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Original research

Change in N-terminal pro-B-type natriuretic peptide at 1 year predicts mortality in wild-type transthyretin amyloid cardiomyopathy

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ABSTRACT

Objectives Wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) is a progressive and fatal condition. Although prognosis can be determined at the time of diagnosis according to National Amyloidosis Centre (NAC) transthyretin amyloidosis (ATTR) stage, the clinical course varies substantially between individuals. There are currently no established measures of rate of disease progression. Through systematic analysis of functional, biochemical and echocardiographic disease-related variables we aimed to identify prognostic markers of disease progression in wtATTR-CM.

Methods This is a retrospective observational study of 432 patients with wtATTR-CM diagnosed at the UK NAC, none of whom received disease-modifying therapy. The association between mortality from the 12-month timepoint and change from diagnosis to 12 months in a variety of disease-related variables was explored using Cox regression.

Results Change in N-terminal pro-B-type natriuretic peptide concentration (Δ NT-proBNP) at 12 months from diagnosis was the strongest predictor of ongoing mortality and was independent of both change in other disease-related variables (HR 1.04 per 500 ng/L increase (95% CI 1.01 to 1.07); p=0.003) and a range of known prognostic variables at the time of diagnosis (HR 1.07 per 500 ng/L increase (95% CI 1.02 to 1.13); p=0.007). An increase in NT-proBNP of >500 ng/L, >1000 ng/L and >2000 ng/L during the first year of follow-up occurred in 45%, 35% and 16% of patients, respectively.

Conclusion Change in NT-proBNP concentration during the first year of follow-up is a powerful independent predictor of mortality in wtATTR-CM.

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INTRODUCTION

Wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) is an increasingly recognised cause of heart failure. The exact prevalence of wtATTR-CM remains unknown, but high-grade cardiac uptake on ^{99m}Technetium labelled 3,3-diphosphon o-1,2-propanodicarboxylic acid (Tc-DPD) scintigraphy was reported in 3.9% of men over 75 years of age in a recent Spanish study.[1] Advances in imaging techniques[2–4] and development of validated non-biopsy diagnostic criteria for ATTR-CM[5 6] have led to a recent exponential rise in diagnoses of wtATTR-CM throughout the world.[7]

Diagnosis of wtATTR-CM is often delayed and may occur at any time during the disease natural history,[7 8] which is of inexorable progression and death within 10 years of diagnosis.[7] Prognosis can be estimated at the time of diagnosis by stratifying patients by the National Amyloidosis Centre (NAC) transthyretin amyloidosis (ATTR) stage according to the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and estimated Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (eGFR).[9 10] However, there is substantial interpatient variability in the rate of disease progression of wtATTR-CM such that there is an urgent need for a widely applicable marker of disease progression in this population.

We sought to evaluate the change between diagnosis and 12 months of follow-up in a range of disease-related variables to identify the best marker of disease progression and prognosis in wtATTR-CM.

METHODS

Study design

This is a retrospective observational cohort study of 432 patients with symptomatic wtATTR-CM diagnosed at the UK NAC between June 2006 and October 2018. Patients with hereditary ATTR amyloidosis and those receiving any form of disease-modifying therapy were excluded; no patients underwent heart transplantation. Diagnosis was established at NAC in all patients by Tc-DPD scintigraphy coupled with biochemical tests for a clonal dyscrasia on the basis of validated criteria,[5 11] or by histology including immunohistochemistry and proteomic analysis of amyloid, undertaken at NAC. The diagnostic clinical evaluation at NAC as well as routine clinical follow-up performed 12±3 months later also included a full biochemical profile (renal, liver, bone, cardiac biomarkers), echocardiography, and functional assessment including NYHA class and 6 min walk test (6MWT).

All patients provided informed consent for anonymous publication of their data. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Biomarker analysis

NT-proBNP was measured with an electrochemiluminescence sandwich immunoassay on the Elecsys 2010 system (Roche Diagnostics). eGFR was calculated by standard MDRD study equation including correction for race.

Statistical methods

Date of diagnosis (baseline) was defined as date of first review at NAC, and patients were censored at death or last clinical contact. Mortality data were obtained from the National Health Service central care records. Censor date was 18 October 2019.

Change in a range of disease-related variables (labelled as Δ variable throughout the manuscript) between baseline and 12 months was calculated, and the association between each Δ variable and mortality from the 12-month timepoint was explored by univariable Cox regression analyses and subsequently by a multivariable Cox regression analysis in which the best performing biochemical (NT-proBNP), echocardiographic (interventricular septal thickness at end diastole, IVSd) and functional (New York Heart Association (NYHA) class) variables significant in the univariable analyses were included. The 12-month timepoint was selected to identify an early marker of disease progression which would be reached by the majority of patients diagnosed with ATTR-CM; it also matches the timepoint of the primary endpoint measure being used in part A of the ongoing phase III clinical trial ATTRibute-CM. Time-dependent receiver operator characteristic (ROC) curve analyses were performed using both absolute Δ NT-proBNP concentration from baseline and percentage Δ NT-proBNP from baseline to identify the optimal measure of Δ NT-proBNP. The area under the curve was higher for absolute Δ NT-proBNP than for percentage Δ NT-proBNP (0.63 vs 0.60); therefore, absolute Δ NT-proBNP was used for all subsequent analyses. The relationship between Δ NT-proBNP and mortality from the 12-month timepoint was further explored by multivariable Cox regression analyses including a range of previously reported prognostic factors assessed at diagnosis.[12] Landmark Kaplan-Meier survival curves illustrate survival from the 12-month timepoint stratified by different Δ NT-proBNP values.

Data are presented as median (IQR) or number (percentage) unless otherwise stated. A p value of <0.05 was deemed significant. Summary statistics were obtained using SPSS V.25 and all other analyses were performed using Stata V.16.

RESULTS

Patient characteristics

The baseline characteristics of all 432 patients are shown in table 1. The median age at diagnosis of wtATTR-CM was 77 years and 95% were male. The majority of patients (69%) had NYHA class II heart failure at diagnosis and the median 6MWT distance was 358 m. The median (IQR) time from diagnosis to 12±3 month follow-up timepoint was 12 (11–13) months, and the median (IQR) follow-up from the 12-month timepoint was 19 (10–31) months. At censor, 146 patients had died and 286 were alive.

Table 1 Baseline patient characteristics

	n	wtATTR-CM (N=432)
Age at diagnosis (years)	432	77 (73–82)
Male gender	432	409 (95)
Caucasian ancestry	432	402 (93)
NAC ATTR stage I	432	210 (49)
NAC ATTR stage II	432	161 (37)
NAC ATTR stage III	432	61 (14)
NT-proBNP (ng/L)	432	2760 (1568–4904)
eGFR (MDRD, mL/min)	432	60 (49–74)
CKD stage ≤I		24 (6)
CKD stage II		196 (45)
CKD stage IIIa		130 (30)
CKD stage IIIb		66 (15)
CKD stage IV		16 (4)
CKD stage V		0 (0)
Troponin T (ng/L)	389	58 (40–81)
Serum albumin (g/L)	432	44 (42–46)
NYHA heart failure class	432	
I		53 (12)
II		298 (69)
III		77 (18)
IV		4 (1)
Comorbidities	432	
Hypertension		147 (34)
Atrial fibrillation		226 (52)
Diabetes mellitus		54 (13)
Pacemaker		66 (15)
Systolic blood pressure (mm Hg)	432	122 (111–135)
Diastolic blood pressure (mm Hg)	432	72 (67–79)
Body mass index (kg/m^2)	432	26 (24–29)
IVSd (mm)	427	17 (16–18)
LVPWd (mm)	427	16 (15–18)
Left ventricular ejection fraction (%)	423	48 (42–56)
6MWT (m)	313	358 (230–449)
Perugini grade on DPD scan	380	
Grade 2		349 (92)
Grade 3		31 (8)

Results displayed as number (percentage) for categorical variables and median (IQR) for numerical variables.
CKD, chronic kidney disease; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; eGFR, estimated glomerular filtration rate; IVSd, interventricular septal thickness at end diastole; LVPWd, left ventricular posterior wall thickness at end diastole; MDRD, Modification of Diet in Renal Disease; 6MWT, 6 min walk test; NAC ATTR stage, National Amyloidosis Centre transthyretin amyloidosis stage; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; wtATTR-CM, wild-type transthyretin amyloid cardiomyopathy.

Survival impact of change in disease-related variables from baseline to 12 months

Univariable Cox regression analyses identified an association between mortality from the 12-month timepoint and Δ NT-proBNP (p=0.001) and Δ NYHA class (p=0.005) (table 2). Multivariable analysis showed both Δ NT-proBNP (HR 1.04 (95% CI 1.01 to 1.07) per 500 ng/L increase; p=0.003) and increasing NYHA class (HR 1.65 (95% CI 1.11 to 2.47); p=0.014) to be predictive of mortality from the 12-month timepoint, independent of change in other disease-related variables (table 2).

Multivariable Cox regression analysis incorporating Δ NT-proBNP along with a range of baseline variables which are known to be prognostic in wtATTR-CM at the time of diagnosis also showed Δ NT-proBNP (HR 1.07 (95% CI 1.02 to 1.13) per 500 ng/L increase; p=0.007; table 3) to be an independent predictor of mortality along with age and NT-proBNP concentration at diagnosis. When diagnostic eGFR and NT-proBNP as individual variables were exchanged for diagnostic NAC ATTR stage (which is calculated from the same two variables) and this multivariable analysis was repeated, Δ NT-proBNP continued to

Table 2 Association between mortality and change (Δ) from baseline to 12 months in disease-related variables by Cox regression analyses

		Univariable analysis			Multivariable analysis		
Variable	**Median change (IQR)**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Δ NT-proBNP (ng/L)	375 (–258 to 1350)	1.05*	1.02 to 1.07	**0.001**	1.04*	1.01 to 1.07	**0.003**
Δ eGFR (mL/min)	–5 (–12 to 1)	1.00	0.98 to 1.01	0.732			
Δ Albumin (g/L)	–1 (–3 to 1)	1.01	0.95 to 1.06	0.840			
Δ Troponin T (ng/L)	12 (4 to 25)	1.01	1.00 to 1.02	0.055			
Δ IVSd (mm)	0 (0 to 1)	1.15	0.99 to 1.34	0.075	1.03	0.85 to 1.25	0.741
Δ LVPWd (mm)	0 (0 to 1)	1.12	0.98 to 1.27	0.099			
Δ LVEF (%)	–1 (–6 to 4)	1.00	0.98 to 1.02	0.886			
Increasing NYHA class	0 (0 to 1)	1.72	1.18 to 2.52	**0.005**	1.65	1.11 to 2.47	**0.014**
Δ Systolic blood pressure (mm Hg)	–1 (–11 to 9)	1.00	0.99 to 1.01	0.741			
Δ Diastolic blood pressure (mm Hg)	1 (–7 to 7)	1.00	0.98 to 1.01	0.556			
Δ NAC ATTR stage	0 (0 to 0)	1.39	0.94 to 2.06	0.096			
Δ 6MWT (m)	–11 (–70 to 16)	0.85†	0.70 to 1.02	0.080			

Increasing NYHA class is displayed as a binary measure.
P-values meeting statistical significance (p<0.05) are highlighted in bold.
*HR for NT-proBNP is per 500 ng/L increase.
†HR for 6MWT distance is per 100 m increase; the remainder of HRs are per unit increase.
eGFR, estimated glomerular filtration rate; IVSd, interventricular septal thickness at end diastole; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall thickness at end diastole; 6MWT, 6 min walk test; NAC ATTR stage, National Amyloidosis Centre transthyretin amyloidosis stage; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

predict mortality (HR 1.07 (95% CI 1.01 to 1.14) per 500 ng/L increase; p=0.017).

Time-dependent ROC curve analyses identified absolute Δ NT-proBNP concentration from baseline to be a better predictor of mortality than percentage Δ NT-proBNP. The median Δ NT-proBNP was not significantly different between different diagnostic NAC ATTR stages (p=0.19 by Kruskal-Wallis test), and there was no evidence of an association between Δ NT-proBNP and the follow-up interval from diagnosis, which ranged from 9 to 15 months (p=0.13). The proportion of patients with Δ NT-proBNP >500 ng/L, >1000 ng/L and >2000 ng/L at 12 months was 45%, 35% and 16%, respectively. Landmark Kaplan-Meier survival curves stratified for Δ NT-proBNP cut-offs of >500 ng/L or ≤500 ng/L, >1000 ng/L or ≤1000 ng/L, and >2000 ng/L or ≤2000 ng/L are shown in figure 1. Among the 432 patients, 150 (35%) with Δ NT-proBNP >1000 ng/L had a median survival of 29 (95% CI 25 to 33) months compared with 46 (95% CI 38 to 54) months in 282 of 432 (65%) patients with Δ NT-proBNP ≤1000 ng/L (p<0.001). Both Δ NT-proBNP >500 ng/L (HR 1.65 (95% CI 1.18 to 2.31); p=0.003) and >2000 ng/L (HR 2.87 (95% CI 1.93 to 4.27); p<0.001) also predicted ongoing mortality.

Table 3 Multivariable analysis including Δ NT-proBNP at 12 months and a range of variables and baseline patient characteristics known to affect prognosis

		HR	95% CI	P value
Δ NT-proBNP at 12 months*		1.07	1.02 to 1.13	**0.007**
Diagnostic NT-proBNP (ng/L)*		1.07	1.02 to 1.13	**0.006**
Diagnostic troponin T (ng/L)		1.01	1.00 to 1.02	0.147
Diagnostic eGFR (mL/min/1.73 m^2)		1.01	0.99 to 1.03	0.377
Age at diagnosis		1.08	1.02 to 1.13	**0.004**
NYHA class at diagnosis	I	1		
	II	0.74	0.33 to 1.65	0.461
	≥III	0.39	0.14 to 1.15	0.089
IVSd at diagnosis		0.93	0.81 to 1.07	0.321
Body mass index (kg/m^2)		0.95	0.88 to 1.03	0.244
6 min walk test distance at diagnosis (m)†		0.91	0.72 to 1.16	0.457
Atrial fibrillation		0.90	0.50 to 1.63	0.738
Hypertension		1.01	0.54 to 1.89	0.986
Diabetes		2.19	0.99 to 4.86	0.054
Permanent pacemaker in situ		0.73	0.31 to 1.68	0.454
Aortic stenosis‡		1.47	0.53 to 4.11	0.459

Δ NT-proBNP was calculated at the 12-month timepoint; all other variables were assessed at diagnosis.
P-values reaching statistical significance (p<0.05) are highlighted in bold
*HR for NT-proBNP is per 500 ng/L increase.
†HR for 6MWT distance is per 100 m increase.
‡≥Moderate aortic stenosis at diagnosis; the remainder of HRs are per unit increase.
eGFR, estimated glomerular filtration rate; IVSd, interventricular septal thickness at end diastole; 6MWT, 6 min walk test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

DISCUSSION

This study establishes Δ NT-proBNP at 12 months from diagnosis as a powerful independent predictor of ongoing mortality in patients with wtATTR-CM. Importantly, the prognostic relevance of Δ NT-proBNP was independent of a range of biochemical, functional and echocardiographic parameters at diagnosis, including NAC ATTR stage, troponin T, age, NYHA class, 6MWT distance, presence of atrial fibrillation and IVSd thickness.

Limitations of our study include its retrospective design, exclusion of patients who die within the first year of follow-up (approximately 5% of patients in the UK), exclusion of more detailed echocardiographic variables and absence of cardiac magnetic resonance data.[13–16] However, the authors maintain that a biomarker-based prognostic system has great attraction due to its simplicity, lack of operator variability, and universal availability and applicability. There may also be concerns that NT-proBNP concentration is known to be confounded by other factors in the wtATTR-CM population; however, where possible, these were accounted for in our multivariable model. Furthermore, in systemic light chain cardiac amyloidosis, a far more heterogeneous disease than wtATTR-CM, diagnostic NT-proBNP predicts mortality and both response to treatment and disease progression are defined by Δ NT-proBNP, which is

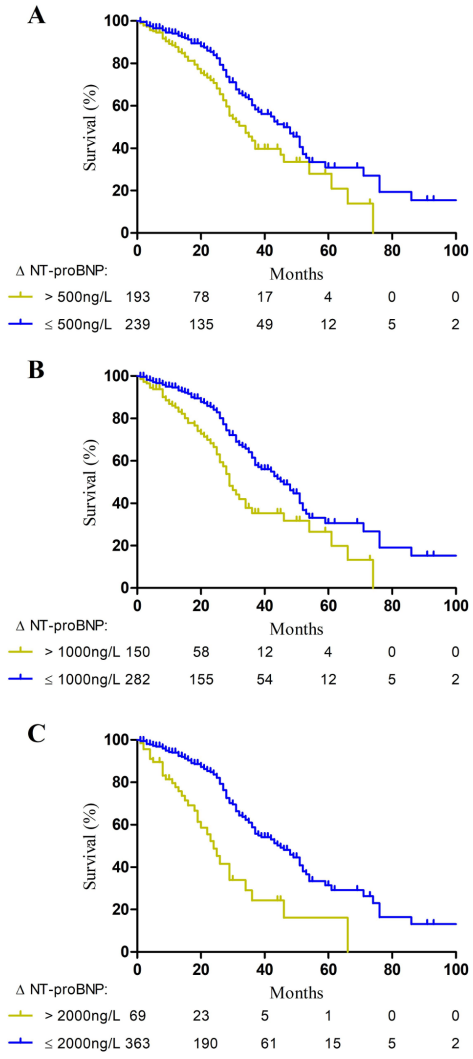

Figure 1 Landmark Kaplan-Meier survival curves stratified by Δ NT-proBNP during the first year of follow-up. Numbers at risk are shown below each curve. (A) Patient survival stratified by Δ NT-proBNP >500 ng/L or ≤500 ng/L (HR 1.65 (95% CI 1.18 to 2.31); p=0.003). (B) Patient survival stratified by Δ NT-proBNP >1000 ng/L or ≤1000 ng/L (HR 1.92 (95% CI 1.37 to 2.70); p<0.001). (C) Patient survival stratified by Δ NT-proBNP >2000 ng/L or ≤2000 ng/L (HR 2.87 (95% CI 1.93 to 4.27); p<0.001). NT-proBNP, N-terminal pro-B-type natriuretic peptide.

strongly associated with morbidity, quality of life and mortality despite the same, and indeed additional, confounders.[17 18] Our study does not include patients on disease-modifying therapy since tafamidis is not available in the UK.

A number of disease-modifying therapies have emerged for ATTR amyloidosis, including diflunisal,[19] tafamidis,[20] patisiran[21 22] and inotersen,[23 24] and several of the relevant clinical trials suggest a role of Δ NT-proBNP in the assessment of response to these disease-modifying treatments. Tafamidis is associated with a reduction in mortality among patients with ATTR-CM, and the ATTR-ACT trial showed a smaller increase in NT-proBNP in the tafamidis group compared with placebo.[20] Post-hoc analysis of the subpopulation with hereditary ATTR-CM accompanying neuropathy in the APOLLO study showed a highly significant reduction in NT-proBNP concentration among patients receiving patisiran compared with those on placebo.[22] Of note, the trial design of ATTRibute-CM, a current global phase III clinical trial evaluating the novel transthyretin (TTR) stabiliser acoramidis in ATTR-CM, includes a part A for which the primary endpoint is a comparison of Δ 6MWT distance from enrolment to 12 months between the treatment and placebo groups.[25] Although Δ 6MWT distance undoubtedly provides a valuable functional assessment, it is noteworthy that it did not predict survival in our cohort.

On the basis of these data, we believe that evaluation of Δ NT-proBNP at 12 months in a cohort with wtATTR-CM receiving disease-modifying therapy is warranted to further assess its potential utility as a marker of treatment response and potential use as a surrogate endpoint in future clinical trials. Multiple disease-modifying therapies may soon be available for wtATTR-CM, including both gene silencer and TTR stabiliser therapies, and early markers of treatment response will be required to guide therapeutic decisions.

In summary, we establish for the first time that Δ NT-proBNP concentration in the first year after diagnosis of wtATTR-CM is a powerful independent predictor of ongoing mortality. Further study of Δ NT-proBNP in a wtATTR-CM cohort receiving disease-modifying therapy is warranted to establish its potential utility as an indicator of treatment response.

Key messages

What is already known on this subject?

- The natural history of wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) is of inexorable progression and death within 10 years of diagnosis.
- Prognosis in the absence of disease-modifying treatment is predicted at diagnosis by the National Amyloidosis Centre transthyretin amyloidosis (ATTR) stage, although there is significant interpatient variability in the rate of disease progression.
- At present there are no established markers of disease progression widely applicable to the wtATTR-CM population.

What might this study add?

- This study establishes change in N-terminal pro-B-type natriuretic peptide in the first year after diagnosis (Δ NT-proBNP) as a powerful independent predictor of mortality in wtATTR-CM.

How might this impact on clinical practice?

- This study highlights a role of Δ NT-proBNP at 12 months in identifying patients with a more aggressive disease phenotype.
- Further study in a cohort receiving disease-modifying treatment is warranted to assess the utility of Δ NT-proBNP as a marker of treatment response and potential surrogate clinical trial endpoint.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval All patients were managed in accordance with the Declaration of Helsinki. The study received IRB approval from the Royal Free Hospital Ethics Committee.

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