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ORIGINAL ARTICLE

Long-term outcomes of phenoclusters in preclinical heart failure with preserved and mildly reduced ejection fraction

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Abstract

Aims The identification of subjects at higher risk for incident heart failure (HF) with preserved ejection fraction (EF) suitable for more intensive preventive programmes remains challenging. We applied phenomapping to the DAVID-Berg population, comprising subjects with preclinical HF, aiming to refine HF risk stratification.

Methods The DAVID-Berg study prospectively enrolled 596 asymptomatic outpatients with EF $>$ 40% with hypertension, diabetes mellitus or known cardiovascular disease. In this cohort, we performed an unsupervised cluster analysis on 591 patients, including clinical, laboratory, electrocardiographic and echocardiographic parameters. We tested the association between each cluster and a composite outcome of HF/death.

Results The median age was 70 years, 55.5% were males and the median EF was 61.0%. Phenomapping provided three different clusters. Subjects in Cluster 3 were the oldest and had the highest prevalence of atrial fibrillation, the lowest estimated glomerular filtration rate (eGFR), the highest N-terminal pro-brain natriuretic peptide (NT-proBNP) and the largest left atrium. During a median follow-up of 5.7 years, 13.4% of subjects experienced HF/death events (N = 79). Compared with Clusters 1 and 2, Cluster 3 had the worst prognosis (log-rank test: Cluster 3 vs. 1 $P < 0.001$; Cluster 3 vs. 2 $P = 0.008$). Cluster 3 was associated with a risk of HF/death 2.5 times higher than Cluster 1 [adjusted hazard ratio (HR) = 2.46, 95% confidence interval (CI) 1.24–4.90].

Conclusions Based on phenomapping, older patients with lower kidney function and worse diastolic function might represent a subset of preclinical HF with EF $>$ 40% who deserve more efforts to prevent clinical HF.

Keywords congestive heart failure; heart failure; kidney disease; metabolic syndrome; preclinical; screening

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Introduction

According to the American College of Cardiology/American Heart Association heart failure (HF) classification, stages A and B encompass patients with HF risk factors and asymptomatic cardiac structural or functional abnormalities, respectively. Thus, stages A and B, despite controversy over the 'preclinical' definition, refer to patients with preclinical HF.[1] Recently, several research groups focused on the attempt to phenotype patients with clinically manifest HF with preserved ejection fraction (HFpEF). Importantly, patients with suspected HFpEF and HF symptoms have validated diagnostic algorithms, such as the H2FPEF or HFA-PEFF scores, as opposed to the patients at risk for HFpEF without dyspnoea.[2,3] Indeed, in a preclinical setting, the identification and phenotyping of subjects at higher risk for incident HF and death is tricky. Clinical, laboratory, electrocardiographic and echocardiographic parameters might be used on purpose.

The prevalence of preclinical HF is high, with one former study estimating a prevalence of 56% in adults older than 45 years old.[4] Importantly, the risk stratification of these individuals is still suboptimal, particularly in the primary care and outpatient settings. As widespread screening for preclinical HF in community-dwelling individuals is not recommended and is not cost-effective,[5] we studied the DAVID-Berg population, comprising asymptomatic individuals aged between 55 and 80 with at least one cardiovascular risk factor among diabetes, hypertension and previous cardiovascular disease (CVD).[6–10]

We hypothesized that performing a cluster analysis in such a population might help to refine the stratification of asymptomatic patients with HF risk factors and identify those more suitable for intensive preventive interventions. These preventive strategies might play a pivotal role in the patient's prognosis, as the progression rate of preclinical HF is high.[11] The objective of this study was to cluster asymptomatic patients with preclinical HF with mildly reduced ejection fraction (HFmrEF)/HFpEF based on clinical, laboratory, electrocardiographic and echocardiographic characteristics, aiming to detect the patient's preclinical phenotype at higher risk for incident HF events.

Methods

Study population

The characteristics of the DAVID-Berg study have been previously published.[6–10] Briefly, DAVID-Berg was a prospective cohort study carried out at three primary care group practices in Bergamo, Italy. In 2008, each primary care physician reviewed the clinical records of all subjects aged 55–80 years (n = 4047). Within this age strata, 113 subjects (2.8%) had known or suspected HF, as defined by the European Society of Cardiology (symptoms and signs of HF associated with objective evidence of a structural or functional abnormality of the heart at rest). Patients without known or suspected HF, without congenital heart disease (n = 3) or without moderate-to-severe valvular heart disease (n = 11) were included. Less than 1% of subjects were unable to attend the general practice clinic for evaluation, mainly for personal disabilities, or were unwilling to participate. Among the remaining asymptomatic subjects, we selected all individuals with HF risk factors defined as one or more of the following: presence of CVD, diabetes mellitus and hypertension. CVD included ischaemic heart disease, cerebrovascular disease and peripheral vessel disease. Specifically:

1 Ischaemic heart disease is defined as angina pectoris with documented ischaemic changes at stress tests, angiographic evidence of coronary stenosis $>$ 70% in at least one epicardial vessel, previous myocardial infarction or previous percutaneous or surgical revascularization.
2 Cerebrovascular disease is defined as a previous transitory ischaemic attack, stroke or asymptomatic carotid stenosis $>$ 50%.
3 Peripheral vessel disease is defined as claudication or asymptomatic iliac/femoral artery stenosis $>$ 50%.
4 Diabetes mellitus is defined as fasting blood glucose $\geq$ 126 mg/dL, 2 h post-challenge serum glucose $\geq$ 200 mg/dL or the use of insulin or oral hypoglycaemic agents.
5 Hypertension is defined as blood pressure $\geq$ 140 mmHg (systolic) or 90 mmHg (diastolic) or on antihypertensive drugs.

Finally, the DAVID-Berg study population comprised 623 subjects who underwent a protocol consisting of history and physical examination (including height, weight and blood pressure measurement), electrocardiogram (ECG), lipid profile, fasting blood glucose, glycosylated haemoglobin, creatinine, N-terminal pro-brain natriuretic peptide (NT-proBNP) and comprehensive echocardiographic evaluation. Renal function was assessed by the estimated glomerular filtration rate (eGFR) with the simplified Modification of Diet in Renal Disease (MDRD) equation. Renal dysfunction was defined as an eGFR $<$ 60 mL/min/1.73 m^2. Metabolic syndrome was defined as an alteration of three or more of the following five components: elevated glucose and glycaemia $\geq$ 110 mg/dL; high-density lipoprotein (HDL) cholesterol of $<$40 mg/dL for males or $<$50 mg/dL for females; triglycerides $\geq$ 150 mg/dL; systolic blood pressure (SBP) $\geq$ 130 or diastolic blood pressure (DBP) $\geq$ 85 mmHg); and abdominal obesity and a waist circumference of $>$102 cm for males or $>$88 cm for females.[12] All patients provided written informed consent to participate in the study, which was approved by the Ethics Committee of the Local Health Authority.

NP-proBNP assessment

In this study, we took into consideration the serum NT-proBNP levels for assessing the natriuretic peptide (NP) activity. NT-proBNP was measured with a point-of-care competitive enzyme immunoassay (Cobas h232, Roche Diagnostic). According to the DAVID-Berg study and previous literature,[9,13] we considered abnormally high NT-proBNP values greater than age-/sex-specific 80th percentiles, as both sex and age significantly impact NT-proBNP plasma values.

Echocardiographic study

The echocardiograms were obtained using a Vivid I GE medical ultrasound machine with a 2.5 MHz transducer (GE Medical System, Horten, Norway). All examinations were performed by expert cardiologists in echocardiography who were blinded to NT-proBNP values. For quality assurance,

randomly (n = 50) chosen echocardiographic examinations were reviewed by the echo core lab at Papa Giovanni XXIII Hospital, Bergamo, Italy, with an intra-class correlation (ICC) of 0.93 for left ventricular ejection fraction (LVEF) and 0.91 for septal mitral annulus E'. All measurements were made in triplicate in patients with sinus rhythm, while in those with atrial fibrillation, we averaged measurements over 10 R–R cycles, in accordance with the recommendations of the European/American Society of Echocardiography.[14] Left ventricular (LV) volumes and LVEF were derived according to the modified biplane Simpson's method in the apical four-chamber and two-chamber views. LV mass (LVM) was calculated from LV linear dimensions and indexed to height$^{2.7}$. LV hypertrophy (LVH) was defined as LVM indexed to height 2.7 $>$ 44 g/m$^{2.7}$ in females and $>$48 g/m$^{2.7}$ in males. LVEF was classified as preserved (≥50%), mildly reduced (41%–49%) or reduced ($<$40%), in accordance with HF and echocardiographic guidelines.[14]

Diastolic function parameters assessed in the DAVID-Berg study were left atrial volume index (LAVI) (abnormal $>$34 mL/m^2), septal E' (abnormal $<$0.07 m/s)[15] and septal E/E' (abnormal $>$15), as previously reported.[9] The arterial elastance (Ea) was defined as the end-systolic pressure to stroke volume ratio, which is an expression of the LV afterload and peripheral resistances. The Ea is normal within the range of 2.2 ± 0.8 mmHg/mL.[16]

Clinical follow-up and outcome

Between September 2008 and June 2014, data on incident HF and all-cause death were prospectively collected. The outcome of interest was a composite of HF events and all-cause death, whichever occurred first. Incident HF was defined as hospital admission for HF [identified by inpatient first diagnosis of the Ninth Revision of the International Classification of Diseases (ICD9) code 428.xx] or as a clinical outpatient event in the case of the appearance of HF signs and symptoms associated with a change in diuretic therapy (introduction of loop diuretics or increase in dose of other classes of diuretics).[17] Inpatient and outpatient events were recorded by adequately trained general practitioners during the time frame of the study and adjudicated by two independent cardiologists in June 2014. If the two cardiologists disagreed, a third cardiologist adjudicated the event.

For this study, only patients with ejection fraction (EF) $>$ 40% were included (Figure 1).

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the included patients: Absolute number and percentage were reported for categorical variables and median and interquartile range (IQR) for continuous variables.

An unsupervised k-median cluster analysis was performed to identify groups of patients with a similar phenotype based on continuous clinical, laboratory, electrocardiographic and echocardiographic parameters. The elbow method was used to detect the optimal number of clusters.

The objective of cluster analysis is to partition a set of observations into mutually exclusive groupings to best represent distinct sets of observations within the sample. In

Figure 1 Flow chart of the DAVID-Berg study. BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction.

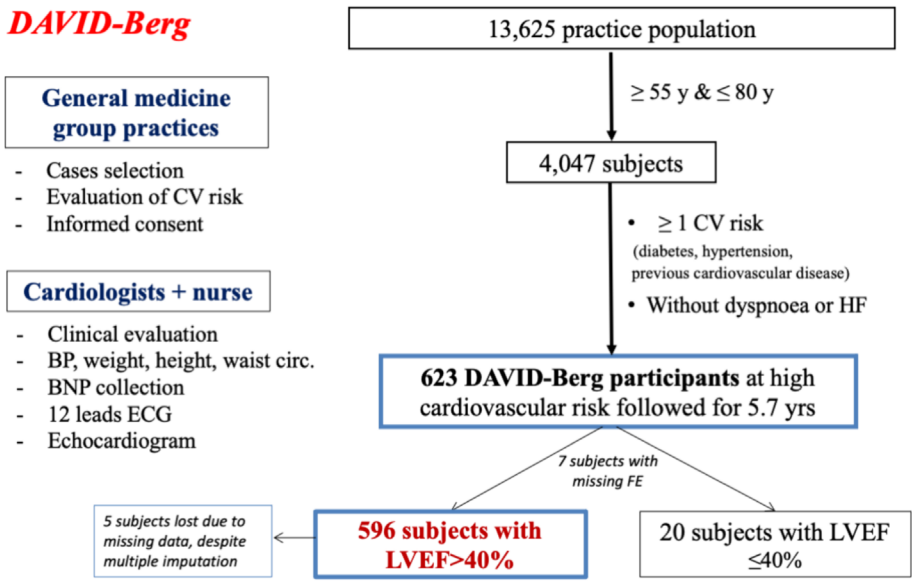


Table 1 Clinical, laboratory, electrocardiographic and echocardiographic characteristics stratified by phenoclusters.

	Total $N = 591$	Cluster 1 $N = 312$	Cluster 2 $N = 202$	Cluster 3 $N = 77$	P_{TOT}	$P_{1\ vs.\ 2}$	$P_{1\ vs.\ 3}$	$P_{2\ vs.\ 3}$
Variables included in the cluster analysis								
Age, median (IQR)	70.0 (64.0–75.0)	67.0 (61.0–72.0)	72.0 (68.0–76.0)	75.0 (69.0–78.0)	<0.001	<0.001	<0.001	0.003
BMI, median (IQR)	28.3 (25.5–31.7)	29.0 (26.4–32.3)	27.5 (24.4–31.4)	27.6 (25.3–30.2)	<0.001	<0.001	0.007	0.92
Systolic BP, median (IQR)	152.0 (134.0–167.0)	148.0 (131.5–162.5)	156.5 (140.0–170.0)	155.0 (136.0–174.0)	0.002	<0.001	0.057	0.73
Diastolic BP, median (IQR)	84.0 (77.0–91.0)	84.0 (78.0–91.0)	83.0 (75.0–91.0)	83.0 (75.0–91.0)	0.64	0.43	0.47	0.88
Heart rate, median (IQR)	73.0 (64.0–83.0)	74.0 (65.0–84.0)	72.5 (63.0–82.0)	70.0 (62.0–81.0)	0.20	0.29	0.082	0.44
Glycaemia, median (IQR)	105.0 (95.0–128.0)	107.0 (97.0–131.0)	104.0 (95.0–126.0)	97.5 (91.0–116.0)	0.002	0.12	<0.001	0.024
Total cholesterol, median (IQR)	201.5 (174.0–228.0)	205.5 (182.0–232.0)	201.0 (168.0–227.0)	183.0 (163.0–207.0)	<0.001	0.016	<0.001	0.050
eGFR, median (IQR)	72.8 (60.3–86.4)	76.7 (63.2–88.3)	68.9 (58.2–83.1)	65.6 (54.7–77.9)	<0.001	<0.001	<0.001	0.17
NT-proBNP, median (IQR)	170.0 (88.0–325.0)	92.0 (60.0–130.5)	279.0 (231.0–380.0)	841.0 (663.0–1195.0)	<0.001	<0.001	<0.001	<0.001
Triglycerides, median (IQR)	124.0 (92.0–163.0)	139.0 (100.0–178.0)	115.0 (89.0–145.0)	106.0 (87.0–139.0)	<0.001	<0.001	<0.001	0.50
QRS DUR, median (IQR)	90.0 (80.0–100.0)	90.0 (80.0–100.0)	90.0 (80.0–102.0)	100.0 (80.0–120.0)	0.069	0.99	0.023	0.045
Ea, median (IQR)	2.4 (1.9–3.0)	2.3 (1.9–2.8)	2.5 (1.9–3.2)	2.5 (1.9–3.1)	0.008	0.003	0.066	0.77
LVM HGT, median (IQR)	53.0 (44.1–63.8)	52.8 (43.1–63.3)	52.3 (44.4–63.7)	56.3 (48.3–66.8)	0.093	0.97	0.037	0.045
LAVI, median (IQR)	27.3 (20.2–35.3)	25.1 (18.5–32.3)	27.9 (21.1–35.0)	36.2 (26.6–48.3)	<0.001	0.010	<0.001	<0.001
LVEDVI, median (IQR)	51.8 (42.8–61.5)	50.6 (42.9–60.4)	52.9 (41.5–64.2)	53.0 (44.8–63.1)	0.52	0.42	0.31	0.71
LVESVI, median (IQR)	20.4 (15.4–26.6)	19.7 (15.1–25.5)	21.1 (16.0–27.1)	20.5 (16.7–28.9)	0.11	0.087	0.10	0.75
LVEF, median (IQR)	61.0 (55.0–67.0)	63.0 (57.0–68.0)	60.0 (54.0–66.0)	59.0 (51.0–65.0)	0.003	0.034	0.002	0.10
E/E′, median (IQR)	10.1 (8.0–12.8)	10.0 (7.8–12.3)	10.3 (7.8–13.2)	10.6 (8.5–14.9)	0.033	0.20	0.011	0.13
Other variables[a]								
Male, *n* (%)	328 (55.5)	186 (59.6)	96 (47.5)	46 (59.7)	0.019	0.007	0.98	0.068
Stage B HF, *n* (%)	536 (90.7)	258 (82.7)	201 (99.5)	77 (100.0)	<0.001	<0.001	<0.001	1.00
EF ≤ 50%, *n* (%)	42 (7.1)	17 (5.5)	16 (7.9)	9 (11.7)	0.14	0.26	0.050	0.33
Hypertension, *n* (%)	523 (89.4)	273 (88.6)	186 (92.5)	64 (84.2)	0.11	0.15	0.29	0.037
Smokers, *n* (%)	72 (12.2)	44 (14.1)	25 (12.4)	3 (3.9)	0.049	0.57	0.014	0.035
Diabetes, *n* (%)	209 (35.4)	114 (36.5)	73 (36.1)	22 (28.6)	0.41	0.93	0.19	0.23
Metabolic syndrome[b], *n* (%)	261 (46.3)	152 (50.8)	83 (42.8)	26 (36.6)	0.047	0.080	0.031	0.37
CKD, *n* (%)	134 (23.9)	55 (18.5)	56 (29.2)	23 (32.4)	0.005	0.008	0.010	0.61
Previous cardiovascular disease, *n* (%)	298 (52.1)	150 (49.8)	108 (55.1)	40 (53.3)	0.50	0.25	0.59	0.79
Peripheral vasculopathy, *n* (%)	138 (26.6)	66 (24.3)	53 (29.4)	19 (28.8)	0.43	0.22	0.45	0.92
TIA/stroke, *n* (%)	87 (16.9)	41 (15.1)	35 (19.8)	11 (16.4)	0.44	0.20	0.79	0.55
Coronary artery disease, *n* (%)	188 (34.0)	93 (32.0)	65 (34.6)	30 (40.5)	0.37	0.55	0.16	0.37
Atrial fibrillation, *n* (%)	21 (3.6)	0 (0.0)	3 (1.5)	18 (23.4)	<0.001	0.060	<0.001	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; Ea, arterial elastance; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LAVI, left atrium volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVM HGT, ratio of left ventricular mass to height; NT-proBNP, N-terminal pro-brain natriuretic peptide; QRS DUR, QRS duration; TIA, transient ischaemic attack.

[a]Not included in the cluster analysis.

[b]Metabolic syndrome was defined as an alteration of three or more of the following five components: elevated glucose and glycaemia ≥ 110 mg/dL; high-density lipoprotein cholesterol of <40 mg/dL for males or <50 mg/dL for females; triglycerides ≥ 150 mg/dL; systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (PAD) ≥ 85 mmHg); and abdominal obesity and waist circumference of >102 cm for males or >88 cm for females.

k-median clustering, each observation is assigned to the group whose median is closest, and then, based on that categorization, new group medians are determined. These steps continue until no observations change groups. To avoid losing observations, we used multiple imputation (with m = 1) to deal with missing data and then performed cluster analysis on the imputed data.

Once phenotype clusters were defined, we compared differences in demographic, clinical, electrocardiographic and echocardiographic characteristics among groups using χ^2 tests (or Fisher's exact tests when appropriate) for categorical variables and analysis of variance (ANOVA) (or the Kruskal–Wallis test when appropriate) for continuous variables.

HF-free survival curves stratified by clusters were calculated by the Kaplan–Meier estimator and compared by the log-rank test.

A univariable Cox regression model was fitted to estimate the association between clusters and the risk of HF/death. The hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were reported.

A multivariable Cox model was fitted to adjust the effect of clusters on HF/death for potential confounders (not already included in cluster analysis) selected through a stepwise approach.

To assess the robustness of the results, a sensitivity analysis was performed (i) to assess the association between clusters and risk of HF with a multivariable Fine and Gray competing-risk regression model, considering death as a competing event [the subdistribution HRs (sHRs) and the corresponding 95% CIs were reported], and (ii) to assess the stability of the clustering by performing multiple imputation of missing data with m = 10. To do this, we performed multiple imputation to obtain 10 different versions of the full dataset; we then performed cluster analysis separately on each of the imputed datasets; we analysed the cluster analysis results for each imputed dataset and evaluated the stability of the clusters obtained from the different imputations using the Rand index. A Rand index of 1 indicates complete agreement between clusters, while a Rand index of 0 indicates complete disagreement.

For all tested hypotheses, two-tailed *P*-values < 0.05 were considered to be significant.

Analyses were performed using STATA software, release 16 (StataCorp LP, College Station, TX, USA).

Results

Among the total DAVID-Berg population (*N* = 623), 596 patients with an LVEF above 40% were eligible for this study: Due to residual missing data in candidate variables for cluster analysis, a total of 591 patients were finally included.

Overall, the median age of the study population was 70 years; 55.5% were males, mostly hypertensive (89.4%); half had a history of CVD; one third had diabetes mellitus; and one fourth had renal dysfunction (Table 1).

According to the elbow method, which indicates k = 3 as the optimal number of clusters, cluster analysis (based on 18 variables reported in Table 1) divided the sample into three groups: Cluster 1 is composed by 312 patients, Cluster 2 by 202 patients and Cluster 3 by 77 patients.

The variables significantly different among the groups were age ($P = 0.019$), body mass index (BMI) ($P < 0.001$), systolic blood pressure ($P < 0.001$), glycaemia ($P = 0.002$), total cholesterol ($P < 0.001$), triglycerides ($P < 0.001$), eGFR ($P < 0.001$), NT-proBNP ($P < 0.001$), arterial elastance ($P = 0.008$), LAVI ($P < 0.001$), LVEF ($P = 0.003$) and E/e' ($P = 0.033$) (Table 1).

Moreover, considering other characteristics (not included in cluster analysis), the three clusters were also different for sex ($P = 0.019$), smokers ($P = 0.049$), metabolic syndrome ($P = 0.047$), chronic kidney disease (CKD) ($P = 0.005$) and atrial fibrillation ($P < 0.001$) (Table 1).

Precisely, as compared with Cluster 2 and even more with Cluster 1, Cluster 3 individuals were older ($P < 0.001$). Furthermore, subjects in Cluster 3 had a lower BMI ($P < 0.001$), a lower frequency of the metabolic syndrome ($P = 0.025$) and a higher frequency of CKD ($P = 0.014$) with a lower eGFR ($P < 0.001$) compared with Cluster 1. The LAVI was significantly higher in Cluster 3 compared with Clusters 1 and 2 (both $P < 0.001$), while there were no differences between Clusters 1 and 2 ($P = 0.12$). The LVEF was significantly lower in Cluster 3, compared with Cluster 1 ($P < 0.001$), and in Cluster 2, compared with Cluster 1 ($P = 0.024$). LV-indexed end-systolic volume was higher in Cluster 3 compared with Cluster 1 ($P = 0.009$), with no other differences between clusters. Finally, we found lower arterial elastance in Cluster 1 compared with Cluster 2 ($P = 0.010$). Figure 2 summarizes the main characteristics of the three phenoclusters.

Risk of HF and death

The composite outcome of interest was incident HF and all-cause death. During a median follow-up of 5.7 years (25th–75th percentiles 5.3–5.9), the composite outcome occurred in 29 (9.3%) subjects in Cluster 1, 28 (13.9%) in Cluster 2 and 22 (28.6%) in Cluster 3 ($P < 0.001$), corresponding to an incidence rate (IR) of 1.7, 2.6 and 5.4 per 100 patient-year (pt-yr), respectively (Table 2).

Figure 3 reports the Kaplan–Meier survival curves for the composite outcome according to the three clusters: Compared with Clusters 1 and 2, Cluster 3 was associated with a significantly worse prognosis (log-rank $P < 0.001$). In particular, patients in Cluster 3 had a 2.5 times higher risk of HF/death (adjusted HR = 2.46, 95% CI 1.24–4.90, $P = 0.010$) than those in Cluster 1.

Figure 2 Phenocluster characteristics. Cluster 1: higher body mass index with a higher prevalence of metabolic syndrome, low N-terminal pro-brain natriuretic peptide (NT-proBNP) and better renal function, no left atrial enlargement. Cluster 2: mainly females with intermediate values of NT-proBNP and estimated glomerular filtration rate (eGFR) with respect to Clusters 1 and 3, no left atrial enlargement. Cluster 3: mainly older males with higher NT-proBNP, lower eGFR and a higher prevalence of atrial fibrillation with an enlarged left atrium.

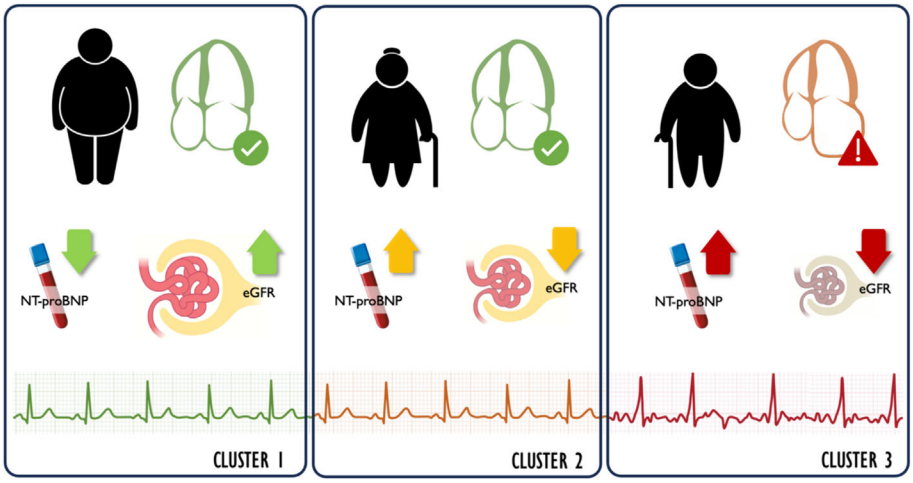


Table 2 Association between clusters and HF/death.

	Events/*N*	IR %pt-yrs (95% CI)	Crude effect Harrell's C: 0.58		Adjusted effect[a] Harrell's C: 0.73	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Cluster						
1	29/312 (9.3%)	1.7 (1.2–2.5)	1.00 (ref)		1.00 (ref)	
2	28/202 (13.9%)	2.6 (1.8–3.7)	1.44 (0.85–2.42)	0.171	1.34 (0.78–2.30)	0.288
3	22/77 (28.6%)	5.4 (3.5–8.1)	2.99 (1.71–5.20)	<0.001	2.46 (1.24–4.90)	0.010

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; pt-yrs, patient-years; ref, reference.
[a]Adjusted effect: multivariable model adjusted for age, smoke, diabetes, atrial fibrillation and metabolic syndrome (variables not included in the cluster analysis).

Sensitivity analysis: (i) Risk of HF

Results of sensitivity analysis further confirmed that patients in Cluster 3 had the highest risk of HF: Compared with Cluster 1, the adjusted sHR of HF was 4.75, 95% CI 2.34–9.66 ($P < 0.001$), considering death as a competing event (Figure S1).

Sensitivity analysis: (ii) Stability of clustering after different imputations

Figure S2 shows the cross-tabulation of the main clusters along the three clusters created after each of the 10 imputations. This analysis shows the good stability of the main clusters compared with those obtained after 10 different imputations of missing values. The Rand index always remained above 0.81 and, in particular, was higher than 0.97 in 6 out of 10 cases, indicating that the clusters obtained after imputation overlapped with the main clusters.

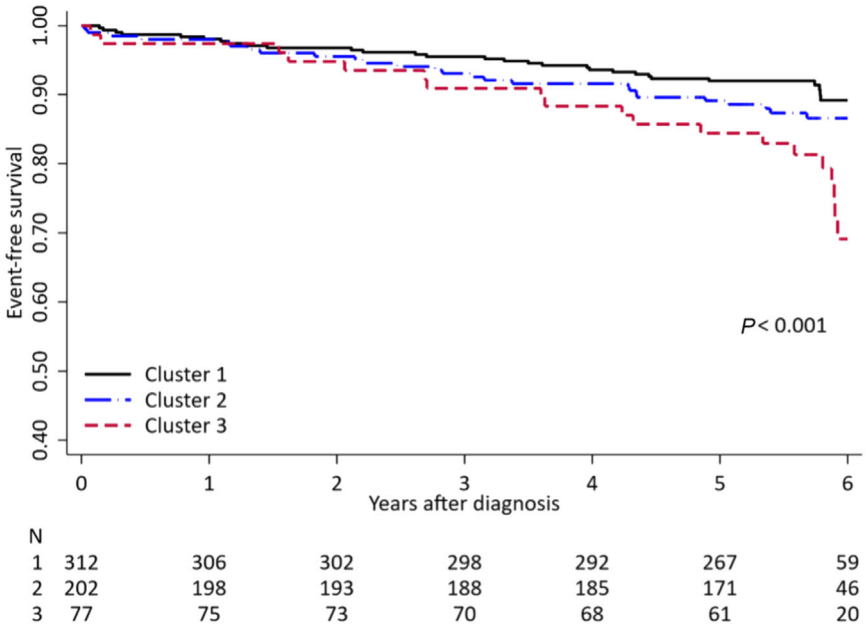
In all 10 imputed datasets, Cluster 3 was significantly associated with a worse outcome (Figure S3).

Discussion

DAVID-Berg data show that patients with preclinical HFmrEF and HFpEF cluster into a phenotype characterized by older age and a higher comorbidity burden, as expressed by lower eGFR, prevalence of diastolic dysfunction and atrial fibrillation, with a consequently higher natriuretic peptide value. These findings are concordant with previously published data on the clinical phase of the disease[18] and suggest targeting a subset of asymptomatic at-risk individuals, comprising elderly people with lower kidney function, for more intensive preventive strategies.

HF prevalence is nowadays increasing due to the ageing of the population and the availability of effective evidence-based therapies or interventions that prolong life expectancy. Thus, HF has become a major global public health issue.[19] Recognizing which at-risk subjects might deserve more effort is challenging, especially in preclinical HFpEF. Different variables have already been acknowledged.

Figure 3 Event (heart failure/death)-free survival according to cluster analysis. Cluster 1 versus 2: $P = 0.139$; Cluster 1 versus 3: $P < 0.001$; and Cluster 2 versus 3: $P = 0.008$.



Nonetheless, at-risk subjects, such as elderly people and/or those with kidney failure, do not routinely perform a cardiological consultation or have a formal indication to check natriuretic peptides. Our data obtained using phenomapping, a statistical method able to simultaneously integrate many pieces of information (clinical data, ECG and echocardiographic ones and laboratory results), should be considered supportive of clinical practice rather than a substitute, and they might be used to strengthen our efforts in the specific phenotype of patients. Data on phenomapping in the preclinical HF population are limited, as opposed to the clinical phase of the disease. However, diagnosing HFpEF can be challenging and is easily misdiagnosed. Signs of right-sided HF and fluid retention are frequently absent, and the presence of comorbidities further complicates the attribution of dyspnoea to HF. As compared with the latest large-scale trial on the HFpEF population,[20,21] apart from the obvious difference in the New York Heart Association (NYHA) class, we observed higher eGFR and lower NT-proBNP levels in our study population despite a higher mean age. Furthermore, patients with clinical HFpEF exhibited a significantly higher burden of atrial fibrillation compared with our preclinical population. These findings align with the concept of HF as a progressive syndrome, and Cluster 3 might fit into the spectrum of HF just before the onset of the clinical disease.

Indeed, phenomapping allowed us to identify a cluster of preclinical HFpEF/HFmrEF patients with a phenotype at higher risk, comprising a higher prevalence of older age, atrial fibrillation, lower kidney function and elevated NT-proBNP. Such a population is representative of the 'older, vascular aging' clinical phenotype, which is frequently encountered even in the clinical phase of the HFpEF syndrome.[22,23] Conversely, a lower risk cluster was characterized by more prevalent obesity and metabolic syndrome. Indeed, such evidence is consistent with phenomapping results previously obtained in a clinical HFpEF population,[18] where the cluster at higher risk of events was similarly characterized by older age, lower BMI, higher NT-proBNP and a higher likelihood of kidney failure.

A possible explanation for our findings might be the strong link between lower kidney function and HFpEF. In fact, CKD is considered a risk factor for incident HFpEF.[24] Indeed, CKD is associated with hypertension and is followed by activation of a systemic inflammatory reaction and endothelial dysfunction, with myocardial stiffening, hypertrophy and interstitial fibrosis.[24] Interestingly, it has been shown that CKD is associated with impaired peak cardiac performance and myocardial remodelling not only in HFpEF but also in a population without symptomatic HF.[25] Besides, altered metabolic pathways induced by renal disease have been held accountable for HFpEF progression.[26,27] The DAVID-Berg results are concordant with this previous evidence and underline the need for intensive HF preventive strategies in individuals with lower eGFR. Among these, therapeutic regimens based on sodium-glucose cotransporter 2 inhibitors (SGLT2is) have

new strong evidence of efficacy in CKD because of their nephroprotective properties and might indeed be considered in preclinical HFmrEF/HFpEF settings, such as the DAVID-Berg study. In fact, SGLT2is have proved to be effective not only in patients with diabetes mellitus (stage A and B HF) and throughout the LVEF spectrum in symptomatic HF[20,21,28] but also in patients with kidney failure.[29–31] Beyond SGLT2is, finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, demonstrated its beneficial effects on CKD progression, cardiovascular events[32,33] and reducing new-onset HF[34] in patients with type 2 diabetes and CKD.[35] Thus, finerenone might also be considered as a possible effective therapy in preclinical HFmrEF and HFpEF.

Moreover, the higher risk cluster was characterized by a larger left atrium. Despite the lack of differences in E/e', the greater dimension of the left atrium may reflect chronic subclinical diastolic dysfunction, which is a strong predictor of incident adverse events such as HF and death.[6] Importantly, in the context of HFpEF, more attention has recently been placed on left atrial remodelling, which is now considered a potential therapeutic target and an endpoint for the evaluation of novel therapies.[36] Even if the progression from diastolic dysfunction to HFpEF is a complex and unsolved issue, emerging evidence suggests that left atrial remodelling might also play a significant role in this transition.[36] These findings overall confirm that echocardiography is justified even in the preclinical HF stage, whenever risky patients are selected, as in DAVID-Berg, and suggest that left atrial remodelling might represent a possible therapeutic target in preclinical HFmrEF/HFpEF.[36]

Finally, concerning natriuretic peptides, the higher risk phenotype (Cluster 3) presented higher values, which may be explained by the following: First, Cluster 3 comprises older DAVID-Berg individuals, and ageing is already acknowledged as the main non-cardiac cause of higher natriuretic peptides.[37] In fact, National Institute for Health and Care Excellence (NICE) HF guidelines recommend higher natriuretic peptide cut-offs according to age.[38] Second, it is well known that patients with cardiovascular risk factors, such as arterial hypertension and previous CVD, have higher natriuretic peptide values.[39] Third, another explanation might be the higher prevalence of atrial fibrillation in the higher risk phenotype, as natriuretic peptide cut-off values change in patients with atrial fibrillation compared with sinus rhythm. Lastly, individuals in Cluster 3 had lower eGFR, which is also associated with higher natriuretic peptide concentrations.[40]

The limitations of our analysis should be noted. First, despite multivariable adjustment, residual confounding cannot be excluded. Second, the inclusion and exclusion criteria of the DAVID-Berg study limit the generalizability of our results to other community settings. In particular, the DAVID-Berg study included only high-risk Caucasian participants. Nonetheless, DAVID-Berg baseline characteristics are similar to those described in other community studies, such as in Olmsted County, Minnesota.[41] The confirmation of DAVID-Berg results in larger studies and other community settings is warranted. Third, patient-reported symptoms might be biased, for example, by self-limitation of physical activity. Thus, it might be argued that not all these subjects were completely asymptomatic. Finally, the dataset enrolled patients in 2008, and follow-up ended in 2014. Thus, this might not entirely reflect contemporary management.

In conclusion, cluster analysis allowed us to define a phenotype of asymptomatic community-dwelling individuals with preclinical HFmrEF/HFpEF at higher risk of a worse outcome, comprising a higher proportion of older subjects with lower kidney function and more prevalent atrial fibrillation/diastolic dysfunction. Of note, this cluster was closely comparable to the previously reported higher risk phenotype of overt HFpEF. Such a preclinical patient phenotype might deserve more screening efforts and therapeutic interventions.

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Conflict of interest statement

The authors declare no conflicts of interest.

Supporting information

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

Figure S1. Cumulative Incidence Function (CIF) and adjusted subdistribution Hazard Ratios (sHR) of HF from a competing risk model (death as competing event). *The competing risk model was adjusted for age, smoke, diabetes, atrial fibrillation, and metabolic syndrome (variables not included in cluster analysis and selected by a stepwise approach).
Figure S2. Cross tabulation of main clusters 1–3 vs. clusters 1–3 created after 10 imputations. The figure shows the proportion of main clusters along the three clusters created after the 10 imputations: it gives a visual indication of whether the groups are significantly different from the main groups. A Rand index of 1 indicates complete agreement between clusters, while a Rand index of 0 indicates complete disagreement.
Figure S3. Event (HF/death)-free survival according to cluster analysis after 10 imputations.

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