Heart failure from ATTRwt amyloid cardiomyopathy is associated with poor prognosis

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Abstract

Aims Amyloid cardiomyopathy is an underappreciated cause of morbidity and mortality. Recent evidence suggests that ATTR wild-type cardiomyopathy (ATTRwt-CM) is probably much more common than widely appreciated. So far, no data are available on comparison of mortality from ATTRwt-CM and other heart failure aetiologies.

Methods and results This was a retrospective, observational, cohort study of 2251 patients and their data collected prospectively from May 2016 to June 2018. Long-term mortality was the main outcome measure. Underlying cardiomyopathies were classified as amyloid CM (6.1%) [ATTRwt 3.0%; light-chain amyloidosis (AL) 3.1%], dilated CM (dCMP) (46.4%), ischaemic heart disease (IHD) (24.4%), hypertensive heart disease (HHD) (14.6%), hypertrophic CM (HCM) (5.1%), and valvular heart disease (VHD) (3.4%). Median duration of follow-up was 7.1 years (interquartile range 3.4–11.3). Five-year overall survival in the whole cohort was 80.1%. In multivariate analysis, individuals with amyloid CM were 3.74 times [95% confidence interval (CI) 2.72–5.14; P < 0.001] more likely to die of any reason than were individuals with dCMP. Mortality was higher in AL-CM compared with ATTRwt-CM [hazard ratio (HR) 2.88; 95% CI 1.48–5.58; P = 0.002]. Mortality rates in patients with ATTRwt-CM were higher than in patients with dCMP (HR 1.96; 95% CI 1.24–3.22; P = 0.007), HCM (HR 2.94; 95% CI 1.28–6.67; P = 0.011), HHD (HR 2.08; 95% CI 1.27–3.45; P = 0.004), VHD (HR 2.38; 95% CI 1.30–4.35; P = 0.005), or left ventricular ejection fraction ≥40% (HR 1.99; 95% CI 1.12–3.52; P = 0.018).

Conclusions Our study demonstrates that amyloid CM is independently associated with various causes of heart failure. ATTRwt-CM had a better long-term prognosis than did AL-CM, but was associated with higher mortality than were dCMP, HCM, HHD, or left ventricular ejection fraction.

Keywords Cardiac amyloidosis; ATTRwt; Prognosis; Cardiomyopathy

Introduction

Amyloidotic cardiomyopathy (CM) is caused by infiltration of the myocardium with extracellular deposited amyloid fibrils resulting from misfolding of various precursor proteins. Acquired monoclonal immunoglobulin light-chain amyloidosis (AL), the hereditary, transthyretin (TTR)-related form (ATTRm), and wild-type (non-mutant) TTR-related amyloidosis (ATTRwt) systemic ‘senile’ amyloidosis account for more than 90% of all amyloid CMs. The principal manifestation of amyloid CM is heart failure with preserved (HFrEF) or mid-range ejection fraction (HfMR EF). Heart failure with reduced ejection fraction may occur in the late stages of the disease. Although widely underappreciated by clinicians, TTR amyloid CM is the most common cause of the infiltrative form of restricted CM. TTR amyloid CM (ATTR-CM) in...
general and ATTRwt in particular have come into focus over the last years, mostly for two reasons: first, recent evidence suggests that ATTRwt is probably much more common than widely recognized. ATTR was evident in patients with HFpEF and in elderly patients with aortic stenosis. In Finland, ATTR was found in 25% of autopsies in very old persons, giving rise to the suspicion that ATTRwt could be the most frequent form of amyloid CM. Second, the recent emergence of novel therapeutics such as tafamidis, which act to prevent transthyretin amyloid formation, and other agents that inhibit transthyretin expression may substantially improve treatment of ATTR-CM that was hitherto limited largely to supportive care. Cardiac involvement in amyloidosis confers significant morbidity and mortality. This, however, is frequently attributed to rapid progression of AL-CM despite substantial improvements in light chain-reducing therapies for AL-CM during the last two decades. ATTR-CM patients have a better prognosis than do AL amyloid patients despite the fact that ATTR presents with thicker myocardial walls. This paradox is thought to be essentially due to the toxicity of circulating free light chains in AL.

A major limitation observed in the previously published literature is the fact that although a difference in prognosis between AL and ATTR patients was repeatedly shown, no data are available that would put long-term outcomes of amyloid subtypes in context with other heart failure aetiologies. This, however, would allow more adequate appreciation of the importance of amyloid CM and in particular ATTRwt among clinicians.

It was the primary aim of this comprehensive retrospective study (i) to provide data on disease progression in patients with cardiac AL and TTRwt-CM and (ii) to compare this with the natural course of most frequent heart failure aetiologies.

Methods

The study cohort consisted of consecutive Caucasian patients, who were seen between May 2000 and June 2018 at a tertiary (Cardiology Department, Medical University of Innsbruck) centre. Thirty-six patients with cardiac amyloidosis were contributed by a secondary centre (Cardiology Department, Ordensklinikum Elisabethinen Linz). A comprehensive baseline assessment was performed in all patients at the time of first presentation including initial clinical evaluation and follow-up as well as laboratory, electrocardiographic, and echocardiographic parameters. Informed consent was waived due to the retrospective nature of the trial. The study was approved by the Ethics Committee of the Medical University of Innsbruck (UN4280, session number 298/4.11).

Diagnostic definitions

Diagnosis of systemic amyloidosis was defined by histological documentation of Congo Red staining and apple-green birefringence under cross-polarized light in at least one involved organ. Cardiac amyloidosis was diagnosed either by means of endomyocardial biopsy, cardiac imaging [echocardiography, cardiac magnetic resonance (CMR) or 99mTC-3,3'-diphosphono-1,2-propanodicarboxyl acid (99mTC-DPD) scintigraphy] and/or by elevation of biomarkers [N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin T] in patients with a positive result of non-cardiac biopsy.

Diagnosis of ATTRwt was defined by positive immunohistochemistry for TTR in the absence of any TTR mutation and of AL by the presence of monoclonal plasma cells in the bone marrow.

Dilated CM (dCMP) was defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment. Right ventricular dilatation and dysfunction may have been present, but were not necessary for diagnosis.

Hypertrophic CM (HCM) was diagnosed by the presence of myocardial hypertrophy in the absence of haemodynamic stress sufficient to account for the degree of hypertrophy and systemic diseases such as amyloidosis or glycogen storage disease. Genetic testing was performed in most but not all patients.

Ischaemic CM [ischaemic heart disease (IHD)] was defined by the presence of any history of myocardial infarction or coronary revascularization or multivessel coronary disease (≥75% stenosis of two or more epicardial vessels) or single-vessel coronary disease with ≥75% stenosis of the left main or proximal left anterior descending artery. Inclusion in the study was limited to patients with left ventricular ejection fraction (LV-EF) < 40% unless severe symptoms of heart failure were present.

Hypertensive heart disease (HHD) was defined as a structural cardiac disorder accompanied by concentric left ventricular hypertrophy associated with diastolic or systolic dysfunction in patients with persistent systemic hypertension and in the absence of other cardiac diseases capable of causing myocardial hypertrophy or cardiac dysfunction.

Valvular CM [valvular heart disease (VHD)] was defined as a structural cardiac disorder caused by congenital or acquired moderate–severe or severe dysfunction of one or more cardiac valves. Patients with severe functional mitral or tricuspid regurgitation were not considered.

Follow-up

Information on vital status was retrieved from next-of-kin interviews, reviews of hospital discharge summaries, and a
search of the National Death Index (Statistics Austria). Follow-up was closed in December 2018, so that each patient was followed for at least 6 months.

**Statistical analysis**

Continuous data were tested for normal distribution using the Kolmogorov–Smirnov test. Categorical variables are presented as percentage (%) and continuous variables as mean [standard deviation (SD)] or median (25th and 75th percentile). Between-group comparisons were performed with ANOVA, Kruskal–Wallis, or Pearson’s \( \chi^2 \) test, as appropriate.

Survival analysis was performed with all-cause mortality as the endpoint. Time of survival was defined from inclusion into database until death or last follow-up. Patients were censored on 30 June 2018. Univariate survival analysis was conducted using the Kaplan–Meier method including the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by Cox regression analysis. Multivariate Cox regression models were established adjusting for age, sex, New York Heart Association (NYHA) class, LV-EF, and NT-proBNP.

A two-sided \( P \) value of 0.05 was considered statistically significant. All calculations were performed using the SPSS statistical package, version 23.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Enrolment**

A total of 2251 consecutive patients were enrolled after four patients with ATTRm-CM were excluded from analysis. The most common diagnosis was dCMP (\( n = 1,044, 46.4\% \)), followed by IHD (\( n = 550, 24.4\% \)), HHD (\( n = 329, 14.6\% \)), amyloid CM (\( n = 137, 6.1\% \)), HCM (\( n = 114, 5.1\% \)), and VHD (\( n = 77, 3.4\% \)). Baseline characteristics for the total cohort and for AL-CM and ATTRwt-CM in particular are shown in Table 1A and 1B, respectively. Patients with ATTRwt-CM were included before tafamidis was available in Austria, whereas AL-CM patients had access to a broad therapeutic armamentarium including autologous stem cell transplantation, if applicable. Diagnosis of CM/heart disease was based on echocardiography, coronary angiography, right heart catheterization, CMR imaging, and endomyocardial biopsy in 100%, 80.9%, 54.3%, 23.4%, and 28.7% of patients, respectively. 99mTc-DPD scintigraphy was performed in 27.1% of patients with amyloid CM, as this technique was not available at our institution before 2016. There was a male predominance (72.1%) in the entire cohort. Mean age at enrolment was 57.5 ± 14.6 years and differed significantly between CMs (\( P < 0.001 \)). Age was highest in amyloid CM (68.7 ± 10.8 years), mostly because of ATTRwt-CM (74.6 ± 6.9 years).

**Association between cause and all-cause mortality**

Overall, 17 201 patient years of follow-up were registered. Median follow-up for the total cohort was 7.1 years (interquartile range 3.4–11.3). After censoring follow-up, 764 (33.9%) of all patients met the endpoint of all-cause mortality. In the total cohort, the unadjusted 5-year mortality rate was 29.9%. Unadjusted 5-year mortality rates for amyloid CM, dCMP, HCM, IHD, HHD, and VHD were 58.7%, 12.9%, 6.8%, 28.2%, 18.0%, and 22.7%, respectively.

Unadjusted and adjusted HRs for all-cause mortality for each aetiological group, as compared with the group with dCMP (in which the HR for death was 1.0, by definition), are provided in a supplementary table. In the unadjusted analysis, survival was more favourable among patients with HCM than among those with dCMP. In contrast, survival was significantly poorer among patients with IHD, HHD, and amyloid CM, whereas survival among patients with VHD did not differ significantly from that in patients with dCMP.

In multivariate Cox proportional hazards analysis adjusting for age, gender, NYHA functional class, and LV-EF, only amyloid CM (HR 3.74; 95% CI 2.72–5.14; \( P < 0.001 \)) and IHD (HR 1.33; 95% CI 1.11–1.59; \( P = 0.002 \)) remained significantly associated with inferior survival (Supporting Information, Figure 1A). Results remained robust when atrial fibrillation, heart rate, mean blood pressure, haemoglobin, and estimated glomerular filtration rate as additional co-variates were added in a second model, which included 2118 patients, and NT-proBNP as another co-variate was added in a third model with 1497 patients (Supporting Information, Table 12). When defining dCMP as the reference (i.e. HR 1), survival was significantly poorer for amyloid CM in all models (Model 1: HR 3.74, 95% CI 2.72–5.14, \( P < 0.001 \); Model 2: HR 2.74, 95% CI 1.62–3.76, \( P < 0.001 \); Model 3: HR 4.35, 95% CI 3.02–6.28, \( P < 0.001 \)).

**All-cause mortality in ATTRwt-CM versus AL-CM**

A higher male prevalence was observed for patients with ATTRwt-CM than for AL-CM patients (86.8% vs. 59.4%). Patients with ATTRwt-CM were older (mean age 74.6 ± 63 years), had a higher prevalence of atrial fibrillation (42.6% vs. 10.1%) and conduction disorders (bundle branch block 30.9% vs. 10.1%, atrioventricular block 32.4% vs. 13.4%), and higher mean arterial pressure (91.6 vs. 84.7 mmHg). Conversely, severity of heart failure was less severe according to NYHA functional class and NT-proBNP levels (4497.7 vs. 6684.9 ng/L) (Table 1B).
Table 1A: Characteristics of the entire study cohort

|                                | Total cohort | Amyloid CM (n = 137) | dCMP (n = 1044) | HCM (n = 114) | IHD (n = 550) | HHD (n = 329) | VHD (n = 77) | P value |
|--------------------------------|--------------|----------------------|-----------------|---------------|---------------|---------------|--------------|---------|
| Demographics                  |              |                      |                 |               |               |               |             |         |
| sex (male)                    | 1622 (72.1)  | 100 (73.0)           | 720 (69.0)      | 64 (56.1)     | 444 (80.7)    | 235 (71.4)    | 59 (76.6)    | <0.001  |
| age (years)                   | 57.5 (14.6)  | 68.7 (10.8)          | 51.3 (15.0)     | 52.3 (15.2)   | 63.3 (10.4)   | 63.6 (10.8)   | 60.1 (12.6)  | <0.001  |
| BMI (kg/m²)                   | 26.0 (4.5)   | 24.9 (3.9)           | 25.6 (4.5)      | 26.6 (5.5)    | 26.2 (3.9)    | 27.7 (4.7)    | 25.2 (4.0)   | <0.001  |
| Diagnosis of CMP              |              |                      |                 |               |               |               |             |         |
| echocardiography              | 2251 (100)   | 137 (100)            | 1044 (100)      | 114 (100)     | 550 (100)     | 329 (100)     | 77 (100)     | <0.001  |
| coronary angiography          | 1822 (80.9)  | 112 (81.8)           | 845 (80.9)      | 65 (57.0)     | 490 (89.1)    | 233 (70.8)    | 77 (100)     | <0.001  |
| right heart catheterization   | 1222 (54.3)  | 108 (78.8)           | 670 (64.2)      | 49 (43.0)     | 211 (38.9)    | 108 (32.8)    | 76 (98.7)    | <0.001  |
| cardiac MRI                   | 526 (23.4)   | 101 (73.7)           | 299 (28.1)      | 63 (55.3)     | 29 (5.3)      | 33 (10.0)     | 1 (1.3)      | <0.001  |
| endomyocardial biopsy         | 647 (28.7)   | 116 (84.7)           | 466 (44.6)      | 15 (13.2)     | 18 (3.3)      | 27 (8.2)      | 5 (6.5)      | <0.001  |
| Cardiac characteristics       |              |                      |                 |               |               |               |             |         |
| NYHA functional class         |              |                      |                 |               |               |               |             | <0.001  |
| class I                      | 607 (27.0)   | 20 (14.6)            | 342 (32.8)      | 43 (37.7)     | 83 (15.1)     | 105 (31.9)    | 14 (18.2)    |         |
| class II                     | 974 (43.3)   | 57 (41.6)            | 438 (42.0)      | 40 (35.1)     | 253 (46.0)    | 157 (47.7)    | 29 (37.7)    |         |
| class III/IV                 | 670 (29.8)   | 60 (43.8)            | 264 (25.3)      | 31 (27.2)     | 214 (38.9)    | 67 (20.4)     | 34 (44.2)    |         |
| LV-EF                        | 34.4 (15.1)  | 50.4 (11.4)          | 32.9 (14.8)     | 57.6 (13.5)   | 28.4 (10.0)   | 34.3 (13.4)   | 34.3 (13.5)  | <0.001  |
| >50%                         | 444 (19.7)   | 84 (61.3)            | 179 (17.1)      | 89 (78.1)     | 24 (4.4)      | 53 (16.1)     | 15 (19.5)    | <0.001  |
| 40-49%                       | 279 (12.4)   | 31 (22.6)            | 136 (13.0)      | 10 (8.8)      | 48 (8.7)      | 48 (14.6)     | 6 (7.8)      |         |
| <40%                         | 1,528 (67.9) | 22 (16.1)            | 729 (69.8)      | 15 (13.2)     | 478 (86.9)    | 228 (69.3)    | 56 (72.7)    |         |
| atrial fibrillation           | 428 (19.0)   | 36 (26.3)            | 181 (17.3)      | 11 (9.6)      | 84 (15.3)     | 91 (27.7)     | 25 (32.5)    | <0.001  |
| bundle branch block           | 532 (23.2)   | 28 (26.7)            | 251 (24.0)      | 11 (9.6)      | 131 (23.8)    | 80 (24.3)     | 22 (28.6)    | 0.015   |
| heart rate (bpm)              | 76.1 (6.5)   | 76.4 (12.2)          | 78.0 (17.6)     | 70.0 (13.9)   | 74.0 (14.6)   | 75.5 (17.1)   | 77.6 (17.1)  | <0.001  |
| Mean BP (mmHg)                | 93.8 (14.8)  | 88.1 (13.6)          | 92.1 (13.6)     | 94.5 (14.6)   | 92.7 (14.1)   | 103.7 (16.1)  | 90.4 (13.2)  | <0.001  |
| Laboratory parameters         |              |                      |                 |               |               |               |             |         |
| NT-proBNP (ng/L)              | 1409 (410–3311) | 3581 (2056–6801) | 1026 (208–2816) | 788 (208–1916) | 1702 (846–3814) | 1072 (401–2491) | 2481 (675–4766) | <0.001  |
| eGFR (ml/min)                 | 74.0 (34.4)  | 62.6 (23.3)          | 80.5 (40.6)     | 75.3 (26.4)   | 66.6 (24.7)   | 71.2 (29.3)   | 69.7 (24.6)   | <0.001  |
| Haemoglobin (G/L)             | 141.9 (17.7) | 132.7 (15.9)         | 143.9 (17.6)    | 143.6 (16.0)  | 140.0 (17.8)  | 143.3 (16.6)  | 138.6 (20.5)  | <0.001  |

AL-CM, AL cardiomyopathy; amyloid CM, amyloid cardiomyopathy; ATTRwt-CM, ATTR wild-type cardiomyopathy; BP, blood pressure; dCMP, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischaemic heart disease; LV-EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VHD, valvular heart disease.

Data from 2251 (1a) and 137 (1b) patients are reported as mean (standard deviation), or median (interquartile range), or number (percentage) related to various heart failure aetiologies.

*NT-proBNP was available in 1571 patients.
Table 1B: Characteristics of patients with amyloid cardiomyopathy

|                                      | ATTRwt-CM (n = 68) | AL-CM (n = 69) | P value |
|--------------------------------------|---------------------|----------------|---------|
| Demographics                         |                     |                |         |
| Sex (male)                           | 59 (86.8)           | 41 (59.4)      | <0.001  |
| Age (years)                          | 74.6 (6.9)          | 63.0 (10.9)    | <0.001  |
| BMI (kg/m²)                          | 25.8 (3.5)          | 24.1 (4.1)     | 0.009   |
| Diagnosis of CMP                     |                     |                |         |
| Echocardiography                     | 68 (100)            | 69 (100)       |         |
| Coronary angiography                 | 57 (83.8)           | 55 (79.7)      | 0.533   |
| Right heart catheterization          | 54 (79.4)           | 54 (78.3)      | 0.869   |
| Cardiac MRI                          | 51 (75.0)           | 50 (72.5)      | 0.736   |
| DPD-TC scintigraphy                 | 27 (42•7)           | 7 (10.4)       | <0.001  |
| Endomyocardial biopsy                | 58 (58.3)           | 58 (84.1)      | 0.841   |
| Cardiac characteristics              |                     |                |         |
| NYHA functional class                |                     |                |         |
| I                                    | 12 (17.6)           | 8 (11.6)       |         |
| II                                   | 34 (50.0)           | 23 (33.3)      |         |
| III/IV                               | 22 (32.4)           | 38 (55.1)      |         |
| LV-EF                                | 49.0 (10.8)         | 51.7 (11.9)    | 0.176   |
| >50%                                 | 38 (55.9)           | 46 (66.7)      | 0.418   |
| 40–49%                               | 18 (26.5)           | 13 (18.8)      |         |
| <40%                                 | 12 (13.2)           | 10 (14.5)      |         |
| Atrial fibrillation                  | 29 (42.6)           | 7 (10.1)       | <0.001  |
| AV block                             | 22 (36.7)           | 9 (13.6)       | 0.003   |
| Bundle branch block                  | 21 (47.7)           | 7 (11.5)       | <0.001  |
| Heart rate (bpm)                     | 72.6 (11.8)         | 79.3 (11.7)    | 0.005   |
| Mean BP (mmHg)                       | 91.6 (12.7)         | 84.7 (13.6)    | 0.003   |
| Laboratory parameters               |                     |                |         |
| NT-proBNP (ng/L)³                    | 3311 (2075–3311)    | 4442 (2037–8030) | 0.201 |
| eGFR (mL/min)                        | 59.6 (17.1)         | 65.6 (27.9)    | 0.133   |
| Haemoglobin (G/L)                    | 135.0 (12.5)        | 131.2 (17.8)   | 0.170   |

AL-CM, AL cardiomyopathy; ATTRwt-CM, ATTR wild-type cardiomyopathy; BP, blood pressure; eGFR, estimated glomerular filtration rate; LV-EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

³NT-proBNP was available in 132 patients.

Median survival from baseline by Kaplan–Meier analysis was 51 months (95% CI 19.4–110.5 months) for ATTRwt-CM and 25.7 months (95% CI 8.9–42.5 months) for AL-CM. Multivariate Cox regression analysis showed that individuals with AL-CM were 2.88 times (95% CI 1.48–5.58; P = 0.002) more likely to die than were patients with ATTRwt-CM. This difference was independent of age, gender, NYHA functional class, and LV-EF.

All-cause mortality in ATTRwt-CM versus other aetiologies

Unadjusted 24-month, 30-month, 36-month, and 60-month mortality rates for ATTRwt-CM were 15.9%, 22.4%, 28.6%, and 48.1%, respectively. ATTRwt-CM was independently associated with poor prognosis in univariate analysis and various multivariate models when dCMP was defined as the reference (Table 2). Conversely, when ATTRwt-CM was defined as the reference (i.e. HR 1), univariate Cox regression analysis showed that mortality in patients with ATTRwt-CM was significantly higher than in patients with dCMP (HR 4.00; 95% CI 2.50–6.25; P < 0.001), HCM (HR 8.33; 95% CI 3.57–20.00; P < 0.001), IHD (HR 1.82; 95% CI 1.15–2.94; P = 0.012), HHD (HR 2.86; 95% CI 1.72–4.54; P < 0.001), or VHD (HR 3.03; 95% CI 1.69–5.56; P < 0.001) (Figure 2). After adjusting for age, gender, NYHA functional class, and LV-EF in a multivariate model, results remained robust when ATTRwt-CM was compared with other aetiologies (HR 5.09; 95% CI 2.96–8.65; P < 0.001). In this model, differences in death rate did not reach statistical significance when ATTRwt was compared with IHD (HR 1.51; 95% CI 0.93–2.44; P = 0.101) (Table 3).

All-cause mortality in ATTRwt-CM versus HfPef/HfMrEF

Unadjusted 5-year mortality rate in 608 CM patients with an LV-EF ≥ 40% without amyloid CM was 11.4%. In univariate analyses, patients with ATTRwt-CM were 4.54 times (95% CI 2.76–7.49; P < 0.001) (Figure 2) more likely to die than were individuals with an LV-EF ≥ 40%. Results remained robust in multivariate analysis adjusted for age, gender, and NYHA functional class (HR 1.99; 95% CI 1.12–3.52; P = 0.018).
Discussion

This study describes a well-characterized cohort of patients with various forms of CMs including cardiac amyloidosis and patients with specific heart diseases. Our study shows that amyloid CM confers the worst prognosis among various aetiologies of heart failure. Although survival with ATTRwt-CM is better than with AL-CM, the natural course of patients with ATTRwt-CM is still less favourable than that of patients with other forms of CMs, specific heart diseases, or HFpEF/HFmrEF. 

Although prognosis in CM has improved over the last years, survival for amyloid CM has been notoriously poor.\textsuperscript{6,24} Five-year mortality rate in our cohort was 58.7% for patients with amyloid CM, irrespective of the underlying subtype. Compared with other aetiologies, patients with amyloid CM were older, in a more advanced stage of heart failure, and had more co-morbidities at the time of diagnosis, which is fairly common as there is often a delay in diagnosis of this condition. Mortality in amyloid CM was significantly poorer, even in multivariate analysis that included a large number of confounders, than in patients with IHD, which is the leading cause of heart failure with reduced ejection fraction. Separate analysis of AL and ATTRwt-CM revealed significantly poorer survival in AL-CM than in ATTRwt-CM. This is well in line with previous studies in patients with amyloid CM.\textsuperscript{1,6,13,14} Our 30-month mortality rate of 22.4% in patients with ATTRwt, who were entirely recruited in the pre-tafamidis area, corroborates grossly with the number reported for the placebo group in the recently published ATTR-ACT study.\textsuperscript{10} Also, median survival rate of 51 months was in the range of recently published cohorts of ATTR-CM.\textsuperscript{25,26} Notably, there was a strong signal for unfavourable disease progression in ATTRwt-CM as compared with all other aetiologies. Differences in death rates between ATTRwt-CM and dCMP, HCM, HHD, as well as VHD were obvious irrespective of age, gender, NYHA functional class, and LV-EF, but were not significant when compared with...
Table 2 Univariate and multivariate Cox regression analysis of all-cause mortality for the entire cohort

| Variables | Unadjusted analysis (n = 2251) | Multivariate analysis Model 1 (n = 2251) | Multivariate analysis Model 2 (n = 2118) | Multivariate analysis Model 3 (n = 1497) |
|-----------|---------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|
|           | Hazard ratio for death (95% CI) | P value                                   | Hazard ratio for death (95% CI)           | Hazard ratio for death (95% CI)           | Hazard ratio for death (95% CI)           |
| dCMP      | 0.48 (0.23–0.97)                | 0.042                                     | 0.2280.79 (0.37–1.71)                    | 0.550.76 (0.33–1.75)                     | 0.519                                     |
| HCM       |                                 |                                           |                                           |                                           |                                           |
| IHD       | 2.17 (1.83–2.56)                | <0.001                                    | 0.0021.34 (1.12–1.61)                    | 0.0021.34 (1.06–1.70)                    | 0.014                                     |
| HHD       | 1.40 (1.13–1.74)                | 0.002                                     | 0.6870.98 (0.78–1.23)                    | 0.8260.92 (0.68–1.25)                    | 0.599                                     |
| VHD       | 1.29 (0.87–1.90)                | 0.206                                     | 0.8330.83 (0.56–1.24)                    | 0.3471.09 (0.67–1.80)                    | 0.726                                     |
| AL-CM     | 7.71 (5.60–10.62)               | <0.001                                    | 0.0014.35 (3.02–6.28)                    | <0.0012.47 (1.62–3.76)                   | <0.001                                    |
| ATTRwt-CM | 3.96 (2.48–6.32)                | <0.001                                    | 0.0072.79 (1.49–5.23)                    | 0.0011.99 (1.04–3.81)                    | 0.039                                     |
| Age       | 1.05 (1.05–1.06)                | <0.001                                    | 0.0011.05 (1.04–1.05)                    | 0.0011.05 (1.04–1.06)                    | <0.001                                    |
| Sex (male)| 1.28 (1.08–1.51)                | 0.005                                     | 0.0211.32 (1.10–1.58)                    | 0.0031.29 (1.03–1.61)                    | 0.025                                     |
| Atrial fibrillation | 1.27 (1.07–1.50)            | 0.006                                     | -                                         | -                                         | 0.374                                     |
| HR (bpm)  | 1.01 (1.00–1.01)                | 0.001                                     | 1.01 (1.01–1.01)                         | <0.0011.01 (1.00–1.01)                   | 0.026                                     |
| Mean BP   | 1.00 (0.99–1.00)                | 0.082                                     | 1.00 (0.99–1.01)                         | 0.3651.01 (1.00–1.01)                    | 0.188                                     |
| NYHA functional class |                        |                                           |                                           |                                           |                                           |
| I         | 1.49 (1.22–1.82)                | <0.001                                    | 0.3101.04 (0.85–1.28)                    | 0.711.00 (0.76–1.32)                     | 0.988                                     |
| II/IV     | 2.27 (1.86–2.77)                | <0.001                                    | <0.0011.27 (1.02–1.59)                   | 0.0361.44 (1.07–1.94)                    | 0.016                                     |
| LV-EF >50%| 0.94 (0.69–1.27)                | 0.680                                     | 0.4321.25 (0.90–1.74)                    | 0.1841.28 (0.87–1.89)                    | 0.206                                     |
| 40–49%    | 1.28 (1.04–1.59)                | 0.022                                     | 0.0081.48 (1.13–1.93)                    | 0.0041.24 (0.89–1.72)                    | 0.207                                     |
| <40%      | 1.01 (1.01–1.02)                | <0.001                                    | 1.01 (1.00–1.01)                         | 0.0941.00 (0.99–1.01)                    | 0.931                                     |
| eGFR (ml/min) |                          |                                           |                                           |                                           |                                           |
| Haemoglobin (G/L) | 1.01 (1.01–1.02)          | <0.001                                    | 1.01 (1.00–1.01)                         | 0.0021.01 (1.00–1.01)                    | 0.047                                     |
| ln NT-proBNP | 1.61 (2.50–1.72)             | <0.001                                    | -                                         | -                                         | 1.32 (1.20–1.45)                          | <0.001                                    |

AL-CM, AL cardiomyopathy; amyloid CM, amyloid cardiomyopathy; ATTRwt-CM, ATTR wild-type cardiomyopathy; BP, blood pressure; dCMP, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischaemic heart disease; LV-EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VHD, valvular heart disease.

Model 1 was adjusted for age, gender, CMP aetiology, NYHA functional class, and LV-EF. Model 2 was adjusted for age, gender, CMP aetiology, NYHA functional class, LV-EF, haemoglobin, eGFR, atrial fibrillation, mean BP, and heart rate. Model 3 was adjusted for age, gender, CMP aetiology, NYHA functional class, LV-EF, NT-proBNP, haemoglobin, eGFR, atrial fibrillation, mean BP, and heart rate.

Figure 2 Hazard ratios for all-cause mortality from univariate analysis for AL-CM, IHD, VHD, HHD, dCMP, HCM, and HfPEF/HfmrEF versus ATTRwt-CM (in which the hazard ratio for death was 1.0, per definition). AL-CM, AL cardiomyopathy; Amyloid CM, amyloid cardiomyopathy; ATTRwt-CM, ATTR wild-type cardiomyopathy; dCMP, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HfPEF/HfmrEF, heart failure with preserved and mid-range ejection fraction; HHD, hypertensive heart disease; IHD, ischaemic heart disease; VHD, valvular heart disease.
IHD. The latter may be explained by a type II error in multivariate analysis because of low numbers in the ATTRwt-CM group. High mortality in ATTRwt-CM was evident despite a large percentage of patients with LV-EF ≥ 40%, namely, 85.5%, as compared with 30.1% and 13.1% in patients with dCMP and IHD, respectively, while previous studies showed higher mortality for HfPEF/HfMRfEF patients as compared to patients with heart failure with reduced ejection fraction (25).

When death rates for ATTRwt-CM were compared with those for HfPEF/HfMRfEF patients, the 3-year mortality rate for ATTRwt-CM, namely, 28.6%, was higher than the 23.4% reported in the Meta-analysis Global Group in Chronic Heart Failure.27 Also, the 2-year mortality rate of 15.9% for ATTRwt-CM was higher than the corresponding 14% rate for a contemporary cohort of HfPEF patients.28 The 5-year mortality rate in patients with an LV-EF ≥ 40% in our cohort was only 11.4% when patients with amyloid CM were excluded from analysis. Individuals with ATTRwt-CM were 4.5 times more likely to die than were individuals with an LV-EF ≥ 40% without amyloid CM.

The findings that survival in patients with ATTRwt-CM was poorer than in heart failure patients with frequent aetiologies and with HfPEF/HfMRfEF undoubtedly call for increased perception of the disease among clinicians. This is especially important because recent evidence indicates that ATTR-CM is prevalent in 13% of HfPEF and 16% of patients with aortic stenosis.5,29 In fact, mortality in those patients with aortic stenosis plus TTR amyloidosis appears to be higher than in patients with aortic stenosis without amyloid CM.30 Prevalence of TTR amyloidosis is most likely to further increase over the next years as advances in non-invasive cardiac imaging such as CMR and 99mTC-DPD scintigraphy will facilitate diagnosis.31,32

In contrast to mutant TTR amyloidosis, it was only during the last 20 years that the amyloidogenic nature of wild-type amyloidosis became apparent.32 It is believed that excess accumulation and subsequent aggregation of amyloid fibrils in ATTRwt are caused by post-translational modifications of the transthyretin or inappropriate chaperone production in the liver that can lead to failure of proteasomal clearance of unfolded transthyretin.33 Recently, tafamidis, a new treatment option that stabilizes the tetrameric structure and prevents dissociation into unstable monomeric units, has been found to reduce all-cause mortality and cardiovascular-related hospitalization and thus for the first time offers effective treatment in patients with ATTRwt.10

### Strengths and limitations

Strengths of our study include the comprehensive clinical characterization and complete follow-up of our cohort. However, some limitations apply to this study. The applicability of our results to the general population of patients with heart failure is limited by the fact that a single centre recruited most of the patients. Although patients were treated according to prevailing guidelines, drug therapy for heart failure was not controlled for in this study. Thus, we are unable to speculate on the extent to which differences in therapy for heart failure may have affected the outcome. This is particularly true for AL-CM patients, in whom treatment has substantially improved over the last 10 to 15 years. Furthermore, patients were enrolled at the time of first

### Table 3 Univariate and multivariate Cox regression analysis of all-cause mortality of ATTRwt-CM compared with other aetiologies

| Variables | Unadjusted analysis (n = 2251) | P value | Multivariate analysis (n = 2251) | P value |
|-----------|-------------------------------|---------|---------------------------------|---------|
| ATTRwt-CM | 1                             |         | 1                               |         |
| dCMP      | 0.25 (0.16–0.40)              | <0.001  | 0.51 (0.31–0.83)                | 0.007   |
| HCM       | 0.12 (0.05–0.28)              | <0.001  | 0.34 (0.15–0.78)                | 0.011   |
| IHD       | 0.55 (0.34–0.87)              | 0.012   | 0.66 (0.41–1.08)                | 0.101   |
| HHD       | 0.35 (0.22–0.58)              | <0.001  | 0.48 (0.29–0.79)                | 0.004   |
| VHD       | 0.33 (0.18–0.59)              | <0.001  | 0.42 (0.23–0.77)                | 0.005   |
| AL-CM     | 1.95 (1.14–3.33)              | 0.015   | 3.04 (1.76–5.25)                | <0.001  |
| Age (per year) | 1.05 (1.05–1.06) | <0.001 | 1.05 (1.04–1.05) | <0.001 |
| Sex (male) | 1.28 (1.08–1.51) | 0.005 | 1.27 (1.07–1.52) | 0.006 |
| NYHA functional class |  |  |  |  |
| I         | 1                             |         | 1                               |         |
| II        | 1.49 (1.22–1.82)              | <0.001  | 1.12 (0.92–1.37)                | 0.269   |
| III/IV    | 2.27 (1.86–2.77)              | <0.001  | 1.45 (1.18–1.79)                | <0.001  |
| LV-EF     |  |  |  |  |
| >50%      | 1                             |         | 1                               |         |
| 40–49%    | 0.94 (0.69–1.27)              | 0.680   | 1.18 (0.96–1.62)                | 0.302   |
| <40%      | 1.28 (1.04–1.59)              | 0.022   | 1.45 (1.13–1.87)                | 0.004   |

AL-CM, AL cardiomyopathy; amyloid CM, amyloid cardiomyopathy; ATTRwt-CM, ATTR wild-type cardiomyopathy; BP, blood pressure; dCMP, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischaemic heart disease; LV-EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VHD, valvular heart disease.
presentation, which may have caused mortality to be overestimated in individual patients due to an already advanced stage of the disease. ATTR-CM, in particular, is notorious for a delay in diagnosis. Even though a large number of confounders were included in multivariate analysis, there are likely multiple other unmeasured confounders that may have influenced differences in mortality between amyloid CM and other aetiologies. Finally, study results are limited to patients with ATTRwt because patients with ATTRm were not included in this study.

Conclusions

Our study demonstrates that cardiac amyloidosis is independently associated with poorer survival among patients with various causes of heart failure. Although ATTRwt-CM had a better long-term prognosis than AL-CM, ATTRwt-CM was still associated with higher mortality than dCMP. HCM, HHD, VHD, and heart failure patients with an LV-EF ≥ 40%. These differences were independent of age, gender, and NYHA functional class. Thus, taking the poor prognosis of ATTRwt CMP and the emerging new treatment strategies into account, a thorough diagnostic workup in heart failure is warranted to detect patient with ATTRwt-CMP.

References

1. Seferovic PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbustini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos E, Kanjhu V, Krijanac G, Limongelli G, Linhart A, Lyon AR, Maksimovic R, Milicic D, Milinkovic I, Noutsias M, Otó A, Otó O, Pavlovic SU, Piepoli MF, Ristic AD, Rosano GMC, Seggewiss H, Asanin M, Seferovic JP, Ruschitzka F, Celukiene J, Jaarsma T, Mueller C, Mourn B, Hill L, Volterrani M, Lopatin Y, Metra M, Baeks J, Mullens W, Chionte O, de Boer RA, Anker S, Rapezzi C, Coats AJS, Tschope C. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; 21: 553–576.

2. Seferovic PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbustini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos E, Kanjhu V, Krijanac G, Limongelli G, Linhart A, Lyon AR, Maksimovic R, Milicic D, Milinkovic I, Noutsias M, Otó A, Otó O, Pavlovic SU, Piepoli MF, Ristic AD, Rosano GMC, Seggewiss H, Asanin M, Seferovic JP, Ruschitzka F, Celukiene J, Jaarsma T, Mueller C, Mourn B, Hill L, Volterrani M, Lopatin Y, Metra M, Baeks J, Mullens W, Chionte O, de Boer RA, Anker S, Rapezzi C, Coats AJS, Tschope C. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; 21: 553–576.

3. Rammos A, Meladinis V, Vovas G, Patsouras D. Restrictive cardiomyopathies: the importance of noninvasive cardiac imaging modalities in diagnosis and treatment—a systematic review. *Radiol Res Pract* 2017; 2017: 2874902.

4. Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, Roger VL, Gertz MA, Dispenzieri A, Zelenrust SR, Redfield MM. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail* 2014; 2: 113–122.

5. Gonzalez-Lopez E, Gallego-Delgado M, Guazzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Borstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015; 36: 2585–2594.

6. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, Berk JL, Plante-Bordeneuve V, Schmidt HHJ, Merlini G. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol* 2015; 66: 2451–2466.

7. Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, Berk JL, Seldin DC. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective. *Obes Curr* 2016; 13: 282–290.

8. Galat A, Guellich A, Bodez D, Slama M, Dijos M, Zeitoun DM, Milleron O, Attias D, Dubois-Rande JL, Mothy D, Audureau E, Teiger E, Rosso J, Monin JL, Damy T. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? *Eur Heart J* 2016; 37: 3525–3531.

9. Tansklen M, Peuralinna T, Polvikoski T, Norkola IL, Sulkanv R, Hardy J, Singleton A, Kiuru-Enni S, Paetau A, Tienari PI, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008; 40: 232–239.

10. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristin AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, Investigators A-AS. Tafamidis treatment for patients with transthyretin amyloid

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Conflict of interest

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Supporting information

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

Table S1. Univariate and multivariate Cox Regression Analysis of all-cause mortality for the entire cohort.
cardiomyopathy. N Engl J Med 2018; 379: 1007–1016.

11. Adams D, Gonzalez-Duarte A, O’Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JI, Lin KP, Vita G, Attarian S, Plante-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH 3rd, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018; 379: 11–21.

12. Benson MD, Waddington-Cruz M, Berk JI, Polydefkis M, Dyck PJ, Wang AK, Plante-Bordeneuve V, Barroso FA, Merlino G, Obici L, Scheinberg M, Brannagan TH 3rd, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceicao I, Schmidt HH, Vita G, Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018; 379: 22–31.

13. Sperry BW, Vranian MN, Hachamovitch R, Joshi H, Ikram A, Phelan D, Hanna M. Subtype-specific interactions and prognosis in cardiac amyloidosis. J Am Heart Assoc 2016; 5: e002877.

14. Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. Arch Intern Med 2005; 165: 1425–1429.

15. Barrett CD, Dobos K, Liedtke M, Tuzovic M, Haddad F, Kobayashi Y, Lafayette R, Fowler MB, Arai S, Schrier S, Witteles JM. A changing landscape of mortality for systemic light chain amyloidosis. JACC Heart Fail 2019; 7: 955–966.

16. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, Gagliardi C, Milantri A, Rapezzi C, Falk RH. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation 2014; 129: 1840–1849.

17. Mishra S, Guan J, Plovie E, Seldin DC, Connors LH, Merlini G, Falk RH, MacRae CA, Liao R. Human amyloidogenic light chain proteins result in cardiac dysfunction, cell death, and early mortality in zebrafish. Am J Physiol Heart Circ Physiol 2013; 305: H95–H1103.

18. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, Apstein CS, Liao R. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circ Res 2004; 94: 1008–1010.

19. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat I, Pankuwit S, Rapezzi C, Seferovic P, Tavazzi I, Keren A. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008; 29: 270–276.

20. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol 2014; 64: 83–99.

21. Felker GM, Shaw LK, O’Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002; 39: 210–218.

22. Lip GY, Felmenden DC, Li-Saw-Hee FL, Bevers DG. Hypertensive heart disease. A complex syndrome or a hypertensive ‘cardiomyopathy’? Eur Heart J 2000; 21: 1653–1665.

23. Nkomo VT, Gardin JM, Skelton TN, Gottlieber JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006; 368: 1005–1011.

24. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016; 387: 2641–2634.

25. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JI, Quarta CC, Grogan M, Lachmann HJ, Bohkari S, Castano A, Durbala S, Johnson GB, Milandri A, Rapezzi C, Falk RH. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation 2014; 129: 1840–1849.

26. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klirich KW, Miller WI, Malezewski JJ, Dispenzieri A. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016; 68: 1014–1020.

27. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012; 33: 1750–1757.

28. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaurefally F, Ng TP, Cameron VA, Poppe K, Lund M, Devlin G, Troughton R, Richards AM, Doughty RN. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J 2018; 39: 1770–1780.

29. Castano A, Narotsky DL, Hamid N, Khaliq OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bohkari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017; 38: 2879–2887.

30. Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, Soman P, Forman DE, Schindler JT, Gleason TG, Lee JS, Schelbert ER. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson 2017; 19: 98.

31. Falk RH, Quarta CC, Durbala S. How to image cardiac amyloidosis. Circ Cardiovasc Imaging 2014; 7: 552–562.

32. Liao R, Ward JE. Amyloid cardiomyopathy: disease on the rise. Circ Res 2017; 120: 1865–1867.

33. Liu PP, Smyth D. Wild-type transthyretin amyloid cardiomyopathy: a missed cause of heart failure with preserved ejection fraction with evolving treatment implications. Circulation 2016; 133: 245–247.