





Comparative prognostic importance of measures of left atrial structure and function in non-ischaemic dilated cardiomyopathy

Daniel J. Hammersley ^{1,2†}, Srinjay Mukhopadhyay^{1,2†}, Xiuyu Chen³, Leanne Cheng^{1,2}, Richard E. Jones^{1,2,4,5}, Lukas Mach^{1,2}, Lara Curran^{1,2}, Momina Yazdani^{1,2}, Alma Iacob^{1,2}, Amrit S. Lota^{1,2}, Zohya Khalique^{1,2}, Antonio De Marvao^{6,7,9}, Resham Baruah², Kaushik Guha⁸, James S. Ware ^{1,2,9}, John Gregson ¹⁰, Shihua Zhao³, Dudley J. Pennell^{1,2}, Upasana Tayal^{1,2}, Sanjay K. Prasad^{1,2‡}, and Brian P. Halliday ^{1,2*‡}

¹National Heart and Lung Institute, Imperial College London, Sydney Street, London SW3 6NP, UK; ²Royal Brompton and Harefield Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK; ³State Key Laboratory of Cardiovascular Disease, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, Fuwai Hospital, Beijing, China; ⁴Essex Cardiothoracic Centre, Basildon, UK; ⁵Anglia Ruskin University, Chelmsford, UK; ⁶British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Medicine and Sciences, King's College London, London, UK; ⁷Department of Women and Children's Health, King's College London, London, UK; ⁸Portsmouth Hospitals NHS Trust, Portsmouth, UK; ⁹Medical Research Council Laboratory of Medical Sciences, Imperial College London, UK; and ¹⁰London School of Hygiene and Tropical Medicine, London, UK

Received 13 June 2023; revised 12 February 2024; accepted 24 February 2024; online publish-ahead-of-print 16 March 2024

See the editorial comment for this article 'Left atrial volume as risk marker: is minimum volume superior to maximum volume?', by O.A. Smiseth *et al.*, <https://doi.org/10.1093/ehjci/jeae136>.

Aims

This study aimed to compare the association between measures of left atrial (LA) structure and function, derived from cardiovascular magnetic resonance (CMR), with cardiovascular death or non-fatal heart failure events in patients with non-ischaemic dilated cardiomyopathy (DCM).

Methods and results

CMR studies of 580 prospectively recruited patients with DCM in sinus rhythm [median age 54 (interquartile range 44–64) years, 61% men, median left ventricular ejection fraction 42% (30–51%)] were analysed for measures of LA structure [LA maximum volume index (LAVI_{max}) and LA minimum volume index (LAVI_{min})] and function (LA emptying fraction, LA reservoir strain, LA conduit strain (LACS), and LA booster strain). Over a median follow-up of 7.4 years, 103 patients (18%) met the primary endpoint. Apart from LACS, each measure of LA structure and function was associated with the primary endpoint after adjusting for other important prognostic variables. The addition of each LA metric to a baseline model containing the same important prognostic covariates improved model discrimination, with LAVI_{min} providing the greatest improvement [C-statistic improvement: 0.702–0.738; χ^2 test comparing likelihood ratio $P < 0.0001$; categorical net reclassification index: 0.210 (95% CI 0.023–0.392)]. Patients in the highest tertile of LAVI_{min} had similar event rates to those with persistent atrial fibrillation. Measures of LA strain did not enhance model discrimination above LA volumetric measures.

Conclusion

Measures of LA structure and function offer important prognostic information in patients with DCM and enhance the prediction of adverse outcomes. LA strain was not incremental to volumetric analysis for risk prediction.

* Corresponding author. E-mail: b.halliday@imperial.ac.uk

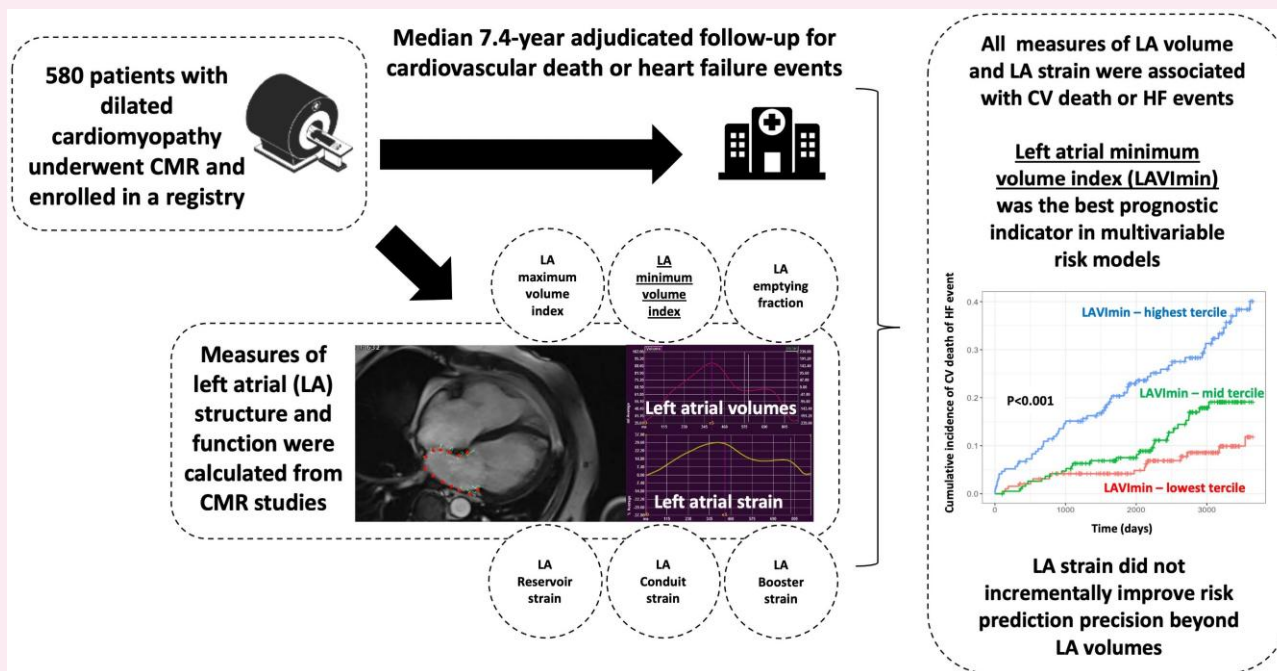
† Joint first authors.

‡ Joint senior authors.

© The Author(s) 2024. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Graphical Abstract



Keywords

dilated cardiomyopathy • left atrium • strain • risk prediction

Introduction

Non-*ischaemic* dilated cardiomyopathy (DCM) is a major contributor to the global burden of heart failure (HF). Whilst advances in treatment have underpinned improved clinical outcomes,¹ DCM remains the leading indication for cardiac transplantation globally.² A major challenge within this group lies in risk prediction, where greater precision may guide more personalized therapy. Left atrial (LA) maximum volume index (LAVI_{max}) is a component of imaging protocols across different modalities and is associated with adverse HF outcomes in DCM.^{3,4} However, it remains unclear whether LAVI_{max} is superior to alternative measures of LA structure and function, which are increasingly available due to improved access and growing expertise in advanced imaging. Such novel measures include LA minimum volume index (LAVI_{min}), LA emptying fraction (LAEF), and phasic LA strain.⁵ The prognostic importance of alternative LA metrics has been evaluated in other conditions; LAVI_{min} was a more powerful predictor of cardiovascular (CV) outcomes than LAVI_{max} in cohorts of patients with HF with preserved ejection fraction and hypertrophic cardiomyopathy (HCM).^{6,7} LAEF predicted survival in a large cohort of patients with HF of mixed aetiology.⁸ LA strain quantifies mechanical atrial deformation aligned to different phases of the cardiac cycle, including LA reservoir strain (LARS) during passive atrial filling, LA conduit strain (LACS) during passive atrial emptying, and LA booster strain (LABS) during active atrial contraction.⁹ LACS was independently associated with adverse CV outcomes in DCM in a further study.¹⁰ However, clarification is required regarding the additive prognostic value of each LA parameter in this population. We studied the incremental predictive value of measures LA structure and function from cardiovascular magnetic resonance (CMR) in relation to a composite endpoint of CV death or non-fatal HF events in a large cohort of patients with DCM.

Methods

Study population

Consecutive patients referred for a CMR between 2009 and 2016 from our clinical service and a network of surrounding hospitals were prospectively enrolled into the Royal Brompton Hospital Cardiovascular Research Centre (RBH CRC) Biobank. The study complied with the Declaration of Helsinki and was approved by the National Research Ethics Service (South Central Hampshire B Research Ethics Committee, Reference 19/SC/0257). All participants provided written consent. Inclusion criteria were confirmed DCM, defined as reduced left ventricular ejection fraction (LVEF) and increased indexed LV end-diastolic volume in relation to age- and sex-adjusted nomograms.¹¹ Exclusion criteria were significant *ischaemic* heart disease (IHD) (defined as stenosis > 50% in a major epicardial coronary artery, inducible *ischaemia* on functional testing, or prior coronary revascularization), adverse loading conditions (uncontrolled hypertension or severe primary valve disease), congenital heart disease, active myocarditis, or an alternative cardiomyopathy. Patients with atrial fibrillation (AF) at the time of CMR ($n = 105$) were excluded from the primary analysis, as a reliable data set for LA strain could not be obtained in such patients. These patients were later included as a comparator group in the survival analysis.

Cardiovascular magnetic resonance

All patients underwent a CMR scan at 1.5 Tesla (Sonata/Avanto, Siemens, Erlangen, Germany). Breath-hold steady-state free precession sequences were performed to produce long- and short-axis cine images. Gadopentetate dimeglumine or gadobutrol (0.1 mmol/kg) was injected intravenously and an inversion recovery gradient echo sequence was undertaken to acquire the LGE images at 10 min. Left and right ventricular

volumes and LV mass were measured using CMRtools (Cardiovascular Imaging Solutions, London, UK) and indexed to body surface area (BSA). Cine images were analysed for LA structure and function using Medis Qstrain (v2.0) and QMass (v8.1) on Medis Suite v3.1 (Medis Medical Imaging Systems, Leiden, the Netherlands) by a single expert operator blinded to clinical outcomes. This involved delineation of the mitral annulus and LA roof in two- and four-chamber views at LV end-diastole and end-systole, from which the LA endocardial borders were semi-automatically contoured and manually adjusted. $LAVI_{max}$ and $LAVI_{min}$ were derived using the biplane area-length method, indexing absolute atrial volumes to BSA. LA appendage and pulmonary veins were excluded. LAEF was derived as $(LAV_{max} - LAV_{min})/LAV_{max} \times 100$. LA contours were tracked automatically via the Qstrain package and phasic strain parameters were obtained for LARS, LACS, and LABS from strain curves. Only a single baseline CMR scan was analysed per patient; follow-up CMR scans in the small subset for whom this was available were not analysed. Reproducibility was assessed in 30 randomly selected cases, which were repeated by the primary operator for intra-observer variation and by a second independent expert operator for inter-observer variation.

Follow-up and endpoints

Clinical follow-up data were obtained from primary care records, hospital medical records, and postal questionnaires. Death certificates and autopsy reports were obtained. Follow-up duration was measured from the CMR date and truncated at 10 years. All events were adjudicated by a panel of experienced cardiologists who were blinded to CMR data. Patients were censored at the time of the first event. The primary endpoint was a composite of CV death or non-fatal major HF events [cardiac transplantation, left ventricular assist device (LVAD) implantation, or HF hospitalization]. Secondary endpoints were (i) all major HF events (composite of HF death and non-fatal HF events), (ii) CV death, and (iii) a sudden cardiac death (SCD) composite endpoint [(SCD or aborted SCD (aSCD))] (see [Supplementary data online](#) for full endpoint definitions).

Statistical analysis

Patient characteristics are presented as frequencies (%) for categorical variables and median [interquartile range (IQR)] for continuous variables. Mann–Whitney test was used to compare continuous variables. Chi-squared test or Fisher's exact test was used to compare categorical variables. Correlation between LA metrics was assessed using Pearson's correlation coefficient. Linearity between LA parameters and the endpoints was assessed using restricted cubic splines with three knots placed at the 10th, 50th, and 90th percentiles. As all LA structure and function parameters were linearly associated with the endpoints (see [Supplementary data online, Figure S1](#)), these were considered as continuous variables in Cox proportional hazard models. Multivariable models adjusted for variables selected *a priori* on the basis of established association with adverse CV outcomes in DCM and included age, sex, New York Heart Association (NYHA) class, myocardial fibrosis presence, and LVEF.¹² A sensitivity analysis included mitral regurgitation severity in addition to these pre-specified variables, to ensure independence of association between parameters of LA structure/function from mitral insufficiency. A second sensitivity analysis was also conducted that integrated LV global longitudinal strain (GLS) into the existing multivariable model, to ensure this did not attenuate the association between LA parameters and the primary endpoint. A pre-specified subgroup analysis was conducted in patients with mild–moderate DCM (patients with $LVEF \geq 35\%$) using the same multivariable model. Improvement in model performance was assessed using Harrel's C-statistic, likelihood ratio test (LKR), Akaike information criterion, and both continuous and categorical net reclassification indices (NRIs). Arbitrary risk cut-offs of <15%, 15–30%, and >30% for categorical NRI were selected based on the incidence of events in the cohort. Intra-class correlation coefficient was used to assess intra- and inter-observer reproducibility. A two-tailed *P*-value of <0.05 was considered significant.

Statistical analyses were conducted on Rstudio (v4.2.2); *survival* and *survminer* packages were used for survival analysis; figures were generated using *ggplot* package; and NRI was calculated using *nricens* package.

Results

Cohort

The primary cohort comprised 580 patients with confirmed DCM in sinus rhythm, of whom most were men [352 patients (61%)] and Caucasian [479 patients (83%)]. The median age was 54 (IQR 44–64) years. Indication for CMR included characterization of LV dysfunction in 431 patients (74%), investigation of arrhythmia in 47 patients (10%), and cardiomyopathy family screening in 35 patients (6%). The remaining 67 patients (12%) underwent CMR for other indications. Significant IHD was excluded by invasive coronary angiogram in 393 patients (68%), computed tomography coronary angiography in 41 patients (7%), and a functional test (stress perfusion CMR, nuclear scan, or stress echocardiogram) in 67 patients (12%). The remaining 79 patients were considered to have a very low clinical probability of IHD and did not undergo investigation to formally exclude: 51% were aged ≤ 40 years, none had prior angina, and none required revascularization or experienced an acute coronary syndrome during follow-up.

At baseline, 83% of patients were treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 70% with beta-blockers, and 37% with mineralocorticoid receptor antagonists. Compared with patients with $LAVI_{min}$ below the median, those with $LAVI_{min}$ above the median were older and had higher NYHA class, and a higher proportion were treated with HF drug therapies and had hypertension or a history of prior AF. Left and right ventricular volumes were higher whilst LVEF and right ventricular ejection fraction (RVEF) were lower in patients with $LAVI_{min}$ above the median compared with those with $LAVI_{min}$ below the median ([Table 1](#)). Patients with AF at the time of CMR excluded from the primary analysis ($n = 105$) were older, and a higher proportion were male, had hypertension, and were treated with beta-blockers and loop diuretics compared with those in sinus rhythm. LVEF and RVEF were lower in those with AF compared with those in sinus rhythm (see [Supplementary data online, Table S1](#)).

LA structure and function metrics

The level of correlation between measures of LA structure and function was variable, ranging from weak correlation between some parameters, including LACS with LABS ($r = 0.19$), to strong correlation between others, including $LAVI_{min}$ with $LAVI_{max}$ ($r = 0.92$) and LAEF with LARS ($r = 0.92$) ([Figure 1](#)). Intra-observer and inter-observer reproducibility for LA measures was good to excellent (see [Supplementary data online, Table S2](#)).

Association between LA structure and function with CV mortality or major HF events

Over a median follow-up of 7.4 years (IQR 4.7–9.3 years), 103 patients (18%) met the primary endpoint, including 20 patients (3.4%) who died from CV causes (8 from HF, 8 from SCD, and 4 from other CV causes) and 83 patients (14.3%) who had non-fatal HF events. On univariable analysis, all measures of LA structure and function were associated with the primary endpoint ([Table 2](#) and see [Supplementary data online, Table S3](#)). Each of these, apart from LACS, remained associated with the primary endpoint on multivariable analysis, adjusting for age, sex, NYHA class, fibrosis presence, and LVEF ([Table 2](#)). The addition of each LA metric to the multivariable model resulted in improved discrimination for the primary endpoint ([Table 3](#)), with the addition of $LAVI_{min}$ offering the highest level of discrimination (C-statistic

Table 1 Patient and cardiovascular magnetic resonance characteristics for the study cohort classified by LA minimum volume index above and below median

	All patients (N = 580)	LAVI _{min} ≤ median (n = 290)	LAVI _{min} > median (n = 290)	P-value
Demographics				
Age	54 (44–64)	52 (41–61)	56 (47–67)	<0.0001
Male	352 (61%)	172 (59%)	181 (62%)	0.44
Caucasian	479 (83%)	251 (87%)	228 (79%)	0.019
Past medical history				
Hypertension	170 (29%)	72 (25%)	98 (34%)	0.018
Diabetes mellitus	74 (13%)	32 (11%)	42 (14%)	0.21
Atrial fibrillation	52 (9%)	18 (6%)	34 (12%)	0.012
Smoker	61 (11%)	39 (13%)	22 (8%)	0.021
Excess alcohol	90 (16%)	43 (15%)	47 (16%)	0.77
Chemotherapy	26 (4%)	11 (4%)	15 (5%)	0.38
Peripartum presentation	10 (2%)	6 (2%)	4 (1%)	0.54
Neuromuscular disease	3 (0.5%)	2 (1%)	1 (0.3%)	0.59
Family history of DCM	91 (16%)	68 (23%)	23 (8%)	<0.0001
Family history of SCD	93 (16%)	57 (20%)	36 (12%)	0.023
NYHA class				
I	268 (46%)	152 (52%)	116 (40%)	0.019
II	218 (38%)	93 (32%)	125 (43%)	
III	87 (15%)	43 (15%)	44 (15%)	
IV	7 (1%)	2 (1%)	5 (2%)	
Medication				
Beta-blocker	406 (70%)	180 (62%)	226 (78%)	<0.0001
ACEi/ARB	482 (83%)	225 (78%)	257 (89%)	0.0005
Mineralocorticoid receptor antagonist	212 (37%)	85 (29%)	127 (44%)	0.0003
Loop diuretic	258 (44%)	97 (33%)	161 (56%)	<0.0001
CMR characteristics				
Left ventricle				
LVEDVi, mL/m ²	119 (102–142)	108 (97–127)	132 (111–162)	<0.0001
LVESVi, mL/m ²	135 (102–189)	56 (47–74)	85 (62–115)	<0.0001
LVMi, g/m ²	85 (72–105)	79 (66–95)	94 (78–111)	<0.0001
LVSVi, mL/m ²	49 (41–57)	50 (44–57)	47 (37–57)	0.049
LVEF, %	42 (30–51)	48 (40–53)	34 (26–46)	<0.0001
Right ventricle				
RVEDVi, mL/m ²	84 (69–99)	81 (67–95)	89 (72–104)	<0.0001
RVESVi, mL/m ²	38 (27–50)	34 (25–43)	43 (29–60)	<0.0001
RVSVi, mL/m ²	45 (37–53)	47 (39–53)	42 (33–52)	0.0009
RVEF, %	55 (46–63)	58 (52–65)	51 (40–61)	<0.0001
Mitral regurgitation				
None	320 (55%)	211 (36%)	109 (19%)	<0.0001
Mild	192 (33%)	69 (12%)	123 (21%)	
Moderate	55 (9%)	9 (2%)	46 (8%)	
Severe	13 (2%)	1 (0.2%)	12 (2%)	
Left atrium				
LAVI _{min} , mL/m ²	22 (15–35)	15 (12–18)	35 (27–50)	<0.0001
LAVI _{max} , mL/m ²	47 (38–60)	38 (31–45)	60 (51–72)	<0.0001
LAEF, %	53 (38–61)	61 (56–65)	38 (27–49)	<0.0001
LARS, %	27.1 (17.0–35.4)	35.0 (29.2–41.1)	17.6 (11.5–24.5)	<0.0001

Continued

Table 1 Continued

	All patients (N = 580)	LAVI _{min} ≤ median (n = 290)	LAVI _{min} > median (n = 290)	P-value
LABS, %	13.1 (8.1–18.4)	17.3 (13.2–22.9)	8.5 (5.4–13.0)	<0.0001
LACS, %	11.3 (6.2–19.0)	17.2 (10.2–23.7)	7.6 (3.7–12.8)	<0.0001
Late gadolinium enhancement	218 (38%)	88 (30%)	130 (45%)	0.0005

Data were presented as median (IQR) or n (%). Bold values in the “P-value column” refer to p values <0.05.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DCM, dilated cardiomyopathy; LA, left atrial; LABS, left atrial booster strain; LACS, left atrial conduit strain; LARS, left atrial reservoir strain; LAEF, left atrial ejection fraction; LAVI_{max}, left atrial maximum volume index; LAVI_{min}, left atrial minimum volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; NYHA, New York Heart Association; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; SCD, sudden cardiac death.

0.702–0.738; χ^2 test comparing LKR: $P < 0.001$). Thus, LAVI_{min} was taken forward as the LA parameter of choice for prognostic purposes. None of the measures of atrial strain improved model discrimination above those of LA volumes. The 5-year categorical NRI following the addition of LAVI_{min} to the baseline model was 0.210 (95% CI: 0.023–0.392), meaning an additional 17% of patients who had an event were reclassified to a more appropriate (higher) risk category and an additional 4% of patients who did not have an event were reclassified to a lower risk category (see [Supplementary data online, Table S4](#)). Patients in sinus rhythm with LAVI_{min} in the highest tertile had higher cumulative incidence of the primary endpoint compared with middle and lowest tertiles (log-rank $P < 0.0001$) ([Figure 2](#)). Interestingly, patients in sinus rhythm with LAVI_{min} in the highest tertile had a similar cumulative incidence for the primary endpoint to patients in AF ([Figure 2](#)). In our first sensitivity analysis that additionally adjusted for mitral regurgitation, all LA parameters remained associated with the primary endpoint, with the addition of LAVI_{min} producing a similar improvement in model discrimination (C-statistic: 0.714–0.738; χ^2 test comparing LKR: $P < 0.001$) (see [Supplementary data online, Tables S5 and S6](#)). In our second sensitivity analysis that additionally adjusted for LV GLS, all LA parameters except LACS remained associated with the primary endpoint, again with the addition of LAVI_{min} resulting in similar improvement in model discrimination (C-statistic: 0.706–0.740; χ^2 test comparing LKR: $P < 0.001$) (see [Supplementary data online, Tables S7 and S8](#)).

Secondary endpoints

Major HF events

In total, 91 (16%) patients experienced a major HF event during follow-up. On univariable analysis, all measures of LA structure and function were associated with major HF events (see [Supplementary data online, Table S9](#)). Apart from LACS, all LA parameters remained associated with major HF events on multivariable analysis (see [Supplementary data online, Table S9](#)). As with the primary endpoint analysis, the degree of model improvement was similar between LA metrics, with LAVI_{min} offering the best discrimination (see [Supplementary data online, Table S10](#)).

CV death

In total, 48 (8%) patients died of CV causes during follow-up. As previous, all LA parameters were associated with CV mortality on univariable analysis. Each LA parameter, except LACS and LABS, remained associated with CV death on multivariable analysis (see [Supplementary data online, Table S11](#)). Model discrimination was similar for the LA parameters that remained associated with CV death on multivariable analysis, with LAVI_{min} offering the best discrimination (see [Supplementary data online, Table S12](#)).

Sudden cardiac death or aborted sudden cardiac death

In total, 38 (7%) patients met the composite SCD endpoint, including 8 SCDs and 30 aSCDs. All LA parameters, except LACS, were associated with this composite endpoint on univariable analysis ([Supplementary data online, Table S13A](#)). On multivariate analysis, these remained associated with the composite SCD endpoint. In contrast to earlier analyses, the addition of LABS resulted in the marginally greater improvement in model discrimination than the other LA parameters, including LAVI_{min} (see [Supplementary data online, Table S14](#)). Notably, guideline-based parameters used to determine primary prevention ICD implantation (LVEF < 35% and NYHA Class >I) were not associated with SCD/aSCD on univariable analysis (see [Supplementary data online, Table S13b](#)).

The prognostic role of atrial structure and function in mild–moderate DCM

In the subgroup with mild–moderate DCM ($n = 389$), 50 (13%) met the primary endpoint (17 due to CV death and 33 due to non-fatal HF events). On univariate analysis, all LA parameters were associated with the primary endpoint. All but LACS remained associated on multivariable analysis (see [Supplementary data online, Table S15](#)). A similar level of discrimination was seen from the addition of each LA parameter on multivariable analysis, including LAVI_{min}. In keeping with our other analyses, LA strain was not a superior discriminant for the primary endpoint to LA volumes in this subgroup (see [Supplementary data online, Table S16](#)).

Discussion

LA structure and function are independently associated with CV death and HF events in patients with DCM

In line with previous studies, we corroborate an important association between the left atrium and incident CV death or HF events in patients with DCM, independently of mitral regurgitation, LV GLS, and conventional markers of DCM phenotype severity. We take forward prior research in this field, including previous work from our group, through direct comparison of multiple measures of LA structure and function to determine parameters that best discriminate adverse CV events. This comparative approach distinguishes this paper from other recent studies evaluating LA parameters in patients with DCM.¹⁰ Whilst the added prognostic value was similar between the measures of LA structure and function in this cohort, LAVI_{min} was the best discriminator for the primary endpoint and additionally identified a subgroup of patients in sinus rhythm with a similar risk of CV death and major HF events to

Table 3 Comparison of multivariable model discrimination for the primary endpoint integrating measures of left atrial structure and function

	C-statistic (95% CI)	AIC	P-value (χ^2 test comparing LKR against Model 1)
Model 1 (age + sex + NYHA class + LGE + LVEF)	0.702 (0.651–0.753)	1195	–
Model 2 (Model 1 + LARS)	0.729 (0.680–0.778)	1184	<0.001
Model 3 (Model 1 + LACS)	0.710 (0.659–0.761)	1193	0.046
Model 4 (Model 1 + LABS)	0.724 (0.677–0.771)	1186	0.001
Model 5 (Model 1 + LAEF)	0.734 (0.685–0.783)	1182	<0.001
Model 6 (Model 1 + LAVI_{max})	0.732 (0.681–0.783)	1178	<0.001
Model 7 (Model 1 + LAVI_{min})	0.738 (0.687–0.789)	1174	<0.001

Bold values correspond to p values <0.05.

AIC, Akaike information criterion; CI, confidence interval; LABS, left atrial booster strain; LACS, left atrial conduit strain; LARS, left atrial reservoir strain; LAEF, left atrial emptying fraction; LAVI_{max}, left atrial maximum volume index; LAVI_{min}, left atrial minimum volume index; LGE, late gadolinium enhancement; LKR, likelihood ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

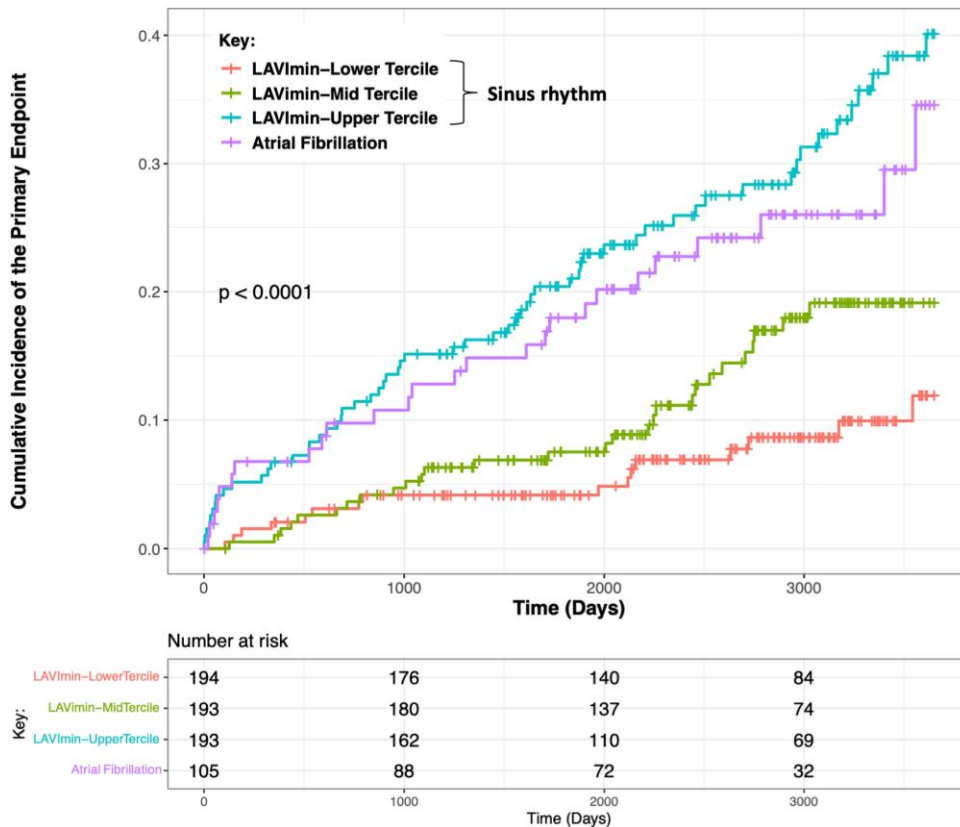


Figure 2 Cumulative incidence of the primary endpoint stratified by tertile of LA minimum volume index for patients with dilated cardiomyopathy in sinus rhythm; patients in AF at the time of cardiovascular magnetic resonance are included as a comparator group. Patients with LA minimum volume index in the highest tertile had higher cumulative incidence of the primary endpoint compared with middle and lowest tertiles but a similar cumulative incidence for the primary endpoint compared with patients in AF.

those in AF. These findings are important as LAVI_{min} is not currently a routine component of CMR reporting protocols. However, it is quick and reproducible to measure and would be simple to integrate into routine practice. It has been proposed that the added value of LAVI_{min} may

relate to a degree of surrogacy for diastolic function, as it is measured at the point of direct continuum with LV end-diastolic pressure through the open mitral valve, and thus may be the most sensitive measure of LV filling pressure.⁵ LAVI_{min} also captures information on both LA size and

contractile function, akin to LV end-systolic volume, which is a stronger prognostic indicator in HF than LV end-diastolic volume or LVEF.¹³ Supporting this hypothesis, we observed stronger correlation between LAVI_{min} than LAVI_{max} with all measures of LA function (Figure 1). Whether the small improvement in discrimination seen with LAVI_{min} compared with LAVI_{max} can enhance risk prediction and clinical outcomes requires further clarification.

Clinical significance of study findings

The clinical application of our findings may include enhanced clinical decision-making through the identification of patients most likely to benefit from early consideration of add-on therapies for HF, including cardiac resynchronization, Vericiguat, or consideration for LVAD or transplantation. Additionally, these may help to identify patients with mild disease at higher risk of adverse CV outcomes, for whom introduction or intensification of drug therapies may be beneficial. A further important finding from this study was that LA strain did not improve risk prediction above LA volumetric analysis in this cohort. The additional analysis time and software required for LA strain measurement are therefore difficult to justify currently in this population.¹⁰

LA parameters are associated with SCD in DCM

A major challenge in the clinical management of patients with DCM relates to risk prediction for SCD.¹⁴ As observed from other recent data,^{15,16} we found no association between LVEF or NYHA class and the SCD composite endpoint in this cohort. By contrast, we found that all measures of LA structure and function, apart from LACS, were associated with the SCD composite endpoint on multivariable analysis. The LA metric that enhanced the prediction of SCD/aSCD the most was LABS, which corroborates the work from Negishi *et al.*,¹⁷ who found LA booster pump function measured by echocardiography was independently associated with ventricular arrhythmias in patients with DCM who had an ICD. Collectively, these findings raise the question of whether LA parameters should be considered for arrhythmic risk stratification in DCM. Further work is required to evaluate utility in this capacity and study the mechanistic link between these indices and arrhythmogenesis. This finding parallels observations in HCM, where increased LA dimension is an established risk factor for SCD and used in clinical practice as a component of arrhythmic risk scoring tools.^{18,19}

Limitations

Patients in this study were enrolled from a single UK referral centre and its hospital network and the study inclusion criteria required a clinical referral for CMR, introducing a potential referral bias. The cohort was predominantly Caucasian patients (83%). Patients with AF at the time of CMR were excluded from the primary analysis as unreliable LA strain measurements in such cases were likely to confound results. A further limitation relates to the fact that CMR images to evaluate LA fibrosis were not obtained; thus, whether such sequences offer additional prognostic utility in DCM is unknown. However, there remains uncertainty about LA fibrosis reproducibility and thus clinical utility. A further limitation relates to the small level of incremental improvement in multivariable model performance from the addition of LAVI_{min} compared with LAVI_{max}; larger multicentre studies are required to understand whether this small difference is clinically meaningful such that it improves prognostication and clinical outcomes. Finally, cardiac biomarkers, including natriuretic peptides, were not routinely measured, and it is possible that their inclusion in multivariable models may interact with the association between LA parameters and outcomes.

Conclusion

LA structure and function are independently associated with adverse outcomes in patients with DCM. Volumetric analysis of the LA adequately captures risk and improves discrimination for CV death or major HF events; LA strain parameters do not offer incremental predictive value beyond these. LAVI_{min} may offer the greatest precision for risk prediction, but further validation is required. The role of LABS in the risk stratification of SCD requires further investigation.

Acknowledgements

We thank the RBH CRC staff, led by Geraldine Sloane. We acknowledge Rohin Reddy, Won Young Yoon, Suprateeka Talukder, Aleksandra Lopuszko, Laura Lazzari, and Andrew Ravendren, who collected the follow-up data.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Funding

This work was supported by a National Heart and Lung Institute grant awarded to S.K.P., D.J.H., R.E.J., U.T., and B.P.H., the British Society for Heart Failure, the British Heart Foundation (FS/CRTF/23/24444 awarded to L.M). Additionally, the study was supported by Rosetrees Trust, Myocarditis UK, and the British Heart Foundation through an Intermediate Clinical Research Fellowship awarded to B.P.H. (FS/ICRF/21/26019) and by the MRC through a Clinician Scientist Fellowship (MRC MR/W023830/1) awarded to U.T. This work was additionally supported by British Heart Foundation (RE/18/4/34215 and SP/17/11/32885), the Royston Centre for Cardiomyopathy Research, Sir Jules Thorn Charitable Trust (21JTA), Medical Research Council (UK), National Institute for Health Research (NIHR), Royal Brompton Cardiovascular Biomedical Research Unit, and NIHR Imperial College Biomedical Research Centre.

Conflict of interest: R.B. has received honoraria from AstraZeneca, Vifor, and Medtronic. K.G. has received honoraria from Bayer, Pfizer, Novartis, AstraZeneca, and Servier Laboratories, a previous unrestricted educational grant from Biotronik, and previous travel assistance from Abbott Laboratories, Medtronic, Biotronik, and Boston Scientific. J.S.W. has acted as a consultant for MyoKardia, Foresite Labs, and Pfizer. D.J.P. has received research funding from Siemens. B.P.H. has received honoraria from Astra Zeneca. The other authors have nothing to declare.

Data availability

The data are available from the corresponding author, on reasonable request. Data will be shared after review and approval by our Biobank scientific board, and terms of collaboration will be reached together with a signed data access agreement.

References

- Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J *et al.* Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2020;**22**:1111–21.
- Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL *et al.* Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**:1077–84.
- Gulati A, Ismail TF, Jabbour A, Ismail NA, Morarji K, Ali A *et al.* Clinical utility and prognostic value of left atrial volume assessment by cardiovascular magnetic resonance in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2013;**15**:660–70.
- Rossi A, Ciccoira M, Zanolla L, Sandrini R, Golia G, Zardini P *et al.* Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2002;**40**:1425–30.

5. Negishi K, Pathan F. Novel left atrial markers for risk stratification of heart failure. *J Am Coll Cardiol* 2022;**79**:1562–4.
6. Shin S-H, Jang J-H, Baek Y-S, Kwon S-W, Park S-D, Woo S-I et al. Prognostic impact of left atrial minimal volume on clinical outcome in patients with non-obstructive hypertrophic cardiomyopathy. *Int Heart J* 2018;**59**:991–5.
7. Shin SH, Claggett B, Inciardi RM, Santos ABS, Shah SJ, Zile MR et al. Prognostic value of minimal left atrial volume in heart failure with preserved ejection fraction. *J Am Heart Assoc* 2021;**10**:e019545.
8. Pellicori P, Zhang J, Lukaszuk E, Joseph AC, Bourantas CV, Loh H et al. Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value. *Eur Heart J* 2015;**36**:733–43.
9. Peters DC, Lamy J, Sinusas AJ, Baldassarre LA. Left atrial evaluation by cardiovascular magnetic resonance: sensitive and unique biomarkers. *Eur Heart J Cardiovasc Imaging* 2021;**23**:14–30.
10. Raafs AG, Vos JL, Henkens MTHM, Slurink BO, Verdonschot JA, Bossers D et al. Left atrial strain has superior prognostic value to ventricular function and delayed-enhancement in dilated cardiomyopathy. *JACC Cardiovasc Imaging* 2022;**15**:1015–26.
11. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2006;**8**:417–26.
12. Halliday BP, Gulati A, Ali A, Newsome S, Lota A, Tayal U et al. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. *Eur J Heart Fail* 2018;**20**:1392–400.
13. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;**76**:44–51.
14. Hammersley DJ, Halliday BP. Sudden cardiac death prediction in non-ischemic dilated cardiomyopathy: a multiparametric and dynamic approach. *Curr Cardiol Rep* 2020;**22**:85.
15. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaitė M et al. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. *Circulation* 2017;**135**:2106–15.
16. Di Marco A, Brown P, Mateus G, Faga V, Nucifora G, Claver E et al. Late gadolinium enhancement and the risk of ventricular arrhythmias and sudden death in NYHA class I patients with non-ischaemic cardiomyopathy. *Eur J Heart Fail* 2023;**25**:740–50.
17. Negishi K, Negishi T, Zardkoohi O, Ching EA, Basu N, Lwilkoff B et al. Left atrial booster pump function is an independent predictor of subsequent life-threatening ventricular arrhythmias in non-ischaemic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1153–60.
18. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation* 2009;**119**:1703–10.
19. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–20.