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# Paravalvular regurgitation after transcatheter aortic valve replacement: incidence, quantification, and prognostic impact

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**INVITED REVIEW**

# Paravalvular regurgitation after transcatheter aortic valve replacement: incidence, quantification, and prognostic impact

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**Abstract**

Transcatheter aortic valve replacement (TAVR) is the standard of care in aortic stenosis with results comparable to surgical aortic valve replacement. However, paravalvular regurgitation (PVR) is more common after TAVR. With the alteration of devices and implantation techniques, the incidence of moderate or more PVR has declined. Mild PVR is still common in around 30% of TAVR patients in low-risk trials. Progression of AS causes myocardial hypertrophy and varying degrees of diastolic dysfunction which may cause heart failure even in combination with small volumes of PVR. Any degree of PVR is associated with an increased risk of overall and cardiovascular mortality. Predictors of PVR are annular eccentricity, severe calcification of the aortic valve, bicuspid aortic valves, and type of prosthesis where balloon-expandable devices are associated with less PVR. PVR is diagnosed using echocardiography, aortic angiogram with or without videodensitometry, haemodynamic parameters, or cardiac magnetic resonance. PVR can be treated using post-dilation, interventional treatment using a vascular plug, or implantation of a second device. Successful post-dilation depends on balloon size which should at least be equal to or >95% of the mean annulus diameter. Implantation of a second device to reduce PVR is successful in ∼90% of cases, either through lengthening of the sealing skirt in case of inadequate position or through further expansion of the index device. Implantation of a vascular plug can successfully reduce PVR and reduce mortality.

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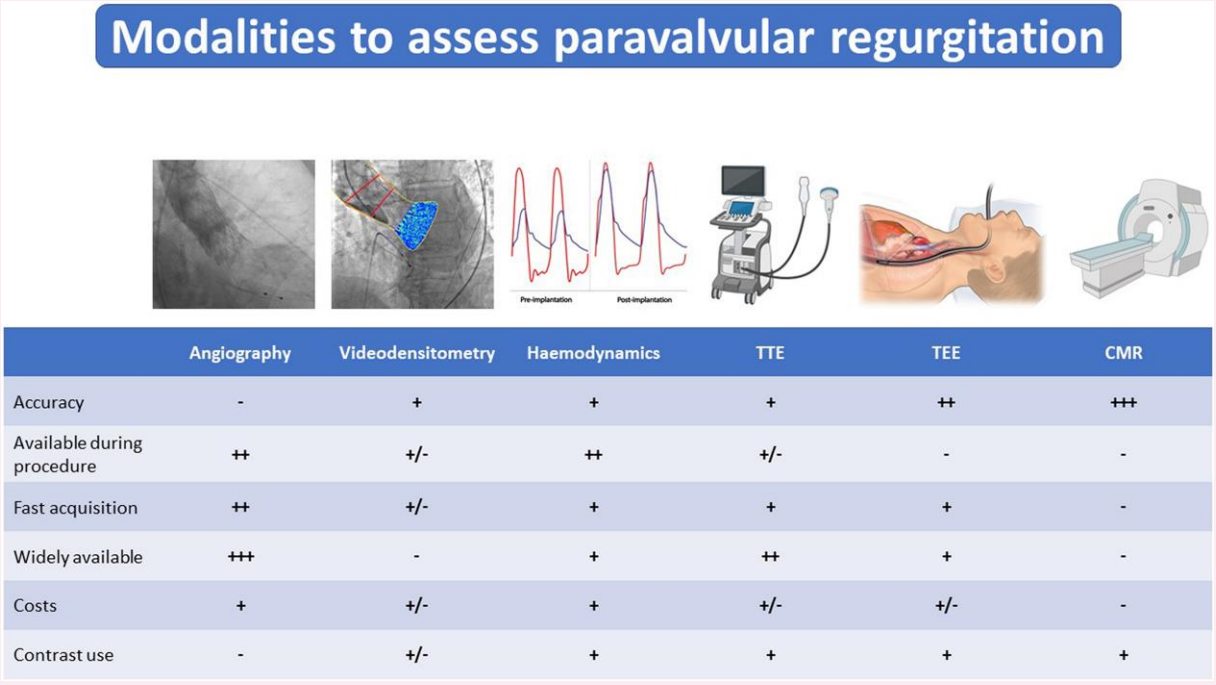
## Graphical Abstract




| | Angiography | Videodensitometry | Haemodynamics | TTE | TEE | CMR |
|---|---|---|---|---|---|---|
| Accuracy | - | + | + | + | ++ | +++ |
| Available during procedure | ++ | +/- | ++ | +/- | - | - |
| Fast acquisition | ++ | +/- | + | + | + | - |
| Widely available | +++ | - | + | ++ | + | - |
| Costs | + | +/- | + | +/- | +/- | - |
| Contrast use | - | +/- | + | + | + | + |

Modalities to assess PVR

**Keywords** aortic stenosis • paravalvular regurgitation • transcatheter aortic valve replacement

# Background

Transcatheter aortic valve replacement (TAVR) is the standard of care in patients with symptomatic severe aortic stenosis (AS) at high and intermediate surgical risk and a suitable alternative to surgical aortic valve replacement (SAVR) in low-risk patients.[1,2] Reported success rates are high. Moreover, haemodynamic properties of TAVR prostheses, including effective orifice area and residual aortic valve gradient, are at least equal to surgical biological valves. Furthermore, the incidence of patient-prosthesis mismatch is lower in patients treated with TAVR compared with patients treated with SAVR.[3] Nonetheless, the incidence and severity of paravalvular regurgitation (PVR) remains significantly higher in patients treated with TAVR compared with SAVR. This is especially important as moderate to severe PVR is associated with increased morbidity and mortality, and even mild PVR might be linked to adverse clinical outcomes.[4,5] In this review, we discuss the incidence, prognostic impact, mechanisms, diagnostic modalities as well as treatment options for PVR.

# Incidence and prognostic impact of PVR

Although the incidence of moderate to severe PVR following TAVR has declined with improved valve design, implantation technique, and operator experience, the latest generation devices implanted in low-risk populations still show moderate to severe PVR in 0.8% in balloon-expandable (BE) devices and in 3.4% in self-expanding (SE) devices at 30 days. In contrast, the incidence of mild PVR is high after TAVR, with incidences of 29% in BE vs. 36% in SE devices at 30 days.[1,2] The relevance of these observations is highlighted by the fact that moderate to severe PVR has consistently been associated with increased mortality.[6–9] Mild PVR is usually asymptomatic and there are conflicting results regarding its association with mortality. This might be explained by the difference in operative risks between patients across studies, as well as differing grading schemes used for PVR quantification (three- vs. four- vs. five-class grading scheme). For example, in the high-risk PARTNER trial (three-class grading scheme), mild PVR was associated with an increased risk of mortality compared with none/trace PVR [hazard ratio (HR) 1.37, 95% CI: 1.14–1.90] while in the intermediate-risk PARTNER 2 trial (five-class grading scheme), this was not [HR mild vs. none/trace PVR 1.09 (95% CI: 0.84–1.41)].[10,11] In the Swiss TAVI registry, mild PVR was associated with an increased risk of mortality at 5 years follow-up (HR 1.56, 95% CI: 1.20–2.02) when using a three-class grading scheme.[5] However, when a five-class grading scheme was applied, only mild-moderate PVR, but not mild PVR, was associated with an increased + risk of mortality. A meta-analysis of 25 predominantly non-comparative studies (without a control group) pooling data of over 21 000 patients reported that mild PVR was associated with a 26% increase in all-cause mortality, and a 28% increase in cardiovascular mortality when compared with none/trace PVR.[4] More recently, a meta-analysis of Kaplan–Meier-derived individual patient data of 38 mostly non-randomized studies with over 25 000 patients, reported that any degree of PVR (even mild PVR) is associated with an increased risk of all-cause mortality, rehospitalization, and cardiovascular mortality as compared with none/trace PVR.[12] Of note, studies included in these meta-analyses varied in the grading schemes used and the timing of PVR assessment, which should be considered when interpreting the results. Moreover, most of the studies included in the meta-analyses comprised unadjusted cohorts, introducing the risk of confounding factors not accounted for in the outcomes.

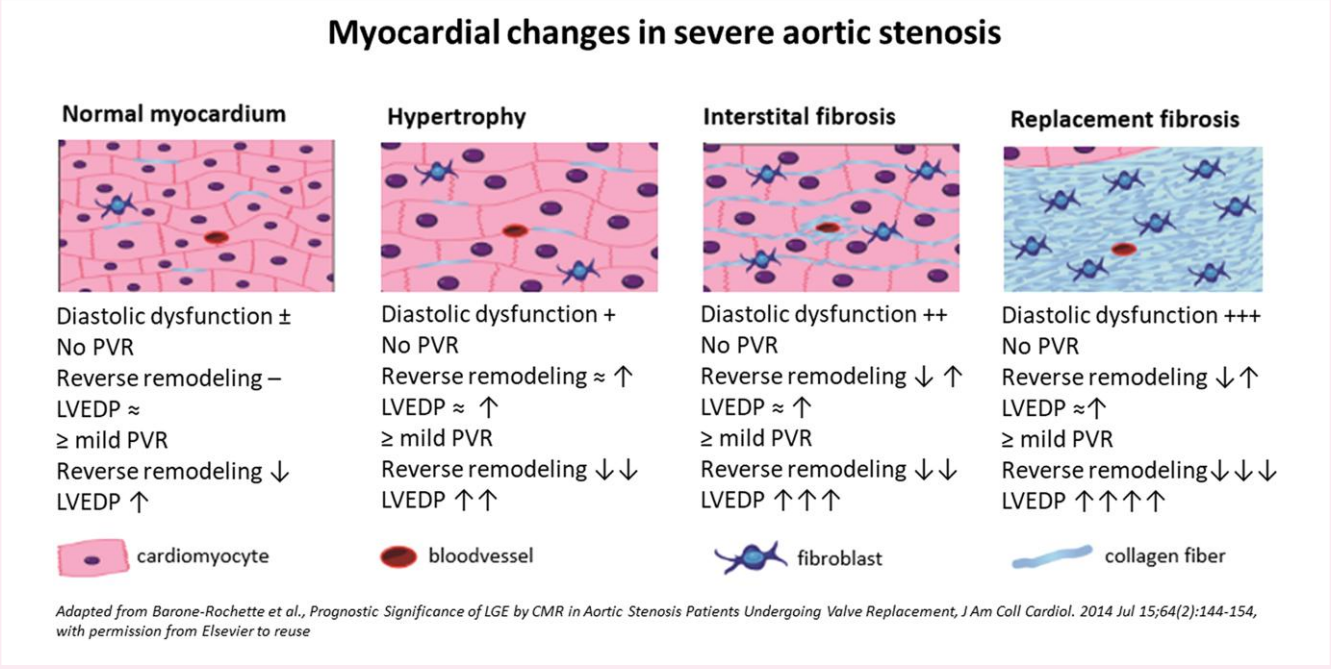



**Figure 1** Myocardial changes in severe AS. PVR, paravalvular regurgitation; LVEDP, left ventricular end-diastolic pressure.

## Potential mechanisms for adverse outcome after PVR

The negative impact of PVR on outcome after TAVR is attributed to the AS-induced remodelling of the left ventricle (LV), resulting in a pressure-overloaded ventricle, in combination with an acute volume overload.[13–15]

The progression of AS increases LV systolic pressures, and in order to maintain wall stress and systolic function, the LV undergoes compensatory hypertrophy.[16] Myocardial hypertrophy increases myocardial stiffness, which in turn decreases compliance. With the progression of AS, abnormalities of the collagen network occur which result in the development of diffuse interstitial fibrosis followed by focal replacement fibrosis and an increase of extra-cellular volume (*Figure 1*).[17–20] This causes diastolic and ultimately also systolic dysfunction, when pressure gradients cannot be overcome by the LV. Indeed, a higher diastolic dysfunction grade at baseline is associated with increased 1- and 2-year mortality in both SAVR and TAVR cohorts.[19,21–23]

Since the degree of diastolic dysfunction differs between patients with severe AS,[24] a regurgitation fraction may lead to varying increments of LV end-diastolic pressure, which subsequently results in diverse clinical patterns ranging from no complaints to overt heart failure.[19,25] This was illustrated by an *in vitro* experimental model, using different aortic regurgitation (AR) fractions in three LV models differing in diastolic properties. In the ventricle with the highest wall stiffness the effect of trace PVR on LV end-diastolic pressure was comparable to the effect of moderate PVR in the ventricle model with the lowest wall stiffness.[26]

The presence of AR at baseline seems to be protective for the effects of PVR after TAVR. In a retrospective study, important PVR (defined as either new, mild PVR without previous AR or moderate to severe PVR in any patient) was compared with unimportant PVR (defined as either no or trace PVR in any patient or mild PVR in patients with previously at least mild AR). Patients with unimportant PVR showed significant improvements in cardiac mechanics as measured by echocardiography, unlike those with important PVR.[27] The varying degrees of diastolic dysfunction found in AS patients might explain the heterogeneity of the effect of mild PVR on morbidity and mortality in TAVR patients.

### Structural changes after aortic valve intervention

Studies have provided strong support for post-intervention remodelling. For example, a small histological study of isolated AS reported that after successful SAVR, hypertrophied myocardium regresses earlier than interstitial fibrosis. Therefore, the net interstitial fibrosis percentage significantly increases early after surgery, resulting in worsened diastolic function. Interestingly, in combined aortic valve disease and isolated AR, the increase in interstitial fibrosis percentage after surgery was not significant.[28] Cardiac magnetic resonance (CMR) studies confirmed that at 6-month follow-up post-SAVR, regression of LV mass is primarily driven by decreases in the volume of the myocardial cells. CMR follow-up after one year showed a reduction in extracellular (matrix) volume, but no change in the volume of focal fibrosis (scar). Though the decrease in myocardial cellular volume exceeded the decrease in extra-cellular matrix volume (resulting in a net increase of percentage extra-cellular volume), improvements were found in diastolic function, NT-proBNP levels, and 6-min walking tests.[29,30] In an observational study using echocardiography for follow-up after TAVR, consistent regression of LV mass index was found in patients with LV hypertrophy at baseline. LV mass index reduction was correlated with higher gradients across the native valve before and lack of significant residual PVR after TAVR. However, regression of hypertrophy was not complete, as only 25% of patients with LV hypertrophy at baseline showed complete normalization of LV mass index. Adverse remodelling was found in 17% of patients, especially in the normal geometry group and in patients with postprocedural more than mild PVR.[31] After TAVR, the decrease in LV mass index is less profound compared with SAVR. This might be explained by the fact that TAVR patients tend to be older with more comorbidities and more extensive myocardial

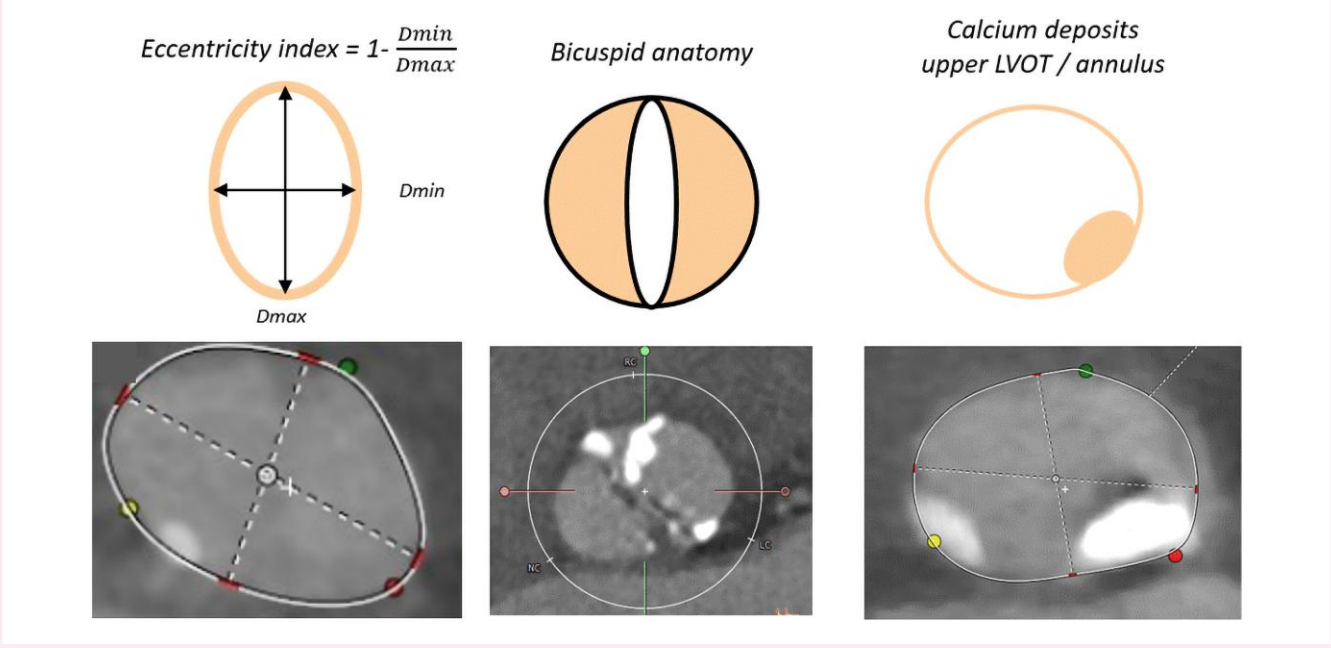



**Figure 2** Anatomical factors predisposing for PVR. From left to right: eccentricity index > 0.35 is an independent predictor of PVR. In bicuspid anatomy, the incidence of mild to moderate PVR after TAVR is significantly higher than in tricuspid anatomy. Volume of calcium deposits at the level of the annulus and upper LVOT, both quantitively and semi-quantitatively, are associated with PVR. PVR, paravalvular regurgitation; TAVR, transcatheter aortic valve replacement; LVOT, left ventricular outflow tract.

disease at baseline, or by the higher prevalence of PVR in the TAVR population, in which the unloading of the LV is incomplete and regression of myocardial mass index is impeded.[3,32]

# Factors predisposing to PVR

## Valve sizing and PVR

Undersizing of the prosthesis relative to the annulus size causes PVR after TAVR. To optimize the sizing of the prosthesis relative to the annulus, the cover index was described. The cover index is defined as {100 × [prosthesis diameter – transoesophageal echo (TEE) derived annulus diameter]/prosthesis diameter}. PVR ≥mild (i.e. PVR ≥ 2/4 in a four-class grading scheme) after TAVR is significantly associated with a lower cover index ($P = 0.002$) and a certain amount of oversizing (and thus a higher cover index) results in lower PVR severities.[33] In another study of SE devices that used three-dimensional (3D) TEE, angiography, and multi-slice CT for measurement of the annulus, the dimensions of the aortic annulus were significantly larger (25.1 ± 2.4 vs. 23.2 ± 1.9 mm; $P < 0.001$) and the cover index significantly lower (10.1 ± 6.1 vs. 16.0 ± 4.6%, $P < 0.001$) in patients with ≥moderate PVR as compared with patients with < moderate PVR.[34] The use of CT-guided sizing of the annulus reduced PVR compared with TEE-guided sizing in patients treated with a BE device (≥moderate PVR 7.5 vs. 21.9%, respectively).[35] Therefore, 3D measurements using multi-slice CT are considered the gold standard for sizing the annulus.

## Annular shape

The aortic annulus is usually oval shaped, while TAVR frames are circular, which might impede the full apposition of the TAVR frame (*Figure 2*).[36,37] Hence, the eccentricity index [defined as 1 – (minimal annular diameter/maximal annular diameter)] was introduced as a measure of annular eccentricity. In first-generation SE devices, an eccentricity index > 0.35 was independently associated with significant PVR.[38] However, other studies in first-generation SE devices were not able to replicate these findings.[39,40] In BE devices, annular eccentricity was associated with PVR, and left ventricular outflow tract (LVOT) eccentricity was an independent predictor of ≥mild PVR. Furthermore, discordant sizing of LVOT and annulus (i.e. oversizing one, undersizing the other) was associated with mild PVR in BE devices, in contrast to concordant under- or oversizing. This is explained by a shorter seal zone of the TAVR frame when the area of sealing is heterogeneous (in discordant sizing) vs. homogenous with a larger area of tissue contact (in concordant sizing). Furthermore, an increased angle of the LVOT to the ascending aorta might affect the radial force of the stent frame and has been associated with relevant PVR in first-generation SE devices.[41]

## Calcification of the native aortic valve and LVOT

Calcification of the native valve leaflets, commissures, and/or annulus might impede proper sealing of the device to circumferential tissue (*Figure 2*), subsequently increasing the risk for PVR. Quantitatively, a total valvular calcium score or Agatston score > 3000 was associated with ≥moderate PVR in first-generation BE and SE devices.[42] Furthermore, sex-specific cut-offs of 4070 in men and 2341 in women are independent predictors of moderate PVR in third-generation devices.[43] Asymmetric calcium deposits in the annular and upper LVOT regions are associated with increased PVR in first- and second-generation BE devices.[44,45] Moderate or severe LVOT calcification is associated with moderate to severe PVR in both SE and BE devices.[46]

## Bicuspid aortic valves

Bicuspid aortic valves (BAV) have larger dimensions of the aortic annulus, sinus of Valsalva, and ascending aorta combined with more

extensive calcification and leaflet asymmetry and a more elliptical aortic orifice as compared with tricuspid aortic valves (*Figure 2*).[47,48] Early experience in small populations with first-generation BE and SE devices in BAV showed less favourable results than in tricuspid valves, with high rates of peri-procedural complications (13–34% moderate to severe PVR, 13–43% of permanent pacemaker implantation, and a 1-year mortality between 4 and 18%).[49,50] Later experience in propensity-matched populations showed that mortality at two years follow-up was comparable (17.2 vs. 19.4%, $P = 0.28$) though procedural success and incidence of relevant PVR still differed significantly in BAV patients compared with tricuspid patients (≥moderate PVR 10.4 vs. 6.8%, $P = 0.04$).[51] The BAVARD registry reported that in tricuspid annuli, the perimeter-derived diameter at the level of the annulus before and after TAVR implantation did not significantly change. However, in bicuspid annuli the diameter was significantly smaller at the level of the annulus after TAVR implantation, suggesting under-expansion of the TAVR frame at the level of the aortic orifice, which is more elliptical in BAV compared with tricuspid valves.[52] It was suggested to take the inter-commissural distance (at the level of the aortic orifice) into account when sizing BAV, especially in cases with a tapered configuration (inter-commissural distance < annular dimensions). However, supra-annular compared with annular sizing in BAV patients showed that annular sizing is accurate in >95% of patients and supra-annular sizing could improve sizing in only 4% but worsen sizing in 40% of patients. Therefore, annular sizing in BAV patients is still preferred over supra-annular sizing.[53]

## Valve type and PVR

Currently, two different types of TAVR design and deployment are used. The Sapien device (Edwards Lifesciences, Irvine, CA, USA) consists of a cobalt-chromium stent frame with bovine pericardial leaflets in intra-annular position, whereas the CoreValve and Evolut devices (Medtronic Inc, Minneapolis. MN, USA) consist of porcine pericardial leaflets mounted on a nitinol frame in supra-annular position.

In PARTNER 1B and the CoreValve extreme risk trials, moderate-to-severe PVR was found in 11.8 and 10.7% and mild PVR in 52.1 and 41.5%, respectively.[6,54–57] Because of the association of moderate-to-severe PVR with mortality, the Sapien 3 and Ultra BE devices are equipped with an adaptive external sealing skirt made of polyethylene terephthalate. The Evolut PRO and PRO+ are equipped with an external pericardial wrap to mitigate PVR (*Figure 3A and B*). When the Sapien 3 is compared with its predecessor Sapien XT, the incidence of moderate to severe PVR and mild or more PVR are reported to be significantly lower in Sapien 3.[58–60] When comparing Evolut PRO with its predecessor Evolut R, the incidence of moderate to severe PVR was comparable.[61,62] In a meta-analysis comparing Evolut R and Evolut PRO with Sapien 3, pooled results showed no difference in ≥moderate PVR rates between these devices [1.3% (95% CI: 1.2–1.4) for Sapien 3 vs. 2.8% (95% CI: 2.5–3.1) for Evolut, risk ratio (RR) 0.49; 95% CI: 0.20–1.17; $P = 0.11$].[63] Significantly higher incidences were reported of mild, but not ≥moderate PVR, in Evolut vs. Sapien (mild PVR: 24.5% in Sapien vs. 40.8% in Evolut, RR 1.63, 95% CI: 1.36–1.96; $P < 0.0001$ and ≥moderate PVR: 2.8% in Sapien vs. 5.4% in Evolut, RR 1.5, 95% CI: 0.97–2.31, $P = 0.07$).[64] These differences in favour of Sapien 3 can be explained by either the higher radial force of the BE frame or the type of PVR sealing used (adaptive sealing in Sapien vs. passive sealing in Evolut PRO).

## Implantation technique and PVR

Implantation depth, both too deep and too shallow, is associated with relevant PVR.[65] In SE TAVR using CoreValve, implantation depth (measured from the non-coronary cusp) below 15 mm resulted in severe PVR because the uncovered part of the TAVR frame is at the annular level. A shallower implantation depth (i.e. 5–10 mm) minimized the chance of moderate or severe PVR.[66] In another study low CoreValve implantation (defined as ≥3 struts below the level of the native annulus) was reported to increase the chances of moderate or severe PVR (OR 3.67, 95% CI: 1.01–13.35).[67] When the prosthesis is implanted too high, PVR results from inadequate apposition of the frame to the aortic annulus and anchoring of the prosthesis is inadequate which results in an unstable position.

# Diagnostic modalities to assess PVR

Several techniques are available to detect and assess severity of PVR (*Graphical Abstract*).

## Angiography

Aortic root angiography as described by Sellers is the oldest and most widely used imaging modality for grading PVR and is readily available during TAVR (*Graphical Abstract*).[68] A pigtail catheter is placed in the ascending aorta just above the newly implanted prosthesis without remaining catheters or wires in the LV. The angiogram is commonly performed in a right anterior oblique 30° view, using 20–40 mL of contrast agent. AR is then classified by visual grading. The reproducibility of classification by visual estimation is relatively low and highly dependent on technical factors, such as the intensity and projection of fluoroscopy, the position of the catheter through which the contrast is administered and the amount and speed of contrast injection that is used.[69,70] Of importance, projection of the descending aorta over the LV can cause inaccuracy of PVR grading. To improve image quality and assessability of aortic angiograms, fluoroscopy using a pigtail catheter to visualize the descending aorta can be used to determine the projection in which overlap of the LV and aorta is avoided.[71]

## Videodensitometry

Quantitative angiography using videodensitometry improves the reproducibility of PVR grading by angiography and can be used both offline and online[72,73] (*Graphical Abstract*). In brief, time–density curves are generated in the LVOT (region of interest) and in the aortic root where the contrast is injected (reference area). From these time–density curves, the area under the time–density curve (AUC) is automatically computed to represent the time–density integral. The regurgitant fraction is then calculated by dividing the AUC of the LVOT by the AUC of the aortic root. This technique has been validated against CMR and echocardiography,[72–74] and videodensitometry-derived AR fraction correlates well with regurgitation fraction as measured by CMR.[72]

## Echocardiography

The Valve Academic Research Consortium-3 recommends to use echocardiography as the primary imaging modality for the assessment of PVR (*Figure 4*, *Graphical Abstract*).[75] Transthoracic echocardiography (TTE) is readily available, cheap, and non-invasive. TTE is useful to identify the presence of PVR using the parasternal long- and short-axis views, the apical long-axis, and five-chamber view to obtain images of valve structure and motion and LV dimensions. Doppler is used to determine jet origin, width, and density as well as the deceleration time of the AR signal and diastolic backflow in the descending aorta. The mechanism of PVR and its morphology differ in TAVR compared with native valve regurgitation since PVR often consists of multiple, eccentric, and irregular shaped jets which may be partly masked by acoustic shadowing of the TAVR frame or native calcification[76] (*Figure 3A*). TTE may therefore not optimally display posterior PVR jets.[77] Of note, the ideal timing of PVR assessment after TAVR remains a matter of debate, with some centres performing the post-TAVR TTE during the index hospitalization, while others have the first post-TAVR TTE performed at the outpatient clinic. Interestingly, regression of PVR over time has been described in both BE and SE devices.[6,9] In a prespecified analysis of

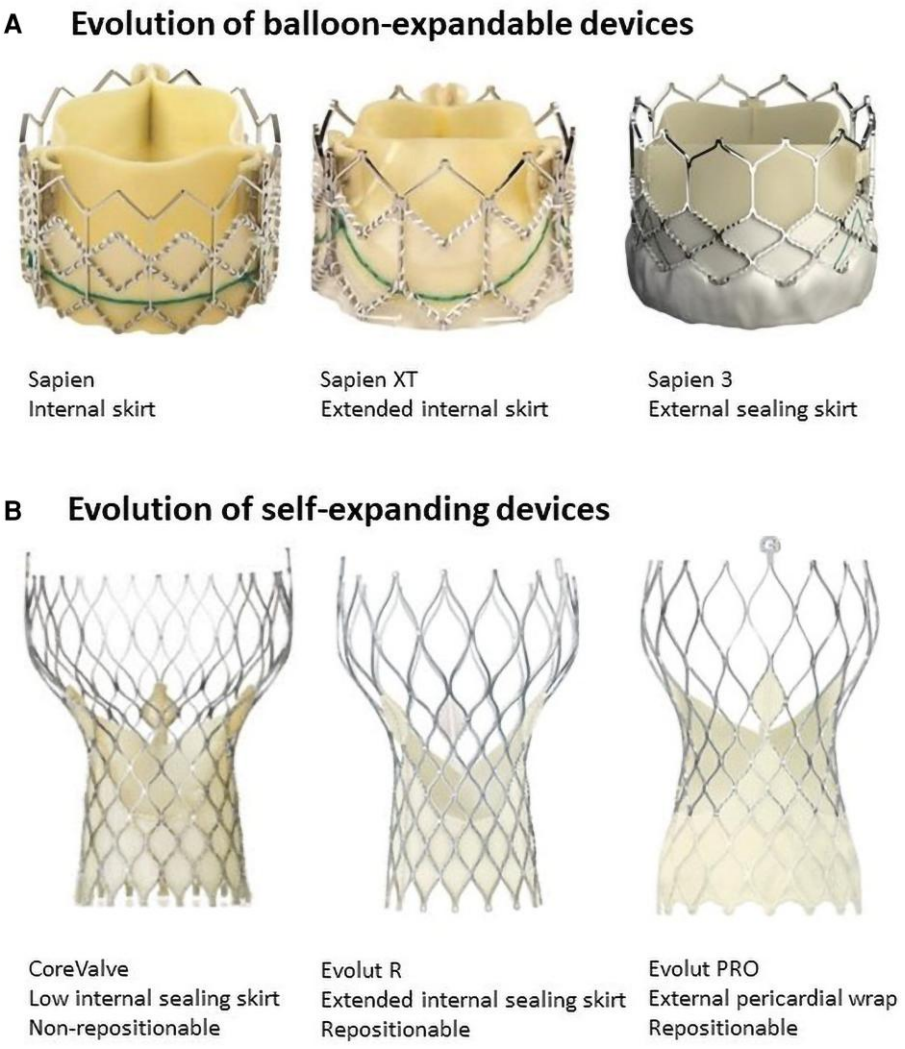



**Figure 3** Changes in TAVR design to mitigate PVR. (*A*) BE devices. From left to right: Sapien, Sapien XT, Sapien 3 with external fabric seal to mitigate PVR. (*B*) SE devices. From left to right: CoreValve: SE, non-repositionable device; Evolut R: SE, repositionable device; Evolut PRO: SE, repositionable device with external pericardial wrap to mitigate PVR.

the PARTNER 2 SAPIEN 3 trial (BE device), 73% of patients with moderate PVR on TTE at discharge improved by at least one PVR grade at 1 year.[9] In the CoreValve US pivotal trial (SE device), this number was as high as 83%.[6] Continuing expansion of the stent frame, tissue overgrowth covering the paravalvular spaces, and aortic root remodelling are mentioned by the authors as potential factors contributing to PVR regression.[78]

TEE is superior to TTE in terms of spatial resolution and image quality and can be used to discriminate PVR from valvular regurgitation, analyse the mechanism of PVR, and diagnose peri-procedural complications such as landing zone haematoma or rupture. However, TEE is invasive and often necessitates sedation of the patient. Moreover, anterior PVR jets can be masked during TEE.[77] The presence of elevated transvalvular velocities is an important clue that should prompt further evaluation with TEE to establish a definitive diagnosis, characterize the severity of the regurgitation, and localize the defect.[79] 3D TEE, using en face views and/or multiplanar reconstruction, may offer a more definitive assessment of valve structure and localization of PVR. In the early days of TAVR, patients were treated under general anaesthesia and as such, TEE imaging for peri-procedural guidance was readily available. With the trend towards minimally invasive TAVR under local anaesthesia or conscious sedation, TTE is the imaging modality of choice.[80,81] TTE-guided TAVR is associated with a similar incidence of PVR at discharge and follow-up compared with TEE-guided TAVR.[82,83] However, it should be noted that in the study by Hayek *et al*., the incidence of intraprocedural post-dilation and second valve implantation was higher in the TTE-guided TAVR group, potentially explaining the lack of difference in PVR between the groups.[83]

The European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend a three-class grading scheme for PVR.[77,84,85] However, in clinical practice a five-class grading scheme is frequently used, dividing mild PVR into mild and mild-moderate PVR, and moderate PVR into moderate and moderate-severe PVR.[86] Usage of this five-class grading scheme reduced inter-core lab variability within the PARTNER 2 registry.[9] Furthermore, a recent study showed that mild-moderate PVR graded using this five-class grading scheme was associated with mortality, as opposed to mild PVR, underlining the clinical importance of this alternative scale.[5]

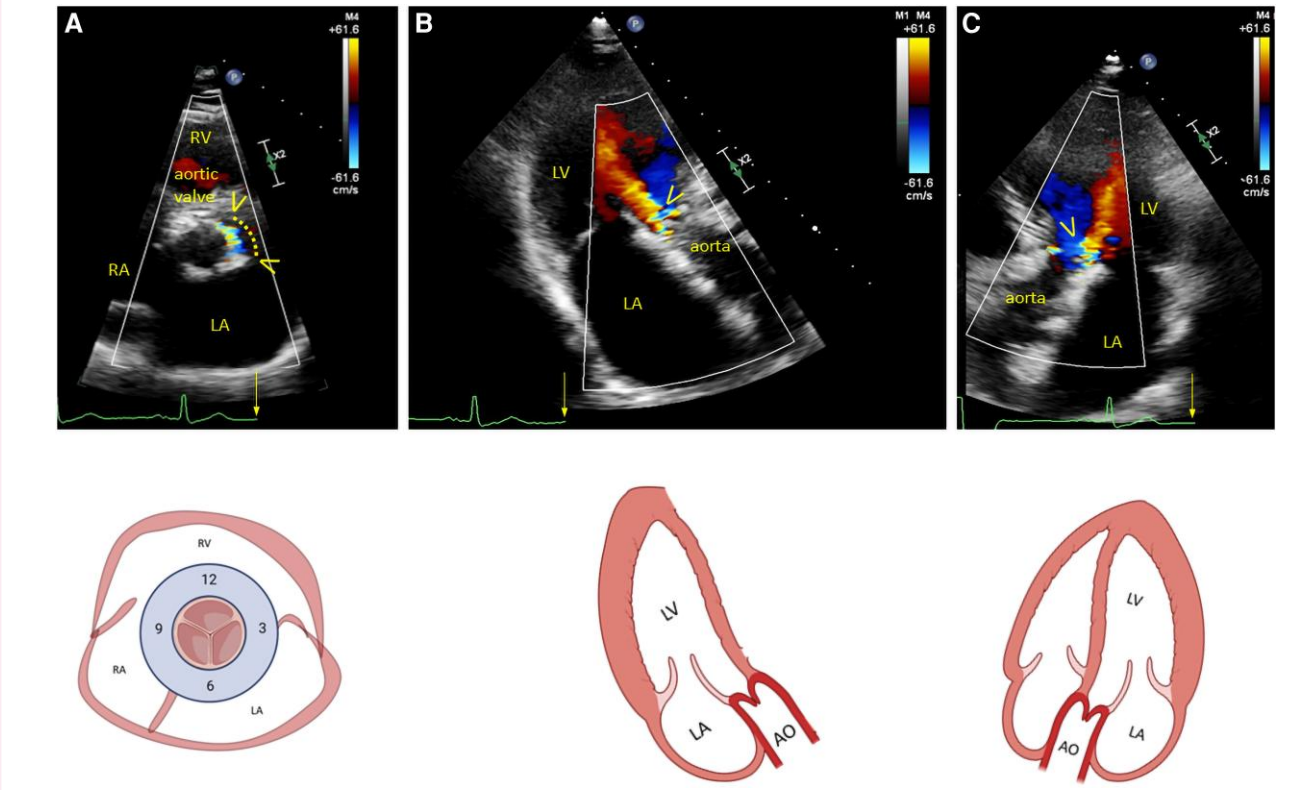



**Figure 4** Echocardiographic grading of PVR. TTE images after TAVR. RV, right ventricle; RA, right atrium; LA, left atrium. Arrowheads indicate PVR. (*A*) Parasternal short axis. The shape of the frame can be determined as well as jet location, circumferential extent (in percentage or minutes), and origin of the jet. (*B*) Apical three-chamber view. (*C*) Apical five-chamber view. Jet density, flow convergence, and pressure-halftime of the regurgitant jet can be determined in these views.

## Invasive haemodynamic parameters

Haemodynamic parameters can be derived from transvalvular pressure tracings post-TAVR. These pressure tracings do not require additional procedural time or contrast agent. Several haemodynamic parameters have been described to estimate PVR and predict prognosis after TAVR (*Table 1* and *Figure 5*), which are the following:

- Diastolic delta (DD): diastolic blood pressure – LV end-diastolic pressure.
- Heart rate-adjusted diastolic delta (HR-DD): (DD/heart rate) * 80.
- Aortic regurgitation index (ARI): (DD/systolic blood pressure) * 100.
- ARI ratio: ARI after implantation/ARI prior to implantation.
- Diastolic pressure time integral (DPTI): [(area between aortic and LV diastolic pressure-time curves/diastolic duration)/systolic blood pressure] * 100.
- Time-integrated aortic regurgitation index (TIARI): (DPTI/LV systolic pressure-time index) * 100.

In previous studies, DD ≤ 18 mmHg,[87] HR-DD < 25,[88] ARI < 25,[34] and ARI ratio < 0.6[89] were all independently associated with an increased risk of mortality after TAVR. These four haemodynamic parameters with their respective cut-off values were subsequently compared for their association with mortality in a large cohort study, in which the ARI ratio was identified as the strongest independent predictor of 1-year mortality.[90] In contrast, the APPOSE trial showed that DD had the best correlation with CMR-assessed PVR, in which DD ≤ 32 mmHg was found to have the highest predictive value for relevant PVR.[91] Regarding DPTI, a value < 27.9 was shown to be an independent predictor of 1-year mortality.[92] A TIARI < 80 was associated with ≥mild PVR with a sensitivity of 86% and a specificity of 83%.[93] Moreover, TIARI was inversely associated with the incidence of balloon post-dilation, and a higher residual TIARI was associated with better survival after TAVR.[94]

## Cardiac magnetic resonance

CMR enables precise and reproducible quantitative measurement of regurgitant volume, irrespective of morphology, number of the PVR jets and type of device used (*Figure 6*).[95] Two-dimensional (2D) phase-contrast velocity encoding (venc) using through-plane velocity quantification is the most frequently adopted CMR technique for PVR assessment, in which 2D flow measurements are acquired during end-expiratory breath-holds. A single venc value is used, which is set at a high venc of ≥180 cm/s, providing accurate measurements of the forward volume, but with a lower accuracy in regurgitant volume (low-flow volume) measurement, due to the lower signal-to-noise ratio. To overcome this issue, a low venc of 75 cm/s can be used for the determination of regurgitant volume. The regurgitant fraction is calculated by dividing the regurgitant volume by the forward volume, multiplied by 100.[96]

Emerging techniques in the field of PVR assessment after TAVR using CMR are 2D multi-venc and four-dimensional (4D) flow.[97] 2D multi-venc flow facilitates the use of a single breath-hold to analyse two or three different venc values by combining these individual venc values into a single reconstruction that can be used for flow quantification.[98] 4D flow provides a comprehensive visualization of the blood flow with

**Table 1 Haemodynamic indices**

| Haemodynamic index | Calculation | Cut-off associated with adverse outcome |
|---|---|---|
| DD | Diastolic blood pressure – LVEDP | DD ≤ 18 mmHg predictor of 30-day and 1-year mortality |
| HR-DD | (DD/heart rate) * 80 | HR-DD < 25 mmHg/BPM predictor of 1-year mortality |
| ARI | (DD/systolic blood pressure) * 100 | ARI < 25 predictor of 1-year mortality |
| ARI ratio | ARI after implantation/ARI prior to implantation | ARI ratio < 0.6 predictor of 1-year mortality |
| DPTI | [(area between aortic and LV diastolic pressure-time curves/ diastolic duration)/systolic blood pressure] * 100 | DPTI ≤ 27.9 predictor of 1-year mortality |
| TIARI | (DPTI/LV systolic pressure-time index) * 100 | TIARI < 80 associated with ≥mild PVR |

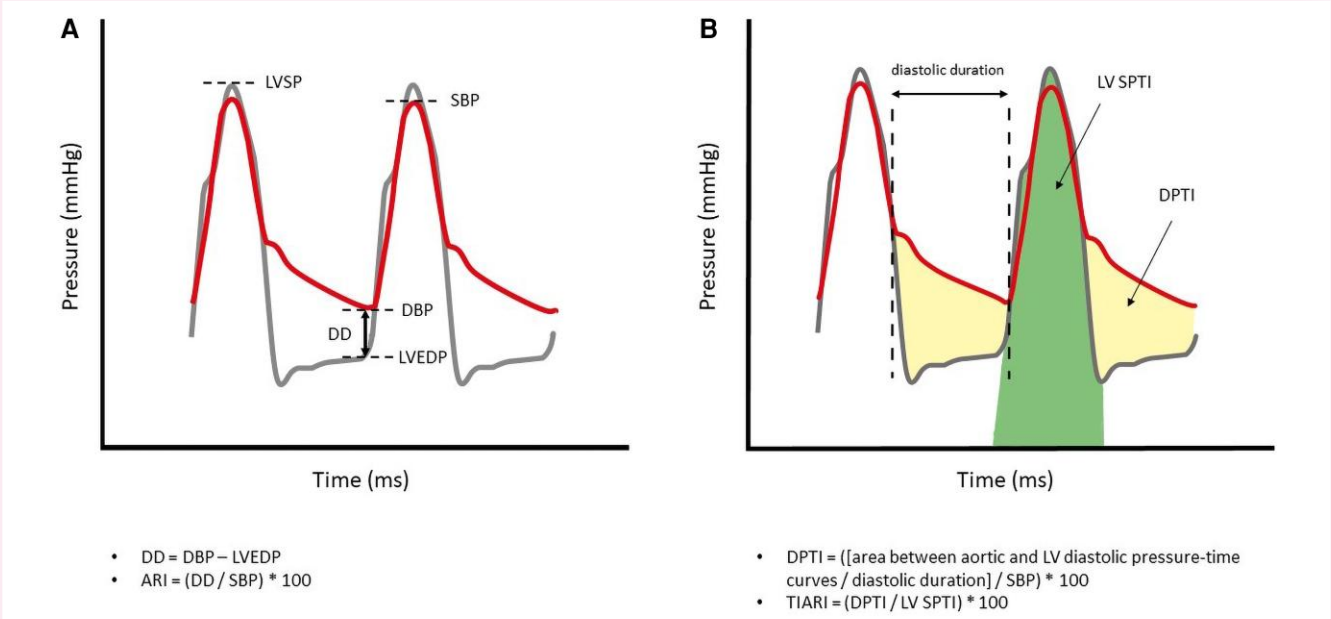



**Figure 5** Haemodynamic parameters used to grade PVR. DD, diastolic delta; DBP, diastolic blood pressure; LVEDP, left ventricular end-diastolic pressure; ARI, aortic regurgitation index; SBP, systolic blood pressure; DPTI, diastolic pressure time integral; LV, left ventricle; SPTI, systolic pressure-time integral.

accurate measurements of the velocity in all spatial directions.[99] In addition, 4D flow is not dependent on breath-holds, allowing the patient to breathe freely.

However, CMR might slightly overestimate the severity of PVR because diastolic coronary flow is included in the calculation of total regurgitant volume.[100] Additionally, 2D flow CMR is not able to differentiate PVR from central valvular regurgitation, which can be resolved by using 4D flow. Studies comparing TTE to CMR reported a low sensitivity of detecting ≥mild PVR in TTE (i.e. 19%)[101] and highlighted that TTE may underestimate PVR grade by at least one stage in 48% of TAVR patients.[76] When comparing 2D TTE and 3D TTE with CMR, there was agreement in PVR grade between 2D TTE and CMR in 76% and between 3D echo and CMR in 86% of patients.[95] In a recent meta-analysis, it was concluded that TTE is sufficient to discriminate between none to mild and moderate to severe PVR and that CMR should be reserved for patients in whom TTE results are equivocal or clinical parameters are not in accordance with the degree of PVR measured by TTE.[102] Other disadvantages of CMR in PVR assessment are the valve-related artefacts (due to the metallic frame of the TAVR device), lower accuracy in patients with irregular heart rhythms (e.g. atrial fibrillation), and the difficulty with interpretation of 4D flow data in case of cardiac motion artefacts and turbulent flow.[85]

## Treatment of PVR

The optimal treatment of PVR is prevention. However, when prevention of PVR was unsuccessful, some treatment options can be considered. These include balloon post-dilation, placement of a second valve, and percutaneous PVR closure by a vascular plug. Treatment of PVR is indicated in the following situations: symptomatic PVR with signs and symptoms of congestive heart failure, or haemolytic anaemia requiring repeated blood transfusions.[103,104] In asymptomatic patients with moderate to severe or severe PVR, treatment of PVR may be considered in case of a progressive decline in left ventricular ejection fraction or a progressive increase in LV dilation.[104,105] Whether the successful

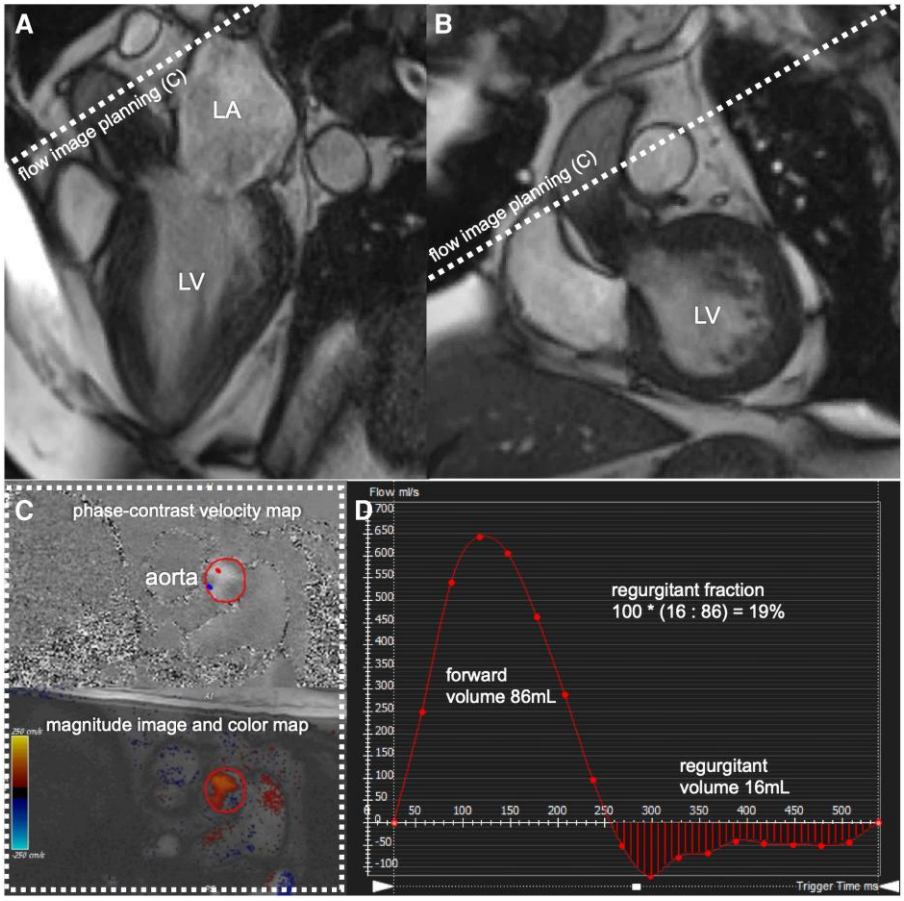



**Figure 6** CMR imaging of PVR. Example of a CMR acquisition of a TAVR valve in the three-chamber cine (*A*) and perpendicular coronal view (*B*) which are used to plan the phase-contrast velocity map (*C*) and magnitude image (*D*) with color-encoded flow map. Flow analysis enables exact quantification of the regurgitant volume (dashed volume of 16 mL) compared with the forward volume (86 mL) providing the regurgitant fraction (19%).

reduction of PVR in asymptomatic patients is associated with improved survival is yet to be investigated.

In case of significant PVR, balloon post-dilation is usually considered first. Post-dilation is easily performed during the index TAVR procedure and is especially effective in case of inadequate apposition or relative undersizing of the valve compared with the native annulus. Post-dilation has been performed in a substantial proportion of patients treated with TAVR, in first-generation prostheses even up to 28%.[106] In PARTNER 1, post-dilation resulted in reduced rates of prosthesis-patient mismatch but also in a higher incidence of ischaemic neurological events up to 7 days after TAVR (4.9 vs. 2.6%, $P = 0.04$).[107] In first-generation SE devices, post-dilation was not associated with higher rates of stroke or mortality in either short- or long-term. Post-dilation succeeded to reduce PVR to mild or less in 63% of patients.[108] In second-generation BE devices, post-dilation successfully reduced PVR by at least one degree in 71% of patients, with residual PVR <mild-moderate in 54% of patients. Post-dilation was associated with a significantly higher occurrence of ischaemic stroke < 24 h after TAVR (8.5 vs. 0.7%, $P = 0.007$).[106] In another study using SE devices, post-dilation was performed when haemodynamic parameters or aortic angiography were indicative of relevant PVR. Post-dilation was safe with no significant difference in 30-day and 1-year mortality between patients who did and did not undergo post-dilation. In all patients treated with post-dilation, PVR reduction of ≥1 degree was obtained, and residual ≥mild PVR was found in 11.6%.[109] Others report a success rate of post-dilation (resulting in ≤mild PVR) of 87.6% of patients treated with SE devices. The most important factor determining post-dilation success was the ratio of the size of the post-dilation balloon vs. the mean annulus diameter as measured by CT. The ratio of the post-dilation balloon diameter to the annulus diameter was greater in patients treated successfully with post-dilation vs. those treated unsuccessfully (post-dilation balloon size/mean annulus diameter $1.04 \pm 0.11$ vs. $0.95 \pm 0.10$, $P = 0.007$) where a post-dilation balloon size of <95% of the mean annulus diameter had a tenfold higher chance of failure to optimize PVR.[110] When asymmetrical large calcium deposits prevent full stent frame apposition, post-dilation has been reported to be associated with peri-aortic haematoma and annular or landing zone rupture, which carries a high mortality.[111] Therefore, post-dilation should be performed with a balloon size that equals at least >95% of the CT-derived mean annulus diameter. However, the risk of landing zone complications in the case of large asymmetric calcium nodules should be taken into account.

Placement of a second valve can resolve significant PVR either by lengthening the sealing skirt in case of inadequate position of the prosthesis (i.e. either too high or too low compared with the native annulus) or by further expanding the malapposed or undersized frame implanted

during the index procedure. In SE first-generation devices, relevant PVR (defined by either an ARI ≤ 25 or >mild PVR graded using angiography) treated with valve-in-valve TAVR resulted in 87.5% of 16 patients in successful reduction of PVR to mild or less.[109] Re-do TAVR for significant PVR was successful at reducing PVR to mild or less in 92% of patients.[112]

Percutaneous PVR closure by a vascular plug is reported to be a safe alternative in patients in whom post-dilation is either not successful during index procedure or is considered high risk because of extensive asymmetrical LVOT or annular calcification. The evidence for percutaneous PVR closure after TAVR is limited. Some small case series have reported high success rates after percutaneous PVR closure with a significant improvement in echocardiographic PVR and reduction of symptoms.[113,114] The largest case series to date, including 24 patients, described a success rate of 89%. The survival rate at 1 year was only 62%, in which most deaths were due to non-cardiac causes, probably reflecting the high-risk profile of these TAVR patients.[115] In a systematic review including 61 procedures in 58 patients, a success rate of 86.9% was reported, without a difference between the type of device (i.e. SE vs. BE). However, mortality remained high at 24.3% at 1-year follow-up.[116] In a retrospective analysis of 72 patients with at least moderate PVR after BE TAVR, 15 out of 72 patients underwent percutaneous closure, of which 13 were successful. Mortality in this successfully treated group was 7.7% compared with 42% in the group of patients treated conservatively ($P = 0.017$).[117] In a multi-centre registry of patients undergoing transcatheter intervention to treat PVR after the index TAVR, the proportion of patients with persisting ≥moderate PVR after a corrective procedure was lowest in patients after redo-TAVR, followed by balloon post-dilation and percutaneous plug closure.[118] In conclusion, although evidence is scarce, treatment of moderate or severe PVR seems feasible and safe with a positive impact on morbidity and mortality. As we currently lack a gold-standard approach for patients with an indication for treatment to reduce PVR severity, future studies addressing and comparing the different approaches are warranted.

# Conclusion

TAVR is also increasingly performed, also in patients with lower surgical risk. Although short-term haemodynamic performance parameters such as effective orifice area and residual gradient of the transcatheter valves outperform those of surgical valves, PVR is still an issue of concern in these devices. The evidence regarding the prognostic impact of mild PVR is conflicting, which might be the result of difficulties in procedural PVR grading in the presence of different LV diastolic dysfunction levels and the preconditioning of the LV by pre-existing AR. Multiple imaging modalities can be used to quantify PVR, each having its own advantages and disadvantages, underlining the importance of a multimodality approach to assess PVR. The decision to treat PVR is based on a shared decision-making process in which a multimodality approach and clinical characteristics play a key role. Treatment options to reduce PVR include balloon post-dilation, implantation of a second valve, and percutaneous closure by a vascular plug. As we currently lack a gold-standard approach to treat patients with relevant PVR, future studies addressing and comparing the different treatment approaches are warranted.

**Conflict of interest:** M.v.W. reports proctor and speaker fees from Abott and speaker fees from Boston Scientific. R.N. reports unrestricted research grants from Biotronik and Philips Volcano and speaker fees from Pfizer, BMS and Sanofi Genzyme. N.v.R. reports research grants from Biotronik, Medtronic, Philips, and Abbott and speaker fees from Abbott, RainMed, Microport, and Bayer. All other authors report no conflicts of interest..

## Data availability

No new data were generated or analysed in support of this research.

# Lead author biography

Marleen van Wely is an interventional cardiologist and a PhD candidate at the Department of Cardiology, Radboud University Medical Center in Nijmegen, the Netherlands. Her thesis involves transcatheter aortic valve implantation procedures, access, risk, and PVL.

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