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Review Article

How to monitor disease progression in ATTR amyloid cardiomyopathy: Implications for clinical practice and trial design

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ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) has been traditionally considered a rare and inexorably fatal condition. However, the development of therapies able to slow or halt ATTR-CM progression and increase survival have transformed the management of this condition. As these treatments become more accessible, the need for clinical indicators of disease progression has become increasingly important to guide clinical decision-making and personalise treatment strategies. Changes in widely available parameters have been shown to track disease evolution, which include worsening heart failure symptoms, outpatient diuretic initiation or intensification, decline in the 6-minute walk test, N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, and structural and functional parameters on cardiac imaging. Given the complexity of ATTR-CM, an integrated, multiparametric approach may provide a more precise assessment of disease trajectories and prognosis. Beyond stabilization and suppression of the circulating transthyretin protein, novel therapeutic approaches, including strategies aimed at clearing amyloid deposits, have shown potential for disease regression, even in patients with advanced involvement. With these advancements, ATTR-CM is shifting from an untreatable disease to a manageable condition where both survival and quality of life can be significantly improved. Future randomised controlled trial of disease-modifying treatments in ATTR-CM might use established criteria of disease progression as surrogate endpoints to have sufficient power and consider endpoints that are still clinically meaningful.

1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the progressive accumulation of insoluble transthyretin (TTR) amyloid fibrils in the myocardial extracellular space [1]. Amyloid deposition in the heart leads to expansion of the extracellular space with associated disruption in myocardial architecture, systolic and diastolic function [2]. ATTR-CM can result from age-related failure of homoeostatic mechanisms in wild-type ATTR-CM (ATTRwt-CM) (non-hereditary form) or destabilizing mutations in variant ATTR-CM (ATTRv-CM) (hereditary form) [1].

In recent years, major advances in disease awareness, repurposed cardiac scintigraphy with bone avid radiotracers and cardiac magnetic resonance imaging have enabled a non-invasive approach to diagnosis of ATTR-CM, which can now be achieved without recourse to tissue biopsy in ≈70 % of cases [3]. As a result, many patients are now diagnosed at an earlier stage, a shorter duration of symptoms being associated with better preserved cardiac structure and function [4,5].

In ATTR-CM, two classes of drugs, namely stabilizers and gene silencers, have offered promise in delaying clinical progression and prolonging survival. TTR stabilizers bind to and enhance the stability of TTR protein in its normal soluble form and are currently the guideline-

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recommended standard therapy for patients with ATTR-CM [6–9]. Recently, vutisiran, a next-generation gene silencer, has shown promising results [10] and was approved by the U.S. Food and Drug Administration in March 2025 for the treatment of ATTR-CM. In Europe, as of early 2026, the drug is under regulatory evaluation and has not yet been formally recommended for routine clinical use in ATTR-CM. Several other therapeutic strategies are in advanced development, including additional gene-silencing agents targeting hepatic TTR production [11–13] and anti-amyloid therapies designed to clear amyloid deposits through immune-mediated degradation [14].

In this rapidly evolving therapeutic landscape, the identification of reliable markers of disease progression is becoming increasingly critical [15]. In 2021, an international panel of experts proposed the first recommendations for assessing disease trajectory [16]. In recent years, multiple clinical, imaging, and biomarker parameters have demonstrated ability to monitor disease progression in ATTR-CM.

The aims of this review are to i) critically summarize the available evidence on markers of disease progression in ATTR-CM, ii) discuss their clinical relevance and limitations in contemporary practice, and (iii) propose a pragmatic framework for monitoring disease progression that can be applied across different clinical settings.

2. Methods

This is a narrative review based on targeted literature searches focusing on studies evaluating longitudinal changes in clinical, biomarker, functional, and imaging parameters in patients with ATTR-CM, with priority given to validated disease-progression criteria derived from large cohorts at international referral centres.

2.1. Clinical disease progression and progression of amyloid infiltration

A critical approach to available evidence on monitoring disease progression in ATTR-CM first requires careful reflection. Clinical progression can be captured through worsening symptoms, functional decline, outpatient diuretic intensification, or heart failure hospitalization and reflects changes that are directly meaningful to patients and clinicians. However, ongoing myocardial amyloid deposition represents a distinct biological process that may not necessarily, or immediately, translate into clinical deterioration.

This distinction is essential as increases in myocardial amyloid burden are not always accompanied by meaningful clinical worsening, and conversely, clinical deterioration may occur despite a stable cardiac amyloid load due to other mechanisms.

Similarly, circulating biomarkers primarily reflect biological activity or myocardial injury, whereas renal parameters capture trajectories of organ function that may be influenced by both cardiac and non-cardiac factors.

Most available parameters were developed to identify clinical progression, rather than to directly quantify amyloid burden, and this review primarily focuses on such clinically oriented markers. Structural measures derived from imaging, particularly CMR-based extracellular volume, are discussed as complementary tools that more closely reflect amyloid burden but have different feasibility and interpretative limitations (Table 1 and Fig. 1).

2.2. Clinical symptoms and function capacity

2.2.1. Heart failure hospitalization

HF-related hospitalization is widely used as a clinical endpoint in general HF trials and has been increasingly used in recent trials of disease-modifying treatments in ATTR-CM. In a post-hoc analysis of the ATTR-ACT trial [17], the most common cause of cardiovascular-related death and hospitalization was HF. In a recent post-hoc analysis of the ATTRibute-CM trial [18], HF hospitalization is associated with higher mortality in patients with ATTR-CM. Patients with no cardiovascular hospitalization (CVH) had a 30-month survival rate of 86.7 % (95 % CI, 82.9 %–89.7 %) versus 60.1 % (95 % CI, 52.8 %–66.7 %) in patients who had at least one CVH during the study. More recently, among contemporary patients with ATTR-CM (predominantly treated with tafamidis), those experiencing HF hospitalization had a subsequent higher rate of all-cause mortality of 29.8 per 100 person-years compared to those patients without worsening HF events (5.0 per 100 person-years) [19].

2.2.2. Outpatient diuretic intensification

The clinical course of HF is characterized by episodes of worsening symptoms and signs.

Outpatient diuretic intensification (ODI), defined as initiation or dose escalation of loop diuretics, often represent a clinical response to fluid overload that may delay or even prevent hospitalization. In ATTR-

Table 1
Markers of disease progression in transthyretin amyloid cardiomyopathy.

Markers of disease progression in transthyretin amyloid cardiomyopathy				
Markers **Clinical domain**	**Definition of progression**	**HR for death (95 %CI)**	**Sample size (n)**	**Follow up assessment**
QoL by KCCQ-OS	Decrease >5 points	2.5 (1.12–5.60) *	205	12 mo
6MWT distance	Decrease >35 m (absolute reduction)	1.80 (1.51–2.15)	2141	12 mo
	Decrease >5 % (relative reduction)	1.89 (1.59–2.24)		
CPET	Decrease in peak VO_2 >1.5 ml/kg/min	1.59 (1.15–2.20)	365	12 mo
	Increase in VE/VCO_2 > 5	1.56 (1.12–2.28)		
ODI	Any initiation or increment in the LD dose	1.79 (1.58–2.04)	2275	12 mo
Biomarker domain				
NT-proBNP progression	Increase of >700 ng/L and >30 %	1.81 (1.59–2.05)	2275	12 mo
Troponin T	Increase of >10 ng/L and >20 %	1.84 (1.44–2.34)	2275	12 mo
Decline in eGFR	Decrease of >20 %	1.71 (1.43–2.04)	2001	12 mo
Urinary ACR	Increase of ≥30 %	1.84 (1.06–3.19)	1181	12 mo
Cardiac imaging domain				
LVOT-VTI (AI-derived on echocardiogram)	Decrease of ≥5 %	1.44 (1.17–1.76)	752	12 mo
Mitral regurgitation (on echocardiogram)	Worsening by ≥1 grade	1.43 (1.14–1.80)	877	12 mo
Tricuspid regurgitation (on echocardiogram)	Worsening by ≥1 grade	1.38 (1.10–1.75)		12 mo
Myocardial ECV (on CMR)	Increase ≥5 %	2.02 (1.08–3.78)	189	12 mo

Legend. 6MWT = 6-minute walk test; ACR = Albumin to creatinine ratio; CI = Confidence Interval; CMR = Cardiac magnetic resonance; CPET = Cardiopulmonary exercise test; ECV = Extracellular volume; eGFR = Estimated glomerular filtration rate; HR = Hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire – overall summary; LD = Loop diuretic; LVOT-VTI = Left ventricular outflow tract velocity-time integral; mo = months; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ODI = Outpatient diuretic intensification; QoL = Quality of life; VE/VCO_2 =Ventilatory Efficiency / Volume of Carbon Dioxide Expired; VO_2 = oxygen consumption.

* A decline >5 points in KCCQ-OS predicted a composite of all-cause mortality and HF hospitalization.

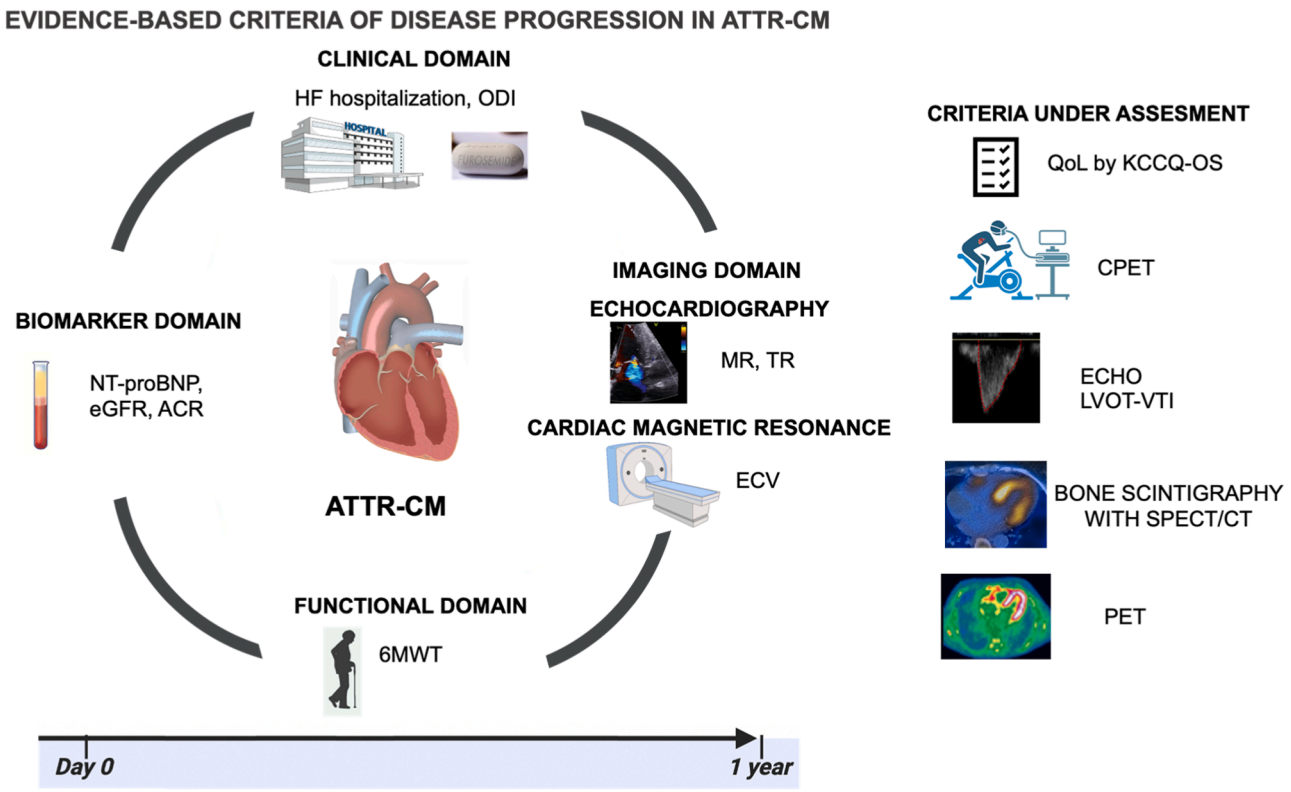

Fig. 1. Evidence-based Criteria of Disease Progression in ATTR-CM and Emerging Markers. Legend: 6MWT = 6-minute walk test; ACR = Albumin to creatinine ratio; ATTR-CM, Transthyretin Amyloid Cardiomyopathy; eGFR = Estimated glomerular filtration rate; CMR = Cardiac magnetic resonance; CPET = Cardiopulmonary exercise test; ECV = Extracellular volume; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire – overall summary; LD = Loop diuretic; LVOT-VTI = Left ventricular outflow tract velocity-time integral; MR = Mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ODI = Outpatient diuretic intensification; QoL = Quality of life; PET = Positron emission tomography; SPECT = Single-photon emission computed tomography; TR = Tricuspid regurgitation.

CM, ODI occurring within the first year after diagnosis has been independently associated with a 1.8-fold increased risk of all-cause mortality, with a clear dose-dependent association, whereby greater increases in diuretic dose confer higher risk [20].

ODI may thus serve as an early and potentially modifiable marker of disease progression. When assessed alongside worsening NT-proBNP, ODI can be incorporated into a simple and broadly applicable risk model: the presence of either marker is associated with a 1.9-fold increase in the risk of all-cause mortality, whereas the coexistence of both markers confers a 3.0-fold increase [20].

ODI has also been evaluated in recent randomized trials investigating disease-modifying therapies for ATTR-CM. In a prespecified analysis of the HELIOS-B trial, ODI was associated with a 2.5-fold higher risk of all-cause mortality or CV events, consistent across the overall study population, patients on monotherapy and those receiving tafamidis at baseline [21]. ODI was further associated with greater deterioration in 6 MWT, KCCQ score and NT-proBNP levels. Vutrisiran therapy significantly reduced the risk of ODI, whether analysed as time to fist event or as a recurrent event, and lowered the risk of the expanded composite endpoint comprising all-cause mortality, cardiovascular events and ODI [21]. As patients are increasingly diagnosed at earlier stages, incorporating ODI as a surrogate endpoint in clinical trials may increase the ability to capture clinically meaningful events, enhance statistical power, and ultimately reduce sample size and follow up requirements.

2.2.3. 6-Minute walking test

The 6-minute walking distance (6MWD) is a widely validated measure of functional exercise capacity in patients with HF and is increasingly used both in clinical practice and as a surrogate endpoint in clinical trials [22–24]. In ATTR-CM, baseline 6MWT is independently associated with prognosis, with patients walking <350 m (m) experiencing a 2.2-fold higher risk of all-cause mortality [25]. Serial assessment of the 6MWT provides valuable insights into disease progression, with an absolute reduction of >35 m or a relative decline of >5 % at 12 months consistently associated to a 1.8-fold and 1.9-fold increase, respectively, in the risk of all-cause mortality across different genotypes and disease stages [25].

The 6MWT has been widely used as a secondary endpoint in phase 3 randomized controlled trials to assess the efficacy of ATTR-specific disease modifying therapies. Over 30 months of follow-up, tafamidis, acoramidis, patisiran and vutrisiran attenuated the mean decline in the distance walked during the 6MWT by 75.7 m, 39.6 m, 15 m and 27 m, respectively, as compared to placebo groups [7,8,10,26,27]. Importantly, the magnitude of treatment effect on 6MWT is closely influenced by the rate of decline in the placebo groups, limiting direct comparisons across trials.

3. Blood markers

3.1. Cardiac biomarkers

3.1.1. N-terminal pro-B-type natriuretic peptide

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a commonly used circulating biomarker for establishing the diagnosis, refining risk stratification and monitoring heart failure [6,28]. In acute settings, elevated natriuretic peptide levels are strong predictors of adverse outcomes, while in outpatient management, changes in NT-proBNP serve as an important indicator of treatment response, risk of hospital readmission and mortality [28].

In ATTR-CM, NT-proBNP has been incorporated in all major prognostic staging systems, with higher baseline levels consistently associated to increased risk of mortality [29–31]. A large multicentre study

demonstrated that an absolute increase of >700 ng/L or a relative increase of >30 % in NT-proBNP at 12 months was associated with a 1.8-fold higher risk of all-cause mortality [20]. This association was consistent across TTR genotypes, treatment with disease-modifying drugs and participation in clinical trials. Given its accessibility and reproducibility, NT-proBNP progression could be widely adopted as a reliable marker for longitudinal monitoring in ATTR-CM.

Changes in NT-proBNP have been widely used as secondary endpoints in multiple phase 3 trials of disease-modifying treatments for ATTR-CM. Across all major randomized trials, patients receiving active treatment consistently showed stabilization or an attenuated increase in NT-proBNP levels compared to placebo. Specifically, in the ATTR-ACT trial [7], tafamidis significantly reduced the rise in NT-proBNP at both 12 months (least-squares mean difference: −735.14 ng/L, 95 % CI [−1249.16 to −221.13]) and 30 months (−2180.54 ng/L, 95 % CI [−3326.14 to −1034.95]) compared with placebo. In the APOLLO-B trial [27], patisiran attenuated the rise in NT-proBNP rise at 12 months compared to placebo (median increase of 131 ng/L vs 518 ng/L). In the ATTRibute-CM trial [8], worsening in NT-proBNP was integrated in the hierarchical primary endpoint, contributing to the highest win/-loss ratio (23.3 % vs. 7.0 %) in favour of acoramidis, which also demonstrated a favourable NT-proBNP trajectory (geometric fold-change ratio of 0.53). In the HELIOS-B trial [10], vutrisiran reduced NT-proBNP elevation at 30 months (geometric fold-change ratio: 0.68, 95 % CI [0.61 to 0.76]). Notably, these differences emerged within months of treatment initiation (often preceding the onset of clinical events), supporting the role of NT-proBNP as a sensitive and early marker of treatment response.

3.1.2. Troponin

Cardiac troponin (cTn) is the biomarker of choice for the detection of ongoing myocardial injury [32]. In ATTR-CM, elevation in cTn have been consistently associated with an increased risk of mortality [29,31]. The largest analysis of serial troponin measurements to date evaluated 605 patients with ATTR-CM from a multicentre cohort, with serum cTn-T levels measured 12 months apart. An absolute increase of 10 ng/L or a relative increase > 20 % was associated with a 2.6-fold higher risk of mortality (HR, 2.55; 95 % CI, 1.27–5.07; P=0.008) [20]. In the APOLLO-B trial [27], patients treated with patisiran showed a favourable change in troponin I levels at 12 months (adjusted geometric mean ratio: 0.87, 95 % CI [0.80 to 0.95]). Similarly, the HELIOS-B trial [10] demonstrated a favourable change in troponin I levels in patients treated with vutrisiran over 30 months (adjusted geometric mean ratio: 0.68, 95 % CI [0.62 to 0.75]). However, the broader use of troponin as a prognostic or progression marker is limited by assay variability across laboratories [32]. A first step in the direction of a broader use of cTn-I in clinical practice has been recently undertaken by an Italian multicentre study in patients with ATTRwt-CM that examined high-sensitivity troponin I (hs-cTnI) across three different assays and confirmed its strong, independent prognostic association with all-cause mortality [33]. A uniform threshold of 80 ng/L for hs-cTnI across these assays optimized risk stratification within a staging system that also incorporated natriuretic peptides [33]. While cTn primarily reflects myocardial injury rather than amyloid load per se, these data suggest that serial troponin could be used to monitor disease activity and potentially treatment response.

3.2. Kidney function

3.2.1. Estimated glomerular filtration rate (eGFR)

Creatinine-based estimated glomerular filtration rate (eGFR) is the standard metric for evaluating renal function and remains central in HF management. Chronic kidney disease (CKD) is common in HF and independently predicts adverse outcome. In ATTR-CM, eGFR is a validated prognostic marker included in a well-established staging system combining eGFR with NT-proBNP to stratify patient risk [29].

Cardiac and renal functions are interdependent. Worsening HF may compromise renal function through reduced perfusion, venous congestion, hemodynamic impairment, and neurohormonal activation. Although some fluctuations in eGFR are expected during decongestion, longitudinal eGFR decline often mirrors HF progression. In a cohort of 2001 patients with ATTR-CM, a decline in eGFR > 20 % over 12 months was associated with a 1.7-fold increase in mortality risk [34]. This association was consistent across the three primary genotypes (wild-type, p.(V142I), and non-p.(V142)) and disease stages. Notably, worsening renal function identified progression even in patients receiving disease-modifying therapy or enrolled in trials [34]. The impact of treatment on renal function was examined in a post-hoc analysis of the ATTR-ACT trial [35], where tafamidis therapy slowed the decline in eGFR (least squares mean difference: 3.99 mL/min/1.73 m^2; 95 % CI [1.31 to 6.68]) and increased the likelihood of CKD stage improvement (17.7 % vs. 7.2 %) compared to placebo. These findings suggest that while eGFR decline indicates adverse outcomes, disease-modifying agents may mitigate renal deterioration.

3.2.2. Urinary albumin-to-creatinine ratio

eGFR may not always accurately reflect renal function as serum creatinine is influenced by extra-renal factors. By contrast, albuminuria is a direct marker of structural glomerular damage and often precedes measurable decline in eGFR. In general HF, albuminuria predicts subsequent hospitalization and mortality, and these associations extend to ATTR-CM [36,37]. The presence of microalbuminuria and macroalbuminuria has been associated with a 1.5-fold and 1.9-fold increased risk of mortality, respectively [38]. In 330 patients with serial urinary albumin-to-creatinine ratio, an increase of ≥30 % over 12 months was indicative of disease progression and conferred a 1.8-fold higher mortality risk [38].

After years of uncertainty regarding conventional HF therapies in ATTR-CM, emerging evidence suggests sodium–glucose co-transporter-2 (SGLT2) inhibitors may offer benefit [39]. These agents have been shown to attenuate eGFR decline and reduce albuminuria, particularly in patients with diabetic CKD [40]. As SGLT2 inhibitors become more integrated into HF treatment strategies for ATTR-CM, progression criteria based on renal parameters such as eGFR or albuminuria may need redefinition [41].

3.2.3. Changes in disease stage

The National Amyloidosis Centre (NAC) disease staging system, which incorporates NT-proBNP and eGFR, effectively categorizes patients into prognostic groups at the time of diagnosis [29,30]. Progression to a higher disease stage during follow-up has also been associated to worse outcomes, with an increase from stage I at 12 months correlating with a 2.6-fold higher risk of mortality [42].

3.3. Cardiac imaging parameters

3.3.1. Echocardiography

Echocardiography is the first line imaging modality that most frequently raises suspicion of ATTR-CM [43–45] and can also aid disease monitoring through serial assessments. In a large cohort of 877 patients with ATTR-CM, worsening stroke volume (SV), mitral regurgitation (MR) and tricuspid regurgitation (TR) over 12 months were strong predictors of mortality [45]; findings corroborated in subsequent studies [46,47]. Progressive amyloid deposition stiffens the myocardium, increases ventricular wall thickness, reduces end-diastolic volume and, consequently, and diminishes SV [48]. In this scenario, even minor worsening in MR and TR severity can break the haemodynamic equilibrium, further reducing forward SV and worsening prognosis [45,48].

However, the ability of serial echocardiography to monitor disease progression is limited by intra- and interobserver variability associated with manual measurements. Artificial intelligence (AI)–based automation may improve measurement precision and reproducibility, and

identify additional markers of progression. In the largest study using fully-automated, machine learning-based echocardiographic study including 752 patients with ATTR-CM, a change in left ventricular outflow tract velocity-time integral (LVOT-VTI) was the only independent and robust predictor of mortality: a relative reduction >5 % at 12 months was associated with a 1.5-fold higher risk of all-cause mortality [49]. Unlike Simpson's biplane or Doppler SV estimate, LVOT-VTI is less affected by geometric assumptions and as the cross-sectional area of the LVOT remains stable over time in a given patient.

In a post-hoc analysis of the ATTR-ACT trial [50], tafamidis therapy was associated to a significantly attenuated decline in SV (least squares mean difference: 7.02 mL) compared to placebo. Altogether, these findings support the use of LVOT-VTI as a potential marker to track treatment response. In a recent analysis of echocardiographic data from the HELIOS-B phase 3 trial of vutrisiran, markers of left and right ventricular systolic and diastolic function were found to be independently associated with the all-cause death and CV events (HR per unit increase, LVEF, 0.90 per 5 % increase; absolute global longitudinal strain, 0.92 per 1 % increase; tricuspid annular systolic myocardial velocity, 0.94 per 1-cm/s increase; average E/e', 1.03 per 1-U increase) [51].

3.3.2. Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) with multiparametric mapping provide comprehensive assessment of cardiac structure, function, and tissue characterization [52]. By isolating the signal from the extracellular volume (ECV), CMR with late gadolinium enhancement (LGE) provides an accurate measure of myocardial amyloid deposition that is a strong independent predictor of mortality. Longitudinal CMR studies have predominantly been conducted in patients with light-chain cardiac amyloidosis, where native T1 mapping has proven useful in monitoring response to chemotherapy and predict survival [53], and ECV quantification provided an estimate of the myocardial amyloid load (with excellent inter-observer reproducibility), and independently predicted survival [54,55].

Emerging evidence supports similar applications in ATTR-CM, supporting the use of CMR parameters for monitoring disease and treatment response. Patisiran and the anti-amyloid antibody NI006 reduced myocardial ECV, suggesting the potential for regression of amyloid.

A landmark study of serial CMR imaging in 189 patient with ATTR-CM [56] demonstrated progressive myocardial ECV increase in untreated individuals, associated with structural and functional deterioration. Disease progression, defined as an increase in ECV of 5 % or greater, occurred in 36 % of patients after 1 year, and was associated with a 2.0-fold increased risk of mortality, even after adjusting for established markers of disease progression [56]. Treatment with patisiran stabilized or reduced myocardial ECV in the majority of patients. Changes in myocardial ECV preceded changes in cardiac structure and function, and major clinical events including cardiovascular-related hospitalisations and mortality. Leveraging ECV measurements in the clinical trial setting would facilitate the assessment of novel agents over a shorter duration of follow-up, would allow mechanistic understanding of the impact on cardiac amyloid load and could enable more rapid approval of safe and effective treatments.

As a result, serial CMR assessments with ECV quantification are increasingly incorporated into clinical trials evaluating the impact of ATTR-specific therapies.

3.4. Emerging tools for monitoring disease progression

3.4.1. Quality of life with the Kansas city cardiomyopathy questionnaire

ATTR-CM significantly impact patients' health status and quality of life (QoL) [57]. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a validated 23-item patient-reported outcome measure (PROM) developed to measure the burden of chronic HF from the patient's perspective. The KCCQ is independently associated with mortality and HF hospitalization in the general HF population, and there is evidence for its prognostic value in ATTR-CM.

In the ATTR-ACT trial [7], tafamidis was associated with a slower decline in KCCQ scores compared to placebo over 30 months, with a statistically significant difference emerging as early as 6 months. In the APOLLO-B trial [27], patisiran resulted in a modest improvement in KCCQ scores, whereas the placebo group experienced a decline, resulting in a statistically significant difference at 12 months. In both the ATTRibute-CM [8] and HELIOS-B trials [10], acoramidis and vutrisiran effectively mitigated the deterioration in health status compared to placebo over 30 months. The least squares mean difference in KCCQ scores was 9.9 points with acoramidis and 5.8 points with vutrisiran, further supporting the sensitivity of KCCQ in tracking treatment response. A decrease in KCCQ - overall score > 5 points at 12 months has been independently associated with a 2.5-fold higher risk in all-cause mortality and HF hospitalization [58,59], but this criterion requires prospective validation.

3.4.2. Cardiopulmonary exercise test

Cardiopulmonary exercise testing (CPET) is the gold standard for evaluating functional capacity and determining the underlying mechanisms which drive exercise intolerance in ATTR-CM [60]. Recent studies have demonstrated the clinical and prognostic significance of both peak oxygen consumption (pVO_2) and ventilatory efficiency (VE/VCO_2) [61–64] in patients with ATTR-CM. These parameters have been shown to correlate with disease severity, functional status, and long-term outcomes in patients with ATTR-CM and, as a result, have emerged as potential indices for monitoring ATTR-CM progression [63].

Although no criteria of disease progression have been formally validated in ATTR-CM, preliminary data suggest potential prognostic relevance. A recent study presented at the ESC HFA Congress 2025 [65] reported that an absolute reduction >1.5 ml/Kg/min in the pVO_2 and an absolute increase >5 in (VE/VCO_2) at 12 months from diagnosis were independently associated with a higher risk of all-cause mortality and HF hospitalization. These thresholds should be considered exploratory and hypothesis-generating. In a seminal phase 3 trial of myosin inhibitor mavacamten for the treatment of obstructive hypertrophic cardiomyopathy, 1.5 mL/Kg/min or greater increase in pVO_2 was used as a primary end-point, hence, there is a precedent for use of this parameter in phase 3 clinical trials [66].

Integrating CPET-based disease progression in clinical practice could help identify clinically meaningful and modifiable events earlier in patients with ATTR-CM, with some advantages compared to 6MWT. For instance, pVO_2, unlike the 6MWT, is minimally affected by training or familiarization effects with repeated measures in HF. Moreover, CPET enables precise assessment of maximal exercise capacity, confirming when a subject surpasses their anaerobic threshold. Notably, the use of CPET is limited by availability, need for standardization across centres, and feasibility in older or frail ATTR-CM populations. CPET can be used to monitor disease progression and assess response to disease-modifying therapies, mostly in specialised centers, and may help shape the design of future trials of ATTR-specific therapies by providing a sensitive and mechanistically informative measure of treatment effect [67].

3.5. How to stratify disease progression in clinical practice

Despite major advances, defining and monitoring disease progression in ATTR-CM remains challenging. Most progression criteria have been derived from retrospective analyses of large but heterogeneous cohorts, including untreated patients, individuals receiving disease-modifying therapies and clinical trial participants (both placebo and treatment arms). Many cohorts were enriched with "historical" patients diagnosed at more advanced stages than those typically encountered today, potentially limiting generalizability to contemporary clinical practice. In addition, most criteria were validated predominantly in White male populations and require further validation across sexes, ethnic groups and genotypes.

Studies developing progression criteria consistently showed that associations between progression markers and clinical outcomes did not substantially differ between ATTRwt and ATTRv populations. However, given variability in patient characteristics, therapeutic exposure, and rates of progression, these thresholds may not be universally applicable at the individual level. Clinical judgment and consideration of patient-specific factors are therefore essential. Importantly, assessments should be performed during periods of clinical and rhythm stability and away from confounding conditions such as hospitalizations, acute infections, rhythm disturbances, or extracardiac comorbidities (e.g. anaemia or acute renal dysfunction), as failure to account for these factors may lead to misclassification.

This is particularly relevant for circulating biomarkers. NT-proBNP is a robust and widely accessible marker of prognosis and disease trajectory, but increases may also occur in association with de novo atrial fibrillation. While NT-proBNP retains prognostic value in patients with concomitant atrial fibrillation, it remains unclear whether NT-proBNP progression driven by new-onset arrhythmia reflects true ATTR-CM progression; therefore, changes should ideally be interpreted during periods of rhythm and clinical stability.

The expanding use of conventional HF therapies in ATTR-CM is also reshaping biomarker trajectories. SGLT2 inhibitors may attenuate rises in NT-proBNP, reduce the need for loop diuretic escalation, and slow eGFR decline, while disease-modifying therapies may stabilize or improve biomarkers and imaging parameters [39]. In addition, acoramidis and SGLT2 inhibitors may induce an early, transient decline in eGFR that subsequently stabilizes; early post-initiation changes should not be automatically interpreted as disease progression. Accordingly, criteria validated in untreated cohorts may require recalibration in patients receiving modern therapies.

Timing of reassessment is critical. Although most criteria were developed using 12-month intervals, earlier reassessments at 6 months may allow timely therapeutic adjustments and enrich clinical trial endpoints. In a recent retrospective study [68], worsening cardiac disease, defined by ODI and/or NT-proBNP progression at 6 months from ATTR-CM diagnosis, independently predicted mortality and cardiovascular hospitalisation even in contemporary tafamidis-treated patients, although larger confirmatory studies are needed.

From a practical perspective, access to advanced monitoring tools such as CMR with ECV mapping, CPET, AI-based echocardiography, or serial patient-reported outcome measures is not universal. A pragmatic tiered approach is therefore appropriate (Table 2). A core dataset feasible in most centres at baseline includes HF hospitalization and ODI (clinical criteria), NT-proBNP and eGFR (biomarkers), and functional assessment with the 6MWT and health-related quality of life, ideally reassessed during clinical stability and compared with values obtained approximately 12 months earlier. Advanced assessment in specialized centres may incorporate automated echocardiographic parameters (including LVOT-VTI), CMR with ECV quantification, CPET, and, in selected cases, positron-emission tomography. Follow-up frequency and intensity should then be adapted according to baseline risk and observed trajectory, with particular attention to changes that are reproducible and clinically meaningful. Importantly, discordant signals across domains should prompt confirmatory reassessment and evaluation of potentially reversible contributors rather than immediate therapeutic escalation.

Future directions include wider use of automated echocardiography to reduce variability, increasing integration of CPET to capture disease trajectories not evident on the 6MWT, and greater reliance on CMR-derived ECV as a sensitive marker of amyloid burden. The role of cardiac scintigraphy for short-term monitoring [69,70] and the utility of frailty as a progression marker require further dedicated longitudinal studies [71].

Table 2
Suggested monitoring schedule in transthyretin amyloid cardiomyopathy.

Suggested monitoring schedule in transthyretin amyloid cardiomyopathy			
Domain	**Baseline**	**Follow up**	Actionable progression
Clinical status	Symptoms, NYHA class, HF history, ODI	Every visit	New HF hospitalization or ODI: reassess volume status, therapeutic adherence, new arrhythmias
Biomarkers	NT-proBNP, eGFR (± troponin)	Every 3–6 months	Confirm change on repeat testing during clinical stability
Functional capacity	6MWT, QoL (± CPET)	Every 6–12 months	If functional decline: review HF therapy, rhythm, comorbidities
Imaging (echo)	Echocardiography with strain analysis	12-months or risk-based	Worsening MR/TR, declining SV/LVOT-VTI: integrated clinical reassessment
Advanced assessment (selected centres)	CMR with ECV mapping and CPET (selected cases)	Risk or trajectory-based	CPET deterioration and/or rising native T1/ECV: consider integrated reassessment\consider therapy escalation \trial enrolment

Legend. 6MWT = 6-minute walk test; CMR = Cardiac magnetic resonance; CPET = Cardiopulmonary exercise test; ECV = Extracellular volume; eGFR = Estimated glomerular filtration rate; HF = Heart failure; LVOT-VTI = Left ventricular outflow tract velocity-time integral; MR = Mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; ODI = Outpatient diuretic intensification; QoL = Quality of life; SV = Stroke volume; TR = Tricuspid regurgitation.

4. Conclusions

With the advent of multiple effective disease-modifying therapies for ATTR-CM, identification of patients with disease progression has become an urgent clinical need. Many commonly used markers are independently associated with mortality, indicating that each captures distinct aspects of progression. Therefore, the most reliable strategy to monitor disease progression is multiparametric: serial biochemical testing, repeated assessment of symptoms and functional capacity, and cardiac imaging provide complementary windows on the disease process.

Since most of these markers are widely accessible, easy to measure, and applicable across clinical settings, they can be integrated into routine practice to support patient management, when interpreted within the clinical context and local resource availability. However, these measures should be regarded as candidate or intermediate indicators of disease progression rather than established surrogate endpoints, as they may be influenced by non–ATTR-CM–specific factors and require further validation across therapeutic classes. Optimal implementation will depend on thoughtful clinical interpretation and an understanding of the inherent limitations of current prognostic criteria.

Data sharing statement

There is no original data generated for this study.

Declaration of competing interest

Sarah Cuddy has received consulting income and speaking honoraria from Astra Zeneca, Alexion, Eidos (BridgeBio), Intellia, Alnylam, and Pfizer. Julian D Gillmore has received consulting income from Ionis, Alexion, Eidos, Intellia, Alnylam, and Pfizer. Marianna Fontana is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/21/33,447) and has consulting income from Intellia, Novo-Nordisk, Pfizer, Eidos, Prothena, Akcea, Alnylam, Caleum,

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