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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis

An Expert Statement

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ABSTRACT

The VARC (Valve Academic Research Consortium) for transcatheter aortic valve replacement set the standard for selecting appropriate clinical endpoints reflecting safety and effectiveness of transcatheter devices, and defining single and composite clinical endpoints for clinical trials. No such standardization exists for circumferentially sutured surgical valve paravalvular leak (PVL) closure. This document seeks to provide core principles, appropriate clinical endpoints, and endpoint definitions to be used in clinical trials of PVL closure devices. The PVL Academic Research Consortium met to review evidence and make recommendations for assessment of disease severity, data collection, and updated endpoint definitions. A 5-class grading scheme to evaluate PVL was developed in concordance with VARC recommendations. Unresolved issues in the field are outlined. The current PVL Academic Research Consortium provides recommendations for assessment of disease severity, data collection, and endpoint definitions. Future research in the field is warranted. (J Am Coll Cardiol 2017;69:2067–87) © 2017 American College of Cardiology Foundation and European Society of Cardiology.

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

AE = adverse event

CMR = cardiac magnetic resonance

CT = computed tomography

LA = left atrial/atrium

LV = left ventricle/ventricular

PVL = paravalvular leak

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

The clinical effect of paravalvular leak (PVL) following circumferentially sutured surgical cardiac valve replacement varies significantly depending on the type of valve prosthesis and the implant location. Because the long-term outcomes of this complication, as well as surgical or transcatheter interventions for PVL, are largely unknown, there is a fundamental need for these studies. The absence of comprehensive retrospective or prospective data arises from the lack of uniform definitions to establish disease severity, clinical endpoints to assess safety and efficacy, and appropriate single and composite endpoints to assess outcomes. In addition, cohort/statistical considerations may be specific to this disease process.

Following publication of the first standardized definitions and endpoints associated with cardiac valvular operations (1,2), the Valve Academic Research Consortium (VARC) has collaborated with the U.S. Food and Drug Administration and device manufacturers to periodically update consensus definitions for clinical endpoints in valve implantation. Accordingly, the Paravalvular Leak Academic Research Consortium (PVLARC) working group harnessed Academic Research Consortium (ARC) methodologies and assembled to discuss current knowledge and evidence concerning clinical studies of PVL therapies. Representatives from the U.S. Food and Drug Administration, device manufacturers, and academic research organizations in the United States and Europe joined a panel of clinical cardiologists, interventional cardiovascular specialists, imaging experts, cardiovascular surgeons, and regulatory and clinical trial experts at the American College of Cardiology Heart House in February 2015 to review and summarize the current state of knowledge on surgical PVL. As a result of this effort, this document provides consensus expert opinion on core principles and endpoint definitions for clinical studies of PVL (**Central Illustration**). This document focuses exclusively on PVL following valve replacement with circumferentially sutured surgical prosthetic valves, defined as an abnormal communication between the sewing ring of a surgical prosthesis and the native annulus. PVL related to transcatheter valve prostheses is comprehensively discussed in the VARC-2, Mitral Valve Academic Research Consortium, and various reviews (3,4). The Online Appendix discusses unanswered questions related to this intervention, which could form the basis for clinical studies.

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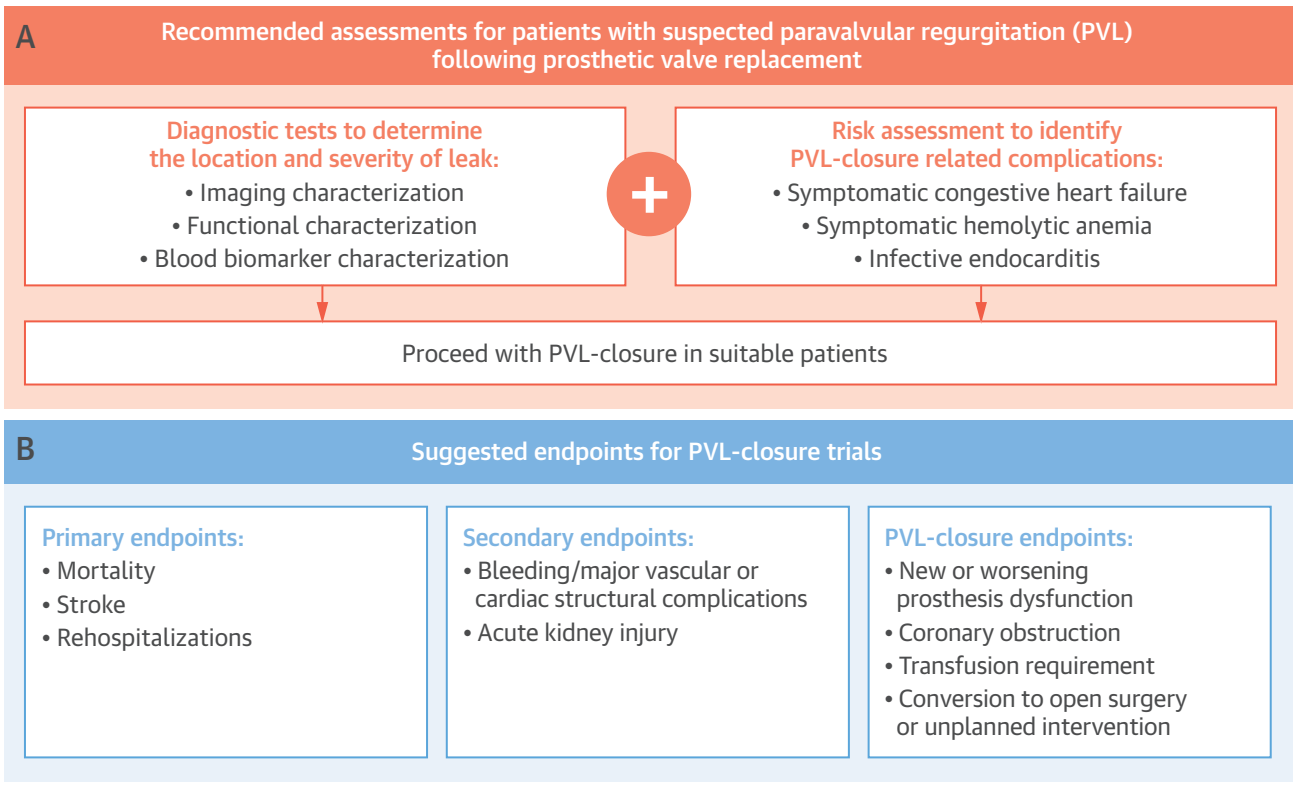
CENTRAL ILLUSTRATION **Approach to PVL of Surgical Valve Prosthesis**



Ruiz, C.E. et al. J Am Coll Cardiol. 2017;69(16):2067–87.

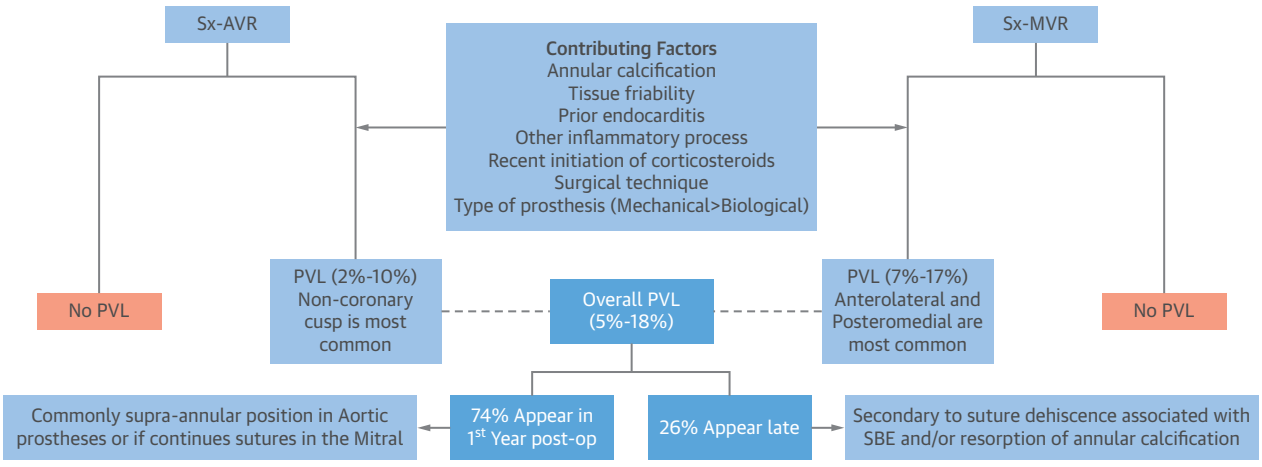
(A) The approach to patients with suspected paravalvular regurgitation (PVL) following surgical valve replacement. Imaging plays a major role in identifying the severity and approach to PVL closure. **(B)** Suggested endpoints for trials or registries of PVL closure.

CORE PRINCIPLES I: CLINICAL

PVLs of varying clinical significance are detected in 5% to 18% of all implanted surgical valves, with an incidence of 2% to 10% in the aortic position and 7% to 17% in the mitral position (5–7). Risk factors for PVL development include: annular calcification, tissue friability, prior endocarditis, or other inflammatory processes and recent initiation of corticosteroid therapy (8–11). Multiple procedural factors may increase the risk of PVL: implantation type (mechanical implants are a greater risk than bioprosthetic implants), position (supra-annular prostheses are a greater risk than annular aortic prostheses), and surgical technique (continuous sutures are a greater risk than interrupted sutures for mitral prostheses) (6,7). A majority (74%) of PVL occurs within the first year of valve implantation (12). Late PVL is commonly related to suture dehiscence associated with infective endocarditis or the gradual resorption of annular calcifications that are not completely debrided (13). **Figure 1** summarizes the prevalence and etiology of PVL.

Percutaneous PVL repair offers an alternative to traditional surgery, especially for patients who are considered to be at high surgical risk (14). Two large single-center studies involving 57 and 141 patients with PVL, respectively, reported overall success rates for percutaneous PVL of 77% to 86.5%, and clinical success ranging from 67% to 77% (15,16). A recent Bayesian meta-analysis, using cardiac mortality as a primary endpoint, evaluated 12 clinical studies involving 362 patients (17). Compared with failed PVL reduction, successful transcatheter closure, defined as the delivery of a reduction device free of mechanical prosthesis interference and resulting in an immediate ≥1-grade regurgitation reduction, translated into lower cardiac mortality (odds ratio [OR]: 0.08; 95% confidence interval [CI]: 0.01 to 0.90) and superior improvement in New York

FIGURE 1 Prevalence and Etiology



The prevalence and etiology of PVL are summarized in this chart. AVR = aortic valve replacement; MVR = mitral valve replacement; PVL = paravalvular leak; SBE = subacute bacterial endocarditis; Sx = surgical.

Heart Association [NYHA] functional classification or hemolysis (OR: 9.95; 95% CI: 2.1 to 66.7), with fewer repeat operations (OR: 0.08; 95% CI: 0.01 to 0.40). Following PVL closure, improvement in heart failure (HF) symptoms is typically limited to patients with no or mild residual regurgitation (18). Patients with hemolytic anemia may not improve following PVL closure. Hein et al. (19) observed that 33% of patients with transfusion-requiring hemolysis had worsening hemolysis after transcatheter-attempted closure, and there was newly developed hemolysis in 10% of all patients. Persistent hemolytic anemia after attempted PVL closure predicts poor survival and need for cardiac surgery (20). A recent single-site study of the effect of changes in procedural technique, use of advanced imaging modalities (i.e., 3-dimensional [3D] echocardiography), and device choice (smaller nitinol braided devices) on outcomes showed a significant learning curve effect on procedure and fluoroscopy time, complications (30-day major adverse cardiovascular events), and hospital length of stay (21). The predominant mechanism of device failure in this study was bioprosthetic leaflet impingement, highlighting the need for defect-specific devices.

The current American College of Cardiology (ACC)/American Heart Association (AHA) indications for percutaneous PVL repair include patients with prosthetic valves and symptomatic HF (NYHA functional class III to IV) and persistent hemolytic anemia, who have anatomic features that are suitable for percutaneous surgery in centers of expertise (14). Closure of less-severe PVL remains controversial. Percutaneous repair is contraindicated in patients with active endocarditis or significant dehiscence involving more than one-fourth to one-third of the valve ring (22).

CLINICAL PRESENTATION AND RISK ASSESSMENT OF PVL. Approximately 2% to 5% of PVL are clinically relevant, and are associated with complications of congestive HF, hemolytic anemia, and infective endocarditis (5,11,23). Most PVLs are small and asymptomatic; however, approximately 90% of patients with symptomatic leaks typically present with congestive HF (13,22), which can be precipitated or worsened by anemia (13). Hemolytic anemia resulting from shear stress on the red blood cells is the second most common presentation of PVL, affecting one-third to three-quarters of patients with symptomatic PVL (8,13). Symptoms of anemia can be severe and may require transfusion, and patients may experience poor quality of life (QOL) (24,25). PVL can also increase the risk for infectious endocarditis (26).

Mortality rates of 7% to 11% have been observed in contemporary single-site studies among those

undergoing surgical reoperation for PVL (27,28), and reports of perioperative complications (e.g., infection, stroke, and myocardial infarction) appear higher for surgical repair than for percutaneous closure (29). However, a direct comparison of closure techniques has never been performed. Surgical risk may be especially high in patients with PVL who are severely symptomatic and have significant comorbidities (8), or in whom dehiscence involves a substantial portion of the sewing ring (30). After attempted transcatheter PVL closure, residual leak of moderate degree or more is associated with a higher risk of need for cardiac surgery or of death (18).

The Society of Thoracic Surgeons risk score and the EuroSCORE II system are widely used for surgical risk evaluation in cardiac surgery; however, such scores have been validated only in standard surgical-risk patients (3), and they may fail to adequately capture risk factors for patients undergoing PVL closure. These factors must be considered by the heart team when deciding on the appropriateness of intervening. **Table 1** outlines the recommended evaluation of patients before PVL closure. Online Table 1 summarizes the studies supporting the clinical data and pre-procedural work-up before PVL closure. Online Table 2 summarizes the studies supporting the proposed post-procedural evaluation.

Current guidelines suggest an initial transthoracic echocardiogram (TTE) be performed 6 weeks to 3 months after valve implantation to assess the effects of surgery and to serve as a baseline for comparison (14). For bioprosthetic valves, routine echocardiographic surveillance is considered appropriate ≥3 years after implantation if there is no known or suspected valve dysfunction (31). It is the opinion of the writing group that after the initial baseline postoperative evaluation, which would include imaging and laboratory testing, yearly follow-up is necessary to better characterize the true prevalence of PVL and its consequences, such as hemolysis. After PVL closure, yearly follow-up assessment is also indicated to determine continued safety and efficacy. A comprehensive evaluation would include clinical and functional assessment (i.e., with echocardiography), as well as laboratory evaluation of hemolysis. The role of routine assessment of biomarkers has not been studied.

TABLE 1 Recommended Evaluation

Pre-procedural evaluation	
Demographics	• Age, sex, • Date of prior surgery, surgical intervention (AVR, MVR) with type/size valve
Clinical history	• History of endocarditis • NYHA functional class • STS score and/or logistic EuroSCORE • Hemolysis evaluation (with transfusion requirement) • BNP, NT-proBNP • Medications
Imaging	• Prosthetic valve function • Location and number of PVL • Severity of PVL • Ventricular and atrial size/function • Pulmonary artery pressures
Intraprocedural evaluation	
Approach	• Transapical, transfemoral, retrograde aortic
Closure devices	• Type, number, location
Imaging (echo/CT)	• Prosthetic valve function • Location and number of residual PVL • Severity of residual PVL • Ventricular and atrial size/function • Pulmonary artery pressures
Procedure data	• Contrast use, fluoroscopic time
Adverse events	• Death, stroke, bleeding, AKI, vascular complications, device complication (i.e., unplanned surgery or intervention, prosthetic valve interference, coronary obstruction, embolization)
Discharge evaluation	
Clinical	• NYHA functional class • Hemolysis evaluation (with transfusion requirement) • BNP, NT-proBNP • Medications
Imaging (echo)	• Prosthetic valve function • Location and number of residual PVL • Severity of residual PVL • Ventricular and atrial size/function • Pulmonary artery pressures
Follow-up evaluation (30-day and 1-yr)	
Clinical	• NYHA functional class • Hemolysis evaluation (with transfusion requirement) • BNP, NT-proBNP • Medications

AKI = acute kidney injury; AVR = aortic valve replacement; BNP = B-type natriuretic protein; CT = computed tomography; Echo = echocardiography; MVR = mitral valve replacement; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PVL = paravalvular leak; STS = Society of Thoracic Surgeons.

CORE PRINCIPLES II: DIAGNOSTIC TESTING FOR ASSESSMENT OF LOCATION AND SEVERITY OF PVL

A variety of diagnostic tests should be performed to determine whether regurgitation following prosthetic valve replacement is functional or abnormal and, if abnormal, whether it is central or paravalvular and the regurgitant severity. Echocardiography is the diagnostic test of choice for assessment of prosthetic valve function; however, several imaging modalities, each with its own individual merits (**Table 2**), can be used to assess the spatial and anatomic dimensions of PVL in surgical prosthetic valves (14,32) (Online Table 3).

ECHOCARDIOGRAPHY. Echocardiography is the imaging modality of choice for the comprehensive evaluation of surgical valve function, left and right heart chamber size and function, and pulmonary artery pressures (14,32,33). Echocardiographic assessment of qualitative and quantitative measures

TABLE 2 Imaging Recommendations for Surgical PHV Dysfunction*

Modality	Key Points	Imaging Goals	Limitations	Caveats
TTE with Doppler	• First-line imaging modality for diagnosis	• PHV structure and function • Aortic root size • LV and RV size and function • LA size • Concomitant valve disease (i.e., TR) • Estimate of PA pressure	• Acoustic shadowing or noise limits imaging of LA as well as the posterior aortic annulus	• May be superior to TEE for imaging the anterior aortic PHV sewing ring
TEE with Doppler	• Adjunctive imaging modality for diagnosis • First-line imaging for intra-procedural guidance	• PHV structure and function • Aortic root size • LV and RV size and function • LA size • Concomitant valve disease (i.e., TR) • Estimate of PA pressure	• Acoustic shadowing or noise limits imaging of the anterior aortic annulus	• Superior to TTE for mitral and tricuspid PHV • May be superior to TTE for imaging the posterior aortic PHV sewing ring
3D echocardiography	• Adjunctive imaging modality for TTE and TEE	• Size and location of the paravalvular regurgitant jet(s)	• May be limited by current equipment frame rates	• Real-time acquisition of 2D, 3D, and Doppler imaging • TEE more accurate than TTE
Cinefluoroscopy	• For suspected abnormality	• Mobility of the prosthetic discs for mechanical PHV		
Cardiac CT	• For suspected/confirmed abnormality	• Calcification, structural and nonstructural deterioration of bioprosthetic PHV† • Mobility of discs for mechanical PHV • Location/size of paravalvular leak (i.e., sewing ring incompetence)	• Artifacts from metallic structures • Contrast • Radiation exposure • Poor temporal resolution	• Pannus may be more accurately diagnosed using this modality
CMR	• For suspected/confirmed abnormality	• Quantification of ventricular volumes • Quantification of regurgitant volume • Quantitation of effective orifice area‡	• Artifacts from metallic structures • Requires patient compliance • Pacemakers/defibrillators are relative contraindications • Averaging of beats resulting in both difficulty imaging with arrhythmias and poor temporal resolution	• Limited utility for paravalvular regurgitation

*After Lancellotti et al. (60) and Nishimura et al. (14). †Structural deterioration defined as: dysfunction or deterioration intrinsic to the valve, including calcification, leaflet tear, or flail. Nonstructural deterioration, defined as abnormalities not intrinsic to the valve itself, including suture dehiscence with associated paravalvular regurgitation, problems related to retained native mitral apparatus, prosthesis-patient mismatch, or pannus formation. ‡By planimetry or phase-contrast (69).

2D = 2-dimensional; 3D = 3-dimensional; CMR = cardiac magnetic resonance; CT = computed tomography; LA = left atrium; LV = left ventricle; PA = pulmonary artery; PHV = prosthetic heart valve; RV = right ventricle; TEE = transesophageal echocardiography; TR = tricuspid regurgitation; TTE = transthoracic echocardiography.

in PVL requires an integrative process utilizing 2-dimensional (2D), 3D, and Doppler echocardiographic modalities, as well as TTE and transesophageal echocardiography (TEE) (33-35).

TTE provides a superior assessment of transvalvular gradients, chamber sizes, and function compared with TEE. TEE is ideal for mechanistic evaluation of prosthetic valve regurgitation, and is superior to TTE for imaging of mitral prosthetic valve regurgitation. However, TEE requires conscious sedation or anesthesia and is expert-driven, both for quality of image acquisition and interpretation (36). Prosthetic material causes numerous ultrasound artifacts that may reduce diagnostic sensitivity (33). For the evaluation of aortic valve prostheses, both modalities may be required because acoustic shadowing prevents imaging of the posterior sewing ring from TTE parasternal long-axis images and the anterior sewing ring from TEE midesophageal views. Like TTE, TEE is less reliable for prognostic evaluation of PVL in the intermediate range (37), with considerable overlap of mild and moderate PVL.

Although the first-line diagnostic test is 2D echocardiography, 3D echocardiography plays a significant role in determining the precise location and size of the PVL. In addition, 3D TEE is an essential tool for intraprocedural guidance. Limitations of 3D TEE remain: artifacts of ultrasound imaging (i.e., echocardiographic dropout, acoustic shadowing, and reverberation artifacts), and reduced temporal and spatial resolution (35). Multibeat acquisitions that stitch together smaller subvolumes will allow for visualization of larger regions of the heart with higher temporal and spatial resolution, but with the loss of real-time imaging (the subvolumes are created by sequential RR cycles) and the creation of stitching

(or reconstruction) artifacts when subvolumes are not precisely aligned (38).

ECHOCARDIOGRAPHIC ASSESSMENT PARAMETERS FOR PVL. Assessing prosthetic structural parameters. The initial assessment of PVL includes an evaluation of prosthetic valve structural integrity. Sewing ring stability and motion, or any abnormal space between the sewing ring and native annulus, may be the first indication of PVL. For the mitral prosthesis, native annular deformation or retained native leaflets may result in the appearance of increased valve mobility. On echocardiography (as well as cinefluoroscopy), significant dehiscence is suggested by excessive rocking motion of the mitral prosthesis >15° compared with the annulus (36). For the aortic prosthesis, motion is restricted by the smaller aortic space; thus, motion discordant with the motion of the adjacent aortic root and native annulus usually indicates significant (40% to 90% of the annular circumference) dehiscence (39).

Grading of paravalvular regurgitation. Accurate echocardiographic assessment of prosthetic valve regurgitation should include an assessment of the location (central versus paravalvular) and quantification of regurgitant severity. Assessment of PVL can be challenging and requires an integrative approach (33). Although guidelines, consensus statements, and studies have used both a 3-class grading scheme (mild, moderate, severe) and the angiographic 4-class scheme to report the severity of prosthetic regurgitation, these schemes have many pitfalls, and intermediate grades may not be reliably estimated (40,41). A unifying 5-class scheme for PVL regurgitation severity following transcatheter AVR has recently been proposed to improve communication between members of the heart team, resolve differences between grading schemes, and align echocardiographic parameters with clinically-used terminology, and is recommended by the writing group for clinical trials (42). The proposed 5-class schemes for aortic (**Table 3**) and mitral (**Table 4**) PVL provide a mechanism for systematic study of PVL outcomes, and a means for correlating outcomes with prior grading schemes. Importantly, this proposed grading scheme is not intended to replace existing guidelines, but could be used as the initial grading scheme and then collapsed into the 3-class scheme for reporting and/or outcomes analysis. A suggested hierarchy of parameters is summarized in **Figure 2** for prosthetic aortic PVL and **Figure 3** for prosthetic mitral PVL.

A recent multicenter study using cardiac magnetic resonance (CMR) to quantify PVL following transcatheter aortic valve replacement used regurgitant fraction cutoffs recommended by the VARC-2 criteria: none/trace (RF ≤15%), mild (16% to 29%), and moderate/severe (≥30%) (43). By ROC analysis, a regurgitant fraction of ≥30% best identified patients at greatest risk for 2-year mortality and the composite of mortality and rehospitalization for HF. These results, together with the echocardiographic outcomes from the PARTNER II SAPIEN 3 trial, using the granular grading scheme showing increased mortality associated with moderate or greater PVL (44) not only help validate the cutoffs for PVL severity in **Table 3**, but also support the use of the unifying grading scheme nomenclature (42).

Color Doppler. For both mitral and aortic prosthetic regurgitation, qualitative color Doppler features are the primary mode used for assessing PVL severity. A multiparametric and multiwindow assessment is required. The most useful parameters, as listed in **Tables 3 and 4**, include color Doppler jet features such as jet width at the origin (vena contracta) or just beyond within the left ventricular outflow tract, number of jets, the presence of a visible region of flow convergence, and circumferential extent of the jet. Proximal flow convergence can be used to quantify aortic regurgitation (45); however, for PVL, this method is limited by not only adequate imaging windows, but constraint of the jets by the sewing ring and adjacent native structures. Importantly, jet length and area should not be used to quantify aortic regurgitation (33,46).

For mitral prosthetic PVL, vena contracta width and downstream jet size are more difficult to assess; however, the presence of proximal flow convergence is a useful TTE color Doppler parameter that would initiate further evaluation by TEE. Circumferential extent of the jet can be used to grade severity of PVL, with extensive involvement (≥25% to 30%) a possible indication for surgical repair instead of a transcatheter approach.

Pulsed and continuous wave Doppler. For aortic prosthetic PVL evaluation, other parameters of jet density and pressure half-time of the regurgitant jet can be qualitative or semiquantitative supportive measures of PVL severity. The timing and velocity of the diastolic flow reversal in the descending aorta is a further Doppler parameter that can also corroborate PVL severity (42). These parameters are unreliable indicators of AR severity, given their dependence on blood pressure and aortic and ventricular compliance.

For mitral prosthetic PVL, signs of significant increase in flow across the valve (increased mean gradients and high transmitral flow compared with left ventricular outflow tract [LVOT] flow) in the setting of a normal pressure half-time, can be used to indicate

TABLE 3 Assessment of PVL Severity in Prosthetic Aortic Valves

3-Class Grading Scheme	None/Trace	Mild		Moderate		Severe
4-Class Grading Scheme	1	1	2	2	3	4
Unifying 5-Class Grading Scheme	Trace	Mild	Mild to Moderate	Moderate	Moderate to Severe	Severe
Doppler echocardiography						
Structural parameters						
Sewing ring motion*	Usually normal	Usually normal	Normal/abnormal†	Normal/abnormal†	Usually abnormal†	Usually abnormal†
LV size‡§	Normal	Normal	Normal	Normal/mildly dilated	Mildly/moderately dilated	Moderately/severely dilated
Doppler parameters (qualitative or semiquantitative)						
Jet features*						
Extensive/wide jet origin	Absent	Absent	Absent	Present	Present	Present
Multiple jets	Possible	Possible	Often present	Often present	Usually present	Usually present
Proximal flow convergence visible	Absent	Absent	Absent	Possible	Often present	Often present
Vena contracta width, mm (color Doppler)‡	Not quantifiable	<2	2 to <4	4 to <5	5 to <6	≥6
Jet width at its origin, % LVOT diameter (color Doppler)*‖	Narrow (<5)	Narrow (5 to <15)	Intermediate (15 to <30)	Intermediate (30 to <45)	Large (45 to <60)	Large (≥60)
Jet density (CW Doppler)†‡	Incomplete or faint	Incomplete or faint	Variable	Dense	Dense	Dense
Jet deceleration rate (PHT), ms (CW Doppler)‡§¶	Slow (>500)	Slow (>500)	Variable (200–500)	Variable (200–500)	Variable (200–500)	Steep (<200)
Diastolic flow reversal in the descending aorta (PW Doppler)‡§¶	Absent	Absent or brief early diastolic	Intermediate	Intermediate	Holodiastolic (end-diastolic velocity >20 to <30 cm/s)	Holodiastolic (end-diastolic velocity ≥30 cm/s)
Circumferential extent of PVL, % (color Doppler)*	Not quantifiable	<5	5 to <10	10 to <20	20 to <30	≥30
Doppler parameters (quantitative)						
Regurgitant volume, ml/beat‡#	<10	<15	15 to <30	30 to <45	45 to <60	≥60
Regurgitant fraction, %‡	<15	<15	15 to <30	30 to <40	40 to <50	≥50
Effective regurgitant orifice area, mm^2‡**	<5	<5	5 to <10	10 to <20	20 to <30	≥30
CMR						
Regurgitant fraction, %††	<15	<15	15 to <30	30 to <40	40 to <50	≥50

*Parameters that are most frequently used to grade PVL severity by Doppler echocardiography. †Care must be taken to avoid over gaining or incomplete spectral traces (i.e., when the jet moves in and out of the Doppler beam). ‡Parameters that are less often applicable due to pitfalls in the feasibility/accuracy of the measurements or to the interaction with other factors. §Applies to chronic PVL but is less reliable for periprocedural/early post-procedural assessment. ‖These parameters should not be used in patients with eccentric or multiple jets. ¶These parameters are influenced by heart rate, LV, and aortic compliance. #Regurgitant volume is calculated as the difference of stroke volume measured in the LV outflow tract minus the stroke volume measured in the right ventricular outflow tract. **The effective regurgitant orifice area is calculated by dividing the regurgitant volume by the time velocity integral of the AR flow by CW Doppler. ††There are important variabilities in the cutpoint values of regurgitant fraction and volume to grade AR by CMR in published reports.

CMR = cardiac magnetic resonance; CW = continuous wave; LVOT = left ventricular outflow tract; PHT = pressure half-time; PW = pulsed wave; other abbreviations as in Tables 1 and 2.

prosthetic valve dysfunction secondary to regurgitation. Systolic reversal of pulmonary vein flow is a specific sign of significant regurgitation, unless a narrow jet is directed into the vein. The absence of systolic reversal after intervention is important supportive evidence of successful treatment.

Quantitative Doppler echocardiography. High transvalvular velocities or gradients with parameters suggestive of a normal valve area are the initial clues to increased transvalvular flow and possible nonphysiological regurgitation. Pulsed wave and continuous wave Doppler should be used to evaluate relative stroke volumes across both the LVOT and right ventricular outflow tract, and thus quantify the aortic regurgitant volume, regurgitant fraction, and effective regurgitant orifice area (33). Quantifying diastolic stroke volume across the prosthetic mitral valve is limited by flow acceleration at the level of the sewing ring. The 2D-derived left ventricular (LV) stroke volume can be used to quantify regurgitant volume by subtracting the Doppler-derived stroke volume from a nonregurgitant valve. Using 3D-derived LV stroke volume may increase the accuracy of this method; however, it systematically underestimates volumes compared with CMR (47,48).

Direct planimetry of vena contracta area. Offline analysis of 3D color Doppler volumes can be used to planimeter the PVL vena contracta area and accurately measure the dimensions of the regurgitant jet, with a 3D color regurgitant orifice major

TABLE 4 Assessment of PVL Severity in Prosthetic Mitral Valves

3-Class Grading Scheme	Trace	Mild		Moderate		Severe
4-Class Grading Scheme	1	1	2	2	3	4
Unifying 5-Class Grading Scheme	Trace	Mild	Mild-to-Moderate	Moderate	Moderate to Severe	Severe
Doppler echocardiography						
Structural parameters						
Sewing ring motion*	Usually normal	Usually normal	Normal/abnormal†	Normal/abnormal†	Normal/abnormal†	Normal/abnormal†
LA and LV size‡§	Normal	Normal	Normal	Normal/mildly dilated	Mildly/moderately dilated	Moderately/severely dilated
RV size and function‡§	Normal	Normal	Normal	Normal/mildly dilated	Mildly/moderately dilated	Moderately/severely dilated
Estimation of pulmonary artery pressures‡	Normal	Normal	Normal	Variable	Increased	Increased (TR velocity >3 m/s, SPAP ≥50 mm Hg at rest and ≥50 mm Hg with exercise)
Doppler parameters (qualitative or semiquantitative)						
Proximal flow convergence visible*	Absent	Absent/minimal	Absent/minimal	Intermediate	Intermediate	Large
Color Doppler jet area (Nyquist 50–60 cm/s)‡	Absent	Small, central jet (usually <4 cm^2 or <20% of LA area)	Small, central jet (usually <4 cm^2 or <20% of LA area)	Variable	Variable	Large central jet (usually >8 cm^2 or >40% of LA area) or variable when wall impinging
Mean gradient (CW)‡	Normal	Normal	Normal	Increased	Increased	≥5 mm Hg
Diastolic PHT (CW)‡‖	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)
Vena contracta width, mm (color Doppler)‡	Not measurable	<2	2 to <3	3 to <5	5 to <7	≥7
Jet density (CW Doppler)‡¶	Incomplete or faint	Incomplete or faint	Variable	Dense	Dense	Dense
Jet profile (CW Doppler)‡	Parabolic	Parabolic	Variable (partial or parabolic)	Variable (partial or parabolic)	Variable (partial or parabolic)	Holosystolic/triangular
Pulmonary vein flow (PW Doppler)*#	Systolic dominance	Systolic dominance	Systolic dominance	Systolic blunting	Systolic blunting	Systolic flow reversal
MV_{PR} flow:LVOT flow (PW Doppler)‡	Equal (1:1)	Slightly increased	Slightly increased	Intermediate	Intermediate	≥2.5
Circumferential extent of PVL, % (color Doppler)*	Not quantifiable	<5	5 to <10	10 to <20	20 to <30	≥30
Doppler parameters (quantitative)						
RVol, ml/beat‡**	<10	<15	15 to <30	30 to <45	45 to <60	≥60
RF, %‡	<15	<15	15 to <30	30 to <40	40 to <50	≥50
EROA, mm^2‡††	<5	<5	5 to <20	20 to <30	30 to <40	≥40
CMR imaging						
Regurgitant fraction, %‡‡	<15	<15	15 to <30	30 to <40	40 to <50	≥50

*Parameters that are most frequently used to grade regurgitation severity by Doppler echocardiography. †>15° of sewing ring motion that is not consistent with normal phasic motion of the mitral annulus. ‡Parameters that are less often applicable due to pitfalls in the feasibility/accuracy of the measurements or to the interaction with other factors. §For bileaflet mechanical valve, E velocity >1.9 m/s is abnormal. ‖PHT should not be used to calculate valve area in the setting of a prosthetic valve; however, it should be normal in the absence of significant stenosis. ¶Care must be taken to avoid over gaining or incomplete spectral traces (i.e., when the jet moves in and out of the Doppler beam). #Pulmonary vein flow reversal may be influenced by LV systolic and diastolic function, LA size and pressure, atrial arrhythmias, and the presence of mitral inflow obstruction; however, holosystolic flow reversal is specific for severe mitral regurgitation. **Regurgitant volume is calculated as the difference of stroke volume measured in the LV outflow tract minus 2D-derived (total) LV stroke volume. ††EROA is calculated by dividing the RVol by the time velocity integral of the mitral RF by CW Doppler. ‡‡There is important variability in the cutpoint values of regurgitant fraction and volume reported in the literature to grade mitral regurgitant by cardiac magnetic resonance imaging.

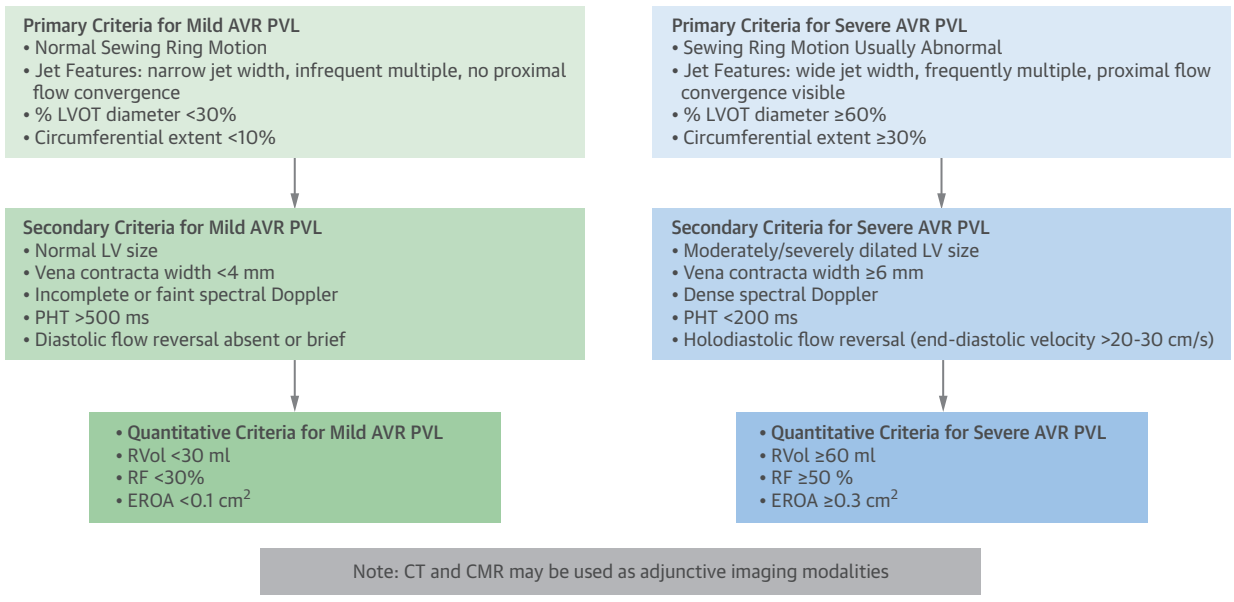
EROA = effective regurgitant orifice area; MV_{PR} = mitral valve prosthetic valve; RF = regurgitant fraction; RVol = regurgitant volume; RVOT = right ventricular outflow tract; SPAP = systolic pulmonary artery pressure; other abbreviations as in Tables 1 to 3.

diameter ≥0.65 cm consistent with greater than moderate PVL (49). Outcomes based on these parameters will require further study.

Sizing paravalvular regurgitation defects. The exact location and size of the defects help determine the optimal approach (transseptal, transapical, or retrograde aortic) and the type and/or size of the device. Measurements of PVL include: 1) precise location of the defect(s); 2) precise radial and circumferential dimensions of the defects, as well as the vena contracta area; 3) orientation of the defect in relation to the sewing ring and prosthetic valve occluders or leaflets; and 4) location and orientation of subvalvular structures.

Although 2D imaging may accurately locate defects and measure radial dimensions, the circumferential extent of the defect is best imaged with 3D TEE (50). Similarly, the regurgitant orifice area can be planimetered on noncolor 3D images (51); however, confirmation by both 2D and 3D color Doppler

FIGURE 2 Summary of Echocardiographic Criteria for Aortic Prosthetic PVL



Parameters used to define severity of aortic prosthetic PVL are listed in this chart as primary and secondary qualitative/semiquantitative parameters, in addition to quantitative parameters. CMR = cardiac magnetic resonance; CT = computed tomography; EROA = effective regurgitant orifice area; LV = left ventricle; LVOT = left ventricular outflow tract; PHT = pressure half-time; RF = regurgitant fraction; RVol = regurgitant volume; other abbreviations as in Figure 1.

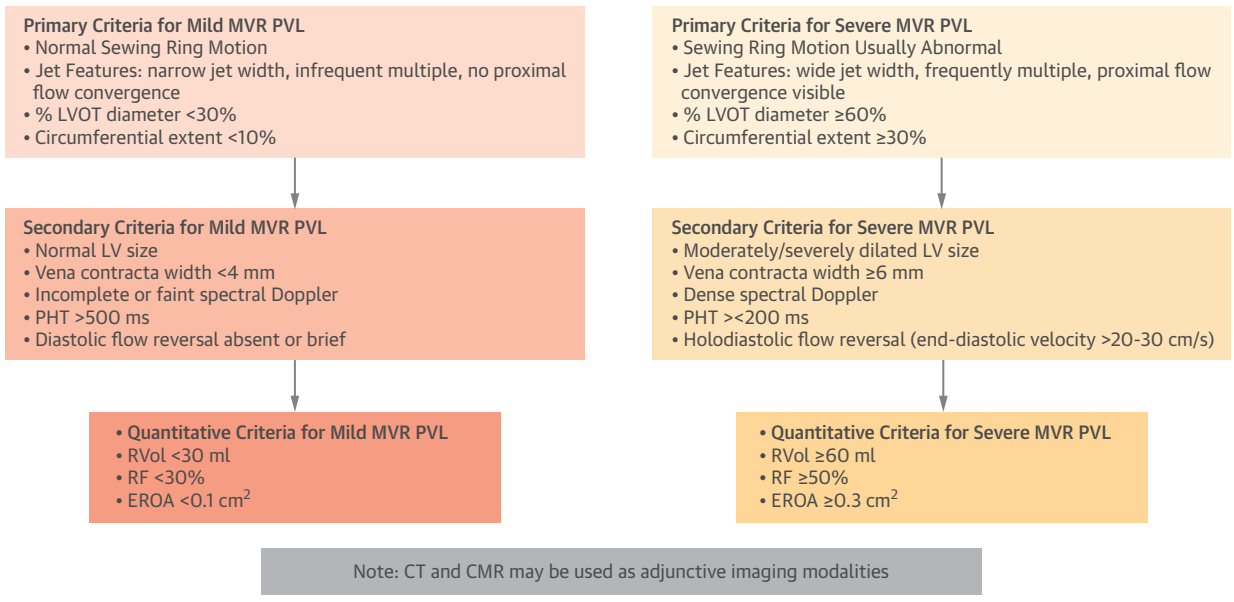
imaging should be performed to exclude an artifact of imaging. In addition, direct measurement of the color Doppler vena contracta area and dimensions by 3D volumes correlates better with standard measures of regurgitant severity compared with noncolor 3D imaging (49), and thus may be superior for localizing and sizing the regurgitant jets, especially when contemplating transcatheter closure (52).

3D TEE is also integral to intraprocedural guidance, and may be especially beneficial in evaluating the success of percutaneous closure of mitral PVL (53,54). The real-time 3D volume of the mitral sewing ring should be positioned in the surgical view with the aortic valve at the top of the mitral ring (12 o'clock) and the left atrial appendage (LAA) at approximately the 9-o'clock position (35,55). Careful 2D and 3D imaging throughout the procedure is required to confirm: 1) catheter and device positioning; 2) full deployment of the device in the intended position; 3) interference of the device with prosthetic valve function or adjacent native anatomy; 4) stable device deployment; 5) residual regurgitation and need for further intervention; and 6) safe removal of catheters and imaging of transseptal shunt. Echocardiographic-fluoroscopic fusion imaging allows real-time overlay of 2D, 3D, or color Doppler images onto the fluoroscopic image, and thus has the potential to improve procedural guidance by rapid localization of PVL defects, and improving communication between the imager and interventionalist (56). Intracardiac echocardiography has also been used for intraprocedural guidance (57).

Other measures of cardiac structure and function. Important clinical information can be gleaned from assessing ventricular and atrial size and function. This is especially important for mitral regurgitation; however, pre-existing abnormalities of chamber size and function should be considered when interpreting changes in these parameters following surgical valve replacement. LV diameters from M-mode or 2D imaging, as well as left atrial (LA) volumes (preferably by biplane Simpson's method) should be measured with chronic severe regurgitation resulting in severe dilation of both the LV and LA. In the setting of symptomatic, severe mitral PVL, an increase in estimated pulmonary artery pressures (tricuspid regurgitation velocity >3 m/s, systolic pulmonary artery pressure ≥50 mm Hg), with resulting right atrial and ventricular dilation, is also seen.

For the aortic prosthesis, current guidelines recommend follow-up assessment of the aortic root and ascending aorta (33). Measurement of LV size and function should be performed, because chronic severe aortic PVL should result in dilation of the LV similar to

FIGURE 3 Summary of Echocardiographic Criteria for Mitral Prosthetic PVL



Parameters used to define severity of mitral prosthetic PVL are listed in this chart as primary and secondary qualitative/semiquantitative parameters in addition to quantitative parameters. MVR = mitral valve replacement; other abbreviations as in Figures 1 and 2.

native aortic regurgitation (AR) (14). Finally, echocardiographic imaging may detect cavitation bubbles, which are frequently seen with normal prosthetic valve function (58). A large number of bubbles may be an indication of hemolysis and be correlated with levels of lactate dehydrogenase (LDH) (59).

NONECHOCARDIOGRAPHIC IMAGING MODALITIES. Cinefluoroscopy and cineangiography. Cinefluoroscopy is a noninvasive, readily-available method for detecting and evaluating mechanical occluder motion when prosthetic valve stenosis is suspected (60–62); however, this modality has limited utility for the diagnosis of PVL location and severity, unless significant dehiscence results in excessive motion of the sewing ring.

Retrograde cineangiography for the assessment of regurgitation has relied on the semiquantitative grading scheme of Sellers et al. (63). Biplane techniques may increase the accuracy of angiographic grading (64). A number of factors confound reliable quantification, resulting in inconsistent correlation with quantitative assessment of AR and significant overlap between angiographic grades (40,41). Finally, angiography cannot elucidate the location or mechanism of PVL, and the writing group considers this a confirmatory method to distinguish less than mild from greater than moderate regurgitation.

Intraprocedurally, retrograde cineangiography may be useful to assess for adequate aortic prosthetic PVL closure, particularly when the defects are in the anterior sewing ring, and thus are poorly-imaged by TEE.

Cardiac computed tomographic assessment of PVL. A recent meta-analysis of multimodality imaging for prosthetic valve dysfunction concluded that computed tomography (CT) allowed adequate assessment of most modern prosthetic heart valves, complementing echocardiographic detection of the etiology of valve obstruction (pannus/thrombus or calcifications) and endocarditis extent (valve dehiscence and pseudoaneurysm), without a clear advantage over echocardiography for the detection of vegetations or periprosthetic regurgitation (61). CT can provide images with improved spatial resolution, which allow for anatomic evaluation of PVL location and can be used to plan interventions (12,15). A recent study showed that CT and 2D TEE had similar diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy) in the detection of PVL (65). CT has significant limitations for PVL assessment: it cannot display blood flow, requires iodinated contrast media and ionizing radiation, and requires expertise in CT post-processing/reconstruction. Nonetheless,

CT is especially strong at anatomically characterizing an area of valvular dehiscence and resultant PVL, especially in the setting of mechanical valves with significant shadowing during sonographic assessment. CT can identify leak location and size of defect, tract trajectory, calcification within the track and adjacent annular tissue, as well as important surrounding cardiac structures, and define the optimal fluoroscopic angles to cross the defect (57). The PVLARC recommends that CT angiography be performed before consideration for reoperation.

Fusion hybrid imaging is also being increasingly integrated into clinical practice (66). With proper gating and multiplanar imaging, CT with fusion imaging can determine the location of PVL, its path and surrounding structures, and the fluoroscopic angles for wiring and catheter cannulation (67). 3D printing of CT data is also increasingly feasible (68), facilitating the understanding of the defect.

CMR imaging for assessment of prosthetic valve function. Studies have shown the feasibility and accuracy of CMR for the assessment of prosthetic valve function (69). Quantitation of regurgitation can be performed by planimetry of the anatomic regurgitant orifice area from the cine CMR acquisitions of the valve (70,71), quantification of forward and backward flow (72), and phase-contrast imaging (61). Phase-contrast velocity mapping (also known as velocity-encoded cine or Q flow) has become the primary mode for assessing regurgitant volume by CMR, and provides information on prosthetic flow patterns and velocities for the visual detection of prosthetic regurgitation. For this purpose, phase-contrast imaging is obtained in a short-axis plane cutting the aorta just above the prosthetic valve to measure the antegrade and retrograde aortic flows, and then to calculate the regurgitant volume and fraction (73).

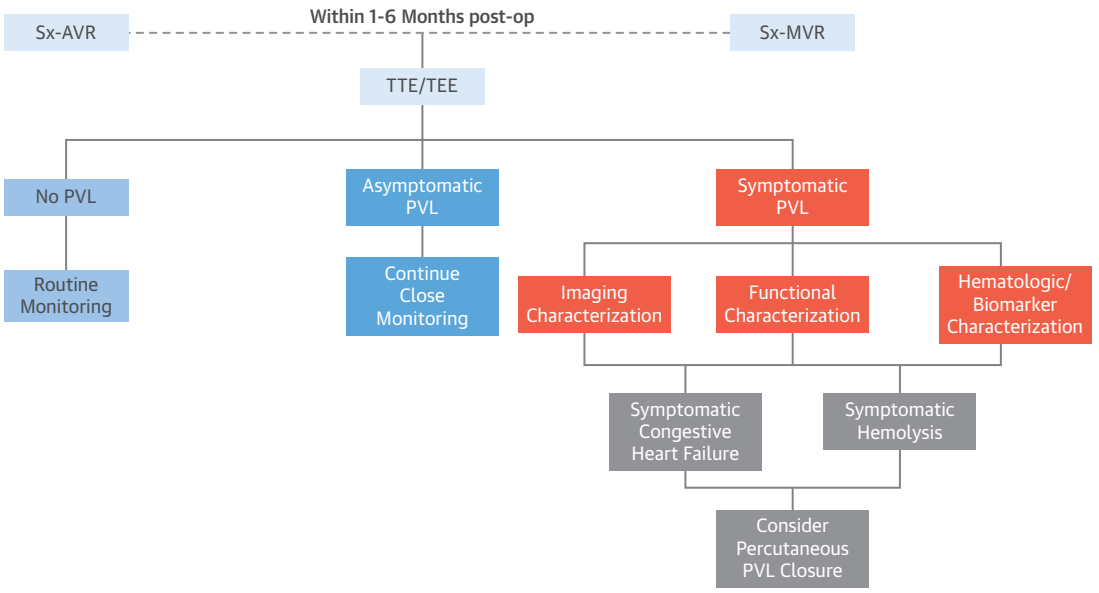
The accuracy of CMR to grade PVL may be altered by arrhythmias, as well as flow turbulences and signal void in the vicinity of the prosthetic valve (especially mechanical valves). Moreover, because the coronary artery diastolic flow is included in the final regurgitant volume assessment, CMR may lead to a slight overestimation of AR, and does not allow precise separation among mild, trace, and no AR. Nonetheless, CMR can been used to not only quantify PVL following transcatheter aortic valve replacement, but also predict outcomes (43). CMR may be particularly useful for corroborating the severity of regurgitation in cases where echocardiography remains inconclusive, and/or when there is discordance between the echocardiographic grading of PVL severity and the patient's symptomatic status and/or degree of LV dilation/dysfunction. The advantages of CMR for PVL assessment include the capacity to measure regurgitant volumes for multiple valve types, irrespective of regurgitant jet number or morphology (74), and high reproducibility of measurements (75). Further outcome studies related to CMR grading of surgically-placed prostheses are urgently needed to confirm the cutpoint values of CMR regurgitant volume and fraction that should be used to grade the severity of chronic PVL.

Nuclear studies. Because implantation of transcatheter devices is contraindicated in the setting of active endocarditis, nuclear studies, such as labeled-leukocyte scintigraphy (76) and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose, may help with the diagnosis of endocarditis in the setting of prosthetic valves (77). ^{18}F-fluorodeoxyglucose PET/CT and PET/CT angiography may improve the diagnostic accuracy of the modified Duke Criteria (78) in patients with suspected infective endocarditis and prosthetic valves (79).

Invasive hemodynamic assessment of PVL. Hemodynamic measurements have also been proposed as a means of quantifying the severity of regurgitation. Although elevated filling pressures reflect the hemodynamic consequences of regurgitation, and thus indicate clinical compromise, there are limitations to invasive hemodynamic assessment. There is poor correlation between AR severity and aortic pressure at end-diastole and pulse pressure (80,81). The dicrotic notch on the downstroke of the arterial pressure waveform is thought to represent slight backward flow in the aorta on closure of the aortic valve; absence of the dicrotic notch is associated with severe AR, but cannot be used to define lesser grades. Grading of AR using hemodynamic tracings has been validated using measurement of the "corrected" diastolic pulse pressure (between the dicrotic notch and end-diastole) or the diastolic slope (slope of the pressure drop following the dicrotic notch) (82), with a direct relationship between these measurements and larger regurgitant volumes. An AR index was recently proposed to assess intraprocedural regurgitation during transcatheter aortic valve implantation (83), but has not been validated in the setting of chronic PVL following surgical valve implantation.

Hemodynamic assessment in the setting of severe mitral regurgitation is typically limited to the nonspecific measurement of right heart pressures and pulmonary capillary wedge pressure, as well as indirect evidence of regurgitant flow (84). Direct LA pressure measurements or assessment of LA to LV pressure gradients are rarely warranted. Neither method can delineate the mechanism of valvular insufficiency.

FIGURE 4 Diagnostic Work-Up



Flow diagram of the suggested diagnostic work-up for patients with surgical prosthetic PVL. TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; other abbreviations as in Figure 1.

NONIMAGING ASSESSMENT. Blood biomarkers of PVL. Recent studies suggest that the high-molecular-weight von Willebrand factor multimeric pattern may be used as a sensor of PVL following valve procedure (85,86). A platelet function analyzer that measures the time for platelet aggregation to occlude a collagen and adenosine diphosphate (ADP)-coated membrane (closure time with ADP), is a point-of-care assay that is very sensitive to high-molecular-weight multimer changes. Investigators have shown that CT closure time with ADP could be used to monitor in real-time valve hemodynamic performance after transcatheter valve replacement, and has prognostic utility (86).

The turbulent flow caused by the leak around the prosthetic valve is presumed to generate excessive shearing forces on red blood cells, resulting in intravascular mechanical hemolysis (24). Factors that increase shear stress, such as important pressure fluctuations during strenuous physical activity, may aggravate the hemolysis. Hemodialysis and the heart-lung bypass machine are other causes of mechanical hemolytic anemia that can be seen in patients with significant PLV. Iron or folate deficiency may further alter the erythrocyte membrane and favor hemolysis.

Specific laboratory studies may help confirm the presence of hemolytic anemia. A hemoglobin or hematocrit is an obvious first step, but significant hemolysis may still be present despite a normal or near-normal hemoglobin/hematocrit count if the bone marrow is capable of compensating for the peripheral red blood cell destruction. In such an instance, the calculation of a reticulocyte production index (or corrected reticulocyte count) may help refine the diagnosis (87). The hemolysis workup should also include serum LDH, haptoglobin, iron and folic acid levels, and peripheral blood smear examination for schistocytes. Consultation with a hematologist is strongly advised. A summary of the approach to diagnostic testing is shown in Figure 4.

CORE PRINCIPLES III: CLINICAL TRIAL DESIGN

DEFINITIONS OF CLINICAL SUCCESS FOR PVL TRIALS. The following are definitions of success for PVL closure.

Technical success (on exit from procedure laboratory).

I. Absence of procedural mortality or stroke;
II. Successful access, delivery, and retrieval of the device delivery system;
III. Proper placement and positioning device(s);

IV. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
V. Continued intended safety and performance of the device, including:
   a. No evidence of structural or functional failure of the prosthetic valve
   b. No specific device-related technical failure issues and complications
   c. Reduction of regurgitation to no greater than mild (1+) paravalvular regurgitation (and without associated hemolysis).

Device success (30-day and all other post-procedural intervals).

I. Absence of procedural mortality or stroke;
II. Original intended device(s) in place;
III. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
IV. Continued intended safety and intended performance of the device:
   a. Structural performance: no migration, embolization, detachment, fracture, worsening of hemolysis, or systemic emboli related to device thrombosis or endocarditis, among others;
   b. Hemodynamic performance: persistent reduction in paravalvular insufficiency without producing central valvular incompetence or stenosis; and
   c. Absence of para-device complications (e.g., erosion of bioprosthetic leaflet or surrounding tissue, LVOT, or valvular gradient increase >10 mm Hg)

Procedural success (<30 days).

I. Device success:
   a. Defined as complete versus incomplete PVL closure;
   b. For incomplete closure (i.e., residual PVL): grading of severity should be performed; and
   c. Appropriate recommendations for change in PVL severity, improvement in HF, or hemolysis should be determined by the specific patients being studied:
      i. For instance, when using a 5-class scheme, procedural success in patients with HF may be defined as less than or equal to mild (or ≤1+ in 4-class) plus reduction of at least 1 class of PVL severity.
      ii. Procedural success for patients presenting with hemolysis may be defined as a reduction of PVL severity that results in resolution of hemolysis.

II. No device- or procedure-related serious adverse events (life-threatening bleed; major vascular or cardiac structural complications requiring unplanned reintervention or surgery; stage 2 or 3 acute kidney injury [includes new dialysis]; myocardial infarction or need for percutaneous coronary intervention or coronary artery bypass graft; severe HF or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support; prolonged intubation >48 h).

Individual patient success (1-year).

I. Device success and all of the following
   a. No rehospitalizations or reinterventions for the underlying condition (e.g., hemolysis or HF); and
   b. Return to prior living arrangement (or equivalent); and
   c. Improvement versus baseline in symptoms (improvement in NYHA functional class ≥1 vs. baseline); and
   d. Improvement versus baseline in functional status (6-min walk test improvement by ≥25 meters vs. baseline) in patients who could complete this test pre-procedure; and
   e. Improvement versus baseline in QOL (e.g., Kansas City Cardiomyopathy Questionnaire or Minnesota Living With Heart Failure improvement by ≥10 vs. baseline).

RELEVANT ENDPOINTS: PRIMARY AND SECONDARY.

The PVLARC Writing Group uses terminology as per the 2014 AAC/AHA Key Data Elements and Definitions for Cardiovascular Events in Clinical Trials (88). In 1988, the cardiovascular surgery societies pioneered the importance of standardized adverse event (AE) definitions in valve disease for adjudicating events in clinical trials, comparing clinical results of therapeutic interventions in valve disease, and standardizing reporting of events to facilitate data analysis (89). More recently, the ARC has contributed guidelines for standardized definitions of AEs in several areas of interventional cardiology, including bleeding (Bleeding Academic Research Consortium [BARC]) (90), transcatheter aortic valve implantation (VARC-2) (3), and mitral valve repair and regurgitation (Mitral Valve Academic Research Consortium) (4).

Building on the previous VARC publications, PVLARC provides definitions to support standardized reporting of the AEs associated with both surgical and transcatheter treatment of PVL. Such standardization is important for clinical trials testing new interventions and for reporting the results of these interventions. An independent clinical events

TABLE 5 Mortality Endpoints

All-cause mortality
Cardiovascular mortality Any of the following criteria: • Death due to proximate cardiac cause (endocarditis, valve interference, cardiac tamponade, worsening heart failure) • Death caused by noncoronary vascular conditions, such as neurological events, pulmonary embolism, aortic dissection, or other vascular disease • All procedure-related deaths, including those related to a complication of procedure or treatment for a complication of procedure • All device-related deaths including structural or nonstructural device dysfunction or embolization or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause
Noncardiovascular mortality • Any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide)

TABLE 6 Stroke and TIA Endpoints

Diagnostic criteria • Acute episode of a focal/multifocal neurological deficit with at least 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, unilateral numbness/sensory loss, dysarthria, aphasia, hemianopsia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke: duration of neurological deficit >24 h and belief by a neurologist that symptoms represent a stroke; *or* <24 h if available neuroimaging documents a new infarct or hemorrhage; *or* the neurological deficit results in death • TIA: duration of neurological deficit <24 h, and neuroimaging does not demonstrate a new infarct or hemorrhage • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with the designated neurologist • Confirmation of the diagnosis by at least 1 of the following: ○ Neurologist or neurosurgical specialist ○ Neuroimaging procedure (CT or magnetic resonance imaging); but stroke may be diagnosed on clinical grounds alone
Stroke classification • Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue • Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage • A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic (e.g., unable to perform imaging)
Stroke definitions • Disabling stroke: an mRS >2 at 90 days from symptom onset; if baseline mRS (>2) and there is an increase of at least 1 point in the mRS category from an individual's pre-stroke baseline • Nondisabling stroke: an mRS score of 0–2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's pre-stroke baseline if his or her baseline is >2

CT = computed tomography; mRS = modified Rankin Scale; TIA = transient ischemic attack.

committee should prospectively define AEs and assess their relatedness to clinical trial interventions. The adjudication of events should not be limited to the acute procedure period (30 days), but also, when appropriate, longer periods (e.g., death months after a disabling stroke due to the procedure).

AE ENDPOINTS. Mortality. Mortality for PVL procedures should be divided into all-cause and cardiovascular mortality. As with other ARC definitions, data on immediate procedural mortality and procedural mortality should also be gathered (Table 5). *Immediate procedural mortality* refers to intraprocedural events that result in immediate or consequent death <72 h after the procedure (3). *Procedural mortality* is all-cause mortality within 30 days or during the index hospitalization (if this is longer than 30 days). Reporting of mortality events is important in PVL closure, and should be reported after 30 days during the follow-up, and then annually for up to 5 years. Adjudication of mortality should be performed using a combination of clinical and other contexts at the time of the index procedure. When possible, national death registries and databases should be used to check for mortality in patients lost to follow-up.

Stroke. *Imaging*. Various multisociety consensus documents (89,91,92) have observed that new diffusion-weighted magnetic resonance imaging sequence abnormalities may be present after cardiovascular procedures; however, the clinical significance of those findings is unknown. Definitions relevant to neurological events are listed in Table 6. Brain imaging is often performed for evaluation of stroke, typically using modalities such as CT for acute hemorrhage, as well as for acute, subacute, and chronic infarction. Magnetic resonance imaging is more sensitive for acute infarction, and can also identify chronic ischemia, as well as both acute and chronic hemorrhage. Imaging as a stand-alone entity should not be used to diagnose a stroke; the diagnosis should be made in conjunction with clinical assessment, preferably by a neurologist.

Primary endpoints. All strokes (ischemic and hemorrhagic) and transient ischemic attacks should be reported as endpoints, as defined in Table 6.

Secondary endpoints. Functional outcome should be a secondary endpoint of the investigation. The modified Rankin Scale is often used for this purpose (93). Functional outcome should be assessed and documented by a certified provider at all scheduled visits in the trial, and at 90 days after stroke onset, as well as at the trial's end of follow-up. Disabling stroke is another secondary endpoint that is usually defined at 90 days from symptom onset (Table 6).

Management. If a potential neurological endpoint occurs, patients should be assessed by a neurologist as soon as possible, and brain imaging should be completed (magnetic resonance imaging or CT). In addition, baseline risk factors should be assessed and documented for patients to identify the cause of the stroke. Strokes that occur after the procedure show

TABLE 7 Bleeding Endpoints

Life-threatening or disabling bleeding • Fatal bleeding (BARC type 5) *or* • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) *or* • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) *or* • Overt source of bleeding with drop in hemoglobin >5 g/dl or whole blood or packed RBC transfusion >4 U (BARC type 3b)
Major bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of 2 or 3 U of whole blood/RBCs, or causing hospitalization or permanent injury, or requiring surgery *and* does not meet criteria of life-threatening or disabling bleeding
Minor bleeding (BARC type 2 or 3a, depending on severity) • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major

BARC = Bleeding Academic Research Consortium; RBC = red blood cell.

TABLE 9 AKI Staging

Stage 1 • Increase in serum creatinine to 150%–199% (1.5–1.99× increase compared with baseline) *or* increase of >0.3 mg/dl (>26.5 mmol/l) • Urine output <0.5 ml/kg/h for 6-12 h
Stage 2 • Increase in serum creatinine to 200%–299% (2.0–2.99× increase compared with baseline) • Urine output <0.5 ml/kg/h for ≥12 h
Stage 3 • Increase in serum creatinine to >300% (>3× increase compared with baseline) *or* • Increase in serum creatinine of ≥4.0 mg/dl (≥353.6 mmol/l) *or* • Initiation of renal replacement therapy *or* • In patients <18 years of age, decrease in eGFR to <35 ml/min/1.73 m^2 *or* • Urine output <0.3 ml/kg/h for ≥24 h *or* • Anuria for ≥12 h

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate.

the importance of investigating adjunctive pharmacotherapy after PVL closure. Medications and doses should be included. Acute stroke management strategies should also be recorded.

BLEEDING COMPLICATIONS. The standard BARC classification of bleeding complications remains applicable to PVL closure (Table 7). An objective assessment is necessary, including risk stratification of bleeding events associated with mortality or chronic sequelae. Bleeding can be divided into life-threatening bleeding, major bleeding, and minor bleeding. Transfusions should be recorded in case report forms.

HEMOLYSIS. Although hemolysis may be commonly seen with mechanical prostheses, it rarely causes overt anemia or requires transfusions (94,95). Severe hemolytic anemia may require repetitive transfusions that would not be related to bleeding and/or hemorrhagic complication, as defined in the previous section. To standardize the reporting of endpoints in oncology/hematology clinical trials, the National Cancer Institute has developed Common Terminology Criteria that could be applied to hemolytic anemia in the context of a cardiovascular intervention. In this context, the severity of anemia is reported by grade on a scale of 1 to 5, as described in Table 8. The number and frequency of transfusions should be recorded. As noted previously, a comprehensive assessment of blood markers of hemolysis should be performed, including serum LDH, serum haptoglobin levels, antiglobulin antibodies, serum iron and folic acid levels, and peripheral blood smear examination for schistocytes.

TABLE 8 Hemolytic Anemia*

Grade	Severity	Definition of Anemia
1	Mild, with mild or no symptoms; no interventions required	Hb <LLN to 10.0 g/dl
2	Moderate; minimal intervention indicated; some limitation of activities	Hb <10.0 g/dl to 8.0 g/dl
3	Severe but not life-threatening; hospitalization required; limitation of patient's ability to care for him/herself	Hb <8.0 g/dl; transfusion indicated
4	Life-threatening; urgent intervention required	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event	Death

*From the U.S. Department of Health and Human Services et al. (114).
Hb = hemoglobin; LLN = lower limit of normal.

ACUTE KIDNEY INJURY. Small changes in kidney function can lead to acute kidney injury (AKI) and increased risk for mortality (96). The Kidney Disease: Improving Global Outcomes system is a modification of the Acute Kidney Injury Network classification that allows for AKI diagnosis up to 7 days after the index procedure (Table 9) (97). AKI is defined as any of the following (not graded):

- Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h; or
- Increase in serum creatinine to ≥1.5× baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 h.

VASCULAR ACCESS-SITE AND ACCESS-RELATED COMPLICATIONS. Major and minor access-site complications are inescapable, but major vascular complications are important clinical endpoints (Table 10). The access site includes any location (arterial or venous) traversed by a guidewire, catheter, or sheath (including the LV apex). *Access-related* is defined as

any adverse clinical consequence associated with the access site. Vascular access can be a combination of femoral arterial or venous access, as well as LV apical access. Pre-planned surgical access or planned endovascular approach to vascular closure is part of the procedure, and is not a complication unless clinical complications are documented (e.g., bleeding, limb ischemia, distal embolization, or neurological impairment). Complications for all sites should be systematically recorded. All vascular complications should be recorded as either access-site related (e.g., femoral artery dissection) or non-access-site related (e.g., aortic dissection or rupture). Complications that fulfill multiple criteria (vascular access site and major bleeding) should be listed under both headings.

OTHER PVL CLOSURE-RELATED COMPLICATIONS. PVLARC recommends definitions for several other endpoints (Table 11).

SURROGATE IMAGING ENDPOINTS. The primary imaging endpoints should be 2D or 3D Doppler echocardiographic assessment of regurgitation severity and its consequences on LV mass, size, and function, as well as estimates of pulmonary artery pressure. Deformation characteristics of the LV have been studied in patients with native aortic regurgitation (98). Myocardial strain and energy dissipation (99) might serve as more sensitive markers of the LV load imposed by the leakage, thus facilitating an earlier stratification of PVL patients and precluding the need to wait for negative remodeling to develop. These markers need to be evaluated.

FUNCTIONAL ASSESSMENT. Multiple well-recognized prognostic indicators describe clinical and functional capacity, including: peak oxygen consumption, which is the standard measurement for assessment of exercise capacity; NYHA functional class, which is the standard grading system of functional status in the clinical setting; and the 6-min walk test, which is considered a realistic assessment of daily physical activity (100). These and other functional parameters have been shown to be prognostic indicators in recent transcatheter aortic valve replacement trials (101–103), and require further study in this population. Given the complex nature of this parameter, the investigation of new means of defining functional capacity, such as activity trackers (104,105), may be useful in this patient population.

QOL ENDPOINTS. A comprehensive assessment of health-related QOL, which incorporates both an HF-specific measure (such as the Minnesota Living With Heart Failure [106] and the Kansas City Cardiomyopathy Questionnaire [107]) and 1 or more generic measures (such as the EuroQOL [108]), is important

TABLE 10 Vascular Complications

Major vascular complications
• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment *or*
• Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage *or*
• The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia, or neurological impairment *or*
• The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia, or neurological impairment *or*
• Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical examination, and/or decreased or absent blood flow on lower extremity angiogram *or*
• Surgery for access site-related nerve injury *or*
• Permanent access site-related nerve injury
Minor vascular complications
• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment *or*
• Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage *or*
• Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication *or*
• Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression transcatheter embolization, or stent-graft)
Percutaneous closure device failure
• Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

TABLE 11 Other PVL Closure-Related Complications

Conversion to open surgery
Unplanned use of cardiopulmonary bypass or hemodynamic support device
Valvular interference
• Angiographic or echocardiographic evidence of a new, partial, or complete interference of the valvular leaflet by the device after release
Coronary obstruction
• Angiographic or echocardiographic evidence of a new, partial, or complete obstruction of a coronary ostium, either by the device or valve after release
Device or valve endocarditis
Any one of the following
• Fulfillment of the Duke endocarditis criteria
• Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during reoperation
• Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy
Device or valve thrombosis
• Any thrombus attached to or near an implanted device that occludes part of the blood flow path through the valve, interferes with valve function, or is sufficiently large to warrant treatment. Of note, device or valve-related thrombus found post-mortem should not be noted as device thrombosis if cause of death was not device- or valve-related.
Valve dehiscence
Complication due to transseptal crossing
New or worsening hemolysis
• Secondary to the device

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PVL = paravalvular leak.

for patients undergoing PVL closure. Compared with the questionnaire-based scores (e.g., EuroQOL five dimensions questionnaire), self-rated assessments (e.g., EQ visual analogue score) tend to be lower at baseline and demonstrate greater improvement thereafter (109), representing a potentially more sensitive marker of health status improvement after therapy. Notably, the attrition of the sickest patients with severe PVL might lead to a spurious improvement of QOL measurements over time. Therefore, a "poor outcome," defined as death or poor QOL, is always preferred to an isolated QOL score (110). Until the data on the specific impact of PVL on health-related QOL become available, PVLARC recommends that an early (30 days) HF-specific assessment be combined with a generic self-rated visual analog, as well as death, in a comprehensive "poor outcome" parameter to rate the overall health status improvement.

TRIAL DESIGN IN PVL. Innovative trial design for transcatheter closure devices should be contemplated to reduce sample size, costs, and operational burden, while maintaining a high degree of scientific validity. Before a trial can be properly designed, the PVL study group must be carefully defined, the clinical question to be addressed should be precisely identified, the device(s) should be selected, and clinical success should be defined. There are several possible trial designs, including comparing PVL reduction by transcatheter therapies to surgical correction in patients with moderate disease, or to medical therapy alone in patients unsuitable for surgery.

Trial design for PVL closure is plagued by unsolved practical and ethical issues. For instance, because of the relative rarity of PVL, sample size is an important consideration. Additionally, a clinical trial of surgical versus percutaneous PVL intervention could be hindered by several factors, including cost, patient reluctance to be randomized (by definition all patients will have had prior thoracotomy), or inability to blind investigators or imaging core laboratories (percutaneous PVL technology has distinct imaging footprints). Furthermore, PVL surgery generally has poor outcomes, with substantial mortality and poor freedom from recurrence. We have a less-robust experience with clinical studies of transcatheter closure. The emergence of some evidence in favor of transcatheter closure of PVL may challenge the basis for clinical equipoise, and would raise questions about how best to design the randomization of vulnerable patients in a clinical trial where epistemic indifference might be lacking.

Nonetheless, these issues also open the door to innovative trial designs for prospective clinical investigation in rapidly evolving fields, such as PVL closure, where what is thought to be true at the start of a trial may no longer be accurate at its end. Because the use of different trial designs may be appropriate for any given study, a discussion of all trial designs is outside the scope of this document. Investigators should understand the rationale behind trial designs such as adaptive randomization (111), Bayesian statistics (112), and randomized registry trials (113).

CONCLUSIONS

This consensus document is derived from multidisciplinary expertise, and represents a first step toward standardization of core principles and endpoint definitions in clinical studies of PVL treatment. Despite limitations to and unresolved questions concerning current trial design, the PVLARC committee recommends these standards for clinical PVL studies in surgical prostheses.

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APPENDIX For an expanded Discussion section as well as supplemental tables, please see the online version of this article.