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ORIGINAL RESEARCH ARTICLE

# Left atrial volume and left ventricular mass indices in heart failure with preserved and reduced ejection fraction

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## Abstract

**Aims** Two key echocardiographic parameters that are currently used to diagnose heart failure (HF) with preserved ejection fraction (HFpEF) are left atrial volume index (LAVi) and left ventricular mass index (LVMi). We investigated whether patients' characteristics, biomarkers, and co-morbidities are associated with these parameters and whether the relationships differ between patients with HFpEF or HF with reduced ejection fraction (HFrEF).

**Methods** We consecutively enrolled 831 outpatients with typical signs and symptoms of HF and elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and categorized patients based upon left ventricular ejection fraction (LVEF): LVEF $<$ 40% (HFrEF), LVEF between 40% and 50% (HF with mid-range ejection fraction), and LVEF $\geq$ 50% (HFpEF). The study includes consecutively enrolled HF patients from an HF outpatient clinic at a tertiary medical centre in the Netherlands. All patients underwent baseline characterization, laboratory measurements, and echocardiography.

**Results** Four hundred sixty-nine patients had HFrEF, 189 HF with mid-range ejection fraction, and 173 HFpEF. The patients with HFrEF were rather male [HFrEF: 323 (69%); HFpEF: 80 (46%); $P < 0.001$], and the age was comparable (HFrEF 67 ± 13; HFpEF 70 ± 14; $P = 0.069$). In HFpEF, more patients had hypertension [190 (40.5%); 114 (65.9%); $P < 0.001$], higher body mass indices (27 ± 8; 30 ± 7; $P < 0.001$), and atrial fibrillation [194 (41.4); 86 (49.7); $P = 0.029$]. The correlation analyses showed that in HFrEF patients, LAVi was significantly associated with age ($\beta$ 0.293; $P < 0.001$), male gender ($\beta$ 0.104; $P = 0.042$), body mass index ($\beta$ −0160; $P = 0.002$), diastolic blood pressure ($\beta$ −0.136; $P < 0.001$), New York Heart Association ($\beta$ 0.174; $P = 0.001$), atrial fibrillation ($\beta$ 0.381; $P < 0.001$), galectin 3 ($\beta$ 0.230; $P < 0.001$), NT-proBNP ($\beta$ 0.183; $P < 0.001$), estimated glomerular filtration rate ($\beta$ −0.205; $P < 0.001$), LVEF ($\beta$ −0.173; $P = 0.001$), and LVMi ($\beta$ 0.337; $P < 0.001$). In HFpEF patients, only age ($\beta$ 0.326; $P < 0.001$), atrial fibrillation ($\beta$ 0.386; $P < 0.001$), NT-proBNP ($\beta$ 0.176; $P = 0.036$), and LVMi ($\beta$ 0.213; $P = 0.013$) were associated with LAVi.

**Conclusions** Although LVMi and LAVi are hallmark parameters to diagnose HFpEF, they only correlate with a few characteristics of HF and mainly with atrial fibrillation. In contrast, in HFrEF patients, LAVi relates strongly to several other HF parameters. These findings underscore the complexity in visualizing the pathophysiology of HFpEF and question the relation between cardiac structural remodeling and the impact of co-morbidities.

**Keywords** Heart failure with preserved ejection fraction (HFpEF); NT-proBNP; Biomarkers; Echocardiography; Left ventricular mass index (LVMi); Left atrial volume index (LAVi)

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# Introduction

Heart failure (HF) is a major health burden worldwide with an increasing incidence of ~2% in industrialized countries.[1,2] Recent population studies show a shift towards an increasing incidence of HF with preserved ejection fraction (HFpEF).[3,4] HFpEF affects more than 50% of the elderly HF population and especially elderly women.[4]

The European Society of Cardiology (ESC) HF guideline states that HFpEF is a challenging diagnosis in comparison with HF with reduced ejection fraction (HFrEF), and at least one structural cardiac abnormality [left ventricular (LV) hypertrophy, left atrial enlargement, or diastolic dysfunction] must be fulfilled for a diagnosis.[5] Important echocardiographic parameters for assessment of structural myocardial changes are LV mass index (LVMi) and left atrial volume index (LAVi).[5] Little is known about whether atrial fibrillation (AF) and biomarkers correlate with echocardiographic parameters in HFpEF. The literature underpinning the assumption that LVMi and/or LAVi are directly linked to HFpEF has been examined in HFpEF patients with specific characteristics.[6,7] We performed a detailed comparison of those parameters of cardiac remodelling with clinical and biochemical correlates in patients with HFrEF and HFpEF. The patients were referred to our HF outpatient clinic with typical signs and symptoms of HF, and the diagnosis was supported by their elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and overall, by typical echocardiographic signs of diastolic dysfunction.

# Methods

## Study population

All HF patients who visited the HF outpatient clinic of the University Medical Center Groningen, a tertiary medical centre in the Netherlands, between March 2014 and December 2017, and fulfilled the inclusion criteria were enrolled. HF patients were aged ≥18 years and received treatment of HF according to the latest ESC guidelines.[5] We studied 831 patients with HF.

## Data registration

Medical doctors and specialized HF nurses acquired the data during the outpatient visit. Besides demographics, medical history, co-morbidities, physical examination, and electrocardiogram, the data also include NT-proBNP and galectin-3 plasma levels.

## Echocardiography

All echocardiographic measurements were in line with the recent echocardiography guidelines.[8] For the echocardiographic evaluation of the different parameters, the average of three consecutive cardiac cycles was determined where possible.

First, the LAVi, defined as atrial volume divided by body surface area, was determined. Left atrial volume was calculated by multiplying the atrial area in two-chamber and four-chamber views (using the biplane area–length method) by 0.85 and dividing the result by the shortest length of the atrium. Based on current recommendations, the LAVi cut-off is 34 mL/m$^2$.[8] In this study, we also present the LAVi in patients who are already receiving HF treatment.

In addition, LVMi was calculated based on the LV end-diastolic diameter, the interventricular septal thickness at end-diastole, and the posterior wall thickness at end-diastole and corrected for body surface area. Published normal ranges for LVMi are 49–115 g/m$^2$ for men and 43–95 g/m$^2$ for women.[8] Therefore, we equally stratified patients according to the median of the complete cohort, which corresponded to 100 g/m$^2$. This is also in line with the 2016 ESC guidelines for HF, which considers an LVMi $>$ 115 g/m$^2$ for men and an LVMi $\geq$ 95 g/m$^2$ for women as a structural alteration.[5]

## Co-morbidities

Co-morbidities are important and common in the pathophysiology of and clinical approach to HFpEF.[9,10] We included co-morbidities if they were self-reported, were noted in the medical history of the patient, or if medication was taken for this typical co-morbidity. The additional inclusion criteria for specific co-morbidities are noted in the Supporting Information.

## Biochemical measurements

Plasma galectin 3 was measured with the Abbott ARCHITECT automated immunoassay analyser (Abbott Park, IL, USA). The plasma NT-proBNP measurements were completed using the Roche Modular system (Roche, Mannheim, Germany).[11]

## Statistical analyses

STATA software (Version 14.0; Stata Corp, College Station, TX, USA) was used for statistical analysis. Normally distributed data are presented as means ± standard deviation, non-normally distributed variables are shown as medians (inter-quartile range), and categorical variables were


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presented as number in per cent. Biomarker levels are shown as log transformation to reach a normal distribution. For normally distributed data, we used Student's *t*-tests to analyse differences between two groups; for non-normally distributed data, the Wilcoxon–Mann–Whitney test and Pearson's $\chi^2$ test for categorical variables were performed. To investigate associations, logistic regression analyses were performed. In a second step, the logistic regression was statistically adjusted for age and sex, while the variable age was only corrected for gender, and the variable gender was only corrected for age. We used a significance level of 0.05 (*P*-value of $<0.05$) and a two-tailed test.

### Ethics

This was a prospectively designed cohort study. Anonymous patient data were entered into a research database, to ensure that no individual patients' data can be traced back by users of the research database. The University Medical Center Groningen medical ethics committee approved this study, and it conforms to the principles of the Declaration of Helsinki and Dutch law.

## Results

### Patient characteristics

We enrolled 469 patients with HFrEF (ejection fraction $<40\%$) and 173 patients with HFpEF ($\geq 50\%$) in the study, 189 patients had HF with mid-range ejection fraction. Patients with HFrEF were younger, more frequently male, and had a lower systolic blood pressure and a higher NT-proBNP compared with the HFpEF patients. An NT-proBNP $>$ 125 pg/mL was present in 97.2% of the HFrEF patients and in 92.5% of the HFpEF patients. Furthermore, patients with HFrEF have a lower body mass index (BMI), a lower incidence of AF, and lower rate of diabetes mellitus and less increase in serum galectin 3 compared with patients with HFpEF. Other important clinical characteristics, such as severity of clinical symptoms [New York Heart Association (NYHA)], were comparable between the two groups. Detailed baseline characteristics and HF treatment can be found in *Table 1A* and *1B*.

### Echocardiography results

#### *Left atrial volume index*

Left atrial volume index was significantly larger in HFrEF patients compared with HFpEF patients (45 ± 17 vs. 41 ± 14; $P = 0.013$) as displayed in *Table 2* and *Figure 1A* and *1B*. LAVi was significantly associated after adjusting for age and sex in HFrEF patients with age, male gender, BMI, systolic and diastolic blood pressure, NYHA class, AF, galectin 3, NT-proBNP, left ventricular ejection fraction (LVEF), and LVMi. Interestingly, in patients with HFpEF, LAVi was only significantly correlated with age, AF, and LVMi (*Table 3*).

#### *Left ventricular mass index*

Left ventricular mass index was significantly increased in patients with HFrEF compared with patients with HFpEF

**Table 1A** Baseline characteristics

| Baseline characteristics | HFrEF EF $<$ 40% (*N* = 469) | HFpEF EF $>$ 50% (*N* = 173) | *P*-value |
|---|---|---|---|
| Demographics | | | |
| Age (years) | 67 ± 13 | 70 ± 14 | 0.069 |
| Male (%) | 323 (69) | 80 (46) | $<0.001$ |
| Systolic blood pressure (mmHg) | 116 ± 20 | 127 ± 21 | $<0.001$ |
| Diastolic blood pressure (mmHg) | 71 ± 11 | 72 ± 11 | 0.14 |
| BMI (kg/m$^2$) | 27 ± 8 | 30 ± 7 | $<0.001$ |
| Medical history | | | |
| NYHA Class (%) | | | |
| I | 50 (10.0) | 15 (8.8) | 0.36 |
| II | 260 (55.4) | 87 (51.2) | |
| III | 150 (32.0) | 63 (37.1) | |
| IV | 9 (1.9) | 5 (2.9) | |
| Atrial fibrillation (%) | 194 (41.4) | 86 (49.7) | 0.029 |
| Ischaemic heart disease (%) | 234 (49.9) | 53 (30.6) | $<0.001$ |
| Hypertension | 190 (40.5%) | 114 (65.9%) | $<0.001$ |
| Diabetes mellitus (%) | 182 (38.8) | 83 (48.0) | 0.098 |
| Plasma (biomarker) | | | |
| Galectin 3 (ng/mL) | 19.6 (15.1, 27.4) | 22.2 (17.1, 29.3) | 0.018 |
| NT-proBNP (ng/L) | 1820 (770, 3826) | 1128 (432, 2143) | $<0.001$ |
| $>$125 ng/L | 456 (97.2%) | 160 (92.5%) | 0.007 |
| eGFR (mL/min/1.73 m$^2$) $<$ 60 | No | Yes | 0.080 |

BMI, body mass index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

**Table 1B** Heart failure medication

| Medication | HFrEF EF < 40% (*N* = 469) | HFpEF EF > 50% (*N* = 173) | *P*-value |
|---|---|---|---|
| ACEi/ARB | 401 (86%) | 124 (72%) | <0.001 |
| Aldosterone antagonist | 265 (57%) | 76 (44%) | 0.005 |
| Beta-blocker | 430 (92%) | 150 (87%) | 0.058 |
| Calcium antagonist | 30 (4%) | 49 (28%) | <0.001 |
| Diuretic | 984 (82%) | 151 (87%) | 0.10 |

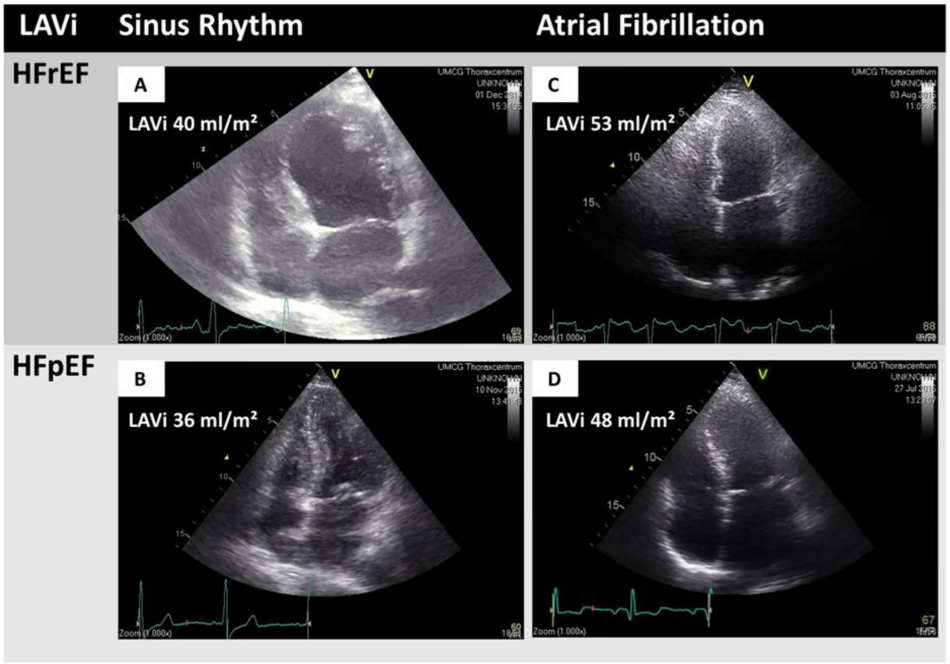
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

**Table 2** Echocardiography HFrEF vs. HFpEF

| Echocardiography | HFrEF EF < 40% (*N* = 469) | HFpEF EF > 50% (*N* = 173) | *P*-value |
|---|---|---|---|
| LVEF % | 27 (8) | 55 (3) | <0.001 |
| LAVi | 45 (17) | 41 (15) | 0.015 |
| LVMi | 118 (34) | 98 (29) | <0.001 |
| E/ Sept, mean | 5.2 (2.0) | 6.6 (2.6) | <0.001 |
| E/ Lat, mean (SD) | 7.5 (4.9) | 9.3 (6.3) | <0.001 |
| E/e, mean (SD) | 13.5 (6.4) | 12.5 (5.5) | 0.13 |

EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; SD, standard deviation.

**Figure 1** Echocardiography examples of heart failure with reduced ejection (HFrEF) (A) vs. heart failure with preserved ejection fraction (HFpEF) (B) ± atrial fibrillation (C/D). LAVi, left atrial volume index.




(118 ± 34 vs. 98 ± 29; $P < 0.001$). LVMi in patients with HFrEF was significantly associated with the several characteristics such as age, male gender, diastolic blood pressure, estimated glomerular filtration rate, LVEF, and LAVi. After adjusting for age and gender, LVMi was only associated with age, male gender, LVEF, and LAVi ($\beta$ 0.31; $P < 0.001$).

In patients with HFpEF, both unadjusted and adjusted linear regressions showed an association of LVMi with BMI, systolic blood pressure, AF, and LAVi (*Table 4*).

## Atrial fibrillation

We performed a sensitivity analysis between subjects with sinus rhythm and AF, because in the previously described analyses, AF was strongly associated with both LAVi and LVMi in both groups. LAVi was higher in patients with HFrEF compared to those with HFpEF (45 vs. 41 mL/m$^2$; $P$ = 0.013). The patients with both subtypes of HF showed a significant increase in LAVi with AF (*Figure 1C* and *1D*) compared with


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**Table 3** Correlation between LAVi, patients' characteristics, and biomarkers

| LAVi | HFrEF | Unadjusted | | Adjusted for age and gender | | HFpEF | Unadjusted | | Adjusted for age and gender | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | *N* | *P* | *β* | *P* | *β* | *N* | *P* | *β* | *P* | *β* |
| Age | 382 | **<0.001** | 0.293 | **<0.001** | 0.294 | 142 | **<0.001** | 0.326 | **<0.001** | 0.313 |
| Male | 382 | **0.042** | 0.104 | **0.029** | 0.107 | 142 | 0.120 | −0.131 | 0.457 | −0.061 |
| BMI | 363 | **0.002** | −0.160 | **0.019** | −0.119 | 135 | 0.768 | −0.026 | 0.930 | 0.007 |
| Systolic blood pressure | 375 | 0.072 | −0.093 | **0.024** | −0.112 | 141 | 0.101 | 0.139 | 0.119 | 0.125 |
| Diastolic blood pressure | 375 | **<0.001** | −0.136 | **0.011** | −0.124 | 141 | 0.664 | 0.037 | 0.400 | 0.067 |
| NYHA | 382 | **0.001** | 0.174 | **0.006** | 0.138 | 142 | 0.954 | −0.005 | 0.314 | −0.083 |
| Atrial fibrillation | 382 | **0.000** | 0.381 | **0.000** | 0.317 | 142 | **0.000** | 0.386 | **0.000** | 0.318 |
| Galectin 3 | 382 | **0.000** | 0.230 | **0.002** | 0.156 | 142 | 0.939 | 0.006 | 0.487 | −0.057 |
| NT-proBNP | 382 | **0.000** | 0.183 | **0.001** | 0.168 | 142 | **0.036** | 0.176 | 0.151 | 0.118 |
| eGFR | 376 | **0.000** | −0.205 | 0.243 | −0.069 | 140 | 0.854 | −0.016 | 0.119 | 0.138 |
| LVEF | 382 | **0.001** | −0.173 | **0.001** | −0.160 | 142 | 0.590 | 0.046 | 0.712 | 0.030 |
| LVMi | 369 | **0.000** | 0.337 | **0.000** | 0.299 | 136 | **0.013** | 0.213 | **0.010** | 0.210 |

BMI, body mass index; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association. Statistically significant *P*-values are displayed in bold typeface.

**Table 4** Correlation between LVMi, patients' characteristics, and biomarkers

| LVMi | HFrEF | Unadjusted | | Adjusted for age and gender | | HFpEF | Unadjusted | | Adjusted for age and gender | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | *N* | *P* | *β* | *P* | *β* | *N* | *P* | *β* | *P* | *β* |
| Age | 425 | **0.038** | 0.101 | **0.038** | 0.098 | 151 | 0.870 | 0.013 | 0.663 | 0.037 |
| Male | 425 | **0.000** | 0.232 | **0.000** | 0.231 | 151 | 0.234 | 0.097 | 0.210 | 0.105 |
| BMI | 405 | 0.192 | −0.650 | 0.458 | −0.036 | 144 | **0.008** | 0.220 | **0.008** | 0.219 |
| Systolic blood pressure | 418 | 0.872 | 0.008 | 0.488 | 0.033 | 150 | **0.001** | 0.266 | **0.001** | 0.266 |
| Diastolic blood pressure | 418 | **0.023** | −0.111 | 0.057 | −0.091 | 150 | 0.273 | 0.090 | 0.247 | 0.096 |
| NYHA | 425 | 0.656 | 0.022 | 0.733 | 0.016 | 150 | 0.257 | 0.093 | 0.242 | 0.101 |
| Atrial fibrillation | 425 | 0.880 | −0.007 | 0.350 | −0.046 | 151 | **0.032** | −0.174 | **0.015** | −0.211 |
| Galectin 3 | 425 | 0.075 | 0.087 | 0.141 | 0.074 | 151 | 0.862 | −0.014 | 0.806 | −0.021 |
| NT-proBNP | 425 | 0.073 | 0.087 | 0.052 | 0.092 | 151 | 0.147 | 0.119 | 0.172 | 0.115 |
| eGFR | 419 | **0.017** | −0.116 | 0.101 | −0.094 | 149 | 0.222 | 0.101 | 0.146 | 0.132 |
| LVEF | 425 | **0.000** | −0.198 | **0.000** | −0.175 | 151 | 0.780 | −0.023 | 0.809 | −0.020 |
| LAVi | 369 | **0.000** | 0.338 | **0.000** | 0.308 | 136 | **0.013** | 0.213 | **0.010** | 0.233 |

BMI, body mass index; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association. Statistically significant *P*-values are displayed in bold typeface.

those in sinus rhythm (HFrEF: 53 vs. 40; $P < 0.001$; HFpEF: 47 vs. 36; $P < 0.001$). LVMi was higher in patients with HFrEF than in those with HFpEF (118 vs. 98; $P < 0.001$). The rhythm, whether sinus rhythm or AF, did not affect the LVMi in HFrEF patients (118 vs. 117; $P = 0.91$). In contrast, patients with HFpEF in sinus rhythm had a higher LVMi compared with HFpEF patients with AF (103 vs. 93; $P = 0.023$) (*Tables 5* and *6*).

**Table 5** Echocardiography HFrEF SR vs. AF

| Echocardiography | HFrEF + SR EF < 40% (*N* = 275) | HFrEF + AF EF > 50% (*N* = 194) | *P*-value |
|---|---|---|---|
| LAVi | 40 ± 13 | 53 ± 19 | <0.001 |
| LVMi | 118 ± 34 | 117 ± 33 | 0.88 |

AF, atrial fibrillation; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVi, left atrial volume index; LVMi, left ventricular mass index; SR, sinus rhythm.

**Table 6** Echocardiography HFpEF SR vs. AF

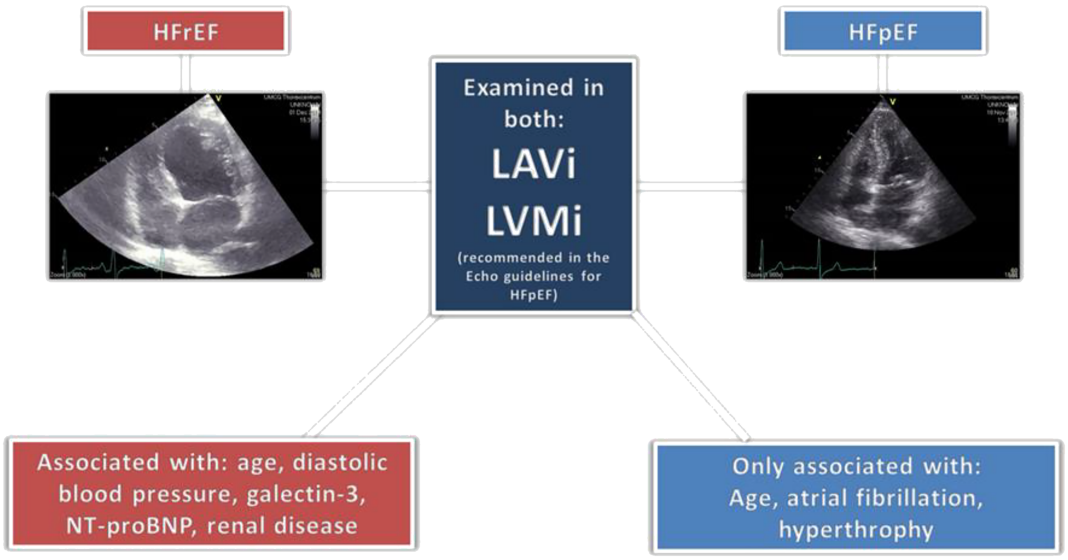
| Echocardiography | HFpEF + SR EF < 40% (*N* = 87) | HFpEF + AF EF > 50% (*N* = 86) | *P*-value |
|---|---|---|---|
| LAVi | 36 ± 12 | 47 ± 15 | <0.001 |
| LVMi | 103 ± 28 | 93 ± 30 | 0.023 |

AF, atrial fibrillation; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LAVi, left atrial volume index; LVMi, left ventricular mass index; SR, sinus rhythm.

## Discussion

Using our large contemporary HF cohort, we performed a correlation analyses in patients with HFrEF and HFpEF to respectively compare the interaction of atrial and ventricular remodelling, represented by guideline-specific echocardiography parameters, together with clinical characteristics and

**Figure 2** Schematic overview. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVi, left atrial volume index; LVMi, left ventricular mass index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.




biomarkers. We demonstrated that LAVi was significantly greater in those with HFrEF, and interestingly, that LAVi correlated stronger with several disease characteristics and NT-proBNP in this population. On the other hand, in HFpEF patients (LVEF $>$ 50%), LAVi was only associated with age, AF, and LVMi. LVMi corresponded to a lesser extent with only few clinical characteristics, and only four correlates in HFrEF and four correlates in HFpEF patients were found (*Figure 2*). We clearly validated that the presence of AF resulted in increased LAVi measurements, both in patients with HFrEF and HFpEF.

Few studies have analysed the correlation of atrial remodelling with characteristics or biomarkers in either HFrEF or HFpEF patients. One study used cardiovascular magnetic resonance in HFpEF patients and showed that left atrial volume max indexed was associated with NT-proBNP, but not with fibrosis-related markers.[12] A prospective multicentre observational study of hospitalized patients with HFpEF without AF showed a modest correlation for echocardiographically measured LAVi and pulmonary capillary wedge pressure, but not for LAVi and NT-proBNP.[13]

In HFpEF patients, a cross-sectional adjusted regression analyses of data from the Aldo-DHF study revealed a significant correlation between LAVi and: age, female gender, AF, mean arterial pressure, heart rate, haemoglobin, intake of angiotensin-converting enzyme inhibitors/angiotensin receptors, and beta-blocker intake. A significant correlation could be demonstrated with LVMi and age, female gender, coronary heart disease, cerebrovascular disease, pulse pressure, heart rate, and estimated glomerular filtration rate. The participants of the Aldo-HF study had HFpEF with either dyspnoea NYHA Class II ($n$ = 363) or III ($n$ = 59).[6] In other HFpEF outpatients ($n$ = 166), a positive correlation of BNP and LAVi was found, but not for BNP and LVMi.[7]

In HFpEF patients, our data showed a significant interaction with NT-proBNP before adjustments were made. After we made adjustments, LAVi in HFpEF patients correlated with age and AF, which agrees with previous findings; however, we cannot confirm an association with diastolic blood pressure, systolic blood pressure, or male gender. Additionally, we found a significant correlation of LAVi and LVMi. Our correlates of LAVi in patients with HFrEF cannot yet be compared with other studies.

Previous works have focused on co-morbidities and the prognostic value of those echo parameters. In these studies, LAVi was found to be greater in HF patients without diabetes mellitus compared with HF patients with diabetes mellitus and larger in HF patients with AF compared with HF patients without AF.[14,15] Ethnicity also seems to contribute to a smaller LAVi, as found when comparing Asian with New Zealander–European in a dual-nation observational HF cohort.[15] Furthermore, LAVi, together with LVMi, ratio of mitral Doppler E velocity to mitral tissue Doppler e′ velocity and tricuspid regurgitation, does not independently predict the prognosis in HFpEF patients.[16] A cross-sectional population-based study of residents $>$44 years of age found that a larger LAVi only has a good predictive value for third-degree and fourth-degree diastolic dysfunction.[17]

Increased LV mass is an independent risk factor for cardiovascular events,[18–20] and we found a significantly higher LVMi in patients with HFrEF. Our results agree with the other studies that demonstrated a significantly higher LVMi in patients

with HFrEF compared with HFpEF.[14,21] Furthermore, our LVMi values in HFpEF patients are similar to those found in three other studies.[22–24] Nevertheless, other studies described ~10 g/m$^2$ lower values.[21,25] In HFrEF, our mean LVMi g/m$^2$ value was ~30 g/m$^2$ lower compared with other documented findings.[21] The differences might be due to different baseline characteristics (mean age and co-morbidities), duration of HF and severity, along with treatment and methods.

Patient characteristics might have influenced the study outcome. For example, contradictory results have been found regarding different LAVi sizes in HFrEF and HFpEF patients. In our study, LAVi was slightly higher in HFrEF compared with HFpEF patients. A marked increase of LAVi in HFrEF compared with HFpEF has been previously described.[26] On the other hand, the work by other researchers demonstrated a comparable LAVi in HFrEF and HFpEF.[14] A different distribution of AF could explain the discrepancies. We had an equal incidence of AF, with 45% in the HFrEF and 46% in the HFpEF group. In the aforementioned paper, 42% of HFpEF patients had AF vs. 26% of HFrEF patients.[26] Furthermore, the duration of AF might complicate the interpretation of the results. For example, it is known that long-standing persistent AF strongly correlates with left atrial pressure.[27] Increased left atrial pressure and left atrial remodelling lead to an increase in LAVi.[28] LAVi has also been shown to be higher in patients with persistent AF compared with paroxysmal AF.[29]

The backbone in the assessment of structural heart disease in HFpEF is to assess LAVi and LVMi (and LV geometry) by echocardiography, in combination with measures of diastolic function.[5,8] With our findings, we specifically point out that LAVi and LVMi, although frequently used echoparameters, do not correlate with certain patient characteristics and biomarkers and are influenced by co-morbidities, especially AF. With our findings, we generate awareness regarding the interpretation of echocardiography in patients with HFpEF and encourage future research to formulate a clear classification of HFpEF.

### Clinical consequences and future perspectives

Our data show that LAVi correlates well with the characteristics and biomarkers of patients with HFrEF in our representative HF cohort. Therefore, the echo measurements seem to be useful in the clinical setting of HFrEF, while LVMi does not correlate well. Although central in the diagnostic workup, LVMi and LAVi do not show clear relations with the tested biomarkers and co-morbid conditions in our HFpEF patients. In summary, LAVi correlates with clinical characteristics and cardiac biomarkers in HFrEF patients, but not in HFpEF. In HFrEF patients, almost all parameters show a significant correlation with LAVi even after adjusting for age and gender.

For the future diagnostic workup of HFpEF patients, the additional measurement of atrial strain in prospective studies seems promising. A recent review about diagnosing LV diastolic dysfunction described a remarkable sensitivity and specificity of left atrial longitudinal strain in HFpEF.[30]

### Strengths and limitations

With 831 patients, we were able to include a representative HF population in the study. Nevertheless, there might be a referral bias because it is a single tertiary centre study. Patients were consecutively enrolled, and we did not perform deformation analysis, invasive pressure measurements, or stress echocardiography. Furthermore, it is difficult to model the various co-morbidities in a time-dependent manner. In other words, some co-morbidities might have existed for years and others may have been diagnosed just recently.

At study enrolment, a few patients had NT-proBNP levels $<$125 pg/mL, presumedly resulting from appropriate HF treatment prior to enrolment.

The participants were also on different HF treatments, which can be considered both as a limitation and as a strength, because it depicts a representative HF population.

## Conclusion

Our data provide new insight in the complexity of HFpEF wherein only few established HF parameters are associated with LAVi and LVMi, which are suggested diagnostic parameters in HFpEF.

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## Conflict of interest

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### Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supporting information

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

**Data S1.** Inclusion criteria of comorbidities is available online.

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