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

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In 1982 John Goodwin was discussing hypertrophiccardiomyopathy1but 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 HF2,3before it became HF with normal EF.4In 2005 the guideline task force of the European Society of Cardiology (ESC) referred to preserved left ventricular EF (PLVEF)3after 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 2008,6since when that label has beenretained7,8(Table1). 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.9Instead, the choice has been based on 'historical'7,8or 'traditional'9grounds. 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 20074and left ventricular volume in 2012.7The concept of HF with mid-range ejection fraction (HFmrEF) was introduced in 20168in 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 scoreThe 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.11The 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 H2FPEF 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 0.84.12At least five studies of the diagnostic performance of the HFA-PEFF score have now been published.13–17Barandiarán Aizpurua et al.13reported 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 f actors incorporated in the HFA-PEFF score.

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 0.73.14The mean age of subjects in that study was only 59 years, and 23% of156 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.15The authors suggested that the HFA-PEFF score may identify early disease, but another possibility is that it may over diagnose HFpEF in the elderly because the criteria in the score are not adjusted forage. 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%).16That 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.17reported that the score was unrelated either to coronary flow reserve or to the6-min walk test distance. They also found differences in the mean HFA-PEFF score between countries. Parcha et al.16reported that the score did not correlate with peak oxygen consumption.

Prognostic utility of the HFA-PEFF and H2FPEF scores

Although the HFA-PEFF and H2FPEF algorithms were both developed for primary diagnosis, at least five studies have now compared their utility instead to estimate prognosis.16,18–21In an elegant and very thorough retrospective cohort study, Verbrugge et al.18included 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.19reported similar performance of the HFA-PEFF score in 804 patients after1year while Selvarajet al.20investigateda population with a much lower pre-test probability of HF. In 641participants aged 67–90 years with unexplained dyspnoea,11%were judged high-risk by the H2FPEF 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.

In the MEDIA study, Huttin et al.21evaluated both scores in515 subjects with HFpEF according to the 2007 ESC consensus criteria (Table1). 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 at1year, both in the derivation cohort (C-statistic0.78) 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 H2FPEF 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. In407 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,t he 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.22The HFA-PEFF and H2FPEF algorithms may diagnose different types of patients20yet fortuitously have similar predictive power. The H2FPEF 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 least14 reports of machine learning used to investigate patients with HFpEF.23–40 They show 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.24,31,32Most studies had no control groups and only two included data collected during27,28or 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 3andFigure1), 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 H2FPEFscores (≤6) were more likely to benefit from spironolactone(hazard ratio 0.47),41while 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.42Knowledge of HFpEF is advancing but we need concerted action stop 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 mono factorial and already amenable to specific treatments. For more complex phenotypes, we should reconsider predefined and often composite end points 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.

References

1. Goodwin JF. The frontiers of cardiomyopathy.Br Heart J1982;48:1–18.

2. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J1998;19:990–1003.

3. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon JL, Nieminen MS, Piérard L, Remme WJ; Task Force for the diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic hear failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. EurHeart J2005;26:1115–1140.

4. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I,Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J2007;28:2539–2550.

5. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme.Lancet2003;362:759–766.

6. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine(ESICM).Eur Heart J2008;29:2388–2442.

7. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH,Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure2012 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart failure association (HFA)of the ESC. Eur J Heart Fail2012;14:803–869.

8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoy-annopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group.

2016ESCGuidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail2016;18:891–975.

9. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Felker GM, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CS, Matsue Y, Metra M, Ohtani T, Piepoli MF, Ponikowski P, Rosano GM, Sakata Y, Seferoví c P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail2021;23:352–380.

10. Fraser AG, Girerd N. Cardiovascular imaging “guidelines” – high time for aparadigm shift. Int J Cardiol2021;329:246–248.

11. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F,Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E,Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J2019;40:3297–3317.

12. Reddy YN, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserve dejection fraction.Circulation2018;138:861–870.

13. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VP. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. Eur J HeartFail2020;22:413–421.

14. Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, Farrell R, Shoenike MW, Sbarbaro J, Malhotra R, Nayor M, Tschöpe C, de Boer RA, Lewis GD, Ho JE. Evaluation of 2 existing diagnostic scores for heart failure with preserved ejection fraction against a comprehensively phenotyped cohort.Circulation2021;143:289–291.

15. Seo Y, Ishizu T, Ieda M, Ohte N; J-LONG Study Investigators. Clinical usefulness of the HFA-PEFF diagnostic scoring system in identifying late elderly heart failure with preserved ejection fraction patients. Circ J2021;85:604–611.

16. Parcha V, Malla G, Kalra R, Patel N, Sanders-van Wijk S, Pandey A, Shah SJ,Arora G, Arora P. Diagnostic and prognostic implications of heart failure with preserved ejection fraction scoring systems. ESC Heart Fail2021;8:2089–2102.

17. Faxen UL, Venkateshvaran A, Shah SJ, Lam CS, Svedlund S, Saraste A, Beussink-Nelson L, Lagerstrom Fermer M, Gan LM, Hage C, Lund LH. Generalizability of HFA-PEFF and H2FPEF diagnostic algorithms and associations with heart failure indices and proteomic biomarkers: insights from PROMIS-HFpEF. J Card Fail2021Feb 26.

https://doi.org/10.1016/j.cardfail.2021.02.005 [Epubahead of print].

18. Verbrugge FH, Reddy YN, Sorimachi H, Omote K, Carter RE, Borlaug BA.Diagnostic scores predict morbidity and mortality in patients hospitalised for heart failure with preserved ejection fraction. Eur J Heart Fail2021;23:954–963.

19. Sotomi Y, Iwakura K, Hikoso S, Inoue K, Onishi T, Okada M, Fujii K, Okamura A, Tamaki S, Yano M, Hayashi T, Nakagawa A, Nakagawa Y, Nakatani D, Yasumura Y, Yamada T, Sakata Y; OCVC-Heart Failure Investigators. Prognostic significance of the HFA-PEFF score in patients with heart failure with preserved ejection fraction. ESC Heart Fail2021;8:2154–2164.

20. Selvaraj S, Myhre PL, Vaduganathan M, Claggett BL, Matsushita K, Kitzman DW, Borlaug BA, Shah AM, Solomon SD. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. JACC Heart Fail2020;8:640–653.

21. Huttin O, Fraser AG, Lund LH, Donal E, Linde C, Kobayashi M, Erdei T, Machu JL, Duarte K, Rossignol P, Paulus W, Zannad F, Girerd N; MEDIA and KaRen Investigators. Risk stratification with echocardiographic bio-markers in heart failure with preserved ejection fraction: the MEDIA Echoscore. ESC Heart Fail2021;8:1827–1839.

22. Rich JD, Burns J, Freed BH, Maurer MS, Burkhoff D, Shah SJ. Meta-Analysis Global Group in Chronic (MAGGIC) heart failure risk score: validation of a simple tool for the prediction of morbidity and mortality in heart failure with preserve dejection fraction .J Am Heart Assoc2018;7:e009594.

23. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction.Circulation2015;131:269–279.24. Kao DP, Lewsey JD, Anand IS, Massie BM, Zile MR, Carson PE, McKelvie RS, Komajda M, McMurray JJ, Lindenfeld J. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response . Eur J Heart Fail2015;17:925–935.

25. Omar AMS, Narula S, Abdel Rahman MA, Pedrizzetti G, Raslan H, Rifaie O,N arula J, Sengupta PP. Precision phenotyping in heart failure and pattern clustering of ultrasound data for the assessment of diastolic dysfunction. JACC CardiovascImaging2017;10:1291–1303.

26. Ahmad T, Lund LH, Rao P, Ghosh R, Warier P, Vaccaro B, Dahlström U, O'Connor CM, Felker GM, Desai NR. Machine learning methods improve prognostication, identify clinically distinct phenotypes, and detect heterogeneity in response to therapy in a large cohort of heart failure patients. J Am Heart Assoc2018;7:e008081.

27. Sanchez-Martinez S, Duchateau N, Erdei T, Kunszt G, Aakhus S, Degiovanni A, Marino P, Carluccio E, Piella G, Fraser AG, Bijnens BH. Machine learning analysis of left ventricular function to characterize heart failure with preserved ejection fraction. Circ Cardiovasc Imaging2018;11:e007138.

28. Tabassian M, Sunderji I, Erdei T, Sanchez-Martinez S, Degiovanni A, Marino P, Fraser AG, D'hooge J. Diagnosis of heart failure with preserved ejection fraction: machine learning of spatiotemporal variations in left ventricular deformation. J Am Soc Echocardiogr2018;31:1272–1284.e9

29. Horiuchi Y, Tanimoto S, Latif AH, Urayama KY, Aoki J, Yahagi K, Okuno T, Sato Y, Tanaka T, Koseki K, Komiyama K, Nakajima H, Hara K, Tanabe K. Identifying novel phenotypes of acute heart failure using cluster analysis of clinical variables. Int J Cardiol2018;262:57–63.

30. Przewlocka-Kosmala M, Marwick TH, Dabrowski A, Kosmala W. Contribution of cardiovascular reserve to prognostic categories of heart failure with preserve dejection fraction: a classification based on machine learning. J Am Soc Echocardiogr2019;32:604–615.e6.

31. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, Yarde M, Wang Z, Bhattacharya PT, Chirinos DA, Prenner S, Zamani P, Seiffert DA, Car BD, Gordon DA, Margulies K, Cappola T, Chirinos JA. Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone. JACC Heart Fail2020;8:172–184.

32. Flint KM, Shah SJ, Lewis EF, Kao DP. Variation in clinical and patient-reported out-comes among complex heart failure with preserved ejection fraction phenotypes .ESC Heart Fail2020;7:811–824.

33. Segar MW, Patel KV, Ayers C, Basit M, Tang WHW, Willett D, Berry J, Grodin JL, Pandey A. Pheno mapping of patients with heart failure with preserved ejection fraction using machine learning-based unsupervised cluster analysis. Eur J HeartFail2020;22:148–158.

34. Chirinos JA, Orlenko A, Zhao L, Basso MD, Cvijic ME, Li Z, Spires TE, Yarde M, Wang Z, Seiffert DA, Prenner S, Zamani P, Bhattacharya P, Kumar A, Margulies KB, Car BD, Gordon DA, Moore JH, Cappola TP. Multiple plasma biomarkers for risk stratification in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol2020;75:1281–1295.

35. Hedman ÅK, Hage C, Sharma A, Brosnan MJ, Buckbinder L, Gan LM, Shah SJ, Linde CM, Donal E, Daubert JC, Mälarstig A, Ziemek D, Lund L. Identification of novel pheno-groups in heart failure with preserved ejection fraction using machine learning.Heart2020;106:342–349.

36. Schrub F, Oger E, Bidaut A, Hage C, Charton M, Daubert JC, Leclercq C, Linde C, Lund L, Donal E. Heart failure with preserved ejection fraction: a clustering approach to a heterogenous syndrome. Arch Cardiovasc Dis2020;113:381–390.

37. Sabbah MS, Fayyaz AU, de Denus S, Felker GM, Borlaug BA, Dasari S, Carter RE, Redfield MM. Obese-inflammatory phenotypes in heart failure with preserve dejection fraction. Circ Heart Fail2020;13:e006414.

38. Stienen S, Ferreira JP, Kobayashi M, Preud'homme G, Dobre D, Machu JL, Duarte K, Bresso E, Devignes MD, López N, Girerd N, Aakhus S, Ambrosio G, Brunner-La Rocca HP, Fontes-Carvalho R, Fraser AG, van Heerebeek L, DeKeu-lenaer G, Marino P, McDonald K, Mebazaa A, Papp Z, Raddino R, Tschöpe C,Paulus WJ, Zannad F, Rossignol P. Enhanced clinical phenotyping by mechanistic bioprofiling in heart failure with preserved ejection fraction: insights from the MEDIA-DHF study (the Metabolic Road to Diastolic Heart Failure).Biomarkers2020;25:201–211.

39. Gu J, Pan JA, Lin H, Zhang JF, Wang CQ. Characteristics, prognosis and treatment response in distinct phenogroups of heart failure with preserved ejection fraction. Int J Cardiol2021;323:148–154.

40. Hahn VS, Knutsdottir H, Luo X, Bedi K, Margulies KB, Haldar SM, Stolina M, Yin J, Khakoo AY, Vaishnav J, Bader JS, Kass DA, Sharma K. Myocardial gene expression signatures in human heart failure with preserved ejection fraction.Circulation2021;143:120–134.

41. Segar MW, Patel KV, Berry JD, Grodin JL, Pandey A. Generalizability and implications of the H2FPEF score in a cohort of patients with heart failure with preserved ejection fraction: insights from the TOPCAT trial.Circulation2019;139:1851–1853.

42. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions.Circulation2019;140:353–365.

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.

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[33]	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[34]	Clinician-assessed HF, Swedish Heart Failure Registry	8591 from total 44886	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, MESA-CHF 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, MESA-CHF study[b]	33, plus 67 controls	36/64	69 ± 7	Principal component analysis	Myocardial velocity and deformation imaging	2	No	No
Horiuchi 2019[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[15]	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[a]	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%)[a]	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[c]	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[c]	356 from total 539	44/56	76 ± 9	Hierarchical cluster analysis	55 clinical and echocardiographic variables	3	2.3	No
Sobbah 2020[37]	Diuretic treatment, high LVFR, 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; LVFR, 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, as 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	Shah	Kao	Omar	Ahmad	Sanchez-Martinez	Tabassian	Horiuchi	Przewlocka-Kosmala	Cohen	Flint	Segar	Chirinos	Hedman	Schrub	Sabbah	Stienen	Gu	Hahn
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, eg, 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 E/e' 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	Shah	Kao	Omar	Ahmad	Sanchez-Martinez	Tabassian	Horiuchi	Przewlocka-Kosmala	Cohen	Flint	Segar	Chirinos	Hedman	Schrub	Sabbah	Stienen	Gu	Hahn
Mitral E velocity		x		x				x											
Mitral E deceleration time				x				x						x					
Mitral E/A ratio												x			x		x		
Mitral annular e' velocity		x		x				x	x					x			x		
Increase in e' after exercise						x	x		x										
E/e' ratio at rest		x		x		x	x		x			x		x				x	
E/e' ratio during or after exercise							x		x										
Left atrial area or volume index		x		x				x		x		x		x	x	x			
Left atrial strain									x										
RV function/tricuspid annular excursion		x												x	x		x		
Tricuspid regurgitation peak velocity/PH								x				x					x		
LV global longitudinal strain rate							x		x						x				
Longitudinal systolic reserve							x												
Chronotropic reserve							x		x										
Peak oxygen consumption									x							x			
6-min walk distance						x	x									x			
Exercise increase in cardiac output									x										
Arterial stiffness/VA coupling									x	x									
Biomarkers/proteomics																			
Natriuretic peptides		x	x		x	x		x				x				x		x	x
Fibrosis/tissue remodelling									x				x			x			x
Inflammatory mediators										x			x			x			x
Immune biomarkers and pathways										x							x		x
Signal transduction and cell interactions																	x		
Regulators of mineral metabolism													x						
Vascular calcification										x									
Myocardial injury													x						
Renin										x									

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 have also been omitted. For comparison, criteria from the MAGGIC score are shown in the first column.

ACE, 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.

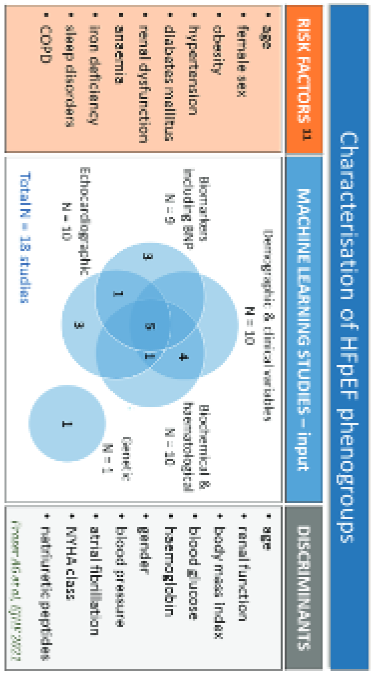
Characterisation of HFpEF phenogroups
RISK FACTORS 11
MACHINE LEARNING STUDIES – input
DISCRIMINANTS
• age
• female sex
• obesity
• hypertension
• diabetes mellitus
• renal dysfunction
• anaemia
• iron deficiency
• sleep disorders
• COPD
Demographic & clinical variables
N = 10
Biomarkers including BNP
N = 9
Biochemical & haematological
N = 10
Genetic
N = 1
Echocardiographic
N = 10
3
4
5
1
1
3
1
Total N = 18 studies
• age
• renal function
• body mass index
• blood glucose
• haemoglobin
• gender
• blood pressure
• atrial fibrillation
• NYHA class
• natriuretic peptides
Fraser AG et al, EJHF 2021

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[21–40] that are summarized 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.