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EDITORIAL COMMENT

Diagnostic recommendations and phenotyping for heart failure with preserved ejection fraction: knowing more and understanding less?

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This article refers to 'Diagnostic scores predict morbidity and mortality in patients hospitalised for heart failure with preserved ejection fraction' by F.H. Verbrugge *et al.*, published in this issue on pages 954–963.

> '*Since any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding in any biological system, further modification and changes are likely to occur as knowledge advances*'.[1]

In 1982 John Goodwin was discussing hypertrophic cardiomyopathy[1] but his statement could apply even more to the ever-expanding tangle of diagnostic and prognostic criteria, classifications, scores, and phenotypes in which we are now enmeshed when considering heart failure (HF) in patients who have a normal left ventricular ejection fraction (EF).

The syndrome was known as diastolic HF[2,3] before it became HF with normal EF.[4] In 2005 the guideline task force of the European Society of Cardiology (ESC) referred to preserved left ventricular EF (PLVEF)[3] after the term had been introduced by the CHARM-Preserved clinical trialists in 2003.[5] 'Heart failure with preserved ejection fraction' (HFpEF) was then adopted by the ESC guidelines in 2008,[6] since when that label has been retained[7,8] (*Table 1*). The cut-point for a normal EF has been kept at >50% without any consensus statement having cited a normative database, and the same shortcoming has been maintained even in the most recent international consensus that proposes four stages and four types of HF.[9] Instead, the choice has been based on 'historical'[7,8] or 'traditional'[9] grounds. Unvalidated variations have also been made in consecutive recommendations for assessing diastolic function, with major impact on prevalence but without evidence of improved performance or utility.[10]

There is growing appreciation that this is not a trivial issue: imprecision of diagnostic criteria for HFpEF has contributed to the heterogeneity of patients recruited into therapeutic trials and to the preponderance of negative outcomes. Rather than reassessing the recommendations completely, however, additional criteria were added such as natriuretic peptides in 2007[4] and left ventricular volume in 2012.[7] The concept of HF with mid-range ejection fraction (HFmrEF) was introduced in 2016[8] in recognition that subjects around the arbitrary cut-point for EF were being excluded from trials, but EF is a continuously distributed variable that alone is neither sufficient to indicate cardiac output nor predictive of left ventricular filling pressures.

Diagnostic utility of the HFA-PEFF score

The most recent ESC consensus statement for diagnosing HFpEF attempted to introduce more concordance by proposing a scoring system for diastolic indices, structural changes, and biomarkers.[11] The HFA-PEFF score was developed after an extensive review of the literature but it had not been validated before publication. An alternative diagnostic score called H_2FPEF was derived from one cohort and tested in another, using a pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg during exercise as the reference; its C-statistic was 0.84.[12]

At least five studies of the diagnostic performance of the HFA-PEFF score have now been published.[13–17] Barandiarán Aizpurua *et al.*[13] reported that it can rule in HFpEF with very high specificity (93%) and positive predictive value (98%) but they determined its accuracy by evaluating patients selected by some of the same factors incorporated in the HFA-PEFF score.

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Table 1 Diagnostic criteria for heart failure with preserved ejection fraction in European Society of Cardiology guidelines

	How to diagnose diastolic HF: European Study Group on Diastolic Heart Failure (1998)[2]	Guidelines for the diagnosis and treatment of chronic HF: executive summary (update 2005)[3]	Consensus statement on the diagnosis of HFnEF by the Heart Failure and Echocardiography Associations of the ESC (2007)[4]	ESC Guidelines for the diagnosis and treatment of acute and chronic HF (2008)[6]	ESC Guidelines for the diagnosis and treatment of acute and chronic HF (2012)[7]	ESC Guidelines for the diagnosis and treatment of acute and chronic HF (2016)[8]	How to diagnose HFpEF: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the HFA of the ESC (2019)[11]
Diagnostic label	Diastolic HF	Diastolic HF	HFnEF	HFpEF	HFpEF	HFpEF	HFpEF
Clinical criteria	Signs or symptoms of congestive HF	Symptoms of HF (at rest or during exercise)	Signs or symptoms of congestive HF	Signs and/or symptoms of chronic HF	Symptoms and signs typical of HF	Symptoms ± signs	Symptoms and/or signs of HF
LVEF	>45%	≥45–50%	>50%	≥45–50%	Normal or only mildly reduced LVEF and left ventricle not dilated	≥50% (40–49% HFmrEF)	≥50%
Diastolic function	Abnormal LV relaxation, filling, diastolic distensibility or diastolic stiffness	Objective evidence of systolic and/or diastolic cardiac dysfunction at rest	Abnormal LV relaxation, diastolic distensibility, or diastolic stiffness	Objective evidence of a structural abnormality or of abnormal LV relaxation or diastolic stiffness at rest	Relevant structural heart disease (LVH/LA enlargement) and/or diastolic dysfunction	At least one additional criterion: LVH and/or LA enlargement, or diastolic dysfunction	Scoring system for major and minor criteria

ESC, European Society of Cardiology; HF, heart failure; HFA, Heart Failure Association; HFmrEF, heart failure with mid-range ejection fraction; HFnEF, heart failure with normal ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

A more realistic evaluation tested the score against invasive haemodynamic studies. Compared with HFpEF defined as a PCWP ≥15 mmHg either at rest or during exercise, the C-statistic of the HFA-PEFF score was 0.73.[14] The mean age of subjects in that study was only 59 years, and 23% of 156 individuals were misclassified. In an older cohort, 72% of 286 subjects aged >75 years with a history of hospitalisation for HF and an EF ≥50%, were classified by the HFA-PEFF score as having an intermediate probability.[15] The authors suggested that the HFA-PEFF score may identify early disease, but another possibility is that it may overdiagnose HFpEF in the elderly because the criteria in the score are not adjusted for age.

The largest reported evaluation of the diagnostic performance of the HFA-PEFF score was performed in patients and matched controls free of cardiovascular disease who had unexplained dyspnoea. They had participated in the TOPCAT and RELAX trials, in which case they were presumed to have HFpEF, or in the ARIC study, in which case they were presumed not to have HF. A low HFA-PEFF score was reported to rule out HFpEF with extremely high sensitivity (99.5%) and negative predictive value (95.7%), while a high HFA-PEFF score ruled in HFpEF with good specificity (82.8%) and positive predictive value (79.9%).[16] That evaluation, however, was also made in a group with high pre-test probability.

Other investigators have tested the HFA-PEFF score against indices of cardiac functional reserve. Faxen *et al.*[17] reported that the score was unrelated either to coronary flow reserve or to the 6-min walk test distance. They also found differences in the mean HFA-PEFF score between countries. Parcha *et al.*[16] reported that the score did not correlate with peak oxygen consumption.

Prognostic utility of the HFA-PEFF and H_2FPEF scores

Although the HFA-PEFF and H_2FPEF algorithms were both developed for primary diagnosis, at least five studies have now compared their utility instead to estimate prognosis.[16,18–21] In an elegant and very thorough retrospective cohort study, Verbrugge *et al.*[18] included 443 consecutive patients with EF ≥50% who had been hospitalised and treated with intravenous diuretics for acute HF. Patients with an identifiable specific aetiology such as ischaemia or valve disease were excluded. Their mean age was 78 years and they constituted a high-risk group since 69% died during an average follow-up of 28 months. Increasing values of each score similarly and strongly predicted increased risk of mortality. Intra-individual variations between the scores are not reported.

Sotomi *et al.*[19] reported similar performance of the HFA-PEFF score in 804 patients after 1 year while Selvaraj *et al.*[20] investigated a population with a much lower pre-test probability of HF. In 641 participants aged 67–90 years with unexplained dyspnoea, 11% were judged high-risk by the H_2FPEF score and 26% were high-risk according to the HFA-PEFF score. The overall prognostic power of each score was good, but only 27 subjects (4%) were designated to be at high risk by both scores while 28% had discordant findings.[20]

In the MEDIA study, Huttin *et al.*[21] evaluated both scores in 515 subjects with HFpEF according to the 2007 ESC consensus

Table 2 Summary of studies that have used machine learning to phenotype heart failure with preserved ejection fraction and assess prognosis

Study	Diagnostic criteria	HFpEF, *n*	M/F, %	Age, years	Machine learning method	Input variables	Pheno-groups	Prognosis mean FU, years	Independent validation, *n*
Shah 2015[23]	Hospitalisation, BNP, Framingham, diastolic dysfunction	397	38/62	65 ± 12	Hierarchical cluster analysis	46 clinical, biochemical, and echocardiographic	3	1–2	107
Kao 2015[24]	EF >45%, NYHA class ≥II, hospitalisation, BNP, Framingham, diastolic function. I-PRESERVE	4113	40/60	67 ± 11	Latent class analysis	11 = age, sex, BMI, AF, CAD, DM, lipids, valve disease, alcohol use, anaemia, eGFR	6	4.1	3203 in CHARM-Preserved
Omar 2017[25]	HF symptoms	73[a] from total 130	72/28	54 ± 16	Cluster analysis	Speckle tracking echocardiography of LV and LA	3	No	44 vs. LVEDP
Ahmad 2018[26]	Clinician-assessed HF. Swedish Heart Failure Registry	8591 from total 44 886	45/55	80 (72–85)	Random forest modelling and k-means cluster analysis	8 = age, creatinine, Hb, weight, HR, systolic BP, mean BP, and income	4	1	No
Sanchez-Martinez 2018[27]	ESC criteria 2007. MEDIA-DHF study[b]	72, plus 33 healthy	49/51	72 (68–78)	Multiple kernel learning	Echocardiographic myocardial velocity imaging at rest and during exercise	2	No	51
Tabassian 2018[28]	ESC criteria 2007. MEDIA-DHF study[b]	33, plus 67 controls	36/64	69 ± 7	Principal component analysis	Myocardial velocity and deformation imaging	2	No	No
Horiuchi 2018[29]	Hospitalisation for acute HF	97 from total 345	65/35	73 ± 14	Non-hierarchical k-means cluster analysis	77 clinical, laboratory, and echocardiographic	3	1	No
Przewlocka-Kosmala 2019[30]	ESC criteria 2007, mild diastolic dysfunction	177, plus 51 controls	27/73	63 ± 8	Hierarchical clustering	LA and RV strain, LV strain rate and E/e′ after peak exercise, HR reserve, galectin-3	2	2	No
Cohen 2020[31]	TOPCAT participants (EF ≥45%)[c]	3445	48/52	69 ± 10	Latent class analysis	8 = age, sex, race, BMI, diabetes, AF, NYHA class, and CKD	3	<5	No
Flint 2020[32]	TOPCAT participants in Americas[c]	1767	50/50	71 ± 10	Latent class analysis	11 clinical variables (same as Kao 2015)	6	2	No

Table 2 (Continued)

Study	Diagnostic criteria	HFpEF, *n*	M/F, %	Age, years	Machine learning method	Input variables	Pheno-groups	Prognosis mean FU, years	Independent validation, *n*
Segar 2020[33]	TOPCAT participants in Americas[c]	654 from total 1767	52/48	71 ± 10	Penalized finite mixture model-based clustering	61 clinical, biochemical, and echocardiographic	3	3.3	198 in RELAX
Chirinos 2020[34]	TOPCAT participants (EF ≥45%)[c]	379 from 3445	54 /46	70 (62–77)	Tree-based pipeline optimizer	49 plasma biomarkers	6	2.9	156 in PHFS
Hedman 2020[35]	Hospitalisation, EF >45%, and elevated BNP. KaRen Study[d]	320 from total 539	44/56	78 (71–83)	Model-based clustering	11 clinical or laboratory variables and 32 echocardiographic variables	6	2.7	No
Schrub 2020[36]	Same as Hedman 2020. KaRen Study[d]	356 from total 539	44/56	76 ± 9	Hierarchical cluster analysis	55 clinical and echocardiographic variables	3	2.3	No
Sabbah 2020[37]	Diuretic treatment, high LVFP, BNP. RELAX, NEAT, INDIE	301	47/53	69 (62–76)	Hierarchical clustering	13 inflammatory biomarkers	3	No	No
Stienen 2020[38]	ESC criteria 2007. MEDIA-DHF study	392	36/64	74 (68–80)	k-means cluster analysis	415 biomarkers	2	1	No
Gu 2021[39]	ESC criteria 2016	970	58/42	70 ± 7	Model-based clustering	11 = age, sex, BMI, AF, hypertension, CAD, DM, eGFR, Hb, E/e′ and BNP	3	5	290
Hahn 2021[40]	ESC criteria 2016 and ESC criteria 2019	41, plus 30 HFrEF and 24 controls	41/59	62 (53–69)	Principal component analysis and hierarchical clustering	5745 genes uniquely altered between HF groups by RNA sequencing of RV septal biopsies	3	1	No

Trial and study acronyms are explained in the cited publications. No = not done (or not reported). Age is given as mean ± standard deviation, or median (interquartile range).
AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; F, female; FU, follow-up; Hb, haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LA, left atrium; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; LVFP, left ventricular filling pressure; M, male; NYHA, New York Heart Association functional class; RNA, ribonucleic acid; RV, right ventricle.
[a]The cluster with highest mean EF had the lowest mean E/e′ and mean LA volume, so some patients although mildly symptomatic may not have had HF.
[b]Both reports from the MEDIA-DHF Exercise study: one unsupervised, and one supervised.
[c]Several reports used data from the TOPCAT study since they can be available to investigators on application.
[d]Both reports from the KaRen Study, with different input variables.

Table 3 Summary of features reported to discriminate between heart failure with preserved ejection fraction phenogroups

	MAGGIC[22]	Shah[23]	Kao[24]	Omar[25]	Ahmad[26]	Sanchez-Martinez[27]	Tabassian[28]	Horiuchi[29]	Przewlocka-Kosmala[30]	Cohen[31]	Flint[32]	Segar[33]	Chirinos[34]	Hedman[35]	Schrub[36]	Sabbah[37]	Stienen[38]	Gu[39]	Hahn[40]
Demographic variables																			
Age	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Gender	x		x		x			x		x	x			x	x	x		x	x
Racial/ethnic group										x	x								
Clinical history and examination																			
Body mass index	x	x	x		x	x	x			x	x	x		x	x	x		x	x
Heart rate		x						x		x				x					
Blood pressure/ hypertension	x	x		x	x			x		x	x	x		x	x				x
Smoking history	x				x					x	x		x						
Ischaemic heart disease					x						x	x		x				x	
NYHA class/severity of symptoms	x			x	x				x	x	x	x	x				x	x	x
Duration of HF/hospitalisations	x							x					x			x	x		x
Oedema								x		x						x			
Chronic obstructive pulmonary disease	x				x					x				x					
Diabetes mellitus/metabolic syndrome	x	x	x		x			x		x	x	x	x	x	x		x	x	x
Atrial fibrillation		x	x		x			x		x	x			x	x		x	x	
History of stroke or TIA					x			x		x									
Peripheral arterial function/disease					x					x		x					x		
Heart valve disease			x		x						x	x			x				
Alcohol use					x						x								
ECG characteristics, e.g. QRS width/QTc		x										x		x					
Laboratory tests																			
Hyperlipidaemia			x								x						x	x	
Haemoglobin/anaemia		x	x		x			x			x	x	x	x		x	x	x	
Renal function/creatinine/eGFR	x	x	x		x			x		x	x	x	x	x	x	x	x	x	x
Drug treatment																			
Beta-blocker	x	x			x					x	x						x		
ACEi/ARB	x	x			x					x	x							x	
Loop diuretic		x			x			x			x	x				x	x		
Aldosterone antagonist								x											x
Statin		x										x							x
Warfarin/anticoagulants												x					x		
Cardiac imaging and function																			
LV ejection fraction	x			x				x				x							
Increase in EF after exercise									x										
LV volumes/dimensions														x					x
LV mass index/LV hypertrophy		x				x				x		x		x	x			x	x
LV untwisting rate									x										
Isovolumic relaxation time														x					

Table 3 (Continued)

	MAGGIC[22]	Shah[23]	Kao[24]	Omar[25]	Ahmad[26]	Sanchez-Martinez[27]	Tabassian[28]	Horiuchi[29]	Przewlocka-Kosmala[30]	Cohen[31]	Flint[32]	Segar[33]	Chirinos[34]	Hedman[35]	Schrub[36]	Sabbah[37]	Stienen[38]	Gu[39]	Hahn[40]
Mitral E velocity		×		×				×											
Mitral E deceleration time				×				×						×					
Mitral E/A ratio												×			×		×		
Mitral annular e′ velocity		×		×				×	×					×			×		
Increase in e′ after exercise						×	×		×										
E/e′ ratio at rest		×		×		×	×		×			×		×				×	
E/e′ ratio during or after exercise							×		×										
Left atrial area or volume index		×		×				×		×		×		×	×	×			
Left atrial strain									×										
RV function/tricuspid annular excursion		×												×	×		×		
Tricuspid regurgitation peak velocity/PH								×				×					×		
LV global longitudinal strain rate							×		×						×				
Longitudinal systolic reserve							×												
Chronotropic reserve							×		×										
Peak oxygen consumption									×							×			
6-min walk distance						×	×									×			
Exercise increase in cardiac output									×										
Arterial stiffness/VA coupling									×	×									
Biomarkers/proteomics																			
Natriuretic peptides		×	×		×	×		×				×				×		×	×
Fibrosis/tissue remodelling									×				×			×			×
Inflammatory mediators										×			×			×			×
Immune biomarkers and pathways										×							×		×
Signal transduction and cell interactions																	×		
Regulators of mineral metabolism													×						
Vascular calcification										×									
Myocardial injury													×						
Renin										×									

This table attempts to indicate input features that were identified by machine learning to discriminate between clusters, and also variables that were then found to vary significantly between the identified clusters. Features have been included if $P < 0.05$, even if the absolute variations were small. When a study was not restricted to subjects with HFpEF, then characteristics have been included for the phenogroup reported to have the highest proportion of HFpEF patients. All information has been retrieved from the cited publications and their supplements, and cross-checked to minimise errors or inaccuracies. Invasive haemodynamic variables, some variables that were identified by only one study, and variables that differed only from controls, have not been included. Genotypic variations investigated and reported by a single study[40] have also been omitted. For comparison, criteria from the MAGGIC score are shown in the first column.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association; PH, pulmonary hypertension; RV, right ventricular; TIA, transient ischaemic attack; VA, ventriculo-arterial.

criteria (*Table 1*). They proposed a new MEDIA echo score incorporating four simple echocardiographic measurements, which together with clinical variables and natriuretic peptides had good predictive power for mortality and recurrent hospitalisation at 1 year, both in the derivation cohort (C-statistic 0.78) and when retested in the KaRen study (C-statistic 0.69). Adding the MEDIA score increased the C-statistics of both the HFA-PEFF and H_2FPEF scores in the same group by 0.09 and 0.12 respectively.

Before implementing these new algorithms widely, it is salutary to note that the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score, using clinical variables and including EF as the only imaging parameter, has similar prognostic value in HFpEF. In 407 patients who had required diuretics during an acute admission with a clinical diagnosis of HF confirmed by Framingham criteria, and who had a normal EF and raised brain natriuretic peptide, the MAGGIC score predicted outcomes at a mean follow-up of 3.6 years with C-statistics of 0.74 for mortality and 0.66 for recurrent cardiovascular hospitalisation.[22]

The HFA-PEFF and H_2FPEF algorithms may diagnose different types of patients[20] yet fortuitously have similar predictive power. The H_2FPEF score is weighted towards atrial fibrillation, observed in 34% of its derivation cohort, whereas the HFA-PEFF score includes measurements of left ventricular long-axis function and natriuretic peptides. Unsurprisingly, both perform less well in people with low or intermediate likelihood of HFpEF – when they would be most useful. There is little need for a score that identifies patients in whom a diagnosis of HF can be made by simpler criteria, or for a score that predicts outcomes without indicating how they might be changed. And of course, performance as a prognostic score does not prove causality.

Phenotyping by artificial intelligence

The optimal diagnostic and prognostic criteria for HF may differ and vary by aetiology, whether the HF is acute or chronic, and whether the EF is normal or reduced. Trying to lump together all patients with the syndrome of HFpEF according to a single diagnostic algorithm has not been conspicuously successful in identifying effective treatments, so it is illogical to refine diagnostic criteria without evidence that their application leads to better outcomes.

An alternative approach that has become extremely popular is to use machine learning to explore specific phenotypes of HFpEF and diastolic function, in the hope of uncovering causative mechanisms of disease for which targeted treatment can be developed – but so far, the trend may be adding to our confusion rather than resolving it. We have identified at least 14 reports of machine learning used to investigate patients with HFpEF.[23–40] They show

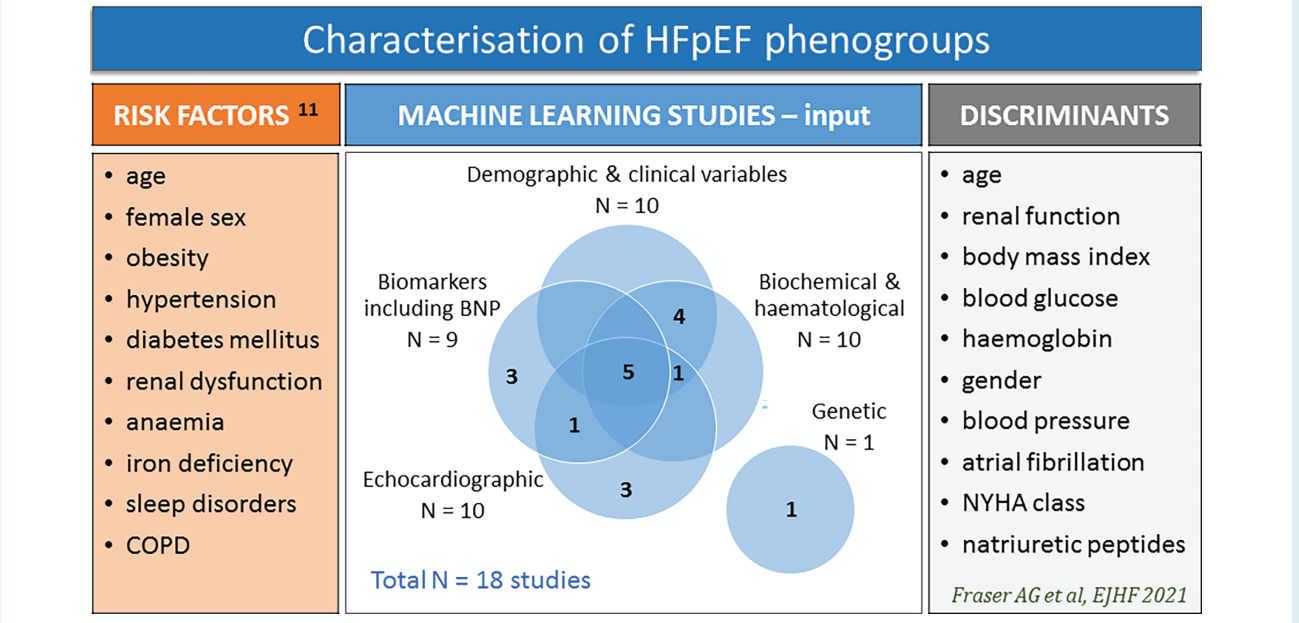

Figure 1 Known risk factors for heart failure with preserved ejection fraction (HFpEF) are listed in the box on the left, in their order in the European Society of Cardiology consensus recommendations.[11] The Venn diagram in the middle box shows which broad types of variables were used as input to the machine learning studies[23–40] that are summarised in *Table 3*. The numbers refer to studies (from a maximum of 18) that assessed each combination of factors. Variables that were found to discriminate between phenogroups of HFpEF are listed in the box on the right, in order of their prevalence; the list includes all those that were reported by 50% or more of the studies. The commonest imaging variables (not shown) were left ventricular hypertrophy, the E/e' index, and left atrial volume, all reported by 44% of studies. Thus in general, the machine learning studies have confirmed known risk factors. BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

considerable diversity of design and inclusion criteria and more variability of input data, as summarised in *Table 2*. Three studies that applied the modelling technique of latent class analysis for a similar objective are also listed.[24,31,32] Most studies had no control groups and only two included data collected during[27,28] or immediately after exercise.[30] None integrated data from all potential sources including demographic and clinical variables, biomarkers and proteomics, structural and functional imaging at rest and during exercise, and genomics, in a population at risk. A minority of studies retested their findings in an independent population.

Different studies have identified between two and six phenogroups of HFpEF. Many relate to known risk factors and elements of HFpEF pathophysiology (*Table 3* and *Figure 1*), while some give new insights. Most studies have identified phenotypes that predict varying outcomes. A few provide the first hints that this approach might identify phenogroups with differential responses to drugs. For example, TOPCAT participants with low H_2FPEF scores (≤6) were more likely to benefit from spironolactone (hazard ratio 0.47),[41] while subjects in phenogroup 3 from a study in China, who had a high prevalence of ischaemic heart disease and type 2 diabetes, had a lower mortality and fewer hospitalisations if they were taking a beta-blocker or angiotensin-converting enzyme inhibitor (absolute risk reductions >10% at 5 years).[39]

Building a bridge to understanding

Diagnostic standards are indeed important, since using dissimilar criteria to select patients for clinical trials has a major impact.[42] Knowledge of HFpEF is advancing but we need concerted actions to improve our understanding and develop new treatments. Unfortunately, none of the consensus recommendations has really been based on a prospective evaluation and evidence of beneficial impact, whether for diagnosis, prognosis, or choice of treatment.

Clinical trialists need to bypass too simple diagnostic recommendations and embrace more detailed characterisation of subjects as they are recruited for new studies. Some less common phenotypes such as amyloidosis and haemochromatosis are rather monofactorial and already amenable to specific treatments. For more complex phenotypes, we should reconsider predefined and often composite endpoints as the only outcomes that can be accepted. What about a really large 'allcomers' HF randomised controlled trial, with fully characterised subjects selected not by EF but because of dyspnoea and reduced exercise capacity, or other independent criteria, and with an adaptive design? Then our diagnostic guidelines and our prognostic scores for HFpEF really would be useful.

Conflict of interest: none declared.

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