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ORIGINAL RESEARCH ARTICLE

Disease progression in cardiac transthyretin amyloidosis is indicated by serial calculation of National Amyloidosis Centre transthyretin amyloidosis stage

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Abstract

Aims Cardiac transthyretin amyloidosis (ATTR-CM) is a progressive and fatal condition. Prognosis can be determined at diagnosis according to the National Amyloidosis Centre (NAC) transthyretin amyloidosis (ATTR) stage. We sought to examine how NAC ATTR stage changes during follow-up and whether it maintains its prognostic value throughout the disease course.
Methods and results We performed a retrospective study of 945 patients with wild-type ATTR-CM (wtATTR-CM) or hereditary ATTR-CM associated with the V122I variant (V122I-hATTR-CM) who were diagnosed and serially evaluated at the UK NAC. Patients who commenced any disease-modifying therapy for amyloidosis were censored at the time of doing so. Landmark Kaplan–Meier survival analyses were performed at diagnosis (n = 945) and at 6 ± 1 (n = 432), 12 ± 3 (n = 562), and 24 ± 3 (n = 316) months and stratified by recalculated NAC ATTR stage at the relevant time point. Cox regression analyses were performed to assess the prognostic significance during follow-up of an increase in NAC ATTR stage from Stage I at diagnosis. Mortality in ATTR-CM was predicted by NAC ATTR stage at each time point [Stage II vs. I, hazard ratios (HRs) 1.95–2.67; $P < 0.001$; Stage III vs. II, HRs 1.64–2.25; $P < 0.001$–0.013]. An increase from NAC ATTR Stage I, which occurred in 21%, 32%, and 44% of evaluable patients at 6, 12, and 24 months of follow-up respectively, was highly predictive of ongoing mortality at each time point (HRs 2.58–3.22; $P < 0.001$) and in each genotypic subgroup (HRs 1.86–4.38; $P < 0.05$). Increase in NAC ATTR stage occurred earlier in V122I-hATTR-CM than in wtATTR-CM (43% vs. 27% at 12 months of follow-up; $P = 0.003$).
Conclusions National Amyloidosis Centre ATTR stage predicts ongoing survival throughout the disease natural history in ATTR-CM, and an increase from NAC ATTR Stage I at diagnosis to a higher NAC ATTR stage predicts mortality throughout follow-up. Serial calculation of NAC ATTR stage suggests a more aggressive phenotype in V122I-hATTR-CM than in wtATTR-CM.

Keywords Amyloidosis; Amyloid; Transthyretin; TTR; Staging; Cardiomyopathy

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Introduction

Cardiac transthyretin amyloidosis (ATTR-CM) may be acquired (wtATTR-CM) or hereditary (hATTR-CM). The commonest hATTR-CM is that associated with the V122I (p.V142I) TTR variant (V122I-hATTR-CM), carried by 3.9% of individuals of African descent.[1] The prevalence of ATTR-CM is not known, but high-grade cardiac uptake on ^{99m}technetium-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy was reported in 3.9% of men over 75 years of age in a recent Spanish study.[2] Advances in imaging techniques[3–5] and development of validated non-biopsy diagnostic criteria for ATTR-

CM[6,7] have led to an exponential rise in diagnoses of ATTR-CM throughout the world.[8]

Without treatment, the natural history of ATTR-CM is one of inexorable progression and death within 3–10 years of diagnosis.[8] Diagnostic delay is common, and patients may be diagnosed at any time during the disease course.[8,9] Recent therapeutic advances, including the TTR stabilizer, tafamidis, and 'gene-silencing' therapies, inotersen[10] and patisiran,[11] show promise in transthyretin amyloidosis (ATTR), although tafamidis is the only such therapy to have specifically been shown to alter the natural history of ATTR-CM.[12] However, a number of Phase 3 clinical trials of these or even newer agents for ATTR-CM are planned or already in progress.

At the time of diagnosis, prognosis of patients with ATTR-CM can be estimated by stratifying them into one of the three National Amyloidosis Centre (NAC) ATTR stages, according to the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and Modification of Diet in Renal Disease estimated glomerular filtration rate (eGFR).[13,14] Median survival in Stage I, II, and III ATTR-CM is approximately 6, 4, and 2 years, respectively.[13] However, serial calculation of NAC ATTR stage in order to determine whether patients progress through the NAC stages during their disease course and if so whether an increase in NAC ATTR stage is of prognostic relevance has not previously been undertaken.

We sought to determine the ability of NAC ATTR stage to predict survival at different times during the disease course in ATTR-CM rather than simply at the time of diagnosis and to determine the prognostic relevance of an increase from NAC ATTR Stage I to a higher NAC ATTR stage throughout patient follow-up.

Methods

Patients

Patients with symptomatic wtATTR-CM or V122I-hATTR-CM, diagnosed between August 2001 and February 2019 on the basis of validated criteria,[6,15] who underwent routine clinical follow-up at NAC, were included in this retrospective study. Patients with other amyloidogenic *TTR* mutations were excluded because of their typical 'mixed' phenotype including amyloid neuropathy. Censor date was 18 October 2019; however, patients receiving any form of disease-modifying therapy were censored at the time of initiation of such treatment in order to exclude the potential influence on survival of therapeutic intervention; this included diflunisal, tafamadis, patisiran, inotersen, and enrolment into interventional clinical trials. Symptomatic heart failure management was according to local protocols.

Nine hundred and forty-five patients were analysed at diagnosis: 432 at 6 ± 1 months from diagnosis, 562 at 12 ± 3 months from diagnosis, and 316 at 24 ± 3 months from diagnosis. The differences in numbers of evaluable patients at each time point were due to a combination of the following: appointments occurring outside the specified time windows, patient death, and insufficient follow-up time before the censor date. A study consort diagram is shown in *Figure 1*.

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

Disease staging

Patients were categorized as NAC ATTR Stage I, defined as NT-proBNP $\leq$ 3000 ng/L and eGFR $\geq$ 45 mL/min/1.73 m^2, or as Stage III, defined as NT-proBNP $>$ 3000 ng/L and eGFR $<$ 45 mL/min/1.73 m^2; with the remainder categorized as Stage II.[13] NAC ATTR stage was calculated at baseline and again at each follow-up attendance within the 6, 12, and 24 month window.

Biomarker analysis

N-terminal pro-B-type natriuretic peptide was measured with an electrochemiluminescence sandwich immunoassay on the Elecsys system 2010 (Roche Diagnostics, Basel, Switzerland); eGFR was calculated by standard Modification of Diet in Renal Disease study equation.

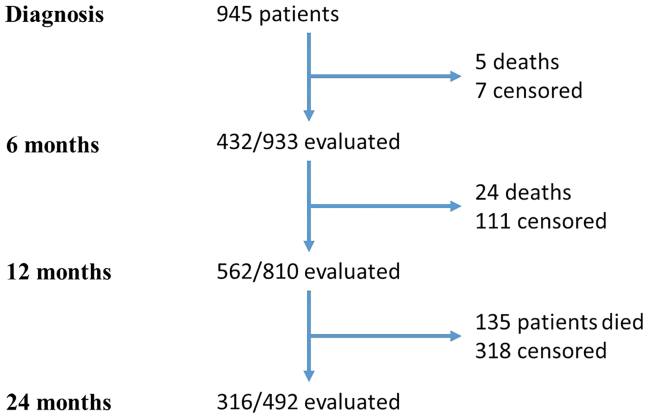
Statistical methods

Date of diagnosis (baseline) was defined as date of first review at NAC. Mortality date was obtained from central National Health Service care records. Patients were categorized into NAC ATTR Stage I, II, and III and further stratified by genotype into wtATTR-CM and V122I-hATTR-CM. Kaplan–Meier (KM) plots were used to illustrate survival stratified by NAC ATTR stage, and Cox proportional hazard regression analysis was used to estimate hazard ratios for mortality in patient subgroups.

Patients with attendances at 6 ± 1, 12 ± 3, and 24 ± 3 months were then restaged based on eGFR and NT-proBNP at the relevant time point. Landmark KM analyses provided survival curves from the relevant time point stratified by NAC ATTR stage recalculated at the relevant time point. Cox proportional hazard regression analysis was used to estimate hazard ratios for mortality from each attendance stratified by NAC ATTR stage, and further subgroup analyses were conducted for both genotypes.

Landmark KM analyses in the subgroup of patients with NAC ATTR Stage I at diagnosis, stratified by whether the

Figure 1 Consort diagram showing evaluable patients at each follow-up time point.



NAC ATTR stage was stable or had increased since diagnosis, were performed at each time point. Cox proportional hazard regression analysis was also used in this patient subgroup to compare mortality from each follow-up time point among those in whom NAC ATTR stage was stable (i.e. still Stage I) and those in whom NAC ATTR stage had increased since diagnosis.

Data are presented as median (inter-quartile range) or number (percentage) unless otherwise stated. A *P*-value of <0.05 was deemed significant unless otherwise stated.

Table 1 Baseline characteristics in patients with wtATTR-CM and V122I-hATTR-CM

	wtATTR-CM (n = 727)	V122I-hATTR-CM (n = 218)	*P*-value
Age at diagnosis (years)	79 (73–83)	77 (72–81)	0.056
Male gender	683 (94%)	154 (71%)	<0.001
Caucasian ancestry	678 (94%)	30 (14%)	<0.001
NAC ATTR Stage I	330 (45%)	106 (49%)	0.464
NAC ATTR Stage II	277 (38%)	73 (34%)	
NAC ATTR Stage III	120 (17%)	39 (18%)	
NT-proBNP (ng/L)	3036 (1717–5310)	2636 (1581–5193)	0.254
eGFR (MDRD, mL/min)	58 (47–71)	57 (46–69)	0.721
CKD Stage I	38 (5%)	13 (6%)	
CKD Stage II	305 (42%)	79 (36%)	
CKD Stage IIIa	235 (32%)	76 (35%)	
CKD Stage IIIb	120 (17%)	34 (16%)	
CKD Stage IV	29 (4%)	16 (7%)	
CKD Stage V	0 (0%)	0 (0%)	
NYHA heart failure class (n = 596, 189)			<0.001
I	54 (9%)	10 (5%)	
II	416 (69%)	112 (59%)	
III	126 (21%)	66 (35%)	
IV	3 (1%)	3 (2%)	
Systolic blood pressure (mmHg)	123 (113–137)	121 (110–135)	0.480
Diastolic blood pressure (mmHg)	74 (68–80)	74 (66–82)	0.612
IVSd (mm)	17 (16–18)	17 (16–18)	0.300
LVPWd (mm)	16 (15–18)	17 (15–18)	0.896
Left ventricular ejection fraction (%)	49 (41–56)	45 (35–51)	<0.001
6MWT distance (m)	363 (274–439)	272 (184–368)	<0.001
Perugini grade on Tc-DPD scan (n = 639, 170)			<0.001
Grade 2	597 (93%)	109 (64%)	
Grade 3	42 (7%)	60 (36%)	
Follow-up (months)	26 (15–39)	24 (15–34)	0.195
Deaths	225 (31%)	114 (52%)	<0.001

6MWT, 6 min walk test; ATTR, transthyretin amyloidosis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IVSd, interventricular septum in diastole; LVPWd, left ventricular posterior wall in diastole; MDRD, Modification of Diet in Renal Disease; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Tc-DPD, ^{99m}technetium-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid; V122I-hATTR-CM, hereditary cardiac transthyretin amyloidosis associated with the V122I variant; wtATTR-CM, wild-type cardiac transthyretin amyloidosis.
Results were displayed as number (percentage) or median (inter-quartile range).

Summary statistics were obtained using SPSS (IBM Corp., 2017), and all other analyses were performed using Stata (Stata Corp., 2019, New York, United States).

Results

Baseline characteristics

Baseline characteristics of 945 patients (727 wtATTR-CM and 218 V122I-hATTR-CM) diagnosed at NAC are shown in *Table 1*. At diagnosis, patients with wtATTR-CM were more commonly male ($P < 0.001$) and had less severe New York Heart Association class heart failure ($P < 0.001$), better left ventricular ejection fraction ($P < 0.001$), higher 6 min walk test distance ($P < 0.001$), and fewer Perugini Grade 3 ^{99m}technetium-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid scans ($P < 0.001$) compared with patients with V122I-hATTR-CM (*Table 1*).

Survival by National Amyloidosis Centre transthyretin amyloidosis stage throughout the disease course

At diagnosis, 436/945 (46%) patients were categorized as NAC ATTR Stage I, 350 (37%) Stage II, and 159 (17%) Stage III, with median survival of 58, 41, and 30 months, respectively [Stage II vs. I, hazard ratio (HR) 1.95; $P < 0.001$; Stage III vs. II, HR 2.25; $P < 0.001$]. In wtATTR-CM, 330 (45%) patients were categorized as Stage I, 277 (38%) Stage II, and 120 (17%) Stage III, with median survival of 63, 46, and 33 months, respectively (Stage II vs. I, HR 2.41; $P < 0.001$; Stage III vs. II, HR 2.46; $P < 0.001$). In V122I-hATTR-CM, 106 (49%) patients were categorized as Stage I, 73 (34%) Stage II, and 39 (18%) Stage III, with median survival of 39, 35, and 26 months (Stage II vs. I, HR 1.62; $P = 0.030$; Stage III vs. II, HR 1.63; $P = 0.062$; *Figure 2A*, *Table 2*, and Supporting Information, *Table S1*).

At 6 months of follow-up, 186/432 (43%) patients were categorized as Stage I, 147 (34%) Stage II, and 99 (23%) Stage III, with median survival from this time point of 56, 36, and 28 months, respectively (Stage II vs. I, HR 2.45; $P < 0.001$; Stage III vs. II, HR 1.86; $P = 0.001$; *Figure 2B*, *Table 2*, and Supporting Information, *Table S1*).

At 12 months of follow-up, 216/562 (38%) patients were categorized as Stage I, 211 (38%) Stage II, and 135 (24%) Stage III, with median survival from this time point of 51, 32, and 23 months, respectively (Stage II vs. I, HR 2.45; $P < 0.001$; Stage III vs. II, HR 1.75; $P < 0.001$; *Figure 2C*, *Table 2*, and Supporting Information, *Table S1*).

At 24 months of follow-up, 105/316 (33%) patients were categorized as Stage I, 119 (38%) Stage II, and 92 (29%) Stage III, with median survival from this time point of 43, 28, and

Figure 2 Landmark Kaplan–Meier analyses showing survival percentages in cardiac transthyretin amyloidosis stratified by National Amyloidosis Centre (NAC) transthyretin amyloidosis stage calculated at the following follow-up time points: (A) diagnosis ($P < 0.001$, log-rank test), (B) 6 month follow-up time point ($P < 0.001$, log-rank test), (C) 12 month follow-up time point ($P < 0.001$, log-rank test), and (D) 24 month follow-up time point ($P < 0.001$, log-rank test). The numbers at risk are displayed below each figure.

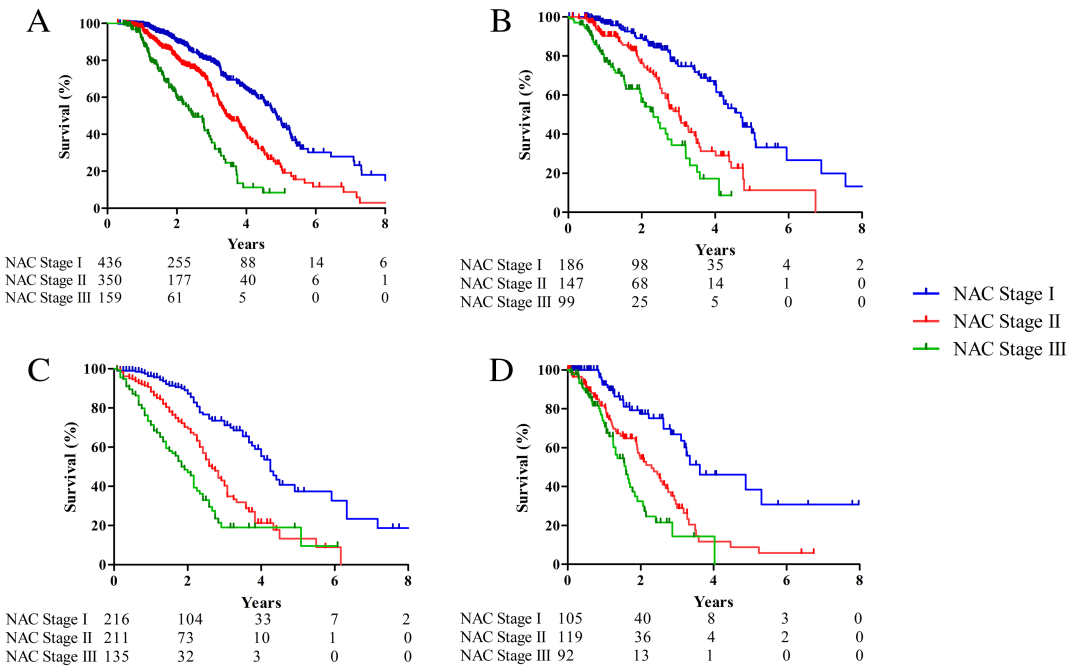


Table 2 Cox regression analyses showing risk of mortality from different follow-up time points in relation to NAC ATTR disease stage calculated at the relevant time point

All patients			wtATTR-CM			V122I-hATTR-CM		
	HR	*P*-value		HR	*P*-value		HR	*P*-value
At diagnosis (*N* = 945)			***N* = 727**			***N* = 218**		
Stage II vs. I	1.95 (1.52–2.49)	<0.001	Stage II vs. I	2.41 (1.77–3.29)	<0.001	Stage II vs. I	1.62 (1.05–2.49)	0.030
Stage III vs. I	4.38 (3.27–5.87)	<0.001	Stage III vs. I	5.92 (4.09–8.56)	<0.001	Stage III vs. I	2.63 (1.59–4.34)	<0.001
Stage III vs. II	2.25 (1.70–2.98)	<0.001	Stage III vs. II	2.46 (1.76–3.42)	<0.001	Stage III vs. II	1.63 (0.97–2.72)	0.062
At 6 month time point (*N* = 432)			***N* = 336**			***N* = 96**		
Stage II vs. I	2.45 (1.67–3.58)	<0.001	Stage II vs. I	2.96 (1.85–4.74)	<0.001	Stage II vs. I	1.90 (0.96–3.74)	0.065
Stage III vs. I	4.55 (2.98–6.96)	<0.001	Stage III vs. I	5.32 (3.11–9.11)	<0.001	Stage III vs. I	2.71 (1.34–5.47)	0.006
Stage III vs. II	1.86 (1.27–2.72)	0.001	Stage III vs. II	1.80 (1.13–2.87)	0.014	Stage III vs. II	1.43 (0.71–2.85)	0.313
At 12 month time point (*N* = 562)			***N* = 432**			***N* = 130**		
Stage II vs. I	2.45 (1.74–3.45)	<0.001	Stage II vs. I	2.36 (1.56–3.55)	<0.001	Stage II vs. I	2.29 (1.21–4.31)	0.011
Stage III vs. I	4.29 (2.99–6.16)	<0.001	Stage III vs. I	4.07 (2.64–6.27)	<0.001	Stage III vs. I	4.32 (2.19–8.53)	<0.001
Stage III vs. II	1.75 (1.28–2.40)	<0.001	Stage III vs. II	1.73 (1.17–2.55)	0.006	Stage III vs. II	1.89 (1.10–3.24)	0.020
At 24 month time point (*N* = 316)			***N* = 251**			***N* = 65**		
Stage II vs. I	2.67 (1.68–4.23)	<0.001	Stage II vs. I	2.53 (1.51–4.24)	<0.001	Stage II vs. I	3.91 (1.29–11.6)	0.016
Stage III vs. I	4.36 (2.66–7.16)	<0.001	Stage III vs. I	3.73 (2.08–6.68)	<0.001	Stage III vs. I	6.48 (2.07–20.3)	0.001
Stage III vs. II	1.64 (1.11–2.42)	0.013	Stage III vs. II	1.47 (0.91–2.38)	0.112	Stage III vs. II	1.66 (0.79–3.48)	0.182

HR, hazard ratio; V122I-hATTR-CM, hereditary cardiac transthyretin amyloidosis associated with the V122I variant; wtATTR-CM, wild-type cardiac transthyretin amyloidosis.

19 months, respectively (Stage II vs. I, HR 2.67; $P < 0.001$; Stage III vs. II, HR 1.64; $P = 0.013$; *Figure 2D*, *Table 2*, and Supporting Information, *Table S1*).

Change in National Amyloidosis Centre transthyretin amyloidosis stage in patients with National Amyloidosis Centre Transthyretin Amyloidosis Stage I disease at diagnosis

Among 436 (46%) patients with NAC ATTR Stage I disease at baseline, 204 were evaluated at 6 months, 2 had died, 2 were censored prior to the 6 month time point, and 228 were alive but not evaluated within the 6 month time point window. Of the 204 evaluable patients, 43 (21%) had an increase in NAC ATTR stage, and the remaining 161 (79%) were still at NAC ATTR Stage I at this time point. Cox regression analysis showed a highly significant increase in ongoing mortality risk among patients with an increase in NAC ATTR stage compared with stable NAC ATTR stage {HR 3.19 [95% confidence interval (CI) 1.76–5.77]; $P < 0.001$}, with consistent results across both genotypes (*Table 3*). Landmark KM survival analysis stratified by stable or increased NAC ATTR stage at 6 months is shown in *Figure 3A*.

Among 436 patients with NAC ATTR Stage I disease at baseline, 283 were evaluated at 12 months, 4 had died, 46 were censored prior to the 12 month time point, and 103 were alive but not evaluated within the 12 month time point window. Of the 283 evaluable patients, 90 (32%) had an increase in NAC ATTR stage, and the remaining 193 (68%) were still at NAC ATTR Stage I at this time point. Cox regression analyses showed a highly significant increase in ongoing mortality risk among patients with an increase in NAC ATTR stage compared with stable NAC ATTR stage [HR 2.58 (95% CI 1.67–3.99); $P < 0.001$] with consistent results across both genotypes (*Table 3*). Landmark KM survival analysis stratified by stable or increased NAC ATTR stage at 12 months is shown in *Figure 3B*.

Among 436 patients with NAC ATTR Stage I disease at baseline, 166 were evaluated at 24 months, 34 had died, 148 were censored prior to the 24 month time point, and 88 were alive but not evaluated within the 24 month time point window. Of the 166 evaluable patients, 73 (44%) had an increase in NAC ATTR stage, and the remaining 93 (56%) were still at NAC ATTR Stage I at this time point. Cox regression analyses showed a highly significant increase in ongoing mortality risk among patients with an increase in NAC ATTR stage compared with stable NAC ATTR stage [HR 3.22 (95% CI 1.87–5.52); $P < 0.001$] with consistent results across both genotypes (*Table 3*). Landmark KM survival analysis stratified by stable or increased NAC ATTR stage at 24 months is shown in *Figure 3C*.

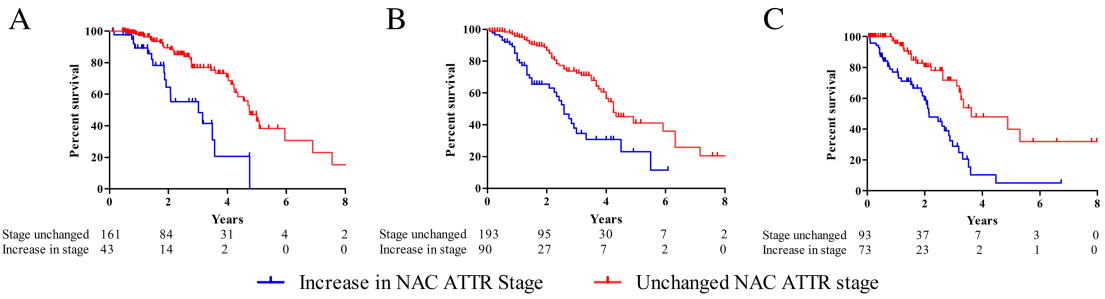
Increase in NAC ATTR stage or death occurred in a significantly higher proportion of NAC ATTR Stage I patients with

Table 3 Cox regression analyses showing risk of ongoing mortality among patients who were at NAC ATTR Stage I at diagnosis according to whether the recalculated NAC ATTR stage was stable or had increased at the relevant time point

	All patients			wtATTR-CM			V122I-hATTR-CM		
	N	HR (95% CI)	*P*-value	*N*	HR (95% CI)	*P*-value	*N*	HR (95% CI)	*P*-value
6 month FU time point	204			152			52		
Stable NAC ATTR Stage I	161	1		123	1		38	1	
Increased NAC ATTR stage	43	3.19 (1.76–5.77)	<0.001	29	2.77 (1.16–6.70)	0.024	14	3.28 (1.37–7.87)	0.008
12 month FU time point	283			210			73		
Stable NAC ATTR Stage I	193	1		152	1		41	1	
Increased NAC ATTR stage	90	2.58 (1.67–3.99)	<0.001	58	1.86 (1.01–3.43)	0.048	32	2.52 (1.28–4.95)	0.007
24 month FU time point	166			134			32		
Stable NAC ATTR Stage I	93	1		78	1		15	1	
Increased NAC ATTR stage	73	3.22 (1.87–5.52)	<0.001	56	2.98 (1.58–5.64)	0.001	17	4.38 (1.38–13.95)	0.012

CI, confidence interval; FU, follow-up; HR, hazard ratio; NAC ATTR, National Amyloidosis Centre transthyretin amyloidosis; V122I-hATTR-CM, hereditary cardiac transthyretin amyloidosis associated with the V122I variant; wtATTR-CM, wild-type cardiac transthyretin amyloidosis.

Figure 3 Landmark Kaplan–Meier survival analyses in patients with National Amyloidosis Centre transthyretin amyloidosis (NAC ATTR) Stage I cardiac transthyretin amyloidosis at diagnosis stratified by whether the recalculated NAC ATTR stage was stable or had increased at each time point. (A) At 6 month follow-up time point, patients with stable NAC ATTR Stage I disease had median ongoing survival of 57 months, and patients with increased NAC ATTR stage had median ongoing survival of 36 months ($P < 0.001$, log-rank test). (B) At 12 month follow-up time point, patients with stable NAC ATTR Stage I disease had median ongoing survival of 51 months, and patients with increased NAC ATTR stage had median ongoing survival of 31 months ($P < 0.001$, log-rank test). (C) At 24 month follow-up time point, patients with stable NAC ATTR Stage I disease had median ongoing survival of 43 months, and patients with increased NAC ATTR stage had median ongoing survival of 26 months ($P < 0.001$, log-rank test). The numbers at risk are displayed below each figure.



V122I-hATTR-CM than wtATTR-CM at the 12 (P = 0.01) and 24 month (P = 0.001) follow-up time points (Supporting Information, *Table S2*). Among 397 wtATTR-CM patients with NAC ATTR Stage II or III disease at diagnosis, 2 (1%), 10 (3%), and 70 (17%) had died at 6, 12, and 24 months of follow-up, respectively. Among 112 V122I-hATTR-CM patients with NAC ATTR Stage II or III disease at diagnosis, 1 (1%), 10 (9%), and 31 (27%) had died at 6, 12, and 24 months of follow-up, respectively.

Discussion

This study shows that NAC ATTR stage, which has been validated as a prognostic tool for ATTR-CM at the time of diagnosis,[13] is applicable throughout the disease course with patients tending to increase their NAC ATTR stage as the condition progresses. The natural history of ATTR-CM is one of relentless progression and eventual death, although the rate of clinical decline varies between individuals. Furthermore, there is often substantial delay in diagnosis of ATTR-CM such that the diagnosis may be made at any time during its natural history.[8,9] Our study shows that patients tend to increase their NAC ATTR stage by 1 point every ~2 years, which is entirely consistent with the published median survival associated with each of the three diagnostic NAC ATTR stages, which differs by about 2 years per stage,[13] and that the prognostic significance of NAC ATTR stage holds up throughout the disease course. Notably, however, the proportion of patients who increased their NAC ATTR stage during follow-up was higher in V122I-hATTR-CM than in wtATTR-CM and, taken together with the higher mortality rate in V122I-hATTR-CM, provides further evidence of a more aggressive phenotype in the hereditary condition.[8,16]

Despite the diagnostic delays highlighted earlier, there is evidence that the recent development and validation of non-invasive diagnosis of ATTR-CM,[6,7] coupled with an increase in disease awareness among cardiologists, partly as a result of therapeutic advances,[12,17] is leading to earlier diagnosis.[8] It seems highly probable that the proportion of patients who are diagnosed with NAC ATTR Stage I will rise to >50% within the next decade. Furthermore, NAC ATTR Stage I encompasses a broad range of disease severity from virtually asymptomatic imaging or histological abnormalities to very significant clinical disease. Our demonstration of the fact that progression from NAC ATTR Stage I to a higher NAC ATTR stage during follow-up is prognostically important is therefore likely to have very substantial clinical relevance. One might even postulate that the absence of an increase in NAC ATTR stage could be used to demonstrate efficacy of novel therapeutic agents in ATTR-CM, although this hypothesis needs further study.

Limitations of our study include the variation in patient numbers, in part as a result of evaluations occurring outside the specified time point windows; however, it is not anticipated that this will introduce bias because appointment delays in our centre almost invariably occur because of issues of capacity rather than on clinical grounds. We maintain that the consistency of the findings across the studied time points indicates that the NAC ATTR stage is applicable at any time during the disease natural history. A further limitation is the relatively small number of patients with V122I-hATTR-CM compared with wtATTR-CM, particularly among those evaluated at later time points.

In summary, we demonstrate for the first time that NAC ATTR stage predicts survival in ATTR-CM throughout follow-up and that an increase in NAC ATTR stage from a diagnostic stage of I predicts mortality throughout the disease natural history.

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Conflict of interest

S.L., A.P., L.C., O.C.C., S.R., J.A.G., D.R., A.M.-N., H.J.L., C.J.W., P.N.H., and M.F. declare that they have no conflict of interest. A.W. and D.F.H. report personal fees from Akcea outside of the submitted work. J.D.G. is an expert advisory board member for Akcea, Alnylam, and Eidos.

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Author contributions

S.L., A.P., M.F., and J.D.G. were responsible for conceiving the study, interpreting the results, and drafting the manuscript. L. C., O.C.C., S.R., J.A.G., D.R., A.W., A.M.-N., H.J.L., C.J.W., D.F. H., and P.N.H. were responsible for the data collection and interpretation.

Supporting information

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

Table S1. Median survival in months from each follow up timepoint according to NAC ATTR Stage calculated at the relevant timepoint.

Table S2. Comparison of change in NAC ATTR Stage and mortality between patients with wtATTR-CM and V122I-hATTR-CM at different timepoints among those with NAC ATTR Stage I at diagnosis.

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