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Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation

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Aims Our aim was to evaluate the invasive haemodynamic indices of high-risk symptomatic patients presenting with 'paradoxical' low-flow, low-gradient, severe aortic stenosis (AS) (PLF-LG) and low-flow, low-gradient severe AS (LEF-LG) and to compare clinical outcomes following transcatheter aortic valve implantation (TAVI) among these challenging AS subgroups.

Methods and results Of 534 symptomatic patients undergoing TAVI, 385 had a full pre-procedural right and left heart catheterization. A total of 208 patients had high-gradient severe AS [HGAS; mean gradient (MG) $\geq$40 mmHg], 85 had PLF-LG [MG $\leq$ 40 mmHg, indexed aortic valve area [iAVA] $\leq$0.6 cm^2 m^{-2}, stroke volume index $\leq$35 mL/m^2, ejection fraction (EF) $\geq$50%], and 61 had LEF-LG (MG $\leq$ 40 mmHg, iAVA $\leq$0.6 cm^2 m^{-2}, EF $\leq$40%). Compared with HGAS, PLF-LG and LEF-LG had higher systemic vascular resistances (HGAS: 1912 $\pm$ 654 vs. PLF-LG: 2006 $\pm$ 586 vs. LEF-LG: 2216 $\pm$ 765 dyne s m^{-5}, $P = 0.007$) but lower valvulo-arterial impedances (HGAS: 7.8 $\pm$ 2.7 vs. PLF-LG: 6.9 $\pm$ 1.9 vs. LEF-LG: 7.7 $\pm$ 2.5 mmHg mL^{-1} m^{-2}, $P = 0.027$). At 30 days, no differences in cardiac death (6.5 vs. 4.9 vs. 6.6%, $P = 0.90$) or death (8.4 vs. 6.1 vs. 6.6%, $P = 0.88$) were observed among HGAS, PLF-LG, and LEF-LG groups, respectively. At 1 year, New York Heart Association functional improvement occurred in most surviving patients (HGAS: 69.2% vs. PLF-LG: 71.7% vs. LEF-LG: 89.3%, $P = 0.09$) and no significant differences in overall mortality were observed (17.6 vs. 20.5 vs. 24.5%, $P = 0.67$). Compared with HGAS, LEF-LG had a higher 1 year cardiac mortality (adjusted hazard ratio 2.45, 95% confidence interval 1.04–5.75, $P = 0.04$).

Conclusion TAVI in PLF-LG or LEF-LG patients is associated with overall mortality rates comparable with HGAS patients and all groups profit symptomatically to a similar extent.

Keywords Transcatheter aortic valve implantation • Aortic stenosis • Hemodynamics

Introduction

Severe aortic stenosis (AS) is defined by current guidelines as an aortic valve area (AVA) $<$1 cm^2 and a mean gradient (MG) $>$40 mmHg in the presence of a normal cardiac output.[1] The management of symptomatic patients presenting with an AVA and gradient pattern discordant with guideline criteria (e.g. MG $\leq$40 mmHg and AVA $<$1 cm^2) is controversial, and can occur among patients with either preserved or low left-ventricular ejection fraction (LVEF).[2–12] Among patients with a low LVEF ($\leq$40%), the combination of a low-gradient ($\leq$40 mmHg) and small AVA ($<$1 cm^2) (LEF-LG) occurs in 5–10% of patients presenting with

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severe AS and is challenging because the prognosis of conservatively managed patients is dismal, yet perioperative mortality is high among those undergoing surgical aortic valve replacement (SAVR).[4,5,7,11] More recently, a new entity, paradoxical low-flow [LVEF ≥50%, but stroke volume index (SVI) ≤35 mL/m^2], low-gradient (≤40 mmHg), severe AS (AVA <1 cm^2) (PLF-LG), has been described and symptomatic patients treated conservatively had a higher mortality compared with those undergoing SAVR.[2,12] Transcatheter aortic valve implantation (TAVI) is an alternative treatment modality for high-risk or inoperable patients with symptomatic severe AS.[13,14] To date, only few data exist on whether patients presenting with symptomatic PLF-LG benefit from TAVI.[15,16] Among patients with LEF-LG, TAVI may be an attractive alternative to SAVR as it is less invasive,[13] LV functional recovery is enhanced among patients with low EF undergoing TAVI,[17] and transcatheter heart valve prostheses have a superior haemodynamic profile.[18] Aortic stenosis is considered a systemic disease and in quantifying overall disease severity, it is essential to consider the interrelation between valvular, arterial, and ventricular variables that may contribute to the pathophysiology and prognosis in patients with AS.[19] Therefore, in a high-risk patient population undergoing TAVI, we sought first, to compare baseline physiological variables using invasively derived haemodynamic indices among patients with low-flow, low-gradient severe AS and either preserved or low LVEF to patients with high-gradient (>40 mmHg) severe AS (HGAS) and secondly, to compare clinical outcomes among these three distinct AS subgroups.

Methods

Patient population

This is a retrospective analysis of prospectively collected data within a dedicated database that includes all patients with severe native-valve AS [indexed AVA (iAVA) ≤0.6 cm^2/m^2 or MG >40 mmHg], who underwent TAVI at our institution between August 2007 and August 2012 (n = 534). All patients were deemed inoperable or at high surgical risk for conventional surgery by a multidisciplinary team consisting of interventional cardiologists and cardiothoracic surgeons. Included in this study were all consecutive patients with: (i) symptomatic severe native-valve AS (iAVA ≤0.6 cm^2 and/or MG > 40 mmHg); (ii) a full pre-procedural right and left heart catheterization within 9 months prior to TAVI; and (iii) complete clinical follow-up data. *Figure 1* summarizes the patient flow. The 354 patients comprising the study population were subdivided into the following three groups:

Group 1: HGAS (MG >40 mmHg) (n = 208)
Group 2: PLF-LG (iAVA ≤0.6 cm^2, MG ≤40 mmHg, SVI ≤35 mL/m^2, LVEF ≥50%) (n = 85)
Group 3: LEF-LG (iAVA ≤0.6 cm^2, MG ≤40 mmHg, LVEF ≤40%) (n = 61).

The cohort study complies with the Declaration of Helsinki, was approved by the local Ethics Committee, and all patients provided informed written consent.

Cardiac catheterization

All patients underwent coronary angiography and right and left heart catheterization for haemodynamic assessment prior to TAVI. Data

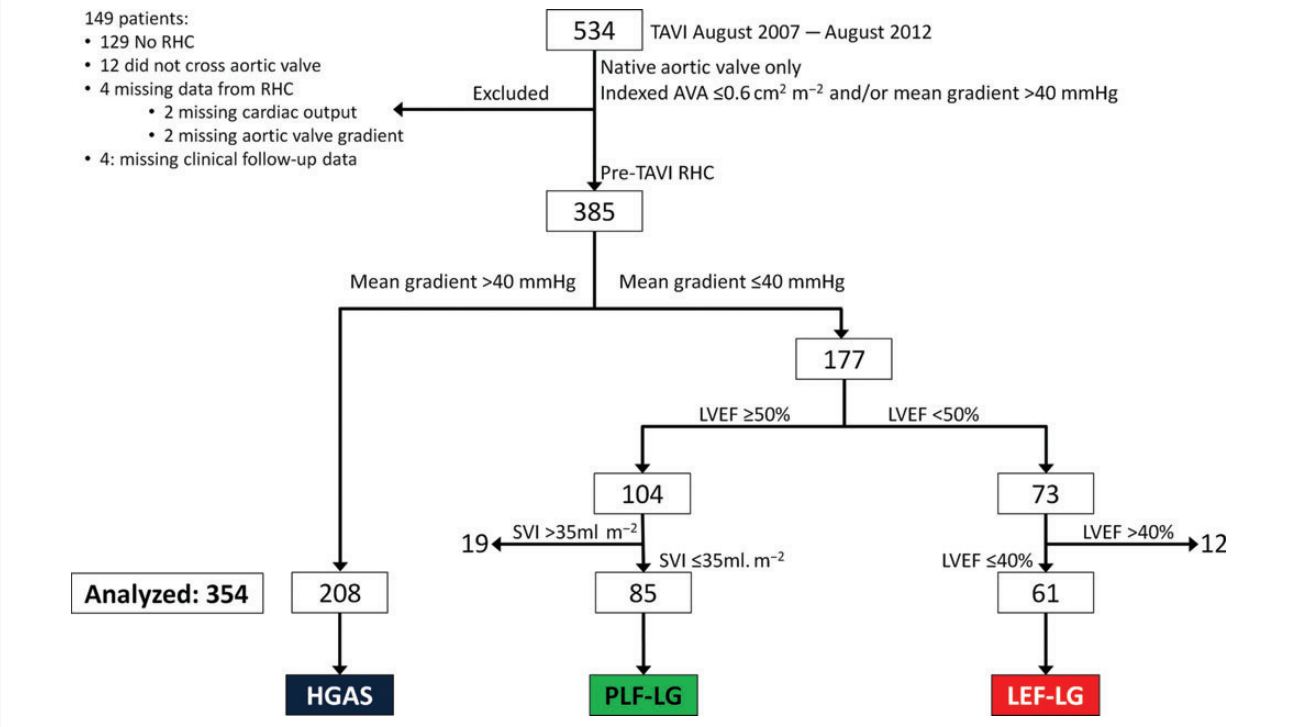


Figure 1 Description of the patient population. TAVI, transcatheter aortic valve implantation; AVA, aortic valve area; RHC, right and left heart catheterization; LVEF, left-ventricular ejection fraction; SVI, stroke volume index; HGAS, high-gradient severe aortic stenosis (AS) (mean gradient >40 mmHg); PLF-LG, paradoxical low-flow, low-gradient (LVEF ≥50%, SVI ≤35 mL m^{-2}, mean gradient ≤40 mmHg), severe AS (indexed AVA ≤0.6 cm^2 m^{-2}); LEF-LG, low-flow, low-gradient (LVEF ≤40%, mean gradient ≤40 mmHg), severe AS (indexed AVA ≤0.6 cm^2 m^{-2}).

were prospectively entered into a dedicated database. Intracardiac pressures were recorded with fluid-filled catheters connected to pressure transducers. Coronary artery disease was defined by a ≥50% lumen diameter narrowing of the left main coronary artery and ≥70% for the major epicardial arteries. Multi-vessel CAD was defined as either left main or two or three major epicardial vessel disease.

Cardiac output

Cardiac output was determined using the Fick method and estimated oxygen consumption (VO2). For calculating Fick cardiac output, systemic arterial and pulmonary arterial oxygen saturation, and haemoglobin were measured directly. The Krakau formula, an equation incorporating both body surface area and age, was the standard equation used for VO2 estimation.[20] Stroke volume (SV) was calculated in all patients as the CO divided by the heart rate (HR) and was indexed to BSA for calculation of the SVI.

Aortic stenosis severity

Left-ventricular pressures were directly measured using fluid-filled, single-lumen pigtail catheters attached to pressure transducers. Aortic valve gradients were measured in all patients by pullback technique from the left ventricle to the ascending aorta. Peak-to-peak gradient was calculated as the difference between the LV systolic pressure (LVSP) and the aortic systolic arterial pressure. Mean gradient, represented by the area under the curve, was digitally calculated by the device software (Schwarzer Systems, Munich, Germany) by superimposing pressure recordings from three consecutive beats for patients in sinus rhythm and five consecutive beats for patients in atrial fibrillation. AVA was derived from the Gorlin equation and calculated as $AVA = (CO/SEP * HR)/44.3\sqrt{\Delta Pm}$, CO indicating cardiac output; HR, heart rate; SEP, systolic ejection period; and ΔPm, mean gradient. Valvular resistance (VR) was calculated as $VR = (\Delta Pm * HR * SEP/CO) * 1.33$.

Arterial afterload

Systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were measured invasively and mean arterial pressure (MAP) was calculated as $MAP = DAP + 1/3(SAP - DAP)$. Systemic arterial compliance (SAC) was calculated as the ratio of the SVI to the pulse pressure (SAP-DAP): $SAC = (SVI)/SAP - DAP$.[21] Systemic vascular resistance (SVR) was calculated using the formula $SVR = [(MAP - RAm) * 80]/[CO]$ with RA_m indicating the mean right atrial pressure.

Global afterload

Valvuloarterial impedance (Z_{va}), a measure of the global afterload impacting on the left ventricle (i.e. valvular + arterial), was calculated using the formula of Briand *et al*[21]: $Zva = LVSP/SVI$, where LVSP is the LV systolic pressure.

Left-ventricular systolic function

Left-ventricular ejection fraction was assessed before TAVI in all patients with transthoracic echocardiography (TTE) using the biplane Simpson method and among 330/354 (93%) patients at the time of LV angiography in the right anterior oblique projection. The remaining 24/354 (7%) did not undergo LV angiography because of renal impairment. For this analysis, LVEF calculated at the time of LV angiography was used for calculations and statistical analysis unless not performed, in which case the LVEF was calculated from the most recent echocardiogram ($n = 24$) performed around the time of cardiac catheterization. In case of a disagreement among these methods, the reviewing cardiologist selected the value that appeared the most representative.

Right heart pressures

Pulmonary hypertension (PH) was defined as a mean pulmonary artery (PA) pressure ≥25 mmHg and was subdivided into pre-capillary PH [left-ventricular end-diastolic pressure (LVEDP) ≤15 mmHg] and post-capillary PH (LVEDP >15 mmHg).

Transcatheter aortic valve implantation procedure

Transcatheter aortic valve implantation was performed using standard techniques as previously described.[22] Vascular access was transfemoral using the Medtronic CoreValve Revalving System (MCRS) (Medtronic, Inc., Minneapolis, MN, USA) or the Edwards SAPIEN valve (ESV) (Edwards Lifesciences, Irvine, CA, USA), transapical for the ESV or the self-expanding Symetis ACURATE TA™ valve (SA) (Symetis Inc., Switzerland) or trans-subclavian using the MCRS.

Clinical follow-up

Adverse events were assessed in hospital, and regular clinical follow-up was performed at 1, 6, and 12 months by means of a clinical visit or a standardized telephone interview. All suspected events were adjudicated by an unblinded clinical event committee comprising a cardiac surgeon and interventional cardiologist. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) responsible for central data audits and maintenance of the database.

Definitions

Clinical endpoints were defined according to the criteria proposed by the Valve Academic Research Consortium (VARC).[23]

Study endpoints

Primary endpoint was all-cause mortality, cardiovascular death, and major adverse cardiovascular and cerebrovascular events (MACCE) (composite of all-cause mortality, major stroke, and myocardial infarction) at 30 days and 1 year. Secondary endpoints included cerebrovascular events (major stroke, minor stroke, transient ischaemic attack) and myocardial infarction (MI) at 30 days and 1 year. In addition, bleeding (life-threatening and major), acute renal failure, access site complications (major and minor), and the VARC combined safety endpoint were assessed at 30 days. New York Heart Association (NYHA) functional class status and Canadian Cardiovascular Society (CCS) angina status were assessed at baseline and 1-year follow-up. Among patients with an LVEF ≤40%, LVEF recovery in patients with a low MG (≤40 mmHg; LEF-LG) was compared with LVEF recovery in patients with a high MG [>40 mmHg; low-flow, high-gradient patients (LEF-HG)] throughout 1 year post-TAVI using TTE. Finally, we assessed the prevalence and impact of patient–prosthetic mismatch (PPM) on all-cause mortality at 1 year.

Statistics

Continuous data are presented as means ± standard deviations (SD), and categorical variables are depicted as percentages and numbers. Categorical variables were compared by means of the χ^2 test (or Fisher's test for two group comparisons), and continuous variables were compared using ANOVA (or unpaired *t*-test for two group comparisons). Left-ventricular ejection fraction was compared among LEF-LG and LEF-HG groups before and after TAVI using the paired-samples *T*-test. NYHA and CCS functional status at 1 year was analysed using χ^2 tests comparing improved vs. not improved survivors across the three patient groups. Time-to-outcome data are presented using

Kaplan–Meier curves, with incidence rates calculated from life-tables, at 30 days and 1-year follow-up, respectively. Univariate and inverse probability treatment weighting (IPTW) adjusted Cox proportional hazards models were used to derive hazard ratio estimates of clinical time-to-outcome comparisons between groups (death, cerebrovascular events, myocardial infarction, and their composites). Univariate Poisson regression models with robust error variances were used to derive risk ratio estimates of all other clinical outcome comparisons between groups. Inverse probability treatment weighting was calculated as the inverse probability of the group weight from a multinomial regression with group as response (HGAS, PLF-LG, or LEF-LG), including the baseline predictors: age, gender, body mass index, previous MI, previous coronary artery bypass grafting, previous percutaneous coronary intervention (PCI), peripheral vascular disease (PVD), and coronary artery disease. All *P*-values and 95% confidence intervals (CIs) are two-sided. Two-sided *P*-values < 0.05 were considered statistically significant. All analyses were performed with STATA (version 12, StataCorp, College Station, TX, USA).

Results

Patient characteristics

Baseline characteristics are given in *Table 1*. Mean age was 82.5 $\pm$ 5.2 years and significantly more females presented with HGAS compared with LEF-LG. No significant differences were observed in the proportion of PLF-LG patients presenting with NYHA class III/IV shortness of breath at baseline compared with HGAS patients (61 vs. 71%, $P = 0.13$). PLF-LG patients, however, were more likely to present with CCS class III/IV angina compared with HGAS patients (24 vs. 10%, $P = 0.004$). Significantly more patients with LEF-LG presented in NYHA class III/IV compared with PLF-LG (82 vs. 61%, $P = 0.012$). LEF-LG patients had a significantly higher incidence of previous MI, moderate mitral regurgitation, and logistic EuroSCORE, compared with both HGAS and PLF-LG. LEF-LG patients also had a significantly higher rate of coronary artery disease compared with HGAS and a significantly higher STS score compared with PLF-LG. Both PLF-LG and LEF-LG groups had significantly higher rates of multi-vessel coronary artery disease, PVD, previous PCI, and higher baseline clopidogrel use compared with HGAS patients.

Haemodynamic characteristics

Haemodynamic characteristics are presented in *Table 2* and *Figure 2*. Median interval between cardiac catheterization and TAVI was 20 days [interquartile range (IQR): 8–40 days]. All patients by definition had severe AS. PLF-LG patients, however, had a significantly larger AVA, iAVA, and lower VR compared with both HGAS and LEF-LG patients. HGAS patients had an overall higher global afterload (Zva) despite a significantly lower arterial afterload (SVR and SAP) compared with both PLF-LG and LEF-LG groups because of a higher valvular load. Conversely, PLF-LG patients had a lower global afterload despite a significantly higher arterial afterload compared with HGAS patients. LEF-LG patients had a lower systolic arterial pressure (pseudonormalization) yet a significantly higher SVR compared with both HGAS and PLF-LG groups. In addition, LEF-LG patients had a significantly higher global afterload compared with PLF-LG, but not HGAS, patients. Mean LVEF was 53%. Compared with HGAS, PLF-LG patients had a significantly higher LVEF despite a significantly lower cardiac output. HGAS patients had significantly higher LVSP, SV, SVI, CO, and CI values compared with PLF-LG and LEF-LG groups, although the latter four variables were all in the low range. Overall, 77% of patients had pulmonary hypertension (PH), which was secondary to left-sided heart disease in most (82%) cases. Incidence of PH was highest among LEF-LG (90%) and lowest among PLF-LG (70%) patients.

Procedural characteristics

Procedural characteristics are given in *Table 3*. Mean procedural time was 77.7 $\pm$ 35.7 min. Transfemoral route and Medtronic CoreValve were used in most cases. More PLF-LG patients had transapical TAVI compared with HGAS. Significantly more patients with HGAS underwent concomitant PCI compared with LEF-LG. Overall VARC device success was 86%. Main reason for the absence of device success was post-procedural paravalvular aortic regurgitation $\geq 2+$ but not a failure to implant the device successfully.

Clinical outcomes

Median follow-up was 370 days (IQR: 43–738 days) and no patients were lost to follow-up. Event rates with crude and adjusted hazard ratios (HR) for all major clinical endpoints at 30 days and 12 months are provided in *Tables 4* and *5*.

Primary endpoint at 30 days

No significant differences in MACCE (10.2 vs. 6.1 vs. 9.9%, $P = 0.58$), cardiovascular death (6.5 vs. 4.9 vs. 6.6%, $P = 0.90$), or all-cause mortality (8.4 vs. 6.1 vs. 9.9%, $P = 0.58$) were observed at 30 days among HGAS, PLF-LG, and LEF-LG groups, respectively.

Secondary endpoints at 30 days

No significant differences were observed in cerebrovascular events, bleeding, acute renal failure, or access site complications between any groups at 30 days (*Table 4*). Combined VARC safety endpoint was 25, 17.6, and 31.1% ($P = 0.17$) in HGAS, PLF-LG, and LEF-LG groups, respectively.

Primary endpoint at 1 year

Survival curves for MACCE, cardiovascular death, and all-cause mortality are shown in *Figure 3*. No significant differences in unadjusted rates of MACCE (21.5 vs. 20.5 vs. 25.8%, $P = 0.74$) and death (17.6 vs. 20.5 vs. 24.5%, $P = 0.67$) were observed at 12 months among HGAS, PLF-LG, and LEF-LG groups, respectively. However, compared with HGAS, a significantly higher rate of cardiovascular mortality at 12 months was observed among LEF-LG patients [8.6 vs. 22.5%, hazard ratio (HR) 2.39, 99% CI 1.11–5.15, $P = 0.03$] and the significance remained after adjustment for age, gender, BMI, previous MI, CABG, PCI, PVD, and coronary artery disease (HR 2.45, 95% CI 1.04–5.75, $P = 0.04$).

Secondary endpoints at 1 year

No significant differences in cerebrovascular events or MI were observed at 1-year follow-up between groups.

NYHA and CCS functional status at 1 year

89.3, 71.7, and 69.2% of surviving LEF-LG, PLF-LG, and HGAS patients, respectively, improved at least one NYHA level at 1 year

Table 1 Baseline clinical characteristics

	All patients ($n = 354$)	HGAS ($n = 208$)	PLF-LG ($n = 85$)	LEF-LG ($n = 61$)	*P*-value
Demographics					
Age (years)	82.5 ± 5.2	82.9 ± 5.2	82.0 ± 5.2	82.0 ± 5.0	0.28
Female gender, *n* (%)	202 (57)	128 (62)[a]	47 (55)	27 (44)[a]	0.053
Physical dimensions					
Body mass index (kg/m^2)	26.6 ± 5.2	26.5 ± 5.1	27.6 ± 5.4[b]	25.5 ± 5.4[b]	0.048
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.67
Cardiac risk factors					
Diabetes mellitus, *n* (%)	101 (29)	55 (26)	27 (32)	19 (31)	0.58
Hypercholesterolaemia, *n* (%)	224 (63)	126 (61)	57 (67)	41 (67)	0.45
Hypertension, *n* (%)	298 (84)	174 (84)	73 (86)	51 (84)	0.89
Current smoker, *n* (%)	36 (10)	23 (11)	7 (8)	6 (10)	0.77
Past medical history					
Coronary artery disease, *n* (%)	209 (59)	111 (53)[a]	53 (62)	45 (74)[a]	0.013
Multivessel disease	128 (40)	62 (33)[a,c]	36 (46)[c]	30 (54)[a]	0.008
Previous myocardial infarction, *n* (%)	52 (15)	19 (9)[a]	13 (15)[b]	20 (33)[a,b]	<0.001
Previous coronary artery bypass graft, *n* (%)	50 (14)	22 (11)	16 (19)	12 (20)	0.07
Previous percutaneous coronary intervention, *n* (%)	84 (24)	36 (17)[a,c]	26 (31)[c]	22 (36)[a]	0.002
Previous stroke, *n* (%)	25 (7)	12 (6)	6 (7)	7 (11)	0.31
Peripheral vascular disease, *n* (%)	70 (20)	29 (14)[a,c]	23 (27)[c]	18 (30)[a]	0.004
Chronic obstructive pulmonary disease, *n* (%)	62 (18)	33 (16)	20 (24)	9 (15)	0.25
Renal failure (GFR < 60 mL min^{-1} 1.73 m^{-2})	241 (68)	137 (66)	56 (67)	48 (79)	0.17
Valvular disease					
Previous valve surgery, *n* (%)	3 (1)	3 (1)	0 (0)	0 (0)	0.35
Moderate aortic regurgitation,[d] *n* (%)	30 (10)	21 (12)	3 (4)	6 (11)	0.18
Moderate mitral regurgitation, *n* (%)	76 (24)	37 (20)[a]	14 (18)[b]	25 (44)[a,b]	<0.001
Severe mitral regurgitation, *n* (%)	10 (3)	4 (2)	2 (3)	4 (7)	0.18
Baseline cardiac rhythm					
Atrial fibrillation, *n* (%)	104 (29)	56 (27)	27 (32)	21 (34)	0.45
Symptoms					
New York Heart Association (NYHA) Functional Class					
NYHA III/IV, *n* (%)	249 (71)	147 (71)	52 (61)[b]	50 (82)[b]	0.024
Canadian Cardiovascular Society (CCS) Angina Status					
CCS III/IV, *n* (%)	49 (14)	21 (10)[c]	20 (24)[c]	8 (13)	0.009
Risk assessment					
Logistic EuroScore (%)	23.6 ± 13.8	20.9 ± 12.4[a]	19.7 ± 9.0[b]	38.0 ± 14.7[a,b]	<0.001
STS score (%)					
Mean	7.0 ± 5.5	6.9 ± 6.2	6.5 ± 3.4[b]	8.2 ± 5.2[b]	0.16
Median (25%–75% IQR)	5.6 (4.0–8.1)	5.3 (3.8–7.8)	5.4 (4.0–8.8)	6.9 (4.6–10.3)	0.016
Medications					
Aspirin, *n* (%)	222 (63)	124 (60)	55 (65)	43 (70)	0.28
Clopidogrel, *n* (%)	64 (18)	26 (13)[a,c]	23 (27)[c]	15 (25)[a]	0.004
Oral anticoagulation, *n* (%)	98 (28)	50 (24)	26 (31)	22 (36)	0.15
Laboratory values					

Continued

Table 1 *Continued*

	All patients ($n = 354$)	HGAS ($n = 208$)	PLF-LG ($n = 85$)	LEF-LG ($n = 61$)	*P*-value
B-type natriuretic peptide (pg/mL)	641.0 ± 846.6	573.0 ± 785.4[c, a]	272.4 ± 287.9 [b,c]	1283.2 ± 1100.3[a,b]	<0.001

Values are *n* (%) or mean ± standard deviation with *P*-values from ANOVAs or counts (%) with *P*-values from χ^2 tests. STS score was left-skewed and therefore also median (25–75% interquartile range) with Kruskall–Wallis test and Mann–Whitney *U*-tests are reported.
STS score, Society for Thoracic Surgeons score.
[a]Significant difference between low-flow, low-gradient severe aortic stenosis (LEF-LG) and HGAS groups.
[b]Significant differences between patients with PLF-LG and LEF-LG groups.
[c]Significant difference between patients with high-gradient severe aortic stenosis (HGAS) and patients with paradoxical low-flow, low-gradient, severe aortic stenosis (PLF-LG) groups.
[d]No patients had severe aortic regurgitation at baseline.

Table 2 **Invasive haemodynamic data**

	All patients ($n = 354$)	HGAS ($n = 208$)	PLF-LG ($n = 85$)	LEF-LG ($n = 61$)	*P*-value
Aortic stenosis severity					
Aortic valve area, cm^2	0.52 ± 0.21	0.47 ± 0.21[a,b]	0.61 ± 0.19[a,c]	0.58 ± 0.19[b,c]	<0.001
Indexed aortic valve area, $cm^2\ m^{-2}$	0.29 ± 0.11	0.26 ± 0.11[a,b]	0.34 ± 0.10[a,c]	0.33 ± 0.10[b,c]	<0.001
Peak-to-peak gradient, mmHg	54.08 ± 27.53	67.88 ± 23.78[a,b]	37.71 ± 14.97[a,c]	29.85 ± 23.60[b,c]	<0.001
Mean gradient, mmHg	44.52 ± 17.09	55.62 ± 12.39[a,b]	31.05 ± 6.58[a,c]	25.46 ± 8.58[b,c]	<0.001
Valvular resistance, dynes cm^{-5}	343.52 ± 209.83	426.79 ± 226.18[a,b]	221.95 ± 85.71[a,c]	231.74 ± 122.66[b,c]	<0.001
Systemic vascular load					
Systolic arterial pressure, mmHg	135.60 ± 29.06	136.56 ± 29.52[a,b]	140.42 ± 27.94[a,c]	125.59 ± 27.06[b,c]	0.007
Diastolic arterial pressure, mmHg	65.97 ± 14.25	65.15 ± 14.37	66.93 ± 13.41	67.44 ± 14.96	0.42
Mean arterial pressure	93.92 ± 18.55	93.61 ± 19.22	96.65 ± 17.68	91.18 ± 17.12	0.20
Systemic vascular resistance, dynes cm^{-5}	1987.30 ± 666.96	1912.09 ± 654.06[a,b]	2006.65 ± 586.92[a,c]	2216.78 ± 765.05[b,c]	0.007
Systemic arterial compliance, mL $mmHg^{-1}$	0.43 ± 0.19	0.45 ± 0.21	0.39 ± 0.13	0.43 ± 0.19	0.11
LV global afterload					
Valvuloarterial impedance, mmHg $mL^{-1}\ m^{-2}$	7.57 ± 2.49	7.80 ± 2.67[a,b]	6.94 ± 1.88[a,c]	7.66 ± 2.50[b,c]	0.027
LV systolic function					
Ejection fraction, %	52.65 ± 15.78	56.48 ± 13.82[a,b]	60.25 ± 6.53[a,c]	29.02 ± 6.73[b,c]	<0.001
LV systolic pressure, mmHg	189.68 ± 35.27	204.43 ± 31.46[a,b]	178.13 ± 28.95[a,c]	155.44 ± 24.43[b,c]	<0.001
LV end diastolic pressure, mmHg	21.38 ± 8.02	21.95 ± 8.21[a,b]	18.84 ± 7.43[a,c]	22.98 ± 7.42[b,c]	0.002
Stroke volume, mL	48.11 ± 15.16	50.91 ± 16.66[a,b]	47.77 ± 9.76[a,c]	39.02 ± 12.23[b,c]	<0.001
Stroke volume index, mL m^{-2}	26.94 ± 7.71	28.55 ± 8.47[a,b]	26.63 ± 4.73[a,c]	21.85 ± 5.97[b,c]	<0.001
Cardiac output, L min^{-1}	3.69 ± 0.96	3.85 ± 1.02[a,b]	3.72 ± 0.74[a,c]	3.11 ± 0.79[b,c]	<0.001
Cardiac index, L $min^{-1}\ m^{-2}$	2.07 ± 0.48	2.16 ± 0.51[a,b]	2.07 ± 0.34[a,c]	1.74 ± 0.36[b,c]	<0.001
Right-sided haemodynamic data					
Mean PA pressure, mmHg	33.51 ± 11.49	32.62 ± 11.58[a,b]	30.22 ± 10.42[a,c]	40.98 ± 9.33[b,c]	<0.001
Pulmonary hypertension,[d] *n* (%)	259 (77)	149 (76)[a,b]	57 (70)[a,c]	53 (90)[b,c]	0.022
Pre-capillary PH, *n* (%)	47 (14)	25 (13)	15 (19)	7 (12)	0.40
Post-capillary PH, *n* (%)	212 (63)	124 (63)[a,b]	42 (52)[a,c]	46 (78)[b,c]	0.007

Values are *n* (%) or mean ± standard deviation.
PA, pulmonary artery; PH, pulmonary hypertension.
[a]Significant difference between patients with high-gradient severe aortic stenosis (HGAS) and patients with paradoxical low-flow, low-gradient, severe aortic stenosis (PLF-LG) groups.
[b]Significant difference between low-flow, low-gradient severe aortic stenosis (LEF-LG) and HGAS groups.
[c]Significant differences between patients with PLF-LG and LEF-LG group.
[d]Pulmonary hypertension = mean PA pressure ≥25 mmHg.

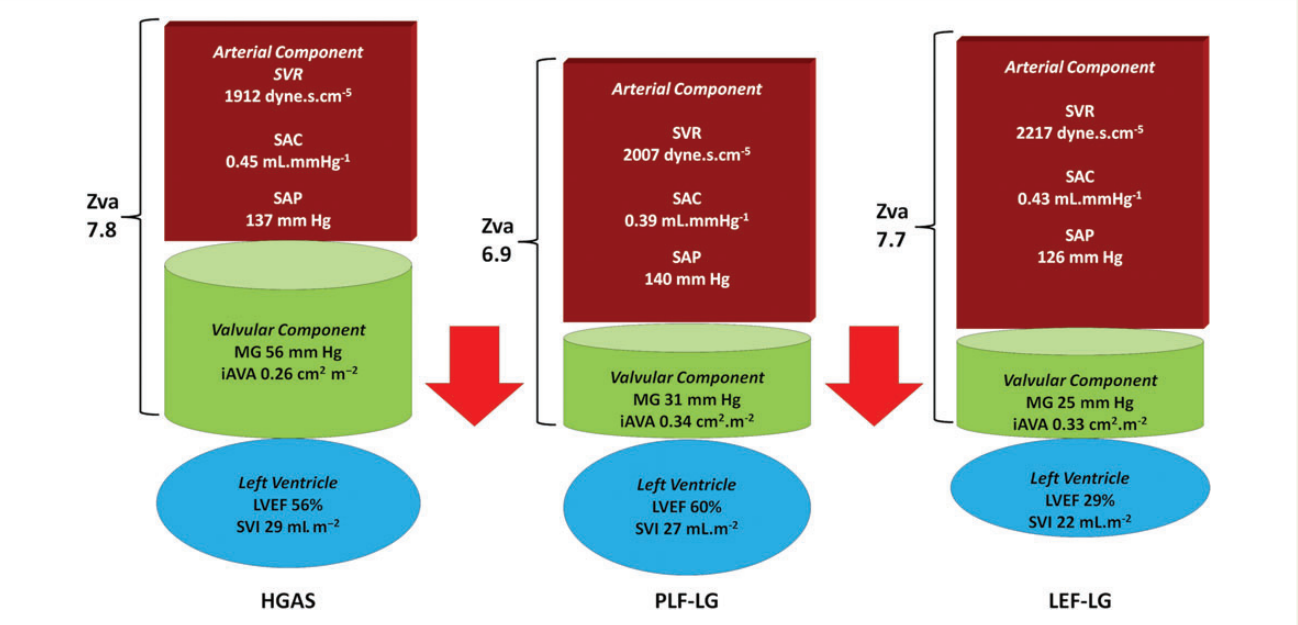


Figure 2 Diagram illustrating the interrelation between the ventricular, valvular, and arterial components among patients with high-gradient, severe aortic stenosis (AS) (HGAS), 'paradoxical' low-flow, low-gradient, severe AS (PLF-LG) and low-flow, low-gradient, severe AS (LEF-LG). PLF-LG and LEF-LG patients had a significantly higher arterial afterload despite a lower valvulo-arterial impedance (Zva). Values taken from *Table 2*. SVR, systemic vascular resistance; SAC, systemic arterial compliance; SAP, systemic arterial blood pressure; MG, mean gradient; iAVA, indexed aortic valve area; LVEF, left-ventricular ejection fraction; SVI, stroke volume index.

Table 3 Procedural characteristics

	All patients ($n = 354$)	HGAS ($n = 208$)	PLF-LG ($n = 85$)	LEF-LG ($n = 61$)	*P*-value
Access route					0.09
Femoral, *n* (%)	291 (82)	179 (86)[a]	64 (75)[a]	48 (79)	0.07
Apical, *n* (%)	59 (17)	28 (13)[a]	20 (24)[a]	11 (18)	0.11
Subclavian, *n* (%)	4 (1)	1 (0)	1 (1)	2 (3)	0.19
Valve type					0.59
Medtronic CoreValve, *n* (%)	200 (56)	119 (57)	43 (51)	38 (62)	0.35
Edwards Sapien valve, *n* (%)	152 (43)	88 (42)	41 (48)	23 (38)	0.43
Symetis valve, *n* (%)	2 (1)	1 (0)	1 (1)	0 (0)	0.63
Revascularization					0.07
Concomitant PCI, *n* (%)	55 (16)	40 (19)[b]	10 (12)	5 (8)[b]	0.06
Staged PCI, *n* (%)	37 (10)	16 (8)	11 (13)	10 (16)	0.10
Procedural specifications					0.49
Device success, *n* (%)	303 (86)	175 (85)	78 (92)	50 (82)	0.17
No device success: valve in series, *n* (%)	6 (2)	3 (1)	2 (2)	1 (2)	0.86
No device success: aortic regurgitation ≥grade 2, *n* (%)	39 (11)	25 (12)	5 (6)	9 (15)	0.18
No device success: access failure, failure of deployment or retrieval, *n* (%)	5 (1)	4 (2)	0 (0)	1 (2)	0.44

Values are *n* (%) or mean ± standard deviation.
PCI, percutaneous coronary intervention.
[a]Significant difference between patients with high-gradient severe aortic stenosis (HGAS) and patients with paradoxical low-flow, low-gradient, severe aortic stenosis (PLF-LG) groups.
[b]Significant difference between low-flow, low-gradient severe aortic stenosis (LEF-LG) and HGAS groups.

Table 4 Clinical outcomes at 30 days and 1-year follow-up

	HGAS (*n* = 208)	PLF-LG (*n* = 85)	LEF-LG (*n* = 61)	PLF-LG vs. HGAS		LEF-LG vs. HGAS		Overall *P*-value
				HR or RR (95% CI)	*P*-value	HR or RR (95% CI)	*P*-value	
30 days follow-up								
All cause death,[a] *n* (%)	16 (8.4)	5 (6.1)	4 (6.6)	0.78 (0.29–2.13)	0.63	0.86 (0.29–2.57)	0.78	0.88
Cardiovascular death,[a] *n* (%)	12 (6.5)	4 (4.9)	4 (6.6)	0.83 (0.27–2.58)	0.75	1.14 (0.37–3.54)	0.82	0.90
Cerebrovascular events								
Major Stroke, *n* (%)	10 (4.9)	1 (1.2)	1 (1.6)	0.24 (0.03–1.90)	0.18	0.34 (0.04–2.63)	0.30	0.26
Minor Stroke, *n* (%)	1 (0.5)	0 (0.0)	1 (1.6)					
Transient ischaemic attack, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)					
Myocardial infarction, *n* (%)	0 (0.0)	0 (0.0)	1 (1.6)					
All cause death, major stroke, or MI,[a] *n* (%)	20 (10.2)	5 (6.1)	6 (9.9)	0.61 (0.23–1.61)	0.32	1.02 (0.41–2.55)	0.96	0.58
Bleeding								
Life-threatening, *n* (%)	35 (16.9)	11 (12.9)	10 (16.4)	0.77 (0.41–1.44)	0.41	0.97 (0.51–1.84)	0.92	0.70
Major, *n* (%)	58 (28.0)	23 (27.1)	14 (23.0)	0.97 (0.64–1.46)	0.87	0.82 (0.49–1.36)	0.44	0.74
Acute renal failure, *n* (%)	8 (3.8)	4 (4.7)	1 (1.6)	1.22 (0.38–3.96)	0.74	0.43 (0.05–3.35)	0.42	0.64
Access site complications								
Major, *n* (%)	19 (9.1)	4 (4.7)	7 (11.5)	0.52 (0.18–1.47)	0.22	1.26 (0.55–2.85)	0.59	0.33
Minor, *n* (%)	26 (12.5)	12 (14.1)	9 (14.8)	1.13 (0.60–2.13)	0.71	1.18 (0.58–2.38)	0.64	0.87
VARC Safety endpoint, *n* (%)	52 (25.0)	15 (17.6)	19 (31.1)	0.71 (0.42–1.18)	0.19	1.25 (0.80–1.94)	0.33	0.17
1-year follow-up								
All cause death,[a] *n* (%)	31 (17.6)	14 (20.5)	12 (24.5)	1.13 (0.60–2.12)	0.71	1.36 (0.70–2.64)	0.37	0.67
Cardiovascular death,[a] *n* (%)	16 (8.6)	8 (12.3)	11 (22.5)	1.25 (0.53–2.92)	0.61	2.39 (1.11–5.15)	0.03	0.08
Cerebrovascular events								
Major stroke, *n* (%)	12 (6.4)	1 (1.2)	1 (1.6)	0.20 (0.03–1.56)	0.13	0.28 (0.04–2.19)	0.23	0.17
Minor stroke, *n* (%)	1 (0.5)	0 (0.0)	1 (1.6)		1.00	3.41 (0.21–54.51)	0.39	0.37
Transient ischaemic attack, *n* (%)	0 (0.0)	2 (4.0)	0 (0.0)		0.08			0.09
Myocardial infarction, *n* (%)	1 (0.7)	0 (0.0)	1 (1.6)		1.00	3.44 (0.21–54.94)	0.38	0.37
All cause death, major stroke, or MI,[a] *n* (%)	38 (21.5)	14 (20.5)	13 (25.8)	0.89 (0.48–1.65)	0.71	1.20 (0.64–2.25)	0.58	0.74

Depicted are counts (incidence rates %). Hazard ratios (HR) [95% confidence intervals (CI)] from Cox regressions for time-to-event data (death to myocardial infarction). In case of zero events, only Fisher's test *P*-values are reported. Risk ratios (RR) from Poisson regression with robust error variances for other event data at 30 days [bleeding to valvular academic research consortium (VARC) safety endpoint]. Other abbreviations as in *Table 1*.
[a]Primary endpoint components.

(compared with no change or worsened $P = 0.09$; *Figure 4A*). All patients with PLF-LG and LEF-LG improved at least one CCS functional class level at 1 year as did 85% of HGAS patients (*Figure 4B*).

Transthoracic echocardiography follow-up among low-flow, low-gradient and low-flow, high-gradient patients

Baseline and follow-up LVEF among patients with LEF-LG ($n = 61$) and the subgroup of patients ($n = 34$) with low-flow (LVEF $\leq$ 40%), high-gradient (>40 mmHg) (LEF-HG) severe AS are shown in *Figure 5*. Compared with baseline, a significant improvement in LVEF was observed at 1-year follow-up among both LEF-LG (baseline LVEF: 28.2 $\pm$ 5.9% vs. 1-year LVEF: 39.4 $\pm$ 13.6%, $P = 0.015$) and LEF-HG (31.8 $\pm$ 7.2 vs. 50.1 $\pm$ 14.2%, $P < 0.0001$) groups after TAVI. Compared with LEF-HG, LVEF improvement was less among LEF-LG patients at 30 days (9.1 $\pm$ 10.5 vs. 21.4 $\pm$ 11.2%, $P < 0.001$) and 1 year (11.2 $\pm$ 14.1 vs. 18.3 $\pm$ 13.0%, $P = 0.17$), although differences were significant only at 30 days.

Patient–prosthetic mismatch

Patient–prosthetic mismatch was defined as a post-procedural indexed AVA $\leq$0.85 $cm^2\ m^{-2}$ using transthoracic echocardiography.

Table 5 Adjusted primary endpoints at 1-year follow-up[a]

	HGAS ($n = 208$)	PLF-LG ($n = 85$)	LEF-LG ($n = 61$)	PLF-LG vs. HGAS		LEF-LG vs. HGAS		Overall *P*-value
				HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	
1-year follow-up								
All cause death, *n* (%)	31 (17.6)	14 (20.5)	12 (24.5)	1.25 (0.65–2.41)	0.50	1.25 (0.59–2.68)	0.56	0.73
Cardiovascular death, *n* (%)	16 (8.6)	8 (12.3)	11 (22.5)	1.49 (0.62–3.61)	0.37	2.45 (1.04–5.75)	0.04	0.12
All cause death, major stroke, or MI, *n* (%)	38 (21.5)	14 (20.5)	13 (25.8)	0.93 (0.50–1.76)	0.83	1.07 (0.53–2.19)	0.85	0.95

Depicted are counts (incidence rates%).
[a]Adjusted for age, gender, body mass index, previous myocardial infarction, previous coronary artery bypass grafting, previous percutaneous coronary intervention, peripheral vascular disease and coronary artery disease. Hazard ratios (HR) [95% confidence interval (CI)] from Cox regressions weighted by inverse probability treatment weighting (IPTW).

The prevalence of PPM and post-procedural valvular haemodynamics are shown in *Table 6*. Post-procedural echocardiographic data were available in 307 out of 354 (87%) patients. Severe and moderate PPM was observed in 2 and 25% of patients, respectively. No significant differences in the incidence of PPM between groups were seen. In addition, no significant differences in 1 year overall mortality were observed among patients with and without PPM (*Table 7*).

Discussion

The main findings can be summarized as follows: first, we confirmed the presence of PLF-AS using invasive haemodynamic indices among a high-risk cohort of patients undergoing TAVI. Most PLF-LG patients were symptomatic, had a high afterload, and the majority demonstrated functional improvement 1 year following the procedure. Clinical outcomes were similar to HGAS patients. Secondly, only limited data are available on clinical outcomes among patients with LEF-LG undergoing TAVI.[24–26] We found that most surviving LEF-LG patients exhibited functional improvement at 1-year follow-up. A significant improvement in LVEF compared with baseline was observed among LEF-LG patients but the LVEF improvement was less when compared with LEF-HG patients. Thirdly, despite being at significantly higher surgical risk, patients with LEF-LG had overall mortality rates similar to lower-risk HGAS and PLF-LG patients. LEF-LG patients, however, were more likely to die from cardiac causes compared with HGAS patients. Finally, PPM did not appear to impact on overall mortality rates at 1 year even among LEF-LG patients. Overall, the majority of patients demonstrated significant functional improvement following TAVI regardless of AS subtype. Therapeutic measures aimed at reducing cardiovascular mortality among LEF-LG patients following TAVI should be identified.

Paradoxical low-flow aortic stenosis

In the present study, patients presenting with PLF-LG were predominantly symptomatic, female, hypertensive octogenarians with a high incidence of multi-vessel coronary artery disease and pulmonary hypertension. Herrmann *et al.*,[15] in a *post-hoc* analysis of the Placement of Aortic Transcatheter Valves (PARTNER) trial, were first to assess the clinical outcomes of patients with PLF-LG severe AS (defined using echocardiographic criteria) undergoing TAVI with the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA). Among the cohort with PLF-LG, those undergoing TAVI had a significantly improved survival when compared with patients undergoing medical management at 1 year (HR 0.38, 95% CI 0.16–0.87, $P = 0.02$). In addition, low flow (SVI $\leq$ 35 mL m^{-2}) was found to be an independent predictor of mortality in all patient cohorts, whereas ejection fraction and gradient were not.[15] The present study complements the PARTNER analysis by confirming the presence of PLF-LG among high-risk patients undergoing TAVI using invasive haemodynamic data. In addition, the latter study did not provide data on the arterial afterload of patients with PLF-LG severe AS, which is thought to play a key role in the pathophysiology of PLF-LG severe AS. We were able to confirm using invasive haemodynamic indices that high-risk PLF-LG patients undergoing TAVI do indeed have an elevated afterload as reflected by a high systemic vascular resistance and valvuloarterial impedance and low systemic arterial compliance. Furthermore, the PARTNER analysis excluded patients with severe obstructive coronary artery disease and no patients received a Medtronic CoreValve both of which were included in the present analysis. It has previously been reported that symptomatic patients presenting with features of PLF-LG were less likely to be referred to SAVR when compared with their high-gradient counterparts.[2,12] One reason for this may be because a low MG among patients presenting with a normal LVEF is perceived to imply a non-severe form of AS. However, MG is directly proportional to the square of flow and inversely proportional to the square of AVA.[12] Therefore, even a small reduction in flow can lead to a substantial reduction in the MG, even though LVEF may remain within the normal range. In the present study, all PLF-LG patients had an LVEF $\geq$50%, an MG in the mild-to-moderate range, yet all had an indexed AVA in the severe range suggesting severe AS. In such clinical scenarios, recent studies have shown that the next important steps are to ensure that AVA is indexed to body surface area (rule out small body size) and to assess the flow status.[2,12,27] All PLF-LG had a low-flow pattern as indicated by an SVI $\leq$35 mL m^{-2}. Following TAVI, the majority demonstrated excellent functional improvement yet only one quarter of patients underwent revascularization, suggesting that the pre-procedural symptoms were directly related to the valve stenosis in a majority of cases.

PLF-LG vs. HGAS

By definition, all patients included in this study had severe AS defined by an indexed AVA $\leq$0.6 cm^2 m^{-2}. Compared with HGAS, however, PLF-LG patients had a significantly larger valve area indicating a less

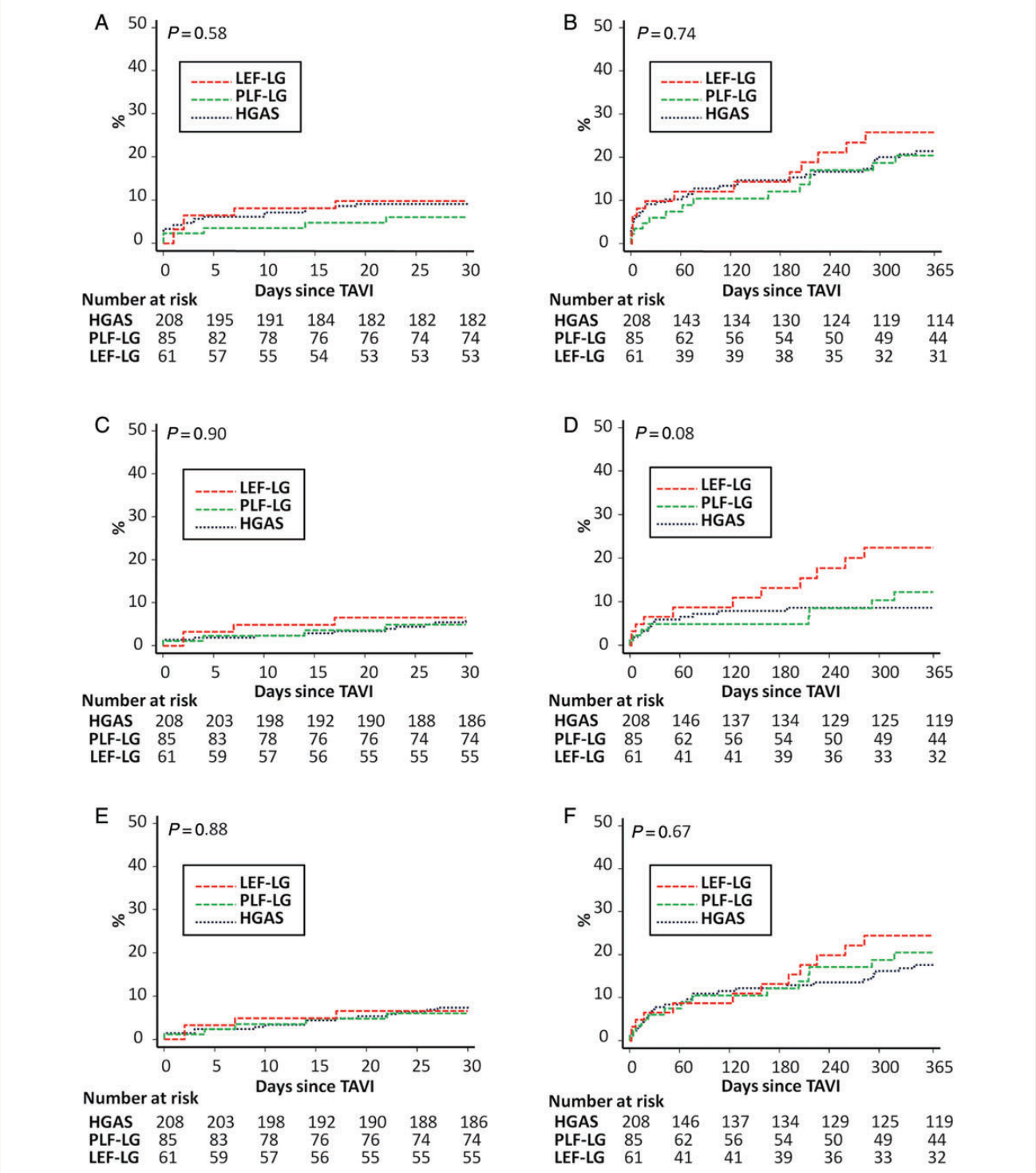


Figure 3 Kaplan–Meier analysis of major adverse cardiovascular and cerebrovascular events (MACCE; composite of death, major stroke, and myocardial infarction) at 30 days (*A*) and 1 year (*B*), cardiovascular death at 30 days (*C*) and 1 year (*D*), and death at 30 days (*E*) and 1 year (*F*) among the three groups. HGAS, high-gradient, severe aortic stenosis (AS); PLF-LG, paradoxical low-flow, low-gradient, severe AS; LEF-LG, low-flow, low-gradient, severe AS.

severe form of AS, although whether this had clinical implications is unclear as there were no significant differences in baseline symptoms. In addition, while the arterial afterload was higher among PLF-LG patients compared with HGAS, global afterload (Zva) was significantly lower. At first glance, these findings appear discordant with previous studies reporting either a similar or smaller sized indexed AVA and a

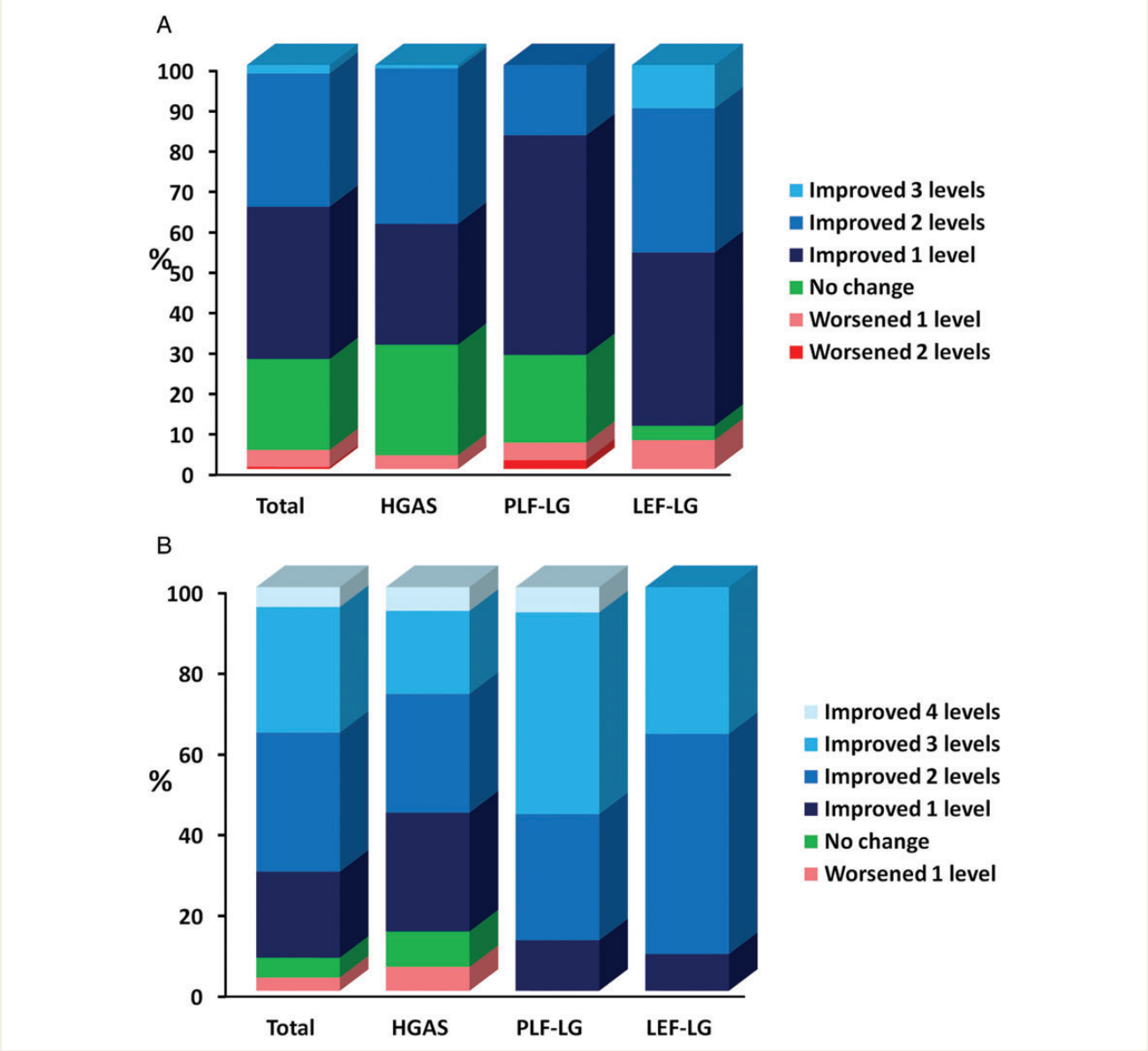
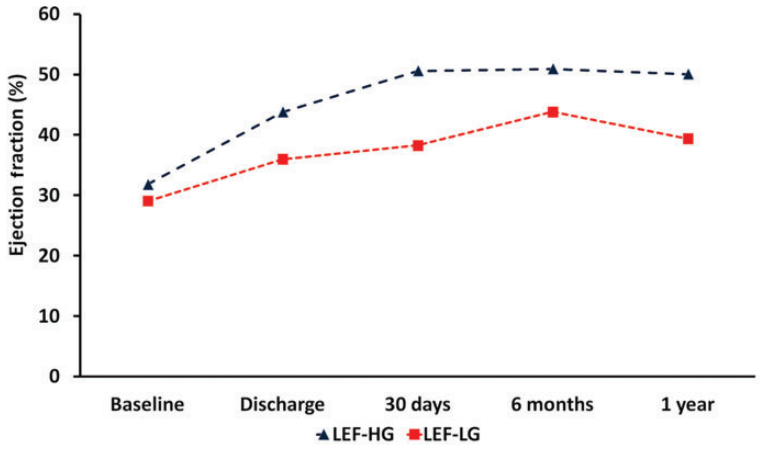


Figure 4 Functional clinical outcome. Functional status expressed by New York Heart Association (NYHA) classification (*A*) and the Canadian Cardiovascular Society (CCS) angina classification (*B*) at 1-year follow-up compared with baseline. Very light blue = improved 4 levels, light blue = improved 3 levels: medium blue = improved 2 levels; dark blue = improved 1 level; green = no change; pink = worsened 1 level; red = worsened 2 levels.

higher Zva among PLF-LG patients compared with normal flow, high-gradient patients.[2,12] Further analysis reveals, however, that most HGAS patients (80.3%) included in this study have in fact a low stroke volume and therefore this group predominantly comprises a low-flow, high-gradient severe AS patient population. This high prevalence of low-flow among HGAS patients is partly explained by the fact that a minority of these patients ($n = 49/208$; 24%) had a low LVEF (<50%). However, even among HGAS patients with a preserved LVEF ($n = 159/208$; 76%), low-flow was observed in a majority of patients (77%). In patients with severe AS and hypertrophied ventricles, an LVEF of 50% may not be entirely normal. In addition, similar to PLF-LG patients, the HGAS patient population comprised elderly hypertensive patients with a high prevalence of coronary artery disease. Therefore, both groups may have had intrinsic myocardial dysfunction caused by a chronically high afterload and/or ischaemic heart disease resulting in a low-flow state, yet the HGAS group had a much greater stenosis severity to the extent that despite low-flow, their gradients remained high (>40 mmHg). Therefore, even though the arterial afterload was significantly lower in comparison with PLF-LG patients, HGAS patients nonetheless had an overall higher global (valvular + arterial) afterload due predominantly to the valvular component. A similar observation was reported in an echocardiographic study by Dumesnil *et al.*,[28] where low-flow, high-gradient patients were found to have a smaller indexed AVA (0.3 vs. 0.5 $cm^2\ m^{-2}$)



	Baseline	Discharge	30 days	6 months	1 year	*P* (baseline vs 30 day)
No. of patients	95 (34–61)	86 (29–57)	51 (20–31)	43 (13–30)	29 (16–13)	
LVEF (LEF-HG group)	31.79±7.19	43.79±9.88	50.59±9.95	50.92±9.85	50.06±14.24	<0.0001
LVEF (LEF-LG group)	29.02±6.73	35.98±11.84	38.26±13.21	43.80±13.86	39.38±13.65	<0.0001

Figure 5 Changes in left-ventricular ejection fraction (LVEF) over time among patients with an LVEF ≤40%, comparing patients with a mean gradient ≤40 mmHg at baseline [low-flow, low-gradient group (LEF-LG): red dashed line] with patients with a mean gradient >40 mmHg at baseline [low-flow, high-gradient group (LFHG); dark blue dashed line].

Table 6 Comparison of post-procedural valvular haemodynamics and patient–prosthetic mismatch between groups

	All patients (*n* = 307)	HGAS (*n* = 179)	PLF-LG (*n* = 77)	LEF-LG (*n* = 51)	*P*-value
Post-procedural valvular haemodynamics					
Aortic valve area, cm^2	1.89 ± 0.55	1.92 ± 0.55	1.83 ± 0.49	1.91 ± 0.64	0.494
Indexed aortic valve area, $cm^2\ m^{-2}$	1.06 ± 0.31	1.08 ± 0.30	1.02 ± 0.27	1.08 ± 0.36	0.356
Mean gradient, mmHg	8.77 ± 3.96	9.40 ± 4.23	8.37 ± 3.39	7.18 ± 3.22	0.001
Patient–prosthetic mismatch grade					0.694
None (iAVA >0.85 $cm^2\ m^{-2}$) (%)	225 (73)	135 (75)	54 (70)	36 (71)	
Moderate (iAVA ≥0.65–0.85 $cm^2\ m^{-2}$) (%)	76 (25)	41 (23)	22 (29)	13 (25)	
Severe (iAVA <0.65 $cm^2\ m^{-2}$) (%)	6 (2)	3 (2)	1 (1)	2 (4)	

Depicted are means ± SD with *P*-values from ANOVAs or counts (%) with *P*-values from χ^2 tests. *n* = 47 patients data missing.
iAVA, indexed aortic valve area.

and a higher Zva (6.0 vs. 5.2 mmHg $mL^{-1}\ m^{-2}$) compared with PLF-LG patients.

Low flow, low gradient, low ejection fraction

LEF-LG occurs in ~5–10% of all patients with severe AS.[14] These patients are challenging to manage because they have a dismal prognosis with medical therapy,[7] yet have a high perioperative mortality (up to 22% in a recent series[4]) undergoing SAVR.[4,7] Transcatheter aortic valve implantation has emerged as an alternative treatment option in this difficult subgroup but to date, only limited data are available regarding the feasibility and outcome of TAVI among these patients.[15,24,25] In a recent *post-hoc* analysis of the PARTNER trial, 2-year mortality was significantly reduced (HR 0.43, *P* = 0.04) with TAVI when compared with medical management among the subset of patients (*n* = 42) with low flow (LF), low LVEF (LEF), and low gradient (LG) from the inoperable B cohort.[15] In addition, there were no significant differences in 2-year mortality rates between TAVI and SAVR among the subset of LF LEF LG patients (*n* = 105) in the high-risk A cohort (HR 1.25, *P* = 0.50).[15] However, in the latter cohort, an early hazard associated with SAVR among LF patients was observed, that persisted to 6 months

Table 7 All-cause mortality at 1-year among patients with and without patient–prosthetic mismatch

	PPM (iAVA ≤0.85 cm^2 m^{-2})	No PPM (iAVA >0.85 cm^2 m^{-2})	HR (95% CI)	*P*-value	*P*-value interaction[a]
All patients	*n* = 82	*n* = 225			
All cause death, *n* (%)	13 (19.3)	27 (15.2)	1.27 (0.65–2.46)	0.48	
Stratified analysis					0.88
HGAS	*n* = 44	*n* = 135			
All cause death, *n* (%)	6 (16.5)	15 (13.6)	1.21 (0.47–3.12)	0.69	
PLF-LG	*n* = 23	*n* = 54			
All cause death, *n* (%)	5 (24.8)	7 (17.7)	1.50 (0.48–4.73)	0.49	
LEF-LG	*n* = 15	*n* = 36			
All cause death, *n* (%)	2 (18.2)	5 (18.5)	0.92 (0.18–4.73)	0.92	

Depicted are counts (incidence rates %).
Hazard ratios (HR) [95% confidence intervals (CI)] from Cox regressions for time-to-event data, testing PPM vs. no PPM.
[a]*P*-value interaction PPM × patient group, decrease of freedom = 2; *n* = 47 patients data missing.

(relative risk 0.60, $P = 0.04$) but was no longer apparent at 1 year. The observations made in this study further support the concept of TAVI as a viable therapeutic option among these high-risk patients and can be summarized as follows: first, TAVI can be safely performed in LEF-LG patients. Despite being at significantly higher risk compared with HGAS patients (logistic EuroSCORE HGAS: 20.9% vs. LEF-LG: 38.0%, $P < 0.001$), LEF-LG patients had similar 30-day and 1-year overall mortality rates compared with lower-risk PLF-LG and HGAS patients. However, LEF-LG patients were at high-risk of cardiac death at 1 year. Therefore, the post-procedural medical management of these patients is important and therapeutic strategies aimed at reducing cardiovascular mortality among this subgroup should be identified. Secondly, LEF-LG patients have a very high arterial afterload despite a low systolic arterial pressure and therefore a normal or low blood pressure reading should not be thought of as equivalent to a normal vascular load among these patients. Thirdly, the majority of patients surviving TAVI exhibited functional improvement at 1 year. Finally, among patients undergoing echocardiographic follow-up, a significant improvement in LVEF was observed following TAVI, although the improvement in LVEF was less in LEF-LG patients when compared with LEF-HG patients. This may have been related to a lack of contractile reserve among a proportion of LEF-LG patients. Further studies are required to assess the impact of the presence or absence of contractile reserve on clinical outcomes among this patient cohort following TAVI. In addition, whether the residual arterial afterload remains higher among LEF-LG patients compared with LEF-HG patients following TAVI is unclear. This may be important as a higher residual arterial afterload may have implications for post-procedural LVEF improvement. Finally, the overall incidence of PPM was 27%, which was lower than that reported by Jilaihawi *et al.* (32%)[29] and Tzikas *et al.* (39%)[30] in a TAVI population. Among SAVR patients, Mohty *et al.*[31] reported that moderate-to-severe PPM was an independent predictor of late mortality among those with a pre-operative LVEF <50%. In addition, Kulik *et al.*[32] reported that PPM (iAVA ≤0.85 cm^2 m^{-2}) had an adverse impact on long-term outcomes among LEF-LG patients undergoing SAVR. In the present study, we found no association between moderate–severe PPM and overall mortality at 1 year among LEF-LG patients undergoing TAVI. Further studies are required to compare the impact of PPM on clinical outcomes among low LVEF patients undergoing TAVI and SAVR.

Limitations

First, this study reflects the experience of a single centre only. However, to the best of our knowledge, this is the first study comparing the invasive haemodynamic characteristics among different subsets of patients with low-gradient AS undergoing TAVI. Secondly, use of the estimated VO2 for cardiac output calculation has been shown to lead to both over- and underestimation of cardiac output and therefore of SVI and AVA measurements. It has been shown that estimates of VO2 based on body size significantly overestimated AVA among elderly patients.[33] Therefore in the present study, it is possible that patients may have had their AVA overestimated. In addition, Gertz *et al.*[33] found that invasive measurements of directly measured VO2 AVAs were less congruent with three-dimensional echocardiography in low-flow states, which may have implications for the present study. Aortic valve gradients were measured by pull-back technique and not by simultaneous measurement of LV and aortic pressures, which is considered optimal. The Gorlin constant, which is assumed to be '1' for aortic tricuspid valves, may contain inherent inaccuracies when calculating AVAs using the Gorlin formula. Importantly, the flow dependency of the Gorlin equation makes AVA assessment most inaccurate in low-flow states. Thirdly, the role of indexing AVA for body size is controversial.[34] However, we chose an iAVA ≤0.6 cm^2 m^{-2} as a cut-off criterion in order to rule out small body size as a potential cause of a low gradient in the presence of a small AVA and preserved LVEF.[27] Fourthly, although the haemodynamic and clinical data were prospectively collected, this is a retrospective study and therefore may be subjected to confounding factors. Fifthly, because this is an invasive haemodynamic study, the findings may not necessarily be concordant with an echocardiographic study.[34] As a result, only patients who underwent a pre-procedural

right and left heart catheterization with aortic valve crossing were included in the present analysis and therefore this is not a consecutive patient series. However, no significant differences in baseline characteristics or clinical outcomes between included and excluded patients were observed (data not shown). Finally, because only a small proportion of patients underwent dobutamine stress echocardiography, we were unable to stratify LEF-LG patients according to the presence or absence of flow reserve.

Conclusions

Patients presenting with PLF-LG and LEF-LG had overall mortality rates comparable with HGAS patients. LEF-LG patients, however, were more likely to die of cardiac causes and therefore therapeutic measures aimed at reducing cardiovascular mortality among these patients following TAVI should be identified. Most surviving patients demonstrated functional improvement regardless of AS subtype.

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