

# Clinical implications of left atrial changes after optimization of medical therapy in patients with heart failure

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## Aims

Limited data exist regarding the prognostic relevance of changes in left atrial (LA) dimensions in patients with heart failure (HF). We assessed changes in LA dimension and their relation with outcomes after optimization of guideline-directed medical therapy (GDMT) in patients with new-onset or worsening HF.

## Methods and results

Left atrial diameter was assessed at baseline and 9 months after GDMT optimization in 632 patients (mean age  $65.8 \pm 12.1$  years, 22.3% female) enrolled in BIOSTAT-CHF. LA adverse remodelling (LAAR) was defined as an increase in LA diameter on transthoracic echocardiography between baseline and 9 months. After the 9-month visit, patients were followed for a median of 13 further months. LAAR was observed in 247 patients (39%). Larger baseline LA diameter (odds ratio [OR] 0.90; 95% confidence interval [CI] 0.87–0.93;  $p < 0.001$ ) and up-titration to higher doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs) (OR 0.56; 95% CI 0.34–0.92;  $p = 0.022$ ) were independently associated with lower likelihood of LAAR. LAAR was associated with an increased risk of the composite of all-cause mortality or HF hospitalization (log-rank  $p = 0.007$  and adjusted hazard ratio 1.73, 95% CI 1.22–2.45,  $p = 0.002$ ). The association was more pronounced in patients without a history of atrial fibrillation ( $p$  for interaction = 0.009).

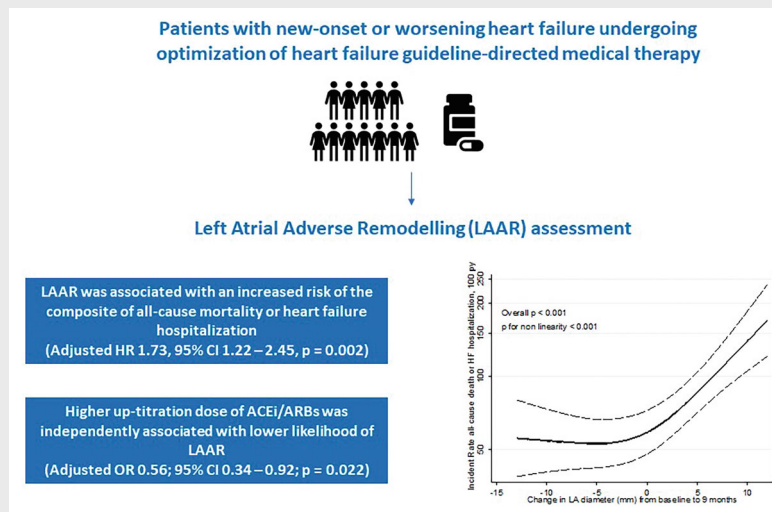
## Conclusion

Among patients enrolled in BIOSTAT-CHF, LAAR was associated with an unfavourable outcome and was prevented by ACEi/ARB up-titration. Changes in LA dimension may be a useful marker of response to treatment and improve risk stratification in patients with HF.

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## Graphical Abstract



Among patients with new-onset or worsening heart failure (HF) undergoing optimization of HF medical therapy, dose up-titration of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) therapy was associated with lower likelihood of left atrial adverse remodelling (LAAR). LAAR is associated with a higher risk of all-cause mortality or hospitalization for HF. CI, confidence interval; OR, odds ratio.

## Keywords

Left atrium • Heart failure • Guideline-directed medical therapy

## Introduction

Heart failure (HF)-related changes in cardiac structure and function help to identify patients at a higher risk of cardiovascular (CV) events.<sup>1,2</sup> Impaired left atrial (LA) structure and function is a well-defined marker of increased risk of hospitalization and mortality in the general population as well as in patients with HF with preserved (HFpEF) and reduced ejection fraction (HFrEF).<sup>3–6</sup>

Therapeutic interventions may attenuate LA enlargement and dysfunction in patients with HF.<sup>7,8</sup> From this perspective, assessment of LA dimensional changes may represent a useful marker of CV risk that captures the effect of treatment on LA pressure and function, which may lead, in turn, to favourable effects on atrial myocytes and extracellular matrix.<sup>8</sup> Many clinical studies have shown the beneficial effect of pharmacological and device therapy on changes of left ventricular (LV) structure and function and found that unfavourable LV remodelling is associated with a higher rate of subsequent CV events.<sup>9,10</sup> However, there is little similar evidence assessing the effects of HF-directed medical therapy on LA changes and the prognostic implications of LA adverse remodelling (LAAR) after drug up-titration.

We prospectively analysed data from a cohort of HF patients enrolled in BIOSTAT-CHF (BIOlogy Study to Tailored Treatment in Chronic Heart Failure),<sup>11</sup> who underwent echocardiographic assessment of LA dimension before and after up-titration of guideline-directed medical therapy (GDMT), to evaluate the incidence, determinants, and outcomes of LAAR, with a particular

focus on the impact of achieved doses of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and  $\beta$ -blockers.

## Methods

## Study population

The study design of the BIOSTAT-CHF study has been described in detail previously.<sup>11</sup> Briefly, an index cohort of 2516 patients with new-onset or worsening HF on loop diuretics and on  $\leq 50\%$  of target dose of ACEi/ARBs and/or  $\beta$ -blockers was recruited from 11 European countries between December 2010 and December 2012 and followed up for a median of 21 months. Patients underwent a 3-month up-titration period where the treating clinicians were encouraged to up-titrate ACEi/ARBs and  $\beta$ -blockers to guideline-recommended target doses (the optimization phase). The subsequent 6 months were the maintenance phase where no further medication changes were mandated unless clinically indicated. Information on ACEi/ARB and  $\beta$ -blocker doses were collected at baseline and 3 months. At 9 months after study entry, patients underwent clinical examination. The study was approved by the ethics committees of all participating centres and all patients provided written informed consent.

## Echocardiography

At the time of study inclusion, patients underwent two-dimensional echocardiography using a commercially available echocardiograph with

a 3.5 MHz probe. The examination was performed by local investigators according to current guidelines and comprised<sup>12,13</sup>: quantification of ventricular and atrial dimensions, LV function and valvular function. LV geometry was defined as: eccentric hypertrophy (LV mass index [LVMI] >95 g/m<sup>2</sup> for women and >115 g/m<sup>2</sup> for men with a relative wall thickness [RWT] ≤0.42), concentric remodelling (LVMI ≤95 g/m<sup>2</sup> for women and ≤115 g/m<sup>2</sup> for men with an RWT >0.42) and concentric hypertrophy (LVMI >95 g/m<sup>2</sup> for women and >115 g/m<sup>2</sup> for men with an RWT >0.42). According to current guidelines, LA dimension was assessed by linear dimension by the LA antero-posterior measurement in the parasternal long-axis view.<sup>12</sup> After the optimization and maintenance phases, patients underwent a two-dimensional echocardiogram at 9 months. Measures of LA dimension were available at both baseline and 9-month echocardiography in 632 patients included in the index cohort (online supplementary Figure S1).

Left atrial adverse remodelling was defined as an increase in LA diameter from baseline to 9-month follow-up (positive delta change).

## Clinical outcomes

The primary outcome of the study was a composite of all-cause mortality or hospitalization for HF. Secondary endpoints were all-cause mortality and HF hospitalization alone. After the study visit at 9 months, there was a clinical follow-up, or patients were contacted via telephone every 6 months until the end of study. The median follow-up duration for the primary endpoint was 13 months (interquartile range [IQR] 8–18). The protocol of BIOSTAT-CHF used clear endpoint definitions, a structured case report form, and source data of all sites were closely monitored.

## Statistical analysis

Summary statistics for clinical characteristics are presented as mean (± standard deviation) or median (IQR) for continuous data, as appropriate, and count (percentage) for categorical data, respectively. Comparisons between groups according to the presence of LAAR were assessed using Student's *t*-test for means, Wilcoxon test for medians, and Chi-squared test for proportions. Change in echocardiographic measures of LA dimension (LA diameter) from baseline to follow-up was calculated as the delta change: 9-month follow-up value – baseline value. Binary logistic regression was performed to assess the determinants of LAAR at 9-month follow-up. First, all clinical variables (Tables 1 and 2) were tested at univariable analysis. A multivariable model was created including variables significantly associated with LAAR at univariable analysis and other variables considered to be relevant according to clinical judgement, avoiding collinearity among the tested predictors. The area under the curve derived from receiver operating characteristic curves (*C*-statistic) and 95% confidence interval (CI) were assessed for the overall multivariable model. The assessment of the prognostic implication of changes in LA dimension and the analysed outcomes was performed after the date of the follow-up echocardiogram performed at 9 months. Cumulative incidence curves were produced using the Kaplan–Meier estimator for the primary and secondary endpoints among patients with or without LAAR. Cox proportional hazards analyses were performed to determine the association of changes in LA dimension and outcomes accounting for baseline value of LA dimension (baseline-adjusted) and further adjustment for the already validated BIOSTAT-CHF risk prediction model,<sup>14</sup> which includes age, previous hospitalization for HF, systolic blood pressure, presence of peripheral oedema, N-terminal pro-B-type natriuretic

peptide (NT-proBNP), haemoglobin, sodium, high-density lipoprotein, and the use of β-blockers at baseline. Given the non-linear association between LA delta change and the composite outcome, LA change was analysed both dichotomously (LAAR vs. no LAAR), and continuously among patients with positive change compared to baseline LA value. The continuous association between the incidence rates of the composite outcome and LA delta change was assessed by restricted cubic splines with three knots, resulting in the lowest model Akaike information criterion (3–6 knots were assessed). All tests were two-sided and a *p*-value <0.05 was considered significant throughout. Analyses were performed with Stata, version 14 (StataCorp, College Station, TX, USA).

## Results

### Study population

Overall, 632 patients with available measurements of LA diameter at baseline and at 9 months were included in the current analysis (online supplementary Figure S1). As compared with the 1884 patients without serial echocardiograms, the 632 patients with serial echocardiographic data were younger and showed a lower prevalence of CV disease and risk factors (online supplementary Table S1).

Mean age was 65.8 ± 12.1 years and 22.3% were women. LAAR was observed in 247 patients (39.1%), whereas a reduction or no changes in LA diameter was observed in 385 patients (60.9%). Among patients with LAAR, 222 (89.8%) showed an increase ≤10 mm and 25 (10.1%) an increase >10 mm. Patients with LAAR were older and more likely to have ischaemic heart disease as a primary cause of HF (Table 1). No significant differences were observed in laboratory data, LV ejection fraction (LVEF) and cardiac structure and function between those with and without LAAR, except for smaller baseline LA diameter among those with LAAR. With respect to treatment, patients with LAAR were less likely to be prescribed any dose of ACEi/ARB (76.5% vs. 84.4%, *p* = 0.013) at baseline and reached lower target doses of ACEi/ARB at 3 months (0.50 ± 0.35 vs. 0.57 ± 0.45, *p* = 0.034). In addition, the proportion of patients receiving ACEi/ARB increased during follow-up from 76.5% to 92.7% in patients with LAAR compared with 84.4% to 94.8% in those without LAAR (*p* = 0.28 for differences between the two groups).

### Predictors of left atrial adverse remodelling

Variables associated with LAAR at univariable analysis are shown in online supplementary Table S2. At multivariable analysis larger baseline LA diameter (odds ratio [OR] 0.90; 95% CI 0.87–0.93, *p* < 0.001), higher ACEi/ARB fraction target dose at 3 months (OR 0.56; 95% CI 0.34–0.92, *p* = 0.022), LV eccentric remodelling (OR 2.13; 95% CI 1.26–3.60, *p* = 0.005), HF ischaemic aetiology (OR 1.78; 95% CI 1.17–2.72, *p* = 0.007), and history of atrial fibrillation (AF) (OR 2.07; 95% CI 1.30–3.28, *p* = 0.002) were significantly associated with LAAR (overall model AUC: 0.73 (95% CI 0.68–0.77) (Table 3). The relationship between ACEi/ARB percentage of target dose at 3 months and LAAR was not modified

**Table 1** Baseline clinical characteristics in the index cohort stratified by left atrial adverse remodelling

	Overall (n = 632)	No LA adverse remodelling (n = 385)	LA adverse remodelling (n = 247)	p-value
Age (years)	65.8 ± 12.1	64.5 ± 12.8	67.8 ± 10.6	< 0.001
Female sex	141 (22.3)	90 (23.4)	51 (20.4)	0.42
BMI (kg/m <sup>2</sup> )	28.0 ± 5.0	28.2 ± 5.3	27.7 ± 4.5	0.25
HF hospitalization in last year	166 (26.3)	99 (25.7)	67 (27.1)	0.69
Smoking				0.97
Past	213 (33.7)	189 (49.1)	122 (49.4)	
Current	311 (49.2)	65 (16.9)	43 (17.4)	
Medical history				
Hypertension	412 (65.2)	244 (63.4)	168 (68.0)	0.23
Diabetes mellitus	181 (28.6)	108 (28.1)	73 (29.6)	0.68
Atrial fibrillation	231 (36.6)	132 (34.3)	99 (40.1)	0.14
HF primary ischaemic aetiology	284 (45.6)	152 (40.3)	132 (53.7)	0.001
Heart valve disease	49 (7.9)	33 (8.8)	16 (6.5)	0.09
Peripheral artery disease	50 (7.9)	24 (6.2)	26 (10.5)	0.050
COPD	93 (14.7)	54 (14.0)	39 (15.8)	0.54
Stroke	45 (7.1)	24 (6.2)	21 (8.5)	0.28
Current malignancy	11 (1.7)	7 (1.8)	4 (1.6)	0.85
CKD	251 (42.6)	147 (40.4)	104 (46.2)	0.16
Device therapy				0.006
Pacemaker	37 (5.9)	21 (5.5)	16 (6.5)	
ICD	39 (6.2)	23 (6.0)	16 (6.5)	
CRT-P	11 (1.7)	4 (1.0)	7 (2.8)	
CRT-D	26 (4.1)	10 (2.6)	16 (6.5)	
NYHA functional class				0.31
I	13 (2.1)	9 (2.4)	4 (1.6)	
II	297 (47.6)	186 (49.1)	111 (45.3)	
III	267 (42.8)	161 (42.5)	106 (43.3)	
IV	47 (7.5)	23 (6.1)	24 (9.8)	
Clinical profile				
Peripheral oedema	110 (20.4)	68 (21.1)	42 (19.4)	0.65
Hepatomegaly	79 (12.5)	49 (12.7)	30 (12.1)	0.83
SBP (mmHg)	127.2 ± 21.8	127.0 ± 21.1	127.4 ± 22.9	0.84
DBP (mmHg)	77.3 ± 12.4	77.5 ± 12.7	77.0 ± 11.9	0.61
HR (bpm)	80.8 ± 20.9	81.1 ± 21.2	80.4 ± 20.5	0.70
Type of visit				0.74
Inpatient hospitalization	343 (54.3)	207 (53.8)	136 (55.1)	
Outpatient clinic	298 (45.7)	178 (46.7)	121 (45.4)	
HF therapy				
ACEi/ARB at baseline	514 (81.3)	325 (84.4)	189 (76.5)	0.013
ACEi/ARB fraction target dose at 3 months (%)	0.54 ± 0.42	0.57 ± 0.45	0.50 ± 0.35	0.034
ACEi/ARB at 9 months	594 (94.0)	365 (94.8)	229 (92.7)	0.28
β-blocker at baseline	532 (84.2)	327 (84.9)	205 (83.0)	0.51
β-blocker fraction target dose at 3 months (%)	0.36 ± 0.29	0.36 ± 0.29	0.37 ± 0.29	0.64
β-blocker at 9 months	608 (96.2)	371 (96.4)	237 (96.0)	0.79
MRA use	364 (57.6)	224 (58.2)	140 (56.7)	0.71
Loop diuretic use	631 (99.8)	385 (100.0)	246 (99.6)	0.21
Digoxin use	128 (20.3)	78 (20.3)	50 (20.2)	0.99

Data are presented as n (%), or mean ± standard deviation.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; LA, left atrial; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

**Table 2** Baseline echocardiographic data and laboratory characteristics stratified by left atrial adverse remodelling

	Overall (n = 632)	No LA adverse remodelling (n = 385)	LA adverse remodelling (n = 247)	p-value
<b>Echocardiographic data</b>				
LVEF (%)	30.0 [25.0–35.0]	30.0 [25.0–35.0]	30.0 [25.0–35.0]	0.42
LVEF categories				0.67
HFrEF (LVEF <40%)	519 (85.6)	314 (85.3)	205 (86.1)	
HFmrEF (LVEF 40–49%)	64 (10.6)	38 (10.3)	26 (10.9)	
HFpEF (LVEF ≥50%)	23 (3.8)	16 (4.3)	7 (2.9)	
Baseline LA diameter (mm)	46.7 ± 8.3	48.5 ± 6.8	44.0 ± 9.5	< 0.001
Moderate–severe mitral regurgitation	306 (48.7)	192 (50.3)	114 (46.3)	0.34
LV baseline geometry				0.31
Normal geometry	121 (22.4)	81 (24.8)	40 (18.8)	
Concentric remodelling	11 (2.0)	6 (1.8)	5 (2.3)	
Concentric hypertrophy	48 (8.9)	31 (9.5)	17 (8.0)	
Eccentric hypertrophy	359 (66.6)	208 (63.8)	151 (70.9)	
LVEDD (mm)	62.5 ± 9.2	62.5 ± 8.8	62.4 ± 9.8	0.90
LVESD (mm)	51.1 ± 10.0	51.2 ± 9.9	50.9 ± 10.1	0.77
LV mass (g/m <sup>2</sup> )	139.5 ± 41.1	138.9 ± 40.2	140.4 ± 42.4	0.67
<b>Laboratory data</b>				
Haemoglobin (g/dl)	13.7 [12.5–14.7]	13.7 [12.6–14.8]	13.7 [12.3–14.6]	0.20
Creatinine (μmol/L)	97.2 [79.6–123.0]	96.3 [79.6–119.5]	102.0 [80.4–127.0]	0.19
eGFR CKD-EPI (ml/min/1.73 m <sup>2</sup> )	65.1 [48.9–83.4]	67.4 [50.2–84.2]	62.1 [46.8–81.0]	0.07
Urea (mmol/L)	9.4 [6.9–14.8]	9.2 [6.6–14.6]	9.9 [7.4–15.0]	0.13
Sodium (mmol/L)	140.0 [137.0–142.0]	140.0 [137.2–142.0]	140.0 [137.0–142.0]	0.81
NT-proBNP (ng/L)	1946.5 [850.8–4537.5]	1829.0 [820.1–4300.5]	2315.0 [905.4–4810.0]	0.16

Data are presented as n (%), mean ± standard deviation, or median [Q25–Q75].

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

by baseline LVEF ( $p$  for interaction = 0.83) and by the change in LVEF or LV diameter at 9 months ( $p$  for interaction = 0.74 and = 0.34, respectively).

### Left atrial adverse remodelling, achieved dose, and outcome

Over a median follow-up period of 13 months (IQR 8–18), the primary outcome occurred in 139 (21%) patients at a rate of 19.9 per 100 person-year (py). Patients with LAAR had a higher rate of the primary outcome during follow-up (16.3% vs. 26.2%, log-rank  $p$  = 0.007; *Figure 1*). Similar results were observed for mortality alone (that occurred in 86 [13.6%] patients at a rate of 11.2 per 100 py) and hospitalization for HF alone (that occurred in 81 [12.8%] patients at a rate of 11.6 per 100 py) (online supplementary *Figure S2*). LAAR was associated with a higher risk of the primary composite endpoint at Cox regression analysis (baseline adjusted hazard ratio [HR] 1.96, 95% CI 1.39–2.77,  $p$  < 0.001) (*Table 4*). This association remained significant also after adjustment for the BIOSTAT-CHF risk prediction model (HR 1.73, 95% CI 1.22–2.45,  $p$  = 0.002). When analysed as a continuous variable, the association between LA delta change and the primary outcome was not linear ( $p$  for non-linearity < 0.001), with a steep increase observed in patients with LAAR over time (overall association  $p$  < 0.001) (*Figure 2* and *Graphical Abstract*). Among patients with an

increase in LA dimension, for each 5 mm increase in LA diameter there was a significant association with the primary composite endpoint, even after adjustment for the BIOSTAT-CHF risk prediction model (HR 1.32, 95% CI 1.11–1.58,  $p$  = 0.002) (*Table 4*). Similar results were observed for each component of the composite endpoint (*Table 4*). The risk of the primary composite endpoint was more pronounced among patients with LAAR >10 mm (HR 6.07, 95% CI 3.09–11.92,  $p$  < 0.001) compared with those with LAAR ≤10 mm (HR 1.78, 95% CI 1.24–2.55,  $p$  = 0.002). The association between LAAR and the primary composite endpoint was not modified by baseline LVEF ( $p$  for interaction = 0.94), HFrEF versus HFpEF ( $p$  for interaction = 0.50), baseline moderate to severe mitral regurgitation ( $p$  for interaction = 0.94), as well as changes in LV diameter or LVEF at 9 months ( $p$  for interaction = 0.061 and = 0.61, respectively). Results were consistent after excluding HFpEF patients (online supplementary *Table S3*). History of AF significantly modified the association between LAAR and outcome ( $p$  for interaction = 0.009) as LAAR was significantly associated with worse outcomes only among patients without a history of AF.

### Discussion

Our analysis of BIOSTAT-CHF, a large, multinational, longitudinal study of patients with new-onset or worsening HF undergoing

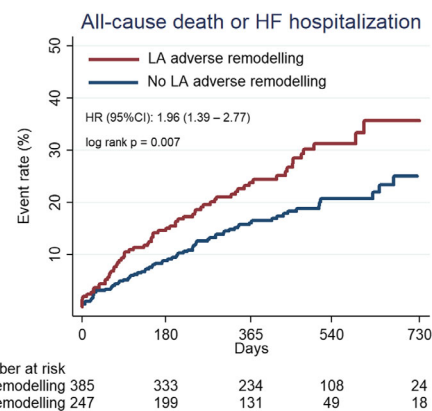
**Table 3** Multivariable analysis of the determinants of left atrial adverse remodelling

	OR (95% CI)	p-value	Z
Baseline LA diameter (mm)	0.90 (0.87–0.93)	<0.001	5.7
ACEi or ARB dose at 3 months	0.56 (0.34–0.92)	0.022	2.3
History of atrial fibrillation	2.07 (1.30–3.28)	0.002	3.1
LV baseline geometry			
Concentric remodelling	1.17 (0.25–5.41)	0.83	0.2
Concentric hypertrophy	1.06 (0.47–2.40)	0.88	0.1
Eccentric hypertrophy	2.13 (1.26–3.60)	0.005	2.8
HF primary ischaemic aetiology	1.78 (1.17–2.72)	0.007	2.7
Men	0.66 (0.39–1.11)	0.122	1.5
Age	1.00 (0.98–1.03)	0.39	0.8
eGFR CKD-EPI (ml/min/1.73 m <sup>2</sup> )	0.99 (0.98–1.00)	0.30	1.0
Baseline LVEF (%)	1.00 (0.97–1.02)	0.99	0.1
Baseline moderate–severe mitral regurgitation (%)	1.06 (0.69–1.64)	0.76	0.3
NYHA class			
II	1.66 (0.38–7.22)	0.49	0.7
III	1.90 (0.43–8.35)	0.39	0.9
IV	2.64 (0.50–13.8)	0.24	1.2

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio.

Overall model area under the curve: 0.73 (95% CI 0.68–0.77).

optimization of HF medical therapy, shows that adverse LA dimensional changes occur in a significant proportion of patients (39%), are associated with lower up-titration of ACEi/ARBs as well as history of AF and ischaemic aetiology, and predict a higher risk

**Figure 1** Kaplan–Meier estimates of all-cause death or heart failure (HF) hospitalization in patients with and without left atrial (LA) adverse remodelling. Unadjusted hazard ratio (HR) with 95% confidence interval (CI) are shown.

of all-cause mortality or hospitalization for HF, with a persistent independent effect also after accounting for clinical confounders. Our data highlight the importance of the longitudinal assessment of LA dimension in clinical practice as a marker of HF treatment response, which may improve prognostic risk stratification (*Graphical Abstract*).

Previous studies have shown the potential beneficial effects of specific treatments to attenuate LAAR, such as with treatment with ACEi in patients with hypertension, after restoration of sinus rhythm in patients with AF, or after mitral valve repair for severe mitral regurgitation.<sup>15–21</sup> A decrease in LA size associated with better clinical outcomes has been shown with cardiac resynchronization therapy or with sacubitril/valsartan administration in patients with HFpEF.<sup>22,23</sup> Similarly, sacubitril/valsartan, compared to valsartan, reduced LA dimension in patients with HFpEF.<sup>24</sup>

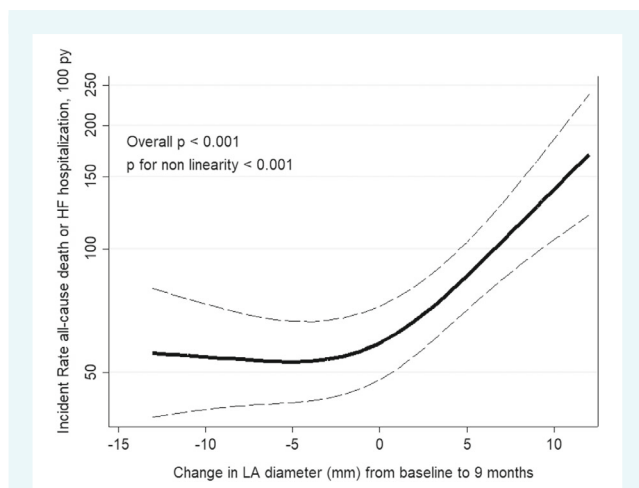
**Table 4** Association of left atrial adverse remodelling and the analysed endpoints

	Unadjusted			Adjusted		
	HR (95% CI)	p-value	Z	HR (95% CI)	p-value	Z
<b>All-cause death or HF hospitalization</b>						
LA adverse remodelling	1.96 (1.39–2.77)	<0.001	3.8	1.73 (1.22–2.45)	0.002	3.1
Δ LA change <sup>a</sup>	1.58 (1.32–1.89)	<0.001	5.1	1.32 (1.11–1.58)	0.002	3.1
<b>HF hospitalization</b>						
LA adverse remodelling	1.85 (1.18–2.91)	0.007	2.7	1.72 (1.10–2.69)	0.017	2.4
Δ LA change <sup>a</sup>	1.60 (1.28–2.00)	<0.001	4.1	1.41 (1.13–1.76)	0.002	3.0
<b>All-cause death</b>						
LA adverse remodelling	2.42 (1.55–3.77)	<0.001	3.9	2.19 (1.40–3.42)	0.001	3.5
Δ LA change <sup>a</sup>	1.51 (1.19–1.92)	0.001	3.5	1.32 (1.04–1.67)	0.019	2.3

CI, confidence interval; HF, heart failure; HR, hazard ratio; LA, left atrial.

Unadjusted and adjusted analysis accounted for baseline LA diameter. Adjusted model was adjusted for the risk model of BIOSTAT-CHF which contains age, previous hospitalization for HF, systolic blood pressure, presence of peripheral oedema, N-terminal pro-B-type natriuretic peptide, haemoglobin, sodium, high-density lipoprotein, and use of β-blockers at baseline.

<sup>a</sup>HRs are shown for 5 mm increase among patients with positive LA change.



**Figure 2** Restricted cubic spline analysis showing the continuous association of change in left atrial (LA) diameter with all-cause death or heart failure (HF) hospitalization (incident rate per 100 person-years [py]).

Recently, sodium–glucose cotransporter 2 inhibitors (SGLT2i) did not clearly show a reduction of LA dimension in diabetic patients with or without HF, but further studies are needed.<sup>25–27</sup>

Taken together, these results show the potential benefit of medical treatment on LA structure changes. Nevertheless, to what extent HF therapy up-titration may promote reverse LA remodelling and its clinical implications, is less known. Hence, our study extends previous reports, offering the opportunity to understand this unmet clinical need in a large group of well selected patients with worsening or new-onset HF enrolled in a prospective study including GDMT optimization. We found that more than half of our population reduced or unchanged LA dimension over time and that the likelihood of LAAR after GDMT optimization was significantly reduced by higher achieved dose of ACEi/ARBs but not  $\beta$ -blockers. On the other hand, an increase in LA dimension of 5 mm over time despite GDMT resulted in a 32% higher risk of all-cause mortality or hospitalization for HF, highlighting the need to attenuate the processes leading to LA enlargement.

Left atrial remodelling is a complex structural and functional process due to a time-dependent adaptive response of atrial myocytes against external electrical, mechanical, and metabolic stressors.<sup>5,28–31</sup> The pathological changes related to these mechanisms may reflect a spectrum of atrial tissue structural alterations leading to atrial impairment, including myocyte hypertrophy, necrosis, inflammation, and changes in the composition of the extracellular matrix.<sup>5,8</sup> By inhibiting the renin–angiotensin–aldosterone system, ACEi/ARB therapy was shown to have a major effect on collagen synthesis, reducing interstitial fibrosis and inflammation.<sup>32,33</sup> Although our analysis cannot provide a pathological evidence of fibrosis reduction among those who did not experience adverse remodelling, and the reverse structural effect after HF therapy may be also related to a passive process due to an improvement of overall cardiac haemodynamics and filling pressure, it is possible that treatment response relies upon the burden of myocardial fibrosis,

as observed for LV reverse remodelling.<sup>9,10</sup> Therefore, patients with less fibrosis and at an early stage of atrial disease may respond more quickly with a decrease in overall chamber compliance and a resultant decrease in LA dimension.<sup>24,34,35</sup> On the other hand, LA assessment may be less sensitive to capture the effect of HF treatment in patients with advanced atrial disease, as those with a history of AF.<sup>8</sup>

The current data show the importance of routine assessment of the left atrium and its change over time may represent *per se* a surrogate of HF treatment response identifying patients with reduced risk of CV events.<sup>8,36</sup> Given the post hoc nature of our study, our data should be interpreted as ‘hypothesis-generating’. The concept that GDMT for HF may have beneficial effects also on LA remodelling and that this may be a marker of better outcomes is novel and warrants prospective replication. Our results suggest that the inclusion of measurements of LA remodelling may be a meaningful surrogate of the effects of treatment on clinical outcomes and may be assessed in clinical trials.

## Study limitations

This is a post hoc analysis of a prospective study with several limitations. First, echocardiographic images were not evaluated by a core laboratory and inter- and intraoperator variability was not assessed. Echocardiographic data at baseline and 9-month follow-up were available in 632 (25.1%) patients enrolled in the index cohort of BIostat-CHF, potentially limiting our power to detect up-titration treatment effect on LA dimension changes and subsequent outcomes. Also, some imbalance in clinical characteristics between patients with and without LA assessment at 9 months was observed, potentially limiting the extrapolation of results to all HF patients. Cautions should be adopted when applying our results to the entire spectrum of LVEF, as we included only a small proportion of patients with HFpEF. Available data did not include neither volumetric measurement of the left atrium nor functional parameters, such as strain derived from speckle tracking echocardiography.<sup>30,37</sup> Further studies are required to globally assess the changes in LA structure and function according to HF therapy. Timing of diuretics to echocardiography was not known, potentially influencing the assessment and interpretation of LA structure.<sup>38</sup> Furthermore, since the study was designed before the evidence of new effective HF treatments (sacubitril/valsartan and SGLT2i), we could not assess the effect of these drugs on LA remodelling. Finally, clinical events were centrally adjudicated, but were not evaluated by independent investigators.

## Conclusions

Our analysis of BIostat-CHF shows that LAAR is associated with an increased risk of all-cause mortality or HF hospitalization and that up-titration of ACEi/ARBs may attenuate LA enlargement. Our results suggest that routine assessment of LA dimensions may identify patients with HF and a favourable response to treatment. Favourable LA remodelling may be a useful surrogate of a reduced risk of CV events and its role warrants further prospective validation.

## Supplementary Information

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

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