

Long-term outcomes of catheter-based intervention for clinically significant paravalvular leak

Leor Perl^{1*}, MD; Amir Cohen¹, MD; Alexander Dadashev¹, MD; Yaron Shapira¹, MD; Hana Vaknin-Assa¹, MD; Vered Yahalom², MD; Alexander Sagie¹, MD; Ran Kornowski¹, MD; Rafael Hirsch¹, MD

1. Cardiology Department, Rabin Medical Center and "Sackler" School of Medicine, Tel Aviv University, Petach Tikva, Israel;
2. Blood Services & Apheresis Institute, Rabin Medical Center and "Sackler" School of Medicine, Tel Aviv University, Petach Tikva, Israel

L. Perl and A. Cohen contributed equally to this manuscript.

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KEYWORDS

- degenerative valve
- miscellaneous
- paravalvular leak
- prior cardiovascular surgery
- specific closure device/technique

Abstract

Background: In most centres, clinically significant percutaneous paravalvular leak (PVL) closure following valve replacement surgery is reserved for those considered high-risk for surgery. There is a paucity of data regarding the long-term outcomes of these patients.

Aims: Our goals were to assess the long-term outcomes of patients undergoing percutaneous PVL closure.

Methods: A total of 100 consecutive transcatheter PVL closure procedures (74 mitral, 26 aortic) were performed in 95 patients between February 2005 and August 2019 at our hospital. Data collected included procedural success rates, indication-specific outcomes and mortality.

Results: Mean follow-up was 5.6±6.1 years, mean age 62.6±15.2 years, and 45.4% were female. The device was successfully implanted in 88 procedures (88.0%). Patients who presented with heart failure (n=57) had a significant improvement in NYHA classification (29.2% Class III/IV versus 100.0%, p<0.001). For patients who presented with haemolytic anaemia (n=38), haemoglobin increased (11.94±1.634 vs 9.72±1.49, p<0.001) and LDH levels were reduced (1,354.90±1,225.55 vs 2,039.40±1,347.20, p<0.001) following the procedure. Rates of mortality were 3.8% at 90 days, 15.6% after 1 year, and 27.2% after 5 years.

Conclusions: For patients who are deemed intermediate- to high-risk for repeat surgery, transcatheter PVL closure shows reasonable clinical success rates, with a significant improvement in symptoms, and a relatively low rate of periprocedural complications.

*Corresponding author: Department of Cardiology, Rabin Medical Center, Beilinson Hospital, 39 Jabotinsky St, Petach Tikva, 4941492, Israel. E-mail: leorperl@gmail.com

Abbreviations

AVR	aortic valve replacement
HA	haemolytic anaemia
HF	heart failure
MVR	mitral valve replacement
NYHA	New York Heart Association
PVL	paravalvular leak
STS	Society of Thoracic Surgeons
TEE	transoesophageal echocardiogram
TTE	transthoracic echocardiogram

Introduction

Following heart valve surgery, 2-18% of patients will ultimately develop significant paravalvular leak (PVL)¹⁻⁶. It occurs more commonly following mitral valve replacement (MVR) than after aortic valve replacement (AVR) and following mechanical rather than biological prosthetic valve implantation². The occurrence of PVL is also increased following incident infective endocarditis, and is related to a supra-annular versus an annular aortic prosthesis, suturing technique, extensive annular calcification and tissue friability^{2,7,8}.

Most PVLs occur shortly after surgery, are usually small and may close spontaneously due to epithelialisation. However, the development of a new valve regurgitation should raise suspicion of PVL. In addition, prosthetic valve endocarditis or a prosthetic valve failure must be ruled out. While some go undetected, 2-5% of all valvular surgery patients are expected to suffer from symptoms related to it. The main signs and symptoms associated with significant PVL are dyspnoea, heart failure (HF) and/or left ventricular enlargement, haemolysis and symptomatic anaemia. Importantly, PVL rates continue to increase over time, with significant increase in rates after 10 and 20 years⁹. Nevertheless, there is a paucity of data regarding the long-term natural history of patients with PVL¹⁻⁶, as well as following percutaneous treatment of PVL¹⁰⁻¹³.

Recent guidelines recommend repeat operation if PVL is related to endocarditis or causes significant haemolytic anaemia (HA), requiring repeated blood transfusions or leading to severe symptoms (class I, level of evidence C), whereas percutaneous PVL closure may be considered for high-risk cases only (class IIb, level of evidence C)¹⁴. However, a recent single-centre study examined the long-term outcomes of patients with PVL after mitral valve and aortic valve surgery who were considered eligible for a reoperation. Most underwent surgery, yet the outcomes for both the short- and long-term mortality were relatively poor (3% in-hospital mortality and 47% mortality at 6.6±4 years)¹⁵. In general, supportive data for either the surgical or the percutaneous approach to PVL repair are relatively scarce. We thus aimed to assess the long-term outcomes (up to five years) of percutaneous PVL closure at our tertiary centre, focusing on outcomes of mitral versus aortic PVL.

Methods

PATIENTS AND SETTING

This observational study is based on a prospective registry of all-comers for percutaneous PVL closure procedures, derived from the Rabin Medical Center, Israel, between February 2005 and August 2019. All patients suffered from symptomatic PVL following mitral valve or aortic valve surgery. Patients who were not deemed suitable for percutaneous PVL closure were those with suspected or proven bacterial endocarditis and those with very large leaks, encompassing more than one quarter of the valve perimeter. Most of these patients had reoperation and are not included in our study.

Patient data, cardiovascular risk factors, and procedural dates were entered into a database at the time of the procedure. All patients had a comprehensive transthoracic echocardiogram (TTE) and transoesophageal echocardiogram (TEE) at the time of initial assessment. Echocardiographic data at 1.5-2.0 years were available for 77 procedures (77.0%) performed in 74 (77.9%) patients, enabling us to determine the degree of residual leak.

Ethics approval was granted for this study by the institutional review board.

PROCEDURE

All procedures were performed with the informed consent of the patient, following Heart Team discussion. The procedures were carried out under general anaesthesia for all mitral PVLs and most aortic PVLs using fluoroscopic and TEE guidance. In some of the aortic PVLs, the procedure was performed in conscious patients, using intra-cardiac echo (ICE) (n=7) or TTE (n=1) guidance. A routine TTE was performed in all patients on the following day. The different techniques, approaches and devices used for PVL closure have been described extensively before and are beyond the scope of this paper. However, some principles of PVL closure that we adopted are outlined in **Supplementary Appendix 1**.

OUTCOMES

The date of percutaneous PVL closure at our institution was defined as the beginning of the observational period. Peri-procedural outcomes were recorded. Immediate and in-hospital clinical events were prospectively recorded in the institutional database. During follow-up, patients completed standardised questionnaires on clinical events at six-month intervals either by telephone or in the out-patient clinic. When indicated, records from peripheral hospitals were acquired to verify the events. All events were further confirmed and adjudicated by the institutional clinical events adjudication committees. Survival status, as well as cause of death, in case it had occurred, was ascertained from municipal civil registries at one and five years.

Clinically significant haemolytic anaemia was defined as symptomatic anaemia (haemoglobin <13 g/dl in women or <15 g/dl in men) requiring transfusion, with laboratory evidence of intravascular haemolysis. HF was diagnosed by our HF team and was assessed according to the New York Heart Association (NYHA) classification. Renal failure was defined as glomerular

filtration rate below 50 mL/min/1.73 m², calculated according to the Modification of Diet in Renal Disease formula.

The degree of PVL was defined as mild, mild to moderate, moderate, moderate to severe or severe. Procedures were defined as successful, partially successful, or unsuccessful – determined by whether any echocardiographic visible leakage was observed following the procedure. An unsuccessful procedure was diagnosed in cases of no change in the leakage observed directly after the procedure or failure to insert the device. Partial success was defined as showing some improvement in the leakage, or when not all leaks were taken care of in patients with more than one leak around the same valve. Success was affirmed in cases with no more than mild residual leak. For those patients with available echocardiographic information at long-term follow-up, we assessed the degree of PVL after 1.5-2.0 years.

Comparison was made between patients with PVL following AVR versus MVR, as well as according to the main indication for intervention – HF or anaemia. Primary endpoints included mortality at 90 days, 1 year and 5 years. Secondary endpoints comprised procedural success rates, rates of procedural complications, and improvement in NYHA class (for those with predominant HF), haemoglobin, lactate dehydrogenase (LDH) and number of packed red blood cell units (PC) transfused (for those with predominant anaemia).

STATISTICAL ANALYSIS

Demographic, procedural and outcome data were divided according to the valve treated – following AVR or MVR. Continuous data are summarised as mean and standard deviation, or median and interquartile range (IQR), and categorical data as frequency (%). The Student's t-test or analysis of variance was used to compare continuous variables between groups, and the ANOVA test was used for categorical variables. The normality of variable distributions was assessed using the Kolmogorov-Smirnov test. Time-to-event curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Effect sizes are presented as odds ratio and 95% confidence interval (CI). All statistical analyses were performed with SPSS, Version 26 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

One hundred procedures were performed in 95 patients. Mean age was 62.6±15.2 years, and 42.0% were female patients. The mean Society of Thoracic Surgeons (STS) score was 7.5±5.5. Seventy-four (74) cases (74.0%) were performed for mitral PVL, 26 (26.0%) for aortic PVL. Of these procedures, 78 (78.0%) were performed as the initial correction of PVL, 12 (12.0%) were carried out after one surgical PVL correction and 10 (10.0%) were performed following two repeat surgeries (Table 1). Mitral PVL, as compared to aortic PVL cases, had a higher percentage of women (44.3 vs 37.5%, p=0.046), higher values of LDH at baseline (1,778.3±1,241.8 vs 1,102.2±865.9, p=0.04) (Table 1) but

Table 1. Baseline characteristics.

Patient characteristics	Total (n=100)	Mitral PVL (n=74)	Aortic PVL (n=26)	p-value	
Age, years	62.6±15.2	64.2±11.8	58.3±8.8	0.102	
Sex, female, %	42.0	44.3	37.5	0.046	
Diabetes mellitus, %	26.0	26.7	25.0	0.940	
Body mass index, kg/m ²	26.5±33.5	26.0±42.9	28.1±31.8	0.084	
Hypertension, %	32.0	30.0	37.5	0.457	
Atrial fibrillation, %	55.0	57.1	50.0	0.506	
CABG, %	11.0	10.0	13.3	0.770	
Ischaemic heart disease, %	28.0	24.3	34.4	0.294	
Peripheral vascular disease, %	15.0	11.1	25.0	0.012	
Obstructive sleep apnoea, %	24.0	29.0	9.4	0.160	
COPD, %	11.0	11.4	9.4	0.759	
Dyslipidaemia, %	27.0	22.9	37.5	0.151	
Hypothyroidism, %	9.0	10.0	6.3	0.540	
Smoking history, %	42.0	38.2	24.5	0.332	
Renal failure, %	27.0	25.7	31.3	0.566	
Coumadin, %	77.0	74.2	86.4	0.081	
Aspirin, %	35.0	32.5	33.6	0.252	
Presenting symptoms					
Anaemia, %	41.0	45.7	35.7	0.094	
Heart failure, %	86.0	84.6	89.8		
Society of Thoracic Surgeons score	7.5±5.5	7.7±5.8	7.2±4.9	0.122	
Time from previous valvular surgery, years	6.6±5.4	6.7±5.8	6.2±4.9	0.562	
Previous surgeries for PVL, %	None	78.0	78.9	76.9	0.898
	One	12.0	11.8	11.5	
	Two	10.0	9.2	11.5	
Laboratory results					
Haemoglobin, mg/dL	10.8±1.7	10.3±1.6	11.7±1.9	0.214	
Creatinine, mg/dL	1.1±0.6	1.1±0.6	1.2±0.6	0.456	
Lactate dehydrogenase, mg/dL	1,561.1±921.8	1,778.3±1,241.8	1,012.2±865.9	0.042	
Total bilirubin, mg/dL	1.8±0.9	1.9±1.2	1.5±0.8	0.085	
CABG: coronary artery bypass graft surgery; COPD: chronic obstructive pulmonary disease; PVL: paravalvular leak					

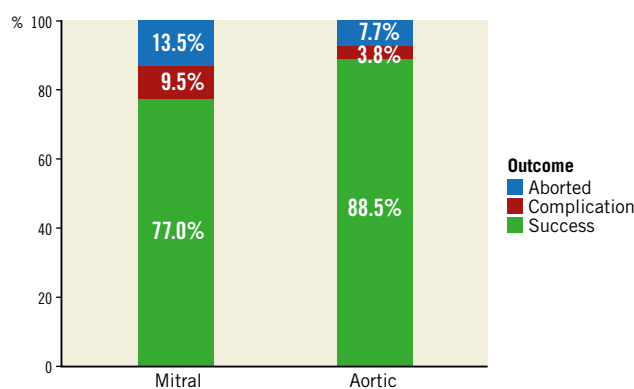
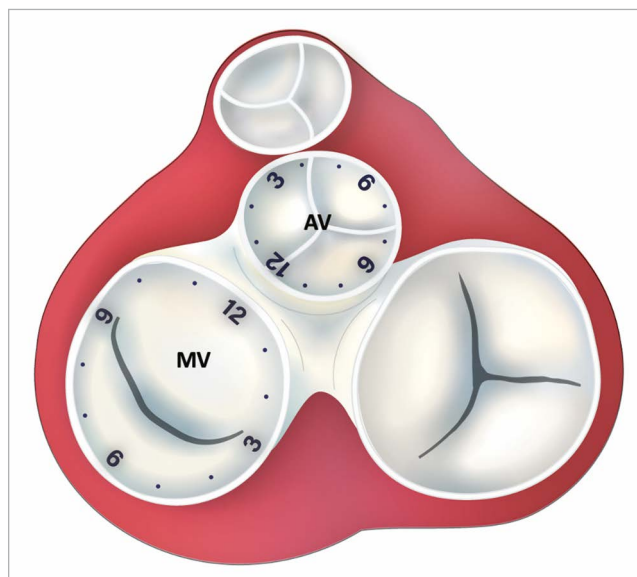
lower rates of reduced left ventricular ejection fraction (p=0.03) (Table 2). Eighty-six percent (86.0%) of the patients suffered from HF prior to the procedure (84.6% for mitral and 89.8% for aortic PVL), and 41.0% from HA (45.7 vs 35.7%, p=0.094 for presenting symptoms) (Table 1).

The device was successfully implanted in 88 procedures (88.0% for the complete cohort, 88.5% for aortic PVL, 77.0% for mitral PVL) (Figure 1). The transseptal approach was the most common one for mitral PVL (73.0%), whereas the retrograde approach was the sole approach in cases of aortic PVL. The transapical approach was the least common method (9.0% of all cases) (Table 2). The

Table 2. Procedural characteristics.

Procedural characteristics	Total (n=100)	Mitral PVL (n=74)	Aortic PVL (n=26)	p-value	
Approach					
Transseptal, %	57 (57.0)	54 (73.0)	0 (0.0)	0.022	
Retrograde, %	36 (36.0)	12 (16.2)	26 (100.0)		
Transapical, %	9 (9.0)	8 (10.8)	0 (0.0)		
Mechanical versus biological, %	80 (80.0)	61 (82.4)	18 (69.2)		
Location of mitral valve leak					
10-12 o'clock		38 (51.4)			
6-9 o'clock		23 (31.1)			
1-5 o'clock		13 (17.6)			
Number of leaks					
Mean number of PVL corrected	1.1±0.9	1.1±0.9	1.2±0.9	0.225	
Total number of PVL identified	1.4±1.0	1.5±1.1	1.3±1.0	0.418	
Mean number of devices used per PVL	1.1±0.9	1.1±0.9	1.2±0.8	0.348	
Device used					
Occlutech PLD, %	3 (3.0)	3 (4.1)	0 (0.0)	0.012	
AMPLATZER VP II, %	16 (16.0)	10 (13.5)	6 (23.1)		
AMPLATZER VP III, %	55 (55.0)	41 (55.4)	14 (53.8)		
Nit-Occlud, %	2 (2.0)	2 (2.7)	0 (0.0)		
AMPLATZER Duct Occluder, %	7 (7.0)	7 (9.5)	0 (0.0)		
Not implanted, %	17 (17.0)	11 (14.9)	6 (23.1)		
Echocardiographic data					
Systolic PA pressure pre, mmHg	47.2±16.3	53.2±17.1	39.1±16.2	0.122	
Systolic PA pressure post, mmHg	43.5±15.6	49.2±14.6	35.3±17.3	0.081	
Mean transvalvular gradient pre, mmHg	13.4±8.8	6.9±2.9	22.8±15.9	0.024	
Peak transvalvular gradient pre, mmHg	26.7±14.1	18.3±5.7	39.0±26.3	0.035	
Mean transvalvular gradient post, mmHg	8.1±6.5	4.2±3.3	15.4±10.3	0.242	
Peak transvalvular gradient post, mmHg	17.9±11.6	14.3±6.6	24.3±14.5	0.418	
LVEF, %	Normal (>55%)	64.6	70.5	52.1	0.031
	Mild (45-54%)	15.7	12.5	22.2	
	Moderate (30-44%)	11.8	11.5	12.5	
	Severe (<30%)	7.9	5.5	13.2	
LVEF: left ventricular ejection fraction; PA: pulmonary artery; PVL: paravalvular leak(s)					

most common location for mitral PVL was 10-12 o'clock (51.4% of cases) (**Central illustration**). The most common device used (55.0% of all cases) was the AMPLATZER™ Vascular Plug III (St. Jude Medical, St. Paul, MN, USA). There were no major differences in the number of leaks identified, number treated or number of plugs per PVL between mitral and aortic PVL (**Table 2**).

**Figure 1. Outcomes by valve treated.****Central illustration.** Anatomical location of PVL according to the clock scheme. AV: aortic valve; MV: mitral valve

The leading cause of procedural failure was the inability to cross the leak or to advance the equipment (10.0% of all cases, 11.8% for mitral, 7.7% for aortic PVL). Major periprocedural complications occurred in 8.0% of the patients (9.5% for mitral, 3.8% for aortic PVL) (**Figure 1, Supplementary Appendix 2**).

The median follow-up was 66 months (IQR 18-92). Rates of PVL below moderate (the definition for success at the end of the procedure) remained high – 59 of the 77 (76.6%) procedures for which we had echocardiographic information at 1.5-2.0 years were estimated as mild or below. Rates of mortality were 3.8% at 90 days, 15.6% after 1 year, and 27.2% after 5 years. Mortality was higher for patients undergoing transcatheter PVL closure of the mitral valve (log-rank $p<0.01$) (**Figure 2**) and for patients who underwent an unsuccessful transcatheter PVL closure (log-rank $p<0.01$) (**Figure 3**). NYHA class was reduced after the procedure (reduction from 97.6% NYHA III-IV at baseline to 28.6% at first follow-up for patients with mitral PVL and from 88.4% to 27.3% in aortic

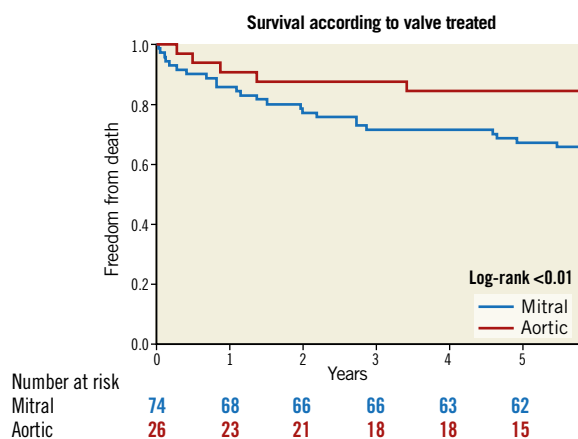


Figure 2. Kaplan-Meier survival estimates of all-cause mortality by valve treated.

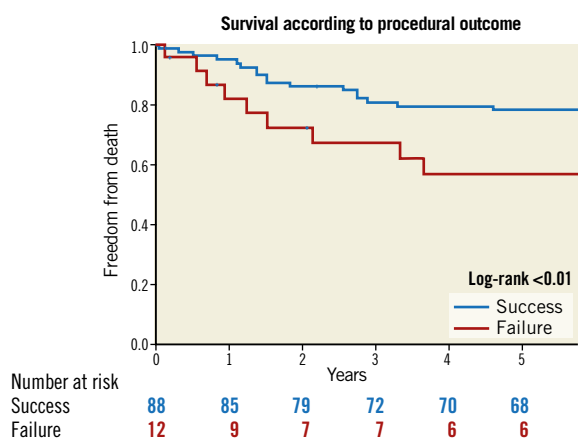


Figure 3. Kaplan-Meier survival estimates of all-cause mortality by procedural outcome.

PVL, $p < 0.01$ for both) (Figure 4) and after 3 years (of 55 patients with available information, NYHA III-IV was described in only 19 [34.5%]). LDH levels were reduced following the procedure (from $1,778.3 \pm 1,241.8$ to $1,282.5 \pm 891.2$ in patients with mitral PVL and $1,012.2 \pm 865.9$ to 720.3 ± 831.9 in patients with aortic PVL, $p < 0.01$ for both) (Figure 5) and after 3 years ($1,023.4 \pm 881.3$, $n = 48$). Levels of haemoglobin increased immediately after the procedure (from 10.3 ± 3.9 to 11.5 ± 4.2 in patients with mitral PVL, $p = 0.03$, and from 11.7 ± 8.2 to 13.0 ± 8.6 in patients with aortic PVL, $p = 0.04$) (Figure 6) and to 12.4 ± 8.3 after 3 years ($n = 50$). Of the mitral PVL patients, 37.5% required packed red blood transfusion during the year prior to the procedure versus 14.8% in the following year ($p < 0.001$, mean number of PC received 4.8 ± 3.8 before versus 1.2 ± 1.0 after the procedure, $p < 0.001$). For patients with aortic PVL, only 22.1% required PC transfusion versus 9.4% after the procedure ($p = 0.03$), for a mean number of PC of 2.8 ± 1.0 versus 0.7 ± 0.8 ($p < 0.001$). After 3 years, haemolysis had worsened in 7 patients (14.0%). These patients were all treated conservatively.

Patients who presented primarily with HF had significant improvement in the NYHA class (100% were Class III-IV

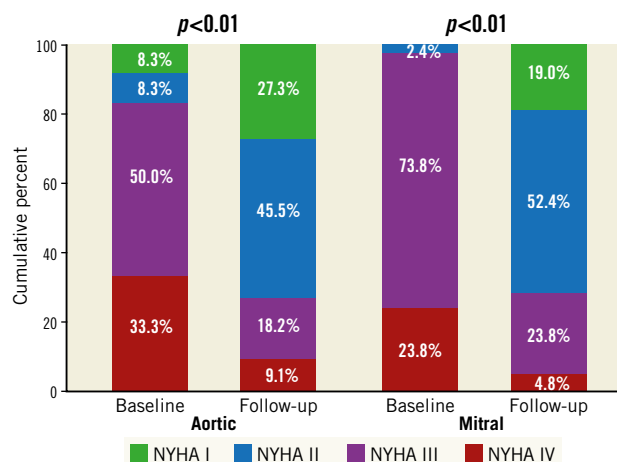


Figure 4. NYHA class by valve treated.

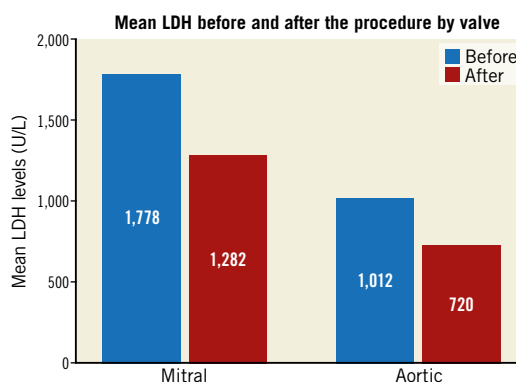


Figure 5. Mean LDH by valve treated.

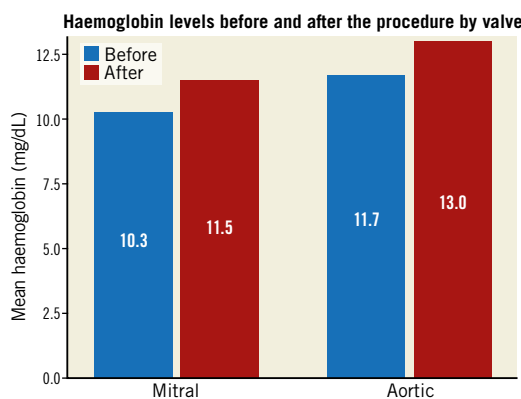


Figure 6. Mean haemoglobin by valve treated.

prior to the procedure, versus 29.2% at follow-up, $p < 0.001$). In patients who presented with HA as a main indication, there was a significant reduction in LDH level ($1,354.90 \pm 1,225.55$ vs $2,039.40 \pm 1,347.20$, $p < 0.001$) following the procedure, as well as an increase in haemoglobin (11.94 ± 1.634 vs 9.72 ± 1.49 , $p < 0.001$). A distinct group suffered from both HF and HA. In

this “mixed group” (n=44), NYHA Class III-IV was reduced from 92.3% at baseline to 28.5% following the procedure ($p<0.01$) and LDH was reduced from $1,901.24\pm 1,019.12$ to $1,305.36\pm 899.44$, $p<0.001$). There was also a reduction in the number of PC received (33.7% prior to vs 13.5% post procedure, $p<0.001$ and 4.2 ± 2.4 mean number of PC prior to vs 1.9 ± 1.3 after the procedure, $p<0.001$).

Cox regression identified four factors significantly impacting on mortality: age (HR 1.15 for each additional year, 95% CI: 1.01-1.76, $p=0.045$), mitral versus aortic valve (HR 1.82, 95% CI: 1.04-3.36, $p=0.033$), procedure failure (HR 2.01, 95% CI: 1.54-11.02, $p=0.011$) and the NYHA class following the procedure (HR 1.15 for each class increase, 95% CI: 1.03-2.64, $p=0.021$) (Table 3). There was no difference in outcomes according to the surgical risk score, type of device or the anatomical approach. Finally, the association between residual leak (more than mild) at 1.5-2.0 years and mortality at 5 years was assessed using an univariate analysis, demonstrating strong relationship (HR 2.76, 95% CI: 1.33-7.28).

Table 3. Cox regression for death.

Parameter	HR	95% confidence interval		p-value
Sex	1.276	0.235	6.924	0.778
Age (for each year)	1.146	1.010	1.763	0.045
Procedure failure	2.010	1.540	11.022	0.011
Mitral versus aortic valve	1.820	1.044	3.360	0.033
Renal failure	2.399	0.488	11.797	0.282
Anaemia	3.138	0.610	16.144	0.171
Atrial fibrillation	2.251	0.245	20.661	0.473
Hypertension	0.359	0.048	2.713	0.321
Diabetes mellitus	8.808	0.653	118.793	0.101
NYHA class post	1.153	1.032	2.639	0.021
LVEF pre	1.138	0.612	11.124	0.181

HR: hazard ratio; LVEF: left ventricular ejection; NYHA: New York Heart Association

Discussion

In this current work, we assessed the long-term outcomes of patients undergoing percutaneous PVL closure at our medical institution. Our results show that rates of mortality were comparable and perhaps better than the outcomes of most studies assessing a surgical approach to PVL closure^{1,3,15-17}. We have also seen significant differences in outcomes according to the valve treated, as mitral PVL closure results in worse prognosis when compared with aortic leak closure. Long-term prognosis also depends on the age of the patient, the success of the procedure and the NYHA classification at the first follow-up. Finally, we have witnessed improved measurements of HF and HA, in particular when each parameter is assessed within the group of patients referred for the procedure for that specific indication.

Following valve replacement surgery, the presence of PVL is not infrequent and increases the risk of mortality, repeat admissions and reoperation¹⁻⁶. The exact mechanism of the appearance of PVL in some patients is uncertain and likely to be multifactorial. It has been suggested that some PVLs recede in the early postoperative period, especially with MVRs, due to endothelialisation of small PVLs or suture tracts⁷.

According to the European Society of Cardiology guidelines, the default treatment for PVL should be repeat surgery, whereas percutaneous PVL closure is reserved for inoperable or high-risk candidates¹⁴. Therefore, outcomes for patients undergoing percutaneous PVL closure are expected to be worse than repeat surgery. However, recent studies have demonstrated less than optimal outcomes for repeat surgery for PVL. Patients at particular risk include those with a high STS score, a high right ventricular systolic pressure, PVL of an infectious aetiology, and cases where PVL surgery resulted in recurrence of the leak^{12,15}. In addition to the immediate risk of reoperation, the less-than-optimal outcomes in surgery for PVL are related to the fact that the tissues around the leakage are often calcified and friable – increasing the risk of recurrent leaks^{18,19}. In fact, several studies have demonstrated lower rates of complications in patients treated by percutaneous PVL closure, and some even suggested it as the treatment of choice^{16,17,20,21}.

As for the potential benefits of percutaneous PVL closure, there are two main factors – reduction in mechanisms related to HF, and improvement in HA. One previous study²² showed a modest improvement in haemolysis marker after PVL closure. In that cohort, the benefit was significantly higher in patients with a mechanical valve. A recent study assessing the Occlutech® PLD Occluder (Occlutech GmbH, Jena, Germany) demonstrated a significant reduction of haemolysis-related blood transfusions following the procedure²³. Heart failure was shown to improve in most studies assessing the effect of PVL correction^{12,24,25}. One study also demonstrated a significant association between reduction in left atrial pressure and outcomes²⁶, reminding us of the important impact of the haemodynamic changes associated with reduction of PVL. Interestingly, in our study, when divided by each of the two indications, we witnessed a significant improvement in these two factors – haemoglobin was raised (and LDH reduced) in patients presenting with HA, and the NYHA class had improved in patients presenting with congestive HF.

The mean STS score in our study was 7.5 ± 5.5 , somewhat higher than the risk in the other large trials of percutaneous PVL closure^{15,27,12}, but still within the intermediate- to high-risk range. Guidelines currently advocate routine follow-up of patients with prosthetic valves, which includes blood tests for HA, as well as TTE and, if needed, TEE to detect a PVL. Reoperation is recommended if the PVL is related to endocarditis or causes HA requiring repeated blood transfusions or leading to severe symptoms. Percutaneous closure of a PVL has a class IIb recommendation, due to inconsistent evidence of efficiency¹⁴. Therefore, it is important to continue to gather long-term information from medical centres such as ours, which treat patients of varying risk profile by

the percutaneous approach, demonstrating no more than modest risk throughout the five-year follow-up. Our findings, in line with previous trials, support consideration of transcatheter PVL repair in a wide range of patients, including in those who are, indeed, candidates for surgery as well.

Limitations

The study is a single-centre observational study; thus we have not compared outcomes to surgical PVL correction. Therefore, our findings cannot be generalised to centres contemplating one of the two approaches. However, since our medical centre is more inclusive in its decisions to perform percutaneous PVL closure, the outcomes presented here warrant careful consideration of this approach in PVL all-comers except for those with active infection. More head-to-head comparisons of the two options may impact on future guidelines.

Conclusions

Transcatheter PVL closure in patients with intermediate to high risk for reoperation shows reasonable clinical success rates, demonstrating significant improvement in symptoms and in haemolytic anaemia, as well as a relatively low rate of periprocedural complications. Younger patients, those who were treated for aortic PVL, who undergo a successful percutaneous PVL closure, and enjoy elevated NYHA class at the first follow-up have better outcomes. These findings need expanded validation.

Impact on daily practice

What is known? Following valvular surgery, paravalvular leak (PVL) is not uncommon. Transcatheter PVL closure is usually reserved for intermediate to high surgical risk patients in cases of symptomatic heart failure or haemolytic anaemia. What is new? In this long-term observational prospective cohort study, we have seen reasonable outcomes and improvement in symptoms according to the indication for the procedure. Aortic PVL patients have better prognosis than mitral PVL patients. What is next? More information on the correct strategy to correct PVL in these intermediate- to high-risk patients is warranted. In addition, studies comparing the different devices used for PVL may assist in our decision to treat patients with PVL.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Additional information on the procedural technique.

Supplementary Appendix 2. Procedural failure and complications.

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Supplementary data

Supplementary Appendix 1. Additional information on the procedural technique

Mitral PVLs located anterolaterally (10-12 o'clock according to the surgeons' view) were approached antegradely, through a transseptal puncture. Leaks near the atrial septum (1-5 o'clock according to the surgeons' view) were usually approached retrogradely, either through the aortic valve (if not replaced by a mechanical prosthesis) or through a surgical transapical access. Posterolateral leaks (6-9 o'clock according to the surgeons' view) were approached either way, with the transseptal approach made easier with a steerable sheath (Agilis™; St. Jude Medical, St. Paul, MN, USA). The anatomic locations of the PVL according to the clock scheme are shown in the **Central illustration**. Since the advent of 3D TEE, this was deemed mandatory for mitral PVL closure. Contrast angiography was not used at all for mitral PVL closure.

Aortic PVLs were closed retrogradely from the aorta. Unlike in mitral PVLs, contrast injections were used regularly in addition to echocardiographic monitoring. In some cases, failure of one approach led to a second and sometimes even a third attempt at PVL closure, using a different approach, device, or both.

Over the duration of the study, several changes have taken place in equipment and technique. Devices included the AMPLATZER™ Duct Occluder (ADO), the AMPLATZER™ Vascular Plug II (AVP II), the AMPLATZER™ Vascular Plug III (AVP III) (all St. Jude Medical) the Occlutech® PLD Occluder (Occlutech GmbH, Jena, Germany) and the Nit-Occlud® coils (pfm medical, Cologne, Germany). In recent years we had at our disposal a large variety of better suited devices, e.g., the AMPLATZER Plugs II and III and the Occlutech PLD device - which is the only one designed specifically for this purpose. Also, in recent years, we opted to use multiple smaller devices for aortic leak closure rather than large single ones.

Supplementary Appendix 2. Procedural failure and complications

The leading cause of procedural failure was the inability to cross the leak or to advance the equipment (10.0% of all cases, 11.8% for mitral, 7.7% for aortic PVL). Of these 12 cases, 6 had undergone successful repeat percutaneous PVL closure, 3 were directed to redo surgery, 1 patient was complicated by a tamponade and death, and 2 were treated conservatively. There were 8 cases (8.0%) of partial success - residual leak which remained moderate or above despite successful deployment of the device and at least some improvement. Of these, 7 (7.0%) were caused by remaining small PVL in addition to larger ones treated successfully. Major periprocedural complications occurred in 8.0% of the patients (9.5% for mitral, 3.8% for aortic PVL) (**Figure 1**), minor events in another 6.2% of cases (for a total of 16.3% for mitral, 12.4% for aortic PVL). Major complications included two perforations - one which resulted in a tamponade and a fatal outcome during the same day and a sealed perforation which was detected incidentally by computed tomography scan of the chest a few days later, in an asymptomatic patient; one patient who was treated by the transapical approach had suffered a dissection of the left atrium, resulting in an abortion of the procedure and surgical correction of the dissection; one ADO device was dislodged to the left atrium and was retrieved safely; there was one case of coronary air embolism which required a short resuscitation but fortunately did not result in clinically evident long-term adverse events; two significant vascular complications - one patient suffered from an inguinal bleeding and one from a retroperitoneal haemorrhage; finally there were two cases of arrhythmia - one procedure had ended due to ventricular tachyarrhythmia and one was complicated by temporary bradycardia which did not result in any adverse events with the patient being treated successfully for the PVL. One AVP II device slightly limited the degree of opening of an aortic valve leaflet, without haemodynamic or clinical consequences. Minor events included the following: a small haematoma from the radial arterial line; one patient who suffered from leaflet entrapment causing the procedure to be aborted without any clinical sequelae; one case of valve disc motion interference which was improved following release of the PVL occluder device; an allergic reaction manifested by a skin rash treated by steroids and antihistamines; another case involving contact dermatitis treated by topical steroids; and a mild case of haematuria in one patient with benign prostatic hyperplasia, who recovered following conservative treatment.