Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 11, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.08.1039

STATE-OF-THE-ART PAPER

Paravalvular Leak After Transcatheter Aortic Valve Replacement

The New Achilles' Heel? A Comprehensive Review of the Literature

Philippe Généreux, MD,*†‡ Stuart J. Head, MSc,§ Rebecca Hahn, MD,*† Benoit Daneault, MD,*† Susheel Kodali, MD,*† Mathew R. Williams, MD,*† Nicolas M. van Mieghem, MD,‖ Maria C. Alu, MM,* Patrick W. Serruys, MD, PhD,‖ A. Pieter Kappetein, MD, PhD,§ Martin B. Leon, MD*†

New York, New York; Montréal, Québec, Canada; and Rotterdam, the Netherlands

Paravalvular leak (PVL) is a frequent complication of transcatheter aortic valve replacement (TAVR) and is seen at a much higher rate after TAVR than after conventional surgical aortic valve replacement. Recent reports indicating that PVL may be correlated with increased late mortality have raised concerns. However, the heterogeneity of methods for assessing and quantifying PVL, and lack of consistency in the timing of such assessments, is a hindrance to understanding its true prevalence, severity, and effect. This literature review is an effort to consolidate current knowledge in this area to better understand the prevalence, progression, and impact of post-TAVR PVL and to help direct future efforts regarding the assessment, prevention, and treatment of this troublesome complication. (J Am Coll Cardiol 2013;61:1125–36) © 2013 by the American College of Cardiology Foundation

Transcatheter aortic valve replacement (TAVR) has become the treatment of choice for inoperable patients with severe aortic stenosis (1) and is comparable to surgical aortic valve replacement (SAVR) for patients at high risk (2). However, paravalvular leak (PVL) is more frequently seen after TAVR than after SAVR, and its potential association with mortality has raised concerns (3–6). Moreover, recent reports have suggested that PVL could negatively impact mid- and long-term prognosis following TAVR (7,8). Although concerning, the lack of standardized quantitative and qualitative methods to assess and categorize PVL and the heterogeneity in the timing of post-procedural assessment of PVL warrant caution in interpretation of these data. Therefore, we sought to perform a systematic review of the current literature to better define the rate, progression over time, predictors, and consequences of PVL after TAVR. Furthermore, recommendations for measuring PVL are provided to improve consistency throughout the literature.

Rate of PVL

Multiple studies have reported the frequency and severity of PVL after TAVR (9). There is, however, significant heterogeneity that is caused by differences in: 1) imaging modalities (transthoracic echocardiography, transesophageal echocardiography, angiography); 2) timing of assessment (immediately after implantation, before discharge, at 30 days); 3) transcatheter heart valve (THV) system; 4) grading scale; and 5) adjudication of events. When PVL was evaluated before hospital discharge and without central core laboratory analysis, its absence was reported in 6% to 59% of patients, whereas moderate or severe PVL was seen in 0% to 24% (1–5,10–16) (Table 1).

Thus far, only the PARTNER (Placement of Aortic Transcatheter Valve) trial has used a central echocardiography core laboratory to evaluate PVL (1,2). PVL was graded in accordance with the American Society of Echocardiography recommendations for native valves (17) because there were no recommendations for prosthetic valve assessment at the start of the trial. In addition, because of the inevitable eccentric nature of the jet and the frequent "spray" of the jet contour in the outflow tract, the color Doppler in the available parasternal short-axis view(s) was weighted in a subjective fashion more heavily than

From the *Columbia University Medical Center/New York Presbyterian Hospital, New York, New York; †Cardiovascular Research Foundation, New York, New York; ‡Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada; §Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands; and the ‖Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands. Dr. Généreux has received speaker honoraria, consulting fees, and research grants from Edwards Lifesciences. Dr. Kodali has received consulting fees from Edwards Lifesciences and St. Jude Medical. Dr. Kappetein is member of a steering committee of the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial sponsored by Medtronic. Dr. Leon is a nonpaid member of the scientific advisory board of Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Généreux and Head are joint first authors.

Manuscript received June 27, 2012; revised manuscript received August 7, 2012, accepted August 21, 2012.

Abbreviations and Acronyms

AR = aortic regurgitation
AV = atrioventricular
LV = left ventricle/ventricular
PVL = paravalvular leak
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve

other signals in providing an integrated assessment. The following definition was applied: no PVL (no regurgitant color flow), trace (pinpoint jet in atrioventricular [AV] short-axis view), mild (jet arc length <10% of the AV annulus short-axis view circumference), moderate (jet arc length 10% to 30% of the AV annulus short-axis view circumference), and severe (jet arc length >30% of the AV annulus short-axis view circumference). In the PARTNER trial, trace/mild PVL was found in 66% of patients and moderate/severe in 12% (1,2).

Thus far, no prospective direct comparison of the rate of PVL after TAVR has been published between the 2 most frequently used THV systems (balloon-expandable THV, Edwards Lifesciences, Irvine, California; self-expandable CoreValve THV, Medtronic, Minneapolis, Minnesota). However, moderate to severe post-procedural PVL seems to be slightly higher with the CoreValve (9% to 21%) (4–6,18–20) than the Edwards (6% to 13.9%) (1–3,5,18,21,22) device. Recent 1-year data presented from the FRANCE 2 (French Aortic National CoreValve and Edwards 2) Registry seemed to confirm this finding—the use of self-expandable prosthesis was identified as one of the major determinants of significant PVL after TAVR. At patient discharge, self-expandable prosthesis was associated with a moderate to severe PVL rate of 19.8%, compared with 12.2% for balloon-expandable prosthesis (p value not available) (23).

Progression Over Time

One of the initial concerns about PVL was potential worsening during extended follow-up. Because a large percentage of patients are discharged with trace or mild PVL, worsening of PVL could have important consequences on the volume load imposed on the left ventricle (LV), ultimately resulting in significant heart failure. In addition, if many cases progress to clinically significant leakage, hemolysis requiring repeated transfusions or reoperation may further complicate the course of patients.

Despite the lack of "common language" among previous reports in assessment of PVL severity, several studies have reported comparable findings with respect to time trends of PVL severity. Webb et al. (24) reported the evolution of PVL over time in a cohort of 168 patients and found that PVL was generally mild and remained stable between 30-day and 1-year follow-ups, a result that has been confirmed by other studies (Table 2). A recent report by Ussia et al. (16) showed that rates of mild (53%) and moderate (15%) post-procedural PVL had been reduced to 47% and 10%, respectively, at a follow-up of 3 years. Some attrition of the "sickest" patients might have been due to patients with worsening PVL dying, but there were no cases of worsening from mild to moderate/severe regurgitation in individual patient progression of PVL.

Data from the PARTNER trial suggested, however, that PVL at 2 years had increased by ≥1 grade in 22.4% of patients, whereas it remained unchanged in 46.2% and improved by ≥1 grade in 31.5% of patients (Fig. 1) (8). So far, no studies have explored the mechanisms behind improvement or worsening of PVL in individual patients, and measurement methods may explain, at least in part, these changes.

Impact on Clinical Outcomes

After SAVR, moderate to severe residual aortic regurgitation (AR) occurs infrequently in approximately 4% of patients (25). A recent study showed that AR after SAVR was an independent predictor of long-term mortality with a hazard ratio of 1.7 (95% CI: 1.2 to 2.3). The TAVR community has focused extensively on the effect of AR on survival because its prevalence is much higher after TAVR than after SAVR (8). A number of studies have identified AR ≥2+ to be an independent predictor of short- and long-term mortality (Table 3) (3). Furthermore, patients with AR ≥2+ were 10 times more likely to be nonresponders to therapy at 6 months' follow-up; nonresponsiveness was defined as either death or New York Heart Association classification ≥2.

Few studies have devoted analyses specifically to PVL. This is not surprising because the low post-operative rate of PVL in surgical series makes statistical analysis not meaningful. However, even in TAVR after which post-procedural AR is largely paravalvular, there have been only a few large registries and randomized trials focused on PVL. Data on 663 patients from the Italian registry found that PVL grade ≥2+ was not associated with early 30-day mortality, but multivariate analysis did find a hazard ratio of 3.79 for patients with PVL ≥2+ for late mortality beyond 30 days (6). More disturbingly, although it was generally believed that only moderate or severe regurgitation would impact long-term outcomes (26), the recently published 2-year results from the PARTNER trial showed that even mild PVL was associated with significant mortality (Fig. 2) (8). Multivariable analyses did not identify AR or PVL as independent predictors of mortality in this trial, but, interestingly, there is a trend toward improved survival in patients undergoing TAVR compared with SAVR if PVL was negligible (70% vs. 65%).

Importantly, based on the current literature, the direct causal relationship between PVL and mortality (vs. PVL being a marker for other factors) still needs to be determined. Careful analyses of baseline patient characteristics, the repercussion of all degrees of PVL on LV geometry and remodeling, and the determination of the precise cause of death (cardiovascular vs. noncardiovascular) are needed to

confirm the strength and the nature of this relationship. At this point, any previous observations linking PVL (especially mild) with mortality should be considered hypothesis generating.

Predictors of PVL

Significant PVL most commonly results from: 1) incomplete prosthesis apposition to the native annulus due to patterns or extent of calcification (11,27–30) or annular eccentricity (26); 2) undersizing of the device (10,31,32); and/or 3) malpositioning of the valve (33). These observations seem to be true for both balloon-expandable and self-expandable THVs.

Valve sizing has been shown to be one of the strongest predictors of PVL. A low cover index reflecting a lower degree of oversizing of the prosthesis based on transthoracic echocardiography annulus measurement predicts significant PVL (10). More recently, studies have evaluated the use of multidetector computed tomography (MDCT) for THV sizing, and MDCT showed good predictability and reduced rates of significant PVL (34–37). Furthermore, larger and eccentric annuli were identified as predictors of PVL in multiple studies and most likely reflect inadequate sizing of the THV (3,15,26). A smaller aortic valve area was found to predict PVL in one study, but this was likely because the smaller area indicates a greater degree of calcification (3). The extent of calcification and asymmetrical distribution, as well as the location of calcium on the aortic wall, valve commissure, or THV landing zone, as a predictor for PVL has been confirmed in several studies (11,26,29,37,38).

In studies specifically evaluating the CoreValve (Medtronic), a lower depth of implantation and a greater angle between the aorta and LV outflow tract were found to predict PVL (14,15).

Assessment of Paravalvular Regurgitation

Angiographic and hemodynamic assessment. Aortic root angiography is an established tool for qualitative and semiquantitative assessment of AR (39). It is readily available during the TAVR procedure and can be quickly and safely executed to provide essential information and initiate adjunctive maneuvers if needed in case of significant (para) valvular AR. Typically, Sellers criteria are applied to grade AR (40): 1) grade 1 or mild AR corresponds to a small amount of contrast entering the LV during diastole without filling the entire cavity and clearing with each cardiac cycle; 2) grade 2 or moderate AR corresponds to contrast filling of the entire LV in diastole but with less density compared with contrast opacification of the ascending aorta; 3) grade 3 or moderate to severe AR corresponds to contrast filling of the entire LV in diastole equal in density to the contrast opacification of the ascending aorta; and 4) grade 4 or severe AR corresponds to contrast filling of the entire LV in diastole on the first beat with greater density compared with the contrast opacification of the ascending aorta. During the contrast injection, no material may cross the aortic valve leaflets (e.g., guidewires, catheters) because incomplete valve closure may artificially be generated, thus resulting in AR. Particularly with self-expanding systems, it is important to wait some time (empirically 10 min) after deployment of the bioprosthesis to allow the system to expand to its maximum. The downside of qualitative aortography AR assessment is that it relies on subjective interpretation of unidimensional images; therefore, interobserver and intraobserver variability can be an issue and additional contrast volume required. Moreover, it is difficult to determine the contribution of PVL and central AR.

Classic findings of acute AR (acute drop in the aortic diastolic pressure with or without elevated LV end-diastolic pressure [LVEDP]) may be seen after TAVR and may be suggestive of moderate to severe AR. However, these findings must be interpreted with caution because the concomitant use of sedatives, vasopressors, inotropes, and intravenous fluids all impact hemodynamics, and the presence of material through the aortic valve (e.g., wire) may interfere temporarily with the THV function. Recently, the AR index, the ratio of the end-diastolic gradient across the aortic valve bioprosthesis to systolic blood pressure ([ADP − LVEDP]/ASP; ADP-aortic diastolic pressure, ASP-aortic systolic pressure), was described (41). An AR index <25 was associated with 1-year mortality. Although this association is interesting, more data and validation are needed to establish the role of this new index in the therapeutic decision process after TAVR.

Echocardiographic assessment. Although the native valve regurgitation quantitative grading scheme has been advocated for the evaluation of prosthetic valve regurgitation (42), there are limited data to support the use of these parameters following TAVR. The majority of semiquantitative parameters for assessing AR apply to central regurgitant jets, which are more uniform, making semiquantitative grading schemes more reliable.

Unlike central jets, paravalvular regurgitant jets are commonly eccentric with crescentic, irregular orifices. Because these jets occur between the annulus and sewing ring, jet areas and lengths may not represent the same severity of regurgitation compared with central jets and these parameters cannot be used to reliably assess regurgitant severity. Although guidelines suggest using the circumferential extent of the regurgitant jet as a semiquantitative measure of severity (42), this parameter has not been validated against any quantitative parameters of regurgitation. Even if we accept the limited validation of this scheme for surgical prostheses, the anatomy and physiology of THVs are different than that of surgical valves. In the balloon-expandable valve, paravalvular regurgitation should be assessed just below the skirt; for central jets, the regurgitation should be assessed at the coaptation point of the leaflets. In addition, there is no scheme that specifically addresses the unusual regurgitation that accompanies the THV. The intact calcified cusps and annulus signifi-

Table 1 Selected Publications Reporting AR After TAVR

First Author, Year (Ref. #)	n	Approach	Prosthesis	Imaging Modality	Severity Gradation	Adjunctive Techniques	AR Post-TAVR	Predictors of AR by Multivariable Analysis
Detaint, 2009 (10)	74	TF = 46 (62%) TA = 28 (38%)	ES	Echocardiogram (TEE) Site reported (blinded echocardiographist)	0 = absent 1 = trace/mild 2 = mild/moderate 3 = moderate/severe 4 = severe	Post-dilation = 5/74 Valve-in-valve = 2/74	Early post-TAVR (TEE) 0 = 5 (7.0%) 1 = 53 (72.0%) 2 = 12 (16.0%) 3 = 4 (5.0%) 4 = 0 (0%)	≥2/4 AR • Low cover index • Operator's experience
Abdel-Wahab, 2011 (3)	690	TF = 644 TA = 26 SC = 22 TAo = 5	ES = 110 (16%) MCV = 580 (84%)	Angiogram Site reported	0 = absent 1 = trace/mild 2 = mild/moderate 3 = moderate/severe 4 = severe	—	Early post-TAVR (angiogram) 0 = 191 (27.7%) 1 = 380 (55.1%) 2 = 103 (14.9%) 3 = 14 (2.0%) 4 = 2 (0.3%)	≥2/4 AR • AVA baseline • Annulus baseline • Cardiogenic shock • Renal failure • Male
Sherif, 2010 (14)	50	TF	MCV	Angiogram Echocardiogram Site reported	1 = trivial/mild 2 = moderate 3 = moderate/severe 4 = severe	—	Early post-TAVR (angiogram) 0 = 3 (6.0%) 1 = 27 (54.0%) 2 = 13 (26.0%) 3 = 7 (14.0%) 4 = 0 (0%) Early post-TAVR (TTE) 0 = 9 (18.0%) 1 = 24 (48.0%) 2 = 13 (26.0%) 3 = 4 (8%) 4 = 0 (0%)	≥2/4 AR • Increase angle of LVOT and ascending aorta • Depth of device in relation to noncoronary cups
John, 2010 (78)	100	TF = 97 (97%) SC = 3 (3%)	MCV	Angiogram Echocardiogram	0 1+ 2+ 3+ 4+	Post-dilation = 34/100 Snare technique = 4/100 Valve-in-valve = 3/100	Early post-TAVR (angiogram) 0 = 35 (35.4%) 1+ = 28 (28.3%) 2+ = 19 (19.2%) 3+ = 8 (0.8%) 4+ = 0 (0%) Early after adjunctive technique (angiogram) 0 =38 (38.4%) 1+ = 49 (49.5%) 2+ = 11 (11.1%) 3+ = 1 (0.1%) 4+ = 0 (0%)	AgS and DLZ-CS showed significant correlation with grade of PVL after initial MCV deployment
Takagi, 2011 (15)	79	TF = 62 (78.5%) SC = 17 (21.5%)	MCV	Angiogram Echocardiogram Site reported	0 = absent 1 = mild 2 = moderate 3–4 = severe	Post-dilation = 21/79 Snare technique = 1/79 Valve-in-valve = 2/79	Final result (angiogram) 0 = 21 (26.6%) 1 = 42 (53.2%) 2 = 13 (16.5%) 3 = 3 (3.8%) 4 = 0 (0%)	≥2/4 AR • Larger annulus diameter • Low implantation • Peripheral vascular disease

Continued on the next page

Table 1 Continued

First Author, Year (Ref. #)	n	Approach	Prosthesis	Imaging Modality	Severity Gradation	Adjunctive Techniques	AR Post-TAVR	Predictors of AR by Multivariable Analysis
Tamburino, 2011 (6)	663	TF	MCV	Echocardiogram Site reported, events reviewed by independent CEC	—	Post-dilation = 68/663 Valve-in-valve = 139/663 Conversion to open surgery = 5/663	Post-TAVR ≥2 PVL = 139 (21.0%)	—
Gotzmann, 2011 (4)	145	TF/SC	MCV	Echocardiogram Angiogram (if poor TTE quality) Site reported	Mild Moderate Severe	—	Early post-TAVR Mild = 64 (44%) Moderate = 23 (16%) Severe = 2 (1%) Early post-TAVR 30-day survivors only Mild = 55 (45%) Moderate = 16 (13%) Severe = 0 (0%)	—
Moat, 2011 (5)	870	TF = 599 Other = 271	ES = 410 (47%) MCV = 459 (53%)	Angiogram Site reported	—	Conversion to open surgery = 6/850	AR ≥1 = 516 (61%) AR >2 = 115 (13.6%)	—

AgS = Agatston score; AR = aortic regurgitation; AVA = aortic valve replacement; CEC = clinical events committee; DLZ-CS = device-landing zone calcification score; ES = Edwards Sapien; LVOT = left ventricular outflow track; MCV = Medtronic CoreValve; PVL = paravalvular leak; SC = subclavian; TA = transapical; TAo = transaortic; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiography; TF = transfemoral; TTE = transthoracic echocardiography.

cantly influence the location and shape of paravalvular jets; typically, these jets appear smaller and more irregular at the level of the intact/calcified cusps and larger just apical to the THV stent.

Quantitative assessment of total AR, or advanced imaging techniques for assessing paravalvular regurgitant orifices, may be a more accurate way of assessing severity and thus a more accurate assessment of risk. Quantitative Doppler uses comparative flow measurements across a regurgitant valve and a nonregurgitant valve to calculate regurgitant volume or fraction (17). The effective regurgitant orifice area is then calculated by dividing the regurgitant volume by the velocity time integral of the regurgitant jet continuous wave spectral profile. Alternatively, the LV stroke volume calculated by 2-dimensional (2D) biplane Simpson method of discs (43) can be used in place of total (regurgitant plus forward) stroke volume; however, systematic underestimation of ventricular volumes has been reported for this method. Although this quantitative assessment has been largely validated in the literature (44–51), has shown reproducibility, and is endorsed by scientific authorities (17,52), it should be acknowledged that this assessment is based on 4 parameters, any one of which may be determined with significant inaccuracy.

Three-dimensional (3D) echocardiography can overcome the limitations of 2D and standard Doppler measurements for quantifying regurgitation (43). Pitfalls of 2D LV imaging, including foreshortening, malrotation, and angulation, can be overcome by 3D imaging. However, limitations of 3D imaging (lower line density and low volume rates) may reduce the utility of this method for assessing total stroke volume. Color Doppler 3D volumes can be useful for the identification and localization of regurgitation jets, as well as planimetry of the vena contracta area (53,54). This imaging modality may be particularly useful for post-TAVR assessment of PVL (55,56).

With the increased use of multimodality imaging capable of 3D reconstruction of the aortic root (36,57–62), there has been intense interest in the shape of the annulus and appropriate sizing of the transcatheter heart valve to reduce PVL. The oval shape of the annulus has been well documented (36,60,61,63–65), and a single sagittal plane measurement is significantly smaller than the coronary plane measurement. Algorithms using 3D imaging tools have been suggested to improve annular sizing and reduce PVL (34,35).

Recently, the Valve Academic Research Consortium (VARC) published the VARC II definitions and suggested the use of TAVR-specific criteria for the assessment of AR and/or PVL after TAVR (Table 4) (66). Figures 2 and 3 illustrate echocardiographic assessment of PVL after TAVR. Figure 4 illustrates a case using 3D echocardiography assessment of PVL.

Treatment for Significant PVL

Improved positioning of the TAVR could require advanced imaging techniques for angiographic planning; having the best coplanar view will ensure accurate fluoroscopic local-

Table 2 Progression of Aortic and/or Paravalvular Regurgitation Over Time

First Author, Year (Ref. #)	n	Significant Post-Procedural	Significant at 6 Months	Significant at 1 Year	Significant at 2 Years	Significant at 3 Years
Paravalvular leakage						
Webb, 2009 (24)	168	30 days 2+ = 37% 3+ = 5%	—	"Stable"	—	—
Muñoz-Garcia, 2011 (79)	144	72 h Mild = 40% Moderate = 23%	Mild = 47% Moderate = 19%	—	—	—
Ussia, 2012 (16)	181	Post-procedure Mild = 53% Moderate = 15%	—	Mild = 48% Moderate = 18%	Mild = 50% Moderate = 17%	Mild = 47% Moderate = 10%
Ye, 2010 (80)	71	30 days Mild = 26% Moderate = 5%	—	—	—	"Remained unchanged and clinically insignificant during follow-up"
Takagi, 2011 (15)	79	30 days 1+ = 51% 2+ = 20% 3+ = 3%	1+ = 49% 2+ = 27% 3+ = 0%	—	—	—
Ewe, 2011 (81)	107	Post-procedure 1+ = 58% 2+ = 16% 3+ = 5%	≥6 months 1+ = 51% 2+ = 31% 3+ = 0%		—	—
Godino, 2010 (82)	137	Post-procedure 1+ = ≈60% 2+ = ≈12% 3+ = 4% 4+ = 2%	1+ = ≈65% 2+ = ≈9% 3+ = ≈5% 4+ = 0%	—	—	—
Aortic regurgitation						
Bauer, 2010 (83)	88	2+ = 29% 3+ = 7%	—	2+ = 24% 3+ = 0%	2+ = 23% 3+ = 0%	—
Rajani, 2010 (84)	46	Within 5 days Mild = 33% Moderate = 19% Moderate/severe = 5%	—	Mild = 31% Moderate = 8% Moderate/severe = 15%	—	—
Clavel, 2009 (85)	50	Discharge Trivial = 38% Mild = 42% Moderate = 8% Severe = 0%	6–12 months Trivial = 26% Mild = 46% Moderate = 6% Severe = 0%		—	—
Lefevre, 2011 (86)	130	Discharge 2+ = 42% 3+ = 5%	—	2+ = 25% 3+ = 0%	—	—
Buellesfeld, 2011 (20)	126	30 days 1+ = 32% 2+ = 9% 3+ = 0%	1+ = 39% 2+ = 6% 3+ = 0%	1+ = 34% 2+ = 3% 3+ = 0%	1+ = 37% 2+ = 0% 3+ = 0%	—
Bleiziffer, 2012 (87)	227	Discharge Mild = 31% Mild/moderate = 13% Moderate = 8% Moderate/severe = 3%	Mild = 45% Mild/moderate = 11% Moderate = 6% Moderate/severe = 0% Severe = 0%	Mild = 40% Mild/moderate = 16% Moderate = 6% Moderate/severe = 0.5% Severe = 0.5%	Mild = 41% Mild/moderate = 15% Moderate = 5% Moderate/severe = 1% Severe = 1%	—
Koos, 2011 (29)	57	After implant 1+ = 77% 2+ = 9% 3+ = 5%	Mean 83 ± 80 days 1+ = 82% 2+ = 5% 3+ = 0%	—	—	—
D'Onofrio, 2011 (88)	504	Discharge 1+ = 30% 2+ = 9%	—	Mean 9.2 ± 6.5 months "No changes in the degree of AR were found"	—	—
Gurvitch, 2010 (21)	70	Post-procedure Trivial = 40% Mild = 44% Moderate = 6%	—	—	—	Trivial = 60% Mild = 33% Moderate = 3%
Walther, 2011 (22)	168	—	3–6 months 1+ = 51% 2+ = 1% 3+ = 0%	1+ = 46% 2+ = 5% 3+ = 0%	—	—

Figure 1 **Change in Paravalvular Leak Severity Over 2-Year Follow-Up**

Adapted with permission from Kodali et al. (8).

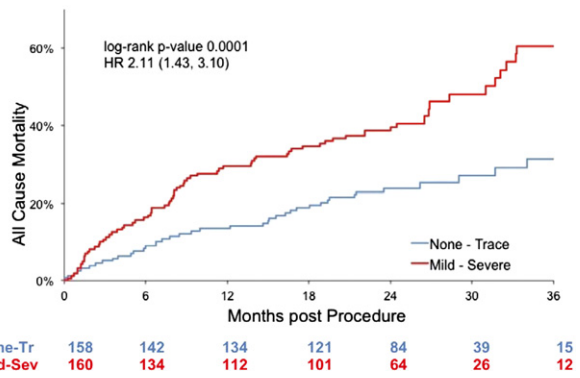

Figure 2 **Impact of Paravalvular Leak on 2-Year All-Cause Mortality**

Reprinted with permission from Kodali et al. (8). HR = hazard ratio.

ization of the valve before implantation. In addition, simultaneous "real-time" imaging, such as echocardiogram (both 2D and 3D), 3D angiographic reconstruction via rotational aortic root angiogram (67), and the use of novel imaging systems (68,69), may assist in choosing intraprocedurally the optimal projection for THV positioning and deployment, leading potentially to less frequent PVL.

Intraprocedurally, several interventional alternatives to reduce regurgitation are available (70). Severe calcification of the native valve might prevent the implanted valve from expanding completely against the annulus, leaving residual orifices through which PVL may occur. Post-implantation balloon dilation of the valve might be effective in reducing PVL and may be considered the initial option for patients with PVL (71). A slightly oversized balloon is recommended to fully expand the valve. Studies have shown that post-dilation can be safely performed, with a reduction of the regurgitation in a majority of patients (38). Calcification of the valve significantly influences the success of this intervention. However, in some patients, post-dilation has no effect in reducing AR (15); in addition, post-dilation has been shown to be associated with a higher incidence of cerebrovascular events (38). The effect of post-dilation on survival has yet to be determined.

Especially with the CoreValve, implantation of the valve that is too low is associated with PVL. Repositioning to a higher implantation depth could therefore reduce PVL. However, no retrievable valve is currently available on the market. Therefore, a snaring maneuver has been described, in which the valve is pulled up by attaching a snare to one of the frame loops (72,73). Although successful cases have been reported (74), the valve may also move to the original (too low) position as soon as tension is released (70). An extra word of caution is warranted when the snaring technique is considered in patients with extensively calcified valves because chunks of calcium may detach as a result of friction. Furthermore, there is a risk of damaging the ascending aorta during the snaring maneuver.

A valve-in-valve procedure may be necessary in some cases in which post-dilation or other techniques do not improve the degree of PVL. This is specifically indicated for patients in whom the valve was suboptimally positioned (i.e., too shallow or too deep). In the Italian registry, a valve-in-valve procedure was used in 3.6% of 663 patients

Table 3 **Outcomes Associated With Aortic and/or Paravalvular Regurgitation**

First Author, Year (Ref. #)	n	Variable	Outcome	Univariate Analysis	Multivariate Analysis
Abdel-Wahab, 2011 (3)	690	AR ≥2	In-hospital mortality	OR = 2.50 (95% CI 1.37–4.55)	OR = 2.43 (95% CI 1.22–4.85)
Gotzmann, 2011 (4)	122	AR ≥2	6-month mortality	—	OR = 4.26 (95% CI 1.59–11.45)
			No clinical improvement		OR = 10.1 (95% CI 3.20–31.94)
Takagi, 2011 (15)	41	AR ≥2	6-month mortality	12.2% vs. 25.0% (p = 0.25)	—
Hayashida, 2012 (89)	260	AR ≥2	Median 217 days (IQR: 54–401)	HR = 1.97 (95% CI 1.19–3.28)	—
Leber, 2011 (90)	69	AR >2	1-year mortality	9% vs. 37.5% (95% CI p = 0.07)	—
Moat, 2011 (5)	870	AR ≥2	1-year mortality	HR = 1.49 (95% CI 1.00–2.21)	HR = 1.66 (95% CI 1.10–2.51)
Sinning, 2012 (91)	152	PVL ≥2	1-year mortality	HR = 4.0 (95% CI 2.1–7.5)	HR = 4.9 (95% CI 2.5–9.6)
Tamburino, 2011 (6)	663	PVL ≥2	Late mortality	—	HR = 3.79 (95% CI 1.57–9.10)
Sinning, 2012 (41)	146	Moderate/severe PVL	1-year survival	HR = 3.9 (95% CI 2.0–7.5)	HR = 2.4 (95% CI 1.0–5.4)
Unbehaun, 2012 (26)	358	No vs. trace vs. mild AR	2-year survival	66% vs. 72% vs. 67% (p = 0.77)	—
Kodali, 2012 (8)	158	Mild to severe AR	2-year survival	HR = 1.75 (95% CI 1.17–2.61)	Not significant
		Mild to severe PVL	2-year survival	HR = 2.11 (95% CI 1.43–3.10)	Not significant

HR = hazard ratio; IQR = interquartile range; OR = odds ratio; other abbreviations as in Table 1.

Table 4 VARC II Recommendations for Evaluation of Aortic and/or Paravalvular Regurgitation After TAVR

	Mild	Moderate	Severe
Semiquantitative parameters			
Diastolic flow reversal in the descending aorta—pulsed wave	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)*	<10	10–29	≥30
Quantitative parameters†			
Regurgitant volume (ml/beat)	<30	30–59	≥60
Regurgitant fraction (%)	<30	30–49	≥50
Effective regurgitant orifice area (cm^2)	0.10	0.10–0.29	≥0.30

*Not well validated and may overestimate severity compared with quantitative Doppler. †For LVOT >2.5 cm, significant stenosis criteria is <0.20. Adapted with permission from Kappetein et al. (66). VARC = Valve Academic Research Consortium; other abbreviations as in Table 1.

(75). Compared with patients who were implanted with a single valve, those who underwent valve-in-valve had similar safety and efficacy over a 1-year follow-up. Encouraging results have been reported from other series as well (76).

As a final option for patients with continued severe PVL in whom interventional therapy does not suffice, conversion to conventional SAVR may be needed (77). SAVR may be undesirable because these patients are generally at high or extreme risk, but the procedure may be unavoidable in some cases.

Emerging TAVR Technologies

Currently, there is no proven or generally accepted treatment for PVL. However, there are emerging THV systems and technologies that are promising in minimizing PVL after TAVR (Fig. 5). These devices may reduce PVL by better supra-, infra-, or intra-annular sealing (cuff) or by allowing controlled deployment, repositioning, or removal of the THV. Preimplantation calcification debulking (surgically or not) also remains one of the most interesting areas

Figure 3 Quantitative Doppler Echocardiography Can Be Used to Calculate the Regurgitant Orifice and Volume

(A) Post–transcatheter heart valve (THV) left ventricular outflow tract (LVOT) diameter (just apical to the THV stent). **(B)** Right ventricular outflow tract (RVOT) diameter. **(C)** LVOT Doppler with sample volume located just apical to the THV stent aligned in the short-axis view of the LVOT pulsed Doppler signal just below the THV stent. Stroke volume (SV) across the THV = LVOT area × LVOT velocity time integral (VTI) = 56 ml. **(D)** RVOT VTI yields an SV across the RVOT of 43 ml. The regurgitant volume = LVOT SV − RVOT SV = 13 ml. AR = aortic regurgitation; PG = pressure gradient.

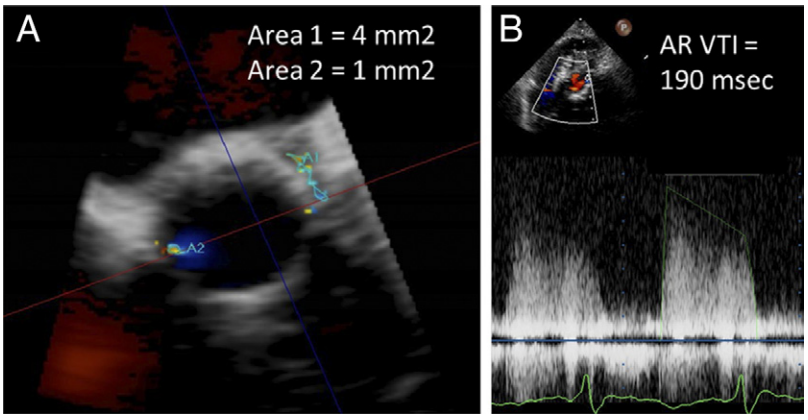

Figure 4 **3-Dimensional Echocardiography Can Be Used to Quantitate the Regurgitant Orifice and Volume**

(A) Multiplanar reconstruction of a 3-dimensional color Doppler volume set, aligned in the short-axis view of the LVOT just below the THV stent. The planimetered regurgitant orifices are 4 mm^2 and 1 mm^2, consistent with a total effective regurgitant orifice area (EROA) of 5 mm^2. **(B)** Aortic regurgitant continuous wave spectral Doppler with AR VTI of 190 ms. The regurgitant volume = EROA × AR VTI = 10 ml (same patient as in Fig. 3). Abbreviations as in Figure 3.

of development to ensure adequate THV expansion and annulus sealing.

Limitations of the Current Literature

Many limitations of the current literature should be acknowledged. Although some studies have used echocardiography, others have used angiography to assess PVL immediately after THV implantation, making comparison between studies difficult. Most of the studies have used site self-reported PVL severity and lack independent adjudication of clinical events. Although the PARTNER trial had the advantage of a central echocardiography core laboratory

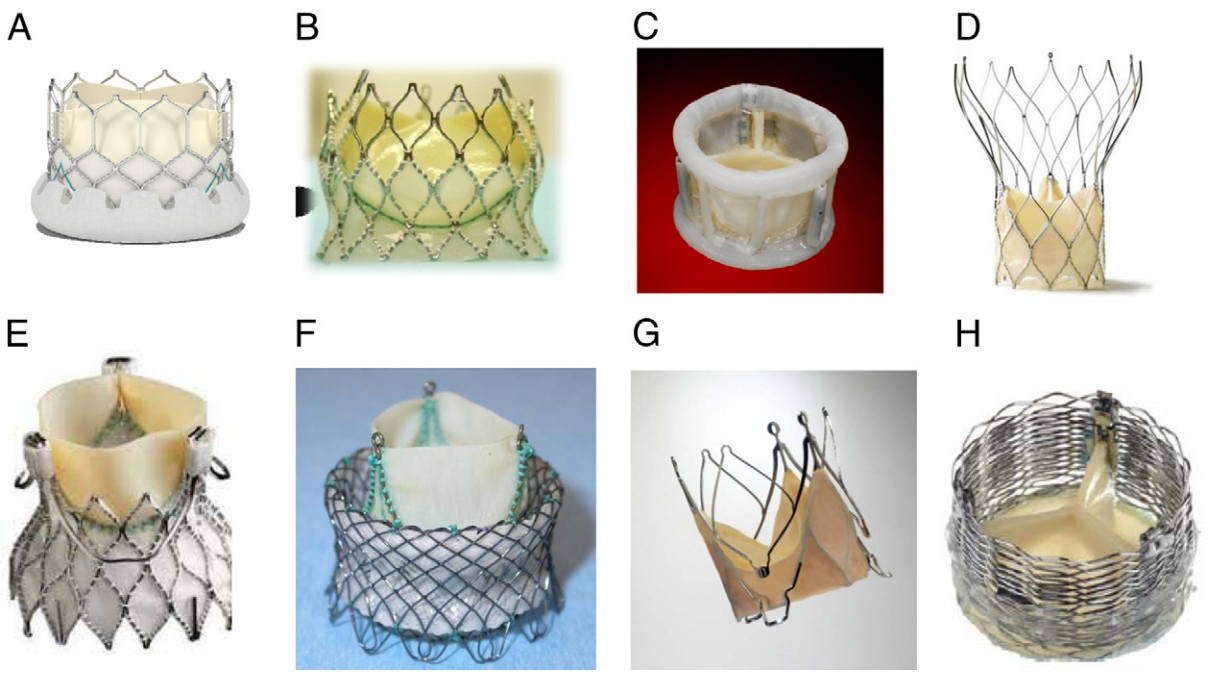

Figure 5 **Emerging TAVR Devices Involving Improved Technologies, Potentially Minimizing PVL After TAVR**

(A) SAPIEN 3 (Edwards Lifesciences, Irvine, California). **(B)** CENTERA (Edwards Lifesciences). **(C)** Direct Flow Medical (Direct Flow Medical, Santa Rosa, California). **(D)** Portico (St. Jude Medical, St. Paul, Minnesota). **(E)** Engager (Medtronic, Minneapolis, Minnesota). **(F)** Heart Leaflet Technologies (Heart Leaflet Technologies, Maple Grove, Minnesota). **(G)** JenaValve (JenaValve Technology, Munich, Germany). **(H)** Sadra Lotus Medical (Boston Scientific SciMed Inc., Maple Grove, Minnesota).

and adjudication of clinical events, we are still waiting for in-depth analysis of the outcomes associated with PVL. Baseline characteristics of patients with no/trace PVL may be different than those with mild to severe PVL and may explain the difference in mortality and the absence of PVL as a predictor for mortality in several reported multivariable analyses. Finally, better criteria to establish PVL severity are needed to ensure appropriate classification and uniformity among studies.

Conclusions

The association of PVL after TAVR with mortality has made it the new "in vogue" Achilles' heel of TAVR. Although post-procedural moderate to severe PVL can understandably be a predictor of a worse outcome, the association with mild PVL may be debatable. Given the limitations of the current literature, the nature and strength of the relationship between PVL and mortality are still to be determined. Future studies should standardize the evaluation of PVL and ensure an appropriate classification of its severity. Upcoming THV systems should be designed to minimize PVL, and emerging technology, such as noninvasive calcification debulking of the aortic valvular complex, brings promises of lower PVL rates after TAVR, potentially as low as those after SAVR.

Reprint requests and correspondence: Dr. Martin B. Leon, Columbia University Medical Center, New York-Presbyterian Hospital, 177 Fort Washington Avenue, New York, New York 10032. E-mail: mleon@crf.org.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364:2187–98.
3. Abdel-Wahab M, Zahn R, Horack M, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German Transcatheter Aortic Valve Interventions Registry. Heart 2011;97:899–906.
4. Gotzmann M, Pljakic A, Bojara W, et al. Transcatheter aortic valve implantation in patients with severe symptomatic aortic valve stenosis—predictors of mortality and poor treatment response. Am Heart J 2011;162:238–45.
5. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58: 2130–8.
6. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299–308.
7. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012; 366:1705–15.
8. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.
9. Généreux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using Valve Academic Research Consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317–26.
10. Detaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus discongruence. J Am Coll Cardiol Intv 2009;2:821–7.
11. Ewe SH, Ng AC, Schuijf JD, et al. Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation. Am J Cardiol 2011;108:1470–7.
12. Gurvitch R, Webb JG, Yuan R, et al. Aortic annulus diameter determination by multidetector computed tomography: reproducibility, applicability, and implications for transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2011;4:1235–45.
13. Piazza N, Schultz C, de Jaegere PP, Serruys PW. Implantation of two self-expanding aortic bioprosthetic valves during the same procedure—insights into valve-in-valve implantation ("Russian doll concept"). Catheter Cardiovasc Interv 2009;73:530–9.
14. Sherif MA, Abdel-Wahab M, Stocker B, et al. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. J Am Coll Cardiol 2010;56:1623–9.
15. Takagi K, Latib A, Al-Lamee R, et al. Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. Catheter Cardiovasc Interv 2011;78:432–43.
16. Ussia GP, Barbanti M, Petronio AS, et al. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012;33:969–76.
17. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
18. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (French Aortic National CoreValve and Edwards) Registry. Eur Heart J 2011;32:191–7.
19. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J 2011;32:198–204.
20. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. J Am Coll Cardiol 2011;57:1650–7.
21. Gurvitch R, Wood DA, Tay EL, et al. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation 2010;122:1319–27.
22. Walther T, Kasimir MT, Doss M, et al. One-year interim follow-up results of the TRAVERCE trial: the initial feasibility study for trans-apical aortic-valve implantation. Eur J Cardiothorac Surg 2011; 39:532–7.
23. Van Belle E. Perivalvular aortic regurgitation: the main determinant of 1-year mortality after a successful TAVI procedure—insights from the FRANCE 2 Registry. Presented at: EuroPCR; May 15–18, 2012; Paris, France.
24. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation 2009;119:3009–16.
25. Sponga S, Perron J, Dagenais F, et al. Impact of residual regurgitation after aortic valve replacement. Eur J Cardiothorac Surg 2012;42:486–92.
26. Unbehaun A, Pasic M, Dreysse S, et al. Transapical aortic valve implantation: incidence and predictors of paravalvular leakage and transvalvular regurgitation in a series of 358 patients. J Am Coll Cardiol 2012;59:211–21.
27. Colli A, D'Amico R, Kempfert J, Borger MA, Mohr FW, Walther T. Transesophageal echocardiographic scoring for transcatheter aortic valve implantation: impact of aortic cusp calcification on postoperative aortic regurgitation. J Thorac Cardiovasc Surg 2011;142:1229–35.
28. Haensig M, Lehmkuhl L, Rastan AJ, et al. Aortic valve calcium scoring is a predictor of significant paravalvular aortic insufficiency in transapical-aortic valve implantation. Eur J Cardiothorac Surg 2012; 41:1234–40.

29. Koos R, Mahnken AH, Dohmen G, et al. Association of aortic valve calcification severity with the degree of aortic regurgitation after transcatheter aortic valve implantation. Int J Cardiol 2011;150:142–5.
30. Yared K, Garcia-Camarero T, Fernandez-Friera L, et al. Impact of aortic regurgitation after transcatheter aortic valve implantation: results from the REVIVAL trial. J Am Coll Cardiol Img 2012;5:469–77.
31. Buzzatti N, Maisano F, Latib A, et al. Computed tomography-based evaluation of aortic annulus, prosthesis size and impact on early residual aortic regurgitation after transcatheter aortic valve implantation. Eur J Cardiothorac Surg 2013;43:43–51.
32. Schultz CJ, Tzikas A, Moelker A, et al. Correlates on MSCT of paravalvular aortic regurgitation after transcatheter aortic valve implantation using the Medtronic CoreValve prosthesis. Catheter Cardiovasc Interv 2011;78:446–55.
33. Block PC. Leaks and the "great ship" TAVI. Catheter Cardiovasc Interv 2010;75:873–4.
34. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. J Am Coll Cardiol 2012;59:1275–86.
35. Willson AB, Webb JG, Labounty TM, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. J Am Coll Cardiol 2012;59:1287–94.
36. Jabbour A, Ismail TF, Moat N, et al. Multimodality imaging in transcatheter aortic valve implantation and post-procedural aortic regurgitation comparison among cardiovascular magnetic resonance, cardiac computed tomography, and echocardiography. J Am Coll Cardiol 2011;58:2165–73.
37. Schultz C, Rossi A, van Mieghem N, et al. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. EuroIntervention 2011;7:564–72.
38. Nombela-Franco L, Rodes-Cabau J, Delarochelliere R, et al. Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol Intv 2012;5:499–512.
39. Michel PL, Vahanian A, Besnainou F, Acar J. Value of qualitative angiographic grading in aortic regurgitation. Eur Heart J 1987;8 Suppl C:11–4.
40. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. Am J Cardiol 1964;14:437–47.
41. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–41.
42. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22:975–1014.
43. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:3–46.
44. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man. Clinical validation. Circulation 1983;67:593–602.
45. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984;70:425–31.
46. Labovitz AJ, Buckingham TA, Habermehl K, Nelson J, Kennedy HL, Williams GA. The effects of sampling site on the two-dimensional echo-Doppler determination of cardiac output. Am Heart J 1985;109:327–32.
47. Dittmann H, Voelker W, Karsch KR, Seipel L. Influence of sampling site and flow area on cardiac output measurements by Doppler echocardiography. J Am Coll Cardiol 1987;10:818–23.
48. Darmon PL, Hillel Z, Mogtader A, Mindich B, Thys D. Cardiac output by transesophageal echocardiography using continuous-wave Doppler across the aortic valve. Anesthesiology 1994;80:796–805.
49. Stoddard MF, Prince CR, Ammash N, Goad JL, Vogel RL. Pulsed Doppler transesophageal echocardiographic determination of cardiac output in human beings: comparison with thermodilution technique. Am Heart J 1993;126:956–62.
50. Maslow A, Comunale ME, Haering JM, Watkins J. Pulsed wave Doppler measurement of cardiac output from the right ventricular outflow tract. Anesth Analg 1996;83:466–71.
51. Gorcsan J 3rd, Diana P, Ball BA, Hattler BG. Intraoperative determination of cardiac output by transesophageal continuous wave Doppler. Am Heart J 1992;123:171–6.
52. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167–84.
53. Chin CH, Chen CH, Lo HS. The correlation between three-dimensional vena contracta area and aortic regurgitation index in patients with aortic regurgitation. Echocardiography 2010;27:161–6.
54. Fang L, Hsiung MC, Miller AP, et al. Assessment of aortic regurgitation by live three-dimensional transthoracic echocardiographic measurements of vena contracta area: usefulness and validation. Echocardiography 2005;22:775–81.
55. Goncalves A, Almeria C, Marcos-Alberca P, et al. Three-dimensional echocardiography in paravalvular aortic regurgitation assessment after transcatheter aortic valve implantation. J Am Soc Echocardiogr 2012;25:47–55.
56. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. J Am Soc Echocardiogr 2011;24:937–65.
57. Koos R, Altiok E, Mahnken AH, et al. Evaluation of aortic root for definition of prosthesis size by magnetic resonance imaging and cardiac computed tomography: implications for transcatheter aortic valve implantation. Int J Cardiol 2012;158:353–8.
58. Leipsic J, Gurvitch R, Labounty TM, et al. Multidetector computed tomography in transcatheter aortic valve implantation. J Am Coll Cardiol Img 2011;4:416–29.
59. Santos N, de Agustin JA, Almería C, et al. Prosthesis/annulus discongruence assessed by three-dimensional transoesophageal echocardiography: a predictor of significant paravalvular aortic regurgitation after transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imaging 2012;13:931–7.
60. Schultz CJ, Moelker AD, Tzikas A, et al. Cardiac CT: necessary for precise sizing for transcatheter aortic implantation. EuroIntervention. 2010;6 Suppl G:G6–13.
61. Tops LF, Wood DA, Delgado V, et al. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. J Am Coll Cardiol Img 2008;1:321–30.
62. Tzikas A, Schultz CJ, Piazza N, et al. Assessment of the aortic annulus by multislice computed tomography, contrast aortography, and transthoracic echocardiography in patients referred for transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2011;77:868–75.
63. Hamdan A, Guetta V, Konen E, et al. Deformation dynamics and mechanical properties of the aortic annulus by 4-dimensional computed tomography. J Am Coll Cardiol 2012;59:119–27.
64. Ng ACT, Delgado V, van der Kley F, et al. Comparison of aortic root dimensions and geometries before and after transcatheter aortic valve implantation by 2-and 3-dimensional transesophageal echocardiography and multislice computed tomography. Circ Cardiovasc Imaging 2010;3:94–102.
65. Schultz CJ, Weustink A, Piazza N, et al. Geometry and degree of apposition of the CoreValve revalving system with multislice com-

puted tomography after implantation in patients with aortic stenosis. J Am Coll Cardiol 2009;54:911–8.
66. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve replacement: the Valve Academic Research Consortium-2 consensus document. Eur J Cardiothorac Surg 2013;145:6–23.
67. Binder RK, Leipsic J, Wood D, et al. Prediction of optimal deployment projection for transcatheter aortic valve replacement: angiographic 3-dimensional reconstruction of the aortic root versus multidetector computed tomography. Circ Cardiovasc Interv 2012; 5:247–52.
68. Tzikas A, Schultz C, Van Mieghem NM, de Jaegere PP, Serruys PW. Optimal projection estimation for transcatheter aortic valve implantation based on contrast-aortography: validation of a prototype software. Catheter Cardiovasc Interv 2010;76:602–7.
69. Dvir D, Lavi I, Eltchaninoff H, et al. Multicenter evaluation of Edwards Sapien positioning during transcatheter aortic valve implantation with correlates for device movement during final deployment. J Am Coll Cardiol Intv 2012;5:563–70.
70. Eggebrecht H, Doss M, Schmermund A, Nowak B, Krissel J, Voigtlander T. Interventional options for severe aortic regurgitation after transcatheter aortic valve implantation: balloons, snares, valve-in-valve. Clin Res Cardiol 2012;101:503–7.
71. Holmes DR Jr, Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:1200–54.
72. Majunke N, Doss M, Steinberg DH, et al. How should I treat a misplaced self-expanding aortic bioprosthetic valve? EuroIntervention 2010;6:537–42.
73. Vavuranakis M, Vrachatis D, Stefanadis C. CoreValve aortic bioprosthesis: repositioning techniques. J Am Coll Cardiol Intv 2010;3: 565–6.
74. Ussia GP, Barbanti M, Sarkar K, et al. Transcatheter aortic bioprosthesis dislocation: technical aspects and midterm follow-up. EuroIntervention 2012;7:1285–92.
75. Ussia GP, Barbanti M, Ramondo A, et al. The valve-in-valve technique for treatment of aortic bioprosthesis malposition: an analysis of incidence and 1-year clinical outcomes from the Italian CoreValve Registry. J Am Coll Cardiol 2011;57:1062–8.
76. Gerckens U, Latsios G, Mueller R, et al. Procedural and mid-term results in patients with aortic stenosis treated with implantation of 2 (in-series) CoreValve prostheses in 1 procedure. J Am Coll Cardiol Intv 2010;3:244–50.
77. Raffa GM, Malvindi PG, Settepani F, et al. Aortic valve replacement for paraprosthetic leak after transcatheter implantation. J Card Surg 2012;27:47–51.
78. John D, Buellesfeld L, Yuecel S, et al. Correlation of device landing zone calcification and acute procedural success in patients undergoing transcatheter aortic valve implantations with the self-expanding CoreValve prosthesis. J Am Coll Cardiol Intv 2010;3:233–43.
79. Muñoz-García AJ, Alonso-Briales JH, Jiménez-Navarro MF, et al. Mechanisms, treatment and course of paravalvular aortic regurgitation after percutaneous implantation of the CoreValve aortic prosthesis. Int J Cardiol 2011;149:389–92.
80. Ye J, Cheung A, Lichtenstein SV, et al. Transapical transcatheter aortic valve implantation: follow-up to 3 years. J Thorac Cardiovasc Surg 2010;139:1107–13.
81. Ewe SH, Delgado V, Ng AC, et al. Outcomes after transcatheter aortic valve implantation: transfemoral versus transapical approach. Ann Thorac Surg 2011;92:1244–51.
82. Godino C, Maisano F, Montorfano M, et al. Outcomes after transcatheter aortic valve implantation with both Edwards-Sapien and CoreValve devices in a single center: the Milan experience. J Am Coll Cardiol Intv 2010;3:1110–21.
83. Bauer F, Lemercier M, Zajarias A, Tron C, Eltchaninoff H, Cribier A. Immediate and long-term echocardiographic findings after transcatheter aortic valve implantation for the treatment of aortic stenosis: the Cribier-Edwards/Edwards-Sapien valve experience. J Am Soc Echocardiogr 2010;23:370–6.
84. Rajani R, Kakad M, Khawaja MZ, et al. Paravalvular regurgitation one year after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2010;75:868–72.
85. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol 2009;53:1883–91.
86. Lefevre T, Kappetein AP, Wolner E, et al. One year follow-up of the multi-centre European Partner Transcatheter Heart Valve Study. Eur Heart J 2011;32:148–57.
87. Bleiziffer S, Mazzitelli D, Opitz A, et al. Beyond the short-term: clinical outcome and valve performance 2 years after transcatheter aortic valve implantation in 227 patients. J Thorac Cardiovasc Surg 2012;143:310–7.
88. D'Onofrio A, Rubino P, Fusari M, et al. Clinical and hemodynamic outcomes of "all-comers" undergoing transapical aortic valve implantation: results from the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA). J Thorac Cardiovasc Surg 2011;142:768–75.
89. Hayashida K, Morice MC, Chevalier B, et al. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. J Am Coll Cardiol 2012;59: 566–71.
90. Leber AW, Kasel M, Ischinger T, et al. Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system. Int J Cardiol 2011 Dec 22 [E-pub ahead of print].
91. Sinning JM, Scheer AC, Adenauer V, et al. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J 2012;33:1459–68.

Key Words: aortic stenosis ■ paravalvular leak ■ TAVI ■ TAVR.