Paravalvular Aortic Leak After Transcatheter Aortic Valve Replacement

Current Knowledge

Stamatios Lerakis, MD; Salim S. Hayek, MD; Pamela S. Douglas, MD

Transcatheter aortic valve replacement (TAVR) is now well-established as the standard of care for patients with severe symptomatic aortic stenosis who are deemed inoperable,[1] and is seen as an alternative treatment option to surgical aortic valve replacement (SAVR) in a subset of patients with high postoperative mortality.[2] The native valve is typically not removed but instead crushed by the superimposed bioprosthesis, which can result in an incomplete seal of the bioprosthetic valve and aortic annulus, with subsequent occurrence of paravalvular leak (PVL). Two types of Transcatheter Heart Valves (THV) that have been widely used, the balloon-expandable Edwards valve (Cribier-Edwards, Edwards SAPIEN and Edwards SAPIEN XT) by Edwards Lifesciences, and the self-expandable CoreValve by Medtronic, have been described in detail elsewhere.[3,4] Despite the evolving technology of transcatheter valves, PVL post-TAVR is common, with a wide range of reported incidences (Table 1). Most importantly, PVL has been associated with increased short- and long-term mortality post-TAVR, and is seen as a barrier to more widespread use of this promising technique.[5–13] This article describes the incidence, causes, and predictors of PVL, as well as its impact on clinical outcomes. Methods of prevention, diagnosis, and treatment of PVL are also reviewed.

Definition and Incidence

Aortic regurgitation is characterized as either central or paravalvular. Pathological central regurgitation occurs in diseased native valves or damaged prosthetic valves, whereas minor central regurgitation is often a physiological feature of some bioprosthetic valves by virtue of their design. On the other hand, PVL is a complication only of aortic valve prostheses and occurs more commonly post-TAVR (Figure 1) than after SAVR.

Various multicenter registries and trials have reported data on incidence of PVL post-TAVR at different time points (Table 1). The overall incidence of PVL post-TAVR ranges between 50% and 85%, which is significantly higher than what has been observed in SAVR, reported between 1% and 47.6%, with only 4.2% consisting of more than mild PVL.[14] Although the majority of post-TAVR PVL is mild (7.8–40.8%), moderate (5–37.9%) and severe (0.5–13.6%) PVL occur frequently.[1,2,6,8,10,11,13,15–26] The largest meta-analysis of TAVR outcomes estimates the incidence of residual moderate or severe aortic regurgitation after TAVR to be 7.4%.[27] The UK TAVR registry suggests moderate-severe PVL occurred more commonly with CoreValve implants (17.3%, versus 9.6% with the Edwards implants).[13] This finding has not been replicated in other studies. One study by Ewe et al[21] did not find a statistically significant difference in incidence of PVL between transfemoral and transapical TAVR at 30 days and 6 months. The wide range of PVL incidence reported is not surprising and is likely a result of the lack of standardization across centers in the TAVR technique, differences in operator experience, types and sizes of valves used, in addition to the different imaging modalities used and challenges in grading PVL. Unbehaun et al[6] used a modified TAVR procedure after which no patient had severe PVL and only 2 had moderate PVL, of a relatively large cohort of 358 patients.

It is unclear whether PVL progresses in severity with time. The studies reporting the rate of PVL for multiple follow-up time points show decreasing incidences of moderate–severe PVL. Although the decrease could be attributed to the death of patients with higher-grade PVL who are at higher mortality risk, a reduction of severity from moderate to mild may also relate to geometric remodeling of the annulus[2,5,20,21] (Table 1). Rates of mild PVL generally remained stable; there was no evidence of an increase in PVL over time.

Clinical Impact of Paravalvular Leak

Despite the difficulties in accurately characterizing PVL, the wide range of incidences reported, and the relative short period of follow-up, its impact on short- and long-term mortality has been consistently reported across studies (Table 2). Data from a large cohort of 3201 SAVR patients with a mean follow-up of 4.5±3.4 years confirm that patients with moderate–severe aortic regurgitation (AR>1/4) had lower survival at 1, 5, and 10 years (91.4 versus 96.7%, 77.5 versus 82.4%, and 44.1 versus 54.5%; $P<0.01$).[14] Other data on clinical outcomes related to PVL extend from the postoperative period to up to 2 years. Moderate–severe PVL is an independent predictor of mortality in the postoperative period to 30 days, at 1 year, and at 2 years[5–11,13] (Table 2). Recently, Kodali et al from the Placement of AoRTic

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Table 1. TAVR Studies and Registries Reporting Incidence of PVL in >100 Patients

Valve	Registry/Trial	Diagnostic Modality	Postprocedure/30 Days	6 Months	1 Year	2 Years	3 Years
Edwards	Rodes-Cabau et al[15] Canadian, 2010	Echocardiography	n=339 Mild: 78% Moderate: 5% Severe: 1%	—	—	—	—
	Thomas et al[16] SOURCE, 2010	Echocardiography	n=1038 Moderate–Severe: 1.9%	—	—	—	—
	Leon et al[1] PARTNER nonoperable cohort, 2010	Echocardiography	n=144 None: 14% Mild: 68% Moderate–Severe: 12%	—	n=98 None: 23% Mild: 59% Moderate–Severe: 11%	—	—
	Smith et al[2] PARTNER high-risk cohort, 2011	Echocardiography	n=287 None: 22.6% Mild: 65.2% Moderate–Severe: 12.2%	n=240 None: 26.3% Mild: 62.5% Moderate–Severe: 11.3%	n=222 None: 32.9% Mild: 60.4% Moderate–Severe: 6.8%	n=143 Moderate–Severe: 6.9%	—
	Nombela-Franco et al,[17] 2012	Echocardiography	n=211 Mild: 30.8% Moderate: 37.9% Severe: 11.3%	—	—	—	—
	Gripari et al,[18] 2012	Echocardiography	n=135 None: 31.1% Mild: 48.1% Moderate: 18.5% Severe: 2.2%	—	—	—	—
	Unbehaun et al,[6] 2012	Echocardiography, Angiography	n=358 None: 51.6% Mild: 47% Moderate: 0.6% Severe: 0%	—	—	—	—
	Walther et al,[19] 2012	Echocardiography	n=150 None: 36% Mild: 30.7% Moderate: 22.8% Severe: 7%	—	—	—	—
	Webb et al,[20] 2009	Echocardiography	n=168 Mild: 58% Moderate: 37% Severe: 5%	None–Mild: 77% Moderate: "Unchanged" Severe: 0%	None–Mild: 66% Moderate: "Unchanged" Severe: 0%	…	…
	Ewe et al,[21] 2011	Echocardiography	TF, n=45 None: 8.9% Mild: 26.7% Moderate: 53.3% Severe: 11.1% TA, n=59 None: 3.4% Mild: 25.4% Moderate: 57.6% Severe:13.6%	TF, n=33 None: 51.5% Mild: 36.4% Moderate: 51.5% Severe: 0% TA, n=39 None: 64.1% Mild: 33.3% Moderate: 2.6% Severe: 0%	TF, n=26 None: 57.7% Mild: 38.5% Moderate: 3.8% Severe: 0% TA, n=23 None: 73.9% Mild: 26.1% Moderate: 0% Severe:0%	…	…

Table 1. Continued

Valve	Registry/Trial	Diagnostic Modality	Postprocedure/30 Days	6 Months	1 Year	2 Years	3 Years
CoreValve	Ussia et al[22] Italian 3-years, 2012	Echocardiography	n=178 Mild: 52.8% Moderate: 15.2% Severe: None	—	n=129 Mild: 48.1% Moderate: 17.8% Severe: None	—	n=89 Mild: 42% Moderate: 9% Severe: None
	Buellesfeld et al,[23] 2011	Echocardiography	n=126 None: 59% Mild: 32% Moderate: 9% Severe: 0%	n= N/A None: 55% Mild: 39% Moderate: 6% Severe: 0%	n= N/A None: 63% Mild: 34% Moderate: 3% Severe: 0%	n= N/A None: 63% Mild: 34% Moderate: 3% Severe: 0%	—
	Sinning et al,[8] 2012	Echocardiography, Angiography	n=146 None: 36.3% Mild: 48.6% Moderate: 12.3% Severe: 2.7%	—	—	—	—
Mixed	Eltchaninoff et al[24] FRANCE, 2011 Edwards 68% CoreValve 32%	Echocardiography, Angiography	n=244 Absent/Mild: 90.5% Moderate: 9% Severe: 0.5%	—	—	—	—
	Gilard et al[25] FRANCE2, 2012 Edwards 66.9% CoreValve 33.1%	Echocardiography	n=1846 Mild: 47.4% Moderate: 16.3% Severe: 0.8%	n=983 Mild: 46% Moderate: 16.1% Severe: 0.8%	n=426 Mild: 47.2% Moderate: 18.5% Severe: 1.2%	—	—
	Abdel-Wahab et al[11,12] Germany, 2011 Edwards 15.6% CoreValve 88.4%	Angiography	n=689 None: 27.6% Mild: 54.9% Moderate: 15.2% Severe: 2.3%	—	—	—	—
	Moat et al[13] UK, 2011 Edwards 47.1% CoreValve 52.9%	Angiography	n=870 None: 39% Mild: 47.4% Moderate–Severe: 13.6% (Edwards 9.6%, CoreValve 17.3%)	—	Moderate–Severe: 12.3%	—	—
	Fraccaro et al,[26] 2012	Echocardiography	n=384 Moderate–Severe: 4%	—	—	—	—
	Hayashida et al,[10] 2012 Edwards 85.4% CoreValve 14.6%	Echocardiography	n=260 Moderate–Severe: 30.8% Severe: 4.2%	…	…	…	…

PARTNER indicates Placement of AoRTic TraNscathetER valve trial; TA, transapical; and TF, transfemoral.

TraNscathetER (PARTNER) valve trial high-risk cohort suggested that any PVL regurgitation (mild–moderate–severe) was associated with increased mortality at 2 years, although this association was not analyzed in multivariate

Causes and Predictors of Paravalvular Regurgitation

During SAVR the positioning of the prosthesis is performed under direct anatomic observation, allowing excision of the

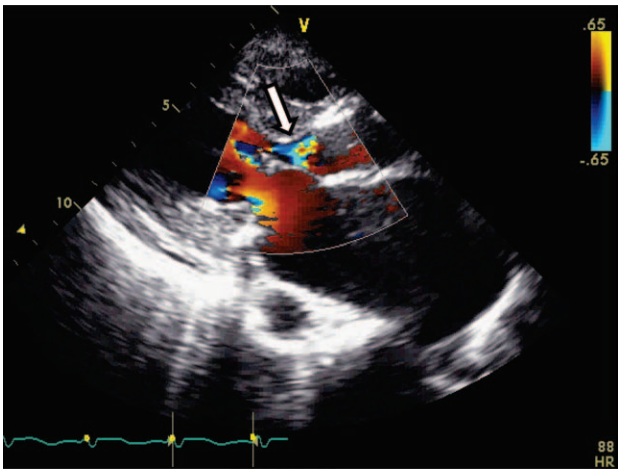

Figure 1. Parasternal longitudinal axis transthoracic echocardiography view showing mild paravalvular leak post–transcatheter heart valve deployment. **Arrow** indicates the site of paravalvular leak.

of the prosthetic valve within the aortic annulus. The minimally invasive nature of TAVR precludes removal of the heavily calcified native valve and direct observation of the annulus. It entails using preprocedural imaging to estimate the size of the aortic root, and indirectly implanting a circular bioprosthesis in a dynamic, oval-shaped aortic annulus. The technique relies on fluoroscopy and intraprocedural echocardiography for positioning. Thus, it is not surprising to expect a higher frequency of PVL in TAVR as a result of the risks of inappropriate sizing of the prosthesis, its malpositioning, and the hindrance of the old calcified valve (Table 3).

The diameter of the aortic annulus is measured before and during the procedure to determine the choice and size of the THV. To assess valve-annulus congruence, a cover index integrating aortic annulus diameter (A) and prosthetic diameter (P; 100×[A–P]/P) was used. Moderate-severe regurgitation was not seen with a cover index >8% in this study of 74 patients. These findings were reproducible in a study using intraprocedural 3D tranesesophageal echocardiography (TEE) in addition to transthoracic echocardiography (TTE) to evaluate the THV.[18] In another prospective study, annulus–prosthesis mismatch was defined as a native annulus diameter larger than normal on label diameter limit for the prosthesis and was associated with higher grade PVL.[28] Larger aortic annulus size measured by MRI and computed tomography (CT) but not TTE was also predictive of PVL.[29] These studies suggest a certain amount of oversizing is indeed necessary to prevent PVL. Indeed, Detaint et al[30] reported that patients with aortic annulus <22 mm by echocardiography had no moderate–severe PVL after TAVR. Although echocardiography is the most widely used method for measuring the annulus, multi-detector computed tomography (MDCT) allows

Table 2. PVL as a Predictor of Outcomes: Reported Mortality/Survival Rates and Hazard Ratios in Studies With >100 Patients

Valve	Registry/Trial	Severity	Outcome	Time	HR/Survival/Mortality
Edwards	Unbehaun et al,[6] 2012, n=358	None, Trace, Mild–Moderate	Survival	2-year	None: 66% Trace: 72%
	Kodali et al[5]; PARTNER high risk cohort, 2012 n=699	Mild–Moderate–Severe	Mortality	2-year	HR 2.11 [1.43–3.10]
CoreValve	Gotzmann et al,[7] 2012 n=198	None–Mild, Moderate–Severe	Mortality	30 day	None–Mild: 6%, Moderate–Severe 21%; HR 3.81 [1.384–10.482]
				1 yr	None–Mild: 16%, Moderate–Severe 57%; HR 5.48 [2.807–10.683]
	Sinning et al,[8] 2012 n=146	None–Mild, Moderate–Severe	Mortality	30 day	None–Mild: 4%, Moderate–Severe: 22.7%
				1 yr	None–Mild: 25%. Moderate–Severe 63.6% HR 3.9 [2.0–7.5]
	Tamburino et al[9] Italian, 2011 n=661	Moderate–Severe	Mortality	30 days – 1 yr	HR 3.785 [1.57–9.10]
Mixed	Hayashida et al,[10] 2011, n=260	Moderate–Severe	Mortality	6 mo	HR 1.97 [1.19–3.28]
	Edwards 85.4%				
	CoreValve 14.6%				
	Abdel-Wahab et al[11,12] German, 2011	None, Mild, Moderate, Severe	Mortality	In-Hospital	None: 4.9%
	Edwards 15.6%				Mild: 6.1%
	CoreValve 88.4%				Moderate 15.5%
	n=689				Severe: 12.5%
					Moderate–Severe: 2.43 [1.22–4.85]
	Moat et al[13] UK, 2011	Moderate–Severe	Mortality	1 yr	HR 1.49 [1.00–2.21]
	Edwards 47.1%				
	CoreValve 52.9%				
	n=870				

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