

POSITION STATEMENT

Monitoring Disease Progression in Patients With Transthyretin Amyloid Cardiomyopathy



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HIGHLIGHTS

- Experts recognized the need to update the 2021 criteria for monitoring disease progression in ATTR-CM.
- The updated proposed criteria include 6 parameters, with corresponding thresholds and monitoring frequency recommendations.
- It is currently unknown whether disease progression is an indicator for modifications to ATTR-CM treatment.
- Future studies should investigate whether changes in ATTR-CM disease-modifying treatment improve outcomes in patients demonstrating disease progression.

ABSTRACT

Recognizing the lack of disease monitoring recommendations in transthyretin amyloid cardiomyopathy (ATTR-CM), international experts convened in 2021 to propose criteria for monitoring disease progression. Data have since been published demonstrating the prognostic value of certain parameters in ATTR-CM. Additionally, increased awareness and advances in diagnostic methods have led to a shift toward diagnosis at earlier stages of disease. In light of these developments, international experts with experience in treating ATTR-CM reviewed the available data, considered the feasibility of implementing evaluations in clinical practice, and proposed an update to the 2021 criteria. The criteria, with meaningful thresholds and monitoring frequency recommendations, are specifically designed to measure disease progression in patients with ATTR-CM, rather than to define progression of amyloid deposition. It remains unknown whether disease progression is an indicator for modifications to ATTR-CM treatment. Future studies should investigate whether changes in ATTR-CM disease-modifying treatment improve outcomes in patients demonstrating disease progression. (JACC Heart Fail. 2026;14:102766) © 2026 Published by Elsevier on behalf of the American College of Cardiology Foundation.

**ABBREVIATIONS
AND ACRONYMS****6MWT** = 6-minute walk test**ATTR-CM** = transthyretin amyloid cardiomyopathy**ATTRv-CM** = variant transthyretin amyloid cardiomyopathy**ATTRwt-CM** = wild-type transthyretin amyloid cardiomyopathy**CKD** = chronic kidney disease**CVH** = cardiovascular-related hospitalization**eGFR** = estimated glomerular filtration rate**GLS** = global longitudinal strain**HF** = heart failure**KCCQ-CSS** = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score**KCCQ** = Kansas City Cardiomyopathy Questionnaire**KCCQ-OSS** = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score**LTE** = long-term extension**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**ODI** = outpatient diuretic intensification**QoL** = quality of life

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and life-threatening disease characterized by infiltrative deposits of misfolded transthyretin protein in the extracellular space of the myocardium.^{1–3} Amyloid deposition leads to increased ventricular stiffness and expansion of the extracellular space, which may result in a progressively smaller ventricular cavity size and fixed stroke volume.^{1,2,4}

Variant transthyretin amyloid cardiomyopathy (ATTRv-CM) is hereditary and can present as a multisystem disease in people from early middle age onwards, whereas sporadic, noninherited, wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) primarily affects the heart and is predominantly seen in people >60 years of age.⁵ Historically, ATTR-CM was considered a rare disease with limited treatment options and a fatal prognosis; however, it is now recognized as a more common cause of heart failure (HF) than previously thought.^{6–10} ATTR-CM has also traditionally been described as a disease affecting older men, although the prevalence in women may be underestimated.⁹ The natural history of ATTR-CM is variable but somewhat dependent on its cause. Prognosis is universally poor in untreated patients, with a median untreated survival time from diagnosis of 2.6 years for patients with V122I-ATTRv-CM, 4.8 years for patients with ATTRwt-CM, and up to 5.8 years for patients with non-V122I-ATTRv-CM.^{11,12} Both ATTRv-CM and ATTRwt-CM are also associated with markedly poor quality of life (QoL) at the time of

diagnosis and progressive deterioration thereafter when untreated, with patients frequently being hospitalized.¹¹ Therefore, accurate and prompt diagnosis and treatment initiation are key to improving clinical outcomes in patients with ATTR-CM.

Recognizing the lack of disease monitoring recommendations in ATTR-CM, in 2021 a group of international experts proposed criteria for monitoring disease progression in patients with ATTR-CM.¹³ Since then, data have been published that demonstrate the prognostic value of various disease progression parameters in patients with ATTR-CM.^{14–25} In addition, the disease landscape has changed in recent years. Heightened awareness among cardiologists and advances in noninvasive diagnostic imaging have led to a shift toward a population diagnosed with ATTR-CM at earlier stages,^{6,7,11,26,27} as well as an overall increase in the number of diagnosed patients, particularly those with ATTRwt-CM.¹¹

In light of these developments, international experts with experience in treating ATTR-CM discussed the need to update the 2021 criteria, reviewed studies examining the prognostic value of monitoring parameters, and considered the feasibility of implementing evaluations in clinical practice. Accordingly, they proposed updated criteria, comprising parameters, thresholds, and monitoring frequency recommendations. This report summarizes the expert panel's final proposed recommendations.

METHODS AND SELECTION OF TOOLS

Panels of experts with experience in treating amyloidosis and ATTR-CM convened in 2 sponsored meetings. One meeting included a group of experts from France, Italy, Japan, Spain, the United

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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](#).

TABLE 1 Updated Criteria for Evaluating Disease Progression in Patients With ATTR-CM				
	Category	Threshold	Frequency	Is There Evidence Supporting the Prognostic Value of the Parameter?
HF-related hospitalization	Clinical	≥1 event	12 mo	Yes ¹⁸⁻²⁰
ODI	Clinical	Initiation of any new oral loop diuretic agent (among those not taking loop diuretic agents) or a sustained increase in dose of ≥30 days (among those taking diuretic agents) occurring in ambulatory care	12 mo	Yes ^{15,24,25}
NT-proBNP	Biomarker	Increase of >700 pg/mL with a relative increase of >30% ^a	12 mo	Yes ^{15,25}
eGFR	Biomarker	Relative decrease of >20% ^a	12 mo	Yes ^{17,25}
6MWT	Functional	Decrease of >35 m	12 mo	Yes ¹⁶
QoL				
KCCQ (preferred parameter for QoL)	Functional	>5-point decrease	12 mo	Yes ^{21,22}
NYHA functional class (if KCCQ not available)	Functional	Increase in class	12 mo	Yes ²³

^aThe measurement should be taken during a period of clinical stability. Alternatively, 2 measurements taken approximately 4 weeks apart may help to ensure that transient changes are not mistaken for progression.

6MWT = 6-minute walk test; ATTR-CM = transthyretin amyloid cardiomyopathy; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ODI = outpatient diuretic intensification; QoL = quality of life.

Kingdom, and the United States. The other meeting included experts from across the United States. The experts were selected based on their expertise in treating patients with ATTR-CM, geographical distribution, and broad range of academic and clinical experience. No participant in either meeting was appointed by a national society or regulatory authority.

To better understand experts' opinions before the meetings, a survey was circulated, and anonymized responses across both meeting cohorts were collated. Both meetings followed an identical structured approach to the discussion. Firstly, experts revisited the criteria from the 2021 publication and reviewed data from relevant studies, including those evaluating the prognostic value of parameters in ATTR-CM. The experts were then asked to discuss whether there was a need to update the 2021 criteria and, if so, to highlight any changes they would make. The experts started by assessing the domain structure of the 2021 criteria, before delving into the specific parameters. In the pursuant months, the meeting expert cochairs met to agree upon and further develop the recommendations from the 2 meetings before giving the broader author group the opportunity to input, refine, and agree upon the final proposed recommendations we present here.

RESULTS

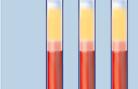
MONITORING DISEASE PROGRESSION IN PATIENTS WITH ATTR-CM. An important distinction was made between amyloid deposition progression

(eg, increased amyloid deposition that results in changes in left ventricular wall thickness) and disease progression in patients with ATTR-CM (eg, worsening of HF symptoms), which could be independent of any further amyloid deposition. The criteria presented here focus specifically on the monitoring of disease progression of patients with ATTR-CM and not amyloid deposition progression.

Considering the differentiation between disease progression and amyloid deposition progression, it was agreed that disease progression as defined in this paper should not necessarily prompt stopping or changing ATTR-CM disease-modifying treatment or define "failure" of a current treatment. The experts felt that stopping or changing ATTR-CM treatment would not necessarily address the factor driving progression (eg, worsening HF, arrhythmia, aging) and that there is currently no evidence that switching or combining ATTR-CM therapy improves clinical outcomes.

UPDATED DISEASE MONITORING CRITERIA. The updated recommended criteria comprise 6 parameters listed as independent variables (Table 1): HF-related hospitalization, outpatient diuretic intensification (ODI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR), 6-minute walk test (6MWT), and QoL (measured by the Kansas City Cardiomyopathy Questionnaire [KCCQ], or NYHA functional class if KCCQ is not available). The rationale for including these parameters is that they are relatively feasible to capture in routine clinical practice and there is

CENTRAL ILLUSTRATION Criteria for Evaluating Disease Progression in Patients With ATTR-CM**List of Parameters, Thresholds, and Categories**

HF-Related Hospitalization	Outpatient Diuretic Intensification	NT-proBNP	eGFR	6MWT	QoL
Clinical	Biomarkers				Functional
 ≥1 event	 Initiation of any new oral loop diuretic ^a or a sustained increase in dose of ≥30 days ^b in ambulatory care	 Increase of >700 pg/mL with a relative increase of >30% ^c	 Relative decrease of >20%	 Decrease of >35 meters	 >5-point decrease in KCCQ or, if KCCQ not available, increase in NYHA functional class

Disease progression can be considered if at least 2 parameters meet their defined thresholds

Parameters should be evaluated every 12 months and compared with the results from 12 months prior

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^aAmong those not taking loop diuretic agents. ^bAmong those taking diuretic agents. ^cThe measurement should be taken during a period of clinical stability. Alternatively, 2 measurements taken approximately 4 weeks apart may help to ensure that transient changes are not mistaken for progression. 6MWT = 6-minute walk test; ATTR-CM = transthyretin amyloid cardiomyopathy; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; QoL = quality of life.

evidence supporting their prognostic value in patients with ATTR-CM.¹⁵⁻²⁵

The experts proposed that progression in at least 2 of the defined parameters could be considered disease progression (**Central Illustration**). Progression of a parameter would require that it meet the threshold defined in **Table 1**. Parameters should be evaluated every 12 months and compared with results from the previous 12 months, rather than compared with a patient's baseline results. In addition, they should not be compared with values measured over the course of the 12 months, to avoid using random fluctuations and oversampling to determine disease progression.

There is evidence supporting the prognostic value of each parameter within the proposed criteria (**Table 2**). However, using only 1 parameter may risk overestimating patients with disease progression. Furthermore, 1 study found that incrementally adding certain validated parameters (ODI, NT-proBNP progression, and 6MWT worsening) increases the risk of mortality in patients with ATTR-CM.¹⁶

The study analyzed the additive prognostic value of ODI, NT-proBNP progression, and 6MWT worsening (as an absolute reduction of >35 m) and found that 2 markers of progression increased the risk of mortality compared with 1 marker of progression (HR: 1.50 [95% CI: 1.21-1.85]; $P < 0.001$).¹⁶ Balancing the need to avoid overestimating progression in clinical practice with the need to be informed by data, the experts proposed at least 2 parameters within the criteria for considering disease progression. The experts additionally encourage validation of this proposal in future studies.

HF-RELATED HOSPITALIZATION. HF-related hospitalization is widely used as a clinical endpoint in HF and ATTR-CM trials, and there is evidence supporting its prognostic use in patients with ATTR-CM.^{18-20,28} A post hoc analysis of the ATTRibute-CM trial (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy; [NCT03860935](#)) (a phase 3 study investigating the efficacy and safety of acoramidis vs placebo in patients with ATTR-CM) was carried out to investigate the relationship

TABLE 2 Selected Studies Investigating the Prognostic Value of the Parameters Included in the Proposed Criteria for Monitoring Disease Progression in Patients With ATTR-CM

First Author, Year	Study Design	Parameter Definition or Threshold	Sample Size	Follow-Up Period	Key Findings
HF-related hospitalizations					
Masri et al, ¹⁸ 2024	Post hoc analysis of phase 3 study (initial reports)	CVH: nonelective admission to an acute care setting for cardiovascular-related morbidity (resulting in a >24-h stay) or an unscheduled medical visit of <24 h due to HF requiring treatment with intravenous diuretic agents	611	30 mo	Patients with no CVH during the study had a 30-mo survival rate of 86.7% (95% CI: 82.9%-89.7%) vs 60.1% (95% CI: 52.8%-66.7%) in patients who had at least 1 CVH during the study ($P < 0.0001$)
Zeldin et al, ²⁰ 2024	Retrospective cohort study	HF hospitalization event	303	30 mo	Patients who experienced HF hospitalization had higher rates of subsequent all-cause mortality (29.8 per 100 person-years; 95% CI: 17.7-50.3) vs those with no HF hospitalization or ODI events (5.0 per 100 person-years; 95% CI: 3.0-8.3; $P < 0.0001$ on log-rank test)
ODI					
Ioannou et al, ¹⁵ 2024	Retrospective, multinational, longitudinal study	ODI: any post-diagnosis initiation or increment in the dose of loop diuretic agent (standardized to furosemide equivalent)	2,275	12 mo	ODI was associated with a 1.9-fold higher risk of mortality (HR: 1.88 [95% CI: 1.62-2.18]; $P < 0.001$) in the NAC development cohort and a 2.1-fold higher risk of mortality (HR: 2.05 [95% CI: 1.53-2.74]; $P < 0.001$) in the external validation cohort
Fontana et al, ²⁴ 2025	Prespecified analysis of phase 3 study	Outpatient worsening HF: an initiation of or a sustained increase (any increase for ≥ 7 d) in daily dose of oral loop diuretic agents; no minimum increase in the daily dose of diuretic agents was required	654	36 mo	Outpatient worsening HF was associated with an increased risk of worse clinical outcomes, including all-cause mortality (HR: 2.45; 95% CI: 1.70-3.52)
Sinigiani et al, ²⁵ 2025	Multicenter, longitudinal, observational study	ODI: any initiation or dose increasing of loop diuretic drugs	683	12 mo	ODI was associated with an increased risk of adverse clinical outcomes (HR: 1.92 [95% CI: 1.01-3.68]; $P = 0.046$) in early-stage ATTRwt-CM patients treated with tafamidis
NT-proBNP					
Ioannou et al, ¹⁵ 2024	Retrospective, multinational, longitudinal study	NT-proBNP progression: increase of both >700 pg/mL and >30%	2,275	12 mo	In the validation cohort (n = 677), NT-proBNP progression was associated with mortality (HR: 1.75 [95% CI: 1.32-2.33]; $P < 0.001$)
Sinigiani et al, ²⁵ 2025	Multicenter, longitudinal, observational study	NT-proBNP progression: absolute increase >700 ng/L and a relative increase >30%	683	12 mo	NT-proBNP progression was associated with poor prognosis in the 12-mo landmark analysis (HR: 3.32 [95% CI: 1.73-6.38]; $P < 0.001$) in early-stage ATTRwt-CM patients treated with tafamidis
eGFR					
Ioannou et al, ¹⁷ 2025	Retrospective, observational cohort study	Decline in kidney function: >20% relative reduction in eGFR	2,001	12 mo	A relative reduction in eGFR of >20% was associated with a 1.7-fold higher risk of mortality (HR: 1.71 [95% CI: 1.43-2.04]; $P < 0.001$)
Sinigiani et al, ²⁵ 2025	Multicenter, longitudinal, observational study	Decline in kidney function: >20% decrease in eGFR	683	12 mo	Decline in kidney function was associated with an increased risk of adverse outcomes (HR: 2.14 [95% CI: 1.13-4.08]; $P = 0.02$) in early-stage ATTRwt-CM patients treated with tafamidis
6MWT					
Ioannou et al, ¹⁶ 2024	Retrospective, observational cohort study	6MWT worsening: absolute reduction of >35 m ^a	2,141	12 mo	An absolute reduction in 6MWT of >35 m at 1 year was associated with an increased risk of mortality (HR: 1.80 [95% CI: 1.51-2.15]; $P < 0.001$)
KCCQ					
Levy et al, ²² 2025	Landmark analysis (initial results)	KCCQ-OSS worsening: decrease of >5 points	205	12 mo	A decrease in KCCQ-OSS of >5 points was associated with an increased risk of all-cause mortality and HF-related hospitalization after 12 mo, after adjustment for other measures of disease severity (HR: 2.5 [95% CI: 1.12-5.6]; $P = 0.026$)

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TABLE 2 Continued						
First Author, Year	Study Design	Parameter Definition or Threshold	Sample Size	Follow-Up Period	Key Findings	
NYHA functional class						
Law et al, ²³ 2022	Retrospective, observational study	NYHA functional class: increase in class	432	12 mo	An increase in NYHA functional class at 1 year predicted mortality (HR: 1.65 [95% CI: 1.11-2.47]; $P = 0.014$)	

^aThe relative reduction threshold for 6MWT investigated in the study was not included in the proposed criteria for monitoring disease progression in patients with ATTR-CM.

ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; CVH = cardiovascular-related hospitalization; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire—Overall Summary Score; NAC = National Amyloidosis Centre; other abbreviations as in Table 1.

between cardiovascular-related hospitalization (CVH) and mortality in the modified intent-to-treat population ($N = 611$).¹⁸ CVH included a nonelective admission to an acute care setting for cardiovascular-related morbidity (resulting in a >24 -hour stay) or an unscheduled medical visit of <24 hours due to HF requiring treatment with intravenous diuretic agents.¹⁸ Initial reports of the analysis found that patients with no CVH during the study had a 30-month survival rate of 86.7% (95% CI: 82.9%-89.7%) vs 60.1% (95% CI: 52.8%-66.7%) in patients who had at least 1 CVH during the study ($P < 0.0001$), suggesting that CVH is associated with higher mortality in patients with ATTR-CM.¹⁸ Furthermore, a post hoc analysis of ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy; [NCT01994889](#)) (a Phase 3 study investigating the efficacy and safety of tafamidis vs placebo in patients with ATTR-CM; tafamidis $n = 264$; placebo $n = 177$) found that most of the deaths among patients were cardiovascular related. The analysis also found that the most common cause of cardiovascular-related death and hospitalization was HF.¹⁹ Additionally, a retrospective cohort study of patients with ATTR-CM who presented to the Columbia University Irving Medical Center ($N = 303$) (most of whom were prescribed a disease-modifying therapy) found that patients who experienced HF hospitalization had higher rates of subsequent all-cause mortality (29.8 per 100 person-years; 95% CI: 17.7-50.3) vs those with no HF hospitalization or ODI events (5.0 per 100 person-years; 95% CI: 3.0-8.3; $P < 0.0001$ on log-rank test).²⁰

Given these data, the updated criteria include HF-related hospitalization. This clinical parameter is straightforward to assess during a patient visit, because an event is typically recorded in a patient's notes during or immediately after the hospitalization. The recommended threshold for HF-related hospitalization is ≥ 1 event within 12 months.

OUTPATIENT DIURETIC INTENSIFICATION. ODI is a frequent first manifestation of worsening HF and is a known strong independent predictor of prognosis in patients with HF.^{29,30} The prognostic validity of ODI in ATTR-CM was investigated in a retrospective, multinational, longitudinal study of 2,275 patients diagnosed with ATTR-CM, of whom 515 were prescribed disease-modifying therapy or enrolled into clinical trials, and assessed 1 year after their start date.¹⁵ ODI was defined as any post-diagnosis initiation or increment in the dose of loop diuretic agent (standardized to furosemide equivalent). In a 1-year landmark survival analysis, ODI was associated with a 1.9-fold higher risk of mortality (HR: 1.88 [95% CI: 1.62-2.18]; $P < 0.001$) in the NAC (National Amyloidosis Centre) development cohort and a 2.1-fold higher risk of mortality (HR: 2.05 [95% CI: 1.53-2.74]; $P < 0.001$) in the external validation cohort. This associated risk of mortality was also dose dependent; patients who experienced the greatest degree of ODI had the greatest risk of mortality.¹⁵ In addition, in a prespecified analysis of the HELIOS-B trial (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; [NCT04153149](#)) ($N = 654$) (of whom 326 patients received vutrisiran and 328 received placebo during a 36-month period), ODI was associated with an increased risk of worse clinical outcomes, including all-cause mortality (HR: 2.45; 95% CI: 1.70-3.52).²⁴ In this analysis, ODI was defined as an initiation or sustained increase for ≥ 7 days in daily dose of oral loop diuretic agents.²⁴ Additionally, a recent multicenter, longitudinal, observational study investigated outcomes in 683 early-stage ATTRwt-CM patients treated with tafamidis at 19 ATTR-CM outpatient clinics in Italy.²⁵ Clinical data were collected at tafamidis initiation and at 12 months.²⁵ The 12-month landmark analysis assessed the prognostic value of various progression markers and reported that ODI, defined as any initiation or dose increase of loop diuretic agents, was associated with an increased risk of adverse clinical outcomes (HR: 1.92 [95% CI: 1.01-3.68]; $P = 0.046$).²⁵

ODI is included in the updated criteria because it has been validated in a study of patients with ATTR-CM and is feasible to capture in clinical practice.¹⁵ It was agreed to use the definition of ODI from a pre-specified analysis of the phase 3 DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; NCT03619213) trial: initiation of any new oral loop diuretic agent (among those not taking loop diuretic agents) or a sustained increase in dose of ≥ 30 days (among those taking diuretic agents) occurring in ambulatory care.²⁹ Assessing ODI to determine disease progression should be carried out every 12 months and compared with the patient's diuretic treatment status 12 months prior.

NT-proBNP. NT-proBNP measurement is used to determine a diagnosis of HF, as well as being used for risk stratification and prognosis.³¹⁻³⁴ In the previously published criteria, a relative (30%) increase with an absolute (300 pg/mL) increase in NT-proBNP was recommended to detect disease progression in patients with both early-stage and more advanced ATTR-CM.¹³ These recommendations were based solely on data from the placebo arm of the ATTR-ACT trial of tafamidis and the expertise of the investigators.¹³

Subsequently, data have been published that demonstrate the prognostic utility of NT-proBNP in patients with ATTR-CM.¹⁵ In the same study that evaluated the validity of ODI as a prognostic predictor of mortality, NT-proBNP was also assessed.¹⁵ Optimal cutoffs for absolute and relative increases in NT-proBNP at 1 year were determined in a development cohort ($n = 1,598$) as an absolute increase of >700 pg/mL and a relative increase of $>30\%$. To account for its biological variability, NT-proBNP progression was defined as an increase that was both >700 pg/mL and $>30\%$. In the validation cohort ($n = 677$), NT-proBNP progression was associated with mortality (HR: 1.75 [95% CI: 1.32-2.33]; $P < 0.001$). Furthermore, compared with the previously published criteria cutoffs, these validated cutoffs produced the most consistent HRs across different genotypes and across both development and validation cohorts.¹⁵ In addition, the aforementioned study investigating outcomes in early-stage ATTRwt-CM patients treated with tafamidis at 19 Italian centers also assessed NT-proBNP progression.²⁵ NT-proBNP progression, defined in this study as an absolute increase of >700 ng/L and a relative increase of $>30\%$, was associated with poor prognosis in the 12-month landmark analysis (HR: 3.32 [95% CI: 1.73-6.38]; $P < 0.001$) in early-stage ATTRwt-CM patients treated with tafamidis,²⁵

further supporting the prognostic utility of NT-proBNP in patients with ATTR-CM.

These published data validate the prognostic utility of NT-proBNP in patients with ATTR-CM.¹⁵ Given that it is also feasible to capture this parameter in clinical practice, NT-proBNP is included in the updated criteria. The updated recommended threshold is an absolute increase of >700 pg/mL with a relative increase of $>30\%$.

NT-proBNP should be measured at 12 months and compared with the results from 12 months prior. The measurement should be taken during a period of clinical stability. Alternatively, 2 measurements taken approximately 4 weeks apart may help to ensure that transient changes in NT-proBNP are not mistaken for progression. Health care professionals should work holistically to determine whether changes are due to other potentially reversible factors, such as a major dietary increase in sodium intake or acute changes in kidney function.

eGFR. Chronic kidney disease (CKD) and HF are common co-occurring conditions, with one often exacerbating the other through various interlinked mechanisms. eGFR, a marker of worsening kidney function, has been used in combination with NT-proBNP to define a prognostic staging system in patients with ATTR-CM, suggesting that the interconnected relationship between ATTR-CM and CKD may be similar to that of HF and CKD.¹⁷

As such, it was posited that a decline in eGFR may be a marker for disease progression in patients with ATTR-CM. This was investigated in a retrospective, observational cohort study of 2,001 patients diagnosed with ATTR-CM (of whom 347 were prescribed disease-modifying therapy or enrolled into clinical trials, and assessed 1 year after their start date).¹⁷ The optimal cutoff for the percentage reduction in eGFR at 1 year was determined as a 20% relative reduction.¹⁷ The study found that a relative reduction in eGFR of $>20\%$ was associated with a 1.7-fold higher risk of mortality (HR: 1.71 [95% CI: 1.43-2.04]; $P < 0.001$).¹⁷ The risk was similar across genotypes and NAC disease stages, and was consistent after adjusting for NT-proBNP and ODI.¹⁷ The previously mentioned study in early-stage tafamidis-treated ATTRwt-CM patients from 19 Italian centers also assessed eGFR.²⁵ In the 12-month landmark analysis, a $>20\%$ decline in eGFR was shown to be associated with an increased risk of adverse outcomes (HR: 2.14 [95% CI: 1.13-4.08]; $P = 0.02$).²⁵ These results validate a decrease in eGFR of $>20\%$ as an independent marker of disease progression in ATTR-CM.¹⁷ As with NT-proBNP, eGFR is feasible to capture in clinical practice.

Reflecting these published data, the updated criteria include eGFR and recommend a decrease of >20% as the threshold. eGFR should be measured every 12 months and compared with the results from 12 months prior. It is recommended that the measurement should be taken during a period of clinical stability. Alternatively, 2 measurements taken approximately 4 weeks apart may help to ensure that transient changes in eGFR are not mistaken for progression. Health care professionals should work holistically to determine whether changes are due to other potentially reversible factors, such as dehydration or hypotension. In addition, an acute, reversible drop in eGFR may occur in some patients after initiating certain treatments. For example, initiation of acoramidis may result in a decrease in eGFR that typically occurs within 1 month of starting treatment and then stabilizes; this decrease is nonprogressive, reversible following treatment discontinuation, and not associated with kidney injury, consistent with a kidney hemodynamic effect.^{35,36} In addition, certain sodium-glucose cotransporter-2 inhibitors are associated with an initial, transient drop in eGFR that likely reflects the protective mechanism of action of these agents and is not associated with long-term kidney function loss or acute kidney injury.³⁷ Similarly, an acute, reversible drop in eGFR may be observed after initiation of treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors; trial results have shown that the decrease is not associated with adverse outcomes and that even a 20% to 30% drop in eGFR is not associated with a reduced treatment effect.^{37,38}

6MWT. ATTR-CM is associated with a progressive decline in functional capacity, especially when untreated.^{12,28,39} This functional deterioration may be driven by cardiac and extracardiac manifestations, such as musculoskeletal symptoms. Physical assessments, including the number of meters walked in 6 minutes, or the 6MWT, are an objective and comprehensive way to evaluate functional capacity. The 6MWT is commonly used in patients with HF both in clinical trials and clinical practice settings.¹⁶ It has also been used as a primary or secondary endpoint in ATTR-CM phase 3 clinical trials.^{28,40-42}

Since the publication of the previous criteria, published data have validated the 6MWT as a prognostic variable in patients with ATTR-CM. In a retrospective, observational cohort analysis of 2,141 patients with ATTR-CM from the NAC (of whom 212 were prescribed disease-modifying therapy and

259 were enrolled into clinical trials), the optimal thresholds for the baseline 6MWT distance and change in 6MWT distance at 1 year were established. A baseline 6MWT distance of <350 m was associated with a 2.2-fold higher risk of mortality (HR: 2.15 [95% CI: 1.85-2.50]; $P < 0.001$). An absolute reduction of >35 m and a relative reduction of >5% at 1 year were associated with an increased risk of mortality (HR: 1.80 [95% CI: 1.51-2.15]; $P < 0.001$ and HR: 1.89 [95% CI: 1.59-2.24]; $P < 0.001$, respectively).¹⁶

The recommended threshold of the 6MWT for defining disease progression was therefore based on these data and is an absolute reduction of >35 m. Although a relative change of 5% in the 6MWT was also validated in this same patient cohort, the expert panel agreed to include only the absolute value because it is simpler to use as part of the criteria, and absolute changes in 6MWT are typically used in other areas of cardiology. 6MWT should be assessed at 12 months and compared with the results from 12 months prior.

QUALITY OF LIFE. QoL may be assessed using tools such as the KCCQ, an established chronic disease measure in clinical trials.⁴³ The KCCQ score includes domains of physical and social limitations, symptoms, and self-efficacy.⁴³ Initial reports have been presented of a landmark analysis investigating worsening Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS) as a marker of disease progression.²² This analysis included 205 patients with ATTR-CM who were prescribed disease-modifying therapies and had baseline and follow-up KCCQ-OSSs.²² The investigators found that a decrease in KCCQ-OSS of >5 points was associated with an increased risk of all-cause mortality and HF-related hospitalization after 12 months, after adjustment for other measures of disease severity (HR: 2.5 [95% CI: 1.12-5.60]; $P = 0.026$).²²

An interim analysis of the ATTR-ACT and long-term extension (LTE) study (Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy; [NCT02791230](#)) examined the progression of KCCQ-OSS and Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS). The analysis included patients who received tafamidis meglumine 80 mg in ATTR-ACT before transitioning to tafamidis free acid 61 mg in the LTE study following a protocol amendment ($n = 110$), and patients who received placebo in ATTR-ACT before switching to tafamidis free acid 61 mg in the LTE study ($n = 82$).²¹ Tafamidis free acid 61 mg is bioequivalent to tafamidis meglumine 80 mg; they are not interchangeable on a per mg basis.⁴⁴ The analysis

found that the placebo to tafamidis group had a 20-point reduction in least-squares mean KCCQ-OSSs at the end of ATTR-ACT (month 30: -19.60 [SE = 1.94]), but the decline slowed after initiating tafamidis in the LTE study (month 60: -24.70 [SE = 3.04]).²¹ Tafamidis additionally slowed the decline in KCCQ-CSSs in the placebo to tafamidis group (least-squares mean change from baseline -19.90 [SE = 2.01] at month 30 and -25.30 [SE = 3.36] at month 60).²¹ A similar effect with survival was observed in the LTE study.²¹

If measuring KCCQ is not possible, NYHA functional class may be used. The prognostic value of NYHA functional class was analyzed in a retrospective, observational study of 432 patients with ATTRwt-CM (none of whom received disease-modifying therapy). The study found that an increase in NYHA functional class at 1-year predicted mortality (HR: 1.65 [95% CI: 1.11-2.47]; $P = 0.014$), independent of changes in other variables.²³

Based on the available data, the updated criteria recommend a >5-point decrease as the threshold for KCCQ score. An increase in class was decided as the threshold for NYHA functional class. KCCQ (or NYHA if KCCQ is not available) should be assessed at 12 months and compared with the results 12 months prior.

DISCUSSION

DEFINING DISEASE PROGRESSION AND CONSIDERING THE IMPLICATIONS.

The proposed criteria presented here focus specifically on the monitoring of disease progression of patients with ATTR-CM and not amyloid deposition progression. The experts agreed that in doing so, they avoid the association of these criteria with any implication of changing ATTR-CM disease-modifying treatment but still provide a framework to identify patients who are experiencing a worsening of their disease. Therefore, disease progression according to these criteria should not prompt stopping treatment, because progression may be due to various factors beyond amyloid progression. Similarly, there are no published data demonstrating a benefit in patient outcomes among patients who exhibit disease progression and in whom specific therapies are switched or combined. As a result, these criteria should be used solely to identify when a patient is experiencing a worsening of their disease course. Moreover, these criteria could provide a future framework for designing prospective studies to evaluate whether changes in disease-modifying treatment (such as switching or combining treatments) improve clinical outcomes.

In clinical practice, identifying which patients with ATTR-CM are experiencing disease progression can help cardiologists to better understand the patient's prognosis and individualize their long-term care plan accordingly. Specifically, patients exhibiting disease progression may benefit from more frequent follow-up appointments, which may involve standard assessments (eg, of their volume status, blood pressure, and arrhythmia) and lifestyle recommendations, as well as a review—and potential optimization—of their non-ATTR-CM-specific therapies.

APPLYING THE CRITERIA IN CLINICAL PRACTICE.

The prognostic thresholds of the parameters included in the criteria are mostly derived from cohort data. Given variability in patient characteristics, therapies, and rates of progression across ATTR-CM genotypes, these thresholds may not be universally applicable to all individual patients. Therefore, clinical judgment and consideration of patient factors are recommended when interpreting and applying the criteria in practice.

RATIONALE FOR THE OMISSION OF CERTAIN PARAMETERS.

In formulating these criteria, the experts acknowledge the need for them to be as widely implementable as possible. As such, it is important to provide the rationale for omitting certain parameters that may have been expected to be included.

In contrast to the previously published criteria,¹³ imaging parameters were excluded. Echocardiography is widely used in the diagnosis of ATTR-CM, with a range of echocardiography parameters providing meaningful indications of ATTR-CM (eg, stroke volume, inferior vena cava diameter, Doppler assessment including E/e' and transmural flow, global longitudinal strain [GLS], and pericardial effusion). It was previously suggested that echocardiography parameters may also be suggestive of disease progression (eg, increase in left ventricular wall thickness, decrease in left ventricular systolic function, and worsening of longitudinal strain),^{6,13,45} although it was noted that the value of different echocardiographic parameters varies according to disease stage.¹³ The experts centered their rationale for omitting imaging parameters on their experience of high interobserver variability and the inherent difficulty in accurately interpreting imaging results over time. This parallels results from a retrospective study of GLS in stable patients undergoing chemotherapy ($N = 30$), which found that variability of GLS assessments made by sonographers over time was 1.28%, whereas in a subset of 10 random patients, interobserver test-retest variability measured by expert observers was 1.12% ($P = 0.17$).⁴⁶ Additionally, a

prospective study of 887 patients with ATTR-CM who had available serial echocardiography findings concluded that only mitral and tricuspid regurgitation were independently associated with mortality.¹⁴ It was also noted that clinical trials in patients with ATTR-CM—as well as cardiomyopathy subgroup analyses of trials in patients with variant transthyretin amyloidosis—have reported imaging parameter data such as left ventricular ejection fraction, left ventricular wall thickness, and longitudinal strain.^{28,40,47-49} Some results suggest that changes in imaging parameters over time between treated and placebo groups were statistically insignificant; others reported a significant difference but—according to the experts—one that was numerically small.^{28,40,47-49} In addition, the multicenter, longitudinal, observational study conducted in 19 Italian centers concluded that imaging-derived markers, particularly interventricular septum, left ventricular ejection fraction, and E/e', did not show any prognostic value in early-stage ATTRwt-CM patients treated with tafamidis.²⁵ In light of these data, it was felt that imaging parameters may not accurately capture actual disease progression, especially in individual patients in whom changes over time may be smaller than the group effects reported in clinical trials. The experts noted a lack of data on progression and also a lack of feasibility with regard to implementing cardiac magnetic resonance-based parameters as part of routine monitoring.

Arrhythmia-related parameters, such as electrocardiography and the need for a pacemaker, were not included, mainly due to a lack of evidence and uncertainty around their value as markers of disease progression. An analysis of the ATTR-ACT trial found that baseline or historical atrial fibrillation/atrial flutter was common in patients with ATTR-CM but not prognostic of all-cause mortality when extensively adjusting for other measures of disease severity.⁵⁰ However, it is currently unknown whether the onset of a de novo arrhythmia is a marker of mortality in patients with ATTR-CM. Another unanswered question is whether the rise in NT-proBNP that is frequently observed in a patient with a de novo arrhythmia is indicative of disease progression in patients with ATTR-CM. In the same study that assessed the prognostic value of NT-proBNP and ODI, a subanalysis was carried out to investigate whether the NT-proBNP cutoffs were suitable to predict the risk of mortality in patients with concomitant atrial fibrillation (n = 1,150).¹⁵ The subanalysis found that NT-proBNP progression was

associated with a 1.8-fold higher risk of mortality (HR: 1.78 [95% CI: 1.49-2.12]; P < 0.001).¹⁵ Although the data support the prognostic value of NT-proBNP in patients with concomitant atrial fibrillation, it remains unclear whether NT-proBNP progression associated with a new arrhythmia is indicative of disease progression in patients with ATTR-CM.

There is evidence for the prognostic value of troponin-T in patients with ATTR-CM.¹⁵ However, troponin-I has not yet been validated; therefore, the optimal cutoff for troponin-I at 1 year to predict worse prognosis is currently unknown and cannot be defined based on data for troponin-T. Given that many clinical centers assess troponin-I instead of troponin-T, troponin was excluded from the criteria to avoid disease progression being influenced by the availability of troponin assays in a center. Regarding the evidence for troponin-T, the prognostic value of this parameter was validated in the same study that assessed NT-proBNP and ODI as prognostic predictors of mortality.¹⁵ In the study, high-sensitivity troponin-T measurements were available in a subset of patients. In the development cohort (n = 459), the optimal cutoffs at 1 year were determined as a 10 ng/L absolute increase and a 20% relative increase. Therefore, troponin-T progression was defined as an increase that was both >10 ng/L and >20%. In the validation cohort (n = 146), an increase in troponin-T using these cutoffs was associated with a 2.6-fold higher risk of mortality (HR: 2.55 [95% CI: 1.27-5.07]; P = 0.008).¹⁵ Given these data, troponin may be considered for future criteria if evidence supporting the independent prognostic use of troponin-I become available.

Although NAC staging may have prognostic value and would be indicative of kidney function, calculating the staging includes (and therefore would duplicate) NT-proBNP and eGFR, which are already included in the criteria.

The experts also considered frailty, reviewing a report of a study of 880 patients with ATTR-CM that identified an association between baseline frailty and worse clinical indicators.⁵¹ However, the study did not report longitudinal follow-up data evaluating the prognostic value of frailty over time. Given the lack of long-term data, the experts did not include frailty in the criteria.⁵¹

PROPOSED FUTURE STUDIES. The experts propose a large, multicenter, international, longitudinal study measuring whether the parameters and respective thresholds as listed in this publication are predictive of mortality. In addition, the study should analyze how many parameters of progression are required to

consider that a patient is progressing, whether the parameters are independent of each other, and whether certain parameters are significantly stronger predictors of mortality than others. It may also be valuable to assess the independent prognostic value of parameters not listed in this publication's criteria (such as, arrhythmias and frailty), and whether the criteria are equally predictive of mortality across all patients or if there are differences according to patients' ethnicity, age, type of transthyretin amyloidosis, and treatments. The authors additionally encourage a study to determine the prognostic value of NT-proBNP progression associated with de novo arrhythmia.

Another area of interest is the ability of parameters to predict outcomes other than mortality, such as CVH, HF-related hospitalizations, and days alive and out of hospital. A multicenter study measuring the same parameters at certain intervals and recording the outcomes may also provide helpful insights into disease progression in ATTR-CM. Research assessing the validity of troponin-I as an independent parameter is also warranted.

In terms of treatment implications, studies should evaluate whether changes in disease-modifying treatment (such as, switching or combining treatments) improve clinical outcomes in patients demonstrating disease progression. Another unanswered treatment-related question is whether to change, maintain or deprescribe disease-modifying treatments in patients with NYHA functional class IV.

Finally, there is a need for studies to determine which patient-reported outcome measures best predict disease progression in patients with ATTR-CM. The studies should also investigate whether patient-reported outcome measures with prognostic value in ATTR-CM are feasible to use in routine clinical practice and acceptable for patients.

CONCLUSIONS

These updated proposed criteria for the monitoring of disease progression in patients with ATTR-CM incorporate recently published data analyzing disease parameters,¹⁵⁻²⁵ while also considering their ease of implementation. These data include validated prognostic parameters and provide useful thresholds that can be used to define disease progression in this challenging and heterogeneous disease.

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