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# Risk stratification with echocardiographic biomarkers in heart failure with preserved ejection fraction: the media echo score

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## Abstract

**Aims** Echocardiographic predictors of outcomes in heart failure with preserved ejection fraction (HFpEF) have not been systematically or independently validated. We aimed at identifying echocardiographic predictors of cardiovascular events in a large cohort of patients with HFpEF and to validate these in an independent large cohort.

**Methods and results** We assessed the association between echocardiographic parameters and cardiovascular outcomes in 515 patients with heart failure with preserved left ventricular (LV) ejection fraction (>50%) in the MEtabolic Road to DIAstolic Heart Failure (MEDIA) multicentre study. We validated our findings in 286 patients from the Karolinska-Rennes Prospective Study of HFpEF (KaRen). After multiple adjustments including N-terminal pro-brain natriuretic peptide (NT-proBNP), the significant predictors of death or cardiovascular hospitalization were pulmonary arterial systolic pressure > 40 mmHg, respiratory variation in inferior vena cava diameter > 0.5, E/e' > 9, and lateral mitral annular s' < 7 cm/s. The combination of these four variables differentiated patients with <10% vs. >35% 1 year risk. Adding these four echocardiographic variables on top of clinical variables and NT-proBNP yielded significant net reclassification improvement (33.8%,  $P < 0.0001$ ) and increase in C-index (5.3%, a change from 72.2% to 77.5%,  $P = 0.015$ ) of similar magnitude as the addition of NT-proBNP on top of clinical variables alone. In the KaRen cohort, these four variables yielded a similar improvement in net reclassification improvement (22.3%,  $P = 0.014$ ) and C-index (4.0%,  $P = 0.029$ ).

**Conclusions** Use of four simple echocardiographic parameters (within the MEDIA echo score), indicative of pulmonary hypertension, elevated central venous pressure, LV diastolic dysfunction, and LV long-axis systolic dysfunction, independently predicted prognosis and improved risk stratification additionally to clinical variables and NT-proBNP in HFpEF. This finding was validated in an independent cohort.

**Keywords** Heart failure, diastolic; Preserved ejection fraction; Echocardiography; Cardiac oedema; Diastolic function; Risk prediction; Cardiovascular diseases

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## Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous syndrome resulting from multiple aetiologies characterized by acutely or chronically increased

cardiac filling pressures.<sup>1</sup> Diagnostic algorithms were proposed by Paulus *et al.* and later criteria for diastolic dysfunction by Nagueh *et al.*<sup>2,3</sup> Recently, the HFA-PEFF<sup>4</sup> and H<sub>2</sub>FPEF<sup>5</sup> scores have emerged as important integrative diagnostic tools for HFpEF. Considerable efforts have been made to

identify patients with HFpEF at greatest risk, in whom closer monitoring and/or more intense treatment might improve outcomes, and to identify potential mechanisms that might be targets for therapy.<sup>6</sup> Among a number of stratification tools, cardiac imaging, usually currently used for diagnostic purposes, could be pivotal for improving the correlation between diagnostic information and prognosis and potentially also treatment response in HFpEF.<sup>7</sup>

Importantly, no single echocardiographic parameter is sufficiently accurate and reproducible to be used in isolation for stratifying risk in an individual patient with HFpEF. Recent secondary analyses of large trials in HFpEF identified many echocardiographic variables that might provide additional prognostic insights and predict poor outcomes, including indicators of ventricular and atrial remodelling and left ventricular (LV) filling.<sup>8–12</sup> Congestion and reduced diastolic compliance, rather than reduced LV contractility, appear important for diagnosis and for prediction of cardiac events.<sup>13</sup> Other studies suggest that right ventricular function and load are also important.<sup>14–17</sup> If a number of isolated echocardiographic parameters associated with outcome have been reported, the set of echocardiographic variables most associated with outcome in patients with HFpEF is yet to be better determined. Important progress has been made in HFpEF using multiple variable algorithms, such as the HFA-PEFF<sup>4</sup> and H<sub>2</sub>FPEF scores,<sup>5</sup> but this approach primarily intends to improve diagnosis rather than prognosis assessment.

We speculated that detailed echocardiographic phenotyping of well-characterized patients with HFpEF could yield parameters that correlate with natriuretic peptides and be associated with hospitalization and death from cardiovascular causes. This hypothesis was tested in the prospective cohort of the European MEtabolic Road to DIAstolic Heart Failure (MEDIA) project.<sup>18</sup> We validated our findings in the Swedish–French KaRen HFpEF cohort.<sup>19</sup>

## Methods

### MEDIA project study population

A total of 515 patients with HFpEF were enrolled prospectively from 2011 to 2013 into the MEDIA multicentre study, in 13 participating university hospitals in Europe.

Inclusion criteria according to the then current consensus statement of the European Society of Cardiology<sup>2</sup> were (i) age > 18 years; (ii) signs and symptoms of HF with a preserved LV ejection fraction (LVEF) (>50%) and an LV end-diastolic volume index (LVEDVi) < 97 mL/m<sup>2</sup>; (iii) elevated serum concentration of brain natriuretic peptide [BNP concentration > 100 pg/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP) > 300 pg/mL]; and (iv) patients being able and willing to provide written informed consent.

We excluded all patients with acute myocardial infarction, haemodynamically significant valvular disease, chronic dialysis, chronic liver disease, or any concomitant malignant disease during the previous 5 years.

The primary objective was to evaluate the value of imaging and biological markers to predict cardiovascular prognosis in patients with HFpEF. One of the secondary objectives was to evaluate cardiovascular outcomes including a combined endpoint of death and all cardiovascular hospitalization (whether for HF or another cardiovascular cause).

The study conforms to the principles of the Declaration of Helsinki<sup>20</sup> and was approved by relevant ethics bodies. All subjects provided written informed consent. Patients provided a detailed clinical history, and blood tests (including haematology, biochemistry profile, and NT-proBNP), electrocardiograms, and echocardiograms were obtained on the same day in most patients.

### Echocardiography

All patients underwent echocardiography according to a common protocol, and images were stored in a digital cine-loop format for offline analysis according to the recommendations.<sup>21</sup>

Left ventricular structure and function were evaluated from standard apical four-chamber, apical two-chamber, and parasternal long-axis and short-axis views. Ventricular dimensions, wall thickness, mass, and geometry were determined from 2D parasternal short-axis and long-axis views. LV volumes, stroke volume, and ejection fraction were calculated using the biplane method of disks (modified Simpson's rule). All cardiac chamber volumes and mass measures were indexed to body surface area.

Additional information regarding echocardiographic methods can be found in Supporting Information.

Echocardiographic data were complete in >75% of patients, apart from the following variables: medial *s'*, Ard-Ad, S/D, isovolumic relaxation time (IVRT), and E/Vp (which were available in 59%, 63%, 50%, 65%, and 51% of the population, respectively).

### Natriuretic peptide analysis

Peripheral venous blood samples for natriuretic peptide analysis were obtained on the same day as echocardiography. Raised serum BNP (>100 pg/mL) and NT-proBNP (>300 pg/mL) were used as inclusion criteria, but some subjects were recruited who had normal natriuretic peptide levels as long as they had sufficient other diagnostic criteria to fulfil the requirements for HFpEF.<sup>2</sup> As biomarker endpoint, we used NT-proBNP, both as a continuous variable and a categorical variable using age-specific cut-off values [<50 years

(450 pg/mL), between 50 and 75 years (900 pg/mL), and >75 years (1800 pg/mL)<sup>22</sup>. NT-proBNP measurements were performed on automated analysers after the completion of the study.

## Cardiovascular events

The primary outcome was a composite of admission for worsening HF or cardiovascular causes and cardiac death. Admission for HF was defined as an admission for worsening of relevant symptoms resulting in substantial intensification of treatment for HF. Follow-up was 100% complete with vital status (in September 2015). Primary outcome events were adjudicated by a dedicated committee.

## Replication in the KaRen cohort

It is increasingly recognized that given the heterogeneity of HFpEF, prognostic variables from single studies have been inconsistent and variable and add limited information. Therefore, we performed a validation in an independent cohort, the Swedish–French prospective KaRen study. KaRen included patients with acute signs and symptoms of HF, according to the Framingham criteria, EF  $\geq$  45% and BNP > 100 pg/mL or NT-proBNP >300 pg/mL, between 1 May 2007 and 1 December 2011 in 10 French and 3 Swedish university hospitals.<sup>19</sup> These patients were subsequently seen 4–8 weeks after the acute HF episode for detailed echocardiography and clinical assessment.

## Statistical analyses

Continuous variables are shown as means  $\pm$  standard deviations as specified, and categorical variables are presented as counts and percentages. Logistic regression models were performed to assess the associations between echocardiographic parameters and high level of natriuretic peptides.

Cox proportional hazards models were used to identify factors associated with an increased risk of death and hospitalization (cardiovascular and HF). The follow-up time for each patient was calculated from the date of their first evaluation to the date of reaching death or hospitalization for cardiovascular cause or to the date of their most recent evaluation. Odds ratios and hazard ratios (HRs) are presented with their 95% confidence intervals. In order to account for potential confounding, models were adjusted firstly for age, NT-proBNP (either as a log-transformed continuous variable or as a categorical variable using the thresholds detailed earlier<sup>22</sup>), and glomerular filtration rate and secondly for the same variables and also for body mass index, atrial fibrillation rather than sinus rhythm, and clinical presentation (acute rather than non-acute). We also

computed a multivariable model using a backward selection procedure to determine a subset of variables that were independently associated with high levels of natriuretic peptides (logistic model) or with the primary composite outcome (Cox model). We included in the multivariable model echocardiographic parameters and potential confounding variables that were associated with the dependent variable in univariable analysis (for which  $P$  was <0.10). We used a missing value indicator approach due to some missing values for echocardiographic variables. Multicollinearity was assessed using variance inflation factor in logistic and Cox regression models.

The increased discriminative value associated with the addition of NT-proBNP and echocardiographic variables on top of the aforementioned covariates was evaluated using increase in C-index and continuous net reclassification improvement (cNRI). Changes from a baseline clinical model (including age, estimated glomerular filtration rate, atrial fibrillation, and HF status) were assessed. We also compared the performance of our MEDIA echo score with the HFA-PEFF<sup>4</sup> and H<sub>2</sub>FPEF<sup>5</sup> scores.

All statistical analyses were carried out using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software (the R Foundation for Statistical Computing). The two-tailed significance level was set at  $P < 0.05$ .

## Results

### Baseline clinical characteristics in the MEDIA project (Table 1)

Participants were  $74 \pm 10$  years old, 38% were male, and 71% were in New York Heart Association Class 2. Co-morbidities included hypertension (88%), coronary artery disease (32%), atrial fibrillation (30%), diabetes (39%), and chronic obstructive pulmonary disease (16%). Fifty-one (10%) patients were included in the acute phase during hospitalization for HF, and 71 (14%) in the first month following a hospitalization for HF (<30 days). The remainder (391, 76%) were ambulatory patients from the outpatient clinic.

### Echocardiographic characteristics (Table 2)

Mean LVEF was  $60.9 \pm 7.2\%$ , and mean indexed LVEDVi was  $44.8 \pm 14.9$  mL/m<sup>2</sup>. Longitudinal diastolic  $e'$  velocities at the septum were <8 cm/s in 81.2% and at the lateral wall <10 cm/s in 73.3%. Approximately half (42.5%) of the patients had a mean  $E/e' > 13$ . S/D was <1 in 36.3% of the patients, and A reverse–A duration (Ard-Ad) was >30 ms in 24.9%.

**Table 1** Clinical and demographic characteristics in the MEDIA project and KaRen cohort

Variable	MEDIA (n = 515)	KaRen (n = 356)
Age (years)	74 ± 10	77 ± 9
Female sex	322 (62.5%)	201 (56.5%)
Body mass index (kg/m <sup>2</sup> )	30.3 ± 6.0	28.8 ± 5.8
Waist circumference (cm)	105 ± 14	NA
Systolic blood pressure (mmHg)	139 ± 23	139 ± 22
Diastolic blood pressure (mmHg)	75 ± 13	74 ± 12
Heart rate (b.p.m.)	70 ± 16	70 ± 16
Glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	66.2 ± 24.5	61.9 ± 27.0
HF status at inclusion		
Recruited during acute admission	51 (9.9%)	—
After discharge (<30 days)	71 (13.8%)	—
Ambulatory—chronic	391 (76.2%)	—
Co-morbidities		
Diabetes	198 (38.7%)	115 (32.3%)
Hypertension	448 (87.7%)	282 (79.4%)
Coronary artery disease	158 (31.6%)	118 (34.0%)
Atrial fibrillation	146 (29.9%)	89 (25.0%)
Chronic obstructive pulmonary disease	83 (16.4%)	45 (12.6%)
Anaemia	144 (31.9%)	126 (38.9%)
New York Heart Association functional class		
I	23 (4.5%)	41 (12.4%)
II	357 (70.6%)	204 (61.8%)
III	94 (18.6%)	76 (23.0%)
IV	32 (6.3%)	9 (2.7%)
Biomarkers		
NT-proBNP (pg/mL)		
Overall	560 (211–1530)	1409 (518–2630)
Recruited during acute admission	1218 (1130–7895)	—
After discharge (<30 days)	958 (302–2266)	—
Ambulatory—chronic	498 (204–1477)	—
HFpEF scores		
HFA-PEFF score	5 (4–6)	5 (4–6)
H <sub>2</sub> FPEF score	5 (3–6)	4 (3–6)
Medication		
ACEI/ARB	405 (79.4%)	243 (68.6%)
Beta-blockers	361 (70.5%)	244 (68.9%)
Diuretics	390 (76.9%)	295 (83.3%)
MRA	55 (10.8%)	NA
Outcomes		
30 day mortality	2 (0.4%)	4 (1.1%)
1 year mortality	22 (4.5%)	33 (9.3%)
30 day admission for HF	4 (0.8%)	24 (6.7%)
1 year admission for HF	33 (6.7%)	77 (21.6%)
1 year admission for cardiovascular cause or HF	82 (16.6%)	NA

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide. Values are mean ± standard deviation or median (Q1–Q3) for continuous variables and frequency (%) for categorical variables.

### Associations between echocardiographic variables and N-terminal pro-brain natriuretic peptide (Figure 1 and Tables S1 and S2)

**Left ventricular and right ventricular structure and function**  
Left ventricular longitudinal function (s') was significantly associated with elevated NT-proBNP in multivariable analysis (Table S1 and Figure 1).

#### Indexes of relaxation

A longer IVRT (>100 ms) was associated with elevated NT-proBNP, both in univariable analysis and after adjustment

(Table S1 and Figure 1). In contrast, e' velocities were not associated with elevated NT-proBNP in multivariable analysis (as in Model 2).

#### Congestion parameters (including estimated left ventricular elevated filling pressure and left atrial volume)

In multivariable analysis (as in Model 2), E/e' > 15, S/D, short DT, and dilated left atrial (LA) (which can also be an indicator of structural remodelling) were all significantly associated with elevated NT-proBNP. Markers of pulmonary hypertension and right atrial pressure including pulmonary artery systolic pressure (PASP) > 40 mmHg and increased inferior

**Table 2** Echocardiographic measurements in the MEDIA project and KaRen cohort

Variable	MEDIA (n = 515)	KaRen (n = 356)
<b>LV structure</b>		
Septal wall thickness (mm)	12.2 ± 2.5	11.6 ± 2.2
Posterior wall thickness (mm)	11.1 ± 2.2	11.0 ± 1.9
LV end-diastolic diameter (mm)	48.5 ± 6.3	47.3 ± 6.2
LV end-systolic diameter (mm)	30.8 ± 5.9	32.1 ± 6.5
LV mass index (g/m <sup>2</sup> )		
Overall	119 ± 40	126 ± 36
Male	129 ± 39	137 ± 39
Female	113 ± 39	117 ± 31
RWT	0.47 ± 0.12	0.47 ± 0.12
<b>LV function</b>		
LVEF (%)	60.9 ± 7.2	62.4 ± 6.9
Global longitudinal strain (%)	NA	-14.6 ± 4.0
LVEDVi (mL/m <sup>2</sup> )	44.8 ± 14.9	50.3 ± 14.7
LVEDVi ≥ 74 (M)/61 (F) mL/m <sup>2</sup>	39 (8.2%)	40 (12.6%)
LVESVi (mL/m <sup>2</sup> )	18.2 ± 8.2	19.3 ± 7.6
SV index (SV indexed for BSA)	36.4 ± 10.1	NA
SV index (LVEDVi-LVESVi)	26.6 ± 9.7	31.1 ± 8.8
Cardiac output (TVI PW) indexed	2.4 ± 0.6	2.5 ± 0.6
Systolic velocity of mitral annulus		
s' lateral (cm/s)	7.3 ± 2.0	7.3 ± 2.0
s' medial (cm/s)	6.3 ± 1.8	5.9 ± 1.7
Mitral annular plane systolic excursion (mm)	13.6 ± 3.6	NA
<b>Atrial variables</b>		
Left atrial area (cm <sup>2</sup> )	25.7 ± 13.0	NA
LAVi (mL/m <sup>2</sup> )	43.3 ± 15.2	49.0 ± 16.0
<b>Left ventricular diastolic function</b>		
Early wave mitral valve flow velocity (E) (m/s)	91.8 ± 27.4	92.8 ± 28.6
Late wave mitral valve flow velocity (A) (m/s)	82.2 ± 28.0	68.5 ± 31.2
E/A ratio	1.18 ± 0.69	1.79 ± 1.29
DT (ms)	205 ± 65	194 ± 76
e' lateral (cm/s)	8.3 ± 2.7	9.6 ± 3.4
e' medial (cm/s)	6.1 ± 1.9	6.4 ± 2.3
Mean e'	7.3 ± 2.1	8.0 ± 2.5
E/e' ratio	13.4 ± 5.1	12.7 ± 5.6
E/e' ratio lateral	12.0 ± 5.0	10.8 ± 5.1
E/e' ratio medial	16.0 ± 6.6	16.0 ± 7.5
Velocity of systolic pulmonary venous flow—S	0.56 ± 0.23	NA
Velocity of diastolic pulmonary venous flow—D	0.56 ± 0.40	NA
S/D	1.23 ± 0.58	NA
A reverse—A duration (Ard-Ad; ms)	0.2 ± 39.9	NA
E/Vp	1.83 ± 0.84	NA
IVRT (ms)	89.4 ± 26.1	92.1 ± 30.6
<b>RV function</b>		
Tricuspid regurgitation velocity (m/s)	2.63 ± 0.63	2.87 ± 0.64
Estimated pulmonary arterial pressure (mmHg)	34.8 ± 12.2	44.1 ± 17.3
IVC diameter—IVC rest (mm)	16.7 ± 5.0	18.4 ± 5.4
IVC during respiration/sniff—IVC insp/sniff	9.2 ± 5.8	11.5 ± 5.8
Ratio IVC insp/IVC rest	0.55 ± 0.58	0.59 ± 0.19
TAPSE (mm)	20.5 ± 4.9	17.2 ± 4.7

BSA, body surface area; DT, deceleration time; IVC, inferior vena cava; IVRT, isovolumic relaxation time; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; NA, not available; RV, right ventricular; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion. Values are mean ± standard deviation.

vena cava (IVC) diameter at rest were also significantly associated with elevated NT-proBNP in multivariable analysis.

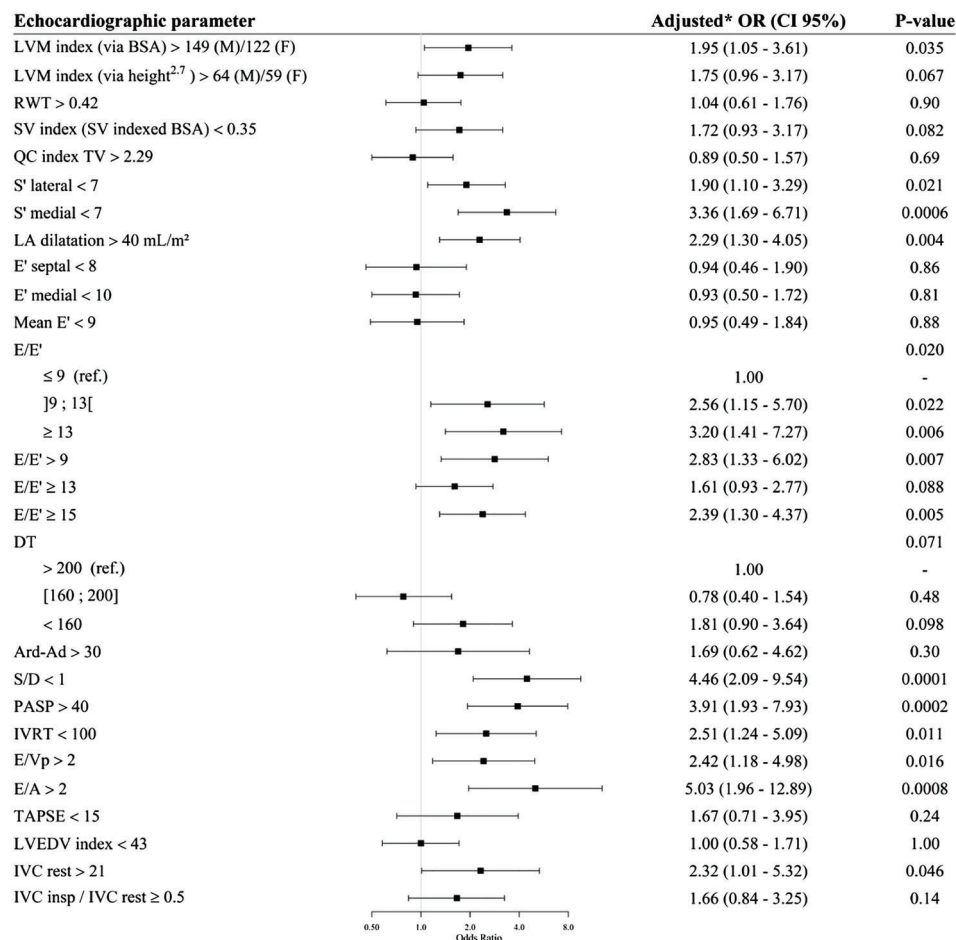
#### Integrative assessment (Table S2)

Five echocardiographic variables were found to be significantly associated with NT-proBNP in a multi-echocardiographic marker model after backward selection. These were two functional variables (stroke volume and s' medial) and three congestion variables (IVC, PASP, and IVRT).

#### Associations between echocardiographic variables and primary endpoint (Figure 2 and Tables S3 and S4)

During a median follow-up of 361 days, hospitalization for cardiovascular causes occurred in 82 patients (16.6%), among which 33 (6.7%) were admissions for HF. One hundred one patients (20.9%) reached a primary study endpoint.

**Figure 1** Associations between echocardiographic measurements and high levels of N-terminal pro-brain natriuretic peptide (> 450 pg/mL in patients below 50 years, >900 in patients aged 50–75 years, and >1800 in patients over 75 years). \*Adjusted on age, estimated glomerular filtration rate, body mass index, atrial fibrillation, and clinical presentation.



\*adjusted on age, eGFR, BMI, AF and clinical presentation

### Left ventricular and right ventricular structure and function

In the multivariable analysis, after adjusting for relevant confounders, lateral s' velocity remained significantly associated with the primary endpoint [HR = 2.26 (1.11–4.61),  $P = 0.025$ ].

### Indexes of relaxation

Increased IVRT duration (>100 ms) was significantly associated with the primary endpoint in both univariable and adjusted analyses, whereas e' velocity was not.

### Congestion parameters (including elevated estimated left ventricular filling pressure)

In multivariable analysis (Model 2), E/A > 2 [2.55 (HR = 1.13–5.76)], PASP > 40 [HR = 2.30 (1.30–4.06)], IVC inspiration/rest > 0.5 (i.e. decreased collapsibility) [HR = 2.73 (1.29–5.77)], S/D ratio [HR = 3.66 (1.53–8.79)], and LA dilatation [>40 mL/m<sup>2</sup>, 1.81 (1.02–3.20)] were significantly associated

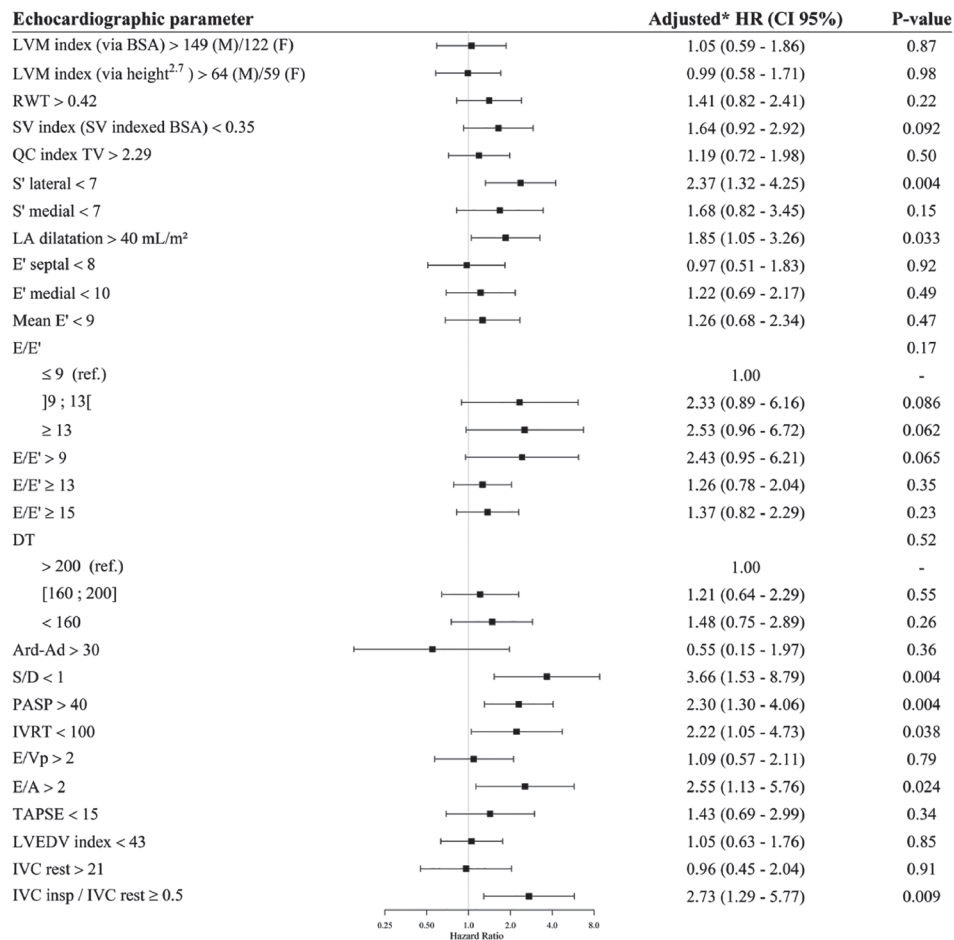
with higher risk of the primary endpoint. E/e' > 9 tended to be associated with the primary endpoint [HR = 2.42 (0.95–6.21),  $P = 0.065$ ].

We did not identify significant interactions (all  $P > 0.10$ ) between HF hospitalization status at baseline or presence of atrial fibrillation and echocardiographic variables with regard to rates of the composite outcome, suggesting a homogeneous effect of these echocardiographic variables across both HF and atrial fibrillation status.

### Integrative echocardiographic approach to risk of cardiovascular hospitalization and mortality (Figures 3 and 4)

After adjusting for categories of NT-proBNP, the three echocardiographic variables that were retained by the vselection procedure were PAPS [HR = 1.91 (1.19–3.07)],

**Figure 2** Associations between echocardiographic parameters and time to cardiovascular/heart failure hospitalization or all-cause death. \*Adjusted for dichotomous N-terminal pro-brain natriuretic peptide, age, estimated glomerular filtration rate, gender, left ventricular ejection fraction, atrial fibrillation, and clinical presentation.



\*adjusted for dichotomous NT-ProBNP, age, eGFR, gender, LVEF, AF, and clinical presentation

E/e' > 9 [HR = 2.81 (1.20–6.58)], and decreased IVC collapsibility [HR = 1.80 (1.01–3.19)]. After adjusting for log-transformed continuous values of NT-proBNP, s' lateral < 7 was retained in the model [HR = 2.00 (1.14–3.51)] along with E/e' > 9 and reduced variation in IVC diameter (Figure 3, Panel A).

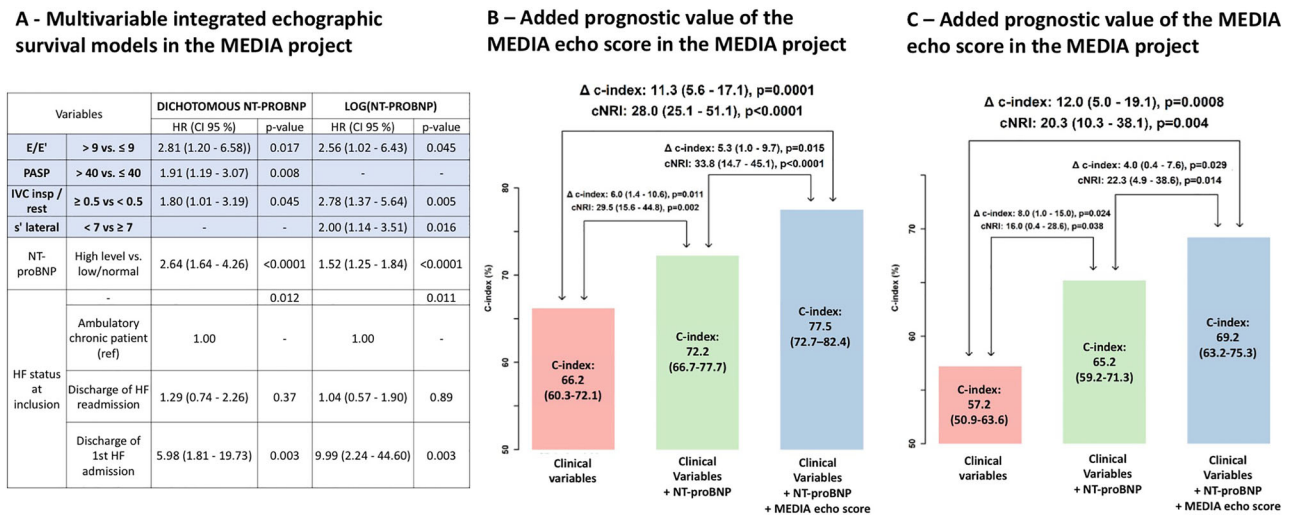
We estimated the risk for the composite event according to the number of parameters reaching the cut-off among the four echocardiographic variables retained in the multivariable survival models (central figure). When considering only echocardiographic variables, at 1 year, 37.8% (27.9–46.3%) of the patients with an echo score of 3 or higher (i.e. at least three markers among PAPS > 40, decreased IVC collapsibility, E/e' > 9, and lateral s' < 7 cm/s) had an event, whereas patients with a score 0/1 had less than 10% risk [7.9% (2.4–13.1%)] (central figure).

### Predictive accuracy of echo parameters in predicting cardiovascular events at follow-up (Figure 3)

The addition of NT-proBNP to a clinical model (including age, estimated glomerular filtration rate, atrial fibrillation, and HF status) improved the net reclassification improvement (NRI = 29.5%,  $P = 0.002$ ) and C-index (delta C-index 6.0%,  $P = 0.011$ ) for cardiovascular events. When further adding the four echocardiographic parameters (PAPS > 40, decreased IVC collapsibility, E/e' > 9, and lateral s' < 7 cm/s), prediction continued to improve significantly (NRI = 33.8%,  $P < 0.0001$ ; delta C-index 0.053,  $P = 0.015$ ) (Figure 3, Panel B); this rise was of similar magnitude to the one observed with the addition of NT-proBNP to the clinical variables.



**Figure 3** Multivariable integrated echocardiographic models in the MEDIA project (Panel A) and its added prognostic value in the MEDIA project (Panel B) and the KaRen cohort (Panel C). Panel A: Cox regression model using subset of variables retained after backward selection (using missing-indicator method) with N-terminal pro-brain natriuretic peptide (NT-proBNP) as a dichotomous or linear variable; Panels B and C: Improvement in prognostic value for the primary endpoint on top of clinical model (including age, estimated glomerular filtration rate, atrial fibrillation, and heart failure status), assessed by net reclassification improvement (NRI) and C-index.



### Added predictive accuracy of MEDIA echo score on top of the HFA-PEFF and H<sub>2</sub>FPEF algorithms (Figure 3)

The C-index of the MEDIA echo score derived from the four echocardiographic parameters (PAPS > 40, decreased IVC collapsibility, E/e' > 9, and lateral s' < 7 cm/s—1 point for each variable) was 0.703 (0.675–0.730). The predictive accuracy of the model including this MEDIA echo score was significantly higher to the ones including the HFA-PEFF score [C-index 0.611 (0.582–0.640); delta C-index 0.092 (0.009–0.175), P = 0.03] or the H<sub>2</sub>FPEF score [C-index 0.583 (0.550–0.617); delta C-index 0.120 (0.049–0.190), P < 0.001] for cardiovascular events (central figure).

### Association of echo variables with outcome and predictive accuracy of the MEDIA echo score according to natriuretic peptide levels

To determine whether the pattern of association of echo variables with outcome was dependent on natriuretic peptide levels, we constructed a Cox model adjusted of HF status at inclusion including the four echo parameters separately in patients with high levels of NT-proBNP (age-dependent threshold detailed in the Methods section) and patients with lower levels of NT-proBNP. E/e' > 9, s' lateral < 7 cm/s, and decreased IVC collapsibility were significantly associated with outcome in patients with lower levels of NT-proBNP [HR = 7.54 (1.01–56.47), P = 0.049; HR = 3.52 (1.57–7.87), P = 0.002; and HR = 3.73 (1.35–10.33), P = 0.011,

respectively]. In patients with high levels of NT-proBNP, PASP > 40 was the only significant factor [HR = 2.68 (1.27–5.68), P = 0.01], whereas decreased IVC collapsibility tended to be associated with outcome [HR = 2.84 (0.94–8.62), P = 0.07].

The prognostic value of the MEDIA echo score was more important in patients with lower levels of NT-proBNP [C-index 0.729 (0.648–0.810)] than in patients with high levels of NT-proBNP [C-index 0.602 (0.513–0.690)]. The survival curves in patients with high levels or lower levels of NT-proBNP are presented in Figure S1.

### Replication in the KaRen cohort

The characteristics of the KaRen cohort have been previously reported.<sup>23</sup> Briefly, the 539 included patients had very similar characteristics than the MEDIA cohort (mean age 77 ± 9; 56% women, hypertension 78%; Table 1).

In the KaRen cohort, we identified a similar significant improvement in prediction when adding NT-proBNP on top of the clinical model. In addition, the added value of the four echocardiographic variables appeared of similar magnitude with significant C-index (4.0%, P = 0.029) and NRI (22.3%, P = 0.014) increases (Figure 3, Panel C).

### Discussion

We have demonstrated that in a typical population of older patients with HFpEF, the main echocardiographic predictors

of cardiovascular hospitalization and/or death were related to pulmonary hypertension, high right atrial pressure, and raised  $E/e'$ . Importantly, longitudinal LV systolic function as assessed by tissue doppler imaging (TDI)  $s'$  was also associated with clinical outcomes. Importantly, we found that a score of these four variables distinguished patients with HFpEF at low risk (<10% at 1 year) from those at high risk (>35% at 1 year), and it improved risk stratification on top of NT-proBNP (as assessed with C-index and NRI). We found no evidence of interaction with atrial fibrillation or clinical settings (acute/chronic), which suggests that this simple echocardiographic approach could be widely applicable in routine practice. Finally, and in contrast to prior studies, our findings were confirmed in independent validation in a separate large and well-characterized HFpEF cohort.

### Echocardiographic markers associated with N-terminal pro-brain natriuretic peptide

$E/e'$  ratio, which is widely used as a surrogate measure for mean pulmonary capillary wedge pressure, was not retained as a key echocardiographic predictor of elevated NT-proBNP, whereas PASP and IVC measurements were eventually significantly associated in the final multivariable model. Our findings are robust because they were very consistent after controlling for the numerous possible confounding factors available in our study, such as cardiac rhythm and whether patients had presented with pulmonary oedema or with dyspnoea on exertion.

### Prognostic value of echocardiographic estimates of left ventricular elevated filling pressure and venous pressure

The American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure suggested an NT-proBNP-guided treatment strategy for optimization of cardioprotective therapy but disfavoured routine repeated echocardiography in stable patients. The 2016 Heart Failure Association guidelines mention natriuretic peptides and echocardiography only as diagnostic tools.<sup>24</sup> Consensus recommendations for the diagnosis of diastolic function rely heavily on the  $E/e'$  ratio,<sup>2,4,24,25</sup> which is reported as a validated prognostic marker.<sup>24,25</sup> Although used in trials to identify the effects of treatment,<sup>26</sup> changes only in  $E/e'$  (or any other single echocardiographic measurement) are not accepted surrogates for clinical benefit and, therefore, not sufficient evidence for approval of a new drug in HFpEF.<sup>27</sup> Actually, the diagnostic accuracy of  $E/e'$  to predict LV elevated filling pressure is still debated,<sup>28</sup> and a recent meta-analysis concluded that it cannot reliably estimate filling pressure in patients with preserved LVEF.<sup>29</sup> Despite these

limitations, we confirm herein the additional prognostic value of  $E/e'$ , with however a rather unusual threshold (>9) in patients with known HF (used instead of the usual threshold of eight in light of our data distribution). In addition to  $E/e'$ , PASP, another (indirect) marker of filling pressure, was retained as an important and significant risk-stratifying variable. Importantly, in our analysis, PASP was significantly associated with outcome only in patients with the most abnormal NT-proBNP values, which suggests that this marker is most important in the sickest patients. In contrast,  $E/e'$  was most associated with outcome in patients with lower NT-proBNP values. In a way, these two echocardiographic markers appear to complement one another in different settings. Yet the prognostic value of the MEDIA echo score was more pronounced in patients with lower NT-proBNP values.

Two out of four echo variables of the prognostic model we are reporting in this paper are actually indicators of elevated LV filling pressures, which fits the major issue of pulmonary congestion, resulting in dyspnoea in patients with HFpEF, and is also a key driver of both symptoms and outcomes in HFpEF.<sup>30</sup> In addition, IVC was retained in the multivariable model, which further reinforces the value of congestion echo-based variables to stratify the risk of patients with HFpEF.

As emphasized previously, chronic LA remodelling is the final step of chronic intra-cavitary pressure overload<sup>31</sup>; in our analysis, LA dilatation was significantly associated with outcome when adjusting on confounding factors. However, it was not retained in our final model by the variable selection procedure, possibly because it is an integrative factor that may overlap with other diastolic function variables.

### Prognostic value of left ventricular remodelling and systolic dysfunction in heart failure with preserved ejection fraction

In data collected from trials, in hypertension with LV hypertrophy<sup>32</sup> or in HFpEF,<sup>8,10</sup> LV mass and other measures of remodelling had important prognostic implication. In our study, neither the univariable nor the multivariable tests demonstrated any significant relationship between LV mass and relative wall thickness with subsequent hospitalization or death at 1 year.

In patients with HFpEF, a varying degree of impaired longitudinal systolic function has been demonstrated.<sup>33,34</sup> LVEF is an imperfect marker of systolic function: it has high inter-observer variability, it is load dependent, and, in isolation, it does not reflect the LV remodelling pattern. Although longitudinal strain generally correlates with LVEF, this correlation is relatively modest in patients with HFpEF. Strain imaging detects impaired systolic function despite preserved global LVEF in HFpEF that may contribute to the pathophysiology of the HFpEF syndrome.<sup>35</sup> In a sub-study of the TOPCAT

trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), global longitudinal strain (GLS) was the strongest echocardiographic predictor of the composite outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization.<sup>11</sup> Consistently, in our study,  $s'$  was an important prognostic marker. This simple variable does provide information on longitudinal function and could be a pragmatic routine approach to systolic function in patients with HFpEF. Of note, longitudinal systolic function has already been reported to be associated with the transition from hypertensive heart disease to HFpEF.<sup>35</sup>

## Clinical perspectives

After adjusting for a number of important prognostic markers (including NT-proBNP), we demonstrated that a limited set of four echocardiographic variables ( $E/e'$ , PASP, IVC, and  $s'$ ) had predictive value in HFpEF. Of note, the prognostic value of our MEDIA echo score appeared superior (as assessed with C-index) than the one of the HFA-PEFF and H<sub>2</sub>FPEF (which are primarily diagnostic algorithms). The major question is whether these variables could also guide the management of patients with HFpEF. Current treatments are empirical<sup>9,26</sup> or given for specific indications such as using diuretics to treat fluid retention, giving agents to control systemic blood pressure, and treating underlying ischaemia. There is evidence that residual congestion at discharge from HF hospitalization is associated with poor outcome.<sup>36</sup> We found that echocardiographic variables assessing congestion predicted outcomes in patients with chronic symptoms as well as those included during a hospitalization for acute symptoms. Therefore, preventing congestion should be beneficial in patients with HFpEF regardless of the context. Indeed, tailoring diuretic and nitrate therapy to changes in pulmonary pressure monitored by an implantable device improves clinical outcome, including in patients with HFpEF.<sup>26,37</sup> Our study suggests that tailoring anti-congestion therapy using simple echocardiography measures of  $E/e'$ , PASP, and IVC is a strategy worth investigating in an appropriate clinical trial.

## Translational outlook

As highlighted earlier, we found that most of the key echocardiographic variables identified in our study are related to congestion. However, congestion animal models are scarce. Our results could suggest that better understanding congestion resolution in controlled settings (such as animal models) would be of interest given the dominance of congestion in HFpEF prognosis.

## Strengths and limitations of the study

A particular strength of our study is that it reflects real-life clinical HFpEF practice. On average, patients were older than in many studies (with a mean age of 74 years), and two-thirds were female. There were high proportions of subjects with co-morbidities (which can also be HFpEF aetiologies), including hypertension in nearly 90% of subjects and diabetes mellitus in more than one-third. Thirty per cent of patients were in atrial fibrillation. In addition, the validation in an external large and well-characterized cohort (the KaRen cohort) strengthens the validity and generalizability of our results. Importantly, the clinical setting and inclusion criteria of the two cohorts were partly different, which further strengthen the generalizability of our results.

Echocardiography was performed in centres with a high level of expertise and with a common protocol, but some studies included in the analysis were not complete with all the measurements.

Our study only focused on rest echocardiography. Exercise echocardiography and lung ultrasound evaluation have emerged as useful diagnostic and prognostic tools in patients with HFpEF.<sup>38,39</sup> Further studies should determine how these imaging tools should be integrated to best evaluate patients with HFpEF.

Patients could be included in the MEDIA cohort if LVEDVi was  $<97$  mL/m<sup>2</sup> and could consequently have mildly or moderately dilated LV upon current standards. However, approximately 10% of the patients we considered in our analysis had LVEDVi  $\geq 4$  (M)/61 (F) mL/m<sup>2</sup>.

## Conclusions

In the MEDIA cohort, we identified four echocardiographic variables (PASP,  $E/e'$ ,  $s'$ , and IVC), three of which are mostly associated with congestion, that independently predicted clinical outcome, regardless of the clinical setting (ambulatory or at acute HF discharge). This important finding was validated in the independent KaRen cohort. These results suggest that haemodynamic evaluation of patients using echocardiography (using the MEDIA echo score) could pave the way to future echo-based therapeutic intervention trials.

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## Conflict of interest

L.H.L. related to present manuscript: none; unrelated: research grants to author's institution and speaker's and/or consulting fees: AstraZeneca, Boehringer Ingelheim, Novartis, Bayer, Vifor Pharma, Boston Scientific, Sanofi, Myokardia, Pharmacosmos, Mundipharma, Orion Pharma, Merck/MSD, and Medscape. N.G. reports consulting fees, unrelated to this manuscript, from AstraZeneca, Boehringer Ingelheim, and Novartis. P.R. reports personal fees from Relypsa, Inc., a Vifor Pharma Group Company; AstraZeneca; Bayer; CVRx; Fresenius; Novartis; Grunenthal; Servier; Stealth Peptides; Vifor Fresenius Medical Care Renal Pharma; Idorsia; and Novo Nordisk, outside the submitted work; and cofounder: CardioRenal. F.Z. reports personal fees from AstraZeneca, Janssen, Bayer, Novartis, Boston Scientific, Resmed, Amgen, CVRx, General Electric, Boehringer, AstraZeneca, and Vifor Fresenius, outside the submitted work, and cofounder: CardioRenal.

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## Supporting information

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

**Table S1:** Associations between echocardiographic measurements and high level of NT-proBNP (NT-proBNP > 450 pg/mL in patients below 50 years, >900 in patients aged 50–75 years, >1800 in patients over 75 years).

**Table S2:** Logistic regression model to predict high level of NT-proBNP on subset of variables retained after backward selection

**Table S3:** Associations between echocardiographic parameters and time to cardiovascular/HF hospitalization or all-cause death.

**Table S4:** Hazard ratio for primary outcome based on echocardiographic parameters analyzed as continuous variables

**Figure S1:** Kaplan–Meier estimates of time to the combined end-point of all-cause death and cardiovascular/HF hospitalization according to the number of echocardiographic criteria met (E/e', PASP, IVC insp/IVC rest ratio, s' lateral) in the MEDIA project according to NT-proBNP levels.

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