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ORIGINAL ARTICLE

HFA-PEFF score: prognosis in patients with preserved ejection fraction after transcatheter aortic valve implantation

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Abstract

Aims Many transcatheter aortic valve implantation (TAVI) candidates have underlying heart failure with preserved ejection fraction (HFpEF) in addition to symptomatic aortic stenosis. Diagnosis of HFpEF is challenging. The Heart Failure Association of the European Society of Cardiology proposed the HFA-PEFF score as part of a novel diagnostic algorithm. This study assessed the prognostic value of the HFA-PEFF score in patients with preserved ejection fraction after TAVI.

Methods and results This single-centre study included 570 consecutive TAVI patients with a preserved left ventricular ejection fraction of ≥50%. Patients with an HFA-PEFF score of ≥5 [*n* = 239 (41.9%)] were compared with those with <5 points [*n* = 331 (58.1%)]. The primary outcome was a composite of all-cause mortality or first heart failure rehospitalization within 1 year after TAVI. Secondary endpoints were the individual components of the primary outcome. Patients with an HFA-PEFF score ≥ 5 had higher rates of comorbidities commonly associated with HFpEF, a higher rate of new pacemaker implantation after TAVI, were at increased risk of the primary composite endpoint (25.5% vs. 10.0%, $P < 0.001$), and rehospitalization for heart failure (11.7% vs. 3.9%, $P < 0.001$). Multivariable analysis confirmed an HFA-PEFF score ≥ 5 as an independent risk factor for the composite endpoint [hazard ratio 2.70, 95% confidence interval (CI) 1.70–4.28, $P < 0.001$] and for all-cause mortality (hazard ratio 2.58, 95% CI 1.46–4.53, $P = 0.001$).

Conclusion The HFA-PEFF score is associated with all-cause mortality and heart failure rehospitalization in patients with preserved ejection fraction after TAVI. This practical tool can easily be incorporated into risk stratification algorithms for TAVI patients.

Keywords Aortic stenosis; Transcatheter aortic valve implantation; Heart failure; Preserved ejection fraction; Mortality; Rehospitalization

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Introduction

Aortic stenosis (AS) is the most frequent valvular heart disease in Europe and North America.[1] The prevalence of AS increases with age and has been reported to be 3.4% for severe AS in the population aged > 75 years.[2] AS leads to a gradual increase in pressure overload, thereby inducing a complex process of adaptive hypertrophic remodelling.[3] Cardiac compensatory mechanisms initially maintain adequate wall stress, but later become maladaptive and translate

into structural damage in advanced stages of AS.[4] Left ventricular diastolic dysfunction plays a pivotal role in the pathophysiology, as it occurs early in AS and worsens with disease progression.[3] Transcatheter aortic valve implantation (TAVI) has been shown to potentially induce a process of reverse remodelling leading to structural and functional improvements.[5,6]

A substantial proportion of TAVI patients may have underlying heart failure with preserved ejection fraction (HFpEF) in addition to AS, due to the fact that both entities share common risk factors, such as age, hypertension, diabetes and chronic kidney disease.[7,8] Although mortality and heart failure hospitalization rates of patients with HFpEF are known to be high, the prognostic implications of HFpEF are not adequately reflected by current risk prediction models, such as the Society of Thoracic Surgeons score (STS) and guidelines for the management of patients undergoing TAVI.[9–11] HFpEF is a complex clinical syndrome and its diagnosis remains challenging. In this context, the Heart Failure Association (HFA) of the European Society of Cardiology has proposed the HFA-PEFF score as part of a novel diagnostic algorithm in patients with suspected HFpEF.[12]

The objective of this study was to assess the prognostic value of the HFA-PEFF score in patients with preserved ejection fraction after TAVI. The hypothesis was that the HFA-PEFF score identifies patients who are at elevated risk for adverse outcomes after TAVI.

Methods

Study design

A total of 1428 patients undergoing TAVI were prospectively enrolled in an observational study at the University Hospital Schleswig-Holstein, Kiel, Germany, between January 2014 and January 2020. All patients provided written informed consent. The study was approved by the Ethics Committee of the University of Kiel and conformed to the principles outlined in the Declaration of Helsinki. For the current study, consecutive TAVI patients with symptomatic AS and a preserved left ventricular ejection fraction (LVEF) of $\geq$50% were assessed for eligibility. LVEF was determined by standard transthoracic echocardiography using biplane images in all patients. Exclusion criteria were concomitant severe mitral or tricuspid regurgitation, non-transfemoral access, congenital bicuspid aortic valve, insufficient clinical or echocardiographic data, or inability to give consent. Outcomes were analysed by comparison between patients with an HFA-PEFF score $\geq$ 5 and patients with an HFA-PEFF score $<$ 5.

The primary outcome was a composite of all-cause mortality or a first heart failure rehospitalization within 1 year after TAVI. The secondary endpoints were the individual components of the primary outcome. All-cause mortality, rather than cardiovascular mortality, was used as an endpoint, because (i) the correct classification of death in the TAVI population is challenging due to the high burden of comorbidities and (ii) a complete knowledge of medical details in deceased patients would be necessary for a correct classification, which can often not be obtained in this elderly patient population. The pre-specified follow-up period for this study was 1 year and was available for all patients.

Procedural details

The decision to perform TAVI was based on evaluation by the heart team and was in accordance with the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease.[9] All TAVI procedures were performed using either balloon-expandable SAPIEN3/SAPIEN3 Ultra (Edwards Lifesciences, Irvine, California, USA) or self-expanding CoreValve Evolut R/PRO (Medtronic, Minneapolis, Minnesota, USA) devices. The optimal type and size of transcatheter heart valve were determined using pre-procedural multidetector CT measurements and the 3mensio Structural Heart software (3mensio Medical Imaging BV, Bilthoven, The Netherlands).

Data acquisition

Patient characteristics, laboratory results, echocardiography data and medication were recorded. Follow-up was conducted by in-person visits to our cardiology outpatient clinic, direct phone calls or by contacting the patient's general practitioner or cardiologist. Specific outcomes for TAVI adhered to the Valve Academic Research Consortium-3 (VARC-3) criteria.[13] Rehospitalization for heart failure was diagnosed if a patient was hospitalized with typical symptoms and objective signs of worsening heart failure.

HFA-PEFF score

The HFA-PEFF score has previously been described in detail as part of the HFA-PEFF diagnostic algorithm for suspected HFpEF.[12] In brief, the HFA-PEFF score comprises the three following domains: (i) functional, (ii) morphological and (iii) biomarker. Each domain has major and minor criteria and can contribute a maximum of 2 points. Thus, the highest HFA-PEFF score is 6. An HFA-PEFF score of $\geq$5 is considered to be diagnostic of HFpEF.

For the calculation of the HFA-PEFF score, we used laboratory and echocardiography data at the time of discharge after the TAVI procedure. As explicitly stated in the consensus

document, the HFA-PEFF score was designed as a practical tool that can be calculated even if not all parameters are available. Thus, we performed a stepwise HFA-PEFF score calculation process. For the functional domain we used average E/e' and pulmonary artery systolic pressure. The morphological domain was primarily based on the left ventricular mass index, as left atrial diameter rather than left atrial volume index (LAVI) was routinely stated in the echocardiography reports. If left ventricular mass index was $<$149/122 g/m^2 (the threshold for a major criterion in male/female patients) or $\leq$115/95 g/m^2 (the threshold for a minor criterion in male/female patients), LAVI was retrospectively measured in apical four-chamber and two-chamber views. For the biomarker domain, we used N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (pro BNP II, Roche Diagnostics, Mannheim, Germany). Global longitudinal strain data were not available.

Statistical analyses

Only patients with a full dataset and complete follow-up were included in the analysis. Baseline characteristics were summarized as means with standard deviation, medians with interquartile ranges, or counts with percentages. Intergroup comparisons were made using the Student's *t*-test, Mann–Whitney *U* test, χ^2 test or Fisher's exact test, as appropriate. Rates of the primary and secondary outcomes during follow-up were assessed using Kaplan–Meier analyses and log-rank tests. For the Cox proportional hazards models, all variables that were significant in the univariable analysis (P value < 0.25) were used in a backward selection process based on the likelihood ratio criteria. Results were summarized as adjusted hazard ratios (HR) with 95% confidence intervals (CI). Continuous variables were dichotomized to keep the Cox model simple. For each variable, the proportional hazards assumption was confirmed by testing for interactions between Schoenfeld residuals and the log-transformed time. Statistical analyses were performed using R software, Version 4.0.4, and GraphPad PRISM, Version 8. A two-tailed P value < 0.05 was considered statistically significant.

Results

A total of 570 consecutive TAVI patients with preserved ejection fraction were eligible for the study. Based on echocardiography and laboratory data at discharge, 239 patients (41.9%) had an HFA-PEFF score ≥ 5, whereas 331 patients (58.1%) had an HFA-PEFF score < 5.

Patient characteristics and periprocedural outcomes

Baseline characteristics are presented in *Table 1*. Patients with an HFA-PEFF score ≥ 5 were significantly older and had a higher body mass index (BMI) than patients with an HFA-PEFF score < 5. In addition, the HFA-PEFF score ≥ 5 group had significantly higher rates of atrial fibrillation, diabetes, chronic obstructive pulmonary disease (COPD) and pulmonary hypertension. Patients with an HFA-PEFF score ≥ 5 also presented with worse renal function, a higher STS score and higher NT-proBNP levels at discharge. Moreover, LV mass and E/e' ratio were significantly higher. Severely dilated left atrium as well as moderate mitral and tricuspid regurgitation were also more prevalent in patients with a high HFA-PEFF score. Notably, there was no significant difference in terms of gender between the groups. The majority of patients (=70.4%) had New York Heart Association class III or IV. Patients with an HFA-PEFF score ≥ 5 showed higher rates of New York Heart Association class III/IV at baseline compared with patients with an HFA-PEFF score < 5 ($P < 0.001$).

Medication at discharge and data on procedural outcomes are summarized in *Table 2*. Beta-blockers and diuretics were more frequently prescribed in patients with an HFA-PEFF score ≥ 5. New permanent pacemaker implantation was the only VARC-3-related outcome that was more often observed in patients with a high HFA-PEFF score.

Primary and secondary study outcomes

All-cause mortality or heart failure rehospitalization within 1 year after TAVI (the primary endpoint) occurred in 61 patients (25.5%) in the HFA-PEFF score ≥ 5 group compared with 33 patients (10.0%) in the HFA-PEFF score < 5 group ($P < 0.001$) (*Figure 1A*). A total of 40 deaths (16.7%) in patients with an HFA-PEFF score ≥ 5 were observed, which is a significantly higher all-cause mortality rate compared with 20 deaths (6.0%) among patients with an HFA-PEFF score < 5 ($P < 0.001$) (*Figure 1B*). Based on available patient records, confirmed non-cardiovascular death occurred in nine patients (=15%) of the total study population. Causes of non-cardiovascular death included infectious disease/septic shock (five patients), advanced pulmonary disease (two patients), malignancy (one patient) and gastrointestinal bleeding (one patient). In addition, heart failure rehospitalization was reported in 28 patients (11.7%) in the HFA-PEFF score ≥ 5 group as opposed to 13 patients (3.9%) in the HFA-PEFF score < 5 group ($P < 0.001$).

The results of univariable and multivariable Cox regression analyses are presented in *Tables 3* and *4*. Ten variables were found to be significantly associated with the primary composite outcome of all-cause mortality or heart failure rehospital-

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Table 1 Baseline characteristics

	Total (n = 570)	HFA-PEFF score ≥ 5 (n = 239)	HFA-PEFF score < 5 (n = 331)	P value
Age (years)	82.1 (78.9–85.5)	83.1 (79.6–86.9)	81.4 (78.6–84.6)	<0.001
Male, *n* (%)	229 (40.2)	87 (36.4)	142 (42.9)	0.118
BMI (kg/m^2)	26.4 (23.7–29.8)	27.4 (24.5–31.3)	25.7 (23.1–29.3)	<0.001
NYHA class, *n* (%)				<0.001
I/II	169 (29.6)	52 (21.8)	117 (35.3)	
III/IV	401 (70.4)	187 (78.2)	214 (64.7)	
Significant CAD, *n* (%)	252 (44.2)	109 (45.6)	143 (43.2)	0.569
Previous PCI, *n* (%)	227 (39.8)	99 (41.4)	128 (38.7)	0.508
Previous CABG, *n* (%)	45 (7.9)	18 (7.5)	27 (8.2)	0.785
COPD, *n* (%)	73 (12.8)	40 (16.7)	33 (10.0)	0.017
Diabetes mellitus, *n* (%)	152 (26.7)	79 (33.1)	73 (22.1)	0.003
Dyslipidaemia, *n* (%)	288 (50.5)	111 (46.4)	177 (53.5)	0.098
Atrial fibrillation, *n* (%)	206 (36.1)	150 (62.8)	56 (16.9)	<0.001
Paroxysmal	66 (11.6)	47 (19.7)	19 (5.7)	
Persistent/permanent	140 (24.6)	103 (43.1)	37 (11.2)	
Hypertension, *n* (%)	511 (89.6)	219 (91.6)	292 (88.2)	0.187
PAD, *n* (%)	43 (7.5)	21 (8.8)	22 (6.6)	0.340
Severe PHT (PASP > 55 mmHg), *n* (%)	59 (10.4)	56 (23.4)	3 (0.9)	<0.001
RV dysfunction, *n* (%)	38 (6.7)	30 (12.6)	8 (2.4)	<0.001
STS score (%), *n* (%)	4.0 (2.4–5.1)	4.3 (3.0–5.9)	3.2 (2.1–4.6)	<0.001
eGFR (mL/min/1.73 cm^b)	55 ± 19	49 ± 19	59 ± 18	<0.001
NT-proBNP (pg/mL)	877 (406–2,153)	1788 (823–3,483)	560 (286–1,181)	<0.001
LV mass(g)	221 (191–260)	246 (217–286)	202 (180–238)	<0.001
AVA (cm^2)	0.8 (0.6–0.9)	0.8 (0.6–0.9)	0.8 (0.6–0.9)	0.203
MPG (mmHg)	40 (30–52)	39 (29–52)	40 (32–52)	0.171
LA size, *n* (%)				
Within reference	65 (11.4)	0 (0)	65 (19.6)	…
Mildly abnormal[a]	376 (66.0)	148 (61.9)	228 (68.9)	0.084
Moderately abnormal[b]	66 (11.6)	41 (17.2)	25 (7.6)	0.004
Severely abnormal[c]	63 (11.1)	50 (20.9)	13. (3.9)	<0.001
Mitral regurgitation, *n* (%)				0.001
Moderate	62 (10.9)	38 (15.9)	24 (7.3)	
Mild or trace	508 (89.1)	201 (84.1)	307 (92.7)	
Tricuspid regurgitation, *n* (%)				<0.001
Moderate	51 (8.9)	40 (16.7)	11 (3.3)	
Mild or trace	519 (91.1)	199 (83.3)	320 (96.7)	
E/e' ratio	12 (9–14)	14 (12–17)	10 (8–12)	<0.001

AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LA, left atrium; LV, left ventricular; MPG, mean pressure gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; pEF, preserved ejection fraction with no heart failure; PHT, pulmonary hypertension; RV, right ventricular; STS, Society of Thoracic Surgeons.
Values are presented as counts (percentages), mean ± SD or median (interquartile range).
[a]LA diameter index = 2.4–2.6 cm/m^2 or LA volume index = 29–33 mL/m^2.
[b]LA diameter index = 2.7–2.9 cm/m^2 or LA volume index = 34–39 mL/m^2.
[c]LA diameter index ≥ 3.0 cm/m^2 or LA volume index ≥ 40 mL/m^2.

ization in the univariable analysis ($P < 0.25$, respectively). Of these, five parameters were included in the final multivariable analysis. An HFA-PEFF score ≥ 5 was confirmed as the most significant risk factor for the primary composite endpoint (HR 2.70, 95% CI 1.70–4.28, $P < 0.001$) (*Table 3*). Other significant risk factors included BMI > 26.4 kg/m^2 (HR 0.63, 95% CI 0.42–0.95, $P = 0.029$), male gender (HR 1.70, 95% CI 1.13–2.55, $P = 0.011$) and COPD (HR 1.77, 95% CI 1.07–2.92, $P = 0.027$) (*Table 3*). In addition, an HFA-PEFF score ≥ 5 was determined as a significant risk factor for all-cause mortality (HR 2.58, 95% CI 1.46–4.53, $P = 0.001$) after adjustment for BMI, male sex, moderate tricuspid regurgitation, STS score ≥ 4%, and COPD (*Table 4*).

Discussion

The main finding of this study was that the HFA-PEFF score is significantly associated with all-cause mortality and heart failure rehospitalization in patients with preserved ejection fraction after TAVI. This is the first report on the potential role of the HFA-PEFF score in the context of TAVI.

Most patients referred for TAVI have a preserved ejection fraction, including those who have underlying HFpEF in addition to symptomatic AS. The prognostic implications of HFpEF are currently not accounted for in clinical practice or by risk scores.[9–11] Patients with HFpEF have a lower risk of mortality and a composite of death and heart failure rehospitalization

Table 2 Procedural variables, medication at discharge and outcomes

	Total (n = 570)	HFA-PEFF score ≥ 5 (n = 239)	HFA-PEFF score < 5 (n = 331)	P value
Valve type, *n* (%)				0.494
Self-expanding valve	310 (54.4)	134 (56.1)	176 (53.2)	
Balloon-expandable valve	260 (45.6)	105 (43.9)	155 (46.8)	
Procedural duration (min)	48 (40–60)	49 (40–68)	48 (39–58)	0.065
Contrast medium (mL)	84 (68–103)	83 (65–100)	85 (70–105)	0.389
Medication at discharge, *n* (%)				
ACE-I/ARB	461 (80.9)	195 (81.6)	266 (80.4)	0.713
ß-Blocker	402 (70.5)	188 (78.7)	214 (64.7)	<0.001
MRA	48 (8.4)	22 (9.2)	26 (7.9)	0.567
Diuretics	385 (67.5)	187 (78.2)	198 (59.8)	<0.001
Loop diuretics	353 (61.9)	168 (70.3)	185 (55.9)	0.003
Dihydropyridine CCBs	197 (34.6)	75 (31.4)	122 (36.9)	0.175
VARC-3, *n* (%)				
Myocardial infarction	2 (0.4)	2 (0.8)	0 (0)	…
Stroke with disability	4 (0.7)	1 (0.4)	3 (0.9)	0.643
AKIN stage 3/4	5 (0.9)	2 (0.8)	3 (0.9)	>0.999
Conversion to open surgery	0 (0)	0 (0)	0 (0)	…
New permanent pacemaker	80 (14.0)	54 (22.6)	26 (7.9)	<0.001
Type 3 (life-threatening) bleeding	18 (3.2)	4 (1.7)	14 (4.2)	0.095
Study endpoints, *n* (%)				
Primary composite outcome	94 (16.5)	61 (25.5)	33 (10.0)	<0.001
All-cause mortality	60 (10.5)	40 (16.7)	20 (6.0)	<0.001
Heart failure rehospitalization	41 (7.2)	28 (11.7)	13 (3.9)	<0.001

AKIN, Acute Kidney Injury Network; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; pEF, preserved ejection fraction with no heart failure; VARC-3, Valve Academic Research Consortium 3.
Values are presented as counts (percentages) or median (interquartile range).

Figure 1 Kaplan–Meier analyses for the primary composite endpoint *(A)* and the secondary endpoints of all-cause mortality *(B)* and heart failure rehospitalization *(C)*.

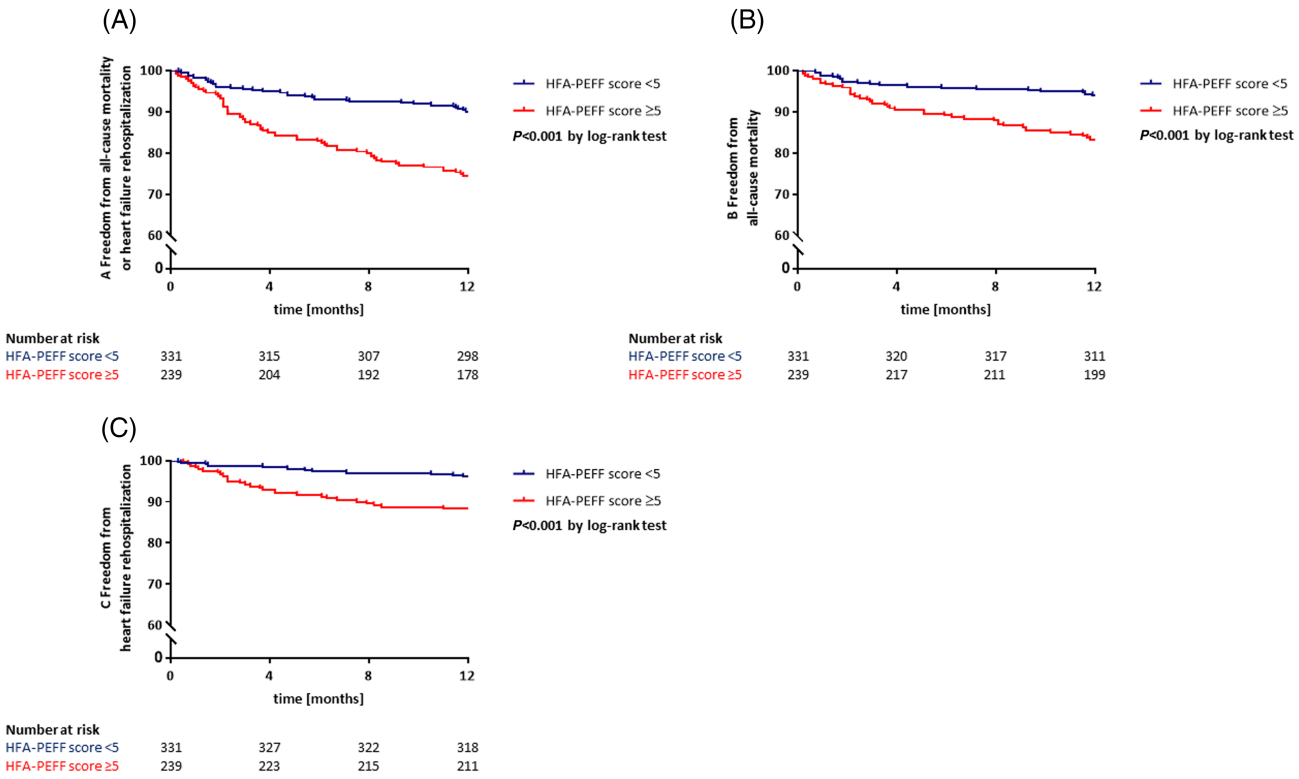

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Table 3 Univariable and multivariable analyses for the composite of all-cause mortality or heart failure rehospitalization after TAVI

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HFA-PEFF score ≥ 5	2.80 (1.83–4.28)	<0.001	2.70 (1.70–4.28)	<0.001
BMI > 26.4 kg/m^2	0.74 (0.49–1.11)	0.150	0.63 (0.42–0.95)	0.029
Male gender	1.60 (1.07–2.40)	0.022	1.70 (1.13–2.55)	0.011
Atrial fibrillation	1.72 (1.15–2.58)	0.009		
Severe PHT (PASP > 55 mmHg)	2.82 (1.74–4.59)	<0.001	1.50 (0.88–2.57)	0.135
Moderate TR	1.92 (1.09–3.38)	0.025		
STS score $\geq 4\%$	1.47 (0.98–2.22)	0.062		
COPD	2.15 (1.32–3.50)	0.002	1.77 (1.07–2.92)	0.027
eGFR < 60 mL/min/1.73 cm^2	1.49 (0.95–2.33)	0.081		
Significant CAD	1.47 (0.98–2.20)	0.063		
NYHA class III/IV at baseline	1.34 (0.83–2.14)	0.230		

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PHT, pulmonary hypertension; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TR, tricuspid regurgitation.
Results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI).

Table 4 Univariable and multivariable analyses for all-cause mortality after TAVI

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HFA-PEFF score ≥ 5	2.93 (1.71–5.00)	<0.001	2.58 (1.46–4.53)	0.001
Age > 82.1 years	1.52 (0.91–2.55)	0.110		
BMI > 26.4 kg/m^2	0.72 (0.43–1.20)	0.210	0.66 (0.39–1.12)	0.122
Male gender	1.73 (1.04–2.87)	0.035	1.97 (1.17–3.31)	0.010
Atrial fibrillation	1.97 (1.19–3.27)	0.009		
Severe PHT (PASP > 55 mmHg)	2.88 (1.58–5.24)	<0.001		
Moderate TR	2.43 (1.26–4.67)	0.008	1.75 (0.88–3.49)	0.110
STS score $\geq 4\%$	2.13 (1.25–3.62)	0.005	1.65 (0.94–2.90)	0.082
COPD	2.69 (1.52–4.77)	<0.001	2.20 (1.21–4.01)	0.010
eGFR < 60 mL/min/1.73 cm^2	1.64 (0.92–2.90)	0.092		
CAD	1.46 (0.88–2.42)	0.140		

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; PASP, pulmonary artery systolic pressure; PHT, pulmonary hypertension; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TR, tricuspid regurgitation.
Results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI).

compared with patients with a reduced ejection fraction; however, the risk remains substantial.[10,11] It has been recommended that the diagnosis of HFpEF should be based on assessment of a combination of echocardiographic measurements of cardiac structure and function, and NT-proBNP levels. The HFA-PEFF diagnostic algorithm provides a score based on these three domains, which can be calculated using various criteria within each domain, making it practical for use in a routine clinical setting.[12]

Several studies have confirmed that the HFA-PEFF score is a reliable diagnostic tool for identifying HFpEF.[14–16] Is has demonstrated prognostic value for clinical outcomes in patients hospitalized with decompensated HFpEF and in patients with unexplained dyspnoea who have a score above the diagnostic threshold.[17–19] Conversely, Abramov and Parwani have commented that the prognostic implications of scores, such as the HFE-PEFF score, might be due to the patient's comorbidity burden rather than a result of a particular cardiac pathology.[20] As a consequence, optimal treatment of the comorbidities such as hypertension, diabetes and pulmonary disease is crucial. In addition, the HFA-PEFF score may also be influenced by parameters other than HFpEF. As an example, E/e' ratio and NT-proBNP concentrations can be modulated by chronic kidney disease, thus increasing the HFA-PEFF score. This needs to be taken into consideration when using these parameters.[21]

We hypothesized that the HFA-PEFF score would identify patients who were at increased risk of adverse outcomes after TAVI. We found that patients with an HFA-PEFF score ≥ 5 had a significantly increased risk of death, rehospitalization for heart failure, and the composite of both outcomes, compared with patients with an HFA-PEFF score < 5. Multivariable analysis confirmed an HFA-PEFF score ≥ 5 as an independent risk factor for the composite endpoint and for

all-cause mortality. Other significant factors in our study included lower BMI, male gender, severe pulmonary hypertension and COPD, which have been previously reported as predictors of poor outcomes after TAVI.[22]

To the best of our knowledge, this is the first report on the prognostic value of the HFA-PEFF score in patients with AS and preserved ejection fraction treated with TAVI. A recent study found that the H_2FPEF score, another score that has been developed to facilitate the diagnosis of HFpEF, was an independent predictor of all-cause mortality and a composite of cardiovascular mortality or heart failure rehospitalization in patients with preserved ejection fraction undergoing TAVI.[23] The H_2FPEF score is based on evaluation of clinical and echocardiographic characteristics, whereas the HFA-PEFF score includes echocardiographic morphological and functional parameters and a biomarker.[12,24]

In contrast to the aforementioned study, the parameters for the calculation of the HFA-PEFF score in our analysis were obtained after TAVI, that is, after the correction of AS. In our study, we found that the HFA-PEFF score identified TAVI patients with common comorbidities associated with HFpEF, such as diabetes, COPD and pulmonary hypertension. This was also observed in the study using the H_2FPEF score in TAVI patients.[23] It should be noted that the HFA-PEFF score in our study was presumably still influenced by the haemodynamic effects caused by long-standing AS. Based on our study design, caution should thus be exercised when making a definitive diagnosis of HFpEF in our patient cohort despite the fact that the patient characteristics are highly indicative of HFpEF. However, as stated in the consensus paper on the diagnosis of HFpEF, significant valvular heart disease must be excluded before diagnosing HFpEF.[12] Future studies should therefore investigate the value of the HFA-PEFF score obtained during further follow-up after TAVI. With respect to VARC-3 outcomes after TAVI, we found a higher rate of new permanent pacemaker implantation in patients with an HFA-PEFF score ≥ 5, while there was no statistically significant difference in the use of balloon-expandable vs. self-expandable prostheses. In our opinion, this finding is likely to reflect an advanced stage of adverse cardiac remodelling including a more vulnerable conduction system in patients with an HFA-PEFF score $\geq$ 5. A difference in pacemaker implantations was not noted between patients with high vs. low scores in the study investigating the H_2FPEF score.[23]

Patients with HFpEF have a worse prognosis than those without heart failure, and patients in the advanced stages of AS and HFpEF have been reported to be at increased risk. Some studies have found that among TAVI patients with severe AS, in-hospital mortality rates were similar in those with HFpEF and those with heart failure with a reduced ejection fraction, while others have found a better prognosis at 1 year in those with HFpEF compared with those with reduced ejection fraction.[25,26] Notably, in patients with HFpEF, treating moderate AS may be beneficial, due to the fact that AS is a modifiable driver of diastolic dysfunction. AS causes increased left ventricular afterload, which leads to left ventricular hypertrophy and results in diastolic dysfunction.[27] Diastolic dysfunction develops early in the course of AS and worsens as the disease progresses.[3] TAVI can potentially induce reverse remodelling, which can lead to structural and functional improvements.[5,6] Treating patients earlier in the AS disease course may help limit diastolic dysfunction and potentially reduce the negative impact of HFpEF. Valvular heart disease, such as AS, may mimic HFpEF, making the diagnosis of HFpEF particularly challenging in this context. While TAVI leads to a successful resolution of AS, the HFA-PEFF score may be helpful for risk stratification after the procedure. In the recently published EMPEROR-preserved study, empagliflozin reduced the combined risk of cardiovascular death or heart failure rehospitalization in patients with HFpEF (defined as an LVEF $\geq$ 40%), regardless of their diabetes status.[28] As a consequence, the HFA-PEFF score may also be useful for identifying TAVI patients with HFpEF who may benefit from specific treatment in addition to the TAVI procedure, including the use of empagliflozin.

Limitations

Several limitations of the study should be acknowledged. First, our study is limited by its single-centre design. Second, echocardiography data were obtained and evaluated by several examiners resulting in measurement variability. In this context, global longitudinal strain data (a minor criterion in the functional domain of the HFA-PEFF score) were not available. Left atrial diameter rather than LAVI was routinely reported in most patients. Third, reassessment of the HFA-PEFF score as well as advanced HFpEF workup (as suggested by the HFA consensus document) during follow-up, which may have resulted in better classification of patients, was not performed. Fourth, follow-up data to evaluate reverse remodelling, physical capacity and quality of life were not sufficiently available. Despite these limitations, our study demonstrates for the first time that the HFA-PEFF score may aid in improving risk stratification of AS patients treated with TAVI.

Conclusion

The HFA-PEFF score is associated with all-cause mortality and heart failure rehospitalization in patients with preserved ejection fraction after TAVI. The HFA-PEFF score is a practical tool that can easily be incorporated into risk stratification algorithms for patients after TAVI.

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Conflict of interest

G. Lutter is a consultant for Edwards Lifesciences, Medtronic, Boston Scientific and Abbott. D. Frank is a consultant for Edwards Lifesciences and Medtronic and has received research funding from Edwards Lifesciences. P. Bramlage has received research funding from Edwards Lifesciences. All other authors have no commercial or financial relationships that could be construed as a potential conflict of interest.

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