**THE PRESENT AND FUTURE**

STATE-OF-THE-ART REVIEW

# Transcatheter Therapies for the Treatment of Valvular and Paravalvular Regurgitation in Acquired and Congenital Valvular Heart Disease

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**ABSTRACT**

Transcatheter therapies in structural heart disease have evolved tremendously over the past 15 years. Since the introduction of the first balloon-expandable valves for stenotic lesions with implantation in the pulmonic position in 2000, treatment for valvular heart disease in the outflow position has become more refined, with newer-generation devices, alternative techniques, and novel access approaches. Recent efforts into the inflow position and regurgitant lesions, with transcatheter repair and replacement technologies, have expanded our potential to treat a broader, more heterogeneous patient population. The evolution of multimodality imaging has paralleled these developments. Three- and 4-dimensional visualization and concomitant use of novel technologies, such as fusion imaging, have supported technical growth, from pre-procedural planning and intraprocedural guidance, to assessment of acute results and follow-up. A multimodality approach has allowed operators to overcome many limitations of each modality and facilitated integration of a multidisciplinary team for treatment of this complex patient population. (J Am Coll Cardiol 2015;66:169–83) © 2015 by the American College of Cardiology Foundation.

The recent "epidemic" of valve heart disease (VHD) has growing clinical impact and significant economic burden. Increasing longevity of the population is mostly responsible for the rise in incidence and prevalence of VHD. Advancements in valve surgery and, more recently, in transcatheter valve techniques, are rapidly shifting therapeutic management by enabling less invasive options for patients. In addition, concurrent progress in imaging technologies has provided higher-fidelity information about valvular anatomy and function, and has allowed improved image integration for pre-procedural planning and guidance. Recognition of the applicability and effectiveness of catheter-based valve therapies has further increased interest in these treatment modalities. This state-of-the-art review is

focused on examining current transcatheter therapies for acquired and congenital valvular regurgitation, as well as for regurgitant lesions after valve replacement or repair (Central Illustration).

## CLINICAL IMPLICATIONS OF VALVULAR REGURGITATION

**OUTFLOW VALVES.** Aortic regurgitation (AR) may develop with native valves or in patients who have undergone previous surgical or transcatheter valve interventions. Transvalvular AR results from mechanical leaflet malfunction or structural degeneration following aortic valve replacement, repair, or a valve-sparing procedure. However, a paravalvular leak (PVL) is an abnormal communication between the sewing ring of a surgical prosthesis or sealing skirt of transcatheter prosthesis and the native leaflets. Although the true incidence of aortic PVLs following surgery is unknown, rates as high as 11% have been reported (1,2). PVL is more common following transcatheter aortic valve replacement (TAVR), with rates as high as 85%, but the pooled estimate of residual moderate or severe PVL is 7.4% (3). Predictors of PVL include calcium burden and location, valve undersizing or underexpansion, and depth of implantation (4). AR leads to left ventricular (LV) volume overload, ventricular dilation, and failure (5). The clinical presentation of PVL may be similar to native AR; however, prosthetic dysfunction or PVL may also cause intravascular hemolysis.

Pulmonary regurgitation (PR) is commonly seen in patients with congenital heart disease, particularly with a previous repaired tetralogy of Fallot or significant pulmonary valve stenosis for which balloon or open valvuloplasty has been performed (6). Surgical repair may involve a transannular patch and/or resection of the pulmonary valve leaflets. Patients with a history of pulmonary valve replacement using either a biological conduit (i.e., homograft) or bioprosthetic tissue valve as part of the original repair or a subsequent surgery are also at risk for conduit valve dysfunction over time (7). Right ventricular (RV) volume overload resulting from chronic PR eventually causes RV dilation, progressive systolic and diastolic dysfunction, and tricuspid regurgitation (TR) that are due to annular dilation. This can result in exercise intolerance, heart failure, arrhythmias, and risk for sudden cardiac death (8). RV enlargement may also lead to adverse RV/LV interaction, resulting in dysfunction (9). Timely consideration of pulmonary valve replacement, together with other interventions as needed for any potential abnormalities of RV afterload (e.g., central or peripheral pulmonary artery [PA] stenosis, pulmonary arterial hypertension), is integral in optimizing long-term outcomes (10).

**INFLOW VALVES.** Native mitral regurgitation (MR) or MR after mitral valve replacement or mitral valve repair is not uncommon. The incidence of prosthetic regurgitation depends on the type of prosthesis either bioprosthetic or mechanical. Like aortic PVLs, the true incidence of mitral PVLs is unknown; however, rates as high as 32% have been reported (11). Volume overload from MR induces progressive unfavorable remodeling of the LV and left atrium. At later stages, patients develop pulmonary hypertension, congestive heart failure, and atrial fibrillation (12). Hemodynamics and clinical implications of prosthetic MR are similar to that of native valve regurgitation, with the clinical course depending on the severity and chronicity of the MR, as well as the underlying etiology that led to its development. Hemolytic anemia is a well-recognized complication of mitral prosthetic regurgitation, especially with mechanical valves, and is commonly seen in mitral PVL.

TR, by contrast, results in elevated right atrial pressure and progression to right heart failure with venous engorgement, peripheral edema, ascites, protein-losing enteropathy, cardiac cirrhosis, and cardiac cachexia. The presence of residual TR in patients undergoing other valve interventions is commonly associated with suboptimal outcomes (13). Additionally, patients who develop progressive TR late after left-sided valve surgery represent a particular challenge (14). In this subgroup, despite medical management, surgical correction is associated with a higher risk of morbidity and mortality as a result of the presence of variable degrees of RV dysfunction, pulmonary vascular disease, and right heart failure. The pre-operative condition of the RV and the severity of secondary renal and hepatic impairment are predictors of survival.

## IMAGING OF VALVULAR REGURGITATION

Echocardiography is the gold-standard imaging modality for the evaluation of regurgitant valvular and PVL lesions (15,16). Severity is assessed on the basis of qualitative and quantitative measures. Qualitative measurements include the area of regurgitant color flow, the density and contour of the regurgitant signal, and other indexes such as the time velocity

**CENTRAL ILLUSTRATION** Flowchart of Transcatheter Therapeutic Options for the Treatment of Outflow and Inflow Valves

### Therapies for **aortic regurgitation** with...

**...native valves**
- No approved options for repair
- Transcatheter aortic valve replacement (TAVR): Jena-Valve and off-label TAVR

**...mechanical prosthetic valves**
- No approved options for repair or replacement

**...biological prosthetic valves**
- Valve-in-valve (ViV) off-label TAVR

**...paravalvular leaks (PVL)**
- Off-label Amplatzer vascular plug IV (AVP IV)

### Therapies for **pulmonic regurgitation** with...

**...native valves**
- No approved options for repair
- Off-label transcatheter pulmonic valve replacement (TPVR): Medtronic Melody valve and Edwards SAPIEN pulmonic transcatheter heart valve

**...implanted conduits or biological prosthetic valves**
- TPVR

**...paravalvular leaks (PVL)**
- Off-label Amplatzer vascular plugs

### Therapies for **mitral regurgitation** with...

**...native valves**
- Edge-to-edge repair: Mitraclip
- Annuloplasty rings: Carillon (Direct); Mitralign, Accucinch device and Cardioband (Indirect)
- Chordal implants: NeoChord and V-Chordal
- Transcatheter mitral valve replacement (TMVR): CardiAQ mitral valve, Fortis mitral valve, TIARA mitral valve and Tendyne mitral valve

**...mechanical prosthetic valves**
- No approved options for repair or replacement

**...biological prosthetic valves**
- ViV off-label TAVR for prosthesis
- Valve-in-ring (ViR) off-label TAVR for annuloplasty

**...paravalvular leaks (PVL)**
- Off-label Amplatzer vascular plugs

### Therapies for **tricuspid regurgitation** with...

**...native valves**
- Repair: Mitralign and TriCinch system
- Transcatheter tricuspid valve replacement (TTVR) concepts: Heterotopic balloon or self-expanding implants and custom-made stent valves

**...mechanical prosthetic valves**
- No approved options for repair or replacement

**...biological prosthetic valves and annuloplasty rings**
- Off-label TAVR

**...paravalvular leaks (PVL)**
- Off-label Amplatzer vascular plugs

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Flowchart of novel transcatheter therapeutic options for the treatment of regurgitant native and prosthetic cardiac valves in the outflow (aortic and pulmonic) and outflow (mitral and tricuspid) positions.

index; quantitative measurements include the diameter of vena contracta, effective regurgitant orifice area, regurgitant volume, and regurgitant fraction (16-18). Assessment of ventricular function including ejection fraction, fractional area change, ventricular 2-dimensional strain/speckle tracking, and tricuspid annular plane systolic excursion can also be obtained.

In transthoracic echocardiography, the position of the interrogated valve plays an important part in the accuracy of evaluation. The farther the distance of the valve from the anterior chest wall, the higher the likelihood of underestimating the severity of regurgitation. Furthermore, the presence of a prosthetic valve may cause a shadowing artifact, making assessment a challenge. Transesophageal echocardiography (TEE) can solve some of these limitations. Advancements in real-time 3-dimensional echocardiography provide superb visualization of cardiac abnormalities, as well as wires, catheters, and devices; it also provides real-time assessment for any complications such as perforations, pericardial tamponade, and device embolization.

Quantification methods used in assessment of the severity of prosthetic regurgitation are similar to those used for native valve regurgitation; however, a few caveats exist. Differentiation between transvalvular and paravalvular regurgitation can be challenging, as the origin of the jet may sometimes be masked. For similar reasons, vena contracta may be difficult to accurately measure, particularly with eccentric paravalvular jets. The circumferential extent of the PVL, obtained by careful analysis of color Doppler data from different views, can be used as a semiquantitative assessment of PVL severity. When all parameters fit into 1 category, severity of the regurgitation (native, prosthetic, or paravalvular) can be determined. When a discrepancy exists, combining all available data with data obtained by other imaging modalities is of paramount importance for accurate diagnosis (18).

Computed tomography angiography (CTA) enables the evaluation of both cardiac structure and function, and more recently, has been integral for the characterization of both native and prosthetic cardiac valves in the pre-procedural planning and guidance of transcatheter valve therapies (19). CTA can provide detailed analysis of valvular, paravalvular, ventricular, and vascular anatomy. Direct planimetry of the regurgitant orifice area can be performed with good correlation to regurgitant severity by TEE (20). In addition, quantification of regurgitant fraction and volume on the basis of left and right stroke volumes can be performed with high correlation to transthoracic echocardiography

severity (21). Functional evaluation of mechanical valves and detection of pannus, prosthetic leaflet thickening, thrombus adherence and/or calcification, abnormal leaflet mobility, and the presence of surrounding pseudoaneurysm or PVL(s) is also possible (22). This information may help to determine the cause of regurgitation and to differentiate transvalvular from paravalvular types in patients with prosthetic valves.

Moreover, CTA can be employed to determine PVL size and shape, course of tract, degree of calcification, interaction with other cardiac structures, and best access for transcatheter repair. Evaluation of prostheses in the aortic position is a challenge, as both echocardiography and CTA may have significant limitations as a result of acoustic shadowing and attenuation artifacts. Fluoroscopy and angiography are essential diagnostic modalities. Aortic root angiograms with selective contrast injections in varying fluoroscopic projections may help to differentiate flow across the center of the valve prosthesis (transvalvular) from flow around the valve prosthesis (PVL) and, with hemodynamics, aide in assessment of severity.

Furthermore, cardiac magnetic resonance (CMR) allows for assessment of valvular morphology, quantitative volumes, and cardiac function without the need for optimal acoustic windows. CMR appears safe with most bioprosthetic valves; however, it is generally less useful for mechanical prostheses because of significant local mechanical artifacts. In patients who have transcatheter heart valves (THVs), CMR may have a more significant role. Echocardiography often misclassifies the severity of PVL after TAVR, and in suspected cases, CMR may provide more accurate quantification of severity (23,24). In patients with right-sided valve dysfunction, CMR is considered the gold standard for measuring RV volume, an important parameter for determining the optimal timing of intervention in chronic PR (25).

Nonetheless, each imaging modality described provides its own unique detailed anatomic information and spatial relationships of cardiac structures for transcatheter therapies. However, each modality has its own inherent practical limitations, which are secondary to its physical properties and further affected by the underlying nature of the organs and tissues. It is practically impossible for a single imaging modality to capture all necessary details that would ensure clinical accuracy and robustness of analysis while simultaneously being useful for guiding interventions. The obvious approach is to integrate images from multiple modalities to make a more reliable and accurate assessment. Fusion imaging combines the relevant

**FIGURE 1** Application of Multimodality Fusion Imaging Technology for the Planning and Guidance of Transcatheter Heart Valve Implantation
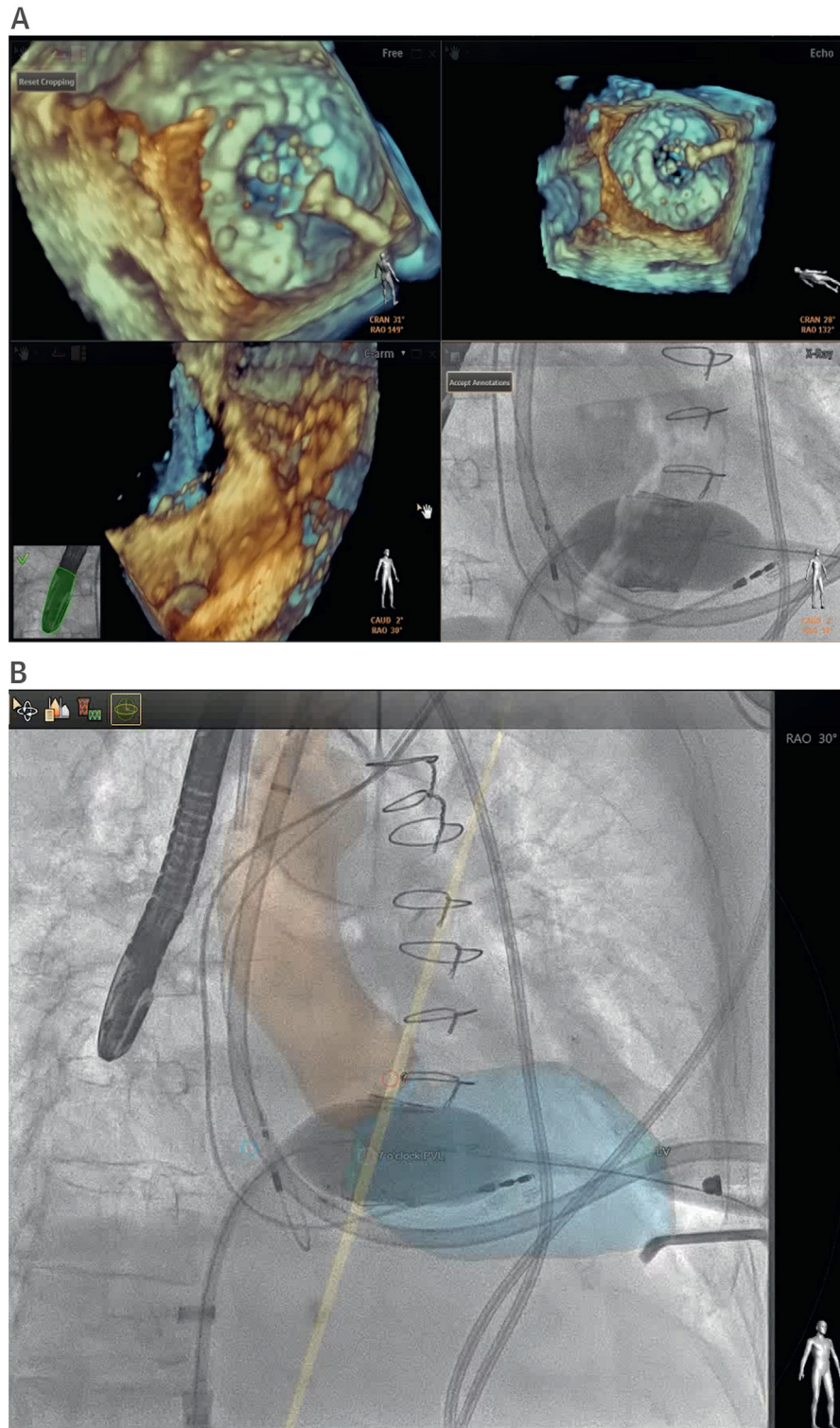


(A) TEE-fluoroscopy and (B) CTA-fluoroscopy (EchoNavigator and HeartNavigator, Philips Healthcare, Best, the Netherlands) fusion imaging. CTA = computed tomography angiography; TEE = transesophageal echocardiography.

**FIGURE 2  Current Transcatheter Technologies Available for the Treatment of Regurgitant Lesions in Native and Prosthetic Outflow Valves**



TAVR = transcatheter aortic valve replacement; TPVR = transcatheter pulmonary valve replacement; ViV = valve-in-valve.
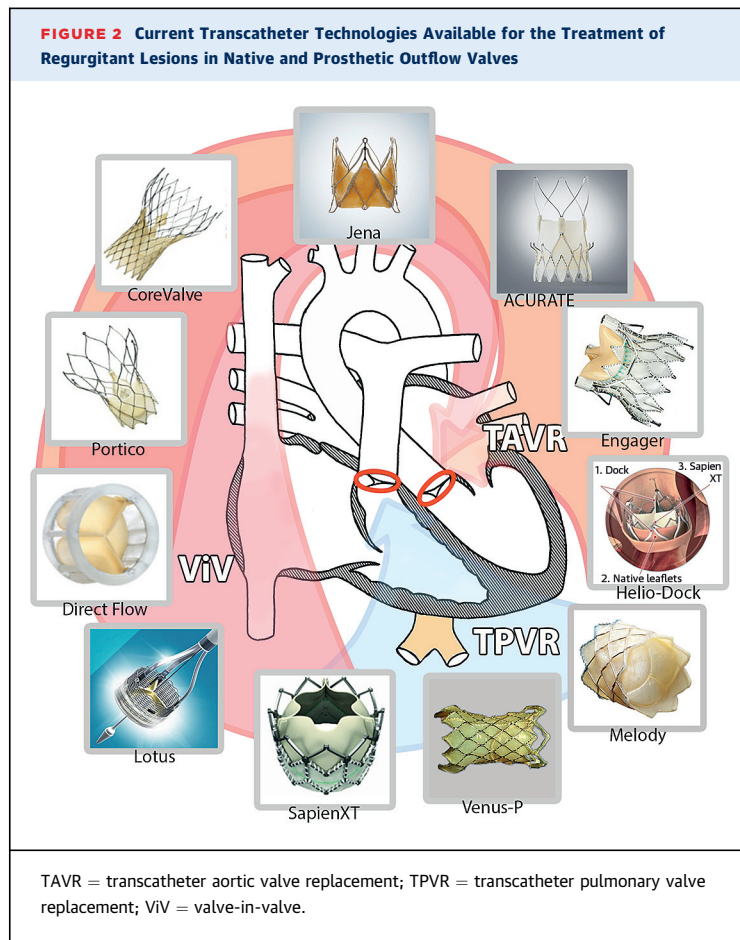
information from 2 or more imaging sources into a single image display, after appropriate coregistration of each imaging dataset has been obtained.

To date, image registration and the fusion of relevant features have been successfully performed with CTA-fluoroscopy and TEE-fluoroscopy (26,27). Fusion imaging provides improved spatial information, and allows precise localization of abnormalities through incorporation of 3-dimensional data while preserving the temporal resolution of fluoroscopy (**Figure 1**). This ability to provide real-time imaging guidance in the cardiac catheterization laboratory has the potential to improve accuracy and safety while reducing radiation exposure, contrast volume, and procedural time. Fusion guidance has been utilized for directed transcatheter access, as well as for procedural interventions in the treatment of both valvular and paravalvular regurgitation (28-31).

## TRANSCATHETER THERAPIES FOR AR

**NATIVE VALVES.** Currently, there are no approved THVs for the treatment of native valve AR in the United States. TAVR is an established treatment for calcific trileaflet aortic stenosis, where leaflet and/or annular calcification aids in anchoring the THV. Primary AR often lacks this calcification; in its absence, valve fixation is a challenge, particularly when the aortic annulus is dilated (32,33). THVs have been used off-label in selected high-risk or extreme-risk AR patients, preferably with the self-expanding types (**Figure 2**). Prostheses are typically oversized relative to the annulus to maximize radial strength and optimize anchoring (34,35). To date, the largest multicenter registry of 42 patients implanted with the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) showed a Valvular Associate Research Consortium (VARC)-defined success of 74.4%, with comparable rates of stroke, vascular complications, bleeding, and mortality to TAVR in aortic stenosis. Residual PVL ≥+2 and the need for valve-in-valve (ViV) implantation were 21% and 19%, respectively, demonstrating early feasibility of this therapeutic application in the context of procedural complexities (36).

The Jena-Valve THV (JenaValve Technology, Munich, Germany) is a second-generation, transapical TAVR valve that has obtained regulatory approval to treat patients with primary AR in native tricuspid aortic valves (**Figure 2**). Its unique design, with active clip fixation of the aortic leaflets, allows for secure implantation, even in the absence of calcification (37). Hemodynamic and clinical outcomes are promising, without any major adverse events. Early experience for treatment of AR revealed 97% VARC-defined success, with all patients having ≤ mild residual PVL (37).

Other novel devices being evaluated for AR include the Engager THV (Medtronic), the ACURATE THV (Symetis SA, Ecublens, Switzerland), and the Helio-Dock (Edwards Lifesciences, Irvine, California) (38,39) (**Figure 2**). The Engager THV is a transapically delivered, self-expanding valve (like the Jena-Valve), which has control arms designed to be placed into the aortic sinuses and secure the aortic leaflets (40). Similarly, the ACURATE THV is a transapically delivered, self-expanding valve; however, it consists of upper and lower crowns that enable valve fixation in a subcoronary and supra-annular position (41). This unique implantation method does not clip, but rather generates a waist for the leaflets, facilitating device self-positioning and anchoring. The Helio-Dock is a self-expandable, cloth-covered, nitinol frame that is delivered transfemorally and engages the aortic leaflets, embedding itself deeply within the 3 aortic sinuses. Transapical placement of a SAPIEN XT (Edwards Lifesciences) is subsequently deployed

across the annulus, utilizing the superelastic dock to increase friction and secure the THV (**Figure 2**).

Additional procedural considerations need to be taken into account when applying transcatheter therapies to native AR. Unlike TAVR with the absence of aortic root calcification, there is a lack of fluoroscopic landmarks for the aortic annulus, making aortography, TEE, and fusion imaging even more important during implantation. Rapid ventricular pacing helps to stabilize THV positioning during deployment, as cardiac motion is hyperdynamic and flow is increased during AR.

**PROSTHETIC VALVES.** More common, and recently achieving U.S. Food and Drug Administration approval, is the use of ViV in patients with degenerated bioprosthesis. Virtually all commercially available valves have been used in this context (**Figure 2**) (42). The presence of a previously implanted prosthesis provides an ideal landing platform for THVs. ViV is generally easier in patients with stented (as compared with stentless) bioprostheses, and successful implantation has been performed in patients with degenerated homografts (43–45). The VIVID (ViV International Data) registry, the largest experience presently published, includes 459 patients who underwent ViV implantation (30% AR alone, 30% combination) with more self-expanding THVs used for regurgitant failure (42). Procedural success was reported to be as high as 93%, with 1-year survival of 83%, and improved outcomes with primary prosthetic AR (46). The incidence of patient–prosthesis mismatch appeared lower in patients with predominant AR at baseline (19% vs. 36%; p < 0.001). It is important to note that there are currently no published data on the mechanical interaction of surgical valves with THVs and the long-term behavior of ViV implants (47). ViV implants have also been used to treat degenerated or malpositioned TAVR prostheses (48,49).

**PVL IN SURGICAL AORTIC VALVES.** For surgical PVLs, surgery has been the traditional approach, and involves either repair or re-replacement. This depends on the surgical findings related to the etiology, condition of the native annulus, size and location of the leak(s), and surgical exposure. Failure rates range from 12% to 35%, with mortality rates that increase with reintervention; because the underlying pathological process remains unchanged, recurrence is common (50). TAVR patients are typically of high surgical risk, and avoidance of open surgery is important. Transcatheter approaches to surgical PVL closure have been applied since 1992 with good results and, more recently, to PVL after TAVR (51,52).

Aortic bioprosthetic or mechanical PVLs are typically approached by a retrograde technique (53). Most aortic leaks require a single device for closure, although more can be placed, if necessary. Care must be taken not to allow for device overhanging, as this can potentially lead to obstruction of the coronary ostia, alter valvular flow in the setting of a narrow LV outflow tracts, or cause prosthetic dysfunction, particularly with mechanical prostheses. The most commonly used devices are Amplatzer vascular plugs (St. Jude Medical, St. Paul, Minnesota) off-label, although any appropriately shaped Amplatzer family of occluders has been used (**Figure 3**). Imaging assessment of leak reduction is performed at all times during the procedure, and once the operator is satisfied with both reduction in degree of leak to mild (or less, if possible) and normal leaflet function (particularly for a mechanical valve), the devices are released.

In a recent meta-analysis that included 12 clinical studies and totaled 362 patients, overall technical and procedural success rates were 86.5% and 76.5%, respectively (54). Thirty percent of PVLs were in the



**FIGURE 3** Current Transcatheter Technologies Used Off-Label for the Treatment of PVLs

PVL = paravalvular leak; TMVR = transcatheter mitral valve replacement; ViV = valve-in-valve.
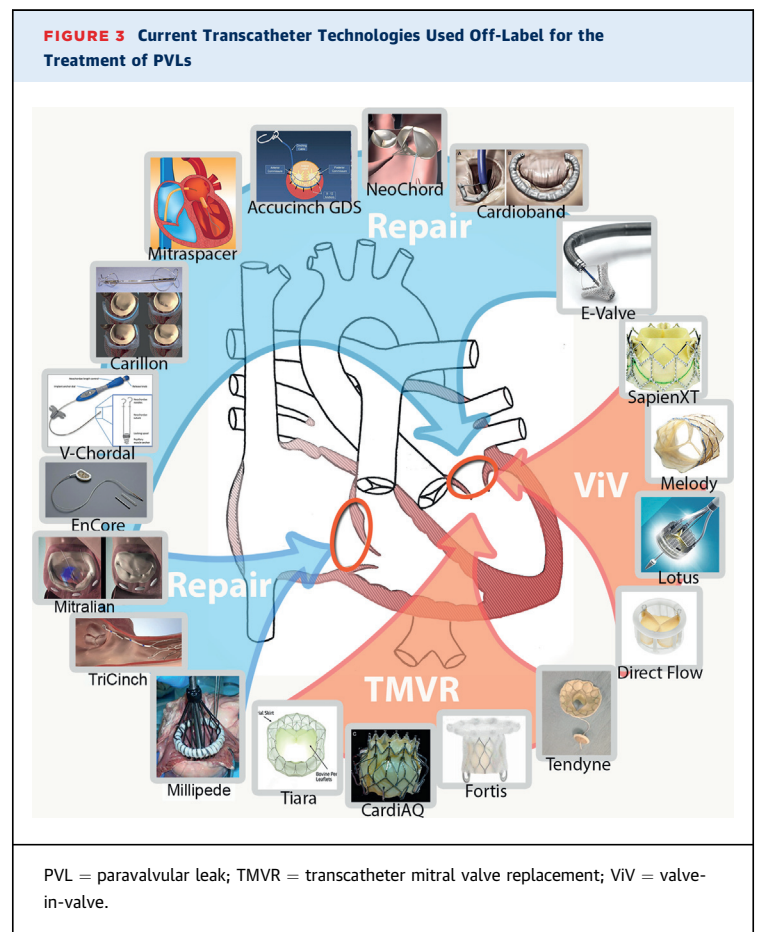
aortic position, with associated technical and procedural success rates of 86.9% and 84.1%, respectively. Successful closure was associated with a lower cardiac mortality (odds ratio [OR]: 0.08; 95% confidence interval [CI]: 0.01 to 0.90), significant improvement in congestive heart failure or hemolysis (OR: 9.95; 95% CI: 2.1 to 66.7), and fewer repeat surgeries (OR: 0.08; 95% CI: 0.01 to 0.4) compared with failed interventions.

**PVL IN TRANSCATHETER AORTIC VALVES.** Treatment options for TAVR PVLs are focused on the timing of onset and can be divided into acute and chronic (55). When moderate or severe PVL is diagnosed acutely at the time of valve implantation, therapeutic steps may include post-dilation to a larger diameter or ViV implantation. If valve malposition or underexpansion is suspected, repeat balloon dilation or implantation of a second valve lower in the LV outflow tract may be considered (56). Redilation is required in approximately 10% of cases, and a second valve is required in 5%, when using a balloon-expandable prosthesis (57,58).

In the chronic setting, when moderate or severe PVL is confirmed, strict attention to afterload reduction and diuresis is critical, particularly because the LV is noncompliant as a result of years of aortic stenosis. If further therapeutic intervention is indicated, then percutaneous retrograde cannulation of the defect with subsequent implantation of closure devices is technically feasible and has been demonstrated to be effective in a small case series (59). Retrograde crossing may be quite challenging because of the presence of native valve leaflets and calcification. No single ideal plug has been identified, although the Amplatzer Vascular Plug IV off-label is preferred for post-TAVR leak closure because of its smaller profile and suitability for delivery via a standard diagnostic catheter (52). Care must be taken to not disrupt TAVR valve position, particularly in a high implant. Next-generation valves, such as the Edwards SAPIEN 3 THV, are associated with a markedly lower incidence of PVL (60). The self-expanding Lotus THV (Boston Scientific, Natick, Massachusetts), which is recapturable and repositionable, similarly has an adaptive seal to allow optimal closure of the paravalvular space (61).

## TRANSCATHETER THERAPIES FOR PR

**NATIVE AND PROSTHETIC VALVES.** Timing of intervention is based on symptomatology, RV volume, and function (62,63). Transcatheter pulmonary valve replacement (TPVR) is designed for treatment of circumferential right ventricular outflow tract

(RVOT) conduit dysfunction when there is evidence of significant pulmonary stenosis and/or regurgitation. TPVR provides an additional therapeutic option, thereby extending conduit lifespan and avoiding the need for repeat median sternotomy (**Figure 2**) (64,65). The Melody THV (Medtronic) was the first to receive approval. A second TPVR option is now available: the SAPIEN pulmonic THV (Edwards Lifesciences) received the CE mark in 2010 and is currently under investigation in the United States (65,66).

Short-term and medium-term outcomes of the Melody valve worldwide suggest significant hemodynamic and clinical improvements, with good durability (67-69). Improvements in RV end-diastolic volume have been demonstrated, and the impact of longer-term remodeling on functional status is being evaluated (70). To date, TPVR in patients affected by isolated PR has demonstrated less rewarding symptomatic, hemodynamic, and functional improvement than that affected by RVOT obstruction with or without associated PR (71). The U.S. IDE (Investigational Device Exemption) and Post-Approval Study trials revealed a >90% 1-year freedom from reintervention or valvular dysfunction. Any evidence of dysfunction should prompt a thorough investigation for stent fracture or endocarditis (72,73). Stent fracture is the primary cause for reintervention, because of close apposition of the RVOT to the sternum, with excessive loading forces and the intrinsic characteristics of balloon-expandable stent metals (74). Prestenting of the landing zone before Melody THV placement has significantly reduced stent fracture rates (72,73).

There remains a subset of patients with native RVOT anatomy or a transannular patch yet to undergo surgical RV-to-PA conduit or bioprosthetic valve placement where TPVR is desired. The goal is to provide a THV that will reduce RVOT size while incorporating a pulmonary valve, or to better conform to an irregular, noncircumferential RVOT (potentially utilizing hybrid, off-pump, surgical collaboration for RVOT reduction) (75). Expansion of sizes/types of TPVR valves will facilitate broader applications to a growing population of both young and older patients with RVOT dysfunction (65,75-77). Off-label use of the Melody or SAPIEN XT THV has been reported in native RVOTs with appropriate anatomy, noncircumferential RVOT conduits, and bioprosthetic valve failure in the right-sided and, more recently, in the left-sided positions (76). Additionally, the newly designed Venus-P valve (Venus Medtech, Shanghai, China) has been implanted first-in-man (FIM) in the native RVOT with a good result (**Figure 2**) (78).

**PVL IN SURGICAL OR TRANSCATHETER PULMONIC VALVES.** PVL in surgical prostheses or following TPVR is very uncommon and typically less clinically important. A rare report of transcatheter pulmonary PVL closure has been reported (79). If needed, a standard right heart approach is undertaken, either via the right internal jugular or femoral veins, with techniques similar to aortic or mitral PVL closure. Unlike left-sided PVLs, there is an inability to create an arteriovenous loop to provide support for sheath delivery; stable wire position in the distal PA is essential.

## TRANSCATHETER THERAPIES FOR MR

**NATIVE VALVES.** Most transcatheter therapies for the mitral valve have been developed on the grounds of an established surgical procedure. MitraClip (Abbott Vascular, Menlo Park, California) (**Figure 4**) is the most adopted technology, utilized in nearly 20,000 high-risk or inoperable patients worldwide. The device consists of a cobalt-chromium clip that reproduces the Alfieri repair, a surgical technique in which opposing leaflets at the site of MR are sutured (80). A transseptally delivered, multisteering catheter is directed toward the mitral valve; the clip is then opened and oriented perpendicular to the coaptation line in order to grasp the free edges of the opposing leaflets, creating a double-orifice mitral valve. It is repositionable and retrievable, and multiple clips can be deployed to achieve optimal results. In the EVEREST study (Endovascular Valve Edge-to-edge REpair STudy), the MitraClip had a superior safety profile when compared with surgical repair, mostly on the basis of a lower risk of transfusions (81). In recent registries, procedural success has largely increased, with a decrease in residual MR, improvement of New York Heart Association functional class, and improved quality of life indicators (82,83).

Satisfactory outcomes have been reported when used in patients with advanced heart failure, non-responders to cardiac resynchronization therapy, and in combination with TAVR (84,85). MitraClip therapy has also been successfully adopted following surgical mitral valve repair, including in patients with ring annuloplasty and/or leaflet repair and in patients who developed late systolic anterior motion with LV outflow tract obstruction (86,87). As with any therapy, appropriate patient selection is crucial; leaflet disruption or calcification at the site of MR, poor leaflet mobility, small orifice area, and multiple jets are the main factors causing suboptimal outcomes. In those requiring surgery, the surgery occurred within 6 months after implantation and surgical options are



**FIGURE 4** Current Transcatheter Technologies Available for the Treatment of Regurgitant Lesions in Native and Prosthetic Inflow Valves

ADO = Amplatzer Ductal Occluder; AVP = Amplatzer Vascular Plug; mVSD = Amplatzer muscular VSD occluder.
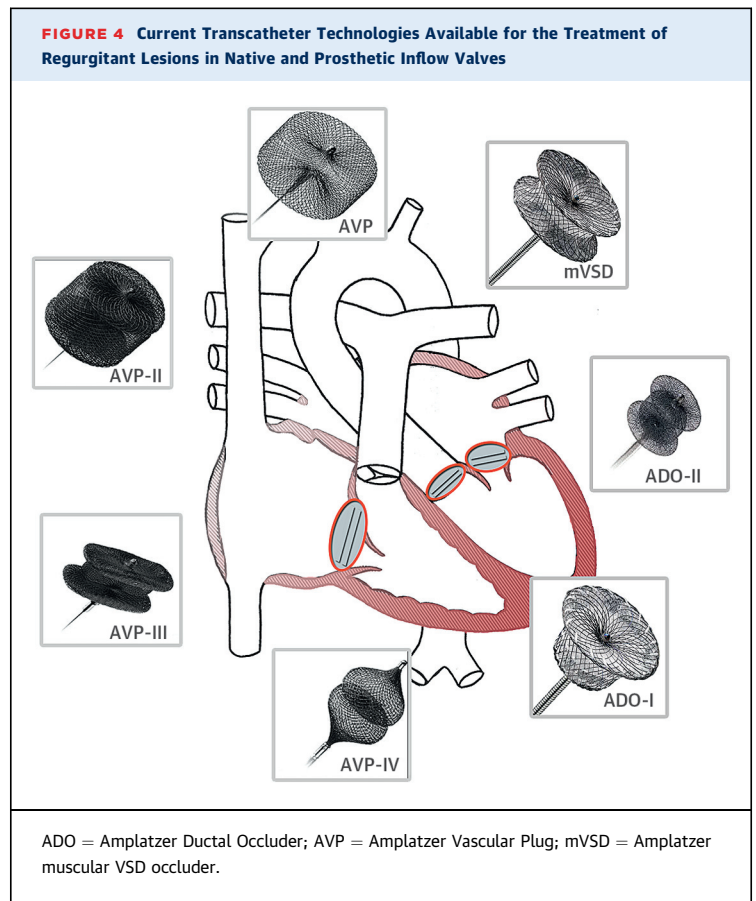
preserved, with 84% able to undergo successful surgical repair (88). Another device that improves leaflet coaptation is the Mitra-Spacer (Cardiosolutions, Stoughton, Massachusetts), a polymer spacer that positions itself at the coaptation zone, filling the regurgitant orifice and providing a sealing surface for the leaflets. Anchored to the LV apex, the device can be delivered via a transseptal or transapical approach. It does not alter the mitral apparatus and can be fully removed; potential complications include thrombus formation or iatrogenic mitral stenosis.

Indirect annuloplasty utilizes the coronary sinus to reshape the mitral annulus. Its close proximity allows for device placement that will shorten the posterior annulus, decreasing the septal-lateral dimension. As a result of suboptimal and unpredictable efficacy, and the risk of coronary obstruction and device perforation, initial outcomes have not been satisfactory (89,90). The Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, Washington) (**Figure 4**), 2 self-expanding nitinol anchors connected by a fixed-length, tension-adjustable cable recently achieved the CE mark (91). The TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) trial

compared this device to medical therapy in patients with functional MR (92). The implanted cohort demonstrated significant reductions in MR and a corresponding reduction in LV diastolic and systolic volumes. Beyond coronary sinus annuloplasty, other indirect annuloplasty approaches have been attempted to reshape/remodel the annulus, including external compression of the atrioventricular groove, the implantation of cinching devices, and application of radiofrequency or ultrasound energy to shrink annular collagen (93-96). Many of these technologies have already been abandoned because of their lack of efficacy and/or safety.

By contrast, direct annuloplasty is the most promising approach for transcatheter repair because it closely reproduces the gold-standard surgical technique. The Mitralign system (Mitralign, Tewksbury, Massachusetts) (Figure 4) has been designed to perform selective plications in the posterior annulus by deploying couples of transannular pledgeted anchors. Tension is applied to sutures connecting the anchors to decrease posterior annular size. Patient enrollment in the CE mark trial is completed, but the device is still not available. The Accucinch system (Guided Delivery Systems, Santa Clara, California) (Figure 4) utilizes a similar technique by implanting a series of 12 retrievable anchors in the subannular space, extending from trigone to trigone. Enrollment into the CINCH2 safety and feasibility trial is underway. The Cardioband system (Valtech Cardio, Or-Yehuda, Israel) (Figure 4) is the closest transcatheter device to a surgical ring (97). It is delivered from a transseptal approach, and a Dacron band is implanted from trigone to trigone using multiple annular anchors. The anchors are delivered under echocardiographic and fluoroscopic guidance, starting from the anterolateral and progressing to the posteromedial commissure. Early clinical experience is promising (97,98). However, the major limitation of these devices is that they are partial rings. Currently, placement of a complete mitral annuloplasty ring is being evaluated using the Millipede (Millipede, Ann Arbor, Michigan) and enCor (Valcare, Irvine, California) systems (Figure 4). Both are delivered via a transseptal approach and fixed into the periannular space.

Lastly, chordal implants are synthetic sutures that can be used to correct leaflet prolapse, usually as a result of ruptured or torn chordae. Implants are attached to the free leaflet margins and anchored to the papillary muscles or LV myocardium. The NeoChord system (NeoChord, Eden Prairie, Minnesota) (Figure 4) allows for open surgical transapical deployment (99). The TACT (Transapical Artificial Chordae Tendinae) trial enrolled 30 patients with severe, isolated posterior leaflet prolapse who underwent placement of at least 1 artificial NeoChord. Procedural success was noted in 87% of patients, with 65% achieving MR reduction to ≤2+ at 30 days. NeoChord has achieved the CE mark. V-Chordal (Valtech Cardio) (Figure 4), originally designed for an off-pump transatrial approach, allows for chordal implantation, with the ability to adjust chordal length under physiological conditions to optimize leaflet coaptation. The FIM trial of 7 patients revealed complete procedural success with efficacy at 2 years. The newer transseptal system has a cinching device that secures 2 chords for each implant. Pre-clinical trials are underway.

Adding to developments in valve repair, transcatheter mitral valve replacement (TMVR) is rapidly evolving. Unlike the aortic valve and TAVR, the complexities of the mitral apparatus make TMVR a challenge. Concerns include the larger annular sizes and asymmetrical anatomy, the need for valve anchoring, and the potential for developing LV outflow tract obstruction and PVL; durability issues dealing with stent fracture, tissue erosion and degeneration require evaluation. Novel valve designs such as a D-shaped frame/orifice, atrial skirt, self-expanding frame, and active fixation systems focus on these issues. Nonetheless, TMVR is still in its infancy, with limited FIM experience (100-103). Four devices have been tested in early clinical trials, the CardiAQ (CardiAQ Valve Technologies, Irvine, California), Fortis (Edwards Lifesciences), TIARA (Neovasc, Vancouver, British Columbia, Canada), and the Tendyne (Tendyne Holdings, Roseville, Minnesota) THVs (Figure 4), but with suboptimal outcomes, highlighting the steep learning curve and the importance of patient selection.

**PROSTHETIC VALVES.** Although transcatheter mitral technologies remain in early clinical stages, current THVs are being implanted successfully within surgical mitral platforms, such as degenerative bioprostheses and complete annuloplasty rings (valve-in-ring [ViR]). The SAPIEN XT (Edwards Lifesciences) and Melody (Medtronic) THVs are currently utilized off-label in the mitral position (104-107). Data from the VIVID registry for mitral ViV/ViR will soon elucidate the efficacy and safety of this technique. To date, the results of 7 Melody ViV implantations within a high-pressure, left-sided hemodynamic environment (1 mitral, 6 aortic) revealed complete freedom from regurgitation and an 86% freedom from significant stenosis at 1-year follow-up (99). The majority of implantations are performed using a surgical transapical approach. Proper patient screening and device selection are crucial for success, with a reduction in

residual gradients and avoidance of LV outflow tract obstruction.

**PVL IN SURGICAL MITRAL VALVES.** Mitral bio-prosthetic and mechanical PVLs are typically approached using an antegrade cannulation technique through transseptal puncture. Access to the mitral valve can be a challenge, especially for posteriorly and medially located PVLs as a result of unfavorable angulation, and in the presence of mechanical aortic valves. Transapical access (TA) can facilitate more precise and accurate navigation within the LV, and ultimately can lead to a decrease in fluoroscopy and procedural times for mitral PVL closure of nearly 35% (26). TA mitral PVL closure can be performed through either an open surgical hybrid or a percutaneous approach, and with high procedural success rates (26,108-110). Given previous cardiac surgery that requires pericardiotomy in this patient population, transcatheter techniques with safe closure can be achieved using off-label Amplatzer devices (St. Jude Medical) (Figure 3). Furthermore, with the use of CTA-fluoroscopy fusion imaging, percutaneous TA puncture can be achieved with an accuracy of within 5 mm of the intended entry site and approximately 15 mm away from the left anterior descending artery (28). The transapical retrograde approach has increasing utility and is the preferred approach at some centers, especially in the presence of double mechanical prosthetic valves.

Like aortic PVL closure, the Amplatzer family of occluders (St. Jude Medical), are utilized off-label to close the defect. One must pay attention so as not to impinge on the prosthetic valve leaflets, and multiple smaller devices may be required to better conform to the paravalvular space. In the same meta-analysis of 12 clinical studies totaling 362 patients described earlier, 70% of PVLs were in the mitral position, with technical and procedural success rates of 82.3% and 73.3%, respectively (54). Twelve percent of the closures were performed using a transapical approach, with a reported success rate of 100%, compared with success rates of 78.4% with an antegrade transseptal approach, and 66.4% with a retrograde transaortic approach.

Mitral annuloplasty ring failure may occur with evidence of significant para-annular ring regurgitation (PAR). PAR can be divided into 2 types: partial dehiscence of the prosthetic ring from the mitral annulus, and tearing of mitral annular tissue without ring dehiscence (111). Little is known about percutaneous options for mitral PAR closure and its resultant complications. Single case reports have identified the potential utility of transcatheter closure with an Amplatzer device for leaks from partial dehiscence, and ViR implantation for leaks from tearing using a Melody THV (Medtronic) with a novel, neochordal tethering approach to the transapical access site (106,107). The longer covered valved stent allows the native leaflets to seal over the stent during systole. This approach provides proof-of-concept that appropriate sealing can occur at the leaflet level without annular apposition, potentially suggesting a future role of transcatheter mitral valve replacement technologies.

**PVL IN TRANSCATHETER MITRAL VALVES.** The high rates of moderate or severe PVL associated with TAVR compared with surgical prostheses and its impact on clinical outcomes pose concerns for TMVR (112). Given the complex nature of the mitral apparatus, PVL may be more common than with TAVR and lead to higher rates of hemolysis, making TAVR less well tolerated. Novel valve designs have been developed, including an atrial skirt and/or D-shaped structure to better conform to the native saddle-shaped annulus, with a focus on reducing PVLs. FIM implantations of TMVR are promising, but it is too early to elucidate the potential scope of this problem (100-103).

## TRANSCATHETER THERAPIES FOR TR

**NATIVE AND PROSTHETIC VALVES.** Surgical treatment of functional TR has been largely focused on annuloplasty with specifically designed right-sided devices; repair or replacement (with or without chordal or papillary reconstruction) is performed less frequently and most often involves patients with congenital heart disease, organic lesions, or advanced annular dilation. When the anatomy is appropriate, transcatheter therapy may be an attractive alternative to surgery for patients deemed high risk. Limited data are available about the feasibility and efficacy of percutaneous tricuspid valve therapies. The use of the MitraClip from a transjugular approach has been reported in 1 patient with corrected transposition of the great arteries and a left-sided, anatomically tricuspid mitral valve (74). The trileaflet design, higher chordal density, and wide malcoaptation gaps from annular dilation make MitraClip an uncertain solution for native functional and congenital TR.

Two other devices have been successfully implanted FIM to treat the valvular components of functional TR. The Mitralign device (Figure 4), originally designed to remodel the mitral annulus, has been successfully implanted in 2 patients for severe TR, with slight modifications of the delivery system (113).

The device is used to plicate the posterior (diaphragmatic) annulus, replicating the bicuspidization Kay procedure. In-hospital results were favorable, with dramatic reductions in right atrial pressure and annular area, and improvement in LV stroke volume. The TriCinch System (4TECH Cardio, Galway, Ireland) (Figure 4) is a percutaneous device designed to cinch the anteroposterior dimension of the annulus in order to improve coaptation (annular cinching). The delivery system allows transfemoral fixation of a stainless-steel corkscrew into the anteroposterior TV annulus, which is connected through a Dacron band to a self-expanding nitinol stent placed in the hepatic region of the inferior vena cava. It has been implanted in a limited number of patients with isolated functional TR. In addition, the Millipede, currently in pre-clinical trials, is a similar device for the mitral position with a complete tricuspid ring and may offer simpler device delivery.

Transcatheter tricuspid valve replacement has not been performed to date, although several concepts are in the pre-clinical phase. Heterotopic implantation of a balloon or self-expanding valve in the inferior vena cava, cranial to the hepatic veins, has been done in a limited number of end-stage patients, aiming at reducing venous hypertension in the hepatorenal system. Likewise, the addition of a valve in the superior vena cava would prevent transmission of systolic waveforms of right atrial hypertension into the superior central systemic venous system. However, with this approach, the right atrium undergoes a potentially detrimental ventricularization process. Some experience has accumulated with balloon-expandable THV implantation in rings (ViR) or in degenerated bioprostheses (ViV) in the tricuspid position (114,115).

**PVL IN SURGICAL TRICUSPID VALVE.** Hemodynamically significant tricuspid PVL, like native tricuspid regurgitation, is rare relative to its occurrence with other cardiac valves. Whether this is a result of few patients receiving tricuspid valve replacements, or technical issues of implantation in this position remains unclear. Limited data suggest that typical clinical manifestations are severe hemolysis and hepatic dysfunction. Recently, successful transcatheter closure has been reported with both bioprosthetic and mechanical prostheses (116-119). Similar to pulmonic PVL, access requires a right heart approach with stable wire positioning.

## FUTURE DIRECTIONS

The future of transcatheter therapies for valvular and paravalvular regurgitation is a matter of fusion—of imaging, of device technologies, and of operator skillsets. The fusion of imaging offers novel opportunities in the diagnosis, planning, and guidance of interventions. Combining structural and functional data is crucial for appropriate patient risk stratification and selection. The merging of multiple imaging modalities can unify information for the operator to aid in improving procedural efficacy and safety. Interdisciplinary collaboration and progression to less invasive techniques has enabled the fusion of technologies, with a steady increase in available hybrid therapies. Although most surgical procedures will likely be performed percutaneously with dedicated devices, the knowledge and experience gained from transcatheter interventions may enhance current surgical tools; a steady trend toward sutureless technologies is a clear example. Moreover, a unified growth in shared technology is inevitable. Finally, but most importantly, this evolution has influenced a new breed of operators and fusion of multidisciplinary skillsets, all focused on achieving optimal results for patients with VHD.

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