

# Stratifying Disease Progression in Patients With Cardiac ATTR Amyloidosis



Adam Ioannou, MBBS, BSc,<sup>a</sup> Francesco Cappelli, PhD,<sup>b</sup> Michele Emdin, MD, PhD,<sup>c,d</sup> Christian Nitsche, MD, PhD,<sup>e</sup> Simone Longhi, MD, PhD,<sup>f</sup> Ahmad Masri, MD,<sup>g</sup> Alberto Cipriani, MD, PhD,<sup>h,i</sup> Mattia Zampieri, MD,<sup>b</sup> Federica Colio, MD,<sup>b</sup> Michael Poledniczek,<sup>e</sup> Aldostefano Porcari, MD,<sup>a,j</sup> Yousuf Razvi, MBChB, BSc,<sup>a</sup> Alberto Aimo, PhD,<sup>c,d</sup> Giuseppe Vergaro, MD, PhD,<sup>c,d</sup> Laura De Michieli, MD, PhD,<sup>h</sup> Muhammad U. Rauf, MBBS,<sup>a</sup> Rishi K. Patel, MBBS, BSc,<sup>a</sup> Eugenia Villanueva, MD,<sup>a</sup> Yael Lustig,<sup>a</sup> Lucia Venneri, MD, PhD,<sup>a</sup> Ana Martinez-Naharro, PhD,<sup>a</sup> Helen Lachmann, MD,<sup>a</sup> Ashutosh Wechalekar, MD,<sup>a</sup> Carol Whelan, MD,<sup>a</sup> Aviva Petrie, MSc,<sup>k</sup> Philip N. Hawkins, MD, PhD,<sup>a</sup> Scott Solomon, MD,<sup>l</sup> Julian D. Gillmore, MD, PhD,<sup>a</sup> Marianna Fontana, MD, PhD<sup>a</sup>

## ABSTRACT

**BACKGROUND** Transthyretin cardiac amyloidosis (ATTR-CA) is a progressive cardiomyopathy. The clinical course varies among individuals and there are no established measures to assess disease progression.

**OBJECTIVES** The goal of this study was to assess the prognostic importance of an increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and outpatient diuretic intensification (ODI) as markers of disease progression in a large cohort of patients with ATTR-CA.

**METHODS** We evaluated landmark survival analysis based on worsening of NT-proBNP and requirement for ODI between time of diagnosis and a 1-year visit, and subsequent mortality in 2,275 patients with ATTR-CA from 7 specialist centers. The variables were developed in the National Amyloidosis Centre (NAC) cohort (n = 1,598) and validated in the external cohort from the remaining centers (n = 677).

**RESULTS** Between baseline and 1-year visits, 551 (34.5%) NAC patients and 204 (30.1%) patients in the external validation cohort experienced NT-proBNP progression (NT-proBNP increase >700 ng/L and >30%), which was associated with mortality (NAC cohort: HR: 1.82; 95% CI: 1.57-2.10;  $P < 0.001$ ; validation cohort: HR: 1.75; 95% CI: 1.32-2.33;  $P < 0.001$ ). At 1 year, 451 (28.2%) NAC patients and 301 (44.5%) patients in the external validation cohort experienced ODI, which was associated with mortality (NAC cohort: HR: 1.88; 95% CI: 1.62-2.18;  $P < 0.001$ ; validation cohort: HR: 2.05; 95% CI: 1.53-2.74;  $P < 0.001$ ). When compared with patients with a stable NT-proBNP and stable diuretic dose, a higher risk of mortality was observed in those experiencing either NT-proBNP progression or ODI (NAC cohort: HR: 1.93; 95% CI: 1.65-2.27;  $P < 0.001$ ; validation cohort: HR: 1.94; 95% CI: 1.36-2.77;  $P < 0.001$ ), and those experiencing both NT-proBNP progression and ODI (NAC cohort: HR: 2.98; 95% CI: 2.42-3.67;  $P < 0.001$ ; validation cohort: HR: 3.23; 95% CI: 2.17-4.79;  $P < 0.001$ ).

**CONCLUSIONS** NT-proBNP progression and ODI are frequent and consistently associated with an increased risk of mortality. Combining both variables produces a simple, universally applicable model that detects disease progression in ATTR-CA. (J Am Coll Cardiol 2024;83:1276-1291) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on [www.jacc.org/journal/jacc](http://www.jacc.org/journal/jacc).

From the <sup>a</sup>National Amyloidosis Centre, University College London, London, United Kingdom; <sup>b</sup>Tuscan Regional Amyloidosis Centre, Careggi University Hospital, Florence, Italy; <sup>c</sup>Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy; <sup>d</sup>Fondazione Toscana Gabriele Monasterio, Pisa, Italy; <sup>e</sup>Division of Cardiology, Department of Internal Medicine, Medical University of Vienna, Vienna, Austria; <sup>f</sup>Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; <sup>g</sup>OHSU Center for Hypertrophic Cardiomyopathy and Amyloidosis, Portland, Oregon,

**T**ransthyretin cardiac amyloidosis (ATTR-CA), is a progressive and ultimately fatal cardiomyopathy, characterized by the deposition of misfolded transthyretin, in the form of amyloid fibrils, within the myocardial extracellular space.<sup>1,2</sup> The sporadic, noninherited, wild-type (wtATTR-CA) is a condition of older, predominantly male individuals; whereas the hereditary form (hATTR-CA) can present earlier in life with a varying clinical phenotype, often comprising both cardiomyopathy and polyneuropathy.<sup>3,4</sup>

SEE PAGE 1292

The only drug currently approved for the treatment of ATTR-CA is tafamidis, which stabilizes the TTR tetramer to prevent dissociation into amyloidogenic monomers that deposit in the myocardium.<sup>5</sup> However, several novel compounds that inhibit TTR synthesis and subsequent amyloid formation are in advanced stages of development and likely to become available soon in clinical practice.<sup>6</sup> Indicators of worsening disease might highlight the need to switch to alternative agents with different mechanisms of action or consider combination therapy, and will be crucial in guiding treatment decisions. Hence, there is an urgent clinical need to identify widely applicable markers of disease progression. Advances in diagnostic techniques have translated into patients with ATTR-CA being diagnosed at earlier disease stages, with substantially lower mortality. These changes have important implications for clinical trial design and have spurred an increasing need to identify markers of disease progression that could be used alongside traditional endpoints as an extended composite outcome and capture a higher number of events.<sup>7</sup>

An increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP) is common in patients with heart failure who experience disease progression.<sup>8</sup> Although an increase in NT-proBNP has been identified as a marker of disease progression in a small cohort of patients with wtATTR-CA, this is yet to be validated and has not been applied to patients with hATTR-CA, or patients prescribed disease-modifying

therapy.<sup>9</sup> A recent consensus document suggested adopting the NT-proBNP thresholds used to monitor treatment response in cardiac light-chain amyloidosis.<sup>10</sup> However, considering the differences in phenotype, prognosis, and treatment paradigm, it is plausible that alternative thresholds are more appropriate in ATTR-CA. In response to disease progression and worsening heart failure symptoms, outpatient diuretic intensification (ODI) is also common and directly affects NT-proBNP levels. ODI is also a strong independent predictor of prognosis in patients with heart failure, but the clinical significance of ODI in patients with ATTR-CA is yet to be characterized.<sup>11-13</sup>

The aims of this study were to assess the prognostic importance of an increase in NT-proBNP and ODI as markers of disease progression in a large cohort of patients with ATTR-CA.

## METHODS

**PATIENT POPULATION.** This is a retrospective multinational longitudinal study of patients diagnosed with ATTR-CA between 2005 and 2022 from 7 specialist referral centers: National Amyloidosis Centre (UK), Portland, Oregon (USA), Vienna (Austria), and 4 Italian centers (Bologna, Florence, Padua, and Pisa). Patients who underwent a comprehensive assessment at the time of diagnosis, and at 1-year of follow-up were eligible for inclusion. The diagnosis of ATTR-CA was established on the basis of validated diagnostic criteria.<sup>10</sup> All patients underwent genetic sequencing of the *TTR*-gene. The study was conducted according to the Declaration of Helsinki and informed consent was obtained under the institutional review board policies of the relevant hospital administrations.

**OUTPATIENT DIURETIC INTENSIFICATION.** At the time of diagnosis and the subsequent 1-year follow-up assessment, the dose of oral loop diuretic was standardized to furosemide equivalents.<sup>14</sup> ODI was defined as any postdiagnosis initiation or increment in the dose of loop diuretic (furosemide equivalent).<sup>11,12</sup>

## ABBREVIATIONS AND ACRONYMS

**ATTR-CA** = transthyretin cardiac amyloidosis

**hATTR-CA** = hereditary transthyretin cardiac amyloidosis

**NAC** = National Amyloidosis Centre

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**ODI** = outpatient diuretic intensification

**wtATTR-CA** = wild-type transthyretin cardiac amyloidosis

USA; <sup>b</sup>Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; <sup>c</sup>Cardiology Unit, University Hospital Padua, Padua, Italy; <sup>d</sup>Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; <sup>e</sup>University College London, Biostatistics Unit, UCL Eastman Dental Institute, London, United Kingdom; and the <sup>f</sup>Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

**STATISTICAL ANALYSIS.** Statistical analysis was performed using Stata (2021 Stata Statistical Software: Release 17, StataCorp LLC). All continuous variables were tested for normality (Shapiro-Wilk test) and presented as mean  $\pm$  SD if the distribution was normal or median (Q1-Q3) otherwise. The independent samples Student's *t*-test was used to compare means if the data were normally distributed in each group, or its nonparametric equivalent (Mann-Whitney *U* test) was used to compare the distributions of the 2 groups. Categorical data are presented as absolute numbers (n) and frequencies (%) and compared using the chi-square test.

To investigate and validate whether an increase in NT-proBNP and ODI at 1 year were associated with disease progression, the population was separated into a development cohort, comprising the patients from the National Amyloidosis Centre (NAC), and a validation cohort, comprising patients from the remaining centers. The optimal cutpoint for the absolute change in NT-proBNP and percentage change in NT-proBNP at 1 year were established using time-dependent receiver operating characteristic curves in the development cohort. The optimal cutpoint determined by the Youden method for an absolute change was 735 ng/L (sensitivity: 46.4%, specificity: 73.7%), and percentage change was 28.7% (sensitivity: 46.9%, specificity: 61.4%). Cutpoints of an absolute increase  $>700$  ng/L (sensitivity: 47.2%, specificity: 72.5%), and relative percentage increase  $>30.0\%$  (sensitivity: 46.3%, specificity: 61.9%) were both good discriminators of survival by the log-rank test. Based on the biological variability of NT-proBNP, progression of NT-proBNP was defined as an increase that was both  $>700$  ng/L and  $>30.0\%$ .<sup>15</sup>

Landmark survival analysis was carried out by assessing the relationship between initiation or intensification of oral diuretic (ODI) or worsening of NT-proBNP at the 1-year follow-up time point, with all-cause mortality from the 1-year follow-up time point onward. Mortality data were obtained via national databases. Survival was evaluated using Cox proportional hazards regression analysis, providing estimated HRs with 95% CIs. The proportional hazards assumption was checked and confirmed using weighted Schoenfeld residuals. The association between the variables (NT-proBNP progression and ODI) and mortality was first evaluated in the NAC cohort, and then corroborated using the validation cohort, composed of patients from the remaining centers. Significant results were followed by internal validation. Cox proportional hazards regression analysis was repeated in the whole study population, and internal validation of the model was achieved by

performing a bootstrapping procedure with 500 repeats, affording a comparison of the percentile and bias-corrected methods to ensure the results were unbiased.

A second landmark analysis comprised patients prescribed disease-modifying therapy or enrolled into clinical trials, who underwent assessment at the start date, and follow-up assessment at 1 year. This assessed the relationship between ODI or NT-proBNP worsening at the 1-year follow-up time point, with all-cause mortality from the 1-year follow-up time point onward.

The likelihood ratio test was used to evaluate the contribution of adding ODI to NT-proBNP progression. Harrell's c-statistic was calculated to measure the discriminatory ability of ODI and NT-proBNP progression. The c-statistics were compared by randomly dividing the data set into 2 cohorts (1:1). The models were fitted to the first cohort, and the c-statistics compared in the second cohort using a Student's *t*-test after creating Jackknife standard errors. Kaplan-Meier curves were constructed to view survival in different groups from the 1-year time point. Statistical significance was defined as  $P < 0.05$ .

## RESULTS

The total study population comprised 2,275 patients. The development cohort comprised 1,598 patients diagnosed at the NAC, of whom 1,100 (68.8%) had wtATTR-CA, 252 (15.8%) had p.(V142I) hATTR-CA, and 236 (14.8%) had non-p.(V142I) hATTR-CA. The median time from baseline to follow-up assessment was 12.1 months, and the median follow-up duration from the 1-year time point was 32.7 months, during which 183 patients were enrolled into clinical trials and 173 were prescribed disease-modifying therapy (inotersen = 6, patisiran = 93, tafamidis = 74). The validation cohort comprised 677 patients diagnosed at 6 external tertiary referral centers, of whom 608 (89.8%) had wtATTR-CA, 10 (1.5%) had p.(V142I) hATTR-CA, and 59 (8.7%) had non-p.(V142I) hATTR-CA. The median time from baseline to follow-up assessment was 12.5 months, and the median follow-up from the 1-year time point was 22.6 months, during which 68 patients were enrolled into clinical trials (39 of whom were also prescribed tafamidis) and 255 were prescribed disease-modifying therapy (inotersen = 3, patisiran = 5, tafamidis = 247). The baseline characteristics are summarized in [Table 1](#).

**NT-proBNP PROGRESSION.** At 1-year post diagnosis, 551 (34.5%) of NAC patients and 204 (30.1%) of patients in the external validation cohort experienced NT-proBNP progression. In patients who experienced

**TABLE 1** Baseline Characteristics for the Study Population

	NAC Cohort (n = 1,598)	Wild-Type ATTR-CA Subgroup (n = 1,110)	p.(V142I) hATTR-CA Subgroup (n = 252)	Non-p.(V142I) hATTR-CA Subgroup (n = 236)	External Validation Cohort (n = 677)
Age, y	75.7 ± 8.1	77.8 ± 6.4	75.2 ± 7.3	66.2 ± 9.6	78.4 ± 7.4
Male	1,380 (86.4)	1,039 (93.6)	175 (69.4)	166 (70.3)	587 (86.7)
Ethnicity					
Caucasian	1,262 (79.0)	1,030 (92.8)	31 (12.3)	201 (79.0)	666 (98.4)
Afro-Caribbean	308 (19.3)	73 (6.6)	213 (84.5)	22 (9.3)	11 (1.6)
Asian	21 (1.3)	7 (0.6)	5 (2.0)	9 (3.8)	0 (0.0)
Other	7 (0.4)	0 (0.0)	3 (1.2)	4 (1.7)	0 (0.0)
AF/AFL	776 (48.6)	612 (55.1)	97 (38.5)	67 (28.4)	374 (55.2)
IHD	287 (18.0)	239 (21.5)	34 (13.5)	14 (5.9)	147 (21.7)
Diabetes mellitus	234 (14.6)	164 (14.8)	55 (21.8)	15 (6.4)	122 (18.0)
Stroke/TIA	150 (9.4)	107 (9.6)	31 (12.3)	12 (5.1)	58 (8.6)
CKD stage 3-5	735 (46.0)	541 (48.7)	148 (58.7)	46 (19.5)	357 (52.7)
Cardiac devices					
PPM	193 (12.1)	127 (11.4)	26 (10.3)	40 (16.9)	101 (14.9)
ICD	37 (2.3)	26 (2.3)	6 (2.4)	5 (2.1)	22 (3.2)
CRT-D	19 (1.2)	13 (1.2)	1 (0.4)	5 (2.1)	11 (1.6)
CRT-P	29 (1.8)	25 (2.3)	0 (0.0)	0 (0.3)	6 (0.9)
Heart failure severity					
NYHA functional class					
I	220 (13.7)	153 (13.7)	11 (4.3)	57 (24.2)	142 (21.0)
II	984 (61.6)	702 (63.2)	146 (57.9)	136 (57.6)	376 (55.5)
III	311 (19.5)	196 (17.6)	86 (34.1)	29 (12.3)	154 (22.7)
IV	19 (1.2)	10 (0.9)	6 (2.3)	3 (1.3)	5 (0.7)
Missing	63	49	3	11	0
NAC stage					
1	867 (54.3)	581 (52.3)	126 (50.0)	160 (67.8)	373 (55.1)
2	531 (33.2)	387 (34.2)	81 (32.1)	63 (26.7)	196 (28.9)
3	200 (12.5)	142 (12.8)	45 (17.9)	13 (5.5)	108 (15.9)
NT-proBNP, ng/L	2,471 (1,309-4,578)	2,555 (1,423-4,588)	2,615 (1,488-5,163)	1,939 (710-3,703)	2,127 (953-4,439)
eGFR, mL/min/1.73 m <sup>2</sup>	62 (50-77)	60 (48-74)	56 (46-68)	81 (64-90)	57 (46-73)
Echocardiographic parameters					
IVSd, mm	16.7 ± 2.5	16.8 ± 2.4	16.9 ± 2.3	16.2 ± 2.9	17.8 ± 3.5
PWTd, mm	16.3 ± 2.6	16.4 ± 2.5	16.6 ± 2.3	15.8 ± 2.9	14.9 ± 5.0
LVEF, %	48.7 ± 10.5	49.1 ± 10.1	44.6 ± 11.1	51.2 ± 10.7	52.5 ± 10.4
Medications					
Beta-blockers	868 (54.3)	633 (57.0)	157 (62.3)	78 (33.1)	389 (57.5)
ACEI/ARBs	917 (57.3)	670 (60.4)	170 (67.5)	77 (32.6)	371 (55.1)
ARNI	13 (0.8)	10 (0.9)	3 (1.2)	0 (0.0)	16 (2.4)
MRAs	650 (40.7)	450 (40.5)	142 (56.3)	58 (24.6)	225 (33.2)
SGT2i	29 (1.8)	19 (1.7)	4 (1.6)	6 (2.5)	12 (1.8)
Loop diuretic	1,118 (70.0)	783 (70.5)	208 (82.5)	127 (53.8)	461 (68.2)
Thiazide diuretic	67 (4.2)	44 (4.0)	17 (6.7)	6 (2.5)	43 (6.4)

Values are mean ± SD, n (%), n, or median (Q1-Q3). Patients in the non-p.(V142I) hATTR-CA subgroup had the following variants: p.(Thr80Ala) = 131, p.(Val50Met) = 21, p.(Ser97Tyr) = 16, p.(Ile127Val) = 10, p.(Ile88Leu) = 6, p.(Glu62Asp) = 5, p.(Glu109Lys) = 5, p.(Gly67Val) = 4, p.(Ala117Ser) = 3, p.(Gly26Ser) = 3, p.(Gly67Arg) = 3, p.(Arg54Gly) = 2, p.(Ile127Phe) = 2, p.(Ser43Asn) = 2, p.(Tyr134Cys) = 2, p.(Tyr89Phe) = 2, p.(Ala120Ser) = 1, p.(Asp58Tyr) = 1, p.(Asp58Val) = 1, p.(Cys30Gly) = 1, p.(Glu74Leu) = 1, p.(Glu74Lys) = 1, p.(Glu109Gln) = 1, p.(Glu112Lys) = 1, p.(Gly67Glu) = 1, p.(Gly73Ala) = 1, p.(Gly73Glu) = 1, p.(His110Asp) = 1, p.(Ile93Val) = 1, p.(Ile104Ser) = 1, p.(Ile104Thr) = 1, p.(Phe64Leu) = 1, p.(Ser70Arg) = 1, p.(Tyr116Ser) = 1, p.(Val40Ile) = 1. The external validation cohort comprised 608 patients with wtATTR-CA, 12 patients with p.(V142I) hATTR-CA, and 57 patients with non-p.(V142I) hATTR-CA. Patients with non-p.(V142I) hATTR-CA had the following variants: p.(Ile88Leu) = 26, p.(His128Arg) = 9, p.(Val50Met) = 3, p.(Glu94Gln) = 2, p.(Glu109Gln) = 2, p.(Thr80Ala) = 2, p.(Phe84Leu) = 2, p.(Phe104Ile) = 2, p.(Thr89Ile) = 2, p.(Arg25His) = 1, p.(Glu82Lys) = 1, p.(Glu101Ala) = 1, p.(Gly87Glu) = 1, p.(Gly97Arg) = 1, p.(His130Asn) = 1, p.(Ser97Tyr) = 1.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CKD = chronic kidney disease; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; eGFR = estimated glomerular filtration rate; hATTR-CA = hereditary transthyretin cardiac amyloidosis; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; IVSd = interventricular septum in diastole; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPM = permanent pacemaker; PWTd = posterior wall thickness in diastole; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TIA = transient ischemic attack; wtATTR-CA = wild-type transthyretin cardiac amyloidosis.

NT-proBNP progression, the median NT-proBNP increased from 2,613 ng/L (Q1-Q3: 1,463-4,604 ng/L) to 4,860 ng/L (Q1-Q3: 3,112-8,822 ng/L). Patients who experienced NT-proBNP progression were older, and had a higher prevalence of p.(V142I) hATTR-CA. Patients who experienced NT-proBNP progression had a greater left ventricular wall thickness and lower estimated glomerular filtration rate than those who did not. Patients who experienced NT-proBNP progression were more commonly prescribed renin-angiotensin system blockers and loop diuretics than those who did not (Table 2).

In the NAC cohort, patients who experienced NT-proBNP progression had a higher death rate (25.0 deaths per 100 person-years [py]; 95% CI: 22.4-27.8 deaths per 100 py) than those who did not (14.0 deaths per 100 py; 95% CI: 12.8-15.4 deaths per 100 py). NT-proBNP progression was associated with a 1.8-fold higher risk of mortality (HR: 1.82; 95% CI: 1.57-2.10;  $P < 0.001$ ). The increased risk of mortality associated with NT-proBNP progression was consistent across patients with wtATTR-CA (HR: 1.68; 95% CI: 1.40-2.00;  $P < 0.001$ ), p.(V142I) hATTR-CA (HR: 1.72; 95% CI: 1.27-2.32;  $P < 0.001$ ), and non-p.(V142I) hATTR-CA (HR: 2.33; 95% CI: 1.52-3.57;  $P < 0.001$ ).

In the external validation cohort, patients who experienced NT-proBNP progression had a higher death rate (18.4 deaths per 100 py; 95% CI: 14.8-22.9 deaths per 100 py) than those who did not (10.6 deaths per 100 py; 95% CI: 8.8-12.8 deaths per 100 py). NT-proBNP progression was associated with a 1.8-fold higher risk of mortality (HR: 1.75; 95% CI: 1.32-2.33;  $P < 0.001$ ) (Figure 1).

These findings were confirmed in the internal validation, whereby the association between NT-proBNP progression and mortality was assessed in the whole study population (HR: 1.81; 95% CI: 1.59-2.05;  $P < 0.001$ ) and the bootstrapped results indicated that the coefficients remained constant across the resamples, suggesting robustness in the association between NT-proBNP progression and mortality. NT-proBNP progression was associated with an increased risk of mortality in patients with NAC stage 1 disease (HR: 2.34; 95% CI: 1.90-2.89;  $P < 0.001$ ) and NAC stage 2 disease (HR: 1.52; 95% CI: 1.24-1.86;  $P < 0.001$ ), but not in those with NAC stage 3 disease (HR: 1.29; 95% CI: 0.97-1.72;  $P = 0.08$ ); however, assessment in this subgroup was limited by the small sample size. Nevertheless, the 95% CI contains values that suggest NT-proBNP progression could be associated with an increased risk of mortality. NT-proBNP

progression was also associated with an increased risk of mortality in a subgroup of obese patients and in patients with concomitant atrial fibrillation (Supplemental Material).

When compared with the NT-proBNP cutoffs recommended in the consensus document, the novel definition of NT-proBNP progression demonstrated improved discrimination in the external validation cohort (Harrell's c-statistic: 0.53; 95% CI: 0.48-0.59 vs 0.56; 95% CI: 0.50-0.61;  $P = 0.033$ ). Comparison between the novel definition of NT-proBNP progression and both NT-proBNP cutoffs recommended in the consensus document and cutoffs previously used in patients with wtATTR-CA, demonstrated that the novel definition of NT-proBNP progression produced the most consistent HRs across different genotypes, and across the NAC cohort and the external validation cohort (Supplemental Table 1).

In the whole study population, 515 patients were prescribed disease-modifying therapy or enrolled into clinical trials; and had assessments at the start date, and 1 year after the start date (Supplemental Figure 1). In this subgroup, 131 (25.4%) patients experienced NT-proBNP progression, and patients who experienced NT-proBNP progression had a higher death rate (17.5 deaths per 100 py; 95% CI: 12.5-24.5 deaths per 100 py) than those who did not (5.7 deaths per 100 py; 95% CI: 4.1-8.0 deaths per 100 py). NT-proBNP progression was associated with a 3.0-fold higher risk of mortality (HR: 3.02; 95% CI: 1.87-4.87;  $P < 0.001$ ) (Figure 2A).

**OUTPATIENT DIURETIC INTENSIFICATION.** At 1 year, 451 (28.2%) NAC patients and 301 (44.5%) patients in the external validation cohort experienced ODI. Patients who experienced ODI were older and had a higher prevalence of p.(V142I) hATTR-CA and atrial fibrillation compared with those who did not experience ODI. Patients who experienced ODI had a worse functional capacity as evidenced by NYHA functional class and more severe cardiac phenotype evidenced by a higher median NT-proBNP, and greater wall thickness than those who did not. Among patients receiving loop diuretics the median furosemide dose at baseline was similar between the patients who experienced ODI and those who did not in both the NAC cohort (40 mg [40-80 mg]), and the external validation cohort (40 mg [25-75 mg]) (Table 3).

In the NAC cohort, patients who experienced ODI had a higher death rate (26.5 deaths per 100 py; 95% CI: 23.6-29.7 deaths per 100 py) than those who did not (14.3 deaths per 100 py; 95% CI: 13.1-15.7

**TABLE 2 Comparison of Patients Who Experienced NT-proBNP Progression With Those Who Did Not**

	NAC Cohort			External Validation Cohort		
	Stable NT-proBNP (n = 1,047, 65.5%)	NT-proBNP Progression (n = 551, 33.5%)	P Value	Stable NT-proBNP (n = 473, 69.9%)	NT-proBNP Progression (n = 204, 30.1%)	P Value
Age, y	75.2 ± 8.6	76.6 ± 7.3	0.004	77.8 ± 7.7	79.8 ± 6.6	0.002
Male	900 (86.0)	480 (87.1)	0.523	411 (86.9)	176 (86.3)	0.828
Genotype			<0.001			0.433
Wild type	737 (70.4)	373 (67.7)		422 (89.2)	186 (91.2)	
p.(V142I)	138 (13.2) <sup>a</sup>	114 (20.7)		6 (1.3)	4 (2.0)	
Non-p.(V142I)	172 (16.4) <sup>a</sup>	64 (11.6)		45 (9.5)	14 (6.9)	
AF/AFL	522 (49.9)	254 (46.1)	0.153	256 (54.1)	118 (57.8)	0.372
IHD	191 (18.2)	96 (17.4)	0.685	100 (21.1)	47 (23.0)	0.584
Diabetes mellitus	135 (12.9)	99 (18.0)	0.006	89 (18.8)	33 (16.2)	0.412
Stroke/TIA	97 (9.3)	53 (9.6)	0.817	41 (8.7)	17 (8.3)	0.886
CKD stage 3-5	438 (41.8)	297 (53.9)	<0.001	240 (50.7)	117 (57.4)	0.114
Cardiac devices						
PPM	118 (11.3)	75 (13.6)	0.172	70 (14.8)	31 (15.2)	0.894
ICD	26 (2.5)	11 (2.0)	0.538	12 (2.5)	10 (4.9)	0.111
CRT-D	15 (1.4)	4 (0.7)	0.215	6 (1.3)	5 (2.5)	0.264
CRT-P	18 (1.7)	11 (2.0)	0.693	4 (0.8)	2 (1.0)	0.864
Heart failure severity						
NYHA functional class			0.022			0.350
I	160 (15.3) <sup>a</sup>	61 (11.1)		104 (22.0)	38 (18.6)	
II	623 (59.5) <sup>a</sup>	361 (65.5)		263 (55.6)	113 (55.4)	
III	204 (19.5)	107 (19.4)		104 (22.0)	50 (24.5)	
IV	16 (1.5)	3 (0.5)		2 (0.4)	3 (1.5)	
Missing	44	19		0	0	
NAC stage			0.007			0.460
1	597 (57.0) <sup>a</sup>	270 (49.0)		268 (56.7)	105 (51.5)	
2	331 (31.6)	200 (36.3)		132 (27.9)	64 (31.4)	
3	119 (11.4)	81 (14.7)		73 (15.4)	35 (17.2)	
NT-proBNP, ng/L	2,291 (1,150-4,482)	2,732 (1,612-4,717)	<0.001	1,984 (854-4,489)	2,365 (1,090-4,238)	0.153
eGFR, mL/min/1.73 m <sup>2</sup>	64 (52-79)	58 (47-72)	<0.001	59 (47-74)	56 (43-71)	0.039
Echocardiographic parameters						
IVSd, mm	16.6 ± 2.5	17.0 ± 2.3	0.009	16.6 ± 3.6	18.2 ± 3.3	0.021
PWTd, mm	16.2 ± 2.7	16.6 ± 2.4	0.011	14.7 ± 5.6	15.3 ± 3.3	0.001
LVEF, %	49.0 ± 10.7	48.3 ± 10.1	0.163	52.7 ± 10.6	51.9 ± 10.0	0.275
Medications						
Beta-blockers	551 (52.6)	317 (57.5)	0.061	270 (57.1)	119 (58.3)	0.763
ACEI/ARBs	575 (54.9)	342 (62.1)	0.006	244 (51.6)	129 (63.2)	0.005
ARNI	12 (1.2)	1 (0.2)	0.031	12 (2.5)	4 (2.0)	0.651
MRAs	418 (39.9)	232 (42.1)	0.399	143 (30.2)	82 (40.2)	0.012
SGT2i	19 (1.8)	10 (1.8)	0.999	8 (1.7)	4 (2.0)	0.807
Loop diuretic	701 (67.0)	417 (75.7)	<0.001	304 (64.3)	158 (77.5)	<0.001
Thiazide diuretic	36 (3.4)	31 (5.6)	0.038	29 (6.1)	14 (6.9)	0.720

Values are mean ± SD, n (%), n, or median (Q1-Q3). <sup>a</sup>P values for pairwise comparison <0.05. Abbreviations as in Table 1.

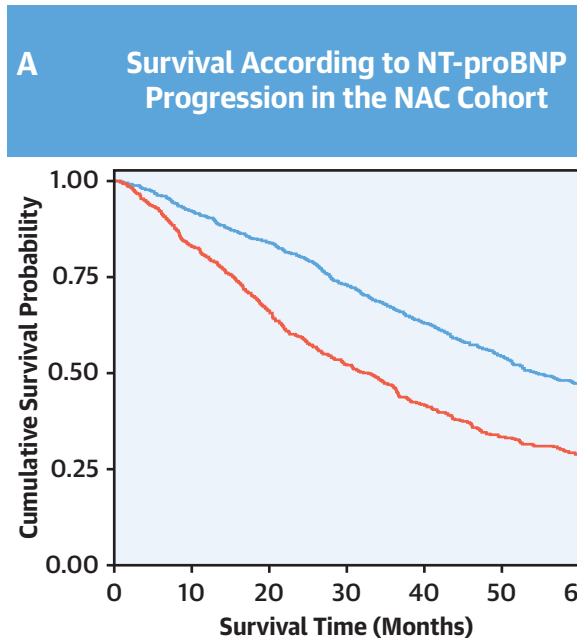
deaths per 100 py). ODI was associated with a 1.9-fold higher risk of mortality (HR: 1.88; 95% CI: 1.62-2.18; *P* < 0.001). The associated risk of mortality was dose-dependent, with patients who experienced the greatest degree of ODI having the highest risk of mortality (Supplemental Material, Figure 3). The increased risk of mortality associated with ODI was

consistent across patients with wtATTR-CA (HR: 1.76; 95% CI: 1.48-2.11; *P* < 0.001), p.(V142I) hATTR-CA (HR: 1.47; 95% CI: 1.08-2.01; *P* = 0.013), and non-p.(V142I) hATTR-CA (HR: 3.65; 95% CI: 2.29-5.81; *P* < 0.001).

In the external validation cohort, patients who experienced ODI had a higher death rate (18.0 deaths

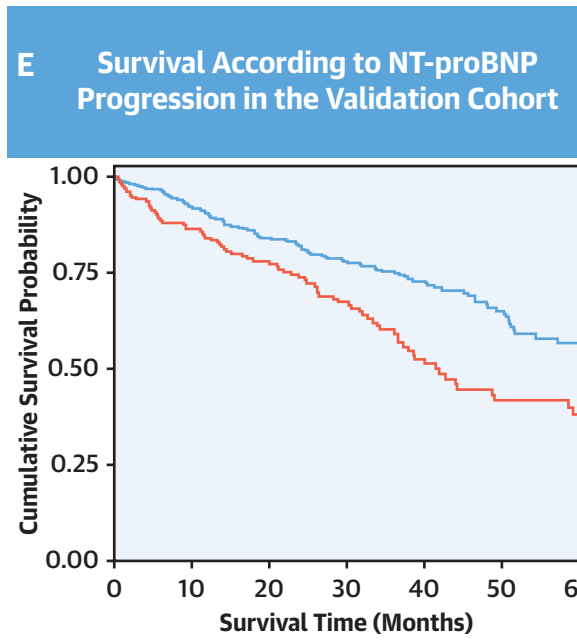


**FIGURE 1** NT-proBNP Progression and Survival



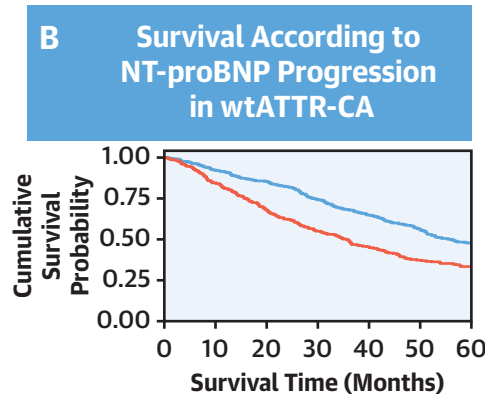
Number at risk:

Stable	1,047	858	716	605	494	368	246
Progression	551	404	304	234	184	132	94



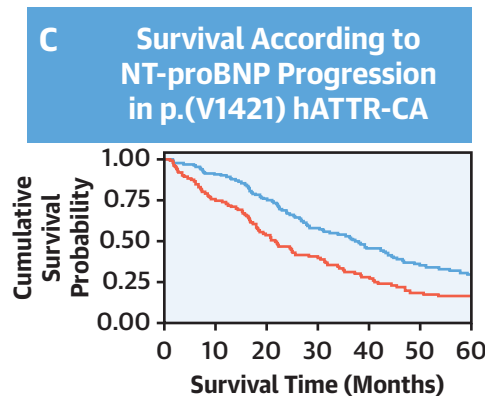
Number at risk:

Stable	473	360	256	197	121	74	41
Progression	204	157	109	79	42	28	18



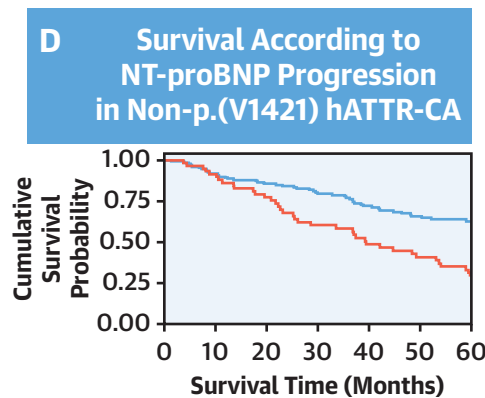
Number at risk:

Stable	737	605	508	436	359	268	170
Progression	373	270	207	166	134	95	70



Number at risk:

Stable	138	118	94	70	53	34	23
Progression	114	81	55	37	25	16	13



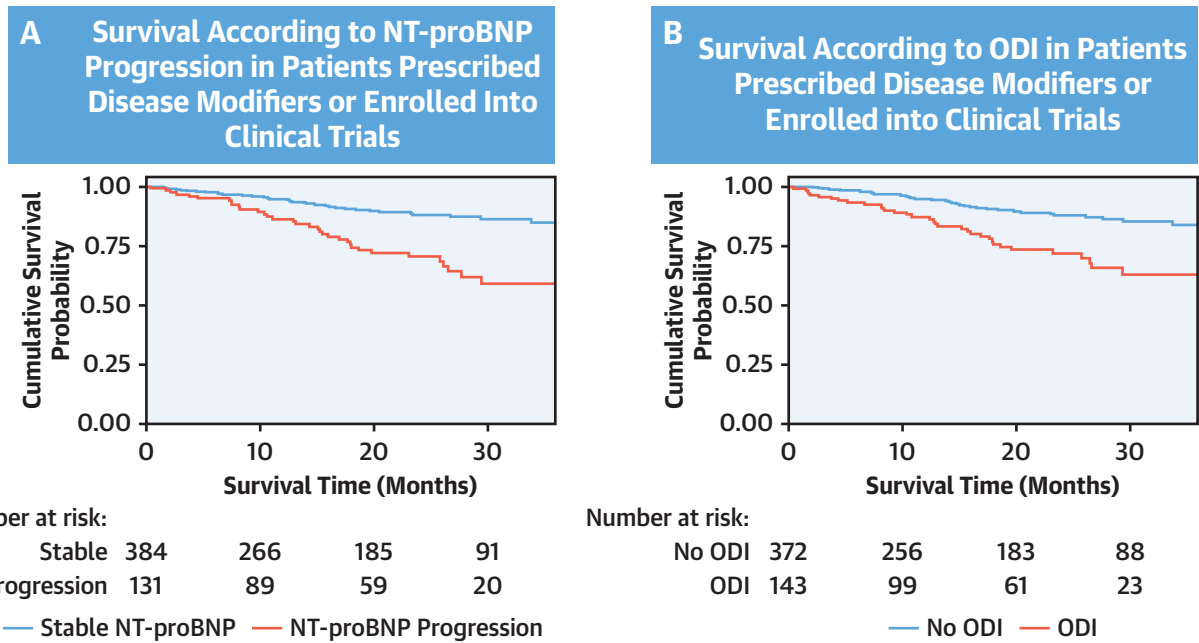
Number at risk:

Stable	172	135	114	99	82	66	53
Progression	64	53	42	31	25	21	11

— Stable NT-proBNP — NT-proBNP Progression

Landmark Kaplan-Meier curves demonstrating the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) progression at 1 year and subsequent survival. (A) Overall National Amyloidosis Centre (NAC) cohort, (B) wild-type transthyretin cardiac amyloidosis (wtATTR-CA) subgroup, (C) p.(V142I) hereditary transthyretin cardiac amyloidosis (hATTR-CA), (D) non-p.(V142I) hATTR-CA, and (E) external validation cohort.

**FIGURE 2** Disease Progression in Clinical Trials and Disease-Modifying Therapy



Landmark Kaplan-Meier curves demonstrating the association between (A) N-terminal pro-B-type natriuretic peptide (NT-proBNP) progression and (B) outpatient diuretic intensification (ODI) at 1 year, and subsequent survival in patients enrolled into clinical trials or prescribed disease-modifying therapy.

per 100 py; 95% CI: 15.1-21.7 deaths per 100 py) than those who did not (8.8 deaths per 100 py; 95% CI: 7.0-11.1 deaths per 100 py). ODI was associated with a 2.1-fold higher risk of mortality (HR: 2.05; 95% CI: 1.53-2.74;  $P < 0.001$ ) (Figure 4).

These findings were confirmed in the internal validation, whereby the association between ODI and mortality was assessed in the whole study population (HR: 1.79; 95% CI: 1.58-2.04;  $P < 0.001$ ), and the bootstrapped results indicated that the coefficients remained constant across the resamples, suggesting robustness in the association between ODI and mortality. ODI was also associated with an increased risk of mortality in patients with NAC stage 1 disease (HR: 1.89; 95% CI: 1.52-2.34;  $P < 0.001$ ), NAC stage 2 disease (HR: 1.52; 95% CI: 1.25-1.86;  $P < 0.001$ ), and NAC stage 3 disease (HR: 1.41; 95% CI: 1.07-1.87;  $P = 0.015$ ).

In the whole study population, 515 patients were prescribed disease-modifying therapy or enrolled into clinical trials; and had assessments at the start date, and 1 year after the start date. In this subgroup, 143 (27.7%) patients experienced ODI, and patients who experienced ODI had a higher death rate (16.3 deaths per 100 py; 95% CI: 11.7-22.8 deaths per

100 py) than those who did not (5.9 deaths per 100 py; 95% CI: 4.2-8.2 deaths per 100 py). ODI was associated with a 2.8-fold higher risk of mortality (HR: 2.77; 95% CI: 1.72-4.45;  $P < 0.001$ ).

**COMBINED ODI AND NT-proBNP PROGRESSION.** In a multivariable analysis with covariates of age and NAC disease stage, both NT-proBNP progression (HR: 1.64; 95% CI: 1.42-1.89;  $P < 0.001$ ) and ODI (HR: 1.60; 95% CI: 1.38-1.85;  $P < 0.001$ ) were independently associated with mortality, and this was consistent across patients with wtATTR-CA, p.(V142I) hATTR-CA, and non-p.(V142I) hATTR-CA (Supplemental Tables 2 and 3). The likelihood ratio test demonstrated that the addition of NT-proBNP progression to ODI added a significant contribution to the multivariable model (chi-square = 56.36;  $P < 0.001$ ) and significantly improved the discriminatory ability of the classification compared with ODI alone (Harrell's c-statistic: 0.61; 95% CI: 0.58-0.64 vs 0.57; 95% CI: 0.55-0.60;  $P < 0.001$ ).

Within the NAC cohort, patients who had a stable NT-proBNP and stable diuretic dose at 1 year had a death rate of 11.5 deaths per 100 py (95% CI: 10.3-13.0



**TABLE 3** Comparison of Patients Who Experienced Outpatient Diuretic Intensification to Those Who Did Not

	NAC Cohort			External Validation Cohort		
	No ODI (n = 1,147, 71.8%)	ODI (n = 451, 28.2%)	P Value	No ODI (n = 376, 55.5%)	ODI (n = 301, 44.5%)	P Value
Age, y	75.2 ± 8.5	76.9 ± 7.1	<0.001	77.6 ± 7.9	79.4 ± 6.7	0.003
Male	979 (85.4)	401 (88.9)	0.062	328 (87.2)	259 (86.0)	0.651
Genotype			<0.001			0.252
Wild type	785 (68.4)	325 (72.1)		341 (90.7)	267 (88.7)	
p.(V142I)	168 (14.6) <sup>a</sup>	84 (18.6)		3 (0.8)	7 (2.3)	
Non-p.(V142I)	194 (16.9) <sup>a</sup>	42 (9.3)		32 (8.5)	27 (9.0)	
AF/AFL	539 (47.0)	237 (52.5)	0.045	190 (50.5)	184 (61.1)	0.006
IHD	192 (16.7)	95 (21.1)	0.043	77 (20.5)	70 (23.3)	0.078
Diabetes mellitus	157 (13.7)	77 (17.1)	0.085	59 (15.7)	63 (20.9)	0.114
Stroke/TIA	105 (9.2)	45 (10.0)	0.611	33 (8.8)	25 (8.3)	0.828
CKD stage 3-5	510 (69.4)	225 (30.6)	0.050	189 (50.3)	168 (55.8)	0.151
Cardiac devices						
PPM	139 (12.1)	54 (12.0)	0.936	62 (16.5)	39 (13.0)	0.200
ICD	24 (2.1)	13 (2.9)	0.345	12 (3.2)	10 (3.3)	0.924
CRT-D	12 (1.1)	6 (1.3)	0.744	5 (1.3)	6 (2.0)	0.497
CRT-P	22 (1.9)	7 (1.6)	0.622	3 (0.8)	3 (1.0)	0.784
Heart failure severity						
NYHA functional class			0.044			<0.001
I	174 (15.2) <sup>a</sup>	47 (10.4)		95 (25.3) <sup>a</sup>	47 (15.6)	
II	699 (60.9)	285 (63.2)		207 (55.1)	169 (55.1)	
III	212 (18.5)	99 (22.0)		74 (19.7) <sup>a</sup>	80 (26.6)	
IV	12 (1.0)	7 (1.6)		0 (0.0) <sup>a</sup>	5 (1.7)	
Missing	50	13		0	0	
NAC stage			<0.001			<0.001
1	662 (57.7) <sup>a</sup>	205 (45.5)		233 (62.0) <sup>a</sup>	140 (46.5)	
2	350 (30.5) <sup>a</sup>	181 (40.1)		88 (23.4)	108 (35.9)	
3	135 (11.8)	65 (14.4)		55 (14.6)	53 (17.6)	
NT-proBNP, ng/L	2,309 (1,218-4,163)	3,095 (1,656-5,590)	<0.001	1,786 (706-3,697)	2,782 (1,293-5,155)	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	62 (50-77)	59 (48-76)	0.062	60 (47-75)	57 (44-71)	0.090
Echocardiographic parameters						
IVSd, mm	16.6 ± 2.5	17.1 ± 2.3	<0.001	17.6 ± 3.7	18.1 ± 3.2	0.005
PWTd, mm	16.2 ± 2.7	16.7 ± 2.2	<0.001	14.3 ± 3.2	15.7 ± 6.5	<0.001
LVEF, %	49.0 ± 10.5	48.0 ± 10.3	0.070	53.0 ± 10.5	51.8 ± 10.3	0.076
Medications						
Beta-blockers	607 (52.9)	261 (57.9)	0.074	210 (55.9)	179 (59.5)	0.344
ACEI/ARBs	664 (57.9)	253 (56.1)	0.514	198 (52.7)	175 (58.1)	0.154
ARNI	11 (1.0)	2 (0.4)	0.302	11 (2.9)	5 (1.7)	0.282
MRAs	453 (39.5)	197 (43.7)	0.125	125 (33.2)	100 (33.2)	0.995
SGT2i	23 (2.0)	6 (1.3)	0.363	7 (1.9)	5 (1.7)	0.844
Loop diuretic	818 (71.3)	300 (66.5)	0.060	250 (66.5)	212 (70.4)	0.274
Thiazide diuretic	53 (4.6)	14 (3.1)	0.173	22 (5.9)	21 (7.0)	0.543

Values are mean ± SD, n (%), n, or median (Q1-Q3). <sup>a</sup>P values for pairwise comparison <0.05.  
ODI = outpatient diuretic intensification; other abbreviations as in Table 1.

deaths per 100 py), compared with 21.9 deaths per 100 py (95% CI: 19.8-24.4 deaths per 100 py) in patients who experienced either NT-proBNP or ODI progression, and 33.2 deaths per 100 py (95% CI: 28.0-39.3 deaths per 100 py) in patients who experienced both NT-proBNP progression and ODI. Compared with patients with a stable diuretic dose and stable NT-proBNP, those who experienced either

NT-proBNP progression or ODI had a 1.9-fold higher risk of mortality (HR: 1.93; 95% CI: 1.65-2.27;  $P < 0.001$ ), and those who experienced both NT-proBNP progression and ODI had a 3.0-fold higher risk of mortality (HR: 2.98; 95% CI: 2.42-3.67;  $P < 0.001$ ). When compared with patients who experienced either NT-proBNP progression or ODI, those who experienced both had a 1.5-fold higher risk of

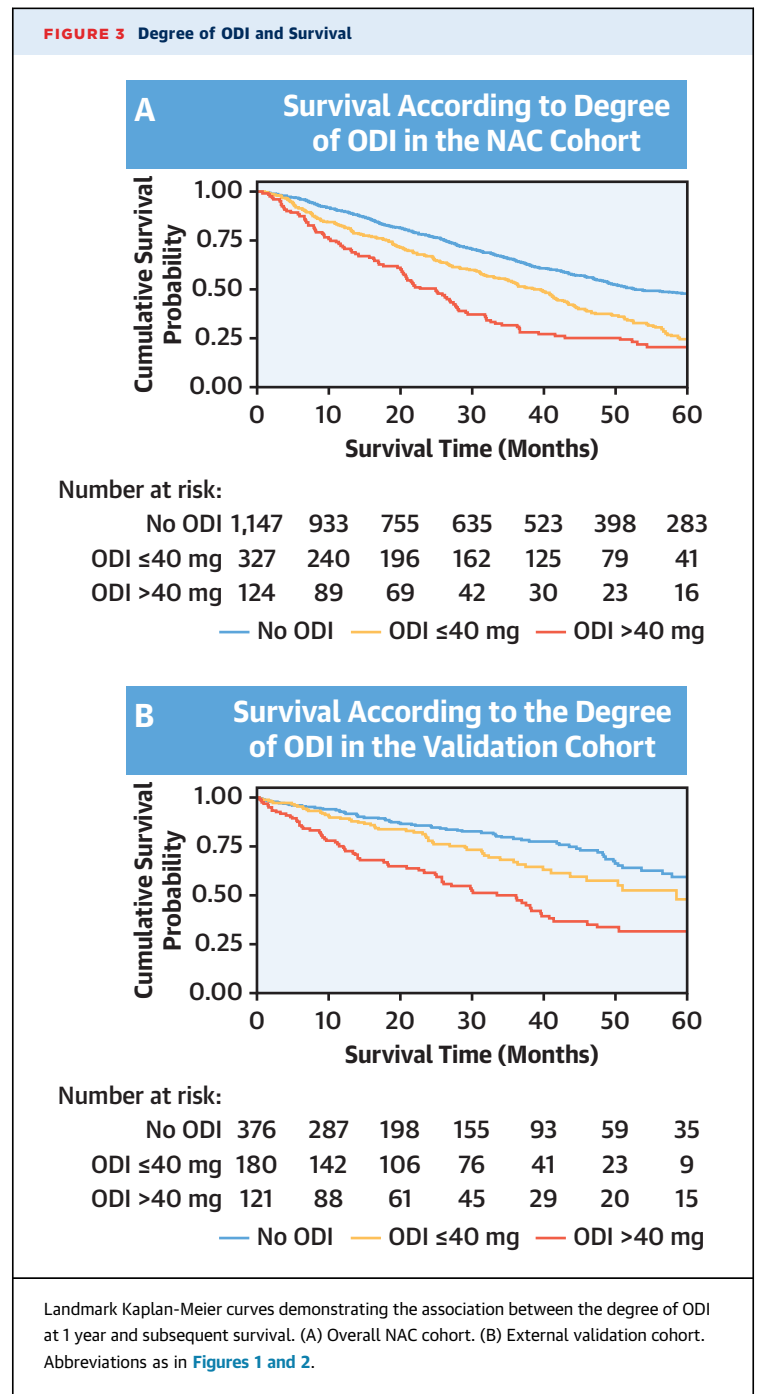
mortality (HR: 1.54; 95% CI: 1.26-1.88;  $P < 0.001$ ). The increased risk of mortality associated with both NT-proBNP progression and ODI was consistent across patients with wtATTR-CA, p.(V142I) hATTR, and non-p.(V142I) hATTR (Supplemental Material).

In the external validation cohort, patients who had a stable NT-proBNP and stable diuretic dose at 1 year had a death rate of 7.4 deaths per 100 py (95% CI: 5.5-9.92 deaths per 100 py), compared with 14.4 deaths per 100 py (95% CI: 11.7-17.6 deaths per 100 py) in patients who experienced either NT-proBNP progression or ODI, and 23.7 deaths per 100 py (95% CI: 18.1-31.1 deaths per 100 py) in patients who experienced both NT-proBNP progression and ODI. Compared with patients with a stable diuretic dose and stable NT-proBNP, those who experienced either NT-proBNP progression or ODI had a 1.9-fold higher risk of mortality (HR: 1.94; 95% CI: 1.36-2.77;  $P < 0.001$ ), and those who experienced both NT-proBNP progression and ODI had a 3.2-fold higher risk of mortality (HR: 3.23; 95% CI: 2.17-4.79;  $P < 0.001$ ). When compared with patients who experienced either NT-proBNP progression or ODI, those who experienced both had a 1.7-fold higher risk of mortality (HR: 1.66; 95% CI: 1.19-2.33;  $P = 0.003$ ) (Figure 5).

These findings were confirmed in the internal validation, whereby the association between the combined variables and mortality was assessed in the whole study population (stable NT-proBNP and stable diuretic dose vs either NT-proBNP progression or ODI: HR: 1.88; 95% CI: 1.62-2.17;  $P < 0.001$ ; stable NT-proBNP and stable diuretic dose vs NT-proBNP progression and ODI: HR: 2.88; 95% CI: 2.40-3.45;  $P < 0.001$ ), and the bootstrapped results indicated that the coefficients remained constant across the resamples, suggesting robustness in the association between the combined variables and mortality. The increased risk of mortality associated with both NT-proBNP progression and ODI was consistent across patients with NAC stage 1, 2, and 3 disease (Supplemental Material).

## DISCUSSION

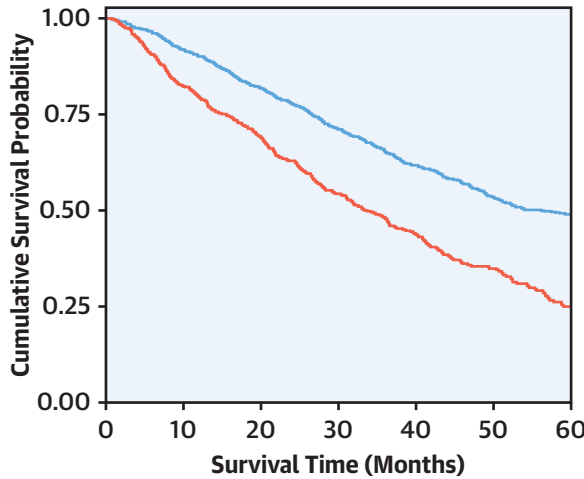
This multicenter longitudinal study of >2,000 patients with ATTR-CA demonstrated that: 1) an increase in NT-proBNP of >700 ng/L and >30% was frequent (1 in 3 patients) and consistently associated with an increased risk of mortality; 2) ODI was similarly frequent (1 in 3 patients) and consistently associated with an increased risk of mortality; and 3) the combination of an increase in NT-proBNP of >700 ng/L and >30%, and ODI enabled further



refinement of risk. These results were consistent across the overall population and different genotypes. Both variables are extremely informative on the rate of disease progression and associated prognosis, and therefore could be highly relevant both in clinical practice to stratify disease progression, and as a modifiable endpoint in clinical trials of patients with ATTR-CA.

**FIGURE 4 ODI and Survival**

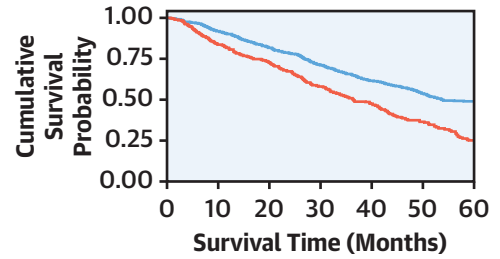
**A Survival According to ODI in the NAC Cohort**



Number at risk:

No ODI	1,147	933	755	635	523	398	283
ODI	451	329	265	204	155	102	57

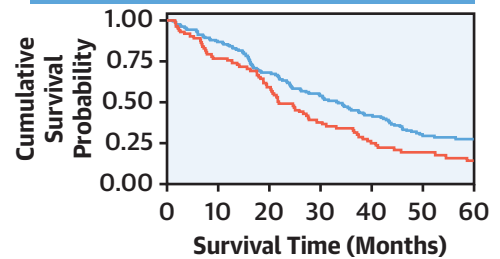
**B Survival According to ODI in wtATTR-CA**



Number at risk:

No ODI	785	635	514	442	368	280	194
ODI	325	240	201	160	125	83	46

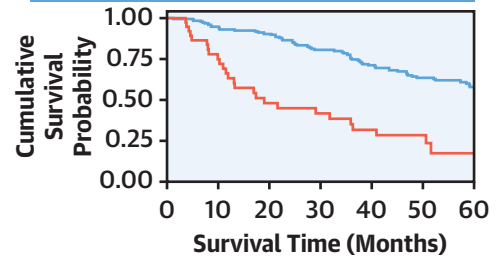
**C Survival According to ODI in p.(V142I) hATTR-CA**



Number at risk:

No ODI	168	136	101	76	58	37	27
ODI	84	63	48	31	20	13	9

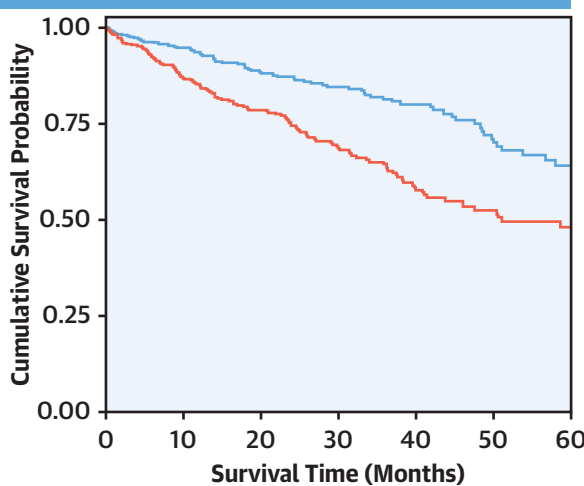
**D Survival According to ODI in Non-p.(V142I) hATTR-CA**



Number at risk:

No ODI	194	162	140	117	97	81	62
ODI	42	26	16	13	10	6	2

**E Survival According to ODI in the Validation Cohort**



Number at risk:

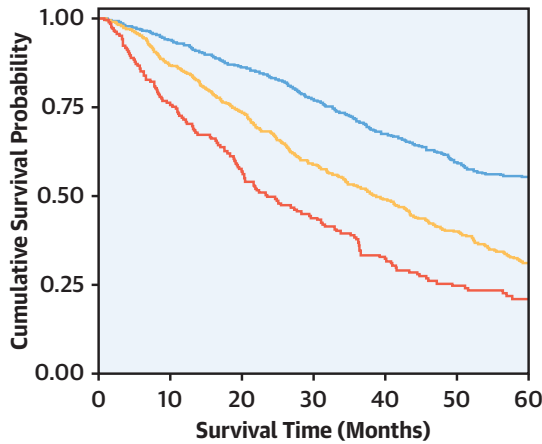
No ODI	376	287	198	155	93	59	35
ODI	301	230	167	121	70	43	24

— No ODI — ODI

Landmark Kaplan-Meier curves demonstrating the association between ODI at 1 year and subsequent survival. (A) Overall NAC cohort, (B) wtATTR-CA subgroup, (C) p.(V142I) hATTR-CA, (D) non-p.(V142I) hATTR-CA, and (E) external validation cohort. Abbreviations as in [Figures 1 and 2](#).

**FIGURE 5** Combination NT-proBNP Progression and ODI

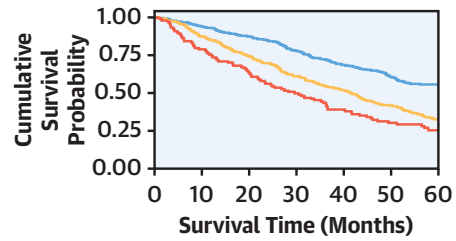
**A** Survival According to NT-proBNP Progression and ODI in the NAC Cohort



Number at risk:

—	780	654	544	472	390	302	213
—	634	483	383	296	237	162	103
—	184	125	93	71	51	36	24

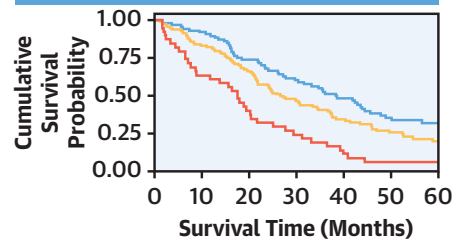
**B** Survival According to NT-proBNP Progression and ODI in wtATTR-CA



Number at risk:

—	538	453	377	331	276	215	144
—	446	334	268	216	175	118	76
—	126	88	70	55	42	80	20

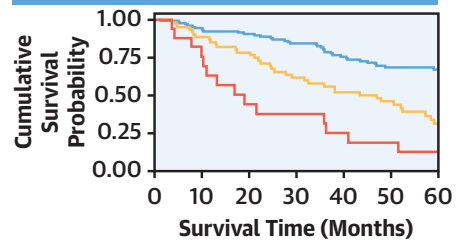
**C** Survival According to NT-proBNP Progression and ODI in p.(V142I) hATTR-CA



Number at risk:

—	94	80	62	49	38	24	17
—	118	94	71	48	35	23	16
—	40	25	16	10	5	3	3

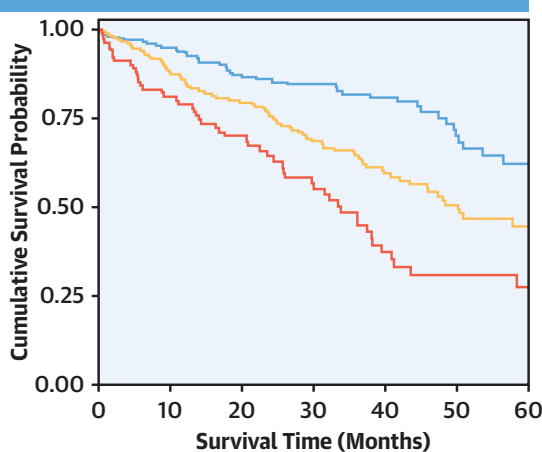
**D** Survival According to NT-proBNP Progression and ODI in Non-p.(V142I) hATTR-CA



Number at risk:

—	148	121	105	92	76	63	52
—	70	55	44	32	27	21	11
—	18	12	7	6	4	3	1

**E** Survival According to NT-proBNP Progression and ODI in the Validation Cohort



Number at risk:

—	280	212	145	116	72	44	26
—	289	223	164	120	70	45	24
—	108	82	56	40	21	13	9

— Neither NT-proBNP Progression or ODI  
 — Either NT-proBNP Progression or ODI  
 — Both NT-proBNP Progression and ODI

Landmark Kaplan-Meier curves demonstrating the association between the NT-proBNP progression and ODI at 1 year and subsequent survival. (A) Overall NAC cohort, (B) wtATTR-CA subgroup, (C) p.(V142I) hATTR-CA, (D) non-p.(V142I) hATTR-CA, and (E) external validation cohort. Abbreviations as in Figures 1 and 2.

ATTR-CA is an inexorably progressive cardiomyopathy, and patients experience worsening heart failure signs and symptoms throughout the course of the disease. However, rate of disease progression is extremely variable, likely reflecting the complex nature of ATTR-CA. Determinants of disease progression are multifactorial, and depend on the underlying genotype, treatment, and comorbidities, hence there is an urgent need to define the disease course and stratify progression at an individual patient level.<sup>7,16,17</sup> Since its discovery, NT-proBNP has been widely used in heart failure to stratify risk and as a marker of treatment response, with favorable changes being associated with a reduced risk of adverse cardiovascular events.<sup>8</sup> Likewise, changes in NT-proBNP have been used in the assessment of ATTR amyloid-specific disease-modifying therapies. The ATTR-ACT (Transferrin Amyloidosis Cardiomyopathy Clinical Trial), ATTRIBUTE-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloidosis Cardiomyopathy) trial, and APOLLO-B (A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy [ATTR Amyloidosis With Cardiomyopathy]) trial demonstrated that tafamidis, acoramidis, and patisiran, respectively, were all associated with a smaller increase in NT-proBNP compared with placebo.<sup>5,18,19</sup> However, there is no NT-proBNP cutoff that can be used at an individual patient level to stratify disease progression across all genotypes. The cutoffs used in a small cohort of patients with wtATTR-CA are yet to be validated or applied to patients with hATTR-CA, or patients prescribed disease-modifying therapy, whereas the cutoffs proposed in a recent consensus document are not supported by data from patients with ATTR-CA.<sup>9,10</sup>

The current study established that NT-proBNP progression (defined as an absolute increase >700 ng/L and relative increase >30%) at 1 year was frequent, occurring in roughly one-third of patients at the NAC, and roughly one-third of patients in the external validation cohort. NT-proBNP progression was more frequent in patients prescribed renin-angiotensin system blockers and loop diuretics, possibly reflecting more advanced cardiac disease at diagnosis.<sup>16</sup> NT-proBNP progression was consistently associated with a 1.8-fold higher risk of mortality in both cohorts, and the subgroup of patients with concomitant atrial fibrillation. NT-proBNP progression conferred the highest risk in patients with non-p.(V142I) hATTR-CA, and lowest risk in patients with p.(V142I) hATTR-CA. When compared with the thresholds recommended in the most recent consensus document and the cutoff proposed for patients with wtATTR-CA,<sup>9,10</sup> our novel definition of

NT-proBNP progression demonstrated improved discrimination and remarkable consistency with regard to HRs across the NAC cohort and external validation cohort. The novel thresholds were associated with an increased risk of mortality in all 3 genotypes, and also identified patients at an increased risk despite being prescribed disease-modifying therapy or enrolled into clinical trials. These results should support the widespread adoption of these NT-proBNP cutoffs to identify patients experiencing disease progression.

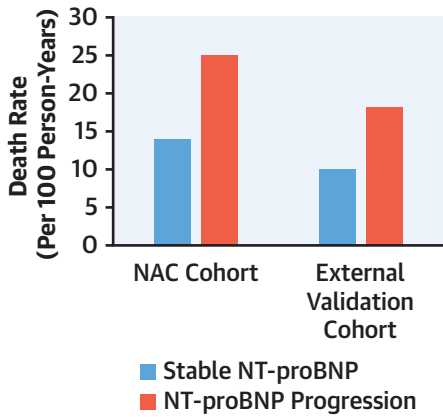
Worsening heart failure is often handled in the outpatient setting with intensification of loop diuretic therapy. ODI is frequent in patients with ATTR-CA, with more than one-quarter of patients at the NAC and almost one-half of the external validation cohort experiencing ODI in the first year after diagnosis.<sup>11,12</sup> ODI was associated with a 1.9-fold higher risk of mortality in the overall NAC cohort, and 2.1-fold higher risk of mortality in the external validation cohort, hence confirming the remarkable consistency with regard to associated risk across multiple international specialist centers, in spite of possible differences in individual clinical practices and the propensity to escalate diuretic therapy. The associated risk varied among the genotypes, and ranged from a 1.5-fold higher risk in patients with p.(V142I) hATTR-CA to a 3.7-fold higher risk in patients with non-p.(V142I) hATTR-CA. The observed differences are probably related to differences in the cardiac phenotype, with the p.(V142I) genotype being associated with more advanced and rapidly progressive cardiac disease, whereas patients with non-p.(V142I) hATTR present with a milder cardiac phenotype.<sup>7</sup> NT-proBNP progression and ODI occur less frequently in patients with a milder cardiac phenotype, compared with patients with more advanced disease. Therefore, these markers possibly provide a more specific signal that is more representative of disease progression in patients with milder disease. This is supported by the associated risk being highest in patients with NAC stage 1 (mild) disease, and lowest risk in patients with NAC stage 3 (severe) disease.

In the setting of ATTR-CA, multiple underlying pathophysiological processes are responsible for the elevation of serum NT-proBNP, including direct cardiac amyloid infiltration, neurohormonal activation, renal filtration, and fluid status, and this forms the basis of the strong prognostic significance of NT-proBNP in cardiac amyloidosis.<sup>20</sup> In response to disease progression, ODI is frequent and strongly associated with mortality, but also influences NT-proBNP levels, with a variable response in

### CENTRAL ILLUSTRATION N-Terminal Pro-B-Type Natriuretic Peptide Progression and Outpatient Diuretic Intensification Detect Disease Progression

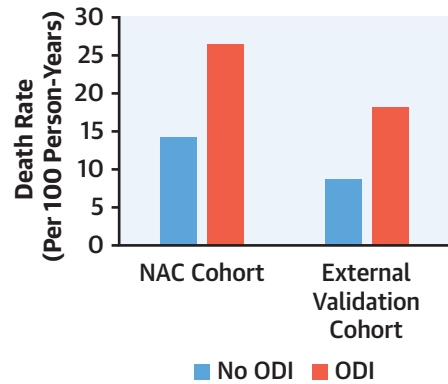
#### NT-proBNP Progression

NT-proBNP progression is associated with a 1.8-fold higher risk of mortality in the NAC cohort and external validation cohort



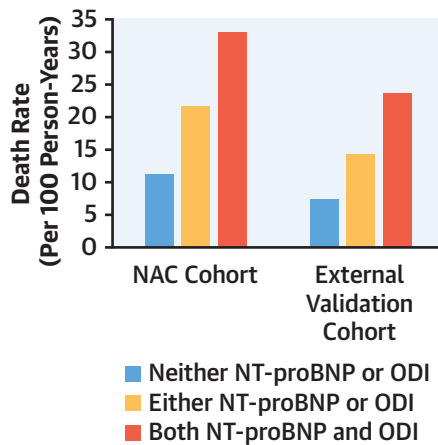
#### Outpatient Diuretic Intensification

ODI is associated with a 1.9-fold higher risk of mortality in the NAC cohort and 2.1-fold higher risk of mortality in the external validation cohort



#### NT-proBNP Progression and Outpatient Diuretic Intensification

Combining both variables produces a simple, universally applicable model that detects disease progression in ATTR-CA



Ioannou A, et al. J Am Coll Cardiol. 2024;83(14):1276-1291.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) progression and outpatient diuretic intensification (ODI) are associated with an increased risk of mortality. Combining both variables produces a simple, universally applicable model that detects disease progression in the National Amyloidosis Centre (NAC) and external validation cohorts.

different individuals, ranging from reduction, to stabilization or increase in NT-proBNP.<sup>13</sup> Therefore, the combination of the presence or absence of diuretic intensification and change in NT-proBNP provides

incremental information compared with each individual variable, and allows further refinement of the risk of mortality (Central Illustration). Despite recent advances in diagnostics that have resulted in most



patients being diagnosed earlier in the disease process, a significant proportion are still diagnosed with advanced cardiac disease.<sup>7</sup> Although both NT-proBNP progression and ODI confer the highest risk in patients with milder cardiac disease, importantly the combination of these variables remains associated with an increased risk of mortality across the spectrum of disease severity.

Considering the rapidly evolving therapeutic landscape, where several novel compounds are likely to become available, there remains an unmet clinical need to define markers of disease progression. Troponin-T progression (defined as an increase >10 ng/L and >20%) was associated with mortality in a subgroup of patients who had serial measurements at baseline and 1 year (Supplemental Figures 2 and 3); however, the widespread use of troponin as a marker of disease progression is significantly limited by the current worldwide use of multiple different troponin assays, with different specialist centers favoring different assays.<sup>20</sup> Serial echocardiographic assessments lack the precision to track disease progression, and although worsening stroke volume and mitral and tricuspid regurgitation are associated with mortality, these parameters are challenging to quantify, and subject to significant intraobserver and interobserver variability.<sup>21</sup> Although cardiac magnetic resonance with multiparametric mapping has demonstrated utility in tracking treatment response in cardiac light-chain amyloidosis, this imaging modality is costly, only available in highly specialized centers, and cannot be used in patients with cardiac devices.<sup>22,23</sup> The identification of NT-proBNP progression and ODI as surrogate markers of disease progression in ATTR-CA is of great importance. Because of their simplicity, lack of operator variability, wide availability, and universal applicability across genotypes, these novel measures of disease progression could easily be applied to clinical practice with significant implications in terms of guiding optimization of treatment strategies, and also as potential endpoints in clinical trials. NT-proBNP progression and ODI are common occurrences in ATTR-CA, and their inclusion may lead to an important increment in event rates, which could in turn influence contemporary trial design, with fewer patients and a reduced follow-up duration being required to evaluate the efficacy of novel agents.

**STUDY LIMITATIONS.** There is a survival bias in that this study only included patients with follow-up 1 year after diagnosis, and therefore it may be that the extent of differences is underestimated, and rapid

disease progression may have resulted in death before the follow-up assessment. There is a possible selection bias as patients who were too unwell to attend an assessment would not have been included. Inclusion was limited to specialist referral centers, and therefore validation of these markers in a community or general cardiology setting is important. The definition of ODI was limited to new initiation or dose increase of loop diuretics, as they represent the mainstay of volume control in heart failure. Augmentation using thiazide diuretics was not considered, given inherent limitations in dose conversion between loop and nonloop diuretics.

## CONCLUSIONS

In this large cohort of patients with ATTR-CA, NT-proBNP progression and ODI were frequent and consistently associated with an increased risk of mortality. Combining both variables produces a simple, universally applicable model that detects disease progression. NT-proBNP progression and ODI represent novel outcomes that, if included in contemporary clinical trials, could allow the capture of more clinically meaningful and potentially modifiable events at earlier stages of disease.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Fontana is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/21/33447); and has received consulting income from Intellia, Novo Nordisk, Pfizer, Eidos, Prothena, Akcea, Alnylam, Caleum, Alexion, Janssen, Ionis, and AstraZeneca. Dr Gilmore has received consulting income from Ionis, Eidos, Intellia, Alnylam, and Pfizer. Dr Wechalekar has received consulting income from Alexia, AstraZeneca, Janssen, Attralus, and Prothena. Dr Cappelli has received consulting income from Alnylam, Pfizer, AstraZeneca, Bridgebio, and Novo Nordisk. Dr Cipriani has received consulting income from AstraZeneca. Dr Solomon has received research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Cytokinetics, Eidos, Gossamer, GSK, Ionis, Lilly, Myokardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and has served as a consultant for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Marianna Fontana, National Amyloidosis Centre, University College London, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, United Kingdom. E-mail: [m.fontana@ucl.ac.uk](mailto:m.fontana@ucl.ac.uk).

## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND

**PROCEDURAL SKILLS:** Elevation of plasma NT-proBNP and ODI in patients with cardiac ATTR amyloidosis are associated with disease progression and increased mortality.

### TRANSLATIONAL OUTLOOK:

Incorporation of NT-proBNP progression and ODI in clinical studies could facilitate earlier recognition of clinically meaningful and potentially modifiable events in patients with cardiac ATTR amyloidosis.

## REFERENCES

1. Ioannou A, Patel RK, Razvi Y, et al. Multi-imaging characterization of cardiac phenotype in different types of amyloidosis. *J Am Coll Cardiol Img.* 2022;14:464-477.
2. Ruberg FL, Grogan M, Hanna M, et al. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2019;73:2872.
3. Porcari A, Razvi Y, Masi A, et al. Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy. *Eur J Heart Fail.* 2023;25:515-524.
4. Patel RK, Ioannou A, Razvi Y, et al. Sex differences among patients with transthyretin amyloid cardiomyopathy - from diagnosis to prognosis. *Eur J Heart Fail.* 2022;24:2355-2363.
5. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018;379:1007-1016.
6. Ioannou A, Fontana M, Gillmore JD. RNA targeting and gene editing strategies for transthyretin amyloidosis. *BioDrugs.* 2023;37:127-142.
7. Ioannou A, Patel RK, Razvi Y, et al. Impact of earlier diagnosis in cardiac ATTR amyloidosis over the course of 20 years. *Circulation.* 2022;146:1657-1670.
8. Masson S, Latini R, Anand IS, et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). *J Am Coll Cardiol.* 2008;52:997-1003.
9. Law S, Petrie A, Chacko L, et al. Change in N-terminal pro-B-type natriuretic peptide at 1 year predicts mortality in wild-type transthyretin amyloid cardiomyopathy. *Heart.* 2022;108:474-478.
10. Garcia-Pavia P, Bengel F, Brito D, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. *Eur J Heart Fail.* 2021;23:895-905.
11. Ferreira JP, Liu J, Claggett BL, et al. Outpatient diuretic intensification as endpoint in heart failure with preserved ejection fraction trials: an analysis from TOPCAT. *Eur J Heart Fail.* 2022;24:378-384.
12. Chatur S, Vaduganathan M, Claggett BL, et al. Outpatient worsening among patients with mildly reduced and preserved ejection fraction heart failure in the DELIVER trial. *Circulation.* 2023;148:1735-1745.
13. Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21:137-155.
14. Cheng RK, Levy WC, Vasbinder A, et al. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. *J Am Coll Cardiol CardioOnc.* 2020;2:414-424.
15. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol.* 2012;30:4541-4549.
16. Ioannou A, Massa P, Patel RK, et al. Conventional heart failure therapy in cardiac ATTR amyloidosis. *Eur Heart J.* 2023;44:2893-2907.
17. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation.* 2019;140:16-26.
18. European Society of Cardiology. Trial demonstrates potential of acoramidis for transthyretin amyloid cardiomyopathy. Accessed October 9, 2023. <https://www.escardio.org/The-ESC/Press-Office/Press-releases/Trial-demonstrates-potential-of-acoramidis-for-transthyretin-amyloid-cardiomyopathy>
19. Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med.* 2023;389:1553-1565.
20. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J.* 2018;39:2799-2806.
21. Chacko L, Karia N, Venneri L, et al. Progression of echocardiographic parameters and prognosis in transthyretin cardiac amyloidosis. *Eur J Heart Fail.* 2022;24:1700-1712.
22. Ioannou A, Patel RK, Martinez-Naharro A, et al. Tracking multiorgan treatment response in systemic AL amyloidosis with cardiac magnetic resonance derived extracellular volume mapping. *J Am Coll Cardiol Img.* 2023;16:1038-1052.
23. Ioannou A, Patel RK, Martinez-Naharro A, et al. Tracking treatment response in cardiac light-chain amyloidosis with native T1 mapping. *JAMA Cardiol.* 2023;8:848-852.

**KEY WORDS** cardiac ATTR amyloidosis, disease progression, NT-proBNP, outpatient diuretic intensification

**APPENDIX** For supplemental material, figures, and tables, please see the online version of this paper.