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Transcatheter aortic valve replacement in patients with paradoxical low-flow, low-gradient aortic stenosis: Incidence and predictors of treatment futility☆

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ABSTRACT

Background: Few and controversial data exist on the outcomes of patients with paradoxical low-flow, low-gradient aortic stenosis (PLFLG-AS) following transcatheter aortic valve replacement (TAVR). This study aims to better characterize clinical outcomes and predictors of treatment futility in PLFLG-AS patients undergoing TAVR.

Methods: In this multicenter study, 318 patients with PLFLG-AS undergoing TAVR were categorized according to treatment futility, defined as all-cause mortality, poor functional status (NYHA class III-IV) or deterioration in functional class at 1-year follow-up. Clinical outcomes and the factors associated with treatment futility were assessed.

Results: The mean age of the patients was 81.0 ± 8.3 years and 50.3% were women. At 1-year follow-up, 17.6% died and 12.9% had heart failure hospitalization. Residual impaired functional capacity (NYHA ≥ II) was present in 54.4% of patients who were alive at 1-year, and 9.8% remained in NYHA III/IV. The primary endpoint was observed in 103 (32.4%) patients, of which 54% died and 46% had a poor or worsening functional class. Factors independently associated with treatment futility were the presence of atrial fibrillation (AF) (OR:1.79, 95%CI, 1.04–3.10), chronic obstructive pulmonary disease (COPD) (OR:2.66, 95%CI, 1.50–4.74) and a lower SVi (OR per each decrease in 10 ml/m^2:1.89, 95%CI, 1.06–3.45). The risk of treatment futility of patients with AF, COPD and a SVi < 30 ml/m^2 was 66.38% (95%CI, 54.29%–78.48%).

Conclusion: Close to one-third of patients with PLFLG-AS failed to derive a benefit from TAVR. The presence of AF, COPD and a low SVi were predictors of treatment futility. Being able to identify patients less likely to improve after the procedure may help to guide management and improve outcomes in patients with PLFLG-AS.

1. Introduction

A relatively high proportion of patients (25–35%) [1] with preserved left ventricular ejection fraction (LVEF ≥ 50%) and severe aortic stenosis (AS) on the basis of aortic valve area (AVA < 1 cm^2, indexed AVA < 0.6 cm^2/m^2), have a low-flow state (indexed stroke volume [SVi]: <35 ml/m^2) with lower than expected transvalvular gradients (i.e. <40 mmHg). This entity, known as paradoxical low-flow low-gradient

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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(PLFLG) AS, is associated with poorer outcomes compared to high gradient AS [2]. The optimal management of these patients is complex and controversial. While numerous studies have shown that surgical aortic valve replacement is associated with a survival benefit [2], others have reported limited improvement [3]. Since these subset of AS patients are generally older and at increased risk of perioperative morbimortality and patient-prosthesis mismatch after surgery [1], there is a growing interest in the role of transcatheter aortic valve replacement (TAVR) as an alternative therapeutic approach. Indeed, a post-hoc analysis of the PARTNER trial found that TAVR was associated with improved 1-year survival in PLFLG patients [4]. On the other hand, other studies reported that PLFLG AS may represent a subgroup with worse clinical outcomes, with TAVR being futile in up to 25% of such patients [5,6]. However, there is a paucity of data regarding the factors associated with poorer outcomes in PLFLG-AS patients undergoing TAVR, with the only study focusing on the issue of futility being limited by the relatively small number of patients [6].

The objective of this study was to validate these previous findings in a larger scale study and to better define the incidence and predictors of treatment futility associated with PLFLG-AS patients undergoing TAVR.

2. Methods

2.1. Study population

Consecutive patients with symptomatic PLFLG-AS undergoing TAVR between 2006 and 2018 from 9 centers were included in the study. PLFLG-AS was defined by an AVA < 1 cm^2 and/or indexed AVA < 0.6 cm^2/m^2, SVi < 35 ml/m^2, mean aortic gradient <40 mmHg and a preserved LVEF (>50%). Indications for TAVR, device type and approach were left at the discretion of the heart team at each participating center. All patients provided signed informed consent for the procedures.

Clinical and echocardiographic data was prospectively collected and entered in a dedicated TAVR database at each participating center. Patients had a clinical follow-up at 1 and 12 months following the procedure.

2.2. Echocardiographic evaluation

Transthoracic echocardiographic exams were performed at baseline, hospital discharge and at 12 months. For the assessment of AS severity, a multi-window approach was used to record peak and mean aortic velocities. Pressure gradients were derived using the modified Bernoulli equation and AVA was calculated using the continuity equation. Left ventricular (LV) SV was calculated as the product of LV outflow tract area and velocity time integral using pulsed-wave Doppler, and was indexed for body surface area. Valvulo-arterial impedance (Zva) was calculated as the sum of systolic blood pressure and mean transaortic valve gradient divided by the LV SVi.

2.3. Endpoints

The primary endpoint was treatment futility defined as any of the following: 1) all-cause mortality within the first 12-months after TAVR, 2) poor functional status (NYHA class III-IV) at 1-year post TAVR, or 3) deterioration in functional status from baseline to 1-year follow-up. Secondary outcomes were all-cause mortality, cardiovascular mortality, and the composite of all-cause mortality and HF hospitalization at 1-year follow-up. Clinical events were recorded and defined according to the VARC-2 criteria [7].

2.4. Statistical analysis

Categorical variables were expressed as a number (percentage) and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]: 25–75th percentile). Assessment of normality was performed using the Shapiro-Wilk test. Comparison of qualitative variables was performed with the X2 or Fisher exact-test. Quantitative variables were analyzed with a 2-sided Student's *t*-test or median test. A logistic regression model was performed to determine independent predictors of treatment futility. Those variables from the univariable analysis with a p value < 0.05 were entered into a multivariable logistic regression analysis. Clinical events over time were also analyzed with the Kaplan–Meier method, and the log-rank test was applied for comparison between groups. Analyses were performed using STATA (version 14.2; StataCorp LLC, College Station, Tx, USA).

3. Results

A total of 334 patients with PLFLG-AS underwent TAVR during the study period (out of 3989 TAVR procedures, 8.4%). Of these, 16 (4.8%) patients lost to follow-up were excluded due to the impossibility of treatment futility assessment, leading to a final study population of 318 patients. The clinical, echocardiographic and procedural characteristics of the study population are summarized in Table 1. The mean age of the overall cohort was 81 ± 8 years, 50% of patients were women and 84% had hypertension. The cohort had a normal mean LVEF 60 ± 6%, a low mean SVi 29 ± 5 ml/m^2 and a high global LV afterload (mean Zva: 6 ± 1 $mmHg \cdot mL^{-1} \cdot m^{-2}$). The mean predicted risk of mortality was 5.5 ± 5.0% as assessed by EuroSCORE II. Baseline characteristics and outcomes of the cohort according to the first (2006–2010, n = 65) and second (2011–2018, n = 253) half of the study periods are detailed in Supplementary Table 1. Patients enrolled during the second study half had a lower 30 day and 1-year mortality: 13.8% vs 4.0%, p < 0.01, and 27.7% vs 15.0%, p = 0.02, respectively. As expected, patients in the contemporary cohort underwent TAVR more frequently by a transfemoral approach (75.1% vs 53.8%, p < 0.01) and with newer generation valves (85.7% vs 16.9%, p < 0.01).

At 1-year follow-up, a total of 56 (17.6%) patients had died, 31 (9.7%) due to cardiovascular reasons, 41 (12.9%) patients were hospitalized for HF, and 90 (28.3%) patients presented with the combined end-point of all-cause mortality and HF hospitalization. The Kaplan-Meier curves for global and cardiac mortality and rehospitalization due to heart failure at 1-year follow-up are shown in Fig. 1.

Changes in NYHA class over time are detailed in Supplemental Fig. 1. Before TAVR, 313/318 (98.5%) patients had impaired functional capacity (NYHA II: 23.9%, NYHA III-IV: 74.6%). Medical treatment, including heart failure medication, did not differ significantly between patients in NYHA class I/II and those in NYHA class III/IV (Supplementary Table 2). At 1-year follow-up, functional class improved in 191 (60.1%) patients, remained unchanged in 65 (20.4%) and worsened in 6 (1.9%). Residual impaired functional capacity (NYHA ≥ II) was present in 173 patients (54.4% of those alive at 1-year follow-up).

3.1. Treatment futility

A total of 103 (32.4%) patients met the primary endpoint of treatment futility. Of these, 56 (54.4%) had died and 47 (45.6%) had a poor or worsening functional class at 1-year follow-up. The clinical and procedural characteristics of patients according to the occurrence of treatment futility are shown in Table 1. The proportion of patients recruited during the first and second study periods, as well as the proportion of old/new generation prosthesis, was similar among patients who met the primary end-point (futility) and those who did not. Patients who did not derive a benefit from TAVR displayed a higher prevalence of comorbidities such as peripheral artery disease (PAD) (34% vs 21%, p = 0.04), atrial fibrillation (AF) (60% vs 42%, p < 0.01) and chronic obstructive pulmonary disease (COPD) (42% vs 18%, p < 0.01). These patients exhibited a lower exercise capacity (6-minute walking-test [6MWT]: 132 ± 66 vs 219 ± 111 m, p < 0.01), a lower baseline SVi (28 ± 5 vs 30 ± 5 $ml/min/m^2$, p < 0.01), were less frequently treated via a transfemoral approach (61% vs 73%, p < 0.01), and exhibited a

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Table 1
Clinical, echocardiographic, procedural characteristics and 30-day outcomes of the study population, overall and according to treatment futility (N = 318).

	All patients (n = 318)	Futility (N = 103)	No futility (N = 215)	p value
Clinical variables				
Age (years), mean ± SD	81.0 ± 8.3	82.2 ± 7.9	80.3 ± 8.3	0.056
Female, n (%)	160 (50.3)	50 (48.5)	110 (51.2)	0.662
BMI (kg/m^2), mean ± SD	28.1 ± 8.5	27.1 ± 5.8	28.6 ± 9.4	0.130
Diabetes mellitus, n (%)	105 (33.0)	28 (27.2)	77 (35.8)	0.126
Hypertension, n (%)	268 (84.3)	87 (84.5)	181 (84.2)	0.949
Active smokers, n (%)	70 (22.0)	29 (28.2)	41 (19.1)	0.067
Peripheral artery disease, n (%)	80 (25.2)	35 (34.0)	45 (20.9)	0.036
Coronary artery disease, n (%)	183 (57.5)	61 (59.2)	122 (56.7)	0.620
Prior myocardial infarction, n (%)	57 (17.9)	23 (22.3)	34 (15.8)	0.062
Prior CABG, n (%)	68 (21.4)	20 (19.4)	48 (22.3)	0.302
Atrial fibrillation, n (%)	153 (48.1)	62 (60.2)	91 (42.3)	0.003
COPD, n (%)	82 (25.8)	43 (41.7)	39 (18.1)	<0.001
Hemoglobin (g/dl), mean ± SD	12.0 ± 1.6	11.7 ± 1.7	12.1 ± 1.6	0.050
CKD (eGFR˙60Ml/min/m^2), n (%)	182 (57.2)	59 (57.3)	123 (57.2)	0.990
EuroSCORE 2, mean ± SD	5.6 ± 5.0	6.0 ± 4.3	5.4 ± 5.3	0.396
Functional status assessment				
Baseline 6MWT (m)[a]	187.4 ± 105.6	132.0 ± 66.3	219.0 ± 111.0	<0.001
DASI index[b]	13.2 ± 8.1	11.8 ± 6.8	14.0 ± 8.7	0.140
Echocardiographic variables				
LVEF (%), mean ± SD	60.2 ± 6.4	59.3 ± 5.9	60.6 ± 6.7	0.107
Mean aortic gradient (mmHg), mean ± SD	31.8 ± 6.2	30.5 ± 6.1	31.0 ± 6.3	0.573
Aortic valve area (cm^2), mean ± SD	0.7 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.023
Aortic annulus (mm), mean ± SD	21.0 ± 2.4	21.2 ± 2.3	20.9 ± 2.4	0.352
Moderate or severe MR, n (%)	49 (15.4)	17 (16.5)	32 (14.8)	0.457
Moderate or severe AR, n (%)	17 (5.3)	3 (3.0)	14 (6.5)	0.257
Moderate or severe TR, n (%)	21 (16.4)	6 (5.8)	15 (7.0)	0.113
Stroke volume indexed (ml/m^2), mean ± SD	29.5 ± 5.4	27.9 ± 4.8	30.2 ± 5.5	<0.001
Zva (mmHg·mL^{-1}·m^{-2}), mean ± SD	5.7 ± 1.1	5.8 ± 1.1	5.6 ± 1.1	0.429
PAP (mmHg), mean ± SD	42.3 ± 15.9	43.8 ± 15.0	41.5 ± 16.3	0.273
Computed tomography variables[c]				
AVC (AU), median (IQR)	1788 (998–2740)	2060 (1178–3526)	1688 (957–2578)	0.037
AVC high score[d], n (%)	93/172 (54.1)	30/52 (57.7)	63/120 (52.5)	0.530
AVCi (AU/m^2), median (IQR)	944 (587–1583)	1099 (661–1946)	924 (555–1440)	0.063
Perimeter (mm), mean ± SD	67.3 ± 21.5	75.1 ± 11.7	65.1 ± 23.1	0.080
Maximal annulus diameter (mm), mean ± SD	26.0 ± 3.1	26.2 ± 3.4	26.0 ± 2.9	0.677
Minimal annulus diameter (mm), mean ± SD	21.6 ± 2.4	21.9 ± 2.4	21.5 ± 2.4	0.324
Procedural variables				
Prosthesis type				
Balloon expandable, n (%)	235 (73.9)	77 (74.8)	158 (73.5)	0.809
Generation				
Old-generation, n (%)	90 (28.3)	32 (31.1)	58 (27.0)	0.449
New-generation, n (%)	228 (71.7)	71 (68.9)	157 (73.0)	
Approach				
TF, n (%)	225 (70.8)	63 (61.2)	162(73.3)	0.009
Study-period				
First study half (2006–2010), n (%)	65 (20.4)	24 (23.3)	41 (19.01)	0.381
Second study half (2011–2018), n (%)	253 (79.6)	79 (76.7)	174 (80.9)	
Postprocedure echocardiography				
Aortic mean gradient (mmHg), mean ± SD	9.1 ± 5.3	9.4 ± 7.6	8.9 ± 4.0	0.497
Aortic valve area (cm^2), mean ± SD	1.55 ± 0.44	1.52 ± 0.40	1.58 ± 0.46	0.301
Residual moderate to severe AR, n (%)	12 (3.8)	6 (5.8)	6 (2.8)	0.128
Residual moderate to severe MR, n (%)	32 (10.3)	16 (17.0)	16 (7.4)	0.010
30-Day outcomes				
Death, n (%)	19 (6.0)	19 (18.4)	0 (0)	<0.001
HF-rehospitalization, n (%)	11(3.5)	5 (4.9)	6 (2.8)	0.336
Stroke, n (%)	7 (2.2)	4 (3.9)	3 (1.4)	0.157
Myocardial infarction, n (%)	8 (2.5)	4 (3.9)	4 (1.9)	0.281
Major/life threatening bleeding, n (%)	32 (10.1)	16 (15.5)	16 (7.4)	0.025

Abbreviations: AR, aortic regurgitation; AU, Agatston-unit. AVC, aortic valve calcification; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; HF, Heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; SD, standard deviation; TF, transfemoral. eGFR, estimated glomerular filtration rate.

[a] Data available in 110 patients.

[b] Data available in 142 patient.

[c] Data available in 172 patients.

[d] AVC high-score was defined as >1274 AU in women and >2065 AU in men.

higher rate of residual moderate/severe mitral regurgitation (17% vs 7%, p = 0.01) and major bleeding complications (16% vs 7%, p = 0.03). Overall aortic valve calcification (AVC) was slightly higher in the futility group (2060 [1178–3526] AU vs. 1668 [957–2578] AU, p = 0.04), however, the proportion of patients with severe AVC, defined as ≥1274 AU in women and 2065 AU in men, did not differ (58% vs 53%, p = 0.53).

The main clinical, procedural, and imaging factors associated with treatment futility are summarized in Table 2. In the multivariable model, factors independently associated with a failure to derive a benefit from TAVR were the presence of AF (OR:1.79, 95%CI, 1.04–3.10), COPD (OR:2.66, 95%CI, 1.50–4.74) and a lower SVi (OR per each 10 ml/m^2 decrease in SVi:1.89, 95%CI, 1.06–3.45). The probability of

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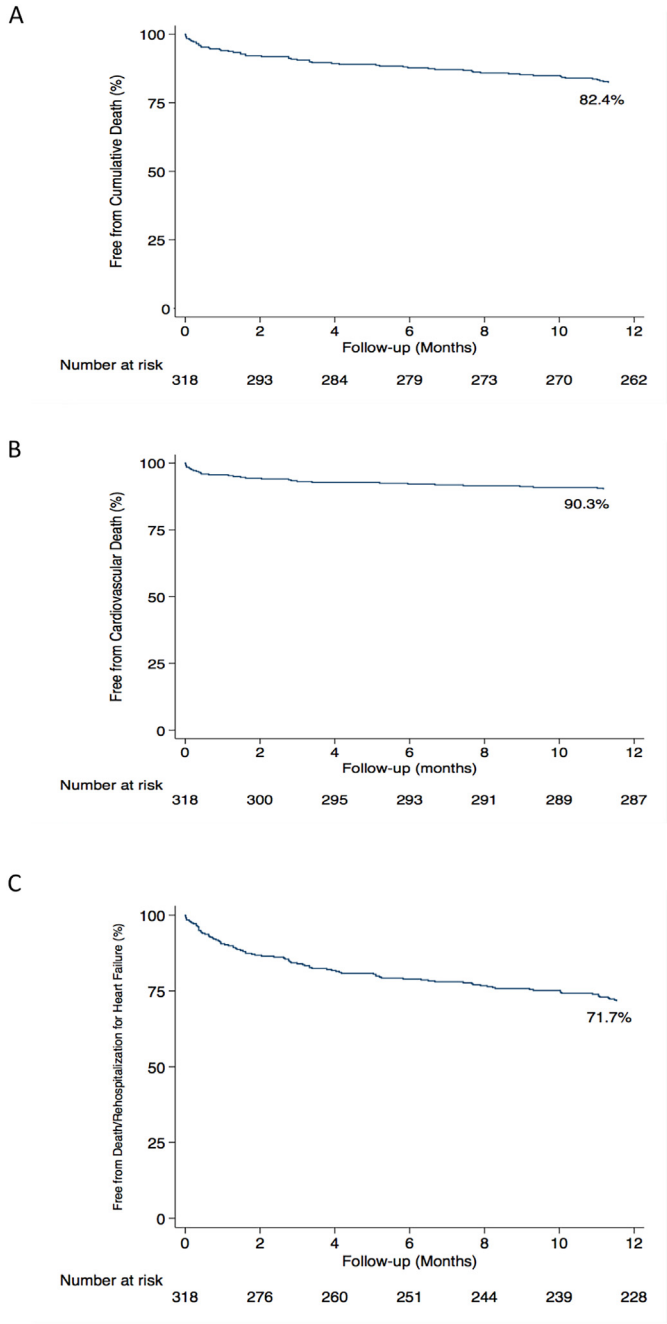

Fig. 1. Kaplan-Meier curves for A) overall-mortality, B) cardiovascular mortality and C) for the combined endpoint of overall-mortality and heart failure rehospitalization at 1-year follow-up.

treatment futility according to the presence of any possible combination of baseline risk factors (AF, COPD and SVi ≤30 ml/m^2) are depicted in Fig. 2. The risk of failing to derive a benefit from TAVR in the presence of the 3 risk factors was 66.38% (95%CI, 54.29%–78.48%). The Kaplan-Meier curves for all-cause mortality at 1-year follow-up according to the presence of risk factors of treatment futility are shown in Supplemental Fig. 2. Higher mortality rates at 1-year follow-up were observed in those patients with AF (26% vs. 10%, $p < 0.01$), COPD (23% vs. 16%, $p < 0.01$) and SVi < 30 ml/m^2 (25% vs. 12%, $p = 0.02$).

4. Discussion

The results of this study showed that one-third of intermediate-risk patients with PLFLG-AS undergoing TAVR failed to derive a benefit from the procedure. The presence of baseline factors like COPD, AF and a lower SVi determined an increased risk of treatment futility, with the vast majority of patients either dying or exhibiting poor functional status at 1-year follow-up in the presence of the 3 risk factors.

With the increasing emphasis on value-based healthcare spending, there is a need to better identify those patients with a negative risk-cost and risk-benefit trade-off in whom TAVR is not expected to positively impact either survival or functional status. The primary endpoint of treatment futility was met by one-third of patients, of which about half died and the other half had a poor or worsening functional class at one year follow up. Previous studies incorporating both a mortality and a patient reported health-status component into their definition of futility have reported poor outcomes after TAVR ranging from 15%-to-50% [8–11]. This large variability is attributed, in part, to the lack of a consensus regarding the definition of futility and to differences in the population being studied. Using data from the PARTNER (Placement of Aortic Transcatheter Valve) trials [8], Arnold et al. were the first to develop an analytic risk predictor based on the Kansas City Cardiomyopathy Questionnaire (KCCQ). Poor outcome was defined as death, KCCQ score < 45 (comparable to NYHA-class IV) or worsening in quality of life (decrease of ≤10 points in the KCCQ from baseline). According to this definition, approximately 33% of patients treated with TAVR had a poor outcome at 6-months [8,9]. When looking at 1-year outcomes and using a threshold of KCCQ < 60 (similar to NYHA III/IV), the risk of a poor-outcome was as high as 50% in inoperable/high-surgical risk patients and 39% in an unselected population that also included patients at lower-risk [8,9,12]. In another more contemporary study including patients with an intermediate operative risk-score (similar to those included in our study), TAVR futility occurred in 29% of the cohort [10]. The authors defined futility as death within the first year after the procedure or lack of improvement in functional class [10]. Lastly, unlike the aforementioned studies, Zusman et al. [11] found a much lower rate (15%) of futile 1-year outcomes using a composite of 1-year mortality, stroke, lack of functional-class improvement and readmissions. Even though none of these studies focused specifically in PLFLG-AS, the results seem to suggest that these patients have an increased risk of futility when compared to the overall intermediate-risk population undergoing TAVR. Indeed, in the present study, PLFLG-AS patients exhibited a higher overall 1-year mortality compared to that of patients included in PARTNER 2 and SURTAVI (Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients) trials: 18% vs 12% and 7%, respectively [13,14]. Additionally, even though TAVR improved functional status in a significant proportion of cases, up to 10% remained in NYHA class III/IV at 1-year, as much as twice the rate reported in the SURTAVI study.

Non-cardiac and cardiac baseline co-morbidities like COPD, AF and a lower stroke volume determined an increased risk of futile TAVR among PLFLG-AS patients. COPD is a common comorbidity in patients undergoing TAVR (~35%) that has been consistently found to be associated with increased early and long-term mortality [15–18]. The main predictors of futility in patients with COPD seem to differ from the general TAVR population and include the degree of airway obstruction, a shorter distance walked in the 6MWT and oxygen dependency [19–21]. The higher surgical risk and excess mortality reported in this subset of patients may not be entirely attributable to AS, but could also be related to the high burden of comorbidities that are prevalent in this age group. The presence of AF was found in close to half of patients in our cohort and independently predicted poor outcomes. Previous reports have also shown that pre-existing and new-onset AF have an adverse impact on morbidity and mortality after-TAVR [15,22,23]. Nonetheless, whether AF per se, or its related treatment, is the cause of these adverse events or only represents a marker of more advanced underlying cardiac disease is unclear. Typically, patients with this entity have an increased global afterload combined with significant concentric ventricular remodeling, a restrictive physiology and a decrease in intrinsic myocardial function that leads to a decrease in SVi despite a preserved LVEF [24]. This notion

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Table 2
Predictors of treatment futility

	Univariable model		Multivariable model[a]	
	OR (95% CI)	p value	OR (95% CI)	p value
Clinical variables				
Age (year)	1.03 (0.99–1.06)	0.058		
Female	0.90 (0.56–1.44)	0.662		
BMI (kg/m^2)	0.97 (0.93–1.01)	0.129		
Diabetes mellitus	0.67 (0.40–1.12)	0.127		
Hypertension	1.02 (0.53–1.95)	0.949		
Active smokers	1.67 (1.02–3.05)	0.069		
Peripheral artery disease	2.06 (1.22–3.48)	0.014	1.41 (0.72–2.76)	0.335
Coronary artery disease	1.09 (0.68–1.76)	0.709		
Prior myocardial infarction	1.46 (0.15–2.64)	0.208		
Prior CABG	0.82 (0.46–1.47)	0.501		
Atrial fibrillation	2.06 (1.28–3.32)	0.003	1.79 (1.04–3.10)	0.036
COPD	3.18 (1.88–5.37)	<0.001	2.66 (1.50–4.74)	0.001
Hemoglobin (g/dl)	0.86 (0.74–1.01)	0.059		
CKD (eGFR < 60 Ml/min/m^2)	1.00 (0.21–1.61)	0.990		
EuroSCORE 2	1.02 (0.97–1.08)	0.397		
Echocardiographic variables				
LVEF (%)	0.97 (0.93–1.01)	0.106		
Mean aortic gradient (mmHg)	0.99 (0.95–1.03)	0.572		
Aortic valve area (cm^2)	0.12 (0.02–0.75)	0.024	0.54 (0.06–4.82)	0.581
Aortic annulus (mm)	1.06 (0.94–1.19)	0.352		
Moderate or severe MR	1.10 (0.58–2.09)	0.771		
Moderate or severe AR	0.42 (0.12–1.50)	0.181		
Stroke volume indexed[b]	2.33 (1.45–3.85)	<0.001	1.89 (1.06–3.45)	0.032
Procedural variables				
Prosthesis type				
Balloon expandable	1.07 (0.62–1.83)	0.809		
Approach				
TF	0.51 (0.31–0.85)	0.010	0.69 (0.36–1.31)	0.255
Generation				
Old-generation	0.82 (0.49–1.37)	0.449		
Study period				
First study half	0.64 (0.39–1-05)	0.077		
Postprocedure echocardiography				
Aortic mean gradient, (mmHg)	1.02 (0.97–1.06)	0.503		
Aortic valve area (cm^2)	0.72 (0.38–1.34)	0.300		
Residual moderate to severe AR	2.52 (0.79–8.05)	0.118		
Residual moderate to severe MR	2.44 (1.17–5.12)	0.018	1.38 (0.60–3.16)	0.449

Abbreviations same as Table 1.
[a] Adjusted for clustering of patients within centers.
[b] per each 10 ml/m^2 decrease in stroke volume indexed.

is further reinforced by the high valvulo-arterial impedance (>5 mmHg·mL^{-1}·m^{-2}) observed in our cohort and, despite all patients having by definition a normal LVEF, the low SVi may indicate a component of intrinsic myocardial dysfunction. In fact, LVEF by itself should not be construed as being equivalent to normal LV flow output and does not represent the true extent of myocardial impairment. In our study, SVi was independently associated with worse outcomes, and patients who did not benefit from TAVR had a lower mean SVi. Several

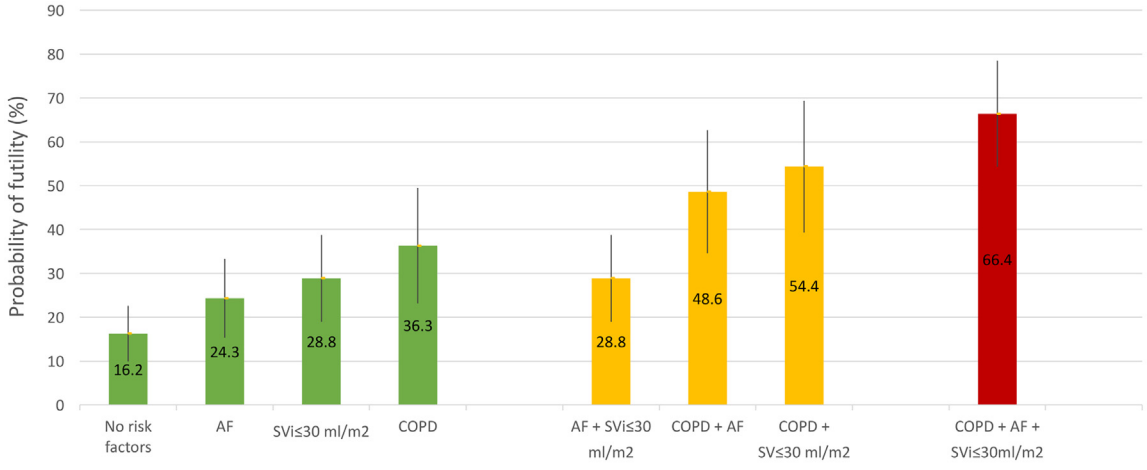

Fig. 2. Probability of treatment futility according to the presence of any possible combination of baseline risk factors (AF, COPD and SVi ≤30 ml/m^2). AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; SVi: stroke volume indexed.

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previous studies have found that a low-flow, defined as SVi < 35 ml/m^2, is associated with poor prognosis in PLFLG-AS [24,25]. Furthermore, when patients were dichotomized according to baseline SVi, those with a SVi < 30 ml/m^2 had a significantly higher mortality rate and, interestingly, the same SVi cut-off was a strong independent predictor of mortality in a recently published large TAVR registry [26].

In the herein cohort, the combination of AF, COPD and a SVi < 30 ml/m^2 conferred a 66% risk of treatment futility (Fig. 2), which underlines the need for a thorough pre-procedural evaluation and optimal patient selection in order to improve outcomes. It is worth mentioning that one possible contributing factor to the poor outcomes observed among patients with PLFLG-AS is underlying undiagnosed amyloidosis. Wild-type transthyretin (ATTR) cardiac amyloidosis share a common demographic with degenerative calcific aortic stenosis, and may be present in 16% of elderly patients undergoing TAVR [27]. The diagnosis is challenging since both entities present with excessive cardiac remodeling and/or a restrictive physiology that may lead to a low-flow pattern. However, the diagnosis is of paramount importance since ATTR amyloidosis has a detrimental impact on prognosis and new therapies, which have shown to reduce mortality and improve functional capacity, have recently become available [28]. A part from screening for amyloidosis, one of the main challenges in this population is to accurately differentiate between "true-severe" PLFLG-AS from moderate-AS, with pseudo-severe AS accounting for approximately one-third of cases [29]. This distinction is of paramount importance since patients with true-severe AS generally benefit from aortic valve replacement, whereas those with pseudo-severe AS do not and should be treated medically [30]. Similar to patients with classical LF-LG AS, a low-dose dobutamine stress echocardiography could be performed to unmask this situation. However, it should not be used in those with a restrictive physiology, which is a frequent finding in this population, and may be inconclusive in a significant proportion of cases [1]. Hence, AVC by multidetector computed tomography may be the preferred approach in this context and should be performed systematically. AVC load not only can be used as a complementary test to accurately identify AS severity, but may also provide important prognostic information [31]. Patients belonging to the futility group had a higher AVC load compared to those who did not. PLFLG-AS is believed to represent a more advanced stage of AS with preserved LVEF ("D3" of the AHA/ACC), and the presence of more calcification may be a marker of chronicity. However, the proportion of patients that achieved the threshold for severity based on AVC did not differ between groups, which also strengths the hypothesis that the excess mortality reported in PLFLG-AS may not be entirely due to valvular disease, but is also likely related to extracardiac comorbidities and/or to impaired systolic left ventricular function unrelated to aortic stenosis, which is common in this age group.

4.1. Study limitations

Even though data was prospectively collected, the analysis was retrospective and subject to bias inherent to the design type. Second, dobutamine stress echocardiography and AVC score using computed tomography was not performed systematically and it is possible that patients with pseudo-severe AS were included in the study. Third, although COPD was diagnosed at each participating center on the basis of pulmonary function tests and/or requirements for bronchodilator therapy, we did not collect data on the degree of airflow obstruction and thus were unable to examine the link between these parameters and futility. Fourth, functional tests such as the 6MWT and DASI index were missing in several patients, and we were unable to analyze the role of these variables as predictors of treatment futility. Lastly, additional echocardiographic parameters for evaluating right ventricular dysfunction were not obtained, such as right ventricular ejection fraction and strain.

In conclusion, this study showed that PLFLG-AS patients undergoing TAVR have a significant risk of treatment futility. Independent predictors associated with a lack of benefit following the procedure were the presence of AF, COPD and a lower SVi. These predicting factors could be used to assess the anticipated benefit of TAVR and help tailor peri-procedural and follow-up strategies to be implemented in order to improve clinical outcomes. Also, being able to better identify the individuals less likely to benefit from TAVR may help guide treatment decisions and manage patient expectations.

CRediT authorship contribution statement

Afonso B. Freitas-Ferraz: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Luis Nombela-Franco:** Resources, Writing - review & editing. **Marina Urena:** Resources, Writing - review & editing. **Frederic Maes:** Resources, Writing - review & editing. **Gabriela Veiga:** Resources, Writing - review & editing. **Henrique Ribeiro:** Resources, Writing - review & editing. **Victoria Vilalta:** Resources, Writing - review & editing. **Iria Silva:** Resources, Writing - review & editing. **Asim N. Cheema:** Resources, Writing - review & editing. **Fabian Islas:** Resources, Writing - review & editing. **Quentin Fischer:** Resources, Writing - review & editing. **Victor Fradejas-Sastre:** Resources, Writing - review & editing. **Vitor Emer Egypto Rosa:** Resources, Writing - review & editing. **Eduard Fernandez-Nofrerias:** Resources, Writing - review & editing. **César Moris:** Resources, Writing - review & editing. **Lucia Junquera:** Resources, Writing - review & editing. **Siamak Mohammadi:** Resources, Writing - review & editing. **Philippe Pibarot:** Resources, Writing - review & editing. **Josep Rodés-Cabau:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration, Supervision.

Declaration of competing interest

Dr. Rodés-Cabau has received institutional research grants from Edwards Lifesciencies, Medtronic and Boston Scientific. Dr. Pibarot reports having Core Lab contracts with Edwards Lifesciences for which he receives no direct compensation, and receiving grants from Edwards Lifesciences and Medtronic during the conduct of the study. The rest of authors do not report any potential conflict of interest with respect to the content of this study.

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Appendix A. Supplementary data

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