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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Characteristics and natural history of early-stage cardiac transthyretin amyloidosis

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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 $\leq$500 ng/L or $\leq$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.

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Structured Graphical Abstract

Key Question

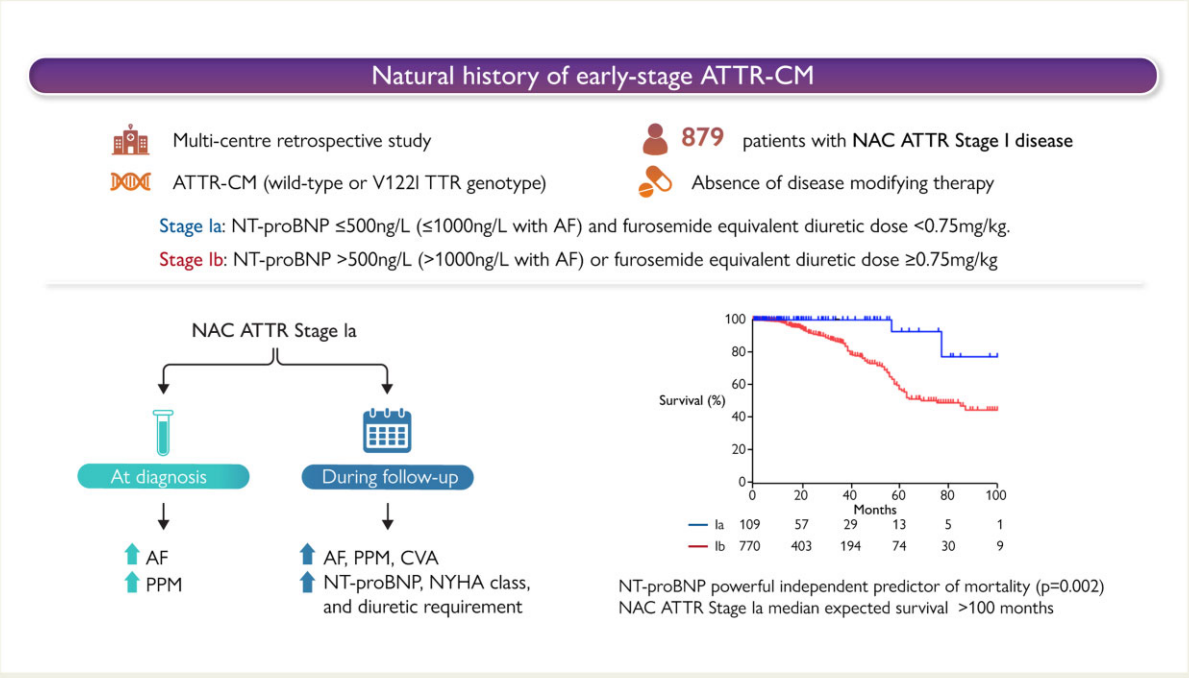
There is little data on the natural history of early-stage transthyretin amyloid cardiomyopathy (ATTR-CM). We sought to characterise the natural history and outcome of patients diagnosed with early-stage ATTR-CM.

Key Finding

Patients diagnosed with NAC Stage Ia ATTR-CM had an expected survival comparable to the matched general UK population. However, Stage Ia patients had substantial cardiovascular morbidity at diagnosis which increased 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.



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

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.[4,7] 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.[7] NAC ATTR Stage I was defined as an NT-proBNP ≤ 3000 ng/L and eGFR ≥ 45 mL/min/1.73 m^2 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.[4]

Patients were systemically 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.[4] 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 (^{99m}Tc-DPD and ^{99m}Tc-HMDP) scintigraphy

Patients were scanned after intravenous injection of ∼700 MBq of ^{99m}Tc-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 ^{99m}Tc-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 ^{99m}Tc-HMDP scintigraphy, previously reported to be equivalent to Perugini Grade ≥2,[8,14] 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.*[15] 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.[16,17]

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.[18]

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.[4,19,20] 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,[20] 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 with 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), ATTRibute-CM (>300 ng/L), APOLLO-B (>300 and >600 ng/L in atrial fibrillation), HELIOS-B (>300 and >600 ng/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)].[10,21–23] 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

NT-proBNP as a continuous variable and loop diuretic dosage by NAC ATTR Stages Ia and Ib as categorical variables. The proportional hazards assumption was checked and satisfied.

Cox regression analyses on the UK cohort alone could not be performed due to there being no deaths in Stage Ia patients from this subgroup; this prevented the creation of a multivariable Cox regression model on this group with subsequent external validation using the Amyloidosis Mondor Network cohort. We, therefore, divided the whole cohort into an 80% training group and 20% validation group to validate our multivariable Cox regression model containing NAC ATTR Stages Ia and Ib using the method reported by Royston.[24] We assessed the Cox proportional hazards regression model on the training data and calculated R^2 for survival models, a measure of the explained variation in such models. The performance of R^2 was evaluated using 1000 bootstrap samples on the validation data. The difference in R^2 values between the training group and validation group was 0.047 [95% confidence interval (CI) −0.25 to 0.34] consistent with no real difference. In addition, a type of model calibration was performed by evaluation of R^2, allowing regression on the predicted index in the validation sample. The model was developed on the training sample and calibrated on the index in the validation sample using 1000 bootstrap samples. The calibration slope was 0.85 suggesting the model is adequately calibrated.

Patient characteristics at diagnosis stratified by NAC ATTR Stages Ia and Ib were compared by Kruskal–Wallis test (numerical variables) and χ^2 test (categorical variables). Patients were also stratified by Perugini grading of cardiac uptake on bone scintigraphy. Patient characteristics of those with NAC ATTR Stage Ia disease were subsequently stratified by presenting symptom into cardiovascular, defined as symptoms of cardiac failure, symptomatic arrhythmia, or cerebrovascular accident, and non-cardiovascular presentations. Kaplan–Meier (KM) survival analyses were performed to estimate median survival and illustrate survival percentages stratified by NAC ATTR Stage. Further KM survival analyses were performed on patients with NAC ATTR Stage Ia stratified by presenting symptom; survival is reported at 80 months of follow-up in these analyses as 100 months of follow-up was not reached in the cardiovascular presentation group. Log-rank tests were performed to compare patient survival between subgroups.

United Kingdom general population survival data were obtained from the Office of National Statistics. Each study patient was assigned an expected survival equivalent to the mean survival for a person of the same age and gender, from the year of diagnosis. These UK individuals were deemed to have died at their expected survival time if that time was <100 months. Any UK individual whose expected survival time was equal to or >100 months was taken as censored at 100 months. A KM survival curve was created for the expected survival times and this was superimposed on the KM survival curves. United Kingdom general population control groups were matched to the NAC ATTR Stage Ia group and the NAC ATTR Stage Ib separately to provide group-specific matching given the significant difference in patient age between Stages Ia and Ib. Survival comparisons with the matched UK population controls were restricted to the UK patient cohort due to differences in population life expectancy between France and the UK.

Data are presented as median (interquartile range) or number (percentage) unless otherwise stated. A *P*-value of <0.05 was deemed significant. Summary statistics were obtained using SPSS v25 (IBM Corp, 2017) and all other analyses were performed using Stata v16 (Stata Corp, 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

Results

Patient characteristics

There were 879 patients with NAC Stage I ATTR-CM at diagnosis included in the analyses (623 from UK and 256 from France); 109 (12%) were Stage Ia and 770 (88%) were Stage Ib. In the UK cohort, 74 (12%) were Stage Ia and 549 (88%) were Stage Ib. Baseline characteristics of all patients are shown in *Table 1* along with a comparison between those with Stages Ia and Ib disease. NAC ATTR Stage Ia patients were more commonly ATTRwt, and had better biochemical, functional, and echocardiographic parameters of disease compared with Stage Ib patients. A greater proportion of NAC ATTR Stage Ib patients had Perugini Grade ≥2 radionuclide scans compared with patients with Stage Ia 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 Ia and Ib, 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.[25–30]

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 Ib (*Table 3*: categorical variable vs. Stage Ia; 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 Ia disease was not met at 100 months, and was 75 months (95% CI: 57–93) among those with Stage Ib 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 Ia disease was not met at 100 months, and there was no evidence of a difference in survival between UK NAC Stage Ia patients and matched UK general population controls ($P = 0.297$; *Figure 1B*). The median estimated survival of UK patients with NAC ATTR Stage Ib 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)	
Male sex, *n* (%)		775 (88)	101 (93)	674 (88)	0.121
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 m^2)		70 (59–81)	76 (66–88)	69 (58–81)	<0.001
Chronic kidney disease stage, *n* (%)	I	120 (14)	26 (24)	94 (12)	0.001
	II	530 (60)	64 (59)	466 (61)	
	IIIa	229 (26)	19 (17)	210 (27)	
Alkaline phosphatase (μ/L) ($n = 866$)		81 (63–103)	72 (58–91)	82 (65–105)	<0.001
Gamma GT (μ/L) ($n = 856$)		58 (31–112)	33 (22–62)	63 (34–117)	<0.001
Serum albumin (g/L) ($n = 740$)		44 (42–46)	44 (42–47)	44 (42–46)	0.093
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* (%)	1	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

Table 1 Continued

		All patients	Controls	Stage Ia	Stage Ib	*P*-value
Carpal tunnel syndrome, *n* (%)	Unilateral	119 (14)	<8.1%[30]	16 (15)	103 (13)	0.710
	Bilateral	423 (48)	<8.1%[30]	66 (61)	357 (46)	0.006
Spinal stenosis, *n* (%)		114 (13)		20 (18)	94 (12)	0.074
Joint replacement, *n* (%)		174 (20)		25 (23)	149 (19)	0.379
Atrial fibrillation, *n* (%)		271 (31)	8%[25]	33 (31)	238 (32)	0.846
PPM, *n* (%)		132 (15)	3%[26]	14 (13)	118 (15)	0.497
ICD, *n* (%)		47 (5)	—	1 (1)	46 (6)	0.028
Hypertension, *n* (%)		388 (44)	64%[27]	47 (43)	341 (44)	0.810
Ischaemic heart disease, *n* (%)		136 (16)	16%[28]	10 (9)	126 (16)	0.052
Stroke or TIA, *n* (%)		96 (11)	9%[28]	9 (8)	87 (11)	0.341
Diabetes mellitus, *n* (%)		143 (16)	14%[29]	22 (20)	121 (16)	0.237

Values are displayed as median (interquartile range) unless otherwise stated. *P*-values represent comparison testing between NAC ATTR Stages Ia and Ib by Kruskal–Wallis test for numerical variables and χ^2 test for categorical variables. NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; IVSd, interventricular septal wall thickness at end-diastole; LVPW, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; TIA, transient ischaemic attack. Controls report the disease prevalence in matched general population groups from a variety of published sources. Number reported where missing data are present within a given variable. NAC ATTR Stage Ia is defined as: NT-proBNP ≤ 500 ng/L or ≤1000 ng/L in the presence of atrial fibrillation with a loop diuretic equivalent requirement of <0.75 mg/kg, and NAC ATTR Stage Ib is defined as: NT-proBNP > 500 ng/L or >1000 ng/L in the presence of atrial fibrillation or a loop diuretic equivalent requirement of ≥0.75 mg/kg.

(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 ischaemic 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 non-specified 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 m^2/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, cardiac 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 ischaemic 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 (acoramidis) 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	Ia	11 (50)	98 (11)	
	Ib	11 (50)	759 (89)	
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 m^2)		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 ^{99m}Tc-HMDP scintigraphy considered equivalent to Perugini Grade ≥2 cardiac uptake ^{99m}Tc-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 χ^2 test for categorical variables.

Table 3 Multivariable Cox regression analyses of mortality indicators at diagnosis in NAC Stage I ATTR-CM

		Multivariable		
		HR	95% CI	*P*-value
NAC ATTR Stage	Ia	1	1.23–20.87	0.025
	Ib	5.06		
Age (per 10 years)		1.14	0.85–1.52	0.374
Male sex		1.28	0.70–2.37	0.424
V122I-ATTRv amyloid type		2.33	1.54–3.53	<0.001
Troponin T (per 100 ng/L)		2.76	1.92–3.97	<0.001
NYHA class	I	1		
	II	1.96	0.90–4.29	0.091
	III	1.78	0.75–4.27	0.194

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, and NAC ATTR Stage Ib is defined as: NT-proBNP > 500 or >1000 ng/L in the presence of atrial fibrillation or a loop diuretic equivalent requirement of ≥0.75 mg/kg. NYHA, New York Heart Association; Harrell's *c*-statistic 0.75.

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 context 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%,

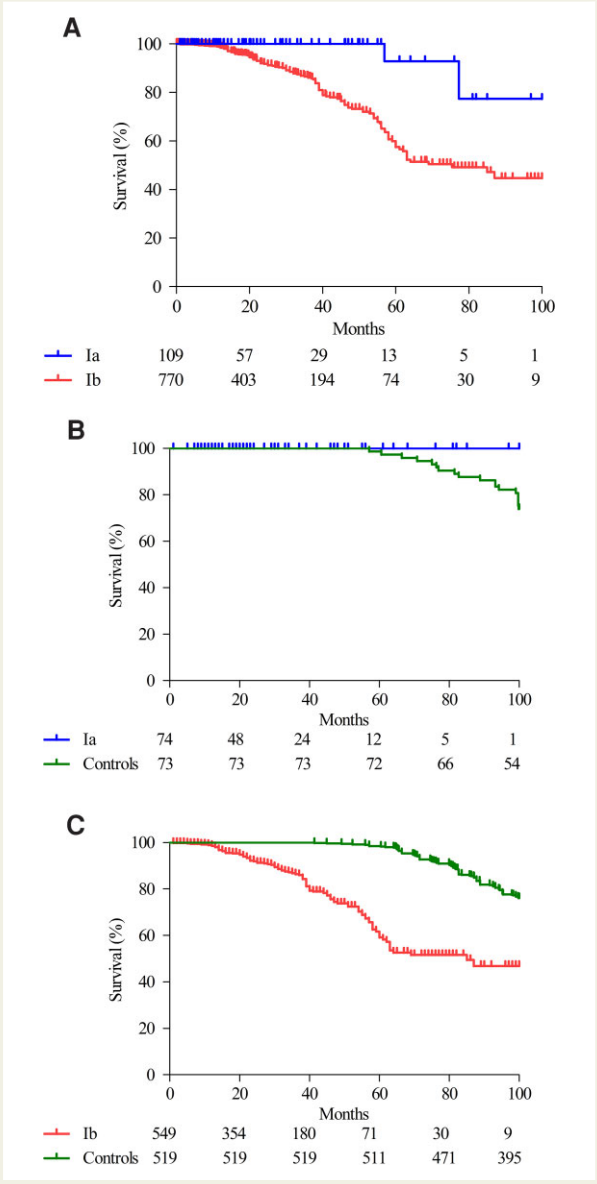


Figure 1 (*A*) Kaplan–Meier survival curves stratified by National Amyloidosis Centre transthyretin amyloid stage for the whole cohort. Median estimated survival among patients with Stage Ia was not met at 100 months and was 75 months (95% CI: 57–93) in patients with Stage Ib ($P = 0.0002$). (*B*) Survival of the UK National Amyloidosis Centre cohort with Stage Ia compared with matched UK general population controls. Median estimated survival was not met in either group at 100 months; there was no evidence of a difference in survival between the two groups ($P = 0.297$). (*C*) Survival of the UK National Amyloidosis Centre cohort with Stage Ib compared with matched UK general population controls. Median estimated survival among patients with Stage Ib was 85 months (95% CI: undefined), and was not met at 100 months in a matched UK general population control group; patient survival was reduced in the Stage Ib group compared with UK general population controls ($P < 0.0001$).

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* (%)	39 (85)	60 (95)	0.062
	V122I-ATTRv, *n* (%)	7 (15)	3 (5)	
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/HDMP 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				
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 cardiac uptake by radionuclide imaging, even in patients without a primary 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 ATTRv-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 Ia ATTR-CM, defined here as an eGFR $\geq$ 45 mL/min, NT-proBNP $\leq$ 500 ng/L (or $\leq$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 Ia ATTR-CM and increases further during patient follow-up. Whether early therapeutic intervention with specific anti-amyloid therapies in patients diagnosed with Stage Ia 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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