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Prognostic impact of echocardiographic mean transvalvular gradients in patients with aortic stenosis and low flow undergoing transcatheter aortic valve implantation

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Abstract

Background: Blunted left ventricular hemodynamics reflected by a low stroke volume index (SVI) ≤35 mL/m^2 body surface area (low flow [LF]) in patients with severe aortic stenosis (AS) are associated with worse outcomes even after correction of afterload by transcatheter aortic valve implantation (TAVI). These patients can have a low or high transvalvular mean pressure gradient (MPG). We investigated the impact of the pre-interventional MPG on outcomes after TAVI.

Methods: Patients with LF AS were classified into those with normal (EF ≥ 50%; LF/NEF) or reduced ejection fraction (EF < 50%; LF/REF) and were then stratified according to an MPG < or ≥ 40 mmHg. Patients with SVI >35 mL/m^2 (normal flow; NF) served as controls.

Results: 597 patients with LF/NEF, 264 patients with LF/REF and 975 patients with NF were identified. Among all groups those patients with a low MPG were characterized by higher cardiovascular risk. In patients with LF/REF, functional improvement post-TAVI was less pronounced in low-MPG patients. One-year survival was significantly worse in LF AS patients with a low vs. high MPG (LF/NEF 16.5% vs. 10.5%, $p = 0.022$; LF/REF 25.4% vs. 8.0%, $p = 0.002$), whereas no differences were found in NF patients (8.7% vs. 10.0%, $p = 0.550$). In both LF AS groups, a low pre-procedural MPG emerged as an independent predictor of mortality.

Conclusions: In patients with LF AS, an MPG cut-off of 40 mmHg defines two patient populations with fundamental differences in outcomes after TAVI. Patients with LF AS and a high MPG have the same favorable prognosis as patients with NF AS.

KEYWORDS

aortic valve, transvalvular gradient, transcatheter aortic valve replacement, low flow, prognosis

1 | INTRODUCTION

Severe aortic stenosis (AS) leads to an increased left ventricular (LV) pressure and to various levels of LV hypertrophy. LV hypertrophy itself can induce diastolic dysfunction, causing a reduction in LV stroke volume (SV). Moreover, LV hypertrophy is associated with distorted myocardial blood supply, and once hypertrophy fails to compensate for the increased afterload, the LV undergoes remodeling that leads to a deteriorated systolic function and finally to a reduction in ejection fraction (EF).[1] While this pathophysiologic sequence has obvious parallels with the development of heart failure with preserved or reduced EF, it more formally defines patient populations with AS and specific hemodynamic characteristics. According to current guidelines, low-flow (LF) hemodynamics in patients with AS is defined as a SV indexed to body surface area (SVI) ≤35 mL/m^2.[2] Such patients can present with reduced (<50%) or preserved (≥50%) EF.[2] The outcome of patients with LF AS is similar to that of patients defined to have concomitant heart failure[3] and is generally limited compared with those patients with normal flow (NF), even after correction of afterload by TAVI.[4]

Low SV can lead to reduced transaortic flow velocities measured by echocardiography that translate into low transvalvular gradients by the simplified Bernoulli equation. Thus, LF and low gradients are often diagnosed simultaneously and characterize a patient population at highest risk.[5] However, a LF status does not necessarily lead to a low mean pressure gradient (MPG),[6,7] and it appears that the MPG plays an essential and independent role in risk stratification and is clearly associated with post-interventional outcomes.[8] We therefore investigated potential predictors of a low versus high MPG in a TAVI registry population and further analyzed the prognostic impact of the pre-TAVI MPG in patients with LF AS.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

In this retrospective, observational study, all data derived from a TAVI registry at a single center. From 2011 until 2019, patients who underwent TAVI for symptomatic AS were consecutively included as a result of the local heart team decision at our center. Follow-up visits were scheduled at 30 days and 1 year post-TAVI. The data were collected in a standardized and anonymized format. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and approval for this study was obtained from the ethics committee of the Justus-Liebig University Giessen. Due to the retrospective nature of this study, a waiver of written informed consent was issued by the ethics committee.

Two different cohorts were created (Figure 1): a) for the exploratory analysis of baseline characteristics of patients with low vs. high MPG, and b) for the analysis of outcomes in LF patients. In the latter cohort only patients with transfemoral access and LF AS were classified into those with reduced EF (EF <50%; LF reduced EF [LF/REF]) and those with preserved EF (EF ≥50%; LF normal EF [LF/NEF]). Patients in each group were then further dichotomized into those with an MPG < or ≥ 40 mmHg. Patients with SVI >35 mL/m^2 were classified as NF patients and served as controls.

2.2 | Outcome variables

The primary endpoint was death from any cause. Patients with follow-up time longer than 1 year were censored as alive after 365 days. Cardiovascular death and clinical events during a 30-day

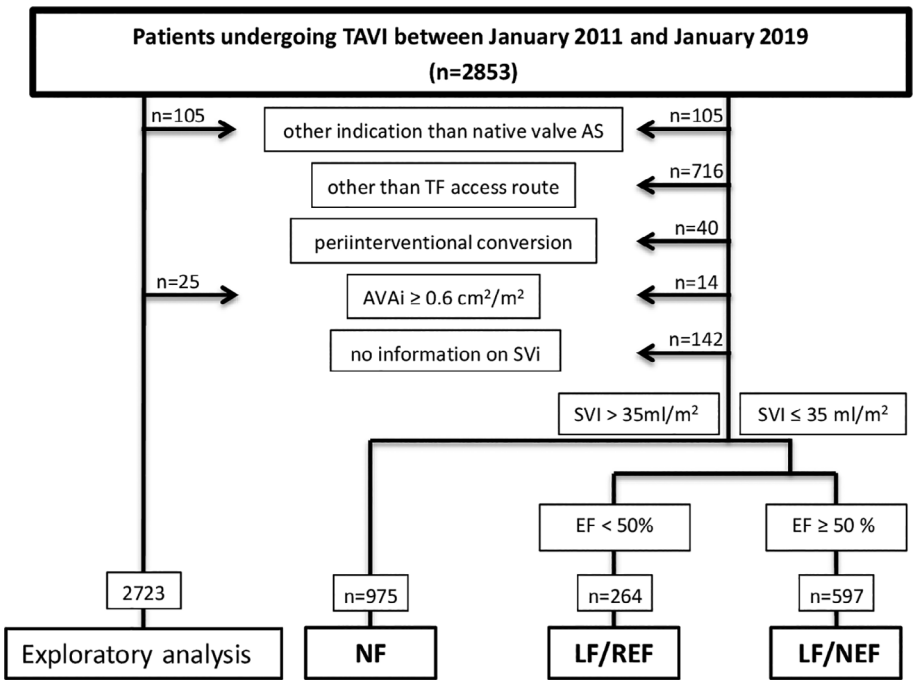

FIGURE 1 Flow chart illustrating the creation of the study populations. Abbreviations: AS, aortic stenosis; AVAi, aortic valva area index; EF, ejection fraction; LF/NEF, low flow, normal EF; LF/REF, normal flow, reduced EF; MPG, mean pressure gradient; NF, normal flow; SVI, stroke volume index; TF, transfemoral

TABLE 1 Patient characteristics – exploratory study population

	Low MPG $n = 1079$	High MPG $n = 1644$	p
Demographic data			
Female	506 (46.9)	935 (56.9)	<0.001
Age, y	81.3 (77.9–84.9)	82.5 (79.1–85.8)	<0.001
BMI, kg/m^2	26.9 (24.1–30.3)	26.8 (24.1–30.5)	0.714
GFR, ml/min/1.73 m^2	57 (42–78)	69 (49–87)	<0.001
NYHA class III / IV	926 (85.8)	1353 (82.3)	0.015
Prior cardiac decompensation	419 (38.8)	442 (26.9)	<0.001
Risk factors			
Arterial hypertension	1009 (93.5)	1517 (92.3)	0.223
Diabetes mellitus	421 (39.0)	488 (29.7)	<0.001
Dyslipidemia	444 (41.1)	624 (38.0)	0.095
COPD	214 (19.8)	332 (20.2)	0.818
EuroScore II, %	6.6 (3.8–11.4)	4.0 (2.5–6.7)	<0.001
Cardiovascular disease			
CAD	729 (67.6)	974 (59.2)	<0.001
CABG	254 (23.5)	177 (10.8)	<0.001
Prior myocardial infarction	201 (18.6)	192 (11.7)	<0.001
History of atrial fibrillation	579 (53.7)	553 (33.7)	<0.001
NT-proBNP serum levels (pg/ml)	2516 (1104–5688)	1965 (805–5488)	0.046
	n = 299	*n = 422*	
Prior stroke	170 (15.8)	222 (13.5)	0.102
Peripheral artery disease	230 (21.3)	266 (16.2)	0.001

Note: Data represent *N* (%) or median (interquartile range). Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MPG, mean pressure gradient; NYHA, New York Heart Association.

TABLE 2 Doppler Echocardiographic and MDCT Data – exploratory study population

	Low MPG $n = 1079$	High MPG $n = 1644$	p
Echocardiographic data			
Ejection fraction, %	60 (34–65)	65 (60–65)	<0.001
LV hypertrophy	695/918 (75.7)	1155/1399 (82.6)	<0.001
SVI, ml/m^2 ($n = 2504$)	32.2 (26.0–39.1)	37.5 (31.1–44.2)	<0.001
MPG, mmHg	29 (23–35)	50 (44–59)	<0.001
MR ≥2+	167 (15.5)	192 (11.7)	0.004
TR ≥2+	146 (13.5)	146 (8.9)	<0.001
MR ≥2+ & TR ≥2+	61 (5.7)	57 (3.5)	0.006
SPAP, mmHg ($n = 1808$)	44 (36–54)	44 (37–57)	0.495
MDCT data			
Agatston Score women, AU	1533 (1053–2162)	2517 (1814–3401)	<0.001
Agatston Score men, AU	2426 (1789–3248)	3654 (2778–4876)	<0.001

Note: Data represent *N* (%) or median (interquartile range). Abbreviations: LV, left ventricular; MDCT, multidetector computed tomography; MPG, mean pressure gradient; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure; SVI, stroke volume index, TR, tricuspid regurgitation.

TABLE 3 Patient characteristics - NF and LF study populations

	NF			LF/NEF			LF/REF		
	low MPG $n = 298$	high MPG $n = 677$	*p*-value	low MPG $n = 255$	high MPG $n = 342$	*p*-value	low MPG $n = 189$	high MPG $n = 75$	*p*-value
Demographic data									
Female	164 (55.0)	385 (56.9)	0.595	150 (58.8)	210 (61.4)	0.524	53 (28.0)	37 (49.3)	0.001
Age, y	82 (79–85)	82 (79–85)	0.474	82 (79–86)	83 (80–86)	0.095	80 (76–83)	83 (80–87)	<0.001
BMI, kg/m^2	26.5 (23.9–29.4)	26.7 (23.9–29.6)	0.708	27.5 (24.4–31.2)	27.2 (24.6–31.5)	0.983	26.9 (24.2–30.4)	26.4 (24.0–31.2)	0.778
GFR, ml/min/1.73 m^2	62,846–85)	73 (52–92)	<0.001	56 (42–81)	66 (49–85)	0.001	54 (39–68)	59 (50–77)	0.009
NYHA class III / IV	244 (81.9)	527 (77.8)	0.154	214 (83.9)	271 (79.2)	0.147	163 (86.2)	70 (93.3)	0.107
Prior cardiac decompensation	95 (31.9)	132 (19.5)	<0.001	87 (34.1)	90 (26.3)	0.039	101 (53.4)	42 (56.0)	0.706
Risk factors									
Arterial hypertension	283 (95.0)	619 (91.4)	0.053	236 (92.5)	314 (91.8)	0.741	171 (90.5)	65 (86.7)	0.365
Diabetes mellitus	112 (37.6)	173 (25.6)	<0.001	90 (35.3)	113 (33.0)	0.565	93 (49.2)	19 (25.3)	<0.001
Dyslipidemia	125 (41.9)	245 (36.2)	0.088	95 (37.3)	128 (37.4)	0.966	74 (39.2)	22 (29.3)	0.135
COPD	57 (19.1)	135 (19.9)	0.769	50 (19.6)	66 (19.3)	0.925	24 (12.7)	10 (13.3)	0.890
EucoScore II, %	4.7 (2.9–8.4)	3.3 (2.2–5.5)	<0.001	6.1 (3.6–10.1)	4.4 (2.7–6.8)	<0.001	10.7 (6.1–18.4)	6.9 (4.4–9.6)	<0.001
Cardiovascular disease									
CAD	184 (61.7)	374 (55.2)	0.059	152 (59.6)	193 (56.4)	0.437	142 (75.1)	37 (49.3)	<0.001
CABG	47 (15.8)	51 (7.5)	<0.001	40 (15.7)	25 (7.3)	0.001	50 (26.5)	4 (5.3)	<0.001
Prior myocardial infarction	29 (9.7)	64 (9.5)	0.892	37 (14.5)	24 (7.0)	0.003	56 (29.6)	10 (13.3)	0.006
Atrial fibrillation	117 (39.3)	174 (25.7)	<0.001	168 (65.9)	163 (47.8)	<0.001	115 (60.8)	24 (32.0)	<0.001
ICD	8 (2.7)	3 (0.4)	0.002	2 (0.8)	1 (0.3)	0.400	20 (10.6)	1 (1.3)	0.012
Prior stroke	40 (13.4)	81 (12.0)	0.525	49 (19.2)	41 (12.0)	0.015	25 (13.2)	5 (6.7)	0.130
Peripheral artery disease	34 (11.4)	69 (10.2)	0.569	34 (13.3)	33 (9.6)	0.158	34 (18.0)	1 (1.3)	<0.001

Note: Data represent *N* (%) or median (interquartile range). Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; LF, low flow (stroke volume index ≤35 mL/m^2);MPG, mean pressure gradient; NEF, normal ejection fraction (≥50%); NF, normal flow (stroke volume index >35 mL/m^2); NYHA, New York Heart Association; REF, reduced ejection fraction (<50%).

TABLE 4 Doppler echocardiographic and MDCT data - NF and LF study populations

	NF			LF/NEF			LF/REF		
	low MPG $n = 298$	high MPG $n = 677$	*p*-value	low MPG $n = 255$	high MPG $n = 342$	*p*-value	low MPG $n = 189$	high MPG $n = 75$	*p*-value
Echocardiographic data									
Ejection fraction, %	65 (60–65)	65 (60–65)	<0.001	65 (55–65)	65 (60–65)	<0.001	30 (25–40)	40 (30–45)	0.001
LV hypertrophy, %	209/273 (76.6)	509/611 (83.3)	0.018	150/226 (66.4)	230/296 (77.7)	0.004	131/163 (80.4)	60/65 (92.3)	0.027
SVI, ml/m^2	41 (38–46)	43 (39–48)	0.001	29 (25–32)	30 (26–32)	0.063	24 (20–29)	27 (23–31)	0.001
MPG, mmHg	33 (28–37)	51 (44–61)	<0.001	28 (23–34)	49 (43–58)	<0.001	22 (17–29)	48 (43–56)	<0.001
MR ≥2+	24 (8.1)	57 (8.4)	0.855	33 (13.0)	55 (16.1)	0.293	50 (26.5)	17 (22.7)	0.524
TR ≥2+	27 (9.1)	40 (5.9)	0.073	30 (11.8)	45 (13.2)	0.611	43 (22.8)	17 (22.7)	0.988
MR ≥2+ & TR ≥2+	8 (2.7)	18 (2.7)	0.982	10 (3.9)	19 (5.6)	0.358	19 (10.1)	6 (8.0)	0.607
SPAP, mmHg	42 (35–53)	43 (35–53)	0.324	43 (36–53)	45 (36–61)	0.133	48 (37–56)	49 (41–60)	0.126
	$n = 201$	$n = 415$		$n = 194$	$n = 229$		$n = 148$	$n = 53$	
MDCT data									
Agatston Score, women, AU	1475 (1004–2026)	2314 (1766–3182)	<0.001	1494 (1039–2125)	2608 (1838–3471)	<0.001	1644 (1049–2365)	3627 (2326–4263)	<0.001
Agatston Score, men, AU	2418 (1731–3135)	3640 (2814–4763)	<0.001	2412 (1747–3209)	3738 (2738–5151)	<0.001	2234 (1628–3143)	3789 (3006–5690)	<0.001

Note: Data represent *N* (%) or median (interquartile range). Abbreviations: LF, low flow (stroke volume index ≤35 mL/m^2); LV, left ventricular; MDCT, multidetector computed tomography; MPG, mean pressure gradient; MR, mitral regurgitation; NEF, normal ejection fraction (≥50%); NF, normal flow (stroke volume index >35 mL/m^2); REF, reduced ejection fraction (<50%); SPAP, systolic pulmonary artery pressure; SVI, stroke volume index, TR, tricuspid regurgitation.

TABLE 5 Procedural data - NF and LF study populations

	NF			LF/NEF			LF/REF		
	low MPG $n = 298$	high MPG $n = 677$	*p*-value	low MPG $n = 255$	high MPG $n = 342$	*p*-value	low MPG $n = 189$	high MPG $n = 75$	*p*-value
Balloon-expandable valve	94 (31.5)	233 (34.5)	0.373	93 (36.5)	135 (39.5)	0.455	88 (46.8)	33 (44.0)	0.680
Rapid pacing	233 (78.2)	634 (93.6)	<0.001	196 (76.9)	322 (94.2)	<0.001	164 (86.8)	73 (97.3)	0.011
Procedural time, min	36 (29–45)	36 (29–46)	0.499	35 (26–47)	37(30–48)	0.011	37 (30–48)	38 (29–49)	0.737
Contrast agent, ml	80 (60–116)	90 (69–120)	0.123	80 (60–116)	90 (70–120)	0.104	95 (70–121)	90 (74–120)	0.775
Device success	279 (93.6)	598 (88.5)	0.013	240 (94.1)	296 (86.5)	0.003	168 (88.9)	67 (89.3)	0.917
AVA at discharge, cm^2	1.7 (1.5–1.9)	1.6 (1.4–1.9)	0.158	1.6 (1.4–1.8)	1.5 (1.3–1.8)	0.104	1.6 (1.4–1.8)	1.5 (1.3–1.7)	0.092
Residual aortic regurgitation ≥ II°	6/266 (2.3)	21/633 (3.3)	0.395	10/235 (4.3)	13/320 (4.1)	0.910	6/177 (3.4)	2/69 (2.9)	0.846

Note: Data represent N (%) or median (interquartile range). Abbreviations: AVA, aortic valve area; LF, low flow (stroke volume index ≤35 mL/m^2); NEF, normal ejection fraction (≥50%); NF, normal flow (stroke volume index >35 mL/m^2); MPG, mean pressure gradient; REF, reduced ejection fraction (<50%).

follow-up were defined according to the Valve Academic Research Consortium-2 consensus document.[9]

2.3 | Cardiac imaging

Echocardiographic exams were scheduled before TAVI, before discharge from hospital, and at the 30-day follow-up. Left ventricular mass was calculated by the linear method.[10] LV hypertrophy was defined as LV mass >95 g/m^2 in women and >115 g/m^2 in men.[10] The left ventricular EF was estimated visually. The LV outflow tract diameter was measured in magnified parasternal long-axis views in early systole. Depending on the flow pattern in each patient, the site of measurement of the outflow tract diameter was usually 0.5–1.0 cm apical to the annulus to obtain laminar flow curves, according to current recommendations.[11] Special care was taken that the level of the velocity recording from the apical five-chamber view was at the same anatomic level as that of the LV outflow tract measurements. In patients with atrial fibrillation with similar cycle lengths ("pseudo-regularization"), one measurement of velocities was performed, whereas 3–5 measurements were averaged in those patients with atrial fibrillation with different cycle lengths. SV was determined at the LV outflow tract by multiplying area by the systolic velocity time integral and was indexed to body surface area. Aortic valve area was calculated according to the continuity Equation.[11] Noncontrast multidetector computed tomography was used for measurement of the Agatston Score, as described earlier.[12]

2.4 | Statistical analysis

Continuous data were not normally distributed and are reported as median and interquartile range (IQR). Continuous values were compared by the Mann–Whitney test and categorical variables by the χ^2 test. To analyze the prediction of a low MPG (<40 mmHg), all

TABLE 6 Logistic regression analysis of the exploratory study population for prediction of a low baseline MPG (<40 mmHg)

Variable	OR	CI 95%		*p*
		Lower	Upper	
Male sex	2.798	2.156	3.632	<0.001
Age, years	0.972	0.954	0.991	0.005
GFR, ml/min/1.73 m^2	0.995	0.990	0.999	0.023
History of AF	1.792	1.400	2.292	<0.001
Peripheral artery disease	1.335	1.005	1.773	0.046
Ejection fraction, %	0.970	0.959	0.980	<0.001
SVI, ml/m^2	0.971	0.959	0.983	<0.001
Agatston Score, AU	0.999	0.999	0.999	<0.001

Abbreviations: AF, atrial fibrillation; CI, confidence interval; GFR, glomerular filtration rate; OR, odds ratio; SVI, stroke volume index.

TABLE 7 Outcome data - NF and LF study populations

	NF			LF/NEF			LF/REF		
	low MPG $n = 298$	high MPG $n = 677$	*p*-value	low MPG $n = 255$	high MPG $n = 342$	*p*-value	low MPG $n = 189$	high MPG $n = 75$	*p*-value
30-day clinical outcomes									
Overall mortality	3 (1.0)	18 (2.7)	0.102	9 (3.5)	9 (2.6)	0.526	12 (6.3)	1 (1.3)	0.089
- in-hospital mortality	2 (0.7)	13 (1.9)	0.144	7 (2.7)	5 (1.5)	0.269	8 (4.2)	0	0.070
- cardiovascular mortality	3 (1.0)	16 (2.4)	0.158	8 (3.1)	7 (2.0)	0.400	8 (4.2)	1 (1.3)	0.242
Any VARC2 event	82/289 (28.4)	205/660 (31.1)	0.407	66/245 (26.9)	119/337 (35.3)	0.032	69/184 (37.5)	23/75 (30.7)	0.297
NYHA class at 30 days									
- improved	167/206 (81.1)	403/487 (82.8)		152/182 (83.5)	196/235 (83.4)		92/119 (77.5)	48/50 (96.0)	
- unchanged	32/206 (15.5)	73/487 (15.0)	0.398	26/182 (14.3)	33/235 (14.0)	0.994	24/119 (20.2)	2/50 (4.0)	0.030
- deteriorated	7/206 (3.4)	11/487 (2.3)		4/182 (2.2)	6/235 (2.6)		3/119 (2.5)	0	
1-year clinical outcomes									
Overall mortality	26 (8.7)	68 (10.0)	0.550	42 (16.5)	36 (10.5)	0.022	48 (25.4)	6 (8.0)	0.002
- cardiovascular mortality	20 (6.7)	42 (6.2)	0.765	29 (11.4)	26 (7.6)	0.115	33 (17.5)	4 (5.3)	0.010
New ICD implant	2 (0.7)	1 (0.1)	0.174	0	0		16 (8.5)	3 (4.0)	0.205

Note: Data represent N (%) or median (interquartile range). Abbreviations: ICD, implantable cardioverter defibrillator; LF, low flow (stroke volume index ≤35 mL/m^2); MPG, mean pressure gradient; NEF, normal ejection fraction (≥50%); NF, normal flow (stroke volume index >35 mL/m^2); NYHA, New York Heart Association; REF, reduced ejection fraction (<50%).VARC2, Valve Academic Research Consortium-2.

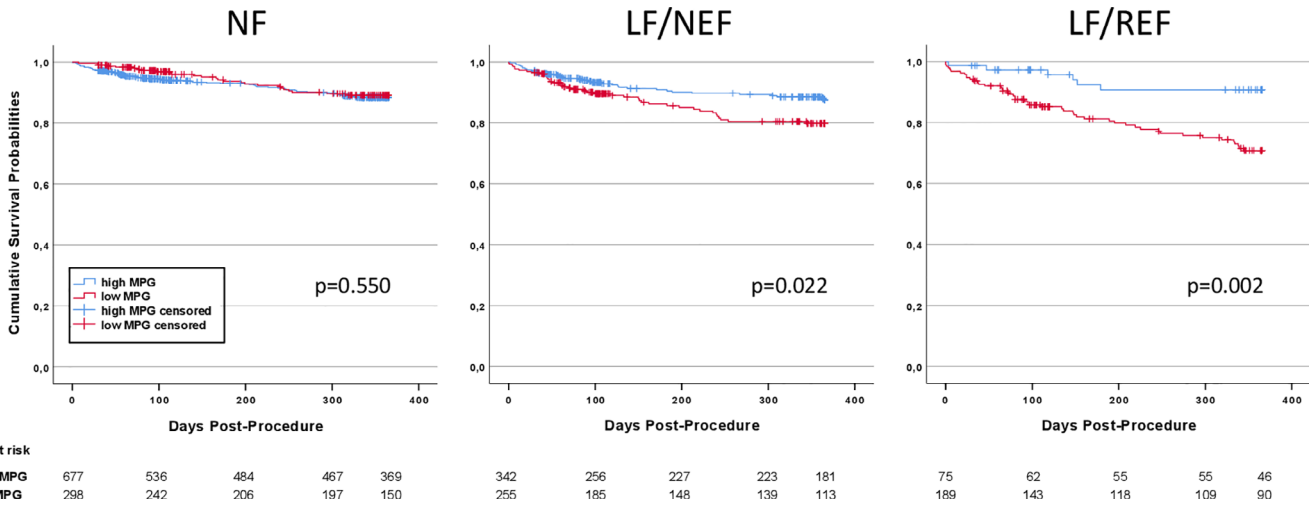

FIGURE 2 Survival curves based on the pre-interventional MPG. Kaplan–Meier analysis of all-cause mortality of patients with NF (normal flow), LF/NEF (low flow, normal EF) and LF/REF (low flow, reduced EF) based on MPG ≥40 mmHg (high MPG) or MPG <40 mmHg (low MPG). Abbreviations: MPG, mean pressure gradient

TABLE 8 Multivarible cox regression analysis for prediction of 1-year mortality of the LF study populations

		CI 95%		
Variable	**HR**	**Lower**	**Upper**	***p***
LF/NEF study population				
Age, years	1.047	1.000	1.095	0.048
Low MPG	2.064	1.300	3.277	0.002
Device success	0.320	0.183	0.559	<0.001
LF/REF study population				
Euro Score II, %	1.071	1.029	1.114	0.001
Low MPG	2.533	1.039	6.179	0.041

Abbreviations: CI, confidence interval; LF/NEF, low flow, normal EF; LF/REF, normal flow, reduced EF; Low MPG, low mean pressure gradient (categorial); OR, odds ratio.

baseline parameters from Tables 1 and 2 with significant ($p < 0.1$) difference between low and high MPG were tested for collinearity and were included in the regression model if the variance inflation factor was <5. Parameters with univariable significance ($p < 0.1$) entered the multivariable regression analysis. Survival curves were constructed using Kaplan–Meier estimates and were compared by the log-rank test. To analyze the prediction of mortality in the LF/NEF and LF/REF groups, all baseline and procedural parameters from Tables 3–5 with significant ($p < 0.1$) difference between low and high MPG together with MPG were tested for collinearity and were included in the regression model if the variance inflation factor was <5. Parameters with univariable significance ($p < 0.1$) entered the multivariable Cox regression analysis. All statistical analyses were carried out using the SPSS statistical package version 26 (IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Exploratory analysis of baseline characteristics

In the exploratory analysis, baseline characteristics of 1079 patients with low MPG and of 1644 patients with high MPG were analyzed (Table 1). Compared with patients with a high MPG, those with a low MPG were more often male, had worse renal function, were more symptomatic, and had a higher prevalence of cardiovascular risk factors and manifest diseases, as mirrored by higher EuroScores (for all comparisons $p < 0.001$). In a subpopulation of 721 patients, NT-proBNP serum levels were higher ($p = 0.046$) in those with low MPG (2516 pg/mL [1104–5688]) than in those with high MPG (1965 pg/mL [805–5488]). The former group also had a lower mean EF and a lower SVI, a higher prevalence of significant atrioventricular valve regurgitation, and a lower amount of aortic valve calcification (Table 2). Independent determinants for a low baseline MPG in this unselected patient population were male sex, lower age, lower glomerular filtration rate, a history of atrial fibrillation, peripheral artery disease, a lower EF, a lower SVI, and a lower Agatston Score (Table 6).

3.2 | Comparison of the LF subgroups

According to LV performance, 975 patients with NF, 597 patients with LF/NEF, and 264 patients with LV/REF were identified. In all three groups, patients with a low MPG had worse renal function and tended to have a higher prevalence of cardiovascular risk factors and manifest cardiovascular disease, as mirrored by a significantly higher EuroScore II (Table 3). Patients with a low MPG displayed a lower EF and SVI and a lower prevalence of LV hypertrophy than

those with a high MPG (Table 4). The prevalence of significant atrioventricular valve regurgitation was identical between groups and patients with low MPG had lower levels of aortic valve calcification than those with high MPG. Intraprocedural rapid pacing was less frequently performed in low-MPG patients (Table 5). In all three groups, 30-day all-cause and cardiovascular mortality was not different between low- and high-MPG patients (Table 7). While functional improvement was identical in patients with a low or high MPG in the NF and in the LF/NEF group, patients in the LF/REF group with a low MPG had a significantly worse functional improvement compared with those in this group with a high MPG. Patients in the NF group had an identical one-year outcome, regardless of low or high MPG. In contrast, striking differences in outcomes were observed in both LF groups between patients with low vs. high MPG. Whereas patients with a high MPG had mortality rates between 8.0 and 10.5%, which was similar to that of patients with NF, those with a low MPG had much higher mortality rates, ranging between 16.5 and 25.4% ($p < 0.001$; Figure 2). Patients with LF/REF and low MPG – meeting the criteria for classical LF, low-gradient AS – had the poorest survival, which was driven by a high cardiovascular mortality. Independent predictors of all-cause mortality in the LF/NEF group were age, a low MPG and lack of device success (Table 8). In the LF/REF group, the EuroScore II and a low MPG predicted mortality. In both groups MPG also emerged as an independent predictor of mortality when included as a linear variable.

4 | DISCUSSION

Our data reveal that patients with severe LF AS do not constitute a uniform population with an inevitably poor prognosis. In fact, such patients can be stratified by their pre-interventional transvalvular MPG into two distinct patient populations that are characterized by different cardiovascular risks and prevalence of cardiovascular diseases. In patients with LF AS and preserved or reduced EF, the MPG emerged as a powerful and independent factor impacting one-year survival, even after correction of afterload by TAVI. It remains speculative, however, whether a low MPG in these patients is a surrogate marker of worse LV performance overall and exerts such a strong influence on outcome.

An analysis of more than 11,000 patients from the Transcatheter Valve Therapies Registry[8] provided important insights into the interplay between EF and MPG in patients undergoing TAVI. Both a reduced EF and a pre-interventional MPG <40 mmHg were independently associated with higher mortality and a higher rate of hospitalization due to heart failure post-TAVI. However, after adjustment of clinical factors, only the MPG remained a strong and independent predictor of adverse events, whereas the EF lost significance. Our results decidedly confirm these data, demonstrating that the MPG determines outcomes in patients independent of EF range. Beyond that, our study provides additional information by reporting stroke volumes, information that was lacking in the former registry which prevented the authors from commenting on the rate of patients with normal versus LF status, which, in turn has a tremendous impact on outcomes.[5] Although it is difficult to define concomitant heart failure in patients with severe AS, as reflected by various definitions of heart failure in this setting,[13–16] we demonstrated that symptomatic patients with LF AS display remarkable similarities with heart failure patients, and that those having a reduced EF (comparable to heart failure with reduced EF) have the worst prognosis.[3] Following this line of reasoning, it is surprising to see that even patients with LF/REF can have an excellent prognosis, comparable to patients with normal SVI if the initial MPG is ≥40 mmHg.

Why does the MPG have such a powerful prognostic impact? Even though atrial fibrillation, low EF, and low SVI emerged as independent predictors of a low MPG in our exploratory analysis, one is tempted to consider these impacts – all of which may lead to a reduced transvalvular flow velocity – under one pathophysiologic model. Several hypotheses have been proposed to explain the interplay between myocardial texture and function in low-gradient patients. Structural or functional aberrations such as ischemic scars, hibernating myocardium, or those seen in idiopathic dilated cardiomyopathy as well as the concept of LV failure and remodeling instead of – or subsequent to – adaptive LV hypertrophy are widely accepted explanations.[1] Recently, Puls et al.[17] reported analyses of LV biopsies from patients with different hemodynamic patterns of severe AS undergoing TAVI. They demonstrated that the burden of myocardial fibrosis correlates with the extent of pathological baseline LV remodeling, and fibrosis emerged as an independent predictor of cardiovascular mortality in these patients. The highest levels of myocardial fibrosis were detected in patients with classical LF, low-gradient AS, comparable to our patients with LF/LEF and low MPG. Myocardial fibrosis in their study was mirrored by reduced strain values. We are aware that parameters of LV performance other than EF are needed to unmask subtle alterations in myocardial function, parameters that are probably related to the level of myocardial fibrosis and possibly related to the MPG. Therefore, further studies on this challenging topic should involve such measurements along with data from "virtual histology" obtained by magnetic resonance tomography.

Atrial fibrillation has consistently been demonstrated to be associated with high-risk AS and is a predictor of all-cause mortality in patients with medically managed AS[18] or in those undergoing TAVI.[5,19] The high prevalence of atrial fibrillation in our patients with low MPG may be interpreted from different perspectives. On one hand, atrial fibrillation may mirror a patient's cumulative cardiovascular risk and advanced stage of cardiac damage. This point of view is supported by the concept of extravalvular cardiac damage in patients with AS, in which atrial fibrillation was classified as being one criterion for stage two cardiac damage or risk class.[20] On the other hand, atrial fibrillation in patients with severe AS is associated with a distinct hemodynamic profile that includes lower stroke volumes.[21] Therefore, the correlation between atrial fibrillation and a low MPG in our patients is also a definite consequence of a particularly low stroke volume and accordingly low aortic flow velocities.

4.1 | Limitations

The EF was not measured but was visually estimated; echocardiographic data on LV diastolic function would have added value to our results. In

addition, information on functional class after one year would have allowed further assessments of long-term changes in clinical outcome.

5 | CONCLUSIONS

In our population of patients with severe LF AS, TAVI led to a symptomatic benefit in the majority. Furthermore, patients with a high MPG exhibited a relatively favorable prognosis like that of patients without NF, whereas a low MPG indicated a tremendous risk that was associated with a poor one-year outcome. Complementary measurements, including histologic and functional characterization of myocardial tissue, could shed more light on underlying pathophysiologic mechanisms.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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