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Prognostic value of the MAGGIC score, H₂FPEF score and HFA-PEFF algorithm in patients with exertional dyspnea and the incremental value of exercise echocardiography

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ABSTRACT

Background: The strategies for improving outcomes in heart failure with preserved ejection fraction (HFpEF) are insufficiently defined, which affects the optimal patient management. The aim of the study was to compare the prognostic value of previously validated the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score with two approaches primarily dedicated to diagnosing HFpEF: the H₂FPEF score (Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension [pulmonary artery systolic pressure>35 mm Hg], Elder age>60, elevated Filling pressures [E/e'>9]) and the HFA-PEFF algorithm (Heart Failure Association - Pre-test assessment; Echocardiography and Natriuretic Peptide Score; Functional testing; Final aetiology) in patients with exertional dyspnea categorized as HFpEF.

Methods: Clinical and biochemical variables, and echocardiographic resting and exercise data from 201 enrollees were retrospectively analyzed. Participants were followed for 48 (24-60) months for HF hospitalization and cardiovascular death.

Results: Seventy-four patients (36.8%) met the study outcome. In sequential Cox analysis, the addition of each of the following: MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 (including only resting echocardiographic evaluation) and step 3 (including also exercise diastolic data) algorithm to the base model comprising BNP and peak VO₂ improved the predictive power for the study endpoint. The Harrel's c-statistic showed a greater predictive ability for the HFA-PEFF step 3 algorithm than each of the other scores (c-index 0.715 vs. 0.637, 0.644 and 0.638 for MAGGIC, H₂FPEF and HFA-PEFF step 2, respectively, all p<0.05). No significant differences were found for other between-score comparisons.

Conclusions: In patients with exertional dyspnea and a possible HFpEF, the H₂FPEF score and HFA-PEFF algorithm limited to resting echocardiography provide prognostic value comparable to the MAGGIC risk score. Extending the HFA-PEFF algorithm with exercise diastolic data is associated with a significant improvement in risk stratification.

Key words: heart failure with preserved ejection fraction; exertional dyspnea; exercise echocardiography; risk stratification

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is one of the major concerns for public healthcare systems due to its rapidly increasing prevalence associated with the ageing of populations and epidemics of obesity, hypertension and diabetes (1). Clinically, exercise intolerance is a hallmark of this disease entity (2). Despite the apparent improvements in recent years, making a correct diagnosis of HFpEF may be challenging, especially in the absence of overt clinical and biomarker evidence of congestion. In addition, the strategies for improving outcomes in this group are not well-defined. Indeed, better definition of subsets at higher clinical risk may be helpful in adjudicating the intensity of follow-up and optimizing therapies (3). Although many of clinical, biochemical, and echocardiographic derangements have been linked to worse outcome (4-6), effective tools, incorporating concurrently several easily available variables, are sought to improve risk stratification in this condition.

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, derived from a large database of patients with heart failure (HF) across the spectrum of ejection fraction (EF) was shown to be useful in the prediction of both morbidity and mortality in HFpEF (7). The H₂FPEF score (Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension [pulmonary artery systolic pressure >35 mm Hg], Elder age >60, elevated Filling pressures [E/e' >9]) proposed by Reddy et al. (8) and the algorithm provided by Heart Failure Association (HFA) of the European Society of Cardiology (the HFA-PEFF diagnostic algorithm [Heart Failure Association - Pre-test assessment; Echocardiography and Natriuretic Peptide Score; Functional testing; Final aetiology]) (9) were primarily

developed to diagnose HFpEF in patients with dyspnea of uncertain origin. Both of these approaches are based on clinical data and echocardiographic measurements that have a documented prognostic significance; therefore, they may have the potential for risk assessment. Up to now, a few studies have demonstrated that higher H₂FPEF scores are associated with worse outcome, however, analogous data for the HFA-PEFF algorithm are scarce (10-13) . Moreover, no comparisons with the existing prognosticating tool – MAGGIC risk score have been carried out to justify the promotion of the above diagnostic strategies as new approaches to risk stratification. In contrast to the H₂FPEF score using only echocardiographic measurements at rest, the HFA-PEFF algorithm has the option to include data from exercise stress echocardiography, which might extend the spectrum of prognostic information.

Accordingly, the aim of the study was to compare the prognostic value of the HFA-PEFF score, H₂FPEF score, and MAGGIC risk score in patients with exertional dyspnea categorized as having HFpEF.

METHODS

Patient selection. In this retrospective analysis, we included data prospectively collected from 201 patients with exertional dyspnea recruited from hospital clinics at a tertiary cardiology center (University Hospital, Wroclaw, Poland), who met the HFpEF criteria in place at the time of recruitment [i.e., between 2012 and 2015]: 1) signs and symptoms of heart failure (dyspnea, fatigue and exercise intolerance) consistent with New York Heart Association (NYHA) functional class II or III; with reduced exercise capacity (<100% of age- and sex-predicted normal ranges for

peak oxygen consumption); 2) preserved LV ejection fraction ($\geq 50\%$); 3) evidence of diastolic dysfunction (14).

The exclusion criteria encompassed: 1) atrial fibrillation or flutter (because of the confounding effect of heart rhythm irregularities on the accuracy of echocardiographic evaluation, especially myocardial deformation and Doppler measurements); 2) ischemic heart disease, defined by the presence of atherosclerotic lesions at coronary angiography or inducible ischemia during exercise testing (because myocardial ischemia itself could reduce exercise capacity without involving diastolic dysfunction); 3) moderate and severe valvular heart disease; 4) confirmed or suspected pulmonary disease (vital capacity $< 80\%$ or forced expiratory volume in 1 second being $< 80\%$ of age- and sex-specific reference values); 5) hemoglobin < 11 mg/dl; 6) other significant comorbidities, including malignancy, renal failure with estimated glomerular filtration rate < 30 ml/min/1.73 m², infections, and autoimmune, skeletal, and thyroid illnesses.

The study protocol included clinical evaluation, cardiopulmonary exercise testing, resting and immediate post-exercise echocardiogram, and blood sampling for laboratory assessments.

Investigations were in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from each participant.

Outcome. Enrollees were followed over a median period of 48 (24-60) months for the composite endpoint of heart failure hospitalization (defined as the first hospital admission due to HF worsening requiring intensification of diuretic therapy) or

cardiovascular death. Event rate was verified by systematic contact with patients or their proxies, as well as by reviewing healthcare records.

Clinical Evaluation. A standard clinical history was taken, including information about risk factors, etiology, and treatment. To predict clinical outcomes, MAGGIC risk score was calculated on the basis of the following variables: age, gender, creatinine, diabetes mellitus, chronic obstructive pulmonary disease, systolic blood pressure, body mass index, NYHA class, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, β -blocker use, heart failure duration, and current smoker (15).

The H₂FPEF score, establishing the likelihood of HFpEF, was computed using weighted, binary variables: obesity, atrial fibrillation, age >60 yrs, ≥ 2 antihypertensives, echocardiographic E/e' ratio >9, and pulmonary artery systolic pressure by echo >35 mmHg. A total score of ≥ 6 points is considered diagnostic of HFpEF (8).

The HFA-PEFF score, a consensus recommendation for HFpEF diagnosis, was calculated as two separate variants (9). After an initial work-up (step 1), echocardiographic assessment of cardiac functional and morphological domains (including mitral annular early diastolic velocity (e'), E/e' ratio, left atrial volume index, LV mass index, LV relative wall thickness, tricuspid regurgitation velocity, and LV global longitudinal strain) and measurement of natriuretic peptide levels permitted calculation of the HFA-PEFF step 2 score. In the next step including functional testing, the combined HFA-PEFF score (HFA-PEFF step 3 score) was computed by adding the points contributed by exercise E/e' ratio reflecting LV

diastolic response to stress to the previous score from step 2. Because of the unavailability of data on exercise tricuspid regurgitant velocity (TRV; this measurement was not a prerequisite for the recognition of abnormal LV filling pressure response to exertion at the time of patients' recruitment), we had to restrict step 3 to the evaluation of exercise E/e' . A total score of ≥ 5 points achieved at step 2 or 3 has been proposed as diagnostic of HFpEF. Exercise echocardiography was performed in all participants, however according to the HFA-PEFF algorithm, additional points from step 3 were added only in patients with an intermediate score (2-4 points) at step 2. The comparison of the assessed scores is presented in Table 1.

Echocardiography. Standard equipment (Vivid e9, General Electric Medical Systems, Milwaukee, Wisconsin) with a phased array 2.5-MHz multifrequency transducer was used for echocardiography imaging. Ultrasound data were analyzed offline after being saved in the digital format on a secure server.

Conventional and Tissue Doppler Imaging. Cardiac dimensions and wall thicknesses were measured according to recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (16). LV volumes and ejection fraction were assessed by the biplane Simpson, whereas LA volumes by the area-length method. LV inflow parameters including peak early (E) and late diastolic flow velocity (A) and deceleration time of early diastolic flow wave (DT) were evaluated from the apical 4-chamber view by pulsed-wave Doppler with the sample volume placed between the tips of the mitral leaflets. Pulsed-wave

tissue Doppler was used to evaluate peak early diastolic tissue velocity (e') at the septal and lateral aspects of the mitral annulus. The E/e' ratio was calculated by dividing the mitral inflow early diastolic velocity by the average e' velocity from both parts of the mitral annulus. Pulmonary artery systolic pressure was assessed only at rest and was calculated as $(4 \times \text{peak tricuspid regurgitation velocity}) + \text{right atrial pressure}$ estimated from the inferior vena cava diameter and its collapsibility with inspiration. Imaging data for this assessment were available in 148 patients.

Speckle Tracking Imaging. LV longitudinal deformation was evaluated by semi-automated 2D speckle tracking using Echopac PC version 113 (GE Healthcare, Horten, Norway) in the three apical views at a temporal resolution of 60-90 frames/s. The peak negative systolic strain value averaged from the 3 strain curves was presented as global longitudinal strain (GLS) and expressed as an absolute value. All echocardiographic analyses were performed by the observers blinded to patient clinical data.

Cardiopulmonary Exercise Testing and Blood Assays. Symptom-limited exercise testing was performed on a treadmill using a modified Bruce protocol with standard ECG and blood pressure monitoring. Ventilation, oxygen uptake, and carbon dioxide production were monitored continuously, and peak oxygen uptake (peak VO_2) was computed as the average oxygen consumption during the last 30 seconds of exercise. Exercise capacity was also presented in metabolic equivalents (METs) based on the peak exercise intensity.

Echocardiographic evaluation of E/e' ratio was also performed immediately after termination of exercise to assess LV diastolic response to exertion, and was preceded by the acquisition of two-dimensional imaging loops. In case of overlapping early and late diastolic Doppler waves (E and A and/or e' and a') at high heart rates, the assessment was delayed until separation of these signals. The average time from the completion of exercise to recording the Doppler diastolic indices was 2.44 ± 0.62 min.

Statistical Analysis. Data are presented as mean \pm SD for normally distributed variables, as median (interquartile range) for skewed variables (BNP), and as counts and percentages for categorical variables. BNP was log-transformed before being analyzed. The associations of MAGGIC risk score, H₂FPEF score and HFA-PEFF step 2 and step 3 algorithms with the study endpoint were evaluated using Cox proportional hazard models adjusted for BNP and peak VO₂. A cause-specific competing risk approach was used for the outcome of interest (HF hospitalization or cardiovascular death) and the competing risk of non-cardiovascular death. Relative risks were expressed as hazard ratios with 95% confidence intervals. The incremental value of each of the tested scores for the prediction of outcome was assessed in nested Cox models by the addition of the parameter of interest (i.e., MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithms to a base model including BNP, and peak VO₂). The change in overall log-likelihood ratio chi-square was used to evaluate the increase in predictive power after the addition of each of the scores. The generalized R-squared was used to examine the explanatory power of each model. The relative quality of models was estimated by

the Akaike information criterion (AIC). The Harrell's c-statistic was used to evaluate model performance.

A receiver operator characteristic (ROC) analysis was used to assess the ability of MAGGIC risk score, H₂FPEF score and HFA-PEFF step 2 and step 3 algorithms to predict the study outcome and to determine the discriminatory cutpoints for these variables, defined as the maximum Youden index. The predictive power of MAGGIC risk score, H₂FPEF score and HFA-PEFF step 2 and step 3 algorithms was evaluated using the Harrell's c-statistic calculated for each univariable model including a single score, and the bootstrap method with 2000 iterations for each test was used to assess the significance of inter-score differences. Event-free survival curves were estimated using the Kaplan -Meier method, and differences were assessed by the log-rank test. All calculations were carried out using standard statistical software (Statistica version 13, TIBICO Software Inc., Palo Alto, CA, USA), and R software ver.4.0.3 [<http://cran.r-project.org/>]). The level of statistical significance was set at p value <0.05.

RESULTS

Patient Characteristics and Events. The studied population was characterized by a predominance of female sex and high frequency of hypertension, diabetes, and obesity or overweight. These characteristics, as well as echocardiographic data are presented in Table 2. The average score was 14.8 for the MAGGIC risk score, 4.5 for the H₂FPEF score, 4.2 for the HFA-PEFF step 2 algorithm, and 4.6 for the HFA-PEFF step 3 algorithm. Using the predefined diagnostic cutoffs recommended for

the identification of HFpEF, 60 (30%) of enrollees had H₂FPEF score ≥ 6 , while 83 (41%) had HFA-PEFF score ≥ 5 at step 2, and 116 (58%) at step 3.

During a median follow-up of 48 months, 74 patients (36.8%) met the composite endpoint of hospitalization due to HF worsening or cardiovascular death. The mortality rate was 10.9% (22 patients). The cause of death was cardiac in 13 cases, cerebral stroke in 3 cases, hematologic malignancy, pneumonia, and septic shock - each in 1 case, and in 3 cases the reason remained undetermined. Table 3 shows incidence rates for the study endpoint for the MAGGIC risk score, H₂FPEF score and HFA-PEFF algorithm categories separated on the basis of the optimal points in ROC analysis.

Outcome. In unadjusted Cox proportional hazard models, the MAGGIC risk score, H₂FPEF score, HFA-PEFF step 2 and step 3 algorithm, as well as BNP, peak VO₂, renal function, E/e', e', GLS, LAVI, E/A were significantly associated with the composite of HF hospitalization or cardiovascular death (Table 4). The significance of the associations of the evaluated scores with the study endpoint persisted after adjustment for BNP and peak VO₂ (Table 5).

In sequential Cox analysis comprising models from Table 5, the addition of each of the following: MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithm to the base model including BNP and peak VO₂ improved the predictive power for the study endpoint (Figure 1). The lower increment in predictive ability demonstrated in this analysis for the HFA-PEFF step 2 score than for the H₂FPEF score (chi² 19.7 vs. 27.8) can be attributable to the fact that the HFA-PEFF algorithm includes natriuretic peptides in its work-up and scoring system.

The addition of points from diastolic exercise echocardiography to the score obtained at step 2 of the HFA-PEFF algorithm in all participants (i.e. irrespective of the step 2 score value) did not provide any prognostic benefit over the step 3 score calculated according to the HFA-PEFF algorithm rules (HR 1.42 95% CI 1.25-1.63; c-statistic 0.701).

Comparison Of the Predictive Potential Of Evaluated Scores. Comparisons of the Harrel's c-statistic showed a greater ability to predict the study endpoint for the HFA-PEFF step 3 algorithm than each of the other analyzed scores (Table 6). No significant differences were found for other between-score comparisons.

Receiver-operating characteristic analysis revealed the highest area under the curve for the HFA-PEFF step 3 algorithm (Figure 2). The optimal cut-off point for the MAGGIC risk score was 17 (sensitivity 51%, specificity 75%), for the H₂FPEF score 5 (sensitivity 66%, specificity 61%), for the HFA-PEFF step 2 algorithm 5 (sensitivity 59%, specificity 69%), and for the HFA-PEFF step 3 algorithm 5 (sensitivity 88%, specificity 60%). Patients with the score equal to or above the above-mentioned thresholds had a significantly higher incidence of HF hospitalization or cardiovascular death (Figure 3).

There was a substantial proportion of discordance among the evaluated scores in predicting adverse outcome. Increased clinical risk was concordantly predicted by all 3 scores in 23 patients, by 2 out of 3 scores in 27 patients (the largest degree of concordance between the HFA-PEFF and H₂FPEF scores), and in 13 patients by a single score only (Table 7). In only 1 patient, the occurrence of adverse outcome was not predicted by any of the evaluated scores.

DISCUSSION

This study demonstrates that in patients with exertional dyspnea meeting the 2007 ESC criteria of HFpEF, the MAGGIC risk score, H₂FPEF score and HFA-PEFF algorithm including only resting echocardiographic evaluation (i.e., limited to the diagnostic work-up step 2) show similar abilities to predict the risk of HF hospitalization or death. The addition of information from diastolic exercise echocardiography (advanced work-up step 3) provides a significant improvement of the prognostic value of HFA-PEFF algorithm. Substantial evidence indicates that HFpEF carries a high cardiovascular risk (17-19). In view of the anticipated increase in the number of HFpEF patients by almost 50% by 2030 (20), it is vital to establish improved management for these patients with the efficient identification of individuals at risk as a priority. The clinical practice needs simple tools that ideally could provide both diagnostic and prognostic information.

The MAGGIC risk score has been validated in HFpEF, showing good discriminatory abilities for the prediction of adverse outcome (7). However, the MAGGIC risk score reflects only clinical risk factors. The 2 recently proposed models for HFpEF identification – the H₂FPEF and HFA-PEFF scores are based on other components that have prognostic value (15). The H₂FPEF score was modeled using invasive hemodynamic measurements as a frame of reference, whereas the HFA-PEFF strategy was prepared as an Expert Consensus Recommendation. Both include echocardiographic parameters with the imaging characteristic more comprehensive in the HFA-PEFF algorithm (9 echo variables vs. only 2 in H₂FPEF).

Unlike the H₂FPEF score, the spectrum of HFA-PEFF components comprises natriuretic peptides and, as an option, LV diastolic response to exercise.

Echocardiography is an essential tool for the diagnosis of LV diastolic dysfunction and HFpEF. This imaging technique is indispensable for the H₂FPEF and HFA-PEFF algorithms. While in the former, the role of echocardiography is limited to quantitation of diastolic markers i.e. E/e' and TRV, in the latter, a more multifaceted set of parameters describing HFpEF-related myocardial impairment is assessed, specifically E/e', TRV, e', GLS, LV mass, wall thicknesses, and left atrial volume. LV filling pressure response to exercise – a part of step 3 of the HFA-PEFF algorithm is evaluated based on echocardiographic measurements of E/e' and TRV at peak stress.

The ability of H₂FPEF score to provide predictive information was recently demonstrated in HFpEF (10, 21, 22) and asymptomatic populations with risk factors (11). However, these data have not been compared with other risk stratification approaches. The only comparison between the H₂FPEF and HFA-PEFF scores showed an equivalent predictive value in patients with unexplained dyspnea (13). It should be emphasized that the calculation of HFA-PEFF score in this study was limited to the evaluation at rest (step 2). The current investigations demonstrated that in the population with exercise intolerance meeting the former HFpEF criteria, the MAGGIC, H₂FPEF and HFA-PEFF step 2 scores exhibited comparable prognostic utility. However, there was considerable discordant risk classification, which argues against the interchangeable use of these algorithms. This is in line with previous studies reporting diagnostic and prognostic discrepancies between the two scores (13, 23). The most important finding of our analysis is that the inclusion

of assessment under an exercise load (the HFA-PEFF step 3) afforded a significant improvement of risk stratification compared to each of the resting models. The HFA-PEFF algorithm extended by E/e' ratio at exercise with an accepted threshold of 5 points was characterized by high sensitivity but poorer specificity (88% and 60%, respectively) in predicting adverse outcome. The optimal point for the H₂FPEF model obtained from ROC analysis was below the diagnostic threshold for this score (5 vs. 6 points), which is consistent with the previous report that the diagnostic and prognostic values of predefined criteria may differ (13). Multivariable modelling with adjustment for the commonly recognized risk predictors – BNP and peak VO₂, revealing the independent and incremental value of the assessed algorithms, supports the usefulness of the H₂FPEF and HFA-PEFF scores for prognostic purposes.

Limited left and right ventricular functional reserve is an important component of the pathophysiology of effort intolerance in HFpEF (3, 24). Accordingly, the identification of abnormal cardiac responses to exercise expands the characterization of patients, especially those with less advanced disease, and improves the completeness of clinical profile defined at rest. Exercise-induced worsening of LV diastolic filling is a major cardiac contributor to reduced functional capacity in HFpEF (25). Pathophysiologically, it is linked with increased LV chamber stiffness (26, 27). Despite the absence of robust evidence supporting the use of E/e' ratio to approximate LV filling pressure during exercise (28), an excessive stress-induced increase in this parameter reflects an abnormal LV diastolic reserve. The prognostic relevance of E/e' ratio response to exercise in dyspneic patients suggests that diminished LV diastolic reserve might be a more important and specific marker

than abnormalities of myocardial performance at rest, and indirectly explains the prognostic superiority of the HFA PEF step 3 algorithm including assessment under stress conditions over the scores based exclusively on the resting evaluation.

If exercise echocardiography cannot be performed, the H₂FPEF score might be considered the preferred tool for predicting patient outcome due to its simplicity and high quality as indicated by the low AIC value. However, the limitations of the H₂FPEF score are that this algorithm does not include BNP – a key marker in heart failure, and the E/e' cutoff is set very low, worsening diagnostic specificity.

Implications. The diagnostic algorithms initially dedicated to HFpEF diagnosis have the potential to identify patients with an increased likelihood of adverse outcomes, which reinforces the utility of these models as clinical tools. Our finding that the addition of exercise echocardiography to diagnostic procedures in patients with exertional dyspnea improves the prognostic evaluation further supports the need for a wider inclusion of stress testing to the recommendations.

Assessment of LV functional reserve improves patient pathophysiological characterization and can directly link patient complaints to abnormal cardiac performance under stress, which is particularly important in subjects with insufficient resting imaging data to recognize impaired diastolic filling as a reason behind exertional dyspnea. The prognostic information provided by the H₂FPEF and HFA-PEFF scores may translate into more appropriate application of treatments for individuals at heightened risk. The prognostic value of diagnostic scores may be helpful in informing the design of future clinical trials.

None of the assessed scores includes right ventricular function parameters. Recent data confirm that right ventricular GLS provides incremental prognostic information

in HFpEF, and it might be worth considering this marker in risk predicting strategies in this entity (29).

Limitations. The lack of TRV measurement at exercise, an additional component of step 3 of the HFA-PEFF algorithm, might have affected the prognostic accuracy. Exclusion of patients with atrial fibrillation and myocardial ischemia might limit generalizability of our results. Although atrial fibrillation is included in both the H₂FPEF and HFA-PEFF scores, the exclusion of subjects with this arrhythmia might have a different effect on the prognostic abilities of these algorithms. Accordingly, our results only apply to patients in sinus rhythm. Reversal of splanchnic vasoconstriction following exercise termination could have led to changes in LV loading, thus affecting the evaluation of LV diastolic response to exertion. However, this was unavoidable with a study protocol including diastolic assessment in the post-exercise period. The prognostic relevance of exercise testing may be less evident in patients with advanced disease, in whom the extension of the HFA-PEFF algorithm by step 3 to make a diagnosis may not be necessary. Finally, since all participants were Caucasian, extrapolation of this study findings to other ethnicities should be made with caution.

Conclusions. In patients with exertional dyspnea and a possible diagnosis of HFpEF according to the 2007 ESC criteria, the H₂FPEF score and HFA-PEFF algorithm limited to step 2 provide prognostic value comparable to the MAGGIC risk score. The inclusion of exercise diastolic data is associated with a significant improvement in risk stratification by the HFA-PEFF algorithm. Accordingly, the HFpEF diagnostic scores, especially the HFA-PEFF algorithm with step 3, where

appropriate, might be used for prognostic purposes to assess the likelihood of unfavorable clinical course in this population.

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Table 1. Comparison of the components of MAGGIC risk score, H₂FPEF score and HFA-PEFF algorithm

Parameter	MAGGIC risk score	H₂FPEF score	HFA-PEFF score step 1 Initial Workup	HFA-PEFF score step 2 Diagnostic Workup	HFA-PEFF score step 3 Advanced Workup
Age	+	+			
Systolic blood pressure	+				
BMI/Obesity	+	+			
Creatinine	+				
NYHA class	+				
Gender	+				
Tobacco smoking	+				
Diabetes	+				
COPD	+				
Time from the first diagnosis of heart failure	+				
Betablockers	+				
ACEI / ARB	+				
At least 2 antihypertensive drugs		+			
Atrial fibrillation		+		different thresholds for natriuretic peptides in atrial fibrillation	

Symptom and/or signs		+	
Comorbidities/Risk factors		+	
ECG		+	
Echocardiography for the exclusion of other reasons		+	
Ergometry/6MWT/CPET		+	
Natriuretic peptides		+	+

Echocardiography

Ejection fraction	+		
E/e' at rest		+	+
Pulmonary artery systolic pressure at rest		+	
e' at rest			+
Tricuspid regurgitation at rest			+
Global longitudinal strain at rest			+
Left atrial volume index			+
Left ventricular hypertrophy			+
E/e' at exercise			+
Tricuspid regurgitation at exercise			+

6MWT, 6 minute walk test; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; E, early mitral inflow; e', early diastolic mitral annular velocity; NYHA, New York Heart Association

Table 2. Baseline demographic, clinical and echocardiographic characteristics of the studied population.

	Values (n=201)
Age, yrs	64.2±8.3
Male sex, n (%)	53 (26%)
BMI, kg/m²	29.6±4.1
NYHA class II, n (%)	156 (78%)
NYHA class III, n (%)	45 (22%)
Hemoglobin, g/dL	13.6±1.1
Hemoglobin, mmol/L	8.44±0.68
Creatinine, mg/dL	1.0±0.2
Creatinine, μmol/L	88.4±17.68
eGFR, mL/min/1.73 m²	66.0±15.6
BNP, pg/mL	48 (25-104)
peak VO₂, mL/min/kg	15.4±4.7
METs per protocol	5.4±2.8
SBP, mmHg	129±16
DBP, mmHg	75±9
LVMI, g/m^{2.7}	110.6±25.6
LAVI, mL/m²	33.8±9.7
EF at rest, %	72.4±8.5
GLS at rest, %	18.4±3.2
E at rest, cm/s	76±19
E/A at rest	0.9±0.4
DT at rest, ms	240±53
e' sept at rest, cm/s	5.9±1.3
e' lat at rest, cm/s	8.0±2.0
E/e' at rest	11.4±3.5
PASP at rest, mmHg	28.0±6.9
LA reservoir strain, %	28.6±8.6
LA contractile strain, %	14.3±5.2
E at exercise, cm/s	118±28

E/A at exercise	1.2±0.5
e' sept at exercise, cm/s	7.0±1.8
e' lat at exercise, cm/s	9.2±2.4
E/e' at exercise	15.1±4.9
MAGGIC risk score	14.8±5.1
H2FPEF score	4.5±1.4
HFA-PEFF step 2 score	4.2±1.2
HFA-PEFF step 3 score	4.6±1.2

Values are mean ± SD or median (interquartile range), or n (%); A, late diastolic mitral flow velocity; BMI, body mass index; BNP, brain natriuretic peptide; DT, deceleration time of E wave; DBP, diastolic blood pressure; E, early mitral inflow; e', early diastolic mitral annular velocity; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LA, left atrial; MET, metabolic equivalents; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SBP, systolic blood pressure; VO₂, oxygen uptake.

Table 3. Event rates for the composite endpoint of HF hospitalization or cardiovascular death using MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithm categories.

	MAGGIC		H2FPEF		HFA-PEFF step 2		HFA-PEFF step 3	
	score <17 (n=131)	score ≥17 (n=70)	score <5 (n=103)	score ≥5 (n=98)	score <5 (n=118)	score ≥5 (n=83)	score <5 (n=85)	score ≥5 (n=116)
Number of events	36	38	25	49	30	44	9	65
Event rate (95% CI)	67.4	169.3	61.2	140	62.5	159.0	23.7	171.5
per 1000 person-year	(45.4-89.4)	(115.5-223.1)	(37.2-85.2)	(100.8-179.2)	(40.1-84.9)	(111.3-204.7)	(8.2-39.2)	(129.8-213.2)

Caption: Categories separated on the basis of the optimal points in ROC analysis.

Table 4. Univariable predictors of HF hospitalization and cardiovascular death in the studied population in Cox proportional hazards analysis.

	HR	95% CI	P value
Age , per 1 year increment	1.05	1.02-1.08	<0.001
BMI , per 1 kg/m ² increment	1.02	0.97-1.08	0.39
Hemoglobin , per 1 g/dL increment	0.80	0.64-1.01	0.06
Creatinine , per 1 mg/dL increment	3.53	1.64-7.61	0.001
eGFR , per 1 mL/min/1.73 m ² increment	0.98	0.96-0.99	0.008
BNP , per 1 pg/mL increment	1.46	1.18-1.80	<0.001
Peak VO₂ , per 1 mL/min/kg increment	0.95	0.91-1.0	0.033
METs per protocol , per 1 unit increment	0.86	0.79-0.95	0.002
SBP , per 1 mmHg increment	1.0	0.98-1.01	0.83
DBP , per 1 mmHg increment	1.01	0.98-1.03	0.46
LVMI , per 1 g/m ^{2.7} increment	1.01	1.00-1.02	0.10
LAVI , per 1 mL/m ² increment	1.02	1.00-1.04	0.037
EF at rest , per 1 % increment	1.0	0.97-1.03	0.86
GLS at rest , per 1 % increment	0.90	0.84-0.97	0.007
E/A at rest , per 1 unit increment	1.76	1.10-2.81	0.02
DT at rest , per 1 ms increment	1.0	1.0-1.01	0.13
e' sept at rest , per 1 cm/s increment	0.71	0.59-0.85	<0.001
e' lat at rest , per 1 cm/s increment	0.77	0.68-0.87	<0.001
E/e' at rest , per 1 unit increment	1.09	1.04-1.15	<0.001
PASP at rest , per 1 mmHg increment	1.07	1.02-1.12	0.005
LA reservoir strain , per 1 unit increment	0.92	0.89-0.95	<0.001
LA contractile strain , per 1 unit increment	0.91	0.87-0.95	<0.001
E/A at exercise , per 1 unit increment	2.27	1.52-3.38	<0.001
e' sept at exercise , per 1 cm/s increment	0.82	0.71-0.94	0.006
e' lat at exercise , per 1 cm/s increment	0.85	0.77-0.94	0.002
E/e' at exercise , per 1 unit increment	1.07	1.03-1.12	<0.001
MAGGIC risk score , per 1 point increment	1.09	1.04-1.14	<0.001
H₂FPEF score , per 1 point increment	1.44	1.22-1.69	<0.001
HFA-PEFF step 2 score , per 1 point increment	1.52	1.24-1.85	<0.001
HFA-PEFF step 3 score , per 1 point increment	2.11	1.64-2.71	<0.001

Abbreviations as in Table 2.

Table 5. Associations of MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithm with the study end-point in Cox proportional hazard models adjusted for BNP and peak oxygen consumption.

	Hazard Ratio	95% CI	P value
Model 1			
BNP	1.42	1.14-1.75	0.001
Peak VO₂	0.96	0.92-1.01	0.10
Model 2			
BNP	1.29	1.02-1.63	0.03
Peak VO₂	0.98	0.93-1.03	0.41
MAGGIC score	1.06	1.01-1.11	0.01
Model 3			
BNP	1.38	1.11-1.74	0.004
Peak VO₂	0.99	0.94-1.04	0.62
H₂FPEF score	1.36	1.16-1.61	<0.001
Model 4			
BNP	1.05	0.74-1.48	0.79
peak VO₂	0.96	0.92-1.01	0.12
HFA-PEFF step 2 score	1.44	1.06-1.95	0.02
Model 5			
BNP	0.99	0.98-1.01	0.65
peak VO₂	0.94	0.72-1.22	0.43
HFA-PEFF step 3 score	2.14	1.61-2.85	<0.001

Abbreviations as in Table 2.

Table 6. Harrel's c-statistic of MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithm for prediction of HF hospitalization or cardiovascular death.

	MAGGIC	H ₂ FPEF	HFA-PEFF step 2	HFA-PEFF step 3	P values					
	(A)	(B)	(C)	(D)	A vs.B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
AUC	0.637	0.644	0.638	0.715	0.45	0.50	0.027	0.45	0.036	0.002
SE	0.056	0.052	0.053	0.043						

Table 7. Concordance of HF hospitalization or cardiovascular death prediction by the evaluated scores in participants with adverse outcome.

HFA-PEFF ≥ 5	HFA-PEFF ≥ 5	HFA-PEFF ≥ 5	H₂FPEF ≥ 5	HFA-PEFF ≥ 5	H₂FPEF ≥ 5	MAGGIC ≥ 17
H₂FPEF ≥ 5	H₂FPEF ≥ 5	MAGGIC ≥ 17	MAGGIC ≥ 17	HFA-PEFF < 5	HFA-PEFF < 5	HFA-PEFF < 5
MAGGIC ≥ 17	MAGGIC < 17	H ₂ FPEF < 5	HFA-PEFF < 5	MAGGIC < 17	MAGGIC < 17	H ₂ FPEF < 5
HFA-PEFF step 3						
23	24	12	1	6	5	2
HFA-PEFF step 2						
18	14	7	6	5	15	7

Data in the table refer to the numbers of patients in the subsets defined by the score threshold values indicating adverse outcome identified as the optimal points in ROC analysis. The boldface script indicates the criteria satisfied in a given subset. In the upper line, concordance was assessed using the HFA-PEFF score calculated on the basis of step 3, whereas in the lower line – using the HFA-PEFF score calculated on the basis of step 2 of this algorithm. The total number of patients in the group with adverse outcome with the HFA-PEFF step 3 score ≥ 5 was 65, with the HFA-PEFF step 2 score ≥ 5 - 44, with the H₂FPEF score ≥ 5 - 53, and with the MAGGIC score ≥ 17 - 38.

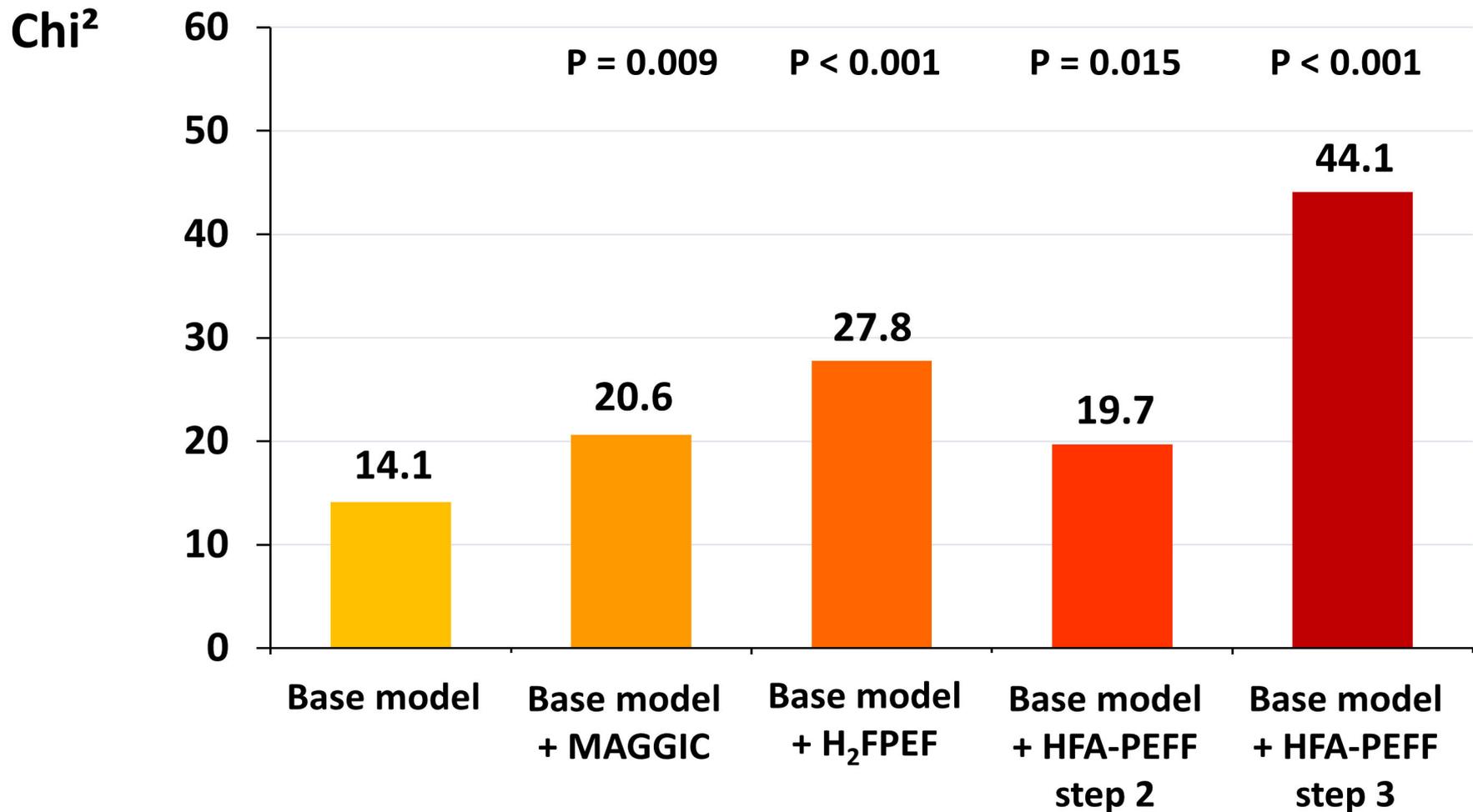
Figure legends

Figure 1. Incremental value of MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithm for prediction of HF hospitalization or cardiovascular death.

Figure 2. Receiver-Operator Characteristic Curves of MAGGIC risk score, H₂FPEF score, and HFA-PEFF step 2 and step 3 algorithm for prediction of HF hospitalization or cardiovascular death.

Caption: Area under the curve \pm SE: for HFA-PEFF step 3 algorithm - 0.766 ± 0.034 ; for HFA-PEFF step 2 algorithm - 0.672 ± 0.040 ; for H₂FPEF score - 0.675 ± 0.039 ; and for MAGGIC risk score - 0.665 ± 0.039 .

Figure 3. Kaplan-Meier estimates of survival-free of HF hospitalization or cardiovascular death according to the optimal cutpoints for MAGGIC risk score, H₂FPEF score, HFA-PEFF step 2 algorithm, HFA-PEFF step 3 algorithm.



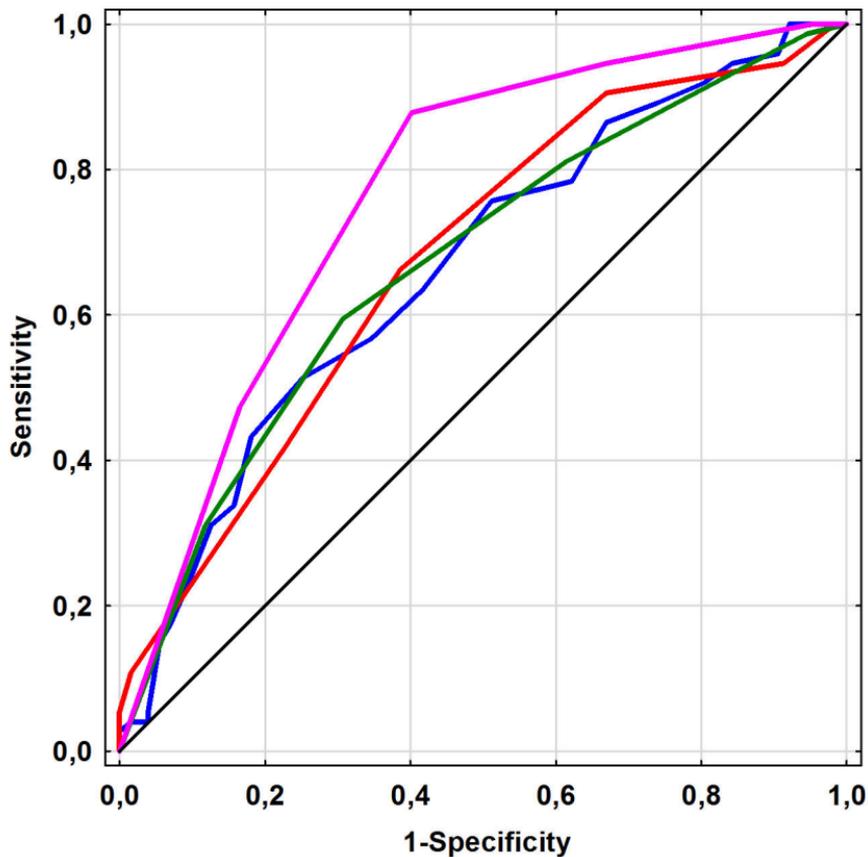
AIC

R²

C-statistic

728	723	716	724	700
0.17	0.24	0.31	0.23	0.45
0.604	0.646	0.669	0.648	0.721

P value- 3 component model (BNP + peak VO₂ + score) vs base 2-component model (BNP + peak VO₂)



— HFA-PEFF step 3 — HFA-PEFF step 2
— H₂FPEF — MAGGIC

