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SHORT REPORT

# Expansion of the National Amyloidosis Centre staging system to detect early mortality in transthyretin cardiac amyloidosis

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**Aims** Transthyretin cardiac amyloidosis (ATTR-CA) is stratified into prognostic categories using the National Amyloidosis Centre (NAC) staging system. The aims of this study were to further expand the existing NAC staging system to incorporate an additional disease stage that would identify patients at high risk of early mortality.

**Methods and results** The traditional NAC staging system (stage 1: N-terminal pro-B-type natriuretic peptide [NT-proBNP] ≤3000 ng/L and estimated glomerular filtration rate [eGFR] ≥45 ml/min; stage 3: NT-proBNP >3000 ng/L and eGFR <45 ml/min; stage 2: remainder) was expanded by the introduction of a new stage 4 (defined as NT-proBNP ≥10 000 ng/L irrespective of eGFR) and studied in 2042 patients. The optimal NT-proBNP cut-point was established using time-dependent receiver operating characteristic curves in the subgroup of patients with NAC stage 3 disease. Mortality at 1 year according to NAC stage was 2.3% ($n = 20/886$) for stage 1, 8.8% ($n = 62/706$) for stage 2, 10.4% ($n = 28/270$) for stage 3, and 30.6% ($n = 55/180$) for stage 4 (log-rank $p < 0.001$). After adjustment for age, mortality hazard for stage 4 was >15-fold higher than that of stage 1 (hazard ratio [HR] 15.5; 95% confidence interval [CI] 9.3–26.1) and >3-fold higher than that of stage 3 (HR 3.4; 95% CI 2.2–5.4). The increased risk of early mortality was consistent across the different genotypes and subclasses of patients based on the severity of heart failure symptoms and echocardiographic parameters.

**Conclusions** The proposed modification of the NAC staging system identifies patients with ATTR-CA at a high risk of early mortality, who may benefit from a more intensive treatment strategy, and who are most likely to experience an event early in the course of a clinical trial.

**Keywords** Staging • Outcome • Transthyretin amyloidosis • Cardiomyopathy

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# Introduction

Transthyretin cardiac amyloidosis (ATTR-CA) is a progressive and ultimately fatal cardiomyopathy, which is an increasingly recognized cause of heart failure.[1,2] The staging system developed at the National Amyloidosis Centre (NAC), based on the combination of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR), has become widely used to stratify patients with ATTR-CA into three prognostic categories. Despite demonstrating utility in both clinical practice and clinical trials, there is a considerable degree of heterogenicity across patients with NAC stage 2 and stage 3 disease. Due to some overlap in the clinical phenotype of patients with NAC stage 2 and stage 3 disease, survival in the first 12 months after diagnosis is similar, with a clear divergence in survival becoming apparent over a longer period of follow-up.[3] Considering this inherent limitation, there remains an unmet clinical need to identify patients at increased risk of early mortality, who may benefit from a more intensive treatment strategy and more frequent follow-up.

The aims of this study were to further expand the existing NAC staging system to incorporate an additional disease stage that would identify patients at high risk of early mortality.

# Methods

Study participants comprised consecutive patients diagnosed with ATTR-CA based on current consensus criteria at the NAC (2005–2022), who did not receive disease-modifying treatment during follow-up. Sequencing of the *TTR* gene was performed in all patients. Patients were managed in accordance with the Declaration of Helsinki and provided written informed consent for analysis and publication of their data (REC reference: 09/H0715/58).

All mortality data were obtained via the UK Office of National Statistics. In order to investigate a novel NT-proBNP cut-off that would identify patients with advanced disease, follow-up was restricted to 12 months, after which patients were censored. The optimal NT-proBNP cut-point was established using time-dependent receiver operating characteristic curves in the subgroup of patients with NAC stage 3 disease. The Youden method identified an optimal cut-point of 10 461 ng/L (sensitivity: 53.5%, specificity: 76.4%), and a cut-point of 10 000 ng/L (sensitivity: 54.1%, specificity: 75.6%) remained a good discriminator of survival by the log-rank test.

The NAC stage was subsequently determined in all patients using the following definition: stage 1: NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min; stage 2: NT-proBNP >3000 ng/L or eGFR <45 ml/min; stage 3: NT-proBNP >3000 ng/L and eGFR <45 ml/min; stage 4: NT-proBNP ≥10 000 ng/L.

Survival was evaluated with Cox proportional hazard regression, providing estimated hazard ratios with 95% confidence intervals. The proportional hazards assumption was checked and confirmed using weighted Schoenfeld residuals. Internal validation of the model was achieved by performing a bootstrapping procedure (500 repeats), affording a comparison of the percentile and bias-corrected methods to ensure the results were unbiased. Harrell's *c*-statistic was calculated to measure the discriminatory ability of each model. To compare *c*-statistics of the new four-stage NAC model with the traditional three-stage NAC model, we randomly divided our data set into a test and validation cohort (1:1). The models were fitted to the training and the *c*-statistics compared in the test cohort. Kaplan–Meier curves were constructed, for which the follow-up time was extended to 36 months, with statistical significance being assessed with a log-rank test. *P*-values were two-sided, and statistical significance was defined as $p < 0.05$.

# Results

Among the 2042 patients studied, 1762 (86%) were male, and the mean (standard deviation) age was 78.3 (7.4) years (*Table 1*). Distribution according to transthyretin amyloidosis (ATTR) subtype was 1506 (74%) ATTR wild-type (ATTRwt), 366 (18%) V142I-associated ATTR variant (ATTRv), and 170 (8%) non-V142I-associated ATTRv. Stratification according to the refined 4-stage NAC system yielded 886 patients in stage 1, 706 in stage 2, 270 in stage 3, and 180 in stage 4. Stage 4 included the following reclassified patients from the traditional 3-stage NAC model: 65 with stage 2 and 115 with stage 3.

## Characteristics of patients with National Amyloidosis Centre stage 4 disease

Patients in the new NAC stage 4 had the highest burden of heart failure symptoms, assigned as New York Heart Association (NYHA) class III/IV in 50.6% of cases, compared with 38.6%, 29.7% and 14.8% in stages 3, 2 and 1, respectively (stage 4 vs. all comparisons $p < 0.05$). By definition, stage 4 patients had the highest NT-proBNP concentrations at median (interquartile range) 14 628 (11 650–19 504) ng/L versus 5665 (4294–7532), 4345 (3323–5904) and 1581 ng/L (940–2214) in stages 3, 2 and 1 (stage 4 vs. all comparisons $p < 0.05$). Severe kidney dysfunction (eGFR <30 ml/min/m$^2$) was present in 25% of NAC stage 4 patients. A continuous worsening of echocardiographic markers of disease severity from stage 1 to 4 was also observed, including an incremental increase in wall thickness and diastolic dysfunction (E/e′), and decrease in systolic function (left ventricular ejection fraction [LVEF] and global longitudinal strain [GLS], all comparisons $p < 0.05$).

## Survival

One-year mortality of the total study population was 8.1% ($n = 165/2042$). Mortality rates according to NAC stage were 2.3% ($n = 20/886$) for stage 1, 8.8% ($n = 62/706$) for stage 2, 10.4% ($n = 28/270$) for stage 3, and 30.6% ($n = 55/180$) for stage 4. After adjustment for age, there was a stepwise increase in risk from stage 2 (vs. stage 1: adjusted hazard ratio [adjHR] 3.83 [2.31–6.35]) to stage 3 (vs. stage 1: adjHR 4.50 [2.52–8.03]), to stage 4 (vs. stage 1: adjHR 15.54 [9.27–26.05]; stage 4 vs. stage 3: adjHR 3.42 [2.17–5.40]; log-rank, $p < 0.001$, online supplementary *Figure S1*). The proportional hazard assumption was satisfied. The new 4-stage NAC system significantly improved the discriminatory ability of the classification compared to the traditional 3-stage system (area under the curve 0.740 [0.701–0.778] vs. 0.706 [0.669–0.743], $p = 0.047$).

In a landmark analysis, with follow-up starting at 12 months and leading up to 36 months, stage 3 had worse outcome compared to stage 2 (adjHR 1.50 [1.16–1.94], $p = 0.002$), and comparable outcome to stage 4 (adjHR 0.89 [0.62–1.27], $p = 0.5$). Over the

**Table 1 Demographics, symptoms, biomarkers, and echocardiographic characteristics at initial presentation**

| | NAC stage 1 (*n* = 886) | NAC stage 2 (*n* = 706) | NAC stage 3 (*n* = 270) | NAC stage 4 (*n* = 180) | *P* value |
|---|---|---|---|---|---|
| **Baseline characteristics** | | | | | |
| Age (years) | 76.6 (7.9)$^{\alpha\beta\gamma}$ | 79.0 (7.0)$^{\delta}$ | 80.7 (5.9) | 80.2 (6.4) | < 0.001 |
| Sex (male) | 768 (86.7%) | 622 (88.1%) | 221 (81.9%) | 151 (83.9%) | 0.059 |
| *Genotype* | | | | | 0.004 |
| ATTRwt | 639 (72.1%) | 534 (75.6%) | 206 (76.3%) | 127 (70.6%) | |
| ATTRv-V142I | 152 (17.2%) | 119 (16.9%) | 54 (20.0%) | 41 (22.8%) | |
| ATTRv−non V142I | 95 (10.7%)$^{\beta}$ | 53 (7.5%) | 10 (3.7%) | 12 (6.7%) | |
| *Ethnicity* | | | | | 0.229 |
| Caucasian | 690 (77.9%) | 562 (79.6%) | 203 (75.2%) | 137 (76.1%) | |
| Afro−Caribbean | 182 (20.5%) | 135 (19.1%) | 61 (22.6%) | 42 (23.3%) | |
| Asian | 6 (0.7%) | 8 (1.1%) | 5 (1.9%) | 1 (0.6%) | |
| Other | 8 (0.9%) | 1 (0.1%) | 1 (0.4%) | 0 (0.0%) | |
| **Heart failure severity** | | | | | |
| NYHA class | | | | | < 0.001 |
| 1 | 169 (20.2%)$^{\alpha\beta\gamma}$ | 49 (7.5%) | 9 (3.7%) | 4 (2.4%) | |
| 2 | 544 (65.0%)$^{\gamma}$ | 413 (62.9%)$^{\varepsilon}$ | 139 (57.7%) | 79 (47.0%) | |
| 3 | 120 (14.3%)$^{\alpha\beta\gamma}$ | 184 (28.0%) | 82 (34.0%) | 75 (44.6%) | |
| 4 | 4 (0.5%)$\beta\gamma$ | 11 (1.7%)$^{\varepsilon}$ | 11 (4.6%) | 10 (6.0%) | |
| Missing | 49 | 49 | 29 | 12 | |
| NT−proBNP, ng/L | 1,581 (940−2,214)$^{\alpha\beta\gamma}$ | 4,345 (3,323−5,904)$^{\delta\varepsilon}$ | 5,665 (4,294−7,532)$^{\phi}$ | 14,628 (11,650−19,504) | < 0.001 |
| eGFR, ml/min/m$^2$ | 68 (57−80)$^{\alpha\beta\gamma}$ | 57 (48−67)$^{\delta\varepsilon}$ | 36 (31−41)$^{\phi}$ | 38 (29−51) | < 0.001 |
| **Echocardiographic parameters** | | | | | |
| IVSd, mm | 16.3 (2.6)$^{\alpha\beta\gamma}$ | 17.2 (2.3)$^{\varepsilon}$ | 16.8 (2.3)$^{\phi}$ | 17.9 (2.5) | < 0.001 |
| PWT, mm | 15.8 (2.6)$^{\alpha\beta\gamma}$ | 16.8 (2.4)$^{\delta\varepsilon}$ | 16.4 (2.5)$^{\phi}$ | 17.6 (2.5) | < 0.001 |
| LVEF, % | 50.5 (9.6)$^{\alpha\beta\gamma}$ | 46.0 (10.6)$^{\varepsilon}$ | 45.9 (10.9)$^{\phi}$ | 41.5 (11.3) | < 0.001 |
| GLS, % | −12.2 (3.8)$^{\alpha\beta\gamma}$ | −9.9 (3.2)$^{\varepsilon}$ | −9.8 (3.2)$^{\phi}$ | −7.9 (2.9) | < 0.001 |
| E/e' | 15.7 (5.8)$^{\alpha\beta\gamma}$ | 17.7 (6.6)$^{\varepsilon}$ | 17.3 (6.3)$^{\phi}$ | 20.2 (7.7) | < 0.001 |

Numbers for numerical variables indicate mean (standard deviation) or median (interquartile range). Categorical variables are displayed as frequency (percentage).
*P*−values for pairwise comparison: $\alpha = P < 0.05$ for 1 vs. 2, $\beta = P < 0.05$ for no 1 vs. 3, $\gamma = P < 0.05$ for 1 vs 4, $\delta = P < 0.05$ for 2 vs 3, $\varepsilon = P < 0.05$ for 2 vs 4, $\phi = P < 0.05$ for 3 vs 4.
NAC indicates National Amyloidosis Centre; ATTRwt, wild−type transthyretin−associated cardiomyopathy; ATTRv, variant transthyretin−associated cardiomyopathy; NYHA, New York Heart Association functional class; NT−proBNP, N−terminal−pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; IVSd, intraventricular septum thickness; PWT, posterior wall thickness; GLS, global longitudinal strain.

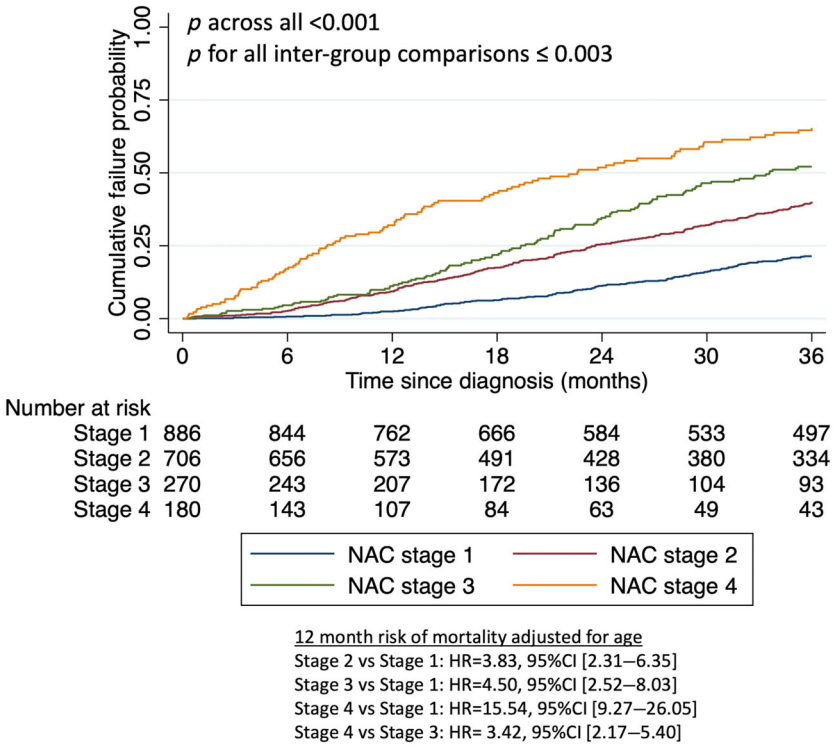


**Figure 1** Kaplan−Meier curves demonstrating the association of National Amyloidosis Centre (NAC) stages with mortality 36 months after initial presentation. CI, confidence interval; HR, hazard ratio.

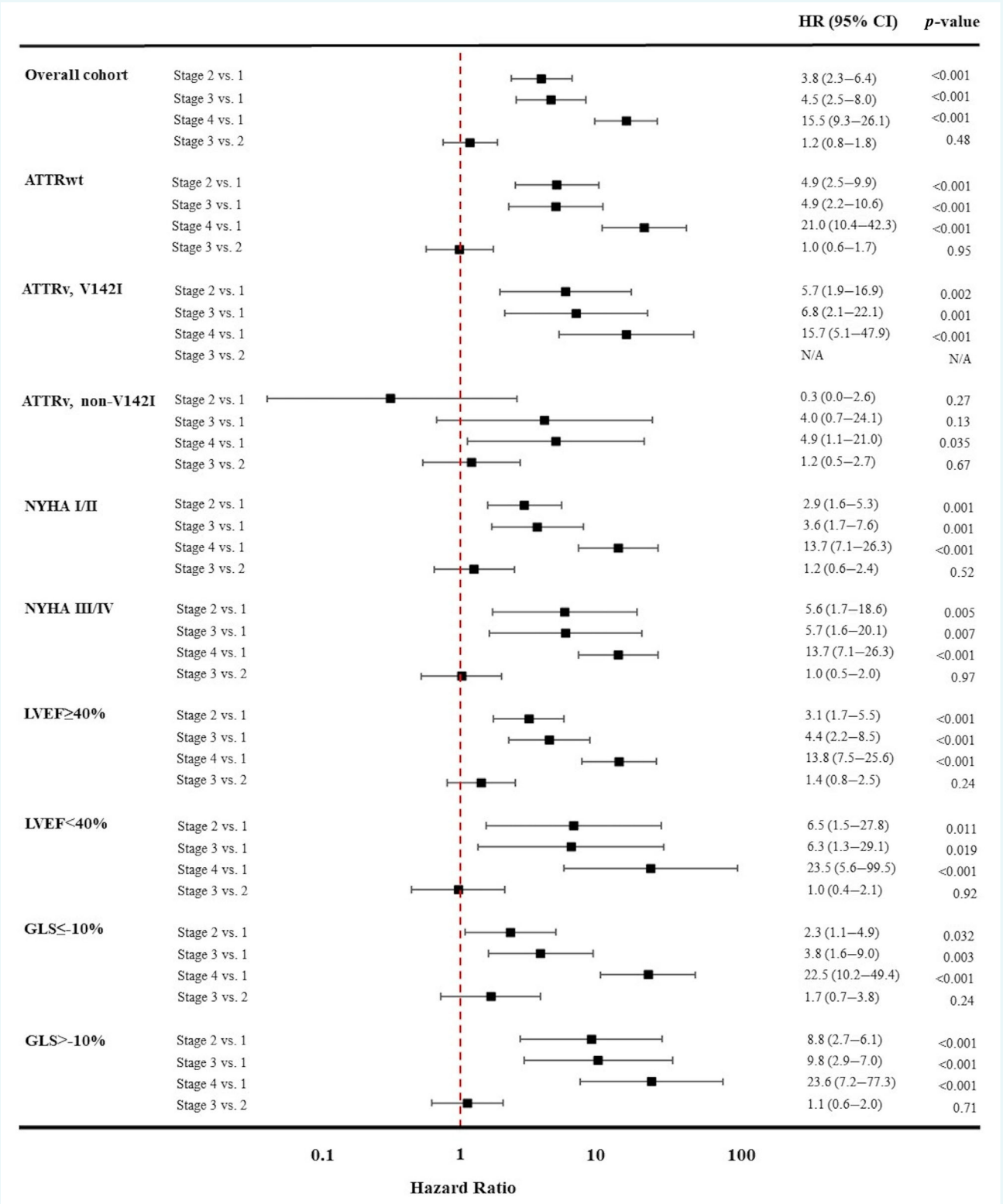


**Figure 2** Forest plots demonstrating the association of different National Amyloidosis Centre stages with 1-year mortality according to pre-specified subgroups. ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

entire follow-up period (0 to 36 months, 603 deaths), an increase in NAC stage was associated with increased mortality hazard (log-rank for all inter-group comparisons $p \leq 0.003$; *Figure 1*). At 36 months, median survival was only reached for stage 3 (33.5 months [28.7–36.0]) and stage 4 (22.5 months [17.5–28.5]).

Prognostic associations for 1-year mortality of the novel staging system were consistent among patients with ATTRwt and V142I-associated ATTRv. Stage 4 was the only stage with a significantly higher 1-year mortality versus stage 1 in patients with non-V142I-associated ATTRv (online supplementary *Figure S2*).

We also performed subgroup analyses at 12-month follow-up for markers of disease severity stratified according to pre-specified cut-offs (LVEF ≥40% vs. <40%, GLS ≤ −10% vs. >10%, NYHA class I/II vs. III/IV). Again, higher NAC stages displayed higher risk hazard consistent across all subgroups (*Figure 2*).

# Discussion

In this study of more than 2000 patients with ATTR-CA, modification of the current NAC staging system enabled the identification of patients with advanced cardiac disease who were at high risk of early mortality.

The NAC staging system represents a simple, widely available and universally applicable stratification tool that accurately classifies patients into prognostic categories.[3] Patients with NAC stage 2 or 3 disease have a similar mortality in the first 12 months, with a clear divergence in survival over a longer duration of follow-up. The addition of NAC stage 4 enables the detection of patients who are at an increased risk of early mortality, but would have previously been classified as having NAC stage 2 or 3 disease. Patients with NAC stage 4 disease had a significantly higher mortality rate than patients in the remaining NAC disease stages, with a 1-year mortality rate of ∼30%, which was >15-fold higher than in patients with NAC stage 1 disease. This increased risk of mortality was consistent across the three different genotypes and pre-specified subgroups.

Identification of this novel high-risk category has important implications on clinical practice, and may help guide treatment decisions considering the ever-expanding landscape of treatment options for patients with ATTR-CA.[4–7] NAC stage 4 patients may require a more intensive treatment strategy with a combination of disease-modifying therapies with different mechanisms of action, and may also represent the cohort of patients most likely to derive benefit from novel treatments designed to remove existing amyloid fibrils from the myocardium.[8,9]

This modification of the NAC staging system may also influence clinical trial design, by enabling the identification of patients at high risk of mortality within the first year of the clinical trial. This could in turn facilitate refinement of the study population size and duration of follow-up needed to evaluate the efficacy of novel treatments.[6,7]

In summary, the proposed modification of the NAC staging system identifies patients with ATTR-CA at high risk of early mortality, who may benefit from a more intensive treatment approach, combination treatment, and who are most likely to experience an event early in the course of a clinical trial. However, this is a single-centre study and therefore requires external validation.

# Supplementary Information

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

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**Conflict of interest**: M.F. reports consultancy/advisory boards for Attralus, Alnylam, Prothena, Akcea, Pfizer, Ionis, Intellia, Alexion, NovoNordisk, Jennsen, AstraZeneca, Lexeo, Cardior; and research grants from Pfizer, Eidos, Alnylam. All other authors have nothing to disclose.

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