Characteristics and natural history of early-stage cardiac transthyretin amyloidosis

Steven Law 1, Melanie Bezard 2, Aviva Petrie 3, Liza Chacko 1, Oliver C. Cohen 1, Sriram Ravichandran 1, Olabisi Ogunbiyi 1, Mounira Kharoubi 3, Sashiananthan Ganeshananthan 1, Sharmananthan Ganeshananthan 1, Janet A. Gilbertson 1, Dorota Rowczynio 1, Ashutosh Wechalekar 1, Ana Martinez-Narahro 1, Helen J. Lachmann 1, Carol J. Whelan 1, David F. Hutt 1, Philip N. Hawkins 1, Thibaud Damy 2, Marianna Fontana 1†, and Julian D. Gillmore 1†

1National Amyloidosis Centre, Division of Medicine, University College London, London, UK; 2Referral Center for Cardiac Amyloidosis, Department of Cardiology, Mondor Amyloidosis Network, GRC Amyloid Research Institute, Clinical Investigation Center 006, DHU A-TVb INSERM U955 all at CHU Henri Mondor, UPEC, Créteil, France; and 3Biostatistics Unit, UCL Eastman Dental Institute, University College London, London, UK

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Abstract

Aims Transthyretin amyloid cardiomyopathy (ATTR-CM) is increasingly diagnosed at an early stage of the disease natural history, defined as National Amyloidosis Centre (NAC) ATTR Stage I. The natural history of early-stage ATTR-CM remains poorly characterized.

Methods and results A retrospective multi-centre observational study of 879 patients with ATTR-CM, either wild-type TTR genotype or carrying the p.V142I TTR variant, and NAC ATTR Stage I biomarkers at the time of diagnosis who did not receive disease-modifying therapy for amyloidosis. Disease characteristics at diagnosis that were independently associated with mortality by Cox regression analysis were N-terminal pro-B-type natriuretic peptide (NT-proBNP), TTR genotype, and troponin T. Patients were categorized into NAC ATTR Stage Ia, defined as a furosemide equivalent diuretic requirement of ≤ 0.75 mg/kg and an NT-proBNP ≤ 500 ng/L or ≤ 1000 ng/L in the presence of atrial fibrillation, and NAC ATTR Stage Ib comprising all remaining Stage I patients. Median estimated survival among the 88% NAC ATTR Stage Ib patients was 75 (95% CI 57–93) months compared with > 100 months in the 12% with Stage Ia disease [hazard ratio for death 5.06 (95% confidence interval 1.23–20.87); P = 0.025] despite significant cardiovascular morbidity at the time of diagnosis which increased during follow-up, including among patients diagnosed in NAC ATTR Stage Ia. Estimated survival among UK NAC ATTR Stage Ia patients was comparable to UK general population controls (P = 0.297).

Conclusion Patients with NAC ATTR Stage I ATTR-CM can be further stratified according to NT-proBNP concentration and diuretic requirement at diagnosis. Patients with Stage Ia ATTR-CM have significant cardiovascular morbidity despite good short- and mid-term survival.
Patients diagnosed with NAC Stage Ia ATTR-CM have an estimated median survival in excess of 100 months in the absence of disease-modifying therapy despite significant cardiovascular morbidity which increases further during follow up.

**Take Home Message**
NAC Stage I ATTR-CM can be further stratified according to NT-proBNP concentration and diuretic requirement at diagnosis. Patients with Stage Ia ATTR-CM have substantial cardiovascular morbidity despite good mid-term survival. The benefit of therapeutic intervention at this early disease stage remains to be determined.

**Natural history of early-stage ATTR-CM**

Patients diagnosed with NAC ATTR Stage Ia amyloidosis have an estimated median survival in excess of 100 months in the absence of disease-modifying therapy despite significant cardiovascular morbidity which increases further during follow up.

**Keywords**
Amyloidosis • Amyloid • Transthyretin • TTR • Staging • Cardiomyopathy

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**Introduction**

Transthyretin amyloid cardiomyopathy (ATTR-CM) is increasingly diagnosed although only a small proportion of those individuals who have ATTR amyloid deposits in their hearts, according to prevalence estimates from post-mortem series, are ever diagnosed with cardiac amyloidosis in life.1–3 Since the diagnosis of ATTR-CM is challenging and often missed, the true disease prevalence remains unknown.

The prognosis of patients who are diagnosed with ATTR-CM can be determined on the basis of National Amyloidosis Centre (NAC) ATTR Stage, which is calculated at the time of diagnosis according to N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and estimated glomerular filtration rate (eGFR).4,5 Initial reports indicated that ~40% of patients were diagnosed in Stage I conferring a prognosis of >5 years in the absence of disease-modifying therapy, with the remainder being Stage II or III associated with progressively worsening prognosis.4 However, the recent improvement in diagnostic imaging techniques coupled with heightened awareness of ATTR-CM among cardiologists due to the availability of life-prolonging therapies, mean that >50% of patients are now diagnosed with NAC Stage I ATTR-CM, a trend which is likely to increase further.6–13

There are few data on the natural history of early-stage ATTR-CM. We sought to characterize the disease course and clinical outcome among patients diagnosed with early-stage ATTR-CM in the absence of disease-modifying therapy.
Methods

Patients
A retrospective analysis was conducted of all patients with ATTR-CM attending two large amyloidosis Centres, the UK NAC and the Amyloidosis Mondor Network, France between 27th August 2009 and 30th July 2020, who fulfilled all of the following inclusion criteria: wild-type TTR gene sequence or TTR mutation encoding the known pathogenic p.V142I variant; NAC ATTR Stage I biomarkers at the time of diagnosis; and absence of administration of disease-modifying therapy during clinical follow-up. ATTR-CM was defined either by validated non-biopsy diagnostic criteria for ATTR-CM or by the presence of ATTR amyloid on histology from any biopsy site coupled with Perugini Grade ≥1 myocardial uptake on radionuclide scan. For clarity, validated non-biopsy criteria for ATTR-CM were defined as all of the following: echocardiogram or cardiac magnetic resonance suggestive of amyloid, Perugini Grade ≥2 radionuclide scan, and absence of a monoclonal protein by serum-free light chain assay and by serum and urine immunofixation. NAC ATTR Stage I was defined as an NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min/1.73 m² at diagnosis. In order to focus on patients with predominant ATTR-CM, those with non-V122I-associated ATTRv amyloidosis were excluded due to the important but variable contributions of peripheral and autonomic neuropathy to both morbidity and mortality in those conditions.

Patients were systematically evaluated at diagnosis and on a 6–12 monthly basis thereafter as clinically indicated. Evaluations consisted of a full clinical history and examination alongside functional, biochemical, electrocardiography, and echocardiographic assessment. Hospitalization data were not reliably captured and therefore excluded from analyses. Throughout the study cardiovascular morbidity is defined by the presence of atrial fibrillation, cerebrovascular accident, permanent pacemaker, diuretic requirement, or New York Heart Association (NYHA) functional Class ≥II.

All patients were managed in accordance with the Declaration of Helsinki and provided informed consent for anonymous publication of their data. The study received IRB approval from the Royal Free Hospital Ethics Committee.

Biomarker analysis
N-terminal pro-B-type natriuretic peptide was measured with an electrochemiluminescence sandwich immunoassay on the Elecsys system 2010 (Roche Diagnostics) and eGFR was calculated by standard Modification of Diet in Renal Disease study equation with correction for ethnicity. National Amyloidosis Centre ATTR disease stage was calculated according to previously published criteria. High-sensitivity troponin T assay was performed with a second-generation assay after 16 December 2015, and before that, with a first-generation troponin T assay.

Radionuclide (99mTc-DPD and 99mTc-HMDP) scintigraphy
Patients were scanned after intravenous injection of ~700 MBq of 99mTc-DPD providing an expected radiation dose of ~4 mSv per patient. Whole-body planar and SPECT/CT images were acquired 3 h post-injection in all patients. Images were acquired using a low energy, high-resolution collimator, and a scan speed of 10 cm/min. Cardiac retention of all 99mTc-DPD scans was determined by two independent experienced readers according to the grading devised by Perugini et al. A heart to mediastinum (H:M) ratio of ≥1.21 on 99mTc-HMDP scintigraphy, previously reported to be equivalent to Perugini Grade ≥4, is reported as Grade ≥2 throughout the manuscript.

Echocardiography
Echocardiography was performed by three echocardiographers with extensive experience of cardiac amyloidosis on General Electric Vivid 7 machines using EchoPac software. All echocardiograms were read and reported by two independent experts in amyloid echocardiography.

Histology, immunohistochemistry, and proteomics
All formalin-fixed paraffin-embedded biopsies were stained with Congo red dye and viewed under crossed polarized light according to the method of Puchtler et al. The definitive amyloid fibril type was established by immunohistochemical staining of amyloid deposits using a panel of monospecific antibodies reactive with serum amyloid A protein, kappa and lambda immunoglobulin light chains, transthyretin, and where necessary, antibodies against apolipoprotein A-I, apolipoprotein A-IV, and fibrinogen Aα-chain, as previously described, and/or by microdissection of amyloid deposits and proteomic analysis, as previously described.

Genetic testing
DNA was extracted from whole blood, amplified by polymerase-chain-reaction assay and the whole coding region of the transthyretin (TTR) gene was sequenced in all patients, as previously described.

Statistical methods
The diagnosis was defined as the date of first review at a specialist amyloidosis centre, and follow-up was defined as the time from diagnosis to date of censoring or death. Patients were censored at the earliest of the following timepoints: 30 July 2020, date of commencement of disease-modifying therapy, enrolment into a clinical trial of disease-modifying therapy, or at 100 months of follow-up.

The association between patient characteristics at diagnosis and survival was explored by univariable Cox regression analyses, and subsequently by multivariable Cox regression analyses including variables known to be associated with survival in ATTR-CM according to the published literature. Due to the independent prognostic power of NT-proBNP at diagnosis coupled with recently published literature demonstrating the independent association between loop diuretic equivalent dose requirement and survival in ATTR-CM, the study population was stratified into two groups defined as: NAC ATTR Stage Ia—NT-proBNP ≤500 or <1000 ng/L in the presence of atrial fibrillation, or a loop diuretic equivalent requirement of <0.75 mg/kg, and NAC ATTR Stage Ib—NT-proBNP >500 or >1000 ng/L in the presence of atrial fibrillation or a loop diuretic requirement of ≥0.75 mg/kg. The NT-proBNP cut-offs were chosen to reflect the NT-proBNP eligibility criteria for recently conducted clinical trials of novel disease-modifying agents in ATTR-CM, some of which require the use of diuretics and acknowledge the effect of atrial fibrillation on NT-proBNP concentration independently of disease severity [ATTR-ACT (>600 ng/L), ATTRbute-CM (>300 ng/L), APOLLO-B (>300 and >600 ng/L in atrial fibrillation), HELIOS-B (>300 and >600ng/L in atrial fibrillation), ION-CS2 (>600 and >1200 ng/L in atrial fibrillation), and ITL-2001-CL-001 (>600 and >1000 ng/L in atrial fibrillation)].

Loop diuretic doses were converted to a total daily furosemide equivalent dose; for example 1 mg bumetanide twice daily was converted to 80 mg as a total daily furosemide equivalent dose. A value of <0.75 mg/kg was selected to identify patients with a relatively low diuretic requirement of <40 mg daily for patients ≥53 and ≤80 kg in weight and ≤60 mg daily for patients of >80 kg typically administered in mild heart failure or for non-heart failure indications. A single cut-off value was chosen for simplicity in order to maximize clinical utility of the staging system. Multivariable Cox regression analyses were subsequently repeated with replacement of
Results

Patient characteristics

There were 879 patients with NAC ATTR Stage I ATTR-CM at diagnosis included in the analyses (623 from UK and 256 from France); 109 (12%) were Stage la and 770 (88%) were Stage lb. In the UK cohort, 74 (12%) were Stage la and 549 (88%) were Stage lb. Baseline characteristics of all patients are shown in Table 1 along with a comparison between those with Stages la and lb disease. NAC ATTR Stage la patients were more commonly ATTRwt, and had better biochemical, functional, and echocardiographic parameters of disease compared with Stage lb patients. A greater proportion of NAC ATTR Stage lb patients had Perugini Grade ≥2 radionuclide scans compared with patients with Stage la disease (99% vs. 90%); both stages were associated with thickening of the ventricular walls [median IVSd 16 mm [interquartile range (IQR) 14–17] and 17 mm (IQR 15–18) for NAC ATTR Stages la and lb, respectively]. Prevalence of atrial fibrillation, a permanent pacemaker, and carpal tunnel syndrome appeared to be high across the whole cohort when compared with those reported in age-matched control populations from a variety of published sources.

Patient characteristics stratified by grade of cardiac uptake on radionuclide scintigraphy are shown in Table 2. Patients with Perugini Grade ≥2 cardiac uptake had worse clinical, biochemical, functional, and echocardiographic parameters of cardiac disease when compared with those with Perugini Grade 1 cardiac uptake.

Patient survival

At a median follow-up of 21 (IQR 8–40) months, 120 (14%) patients had died, and the overall median estimated survival was 87 (95% CI 63—not met) months.

Univariable Cox regression analyses investigating the association between mortality and a range of patient and disease-related variables for the whole cohort are shown in Supplementary material online, Table 1. There was a significant association between mortality and TTR genotype, NT-proBNP, troponin T, serum albumin, IVSd, NYHA class, diabetes mellitus, loop diuretic dose, mineralocorticoid requirement, LVEF, and systolic blood pressure. Multivariable analyses identified higher NT-proBNP (Supplementary material online, Table 2; Harrell’s c-statistic 0.89) or NAC ATTR Stage lb (Table 3; categorical variable vs. Stage la; Harrell’s c-statistic = 0.75), ATTRv, and higher troponin T at diagnosis as independent predictors of mortality. N-terminal pro-B-type natriuretic peptide at diagnosis was the most powerful independent predictor of mortality [HR 4.36 (95% CI 1.69–11.30); P = 0.002, Supplementary material online, Table 2].

Median estimated survival by KM analysis among patients with NAC ATTR Stage la disease was not met at 100 months, and was 75 months (95% CI: 57–93) among those with Stage lb disease (P < 0.001, Structured Graphical Abstract, Figure 1A). When limited to the UK cohort, the median estimated survival of patients with NAC ATTR Stage la disease was not met at 100 months, and there was no evidence of a difference in survival between UK NAC Stage la patients and matched UK general population controls (P = 0.297; Figure 1B). The median estimated survival of UK patients with NAC ATTR Stage lb disease was 85 (95% CI: undefined) months which was significantly reduced when compared with matched UK general population controls (P < 0.0001; Figure 1C).

Cardiovascular and non-cardiovascular morbidity in Stage Ia ATTR amyloidosis

Among the 109 patients from the whole cohort who were NAC ATTR Stage Ia at diagnosis, followed for a median of 28 months...
Table 1  Patient and disease-related characteristics at diagnosis in 879 patients with National Amyloidosis Centre Stage I transthyretin amyloid cardiomyopathy

|                                | All patients (n = 879) | Stage Ia (n = 109) | Stage Ib (n = 770) | P-value Ia vs. Ib |
|--------------------------------|------------------------|--------------------|-------------------|------------------|
| **Age at diagnosis (years)**   | 77 (71–82)             | 75 (71–80)         | 77 (71–80)        | 0.032            |
| **Amyloid type**               |                        |                    |                   |                  |
| ATTRwt, n (%)                  | 698 (79)               | 99 (91)            | 599 (78)          | 0.002            |
| ATTRv, n (%)                   | 181 (21)               | 10 (9)             | 171 (22)          |                  |
| **Year of diagnosis**          |                        |                    |                   |                  |
| 2018–20                        | 420 (48)               | 56 (51)            | 364 (47)          | 0.540            |
| 2015–17                        | 294 (33)               | 37 (34)            | 257 (33)          |                  |
| 2012–14                        | 131 (15)               | 13 (12)            | 118 (15)          |                  |
| 2009–11                        | 34 (4)                 | 3 (3)              | 31 (4)            | 0.121            |
| **Male sex, n (%)**            | 775 (88)               | 101 (93)           | 674 (88)          |                  |
| **Caucasian ancestry, n (%)**  | 684 (78)               | 89 (82)            | 595 (77)          | 0.303            |
| **ATTR histology, n (%)**      | 359 (41)               | 46 (42)            | 313 (41)          | 0.758            |
| Meets non-biopsy criteria, n (%) | 752 (86)              | 83 (76)            | 669 (87)          | 0.003            |
| **NT-proBNP (ng/L)**           | 1496 (913–2254)        | 367 (205–480)      | 1684 (1130–2342)  | <0.001           |
| **Troponin T (ng/L) (n = 861)** | 45 (31–64)            | 27 (20–38)         | 48 (34–66)        | <0.001           |
| eGFR (mL/min/1.73 m²)          | 70 (59–81)             | 76 (66–88)         | 69 (58–81)        | <0.001           |
| Chronic kidney disease stage, n (%) | 120 (14)            | 26 (24)            | 94 (12)           | 0.001            |
| **IVSd (mm) (n = 865)**        | 17 (15–18)             | 16 (14–17)         | 17 (15–18)        | <0.001           |
| **LVPW (mm) (n = 858)**        | 16 (14–18)             | 15 (13–16)         | 16 (14–18)        | <0.001           |
| LVEF (%) (n = 854)             | 51 (45–58)             | 58 (54–61)         | 51 (44–57)        | <0.001           |
| DPD/HDMP grade, n (%)          | 22 (3)                 | 11 (10)            | 11 (1)            | <0.001           |
| ≥2                             | 857 (97)               | 98 (90)            | 759 (99)          |                  |
| Systolic blood pressure (mmHg) (n = 871) | 128 (118–141)       | 131 (122–143)      | 127 (117–140)     | 0.022            |
| Diastolic blood pressure (mmHg) (n = 871) | 75 (69–82)            | 76 (70–84)         | 75 (69–81)        | 0.222            |
| Six-min walk test distance (m) (n = 636) | 360 (255–444)        | 430 (345–506)      | 354 (240–436)     | <0.001           |
| NYHA class, n (%) (n = 870)    |                       |                    |                   |                  |
| I                              | 126 (15)               | 40 (38)            | 86 (11)           | <0.001           |
| II                             | 611 (70)               | 58 (55)            | 553 (72)          |                  |
| ≥III                           | 133 (15)               | 8 (8)              | 125 (16)          |                  |
| Loop diuretic, n (%)           | 536 (61)               | 32 (29)            | 504 (66)          | <0.001           |
| Thiazide diuretic, n (%)       | 52 (6)                 | 9 (8)              | 43 (6)            | 0.270            |
| Mineralocorticoid receptor antagonist, n (%) | 142 (16)             | 8 (7)              | 134 (17)          | 0.008            |
| Digoxin, n (%)                 | 32 (4)                 | 5 (5)              | 27 (4)            | 0.577            |
| ACE inhibitor, n (%)           | 311 (35)               | 30 (28)            | 281 (37)          | 0.067            |
| Angiotensin receptor blocker, n (%) | 166 (19)              | 19 (17)            | 147 (19)          | 0.674            |
| Beta blocker, n (%)            | 304 (35)               | 18 (17)            | 286 (37)          | <0.001           |

Continued
The symptoms accompanied by histological evidence of bladder or prostatic in which ATTR amyloid deposits were identified at biopsy sites (range: 8–46), regular diuretic use increased from 39% of patients at diagnosis to 56% of patients, prevalence of atrial fibrillation increased from 31% at diagnosis to 40% of patients, NYHA Class ≥ II heart failure increased from 62% to 82% of patients, cardiovascular accident or transient ischemic attack from 8% to 15% of patients, and permanent pacemaker implants from 13% to 20% of patients. Of the six permanent pacemakers implanted after diagnosis of ATTR-CM, three were for complete heart block and the remainder for nonspecific bradyarrhythmias. The median NT-proBNP increase during follow-up was 145 ng/L/year (IQR: 47–440) and median eGFR reduction was 2.8 mL/min/1.73 m²/year (IQR: 0–7). Twenty-one of 80 (26%) patients with follow-up biomarkers went from Stage Ia to Stage Ib ATTR-CM and 14 (18%) developed NAC ATTR Stage ≥ II disease during the follow-up period.

Among 63 patients with NAC ATTR Stage Ia disease who had a primary cardiovascular presentation, cardiovascular biomarkers, cardiac imaging, and functional markers of cardiac disease were significantly worse than in the 46 patients with a primary non-cardiovascular presentation (Table 4). Similarly, a significantly higher proportion of patients with a primary cardiovascular presentation required diuretic therapy, had atrial fibrillation and met the non-biopsy diagnostic criteria for ATTR-CM. The commonest cardiovascular presentations were cardiac failure (60%) and atrial arrhythmias (25%) (Table 4).

Non-cardiovascular clinical presentations included urological symptoms accompanied by histological evidence of bladder or prostatic ATTR amyloid, carpal tunnel syndrome with ATTR amyloid deposits in the flexor retinaculum or tenosynovium, and incidental discovery of ATTR amyloid deposits in the gastrointestinal tract. Biopsy sites in which ATTR amyloid deposits were identified in patients with a non-cardiovascular primary clinical presentation are shown in Table 4. Perugini Grade ≥ 2 cardiac uptake was identified by imaging (usually in the context of screening for it) in 76% of patients with a primary non-cardiovascular presentation (Table 4). Follow-up data were available for 43 of 46 Stage Ia patients with a non-cardiovascular primary clinical presentation and after a median follow-up of 19 months (IQR: 8–50), 12 (28%) patients had atrial fibrillation, 8 (19%) had a permanent pacemaker, 6 (14%) had a history of stroke or transient ischemic attack, 29 (69%) had NYHA Class ≥ II heart failure symptoms, and 16 (37%) required diuretic therapy; median NT-proBNP increase was 109 ng/L/year (IQR: 23–276) and 9 of 32 (28%) patients with follow-up biomarkers had progressed to NAC ATTR Stage ≥ Ib. The median estimated survival of patients with NAC ATTR Stage Ia was not met at 80 months in both patients with and without a cardiovascular presentation (P = 0.837).

### Discussion

Increased awareness of ATTR-CM among cardiologists and improved diagnostic techniques are leading to a reduction in diagnostic delays with a consequent increase in the proportion of patients diagnosed with early-stage disease, defined as NAC ATTR Stage I, a trend which is likely to continue.6–9,13 This trend has recently been highlighted by the reported findings from Part 1 of the ATTRibute-CM (acarizimib) study in which the 6 min walk test distance among patients within the placebo arm declined by <10 m in the first year compared with ≥50 m over the same time period among patients on placebo within the older ATTR-ACT trial (tafamidis).10,31 Here
Table 2  Baseline characteristics of patients with National Amyloidosis Centre Stage I transthyretin amyloid cardiomyopathy stratified by grade of cardiac uptake by radionuclide scanning

| Grade 1 (n = 22) | Grade ≥ 2 (n = 857) | P-value |
|------------------|---------------------|---------|
| Age at diagnosis (years) | 79 (72–83) | 77 (71–82) | 0.402 |
| Amyloid type | ATTRwt, n (%) | 19 (86) | 679 (79) | 0.414 |
| | V122I-ATTRv, n (%) | 3 (14) | 178 (21) | |
| Male sex, n (%) | 19 (86) | 756 (88) | 0.791 |
| NAC ATTR Stage | Ib | 11 (50) | 98 (11) | |
| NT-proBNP (ng/L) | 513 (245–1239) | 1522 (939–2267) | <0.001 |
| Troponin T (ng/L) | 20 (14–35) | 46 (32–64) | <0.001 |
| eGFR (mL/min/1.73 m²) | 73 (61–88) | 70 (59–81) | 0.381 |
| Alkaline phosphatase (µ/L) | 76 (55–105) | 81 (63–103) | 0.544 |
| IVSd (mm) | 12 (11–12) | 17 (15–18) | <0.001 |
| LVPW (mm) | 12 (11–13) | 16 (14–18) | <0.001 |
| LVEF (%) | 55 (45–60) | 51 (45–58) | 0.340 |
| Systolic blood pressure (mmHg) | 132 (121–148) | 128 (117–141) | 0.216 |
| Six-min walk test distance (m) | 365 (235–460) | 360 (256–443) | 0.696 |
| NYHA class, n (%) | I | 9 (41) | 117 (14) | 0.001 |
| | II | 12 (54) | 599 (71) | |
| | ≥III | 1 (5) | 132 (16) | |
| Carpal tunnel syndrome, n (%) | Unilateral | 3 (14) | 116 (14) | 0.989 |
| | Bilateral | 12 (55) | 411 (48) | 0.541 |
| Spinal stenosis, n (%) | 3 (14) | 111 (13) | 0.925 |
| Joint replacement, n (%) | 2 (9) | 172 (20) | 0.202 |
| Loop diuretic, n (%) | 8 (36) | 528 (62) | 0.017 |
| Thiazide diuretic, n (%) | 1 (5) | 51 (6) | 0.782 |
| Mineralocorticoid receptor antagonist, n (%) | 1 (5) | 141 (17) | 0.134 |
| Digoxin, n (%) | 1 (5) | 31 (4) | 0.820 |
| ACE inhibitor, n (%) | 3 (14) | 308 (36) | 0.031 |
| Angiotensin receptor blocker, n (%) | 2 (9) | 164 (19) | 0.234 |
| Beta blocker, n (%) | 4 (18) | 300 (35) | 0.101 |
| Atrial fibrillation, n (%) | 7 (32) | 264 (31) | 0.963 |
| PPM, n (%) | 2 (9) | 130 (15) | 0.431 |
| ICD, n (%) | 1 (5) | 46 (5) | 0.866 |
| Hypertension, n (%) | 7 (32) | 381 (45) | 0.237 |
| Ischaemic heart disease, n (%) | 3 (14) | 133 (16) | 0.809 |
| Stroke or TIA, n (%) | 3 (14) | 93 (11) | 0.679 |
| Diabetes mellitus, n (%) | 5 (23) | 138 (16) | 0.406 |

Values displayed as median (interquartile range) unless otherwise stated. Heart:mediastinal ratio of ≥1.21 by 99mTc-HMDP scintigraphy considered equivalent to Perugini Grade ≥2 cardiac uptake 99mTc-DPD. P-values represent comparison testing between patients with a Perugini Grade 1 cardiac uptake vs. those with Perugini Grade ≥2 cardiac uptake at diagnosis by the Kruskal–Wallis test for numerical variables and χ² test for categorical variables.
we outline for the first time, the clinical features and natural history of early-stage ATTR-CM in a large cohort of patients with predominant cardiomyopathic TTR genotypes followed in two large European Amyloidosis Centres.

It is noteworthy, although perhaps unsurprising, that the most important independent predictor of mortality in this cohort was NT-proBNP concentration at diagnosis. A diagnostic NT-proBNP concentration of ≤500 ng/L (or ≤1000 ng/L in the presence of atrial fibrillation) coupled with a loop diuretic equivalent dose requirement of ≥0.75 mg/kg, defined here as NAC ATTR Stage Ia, was present in only 109 (12%) of patients. Despite Perugini Grade ≥2 radionuclide scintigraphy in 90% of such patients, only 58% of Stage Ia patients had a primary cardiovascular clinical presentation. A comparison between patients diagnosed with Stages Ia and Ib disease showed a significantly higher proportion of ATTRwt, lower troponin T, higher eGFR, lower ALP, less thickening of left ventricular walls and better LVEF on echocardiography, and a better functional status according to both NYHA class and 6 min walk test in the former group. Median survival was in excess of 100 months from diagnosis in Stage Ia patients, and there was no evidence of a difference in survival between UK NAC Stage Ia patients and matched UK general population controls.

The most common non-cardiac sites in which ATTR amyloid deposits were identified were flexor retinaculum, gastrointestinal tract, and bladder; flexor retinaculum biopsies were obtained at carpal tunnel surgery and bladder biopsies were usually performed for haematuria, whereas the finding of ATTR amyloid in gastrointestinal tract was often ‘incidental’ in association with a second pathology in the relevant organ (e.g. gastric ulcer).

Cardiovascular morbidity at the time of diagnosis was substantial, even in patients with NAC ATTR Stage Ia disease; NYHA Class ≥II heart failure symptoms, regular diuretic use, atrial fibrillation, permanent pacemaker implants, and CVA/TIAs were present in 62%, 39%,
Table 4  Baseline characteristics of 109 patients diagnosed with NAC ATTR Stage Ia disease stratified by clinical presentation

|                        | Cardiovascular presentation | P-value |
|------------------------|----------------------------|---------|
|                        | No (n = 46)                | Yes (n = 63) |
| Age (years)            | 75 (70–80)                 | 75 (71–80) | 0.988 |
| Male sex, n (%)        | 41 (89)                    | 60 (95)  | 0.227 |
| Caucasian ancestry, n (%) | 35 (76)              | 54 (86) | 0.200 |
| Amyloid type           | ATTRwt, n (%)              |         |       |
|                        | V122I-ATTRv, n (%)         | 7 (15)  | 3 (5)  | 0.062 |
| ATTR histology, n (%)  | 24 (52)                    | 22 (35) | 0.072 |
| Meets non-biopsy criteria, n (%) | 30 (65)                | 53 (84) | 0.022 |
| NT-proBNP (ng/L)       | 263 (155–456)              | 403 (288–668) | 0.001 |
| Troponin T (ng/L)      | 21 (17–30)                 | 32 (24–48) | <0.001 |
| eGFR (mL/min/1.73 m^2) | 76 (71–90)                 | 74 (64–88) | 0.237 |
| IVSd (mm)              | 15 (12–17)                 | 16 (15–17) | 0.024 |
| DPD/HDMR grade, n (%)  | 1                          | 11 (24) | 0 (0)  | <0.001 |
|                        | ≥2                         | 35 (76) | 63 (100) |         |
| NYHA class, n (%)      | I                          | 25 (57) | 15 (24) | 0.003 |
|                        | II                         | 16 (36) | 42 (68) |         |
|                        | ≥III                       | 3 (7)  | 5 (8)  |         |
| Atrial fibrillation, n (%) | 6 (13)                 | 27 (43) | 0.001 |
| Hypertension, n (%)    | 19 (41)                    | 28 (44) | 0.744 |
| Diabetes mellitus, n (%) | 9 (20)                 | 13 (21) | 0.891 |
| Pacemaker, n (%)       | 6 (13)                     | 8 (13)  | 0.958 |
| Stroke or TIA, n (%)   | 3 (7)                      | 6 (10)  | 0.574 |
| Diuretic requirement, n (%) | 10 (22)                | 33 (52) | 0.001 |

**Presentation**

|                        | Cardiovascular presentation |
|------------------------|----------------------------|
| Cardiac failure, n (%) | 38 (60)                    |
| Atrial fibrillation/flutter, n (%) | 16 (25)               |
| Complete heart block, n (%) | 1 (2)                |
| Stroke, n (%)          | 3 (5)                      |
| Chest pain, n (%)      | 3 (5)                      |
| Aortic stenosis, n (%) | 1 (2)                      |
| Syncope                | 1 (2)                      |
| Asymptomatic ECG abnormality, n (%) | 5 (11)               |
| Asymptomatic cardiac imaging abnormality, n (%) | 22 (48)               |
| Histology              | Carpal tunnel, n (%)       | 5 (11) |
|                        | Gastrointestinal, n (%)    | 6 (13) |
|                        | Bladder, n (%)             | 7 (15) |
|                        | Prostate, n (%)            | 1 (2)  |

Values displayed as median (interquartile range) unless stated otherwise. P-values represent comparison testing between NAC ATTR Stage Ia patients with a symptomatic cardiovascular clinical presentation vs. those with a non-cardiovascular clinical presentation at diagnosis by the Kruskal–Wallis test for numerical variables and χ^2 test for categorical variables. NAC ATTR Stage Ia is defined as NT-proBNP ≤ 500 or ≤1000 ng/L in the presence of atrial fibrillation with a loop diuretic equivalent requirement of <0.75 mg/kg.
31%, 13%, and 8% such patients, respectively. Furthermore, despite a relatively short median duration of follow-up in this patient subgroup, the proportion of patients with these cardiovascular morbidities increased following diagnosis including among patients who did not have a primary cardiovascular clinical presentation. These findings lend strong support to the argument for considering disease-modifying therapy with TTR stabilisers or TTR gene silencers at the time of identification of ATTR amyloid in patients with cardiovascular presentation or overt heart failure symptoms.10–12 It remains to be determined, however, whether therapeutic intervention at this early disease stage will lead to a reduction in cardiovascular morbidity.

Study limitations include the relatively smaller size of the ATTRx-CM population compared with ATTRwt-CM population although this probably reflects true disease prevalence in the respective countries. Other limitations include the relatively short median duration of follow-up, the absence of hospitalization data, the use of internal validation rather than external validation, the absence of data on cause of death, the use of expected survival rather than actual survival for general population analyses, the restriction of general population analyses to the UK cohort, and the potential bias introduced by the fact that patients were followed in large specialist amyloidosis centres rather than across general cardiology as well as other specialty clinics.

In conclusion, the short- and mid-term prognosis of patients diagnosed with Stage la ATTR-CM, defined here as an eGFR ≥ 45 mL/min, NT-proBNP ≤ 500 ng/L (or <1000 ng/L in the context of atrial fibrillation), and a loop diuretic equivalent dose requirement of ≤0.75 mg/kg, appears to be good and overall prognosis in the absence of disease-modifying therapy may be comparable to the age and gender-matched general population. However, cardiovascular morbidity is high in patients diagnosed with Stage la ATTR-CM and increases further during patient follow-up. Whether early therapeutic intervention with specific anti-amyloid therapies in patients diagnosed with Stage la ATTR-CM will reduce cardiovascular morbidity and prolong survival remains to be determined.

Supplementary material

Supplementary material is available at European Heart Journal online.

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