Published in final edited form as:

J Card Fail. 2018 August ; 24(8): 504–511. doi:10.1016/j.cardfail.2018.07.001.

Myocardial Contraction Fraction by M-Mode Echocardiography is Superior to Ejection Fraction in Predicting Mortality in Transthyretin Amyloidosis

Jonah Rubin^a, D. Eric Steidley^b, Martin Carlsson^c, Moh-Lim Ong^c, and Mathew S. Maurer^{*a}

^aDepartment of Medicine, Columbia University Medical Center, New York, NY, USA

^bDepartment of Cardiovascular Disease, Mayo Clinic, Phoenix, AZ, USA

^cPfizer Inc., New York, NY, USA

Abstract

Background: Transthyretin amyloidosis (ATTR) is often associated with cardiac involvement manifesting as conduction disease as well as a restrictive cardiomyopathy causing heart failure and death. Myocardial contraction fraction (MCF), the ratio of left ventricular stroke volume (SV) to myocardial volume (MV), is a volumetric measure of myocardial shortening that is superior to EF in predicting mortality in patients with primary amyloid light chain (AL) cardiac amyloidosis. We hypothesized that MCF would be an independent predictor of survival in ATTR.

Methods and Results: MCF was derived from 2D echo-guided M-mode data for 530 subjects in the Transthyretin Amyloidosis Outcomes Survey (THAOS) database (age 61 ± 16 , 74% male; 158 wild-type (ATTRwt) and 372 mutant (ATTRm) with a mean follow up of 1.5 ± 1.7 years). Using multivariate Cox proportional hazards regression models, MCF above and below 25% was highly associated with survival (HR 8.5, 95% CI 4.8 – 14.9, $p < 0.0001$) which was stronger than the association of ejection fraction (EF) dichotomized at 50% (HR 2.8, 95% CI 1.8 – 4.4, $p < 0.0001$). MCF $< 25\%$ remained significantly predictive of survival in a multivariate model that included systolic blood pressure, estimated glomerular filtration rate below vs. above 65 ml/min/m², NYHA class, and health status based on the EQ-5D-3L questionnaire (AUC = 0.83, 95% CI 0.78 -0.89).

Conclusions: MCF was superior to EF in predicting mortality in patients with transthyretin amyloidosis. A predictive model combining MCF with systolic blood pressure, renal function, NYHA class, and health status was strongly associated with survival in patients with ATTR.

Address for Correspondence: Mathew S. Maurer, MD, Clinical Cardiovascular Research Laboratory for the Elderly, Allen Hospital of New York Presbyterian, Columbia University Medical Center, 5141 Broadway, 3 Field West, Room 037, New York, NY, 10034, 212-932-4537, Msm10@cumc.columbia.edu.

ClinicalTrials.gov identifier: NCT00628745

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

myocardial contraction fraction; transthyretin amyloidosis; ATTR; MCF; ejection fraction

Introduction

Transthyretin amyloidosis (ATTR) is a progressive disorder that is characterized by the extracellular cardiac deposition of wild-type or mutant predominantly in the nerves or myocardium. A majority of patients with ATTR have cardiac involvement, which can cause conduction disease or a restrictive cardiomyopathy leading to heart failure and death [1,2]. Amyloid fibril infiltration can result in thickened ventricular walls, increased left ventricular mass, diminished end-diastolic capacitance, and impaired myocardial contraction [3]. Despite advancing disease, cardiac function as assessed by left ventricular ejection fraction (EF) typically remains “normal” or “preserved” [4,5].

The myocardial contraction fraction (MCF) is a volumetric measure of myocardial contraction that indexes cardiac function as the ratio of stroke volume (SV) to myocardial volume (MV) [6]. Myocardial contraction fraction calculated from three-dimensional echocardiography distinguished between physiologic and pathologic hypertrophy [6]. More recently, MCF as calculated based on two-dimensional guided M-mode echocardiography in a community dwelling older adult population was independently associated with adverse cardiovascular outcomes including heart failure, atherosclerotic cardiovascular disease, and death in a population with a normal EF [7]. Since amyloid deposition in the myocardium increases ventricular myocardial volume with subsequent impairment in myocardial shortening, we hypothesized that MCF would be impaired in subjects with ATTR more so than EF and thus, MCF would be a better predictor of mortality. Indeed, MCF has already proven superior to EF in predicting mortality in patients with primary amyloid light chain (AL) cardiac amyloidosis [8].

Methods

Study Population

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an international, longitudinal, observational study of patients with wild-type and mutant transthyretin amyloidosis, as well as asymptomatic carriers of ATTR gene mutations, developed to improve understanding of the natural history of ATTR amyloidosis. The full design, methods, and goals of this registry have been previously described [9]. Briefly, patients provide written consent to have their demographic and clinical data entered electronically to the registry upon enrollment and after each clinic visit. The data is stored on a secure server maintained by Pfizer Inc. The THAOS scientific board approved use of THAOS data for this study, which included all subjects in the registry through January 14, 2016. The target population included all subjects with sufficient echocardiographic data to calculate MCF.

Echocardiographic Indices

Myocardial contraction fraction is the ratio of left ventricular (LV) stroke volume to myocardial volume. Left ventricular end-systolic (ESV) and end-diastolic (EDV) volumes were not directly measured but derived via calculations based on left ventricular dimensions measured by the American Society of Echocardiography (ASE) guidelines and with previously validated techniques using linear dimensions from 2DE [10-12]. Left ventricular EDV was estimated as $4.5 \times (\text{LV end diastolic dimension [LVEDD]})^2$ and LV ESV was estimated as $3.72 \times (\text{LV end systolic dimension})^2$. Volumetric chamber data was not recorded in THAOS. Stroke volume is EDV minus ESV. Left ventricular mass was determined using $(1.04 \times (\text{LVEDD} + \text{interventricular septal thickness} + \text{posterior wall thickness})^3 - (\text{LVEDD})^3)$ as per Devereux et al. [13] and indexed to body surface area [14]. Myocardial volume was defined as LV mass divided by the mean density of myocardium (1.04 g/ml). Ejection fraction was calculated as SV divided by EDV multiplied by 100.

Health status

Health status was evaluated with the EQ-5D-3L [15]. This validated tool relies on patients' self-assessment of their health status in five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In each dimension, patients report whether they suffer from no problems, some problems, or extreme problems, which can define up to 243 distinct health states. These measures can then be converted via a proprietary formula into a summary index that ranges from -0.11 to 1, where 1 indicates perceived perfect health.

Statistical Methods

Clinical, functional, laboratory, and cardiac testing data available at enrollment for the overall population and stratified by survival status were delineated. Additionally, we compared the target population to the remainder of those in the THAOS database, in order to better characterize the target population. Descriptive summaries of the distribution of continuous variables are presented with mean and standard deviation. Binary and categorical variables were summarized in terms of frequencies and percentages. Student's *t*-test was applied to compare variables of interest in those who died compared to those who survived with Welch's *t*-test in the case of unequal variances. Group comparisons with respect to discrete baseline variables used the chi-square test. We compared the association of EF and MCF with time to death from enrollment in THAOS using unadjusted Cox proportional hazards regression models. For multivariate analysis, a stepwise variable selection procedure for Cox proportional hazards model included demographic features (age, gender, race) as well as parameters that are either easily obtainable in clinic and/or have been shown in previous studies to predict outcomes in subjects with cardiac amyloidosis (New York Heart Association (NYHA) class [16,17], presence of a TTR mutation [18], systolic blood pressure (SBP) [16], estimated glomerular filtration rate (eGFR) [19] and health status) along with echocardiographic measures of left ventricular function, EF and/or MCF. Because we utilized a step-wise regression model, hazard ratios for non-significant variables are not retained in the final model and therefore cannot be presented. We excluded from the multivariate analysis, echocardiographic measures which were highly collinear with MCF to avoid model overfitting. Cardiac biomarker BNP predicts mortality for subjects in the

THAOS database [20] but insufficient data for BNP and NT-pro-BNP was available in our target population to include this variable in our analysis. The assumption of proportional hazards was tested with the Lin, Wei, and Ying score process test [21]. These tests indicated no deviation from proportional hazards assumption, as required. Generalized Additive Models (GAM) were applied to assess the appropriate form of the dependence of death on each of the variables. Myocardial contraction fraction, ejection fraction, and estimated glomerular filtration rate (eGFR) calculated via the Cockcroft-Gault equation were evaluated as binary variables with a cutoff of <25%, <50%, and <65 ml/min/m², respectively. These values for MCF and eGFR were determined using the Youden Index for optimal cutoffs based on optimizing sensitivity and specificity [22]. The Youden Index is a commonly used technique to determine the most appropriate cut-off value and corresponds to a point on the Receiver Operating Characteristic curve with the highest vertical distance from the diagonal. The C-statistic was calculated for the composite of those variables that remained significant in multivariate analysis. Net reclassification index was calculated as the percent of patients correctly identified via MCF as having died minus the percentage correctly classified by EF. A two-sided significance level of 5% was applied to all statistical tests. We used SAS software, version 9.4 (SAS institute), for the statistical analyses.

Results

530 subjects from the THAOS registry with wild-type or mutant ATTR and sufficient echocardiographic data to calculate MCF were included in this study. Mean follow up was 1.5 ± 1.7 years. Ninety subjects (17%) died during follow-up period. Seventy-five deaths (5%) occurred in patients with MCF below 25% ($n = 300$) and 15 (6.5%) deaths occurred in those with MCF $\geq 25\%$ ($n = 230$).

Table 1 delineates baseline demographic and clinical data of the target population overall and stratified by survival status. Subjects with measurable MCF were compared to those without MCF measures (Supplementary Table 1). Subjects included in the primary analysis differed from the remainder of the THAOS cohort in that they were older, more often Caucasian and male with higher NYHA Class, more carpal tunnel syndrome, more often wild-type, more frequently hospitalized, and had lower voltage on electrocardiograms. These findings are consistent with echocardiograms performed in subjects with ATTR cardiac amyloidosis. The mean MCF of the target population was $27 \pm 16\%$ and was lower at baseline in those that died during follow-up ($29 \pm 17\%$ vs. $18 \pm 12\%$, $p = <0.0001$). Mean EF was $60 \pm 13\%$ and was lower at baseline in those who died ($62 \pm 13\%$ vs. $55 \pm 13\%$, $p = 0.0001$) but still in the normal range in both cohorts. Fractional shortening (HR 0.94, 95% CI 0.92 – 0.99) and relative wall thickness (HR 20.3, 95% CI 10.2 – 40.4) were also significantly associated with mortality in univariate analysis and the MCF and RWT were highly correlated ($r = -0.80$, $p = <0.0001$).

Variables that were significantly associated with death in univariate and multivariate analysis are in Table 2. In univariate analysis, MCF below 25% was significantly more predictive of mortality (HR 8.46, 95% CI 4.8 – 14.9) compared to EF below 50% (HR 2.78, 95% CI 1.8 – 4.4). A Kaplan-Meier curve demonstrating survival of patients with MCF above vs. below 25 is presented in Figure 1. In multivariate analysis,

MCF below 25% was independently associated with significantly greater risk of death (HR 5.4, 95% CI 1.82 – 15.86, $p = 0.0024$) -as was estimated GFR, systolic blood pressure (SBP), NYHA class, and health status. The C-statistic for the multivariate model including MCF, MAP, eGFR, NYHA Class, and EQ-5D-3L had good discrimination for mortality (AUC of 0.83, 95% CI 0.78 - 0.89). Net reclassification of non-survivors by MCF vs. EF was 52%. In the full model, the addition of MCF resulted in a net reclassification of 3.5% of subjects.

Discussion

In this study, MCF calculated from linear dimensions derived from two dimensional echocardiography was superior to EF in predicting survival of subjects with both mutant and wild-type ATTR and in a model combined with SBP, eGFR, NYHA class, and health status, MCF was independently associated with survival.

MCF is a volumetric index of myocardial shortening which captures pathological changes in cardiac function not quantified by measurement of EF. Since myocardial mass, and therefore MV, is constant throughout the cardiac cycle, the MCF is a unitless volumetric measure of myocardial shortening, that is highly correlated with global longitudinal strain [23,24]. Since MCF is analogous to EF, which is also a ratiometric, and has similar normal values, adoption into clinical practice should be facilitated. In ATTR-CA, amyloid infiltration increases myocardial mass, decreases left ventricular capacitance, and impairs myocardial contraction [3]. These changes reduce EDV and ESV, with a concomitant reduction in SV. As MV increases and SV decreases, MCF necessarily decreases. Thus, worsening MCF likely reflects progressive myocardial amyloid infiltration and its pathophysiologic effects may explain why MCF predicts mortality more powerfully than EF. Conversely, EF often remains “normal” or “preserved” [4,5] despite progressive amyloid deposition in the myocardium because EDV and SV are reduced together.

MCF was first described using three dimensional echocardiography, and successfully differentiated between pathologic hypertensive hypertrophic cardiomyopathy and physiologic hypertrophy, in addition to differentiating between normal subjects and athletes [6]. It outperformed the diagnostic capability of conventional echocardiographic measures of myocardial shortening, including ejection fraction, shortening fraction, and mid-wall shortening fraction for distinguishing these cohorts. MCF calculated via cardiac magnetic resonance imaging (CMR) in nonischemic dilated cardiomyopathy is associated with prognosis [25], as well as in the Framingham Heart Study, where a low MCF predicted the composite outcome of death, myocardial infarction, stroke, or new heart failure [26]. Using cMRI, MCF outperformed EF in discriminating ATTR-CA from controls (AUC = 0.94, sensitivity 81%, specificity 94%) [27]. However, the greater availability and lower cost of echocardiography compared to CMR prompted echocardiography-based investigations of the utility of MCF for risk prediction. MCF calculated via 2DE predicted atherosclerotic cardiovascular disease and mortality in patients with no known cardiovascular disease in the Cardiovascular Health Study [7]. MCF using 2D echocardiographic techniques identical to those employed in the current study, predicted mortality in light-chain cardiac amyloidosis (AL-CA) as well [8]. This latter study included only 32 ATTR-CA patients and reported that

an MCF under 30% did not significantly predict mortality (HR 1.26, 95% CI 0.36 – 3.28, $p = 0.87$). However, this study had a small sample size with few events limiting statistical power. Our study of over 500 patients is better powered to assess the predictive power of MCF on mortality for this patient population. A more recent study compared the diagnostic capability of conventional echocardiography-based parameters including MCF for identification of cardiac amyloidosis [28]. Of the parameters based solely on conventional echocardiography, MCF performed best at identifying cardiac amyloidosis with an AUC of 0.8. This study did not assess ability to predict outcomes and included only 40 patients with cardiac amyloidosis (15 ATTR, 35 light-chain). We also found that relative wall thickness (RWT), a well-described measure of chamber structure, was also significantly associated with mortality, as has been shown in another recent publication of subjects with ATTRwt cardiac amyloidosis [29]. RWT and MCF were highly in our data ($r = -0.80$, $p = <0.0001$) but MCF is a novel metric that includes both structural and functional aspects of chamber properties.

Multiple advanced echocardiography techniques can also predict outcomes in patients with AL-CA and a normal EF, and are more sensitive diagnostically than conventional Doppler parameters such as mitral inflow velocities. Mid and basilar ventricular longitudinal strain with apical sparing, and strain rate, have distinguished AL-CA from other causes of LV hypertrophy [30], and strain predicts mortality in patients with AL-CA [31-33]. Tissue Doppler imaging of early and late diastolic parameters (e' and a') can also detect abnormalities unique to infiltrative cardiomyopathy, although with somewhat less sensitivity than strain and strain rate [30,34]. EF measures fail to detect these changes revealed by strain and tissue Doppler but others have found MCF to correlate with strain [18]. Although strain is not available in THAOS, both MCF and strain are measures of myocardial deformation or shortening, which can identify decrements in myocardial function that are not detected by ejection fraction. Wider application of MCF, which does not require advanced echocardiographic techniques, may improve prognostication in a cohort in which available sophisticated echocardiographic measures are either unavailable or not routinely performed. Furthermore, to our knowledge, previous studies correlating advanced echocardiographic parameters with mortality have studied populations of AL-CA, not ATTR-CA.

In multivariate analysis, SBP, $eGFR < 65 \text{ mL/min/m}^2$, and health status were each additional independent predictors of mortality. Mean arterial pressure is a predictor of mortality in the THAOS database among patients in the United States [36]. Low blood pressure has also been associated with greater mortality in patients with light-chain cardiac amyloidosis [16,37] as well as heart failure with reduced ejection fraction [38,39]. Decreases in arterial blood pressure may represent worsening amyloid with lower cardiac stroke volume or even the effects of progressive autonomic dysfunction in affected individuals [40].

Numerous prospective studies have demonstrated the ability of various quality of life (QOL) scores to predict mortality in patients with heart failure [41-43], but often employ lengthy scoring systems. Some of these studies have been criticized for not adjusting for covariates [42]. The EQ-5D-3L is a brief instrument with 5 questions each with 3 options, and has been shown to successfully predict mortality in patients with chronic kidney disease [44] and HIV

[45]. To our knowledge, this score has not been previously used to predict mortality in heart failure. Furthermore, no QOL scores predict mortality in amyloidosis specifically. Our findings suggest that this easily administered QOL score can successfully predict mortality in ATTR and demonstrates that patients' perception of their health status is an important predictive marker of survival. Numerous factors in ATTR may contribute to worsened health status in the five measured dimensions including frequent hospitalizations, diminished exercise tolerance, poor functional capacity and reduced independence, as well as comorbidities such as kidney disease or neurologic manifestations. Further analysis of the distribution of EQ-5D-3L scores may reveal if a particular dimension was most frequently identified as problematic to this patient population and may point to a specific pathophysiological change that contributes worsening symptoms and adverse outcomes.

While EQ-5D-3L measures a patient's perception of their health status, NYHA Class is a clinician-determined assessment of a patient's functional status. NYHA Class predicts mortality in patients with heart failure and preserved ejection fraction [46] and our data confirms the value of this classic classification system in subjects with ATTR.

Finally, worsening kidney disease is an independent predictor of mortality as well. Most likely, renal disease in ATTR-CA represents a type 2 cardiorenal syndrome, where progressively worsening perfusion from advancing cardiac disease leads to renal dysfunction. While the concomitance of cardiac and renal dysfunction in patients with known amyloidosis might suggest a type 5 cardiorenal syndrome, in which a singular systemic disease like amyloidosis simultaneously causes heart and kidney dysfunction [47], this appears to be common in AL-CA but less so in ATTR-CA [48,49]. Notably, a recent study successfully developed a staging system for ATTR-CA utilizing eGFR above and below 45mL/min to stratify patients into upper and lower stages and was predictive of survival [19].

There are numerous limitations of this study. We were only able to include patients with transthyretin amyloidosis who had sufficient echocardiographic data to calculate the MCF. Unfortunately, data was missing in a large percentage of subjects. Therefore, the generalizability of our findings to the larger cohort of subjects with TTR amyloidosis is uncertain. However, our target population included patients with clinical evidence of ATTR-CA, a cohort in which cardiovascular measures such as MCF are needed to predict outcomes. Also, as noted, left ventricular mass and volumes were not directly measured and thus true volumetric chamber data is lacking. Although the techniques used to estimate left ventricular volumes and mass have been previously validated, these are estimates and not true measures of ventricular volumes and are subject to error. However, the main objective of the present study was to demonstrate that MCF, even if measured with the simplest method, can predict adverse outcomes. Additionally, measurement of MV relied on assuming a consistent myocardial density of 1.04g/mL regardless of amyloid presence, which is unlikely since myocardial density is known to vary with other conditions such as after infarction, when density has been shown to increase [52]. Finally, lacking data in the THAOS database on other known predictors of outcomes in light-chain cardiac amyloidosis, including strain [31-33], tricuspid phase annular plane systolic excursion [35], left atrial volume and function [53], and Left ventricular wall thickness [54], precluded their direct comparison with MCF.

In conclusion, myocardial contraction fraction measured by 2D echocardiographic guided linear measures was superior to EF in predicting mortality in patients with ATTR. When combined with SBP, eGFR, NYHA class, and health status score from the EQ-5D-3L, MCF remained an independent predictor of mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures: JR and DES have no conflicts of interest to report. MSM receives funding from an NIH K24 AG036778 Midcareer Mentoring Award in Geriatric Cardiology and he or his institution receives funding for research and serving on advisory boards and DSMBs from Pfizer Inc., Alnylam Pharmaceuticals Inc., GSK Inc., ISIS Pharmaceuticals and Prothena Inc. MLO and MC are employees of Pfizer and hold stock and/or stock options. Data for this manuscript are derived from the THAOS registry which is sponsored by Pfizer Inc.

References

- [1]. Westermarck P Aspects of the history and nomenclature of amyloid and amyloidosis In: D PM, A HG, A D, editors. *Amyloid and Related Disorders*. 2 ed. Switzerland: Humana Press; 2015 p. 3–8.
- [2]. Galant NJ, Westermarck P, Higaki JN, et al. Transthyretin amyloidosis: an under-recognized neuropathy and cardiomyopathy. *Clin Sci (Lond)* 2017;131:395–409. [PubMed: 28213611]
- [3]. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation*. 2009;120:1203–12. [PubMed: 19752327]
- [4]. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J*. 2012;164:222–8 e1. [PubMed: 22877808]
- [5]. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation*. 2005;112:2047–60. [PubMed: 16186440]
- [6]. King DL, El-Khoury Coffin L, Maurer MS. Myocardial contraction fraction: a volumetric index of myocardial shortening by freehand three-dimensional echocardiography. *J Am Coll Cardiol*. 2002;40:325–9. [PubMed: 12106939]
- [7]. Maurer MS, Koh WJ, Bartz TM, et al. Relation of the Myocardial Contraction Fraction, as Calculated from M-Mode Echocardiography, With Incident Heart Failure, Atherosclerotic Cardiovascular Disease and Mortality (Results from the Cardiovascular Health Study). *Am J Cardiol*. 2017;119:923–8. [PubMed: 28073429]
- [8]. Tendler A, Helmke S, Teruya S, et al. The myocardial contraction fraction is superior to ejection fraction in predicting survival in patients with AL cardiac amyloidosis. *Amyloid*. 2015;22:61–6. [PubMed: 25510353]
- [9]. Plante-Bordeneuve V, Suhr OB, Maurer MS, et al. The Transthyretin Amyloidosis Outcomes Survey (THAOS) registry: design and methodology. *Curr Med Res Opin*. 2013;29:77–84. [PubMed: 23193943]
- [10]. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–63. [PubMed: 16376782]
- [11]. de Simone G, Devereux RB, Ganau A, et al. Estimation of left ventricular chamber and stroke volume by limited M-mode echocardiography and validation by two-dimensional and Doppler echocardiography. *Am J Cardiol*. 1996;78:801–7. [PubMed: 8857486]

- [12]. Maurer MS, Burkhoff D, Fried LP, et al. Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2007;49:972–81. [PubMed: 17336721]
- [13]. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–8. [PubMed: 2936235]
- [14]. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358–67. [PubMed: 2698218]
- [15]. Scalone L, Ciampichini R, Fagioli S, et al. Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D 5L in patients with chronic hepatic diseases. *Qual Life Res*. 2013;22:1707–16. [PubMed: 23192232]
- [16]. Siepen FAD, Bauer R, Voss A, et al. Predictors of survival stratification in patients with wild-type cardiac amyloidosis. *Clin Res Cardiol*. 2018;107:158–69. [PubMed: 28956153]
- [17]. Austin BA, Duffy B, Tan C, et al. Comparison of functional status, electrocardiographic, and echocardiographic parameters to mortality in endomyocardial-biopsy proven cardiac amyloidosis. *Am J Cardiol*. 2009;103:1429–33. [PubMed: 19427441]
- [18]. Kristen AV, Perz JB, Schonland SO, et al. Non-invasive predictors of survival in cardiac amyloidosis. *Eur J Heart Fail*. 2007;9:617–24. [PubMed: 17350331]
- [19]. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2017.
- [20]. Kristen AV, Maurer MS, Rapezzi C, et al. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - Report from the Transthyretin Amyloidosis Outcome Survey (THAOS). *PLoS One*. 2017;12:e0173086. [PubMed: 28384285]
- [21]. L DY, W LJ, Y Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika*. 1993;80:557–72.
- [22]. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32–5. [PubMed: 15405679]
- [23]. Milani P, Dispenzieri A, Gertz M, et al. Myocardial Contraction Fraction, A New Echocardiographic Parameter for Prediction of Survival in Patients with Light-Chain Amyloidosis. *J Am Coll Cardiol*. 2016;67:1601.
- [24]. Matthews SD, Rubin J, Cohen LP, et al. Myocardial Contraction Fraction: A Volumetric Measure of Myocardial Shortening Analogous to Strain. *J Am Coll Cardiol*. 2018;71:255–6. [PubMed: 29325647]
- [25]. Arenja N, Riffel JH, Fritz T, et al. Diagnostic and Prognostic Value of Long-Axis Strain and Myocardial Contraction Fraction Using Standard Cardiovascular MR Imaging in Patients with Nonischemic Dilated Cardiomyopathies. *Radiology*. 2017;283:681–91. [PubMed: 28156200]
- [26]. Chuang ML, Gona P, Salton CJ, et al. Usefulness of the left ventricular myocardial contraction fraction in healthy men and women to predict cardiovascular morbidity and mortality. *Am J Cardiol*. 2012;109:1454–8. [PubMed: 22381161]
- [27]. Arenja N, Fritz T, Andre F, et al. Myocardial contraction fraction derived from cardiovascular magnetic resonance cine images-reference values and performance in patients with heart failure and left ventricular hypertrophy. *Eur Heart J Cardiovasc Imaging*. 2017;18:1414–22. [PubMed: 28165128]
- [28]. Pagourelas ED, Mirea O, Duchenne J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. *Circ Cardiovasc Imaging*. 2017;10:e005588. [PubMed: 28298286]
- [29]. Connors LH, Sam F, Skinner M, et al. Heart Failure Resulting From Age-Related Cardiac Amyloid Disease Associated With Wild-Type Transthyretin: A Prospective, Observational Cohort Study. *Circulation*. 2016;133:282–90. [PubMed: 26660282]
- [30]. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. *Circulation*. 2003;107:2446–52. [PubMed: 12743000]

- [31]. Koyama J, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. *JACC Cardiovasc Imaging*. 2010;3:333–42. [PubMed: 20394893]
- [32]. Buss SJ, Emami M, Mereles D, et al. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. *J Am Coll Cardiol*. 2012;60:1067–76. [PubMed: 22883634]
- [33]. Bellavia D, Pellikka PA, Al-Zahrani GB, et al. Independent predictors of survival in primary systemic (AL) amyloidosis, including cardiac biomarkers and left ventricular strain imaging: an observational cohort study. *J Am Soc Echocardiogr*. 2010;23:643–52. [PubMed: 20434879]
- [34]. Cappelli F, Porciani MC, Bergesio F, et al. Right ventricular function in AL amyloidosis: characteristics and prognostic implication. *Eur Heart J Cardiovasc Imaging*. 2012;13:416–22. [PubMed: 22180463]
- [35]. Bellavia D, Pellikka PA, Dispenzieri A, et al. Comparison of right ventricular longitudinal strain imaging, tricuspid annular plane systolic excursion, and cardiac biomarkers for early diagnosis of cardiac involvement and risk stratification in primary systematic (AL) amyloidosis: a 5-year cohort study. *Eur Heart J Cardiovasc Imaging*. 2012;13:680–9. [PubMed: 22307866]
- [36]. Maurer MS, Hanna M, Grogan M, et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161–72. [PubMed: 27386769]
- [37]. Kristen AV, Brokbal E, Aus dem Siepen F, et al. Cardiac Amyloid Load: A Prognostic and Predictive Biomarker in Patients With Light-Chain Amyloidosis. *J Am Coll Cardiol*. 2016;68:13–24. [PubMed: 27364045]
- [38]. Lee TT, Chen J, Cohen DJ, et al. The association between blood pressure and mortality in patients with heart failure. *Am Heart J*. 2006;151:76–83. [PubMed: 16368295]
- [39]. Tsimploulis A, Lam PH, Arundel C, et al. Systolic Blood Pressure and Outcomes in Patients With Heart Failure With Preserved Ejection Fraction. *JAMA Cardiol*. 2018.
- [40]. Shah KB, Mankad AK, Castano A, et al. Transthyretin Cardiac Amyloidosis in Black Americans. *Circ Heart Fail*. 2016;9:e002558. [PubMed: 27188913]
- [41]. Hoekstra T, Jaarsma T, van Veldhuisen DJ, et al. Quality of life and survival in patients with heart failure. *Eur J Heart Fail*. 2013;15:94–102. [PubMed: 22989869]
- [42]. Rodriguez-Artalejo F, Guallar-Castillon P, Pascual CR, et al. Health-related quality of life as a predictor of hospital readmission and death among patients with heart failure. *Arch Intern Med*. 2005;165:1274–9. [PubMed: 15956007]
- [43]. Ramos S, Prata J, Rocha-Goncalves F, et al. Quality of Life Predicts Survival and Hospitalisation in a Heart Failure Portuguese Population. *Applied Research Quality of Life*. 2017;12.
- [44]. Jesky MD, Dutton M, Dasgupta I, et al. Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. *PLoS One*. 2016;11:e0165675. [PubMed: 27832126]
- [45]. Mathews WC, May S. EuroQol (EQ-5D) measure of quality of life predicts mortality, emergency department utilization, and hospital discharge rates in HIV-infected adults under care. *Health Qual Life Outcomes*. 2007;5:5. [PubMed: 17254361]
- [46]. Ahmed A, Aronow WS, Fleg JL. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *Am Heart J*. 2006;151:444–50. [PubMed: 16442912]
- [47]. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527–39. [PubMed: 19007588]
- [48]. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation*. 2012;126:1286–300. [PubMed: 22949539]
- [49]. Westermarck P, Bergstrom J, Solomon A, et al. Transthyretin-derived senile systemic amyloidosis: clinicopathologic and structural considerations. *Amyloid*. 2003;10 Suppl 1:48–54. [PubMed: 14640042]
- [50]. Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. *Clin J Am Soc Nephrol*. 2012;7:1337–46. [PubMed: 22537653]
- [51]. Lobato L Portuguese-type amyloidosis (transthyretin amyloidosis, ATTR V30M). *J Nephrol*. 2003;16:438–42. [PubMed: 12832749]

- [52]. Ford WR, Menon V, Bhambhani A, et al. Changes in myocardial density during postinfarction healing: effect on estimation of in vivo left ventricular mass by echocardiographic imaging. *Can J Physiol Pharmacol.* 1997;75:1075–82. [PubMed: 9365816]
- [53]. Mohty D, Boulogne C, Magne J, et al. Prognostic value of left atrial function in systemic light-chain amyloidosis: a cardiac magnetic resonance study. *Eur Heart J Cardiovasc Imaging.* 2016;17:961–9. [PubMed: 27194782]
- [54]. Cueto-Garcia L, Reeder GS, Kyle RA, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. *J Am Coll Cardiol.* 1985;6:737–43. [PubMed: 4031287]

Highlights

- Myocardial contraction fraction predicts mortality in transthyretin amyloidosis.
- Ejection fraction does not independently predict mortality in this disease.
- Net reclassification for mortality by myocardial contraction vs. EF was 52%.
- NYHA Class, GFR, systolic blood pressure, health status also predicted mortality.

Figure 1.
Kaplan-Meier survival curve for subjects with MCF above and below 25%

Table 1.

Clinical, Functional, Laboratory, and Cardiac Testing data at enrollment

	Target Population			Alive		Dead	p-value
	N		n		n		
Clinical							
Age							
At enrollment, y	530	60.7 ± 16.3	440	59.3 ± 16.5	90	68.0 ± 12.9	<.0001
50y, n(%)	530	389 (73)	440	308 (70)	90	81 (90)	<.0001
At diagnosis, y	435	58.4 ± 17.6	372	57.2 ± 18.1	63	65.9 ± 12.1	<.0001
Male, n (%)	530	391 (74)	440	317 (72)	90	74 (82)	0.0455
Race/Ethnicity, n (%)	476		386		90		0.0897
Caucasian		405 (85)		333 (8)		72 (18)	
African descent		30 (6)		19 (63)		11 (37)	
Latin American		24 (5)		21 (88)		3 (13)	
Asian		7 (1)		6 (86)		1 (14)	
Other		10 (2)		7 (70)		3 (30)	
Heart rate, bpm	434	74 ± 12	364	74 ± 120	70	75 ± 13	0.4950
Systolic blood pressure, mmHg	511	121 ± 19	423	122 ± 19	88	114 ± 17	<.0001
CTS, n (%)	446	138 (31)	385	120 (31)	61	18 (30)	0.7943
Mutation	530		440		90		0.0014
Wild type		158 (30)		122 (23)		36 (7)	
Cardiac-amyloid mutation		75 (14)		56 (11)		19 (4)	
Val122Ile		31 (6)		21 (4)		10 (2)	
Ile68Leu		15 (3)		13 (2)		2 (<1)	
Thr60Ala		15 (3)		13 (2)		2 (<1)	
Leu11Met		2 (<1)		1 (<1)		1 (<1)	
Val20Ile		12 (2)		8 (2)		4 (<1)	
All other mutations		297 (56)		262 (49)		35(7)	
Functional							
NYHA Class	524		436		88		<.0001
No Heart Failure		258 (49)		235 (54)		23 (26)	
Class I		29 (6)		28 (6)		1 (1)	
Class II		123 (23)		94 (22)		29 (33)	
Class III		102 (19)		71 (16)		31 (35)	
Class IV		12 (2)		8 (2)		4 (5)	
EQ-5D-3L Score (-0.11 – 1.0)	399	0.77 ± 0.19	346	0.78 ± 0.18	53	0.67 ± 0.23	0.0012
Hospitalizations							
Any	530	121 (23)	440	75 (17)	90	46 (51)	<.0001
Cardiac	530	76 (14)	440	47 (11)	90	29 (32)	<.0001
Laboratory							
eGFR, mL/min/m²	410	89 ± 199	333	96 ± 220	77	59 ± 29	0.0035
BNP	96	734 ± 1961	74	459 ± 1445	22	1659 ± 2999	0.0820

	Target Population		Alive		Dead		p-value
	N		n		n		
NT-pro-BNP	246	6503 ± 25342	208	5084 ± 23009	38	14272 ± 34892	0.1255
<i>Cardiac Testing</i>							
Atrial fibrillation	145	78 (54)	110	59 (54)	35	19 (54)	0.9465
Left atrial size, cm	472	42.2 ± 9.6	392	41.5 ± 9.7	80	45.6 ± 798	<.0001
Low voltage, n (%)	387	83 (22)	328	68 (21)	59	15 (25)	0.4189
Relative wall thickness	530	0.62 ± 0.24	440	0.60 ± 0.23	90	0.76 ± 0.26	<.0001
Fractional wall shortening	530	31.7 ± 11.4	440	32.7 ± 11.1	90	26.9 ± 11.3	<.0001
LVESD, cm	530	30.8 ± 6.4	440	30.6 ± 6.2	90	31.8 ± 7.4	0.1327
LVEDD, cm	530	45.2 ± 6.1	440	45.5 ± 6.0	90	43.4 ± 6.5	0.0033
IVST, cm	511	15.3 ± 4.9	423	14.8 ± 4.9	88	17.6 ± 4.4	<.0001
Posterior wall thickness, cm	530	13.7 ± 4.3	440	13.2 ± 4.1	90	16.0 ± 4.2	<.0001
LV mass, g	530	276 ± 124	440	266 ± 121	90	326 ± 125	<.0001
LV mass index, g/m²	506	147 ± 63	423	141 ± 60	83	179 ± 66	<.0001
EDV, mL	530	93 ± 25	440	95 ± 25	90	87 ± 27	0.0058
ESV, mL	530	37 ± 16	440	36 ± 15	90	40 ± 19	0.0994
SV, mL	530	57 ± 20	440	59 ± 20	90	47 ± 17	<.0001
MV, mL	530	265 ± 119	440	255 ± 116	90	313 ± 120	<.0001
EF	530	60.4 ± 13.0	440	61.5 ± 12.7	90	4 54.8 ± 13.5	<.0001
MCF	530	27.1 ± 16.1	440	28.9 ± 16.9	90	18.1 ± 11.9	<.0001

Results are expressed as mean ± standard deviation where applicable. p values calculated for subjects that lived versus died. eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; CTS, carpal tunnel syndrome; BNP, brain natriuretic peptide; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; IVST, interventricular septal thickness; LV, left ventricular; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; MV, myocardial volume; EF, ejection fraction; MCF, myocardial contraction fraction

Table 2.

Univariate and Multivariate Analyses to Assess Risk of Death

	Univariate Analysis			Multivariate Analysis*		
	Hazard Ratio	95% Confidence Interval	P-Value	Hazard Ratio	95% Confidence Interval	P-Value
Age at enrollment (per year)	1.06	1.04 - 1.07	<.0001			
Age 50 vs < 50 years	8.04	4.0 - 16.1	<.0001			
Male gender	2.49	1.5 - 4.3	0.0010			
Systolic blood pressure (per mmHg)	.97	0.95 - 0.98	<.0001	0.977	0.956 – 0.998	0.035
Wild type ATTR vs Other	3.97	2.5 - 6.4	<.0001			
Cardiac-Mutant type ATTR vs Other	2.83	1.6 - 5.0	0.0003			
NYHA class (per class)	2.11	1.8 - 2.5	<.0001	1.665	1.191 – 2.327	0.0029
EQ-5D-3L score (per 0.1 unit)	.05	0.014 - 0.16	<.0001	0.758	0.658 – 0.874	0.0001
eGFR (<65 vs 65 ml/min/m ²)	4.59	2.8 - 7.4	<.0001	3.169	1.516 – 6.625	0.0022
EF (<50 vs 50)	2.78	1.77 - 4.37	<.0001			
MCF (<25 vs 25)	8.46	4.8 - 14.9	<.0001	5.369	1.817 – 15.86	0.0024

* Variables included in the step-wise multivariate Cox regression model were: Age at enrollment (above and below 50), gender, race, mutation (wild type, cardiac, all other mutations), systolic blood pressure, eGFR (above and below 65), NYHA class, EQ-5D-3L score, EF (above and below 50), MCF (above and below 25). ATTR, transthyretin; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; EF, ejection fraction; MCF, myocardial contraction fraction.