Five things to know about diagnosis of HFpEF

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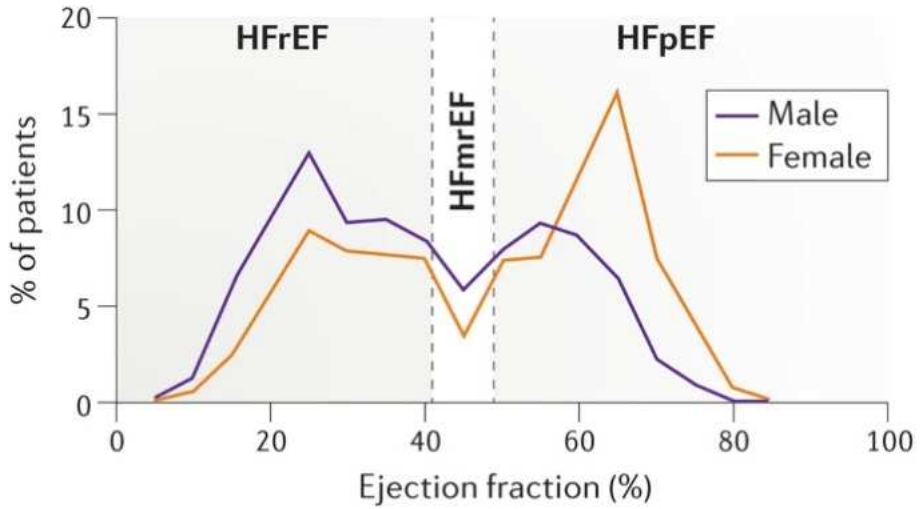
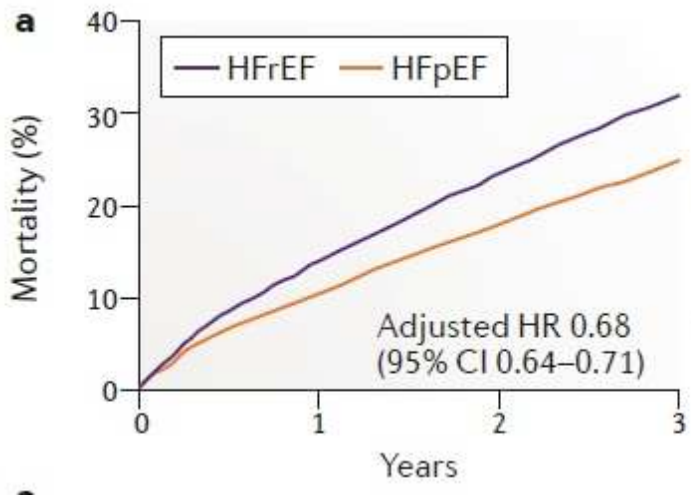
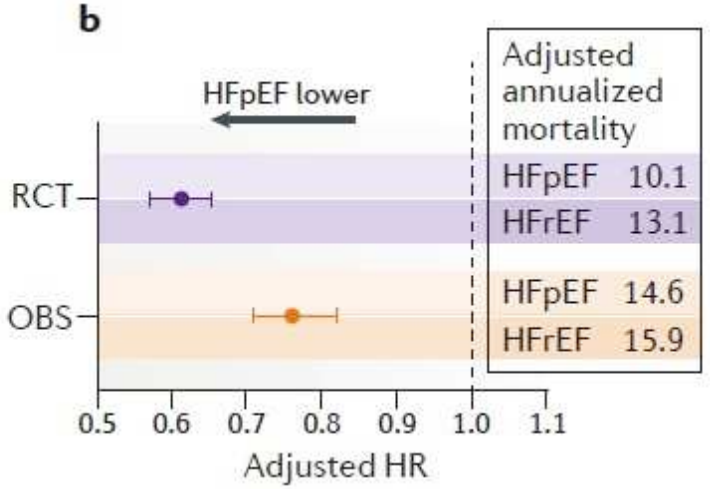
- **Speaker fees**: Roche, Servier, Medtronic







Nature Reviews | Cardiology

Study	Years	Population source	EF definition of HFpEF (%)	Proportion of HF with HFpEF (%)
Redfield *et al.*[21]	1997–2000	Olmsted County, Minnesota, USA	≥50	44 (20/45)
Bursi *et al.*[26]	2003–2005	Olmsted County, Minnesota, USA	≥50	55 (308/556)
Gerber *et al.*[41]	2000–2010	Olmsted County, Minnesota, USA	≥50	52.5* (1,089/2,074)
Lee *et al.*[48]	1981–2004	Framingham Heart Study	>45	41 (220/534)
Ho *et al.*[46]	1981–2008	Framingham Heart Study	>45	43* (196/457)
Ho *et al.*[43]	1979–2002	Pooled from three cohorts‡	>45	48* (795/1,666)
Bhatia *et al.*[40]	1999–2001	Ontario, Canada	>50	31 (880/2,802)
Devereaux *et al.*[44]	1993–1995	Strong Heart Study	≥55	53 (50/95)
Gottdiener *et al.*[32]	1989–1993	Cardiovascular Health Study	≥55	22.3 (60/269)
Philbin *et al.*[33]	1995 & 1997	Community hospital registry	>50	24 (312/1,291)
Brouwers *et al.*[31]	1997–2010	PREVEND study	≥50	34* (125/374)
Gurwitz *et al.*[36]	2005–2008	Cardiovascular Research Network	≥50	52* (6,210/11,994)
Gustaffson *et al.*[37]	1993–1996	Denmark registry	Based on WMI	40 (2,218/5,491)
MacCarthy *et al.*[39]	1993–1995	UK-HEART study	≥50	31 (163/522)
Lenzen *et al.*[38]	2000–2001	Euro HF Survey	≥40	46 (3,148/6,806)
Yancy *et al.*[35]	2001–2004	ADHERE hospitalization database	≥40	50.4 (26,322/52,187)
Owan *et al.*[34]	1987–2001	Hospitalized at Mayo Clinic, Minnesota, USA	≥50	47.1 (2,167/4,596)

"If HFpEF is that difficult to diagnose.. …it does not exist!"

Paulus. Circ 2018;138:871
Dunlay et al. Nat Rev Cardiol 2017;14:591

Box 2 | **Criteria for the diagnosis of heart failure**

Framingham criteria[22]

- Major criteria
  - Paroxysmal nocturnal dyspnoea
  - Orthopnoea
  - Elevated jugular venous pressure
  - Rales
  - Third heart sound
  - Cardiomegaly (chest radiograph)
  - Pulmonary oedema (chest radiograph)
- Minor criteria
  - Extremity oedema
  - Night cough
  - Loss of >4.5 kg in 5 days with diuretics
  - Hepatomegaly
  - Pleural effusion
  - Heart rate >120 bpm
  - Exertional dyspnoea

Diagnosis of heart failure requires two major, or one major and two minor criteria.

Boston criteria[24,110]

- History
  - Dyspnoea: none (0 points), leg fatigue on walking level (1 point), dyspnoea on walking level (2 points), paroxysmal nocturnal dyspnoea (3 points), orthopnoea (4 points), dyspnoea at rest (4 points)
- Physical findings
  - Heart rate <90 bpm (0 points), 91–110 bpm (1 point), >110 bpm (2 points)
  - Jugular venous pressure: <6 mmHg (0 points), >6 mmHg (2 points), >6 mmHg and liver enlarged or pitting oedema (3 points)
  - Pulmonary rales: none (0 points), at bases only (1 point), more than at bases (2 points)
  - Wheezes: no (0 points), yes (3 points)
  - S3 gallop: no (0 points), yes (3 points)
- Chest radiography findings
  - Normal (0 points), upper flow redistribution (2 points), cardiac enlargement (3 points), interstitial oedema (3 points), bilateral pleural effusions (3 points), alveolar oedema (4 points)

Heart failure is considered definite (8–12 points), possible (5–7 points), or unlikely (<5 points).

Gothenburg criteria[23,110]

- Cardiac score
  - Coronary heart disease in past (1 point), within past year (2 points); angina in past (1 point), angina in past year (2 points); leg oedema (1 point); pulmonary rales (1 point); atrial fibrillation (1 point)
- Pulmonary disease score
  - History of bronchitis (1 point), chronic bronchitis in past year (2 points); asthma (1 point), asthma in past year (2 points); coughing, phlegm, or wheezing (1 point); rhonchi at physical exam (1 point)
- Therapy score
  - History of digoxin (1 point) or diuretic (1 point) use

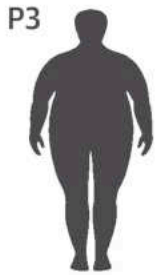
Heart failure graded as 0 (absent) if all three scores are 0; grade 1 (latent) if cardiac score >0 and pulmonary and therapy score = 0; grade 2 (manifest) if cardiac score >0 and either pulmonary or therapy score >0; grade 3 if cardiac score >0 and both pulmonary and therapy scores >0; and grade 4 if person died in heart failure.

Dunlay et al. Nat Rev Cardiol 2017;14:591

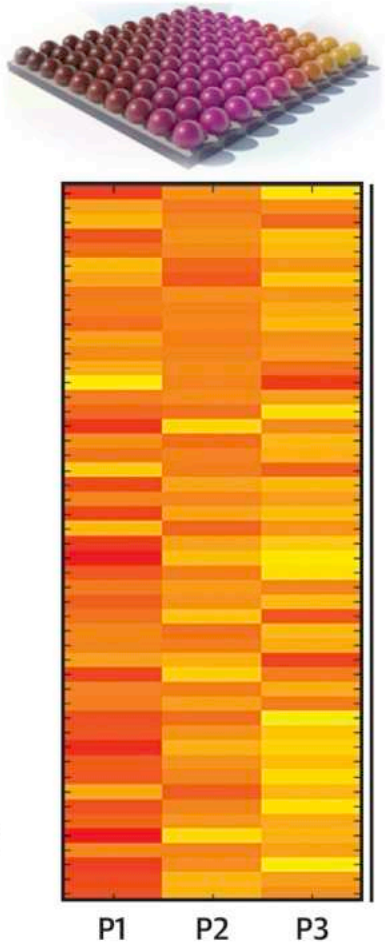
CENTRAL ILLUSTRATION: Clinical Phenogroups in HFpEF

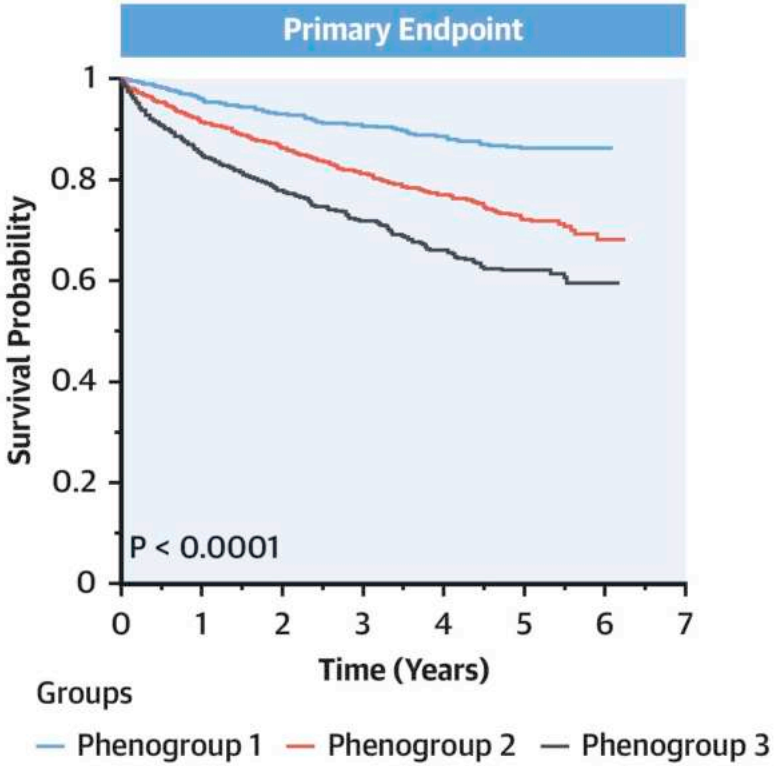
- Normal LV geometry
- Low arterial stiffness
- Low natriuretic peptides
- Markers of COPD (not genuine HFpEF?)
- Low event rate
- Preferentially enrolled in Russia/Georgia

- Concentric remodeling
- Very stiff arteries
- LA enlargement and AF
- High natriuretic peptides
- Innate immunity activation
- High risk of primary endpoint



- Obesity/Diabetes
- Inflammation (TNF-α)
- Abnormal metabolism, liver and renal injury/dysfunction
- High renin
- Highest risk of primary endpoint
- Preferential response to spironolactone



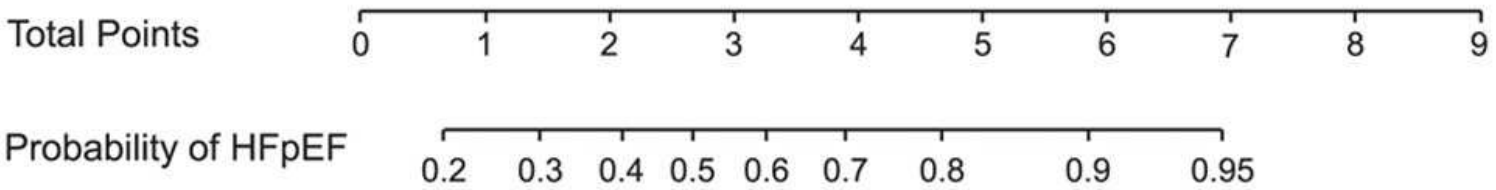


Cohen, J.B. et al. J Am Coll Cardiol HF. 2020;8(3):172-84.

H_2FPEF score

- 414 patients with unexplained dyspnea between 2006-2016 at the Mayo Clinic undergoing invasive exercise testing
- Patients with HFpEF (64%) were identified by elevated pulmonary capillary wedge pressure at rest (≥15 mm Hg) or during exercise (≥25 mm Hg)
- Robust caliibration (P>0.1)
- Validation in 100 patients, AUC 0.89 for points-based score and 0.910 for the continuous variable-based score

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)



Reddy et al. Circ 2018:138:861

Circulation

European Heart Journal (2007) 28, 2539–2550
doi:10.1093/eurheartj/ehm037

Special article

ORIGINAL RESEARCH ARTICLE

A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction

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H_2	Heavy	Body mass index > 30 kg/m^2	2
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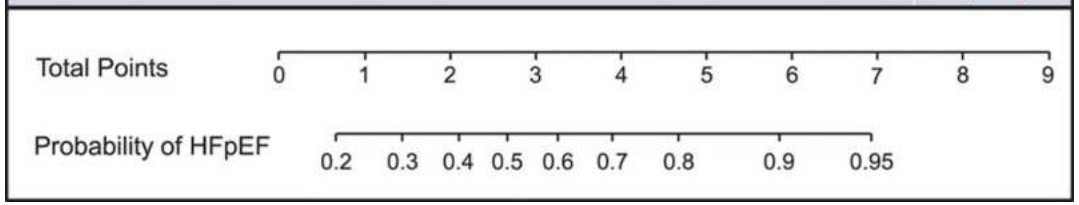
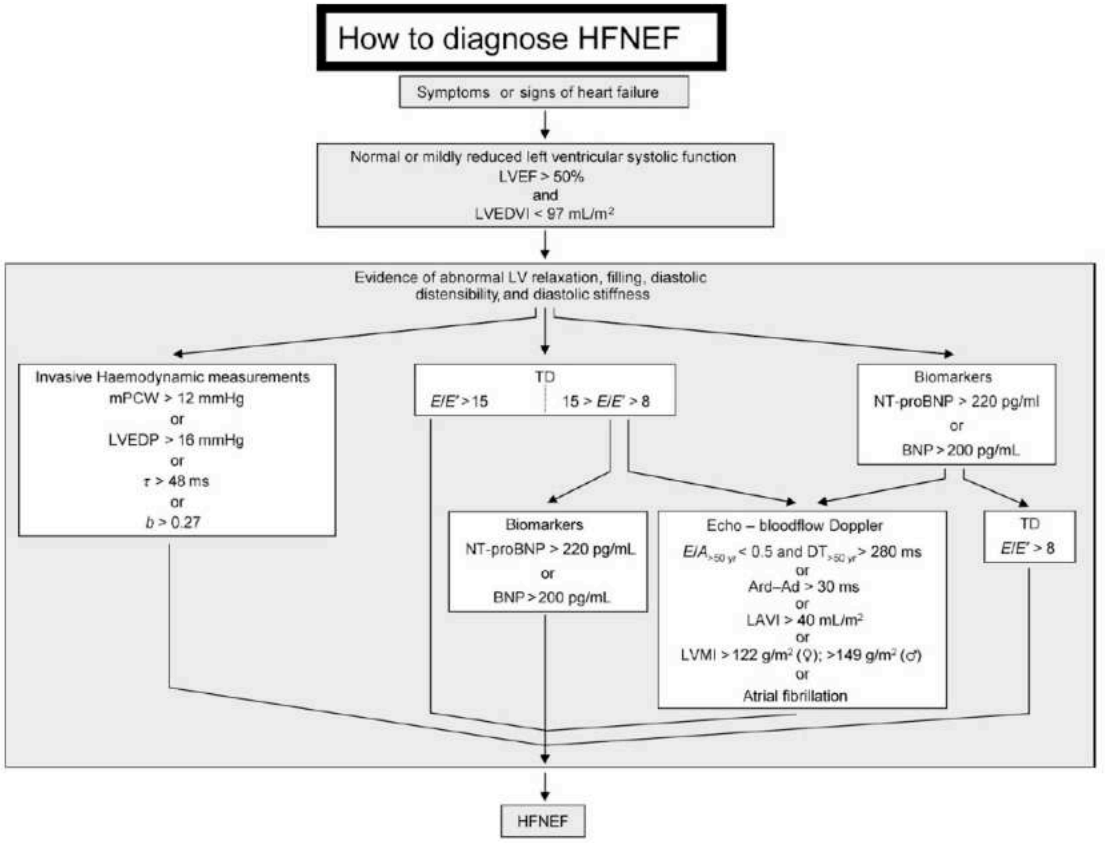


How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology



+0.169 (95% CI 0.120-0.217) in AUC vs

HFA-PEFF diagnostic algorithm

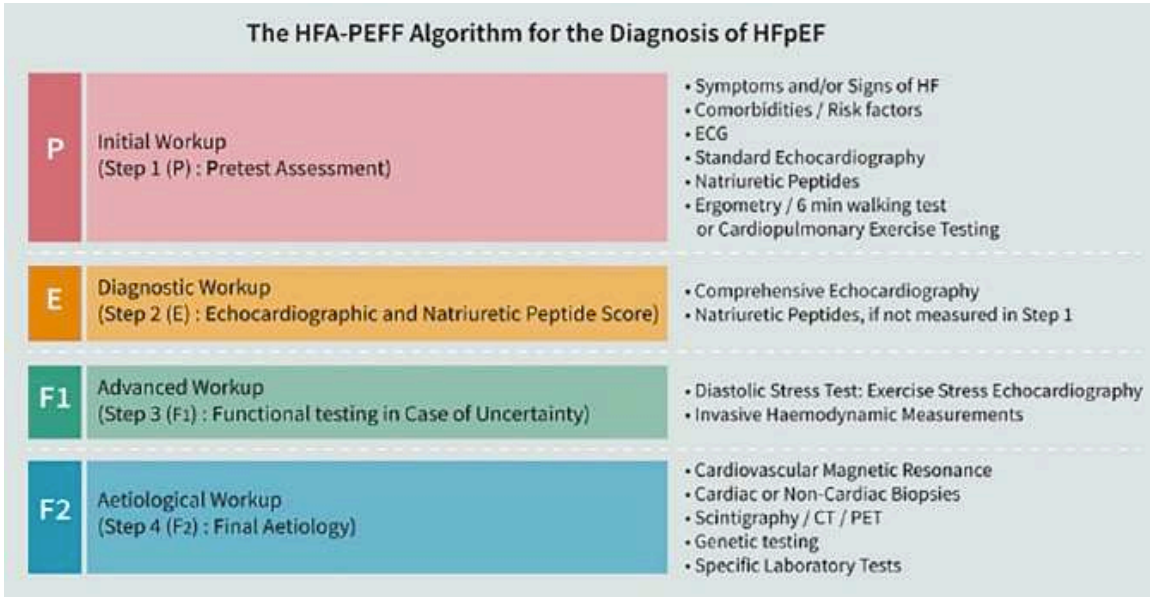
ESC European Society of Cardiology

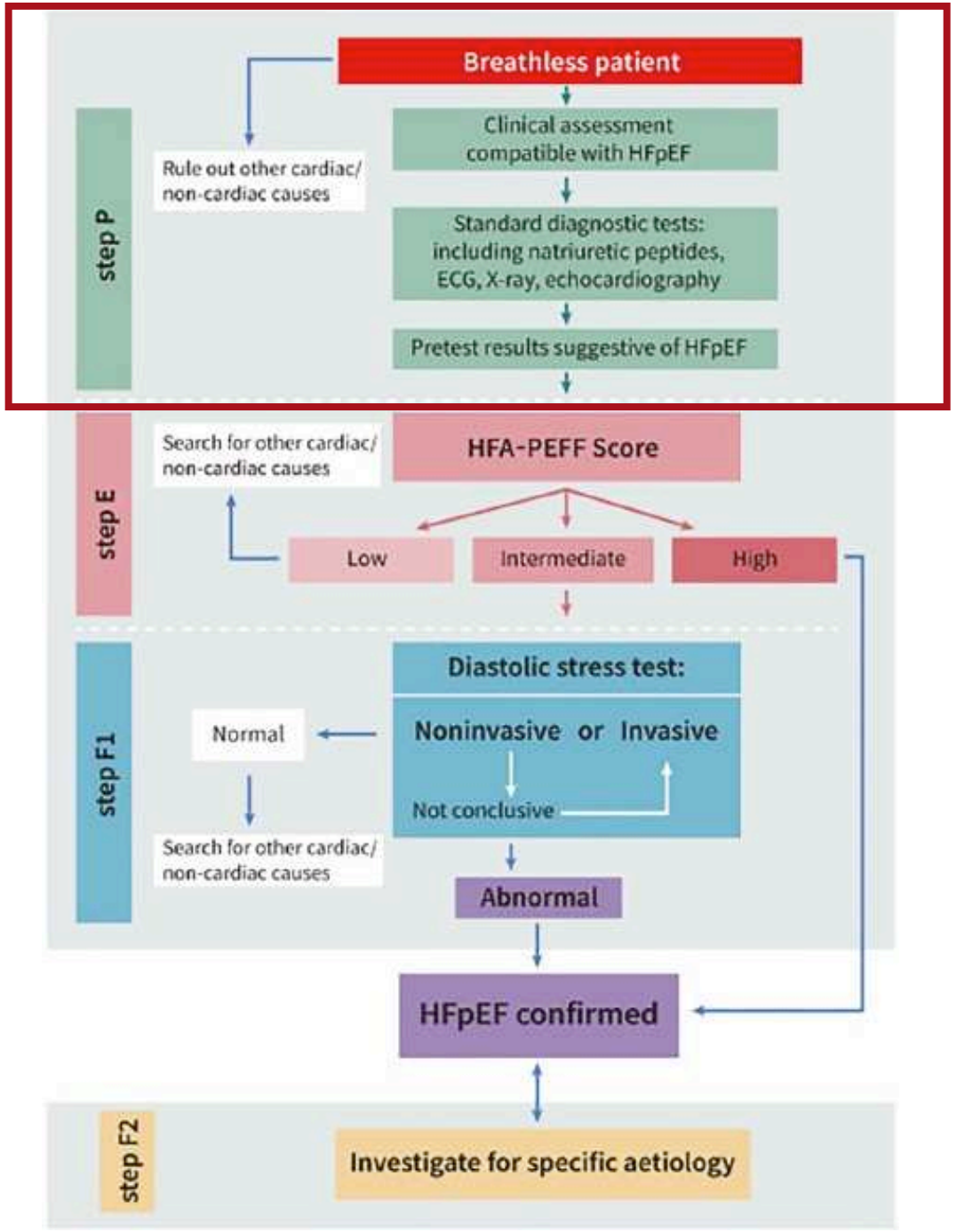
European Journal of Heart Failure (2020) 22, 391–412
doi:10.1002/ejhf.1741

HFA CONSENSUS RECOMMENDATION

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)

Burkert Pieske[1,2,3,4]*, Carsten Tschöpe[1,2,5], Rudolf A. de Boer[6], Alan G. Fraser[7], Stefan D. Anker[1,2,5,8], Erwan Donal[9], Frank Edelmann[1,2], Michael Fu[10], Marco Guazzi[11,12], Carolyn S.P. Lam[13,14], Patrizio Lancellotti[15], Vojtech Melenovsky[16], Daniel A. Morris[1], Eike Nagel[17,18], Elisabeth Pieske-Kraigher[1], Piotr Ponikowski[19], Scott D. Solomon[20], Ramachandran S. Vasan[21], Frans H. Rutten[22], Adriaan A. Voors[6], Frank Ruschitzka[23], Walter J. Paulus[24], Petar Seferovic[25], and Gerasimos Filippatos[26,27]



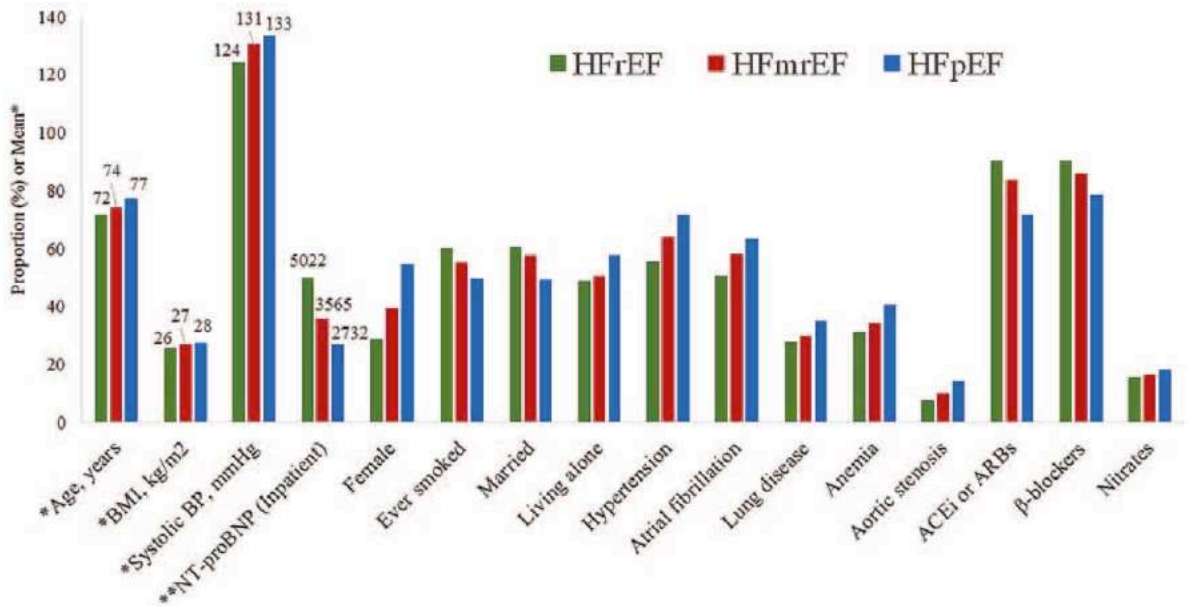

Breathless patient
step P
Rule out other cardiac/ non-cardiac causes
Clinical assessment compatible with HFpEF
Standard diagnostic tests: including natriuretic peptides, ECG, X-ray, echocardiography
Pretest results suggestive of HFpEF
step E
Search for other cardiac/ non-cardiac causes
HFA-PEFF Score
Low
Intermediate
High
step F1
Diastolic stress test:
Noninvasive or Invasive
Not conclusive
Normal
Search for other cardiac/ non-cardiac causes
Abnormal
HFpEF confirmed
step F2
Investigate for specific aetiology

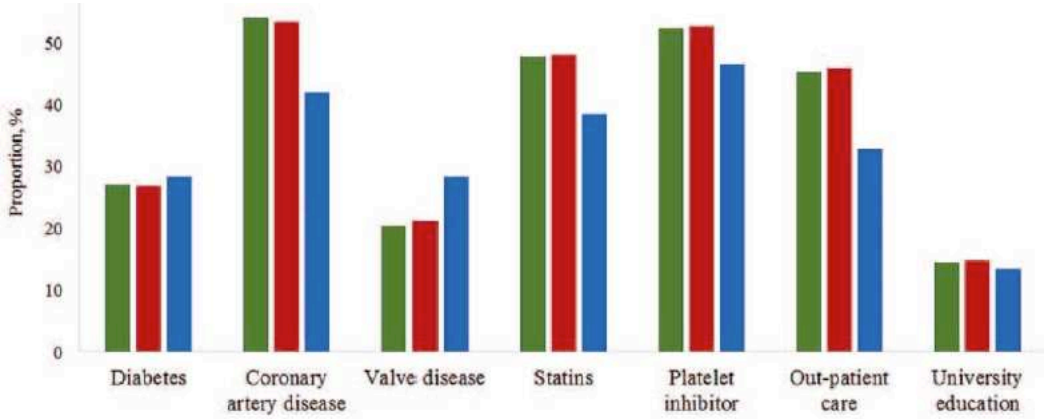
European Journal of Heart Failure (2017) 19, 1624–1634
doi:10.1002/ejhf.945

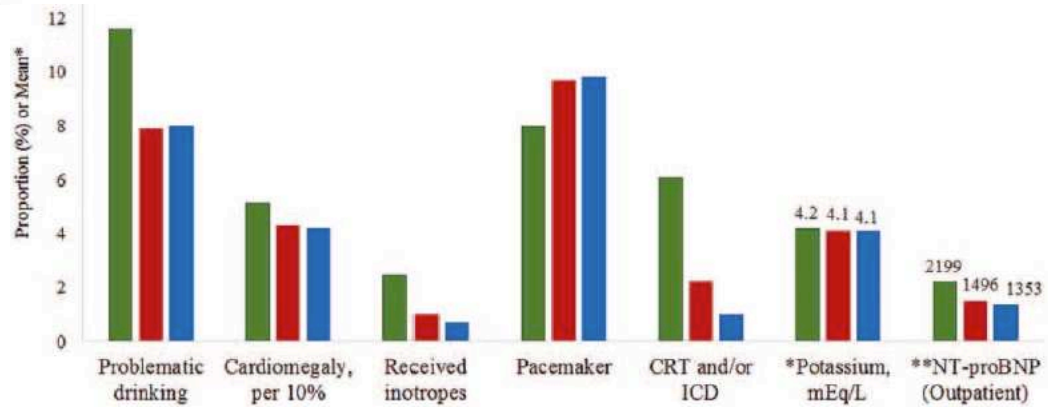
RESEARCH ARTICLE

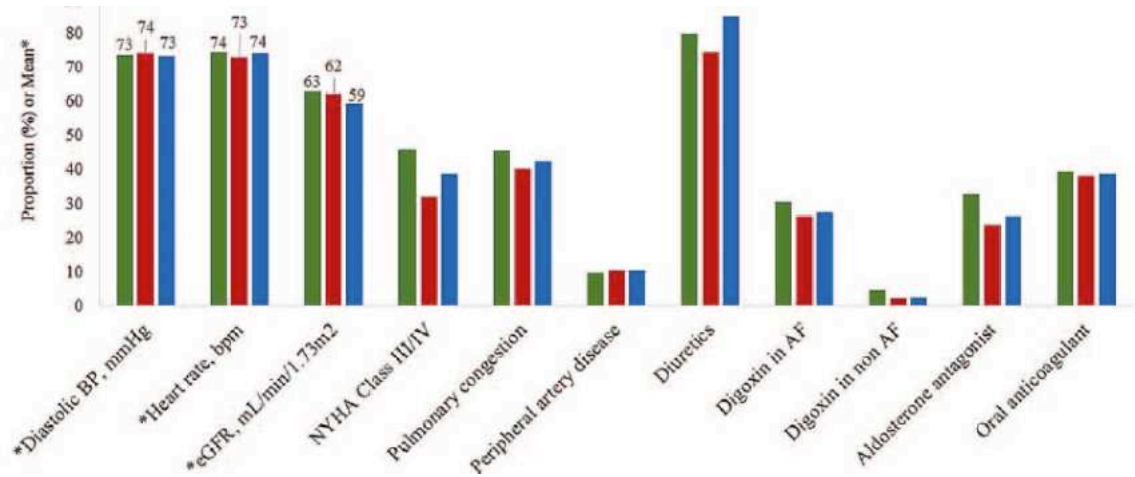
A comprehensive population-based characterization of heart failure with mid-range ejection fraction

Angela S. Koh[1,2], Wan Ting Tay[1], Tiew Hwa Katherine Teng[1,3], Ola Vedin[4], Lina Benson[5], Ulf Dahlstrom[6], Gianluigi Savarese[7], Carolyn S.P. Lam[1,2,8]*, and Lars H. Lund[7]*









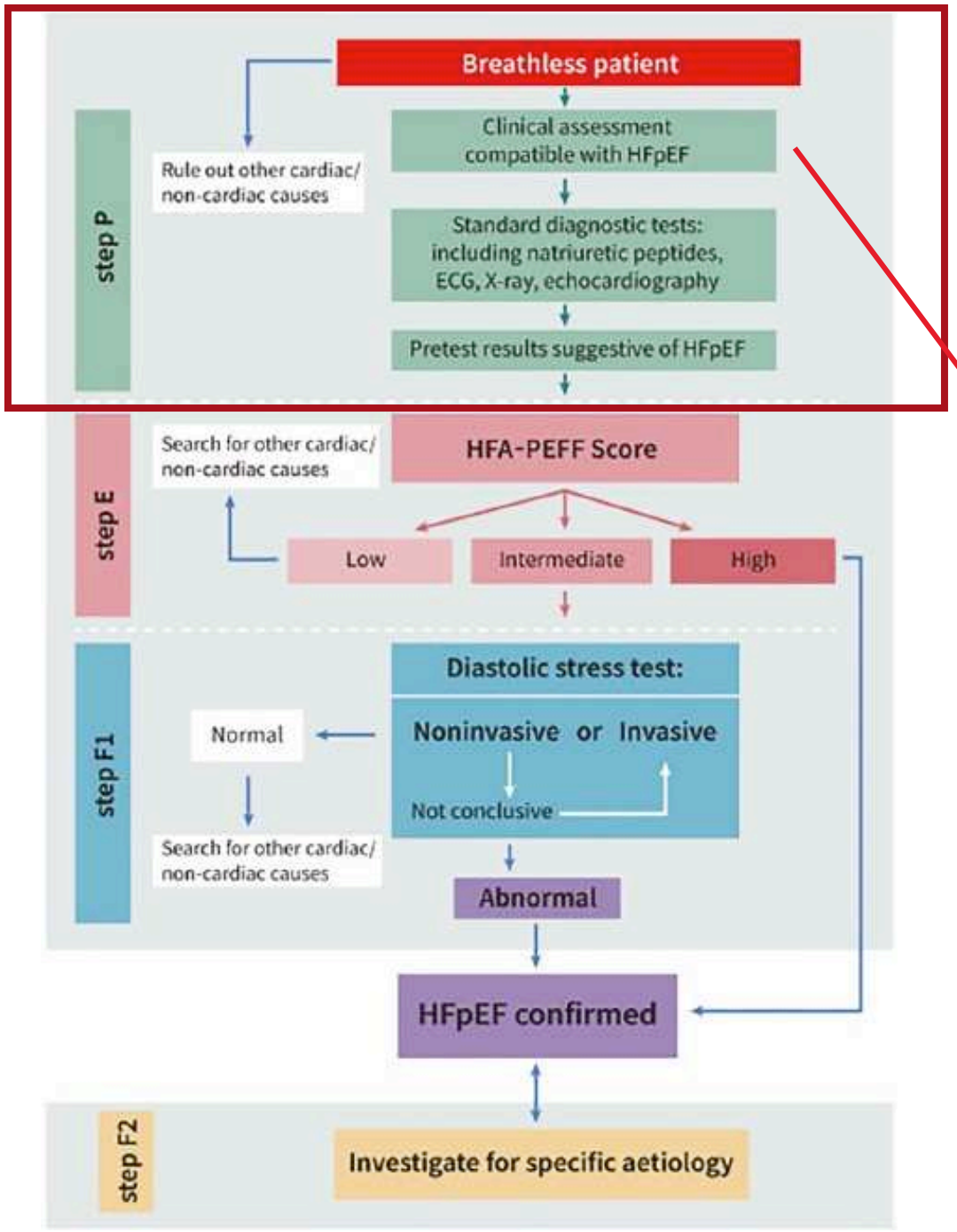


Table 1 **Risk factors and findings consistent with heart failure with preserved ejection fraction in a symptomatic patient**

Advanced age (age ≥ 70 in men or ≥ 75 in women)
Overweight/obesity
Metabolic syndrome/diabetes mellitus
Physical inactivity/deconditioning
Arterial hypertension
Atrial fibrillation
ECG abnormalities (beyond atrial fibrillation)
Elevated natriuretic peptide levels (if available, BNP ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL)

BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.

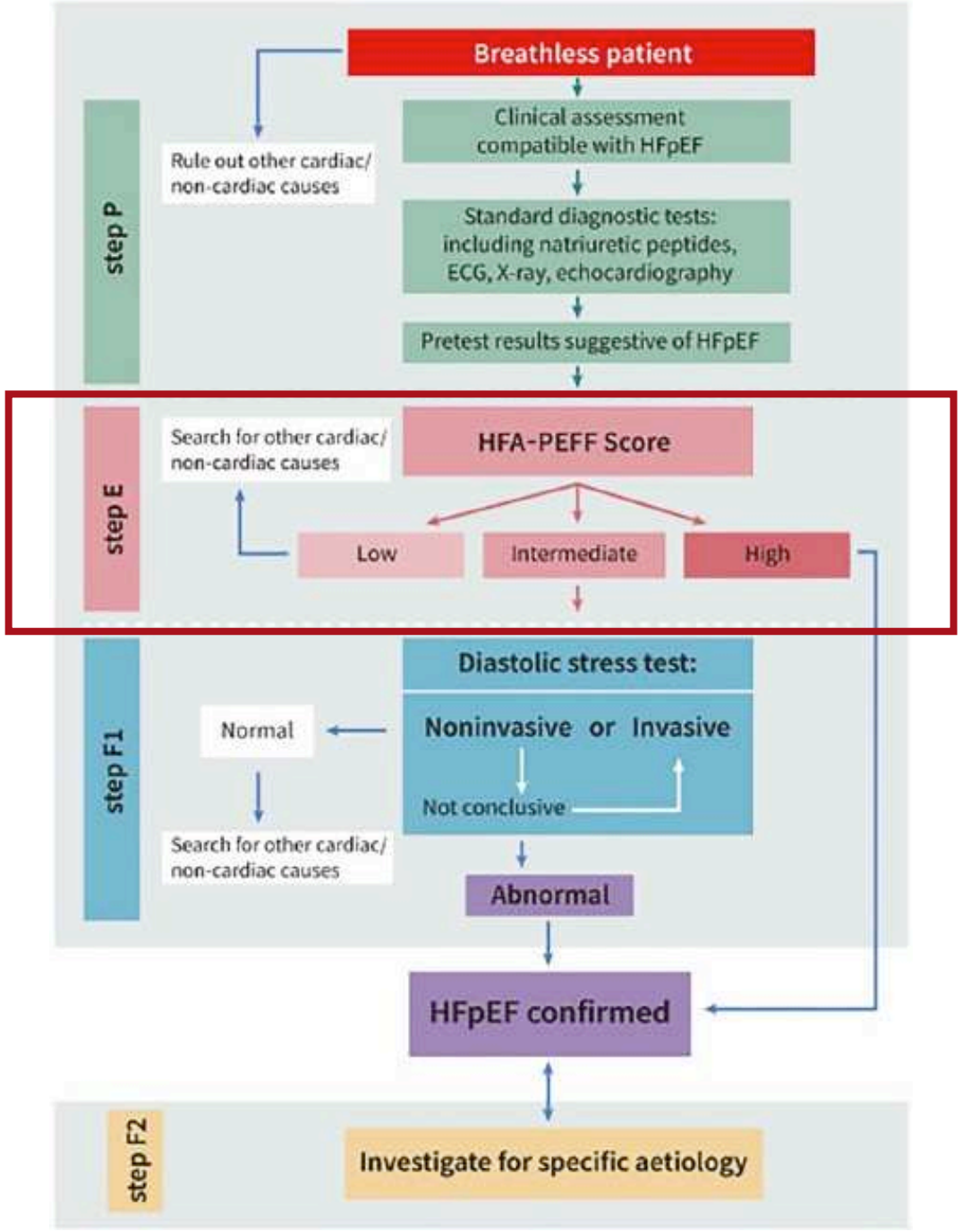
If at least one +

Step E

Step E

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements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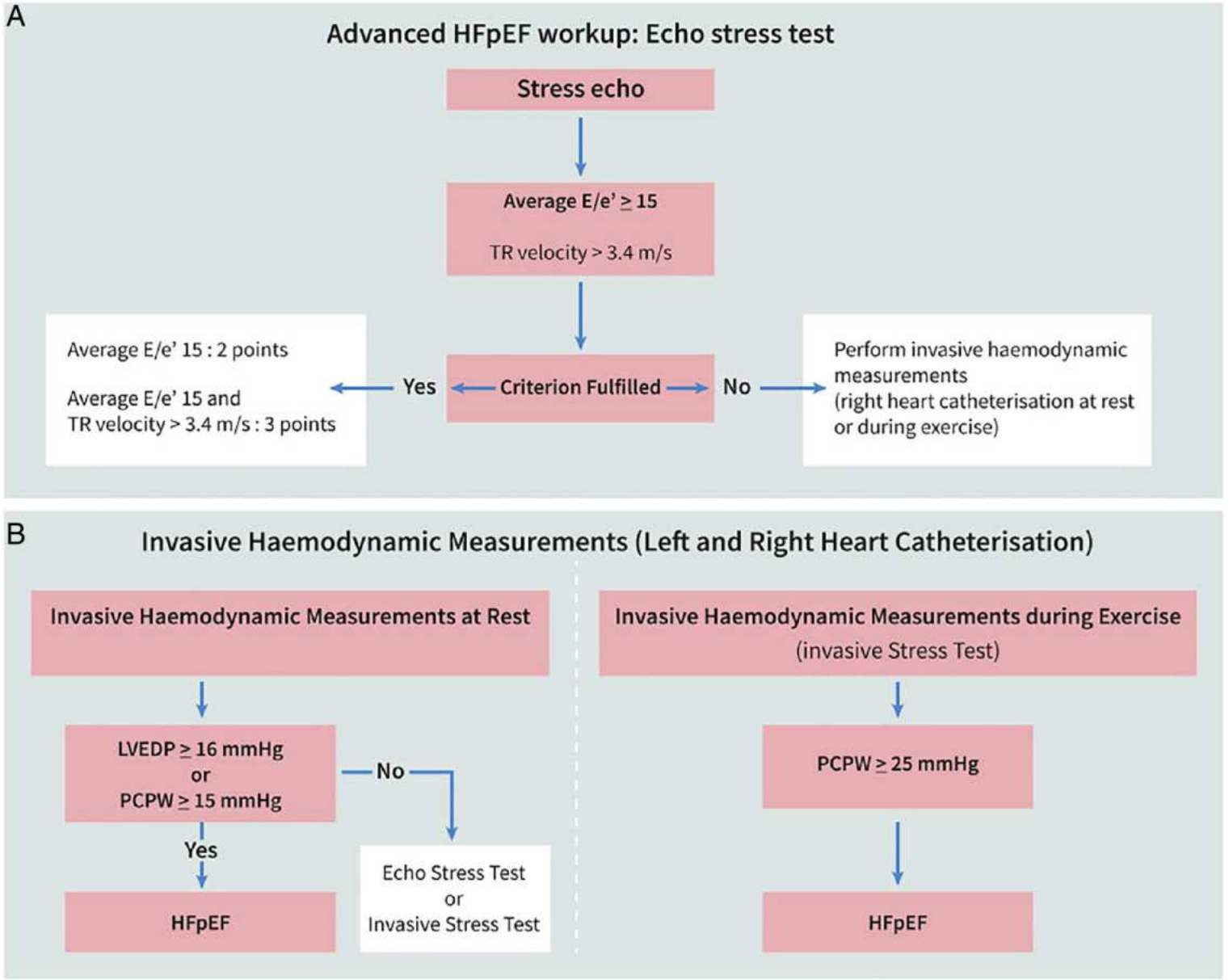
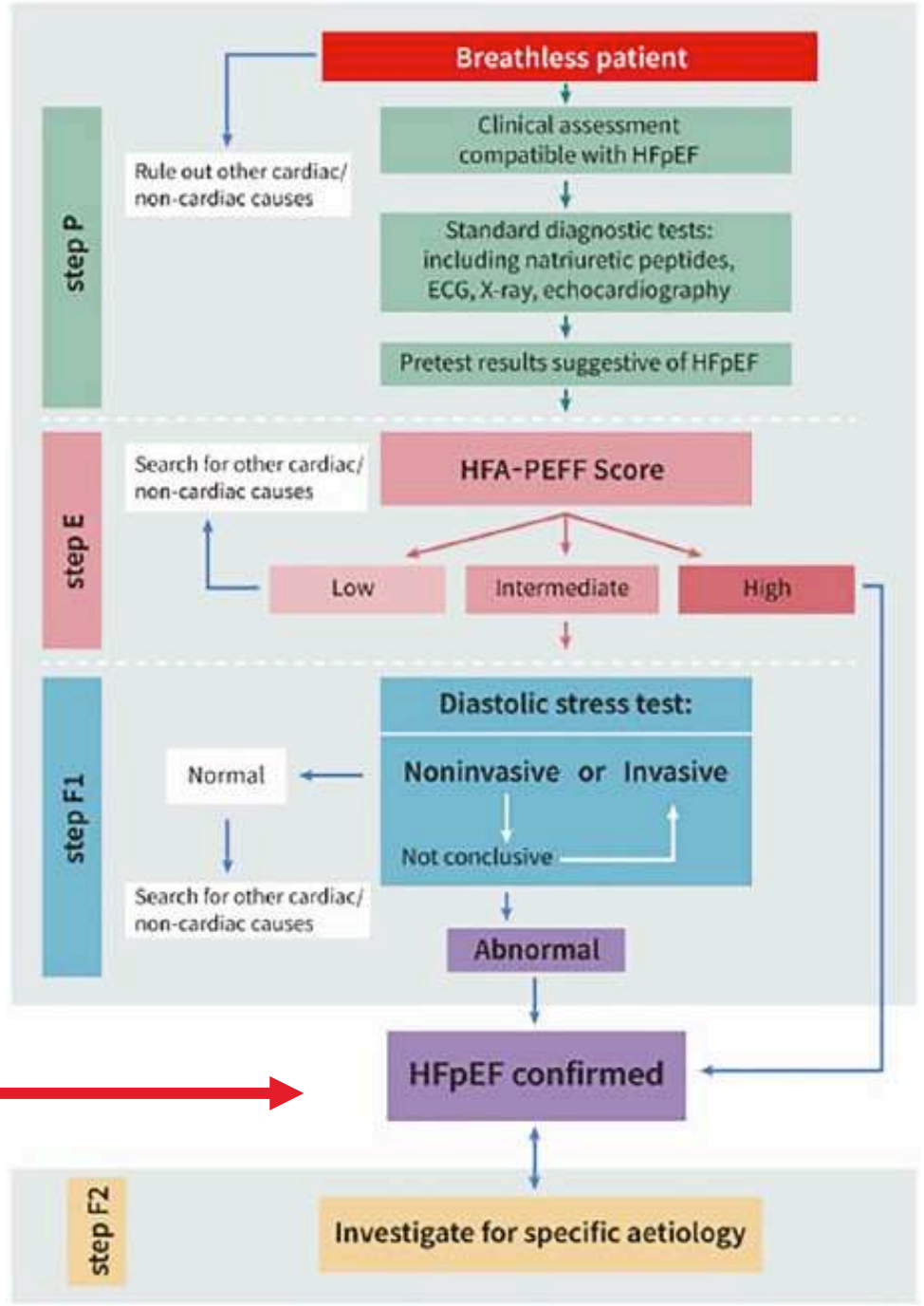
HFpEF confirmed
step F2
Investigate for specific aetiology

Step F1


A
Advanced HFpEF workup: Echo stress test
Stress echo
Average E/e' ≥ 15
TR velocity > 3.4 m/s
Criterion Fulfilled
Yes
Average E/e' 15 : 2 points
Average E/e' 15 and
TR velocity > 3.4 m/s : 3 points
No
Perform invasive haemodynamic measurements
(right heart catheterisation at rest or during exercise)
B
Invasive Haemodynamic Measurements (Left and Right Heart Catheterisation)
Invasive Haemodynamic Measurements at Rest
LVEDP ≥ 16 mmHg
or
PCPW ≥ 15 mmHg
Yes
HFpEF
No
Echo Stress Test
or
Invasive Stress Test
Invasive Haemodynamic Measurements during Exercise
(invasive Stress Test)
PCPW ≥ 25 mmHg
HFpEF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Abnormal
HFpEF confirmed
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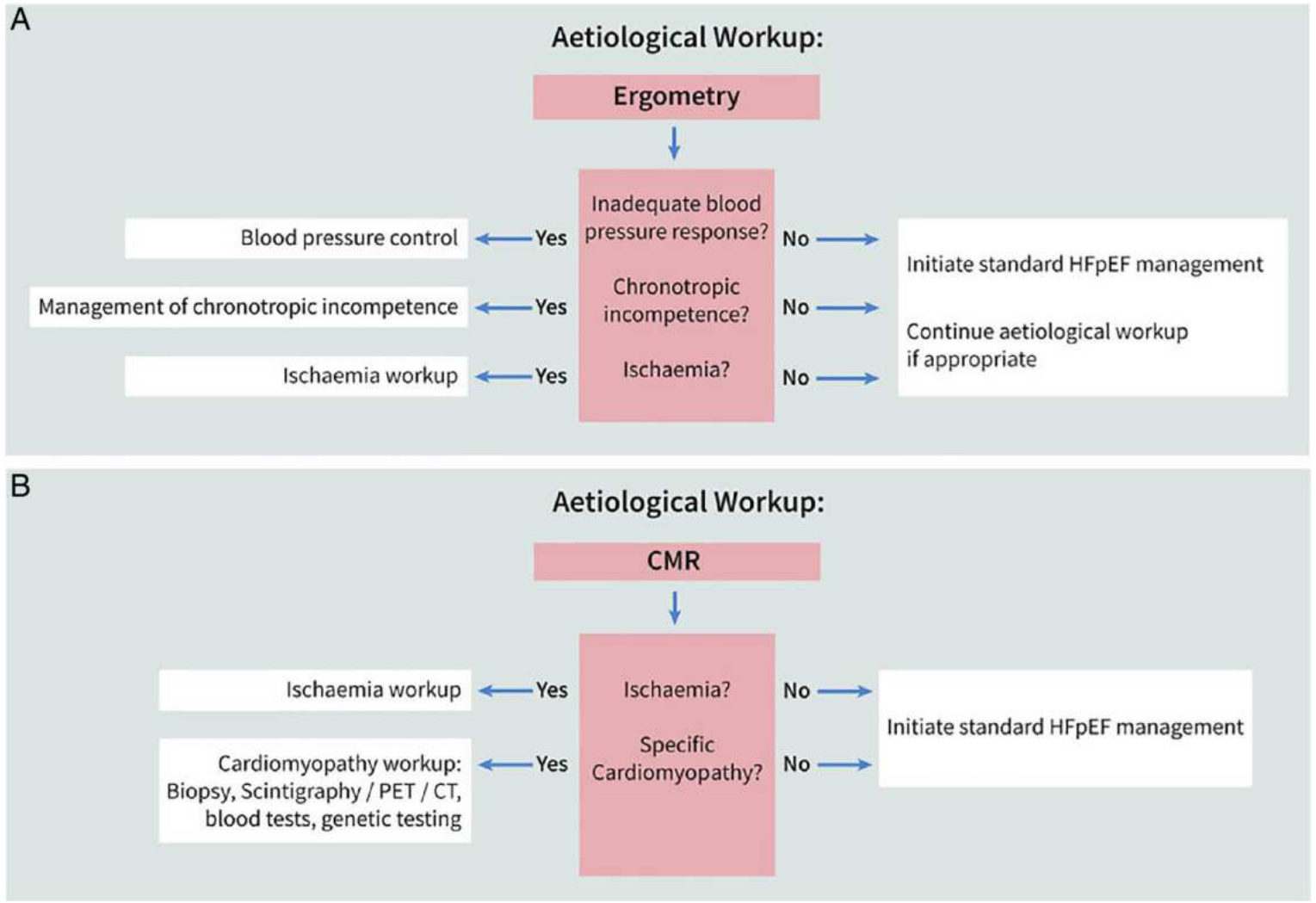
Step F2


A
Aetiological Workup:
Ergometry
Inadequate blood pressure response?
Blood pressure control
Yes
No
Initiate standard HFpEF management
Chronotropic incompetence?
Management of chronotropic incompetence
Yes
No
Continue aetiological workup if appropriate
Ischaemia?
Ischaemia workup
Yes
No
B
Aetiological Workup:
CMR
Ischaemia?
Ischaemia workup
Yes
No
Initiate standard HFpEF management
Specific Cardiomyopathy?
Cardiomyopathy workup: Biopsy, Scintigraphy / PET / CT, blood tests, genetic testing
Yes
No

Step F2

Table 2 Potential specific aetiologies underlying heart failure with preserved ejection fraction-like syndromes in Step 4 (F_2)

Abnormalities of the myocardium		
Ischaemic		Myocardial post-infarction/scar[49] Myocardial stunning[50] Epicardial coronary artery disease[51] Microvascular and endothelial dysfunction[52,53–55]
Toxic	Recreational substance abuse	Such as alcohol,[56] cocaine,[57] and anabolic steroids[58]
	Heavy metals	Such as iron,[59] lead,[60] cadmium,[60] cobalt,[61] copper (Wilson disease)[62]
	Medications	Such as chloroquine,[63] ergotamine,[64] cytostatic drugs (e.g. anthracyclines),[64] immunomodulating drugs (e.g. interferons, monoclonal antibodies such as trastuzumab, cetuximab)[64]
	Radiation	Mean cardiac radiation doses > 3 Gy[65,66]
Immune and inflammatory	Related to infection	Such as cardiotropic viruses,[67,68] HIV,[69–71] hepatitis,[72] helminths,[73] parasites (e.g. Chagas' disease[74])
	Not related to infection	Lymphocytic myocarditis,[75–79] autoimmune diseases (e.g. rheumatoid arthritis,[80] connective tissue disorders like scleroderma,[81] Raynaud's phenomenon,[55] systemic lupus erythematosus,[82] dermato/polymyositis,[83] and hypersensitivity and eosinophilic myocarditis[73,84–87]
Infiltrative	Related to malignancy	Direct infiltrations and metastases[88–90]
	Not related to malignancy	Amyloidosis,[19,91] sarcoidosis,[92,93] primarily and secondary haemochromatosis,[94–96] storage diseases[97] (e.g. Fabry disease,[98,99] Danon disease,[100–102] Pompe disease,[99,102] PRKAG2 deficiency,[99] Gaucher's disease[99])[103,104,105,106]
Metabolic	Hormonal	Such as thyroid diseases,[107,108] parathyroid diseases,[109] acromegaly,[110] GH deficiency,[111] Cushing disease,[112] Conn's disease,[113] Addison disease,[114] phaeochromocytoma,[115] pathologies related to pregnancy and peripartum[116,117]
	Nutritional	Such as deficiencies in thiamine,[118] L-carnitine,[119] selenium,[120] (functional) iron,[121,122] complex malnutrition (e.g. AIDS, infections,[73] anorexia nervosa[73,123,124])
Genetic	Diverse forms	Such as HCM,[97,125,126] restrictive cardiomyopathies,[103,104,106] hypertrophic form of non-compaction cardiomyopathy,[127,128] early forms of muscular dystrophies (Duchenne/Becker disease[129]).
Endomyocardial		HES,[84] EMF,[71,127] endocardial fibroelastosis,[128] carcinoid,[130,131] endocardial calcification (Paget's disease[132])
Abnormalities of loading conditions		
Hypertension		Primary and secondary forms of hypertension[112,113,115,130,131]
Valvular and structural defects	Acquired	Heart valve diseases[133,134]
Valvular and structural defects	Congenital	Septal defects[132,135,136]
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis and pericardial effusion[137,138]
	Endomyocardial	HES,[86] EMF,[73,139] endocardial fibroelastosis,[140] carcinoid,[141,142] endocardial calcification (Paget's disease[143])
High output states		Severe anaemia,[144] sepsis,[145] thyrotoxicosis,[105] arteriovenous fistula,[146] and pregnancy[147]
Volume overload		Renal failure and fluid overload[148,149,150]
Abnormalities of the cardiac rhythm		
Rhythm disorders		Atrial/ventricular arrhythmias, pacing, conduction disorders[38,151–153]

EMF, endomyocardial fibrosis; GH, growth hormone; HCM, hypertrophic cardiomyopathy; HES, hypereosinophilic syndrome (formerly known as Löffler's endocarditis); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; LV, left ventricular; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2.

ESC European Society of Cardiology

European Journal of Heart Failure (2020) 22, 413–421
doi:10.1002/ejhf.1614

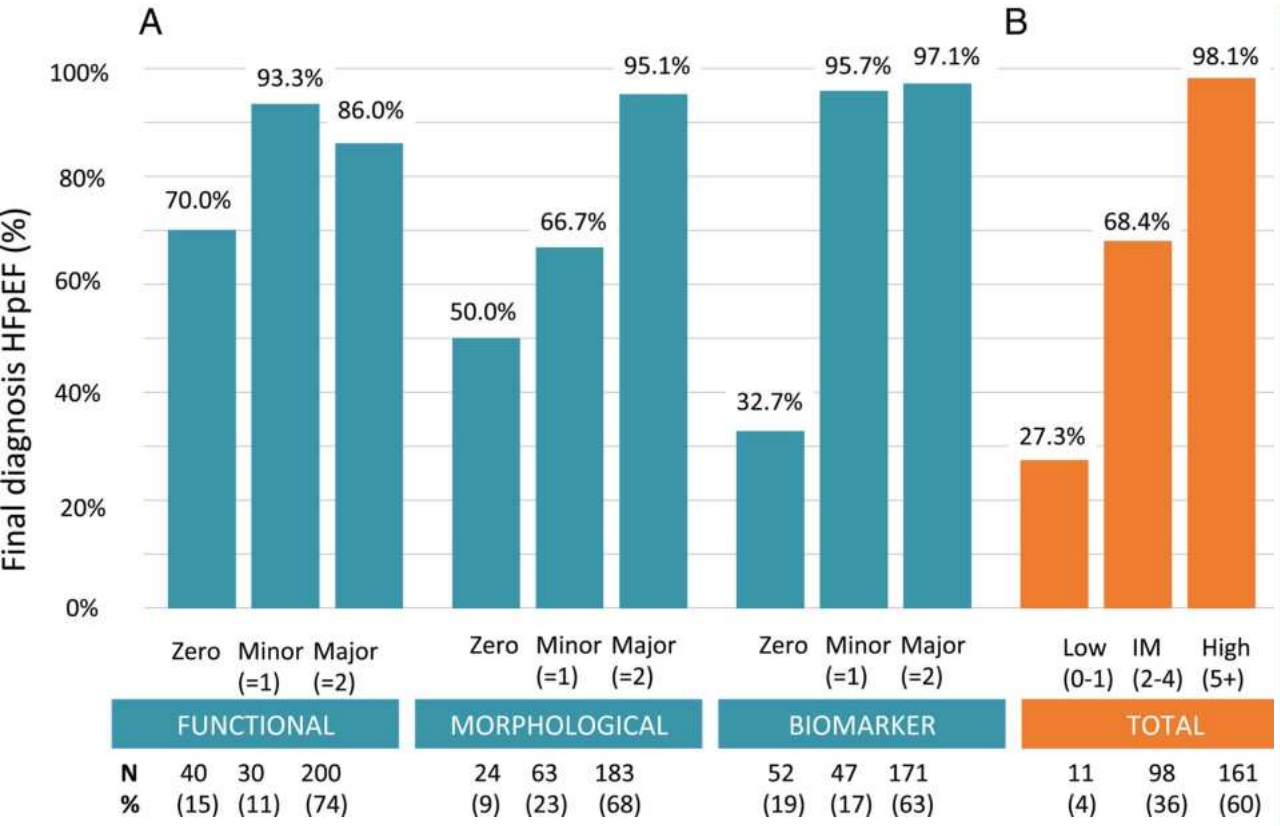
RESEARCH ARTICLE

Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction

Table 3 Diagnostic performance of the HFA-PEFF algorithm

Cut-off for diagnosing HFpEF	Sens	Spec	PPV	NPV
≥ 2 points	99%	19%	87%	73%
≥ 3 points	96%	48%	91%	71%
≥ 4 points	90%	81%	96%	60%
≥ 5 points	69%	93%	98%	36%
≥ 6 points	45%	95%	98%	24%

HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.
This analysis includes 228 HFpEF and 42 non-HFpEF patients from the Maastricht cohort.



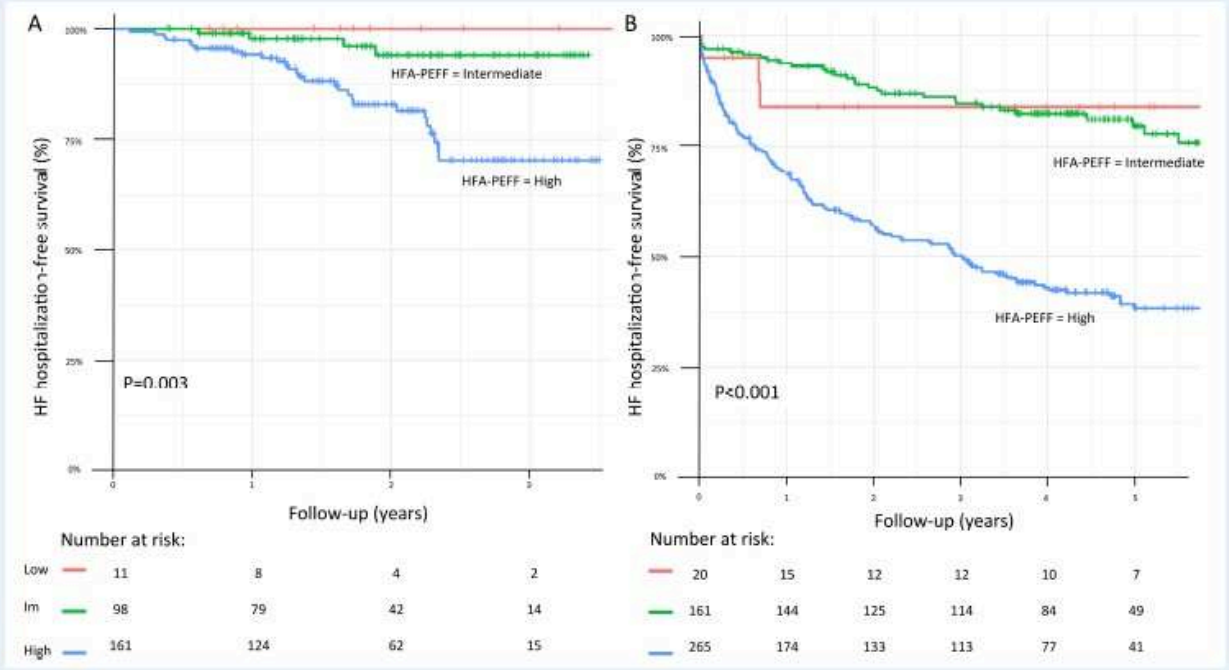
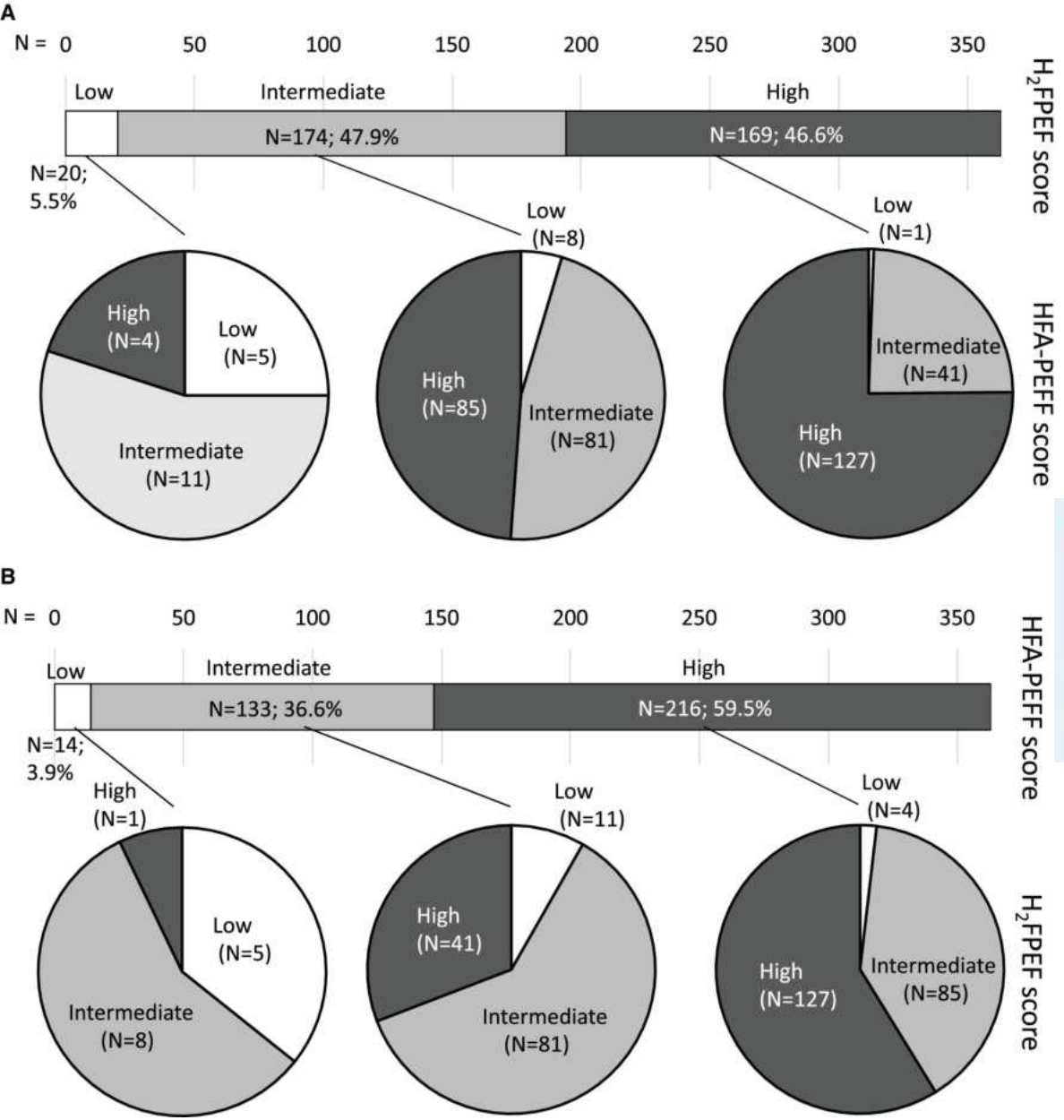


Figure 3 Kaplan–Meier curves for the combined endpoint of heart failure (HF) hospitalization or death. Kaplan–Meier curves are divided by HFA-PEFF category, in the total Maastricht cohort [*A*, including HF with preserved ejection fraction (HFpEF) and non-HFpEF] and in the Northwestern (Chicago) cohort (*B*, HFpEF only). IM, intermediate.

Reclassification from H_2FPEF to HFA-PEFF



Vice versa

41% of patients are differently classified according to the 2 scores

Table 1 Diagnostic performance of the H_2FPEF and HFA-PEFF scores

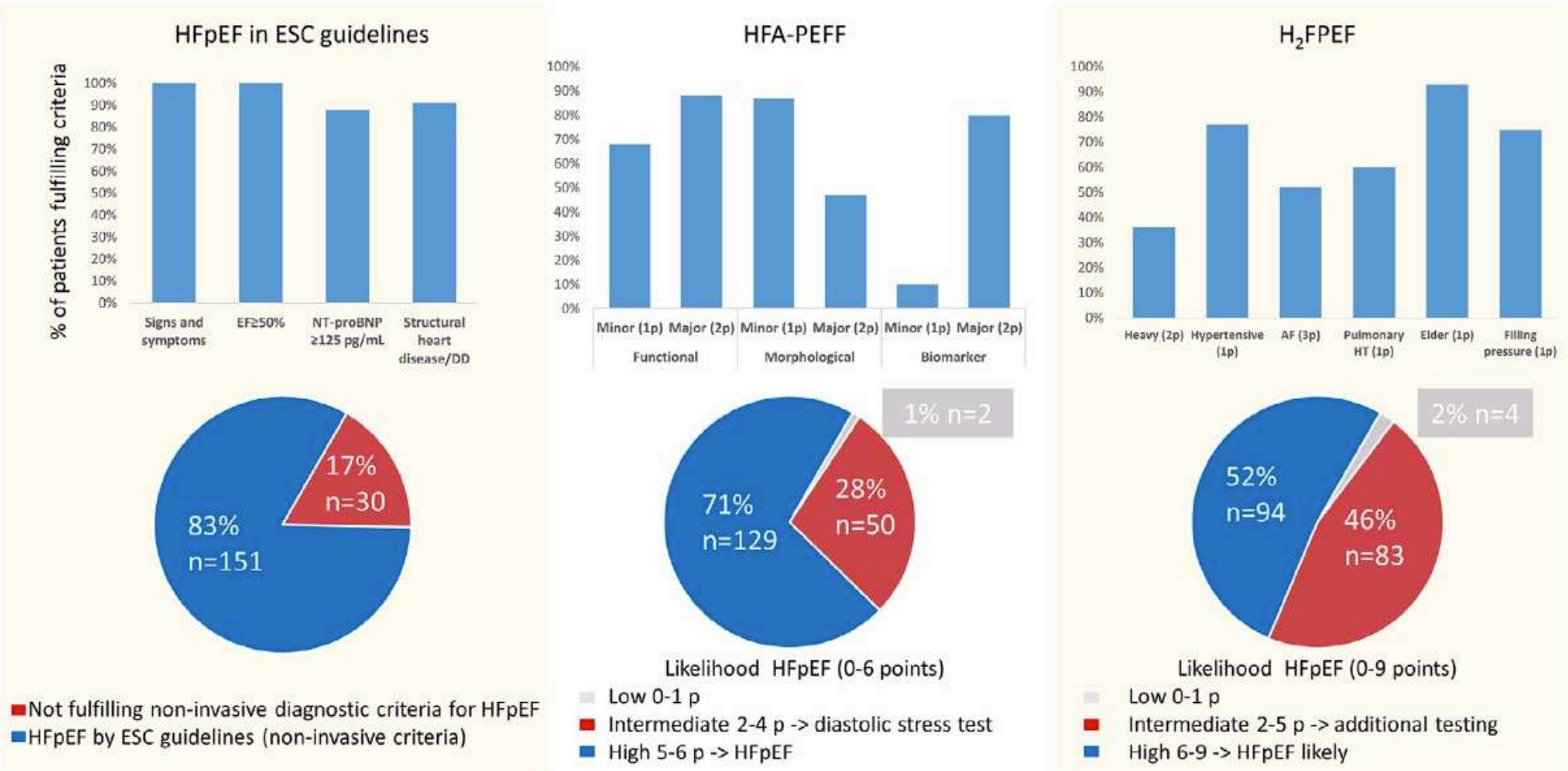
	AUC (95% CI)	Cut-off	Sensitivity	Specificity	NPV	PPV
H_2FPEF	0.77 (0.71–0.83)	≥6	52.7%	82.5%	26.8%	93.5%
HFA-PEFF	0.88 (0.82–0.93)*	≥5	70.0%	90.5%	38.8%	97.2%

Results were similar when excluding imputed data. AUC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
*$P < 0.009$ vs. H_2FPEF.

Sanders-can Wijk et al. EJHF 2020

Generalizability of HFA-PEFF and H_2FPEF Diagnostic Algorithms and Associations With Heart Failure Indices and Proteomic Biomarkers: Insights From PROMIS-HFpEF

PROMIS-HFpEF, EF≥50%: n=181



Faxen UL et al. JCF 2021

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Application of Diagnostic Algorithms for Heart Failure With Preserved Ejection Fraction to the Community

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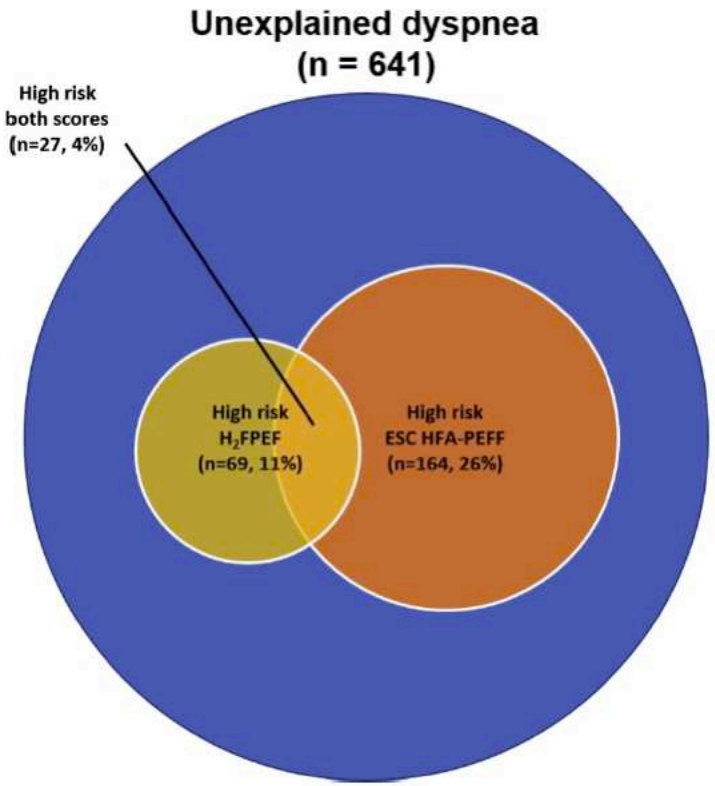

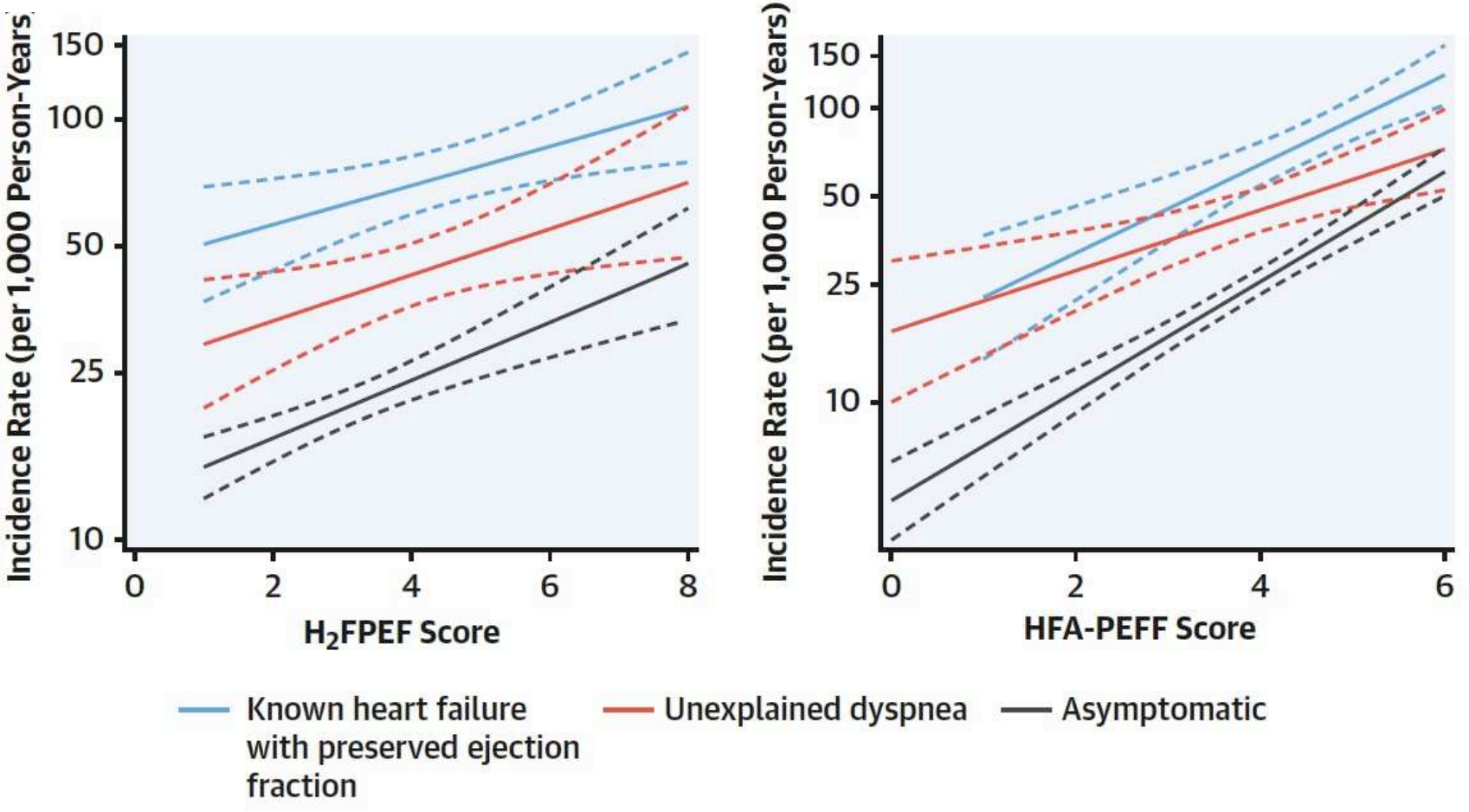

Take-home messages

- HFpEF is underdiagnosed. Limited availability of important diagnostic tools (e.g. exercise testing with invasive hemodynamic evaluation) might be a major contributor and standardized diagnostic algorithm might facilitate the correct diagnosis of HFpEF

- However, HFpEF is a clinical syndrome, with multiple contributing factors, aetiologies, pathophysiological expression, and using one algorythm for diagnosing HFpEF carries the risk of limiting it to a single clinical diagnosis

- High HFA-PEFF score (5-6 points) has been shown to diagnose HFpEF with high specificity (93%), whereas a low HFA-PEFF score (0-1 points) rules out HFpEF with a sensitivity of 99%, with many patients in validation studies falling in an intermediate category (36%)

- HFA-PEFF but also other scores, e.g. H_2FPEF need to be validated against invasive hemodynamic criteria which are the fold standard for the diagnosis of HFpEF

- Combining more than one score, e.g. HFA-PEFF and H_2FPEF which often show discrepancies, might be insightful in daily clinical practice

- When diagnosing HFpEF, other important conditions with heart failure-like symtoms should be directly excluced during the initial workup, e.g. coronary artery disease, significant valvular disease, pulmonary disease, anemia.

- It is also important to remember potential secondary causes of HFpEF which have specific treatments and diagnostic algorythms, i.e. primary cardiomyopathies (e.g. amyloidosis), valvular diseases, pericardial disease, right ventricular failure, volume overload due to kidney/liver disease

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Thanks for the Attention!!!