Cardiac structural and functional consequences of amyloid deposition by CMR and echocardiography and their prognostic roles

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Conflicts of interest: None
Relationships with Industry: None

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Word count (including references and figure captions): 4,935

Structured Abstract

Objectives

This cross-sectional study aimed to: 1) describe the functional and structural cardiac abnormalities that occur across a spectrum of cardiac amyloidosis burden; 2) identify the strongest cardiac functional and structural prognostic predictors in amyloidosis using cardiac magnetic resonance (CMR) and echocardiography.

Background

Cardiac involvement in light chain and transthyretin amyloidosis is the main driver of prognosis and influences treatment strategies. Numerous measures of cardiac structure and function are assessed by multiple imaging modalities in amyloidosis.

Methods

Three-hundred and twenty-two subjects (311 systemic amyloidosis, 11 TTR gene mutation carriers) underwent comprehensive CMR and transthoracic echocardiography. The probabilities of eleven commonly measured structural and functional cardiac parameters being abnormal with increasing cardiac amyloidosis burden were evaluated. Cardiac amyloidosis burden was quantified using CMR-derived extracellular volume (ECV). The prognostic capacities of these parameters to predict death in amyloidosis were assessed using Cox proportional hazards models.

Results

LV mass and MAPSE by CMR along with strain and E/E' by echocardiography have high probabilities of being abnormal at low cardiac amyloid burden. Reductions in bi-ventricular ejection fractions and elevations in bi-atrial areas occur at high burdens of infiltration. The probabilities of indexed stroke volume, MCF and TAPSE being abnormal occur more gradually with increasing extracellular volume.

Ninety patients (28%) died during a median follow-up of 22 months (interquartile range 10-38 months). Univariable analysis showed that all imaging markers studied significantly predicted outcome. Multivariable analysis showed that TAPSE (hazard ratio, 1.46; 95% confidence interval, 1.16-1.85; $P<0.01$) and indexed stroke volume (hazard ratio, 1.24; 95% confidence interval, 1.04-1.48; $P<0.05$) by CMR were the only independent predictors of mortality.

Conclusions

Specific functional and structural abnormalities characterize different burdens of cardiac amyloid deposition. In a multi-modality imaging assessment of a large cohort of amyloidosis patients, CMR-derived TAPSE and indexed stroke volume are the strongest prognostic cardiac functional markers.

Key Words: CMR; echocardiography; amyloidosis; function; prognosis

Abbreviations

AL = light-chain amyloidosis
ATTR = transthyretin-related amyloidosis
CMR = cardiac magnetic resonance
ECV = extracellular volume
EF = ejection fraction
LA = left atrial
LGE = late gadolinium enhancement
LGS = longitudinal global strain

LV = left ventricular
MAPSE = mitral annular plane systolic excursion
MCF = myocardial contraction fraction
RA = right atrial
RV = right ventricular
SV = stroke volume
TAPSE = tricuspid annular plane systolic excursion

Introduction

Systemic amyloidosis is a fatal disease caused by the progressive deposition of abnormal insoluble protein fibrils in the extracellular space, leading to the loss of normal tissue architecture and function (1). Cardiac amyloidosis is due to intramyocardial amyloid infiltration, which leads to progressive structural and functional changes (2,3). The most frequent types of systemic amyloidosis associated with clinically relevant cardiac involvement are: light-chain amyloidosis (AL) due to a clonal plasma cell dyscrasia, which produces the immunoglobulin light chains of the fibrillary deposits; hereditary, transthyretin-related form (ATTRm), which can be caused by over 100 mutations of transthyretin (TTR), a transport protein mainly synthesized by the liver; and wild-type (non-mutant) transthyretin-related amyloidosis (ATTRwt), which mainly affects the hearts of elderly men (1).

Cardiac involvement in both AL and ATTR amyloidosis is the main predictor of mortality and influences therapeutic choices (4,5). Late gadolinium enhancement (LGE) and extracellular volume (ECV) assessment by cardiac magnetic resonance (CMR) are known to be diagnostic and prognostic in cardiac amyloidosis (2). Echocardiography and CMR are both commonly utilized imaging modalities to assess cardiac amyloidosis that generate a plethora of functional and structural metrics aside from tissue characterization parameters. Many of these cardiac functional and structural parameters demonstrate prognostic value when studied in isolation (3,6-12). However, their relative prognostic importance and their behavior in the natural history of cardiac infiltration have never been investigated.

The aims of this study were to 1) describe the functional and structural cardiac abnormalities that occur across a spectrum of cardiac amyloid burden in AL and ATTR cardiac amyloidosis, and 2) identify the strongest cardiac functional predictors of prognosis in systemic amyloidosis.

Methods

Amyloidosis patients. Subjects were recruited at the National Amyloidosis Centre, Royal Free Hospital, London, United Kingdom, from 2010 to 2015. A retrospective, cross-sectional analysis of 433 patients who underwent CMR and echocardiography was performed. Patients with datasets not containing all of the structural and functional cardiac metrics selected for analysis in this study were excluded. The remaining 322 patients were categorized into 3 groups:

(i) **Subjects with AL amyloidosis**: 133 patients with biopsy proven systemic AL amyloid (86 male, 65%; age 66 (57-71) years), with biopsies from the myocardium (n=7, 5%) or other tissues (n=126, 95%).

(ii) **Subjects with ATTR amyloidosis**: 158 patients (139 male, 88%; age 74±8 years) with cardiac ATTR amyloidosis and 20 with suspected cardiac ATTR amyloidosis (12 male, 60%; age 70±15 years) were recruited. The definitions of definite and suspected cardiac ATTR amyloidosis have been previously described (13,14). To summarize, cardiac ATTR amyloidosis was defined as the combination of symptoms with an echocardiogram consistent with or suggestive of cardiac amyloidosis, grade 2 or 3 cardiac uptake on the ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy in the absence of a monoclonal gammopathy or, in the presence of monoclonal gammopathy, a cardiac biopsy positive for TTR. Suspected cardiac ATTR amyloidosis was defined by grade 1 cardiac uptake on ^{99m}Tc-DPD in the absence of monoclonal gammopathy. Seventy-two percent (n = 128) of patients with ATTR amyloidosis had histological proof of ATTR amyloidosis by Congo red and immunohistochemical staining of myocardial (n = 40, 22%) or other tissues (n = 88, 49%). All subjects underwent sequencing of exons 2, 3, and 4 of the *TTR* gene.

(iii) **TTR gene mutation carriers**: In addition, there were 11 subjects with amyloidogenic *TTR* gene mutations (4 male, 36%; age 46±8 years) defined as individuals with no evidence of clinical disease (including no cardiac uptake on Tc-DPD scintigraphy and normal echocardiography, CMR, N-terminal pro-brain natriuretic peptide [NT-proBNP] and Troponin T).

***Exclusion criteria*:** We excluded all patients with datasets not containing all of the structural and functional cardiac metrics selected for analysis. Patients with contraindications to CMR (such as CMR-incompatible devices) were excluded from the original study cohort. Patients with a glomerular filtration rate <30mL/min underwent a non-contrast study protocol (n=5) unless informed consent was obtained for a contrast study protocol for clinical diagnostic purposes (n=4). All ethics were approved by the UCL/UCLH Joint Committees on the Ethics of Human Research Committee, and all participants provided written informed consent.

***Echocardiography acquisition and analysis*:** Echocardiographic assessments were performed using a Vivid E9 ultrasound machine (GE, Healthcare, Milwaukee, Wisconsin, USA). Image quality was optimized by adjusting probe frequency (range 1.7-2.0MHz) and temporal resolution (60-120 frames per second). LV structure, systolic and diastolic assessment was performed according to published recommendations (15-17). This included the analysis of multiple beats in atrial arrhythmia at the discretion of the clinical study operator. All echocardiography analysis was performed by investigators blinded to the CMR results. The echocardiographic functional parameters assessed in the mutivariable model were E/e' and apical four-chamber longitudinal global strain (LGS). For the former measure, Pulsed-Wave (PW) Tissue Doppler Imaging (TDI) of the septal and lateral mitral annuli in the 4-chamber view was performed to obtain peak early diastolic (e') tissue velocities, with septal and lateral velocities averaged to obtain a mean value.

The peak early diastolic transmitral inflow wave (E) was obtained by PW-Doppler with the sample volume placed at the tips of the mitral valve in the apical 4-chamber view. Myocardial deformation was assessed using commercially available speckle-tracking software (EchoPac PC dimension software version 112, GE Healthcare). Between 2 to 3 cardiac cycles from an apical 4-chamber view were acquired with appropriate image optimisation and digitally stored for offline analysis. The endocardium of the LV was manually traced from the medial and lateral mitral valve annuli and a region of interest (ROI) automatically generated to cover the LV myocardium. The ROIs were adjusted to optimize the tracking quality if needed.

***CMR protocol*:** All participants underwent standard CMR on 1.5T clinical scanners (either Avanto or Aera, Siemens Healthcare, Erlangen, Germany). A standard volume and LGE study was performed in all patients. Retrospectively gated balanced steady state free precession (b-SSFP) end-expiratory breath-hold cines were acquired covering the bases to apices of both ventricles in the short-axis for patients in sinus rhythm. Patients with atrial arrhythmia had a similarly planned short-axis biventricular stack of cine images acquired using either prospectively gated b-SSFP cines or real-time cine imaging at the discretion of the clinical study operator. Slice thickness was 7mm with a 3mm slice gap. The gadolinium-based contrast agent used was 0.1mmol/kg of Gadoterate meglumine (gadolinium-DOTA, marketed as Dotarem©, Guerbet SA, Paris, France) for LGE imaging as previously described (2). For native T1 mapping, basal and mid ventricular short axis, and 4-chamber long-axis were acquired using the shortened modified look-locker inversion recovery (ShMOLLI) or modified look-locker inversion recovery (MOLLI) sequences after regional shimming, as previously described(18).

***CMR image analysis*:** All CMR images and maps were analysed offline. All CMR analysis was performed by investigators blinded to the echocardiography results. Endocardial borders of both

ventricles were manually traced at end-diastole and end-systole, the time points of which were identified by the largest and smallest cavity areas respectively. Left ventricular (LV) stroke volume (SV) was the difference between the LV end-diastolic volume (EDV) and LV end-systolic volume (ESV), and ejection fraction (EF) was calculated as (SV/EDV)x100. LV mass was calculated from the end-diastolic frames by manually tracing an epicardial contour. The papillary muscles and trabeculae excluded from the blood pool by the endocardial contour (thus they were included when measuring mass and excluded when measuring cavity volumes). Annular plane systolic excursion for both the mitral (MAPSE) and tricuspid (TAPSE) valves were analyzed for the lateral valvular annulus. Maximal biatrial areas were manually traced at the ventricular end-systolic frames from a 4-chamber cine.

ECV was used as the primary measure of cardiac amyloidosis burden, and was calculated as previously described(19). To summarize, T1 values were obtained by drawing a single region of interest (ROI) in each of the 4 required areas: myocardial T1 estimates (basal to mid septum in 4-chamber map) and blood T1 estimates (LV cavity blood pool in 4 chamber map, avoiding the papillary muscles) before and after contrast administration. Hematocrit was taken in all subjects immediately before each CMR study. ECV was calculated as: myocardial ECV = (1-hematocrit) x ($\Delta R1_{myocardium}/\Delta R1_{blood}$), where R1=1/T1.

***Statistical Analysis*:** Statistical analysis was performed using SPSS 24.0 (IBM Corporation, Armonk, New York, USA) and R programming language (http://r-project.org/). Data were examined for normality using the Kolmogorov-Smirnov normality test. Descriptive statistics are expressed as mean±standard deviation (SD) when normally distributed and median (inter-quartile range, IQR) when non-normally distributed. Proportions are expressed as percentages. Systematic differences between measurements were evaluated with Student's *t*-test (two-tailed)

to compare parametric data, and the Mann-Whitney-U test was used to compare non-parametric data. The χ^2 test or Fisher's exact test (two-sided) was used to compare proportions data as appropriate. Comparisons between groups were performed by 1-way ANOVA for parametric data and by the Kruskal-Wallis 1-way ANOVA for non-parametric data. *P*-values <0.05 were considered statistically significant.

Eleven functional and structural cardiac variables by echocardiography (E/e', LGS) and CMR (indexed LA area, indexed LV mass, indexed RA area, indexed SV, LVEF, MAPSE, RVEF, TAPSE, MCF) were selected a priori based upon clinical relevance. The focus of this study is on the effects of myocardial infiltration on cardiac structure and function, since the prognostic capacities of LGE and ECV assessment in cardiac amyloidosis are already well established (2). Therefore, the statistical analyses included only structural and functional cardiac imaging biomarkers (and no tissue characterization parameters) as the variables under investigation. Biventricular function and biatrial areas were assessed using CMR rather than echocardiography due to the superior accuracy and reproducibility of the former imaging modality for these purposes. MAPSE and TAPSE were also assessed by CMR on the same 4-chamber view as biatrial area measurements as per the standard clinical CMR protocol at our institution. The MCF, defined as the ratio of SV to myocardial volume, has been shown to be prognostic in cardiac amyloidosis(20). Simple logistic regression analysis was performed for evaluating the probability of the selected cardiac structural and functional parameters being abnormal across the spectrum of ECV. Cut-offs for defining abnormalities in these variables were chosen according to published reference guidelines: E/e' >8(21), indexed LA area >15cm^2/m^2(22), indexed RA area >16cm^2/m^2(22), LGS <-20%(23), LVEF <57%(22), RVEF <52%(22), indexed SV

<42mL/m^2(22), indexed LV mass >81g/m^2(22), MAPSE <11mm, TAPSE <16mm, MCF <38%(24).

Survival was evaluated with Cox proportional hazards regression analysis, providing estimated hazard ratios with 95% confidence intervals and Kaplan–Meier curves. The eleven echocardiography and CMR variables along with heart rate at the time of CMR study were first explored with simple Cox regression analysis. The variables that were statistically significant predictors of outcome on simple Cox regression analysis were entered into a multivariable Cox proportional hazards analysis to determine which covariates were independent predictors of mortality. The relationships between candidate predictors was first explored with correlational analysis. Possible collinearity among candidate predictors was subsequently assessed using variance inflation factors with threshold equal 5. Separate multivariable models were performed in order to exclude parameters that are derived from one another (for example, LVEF and MCF both being derived from SV; MCF being derived from SV and myocardial mass). Thus, model A included indexed left ventricular SV and mass (and excluded MCF and LVEF); model B included LVEF and LV mass (SV and MCF were excluded); model C included MCF (SV, LV mass and LVEF were excluded). Sub-analyses of the AL and ATTR amyloidosis patient cohorts were also performed. The Harrell C statistic was calculated for the different models.

Results

Study population characteristics

Details of the 322 subjects are shown in Table 1. The TTR mutations in the 158 patients with definite cardiac ATTR amyloidosis were as follows: V122I, n=30; T60A, n=16; V30M, n=3; E89K, n=2; and E54G, D38Y, F44L and I73V, n=1 each. Of the 20 patients with suspected cardiac ATTR amyloidosis, the TTR mutations were as follows: S77Y, n=3; V122I and V30M,

n=2 each; E54G, G47V, I84S and I107F, n=1 each. Of the 11 asymptomatic individuals with TTR mutations, 6 had TTR V30M, 4 had T60A, and 1 had S77Y. Patients with ATTR amyloidosis were older, had poorer renal function and a higher prevalence of electrocardiographic (ECG) conduction abnormalities. Twenty-three patients were excluded from ECV analysis due to significant renal impairment precluding gadolinium administration (n=5) or due to constraints specific to the clinical circumstances (n=18).

Relationship between non-invasive functional metrics and ECV

The ECV values in the 299 patients who underwent this assessment by CMR were divided into tertiles. Increasing myocardial amyloid burden across these ECV tertiles was associated with several structural and functional changes in both the AL and ATTR patient cohorts (Table 2): more severe diastolic dysfunction and worsening LGS by echocardiography; increased LV mass, increased bi-ventricular end-systolic volumes, decreased bi-ventricular EFs, decreased stroke volume, and worsening bi-ventricular longitudinal function. In ATTR, increasing ECV burden was also associated increased bi-ventricular end-diastolic volumes and increased bi-atrial areas. When using ECV as a marker of cardiac infiltration burden, the CMR and echocardiography functional metrics can be grouped by the probability of becoming abnormal at low or high disease burdens or gradually across the spectrum of myocardial infiltration (Figure 1). Indexed LV mass and MAPSE by CMR along with LGS and E/e' by echocardiography have a high probability of being abnormal at low cardiac amyloid burdens. Conversely, bi-ventricular ejection fractions and bi-atrial areas become abnormal at higher burdens of cardiac infiltration. The probabilities of MCF, TAPSE and indexed stroke volume becoming abnormal increase gradually across the spectrum of ECVs.

Non-invasive functional and structural metrics and prognosis

Ninety patients (28%) died during a median follow-up period of 22 months (interquartile range 10-38 months). All of the imaging metrics studied except for heart rate were predictive of mortality on simple Cox regression analysis (Table 3). Only CMR-derived TAPSE (hazard ratio, 1.46; 95% confidence interval, 1.16-1.85; $P<0.01$) and indexed stroke volume (hazard ratio, 1.24; 95% confidence interval, 1.04-1.48; $P<0.05$) remained independently predictive of mortality in a multivariable Cox model adjusted for age and sex (Table 4, Figure 2). Harrell's C-statistic for this model was 0.73. When performing different multivariable models to avoid statistical coupling of the entered variables, TAPSE remained independently predictive of mortality (Table 4). The marked differences in significance levels from univariable to multivariable analyses are partly due to the correlation amongst covariates (Supplementary Table 1). However, exploring variance inflation factors and using a threshold equal 5 found no evidence of collinearity amongst the parameters entered into the multivariable analyses. Functional parameters by echocardiography and CMR were also entered into multivariable Cox regression models for AL and ATTR patient subgroups (Supplementary Tables 2 and 3, respectively). In ATTR cardiac amyloidosis, TAPSE was consistently significantly associated with mortality (hazard ratio, 1.53; 95% confidence interval, 1.08-2.16; $P<0.05$; Harrell's C-statistic 0.729). Three metrics were consistently significantly associated with mortality in AL cardiac amyloidosis, namely LA area indexed (hazard ratio, 1.53; 95% confidence interval, 1.12-2.09; $P<0.01$), stroke volume indexed (hazard ratio, 1.37; 95% confidence interval, 1.03-1.83; $P<0.05$) and TAPSE (hazard ratio, 1.54; 95% confidence interval, 1.08-2.18; $P<0.05$; Harrell's C-statistic 0.797).

Relationship between right ventricular LGE and TAPSE

Evidence of RV cardiac amyloidosis involvement, defined by the presence of RV LGE, was determined given the significant association of TAPSE with mortality. An increasing prevalence of RV LGE was observed in both AL and ATTR patient cohorts with increasing amyloid burden measured by ECV (Table 2). A total of 229 subjects (70%; 73 (63%) of AL amyloidosis patients, 156 (85%) of ATTR subjects including mutation carriers) on LGE assessment had evidence of RV cardiac amyloidosis, with corresponding significantly lower TAPSE across all patient subgroups (Table 5).

Discussion

In this study we comprehensively describe the structural and functional cardiac abnormalities associated with cardiac infiltration using commonly utilized CMR and echocardiography parameters. To our knowledge, this is also the largest study to identify the strongest prognostic structural and functional cardiac imaging metrics in amyloidosis.

Ejection fraction (EF) is the most ubiquitous marker conventionally used to describe cardiac function, especially in the setting of heart failure. However, symptoms and signs of cardiac decompensation are known to commonly precede significant deterioration in EF in amyloidosis (25). Our data confirm that bi-ventricular EFs tend to be preserved up until higher burdens of cardiac infiltration, with abnormalities in bi-atrial size also reflecting the most advanced stages of the disease process. Echocardiography and CMR functional metrics can be divided into a cascade of three groups that become abnormal sequentially with increasing cardiac amyloid burden as assessed by ECV quantification. Variables more likely to become abnormal at low levels of cardiac infiltration reflect impairment of LV diastolic function and LV longitudinal dysfunction, both of which are not accounted for by global EF. Despite E/e' and myocardial mass being generated by different imaging modalities (echocardiography and CMR

respectively), they become abnormal in parallel across increasing amyloid deposition. This reflects the close relationship between amyloid burden and diastolic dysfunction, particularly in early cardiac involvement. Longitudinal global strain and MAPSE also tend to become abnormal at the lower end of the ECV spectrum. Both of these parameters reflect longitudinal impairment, an early marker of systolic dysfunction that is not accounted for by global EF(26). This is especially pertinent in cardiac amyloidosis due to infiltration starting in the subendocardium, predominantly consisting of longitudinal fibers.

Left ventricular SV, MCF and TAPSE constitute the intermediate group of variables with a probability of being abnormal that rises progressively across the spectrum of increasing amyloid burden. In contrast to EF, SV has a high probability of being abnormal in the earlier stages of cardiac amyloid infiltration. This could be due to the initial increase in myocardial mass conferring a smaller end-diastolic cavity volume. However, the likelihood of SV being abnormal then continues to rise with increasing levels of amyloid burden, possibly reflecting the later development of impaired radial function with progression from subendocardial to transmural amyloid deposition. Thus abnormal SV is likely to represent a composite signal of diastolic dysfunction at low burdens of cardiac amyloidosis and systolic contractile impairment at higher burdens of cardiac infiltration. The progressively increasing likelihood of MCF becoming abnormal with rising ECV reflects the behaviors of the variables from which it is derived, namely SV and myocardial mass. The likelihood of TAPSE being abnormal also increases gradually across the spectrum of rising myocardial infiltration, whereas global RVEF becomes abnormal at high burdens of cardiac involvement. This difference is likely to be due to TAPSE reflecting infiltration of subendocardial longitudinal fibers in the earlier stages of the disease,

whereas radial dysfunction and congestive heart failure manifest late in the natural history of the disease.

Interestingly, TAPSE and indexed SV were the only prognostic markers for mortality in the multivariable model of all amyloidosis patients. TAPSE was the most statistically significant independent marker of prognosis, and was the only prognostic marker common to the sub-group analyses of both AL and ATTR patient cohorts. Right ventricular dysfunction is common in cardiac amyloidosis(7). Furthermore, RV failure is a well-documented independent predictor of prognosis in patients with primary left heart failure(27-29). However, direct RV subendocardial infiltration is likely to be the principal reason behind the prognostic importance of TAPSE in amyloidosis, rather than RV dysfunction as a consequence of LV impairment. This is evidenced by the high prevalence of RV late gadolinium enhancement in both AL and ATTR patient cohorts, and explains why TAPSE rather than RVEF is the key prognostic marker in amyloidosis overall. This is also in contrast to RV pressure-overload states, whereby radial rather than longitudinal contraction more closely reflects global RV function, with global RVEF being a consistently strong predictor of outcome(30-32). The main finding on sub-group analysis of the AL and ATTR patient cohorts was that left atrial area was an additional significant prognostic marker in the AL patient cohort, consistent with previous echocardiography studies in AL amyloidosis (33,34). Thus left atrial dilatation could represent a structural marker of more advanced disease.

Study limitations

The study was retrospective, with approximately one-quarter of patients excluded due to incomplete data acquisition. However, the number of events in the remaining 322 patients is sufficient for the multivariable analyses. The study design was also cross-sectional, with patients

scanned at different stages of presentation and treatment. This might include chemotherapy for patients with AL amyloidosis, with some agents having known cardiotoxic side-effects that could also influence the measurement of the variables under investigation. Furthermore, the assessment of disease progression would require serial assessments of these measures in the same individuals over time. Patients with ATTR amyloidosis might be more likely to present at later stages of cardiac infiltration when symptoms of cardiac failure are manifest, reflected by the smallest proportion of ATTR patients being in the lowest ECV tertile (19%). This might impact upon the changes observed in cardiac markers at low amyloid burdens in this cohort. The inclusion of 20 suspected ATTR cases and 11 asymptomatic TTR gene mutation carriers, all of whom potentially may have subclinical or very early disease, might at least partly offset this limitation. Conversely, the largest proportion of AL patients were in the lowest ECV tertile (62%), again likely representing the manner of clinical presentation. Overall, twenty-three patients did not have ECV measured either due to significant renal dysfunction or clinical constraints at the time of scanning. Patients with implanted cardiac defibrillators or permanent pacemakers were also excluded from CMR study. Given that these patients are known to have an adverse prognosis, their exclusion could affect the survival analysis. However, these limitations all reflect real-world practice and the presentation of patients for clinical evaluation. The simple logistic regression analysis dichotomized each variable as abnormal or normal according to pre-defined cut-off values derived from healthy populations, rather than from patient populations with cardiac amyloidosis. Whilst these cut-off values from a normal population would have less direct clinical relevance to a cardiac amyloidosis predominant population, our aim was to describe the behavioral changes in cardiac markers across the spectrum of cardiac infiltration rather than specify the diagnostic threshold of the cut-off values themselves. Finally, cardiac

biopsy was performed in a minority of patients, but the entire cohort underwent comprehensive composite non-invasive evaluation including DPD scanning. This is our routine clinical protocol, and is known to deliver high diagnostic accuracy.

Conclusions

In the multi-modality cardiac imaging assessment of patients with amyloidosis, TAPSE and left ventricular indexed SV measured by CMR are the most powerful prognostic cardiac functional parameters. They are standard and simply obtained measures, with a likelihood of being abnormal that increases with rising cardiac amyloid burden.

Perspectives

COMPETENCY IN MEDICAL KNOWLEDGE: Cardiac involvement in amyloidosis is the main determinant of prognosis. The behavior and prognostic importance of common cardiac functional and structural markers by echocardiography and CMR have been evaluated in a cross-sectional study of patients with systemic amyloidosis. Both TAPSE and indexed stroke volume: (1) have an increasing likelihood of becoming abnormal with rising cardiac amyloid burden, and (2) are independently prognostic in systemic amyloidosis.

TRANSLATIONAL OUTLOOK: The behavior of cardiac structural and functional parameters can be interpreted in relation to the pathophysiology of amyloidosis across the spectrum of cardiac disease burden. Prospective clinical studies of serial cardiac imaging assessments are required in order to evaluate the progression of structural and functional cardiac measures with increasing myocardial amyloid burden.

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Figure legends

Figure 1: The probability of cardiac structural and functional variables being abnormal across the spectrum of cardiac amyloid burden (as defined by ECV). Variables can be categorized into three groups according to their likelihood of being abnormal; either predominantly at low or high burdens of cardiac infiltration, or with a progressively rising probability of being abnormal across the spectrum of myocardial amyloid burden (intermediate). *LV, left ventricular; SV, stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial; RA, right atrial; ECV, extracellular volume.*

Figure 2: Kaplan–Meier curves for TAPSE (left) and indexed stroke volume (right). Kaplan-Meier curves displaying event-free survival in all patients according to (left) CMR-derived TAPSE ≥16mm or <16mm and (right) indexed stroke volume ≥42mL/m^2 or <42mL/m^2. *SVi, indexed stroke volume; TAPSE, tricuspid annular plane systolic excursion.*

Table 1 – Main clinical characteristics and ECG findings in patients with AL and ATTR amyloidosis

	All Patients (n=322)	AL Patients (n=133)	ATTR Patients (n=189)	ATTR Patients (n=189)		
				Definite (n=158)	Suspected (n=20)	Gene mutation carriers (n=11)
Age, y	71 (63-77)	66 (57-71)‡	74 (68-80)	75 (70-81)	74 (52-83)	45 (42-53)
Female, n (%)	81 (25.2%)	47 (35.3%)‡	34 (18.0%)	19 (12%)	8 (40%)	7 (63.6%)
Ethnicity, n (%)						
White	267 (82.9%)	120 (90.2%)	147 (77.8%)	119 (75.3%)	17 (85.0%)	11 (100%)
Black	48 (14.9%)	6 (4.5%)‡	42 (22.2%)	39 (24.7%)	3 (15%)	0 (0%)
Asian	5 (1.6%)	5 (3.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Arab	1 (0.3%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mixed	1 (0.3%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clinical history of hypertension, n (%)	63 (19.6%)	27 (20.3%)	36 (19.0%)	32 (20.3%)	3 (15.0%)	1 (9.1%)
eGFR, mL.min-^{1}.1.73m^{2}	67 (48-84)	75 (50-90)†	63 (47-79)	59 (45-73)	82 (62-89)	86 (76-100)

Systolic BP, mmHg	120 (110-133)	121 (109-138)	120 (110-130)	119 (110-129)	128 (114-148)	121 (112-132)
Diastolic BP, mmHg	72 (65-80)	72 (65-83)	71 (65-79)	71 (64-79)	70 (67-78)	75 (69-81)
NT-proBNP, pmol/L	220 (86-467)	170 (65-389)*	280 (112-522)	322 (172-591)	27 (13-118)	7 (3-9)
6 MWT, meters	330±136	321±127	335±141	313±133	374±141	526±60
Sinus rhythm, n (%)	155 (48.1%)	31 (23.3%)‡	124 (65.6%)	96 (60.8%)	18 (90.0%)	10 (90.9%)
Heart rate (bpm)	73±13	78±13‡	69±12	69±13	71±11	70±12
PR, ms	184 (157-214)	168 (148-194)‡	195 (162-224)	202 (184-232)	170 (153-195)	144 (130-154)
QRS, ms	102 (92-120)	98 (88-109)‡	106 (94-132)	108 (96-146)	94 (88-112)	88 (84-92)
Sum limb leads voltage, mm	29 (21-39)	26 (19-36)*	30 (23-39)	29 (21-39)	33 (26-52)	37 (30-38)
Sum chest leads voltage, mm	78 (62-100)	73 (57-93)†	82 (64-106)	84 (65-108)	69 (63-88)	72 (57-86)
Medications, n (%)						
Beta-blocker	98 (30.4%)	29 (21.8%)‡	69 (36.5%)	67 (42.4%)	2 (10.0%)	0 (0%)
Loop diuretic	183 (56.8%)	54 (40.6%)‡	129 (68.3%)	124 (78.5%)	5 (25.0%)	0 (0%)
Aldosterone	76	17	59 (31.2%)	57	2 (10.0%)	0 (0%)

antagonist	(23.6%)	(12.8%)‡		(36.1%)		
ACE inhibitor or angiotensin receptor blocker	117 (36.3%)	36 (27.1%)‡	81 (42.9%)	78 (49.4%)	3 (15.0%)	0 (0%)

*P<0.05, †P<0.01, ‡P<0.001 for AL versus ATTR amyloidosis patients.

ACE, angiotensin converting enzyme; AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; BP, blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6 MWT, 6 minute walk test.

All normally distributed data are presented as mean±standard deviation, non-parametric data are presented as median (Q1-Q3) and proportions as n (%).

Table 2 – CMR and echocardiographic findings in patients with AL and ATTR amyloidosis

	All Patients (n=322)	**AL Patients (n=116)**			**ATTR Patients (n=183)**		
ECV	0.56∞ (0.43-0.65)	0.45 (0.37-0.56)			0.61 (0.51-0.69)‡		
ECV tertile		0.23-0.48 (n=72, 62%)	0.49-0.61 (n=31, 27%)	0.62-0.92 (n=13, 11%)	0.23-0.48 (n=35, 19%)	0.49-0.61 (n=59, 32%)	0.62-0.92 (n=89, 49%)
Echocardiography parameters							
IVSd, cm	1.5 (1.3-1.7)	1.2 (1.1-1.3)	1.4 (1.3-1.5)	1.6 (1.5-1.75)†	1.1 (1.0-1.5)	1.6 (1.4-1.7)	1.7 (1.6-1.9)‡
E wave, cm/s	0.81 (0.66-0.95)	0.76 (0.59-0.93)	0.90 (0.79-1.01)	0.82 (0.63-0.95)*	0.76 (0.65-0.87)	0.86 (0.74-1.02)	0.80 (0.69-0.95)*
A wave, cm/s	0.59 (0.37-0.78)	0.71 (0.59-0.88)	0.60 (0.41-0.82)	0.32 (0.21-0.75)†	0.62 (0.55-0.81)	0.61 (0.38-0.74)	0.31 (0.25-0.46)‡
E/A	1.35 (0.92-2.30)	0.93 (0.78-1.37)	1.53 (0.94-2.42)	1.61 (0.95-2.86)†	1.16 (0.95-1.35)	1.50 (1.00-2.39)	2.48 (1.79-3.18)‡
Average e', cm/s	0.06 (0.05-0.08)	0.07 (0.06-	0.06 (0.05-	0.04 (0.03-	0.08 (0.07-	0.05 (0.04-	0.05 (0.04-

		0.09)	0.08)	0.07)†	0.11)	0.07)	0.06)‡
E/e'	14 (9-19)	10 (8-16)	15 (10-19)	21 (10-27)†	9 (6-12)	15 (12-20)	17 (13-21)‡
E-wave deceleration time, ms	181 (148-215)	200 (162-241)	180 (131-207)	166 (115-235)	195 (156-227)	185 (150-225)	165 (139-191)†
Strain, %	13 (9-17)	18 (14-20)	12 (8-16)	9 (7-11)‡	19 (17-20)	12 (10-15)	9 (7-11)‡
CMR parameters							
$LVEDV_i$, mL/m^2	61 (52-70)	59 (52-67)	57 (45-62)	59 (48-67)	60 (50-70)	60 (51-73)	68 (59-80)†
$LVESV_i$, mL/m^2	22 (16-32)	17 (13-23)	17 (11-25)	27 (20-33)†	19 (12-22)	20 (16-33)	33 (25-43)‡
$RVEDV_i$, mL/m^2	63 (54-76)	59 (51-67)	56 (49-65)	61 (52-67)	60 (53-70)	62 (53-76)	72 (63-89)‡
$RVESV_i$, mL/m^2	25 (18-37)	19 (16-25)	21 (14-28)	26 (21-42)*	20 (16-26)	25 (18-30)	38 (31-50)‡
LV SV_i, ml/m^2	37±10	42±8	36±9	30±9‡	41±8	38±8	33±9‡
LVEF, %	63 (50-72)	71 (65-75)	68 (57-76)	57 (42-62)‡	71 (64-77)	64 (56-71)	50 (40-58)‡
RVEF, %	60 (49-68)	67 (60-73)	64 (52-71)	52 (36-57)‡	66 (63-72)	60 (52-67)	47 (36-55)‡
MAPSE, mm	8 (6-10)	10 (8-13)	7 (5-9)	4 (4-6)‡	12 (10-	8 (6-9)	6 (5-8)‡

					13)		
TAPSE, mm	14 (10-19)	19 (14-22)	14 (9-20)	10 (8-14)‡	20 (18-24)	14 (11-17)	11 (8-13)‡
LV mass$_i$,g/m^2	109 (80-137)	79 (63-99)	96 (80-111)	122 (108-144)‡	72 (60-95)	118 (102-139)	145 (124-167)‡
LA area$_i$,cm^2/m^2	15±4	13±3	13±4	15±2*	13±3	16±3	17±3‡
RA area$_i$,cm^2/m^2	13 (10-16)	12 (10-14)	12 (10-14)	10 (9-15)	12 (10-13)	13 (11-15)	16 (14-19)‡
RV LGE∞	229 (77%)	34/72 (47%)	28/31 (90%)	11/13 (85%)‡	13/35 (37%)	57/59 (97%)	86/89 (97%)‡
Precontrast T1, ms	1089 (1049-1127)	1046 (999-1085)	1135 (1100-1175)	1164 (1119-1195)‡	1003 (963-1052)	1086 (1067-1106)	1115 (1091-1142)‡
MCF, %	35.5 (25.4-54.9)	56.3 (42.9-71.4)	38.0 (30.1-51.8)	24.1 (19.8-33.3)‡	62.2 (36.9-72.3)	34.2 (25.5-41.3)	24.2 (19.4-28.3)‡

∞less 23 patients who did not have ECV measured

*P<0.05, †P<0.01, ‡P<0.001 for the distribution of variables across ECV tertiles in the AL and ATTR patient cohorts.

AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; IVSd, interventricular septum

thickness in diastole; LV, left ventricular; RV, right ventricular; EDV_i, end diastolic volume indexed; ESV_i, end systolic volume indexed; SV_i, stroke volume indexed; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LV $mass_i$, left ventricular mass indexed; LA $area_i$, left atrial area indexed; RA $area_i$, right atrial area indexed; RV LGE, right ventricular late gadolinium enhancement, ECV, extracellular volume.

All normally distributed data are presented as mean±standard deviation, non-parametric data as median (Q1-Q3) and proportions as n (%).

Table 3. Simple Cox regression analysis of risk of death in the overall population

Variables	**Univariable**	
	HR (95% CI)	**P**
Heart rate (bpm)	1.01 (0.99-1.02)	0.608
E/e' each 1 unit increment	1.03 (1.01-1.05)	0.005†
LV LGS, each 2% decrement	1.24 (1.13-1.36)	0.000004‡
LV mass indexed, each 10g/m^2 increment[23]	1.07 (1.02-1.13)	0.009†
LA area indexed, each 1.8cm^2/m^2 increment[23]	1.25 (1.10-1.41)	0.001†
RA area indexed, each 1.8cm^2/m^2 increment[23]	1.18 (1.07-1.29)	0.001†
LVEF, each 3% decrement	1.12 (1.07-1.17)	5.0x10^{-7}‡
RVEF, each 3% decrement	1.14 (1.08-1.19)	1.9x10^{-7}‡
SV indexed, each 5mL/m^2 decrement	1.40 (1.24-1.57)	4.8x10^{-8}‡
MAPSE, each 2.2mm decrement	1.43 (1.23-1.66)	0.000002‡

TAPSE, each 3.6mm decrement	1.70 (1.45-2.00)	$1.3x10^{-10}$‡
MCF, each 10% decrement[21]	1.55 (1.32-1.81)	$3.5x10^{-8}$‡

*P<0.05, †P<0.01, ‡P<0.001

LV, left ventricular; LGS, longitudinal global strain; SV, stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial; RA, right atrial; MCF, myocardial contraction fraction.

Table 4. Multivariable Cox regression analysis of risk of death in the overall population

Variables	Model A		Model B		Model C	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
E/e' each 1 unit increment	1.02 (0.98-1.05)	0.40	1.02 (0.98-1.06)	0.33	1.00 (0.96-1.04)	0.99
LV LGS, each 2% decrement	1.02 (0.89-1.18)	0.76	1.03 (0.89-1.19)	0.69	1.08 (0.94-1.25)	0.27
LV mass indexed, each 10g/m^2 increment[23]	0.97 (0.90-1.05)	0.49	0.95 (0.88-1.02)	0.16		
LA area indexed, each 1.8cm^2/m^2 increment[23]	1.18 (0.99-1.40)	0.060	1.11 (0.95-1.30)	0.20	1.08 (0.93-1.26)	0.32
RA area indexed, each 1.8cm^2/m^2 increment[23]	1.02 (0.90-1.16)	0.71	1.02 (0.89-1.16)	0.81	1.02 (0.90-1.15)	0.79
LVEF, each 3% decrement			1.04 (0.96-1.14)	0.33		
RVEF, each 3% decrement	1.02 (0.95-1.10)	0.60	1.00 (0.91-1.09)	0.93	1.02 (0.95-1.09)	0.60

SV indexed, each 5mL/m^2 decrement	1.24 (1.04-1.48)	0.019*				
MAPSE, each 2.2mm decrement	1.00 (0.82-1.22)	0.99	1.03 (0.85-1.26)	0.74	1.02 (0.84-1.24)	0.84
TAPSE, each 3.6mm decrement	1.46 (1.16-1.85)	0.0014†	1.55 (1.23-1.96)	0.00026‡	1.48 (1.17-1.87)	0.0012†
MCF, each 10% decrement[(21)]					1.25 (1.00-1.57)	0.053
C-statistic	0.729 (0.639, 0.819)		0.724 (0.634, 0.814)		0.725 (0.635, 0.815)	

*P<0.05, †P<0.01, ‡P<0.001

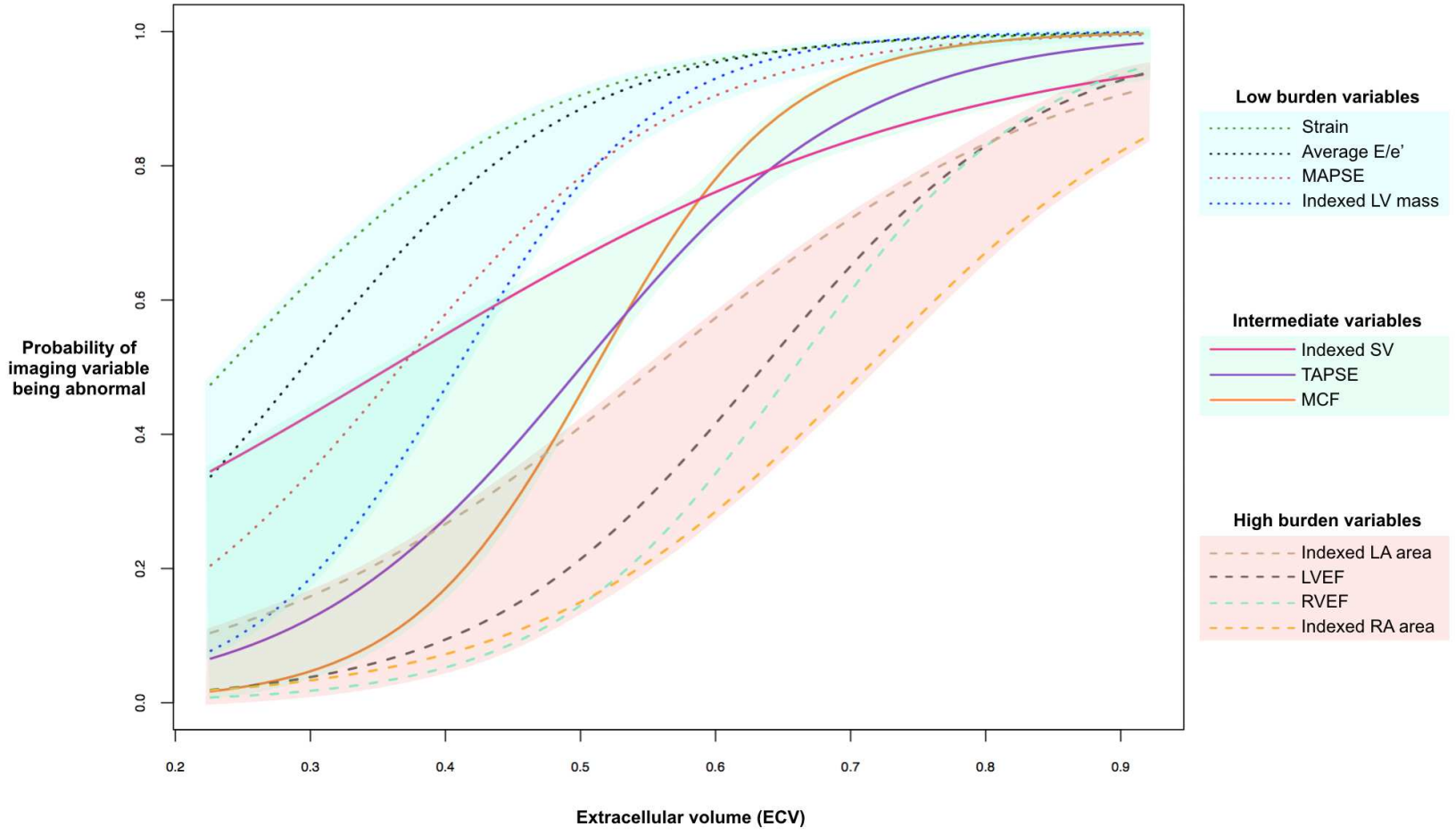
LV, left ventricular; LGS, longitudinal global strain; SV, stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial; RA, right atrial; MCF, myocardial contraction fraction.

Table 5 – Relationship between RV LGE and TAPSE in patients with AL and ATTR amyloidosis

	All subjects (n=299)		**AL (n=116)**		**ATTR (n=183)**	
	RV LGE present	**RV LGE absent**	**RV LGE present**	**RV LGE absent**	**RV LGE present**	**RV LGE absent**
N (%)	229 (77)	70 (23)†	73 (63)	43 (37)*	156 (85)	27 (15)†
TAPSE	12 (9-16)	21 (17-24)†	14 (10-19)	21 (17-24)†	12 (9-15)	20 (18-25)†

*P<0.01, †P<0.001 for differences between RV LGE positive and negative groups.

AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; LGE, late gadolinium enhancement; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion. TAPSE data are presented as median (Q1-Q3) and proportions as n (%).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0.4
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0.2
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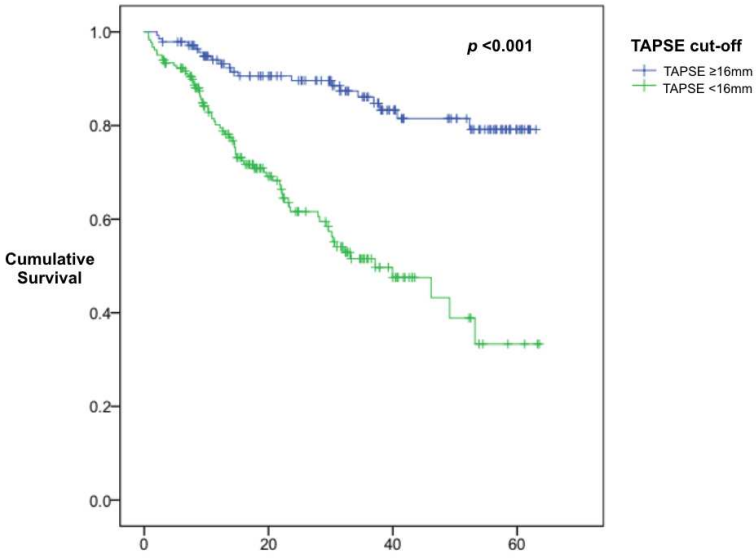
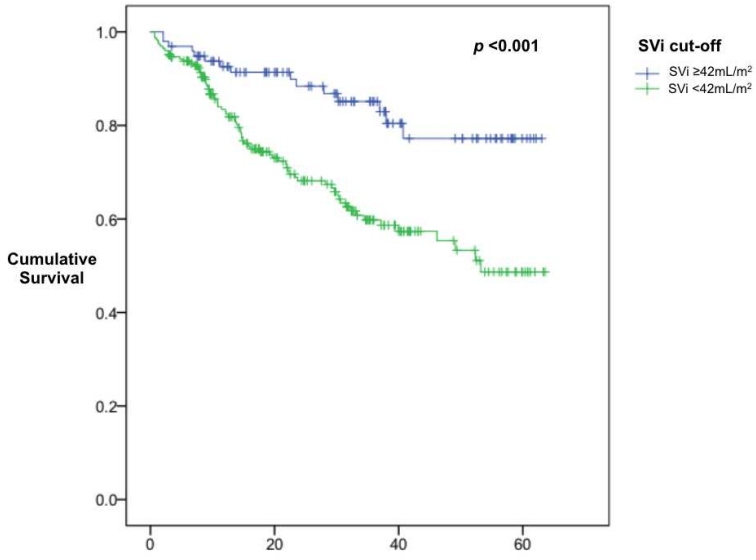
0.4
0.5
0.6
0.7
0.8
0.9
Extracellular volume (ECV)
Low burden variables
Strain
Average E/e'
MAPSE
Indexed LV mass
Intermediate variables
Indexed SV
TAPSE
MCF
High burden variables
Indexed LA area
LVEF
RVEF
Indexed RA area



Number at risk				
TAPSE ≥16mm	140	98	50	9
TAPSE <16mm	182	78	21	3



Number at risk				
SVi ≥42mL/m²	97	67	28	5
SV <42mL/m²	225	109	43	7

Supplementary Table 1. Correlational analyses for all parameters analyzed in the multivariable Cox regression analyses of risk of death

		E/e'	LV LGS	LV mass indexed	LA area indexed	LVEF	RVEF	SV indexed	MAPSE	TAPSE	RA area indexed	MCF
E/e'	**r**		-0.419‡	0.369‡	0.249‡	-0.247‡	-0.266‡	-0.213‡	-0.431‡	-0.324‡	0.07	-0.380‡
	P		4.2×10^{-15}	8.6×10^{-12}	6×10^{-6}	7×10^{-6}	1×10^{-6}	0.00012	5×10^{-16}	2.5×10^{-9}	0.207	1.7×10^{-12}
LV LGS	**r**	-0.419‡		-0.566‡	-0.394‡	0.627‡	0.610‡	0.424‡	0.601‡	0.668‡	-0.408‡	0.603‡
	P	4.2×10^{-15}		1×10^{-28}	2×10^{-13}	1.6×10^{-36}	3.3×10^{-34}	1.7×10^{-15}	5.8×10^{-33}	5.9×10^{-43}	2.5×10^{-14}	3.4×10^{-33}
LV mass indexed	**r**	0.369‡	-0.566‡		0.505‡	-0.485‡	-0.429‡	-0.079	-0.461‡	-0.524‡	0.433‡	-0.773‡
	P	8.6×10^{-12}	1.0×10^{-28}		3.3×10^{-22}	1.9×10^{-20}	8.0×10^{-16}	0.156	2.3×10^{-18}	4.1×10^{-24}	3.8×10^{-16}	3.3×10^{-65}
LA area indexed	**r**	0.249‡	-0.394‡	0.505‡		-0.395‡	-0.432‡	-0.034	-0.304‡	-0.363‡	0.610‡	-0.381‡
	P	6×10^{-6}	2×10^{-13}	3.3×10^{-22}		2.0×10^{-13}	4.7×10^{-16}	0.549	2.5×10^{-8}	1.8×10^{-11}	3.1×10^{-34}	1.5×10^{-12}
LVEF	**r**	-0.247‡	0.627‡	-0.485‡	-.395‡		0.822‡	0.599‡	0.530‡	0.569‡	-0.405‡	0.591‡
	P	7×10^{-6}	1.6×10^{-36}	1.9×10^{-20}	2.0×10^{-13}		2.6×10^{-80}	9.3×10^{-33}	1.1×10^{-24}	4.8×10^{-29}	4.0×10^{-14}	1.2×10^{-31}
RVEF	**r**	-0.266‡	0.610‡	-0.429‡	-0.432‡	0.822‡		0.590‡	0.479‡	0.627‡	-0.427‡	0.550‡
	P	1×10^{-6}	3.3×10^{-34}	8.0×10^{-16}	4.7×10^{-16}	2.6×10^{-80}		1.3×10^{-31}	7.0×10^{-20}	1.6×10^{-36}	1.0×10^{-15}	7.2×10^{-27}
SV indexed	**r**	-0.213‡	0.424‡	-0.079	-0.034	0.599‡	0.590‡		0.452‡	0.514‡	-0.087	0.493‡
	P	0.00012	1.7×10^{-15}	0.156	0.549	9.3×10^{-33}	1.3×10^{-31}		1.3×10^{-17}	4.1×10^{-23}	0.118	3.7×10^{-21}
MAPSE	**r**	-0.431‡	0.601‡	-0.461‡	-0.304‡	0.530‡	0.479‡	0.452‡		0.642‡	-0.248‡	0.590‡
	P	5×10^{-16}	5.8×10^{-33}	2.3×10^{-18}	2.5×10^{-8}	1.1×10^{-24}	7.0×10^{-20}	1.3×10^{-17}		7.3×10^{-39}	7×10^{-6}	1.5×10^{-31}
TAPSE	**r**	-0.324‡	0.668‡	-0.524‡	-0.363‡	0.569‡	0.627‡	0.514‡	0.642‡		-0.373‡	0.643‡
	P	2.5×10^{-9}	5.9×10^{-43}	4.1×10^{-24}	1.8×10^{-11}	4.8×10^{-29}	1.6×10^{-36}	4.1×10^{-23}	7.3×10^{-39}		4.6×10^{-12}	5.2×10^{-39}
RA area indexed	**r**	0.07	-0.408‡	0.433‡	0.610‡	-0.405‡	-0.427‡	-0.087	-0.248‡	-0.373‡		-0.343‡
	P	0.207	2.5×10^{-14}	3.8×10^{-16}	3.1×10^{-34}	4.0×10^{-14}	1.0×10^{-15}	0.118	7×10^{-6}	4.6×10^{-12}		2.7×10^{-10}
MCF	**r**	-0.380‡	0.603‡	-0.773‡	-0.381‡	0.591‡	0.550‡	0.493‡	0.590‡	0.643‡	-0.343‡	
	P	1.7×10^{-12}	3.4×10^{-33}	3.3×10^{-65}	1.5×10^{-12}	1.2×10^{-31}	7.2×10^{-27}	3.7×10^{-21}	1.5×10^{-31}	5.2×10^{-39}	2.7×10^{-10}	

*P<0.05, †P<0.01, ‡P<0.001

LV, left ventricular; LGS, longitudinal global strain; SV, stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial; RA, right atrial; MCF, myocardial contraction fraction.

Supplementary Table 2. Multivariable Cox regression analysis of risk of death in the AL amyloidosis population

Variables	Model A		Model B		Model C	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
E/e' each 1 unit increment	1.02 (0.97-1.08)	0.44	1.03 (0.98-1.10)	0.25	1.02 (0.96-1.07)	0.58
LV LGS, each 2% decrement	0.92 (0.74-1.15)	0.47	0.93 (0.75-1.16)	0.54	0.97 (0.78-1.20)	0.76
LV mass indexed, each 10g/m^2 increment[23]	0.98 (0.86-1.12)	0.78	0.94 (0.82-1.08)	0.38		
LA area indexed, each 1.8cm^2/m^2 increment[23]	1.53 (1.12-2.09)	0.0072†	1.32 (1.01-1.73)	0.039*	1.28 (1.01-1.63)	0.044*
RA area indexed, each 1.8cm^2/m^2 increment[23]	0.94 (0.73-1.21)	0.63	0.90 (0.70-1.16)	0.41	0.89 (0.70-1.14)	0.36
LVEF, each 3% decrement			1.03 (0.91-1.17)	0.64		
RVEF, each 3% decrement	0.95 (0.84-1.08)	0.44	0.99 (0.85-1.16)	0.92	1.02 (0.91-1.14)	0.75
SV indexed, each 5mL/m^2 decrement	1.37 (1.03-1.83)	0.030*				
MAPSE, each 2.2mm decrement	0.85 (0.64-1.13)	0.25	0.88 (0.67-1.18)	0.40	0.90 (0.68-1.19)	0.47
TAPSE, each 3.6mm decrement	1.54 (1.08-2.18)	0.017*	1.69 (1.18-2.42)	0.0039†	1.62 (1.13-2.30)	0.0082†
MCF, each 10% decrement[21]					1.13 (0.83-1.54)	0.43
C-statistic	0.797 (0.699, 0.895)		0.785 (0.687, 0.883)		0.785 (0.687, 0.883)	

*P<0.05, †P<0.01, ‡P<0.001

LV, left ventricular; LGS, longitudinal global strain; SV, stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial; RA, right atrial; MCF, myocardial contraction fraction.

Supplementary Table 3. Multivariable Cox regression analysis of risk of death in the TTR amyloidosis population

Variables	Model A		Model B		Model C	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
E/e' each 1 unit increment	1.01 (0.97-1.06)	0.54	1.02 (0.97-1.07)	0.53	1.00 (0.95-1.05)	0.91
LV LGS, each 2% decrement	1.16 (0.96-1.41)	0.13	1.16 (0.96-1.41)	0.13	1.21 (1.01-1.45)	0.043*
LV mass indexed, each 10g/m^2 increment[23]	0.98 (0.89-1.08)	0.70	0.96 (0.87-1.05)	0.35		
LA area indexed, each 1.8cm^2/m^2 increment[23]	0.99 (0.79-1.23)	0.90	0.96 (0.78-1.19)	0.72	0.93 (0.75-1.14)	0.47
RA area indexed, each 1.8cm^2/m^2 increment[23]	1.10 (0.95-1.28)	0.19	1.10 (0.94-1.28)	0.24	1.10 (0.95-1.28)	0.20
LVEF, each 3% decrement			1.05 (0.93-1.18)	0.41		
RVEF, each 3% decrement	1.01 (0.91-1.12)	0.85	1.01 (0.88-1.15)	0.92	1.03 (0.94-1.12)	0.52
SV indexed, each 5mL/m^2 decrement	1.18 (0.92-1.51)	0.18				
MAPSE, each 2.2mm decrement	1.05 (0.76-1.45)	0.78	1.09 (0.80-1.49)	0.59	0.99 (0.71-1.38)	0.96
TAPSE, each 3.6mm decrement	1.45 (1.02-2.06)	0.039*	1.53 (1.08-2.16)	0.017*	1.42 (1.00-2.02)	0.053
MCF, each 10% decrement[21]					1.38 (0.94-2.03)	0.10
C-statistic	0.728 (0.644, 0.812)		0.729 (0.645, 0.813)		0.725 (0.641, 0.809)	

*P<0.05, †P<0.01, ‡P<0.001

LV, left ventricular; LGS, longitudinal global strain; SV, stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; LA, left atrial; RA, right atrial; MCF, myocardial contraction fraction.

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Article entitled: Cardiac structural and functional consequences of amyloid deposition by CMR and echocardiography and their prognostic roles

Manuscript number: JIMG040917-0441

Corresponding Author: Dr. Knight

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Manuscript number: JIMG040917-0441R

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Article entitled: Cardiac structural and functional consequences of amyloid deposition by CMR and echocardiography and their prognostic roles

Manuscript number: JIMG040917-0441

Corresponding Author: Dr. Knight

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