Prognostic value of the H$_2$FPEF score in patients undergoing transcatheter aortic valve implantation

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Abstract

Aims The aim of this study was to assess the prognostic value of the H$_2$FPEF score in patients undergoing transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) and preserved left ventricular ejection fraction (EF).

Methods and results In this multicentre study, a total of 832 patients from two German high-volume centres, who received TAVI for severe AS and preserved EF ($\geq$50%), were identified for calculation of the H$_2$FPEF score. Patients were dichotomized according to low (0–5 points; $n = 570$) and high (6–9 points; $n = 262$) H$_2$FPEF scores. Kaplan–Meier and Cox regression analyses were applied to assess the prognostic impact of the H$_2$FPEF score. We observed a decrease in stroke volume index (–2.04 mL/m$^2$/point) and mean transvalvular gradients (–1.14 mmHg/point) with increasing H$_2$FPEF score translating into a higher prevalence of paradoxical low-flow, low-gradient AS among patients with high H$_2$FPEF score. One year after TAVI, the rates of all-cause (low vs. high H$_2$FPEF score: 8.0% vs. 19.4%, $P < 0.0001$) and cardiovascular (CV) mortality (1.9% vs. 9.0%, $P < 0.0001$) as well as the rate of CV mortality or rehospitalization for congestive heart failure (6.4% vs. 23.2%, $P < 0.0001$) were higher in patients with high H$_2$FPEF score compared with those with low H$_2$FPEF score. After multivariable analysis, a high H$_2$FPEF score remained independently predictive of all-cause mortality [hazard ratio 1.59 (1.28–2.35), $P = 0.018$] and CV mortality or rehospitalization for congestive heart failure [hazard ratio 2.92 (1.65–5.15), $P < 0.001$]. Among the H$_2$FPEF score variables, atrial fibrillation, pulmonary hypertension, and elevated left ventricular filling pressure were the strongest outcome predictors.

Conclusions The H$_2$FPEF score serves as an independent predictor of adverse CV and heart failure outcome among TAVI patients with preserved EF. A high H$_2$FPEF score is associated with the presence of paradoxical low-flow, low-gradient AS, the HFpEF in patients with AS. By identifying patients in advanced stages of HFpEF, the H$_2$FPEF score might be useful as a risk prediction tool in patients with preserved EF scheduled for TAVI.

Keywords H$_2$FPEF score; HFpEF; Paradoxical low gradient; Aortic stenosis; TAVI

Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) has increased over the last decades, and affected patients suffer from impaired prognosis. Although the diagnosis of HFpEF leads to a similar rehospitalization burden compared with heart failure with reduced ejection fraction (HFrEF), its fatal impact still remains widely unrecognized and, thus, the condition itself underdiagnosed. To overcome this shortcoming, the so-called H$_2$FPEF score has recently been published enabling the diagnosis of HFpEF with high accuracy using simple demographic, clinical, and...
trochocardiographic parameters. Moreover, it has been demonstrated that the H$_2$FPEF score is able to predict adverse outcome in heart failure patients.\textsuperscript{10–13}

Aortic stenosis (AS) is a frequent finding, especially among elderly patients, and severe AS is associated with dismal outcome if left untreated.\textsuperscript{14,15} Pathophysiological, left ventricular (LV) pressure overload due to obstructed outflow through the calcified aortic valve is usually associated with concentric LV hypertrophy.\textsuperscript{16} In more advanced stages of the disease, the persistent pressure load promotes further structural LV alterations, very similar compared with those in HFpEF patients, leading to, for example, diastolic dysfunction, atrial fibrillation, and mitral (MR) or tricuspid regurgitation (TR).\textsuperscript{17} As a consequence, these alterations may result in reduced stroke volume and—although LV ejection fraction (EF) is still preserved—in a ‘paradoxical’ low transvalvular gradient, a state defined as paradoxic low-flow, low-gradient AS (PLF-LG AS).\textsuperscript{18} Thus, it has been suggested that PLF-LG AS is equal to HFpEF in patients with AS.\textsuperscript{19–21} Compared with patients with high-gradient AS (HG-AS), these patients are known to have notably worse outcome after transcatheter aortic valve implantation (TAVI).\textsuperscript{22,23}

Yet in AS patients with preserved EF undergoing TAVI, especially in those with PLF-LG AS, only few baseline parameters have been identified as predictors of outcome.

The aim of this multicentre study was to assess the prognostic impact of the H$_2$FPEF score on adverse outcome in patients with preserved EF undergoing TAVI for severe AS. We hypothesized that a high H$_2$FPEF score is associated with a high prevalence of PLF-LG AS and, thus, with adverse outcome in patients undergoing TAVI.

**Methods**

**Study design and data acquisition**

The study is designed as a retrospective, multicentre analysis of data derived from TAVI registries of two German high-volume centres (University Heart and Vascular Centre Hamburg, Germany; German Heart Centre Munich, Germany). All clinical endpoints were adjudicated according to current Valve Academic Research Consortium 2 (VARC-2) criteria after 30 days. Survival data were obtained, as part of clinical routine, from either in-house data or telephone follow-up of the patient or the referring physician. The investigation conforms to the principles outlined in the Declaration of Helsinki.\textsuperscript{24}

**Patient population**

Between 2013 and 2018, a total of 3852 patients underwent TAVI for severe AS at both centres. Decision to perform TAVI was made by an interdisciplinary heart team for all patients. After exclusion of patients with EF < 50%, severe aortic regurgitation, valve-in-valve procedures, and combined percutaneous mitral valve treatment, 1555 patients fulfilled criteria for potential study inclusion. Of these, 832 patients with severe AS and preserved EF had available data for all six H$_2$FPEF score variables and, thus, formed the final study population. Median follow-up for these patients was 1.08 [95% confidence interval (CI) 1.06–1.11] years. A comparison of baseline characteristics between excluded and included patients is given in Supporting Information, Table S1.

**H$_2$FPEF score calculation**

The original H$_2$FPEF score comprises six weighted variables: obesity (defined as body mass index > 30 kg/m$^2$), atrial fibrillation, age > 60 years, arterial hypertension (defined as treatment with ≥ 2 antihypertensives), elevated LV filling pressures (defined as echocardiographic E/e′ ratio > 9), and echocardiographically derived systolic pulmonary artery pressure > 35 mmHg. According to Reddy et al., the probability for the diagnosis of HFpEF is ≥ 90%, if a patient reaches ≥ 6 score points.\textsuperscript{9} In the present study, calculation of the score was modified adapting to common TAVI registry parameters. Arterial hypertension was defined based on the diagnosis of hypertension according to patient history, and elevated filling pressures were defined as invasively measured pre-procedural LV end-diastolic pressure (LVEDP) ≥ 15 mmHg. In accordance with the original publication, all variables were weighted equally (1 point) with the exception of obesity (2 points) and atrial fibrillation (3 points).\textsuperscript{9}

**Definition of aortic stenosis subtypes**

Severity of AS and classification in HG-AS, PLF-LG AS, or normal-flow, low-gradient (NF-LG) AS were assessed by means of resting transthoracic echocardiography at baseline according to the current European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines.\textsuperscript{18} HG-AS was defined as an effective orifice area (EOA) ≤ 1.0 cm$^2$ and mean transvalvular gradient (Pmean) > 40 mmHg. Severe PLF-LG AS was defined as an EOA ≤ 1.0 cm$^2$, Pmean < 40 mmHg, and stroke volume index (SVI) ≤ 35 mL/m$^2$ and NF-LG AS as EOA ≤ 1.0 cm$^2$, Pmean < 40 mmHg, and SVI > 35 mL/m$^2$. EF was ≥ 50% in all patients. All parameters for AS subtype classification were available in 751 patients; 81 patients were not classified because of missing data.

**Statistical analysis**

The median follow-up time as well as the percentages of deaths were estimated by the Kaplan–Meier potential follow-up estimator.\textsuperscript{25} Binary variables were shown as absolute numbers and percentages and were compared by
using $\chi^2$ test. Continuous variables were shown as mean ± standard deviation or as median (25th percentile, 75th percentile), and for between-group comparisons, the Mann–Whitney U test was used. Unadjusted spline analyses were performed. Survival curves were produced using the Kaplan–Meier method, and curve differences were tested by the log-rank test. For the univariable and multivariable analyses, the following set of variables was used: age, male sex, body mass index, prior stroke, atrial fibrillation, hypertension, prior myocardial infarction, coronary artery disease, diabetes, chronic obstructive pulmonary disease (COPD), systolic pulmonary artery pressure in the categories ≤35 (reference), 36–55, and >55 mmHg, TR ≥ 2, MR ≥ 2, New York Heart Association (NYHA) stage, glomerular filtration rate <60 mL/min, non-transfemoral access, LVEDP, and $H_F$-FPEF score with the low score (0–5 points) as reference. Variables that showed $P$-values <0.25 in the univariable Cox regression analyses were used in a forward selection process based on Akaike information criterion. We performed two different multivariable regressions: one with the $H_A$-Akaike information criterion. We performed two different analyses were used in a forward selection process based on

In patients with high $H_F$-FPEF score, the prevalence of both moderate or severe TR and moderate or severe MR was higher compared with those patients with low $H_F$-FPEF score. Moreover, patients with high $H_F$-FPEF score presented with significantly lower Pmean and lower SVI. Figure 2 shows spline analyses for the association of the $H_F$-FPEF score with Pmean, SVI, and with probabilities of prevalent PLF-LG AS and NF-LG AS. Figure 2A demonstrates spline analysis for the inverse association between Pmean and increasing $H_F$-FPEF score revealing a 1.14 mmHg decrease in Pmean per 1-point increase of the $H_F$-FPEF score. A similar inverse inter-relation was observed for the $H_F$-FPEF score and SVI (Figure 2B). Excluding $H_F$-FPEF score 1–3, SVI decreased by 2.04 mL/m² with each $H_F$-FPEF score point increase.

**Distribution of aortic stenosis subtypes according to $H_F$-FPEF score**

Regarding the distribution of AS subtypes, the proportion of HG-AS was significantly higher in patients with low $H_F$-FPEF score (57.5%) compared with those with high $H_F$-FPEF score (45.1%). Conversely, patients with high $H_F$-FPEF score had a higher prevalence of PLF-LG AS (30.5%) compared with patients with low $H_F$-FPEF score (13.9%). With regard to NF-LG AS, there was no statistical difference between both groups. However, the proportion of NF-LG AS was numerically higher in patients with high $H_F$-FPEF score. Figure 2C and 2D depicts spline analyses for the interrelations of increasing $H_F$-FPEF score with the probability of prevalent PLF-LG AS or NF-LG AS among the subset of patients with low-gradient AS (Pmean < 40 mmHg) (N = 328). With the exception of $H_F$-FPEF score 1–3, the probability of prevalent PLF-LG AS increased by 8% per 1-point increase of the $H_F$-FPEF score while decreasing by 8% for the probability of NF-LG AS.

**Outcome according to $H_F$-FPEF score**

Over the mean follow-up time of 1.08 years (95% CI 1.06–1.11), all-cause mortality occurred in 113 (54.6%) patients ($H_F$-FPEF score 0–5: N = 55; $H_F$-FPEF score 6–9: N = 58). Procedural and 30 day VARC-2 outcome is shown in Supporting Information, Table S2. No differences were found between low and high $H_F$-FPEF scores regarding TAVI access, transcatheter heart valve types, or any 30 day VARC-2 endpoints [i.e. disabling stroke, myocardial infarction, major or life-threatening bleeding, and renal failure (Acute Kidney Injury Network >2), new permanent pacemaker implantation, and more than mild paravalvular leakage]. However, 30 day all-cause mortality was significantly higher in patients with high $H_F$-FPEF score compared with those with low $H_F$-FPEF score (0.9% vs. 5.4%, $P < 0.001$). Figure 3 shows Kaplan–Meier survival estimates according to low and high $H_F$-FPEF scores for all-cause mortality (Figure 3A), cardiovascular (CV) mortality (Figure 3B), rehospitalization for congestive heart failure (CHF) (Figure 3C), and the combined endpoint of CV mortality and rehospitalization for CHF (Figure 3D) at

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**Results**

**Clinical baseline characteristics and distribution of score variables**

Figure 1 shows the $H_F$-FPEF score distribution among the study population. Mean $H_F$-FPEF score was 4.38. For further analyses, patients were dichotomized according to low [0–5 points, $n = 570/832$ (69%)] and high $H_F$-FPEF score [6–9 points, $n = 262/832$ (31%)]. Clinical and echocardiographic baseline characteristics as well as the distribution of score variables among patients with low and high $H_F$-FPEF scores are presented in Table 1. In patients with high $H_F$-FPEF score, there was a higher prevalence of diabetes and COPD compared with those with low $H_F$-FPEF score. Moreover, patients with high $H_F$-FPEF score presented with worse renal function, advanced NYHA stages, and higher estimated surgical risk. There were no differences between both groups regarding age and sex. The prevalence of all other score variables was higher in patients with high $H_F$-FPEF score.

**Echocardiographic findings**

In patients with high $H_F$-FPEF score, the prevalence of both moderate or severe TR and moderate or severe MR was...
1 year after TAVI. The rates of all-cause (low vs. high H$_2$FPEF score: 8.0\% vs. 19.4\%, $P < 0.0001$) and CV mortality (1.9\% vs. 9.0\%, $P < 0.0001$), rehospitalization for CHF (4.3\% vs. 14.5\%, $P = 0.00069$), and CV mortality or rehospitalization for CHF (6.4\% vs. 23.2\%, $P < 0.0001$) were significantly higher in patients with high H$_2$FPEF score compared with those with low H$_2$FPEF score.

**Prognostic impact of H$_2$FPEF score**

The prognostic impact of, both, a high H$_2$FPEF score (6–9 points) (I) and of the single score variables (II) was assessed by multivariable analysis for all-cause mortality ([Table 2](#)) and for the combined endpoint of CV mortality or rehospitalization for CHF ([Table 3](#)).

Multivariable analyses (I) determined a high H$_2$FPEF score as a strong independent predictor of all-cause mortality [hazard ratio (HR) 1.59, 95\% CI 1.08–2.35, $P = 0.018$] and of CV mortality or rehospitalization for CHF (HR 2.92, 95\% CI 1.65–5.15, $P < 0.001$). In separate multivariable analyses (II) with all score variables, but without the score itself, atrial fibrillation was the score variable with the strongest association with all-cause mortality (HR 1.99, 95\% CI 1.34–2.95, $P < 0.001$) ([Table 2](#)). Pulmonary artery hypertension >55 mmHg (HR 3.02, 95\% CI 1.22–7.47, $P = 0.017$), atrial fibrillation (HR 2.01, 95\% CI 1.10–3.67, $P = 0.023$), and elevated LV filling pressure (HR 1.66, 95\% CI 0.92–2.97, $P = 0.09$) showed the strongest association with CV mortality or rehospitalization for CHF ([Table 3](#)) among all score variables.

Moderate or severe TR, chronic renal failure, and non-transfemoral access were further independent predictors of all-cause mortality, while moderate or severe MR and NYHA stage were independently associated with CV mortality or rehospitalization for CHF.

The predictive value of the H$_2$FPEF score was assessed using C-statistics for all endpoints 1 year after TAVI resulting in $C$-indices of 0.66 for all-cause mortality, 0.78 for CV mortality, 0.64 for rehospitalization for CHF, and 0.69 for the combined endpoint of CV mortality or rehospitalization for CHF.

**Discussion**

The present multicentre study assessed the prognostic impact of the H$_2$FPEF score in 832 patients with preserved EF who received TAVI for severe AS. The main findings of this study are as follows. Among TAVI patients with preserved EF:

i A high H$_2$FPEF score (6–9 points) is associated with a higher prevalence of co-morbidities and a higher estimated surgical risk.

ii A high H$_2$FPEF score is associated with lower Pmean and lower SVI resulting in a higher probability of prevalent PLF-LG AS.

iii Rates of all-cause mortality, CV mortality, rehospitalization for CHF, and the combined endpoint of CV mortality or
Table 1 Clinical and echocardiographic baseline characteristics

| Clinical baseline characteristics | All patients (N = 832) | H₂FPEF score 0–5 (N = 570) | H₂FPEF score 6–9 (N = 262) | P-value |
|----------------------------------|------------------------|----------------------------|----------------------------|---------|
| Male sex                         | 359 (43.1)             | 255 (44.7)                 | 104 (39.7)                 | 0.20    |
| STS PROM                         | 4.1 (2.8, 5.7)         | 3.9 (2.7, 5.4)             | 4.3 (3.0, 6.6)             | 0.036   |
| EuroSCORE II                     | 3.6 (2.3, 5.8)         | 3.4 (2.2, 5.5)             | 4.2 (2.6, 7.0)             | <0.001  |
| Diabetes                         | 221 (26.6)             | 131 (23.0)                 | 90 (34.4)                  | <0.001  |
| COPD                             | 116 (13.9)             | 69 (12.1)                  | 47 (17.9)                  | 0.032   |
| GFR (CKD-EPI)                    | 62.3 (46.8, 76.6)      | 65.1 (49.2, 78.7)          | 57.4 (41.8, 70.1)          | <0.001  |
| CAD                              | 603 (72.8)             | 419 (73.8)                 | 184 (70.8)                 | 0.41    |
| Prior MI                         | 63 (7.6)               | 48 (8.4)                   | 15 (5.7)                   | 0.22    |
| Prior CABG                       | 70 (8.4)               | 50 (8.8)                   | 20 (7.6)                   | 0.68    |
| Prior PCI                        | 303 (36.5)             | 213 (37.4)                 | 90 (34.4)                  | 0.44    |
| Prior stroke                     | 111 (13.3)             | 67 (11.8)                  | 44 (16.8)                  | 0.061   |
| Prior PM                         | 29 (6.9)               | 28 (9.6)                   | 1 (0.8)                    | 0.0019  |
| NYHA III/IV                      | 589 (71.0)             | 382 (67.3)                 | 207 (75.3)                 | <0.001  |
| H₂FPEF score variables           |                        |                            |                            |         |
| BMI (kg/m²)                      | 26.2 (23.5, 29.4)      | 25.7 (23.4, 28.7)          | 27.6 (24.1, 31.2)          | <0.001  |
| Hypertension                     | 755 (90.7)             | 499 (87.5)                 | 256 (97.7)                 | <0.001  |
| Atrial fibrillation              | 266 (32.0)             | 32 (5.6)                   | 234 (89.3)                 | <0.001  |
| Moderate PHT (sPAP 36–55 mmHg)   | 502 (60.3)             | 321 (56.3)                 | 181 (69.1)                 | <0.001  |
| Severe PHT (sPAP > 55 mmHg)      | 113 (13.6)             | 51 (8.9)                   | 62 (23.7)                  | <0.001  |
| Age (years)                      | 81.9 (78.0, 85.1)      | 81.6 (77.6, 85.1)          | 82.3 (78.8, 85.2)          | 0.18    |
| LVEDP (mmHg)                     | 12.0 (9.0, 18.0)       | 12.0 (8.0, 17.0)           | 14.0 (10.0, 20.0)          | <0.001  |
| Echocardiographic baseline parameters |                   |                            |                            |         |
| Moderate or severe TR            | 134 (16.1)             | 63 (11.1)                  | 71 (27.1)                  | <0.001  |
| Moderate or severe MR            | 179 (21.5)             | 99 (17.4)                  | 80 (30.5)                  | <0.001  |
| Pm-mean (mmHg)                   | 42.0 (31.0, 51.0)      | 43.0 (33.7, 53.0)          | 39.0 (28.0, 48.7)          | <0.001  |
| Stroke volume index (mL/m²)      | 34.0 (32.0, 46.8)      | 40.7 (34.4, 48.4)          | 35.2 (30.8, 43.7)          | <0.001  |
| HG-AS                            | 423 (53.5)             | 309 (57.5)                 | 114 (45.1)                 | 0.0013  |
| NF-LG AS                         | 187 (25.4)             | 135 (26.8)                 | 52 (22.3)                  | 0.22    |
| PLF-LG AS                        | 141 (19.2)             | 70 (13.9)                  | 71 (30.5)                  | <0.001  |
| Procedural parameters            |                        |                            |                            |         |
| TF access                        | 783 (94.1)             | 536 (94.0)                 | 247 (94.3)                 | 1.00    |
| TA access                        | 33 (4.0)               | 22 (3.9)                   | 11 (4.2)                   | 0.97    |
| TAX access                       | 15 (1.8)               | 11 (1.9)                   | 4 (1.5)                    | 0.90    |
| Other access                     | 1 (0.1)                | 1 (0.2)                    | 0 (0)                      | 1.00    |

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HG-AS, high-gradient aortic stenosis; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; MR, mitral regurgitation; NF-LG AS, normal-flow, low-gradient aortic stenosis; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PHT, pulmonary hypertension; PLF-LG AS, paradoxical low-flow, low-gradient aortic stenosis; PM, permanent pacemaker; P-mean, mean transvalvular pressure gradient; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TA, transapical; TAX, transaxillary; TF, transfemoral; TR, tricuspid regurgitation.

Data presented are the number (percentage) of patients for categorical variables or median values (25th percentile, 75th percentile) for continuous variables.

rehospitalization for CHF were significantly higher in patients with high H₂FPEF score compared with those with low H₂FPEF score 1 year after TAVI.

iv A high H₂FPEF score is an independent predictor of all-cause mortality and CV mortality or rehospitalization for CHF after TAVI.

The coexistence of severe AS and HFpEF is a common, yet underrecognized phenomenon. In a recent analysis of the US National Inpatient Sample registry, 37.0% of all patients receiving TAVI for severe AS and 67.4% of those with known heart failure were diagnosed with HFpEF. In the present study, we investigated characteristics and outcomes of this subset of patients with AS and concomitant HFpEF as diagnosed by the H₂FPEF score. Compared with patients with HFrEF, patients with HFpEF are usually older, more commonly female, more likely to be hypertensive, and less likely to suffer from coronary artery disease. Moreover, HFpEF is associated with co-morbidities that contribute to the progress of diastolic heart failure, such as atrial fibrillation, diabetes, obesity, chronic renal failure, pulmonary hypertension, and COPD. In line with these findings, co-morbidities that were not comprised by the H₂FPEF score, such as diabetes, COPD, and impaired renal function, were associated with a high H₂FPEF score in our study. Thus, our results demonstrate that the H₂FPEF score may well be extended to patients with valvular heart disease as it seems to identify typical HFpEF phenotypes.

Among patients with AS, there seems to be a significant overlap of these HFpEF phenotypes with PLF-LG AS, which
is found in approximately 5–15% of AS patients. Similar to HfPEF, PLF-LG AS is mostly found in elderly patients and typically associated with small ventricular size, LV hypertrophy, and a history of hypertension. Presence of impaired diastolic filling, atrial fibrillation, pulmonary hypertension, and mitral and tricuspid regurgitation in advanced stages of AS result in a reduced stroke volume in these patients. Taking these parallels into account, recent studies proposed to refer to PLF-LG AS as the HfPEF of AS. This is strongly supported by the current study, as we demonstrate that Pmean and SVI decrease with increasing H2FPEF score, and thus, a high proportion of AS patients with high H2FPEF score, in fact, fulfill European Society of Cardiology guideline criteria for PLF-LG AS.

The negative prognostic role of reduced SVI has been well described for both HfPEF patients and patients receiving TAVI for severe AS. Moreover, it has been shown that diastolic dysfunction, a key pathological mechanism in HfPEF, is associated with increased mortality in TAVI patients. However, there was so far no data regarding prognostic implications of HfPEF itself in TAVI patients. Our results suggest that HfPEF, as diagnosed by a high H2FPEF score, is in fact associated with higher risk for all-cause mortality and, even more, for CV mortality and heart failure events after TAVI among patients with severe AS and preserved EF. Thereby, the reduction of SVI and the presence of PLF-LG AS, as an expression of advanced diastolic dysfunction, may well be a driving force for the adverse impact of HfPEF in TAVI patients. In some of these patients, AS represents the sole cause of HfPEF, which may persist even after the resolution of AS by TAVI in those at advanced stages of the disease. In others, however, the evolution of AS may parallel the existence of HfPEF due to pathophysiological processes independent from AS with significant impact on symptoms and outcomes in these patients following AS treatment. Among the individual score variables, the main predictors for CV
death and heart failure events in the present study were atrial fibrillation, pulmonary hypertension, and elevated LV filling pressure. Interestingly, these exact variables are also included in a staging classification of AS-induced cardiac damage, established by Généreux et al., as indicators of advanced and potentially irreversible structural alterations of the heart. Thus, the presented results strengthen the hypothesis that the \( H_2 \)FPEF score may identify a subset of AS patients with preserved EF that suffers from poor prognosis even after AS treatment due to advanced, irreversible HFpEF, either caused by or coexistent to AS. Especially with regard to the prediction of CV and heart failure outcomes, calculation of the \( H_2 \)FPEF score may enhance clinical decision making compared with single and dichotomous parameters (e.g. atrial fibrillation).

**Study limitations**

Some limitations of the present study have to be addressed. First, the retrospective design of the present study puts constraints on any drawn conclusions. Second, for the purpose of the current study, \( H_2 \)FPEF score variables were slightly modified as we used invasively measured LVEDP compared with...
### Table 2 Univariable and multivariable analyses for all-cause mortality after TAVI

|          | Univariable analysis | Multivariable analysis (with H2FPEF score) (N = 832) | Multivariable analysis (with H2FPEF score variables) (N = 832) |
|----------|----------------------|-----------------------------------------------------|---------------------------------------------------------------|
|          | HR (95% CI)          | P-value                                             | HR (95% CI)                                                   | P-value |
| Age      | 1.06 (1.02–1.09)     | 0.0022                                              | 1.03 (0.99–1.06)                                              | 0.18    | 1.03 (0.99–1.07) | 0.20 |
| Male sex | 0.98 (0.68–1.42)     | 0.91                                                |                                                               |         |                                                       |
| BMI      | 0.96 (0.92–1.00)     | 0.047                                               |                                                               |         |                                                       |
| Prior stroke | 1.32 (0.80–2.16)   | 0.28                                                |                                                               |         |                                                       |
| Atrial fibrillation | 2.74 (1.89–3.97) | <0.001                                              |                                                               |         |                                                       |
| Hypertension | 0.81 (0.45–1.48) | 0.50                                                |                                                               |         |                                                       |
| Prior MI | 0.62 (0.25–1.51)     | 0.29                                                |                                                               |         |                                                       |
| CAD      | 0.81 (0.54–1.21)     | 0.30                                                |                                                               |         |                                                       |
| Diabetes | 1.21 (0.81–1.79)     | 0.35                                                |                                                               |         |                                                       |
| COPD     | 1.30 (0.79–2.13)     | 0.30                                                |                                                               |         |                                                       |
| PHT <35 mmHg | 1 (reference)       |                                                     |                                                               |         |                                                       |
| 36–55 mmHg | 1.66 (1.01–2.74)    | 0.047                                               |                                                               |         |                                                       |
| >55 mmHg | 3.31 (1.85–5.91)     | <0.001                                              |                                                               |         |                                                       |
| TR ≥ 2  | 3.55 (2.44–5.17)     | <0.001                                              |                                                               |         |                                                       |
| MR ≥ 2  | 2.34 (1.59–3.43)     | <0.001                                              |                                                               |         |                                                       |
| NYHA     | 1.89 (1.40–2.56)     | <0.001                                              |                                                               |         |                                                       |
| GFR < 60 mL/min | 2.12 (1.45–3.11) | <0.001                                              |                                                               |         |                                                       |
| Non-TF access | 2.51 (1.49–4.23) | <0.001                                              |                                                               |         |                                                       |
| LVEDP > 15 mmHg | 1.42 (0.98–2.07) | 0.063                                               |                                                               |         |                                                       |
| H2FPEF score 0–5 | 2.27 (1.57–3.29) | <0.001                                              |                                                               |         |                                                       |
| H2FPEF score 6–9 | 1.59 (1.08–2.35) | 0.018                                               |                                                               |         |                                                       |

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PHT, pulmonary hypertension; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TR, tricuspid regurgitation.

Score variables were highlighted.

### Table 3 Univariable and multivariable analyses for the combined endpoint of cardiovascular mortality or rehospitalization for congestive heart failure after TAVI

|          | Univariable analysis | Multivariable analysis (with H2FPEF score) (N = 410) | Multivariable analysis (with H2FPEF score variables) (N = 410) |
|----------|----------------------|-----------------------------------------------------|---------------------------------------------------------------|
|          | HR (95% CI)          | P-value                                             | HR (95% CI)                                                   | P-value |
| Age      | 1.05 (0.99–1.10)     | 0.078                                               |                                                               |         |                                                       |
| Male sex | 0.76 (0.44–1.33)     | 0.34                                                |                                                               |         |                                                       |
| BMI      | 1.01 (0.95–1.07)     | 0.74                                                |                                                               |         |                                                       |
| Prior stroke | 1.55 (0.75–3.18)   | 0.23                                                |                                                               |         |                                                       |
| Atrial fibrillation | 3.03 (1.74–5.30) | <0.001                                              |                                                               |         |                                                       |
| Hypertension | 0.79 (0.31–1.98) | 0.61                                                |                                                               |         |                                                       |
| Prior MI | 1.44 (0.57–3.62)     | 0.44                                                |                                                               |         |                                                       |
| CAD      | 0.83 (0.39–1.77)     | 0.63                                                |                                                               |         |                                                       |
| Diabetes | 1.04 (0.56–1.92)     | 0.91                                                |                                                               |         |                                                       |
| COPD     | 1.41 (0.69–2.91)     | 0.34                                                |                                                               |         |                                                       |
| PHT <35 mmHg | 1 (reference)       |                                                     |                                                               |         |                                                       |
| 36–55 mmHg | 2.22 (1.04–4.75)    | 0.039                                               |                                                               |         |                                                       |
| >55 mmHg | 6.32 (2.79–14.32)    | <0.001                                              |                                                               |         |                                                       |
| TR ≥ 2  | 3.67 (1.88–7.15)     | <0.001                                              |                                                               |         |                                                       |
| MR ≥ 2  | 3.32 (1.87–5.90)     | <0.001                                              |                                                               |         |                                                       |
| NYHA     | 1.93 (1.25–2.99)     | 0.0030                                              |                                                               |         |                                                       |
| GFR < 60 mL/min | 1.92 (1.10–3.35) | 0.021                                               |                                                               |         |                                                       |
| Non-TF access | 0.00 (0–inf)        | 1.00                                                |                                                               |         |                                                       |
| LVEDP > 15 mmHg | 2.10 (1.19–3.71) | 0.011                                               |                                                               |         |                                                       |
| H2FPEF score 0–5 | 3.52 (2.01–6.14) | <0.001                                              |                                                               |         |                                                       |
| H2FPEF score 6–9 | 2.92 (1.65–5.15) | <0.001                                              |                                                               |         |                                                       |

Abbreviations as in Table 2.

Score variables were highlighted.
echocardiographically derived measurements (E/e′) that are included in the original score. Nevertheless, invasively measured LVEDP is considered a more precise method for the assessment of LV filling pressures as compared with echocardiographic E/e′. Third, invasive assessment of LVEDP may have been influenced by general anaesthesia in patients with non-transfemoral access.

### Conclusion

Among patients with severe AS and preserved EF undergoing TAVI, the H2FPEF score serves as an independent predictor of adverse outcome. A high H2FPEF score is further associated with lower Pmean and lower SVI translating into a higher rate of PLF-LG AS. Thus, by identifying patients with PLF-LG AS, the H2FPEF of AS, the H2FPEF score might be useful as a risk prediction tool for TAVI patients.

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### Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Comparison of baseline characteristics between excluded and included patients

**Table S2.** Procedural parameters and VARC2 30-day outcome

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