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Does pre-existing aortic regurgitation protect from death in patients who develop paravalvular leak after TAVI?

Andrea Colli [a,*,1], Laura Besola [a,1], Stefano Salizzoni [b], Dario Gregori [a], Giuseppe Tarantini [a], Marco Agrifoglio [c], Alaide Chieffo [d], Tommaso Regesta [e], Davide Gabbieri [f], Francesco Saia [g], Corrado Tamburino [h], Flavio Ribichini [i], Orazio Valsecchi [j], Bruno Loi [k], Alessandro Iadanza [l], Miroslava Stolcova [m], Alessandro Minati [n], Gianluca Martinelli [o], Francesco Bedogni [p], Anna Petronio [q], Michele Dallago [r], Antioco Cappai [s], Augusto D'Onofrio [a], Gino Gerosa [a], Mauro Rinaldi [b]

[a] Department of Cardiology, Thoracic and Vascular Sciences, University of Padua, Padua, Italy
[b] Division of Cardiac Surgery, San Giovanni Battista Hospital 'Molinette', University of Turin, Turin, Italy
[c] Department of Clinical Sciences and Community Health, Cardiac Surgery, University of Milan, Centro Cardiologico Monzino Hospital, Milan, Italy
[d] Division of Metabolic and Cardiovascular Sciences, San Raffaele Scientific Institute, Milan, Italy
[e] Division of Cardiac Surgery, San Martino University Hospital, University of Genova, Genova, Italy
[f] Clinical Surgical Cardiology and Thoracic Vascular Department, Hesperia Hospital, Modena, Italy
[g] Department of Cardiology, Policlinico S. Orsola-Malpighi, University of Bologna, Bologna, Italy
[h] Division of Cardiology, Ferrarotto Hospital, Catania, Catania, Italy
[i] Division of Cardiology of the Department of Medicine, University of Verona, Verona, Italy
[j] Cardiovascular Department, AO Papa Giovanni XXIII, Bergamo, Italy
[k] Interventional Cardiology Unit, AO Brotzu, Cagliari, Italy
[l] Department of Cardiovascular Diseases, Le Scotte University Hospital, University of Siena, Siena, Italy
[m] Interventional Cardiology Unit, Careggi University Hospital, Florence, Italy
[n] Division of Cardiac Surgery, Azienda Ospedaliera-Universitaria, Trieste, Italy
[o] Division of Cardiac Surgery, Santa Maria Hospital, Bari, Italy
[p] Department of Cardiology, Clinical Institute S. Ambrogio, Milan, Italy
[q] Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[r] Division of Cardiology, S. Chiara Hospital, Trento, Italy
[s] Division of Cardiac Surgery, Humanitas Research Hospital, Milan, Italy

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ABSTRACT

Objective: The aim of this study was to investigate interactions among pre-procedural aortic regurgitation (AR), post-procedural paravalvular leak (PVL) and long-term clinical outcomes.
Methods and results: We analyzed data prospectively collected in the Italian Transcatheter balloon-Expandable Registry (ITER) on aortic stenosis (AS) patients. The degree of pre-procedural AR and post-procedural PVL was stratified as: absent/trivial, mild, and moderate/severe. VARC definitions were applied to outcomes. Of 1708 patients, preoperatively, AR was absent/trivial in 40% of the patients, mild in 42%, and moderate in 18%. Postoperatively, PVL was moderate–severe in 5%, mild in 32% of patients, and absent/trivial in 63%. Clinical follow-up, median 821 days (IQR 585.75), was performed in 99.7% of patients. PVL, but not preoperative AR, was a major predictor of adverse outcome (HR 1.33, CI 95% 0.9–2.05, $p = 0.012$ for mild PVL, HR 1.36, CI 95% 0.9–2.05, $p < 0.001$ for PVL ≥ moderate and OR 1.04, $p = 0.97$ respectively). Patients with moderate–severe PVL and preoperative left ventricle (LV) dilatation (LVEDVi > 75 ml/m^2) showed better survival than those without dilatation (HR 8.63, $p = 0.001$).
Conclusions: In patients with severe AS treated with balloon-expandable TAVI, the presence of PVL, but not pre-procedural AR, was a major predictor of adverse outcome. Preoperative LV dilatation seemed to offer some clinical advantages.

* Corresponding author at: Cardiac Surgery Unit, Department of Cardiology, Thoracic and Vascular Sciences, University of Padova Medical School, Via Giustiniani, 2, 35127 Padova, Italy.
E-mail address: colli.andrea.bcn@gmail.com (A. Colli).
[1] Authors contributed equally to the manuscript.

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1. Introduction

Transcatheter aortic valve implantation (TAVI) is a well-established alternative to surgery in inoperable/high-risk patients with severe symptomatic aortic stenosis (AS) [1–3]. Residual aortic regurgitation (AR) due to paravalvular leakage (PVL) following TAVI is associated with increased morbidity and mortality [3,4]. Despite technological advances in TAVI, the presence of any degree of PVL still remains a complication, the incidence of which varies between 2 and 40% [3–4,9–20], regardless of prosthesis type [1–8]. However, the correlations among pre-procedural AR, post-procedural PVL and long-term clinical outcomes are not clearly known. Accordingly, we aimed to assess these potential interactions and to investigate the role of preoperative AR and left ventricle (LV) volumes in terms of long-term outcome in patients with PVL after TAVI.

2. Methods

Between November 2007 and December 2012, patients with severe symptomatic AS evaluated as being at high surgical risk or inoperable underwent TAVI at 33 Italian centers. Patients with preoperative mitral regurgitation (MR) suitable for surgical correction were not considered for the study. Indication for TAVI required consensus by the multidisciplinary Heart Team of each center. All consecutive patients were included in the retrospective voluntary Italian Transcatheter balloon-Expandable Registry (ITER) which complies with the Declaration of Helsinki and was approved by a locally appointed ethics committee. Patients gave written informed consent for participation in the Registry. Any type of access was used. All procedures were performed with the balloon-expandable Edwards-SAPIEN valve prosthesis (Edwards Lifesciences, Irvine, CA), Sapien and Sapien XT. Clinical and echocardiographic data were prospectively recorded and subsequently analyzed.

Preoperative echocardiographic screening for the analysis of aortic valve function was performed by means of transthoracic echocolor-Doppler (TTE); AR was graded in accordance with guidelines as: absent (0), mild (grade 1) or moderate/severe (grade ≥ 2) [21].

The severity of PVL after TAVI was assessed by TTE at discharge, using a combination of qualitative and semiquantitative parameters according to current guidelines [22,23] and was graded as absent (0), mild (grade 1), or moderate/severe (grade ≥ 2). Adverse events were adjudicated according to the VARC definitions [24].

3. Statistical analysis

Continuous variables were expressed as medians, with interquartile range as a measure of variability. Survival curves were generated by means of the Kaplan-Meier method and compared by means of the log-rank test.

The association of factors with PVL status was modeled using a proportional odds model whereas the individual effect of clinical data on long-term survival was evaluated through Cox proportional hazards regression analysis.

The proportional hazard assumption was checked by means of the Grambsh and Therneau test and diagnostic plots were based on the

Table 1
Preoperative clinical features.

Variable	Total (1708)	PVL 0 (1083; 63.4%)	PVL 1 (539; 31.6%)	PVL 2 (86; 5%)	*p* value
Age (years, median/I–III IQ)	82.5(78.4–86)	82.4(78.1–86)	82.8(78.9–86.4)	83.1(80.2–85.9)	0.187
Sex (%)					
Female	1035 (61%)	688 (64%)	302 (56%)	45 (52%)	0.004
Male	673 (39%)	395 (36%)	237 (44%)	41 (48%)	
Hypertension (%)	1381 (81%)	871 (80%)	438 (81%)	72 (84%)	0.725
Diabetes (%)	429 (25%)	272 (25%)	135 (25%)	22 (26%)	0.994
PVD (%)	595 (35%)	393 (36%)	176 (33%)	26 (30%)	0.230
COPD (%)	411 (24%)	261 (24%)	133 (25%)	17 (20%)	0.613
NYHA (%)					
I	50 (3%)	30 (3%)	18 (3%)	2 (2%)	
II	281 (16%)	160 (15%)	104 (19%)	17 (20%)	0.137
III	1177 (69%)	771 (71%)	353 (65%)	53 (62%)	
IV	200 (12%)	122 (11%)	64 (12%)	14 (16%)	
Neurological dysfunction (%)	145 (8%)	88 (8%)	47 (9%)	10 (12%)	0.519
EuroSCORE I (median/I–III IQ)	17(11.5–25.8)	17.2(11.5–25.6)	17.1(12.1–26.9)	15.4(11.2–23)	0.451
EuroSCORE II (median/I–III IQ)	5(3.2–9)	5.2(3.2–9)	5(3.4–9.2)	3.7(2.3–5.9)	0.016
STS Score (median/I–III IQ)	6.5(4.2–11.2)	6.6(4.3–11.5)	6.5(4.5–11)	6.9(3.8–10)	0.803
Cardiac rhythm (%)					
SR	1129 (72%)	810 (75%)	356 (66%)	63 (73%)	0.006
AF	367 (21%)	205 (19%)	144 (27%)	18 (21%)	
PPM	112 (7%)	68 (6%)	39 (7%)	5 (6%)	

PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; SR: sinus rhythm, AF: atrial fibrillation, PPM: permanent pace- maker; IQ: interquartile.

Table 2
Preoperative echocardiographic features.

Variable	Total (1708)	PVL 0 (1083; 63.4%)	PVL 1 (539; 31.6%)	PVL 2 (86; 5%)	*p* value
Maximum transaortic gradient (mm Hg, median/I–III IQ)	80 (67–95)	80 (67–95	77 (65–93.5)	84 (100–70)	0.065
Mean transaortic gradient (mm Hg, median/I–III IQ)	49 (40–59	49 (40–60)	47 (39.8–57)	50 (44–62)	0.026
*AVA*i (cm^2/m^2, median/I–III IQ)	0.4 (0.4–0.5)	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.4 (0.3–0.5)	<0.001
Aortic regurgitation (%)					
0	676 (40%)	481 (45%)	168 (31%)	27 (31%)	
1	707 (42%)	400 (37%)	266 (50%)	41 (48%)	<0.001
2	312 (18%)	192 (18%)	102 (19%)	18 (21%)	
LVEDVi (mL/m^2, median/I–III IQ)	72(55–96)	73(56–97.8)	68 (52–88)	83 (54.5–99.8)	0.082
LVEF (%, median I–III IQ)	55 (46–61)	56 (47–62)	55 (45–60)	55 (45.8–60)	0.004
IVS thickness (mm, median/ I–III IQ)	14 (13–15)	13 (12–15)	14 (13–15)	15 (13–16)	0.011
Mitral regurgitation (%)					
0	590 (35%)	404 (38%)	167 (31%)	19 (22%)	
1	702 (41%)	429 (40%)	226 (42%)	47 (55%)	0.008
2	404 (24%)	241 (22%)	143 (27%)	20 (23%)	
sPAP (mm Hg, median/I–III IQ)	40 (33–50)	40 (32–49)	40 (35–50)	40.5 (33–50)	0.325

*AVA*i: aortic valve area indexed; LVEDVi: left ventricular end-diastolic volume indexed; LVEF: left ventricular ejection fraction; IVS: interventricular septum thickness; sPAP: systolic pulmonary artery pressure., IQ: interquartile.

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Table 3
Intra-procedural and post-procedural complications.

Variable	Total (1708)	PVL 0 (1083; 63.4%)	PVL 1 (539; 31.6%)	PVL 2 (86; 5%)	*p* value
Prosthesis embolization (%)	5 (0.3%)	5 (0.5%)	0 (0%)	0 (0%)	0.235
ECC/ECMO (%)	7 (0.4%)	6 (0.6%)	1 (0.2%)	0 (0%)	0.456
Conversion to full sternotomy (%)	13 (0.8%)	11 (1%)	2 (0.4%)	0 (0%)	0.236
Apex bleeding/rupture (%)	23 (1.3%)	15 (1.4%)	8 (1.5%)	0 (0%)	0.532
CA/CPR (%)	28 (1.6%)	19 (1.8%)	7 (1.3%)	2 (2.3%)	0.695
Coronary ostia occlusion (%)	12 (0.7%)	10 (0.9%)	1 (0.2%)	1 (1.2)	0.214
Aortic dissection (%)	6 (0.4%)	6 (0.6%)	0 (0%)	0 (0%)	0.176
POAF (%)	152 (8.9%)	98 (9%)	45 (8.3%)	9 (10.5%)	0.802
AMI (%)	15 (0.9%)	12 (1.1%)	1 (0.2%)	2 (2.3%)	0.188
Bleeding (%)					
Life threatening	128(7.5%)	92 (8.5%)	30 (5.6%)	6 (7%)	0.248
Major	186(10.9%)	119 (11%)	58 (10.8%)	9 (10.5%)	
Minor	103 (6%)	56 (5.2%)	41 (7.6%)	6 (7%)	
Vascular complications (%)					
Major	133 (8%)	87 (8%)	40 (7%)	6 (7%)	0.561
Minor	120 (7%)	69 (6%)	46 (9%)	5 (6%)	
Stroke (%)					
TIA	16 (1%)	9 (1%)	6 (1%)	1 (1%)	
Minor	11 (0.7%)	6 (1%)	4 (1%)	1 (%)	0.792
Major	12 (0.7%)	10 (1%)	2 (0.4%)	0 (0%)	
New PPM (%)	104 (6%)	67 (6%)	34 (6%)	3 (3%)	0.538
Creatinine peak level at 72 h (m/dL, median, I–III IQ)	1.2 (0.9–1.6)	1.1 (0.9–1.5)	1.2 (0.9–1.6)	1.2 (1–1.6)	<0.001
CVVH (%)	29 (2%)	14 (1%)	11 (2%)	4 (5%)	0.040

ECC: extracorporealcirculation; ECMO: extracorporeal membrane oxygenator; CA: cardiacarrest; CPR: cardio-pulmonaryresuscitation; POAF: postoperativeatrialfibrillation; AMI: acute myocardialinfarction; TIA: transientischemicattack; PPM: permanent pace-maker; CVVH: continuous veno-venous hemofiltration; IQ: interquartile.

Table 4
Discharge echocardiographic data.

Variable	Total (1708)	PVL 0 (1083; 63.4%)	PVL 1 (539; 31.6%)	PVL 2 (86; 5%)	*p* value
Maximum transaortic gradient (mm Hg, median/I–III IQ)	19 (24–15)	19 (15–24)	18 (14–23)	19 (16–25.3)	0.018
Mean transaortic gradient (mm Hg, median/I–III IQ)	10 (8–13)	10 (8–13)	10 (8–12)	11 (8–14)	0.005
LVEF (%, median/I–III IQ)	55 (50–61)	58 (50–62)	55 (48–60)	55 (50–60)	<0.001
sPAP (mm Hg, median/I–III IQ)	35 (30–42)	35 (30–42)	35 (30–43)	37 (30–45)	0.391
Mitral regurgitation (%)					
0	501 (38%)	370 (46%)	116 (26%)	15 (19%)	
1	648 (49%)	342 (43%)	257 (59%)	49 (62%)	<0.001
2	170 (13%)	90 (11%)	65 (15%)	15 (19%)	

LVEF: left ventricle ejection fraction; sPAP: systolic pulmonary artery pressure; IQ: interquartile.

Shoenfeld residual. All variables considered were entered into the model as they were, without any transformation or cut-off. The nonlinear effect of covariates was modeled by means of a restrictive cubic spline function, and its significance was assessed by means of the χ^2 Wald test. The model strategy was determined by following a backward selection strategy among variables reaching a level of at least 0.25 on univariable analysis. Model fit was considered significantly improved on the basis of the Akaike Information Criterion (AIC) applied backward for each model at a significance level of 0.05. To avoid inflation in type-I error due to multiplicity of testing, subgroup analysis was conducted by introducing interaction terms into the main multivariable model, and its significance assessed by means of AIC [25]. Multivariable models were depicted as nomograms, estimated at different survival points (two and six years). To evaluate the goodness of fit of the models, cross-validation and bootstrap (1000 runs) techniques were applied by the use of Somere option. Statistical significance was set at $p \leq 0.05$. The R-System [26] statistical package and the Harrellor>rms [27] libraries were used for analysis.

4. Results

Of the 1904 patients enrolled in the ITER, 191 patients (10%) died within the first 30 postoperative days and were excluded from the study owing to the lack of long-term follow-up. Of these patients only 10 (5.2%) presented moderate PVL and 18 (9.4%) presented a mild PVL, none presented severe PVL. Of those only 3 patients (1.6%)

Table 5
Follow-up data.

Variable	Total (1708)	PVL 0 (1083; 63.4%)	PVL 1 (539; 31.6%)	PVL 2 (86; 5%)	*p* value
Overall mortality (%)	435 (25%)	252 (23%)	158 (29%)	25 (29%)	0.054
Cardiovascular mortality (%)	164 (10%)	92 (9%)	63 (12%)	9 (11%)	0.593
NYHA class (%)					
I	517 (46%)	337 (50%)	164 (42%)	16 (28%)	
II	474 (42%)	267 (40%)	174 (45%)	33 (57%)	0.013
III	115 (10%)	61 (9%)	46 (12%)	8 (14%)	
IV	15 (1%)	7 (1%)	7 (2%)	1 (2%)	

NYHA: New York Heart Association.

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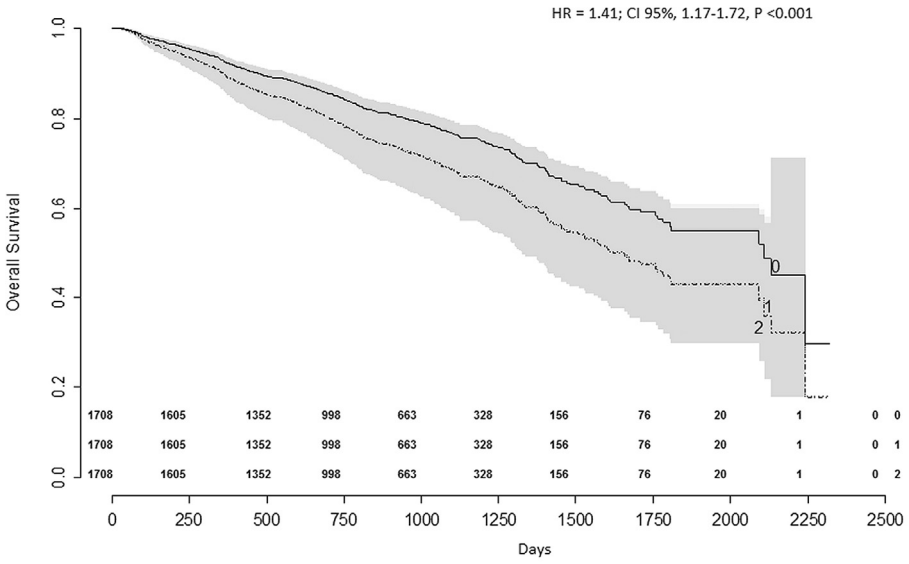

Fig. 1. Kaplan-Meier curve for overall survival according to PVL (0 = no PVL, 1 = mild PVL, 2 = moderate PVL).

Table 6
Independent risk factors for mortality during follow-up on multivariate analysis. Age and gender were always included in the model. Somer's Dxy 0.53. Values are hazard ratios (HR) and their corresponding confidence intervals. *p*-Value refers to the significance of the variable in the final model.

Factor	HR	95% C.I.	*p* value
LVEF ≤ 30%	1.82	1.24–2.66	0.002
Logistic EuroSCORE II	1.28	1.17–1.41	<0.001
Age	0.99	0.87–1.12	0.880
Male sex	1.37	1.13–1.66	0.001
Mild PVL	1.33	1.09–1-63	0.012
PVL ≥ moderate	1.36	0.90–2.05	<0.001
Preoperative AR	1.02	0.83–1.24	0.854

presented a more than moderate postoperative PVL. Another 5 patients (0.3%) were excluded because they were lost to follow-up. A total of 1708 patients (89.7% of the original cohort) were available for the purposes of the present study. Long term echocardiographic follow-up was complete in 1595 patients (94%).

Median age was 82.5 years (IQR 7.6); 61% were female. The median Euroscore II was 5 (IQR 5.8). Clinical follow-up (FU) was accomplished in 99.7% of patients, with a median FU time of 821 days (IQR 586). Preoperatively, New York Heart Association (NYHA) clinical functional class was ≥3 in 1377 (81%) patients. Before TAVI, 40% of the patients had no AR, 42% mild AR and 18% moderate AR. After TAVI, 63% of the patients had trace PVL or no PVL, 32% had mild PVL and 5% had moderate–severe PVL. Tables 1 and 2 show preoperative, clinical and echocardiographic data according to the different degrees of PVL. Operative and postoperative complications are shown in Table 3. Patients with greater PVL were more frequently male ($p = 0.004$) and had higher creatinine levels ($p = 0.006$), lower EuroSCORE II ($p = 0.016$), higher mean transvalvular gradients ($p = 0.026$), more reduced EF ($p = 0.004$), and LV hypertrophy ($p = 0.011$).

Prosthesis sizes and the rate of the transfemoral approach were similarly distributed among PVL groups. Procedural complications were not different among the groups. Only the rate of post-procedural renal insufficiency requiring continuous veno-venous hemofiltration (CVVH)

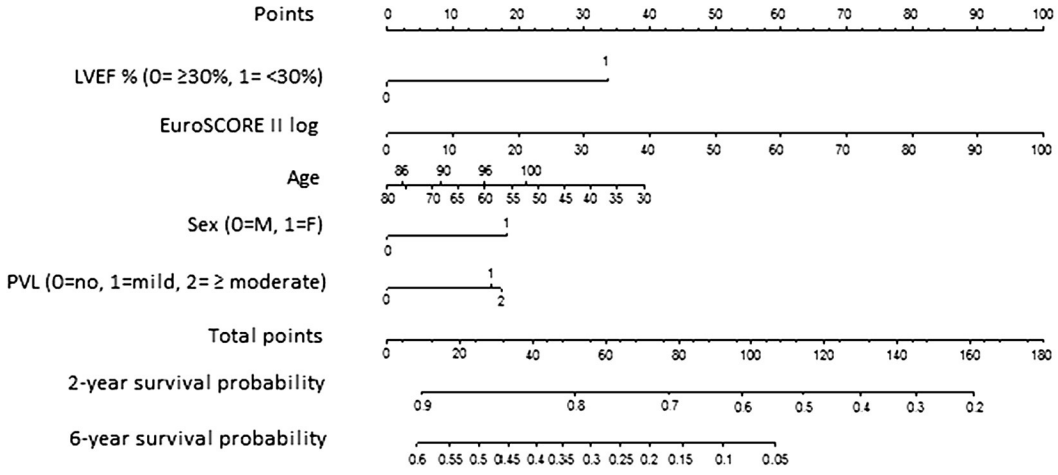

Fig. 2. Predictive nomogram to estimate long-term survival (based on independent risk factors: LVEF < 30%, EuroSCORE II, age, sex, PVL grade). Every variable is weighted with points ranging from 0 to 100. The sum of each score can estimate the 2-years and 6-years survival probability.

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and creatinine peak levels at 72 h were higher in patients with PVL ($p = 0.040$ and $p < 0.001$, respectively). After TAVI, patients with PVL had higher maximum and mean valvular gradients ($p = 0.018$ and $p = 0.005$) and lower LVEF ($p < 0.001$).

We observed a reduction of mitral regurgitation severity in each group; this reduction was less evident in patients with moderate/severe PVL. Complete postoperative echocardiographic data are shown in Table 4.

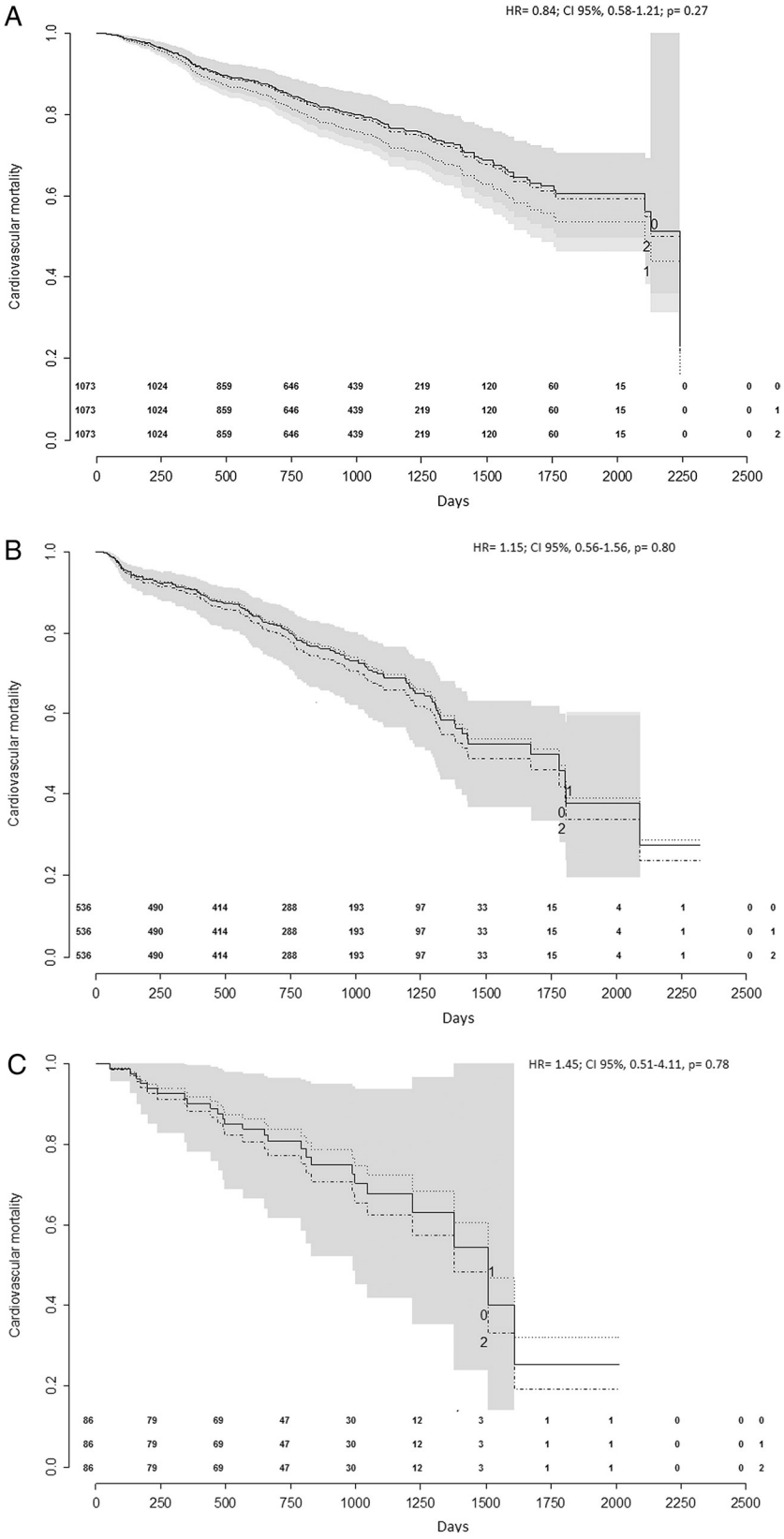

Fig. 3. Survival of patients according to the degree of PVL (Panel A = no PVL, Panel B = mild PVL, Panel C = moderate PVL) and by the presence of preoperative AR (0 = no AR, 1 = mild AR, 2 = moderate AR).

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On FU, overall mortality was 25% (435/1708). Patients with PVL suffered higher mortality than those without PVL (29% vs. 23%, $p = 0.05$) (Table 5). The overall survival rates according to the different degrees of PVL are shown in Fig. 1. Overall mortality was similar for patients with both mild and moderate PVL and significantly higher than patients without PVL ($p < 0.001$). Multivariable analysis demonstrated that PVL, EuroSCORE II, reduced LV ejection fraction and male gender were independent risk factors for death (Table 6, Fig. 3). Clinical status (NYHA class) was affected by the presence of PVL ($p = 0.01$) (Table 5). (See Fig. 2.)

5. Preoperative AR, PVL and outcomes

Pre-existing AR was significantly associated with higher levels of PVL (OR for higher PVL levels 1.74, CI 95%, 1.33–2.28). The presence of preoperative AR was not an independent predictor of outcome (HR = 1.02; CI 95% 0.83–1.24, $p = 0.85$). In patients with PVL, pre-existing AR offered no advantage in terms of either survival (Fig. 3, Panels B and C) or functional status [NYHA functional class, (OR = 0.73; CI 95% 0.13–4; $p = 0.88$)].

Considering the natural pathophysiologic remodeling of the LV in the presence of pre-existing AR, we investigated the correlation between LV volumes [estimated by means of left ventricular end-diastolic volume (LVEDVi)] and long-term survival in patients with PVL of any degree. The presence of LV dilatation before TAVI seemed to offer some clinical advantage. Specifically, a protective effect seemed to emerge at values above 75 mL/m^2 (Fig. 4). In patients with postoperative PVL, an enlarged LV is protective in term of mortality with a stronger impact with the increasing of LVEDVi after the cutoff of 75 ml/m^2. More specifically, to evaluate the real impact of LV dilatation on survival, we divided the study population into two subgroups, according to the type of aortic valve pathology: group A comprising patients with isolated severe AS (trace and mild [1+] AR were included) and group B comprising those with combined aortic valve disease (severe AS with concomitant AR equal or greater than moderate [2+]). On comparing the two groups, we observed that in patients with isolated AS, the presence of LV dilatation was associated with worse prognosis in case of PVL equal or greater than moderate (Fig. 5-Panel A, Log Relative Hazard > 0). By contrast in case of PVL equal or greater than moderate progressive LV dilatation was protective in the group with combined disease (Fig. 5-Panel B, Log Relative Hazard < 0).

6. Discussion

The main findings of our analysis of the interactions among pre-procedural aortic regurgitation (AR), LV dilatation, post-procedural PVL and long-term clinical outcomes of patients treated with balloon-expandable TAVI were that: 1) PVL was an independent risk factor for poor long-term outcome; 2) preoperative AR was associated with higher levels of PVL; 3) preoperative AR was not an independent predictor of outcome in patients who developed PVL; and 4) in patients with PVL, the presence of preoperative LV dilatation before TAVI seemed to be of some clinical advantage in those with combined aortic valve disease, and to be disadvantageous in those with isolated aortic stenosis.

PVL is the Achilles' heel of TAVI. Indeed, many studies have demonstrated its negative effect on both short- and long-term survival [17,28–32]. This effect is one of the most important obstacles to extending TAVI to younger and intermediate-risk patients. The present study confirmed previous findings that mild PVL is common after TAVI procedures, and that moderate to severe PVL is less frequent.

It was formerly believed that only moderate and severe PVL were independent risk factors for mortality. Reports by Kodali [16,18], however, have shown that mild PVL also has a negative impact on survival. This is consistent with our findings, which indicated that the presence of post-operative PVL, independently of its severity, was a risk factor for overall long-term mortality (OR 7.5, $p = 0.02$). These findings are consistent with those reported by other authors [4–9]. Our multivariate analysis was performed both on including and on excluding preoperative AR. Differently from findings reported by Van Belle in FRANCE2 Registry [33], in our series preoperative AR did not prove to be an independent risk factor for all-cause death, nor did it modify the impact of other variables on long-term survival.

Present results may suggest performing a population matched analysis to overcome the potential limitation related to a large retrospective multicenter registry. We observed a significative reduction of MR grade after the procedure but this modification was less evident in patients with moderate/severe PVL probably because of the maintenance of a volume overload due to the PVL itself. This lower reduction could act as another risk factor for the higher long-term mortality observed in

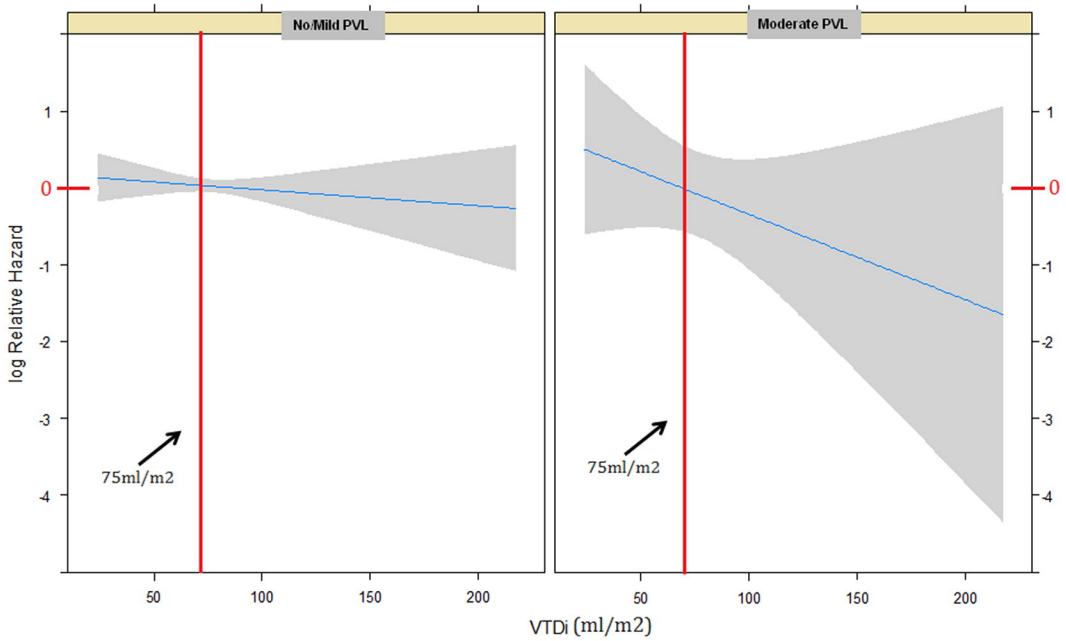

Fig. 4. Effect of left ventricular dilatation on patients according to PVL (no/mild PVL; moderate PVL); Log Relative Hazard values inferior than 0 are related to improved survival.

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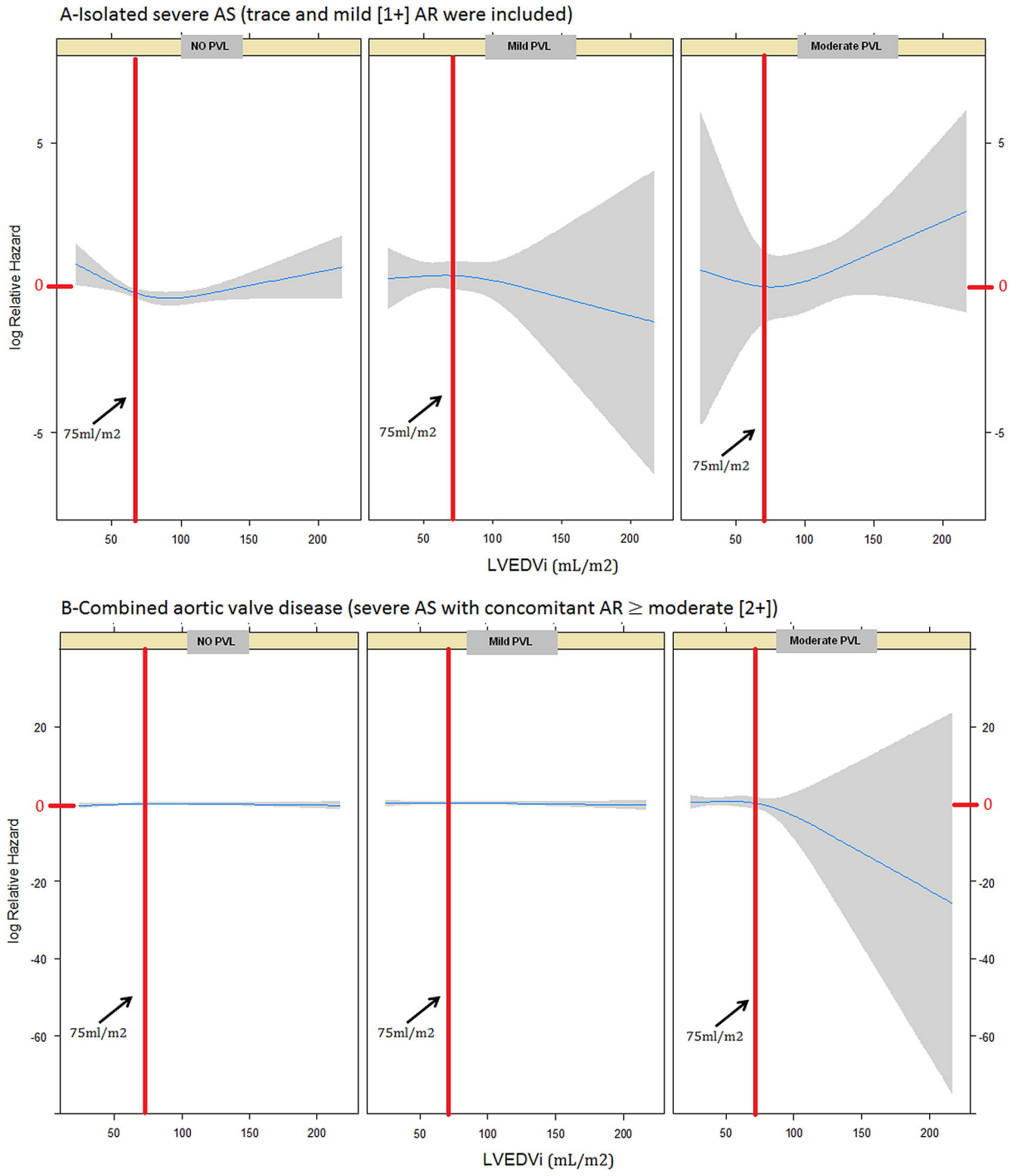

Fig. 5. Effect of left ventricular dilatation in patients according to aortic valve disease (Panel A = isolated aortic valve stenosis; Panel B = combined aortic valve disease) and by grade of PVL (0 = no PVL, 1 = mild PVL, 2 = moderate or greater PVL); Log Relative Hazard values inferior than 0 are related to improved survival.

this group. Anyway, at multivariate analysis, the presence of postoperative MR did not result as significative independent risk factor for mortality. Interestingly, we have observed that patients who presented postoperative PVL presented also a higher incidence of acute renal injury (higher creatinine peak levels at 72 h and use of CVVH). We can speculate that this new observation could be related to the greater amount of contrast used to evaluate the severity of PVL immediately after TAVI implantation and/or after balloon post dilatation used to correct PVL. Unfortunately, the information on contrast and requirement of post dilatation were not collected in the ITER registry.

Our findings revealed an association between the presence of preoperative AR and the development of post-procedural PVL. One possible explanation is that patients with AS associated with relevant AR present in general a significant fusion of the commissures. In this situation the prosthesis deployment could result asymmetrical due to the different resistance offered by the calcified commissures to the valve stent frame. This finding is in accord to the literature reporting that heavy and asymmetrical calcification of the aortic annulus and aortic leaflets can be considered one of the risk factors for post-procedural PVL [16, 17].

Based on the pathophysiology of aortic valve disease, we hypothesized that the existence of concomitant preoperative AR could, as a result of LV adaptation to long-standing volume overload, act as a protective factor in patients who developed PVL. The present study

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did not confirm our hypothesis; indeed, we observed that preoperative AR did not improve survival in the event of PVL.

By contrast, LV dilatation with LVEDVI greater than 75 ml/m^2 was identified as a protective factor. The clinical advantage, considered as improved long-term survival, is related to the presence of preoperative LV dilatation in patients who develops more than mild PVL with a progressive stronger effect in case of higher LVEDVi values. To better define the importance of LV dilatation, we performed a subgroup analysis based on the type of aortic valve disease. We hypothesized that patients with pure AS could present LV dilatation as result of a different pathophysiologic mechanism from that acting in patients with combined aortic valve disease. Indeed, in the case of isolated AS, the presence of LV dilatation reduced long-term survival, while in the case of combined disease, it improved survival.

In patients with AS, LVEDVi does not increase and high-pressure gradients between the LV and the aorta determine LV hypertrophy. This results in impaired relaxation, increased stiffness, myocardial fibrosis and elevated LV end-diastolic pressure, making it difficult to manage the acute volume overload that occurs in the event of PVL. In patients with concomitant AR, by contrast, the volume overload causes an increase of LVEDVi. Thanks to LV compliance and progressive eccentric ventricular remodeling, LV end-diastolic pressure does not increase, making the volume overload determined by PVL tolerable.

The present observations are also supported by a recent publication by Ewe et al. [34], in which it was demonstrated that LV stiffness (measured as interventricular septum thickening) impacted negatively on the survival of patients with PVL.

7. Limitations

Possible limitations of our study are: 1) data from a retrospective registry, 2) the small number of patients with severe AR combined with AS, 3) the lack of data on LV wall thickness and filling pressure values, from which to estimate the real LV wall stress and diastolic performance, and 4) the lack of a core-lab evaluation of preoperative and postoperative Echocardiographic data. The impact of this item was reduced by the strict application of VARC international criteria for the classification of the severity of preoperative AR and postoperative PVL.

8. Conclusions

The postoperative presence of any grade of PVL negatively affects both overall survival and functional class.

Pre-existing AR has no protective effect on survival in the event of post-procedural PVL. LV dilatation has a protective effect on long-term survival in patients with mixed valvular pathology who develop at least a moderate degree of PVL. Dilatation due to prolonged pure AS does not display the same effect.

9. Impact on daily practice

PVL is a challenging complication of TAVI and has significant impact on survival. We tried to identify the type of patients in whom a more than mild postoperative PVL could be accepted. Our findings demonstrate that preexisting AR in a AS patient is never a protective factor; but patients with AS, AR and LV dilatation are those who best tolerate post procedural AR at long-term FU.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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