Left Atrial Reverse Remodeling in Dilated Cardiomyopathy

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Background: Left atrial (LA) dilation is associated with a worse prognosis in several cardiovascular settings, but therapies can promote LA reverse remodeling. The aim of this study was to characterize and define the prognostic implications of LA volume index (LAVI) reduction in patients with dilated cardiomyopathy (DCM).

Methods: Consecutive patients with DCM from two tertiary care centers, with available echocardiograms at baseline and at 1-year follow-up, were retrospectively analyzed. LA dilation was defined as LAVI > 34 mL/m^2, and change in LAVI (ΔLAVI) was defined as the 1-year relative LAVI reduction. The outcome was a composite of death, heart transplantation (HTx), or heart failure hospitalization (HFH).

Results: Five hundred sixty patients were included (mean age, 54 ± 13 years; mean left ventricular ejection fraction, 31 ± 10%; mean LAVI, 45 ± 18 mL/m^2). Baseline LAVI had a non-linear association with the risk for death, HTx, or HFH, independent of age, left ventricular ejection fraction, mitral regurgitation, and medical therapy ($P < .01$). At 1-year follow-up, LAVI decreased in 374 patients (67%; median ΔLAVI, −24%; interquartile range, −37% to −11%). Factors independently associated with ΔLAVI were higher baseline LAVI and lower baseline left ventricular ejection fraction. After multivariable adjustment, ΔLAVI showed a linear association with the risk for death, HTx, or HFH (hazard ratio, 0.96 per 5% decrease; 95% CI, 0.93-0.99; $P = .042$). At 1-year follow-up, patients with reductions in LAVI of >10% and LAVI normalization (i.e., follow-up LAVI ≤ 34 mL/m^2; 31% of the overall cohort) were at lower risk for death, HTx, or HFH (hazard ratio, 0.37; 95% CI, 0.35-0.97; $P = .028$).

Conclusions: In a large cohort of patients with DCM, 1-year reduction in LAVI was observed in a number of patients. The association between reduction in LAVI and death, HTx, or HFH suggests that LA structural reverse remodeling might be considered an additional parameter useful in the individualized risk stratification of patients with DCM.

Keywords: Dilated cardiomyopathy, Left atrium, Left atrial reverse remodeling, Heart failure, Clinical outcome

The complex interactions between the left atrium and the progression of heart failure (HF) have gained increasing interest.[1,2] The left atrium is not a passive structure but actively contributes to the global cardiac performance.[3] Left atrial (LA) adverse remodeling is the consequence of functional and structural alterations in the LA architecture under prolonged pressure and/or volume overload, culminating in the progressive dilation of the left atrium.[4] In HF with reduced ejection fraction (HFrEF), LA unfavorable remodeling is determined by the contribution of different stressors, including raised filling pressures, diastolic dysfunction, mitral regurgitation (MR), and atrial tachyarrhythmias. This maladaptive process has been formerly associated with poor prognosis in several cardiovascular diseases, including HFrEF overall and dilated cardiomyopathy (DCM).[5-8]

In HFrEF, there are effective therapies that counteract the maladaptive processes leading to progressive dilation of the left heart chambers. Indeed, in older series of patients, left ventricular (LV) reverse

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Conflicts of interest: None.

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Abbreviations
AF = Atrial fibrillation
CRT = Cardiac resynchronization therapy
DCM = Dilated cardiomyopathy
HF = Heart failure
HFH = Heart failure hospitalization
HFrEF = Heart failure with reduced ejection fraction
HTx = Heart transplantation
LA = Left atrial
LARR = Left atrial reverse remodeling
LAVI = Left atrial volume index
LV = Left ventricular
LVEF = Left ventricular ejection fraction
MR = Mitral regurgitation

remodeling is a well-recognized result of targeted therapies for HFrEF.[9] Similarly, LA reverse remodeling (LARR) can be promoted by the same treatments, and it is partially a secondary effect of improved LV function.[10] However, previous data on cardiac resynchronization therapy (CRT) in HFrEF overall suggest that the association between LARR and better prognosis can be independent of the improvement in LV function,[11] suggesting that LARR is a positive disease marker in HFrEF.

DCM is a specific cause of LV systolic dysfunction in the absence of any primary pressure or volume-overload state.[12] In DCM the left atrium may be exposed to the progressive adverse remodeling driven by the combination of the primary cardiomyopathic process and the consequences of the hemodynamic impairment. Although the association between LV reverse remodeling and outcome in DCM has been extensively demonstrated,[9] the prevalence and impact of structural LARR on the prognosis of the disease remain unexplored. In the present study, we sought to investigate the 1-year trends of LA volume index (LAVI) and its prognostic effects in patients with DCM.

METHODS

Study Population

Consecutive outpatients enrolled in two European DCM prospective ongoing registries, the Trieste Heart Muscle Disease Registry (between 2006 and 2016) and the Maastricht Cardiomyopathy Registry (between 2004 and 2016), were considered eligible.

The diagnosis of DCM was determined according to the currently accepted criteria.[12] Patients with significant coronary artery disease (>50% stenosis of an epicardial coronary artery, ruled out by coronary angiography or computed tomography), history of significant systemic hypertension, biopsy-proven active myocarditis, alcohol intake > 100 g/d, organic valve disease, previous cardiac surgery, tachycardia-induced cardiomyopathy, peripartum cardiomyopathy, congenital heart disease, or advanced systemic disease affecting prognosis were excluded.

All patients with a complete clinical and echocardiographic evaluations at baseline (i.e., first evaluation at the enrolling center) and at 1-year follow-up (range, 9-15 months) were included in the study and retrospectively analyzed. None of the patients included died or underwent heart transplantation (HTx) or HF hospitalization (HFH) before the 1-year follow-up evaluation. The follow-up period ended on July 31, 2019, or at the date of the study end point; thus every patient had potential follow-up of ≥36 months. All patients were treated according to international guidelines on HF, including device therapy.[13] Baseline therapy was recorded at the end of first evaluation. Chronic kidney disease was defined as Modification of Diet in Renal Disease estimated glomerular filtration rate < 60 mL/min/1.73 m^2.[14] The study was approved by the institutional ethical boards. All patients provided written informed consent.

Echocardiographic Analysis and Definitions

Echocardiograms were recorded on digital media storage at the institutions' echocardiography core laboratories and subsequently analyzed offline for the present study by experienced echocardiographers (V.N., P.M., and A.R.) blinded to patient outcomes and to the measurements reported on the original report. Each patient was analyzed by the same operator at both baseline and follow-up evaluations. Conventional measurements were obtained according to the latest available guidelines.[15] In particular, LA volumes were obtained from optimized apical four-chamber and two-chamber views, avoiding foreshortening of the atrium. LA volume was determined by the disk summation algorithm from both four-chamber and two-chamber views. LAVI measurement was tested in an intra- and interobserver reproducibility study. In a total sample of 80 patients (40 in Trieste, 40 in Maastricht), LAVI was remeasured a second time by the same operator and a third time by a different operator. Intra- and interobserver variability was thus calculated. Results are reported in Supplemental Table 1. Other details regarding echocardiography and reproducibility are reported in Supplemental Methods.

The 1-year relative variation in LAVI was defined as change in LAVI (ΔLAVI) = (1-year LAVI − LAVI baseline)/LAVI baseline × 100 and is reported as a percentage value, as previously validated.[3,11,16] Thus, a negative ΔLAVI value indicates reduction in LAVI for the corresponding patient. Similarly, each Δ parameter was calculated analogously to ΔLAVI. LARR was defined as normal LAVI at follow-up evaluation (i.e., LAVI ≤ 34 mL/m^2) and ΔLAVI of ≥10% (double the mean interobserver variability) and was used in the assessment of cumulative event-free survival. MR reduction was defined as reduction of MR severity from moderate or severe to absent or mild.

Study Outcomes

The primary outcome measure was a composite of all-cause mortality, HTx, or HFH (HFH).

A prespecified subgroup analysis was performed in patients with versus without atrial fibrillation (AF).

Information regarding outcome was obtained from official reports drawn up by hospitals, direct contact with patients, their families or general practitioners, queries of regional health care data warehouse and registers of death of the municipalities of residence. No patients were lost to follow-up concerning information on the outcome.

Statistical Analysis

Descriptive statistics are reported as mean ± SD, median (interquartile range), or counts and percentages as appropriate. For continuous variables, cross-sectional comparisons between groups were made using one-way analysis of variance or the nonparametric Mann-Whitney *U* test as appropriate. The χ^2 or Fisher exact test was used for comparisons of categorical variables between groups. Comparisons between baseline and follow-up variables were performed using the paired *t* test or nonparametric Wilcoxon test for paired variables. Univariable and multivariable Cox regression models were fitted for the primary outcome. When there was evidence of nonlinear effects between a continuous variables and the primary

HIGHLIGHTS

- LA dilation is associated with poor outcomes in HF and DCM.
- Therapies can promote LARR.
- A significant proportion of patients with DCM show LARR over 1-year follow-up.
- LARR is strongly associated with lower risk for poor prognosis.

outcome, the former was modeled using restricted cubic spline analyses with four degrees of freedom (internal knots were put at the first, second, and third quartiles of the variable distribution). Baseline variables associated with 1-year ΔLAVI were identified using univariable and multivariable linear regression models. Nonlinearity was tested using the likelihood ratio test by comparing the model with a linear effect and the model with nonlinear effect. The degree of freedom of the restricted cubic spline was chosen using the adjusted Akaike information criterion: model likelihood ratio − 2 × *df*. Correlations between ΔLAVI and other continuous variables (ΔLV ejection fraction [ΔLVEF], ΔLV end-diastolic volume index, and ΔLV end-systolic volume index) were assessed using Spearman correlation, while correlations between ΔLAVI and dichotomous variables were assessed by fitting independent univariable logistic regression models. Survival curves for the primary outcome were estimated using the Kaplan-Meier estimator and were compared between groups using the log-rank test. When variables measured at follow-up were used as covariates in the time-to-event analyses, follow-up time was measured from the time of the 1-year follow-up evaluation. *P* values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 25 (IBM) and R version 3.6.2 (R Foundation for Statistical Computing), with libraries survival and ggplot2.

RESULTS

Study Population: Baseline and Follow-Up Characteristics

During the study period, 1,187 patients were enrolled in the registries (Trieste, $n = 459$; Maastricht, $n = 773$). Of these, 627 were excluded because 1-year echocardiographic follow-up was not available (patients were dead or missing information) or because of poor-quality imaging (Supplemental Figure 1). No relevant differences regarding the study outcome were found between patients included and those excluded from the present study (Supplemental Table 2). The final study population consisted of 560 patients (mean age, 54 ± 14 years; 365 [65%] men; median disease duration, 3 months [IQR, 1-11 months]). At baseline, mean LAVI was 45 ± 18 mL/m^2, and 389 patients (69%) had LA dilation (i.e., LAVI > 34 mL/m^2). Mean LVEF was 31 ± 10%. Additional baseline characteristics are summarized in Table 1.

At 1-year follow-up (median, 11 months [IQR, 9 to 13 months] after baseline), mean LAVI was 39 ± 17 mL/m^2, and mean LVEF was 40 ± 11%. The median observed ΔLAVI was −24% (IQR, −37% to −11%), with 374 patients (67% of the overall cohort) experiencing any degree of LAVI reduction and 109 patients (19% of the overall cohort and 28% of patients with baseline LAVI > 34 mL/m^2) reaching normal LA dimension at 1-year follow-up.

Functional Correlations and Characteristics Associated with ΔLAVI

ΔLAVI demonstrated weak correlations with 1-year changes in LV metrics (ΔLVEF, Pearson coefficient = −0.243, $P < .001$; ΔLV end-diastolic volume index, Pearson coefficient = 0.314, $P < .001$; ΔLV end-systolic volume index, Pearson coefficient = 0.299, $P < .001$), whereas the reduction in the severity of MR and in the prevalence of restrictive filling pattern was more frequent in patients with decreased LAVI compared with patients with stable or worsened LAVI (Figure 1).

Patients with improved LAVI were more likely to be treated with mineralocorticoid antagonists compared with those with stable or worsening ΔLAVI (46% vs 37%, respectively, $P = .046$), but no other significant differences in other drugs and devices therapies were observed between the two groups (Supplemental Table 3). On linear multivariable regression analysis, the baseline factors independently associated with ΔLAVI were disease duration ($\beta = -0.205$; 95% CI, −0.255 to −0.064; $P = .001$) and baseline LAVI ($\beta = 0.466$; 95% CI, 0.603 to 1.105; $P < .001$; Table 2).

Prognostic Implications of LAVI

Over a median follow-up period of 65 months (IQR, 36-101 months), the primary composite outcome occurred in 123 patients (22% of the overall cohort; 52 deaths, 13 HTx procedures, 58 HFHs).

Baseline LAVI was associated with risk for death, HTx, or HFH on univariable analysis and after adjustment for age, LVEF, moderate to severe MR, and medical therapy, showing a nonlinear effect. In particular, as illustrated in Figure 2, the risk for death, HTx, or HFH progressively increased for LAVI values >42 mL/m^2 ($P < .01$).

At 1-year follow-up, ΔLAVI demonstrated a linear association with risk for death, HTx, or HFH after adjustment for age, baseline LAVI, LVEF, ΔLVEF, baseline MR, MR reduction, AF, and therapy with renin-angiotensin inhibitors and β-blockers (hazard ratio, 0.96 per 5% decrease; 95% CI, 0.93-0.99; $P = .042$; Figure 3). As a confirmatory analysis, we also assessed the association between absolute variation in LAVI (1-year LAVI − baseline LAVI) and the primary end point, obtaining similar results (Supplemental Figure 2).

On subgroup analysis, ΔLAVI remained associated with risk for death, HTx, or HFH regardless of the presence of AF (Supplemental Figure 3).

Finally, LARR (defined as LAVI reduction > 10% and LAVI ≤ 34 mL/m^2 at 1-year follow-up) was observed in 175 patients (31%) of the study population. Survival curve analysis showed a lower incidence of death, HTx, or HFH for patients with LARR compared with those without LARR (Figure 4A). A similar reduction in risk for patients with LARR compared with patients without LARR was observed after the exclusion of patients with normal baseline LAVI (i.e., LAVI ≤ 34 mL/m^2; Figure 4B).

DISCUSSION

In this study, we assessed the 1-year trajectories of LA size in a large contemporary cohort of patients with DCM managed according to evidence-based treatment strategies. The main findings are as follows: (1) baseline LAVI had a nonlinear association with outcome, independent of age, baseline LVEF, MR, and medical therapy; (2) >60% of the study population experienced reductions in LAVI 1 year after enrollment; (3) a larger left atrium and shorter disease duration were the

Table 1 Clinical characteristics of the study population at baseline and at 1-year follow-up

	n	Baseline evaluation (*n* = 560)	*n*	1-y evaluation (*n* = 560)	*P*
Clinical evaluation					
Age, y	560	52 ± 13	—	—	—
Sex, male	560	366 (65)	—	—	—
Center (Maastricht)	560	275 (49)	—	—	—
Heart rate, beats/min	517	76 ± 17	517	69 ± 13	<.001
SBP, mm Hg	485	128 ± 21	485	127 ± 20	.235
NYHA functional class III or IV	545	97 (18)	466	33 (7)	<.001
LBBB	557	125 (23)	—	—	—
Diabetes mellitus	559	65 (12)	—	—	—
eGFR < 60 mL/min/1.73m^2	560	47 (8)	—	—	—
AF	560	110 (20)	—	—	—
Paroxysmal/persistent AF	553	70 (13)	—	—	—
Permanent AF	553	40 (7)	—	—	—
Echocardiography					
LVEF, %	560	31 ± 10	560	40 ± 11	<.001
LVEDD, mm	560	63 ± 9	560	59 ± 8	<.001
LVEDVI, mL/m^2	560	90 ± 30	560	77 ± 29	<.001
IVS, mm	465	10 ± 2	465	10 ± 2	.478
LAVI, mL/m^2	560	45 ± 18	560	39 ± 17	<.001
Moderate or severe MR	548	99 (18)	553	55 (10)	<.001
RFP	467	105 (23)	486	40 (8)	<.001
E/E′ ratio	202	14 (8)	202	10 (5)	<.001
RV dysfunction	448	118 (26)	415	47 (11)	<.001
Medications					
ACE inhibitors, ARBs, or ARNIs	560	479 (86)	560	486 (87)	.562
β-blockers	559	462 (83)	538	498 (93)	<.001
MRAs	558	242 (43)	538	237 (44)	.781
Ivabradine	559	23 (4)	537	25 (5)	.453
Diuretics	559	315 (56)	538	295 (55)	.516
CRT	560	23 (4)	560	62 (11)	<.001
ICD	560	24 (4)	560	84 (15)	<.001

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor neprilysin inhibitor; *eGFR*, estimated glomerular filtration rate; *ICD*, implantable cardioverter-defibrillator; *IVS*, interventricular septum; *LBBB*, left bundle branch clock; *LVEDD*, LV end-diastolic diameter; *LVEDVI*, LV end-diastolic volume index; *MRA*, mineralocorticoid receptor antagonist; *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern; *RV*, right ventricular; *SBP*, systolic blood pressure.
Data are expressed as mean ± SD or as number (percentage). *P* values were estimated using the χ^2 test for categorical variables and Student's *t* test for continuous variables.

baseline factors associated with a larger reduction in LAVI at 1-year follow-up; and (4) LAVI reduction demonstrated a strong association with the long-term morbidity and mortality outcome measure of death, HTx, or HFH, independent of ventricular function, baseline MR, MR improvement, medical therapy, AF, and age.

Maladaptive LA Remodeling in DCM

LA remodeling is a complex process involving structural, functional, electrical, and metabolic changes. In our study we focused on LA macroscopic changes. Several cardiovascular conditions may affect LA structure and function, leading to its progressive enlargement. It is typically considered a marker of LV diastolic dysfunction and can be a predisposing factor for the development of AF or in turn a consequence of long-standing AF.[3,17] Within the spectrum of HF phenotypes, LA dilation and impaired LA function also characterize the progression of HFrEF and have been associated with worse prognosis in patients with HFrEF.[6,8] Beyond AF and diastolic dysfunction, other mechanisms can promote LA enlargement in HFrEF, including age, MR, atrial and ventricular dyssynchrony, congestion, and neurohormonal activation.[3] This study population is characterized by a relatively younger age compared with other ischemic and nonischemic HFrEF populations.[18] This is reasonable, as idiopathic and genetic DCM have younger age at onset compared with secondary causes of HFrEF.[19-21]

We focused on LA size, investigated as LAVI, which can be considered an epiphenomena of the ultrastructural, metabolic, electrical, and functional status of the left atrium. LA dilation, defined as LAVI

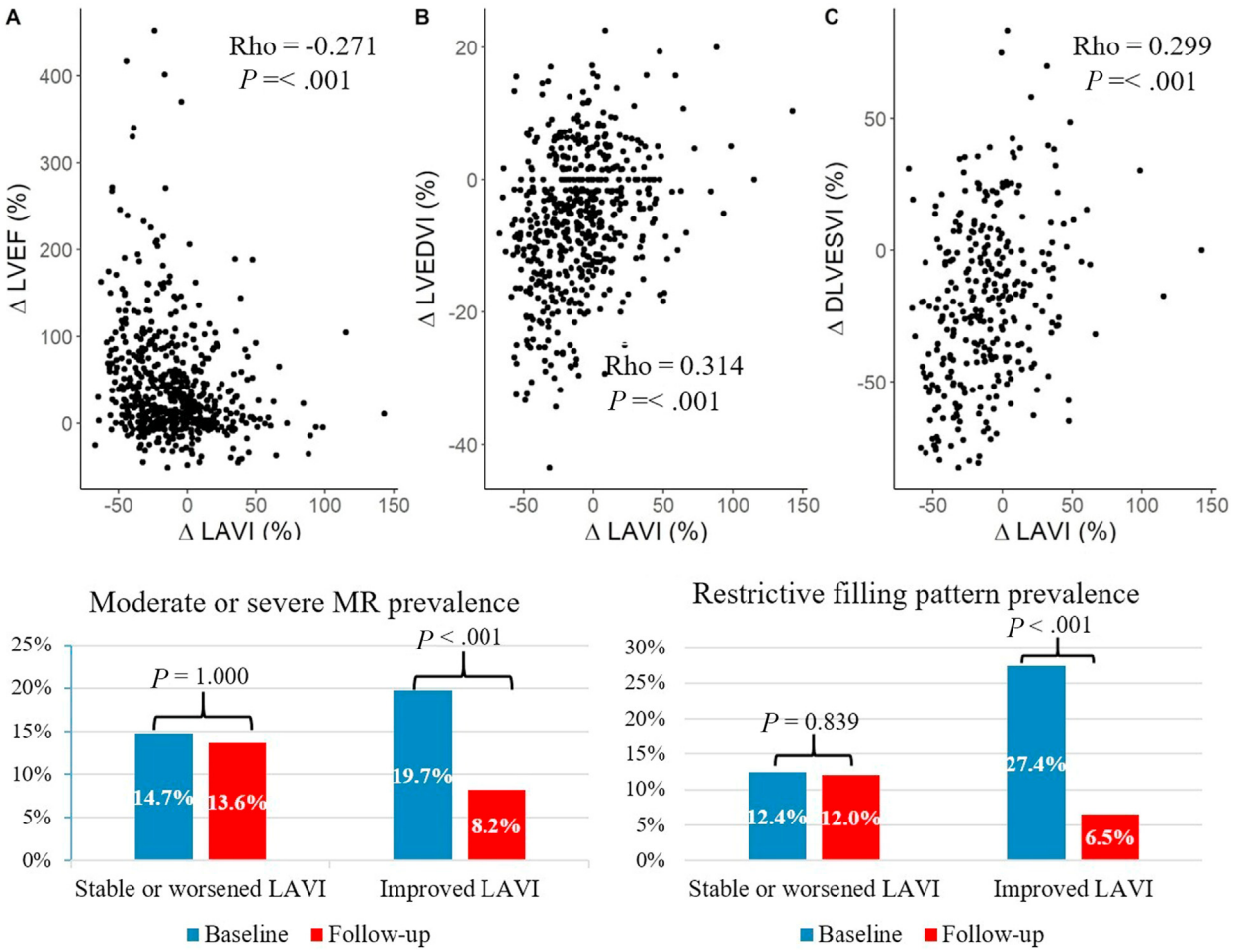

Figure 1 Correlations between ΔLAVI and changes in LVEF **(A)**, LV end-diastolic volume index (LVEDVI) **(B)**, and LV end-systolic volume index (LVESVI) **(C)**. Correlations between ΔLAVI and other continuous variables were assessed using Spearman correlation coefficients (rho); correlations between ΔLAVI and dichotomous variables were assessed using independent univariable logistic regression models.

> 34 mL/m^2, was found to be highly prevalent at baseline (69% of the overall cohort), similarly to previous studies of DCM.[5] According to former studies, patients with larger LA dimensions were at higher risk for adverse events, independent of LV function other important prognosticators, further confirming the relationship between adverse LA remodeling and poor outcomes in DCM.[5] In addition, we observed an increased risk for death, HTx, or HFH for baseline LAVI values exceeding 42 mL/m^2. This value needs to be tested in larger cohorts to validate its application in the specific setting of DCM.

One-Year Trends of LA Dimensions in DCM

The regression of structural LA dilation has been described in observational studies through the control of traditional risk factors for LA remodeling, such as hypertension and AF.[4,16] However, in the setting of HFrEF, and in particular in DCM, the modifications of LA dimension during follow-up were poorly explored.[10,11] Previous studies showed that the reduction in wall stress and the regression of atrial fibrosis obtained with neurohormonal antagonist drugs,[22] the correction of dyssynchrony and the reduction in MR with CRT,[23] and the stability of sinus rhythm obtained through medications or ablation procedures[24] can all contribute to promoting the progressive reverse remodeling of the enlarged left atrium.

In our study, after 1 year of medical therapy, LARR was observed in 31% of patients. We observed that patients with reduced LAVI were more likely to be treated with mineralocorticoid antagonists. No other differences were observed between groups. However, systematic information on doses was not available, and we cannot exclude that patients with larger improvements in LAVI might have been treated with higher doses of neurohormonal antagonist drugs. At baseline, we identified two factors associated with higher reduction in 1-year LAVI: larger LAVI and shorter disease duration. It might seem surprising that the more enlarged left atria had the highest degree of improvement in LAVI at follow-up. The most likely explanation is that in patients with normal or near normal LAVI, the probability of larger improvement is lower, as they already have, or achieve by a small improvement, the normal range of LAVI. The association between disease duration and the degree of LAVI reduction supports the importance for early referral to tertiary centers

Table 2 Univariable and multivariable analysis linear regression model for variables associated with ΔLAVI at 1-year evaluation (560 cases)

	Univariable, β (95% CI)	Multivariable, β (95% CI)
Clinical evaluation		
Age, per year	0.126 (−0.053 to 0.305), P = .167	
Sex, male	0.039 (−5.062 to 5.139), P = .716	
Center (Maastricht)	−1.613 (−6.466 to 3.240), P = .514	
Heart rate	0.085 (−0.060 to 0.229), P = .250	
SBP	−0.003 (−0.125 to 0.119), P = .959	
Disease duration	−0.167 (−0.220 − −0.063), P < .001	−0.205 (−0.255 − −0.064), P = .001
LBBB	−4.855 (−10.880 to 1.170), P = .114	
Diabetes mellitus	1.243 (−6.341 to 8.827), P = .748	
eGFR < 60 mL/min/1.73m^2	−3.245 (−11.993 to 5.504), P = .467	
AF	−0.779 (−6.887 to 5.330), P = .802	
NYHA functional class III or IV	2.136 (−4.336 to 8.608), P = .517	
Echocardiography		
LVEF	−0.591 (−0.829 to −0.352), P < .001	−0.112 (−0.827 to 0.094), P = .118
LVEDVI	0.075 (−0.026 to 0.175), P = .144	
IVS	−0.141 (−1.466 to 1.184), P = .835	
LAVI	0.578 (0.448 to 0.707), P < .001	0.466 (0.603 to 1.105), P < .001
Moderate or severe MR	8.851 (2.605 to 15.096), P = .006	−0.055 (−15.031 to 6.854), P = .462
RFP	13.251 (6.943 to 19.558), P < .001	0.023 (−9.355 to 12.682), P = .766
E/E′ ratio	0.752 (0.214 to 1.290), P = .006	0.004 (−0.632 to 0.664), P = .961
RV dysfunction	4.453 (−1.756 to 10.663), P = .159	
Medications		
ACE inhibitors, ARBs, ARNIs	−1.299 (−8.198 to 5.600), P = .712	
β-blockers	1.625 (−4.793 to 8.042), P = .619	
MRAs	4.866 (−0.022 to 9.754), P = .051	
Ivabradine	3.688 (−8.546 to 15.922), P = .554	
Diuretics	3.556 (−1.336 to 8.449), P = .154	
CRT at baseline	7.392 (−4.822 to 19.606), P = .235	
ICD at baseline	11.318 (−0.628 to 23.265), P = .063	

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor neprilysin inhibitor; *eGFR*, estimated glomerular filtration rate; *ICD*, implantable cardioverter-defibrillator; *IVS*, interventricular septum; *LBBB*, left bundle branch clock; *LVEDVI*, LV end-diastolic volume index; *MRA*, mineralocorticoid receptor antagonist; *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern; *RV*, right ventricular; *SBP*, systolic blood pressure.

specializing in management of cardiomyopathy. Interestingly, AF was not associated with ΔLAVI. This might be explained by the lower overall prevalence and the low proportion of permanent AF compared with the general HFrEF population.

We also assessed the correlations between 1-year ΔLAVI and longitudinal changes in the other relevant echocardiographic parameters. Of note, the correlations of ΔLAVI with the LV metrics were weak, suggesting that changes in ΔLAVI are not the mere consequence of the LV response to treatment. Apparently, a stronger connection was observed with the improvement in MR and diastolic function. The reduction in the severity of MR and the improvement in diastolic function as the result of therapy implementation have been previously reported to occur frequently in DCM and in general at an earlier stage compared with the improvement in LV metrics.[25] The data confirm the tight connection among LV diastolic function, MR, and LA size, suggesting that the all aspects of cardiac performance may dramatically improve over 1 year. Future studies including advanced imaging techniques such as LA strain might explore in depth these aspects in DCM and more generally in HFrEF.

Prognostic Implications of 1-Year LAVI Changes

In the overall HF population, as well as in DCM, the prognostic impact of LARR remains largely unexplored. In a small cohort of CRT recipients with mixed etiologies of HFrEF, LARR occurred in

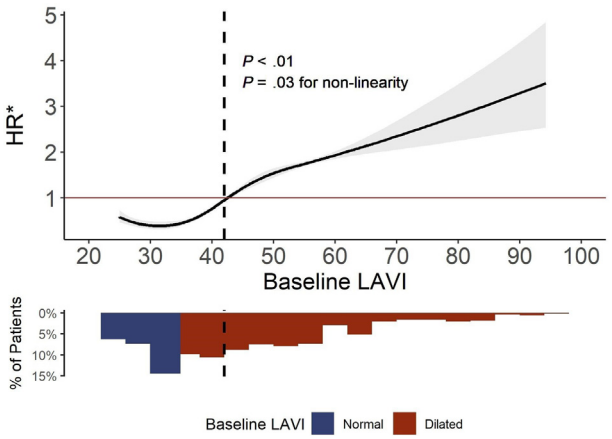

Figure 2 Prognostic effect of LAVI at baseline with respect to a reference value of LAVI at baseline of 42 mL/m^2 (median value of the cohort; *vertical dotted line*). At the *bottom* is reported the number of patients for each LAVI interval. Normal LAVI *(blue)* is defined as LAVI ≤ 34 mL/m^2; dilated line *(red)* defined as LAVI > 34 mL/m^2. *Hazard ratio (HR) for the risk of death, HTx, or HFH is adjusted for age, LVEF, moderate to severe MR, mineralocorticoid antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, neprilysin inhibitors, β-blockers, and diuretics.

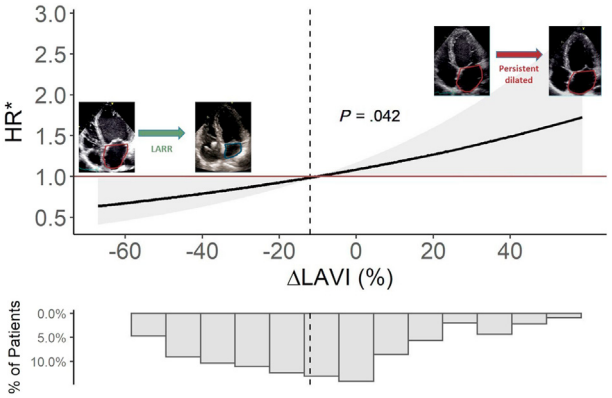

Figure 3 Prognostic role of ΔLAVI after adjustment for baseline LAVI, baseline LVEF, and ΔLVEF. The hazard ratio (HR) is calculated for the risk for death, HTx, or HFH beginning from the 1-year follow-up evaluation with respect to a reference value of ΔLAVI of 12% (median value of the cohort; *vertical dotted line*). At the *bottom* is reported the number of patients for each ΔLAVI interval. *HR is adjusted for age, baseline LAVI, LVEF, ΔLVEF, baseline MR, MR reduction, AF, and therapy with renin-angiotensin inhibitors and β-blockers.

CRT responders and had an association with better outcome, independent of LV systolic improvement.[11] In our study, we demonstrated for the first time that in a large cohort of patients with DCM, 1-year LAVI variation showed a linear association with risk for death, HTx, or HFH, independent of the entity of LA dilation at baseline, baseline and changes in MR and LVEF, the presence of AF, the use of HF medications, and age. Consistent findings were obtained if absolute LAVI variation was used instead of ΔLAVI. Of note, in the prespecified subgroup analysis, ΔLAVI remained associated with death, HTx, or HFH regardless of AF. The finding that the longitudinal trajectories of LAVI are associated with risk for adverse events in DCM highlights the potential role of quantifying changes in LAVI as a marker of response to therapeutic strategies. In DCM, this appears to be of incremental value compared with the baseline clinical and echocardiographic evaluation. Conversely, increasing LAVI at follow-up should be considered as an indirect indicator of worsening clinical status. We demonstrated that the 10% ΔLAVI reduction is a valuable cutoff as a prognosticator, in accordance with the variability of LARR measurements, as shown in the reproducibility study. In our cohort, indeed, patients with LARR (1-year LAVI ≤ 34 mL/m^2 and ΔLAVI ≥ 10%) were at lower risk for adverse outcome compared with those without LARR, irrespective of the presence of LA dilation at baseline. In our cohort, indeed, patients with LAVI reductions >10% and 1-year LAVI ≤ 34 mL/m^2 were at lower risk for adverse outcome compared with patients without LARR, regardless of the presence of LA dilation at baseline.

Limitations

As with all observational studies, our study suffers from selection bias due to its retrospective design. The study population was enrolled at two tertiary care centers for HF, and this indirectly may explain the rate of patient exclusions, as the proportion of patients referred from other institutions was high, and many of these did not return for follow-up to our centers. However, only 4% of the study population was excluded because of poor acoustic windows, supporting the feasibility of LAVI measurements in routine practice. Patients who died before the 1-year reassessment were excluded, which along with the known lower risk reported for patients with DCM compared with ischemic cardiomyopathy[26] explains the low event rate. Former studies published by the Trieste and Maastricht groups were performed in the same registries as the present study. Differences in patient selection and clinical management between centers may introduce a further bias and limit the generalizability of our findings; the comparison of the main characteristics of the population of the two registries shown in Supplemental Table 4 demonstrates that the incidence of the outcome was not different between the two groups. We set our main analyses on LARR as a continuous variable (ΔLAVI) because there was no consensus on a cutoff defining LARR in DCM. Moreover, the linear prognostic effect of ΔLAVI suggests that a precise cutoff could be not the best way to use LAVI evolution for prognostication. We focused our analyses on structural LARR, as functional LA parameters were not systematically available. Some patients underwent HF therapy optimization (in particular, 7% underwent CRT device implantation). Definite conclusions on the impact of therapy with CRT, neprilysin inhibitors, AF cardioversion or ablation, or severe renal impairment cannot be drawn given the limited number of patients receiving these treatments or presenting with these conditions. We were unable to assess the value of advanced LV diastolic parameters, because these data were not available. Although MR was quantified in the majority of the patients, in a limited number of patients the MR was qualitatively assessed. Data on genetics, biomarkers, estimated pulmonary pressure, and advanced imaging, including speckle-tracking, three-dimensional echocardiography, and magnetic resonance, were available in the minority of patients and thus were not considered in our analysis.

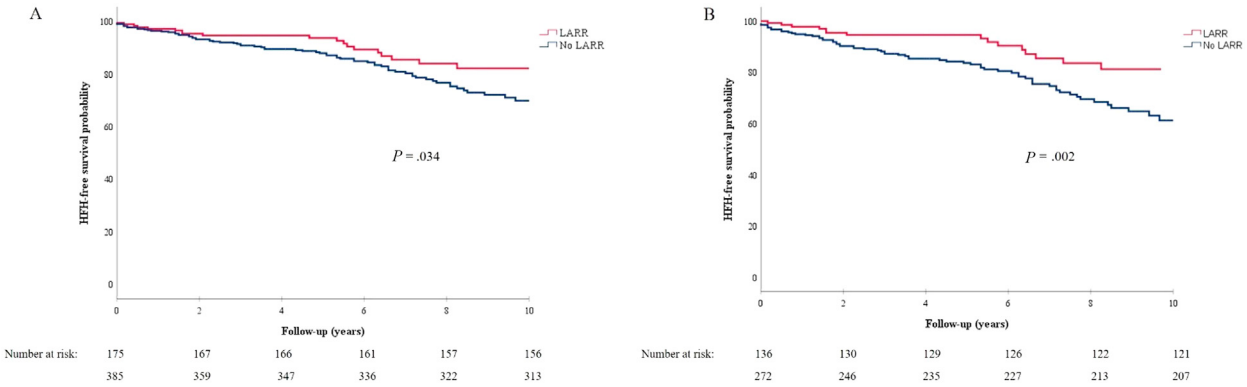

Figure 4 Kaplan-Meier curves for the primary outcome (death, HTx, or HFH) in patients with persistent LA dilation versus LARR (i.e., LAVI $\leq$ 34 mL/m^2 at follow-up and ΔLAVI $\geq$ 10%). Follow-up beginning is considered from the 1-year follow-up evaluation (i.e., time 0 on the graph corresponds to the 1-year follow-up evaluation time). **(A)** Analysis performed on the total population. **(B)** Analysis performed only among patients with LA dilation at baseline (i.e., baseline LAVI > 34 mL/m^2).

CONCLUSION

In a large cohort of patients with DCM, reductions in LAVI were found in the majority of patients, and 1-year changes in LAVI were associated with the long-term risk for death, HTx, or HFH, regardless of other major prognosticators. If confirmed in larger independent series, LARR and its changes might function as an additional prognostic marker in the management of patients with DCM.

ACKNOWLEDGMENT

We acknowledge Cassa di Risparmio di Trieste Foundation for continuous support in research.

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