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SHORT REPORT

A machine learning-derived echocardiographic algorithm identifies people at risk of heart failure with distinct cardiac structure, function, and response to spironolactone: findings from the HOMAGE trial

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Aim

An echocardiographic algorithm derived by machine learning (e′VM) characterizes pre-clinical individuals with different cardiac structure and function, biomarkers, and long-term risk of heart failure (HF). Our aim was the external validation of the e′VM algorithm and to explore whether it may identify subgroups who benefit from spironolactone.

Methods and results

The HOMAGE (Heart OMics in AGEing) trial enrolled participants at high risk of developing HF randomly assigned to spironolactone or placebo over 9 months. The e′VM algorithm was applied to 416 participants (mean age 74 ± 7 years, 25% women) with available echocardiographic variables (i.e. e′ mean, left ventricular end-diastolic volume and mass indexed by body surface area [LVMi]). The effects of spironolactone on changes in echocardiographic and biomarker variables were assessed across e′VM phenotypes. A majority (>80%) had either a 'diastolic changes' (D), or 'diastolic changes with structural remodelling' (D/S) phenotype. The D/S phenotype had the highest LVMi, left atrial volume, E/e', natriuretic peptide and troponin levels (all $p < 0.05$). Spironolactone significantly reduced E/e' and B-type natriuretic peptide (BNP) levels in the D/S phenotype ($p < 0.01$), but not in other phenotypes ($p > 0.10$; $p_{interaction} < 0.05$ for both). These interactions were not observed when considering guideline-recommended echocardiographic structural and functional abnormalities. The magnitude of effects of spironolactone on LVMi,

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left atrial volume and a type I collagen marker was numerically higher in the D/S phenotype than the D phenotype but the interaction test did not reach significance.

Conclusions In the HOMAGE trial, the e′VM algorithm identified echocardiographic phenotypes with distinct responses to spironolactone as assessed by changes in E/e' and BNP.

Keywords Heart failure • Echocardiogram • Collagen • Spironolactone • Biomarkers

Introduction

Cardiac dysfunction often exists and progresses for years before the onset of clinical heart failure (HF).[1] Echocardiographic screening for abnormalities of cardiac structure or function in asymptomatic individuals may predict the future development of HF.[2,3] However, widely accepted echocardiogram-based diagnostic algorithms for assessment of cardiac abnormalities are not yet established as tools to risk stratify patients at risk of future HF.

In a recent report, we used a machine learning approach fueled by echocardiographic variables to develop an algorithm (the e′VM algorithm) which characterizes asymptomatic individuals with distinct cardiac structure and function, different proteomic data, and differing long-term risk of developing HF.[4] However, the study was conducted in a relatively young population with a low comorbidity burden. It is not clear whether this e′VM algorithm provides appropriate information in individuals at high risk of developing HF. In addition, whether the e′VM echocardiographic phenotypes identifies patients more likely to benefit from preventive treatment (such as mineralocorticoid receptor antagonists [MRA]) is unknown.

The Heart OMics in AGEing (HOMAGE) trial evaluated the effect of spironolactone (an MRA) in patients at risk of HF. It provides a unique opportunity to explore whether the e′VM algorithm identifies asymptomatic individuals with different biological profiles who may benefit from spironolactone treatment.[5]

In the present analysis, we explored whether the e′VM algorithm identified patients at risk of HF with different characteristics who had different responses to spironolactone treatment.

Methods

The design and main results of the HOMAGE trial have previously been reported.[5,6] Briefly, the HOMAGE trial was a randomized placebo-controlled, double-blind trial, assigning 527 patients at high risk of HF to receive either spironolactone or placebo for up to 9 months. The current post-hoc analysis included the 416 participants who had available echocardiographic variables which are incorporated in an echocardiography algorithm (i.e. e′ mean, left ventricular end-diastolic volume index [LVEDVi] and left ventricular mass index [LVMi]; e′VM algorithm). To classify e′VM phenotypes, participants were first split by e′ mean: if e′ mean was <10 cm/s, patients were categorized by a combination of thresholds for LVEDVi and LVMi. Phenotypes were labelled: (a) mostly normal (MN); (b) diastolic changes (D); and (c) diastolic changes with structural remodelling (D/S) as shown in online supplementary *Figure S1.*.[4] As mean age of patients in the HOMAGE trial is higher than that in the Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux (STANISLAS) cohort (from which the e′VM algorithm was derived), the thresholds for e′ mean, LVEDVi and LVMi were modified by age using decade-specific limits (online supplementary *Table S1.*).

Echocardiograms were analysed offline by a single experienced operator, blinded to clinical data, using dedicated software (Echo PAC, GE Healthcare) as recently recommended.[7,8] Measurement reproducibility has been reported.[9] Procollagen type I C-terminal propeptide (PICP) was measured by enzyme immunoassay (METRA; Quidel Corporation®), procollagen type III N-terminal propeptide (PIIINP) and collagen type I C-terminal telopeptide (CITP) by radio-immunoassay (Orion Diagnostica®), galectin-3 by enzyme-linked immunosorbent assay (ELISA) (BG Medicine®), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hsTnT) and growth differentiation factor-15 (GDF-15) by electro-chemi-luminescence (ELECSYS® 2010 analyser; Roche Diagnostics, Mannheim, Germany), and B-type natriuretic peptide [BNP] by using Olink Proseek® Multiplex Cardiovascular II, blinded to clinical data and randomization.

Categorical variables are presented as frequencies (percentages) and continuous variables as median (25th and 75th percentiles). Comparisons of baseline characteristics across echocardiographic phenotypes were analysed using analysis of variance, Kruskal–Wallis and χ^2 tests, as appropriate. Analysis of covariance was used for changes in echocardiographic and biomarker variables by the effect of spironolactone after adjustment for age, sex, body mass index (BMI), a prevalence of hypertension, diabetes and estimated glomerular filtration rate. Interaction between spironolactone effect and echocardiographic phenotypes on changes in echocardiographic variables and circulating biomarkers was assessed. Statistical analyses were performed using R version 4.0.2 (R Development Core Team, Vienna, Austria). A two-sided *p*-value <0.05 was considered statistically significant.

Results

The 416 participants included in the present analysis had a similar profile to those included in HOMAGE (data not shown) with a median age of 73 years (25th and 75th centiles 69–78); 24.5% were women (*Table 1*).

Age, BMI, cardiovascular risk factors/diseases (i.e. hypertension, coronary artery disease and renal function) were similar across e′VM phenotypes except for a lower prevalence of diabetes in the MN phenotype, a higher number of women in the D phenotype and higher systolic blood pressure in the D/S phenotype ($p < 0.05$). The D phenotype represented half of the participants ($n = 200$, 48%), and had the smallest left ventricular (LV) and left atrial (LA) volumes. The D/S phenotype ($n = 147$) had the highest LV mass, volumes, LA volumes indexed by body surface area (LAVi), lowest

Table 1 Clinical characteristics according to the e′VM echocardiographic phenotypes

	Overall ($n=416$)	MN type ($n=66$)	D type ($n=200$)	D/S type ($n=150$)	*p*-value
Age, years	74 ± 7	74 ± 6	73 ± 6	74 ± 7	0.96
Women	102 (24.5)	11 (16.7)	62 (31.0)	29 (19.3)	**0.012**
BMI, kg/m^2	29 ± 5	28 ± 5	28 ± 5	29 ± 5	0.34
Smoking	32 (7.7)	4 (6.1)	13 (6.5)	15 (10.0)	0.41
Medical history					
Hypertension	321 (77.2)	51 (77.3)	147 (73.5)	123 (82.0)	0.17
Diabetes	172 (41.3)	16 (24.2)	91 (45.5)	65 (43.3)	**0.008**
Coronary artery disease	299 (71.9)	52 (78.8)	142 (71.0)	105 (70.0)	0.39
Myocardial infarction	166 (39.9)	25 (37.9)	76 (38.0)	65 (43.3)	0.56
Stroke or TIA	19 (4.6)	3 (4.5)	7 (3.5)	9 (6.0)	0.54
COPD	23 (5.5)	5 (7.6)	13 (6.5)	5 (3.3)	0.32
Medications					
ACEi or ARB	326 (78.4)	54 (81.8)	156 (78.0)	116 (77.3)	0.75
Beta-blocker	293 (70.4)	46 (69.7)	138 (69.0)	109 (72.7)	0.75
CCB	83 (20.0)	16 (24.2)	34 (17.0)	33 (22.0)	0.33
Lipid-lowering therapy	342 (82.2)	54 (81.8)	166 (83.0)	122 (81.3)	0.92
Antiplatelet	337 (81.0)	57 (86.4)	156 (78.0)	124 (82.7)	0.26
Clinical profile					
Systolic BP, mmHg	143 ± 21	139 ± 21	141 ± 20	146 ± 21	**0.034**
Heart rate, bpm	62 ± 9	61 ± 10	62 ± 9	61 ± 9	0.47
Laboratory data					
Haemoglobin, g/dl	14.0 ± 1.4	14.0 ± 1.4	14.0 ± 1.3	13.9 ± 1.4	0.86
Sodium, mmol/l	139.1 ± 2.9	138.6 ± 3.5	138.8 ± 2.8	139.7 ± 2.5	**0.003**
Potassium, mmol/l	4.3 ± 0.4	4.3 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	0.44
eGFR, ml/min/1.73 m^2	71 ± 16	69 ± 16	71 ± 16	72 ± 16	0.63
Echocardiographic variables					
LVEDVi, ml/m^2	43 ± 11	44 ± 10	38 ± 8	49 ± 11	**<0.001**
LVEF, %	62 ± 7	62 ± 6	63 ± 7	60 ± 8	**0.001**
LVMi, g/m^2	98 ± 27	93 ± 27	84 ± 15	120 ± 25	**<0.001**
LVMi >115 ml/m^2 in men or LVMi >95 ml/m^2 in women	121 (29.2)	15 (23.4)	19 (9.5)	87 (58.0)	**<0.001**
LAVi, ml/m^2	32 ± 9	34 ± 10	29 ± 7	35 ± 10	**<0.001**
LAVi >34 ml/m^2	141 (34.4)	26 (41.3)	41 (20.7)	74 (49.7)	**<0.001**
E/A ratio	0.9 ± 0.3	1.1 ± 0.4	0.9 ± 0.3	0.8 ± 0.3	**<0.001**
e' lateral, cm/s	8.7 ± 2.8	12.8 ± 2.6	8.2 ± 2.0	7.7 ± 2.3	**<0.001**
e' septal, cm/s	6.0 ± 1.7	7.9 ± 1.9	5.9 ± 1.4	5.4 ± 1.3	**<0.001**
e' septal <7 cm/s or e' lateral <10 cm/s	354 (85.3)	21 (32.3)	187 (93.5)	146 (97.3)	**<0.001**
E/e' mean	9.8 ± 3.3	7.6 ± 2.1	10.0 ± 3.1	10.5 ± 3.6	**<0.001**
E/e' mean >14	40 (9.8)	1 (1.5)	19 (9.6)	20 (13.7)	**0.022**
Echocardiographic strain					
GLS, % ($n=73$)	−17.8 ± 2.4	−18.4 ± 2.7	−17.9 ± 2.3	−17.0 ± 2.7	0.26
LA reservoir strain, % ($n=111$)	24.8 ± 4.8	24.4 ± 4.4	24.9 ± 5.2	24.8 ± 4.2	0.92
LA conduit strain, % ($n=111$)	10.4 ± 3.5	10.6 ± 3.1	10.4 ± 3.5	10.4 ± 4.1	0.98
LA contractile strain, % ($n=111$)	14.4 ± 3.9	13.9 ± 3.5	14.5 ± 4.1	14.4 ± 3.8	0.80
Biomarker profiles					
PIIINP, µg/L	3.9 (3.1–5.0)	3.9 (3.2–5.1)	3.8 (3.0–4.9)	4.1 (3.0–5.3)	0.27
PICP, µg/L	79.4 (64.7–96.0)	77.7 (62.5–92.2)	76.9 (63.2–93.2)	81.7 (68.1–99.7)	0.12
CITP, µg/L	3.7 (2.8–4.8)	3.5 (2.9–4.6)	3.7 (2.8–4.9)	3.7 (2.8–4.8)	0.99
GDF-15, ng/L	1434 (1061–2148)	1449 (963–1878)	1398 (1049–2174)	1466 (1092–2338)	0.28

Table 1 (Continued)

	Overall (*n* = 416)	MN type (*n* = 66)	D type (*n* = 200)	D/S type (*n* = 150)	*p*-value
Galectin-3, μg/L	16.2 (13.5–20.0)	15.4 (12.9–19.5)	16.2 (13.1–19.6)	16.6 (14.1–20.7)	0.13
NT-proBNP, pg/ml	208 (134–342)	166 (125–289)	201 (128–329)	247 (150–450)	**0.003**
BNP (NPX)	2.7 ± 1.1	2.6 ± 1.2	2.6 ± 1.0	2.9 ± 1.2	**0.046**
High-sensitivity troponin T, ng/L	12.8 (8.9–18.1)	12.1 (8.8–16.6)	12.0 (8.0–17.0)	14.2 (10.1–19.4)	**0.007**

Values are expressed as mean ± standard deviation, *n* (%), or median (25th–75th percentile).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CCB, calcium channel blocker; CITP, collagen type-I C-terminal telopeptide; COPD, chronic obstructive pulmonary disease; D, diastolic changes; D/S, diastolic changes with structural remodelling; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; GLS, global longitudinal strain; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MN, mostly normal; NPX, normalized protein expression; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PICP, procollagen type I C-terminal propeptide; PIIINP, procollagen type III N-terminal propeptide; TIA, transient ischaemic attack.

LV ejection fraction (LVEF) (despite having a mean LVEF of 60%), and lowest e' as well as highest E/e' (*Table 1*).

Echocardiographic strain parameters for the left ventricle and atrium were not significantly different across e'VM phenotypes ($p > 0.10$) (*Table 1*).

Patients with the D/S phenotype had the highest serum concentrations of NT-proBNP, BNP, troponin T and hsTnT (all $p < 0.05$). PICP, CITP, PIIINP, GDF-15 and galectin-3 did not differ between phenotypes (*Table 1*).

During the 9-month period, spironolactone effect on E/e', NT-proBNP and BNP was more pronounced in people with the D/S phenotype versus those with the D phenotype (p for interaction < 0.05 for all, *Figure 1* and online supplementary *Table S2*). When considering recommended echocardiographic variables defined by the 2016 American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) guidelines, namely, diastolic dysfunction (DD), LV hypertrophy (>95 g/m^2 in women and > 115 g/m^2 in men), LA enlargement (>34 ml/m^2), abnormal e' by a septal e' <7 cm/s or lateral e' <10 cm/s, and increased E/e' (>14),[7,10] we found no significant interaction with MRA response, except for a more pronounced reduction of NT-proBNP and BNP in patients who had a LA enlargement (p for interaction < 0.05). The magnitude of the effect of spironolactone on serum PICP was higher in the D/S phenotype (delta, −12.6, 95% confidence interval [CI] −20.5 to −4.8, $p = 0.002$) than in the D phenotype (delta, −6.3, 95% CI −12.2 to −0.4, $p = 0.04$), although this differential effect did not reach significance (p for interaction = 0.21) (*Figure 1*). Significant decreases in LVMi and LAVi were also observed only in the D/S phenotype (p for interaction > 0.10). The effect of spironolactone on LVEDVi, systolic blood pressure and PIIINP was similar across the three phenotypes (online supplementary *Table S2*).

Discussion

In the present analysis of the HOMAGE trial, we report that our e'VM classification system derived from echocardiographic data using a machine learning-based algorithm identified subgroups of people at risk of developing HF with different echocardiographic variables, circulating biomarkers of cardiac stress and damage and of collagen metabolism, and response to spironolactone. Specifically, people with the D and D/S phenotypes had higher E/e', and those with the D/S phenotype had greater structural remodelling of the left ventricle and atrium as well as higher levels of circulating biomarkers reflecting congestion (i.e. natriuretic peptides) and myocardial damage (i.e. troponin). The magnitude of the antifibrotic and anti-remodelling effects of spironolactone was more pronounced in the D/S phenotype. These findings underscore the potential value of the e'VM classification for screening asymptomatic, but at-risk, individuals and for identifying those more likely to benefit from spironolactone, which might prevent or delay the onset of HF.

The e'VM algorithm significantly predicted MRA response on E/e', BNP and NT-proBNP, whereas guideline-recommended DD classification, LVH, abnormal e' or increased E/e' did not. The favourable effects of spironolactone were more pronounced in the D/S phenogroup. The changes in collagen peptides were also more pronounced in the D/S phenotype, but without reaching statistical significance. These results suggested that, even in patients prior to the onset of HF, those who had cardiac structure and function remodelling were more likely to experience antifibrotic and natriuretic effects of spironolactone, which is also supported by prior reports.[11,12] In addition, interestingly, we observed a significant interaction between LA enlargement and MRA response on natriuretic peptides, which may be partly supported by the natriuretic effect of spironolactone[13]; however, no significant interaction was identified with E/e'.

Studies examining the impact of MRA therapy on cardiac structure and function in HF with preserved ejection (HFpEF) have yielded conflicting results.[14] In the Aldosterone Receptor Blockage in Diastolic Heart Failure (Aldo-DHF) trial ($n = 442$), patients assigned to receive spironolactone had a greater fall in LV mass and improvement in diastolic function compared to those with placebo.[15] By contrast, in a sub-study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial ($n = 239$), neither cardiac structural nor functional remodelling was affected by spironolactone as compared with placebo.[16] The population enrolled in the HOMAGE trial had

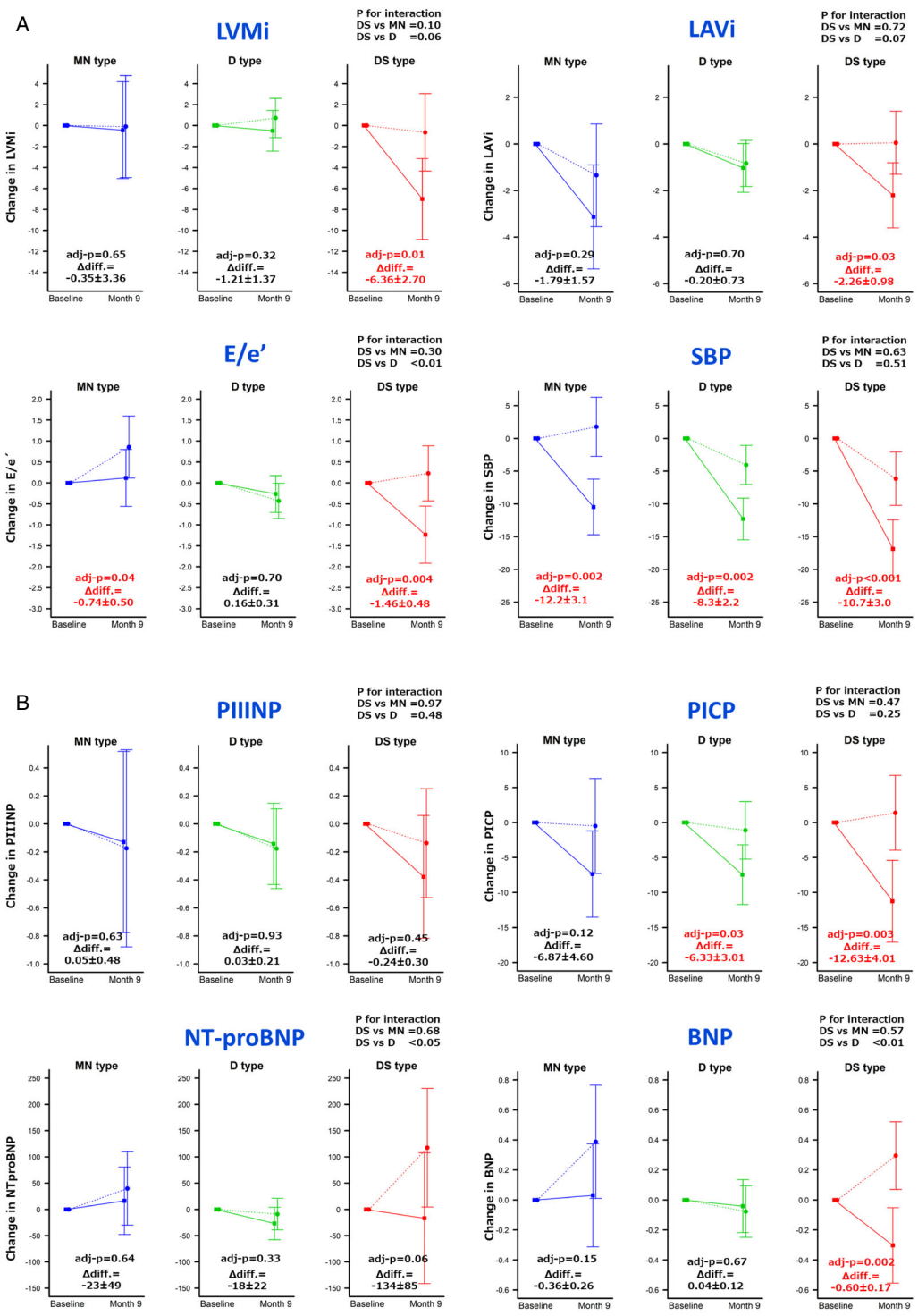

Figure 1 Change in echocardiographic variables, blood pressure and biomarkers in response to spironolactone according to the e′VM phenotypes. (*A*) Changes in left ventricular mass index (LVMi), left atrial volume index (LAVi), E/e' and systolic blood pressure (SBP) over 9 months between spironolactone/placebo groups according to the e′VM classification. (*B*) Changes in collagen biomarkers (i.e. procollagen type III N-terminal propeptide [PIIINP] and procollagen type I C-terminal propeptide [PICP]) and natriuretic peptide (i.e. N-terminal pro-B-type natriuretic peptide [NT-proBNP] and B-type natriuretic peptide [BNP]) over 9 months between spironolactone/placebo groups according to the e′VM classification. *p*-values were adjusted for age, sex, body mass index, a prevalence of hypertension, diabetes mellitus, glomerular filtration rate and baseline echocardiographic/proteomic variables. D, diastolic changes; D/S, diastolic changes with structural remodelling; MN, mostly normal.

similar abnormalities of LV and LA structure and diastolic function as those in large clinical trials of HFpEF.[5] Therefore, our results showing a favourable effect of spironolactone treatment predominantly in the D/S phenotype suggest that the e′VM classification can identify a subgroup in the pre-clinical HFpEF category whose impaired cardiac structure and function are more likely to improve with spironolactone treatment. The results further suggest that the benefit from spironolactone is more likely in patients with some degrees of cardiac structural and functional abnormalities, which may eventually be useful to guide preventive strategies in the future.

The main limitation of the current study was the post-hoc nature, a relatively moderate sample size, and should be regarded as hypothesis-generating; thus, prospective validation with a dedicated trial is warranted to ascertain whether the e′VM-based classification predicts MRA response. Eventually, an e′VM classification-guided preventive HF trial would be worthy of investigation to ascertain whether this new echocardiographic classification can be applied to identify individuals at risk of HF, and those who are more likely to require early initiation of specific disease-modifying agents. Age-based cut-offs, in addition, were supported by prior studies but not guidelines.[17,18] Lastly, we cannot completely rule out early stages of cardiac amyloidosis in some patients enrolled in the trial.

In conclusion, in the HOMAGE trial, the e′VM classification system identified asymptomatic subgroups with distinct abnormalities of cardiac structure and function that are more likely to have chronically elevated filling pressures and myocardial damage/injury. The magnitude of the effects of spironolactone on these cardiac abnormalities and circulating biomarkers differed with classification. These findings may support the use of the e′VM algorithm to identify participants at higher risk of HF and guide preventive HF treatment.

Supplementary Information

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

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