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Surgery Versus Transcatheter Interventions for Significant Paravalvular Prosthetic Leaks

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ABSTRACT

OBJECTIVES This study sought to assess the relative merit of surgical correction (SC) versus transcatheter reduction on long-term outcomes in patients with significant paravalvular leak (PVL) refractory to medical therapy.

BACKGROUND PVL is the most frequent dysfunction following prosthetic valve replacement. Although repeat surgery is the gold standard, transcatheter reduction (TR) of PVL has been associated with reduced mortality.

METHODS From 1994 to 2014, 231 patients underwent SC (n = 151) or TR (n = 80) PVL correction. Propensity matching and Cox proportional hazards regression models were used to assess the effect of either intervention on long-term rates of all-cause death or hospitalization for heart failure. Survival after TR and SC were further compared with the survival in a matched general population and to matched patients undergoing their first surgical valve replacement.

RESULTS Over a median follow-up of 3.5 years, SC was associated with an important reduction in all-cause death or hospitalization for heart failure compared with TR (hazard ratio: 0.28; 95% confidence interval: 0.18 to 0.44; $p < 0.001$). There was a trend towards reduced all-cause death following SC versus TR (hazard ratio: 0.61; 95% confidence interval: 0.37 to 1.02; $p = 0.06$). Neither intervention normalized survival when compared with a general population or patients undergoing their first surgical valve replacement.

CONCLUSIONS In patients with significant prosthetic PVL, surgery is associated with better long-term outcomes compared with transcatheter intervention, but results in important perioperative mortality and morbidity. Future studies are needed in the face of increasing implementation of transcatheter PVL interventions across the world. (J Am Coll Cardiol Intv 2017;10:1959–69) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

NYHA = New York Heart Association

PVL = paravalvular leak

SC = surgical correction

TR = transcatheter reduction

Paravalvular leak (PVL) occurs after valve replacement when there is an incomplete apposition of the prosthesis's sewing ring to the native annulus PVL occurs in 5% and 10% of patients following mitral and aortic valve replacement, respectively, and represents the most frequent nonstructural valve dysfunction (1,2). Although mild PVL could be asymptomatic, moderate-to-severe regurgitation is associated with heart failure (HF), refractory hemolytic anemia, and a high long-term mortality (3). Therefore, surgical correction (SC) of PVL is indicated in these patients, as it has been associated with improved event-free survival when compared with conservative treatment (4,5).

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Recently, transcatheter reduction (TR) of PVL has emerged as an alternative therapy for patients deemed unsuitable for a redo surgery (6). In most single-center series and registries, the procedure reduces the PVL severity and has been associated with variable success rates (7–11). Although the global experience with TR is limited to nonrandomized studies, the available evidence suggests that a successful procedure improves survival and functional class when compared with conservative treatment (12).

With recent advances in transcatheter techniques and the reduction in surgical mortality and morbidity following repeat cardiac surgery, there is a lack of evidence in the respective role of the surgical and the transcatheter approaches to treat severe PVL. In addition, few studies have compared these interventions (13,14). We aimed to assess the relative merit of SC and TR on outcomes at both short- and long-term in symptomatic patients with significant PVL.

METHODS

PATIENT POPULATION. From the start of our transcatheter program (March 1995) to December 2014, consecutive patients with significant PVL who underwent either SC or TR were identified using a dedicated institutional database for prosthetic valve surgery (15) and the discharge summary database, which included the diagnostic and intervention codes from hospital discharge claims as provided to our governmental health administrative database (Régie de l'Assurance Maladie du Québec) (16). During this period, procedures were restricted to 4 surgeons and 2 interventional cardiologists. A PVL was deemed significant if responsible for functionally limiting HF (New York Heart Association [NYHA] functional class III or IV despite guideline-directed medical therapy) or for hemolytic anemia requiring repeated transfusions. Patients were excluded if operated for an active infective endocarditis or if undergoing a surgical PVL correction as part of a cardiac surgery for another primary indication.

DATA COLLECTION AND FOLLOW-UP. Baseline characteristics, procedural details, and outcomes were collected from medical records and from the dedicated prospective database linked to our institutional prosthetic valve cohort (15). As part of this cohort, all patients undergoing a surgical prosthetic valve replacement are followed with an annual visit or phone interview. In addition, a questionnaire is sent annually to their referring physicians. Data collected at follow-up included death, NYHA functional class, need for blood transfusions, hospitalization for HF, and the need for repeated surgery or transcatheter intervention. As this was a retrospective analysis conducted as per institutional guidelines for data security and privacy, a waiver of consent was granted by the Institutional Review Board.

CLINICAL DEFINITIONS. All clinical definitions and endpoints are in line with recently reported PVL Academic Research Consortium Expert Statement (17). Significant HF was defined as a NYHA functional class of III or greater. Significant hemolysis was defined as anemia secondary to intravascular hemolysis at a grade III or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events scale (18). Grade III was defined as severe but not life-threatening anemia (hemoglobin <8.0 g/dl) requiring hospitalization, limiting the patient's ability to care for himself or herself and necessitating transfusions.

A PVL is defined as an abnormal communication between the valvular prosthesis sewing ring and the native tissues that results in a regurgitant jet (19). The severity of the regurgitation was quantified by echocardiography as recommended by the American Society of Echocardiography practice guidelines (20–24). The regurgitant jets were located using the clock-face system in the "surgical view" and their extent was quantified using the number of "leaking hours" involved in the circumferential ring (25). Multiple leaks were defined whenever "leaking hours" were not consecutive.

In patients who underwent SC, procedural success was defined as correction of the regurgitation (residual PVL no greater than mild), freedom from periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident during the index hospitalization. In patients who

underwent TR, procedural success was defined as the delivery of a reduction device with no mechanical prosthesis interference, leading to a post-procedural PVL regurgitation no greater than moderate (≤+2 or 4) and freedom from periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident. Technical success was defined as a delivery of a reduction device without prosthesis interference and irrespective of PVL reduction obtained. In both SC and TR, clinical success was defined as post-procedural NYHA functional class of II or less or improved hemolytic anemia as shown by any improvement to grade II or lower on the National Cancer Institute Common Terminology Criteria for Adverse Events scale.

SC AND TR TECHNIQUES. The prosthesis was replaced in cases of extensive PVL or prosthesis dehiscence. If the site of PVL was small and the prosthesis was otherwise well seated, and surgical repair was performed using interrupted pledged sutures. Most surgeries were performed using a standard sternotomy approach. All procedures were monitored by transesophageal echocardiography for the localization of the PVL and for the adequacy of repair.

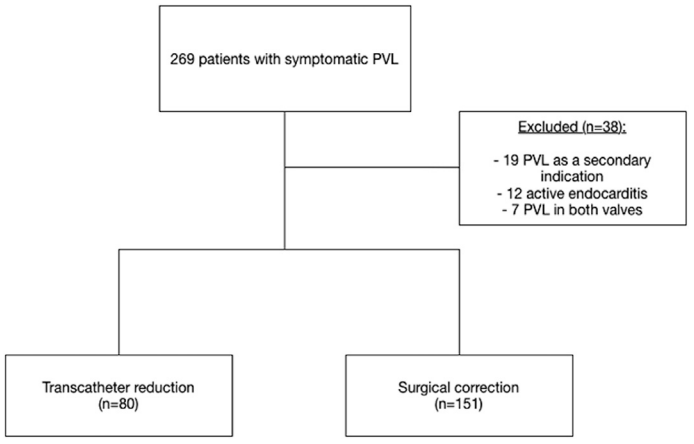
All TR procedures were performed under general anesthesia. Fluoroscopy and transesophageal echocardiography guidance were used for device positioning and to confirm the absence of prosthetic leaflet impingement before final device release. Technical details have been reported previously (26). Briefly, aortic PVLs were performed using a retrograde approach via the femoral artery. Most of mitral PVLs were performed using a femoral transvenous transseptal access.

STATISTICAL ANALYSIS. Continuous variables are described as mean ± SD or median (interquartile range) as appropriate and compared using *t* tests or the Wilcoxon rank sum tests accordingly. Categorical variables are presented as number (percentage), and compared using either chi-square or Fisher exact tests. Kaplan-Meier methods were used to illustrate the freedom from the combined endpoint of all-cause death and hospitalization for HF (primary endpoint), and the freedom from of all-cause death (secondary endpoint) for patients who underwent TR or a SC. No data imputation was performed. Data analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

OUTCOMES MODELING. This study was developed to assess the hypothesis that in patients with significant PVL, surgery would be superior to transcatheter therapy at reducing mortality and decompensated HF at long-term. This combined endpoint was selected as it was felt to better represent the importance and the burden of the disease in the perspective of the patients' oriented outcomes. We developed multivariable models to adjust for known or expected confounding variables in the relation between the PVL treatment group and outcomes. For each model, candidate variables were pre-specified using either clinical experience or previously reported risk factors. The first model was developed to identify predictors of undergoing a TR of PVL (vs. an SC). The purpose of this model was to derive a treatment propensity score to adjust for case mix in the second model, which ascertained the relationship between the type of intervention (SC vs. TR) and the clinical endpoints.

The first model used a logistic regression to identify variables predicting allocation to either transcatheter or surgical groups. The model compared the 80 patients who underwent a TR to the 158 patients who underwent a SC. The candidate predictors included medical history (number of prior cardiac surgery), the primary indication for intervention (hemolysis, congestive HF or both) and the anatomic variables (extension for PVL, multiplicity of leaks and septal location in the case of mitral PVL). For each patient, we derived a propensity score representing the likelihood of undergoing a TR rather than a SC. Adequacy of the propensity score for balancing confounding variables was assessed by confirming that no candidate predictors were significantly different between SC and TR of PVL after adjustment for the propensity score. The model discrimination was evaluated with the *c*-index.

FIGURE 1 Patient Flow Chart



Study flow chart. PVL = paravalvular leak.

TABLE 1 Baseline Characteristics of Patients Undergoing a Surgical Correction and a Transcatheter Reduction

	Surgical Correction (n = 151)	Transcatheter Reduction (n = 80)	p Value
PVL location			0.010
Mitral	98 (64.9)	65 (81.3)	
Aortic	53 (35.1)	15 (18.8)	
Demographics			
Age, yrs	64.0 (54.1-70.7)	67.9 (62.3-74.8)	<0.001
Male	95 (62.9)	40 (50.0)	0.06
BMI, kg/m^2	26.1 (22.2-28.0)	25.0 (21.7-27.8)	0.30
Medical history			
Hypertension	53 (37.1)	48 (60.0)	0.001
Diabetes mellitus	17 (11.4)	13 (16.3)	0.28
Chronic renal insufficiency*	75 (49.7)	58 (72.5)	<0.001
COPD	26 (18.1)	20 (25.0)	0.22
Ischemic heart disease†	38 (25.2)	31 (38.8)	0.03
PCI	7 (4.7)	5 (6.5)	0.56
CABG	12 (8.1)	19 (24.7)	<0.001
Peripheral vascular disease	17 (11.8)	7 (8.9)	0.50
Atrial fibrillation/flutter	76 (52.8)	64 (80.0)	<0.001
Permanent pacemaker	31 (20.5)	34 (43.6)	<0.001
Presenting characteristics			
NYHA functional class III-IV	122 (80.8)	65 (81.3)	0.93
LVEF, %	60 (55.0-60.0)	60 (51.5-60.0)	0.97
PASP, mm Hg	48 (36.0-53.0)	52 (48.5-68.5)	<0.001
Indication for intervention			
Heart failure	100 (66.2)	52 (65.0)	
Hemolysis	2 (1.3)	1 (1.3)	0.98
Both	49 (32.5)	27 (33.8)	
Procedural risk for cardiac surgery			
Number of prior cardiac surgeries			
1	79 (52.3)	26 (32.5)	
2	46 (30.5)	23 (28.8)	<0.001
≥3	26 (17.2)	31 (38.8)	
EuroSCORE (logistic)	10.2 (6.0-16.6)	16.4 (11.4-27.9)	<0.001
EuroSCORE-2 (logistic)	6.2 (3.6-10.3)	9.2 (6.0-13.2)	<0.001
Parsonnet score	22.6 (14.0-38.8)	30.1 (18.9-39.7)	0.15

Values are n (%) or median (interquartile range). *Defined as creatinine clearance <60 ml/min. †Defined as any coronary stenosis >50%.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; PVL = paravalvular leak.

The second model used a Cox proportional hazard regression and investigated the association between the type of PVL intervention (either SC or TR) and endpoints at longest available follow-up. The model accounted for clinical variables known to predict adverse outcomes in patients with HF and was also adjusted for the propensity score derived from the first model. Candidate predictors that showed marginal associations to the outcome on univariate testing ($p < 0.20$) were included in the multivariable analyses and a backward stepwise selection method was conducted. The candidate predictors used included demographics (age, sex), medical history (diabetes, renal insufficiency), procedural characteristics (aortic vs. mitral PVL, urgent procedure, defined as an intervention performed during an admission for clinical impairment, rather than electively), and left ventricular ejection fraction and pulmonary artery systolic pressure. The proportionality assumption was assessed by adding a time-dependent variable to the model. The significance of multivariable regression coefficients was determined with the Wald chi square. Patients who were missing predictor or outcome data for a given model were omitted from that model; no data imputation was performed. None of the modeled variables had more than 2% of missing values.

SENSITIVITY ANALYSES. Because of the variable success rate with the TR, we repeated stratified survival analyses comparing patients who underwent a successful versus failed TR to those who underwent SC.

SURVIVAL OF MATCHED POPULATIONS. To assess the relative and absolute merit of SC and TR of PVL, the survival of patients included in this series was compared with the survival of the general population and to the survival of patients undergoing a first prosthetic valve replacement. Expected survival of a sex- and age-matched general population was obtained using the Hakulinen method (27). General population survival estimates were generated from publicly available Province of Quebec survival tables for each patient according to age and sex. Survival of a matched first-do heart valve replacement cohort was generated using the database of our institutional prosthetic valve cohort (n = 8,515). Patients with and without PVL were matched 1:3 according to sex, age, valve position (mitral or aortic), and prosthesis types (mechanical or biological).

RESULTS

STUDY POPULATION. A total of 231 patients were included, of which 151 (65.4%) underwent SC and 80 (34.6%) underwent TR (Figure 1). A majority of patients underwent an intervention for PVL in the mitral position (n = 163, 70.6%). The median follow-up for all-cause death, rehospitalization, reintervention, and functional class was 3.5 (interquartile range: 0.5-7.2) years, accounting for a total of 1,072 patient-years. Follow-up at 1 year was complete for 99% of patients.

BASELINE CHARACTERISTICS. The baseline characteristics were noticeably different between SC and TR patients (Table 1). Patients who underwent a TR were older and more likely to have a history of chronic renal insufficiency, ischemic heart disease, atrial fibrillation, and pulmonary hypertension. In addition, patients treated by SC had undergone fewer prior cardiac surgeries (1.7 vs. 2.2; $p < 0.001$) and had lower pre-operative European System for Cardiac Operative Risk Evaluation score and Parsonnet scores ($p < 0.001$). However, NHYA functional class, hemolysis, and left ventricular ejection fraction were similar in both groups.

PROCEDURAL CHARACTERISTICS. The procedural characteristics for patients who underwent an SC or TR are summarized in Table 2. Patients treated by TR were more likely to have their PVL graded as moderate to severe (+3) or greater at the baseline. Sixty-eight (45%) patients treated by surgery underwent concomitant surgical procedures, including tricuspid valve annuloplasty (29 patients, 19.2%), coronary artery bypass grafting (coronary artery bypass grafting, 21 patients, 13.9%) or another valve replacement (15 patients, 9.9%). No patients treated by TR underwent concomitant transcatheter interventions.

PERIPROCEDURAL OUTCOMES. The majority of patients (99.3%) treated by SC had no or minimal PVL following their surgery whereas one-half (50%) of patients treated by TR had greater than mild residual PVL. In-hospital all-cause death, myocardial infarction, and cerebrovascular accident were not different between the 2 groups (6.6% in the SC group vs. 2.5% in the TR group; $p = 0.23$; 2.3% in the SC group vs. 0% in the TR group; $p > 0.99$; and 4.6% in the SC group vs. 0% in the TR group; $p = 0.10$; respectively). As per our definition, periprocedural success was therefore achieved in 121 (80.1%) of SC patients compared with 44 (55%) of TR patients ($p < 0.001$). Specific surgical and transcatheter procedural characteristics, as well as their complications rates are presented in Online Tables 1 and 2, respectively.

ALL-CAUSE DEATH AND HOSPITALIZATION FOR HF. At longest available follow-up, SC was associated with a 72% reduced risk for death or hospitalization for HF (Table 3). Similarly, there was a lower incidence of death or hospitalization for HF at 1 year and 3 years (adjusted hazard ratio: 0.45; 95% confidence interval: 0.26 to 0.77; and hazard ratio: 0.33; 95% confidence interval: 0.20 to 0.54, respectively; $p < 0.001$) (Figure 2A, Table 3).

TABLE 2 Procedural Characteristics and Outcomes for Patients Undergoing a Surgical Correction and a Transcatheter Reduction

	Surgical Correction (n = 151)	Transcatheter Reduction (n = 80)	p Value
Prosthesis type			
Biological	14 (9.3)	7 (9.0)	0.94
Mechanical	137 (90.7)	71 (91.0)	
Leak extension*, h	4 (3–4)	4 (2–5)	0.33
Multiple leaks	20 (13.3)	10 (12.5)	0.87
Type of intervention†			
Elective	110 (72.9)	58 (72.5)	0.96
Urgent	41 (27.2)	22 (27.5)	
Critical state‡	5 (3.3)	0 (0.0)	0.17
Concomitant procedures	68 (45.0)	0 (0.0)	<0.001
Regurgitation before			
Mild (+1)	3 (2.0)	2 (2.7)	<0.001
Moderate (+2)	65 (43.6)	10 (13.3)	
Moderate to severe (+3)	71 (47.7)	45 (60.0)	
Severe (+4)	10 (6.7)	18 (24.0)	
Regurgitation after			
None	144 (96.6)	7 (11.3)	<0.001
Mild (+1)	4 (2.7)	24 (38.7)	
Moderate (+2)	1 (0.7)	13 (21.0)	
Moderate to severe (+3)	0 (0.0)	18 (29.0)	
Technical success	–	55 (68.8)	NA
Procedural success§	121 (80.1)	44 (55.0)	<0.001
Death	10 (6.6)	2 (2.5)	0.23
Myocardial infarction	3 (2.3)	0 (0.0)	1.00
Cerebrovascular accident	7 (4.6)	0 (0.0)	0.10
Length of hospital stay, days	9 (7–14)	4 (1–9)	<0.001

Values are n (%) or median (interquartile range). *Expressed as the number of leaking hours in the circumferential ring. †Urgent interventions were defined as those performed during any admission for clinical impairment rather than electively. ‡Defined as per EuroSCORE II criteria as ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure (anuria or oliguria <10 ml/h). §In patients who underwent surgical correction, defined as residual PVL no greater than mild, free of periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident. In patients who underwent transcatheter reduction, defined as the delivery of a reduction device with no mechanical prosthesis interference, leading to a residual PVL regurgitation no greater than moderate (≤+2) and free of periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident. Myocardial infarction and cerebrovascular accident are defined as per Valve Academic Research Consortium-2 criteria (31).

NA = not applicable; other abbreviations as in Table 1.

After adjustment, there was a tendency toward a reduction in all-cause mortality after SC when compared with the TR group at the longest available follow-up (adjusted hazard ratio for SC: 0.61; 95% confidence interval: 0.37 to 1.02; $p = 0.06$). However, there was no difference at 1 and 3 years between the 2 groups (Table 3).

Neither the TR nor the SC succeeded at normalizing the risk of all-cause death when compared with a general population or to patients undergoing their first surgical valve replacement. However, when considering patients who survived the PVL procedure, survival of patient in the SC group was no different to the general population or patients

TABLE 3 Outcomes for Surgical PVL Correction Versus Transcatheter PVL Reduction

	Surgical PVL Correction (n = 151)		Transcatheter PVL Reduction (n = 80)		Unadjusted Analyses		Adjusted Analyses*	
	Patients With Event	KM Estimate	Patients With Event	KM Estimate	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause death or hospitalization for heart failure								
1 yr	26 (17.2)	18.5	35 (43.8)	47.3	0.35 (0.21–0.58)	<0.001	0.45 (0.26–0.77)	0.003
3 yrs	34 (22.5)	25.3	48 (60.0)	69.2	0.28 (0.18–0.44)	<0.001	0.33 (0.20–0.54)	<0.001
Longest follow-up	68 (45.0)	–	57 (71.3)	–	0.26 (0.17–0.38)	<0.001	0.28 (0.18–0.44)	<0.001
All-cause death								
1 yr	21 (13.9)	14.9	14 (17.5)	19.8	0.80 (0.41–1.57)	0.52	1.30 (0.64–2.67)	0.47
3 yrs	26 (17.2)	19.2	25 (31.3)	40.0	0.50 (0.29–0.87)	0.014	0.79 (0.43–1.44)	0.44
Longest follow-up	53 (35.1)	–	38 (47.5)	–	0.41 (0.27–0.64)	<0.001	0.61 (0.37–1.02)	0.06

Values are n (%) or %, unless otherwise indicated. *Models adjusted for the propensity of undergoing a transcatheter PVL reduction (number of prior cardiac surgery, hemolysis, extent of PVL, location and multiplicity of leaks), the type of intervention (transcatheter reduction vs. surgical correction), age, sex, diabetes, creatinine clearance, left ventricle ejection fraction, pulmonary artery systolic pressure and procedural urgency.

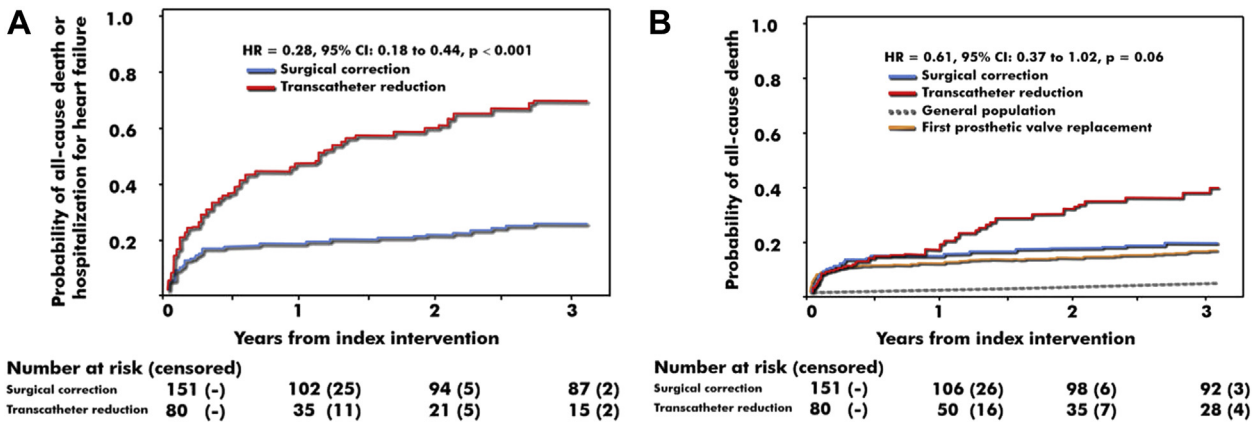
CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; PVL = paravalvular leak.

who underwent a first surgical valve replacement (Figure 2B).

IMPACT ON LONG-TERM SYMPTOMS. SC resulted in better improvement in NYHA functional class. Indeed, at the longest available follow-up, 76.4% of SC patients were in NYHA functional class <II to IV versus 51.3% in the TR group ($p < 0.001$). Hemolytic anemia improved in all patients treated by surgery compared with only 7 (25%) patients treated with TR ($p < 0.001$). New or worsening hemolytic anemia was observed in 15 (18.8%) patients who underwent TR, with no relation with the type of device implanted. Fewer reinterventions were required in patients initially treated with SC (Figure 3). Noticeably, persistence or worsening hemolysis was responsible for 50% of crossovers to surgery in patients initially treated with transcatheter therapy.

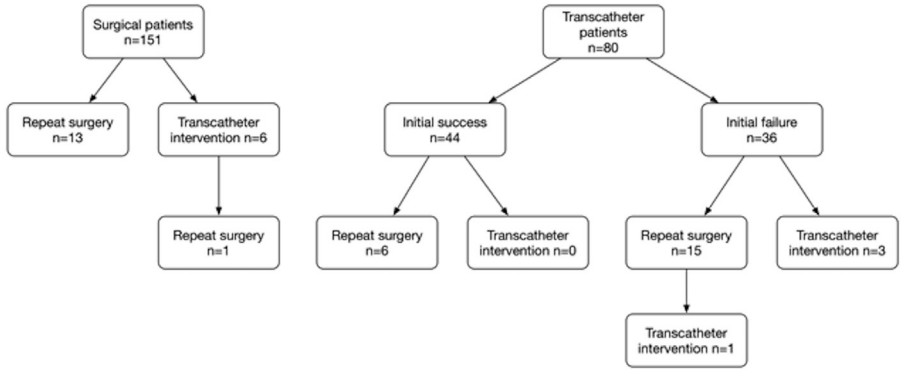
IMPACT OF SUCCESSFUL OR FAILED TR IN LONG-TERM OUTCOMES. After adjustment, SC was associated with a 52% and 79% reduced risk for all-cause death or hospitalization for HF, compared with successful or unsuccessful TR, respectively

FIGURE 2 Probability of the Combined Endpoint of All-Cause Death or Hospitalization for Congestive Heart Failure and Probability of All-Cause Death in the Surgical Correction and the Transcatheter Reduction Groups



(A) Probability of all-cause death or hospitalization for heart failure in the surgical correction group **(blue line)** and in the transcatheter reduction group **(red line)**. **(B)** Probability of all-cause death in the surgical correction group **(blue line)** and in the transcatheter reduction group **(red line)**. All-cause death in a sex- and age-matched general population **(dashed gray line)** and all-cause death in a sex-, age- and location-matched (mitral vs. aortic) population with prior heart valve replacement **(orange line)** are shown. Hazard ratios are presented for the longest available follow-up. CI = confidence interval; HR = hazard ratio.

FIGURE 3 Need for Reintervention



Need for reintervention in the surgical correction and successful and failed transcatheter groups.

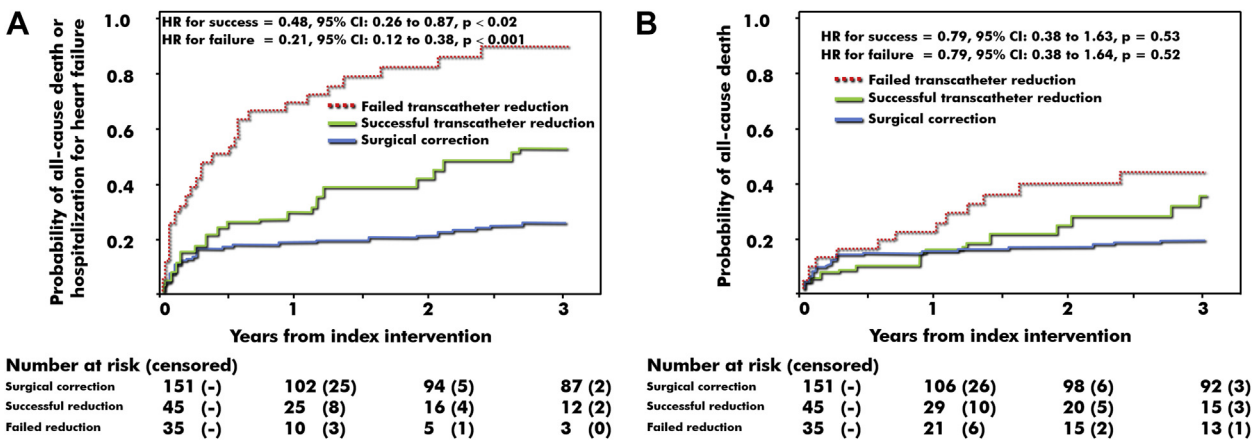
(Figure 4A, Table 4). However, the rates of all-cause death were not different between SC and a successful TR or a failed TR (Figure 4B, Table 4).

DISCUSSION

The relative merit of surgery over transcatheter therapy study should be interpreted with caution given the important case mix presented between study groups. Both in adjusted and unadjusted comparison, surgery is associated with an improvement in the combined occurrence of all-cause death and hospitalization for HF when compared with transcatheter intervention. Despite being associated with better long-term outcomes, surgery results in important perioperative mortality and morbidity and seems only beneficial well beyond 1 year of expected survival. These findings have important clinical implications given the lack of prior evidence to guide the decision making in the assignment of either surgery or transcatheter therapy in this patient population. This is all the more important in view that the present study represents the largest PVL series comparing SC and TR.

Few studies have compared surgery and transcatheter therapy in PVL. Recently, Angulo-Llanos et al. (13) compared 36 patients undergoing PVL SC

FIGURE 4 Probability of the Combined Endpoint of All-Cause Death or Hospitalization for Congestive Heart Failure and Probability of All-Cause Death in the Surgical Correction and Successful and Failed Transcatheter Reduction Groups



Probability of **(A)** all-cause death or hospitalization for heart failure and of **(B)** all-cause death in the surgical correction group **(blue line)**, successful transcatheter reduction group **(green line)**, and failed transcatheter reduction group **(dashed red line)**. CI = confidence interval; HR = hazard ratio.

TABLE 4 Sensitivity Analyses: Outcomes Analysis for Successful and Failed Transcatheter PVL Reduction Versus Surgical Correction

	Surgical PVL Correction (n = 151)		Successful Transcatheter PVL Reduction (n = 45)		Failed Transcatheter PVL Reduction (n = 35)		Unadjusted Analyses			Adjusted Analyses*		
	Patients With Event	KM Estimate	Patients With Event	KM Estimate	Patients With Event	KM Estimate	Transcatheter Reduction Result	HR (95% CI)	p Value	Transcatheter Reduction Result	HR (95% CI)	p Value
All-cause death or hospitalization for heart failure												
1 yr	26 (17.2)	18.5	12 (26.7)	29.3	23 (65.7)	68.9	Success	0.62 (0.32–1.24)	0.18	Success	0.72 (0.35–1.46)	0.36
							Failure†	0.21 (0.12–0.36)	<0.001	Failure†	0.29 (0.16–0.54)	<0.001
3 yrs	34 (22.5)	25.3	19 (42.2)	52.0	29 (82.9)	89.1	Success	0.45 (0.26–0.80)	0.006	Success	0.48 (0.26–0.87)	0.017
							Failure†	0.16 (0.10–0.27)	<0.001	Failure†	0.21 (0.12–0.38)	<0.001
All-cause death												
1 yr	21 (13.9)	14.9	6 (13.3)	15.3	8 (22.9)	25.5	Success	1.08 (0.43–2.66)	0.88	Success	1.48 (0.58–3.77)	0.41
							Failure	0.59 (0.26–1.34)	0.21	Failure	1.17 (0.49–2.81)	0.72
3 yrs	26 (17.2)	19.2	12 (26.7)	37.0	13 (37.1)	44.5	Success	0.60 (0.30–1.20)	0.15	Success	0.79 (0.38–1.63)	0.53
							Failure	0.41 (0.21–0.79)	0.008	Failure	0.79 (0.38–1.64)	0.52

Values are n (%) or %, unless otherwise indicated. *Models adjusted for the propensity of undergoing a transcatheter paravalvular leak (PVL) reduction (number of prior cardiac surgery, hemolysis, extent of PVL, location and multiplicity of leaks), the type of intervention (transcatheter reduction vs. surgical correction), age, sex, diabetes, creatinine clearance, left ventricle ejection fraction, pulmonary artery systolic pressure, and procedural urgency. †Statistically significant differences ($p < 0.05$) were found between successful and failed transcatheter reduction interventions.

Abbreviations as in Table 3.

to 51 transcatheter patients. There were no differences in the adjusted survival free from death or hospitalization for HF. The discrepancy in survival with our study could be explained by a higher early mortality in their surgical group (>30%) when compared with our series (<10%) (28). In parallel, Taramasso et al. (29) suggested that the transapical reduction of PVL is less morbid than surgery in the early period (<30 days) whereas no long-term outcomes were presented. Finally, in a series of 35 patients, Pinheiro et al. (30) showed a tendency toward a reduction in mortality with surgery compared with transcatheter therapy at 1 year (0% vs. 20%; $p = 0.08$), which closely resembles the survival reported in our study. Recently, Wells et al. (14) found in 114 patients that transcatheter intervention and surgery had a nonsignificantly different survival at 1 year (83.9% vs. 75.9%; $p = 0.28$), despite adjusting for baseline characteristics. No extended follow-up information beyond 1 year was provided, but the series had the particularity to include patients with active endocarditis and with pulmonary PVL, for whom virtually no information was available previously.

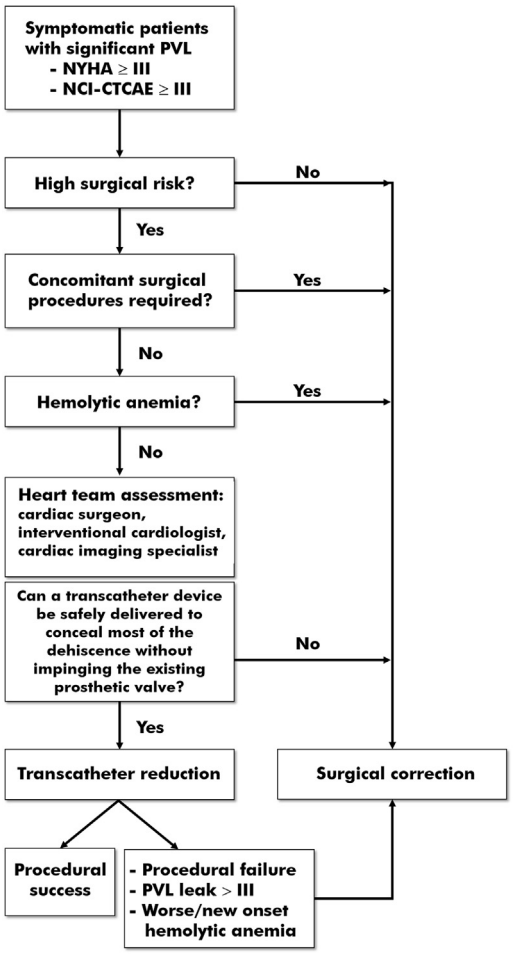
A previously published meta-analysis from Millán et al. (12) showed that a successful TR is associated with a significant improvement in long-term mortality, functional class, and hemolytic anemia when compared with failed TR. Similarly, we observed that a successful TR seems to favorably inflect outcomes compared with a failed reduction, especially in the early years after the intervention. Indeed, there was no difference in the rate of overall death between SC and a successful TR up to 3 years of follow-up. However, when compared with SC, a successful TR was associated with a higher incidence of death and hospitalization for congestive HF. This highlights the impact of residual PVL despite a successful TR as the majority of these patients are left with a mild or moderate paravalvular regurgitation. Therefore, in parallel to recent advances in transcatheter therapies in structural heart disease, further research leading to the development of a specific transcatheter PVL closure device is needed to improve long-term outcomes in this patient's population (6).

In clinical practice, the allocation to SC or TR is not random but typically relates to the perioperative risk and clinical evaluation. Therefore, despite propensity adjustment and multivariate analyses, it remains difficult to fully control for the indication bias. On the one hand, patients selected for surgery had lower procedural risk and were often operated for concomitant indications (e.g., coronary artery bypass grafting or prosthetic valve replacement). On the other hand, patients with initial failed TR frequently underwent subsequent surgical treatment. Despite these confounders, our results bring new insights that could inform clinical practice and trial design in the future. First, we observed that surgery is associated with higher early mortality and requires more than a year to match the clinical benefits observed following successful TR (Table 4). Second, rehospitalization for congestive HF is frequent in this patient population and was the most important driver of the combined endpoint used in our primary analysis. Thirdly, TR might not be an effective therapy to treat

hemolysis and can even worsen this condition following incomplete PVL reduction. The comparison of surgery or transcatheter therapy in patients with similar risk profiles would likely minimize the difference in outcomes observed between both groups. Finally, because none of the available therapies normalized survival, timing of intervention in these patients should be reconsidered. It could be hypothesized that therapy was attempted too late in most patients, therefore precluding normalization of survival.

In the original treatment algorithm proposed by Turi (31), patients with severe prosthetic PVL with low or moderate surgical risk and those with major dehiscence should be referred for surgery, whereas those at high surgical risk or with unfavorable anatomic characteristics for surgery (severe mitral annular calcification or porcelain aorta) should be treated by TR. Adding to this algorithm, our study suggests that the risk-benefit balance should also take into consideration the presence of additional cardiac conditions that warrant SC, such as coronary artery disease or other valve dysfunction (**Figure 5**). As highlighted by previous studies (10,32), we also recommend that patients with severe hemolytic anemia should undergo SC as the transcatheter approach failed to improve this condition in our cohort. Nonetheless, given the improvement in overall survival in successful TR, we believe that transcatheter intervention should be initially attempted in high-risk surgical candidates with limited life expectancy and favorable anatomic features for a transcatheter approach. In such cases, a specialized heart team (including a cardiac surgeon, an interventional cardiologist, and a cardiac imaging specialist) should review the case and evaluated the safety and potential efficacy of a TR. Patients treated with TR should be closely followed-up and be reassessed for surgery in case of significant residual PVL leak (grade 3 or higher), poor functional improvement, or exacerbated or new onset hemolytic anemia. Indeed, previous TR should not be considered a contraindication for repeat surgery.

FIGURE 5 PVL Treatment Proposed Algorithm



Proposed treatment algorithm for symptomatic patients with significant PVL. NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; PVL = paravalvular leak.

STUDY LIMITATIONS. The present investigation is a single-center retrospective study with the inherent limitations of this study design. Several assumptions remain unverified at this moment. For instance, we assumed that hemolysis and HF conveyed the same significance and that mitral versus aortic PVL carried the same prognosis (33,34). Likewise, we assumed that interventions performed at the start of our series yielded the same benefit as the interventions carried later in time, whereas learning curves have been documented (35) and better imaging techniques and devices are currently available. To minimize biases, we adjusted for key variables known to affect survival and performed sensitivity analyses.

Given the variability and the lack of standardization in deciding which patients would benefit from surgery versus transcatheter therapy, treatment assignment cannot be thoroughly predicted retrospectively, despite propensity adjustment. Transcatheter PVL closure techniques and operator experience have evolved throughout the years. Although we cannot exclude that newer devices result in better clinical outcomes, we believe in fact that they have a limited

effect other than extending by which they decrease the severity of the leak, which has been properly phenotyped with the concept of procedural success and accounted for in the multivariate models and the stratified sensitivity analysis. For all these reasons, extrapolation of our results to broader populations should be made with caution.

CONCLUSIONS

In the largest study comparing surgical and transcatheter interventions to treat PVL, we found that despite important perioperative mortality and morbidity, surgery remains associated with better long-term outcomes, mostly driven by a reduction in hospitalization for HF. As transcatheter techniques are improving and expanding across the world, future studies are needed.

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PERSPECTIVES

WHAT IS KNOWN? Significant PVL after prosthetic valve replacement is associated with high mortality and morbidity. Although SC is the gold-standard treatment, TR has emerged as a less invasive alternative but few data is available comparing both techniques.

WHAT IS NEW? Being the largest series reported, our study provides new evidence on clinical outcomes after SC or TR; we found that despite higher perioperative mortality, surgery is associated with better long-term outcomes, mostly driven by a reduction in hospitalizations for HF.

WHAT IS NEXT? Further research comparing SC with TR using specific PVL devices in patients with a similar risk profile is needed to better define the role of both techniques and to improve long-term outcomes in this patient's population.

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APPENDIX For supplemental tables, please see the online version of this paper.