

Monitoring Disease Progression in Transthyretin Amyloid Cardiomyopathy

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Transthyretin amyloid cardiomyopathy is a progressive and fatal cardiomyopathy caused by the deposition of misfolded transthyretin in the form of amyloid fibrils in the myocardium. The advent of various highly efficacious transthyretin amyloid-specific disease-modifying therapies has sparked a growing interest in identifying the clinical indicators of disease progression that will be crucial in guiding treatment decisions. Markers of disease progression include changes in commonly measured biomarkers such as the N-terminal pro-B-type natriuretic peptide and the estimated glomerular filtration rate, a decline in the 6-minute walk test distance, outpatient diuretic intensification, changes in heart failure symptom burden and also changes in various cardiac-imaging parameters. Considering the wide array of markers that can detect disease progression, it is likely that a comprehensive clinical assessment will involve monitoring multiple markers simultaneously. Integrating multiple markers of disease progression offers additional insights beyond individual markers, enabling a refined assessment of disease trajectory and mortality risk. Many of these markers are readily available, simple to measure and universally applicable, making them easy to implement in clinical practice for identifying patients with advancing disease and a heightened risk of mortality.

Keywords

Cardiac imaging, disease progression, estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide, outpatient diuretic intensification, transthyretin amyloid cardiomyopathy

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is an inexorably progressive and ultimately fatal cardiomyopathy characterized by the deposition of misfolded transthyretin (TTR) in the form of amyloid fibrils within the myocardium.¹ Transthyretin amyloid (ATTR) fibrils are insoluble protease-resistant beta-pleated sheets that are stabilized within the extracellular matrix, disrupting the integrity, structure and function of the myocardium.² ATTR-amyloid fibril deposition results in biventricular wall thickening, stiffening of the myocardium and both systolic and diastolic dysfunction.³

ATTR-CM presents with two predominant phenotypes.⁴ In the sporadic, non-inherited, wild-type form (wtATTR-CM), misfolding of TTR occurs secondary to a pathological process that is associated with age-related homeostatic mechanisms.⁵ This is a condition of older, predominantly male individuals and predominantly affects the heart in isolation, with common extra-cardiac sites of infiltration resulting in carpal tunnel syndrome, lumbar spine stenosis and tendinopathies.^{6–8} In the hereditary or variant form (hATTR-CM), misfolding of TTR occurs secondary to a single nucleotide substitution, resulting in a missense mutation that is inherited in an autosomal dominant fashion with variable disease penetrance.² The clinical phenotype varies depending on the underlying TTR gene variant, and patients typically present at a younger age with either cardiomyopathy or a mixed phenotype comprising a length-dependent, peripheral/autonomic polyneuropathy and cardiomyopathy.^{6,9}

Historically, ATTR-CM was considered a rare disease, but an improved understanding of the underlying pathophysiology, coupled with advances in diagnostic techniques and increased awareness, has resulted in a dramatic upsurge in diagnoses.¹⁰ Furthermore, the development of highly specific disease-modifying therapies has transformed the perception of ATTR-CM from a terminal disease process into a treatable cardiomyopathy with multiple therapeutic options. At present, the ATTR-specific disease-modifying therapies that are approved for the treatment of ATTR-CM by the US Food and Drug Administration are tafamidis and acoramidis, which are both TTR stabilizers that prevent the dissociation of TTR into amyloidogenic monomers that subsequently form ATTR fibrils.^{11,12} However, several novel compounds that inhibit TTR synthesis and subsequent ATTR-fibril formation through directly targeting TTR gene expression are likely to become available in the near future and novel anti-amyloid therapies that target fibrils that have already deposited in the heart and accelerate removal through an immune-mediated degradation process are also at advanced stages of development.^{13–16} Clinical indicators of disease progression might highlight the need to switch to alternative disease-modifying therapies with different mechanisms of action or even prompt clinicians to consider the use of combination therapy. In an era of ever-expanding and evolving treatment options, markers of disease progression will be crucial in guiding clinical

decisions. This article explores in detail the current evidence base for markers of disease progression in patients with ATTR-CM.

N-terminal pro-B-type natriuretic peptide

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is widely used in the context of heart failure to risk-stratify patients at the time of diagnosis and also during follow-up.¹⁷ In the acute setting, elevations in natriuretic peptides predict adverse outcomes, while changes in NT-proBNP in the outpatient setting are widely used as a marker of treatment response to prognostic heart failure therapies, with a reduction being associated with a reduced risk of cardiovascular events.^{18,19}

In the context of ATTR-CM, NT-proBNP forms the cornerstone of all prognostic staging systems, with elevations in NT-proBNP at diagnosis being consistently associated with an increased risk of mortality.^{20–22} A multicentre study of 2,275 patients with ATTR-CM demonstrated that an absolute increase of >700 ng/L in NT-proBNP and a relative increase of >30% at 12 months was associated with a 1.8-fold higher risk of mortality. The increased risk associated with NT-proBNP progression was present across the three main genotypes (wild type, p.[V142I] and non-p.[V142I]) and was therefore able to detect disease progression in patients with ATTR-CM and those with a mixed phenotype comprising both cardiomyopathy and polyneuropathy. NT-proBNP progression was also able to detect disease progression in patients who were prescribed disease-modifying therapies or enrolled in clinical trials and was also associated with mortality in patients with concomitant atrial fibrillation and obesity. The wide availability and universal applicability of the definition of NT-proBNP progression across different genotypes and across patients with a range of comorbidities support its widespread adoption to identify patients experiencing disease progression.²³

Changes in NT-proBNP have also been used as an exploratory endpoint in multiple phase III clinical trials of disease-modifying therapies in patients with ATTR-CM. In the ATTR-ACT trial (A MULTICENTER, INTERNATIONAL, PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF DAILY ORAL DOSING OF TAFAMIDIS MEGLUMINE (PF-06291826) 20 MG OR 80 MG IN COMPARISON TO PLACEBO IN SUBJECTS DIAGNOSED WITH TRANSTHYRETIN CARDIOMYOPATHY [TTR-CM]; ClinicalTrials.gov identifier: NCT01994889), treatment with tafamidis resulted in a smaller increase in NT-proBNP at both 12 months (least-squares mean difference: –735.14 ng/L, 95% CI [–1,249.16 to –221.13]) and 30 months compared with placebo (least-squares mean difference: –2,180.54 ng/L, 95% CI [–3,326.14 to –1,034.95]).¹¹ In the APOLLO-B trial (APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy [ATTR Amyloidosis With Cardiomyopathy]; ClinicalTrials.gov identifier: NCT03997383), treatment with patisiran resulted in a smaller increase in NT-proBNP at 12 months compared with placebo (median increase: 131 ng/L, interquartile range (IQR) [–280 ng/L to 817 ng/L] versus 518 ng/L [51 ng/L to 1,544 ng/L]), with a geometric fold-change ratio of 0.80 (95% CI [0.73 to 0.89]).²⁴

A similar result was observed in the HELIOS-B trial (HELIOS-B: A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy [ATTR Amyloidosis With Cardiomyopathy]; ClinicalTrials.gov identifier: NCT04153149), whereby treatment with vutrisiran resulted in a smaller increase in NT-proBNP at 30 months compared with placebo, with a geometric fold-change ratio

of 0.68 (95% CI [0.61 to 0.76]).²⁵ In the ATTRIBUTE-CM trial (A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects With Symptomatic Transthyretin Amyloid Cardiomyopathy [ATTRIBUTE-CM Trial]; ClinicalTrials.gov identifier: NCT03860935), the change from baseline in NT-proBNP formed the third step of a four-step primary hierarchical analysis and followed all-cause mortality and cardiovascular hospitalizations.¹² The change in NT-proBNP was responsible for the highest ratio of wins to losses (23.3% versus 7.0%) in favour of acoramidis. Furthermore, treatment with acoramidis resulted in a favourable change in NT-proBNP compared with placebo, with a geometric fold-change ratio of 0.53 (95% CI [0.46 to 0.60]).¹²

Throughout all the randomized controlled trials of ATTR-specific disease-modifying therapies, patients randomized to treatment tend to experience stabilization or at least a smaller increase in NT-proBNP compared with those randomized to placebo. The difference in the change in NT-proBNP between the two groups is often evident within a few months of randomization and therefore becomes apparent before any adverse cardiovascular events begin to manifest. This reinforces the utility of NT-proBNP as a measure for monitoring disease progression and identifying high-risk patients whose disease trajectory may be altered through an earlier intervention.

Troponin

Serum troponins represent a marker of ongoing myocyte damage and have demonstrated clinical utility in the assessment of acute cardiac conditions such as myocardial infarction and myocarditis.²⁶ Serum troponins are commonly elevated in patients with ATTR-CM, with increased levels at diagnosis being associated with a higher risk of mortality.^{21,27} However, the widespread use of troponin as a prognostic marker and as a marker of disease progression is significantly limited by the current worldwide use of multiple different assays. The largest study of serial troponin measurements in patients with ATTR-CM was conducted in a subset of patients from a large multicentre study who had serum troponin-T measurements 12 months apart. In 605 patients with ATTR-CM, an absolute increase of 10 ng/L and a relative increase of >20% were associated with an increased risk of mortality.²³

Changes in troponin in response to treatment have also been explored in clinical trials. In the APOLLO-B trial, the 12-month change from baseline in troponin I (ratio of adjusted geometric mean factor change) was 0.87 (95% CI [0.80 to 0.95]) in favour of patisiran, and in the HELIOS-B trial, the 30-month change from baseline in troponin I was 0.68 (95% CI [0.62 to 0.75]) in favour of vutrisiran.^{24,25} These findings support the hypothesis that serial troponin measurements could be used to track the amyloid disease burden, and it is possible that the latest generation high-sensitivity troponins will be able to detect even smaller changes in disease activity, but this premise requires further investigation in large-scale prospective multicentre studies to establish clinically meaningful thresholds across the multiple different assays that are used across different healthcare settings and to establish whether these thresholds remain applicable across different genotypes and disease stages.²⁶

Estimated glomerular filtration rate

Creatinine-based estimated glomerular filtration rate (eGFR) represents the most widely used focal metric for the assessment of renal function and forms an integral component of the standard heart failure assessment. In the context of heart failure, chronic kidney disease (CKD) is common and represents an independent predictor of adverse events, including heart failure hospitalizations and mortality.^{28,29} The prognostic

importance of eGFR also extends to patients with ATTR-CM. This principle is most notably demonstrated in a well-established staging system that combines eGFR with NT-proBNP to accurately stratify patients into prognostic categories.²⁰

Cardiac and renal function are closely linked, and worsening heart failure influences renal function through an array of different mechanisms including a reduction in renal blood flow, renal venous congestion, impaired haemodynamics and also neurohormonal activation. It is therefore plausible that in the context of heart failure, changes in renal function reflect changes in heart failure severity.³⁰ In a large study of 2,001 patients with ATTR-CM, a decrease of >20% in eGFR at 12 months was consistently associated with a 1.7-fold higher risk of mortality, with a similar increase in risk observed across the three main genotypes (wild type, p.[V142I] and non-p.[V142I]) and the spectrum of disease stages. The risk of mortality was consistent regardless of sex, body mass index and whether patients had concomitant CKD or diabetes. A decline in renal function was also able to detect disease progression in a subset of patients who were prescribed disease-modifying therapies or enrolled in clinical trials. The wide availability and universal applicability of a decline in eGFR across different demographics, genotypes and a range of comorbidities support its widespread adoption in clinical practice to identify patients experiencing disease progression.³¹

Changes in renal function in response to treatment were studied in a post hoc analysis of the ATTR-ACT trial, whereby treatment with tafamidis was associated with a smaller decline in eGFR (least squares mean difference: 3.99 mL/min/1.73 m²; 95% CI [1.31 to 6.68]) and more commonly associated with an improvement in the CKD stage (17.7% versus 7.2%) compared with placebo.³² These data indicate that although eGFR decline is associated with an increased risk of adverse events, it is potentially modifiable by the use of ATTR-specific disease-modifying therapies.

Urinary albumin-to-creatinine ratio

Despite the widespread use of creatinine-based eGFR as a measure of renal function due to both convenience and low cost, changes in eGFR may not necessarily reflect true changes in GFR and could occur secondary to changes in serum creatinine levels, which can be influenced by extra-renal factors.³³ In contrast, the presence of albuminuria directly reflects morphological glomerular damage, and therefore, albuminuria represents an early marker of renal disease that often precedes a decline in eGFR.

In the context of heart failure, albuminuria is prognostic for heart failure hospitalizations and death.^{34,35} This premise extends to ATTR-CM, whereby the presence of microalbuminuria and macroalbuminuria is associated with a 1.5-fold and 1.9-fold higher risk of mortality, respectively. In a subgroup of 330 patients with repeated urinary albumin-to-creatinine ratio measurements, an increase of ≥30% at 12 months also represented a marker of disease progression and was associated with a 1.8-fold higher risk of mortality.³⁶

Changes in disease stage

The National Amyloidosis Centre disease staging system comprises thresholds for NT-proBNP and eGFR and reliably stratifies patients into prognostic categories at diagnosis.^{20,22} An increase in disease stage in patients with wild-type and p.(V142I) ATTR-CM during follow-up is also predictive of mortality, with an increase in NAC disease stage from stage I at 12 months being associated with a 2.6-fold higher risk of mortality.

This further supports the utility of changes in NT-proBNP and eGFR as markers of disease progression.³⁷

6-minute walk test distance

The 6-minute walk test (6MWT) is a well-established, comprehensive measure of functional exercise capacity that reflects an individual patient's capacity to conduct activities of daily living and provides an objective measurement that is meaningful to both clinicians and patients. This functional assessment has already demonstrated its utility in stratifying the prognosis of patients with heart failure and represents an independent predictor of cardiovascular outcomes.^{38,39}

This is also true in the context of ATTR-CM, where the baseline 6MWT distance is independently associated with mortality. Furthermore, the change in the 6MWT over time represents a marker of disease progression, whereby an absolute reduction of >35 m and a relative reduction of >5% at 12 months are associated with a 1.8-fold and 1.9-fold higher risk of mortality, respectively, with the associated risk remaining consistent across the three main genotypes and the spectrum of disease stages, supporting its applicability across a wide range of patients with ATTR-CM.⁴⁰

The change in 6MWT distance has also been widely used across multiple-phase III randomized controlled trials to demonstrate the efficacy of ATTR-specific disease-modifying therapies. Trials of TTR stabilizers demonstrated that over 30 months, tafamidis and acoramidis reduced the 6MWT distance decline by 75.7 m and 39.6 m, respectively.^{11,12} Trials of TTR gene silencers demonstrated that over 12 months, patisiran reduced the 6MWT distance decline by 14.7 m, and over 30 months, vutrisiran reduced the distance decline by 26.5 m.^{24,25}

The treatment effect on the rate of distance decline largely depends on the rate of deterioration in patients randomized to placebo, making simple comparisons of treatment effects across different trials challenging. This further emphasises the importance of the thresholds detailed above that define a meaningful absolute and relative deterioration in the 6MWT distance that can be used at an individual level to appropriately detect changes in functional capacity that represent significant disease progression.⁴⁰

Outpatient diuretic intensification

Outpatient diuretic intensification (ODI) is defined as any post-diagnosis initiation or increment in the dose of loop diuretics and occurs in response to worsening heart failure symptoms. Increasing diuretic requirements in the outpatient setting not only represent an opportunity to prevent a downstream hospital admission but also reflect a deterioration in the clinical status of the patient secondary to disease progression. ODI is common in patients with heart failure and represents an independent predictor of adverse outcomes.^{41,42} The same principle applies to patients with ATTR-CM, whereby ODI within the first year of diagnosis confers a 1.8-fold higher risk of mortality. The associated risk is dose-dependent, with patients who experienced the greatest increment in their diuretic requirements being at the highest risk of mortality.²³ ODI is an upstream marker of disease progression that often precedes a hospital admission for a heart failure exacerbation that requires intravenous decongestion. It therefore represents an earlier and potentially modifiable marker of disease progression (*Table 1*).^{23,31,36,40,43}

ODI can be combined with other markers of disease progression that provide incremental information to each individual marker of disease progression and, hence, refine the assessment of the rate of

Table 1: Markers of disease progression and associated risk of mortality^{23,31,36,40,43}

Markers of disease progression in transthyretin amyloid cardiomyopathy amyloidosis		
Markers	Definition of progression	Hazard ratio for death (95% confidence interval)
NT-proBNP progression	Increase of >700 ng/L and >30%	1.81 (1.59–2.05) ²³
Decline in eGFR	Decrease of >20%	1.71 (1.43–2.04) ³¹
Urinary ACR	Increase of ≥30%	1.84 (1.06–3.19) ³⁶
Outpatient diuretic intensification	Any initiation or increment in the dose of loop diuretic	1.79 (1.58–2.04) ²³
6MWT distance	Absolute reduction defined as a decrease >35 m	1.80 (1.51–2.15) ⁴⁰
	Relative reduction defined as a decrease >5%	1.89 (1.59–2.24) ⁴⁰
Mitral regurgitation	Worsening of mitral regurgitation by ≥1 grade	1.43 (1.14–1.80) ⁴³
Tricuspid regurgitation	Worsening of tricuspid regurgitation by ≥1 grade	1.38 (1.10–1.75) ⁴³

ACR = albumin to creatinine ratio; eGFR = estimated glomerular filtration rate; 6MWT = 6-minute walk test; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

progression. ODI can be combined with NT-proBNP progression and 6MWT worsening or with NT-proBNP progression and decline in eGFR to produce a comprehensive evaluation of disease progression, whereby each incremental increase in progression markers is associated with a significantly increased risk of mortality.

The inclusion of ODI as part of a composite end-point in clinical trials could result in an important increment in event rates. A post hoc analysis of the APOLLO-B trial open-label extension demonstrated that patients requiring ODI also experienced a significant deterioration in their functional capacity, symptom burden and an increase in NT-proBNP levels.⁴⁴ Treatment with patisiran significantly reduced the risk of outpatient worsening heart failure, and the addition of ODI to an extended composite led to a 52% increase in the total number of patients with events over the 24-month study period.⁴⁴

A similar prespecified analysis of the HELIOS-B trial demonstrated that patients who experienced ODI had a 2.6-fold higher risk of the composite of all-cause mortality and cardiovascular events and a 2.5-fold higher risk of all-cause mortality.⁴⁵ The increased risk was consistent across the overall population, monotherapy population and the population of patients treated with tafamidis at baseline. ODI was also associated with a greater deterioration in 6MWT distance, Kansas City Cardiomyopathy Questionnaire (KCCQ) score and a greater increase in NT-proBNP. Treatment with vutrisiran significantly reduced the risk of ODI in a time to first event analysis and the rate of ODI in a recurrent event analysis and, most importantly, also reduced the risk of the composite of all-cause mortality, cardiovascular events and ODI compared with placebo.⁴⁵ The inclusion of ODI in an expanded composite end-point in future clinical trials may reduce sample size requirements and follow-up duration required to accrue the target number of events by capturing clinically significant events earlier in the disease trajectory.^{44,45}

Kansas City Cardiomyopathy Questionnaire

The KCCQ represents a comprehensive measure of the overall burden of chronic heart failure that patients experience by assessing four main domains: symptoms, physical limitations, social limitations and quality of

life.^{46,47} The KCCQ has been widely studied in the general heart failure population and across multiple different settings, including both acute admissions and outpatient scenarios, and the KCCQ score has been independently associated with mortality and heart failure hospitalizations. Changes in the KCCQ score reflect meaningful improvements and deteriorations in clinical status that are also associated with clinical outcomes.⁴⁷

Although the prognostic importance of the KCCQ in ATTR-CM is yet to be defined, the change in KCCQ has been widely used as a secondary end-point in trials of ATTR-specific disease-modifying therapy. In the ATTR-ACT trial, treatment with tafamidis reduced the decline in KCCQ as compared with placebo over 30 months with a significant difference between the two groups being first observed at 6 months.¹¹ In the APOLLO-B trial, treatment with patisiran resulted in a slight improvement in KCCQ, while there was a decline in the placebo group that resulted in a significant difference between the two groups over 12 months.²⁴ In both the ATTRIBUTE-CM trial and HELIOS-B trial, treatment with acoramidis (least squares mean difference: 9.9 points [95% CI: 6.0 to 13.9]) and vutrisiran (least mean squares difference: 5.8 points [95% CI: 2.4 to 9.2]) reduced the decline in KCCQ compared with placebo over 30 months.^{12,25}

Cardiac imaging parameters

Echocardiography

The increasing clinical need to monitor disease progression in patients with ATTR-CM has spurred a growing interest in using multimodality imaging. Echocardiography remains the most widely available form of cardiac imaging and is therefore widely used in clinical practice. However, in patients with ATTR-CM, only worsening stroke volume, mitral regurgitation and tricuspid regurgitation are associated with an increased risk of mortality (*Table 1*).⁴³ It is possible that the lack of association between the changes in other structural and functional parameters may be influenced by significant intra- and interobserver variability that occurs when measuring changes that occur over time, which can be especially problematic when only small changes are expected. It is possible that the removal of manual contouring through the use of artificial intelligence would lead to a significant increase in precision, and advances in automation could reveal additional parameters that could be used to track disease progression on serial echocardiographic examinations.⁴⁸

Cardiac magnetic resonance

Cardiac magnetic resonance with multiparametric mapping provides similar structural and functional information to echocardiography but has the additional benefit of deep tissue characterization, which enables non-invasive visualization of changes within the myocardial substrate. Changes in cardiac magnetic resonance parameters over time have been most extensively studied in patients with cardiac light-chain amyloidosis. Native T1 is a measure of the myocardial relaxation time and provides a composite signal from the intra- and extracellular space. Serial measures of myocardial native T1 can track the treatment response in cardiac light-chain amyloidosis, with reductions being associated with favourable structural and functional changes along with a reduced risk of mortality.⁴⁹

Intravenous administration of gadolinium-based contrast agents enables isolation of the extracellular signal. Amyloidosis is the exemplar interstitial disease, and hence changes in the extracellular volume (ECV) act as a surrogate marker of changes in the amyloid burden. In the context of cardiac light-chain amyloidosis, reductions in myocardial ECV are associated with favourable cardiac remodelling and a reduced risk of mortality.⁵⁰

A small imaging-based study demonstrated that treatment with patisiran was associated with a reduction in myocardial ECV in patients with ATTR-CM, and more recently, a phase I study demonstrated that treatment with NI006 appeared to result in a reduction in the myocardial ECV.^{16,51} Serial cardiac magnetic resonance examinations are increasingly being used in the context of clinical trials to assess the effect of ATTR-specific disease-modifying therapies on the cardiac amyloid burden. However, the majority of evidence supporting the prognostic importance of changes in ECV is based on studies of patients with cardiac light-chain amyloidosis and, therefore, further research is needed to consolidate this premise in patients with ATTR-CM.⁵²

Bone scintigraphy

Bone scintigraphy with technetium-based bone-avid radiotracers represents a key diagnostic investigation and is a crucial component of the non-biopsy diagnostic pathway for ATTR-CM.⁵³ However, the clinical significance of changes in myocardial uptake over time remains poorly understood. A natural history study did not demonstrate that there were any significant changes in myocardial radiotracer uptake over time, suggesting that bone scintigraphy may not be sensitive enough to detect disease progression.⁵⁴ The majority of other studies have assessed the changes in cardiac uptake in response to treatment, with tafamidis, patisiran and NI006 all being associated with a reduction in myocardial radiotracer uptake.^{16,51,55,56} However, the reduction in uptake occurred alongside inconsistent changes in cardiac structure and cardiac function. The discordance with structural and functional imaging suggests that a reduction in myocardial radiotracer uptake may represent molecular changes in amyloid fibril composition in response to treatment, rather than an absolute reduction in amyloid mass. In two studies, treatment with patisiran and NI006 resulted in a reduction in NT-proBNP and a reduction in cardiac magnetic resonance-derived myocardial ECV, alongside a reduction in myocardial radiotracer uptake on bone scintigraphy.^{16,51} In these studies, although the reduction in cardiac uptake most likely demonstrated a favourable treatment effect, it is noteworthy that the kinetics and dynamics of radiotracers binding to the myocardium, bones and soft tissues fluctuate, and variations in tracer binding in any of these compartments will influence both the visual appearance and mathematical calculation of proportionate myocardial radiotracer uptake. Therefore, reduced myocardial radiotracer uptake should always be supported by improvements in other biochemical or imaging-based measures of cardiac function before the observed changes are ascribed exclusively to a reduction in the cardiac amyloid burden. Further studies using serial bone scintigraphy are needed to evaluate the clinical significance of changes in myocardial radiotracer uptake over time, and until then, any changes observed should be contextualized alongside a comprehensive multimodal assessment.

Future perspectives

Markers of disease progression have emerged as important clinical tools in the assessment of patients with ATTR-CM. Clinical studies have

provided clinicians with multiple markers that have been validated in large and diverse populations comprising patients with wild-type and hereditary ATTR-CM. Many of these markers have been remeasured 12 months after the baseline assessment and, hence, are likely to have been influenced by an unavoidable survival bias, whereby rapid disease progression may have resulted in death before the follow-up assessment, and the extent of differences between progressors and patients with stable disease is underestimated. Future studies should focus on validating these markers at earlier timepoints, such as at 6 months, as this would enable clinicians to detect disease progression sooner and intervene before patients develop advanced cardiac disease.

Many of these markers have been developed and validated in large real-world cohorts, where the majority of historic patients have been untreated. Although the markers have been assessed in subgroups of the study populations who were treated with disease-modifying therapies or enrolled into clinical trials, it is also important to demonstrate that these markers can detect disease progression in a clinical trial setting. ODI has already been applied to the APOLLO-B and HELIOS-B trial populations and demonstrated utility, but it would also be important to investigate the use of other markers in clinical trial populations, as they could be used alongside traditional endpoints as an extended composite outcome and capture a higher number of events.

Conclusions

The emergence of multiple novel efficacious ATTR-specific disease-modifying therapies has resulted in a growing need to identify patients with ATTR-CM experiencing disease progression. Considering the wide array of clinical tools that have been demonstrated to reliably detect disease progression, it is likely that a comprehensive assessment would incorporate serial biochemical measurements, serial evaluations of symptom burden and functional capacity and possibly serial cardiac imaging examinations. Some of the more commonly use markers of disease progression can be applied in combination and remain independently associated with an increased risk of mortality, indicating that each marker is capturing a different aspect of the underlying disease process. For example, NT-proBNP progression, decline in renal function and ODI or NT-proBNP progression, ODI and reduction in 6MWT distance can be used in combination, with each additional increment in markers of progression conferring a significantly increased risk of mortality, across the three main genotypes and the spectrum of disease stages.^{31,40} Combining these markers provides incremental information to each individual marker and allows further refinement of the rate of disease progression and enables identification of patients who are at the highest risk. Many of these markers are widely available, simple to measure and universally applicable across different genotypes and disease stages and, hence, can be easily adopted into clinical practice to identify patients experiencing disease progression and at highest risk of mortality. □

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