Transcatheter Valve-in-Valve and Valve-in-Ring for Treating Aortic and Mitral Surgical Prosthetic Dysfunction

Jean-Michel Paradis, MD, Maria Del Trigo, MD, Rishi Puri, MBBS, PhD, Josep Rodés-Cabau, MD

ABSTRACT

Bioprosthetic valve use has increased significantly. Considering their limited durability, there will remain an ongoing clinical need for repairing or replacing these prostheses in the future. The current standard of care for treating bioprosthetic valve degeneration involves redo open-heart surgery. However, repeat cardiac surgery may be associated with significant morbidity and mortality. With the rapid evolution of transcatheter heart valve therapies, the feasibility and safety of implanting a transcatheter heart valve within a failed tissue valve has been established. We review the historical perspective of transcatheter valve-in-valve therapy, as well as the main procedural challenges and clinical outcomes associated with this new less invasive treatment option. (J Am Coll Cardiol 2015;66:2019–37) © 2015 by the American College of Cardiology Foundation.

Approximately 85,000 heart valve prostheses are implanted in the United States each year, and a total of 275,000 worldwide (1). There are 2 main types of heart valve prostheses: 1) mechanical prosthetic valves, which require lifelong anticoagulation; and 2) tissue valves, which obviate the need for anticoagulation, but do not last as long as their mechanical counterparts. In the United States, the use of bioprosthetic aortic valve replacement increased from 26.7% in 1998 to 50.2% in 2005 (1,2). This major shift in the use of surgical bioprostheses, combined with their shorter durability and the increasing life expectancy of an aging population, is expected to translate into a major increase in the incidence of patients with surgical valve failure in the coming years.

The standard of care for degenerated bioprosthetic valves currently involves reoperative valve replacement. Over the last 2 decades, the mortality associated with redo aortic valve surgery has decreased significantly (3–5). Nevertheless, depending on risk factors and patient status, the recognized mortality of bioprosthetic re-replacement for structural valve failure still ranges from 3% to 23% in most series (3,6). Advanced age, female sex, preoperative New York Heart Association functional class, left ventricular dysfunction, renal failure, pulmonary disease, cognitive impairment, number of prior operations, urgency of operation, and technical difficulties caused by adhesions have each been identified as predictors of higher reoperative risk (4,5,7).

Transcatheter aortic valve replacement (TAVR) is now established as the preferred treatment option for inoperable patients and a valid alternative for high-risk individuals with severe symptomatic native aortic stenosis (8). In recent years, following rapid evolution within the transcatheter valve field, the successful placement of new bioprosthetic valves via a transcatheter approach within degenerative aortic, mitral, tricuspid, and pulmonic surgical bioprostheses has been confirmed (9–13). This study reviews the historical perspective, technical challenges, major
MISMATCH: Valve Replacement and Deterioration

**TRANSVALVULAR WINDING**

valve = transcatheter heart valve
TAVR = transcatheter aortic valve replacement
SVD = structural valve deterioration
SHV = surgical heart valve
SAVR = surgical aortic valve replacement
CT = computed tomography
LVOT = left ventricular outflow tract
PPM = prosthesis-patient mismatch
SAVR = surgical aortic valve replacement
SHV = surgical heart valve
STS = Society of Thoracic Surgeons
SVD = structural valve deterioration
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve

**SURGICAL BIOPROSTHETIC VALVES**

Characteristics of the main surgical bioprostheses are summarized in Table 1. Surgical bioprostheses are usually made of leaflets from bovine pericardium or porcine valve leaflets. Homografts, which are less frequently used, are composed of human tissue. Bioprosthetic valves can be further categorized as stented or stentless. The 3 main components of stented bioprosthetic valves are: 1) valve leaflets, which can be mounted internally or externally; 2) the stent frame, which is composed of polymeric material or alloys; and 3) a circular or scallop-shaped external sewing ring (Figure 1) (7). Surgical heart valves are manufactured as either intra-annular or supra-annular, and the portion visible on fluoroscopy can be either the stent frame or the sewing ring. The sewing ring is located at the bottom or 3 to 5 mm above the bottom of the stent frame in the supra- and intra-annular valve designs, respectively (14).

Stentless valves were developed to optimize the effective orifice area and thus facilitate left ventricular mass regression (15). These valves do not have a base ring or a frame to support the leaflets, are sutured to the root in the actual position of the native valve, and can be of autograft, heterograft, or homograft origin (15,16).

More recently, sutureless valves that avoid the placement of sutures following annulus decalcification have been introduced, with the objective of reducing cross-clamp and cardiopulmonary bypass duration, and facilitating minimally invasive surgery and complex cardiac interventions (17).

**LABELING OF SURGICAL BIOPROSTHETIC VALVES.** Surgical heart valve (SHV) sizing across manufacturers lacks standardization (18). This may lead to confusion because the valve size labeling may correspond to internal or external diameters for stented valves, and to external diameter for stentless valves (7). Consequently, 2 bioprostheses may have distinctive internal and external sewing ring diameters, despite having the same label size. For valve-in-valve therapy, the most relevant parameter relates to valve internal dimensions, which are often significantly smaller than the labeled valve size. Therefore, when envisioning a valve-in-valve procedure, it is imperative for the heart team to elicit the precise diameters of the failing bioprosthetic valve (usually available by reviewing published detailed tables providing valves dimensions (7,19) or by consulting directly with the manufacturer). However, it is important to realize that, by convention, the stent internal diameter represents exclusively the internal dimension of a bare stent covered with fabric or pericardium, without accounting for the effect of artificial leaflets sutured within the stent (20). Indeed, in a study conceived to assess the effect of tissue leaflets on stent internal diameter, the true internal valve diameter was smaller than the actual stent internal diameter in the majority of SHV designs (20). Moreover, calcification or pannus can generate a discrepancy between the expected and the observed internal stent diameters. Multidetector computed tomography (MDCT) and transesophageal echocardiography could be performed to determine the precise dimensions of the SHV. Nevertheless, considering the absence of standardized measures regarding the internal diameter of a variety of SHVs and the variability of the measurements obtained from differing imaging modalities, the exact role of pre-procedural imaging with MDCT or transesophageal echocardiogram (TEE) in the valve-in-valve field is yet to be determined.

**FAILURE OF BIOPROSTHETIC VALVES: MECHANISMS AND INCIDENCE.** Structural dysfunction, due to progressive tissue deterioration, is the main cause of bioprosthetic valve failure. The major pathophysiological mechanism underlying this process is cusp calcification. This mineralization process may engender pure stenosis via cusp stiffening, and may also precipitate regurgitation due to secondary tears. Recent studies have suggested that bioprosthetic valve calcification is an active rather than a passive process, and is modulated by numerous mechanisms, including lipid-mediated inflammation, immune response, and dysfunctional phosphocalcific metabolism (21). Calcium deposits can be located on cuspal tissue (intrinsic calcification), but may also develop in thrombi or endocarditic vegetations (extrinsic calcification) (1). To attenuate calcification and further degeneration, glutaraldehyde valve leaflet pretreatment is widely used.

Another mechanism contributing to the limited lifespan of bioprosthetic valves is progressive collagen deterioration (1). Design-related tearing, rather than leaflet calcification, generally explains the deterioration of bovine pericardial valves (1). The formation of tissue overgrowth (e.g., pannus), thrombus, or paravalvular leaks can usually explain bioprosthetic dysfunction not related to leaflet failure. Usually, valve stenosis is the consequence of calcification, pannus, or thrombus, whereas leaflet destruction or
paravalvular leak will lead to regurgitation. The outcome of the degenerative tissue valves can also be a combination of stenosis and regurgitation.

The mechanisms of aortic bioprosthetic dysfunction are equally distributed as predominantly stenotic, regurgitant, or mixed, with a higher rate of stenotic dysfunction among stented and smaller (≤21 mm) valves, and a predominant regurgitant mechanism among stentless valves (11). In mitral bioprostheses, regurgitation is the predominant mechanism of valve dysfunction (49%), followed by stenosis (21%) and combined mechanisms (30%) (22).

The incidence of aortic and mitral bioprosthesis structural valve deterioration (SVD) requiring re-intervention is 20% to 30% at 10 years and over 50% at 15 years (23,24) (Central Illustration). Because bioprosthetic valve calcification is hastened in younger individuals, the likelihood of primary tissue failure diminishes with age (1,25,26) (Figure 2). Sénége et al. (27) showed that early valve failure is not infrequent and constitutes a life-threatening condition. A younger age at implantation, renal failure, hyperparathyroidism, higher post-operative gradients, prosthesis-patient mismatch (PPM), and mitral valve position are associated with a higher risk of tissue valve deterioration (21,23,24,26). One of the most likely hypotheses for the greater frequency of mitral bioprosthetic failure relative to aortic bioprosthetic failure may be partially related to the higher close-off pressure in the mitral position (usually >100 mm Hg vs. <100 mm Hg in the aortic position). Also, the closure time is expected to be greater with a mitral prosthesis compared with an aortic prosthesis, possibly contributing to a higher degeneration rate (1).

TRANSCATHETER VALVE-IN-VALVE INTERVENTIONS: HISTORICAL PERSPECTIVES

AORTIC POSITION. Following pre-clinical studies evaluating the valve-in-valve technique, the first-in-human cases of valve-in-valve procedures for treating aortic bioprosthetic dysfunction were reported in 2007 using the CoreValve and Cribier-Edwards valve systems (9,28,29). This was followed by publication of several case reports of valve-in-valve procedures combining different transcatheter devices (30-35) and surgical valves, as well as several small single-center and multicenter series (36-39). More recently, retrospective collection of valve-in-valve cases on a voluntary basis from different centers worldwide has led to the publication of the 2 largest series of valve-in-valve procedures to date, including 202 and 459 patients, respectively (10,11). In addition, a prospective registry evaluating the Edwards SAPIEN valve for valve-in-valve procedures has recently been completed (PARTNER VinV registry [PARTNER II Trial: Placement of AoRTic TraNsclathET Valves]; NCT01314313) and another prospective registry using the CoreValve system (Medtronic) is still ongoing (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis With Significant Comorbidities in Very High Risk Subjects Who Need Aortic Valve Replacement; NCT01675440).

To date, the vast majority of valve-in-valve procedures for aortic valve dysfunction have been performed with the Edwards SAPIEN/SAPIEN XT valves (Edwards Lifesciences, Irvine, California) and the CoreValve system (Medtronic, Minneapolis, Minnesota). Nonetheless, most transcatheter valves available for the treatment of native aortic valve stenosis have also been used for treating surgical aortic bioprosthetic dysfunction (Figure 3).

MITRAL POSITION. Data from pre-clinical studies proving the concept of mitral valve-in-valve and valve-in-ring procedures were reported in 2007 (9) and 2009 (40), respectively. The first-in-human cases of valve-in-valve and valve-in-ring procedures for mitral valve or ring dysfunction were reported in 2009 (41) and 2011 (42), respectively. Most cases of mitral valve-in-valve or valve-in-ring have been performed with the balloon-expandable Edwards system, via transapical or antegrade transfemoral approaches. The balloon-expandable Melody valve (Medtronic, Minneapolis, Minnesota) has been used in a minority of cases (43,44). More recently, the use of self-expandable transcatheter valve systems for treating mitral valve dysfunction has also been reported (45) (Figure 3).

AORTIC VALVE-IN-VALVE PROCEDURES

PRE-PROCEDURAL WORK-UP AND PROCEDURAL ASPECTS. The pre-procedural work-up and peri-procedural steps involved in valve-in-valve procedures are similar to those used for patients with native aortic valve stenosis considered for TAVR (46). However, specific aspects of preparation of a valve-in-valve procedure should be considered:

1. **Type of bioprosthesis dysfunction.** A sound knowledge of prior cardiac surgery and failed bioprosthetic valves is essential. A meticulous echocardiographic evaluation is very useful for determining the mode of valve failure. In order to eliminate endocarditis or paravalvular (rather than
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<tr>
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<td>St. Jude Medical</td>
<td>Toronto SPV root</td>
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Adapted with permission from Bapat et al. (19), Bapat et al. (55), and Flameng et al. (81).

SHV = surgical heart valve.
transvalvular) leaks, TEE should be routinely performed in patients with regurgitation as the main mode of valve failure. For those patients presenting predominantly with valve stenosis, a careful review of prior echocardiographic examinations, as well as recent changes in clinical status should be undertaken to differentiate between surgical valve failure and PPM following surgical aortic valve replacement (SAVR). This is of particular importance in those patients with smaller surgical valves (<21 mm), which are frequently associated with higher transvalvular gradients and a greater incidence of moderate-to-severe PPM post-SAVR (47). At best, a valve-in-valve procedure is expected to reduce transvalvular gradients to the values obtained immediately following SAVR, and this should be taken into account in the clinical decision-making process for valve-in-valve procedures.

2. **Valve sizing** remains a challenging aspect of valve-in-valve procedures. As previously discussed, a detailed knowledge of the surgical valve labeling is essential. Importantly, the true inner diameter of the surgical valve, which is usually a few millimeters smaller than the outer diameter, is used for sizing purposes. As transcatheter valves are sutureless devices, ensuring transcatheter valve fixation and stability greatly depends on the principle of relative oversizing of the transcatheter valve with respect to aortic annulus dimensions. Whereas significant paravalvular regurgitation or embolization may result from transcatheter valve undersizing, excessive oversizing can lead to incomplete expansion, incorrect functioning, and/or higher residual gradients (20). To date, in the absence of dedicated sizing guidelines for valve-in-valve procedures, the main principles of sizing (including the degree of oversizing) used for native aortic valves are usually applied (48–50). Thus, performing a 3-dimensional (3D) reconstruction (by computed tomography [CT] or TEE) of the surgical prosthesis in order to obtain an additional measure of the inner diameter and area/perimeter is advisable. Three-dimensional TEE, a technique that can be used intraprocedurally during TAVR and does not require iodinated contrast, has superior temporal resolution, provides physiological information, and essentially eliminates motion-based artifacts. Nonetheless, 3D TEE is hampered by suboptimal lateral resolution in the coronal plane, which diminishes the ability to measure the blood/tissue interface in this plane. In contrast, MDCT, which requires iodinated contrast, typically offers superior tissue/lumen contrast, but may be limited by artifacts because of partial volume-averaging effects (blooming), heart/lung motion, patient motion, and arrhythmias. Both imaging modalities are user-dependent, and prime image acquisition and analysis are essential for satisfactory annular assessment. Indeed, echocardiography and MDCT are often considered complementary imaging modalities.

In addition to those imaging modalities, the use of the **Valve in Valve app** is highly recommended. This free app, developed collaboratively by the technology
3. **Risk of coronary obstruction.** Aortic valve-in-valve procedures have been associated with an increased risk of coronary obstruction, especially in patients with stentless valve dysfunction. In a large series of coronary obstruction cases post-TAVR, the risk of coronary obstruction was >2 times more frequent among valve-in-valve procedures compared with TAVR performed within native valves (51). The main anatomic factors associated with a higher risk of coronary obstruction were low coronary height (<12 mm) and reduced diameter of the sinus of Valsalva (<30 mm). During valve-in-valve cases, a leaflet directly contacting either the coronary ostium, or the aortic root surrounding the coronary ostium most commonly generates coronary obstruction. The major predisposing condition is the proximity of the coronary ostium to the projected final position of the displaced bioprosthetic leaflet after transcatheter heart valve (THV) placement. Therefore, during the pre-procedural work-up, it is often useful to perform aortography to identify patients at risk for coronary obstruction. This should be done in a projection perpendicular to both the SHV and the coronary ostia. Because coronary ostia are typically located midway between 2 surgical valve posts, a projection perpendicular to the coronary ostia is generally attained by perfectly superimposing 2 adjacent posts (1 to 2 technique) (52). Computed tomography or 3D TEE, by allowing 3D anatomic assessment, can also be used in the screening process for the risk of coronary obstruction. However, even if these modalities can assess the geometric axis of the SHV at the level of the coronary artery ostia and can anatomically define the distance between the future THV and the coronary ostia, their role in predicting this potential life-threatening complication is still evolving. When a patient is at high risk of coronary obstruction, the following options should be contemplated: consider redo open heart surgery; use of periprocedural general anesthesia; selection of a smaller or underfilled transcatheter valve; positioning the transcatheter valve in a lower position with respect to the SHV; use of a retrievable device (e.g., Evolut-R, Portico, Lotus); use of a transcatheter valve with clipping mechanism that grasp SHV leaflets (e.g., JenaValve, Engager); and placement of a wire and an undeployed stent within the distal coronary bed, ready to be pulled back and implanted emergently, if needed (52).

4. **Need for balloon pre-dilation.** The role of balloon aortic pre-dilation during valve-in-valve procedures is debatable. Degenerative bioprostheses

### CENTRAL ILLUSTRATION: Valve-in-Valve: Failure of Bioprosthetic Valves and Transcatheter Options for High-Risk Patients

#### Failure of Aortic and Mitral Bioprosthetic Valves

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<th>Incidence of bioprosthesis failure (no. of years after surgery)</th>
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<td>20-30% (10 yrs)</td>
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<td>50% (15 yrs)</td>
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**Standard-of-care for suitable patients**
- Reoperative valve replacement.
- High-risk patients considered for less invasive procedures — See below

#### Transcatheter Valve-in-Valve (VIV) or Valve-in-Ring (Patients at high or prohibitive surgical risk)

**Preprocedural evaluation**
- Evaluate type of bioprosthesis dysfunction;
- valve size; valve positioning; risk of coronary obstruction;
- risk of left ventricular outflow tract (LVOT) obstruction

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<th>Transcatheter aortic VIV</th>
<th>Transcatheter mitral VIV and valve-in-ring</th>
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<tr>
<td>Successful procedure in 95% of patients</td>
<td>Successful procedure in 95% of patients</td>
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<tr>
<td>8% 30-day mortality rate</td>
<td>8.5% 30-day mortality rate</td>
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<tr>
<td>15.1% 1-year mortality rate</td>
<td>20.5% 14-month mortality rate</td>
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**Risks**
- Elevated post-procedural gradient
- Coronary obstruction
- Unknown durability
- Malpositioning

- LVOT obstruction
- Thrombosis
- Significant mitral regurgitation
- Unknown durability
- Malpositioning


Incidence of bioprosthesis valve dysfunction and transcatheter aortic valve-in-valve and valve-in-ring as alternative treatments in those patients at high or prohibitive surgical risk. Aspects of the main pre-procedural evaluation, risks, and results of transcatheter treatment of aortic and mitral bioprosthetic dysfunction are shown.
are friable, and the risks of embolization and stroke or destruction and acute regurgitation with pre-dilation must be weighed against the possibilities of both difficulty in crossing a severely stenotic surgical valve and suboptimal expansion of the THV. Although societal guidelines advise against using balloon dilation for prosthetic left-sided heart valves (53,54), balloon pre-dilation is still performed in about one-fourth of valve-in-valve cases (11). When a retrograde approach is selected (e.g., transarterial or transaortic crossing of an aortic bioprosthesis), cautious pre-dilation with an undersized balloon may be considered, especially in the presence of a bulky and severely calcified stenotic aortic valve. In those cases performed through a transapical approach or in the presence of regurgitant bioprostheses, pre-dilation is generally not recommended. In surgical valves with no fluoroscopic markers or in a Mosaic valve, balloon pre-dilation could be used to locate the exact level of the neoanulus and facilitate transcatheter valve positioning. Finally, balloon pre-dilation can contribute to the evaluation of the geometric relationship between the SHV and the coronary ostia (52).

5. Transcatheter valve positioning. The optimal placement of a transcatheter valve inside a SHV can be defined as a placement where the valve is securely fixed to avoid embolization, with its uncovered portion remaining above the sewing ring of the SHV (14). The use of a reference plane, or “neo-annulus” has been proposed by Bapat et al. (55) to achieve an optimal placement of THV devices inside a given surgical heart valve (Table 1). Indeed, irrespective of the valve design, the narrowest portion of all surgical valves is at the level of its sewing ring, which should be used as a reference level during valve-in-valve cases (55). The relationship between the fluoroscopically visible component of a SHV and the level of the sewing ring must be well acknowledged to optimize transcatheter valve positioning within any SHV. Similar to conventional TAVR, finding a fluoroscopic coplanar or perpendicular view to the bioprosthetic annular plane is helpful. This can be accomplished by finding a fluoroscopic angulation where the radiopaque components of the bioprosthetic basal ring appear as a straight line or the radiopaque components of the valve posts seem to be at the same height (52). The use of TEE can be very useful for valve positioning in the absence of surgical valve leaflet calcification, in the presence of stentless valves, or when the mode of SHV failure is severe regurgitation. Rapid ventricular pacing and the use of repositionable self-expanding devices can also be considered to obtain a perfect depth of implantation. Ideally, the Edwards SAPIEN XT valve should be implanted 4 to 5 mm below the sewing ring of the SHV, whereas the CoreValve should be positioned 5 mm below the neoanunnular plane (14). Interestingly, optimal THV positioning within stented SHVs can usually be obtained with minimal contrast dye injection, or even without any. Several examples of aortic valve-in-valve cases are shown in Figure 4.
EARLY OUTCOMES

PROCEDURAL AND 30-DAY OUTCOMES. Baseline characteristics and outcomes of all published case series including more than 10 aortic valve-in-valve procedures are shown in Table 2 (10,34,36,56–66). The mean age was 78 years, and 58% of patients were men. The mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and Society of Thoracic Surgeons (STS) score were 31.3% and 11.3%, respectively, which represented a much higher risk profile than those reported in most TAVR within native valve series (8). Most surgical valves were stented (82% vs. 18% stentless). The selected routes were transfemoral, transapical, transaxillary, transaortic, and subclavian in 55%, 41.6%, 2%, 1%, and 0.3% of patients, respectively.

The transcatheter valve was successfully implanted in 94.7% of patients, and the mean 30-day mortality rate was 8% (Central Illustration). The mean rate of periprocedural complications was: valve malpositioning/embolization (12.4%); stroke (1.4%); pacemaker implantation (7.6%); and coronary obstruction (2.2%). Interestingly, although the rate of coronary obstruction and valve malpositioning seems to be higher, as compared with TAVR within native valves, pacemaker implantation rates are much lower. We hypothesize that the surgical valve structure may function as a protective factor in such cases, in addition to a higher (more aortic) implantation of the THV. The relatively high malpositioning rate may be due to positioning challenges in those cases with aortic regurgitation as a predominant mechanism of valve failure, which indeed are frequently associated with a lower degree of valve calcification. Also, the lack of fluoroscopic markers in some stentless valves can make the final positioning of the transcatheter valve challenging, and this may translate into a higher rate of valve malpositioning.

VALVE HEMODYNAMICS. The mean transvalvular gradient after aortic valve-in-valve procedures was 15.5 mm Hg (>10 mm Hg in most patients), which is higher than the gradients reported following TAVR within native valves (usually <10 mm Hg) (8,46). The global rate of severe PPM (defined as an effective orifice area <0.65 cm²/m²) following aortic valve-in-valve is 32.1% (Figure 5). That the transcatheter valves are implanted in a nondistensible structure and the amount of material occupying the aortic annulus space (surgical valve + transcatheter valve) may partially explain such results. In addition, some patients already presented with elevated gradients and moderate-to-severe PPM following SAVR (particularly in the group of smaller surgical valves) (47), and this also contributes to the high rate of elevated transvalvular gradients following valve-in-valve procedures.

Dvir et al. (10) evaluated the factors associated with higher transvalvular gradients following valve-in-valve procedures. The use of a balloon-expandable valve (particularly in those patients with surgical valves ≤23 mm) and stenosis (instead of
regurgitation) as a mechanism of surgical valve dysfunction were the factors associated with higher transvalvular gradients post-TAVR (Figure 6). In those patients receiving a CoreValve, a depth of implantation >6 mm below the surgical valve was also associated with higher residual gradients.

The mean rate of paravalvular leaks of at least moderate degree following valve-in-valve procedures is 4%, much lower than the ~10% to 12% reported with first-generation transcatheter valves (8). In fact, up to 74% of the patients had none or trace residual leak following a valve-in-valve procedure, which is similar to the results obtained with the last generation of transcatheter valves for treating native aortic stenosis.

There are some major differential aspects between conventional TAVR and valve-in-valve procedures. Table 3 condenses the relative frequencies of the main complications associated with each type of procedure.

**LATE OUTCOMES**

Only a few valve-in-valve studies have reported 1-year survival rates (10,56,59–65). The mean mortality rate at 1 year has been 15.1% (ranging from 0% to 16.8%) (Table 2). Factors associated with increased 1-year mortality were smaller surgical valves, stenosis as a mechanism of valve dysfunction, and use of the transapical approach (Figure 7) (10). No cases of structural valve failure at midterm follow-up were reported in the most important series of valve-in-valve procedures, but further studies with a longer-term follow-up are needed to determine the degeneration rate of transcatheter valves following these procedures.

**MITRAL VALVE-IN-VALVE AND VALVE-IN-RING PROCEDURES**

Perioperative mortality and morbidity exceeds 15% in patients >75 years of age after reoperation following a first mitral valve intervention (67). Transcatheter valve-in-valve implantation, and, more recently, valve-in-ring procedures have emerged as less invasive alternatives to redo open heart surgery in selected patients deemed at high surgical risk. However, it should be stressed that these new procedures are performed with devices that were initially designed for the aortic or pulmonary valve. Therefore, they are still considered “off-label” and should be performed only as a last resort, when no other feasible options exist.

**PRE-PROCEDURAL WORK-UP AND PROCEDURAL ASPECTS.** Similar to aortic valve-in-valve procedures, an accurate knowledge of the surgical mitral
<table>
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<tr>
<th>First Author, Year (Ref. #)</th>
<th>N</th>
<th>THV Approach</th>
<th>Age (yrs)</th>
<th>Logistic EuroSCORE (%)</th>
<th>STS Score (%)</th>
<th>LVEF (%)</th>
<th>Procedural Success (%)</th>
<th>Mean Gradient Post-ViV (mm Hg)</th>
<th>AR &gt; Moderate Pacemaker</th>
<th>THV Malposition (%)</th>
<th>Coronary Obstruction (%)</th>
<th>PPM (%)</th>
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AR = aortic regurgitation; AS = aortic stenosis; LVEF = left ventricular ejection fraction; NR = not reported; PPM = prosthesis-patient mismatch; STS = Society of Thoracic Surgeons; TA = transapical; TAO = transaortic; TAx = transaxillary; TF = transfemoral; THV = transcatheter heart valve; TS = transseptal; ViV = valve-in-valve.
prosthesis or ring is essential for planning a mitral valve-in-valve or valve-in-ring procedure. The main characteristics of the SHV have already been outlined in a prior section of this review. Regarding the mitral rings, the D-shape of the annuloplasty ring may result in the occurrence of paravalvular leaks following transcatheter valve implantation. Because ring circularization is important to ensure efficient sealing, a transcatheter valve-in-ring procedure should, perhaps, be limited to deformable complete and rigid semilunar annuloplasty devices. Table 4 summarizes all the known surgical mitral rings amenable to a valve-in-ring procedure. Selection of the most appropriate THV is critical. Indeed, especially during valve-in-ring procedures, the capability of the THV to assume a D-shaped morphology, if needed, (e.g., Direct Flow valve) could become an important asset.

PRE-PROCEDURAL CONSIDERATIONS. Akin to aortic valve procedures, patients should undergo a multi-disciplinary team evaluation including cardiologists, cardiothoracic surgeons, anesthesiologists, nurses, and geriatricians. Transthoracic echocardiography and TEE should be performed to assess the severity and mode of bioprosthetic mitral valve failure, as well as left ventricular function. Concomitant coronary disease should be ruled out by a coronary angiogram before the procedure. CT is also very useful to provide information on valve dimensions and other geometric considerations. Left ventricular outflow tract (LVOT) obstruction is one of the potential complications of mitral transcatheter valve procedures, and the proximity between the surgical valve and LVOT, as well as LVOT dimensions should be assessed. However, the exact role of CT measurements in pre-procedural planning needs to be further evaluated (e.g., to better predict the risk of LVOT obstruction).

VALVE SIZING. To optimize anchoring and to limit paravalvular leakage, a minimum of 10% oversizing of the transcatheter valve compared with the true internal diameter of the surgical device is currently recommended (68). It is not appropriate to perform extreme oversizing, as a significantly underexpanded transcatheter valve may lead to incorrect leaflet coaptation, elevated transvalvular gradient, and limited durability.

APPROACH. The majority of mitral valve-in-valve cases are performed within a dedicated hybrid theater or in an operating room under general anesthesia. When the transapical approach is selected, a left mini-thoracotomy is used and purse-string sutures reinforced with pledgets are prepared. The left ventricular apex is punctured, the access sheath is
inserted inside the left ventricle, and a guidewire is advanced under fluoroscopy across the failing bioprosthetic mitral valve into a pulmonary vein. The wire is then exchanged for a stiffer wire. The transcatheter valve (which is crimped in a reverse fashion when an Edwards SAPIEN is used) is then delivered through a standard delivery system. The transcatheter valve is implanted with fluoroscopic and TEE guidance, during rapid ventricular pacing.

When the transseptal approach is chosen, femoral or jugular venous access is obtained. A transseptal puncture is done in a high and posterior position. After placing a sheath in the left atrium, a bolus of heparin is administered and a guidewire is positioned in the left ventricle. Afterward, a stiffer wire with a J curve at the end is gently placed at the left ventricular apex. Pre-dilation is generally avoided. Then, the valve, mounted for an antegrade implantation, is advanced across the atrial septum and then implanted using a slow balloon inflation technique, under rapid ventricular pacing.

**VALVE POSITIONING.** The transcatheter valve should be positioned 3 to 5 mm atrially, relative to the sewing cuff of the SHV (69). For mitral valve-in-ring procedures, it is generally recommended to center the transcatheter valve in relation to the ring, with equal portions within the left atrium and the left ventricle (70). Examples of valve-in-valve and valve-in-ring procedures are shown in Figure 8.

**MITRAL VALVE-IN-VALVE AND VALVE-IN-RING RESULTS**

The reported results of the case series of mitral valve-in-valve and valve-in-ring published to date (43,44,68,70–76) are shown in Table 5. A total of 113 patients (77 valve-in-valve, 36 valve-in-ring) have been reported, with a mean age of 72 years, and a very high surgical risk profile (mean logistic Euroscore and STS scores of 40% and 13.8%, respectively). Most procedures (64%) were performed via a transapical approach and 36% of cases were performed via a transseptal approach. The Edwards SAPIEN XT valve was used in most cases (83%), and the Melody valve was used in 12% of patients. The transcatheter valve was successfully implanted in 94.5% of cases, and mean 30-day mortality rate was 8.2% (Central Illustration). LVOT obstruction occurred in 8.3% of patients undergoing valve-in-ring implantation (n = 3), with no reported cases in valve-in-valve procedures. Mean transvalvular gradient post-valve implantation was 6.3 mm Hg and

![Mortality Rates at 1-Year Follow-Up After Aortic Valve-in-Valve Procedures](image-url)

Mortality rates following aortic valve-in-valve procedures, according to the main mechanism of surgical valve dysfunction (A), surgical valve size (B), and type of transcatheter valve (C). Reprinted with permission from Dvir et al. (10).
residual leaks of at least moderate degree were observed in 3.5% of patients.

The results of a retrospective collection of data from multiple centers worldwide were recently presented (45). This study included a total of 349 and 88 patients who underwent a mitral valve-in-valve and valve-in-ring procedure, respectively. The access route was transapical (78.9%), transseptal after jugular or femoral venous access (18.5%), and direct left atrium (2.5%). The mean age of the study population was 74 years, with 60% women, and a mean STS score of 12.9%. The mechanisms of failure were regurgitation, stenosis, and combined mode in 45%, 23%, and 32% of patients, respectively. The vast majority of the mitral procedures were done under general anesthesia (98.9%) and a balloon pre-dilation was performed in only 24% of cases. Malpositioning of the transcatheter valve occurred in 6.6% of cases.
and LVOT obstruction in 6.9% of cases (2.6% and 8% in valve-in-valve and valve-in-ring procedures, respectively; p = 0.03). At 30 days, the rate of all-cause death was 8.5% (7.7% and 11.4% in valve-in-valve and valve-in-ring procedures, respectively; p = 0.15) and the occurrence of stroke was 2.5% (2.9% and 1.1% in valve-in-valve and valve-in-ring procedures, respectively; p = 0.33). The main procedural results according to the type of procedure (valve-in-valve vs. valve-in-ring) are summarized in Figure 9.

Predictors of suboptimal valve hemodynamic results were also evaluated. The main predictor of post-procedural elevated mitral gradients (≥10 mm Hg) was the presence of a small surgical valve size (label size ≤25 mm). Significant residual mitral regurgitation (≥moderate) was more frequent after mitral valve-in-ring than after valve-in-valve procedures (14.8% vs. 2.6%; p < 0.001) (Figure 9).

The late results (>3 months) of valve-in-valve and valve-in-ring procedures are limited to 7 reports, including a total of 93 patients (43,68,70,71,73,75,76). The mortality rate after a mean follow-up of 14 months was 20.5%. Four cases of valve thrombosis were reported, all >30 days after a valve-in-valve procedure (70,74). During follow-up, 1 patient underwent a second transapical valve-in-valve implantation due to transcatheter valve migration 2 months after an uneventful valve-in-valve procedure (68). There were no cases of late structural valve failure requiring reintervention.

In summary, the preliminary experience with mitral valve-in-valve and valve-in-ring procedures has outlined its feasibility, with acceptable clinical and hemodynamic 30-day and late results, despite the high-risk profile of the treated population. Most procedures were performed via a transapical approach, which is more invasive, yet more direct, and an easier approach for such procedures. However, a progressive shift towards a higher use of the transfemoral/transseptal approach is likely to be seen in the coming years. Of note, valve-in-ring procedures were associated with a much higher risk of major complications, including a higher rate of residual regurgitation and LVOT obstruction. A better understanding of the ring characteristics leading to these greater failure rates is required. Preliminary data suggests that subacute or late valve thrombosis rates may be more frequent in transcatheter valves positioned within the mitral (vs. aortic) position, further outlining that anticoagulation therapy following these procedures may be the preferred antithrombotic strategy. Finally, close clinical follow-up of these patients will be required to determine valve durability and potential late complications.

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<th>N</th>
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<th>Age (yrs)</th>
<th>Logistic EuroScore (%)</th>
<th>STS Score (%)</th>
<th>LVEF (%)</th>
<th>Procedural Success (%)</th>
<th>Valve Embolization (%)</th>
<th>Mean Post-Gradient (mm Hg)</th>
<th>Moderate or Severe Residual MR (%)</th>
<th>Stroke</th>
<th>Short-Term Mortality (30 Days/In-Hospital) (%)</th>
<th>Late Mortality (%)</th>
<th>Follow-Up (months)</th>
<th>Valve Thrombosis (%)</th>
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<td>6</td>
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MR = mitral regurgitation; NR = not reported; other abbreviations as in Table 2.
Valve-in-Ring

Mitral Valve-in-Ring Procedures

VENTRICULAR OUT

Thirty-day rates of death, major stroke, mitral regurgitation, and left ventricular outflow tract (LVOT) obstruction following transcatheter mitral valve-in-valve (n = 349) and valve-in-ring (n = 88) procedures (45).
include a greater implantation rate of SHVs with regurgitation as the predicted main mechanism of degeneration.

Even if current data supports the use of valve-in-valve procedures for most patients, a thorough multidisciplinary heart team approach is strongly recommended for every patient considered for this type of transcatheter therapy. Long-term follow-up and increasing the worldwide clinical experience will be fundamental for establishing the exact role of valve-in-valve implantation for treating degenerative bioprosthetic valves, as well as for addressing the numerous knowledge gaps associated with these innovative procedures.

**REFERENCES**

37. Panoulas VF, Latb A, Colombo A. Transcatheter aortic valve implantation with a Direct Flow Medical valve in a patient with severe aortic
75. Bouleti C, Fassa AA, Himbert D, et al. Transfemoral implantation of transcatheter heart valves after deterioration of mitral bioprosthesis or

**KEY WORDS** bioprosthetic dysfunction, transcatheter aortic valve replacement, valve failure