ORIGINAL RESEARCH

Predictors of Mortality and Symptomatic Outcome of Patients With Low-Flow Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement

Norman Mangner, MD;* Georg Stachel, MD;* Felix Woitek, MD; Stephan Haussig, MD; Florian Schlotter, MD; Robert Höllriegel, MD; Jennifer Adam, MA; Anna Lindner, MD; Friedrich W. Mohr, MD; Gerhard Schuler, MD; Philipp Kiefer, MD; Sergey Leontyev, MD; Michael A. Borger, MD, PhD; Holger Thiele, MD; David Holzhey, MD; Axel Linke, MD

***Background*—**Impaired left ventricular (LV) ejection fraction is a common finding in patients with aortic stenosis and serves as a predictor of morbidity and mortality after transcatheter aortic valve replacement. However, conflicting data on the most accurate measure for LV function exist. We wanted to examine the impact of LV ejection fraction, mean pressure gradient, and stroke volume index on the outcome of patients treated by transcatheter aortic valve replacement.

***Methods and Results*—**Patients treated by transcatheter aortic valve replacement were primarily separated into normal flow (NF; stroke volume index >35 mL/m^2) and low flow (LF; stroke volume index ≤35 mL/m^2). Afterwards, patients were divided into 5 groups: "NF–high gradient," "NF–low gradient" (NF-LG), "LF–high gradient," "paradoxical LF-LG," and "classic LF-LG." The 3-year mortality was the primary end point. Of 1600 patients, 789 (49.3%) were diagnosed as having LF, which was characterized by a higher 30-day (P=0.041) and 3-year (P<0.001) mortality. LF was an independent predictor of all-cause (hazard ratio, 1.29; 95% confidence interval, 1.03–1.62; P=0.03) and cardiovascular (hazard ratio, 1.37; 95% confidence interval, 1.06–1.77; P=0.016) mortality. Neither mean pressure gradient nor LV ejection fraction was an independent predictor of mortality. Patients with paradoxical LF-LG (35.0%), classic LF-LG (35.1%) and LF–high gradient (38.1%) had higher all-cause mortality at 3 years compared with NF–high gradient (24.8%) and NF-LG (27.9%) (P=0.001). However, surviving patients showed a similar improvement in symptoms regardless of aortic stenosis entity.

***Conclusions*—**LF is a common finding within the aortic stenosis population and, in contrast to LV ejection fraction or mean pressure gradient, an independent predictor of all-cause and cardiovascular mortality. Despite increased long-term mortality, high procedural success and excellent functional improvement support transcatheter aortic valve replacement in patients with LF severe aortic stenosis. **(*J Am Heart Assoc*. 2018;7:e007977. DOI: 10.1161/JAHA.117.007977.)**

Key Words: aortic stenosis • low flow • outcome • transcatheter aortic valve implantation • transcatheter aortic valve replacement

Impaired left ventricular (LV) function is a frequent finding in patients with calcific aortic stenosis (AS).[1] LV ejection fraction (LV-EF) has affected survival after surgical aortic valve replacement[2–4] and has consequently been incorporated in statistical models for assessment of operative risk.[5] Conversely, in transcatheter aortic valve replacement (TAVR), which has been a safe and effective treatment for patients at intermediate[6] and high surgical risk,[7] the relationship is less clear.[8–12]

From the Heart Center Leipzig–University Hospital, Leipzig, Germany (N.M., G. Stachel, F.W., F.S., J.A., A. Lindner, G. Schuler, H.T.); Department of Internal Medicine and Cardiology, Heart Center Dresden, Technische Universität Dresden, Dresden, Germany (N.M., F.W., S.H., R.H., A. Linke); Leipzig Heart Institute, Leipzig, Germany (F.W.M.); and Department of Cardiac Surgery, Heart Center Leipzig, University of Leipzig, Leipzig, Germany (P.K., S.L., M.A.B., D.H.).

Accompanying Tables S1 through S4 and Figure S1 are available at http://jaha.ahajournals.org/content/7/8/e007977/DC1/embed/inline-supplementary-material-1.pdf

*Dr Mangner and Dr Stachel contributed equally to this work and are co–first authors.

Correspondence to: Norman Mangner, MD, Heart Center Leipzig–University Hospital, Struempellstraße 39, 04289 Leipzig, Germany.
E-mail: norman.mangner@med.uni-leipzig.de

Received October 27, 2017; accepted February 6, 2018.

Clinical Perspective

What Is New?

- Approximately 50% of the patients undergoing transcatheter aortic valve replacement are in a state of low flow (LF; eg, stroke volume index ≤35 mL/m^2).
- An LF aortic stenosis is associated with a higher all-cause and cardiovascular mortality compared with normal-flow aortic stenosis in patients undergoing transcatheter aortic valve replacement and is, in contrast to left ventricular ejection fraction and mean pressure gradient, an independent predictor of all-cause and cardiovascular mortality.
- Patients with paradoxical LF–low-gradient aortic stenosis have comparable outcomes to patients with classic LF–low-gradient aortic stenosis.
- Despite differences in mortality, surviving patients showed similar improvements in functional capacity across all examined entities of aortic stenosis.

What Are the Clinical Implications?

- Despite the higher long-term mortality in patients with paradoxical LF–low-gradient and classic LF–low-gradient aortic stenosis, these patients have a high transcatheter aortic valve replacement procedural success and low procedural mortality.
- Marked improvement in functional capacity is also evident among survivors.
- Our findings suggest that these patients are, therefore, in need of early treatment because of advanced disease and do not represent a futile patient cohort.

A more comprehensive indicator of LV function is stroke volume index (SVI) because of the fact that in the setting of marked LV hypertrophy and diastolic dysfunction, LV-EF does not reflect the complex capacity of the LV.[13] Reduced stroke volume (eg, low flow [LF]) leads to a reduced pressure gradient despite severe AS creating the entity of "LF–low-gradient (LG) AS."[14] This can be further subdivided into a "classic" type with reduced LV-EF and a "paradoxical" type with preserved LV-EF, with the latter characterized by impaired longitudinal deformation, diastolic dysfunction, and a small LV volume causing the impairment in LV function.[15] LF states are associated with either poor prognosis, if treated medically,[16] or with increased operative mortality, if treated by surgical aortic valve replacement[16–18] or TAVR.[19] Data in TAVR cohorts are characterized by different definitions of AS entities and missing information on SVI, leading to an inconclusive assessment on the impact of LV-EF, mean pressure gradient (MPG), and SVI on outcome.[1,9,10,19–23] Beyond survival, it is also recognized that some patients fail to experience a benefit in functional capacity or morbidity after TAVR.[24] Therefore, the need for identifying the subgroups of patients in whom TAVR is likely to be futile remains a priority.

In this study, we examined the impact of SVI, MPG, and LV-EF on mortality and functional capacity after TAVR in a large, single-center, all-comers cohort.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patient Cohort

From February 24, 2006 to September 17, 2014, a total of 1821 consecutive patients were treated with a transfemoral TAVR in our tertiary center after discussion of the best treatment option in a multidisciplinary heart team.[25] For this analysis, patients were excluded if they were treated because of aortic valve bioprosthesis failure (n=62) or pure aortic regurgitation (n=3) or if they had incomplete baseline echocardiographic data (n=156). Baseline characteristics, procedural data, and outcome data were prospectively collected. Follow-up was performed after 30 days, 12 months, and up to 3 years. Presence of lung disease was defined according to the EuroScore definition.[26] Immunosuppressant medication, diabetes mellitus, coronary heart disease, and peripheral artery disease were defined according to the Society of Thoracic Surgeons Predicted Risk of Mortality score.[27] Society of Thoracic Surgeons Predicted Risk of Mortality score and logistic EuroScore I were calculated. The registry was approved by the Ethics Committee of the University of Leipzig (registration no. 167-10-12072010), and all patients gave written informed consent.

Echocardiography

LV-EF and LV outflow tract diameter were acquired by echocardiography. Doppler velocity measurements of LV outflow tract flow and transvalvular flow were measured, and stroke volume and aortic valve area were calculated using the continuity equation. Peak and mean transaortic gradients were computed using the Bernoulli equation. SVI and aortic valve area index were calculated using the body surface area, as determined by the DuBois formula. Patients were primarily separated into normal flow (NF; SVI >35 mL/m^2) and LF (SVI ≤35 mL/m^2). In a second analysis, patients were further stratified into 4 groups according to a current guideline definition[28]: "NF–high gradient" (NF-HG; SVI >35 mL/m^2, MPG >40 mm Hg), "NF-LG" (SVI >35 mL/m^2, MPG ≤40 mm Hg), "LF-LG" (SVI ≤35 mL/m^2, MPG ≤40 mm Hg), and "LF-HG" (SVI ≤35 mL/m^2, MPG >40 mm Hg). The LF-LG

group was additionally separated into classic LF-LG (cLF-LG; LV-EF <50%) and paradoxical LF-LG (pLF-LG; LV-EF ≥50%).

End Points

The primary end point was 3-year all-cause mortality. Thirty-day all-cause mortality served as a secondary end point. Occurrence of periprocedural myocardial infarction, stroke, renal failure, bleeding, and access site complications was evaluated according to the Valve Academic Research Consortium-2 defintion.[29] Causes of death were categorized into cardiovascular and noncardiovascular causes, also according to Valve Academic Research Consortium-2. Functional capacity was assessed by the New York Heart Association (NYHA) class and was evaluated at baseline and after 6 to 12 months.

Statistical Analysis

The statistical analysis was performed using SPSS Statistics, version 22.0 (IBM Corporation, Armonk, NY). Categorical variables are expressed as numbers and percentage and were compared with the use of χ^2 test. Continuous variables are expressed as median with the corresponding 25th and 75th quartile and were compared using the Kruskal-Wallis test because of nonnormal distribution assessed with the Shapiro-Wilk test. To prove the cutoff value of 35 mL/m^2 for SVI, the optimal cutoff in our cohort was determined by receiver-operating characteristic curve analysis and the Youden index. The 30-day and 3-year mortality rates were analyzed according to the method of Kaplan-Meier, and group comparisons were made applying the log-rank test. Independent predictors of mortality were determined with Cox proportional hazards regression models for all-cause and cardiovascular mortality at 3 years. Clinically relevant variables with a $P<0.1$ in univariate analysis were included in the model. Age was forced into the model for all-cause mortality. Two different models were created: one only including baseline variables and one including baseline and periprocedural variables. LogEuroScore, Society of Thoracic Surgeons Predicted Risk of Mortality score, and body mass index were naturally log transformed because they were nonnormally distributed. NYHA class at baseline and follow-up was analyzed as a paired test. $P<0.05$ was considered significant.

Results

Determination of the Optimal Cutoff for SVI

The optimal cutoff value for SVI, as determined by Youden index, was 34.4 mL/m^2 in our cohort (Figure S1). To keep it comparable to other studies, <35 mL/m^2 was defined as cutoff for the definition of LF.

Baseline Characteristics

Of 1600 patients, 789 (49.3%) were diagnosed as having LF and 811 (50.7%) had NF. After further subdivision, 522 patients (32.6%) had NF-HG, 289 patients (18.1%) had NF-LG, 405 patients (25.3%) had LF-LG, and 384 patients (24.0%) had LF-HG. Of the 405 patients with LF-LG, 225 (14.1% of the total population) had cLF-LG and 180 (11.3%) had pLF-LG. Baseline characteristics and echo parameters are depicted in Table 1, showing substantial differences between groups. Specifically, the proportion of younger and male patients was significantly higher in cLF-LG. Moreover, patients with cLF-LG had a higher logistic EuroScore I, had more cardiovascular comorbidities, and more often had chronic kidney disease. In contrast, patients with pLF-LG were more often women and had the highest prevalence of preexisting atrial fibrillation. All patients were highly symptomatic, with ~70% to 80% having dyspnea, according to NYHA class III/IV. Levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide) were increased in all groups, with highest values found in cLF-LG and LF-HG and comparable levels in NF-HG, NF-LG, and pLF-LG.

Procedural Data and Complications

Types of implanted valves and Valve Academic Research Consortium-2–defined device success did not differ between the groups (Table 2). Analysis of the complication rate at 30 days revealed significant differences between the groups, with higher rates of overall bleeding and access site complications in NF-HG and pLF-LG. The other Valve Academic Research Consortium-2–defined end points, including myocardial infarction, stroke, and kidney injury, did not vary between groups (Table 2).

Mortality and Functional Outcome

Patients with LF exhibited a significantly higher all-cause mortality at both 30 days (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.02–2.11; $P=0.041$) and 3 years (HR, 1.46; 95% CI, 1.22–1.74; $P<0.001$) (Figure 1A), mainly driven by a higher cardiovascular mortality at 3 years (HR, 1.50; 95% CI, 1.22–1.84; $P<0.001$) (Figure 1B). Stratifying patients according to MPG (Figure 2A and 2B), no significant differences for all-cause (HR, 1.14; 95% CI, 0.96–1.37; $P=0.138$) and cardiovascular (HR, 1.05; 95% CI, 0.86–1.29; $P=0.641$) mortality were observed in univariate analysis. In contrast, stratifying patients according to LV-EF, a higher all-cause (HR, 1.31; 95% CI, 1.09–1.56; $P=0.004$) and cardiovascular (HR, 1.32; 95% CI, 1.08–1.62; $P=0.008$) mortality was observed in patients with LV-EF ≤50% at 3 years in univariate analysis (Figure 2C and 2D).

Table 1. Baseline Characteristics

Characteristics	NF-HG (n=522)	NF-LG (n=289)	LF-HG (n=384)	cLF-LG (n=225)	pLF-LG (n=180)	*P* Value
Age, y	81 (77–84)	81 (77–84)	81 (77–85)	79 (74–83)	81 (77–84)	<0.001
Male sex	208/522 (39.8)	140/289 (48.4)	139/384 (36.2)	137/225 (60.9)	58/180 (32.2)	<0.001
Body mass index, kg/m^2	27.2 (24.1–30.9)	27.9 (24.4–31.3)	27.3 (24.5–30.9)	27.1 (23.7–30.5)	28.0 (25.0–32.0)	0.033
Logistic EuroScore I, %	12.7 (9.0–19.4)	14.5 (9.5–23.4)	16.3 (10.7–25.3)	24.1 (15.3–35.9)	14.4 (8.1–22.6)	<0.001
STS score, %	5.9 (3.7–9.5)	6.2 (4.0–9.8)	6.7 (4.3–11.2)	7.6 (5.0–12.0)	7.7 (4.2–11.5)	<0.001
NYHA class III/IV	358/521 (68.7)	221/289 (76.5)	312/384 (81.2)	199/225 (88.4)	139/180 (77.2)	<0.001
CAD	205/484 (42.4)	149/268 (55.6)	161/359 (44.8)	130/207 (62.8)	76/159 (47.8)	<0.001
Previous MI	44/503 (8.7.)	58/282 (20.6)	46/373 (12.3)	68/221 (30.8)	28/174 (16.1)	<0.001
Previous CABG	33/503 (6.6)	50/282 (17.7)	27/373 (7.2)	49/221 (22.2)	18/174 (10.3)	<0.001
Previous PCI	71/503 (14.1)	73/282 (25.9)	54/373 (14.5)	54/221 (24.4)	33/174 (19.0)	<0.001
Arterial hypertension	484/518 (93.4)	270/287 (94.1)	359/381 (94.2)	201/225 (89.3)	172/178 (96.6)	0.044
Diabetes mellitus	199/521 (38.2)	146/289 (50.5)	158/382 (41.4)	111/225 (49.3)	82/179 (45.8)	0.003
Atrial fibrillation/flutter	165/522 (31.6)	115/289 (39.8)	177/384 (46.1)	129/225 (57.3)	114/180 (63.3)	<0.001
Previous stroke	51/518 (9.8)	29/287 (10.1)	27/381 (7.1)	31/225 (13.8)	23/178 (12.9)	0.068
PAD	47/518 (9.1)	35/287 (12.2)	38/381 (10.0)	44/225 (19.6)	19/178 (10.7)	0.001
COPD	83/522 (15.9)	53/289 (18.3)	64/384 (16.7)	39/225 (17.3)	27/180 (15.0)	0.872
CKD stage ≥3b	140/521 (26.9)	95/289 (32.9)	106/384 (27.6)	83/225 (36.9)	61/180 (33.9)	0.028
Chronic hemodialysis	9/521 (1.7)	7/288 (2.4)	4/383 (1.0)	11/221 (5.0)	7/177 (4.0)	0.016
Immunosuppressive therapy	50/522 (9.6)	23/289 (8.0)	30/384 (7.8)	16/224 (7.1)	14/180 (7.8)	0.783
LV ejection fraction, %	62 (55–69)	57 (48–65)	55 (44–64)	35 (26–45)	62 (57–66)	<0.001
Aortic valve area, cm^2	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.5 (0.4–0.6)	0.7 (0.5–0.8)	0.7 (0.6–0.8)	<0.001
Peak gradient, mm Hg	82 (71–96)	55 (47–61)	78 (71–94)	45 (37–55)	51 (43–60)	<0.001
Mean gradient, mm Hg	52 (45–62)	34 (28–38)	51 (45–61)	29 (23–35)	33 (27–37)	<0.001
SVI, mL/m^2	44 (40–50)	42 (38–48)	29 (24–32)	26 (22–30)	28 (25–32)	<0.001
Mitral regurgitation 2/3	32/475 (6.7)	25/269 (9.3)	44/359 (12.3)	53/197 (26.9)	22/168 (13.1)	<0.001
Aortic regurgitation 2/3	82/464 (17.7)	28/260 (10.8)	59/353 (16.7)	21/191 (11.0)	15/161 (9.3)	0.009
NT-proBNP, pg/mL	1419 (655–3366)	1111 (507–3028)	2854 (1344–5900)	4691 (2415–9230)	1658 (707–3382)	<0.001

Variables are expressed as number/total (percentage) or median (25th–75th quartile). CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; cLF-LG, classic low flow–low gradient; COPD, chronic obstructive lung disease; LF-HG, low flow–high gradient; LV, left ventricular; MI, myocardial infarction; NF-HG, normal flow–high gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; pLF-LG, paradoxical low flow-low gradient; STS, Society of Thoracic Surgeons; and SVI, stroke volume index.

Dividing the population into 5 groups according to SVI, MPG, and LV-EF, significantly higher all-cause and cardiovascular mortality rates were observed in patients with cLF-LG, pLF-LG, and LF-HG compared with NF-HG and NF-LG (Figure 3A and 3B; Table 2). The all-cause and cardiovascular mortality rates between cLF-LG and pLF-LG were not different at 3 years.

The factors associated with all-cause and cardiovascular mortality at 3 years are shown in Tables 3 and 4. Despite including not only preprocedural variables (upper part of Tables 3 and 4) but also periprocedural complication rates, the presence of LF remained an independent predictor of all-cause (HR, 1.29; 95% CI, 1.03–1.62; *P*=0.03) and cardiovascular (HR, 1.37; 95% CI, 1.06–1.77; *P*=0.016) mortality. Neither MPG nor LV-EF at baseline was an independent predictor of mortality in these models (Tables S1 through S4).

In terms of functional capacity, significantly more patients with cLF-LG, pLF-LG, and LF-HG were in NYHA class III/IV at baseline in comparison to patients with NF. We found this difference mitigated at 1-year-follow-up, and there was significant symptom improvement in every respective entity between baseline and 1-year follow-up (Figure 4A and 4B). There were no significant differences between the 5 entities on the proportion of patients with improvement of NYHA class at 1-year follow-up (Figure 4C).

Table 2. Procedural Outcomes and Mortality at 30 Days and 3-Year Mortality

Variables	NF-HG (n=543)	NF-LG (n=306)	LF-HG (n=392)	cLF-LG (n=232)	pLF-LG (n=182)	*P* Value
Type of valve						0.673
Self-expandable	376/521 (72.2)	220/289 (76.1)	290/384 (75.5)	170/225 (75.6)	136/180 (75.6)	
Balloon expandable	145/521 (27.8)	69/289 (23.9)	94/384 (24.5)	55/225 (24.4)	44/180 (24.4)	
Procedure time, min	46 (38–60)	45 (36–56)	48 (39–64)	45 (35–58)	43 (34–57)	0.002
Contrast dye, mL	125 (105–154)	120 (100–150)	130 (105–160)	125 (103–150)	120 (100–150)	0.023
Device success	455/502 (90.6)	262/282 (92.9)	333/373 (89.3)	205/221 (92.8)	162/174 (93.1)	0.352
Residual aortic regurgitation ≥2	25/474 (5.3)	10/261 (3.8)	24/341 (7.0)	10/206 (4.9)	7/164 (4.3)	0.459
Residual mean gradient, mm Hg	9 (7–12)	8 (6–11)	9 (6–11)	7 (5–9)	8 (6–11)	<0.001
Aortic valve area, cm^2	1.9 (1.6–2.2)	1.9 (1.6–2.3)	1.8 (1.5–2.2)	1.9 (1.5–2.2)	1.8 (1.5–2.1)	0.014
VARC-2						
Myocardial infarction	8/503 (1.6)	0/282 (0.0)	4/373 (1.1)	1/221 (0.5)	1/174 (0.6)	0.194
Stroke	19/503 (3.8)	15/282 (5.3)	21/373 (5.6)	14/221 (6.3)	5/174 (2.9)	0.347
Renal failure	80/504 (15.9)	47/283 (16.6)	61/376 (16.2)	42/221 (16.2)	35/174 (20.1)	0.650
Bleeding	215/503 (42.7)	111/282 (39.4)	152/372 (40.9)	65/221 (29.4)	74/174 (42.5)	0.014
Access site complication	158/503 (31.4)	68/282 (24.1)	101/373 (27.1)	45/221 (20.4)	56/174 (32.2)	0.011
New PPM/ICD	149/521 (28.6)	84/289 (29.1)	120/384 (31.2)	57/225 (25.3)	56/180 (31.1)	0.588
All-cause mortality						
30 d	35/521 (6.7)	14/287 (4.9)	38/383 (9.9)	20/225 (8.9)	11/180 (6.1)	0.101
3 y	129/521 (24.8)	80/287 (27.9)	146/383 (38.1)	79/225 (35.1)	63/180 (35.0)	<0.001
Cardiovascular mortality						
30 d	33/521 (6.4)	13/286 (4.6)	35/383 (9.2)	18/225 (8.1)	8/180 (4.5)	0.093
3 y	99/521 (19.0)	58/287 (20.2)	119/383 (31.1)	58/225 (25.8)	46/180 (25.6)	<0.001

Variables are expressed as number/total (percentage) or median (25th–75th quartile). cLF-HG indicates classic low flow–high gradient; ICD, implantable cardioverter defibrillator; NF-HG, normal flow–high gradient; NF-LG, NF–low gradient; pLF-LG, paradoxical low flow–low gradient; PPM, permanent pacemaker; and VARC, Valve Academic Research Consortium.

Discussion

The purpose of this study was to examine the impact of SVI, MPG, and LV-EF on procedural complications, mortality, and functional capacity after TAVR in a large, single-center, all-comers cohort. The main findings of this study include the following: (1) ≈50% of the patients undergoing TAVR are in a state of LF (eg, SVI ≤35 mL/m^2); (2) LF is associated with higher all-cause and cardiovascular mortality rates compared with NF; (3) LF, but not LV-EF or MPG, is an independent predictor of all-cause and cardiovascular mortality; (4) patients with pLF-LG had comparable outcomes to patients with cLF-LG; and (5) despite differences in mortality, surviving patients showed similar improvements in functional capacity across all examined entities of AS.

Incidence and Impact of LF on Outcome

The presence of LF is a common finding in patients with severe AS undergoing surgical aortic valve replacement or TAVR and is reported to range between 30% and 55%.[1,19,22,23] The reasons for LF are multifactorial, including impaired myocardial contractility, restrictive physiological features, and afterload mismatch with high valvuloarterial impedance.[1] Nonrandomized data propose that regardless of the origin, patients with LF have worse outcomes both with and without surgery but may still have an advantage from valve replacement compared with optimal medical therapy.[17,30,31]

Le et al evaluated the effect of stroke volume on survival after TAVR in 639 patients,[19] Schewel et al in 676 patients,[23] and Reinthaler et al in 150 patients.[22] All these studies revealed a higher mortality in patients with LF. Our study confirms and expands the knowledge about the impact of LF on the outcome of patients undergoing TAVR by corroborating the findings of these smaller studies and proves the independence of SVI as a predictor of mortality. In our study, periprocedural complications were included in the Cox regression models but were not reported[1,19] or not included in the multivariable analyses in the aforementioned studies,[23] despite the fact that periprocedural complications are known to affect long-term

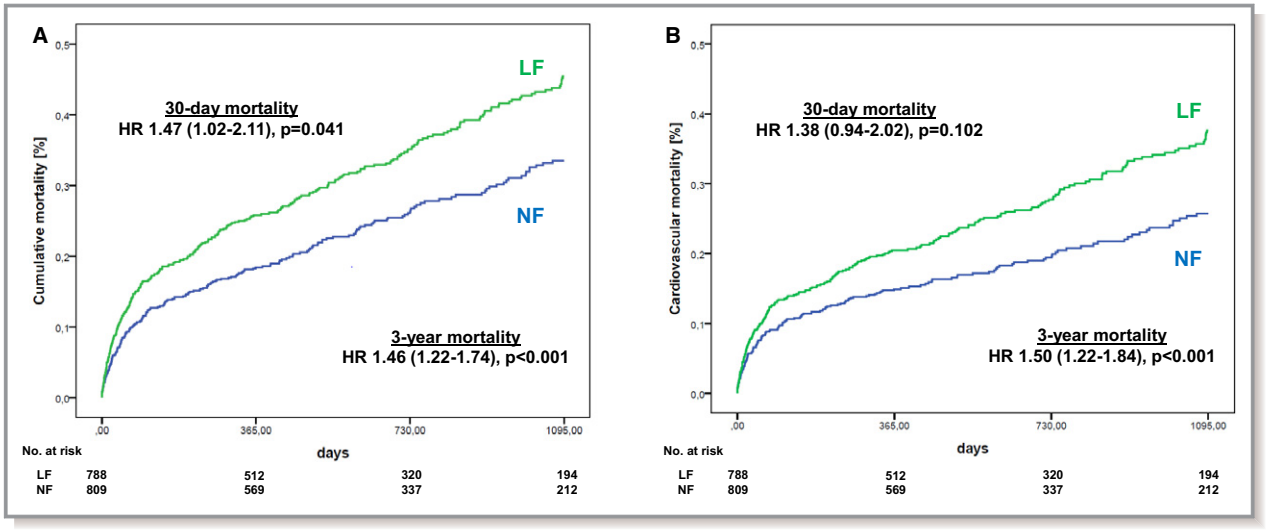

Figure 1. All-cause (A) and cardiovascular (B) mortality according to low flow (LF) vs normal flow (NF). HR indicates hazard ratio.

mortality.[21] The higher rate of bleeding and access site complications in NF-HG and pLF-LG could also be attributed to the higher amount of women in these groups who are known to experience these complications more frequently,[32] but sex was included in our Cox regression model to adjust for this potential confounder. LF is an independent predictor of

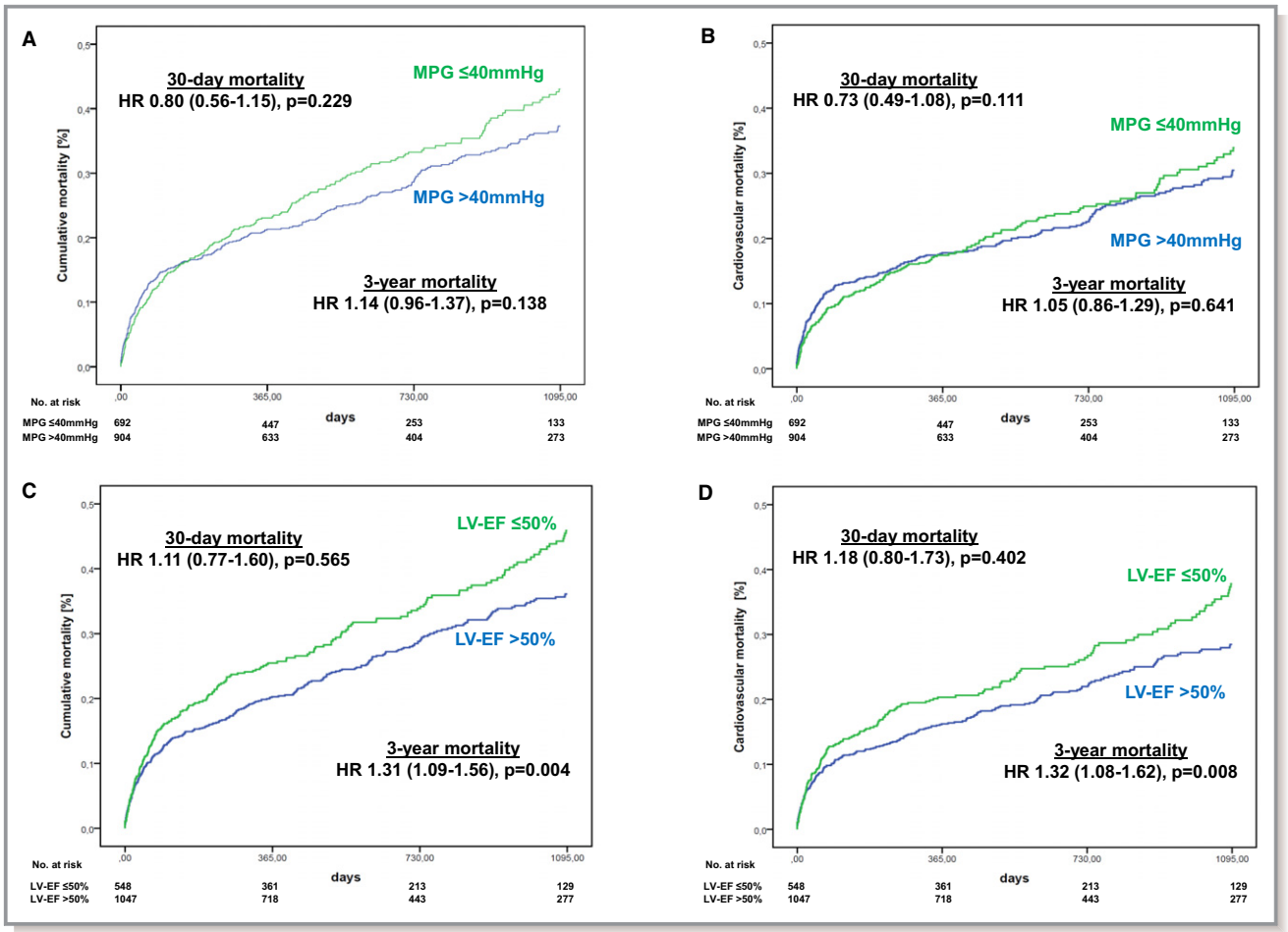

Figure 2. All-cause (A) and cardiovascular (B) mortality according to mean pressure gradient (MPG). All-cause (C) and cardiovascular (D) mortality according to left ventricular ejection fraction (LV-EF). HR indicates hazard ratio.

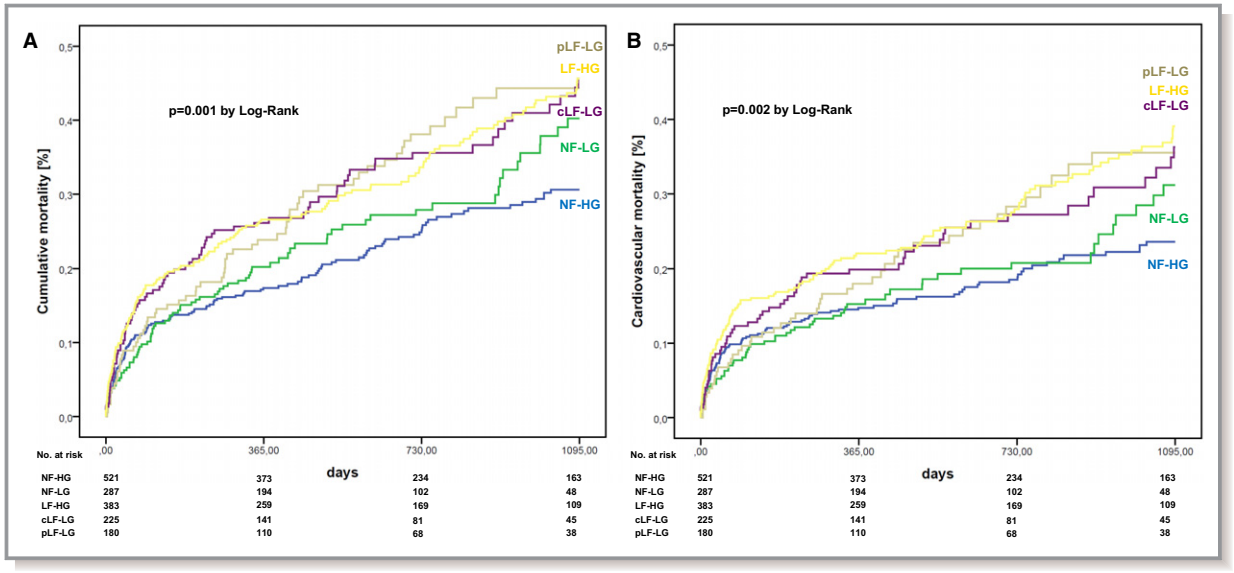

Figure 3. All-cause (A) and cardiovascular (B) mortality according to 5 different aortic stenosis entities: normal flow–high gradient (NF-HG), NF–low gradient (NF-LG), low flow–HG (LF-HG), classic LF-LG (cLF-LG), and paradoxical LF-LG (pLF-LG).

all-cause and cardiovascular mortality in both models, including and excluding periprocedural complications underlining the importance and robustness of this factor. Furthermore, procedural complications even affect the outcome up to 3 years.

Table 3. Factors Associated With All-Cause 3-Year Mortality

Factors	HR (95% CI)	*P* Value
Parameter (including only preprocedural factors)		
Male sex	1.33 (1.08–1.84)	0.008
STS score (per 1% increase)	1.12 (1.07–1.16)	<0.001
NYHA class III/IV	1.46 (1.10–1.93)	0.009
Atrial fibrillation	1.28 (1.04–1.57)	0.019
PAD	1.40 (1.06–1.85)	0.019
CKD stage ≥3b	1.28 (1.02–1.61)	0.033
SVI (low flow vs normal flow)	1.22 (1.00–1.50)	0.05
Parameter (including preprocedural and periprocedural factors)		
STS score (per 1% increase)	1.09 (1.05–1.15)	<0.001
NYHA class III/IV	1.42 (1.05–1.92)	0.024
Atrial fibrillation	1.36 (1.08–1.71)	0.008
PAD	1.49 (1.10–2.02)	0.011
CKD stage ≥3b	1.30 (1.01–1.68)	0.042
SVI (low flow vs normal flow)	1.29 (1.03–1.62)	0.03
Aortic regurgitation ≥2 (post-TAVI)	1.51 (1.03–2.22)	0.036
VARC-2 renal failure	1.81 (1.38–2.37)	<0.001

CI indicates confidence interval; CKD, chronic kidney disease; HR, hazard ratio; NYHA, New York Heart Association; PAD, peripheral artery disease; STS, Society of Thoracic Surgeons; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; and VARC, Valve Academic Research Consortium.

Impact of LV-EF and Pressure Gradient on Outcome

The impact of global LV-EF, a common parameter incorporated in the classic risk scores,[5] and transvalvular pressure gradient

Table 4. Factors Associated With Cardiovascular 3-Year Mortality

Factors	HR (95% CI)	*P* Value
Parameter (including only preprocedural factors)		
Male sex	1.30 (1.04–1.63)	0.021
STS score (per 1% increase)	1.15 (1.10–1.20)	<0.001
NYHA class III/IV	1.38 (1.02–1.87)	0.036
Atrial fibrillation	1.39 (1.11–1.74)	0.004
SVI (low flow vs normal flow)	1.28 (1.02–1.59)	0.033
Parameter (including preprocedural and periprocedural factors)		
Male sex	1.32 (1.01–1.71)	0.039
STS score (per 1% increase)	1.15 (1.10–1.21)	<0.001
Atrial fibrillation	1.56 (1.21–2.02)	0.001
PAD	1.46 (1.04–2.04)	0.029
SVI (low flow vs normal flow)	1.37 (1.06–1.77)	0.016
Aortic regurgitation ≥2 (post-TAVI)	1.54 (1.02–2.33)	0.042
VARC-2		
Stroke	1.84 (1.17–2.90)	0.008
Renal failure	1.83 (1.36–2.47)	<0.001

CI indicates confidence interval; HR, hazard ratio; NYHA, New York Heart Association; PAD, peripheral artery disease; STS, Society of Thoracic Surgeons; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; and VARC, Valve Academic Research Consortium.

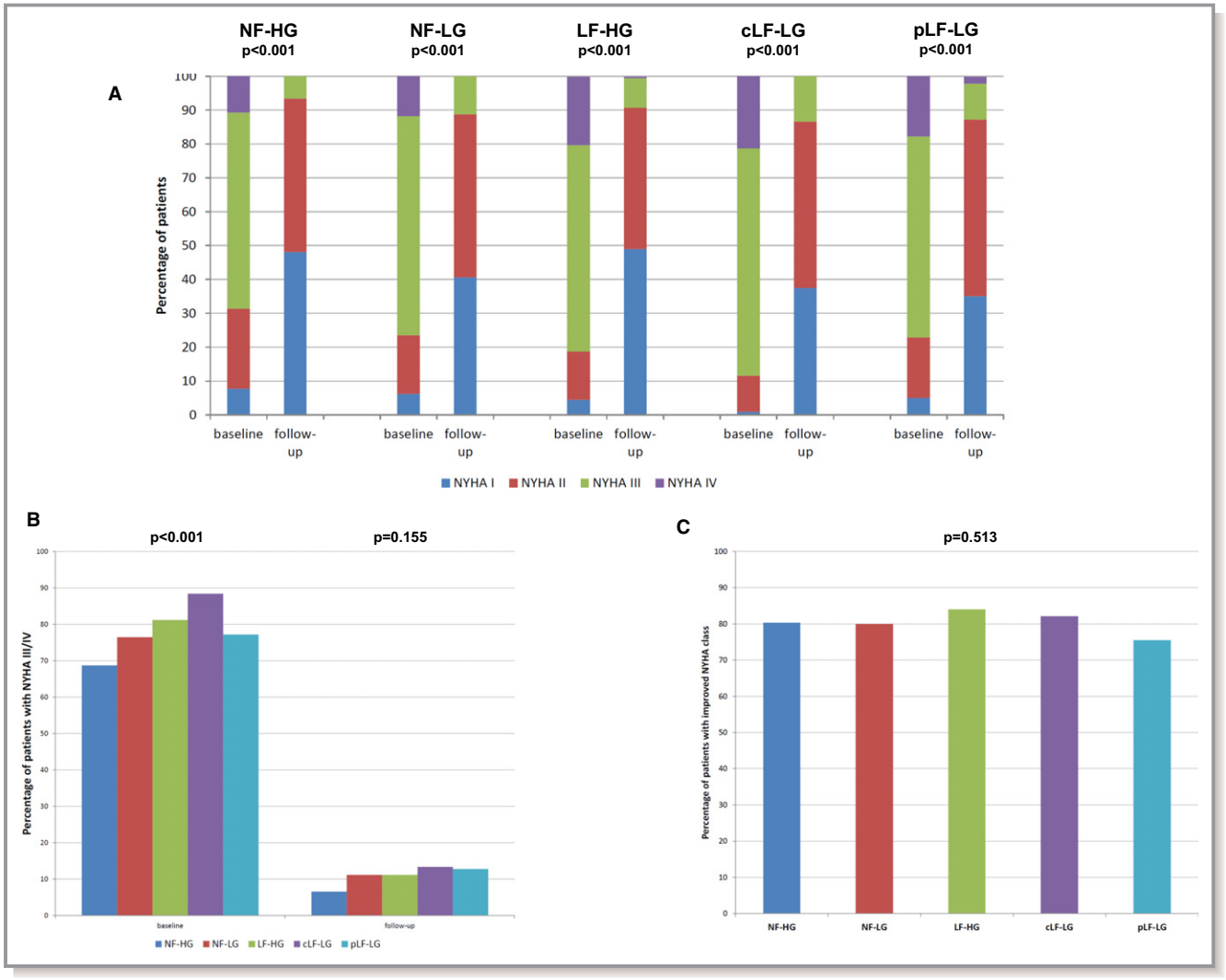

Figure 4. A, Percentage of patients with respective New York Heart Association (NYHA) functional class for each entity at baseline and at 1 year. B, Percentage of patients with NYHA class III or higher for each entity before and after treatment. C, Percentage of patients in each group with NYHA improvement of ≥1 classes after treatment. cLF-LG indicates classic low flow–low gradient; LF-HG, low flow–high gradient; NF-HG, normal flow–high gradient; and pLF-LG, paradoxical low flow-low gradient.

on short-term and midterm survival after TAVR remain a matter of debate, and numerous large studies found conflicting results. For instance, an analysis of 2535 patients from the UK-TAVR registry found reduced midterm survival in patients with LG and EF <50%, whereas patients with normal MPG or preserved EF did not exhibit increased mortality at 2 years.[10] A study with 3908 patients from the German Aortic Valve Registry yielded similar results.[9] A meta-analysis of 12 589 patients found transvalvular gradient to be an independent predictor of 1-year mortality but not LV-EF.[20] In our study, reduced LV-EF was associated with a higher mortality in univariate analysis; however, after adjusting for other risk factors, including SVI, this association lost significance. Transvalvular pressure gradient was not associated with 30-day or 3-year mortality in our analysis. The reason for those divergent findings might be caused by heterogeneous group definitions (eg, LV-EF <30% versus >30% or <50% versus >50%), bias inherent to observational studies, and, most important, missing measurement/incorporation of SVI. LV-EF does not adequately reflect total LV function in a setting of marked LV hypertrophy and relatively small LV volumes typical of high-grade AS.[18] Reduced MPG can be interpreted as an effect of low transvalvular flow secondary to LV dysfunction or concomitant mitral regurgitation, but without knowledge of SVI, this entity cannot be discerned from LG because of only moderately reduced aortic valve area. Therefore, the inverse relationship between baseline gradient and mortality after TAVR is possibly explained by the occurrence of LF, which has not been determined in those studies.[20] All these findings suggest that SVI, as a direct measure of cardiac systolic function, is a more important determinant of outcome than the mechanism leading to the LF state.

"pLF-LG" and "cLF-LG" AS

The impact of pLF-LG on outcome compared with cLF-LG and NF-HG has been conversely debated. Studies show comparable outcomes to NF-HG,[9] a higher mortality in pLF-LG compared with NF-HG but lower compared with cLF-LG,[23] and those with equal mortality rates in pLF-LG and cLF-LG but higher compared with NF-HG.[19] Our findings confirm the high prevalence of pLF-LG and similar worse prognosis of those patients compared with cLF-LG, which is in line with those studies integrating SVI as an essential parameter for group definition.[1,19,22,23] These data support the above mentioned thesis that flow, rather than the mechanism for reduced flow, is the key prognostic factor[1] and that an LF state might be a sign for an advanced disease. The divergence compared with the analysis derived from the German Aortic Valve Registry[9] might be caused by the definition of pLF-LG, including only LV-EF ≥50% and MPG <40 mm Hg but not SVI, which may have led to the inclusion of nonsevere AS in this group. Despite the higher mortality in pLF-LG and cLF-LG after TAVR, those patients derive a mortality benefit from valve replacement compared with medical therapy, which seems to be comparable between TAVR and surgical aortic valve replacement.[1,17]

Beyond mortality, surviving patients in all LF groups had a significant improvement in functional symptoms, which was comparable to NF-HG and NF-LG in our analysis and another study,[23] indicating that treatment needs to be considered in patients with LF, despite a higher mortality compared with patients with NF.

Limitations

Our study has several limitations that should be noted. Data collected were derived from a single-center registry and are, therefore, prone to bias inherent to registries and not necessarily conferrable to other cohorts. There was no core laboratory to analyze echocardiography. Echocardiographic estimation of SVI is susceptible to measurement errors, in particular in elliptic shape of the LV outflow tract, atrial fibrillation, concomitant aortic and mitral regurgitation, or poor image quality.[28] Dobutamine stress echocardiography was not performed on a regular basis. Thus, we were not able to estimate contractile reserve, which is known to affect the outcome of patients with cLF-LG.[31] Only little is known about the role of dobutamine stress echocardiography in pLF-LG.[33] The assessment of calcium score has gained increasing importance in the diagnosis of LF-LG because the degree of valve calcification by computed tomography is related to AS severity and outcome. Unfortunately, calcium score was not available in our registry to further differentiate this entity. However, comparable NT-proBNP values in NF-HG, NF-LG, and pLF-LG and the even higher values in LF-HG and cLF-LG are reassuring that all patients experienced a real severe AS. Finally, NYHA class is a subjective parameter for assessing functional outcome, but more sophisticated examinations (eg, 6-minute walk test and quality-of-life questionnaires) were not performed in our registry.

Conclusion

LF, defined by SVI ≤35 mL/m^2, is a common finding within the AS population. LF, but not LV-EF or MPG, is an independent predictor of all-cause and cardiovascular mortality. The results of this study underline the importance to determine SVI during evaluation of patients with severe AS for diagnosis and risk assessment, as recommended in current guidelines. Despite a significantly higher long-term mortality in patients with pLF-LG and cLF-LG, the high procedural success rates, heightened, yet low, procedural mortality, and the excellent improvement in functional capacity of the surviving patients suggest that these are rather patients in need for an early treatment because of advanced disease than a futile patient cohort. Randomized controlled trials would need to test this hypothesis.

Disclosures

Leontyev reports other funding from St Jude Medical and Medtronic, during the conduct of the study. Borger reports speakers' honoraria and consulting fees from Edwards Lifesciences, Medtronic, and CryoLife. Holzhey reports other funding from Symetis and Medtronic, during the conduct of the study. Linke reports grants and personal fees from Medtronic, personal fees from St Jude Medical, grants from Claret Medical, personal fees and other from Claret Medical, personal fees from Boston Scientific, personal fees from Bard, and personal fees from Edwards, outside the submitted work. The remaining authors have no disclosures to report.

References

1. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani V, Szeto WY, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation*. 2013;127:2316–2326.
2. Ding WH, Lam YY, Duncan A, Li W, Lim E, Kaya MG, Chung R, Pepper JR, Henein MY. Predictors of survival after aortic valve replacement in patients with low-flow and high-gradient aortic stenosis. *Eur J Heart Fail*. 2009;11:897–902.
3. Halkos ME, Chen EP, Sarin EL, Kilgo P, Thourani VH, Lattouf OM, Vega JD, Morris CD, Vassiliades T, Cooper WA, Guyton RA, Puskas JD. Aortic valve replacement for aortic stenosis in patients with left ventricular dysfunction. *Ann Thorac Surg*. 2009;88:746–751.
4. Kuwaki K, Amano A, Inaba H, Yamamoto T, Matsumura T, Dohi S, Matsushita S. Predictors of early and mid-term results in contemporary aortic valve replacement for aortic stenosis. *J Card Surg*. 2012;27:139–145.
5. Wendt D, Osswald BR, Kayser K, Thielmann M, Tossios P, Massoudy P, Kamler M, Jakob H. Society of Thoracic Surgeons score is superior to the EuroSCORE determining mortality in high risk patients undergoing isolated aortic valve replacement. *Ann Thorac Surg*. 2009;88:468–474.
6. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD,

Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620.

7. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.
8. Baron SJ, Arnold SV, Herrmann HC, Holmes DR Jr, Szeto WY, Allen KB, Chhatriwalla AK, Vemulapali S, O'Brien S, Dai D, Cohen DJ. Impact of ejection fraction and aortic valve gradient on outcomes of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2349–2358.
9. Lauten A, Figulla HR, Mollmann H, Holzhey D, Kotting J, Beckmann A, Veit C, Cremer J, Kuck KH, Lange R, Zahn R, Sack S, Schuler G, Walther T, Beyersdorf F, Bohm M, Heusch G, Meinertz T, Neumann T, Welz A, Mohr FW, Hamm CW. TAVI for low-flow, low-gradient severe aortic stenosis with preserved or reduced ejection fraction: a subgroup analysis from the German Aortic Valve Registry (GARY). *EuroIntervention*. 2014;10:850–859.
10. Malkin CJ, Long WR, Baxter PD, Gale CP, Wendler O, Monaghan M, Thomas MT, Ludman PF, de Belder MA, Cunningham AD, Moat NE, Blackman DJ. Impact of left ventricular function and transaortic gradient on outcomes from transcatheter aortic valve implantation: data from the UK TAVI Registry. *EuroIntervention*. 2016;11:1161–1169.
11. Schaefer U, Zahn R, Abdel-Wahab M, Gerckens U, Linke A, Schneider S, Eggebrecht H, Sievert H, Figulla HR, Senges J, Kuck KH. Comparison of outcomes of patients with left ventricular ejection fractions </=30% versus >/=30% having transcatheter aortic valve implantation (from the German Transcatheter Aortic Valve Interventions Registry). *Am J Cardiol*. 2015;115:656–663.
12. Schymik G, Tzamalis P, Herzberger V, Bergmann J, Bramlage P, Wurth A, Conzelmann LO, Luik A, Schrofel H. Transcatheter aortic valve implantation in patients with a reduced left ventricular ejection fraction: a single-centre experience in 2000 patients (TAVIK Registry). *Clin Res Cardiol*. 2017;106:1018–1025.
13. Badiani S, van Zalen J, Treibel TA, Bhattacharyya S, Moon JC, Lloyd G. Aortic stenosis, a left ventricular disease: insights from advanced imaging. *Curr Cardiol Rep*. 2016;18:80.
14. Clavel MA, Pibarot P, Dumesnil JG. Paradoxical low flow aortic valve stenosis: incidence, evaluation, and clinical significance. *Curr Cardiol Rep*. 2014;16:431.
15. Galli E, Leguerrier A, Flecher E, Leclercq C, Donal E. Increased valvulo-arterial impedance differently impacts left ventricular longitudinal, circumferential, and radial function in patients with aortic stenosis: a speckle tracking echocardiography study. *Echocardiography*. 2017;34:37–43.
16. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60:1845–1853.
17. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Senechal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60:1259–1267.
18. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115:2856–2864.
19. Le VF, Freeman M, Webb J, Clavel MA, Wheeler M, Dumont E, Thompson C, De LR, Moss R, Doyle D, Ribeiro HB, Urena M, Nombela-Franco L, Rodes-Cabau J, Pibarot P. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2013;62:782–788.
20. Conrotto F, D'Ascenzo F, D'Amico M, Moretti C, Pavani M, Scacciatella P, Omede P, Montefusco A, Biondi-Zoccai G, Gaita F, Maisano F, Nietlispach F. Outcomes of patients with low-pressure aortic gradient undergoing transcatheter aortic valve implantation: a meta-analysis. *Catheter Cardiovasc Interv*. 2017;89:1100–1106.
21. Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, Guo J, Linke A. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. *Eur Heart J*. 2017;38:2729–2738.
22. Reinthaler M, Schwabe A, Landmesser U, Chung R, Aggarwal S, Delahunty N, Frohlich G, Meier P, Roberts N, Pantazis A, Mullen MJ. "Paradoxical" low-flow, low-gradient severe aortic valve stenosis: an entity with limited improvement following transcatheter aortic valve implantation. *J Heart Valve Dis*. 2014;23:441–449.
23. Schewel J, Schewel D, Frerker C, Wohlmuth P, Kuck KH, Schafer U. Invasive hemodynamic assessments during transcatheter aortic valve implantation: comparison of patient outcomes in higher vs. lower transvalvular gradients with respect to left ventricular ejection fraction. *Clin Res Cardiol*. 2016;105:59–71.
24. Puri R, Iung B, Cohen DJ, Rodes-Cabau J. TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J*. 2016;37:2217–2225.
25. Mangner N, Woitek F, Haussig S, Schlotter F, Stachel G, Hollriegel R, Wilde J, Lindner A, Holzhey D, Leontyev S, Mohr FW, Schuler G, Linke A. Incidence, predictors, and outcome of patients developing infective endocarditis following transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2907–2908.
26. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentii C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg*. 1999;15:816–822.
27. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg*. 2009;88:S23–S42.
28. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392.
29. Kappetein AP, Head SJ, Genereux P, Piazza N, Van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438–1454.
30. Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M, Szymanski C, Cosyns B, Pierard LA. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol*. 2012;59:235–243.
31. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319–324.
32. Conrotto F, D'Ascenzo F, Presbitero P, Humphries KH, Webb JG, O'Connor SA, Morice MC, Lefevre T, Grasso C, Sbarra P, Taha S, Omede P, Grosso MW, Salizzoni S, Moretti C, D'Amico M, Biondi-Zoccai G, Gaita F, Marra S. Effect of gender after transcatheter aortic valve implantation: a meta-analysis. *Ann Thorac Surg*. 2015;99:809–816.
33. Clavel MA, Ennezat PV, Marechaux S, Dumesnil JG, Capoulade R, Hachicha Z, Mathieu P, Bellouin A, Bergeron S, Meimoun P, Arsenault M, Le TT, Pasquet A, Couture C, Pibarot P. Stress echocardiography to assess stenosis severity and predict outcome in patients with paradoxical low-flow, low-gradient aortic stenosis and preserved LVEF. *JACC Cardiovasc Imaging*. 2013;6:175–183.

Supplemental Material

Table S1. Factors associated with all-cause 3-year mortality (including only preprocedural factors).

Parameter	Univariate		Multivariate	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age (per 1 year increase)	1.01 (0.99-1.03)	0.233	0.99 (0.98-1.01)	0.406
Male sex	1.27 (1.07-1.52)	0.007	1.33 (1.08-1.84)	0.008
BMI (per 1kg/m² increase)	0.44 (0.15-1.29)	0.134		
STS (per 1% increase)	1.15 (1.12-1.19)	<0.001	1.12 (1.07-1.16)	<0.001
logES I (per 1% increase)	1.12 (1.08-1.15)	<0.001	1.02 (0.97-1.06)	0.492
NYHA III/IV	1.86 (1.45-2.37)	<0.001	1.46 (1.10-1.93)	0.009
Previous CAD	1.21 (1.01-1.46)	0.042	1.02 (0.0.81-1.29)	0.876
Previous MI	1.33 (1.06-1.66)	0.013	0.93 (0.70-1.22)	0.583
Previous CABG	1.32 (1.02-1.71)	0.032	1.04 (0.73-1.48)	0.838
Previous PCI	1.16 (0.93-1.45)	0.203		
Art. Hypertension	0.88 (0.63-1.22)	0.434		
Diabetes mellitus (yes/no)	1.21 (1.01-1.44)	0.036	0.93 (0.75-1.15)	0.507
Atrial fibrillation	1.56 (1.31-1.86)	<0.001	1.28 (1.04-1.57)	0.019
Previous stroke	0.76 (0.55-1.06)	0.105		
PAD	1.51 (1.18-1.93)	0.001	1.40 (1.06-1.85)	0.019
COPD	1.35 (1.09-1.68)	0.007	0.91 (0.69-1.20)	0.509
CKD stage ≥3b	1.84 (1.54-2.19)	<0.001	1.28 (1.02-1.61)	0.033
Immunosuppressive therapy	1.13 (0.82-1.55)	0.469		
LV-EF (> 50% vs. ≤50%)	1.31 (1.09-1.56)	0.004	0.97 (0.78-1.22)	0.815

SVI (low-flow vs. normal-flow)	1.46 (1.23-1.75)	<0.001	1.22 (1.00-1.50)	0.05
MPG (> 40mmHg vs. ≤40mmHg)	1.14 (0.96-1.37)	0.138		
MR grade ≥2 (baseline)	1.51 (1.18-1.94)	0.001	1.14 (0.86-1.53)	0.365
AR grade ≥2 (baseline)	1.26 (0.99-1.61)	0.059	1.22 (0.94-1.59)	0.132

AR indicates aortic regurgitation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CKD stage, chronic kidney disease stage; COPD, chronic obstructive lung disease; log ES I, logistic EuroScore I; LV-EF, left ventricular ejection fraction; MI, myocardial infarction; MPG, mean pressure gradient, MR, mitral regurgitation; NYHA class, New York Heart Association class; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons score; SVI, stroke volume index.

Table S2. Factors associated with all-cause 3-year mortality (including preprocedural and periprocedural factors).

Parameter	Univariate		Multivariate	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age (per 1 year increase)	1.01 (0.99-1.03)	0.233	1.00 (0.98-1.02)	0.609
Male sex	1.27 (1.07-1.52)	0.007	1.24 (0.99-1.57)	0.067
BMI (per 1kg/m² increase)	0.44 (0.15-1.29)	0.134		
STS (per 1% increase)	1.15 (1.12-1.19)	<0.001	1.09 (1.05-1.15)	<0.001
logES I (per 1% increase)	1.12 (1.08-1.15)	<0.001	1.00 (0.95-1.06)	0.973
NYHA III/IV	1.86 (1.45-2.37)	<0.001	1.42 (1.05-1.92)	0.024
Previous CAD	1.21 (1.01-1.46)	0.042	0.96 (0.74-1.23)	0.724
Previous MI	1.33 (1.06-1.66)	0.013	1.04 (0.75-1.44)	0.805
Previous CABG	1.32 (1.02-1.71)	0.032	1.15 (0.83-1.61)	0.396
Previous PCI	1.16 (0.93-1.45)	0.203		
Art. Hypertension	0.88 (0.63-1.22)	0.434		
Diabetes mellitus (yes/no)	1.21 (1.01-1.44)	0.036	0.97 (0.75-1.24)	0.780
Atrial fibrillation	1.56 (1.31-1.86)	<0.001	1.36 (1.08-1.71)	0.008
Previous stroke	0.76 (0.55-1.06)	0.105		
PAD	1.51 (1.18-1.93)	0.001	1.49 (1.10-2.02)	0.011
COPD	1.35 (1.09-1.68)	0.007	0.99 (0.72-1.34)	0.925
CKD stage ≥3b	1.84 (1.54-2.19)	<0.001	1.30 (1.01-1.68)	0.042
Immunosuppressive therapy	1.13 (0.82-1.55)	0.469		
LV-EF (> 50% vs. ≤50%)	1.31 (1.09-1.56)	0.004	0.95 (0.74-1.21)	0.660

SVI (low-flow vs. normal-flow)	1.46 (1.23-1.75)	<0.001	1.29 (1.03-1.62)	0.03
MPG (> 40mmHg vs. ≤40mmHg)	1.14 (0.96-1.37)	0.138		
MI ≥2 (baseline)	1.51 (1.18-1.94)	0.001	0.98 (0.70-1.38)	0.914
AI ≥2 (baseline)	1.26 (0.99-1.61)	0.059	1.25 (0.94-1.67)	0.129
Self vs. balloon expendable	1.00 (0.81-1.22)	0.965		
AI ≥2 (post-TAVI)	1.41 (0.97-2.04)	0.073	1.51 (1.03-2.22)	0.036
VARC-II MI	4.48 (2.32-8.67)	<0.001	1.45 (0.20-10.41)	0.713
VARC-II Stroke	1.88 (1.34-2.65)	<0.001	1.45 (0.92-2.27)	0.107
VARC-II Renal Failure	2.99 (2.46-3.63)	<0.001	1.81 (1.38-2.37)	<0.001
VARC-II Bleeding	1.35 (1.12-1.61)	0.001	1.04 (0.83-1.32)	0.729
VARC-II Access site complication	1.08 (0.89-1.33)	0.407		
New PPM/ICD	1.19 (0.99-1.44)	0.066	1.21 (0.96-1.52)	0.113

AR indicates aortic regurgitation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CKD stage, chronic kidney disease stage; COPD, chronic obstructive lung disease; ICD, implantable cardioverter defibrillator; log ES I, logistic EuroScore I; LV-EF, left ventricular ejection fraction; MI, myocardial infarction; MPG, mean pressure gradient, MR, mitral regurgitation; NYHA class, New York Heart Association class; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS, Society of Thoracic Surgeons score; SVI, stroke volume index; VARC, Valve Academic Research Consortium.

Table S3. Factors associated with cardiovascular 3-year mortality (including only preprocedural factors).

Parameter	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**P**
Age (per 1 year increase)	1.03 (1.01-1.05)	0.001	1.02 (1.00-1.04)	0.072
Male sex	1.19 (0.97-1.45)	0.097	1.30 (1.04-1.63)	0.021
BMI (per 1kg/m² increase)	0.24 (0.07-0.85)	0.027	0.37 (0.09-1.50)	0.164
STS (per 1% increase)	1.18 (1.13-1.22)	<0.001	1.15 (1.10-1.20)	<0.001
logES I (per 1% increase)	1.14 (1.09-1.18)	<0.001	1.01 (0.97-1.06)	0.603
NYHA III/IV	1.79 (1.36-2.36)	<0.001	1.38 (1.02-1.87)	0.036
Previous CAD	1.19 (0.96-1.47)	0.114		
Previous MI	1.26 (0.97-1.64)	0.080	0.93 (0.69-1.26)	0.644
Previous CABG	1.18 (0.87-1.60)	0.288		
Previous PCI	1.15 (0.89-1.48)	0.292		
Art. Hypertension	0.89 (0.60-1.30)	0.533		
Diabetes mellitus (yes/no)	1.15 (0.94-1.41)	0.170		
Atrial fibrillation	1.67 (1.37-2.05)	<0.001	1.39 (1.11-1.74)	0.004
Previous stroke	0.79 (0.54-1.14)	0.209		
PAD	1.53 (1.16-2.02)	0.003	1.46 (1.04-2.04)	0.029
COPD	1.29 (1.00-1.66)	0.049	0.87 (0.65-1.17)	0.360
CKD stage ≥3b	1.93 (1.58-2.36)	<0.001	1.20 (0.94-1.53)	0.146
Immunosuppressive therapy	1.14 (0.79-1.64)	0.474		
LV-EF (> 50% vs. ≤50%)	1.32 (1.08-1.62)	0.008	0.96 (0.75-1.23)	0.755

SVI (lowflow vs. normal flow)	1.51 (1.23-1.85)	<0.001	1.28 (1.02-1.59)	0.033
MPG (> 40mmHg vs. ≤40mmHg)	1.05 (0.86-1.29)	0.641		
MI ≥2 (baseline)	1.63 (1.24-2.15)	0.001	1.22 (0.91-1.63)	0.188
AI ≥2 (baseline)	1.20 (0.90-1.59)	0.209		

AR indicates aortic regurgitation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CKD stage, chronic kidney disease stage; COPD, chronic obstructive lung disease; log ES I, logistic EuroScore I; LV-EF, left ventricular ejection fraction; MI, myocardial infarction; MPG, mean pressure gradient, MR, mitral regurgitation; NYHA class, New York Heart Association class; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons score; SVI, stroke volume index.

Table S4. Factors associated with cardiovascular 3-year mortality (including preprocedural and periprocedural factors).

Parameter	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	P
Age (per 1 year increase)	1.03 (1.01-1.05)	0.001	1.01 (0.99-1.03)	0.459
Male sex	1.19 (0.97-1.45)	0.097	1.32 (1.01-1.71)	0.039
BMI (per 1kg/m² increase)	0.24 (0.07-0.85)	0.027	0.39 (0.08-1.95)	0.251
STS (per 1% increase)	1.18 (1.13-1.22)	<0.001	1.15 (1.10-1.21)	<0.001
logES I (per 1% increase)	1.14 (1.09-1.18)	<0.001	1.01 (0.95-1.06)	0.875
NYHA III/IV	1.79 (1.36-2.36)	<0.001	1.28 (0.91-1.79)	0.151
Previous CAD	1.19 (0.96-1.47)	0.114		
Previous MI	1.26 (0.97-1.64)	0.080	1.10 (0.80-1.52)	0.551
Previous CABG	1.18 (0.87-1.60)	0.288		
Previous PCI	1.15 (0.89-1.48)	0.292		
Art. Hypertension	0.89 (0.60-1.30)	0.533		
Diabetes mellitus (yes/no)	1.15 (0.94-1.41)	0.170		
Atrial fibrillation	1.67 (1.37-2.05)	<0.001	1.56 (1.21-2.02)	0.001
Previous stroke	0.79 (0.54-1.14)	0.209		
PAD	1.53 (1.16-2.02)	0.003	1.46 (1.04-2.04)	0.029
COPD	1.29 (1.00-1.66)	0.049	0.98 (0.70-1.38)	0.912
CKD stage ≥3b	1.93 (1.58-2.36)	<0.001	1.20 (0.90-1.59)	0.207
Immunosuppressive therapy	1.14 (0.79-1.64)	0.474		
LV-EF (> 50% vs. ≤50%)	1.32 (1.08-1.62)	0.008	0.93 (0.70-1.22)	0.580

SVI (lowflow vs. normal flow)	1.51 (1.23-1.85)	<0.001	1.37 (1.06-1.77)	0.016
MPG (> 40mmHg vs. ≤40mmHg)	1.05 (0.86-1.29)	0.641		
MI ≥2 (baseline)	1.63 (1.24-2.15)	0.001	1.09 (0.76-1.55)	0.643
AI ≥2 (baseline)	1.20 (0.90-1.59)	0.209		
Self vs. balloon expendable	1.10 (0.88-1.38)	0.409		
AI ≥2 (post-TAVI)	1.68 (1.12-2.51)	0.012	1.54 (1.02-2.33)	0.042
VARC-II MI	5.74 (2.96-11.12)	<0.001	2.37 (0.33-17.07)	0.393
VARC-II Stroke	1.89 (1.29-2.78)	0.001	1.84 (1.17-2.90)	0.008
VARC-II Renal Failure	3.19 (2.56-3.97)	<0.001	1.83 (1.36-2.47)	<0.001
VARC-II Bleeding	1.50 (1.22-1.84)	<0.001	1.06 (0.80-1.40)	0.684
VARC-II Access site complication	1.21 (0.97-1.52)	0.091	1.11 (0.84-1.46)	0.475
New PPM/ICD	1.13 (0.91-1.41)	0.254		

AR indicates aortic regurgitation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CKD stage, chronic kidney disease stage; COPD, chronic obstructive lung disease; ICD, implantable cardioverter defibrillator; log ES I, logistic EuroScore I; LV-EF, left ventricular ejection fraction; MI, myocardial infarction; MPG, mean pressure gradient, MR, mitral regurgitation; NYHA class, New York Heart Association class; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS, Society of Thoracic Surgeons score; SVI, stroke volume index; VARC, Valve Academic Research Consortium.

Figure S1. Receiver operating curve for stroke volume index.