Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Changing Treatment Landscape in Transthyretin Cardiac Amyloidosis

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ABSTRACT: The demographics of patients with transthyretin amyloidosis with cardiomyopathy have evolved over the past decade, mostly driven by improved awareness of the disease among clinicians, noninvasive imaging tools for diagnosis, and new, effective treatments. Patients are now diagnosed earlier in their disease course, and treatment is initiated in those with milder disease, leading to improved outcomes. Earlier treatment of patients with milder disease may lead to accelerated disease stabilization and greater preservation of function. In addition, identification of patients with transthyretin amyloidosis with cardiomyopathy at an earlier disease stage translates to healthier study populations at enrollment in clinical trials, with slower disease progression compared with patients in prior trials. In this context, effect sizes between active treatment and placebo arms will likely be smaller than those seen in historic trials, although it is still possible to observe clinically relevant differences. In this review, we discuss how patient characteristics have changed from the ATTR-ACT trial to the more recent APOLLO-B, ATTRibute-CM, and HELIOS-B studies. In addition, we consider how measures of the minimal clinically important difference for particular end points can assist in clinical decision-making and targeting treatment goals. Treatment goals are evolving over time with the need for evidence-based recommendations in this clinical space. Lastly, we address unmet needs and future expectations for the management of transthyretin amyloidosis with cardiomyopathy.

Key Words: amyloidosis ■ cardiomyopathies ■ heart failure ■ quality of life

Transthyretin amyloidosis (ATTR) is a progressive, debilitating, and fatal multisystem disease. It is caused by misfolded transthyretin (TTR) protein accumulating as toxic amyloid deposits in multiple organs[1–3] and commonly presents as cardiomyopathy or polyneuropathy or in some cases as a mixed phenotype.[4,5] Patients with cardiomyopathy typically show a decline in functional capacity and quality of life (QOL) over time due to worsening heart failure, arrhythmias, and conduction disease.[6–9]

Today, patients with ATTR with cardiomyopathy (ATTR-CM) are being diagnosed earlier and with milder disease presentation compared with those diagnosed a decade ago.[10] These advances are due to improvements in disease awareness, availability of disease-modifying treatments, and better diagnostic technologies. These patients are, therefore, receiving treatment earlier in their disease course, resulting in improved preservation of function and overall outcomes compared with historic populations of patients with ATTR-CM.[10] The population of patients with ATTR-CM today is, therefore, considerably different from the population 10 years ago. In particular, patients entering clinical trials seem to be healthier at baseline and those assigned to placebo have slower progression compared with patients in older trials.[10–12]

The aim of this review is to examine how patient baseline characteristics and natural history course of disease progression can indicate how the population of

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For Sources of Funding and Disclosures, see page 907.

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Nonstandard Abbreviations and Acronyms	
6MWT	6-minute walk test
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloidosis with cardiomyopathy
KCCQ	Kansas City Cardiomyopathy Questionnaire
MCID	minimal clinically important difference
NT-proBNP	N-terminal pro-B-type natriuretic peptide
QOL	quality of life
TTR	transthyretin

patients with ATTR-CM has evolved since the seminal ATTR-ACT trial, published in 2018,[13] and to discuss how these impact both treatment expectations and broader considerations for the long-term management of ATTR-CM. We will also discuss how the concept of minimal clinically important difference (MCID) can help clinicians assess treatment responses and consequently inform the management of patients. Finally, we look to the future and the remaining unmet needs of patients with ATTR-CM as this complex patient population continues to evolve.

A literature search was performed with terms related to ATTR-CM and clinical trials or guidelines. All authors agreed to mainly focus on the ATTR-ACT,[13] APOLLO-B,[11] ATTRibute,[12] and HELIOS-B[14] phase 3 clinical trials. Literature on clinical guidelines was supplemented by the authors' clinical expertise and knowledge of relevant expert recommendations.

EVOLVING POPULATION OF PATIENTS WITH ATTR-CM

Both the clinical characteristics and prognosis of the population of patients with ATTR-CM have changed over the past decade due to improvements in diagnosis and treatment, resulting in diagnosis at a milder disease stage with more favorable structural and functional echocardiographic parameters.[10]

There is greater physician awareness of early red flags for referral for ATTR-CM screening, enabling earlier diagnosis at a point of less severe disease progression.[6,15–17] Recent trends in clinical practice have increased referrals for ATTR-CM, resulting in more true positive (patients for whom the diagnosis was confirmed) and false positive (patients for whom the diagnosis was finally excluded) diagnoses. This supports the theory that referring clinicians now have a lower threshold at which to send patients for further investigations, even when ATTR-CM is one of many other differentials.[10]

Availability of improved therapeutics drives clinicians to diagnose patients earlier, as evidenced by the exponential rise in referrals to amyloid centers that we have seen. This may lead to diagnostic tests being performed earlier in the disease course to enable access to treatment. The approval of tafamidis in 2019 in the United States, and in 2020 in the European Union and other parts of the world, was a major milestone for the management of patients with ATTR-CM,[6,15,17,18] although its elevated cost has limited the accessibility of the drug in many countries.[19] Tafamidis was the first broadly effective therapeutic agent that clinicians could offer their patients with ATTR-CM, thus driving a need to identify and appropriately diagnose these patients. Longer-term data and post hoc analyses have confirmed the benefits of tafamidis on the health status of the patients and QOL,[20–23] as well as additional benefits such as reduced decline in renal function.[24]

Advances in diagnostic imaging techniques such as echocardiography with global longitudinal strain, cardiac magnetic resonance imaging, and bone scintigraphy contribute to the earlier diagnosis of ATTR-CM.[25–30] Access to bone scintigraphy and cardiac magnetic resonance imaging, which can diagnose patients even before the appearance of echocardiographic abnormalities,[31,32] has fueled earlier diagnosis in patients presenting with less severe symptoms. Most patients are now diagnosed noninvasively (via laboratory testing and bone scintigraphy), whereas in the era of the ATTR-ACT trial, most patients required endomyocardial biopsy to confirm the diagnosis.[13] Because patients are being diagnosed and treated when they have milder disease compared with patients a decade ago, outcomes have greatly improved.[10] Initiating treatment that can stabilize or slow the progression to more severe disease earlier in the disease course leads to patients with ATTR-CM living longer, healthier lives.[10] Other important factors include improvements in the management of heart failure in patients with ATTR-CM,[33,34] potentially leading to overall better outcomes in these patients.

Clear evidence for the evolution in patients with ATTR-CM can be seen by comparing the patient baseline characteristics in clinical trials over time (Table). In ATTR-ACT, a wide range of characteristics indicated that patients had more severe symptoms, poorer health status, and worse QOL compared with those enrolling in more recent trials (Table).[11–14] When comparing disease characteristics, patients in the ATTR-ACT trial generally had poorer levels of baseline disease severity, as measured by the 6-minute walk test (6MWT), Kansas City Cardiomyopathy Questionnaire (KCCQ)–Overall Summary, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and troponin I levels, and echocardiographic parameters suggesting more advanced disease (Figure 1). ATTR-ACT also had a

Table. Baseline Characteristics Across ATTR-ACT, APOLLO-B, ATTRibute-CM, and HELIOS-B

Characteristic	ATTR-ACT: 2018[13] (N=441)		APOLLO-B: 2023[11] (N=360)		ATTRibute-CM: 2024[12] (N=632)		HELIOS-B: 2024[14] (N=655)	
	Tafamidis (n=264)	Placebo (n=177)	Patisiran (n=181)	Placebo (n=178)	Acoramidis (n=421)	Placebo (n=211)	Vutrisiran (n=326)	Placebo (n=329)
Enrollment dates	December 2013–August 2015		October 2019–May 2021		April 2019–October 2020		December 2019–August 2021	
Age, y	75 (46 to 88)*	74 (51 to 89)*	76 (47 to 85)*	76 (41 to 85)*	77.4 (6.5)†	77.1 (6.8)†	77 (45 to 85)*	76 (46 to 85)*
Male sex, n (%)	241 (91.3)	157 (88.7)	161 (89)	160 (90)	384 (91.2)	186 (88.2)	299 (92)	306 (93)
TTR genotype, n (%)								
ATTRwt	201 (76.1)	134 (75.7)	144 (80)	144 (81)	380 (90.3)	191 (90.5)	289 (89)	289 (88)
ATTRv	63 (23.9)	43 (24.3)	37 (20)	34 (19)	41 (9.7)	20 (9.5)	37 (11)	39 (12)
V122I	N/A	N/A	17 (46)	12 (35)	24 (58.5)	12 (60.0)	24 (65)	25 (64)
eGFR, mL/min per 1.73 m^2	N/A	N/A	71 (58 to 83)*	67 (51 to 84)*	61 (18)†	61 (19)†	64 (50 to 81)‡	65 (53 to 81)‡
Functional status								
6MWT distance, m	350.6 (121.3)†	353.3 (126.0)†	358.0 (295.0 to 420.0)*	367.7 (300.0 to 444.3)*	364 (103)†	351 (102)†	372.0 (103.7)†	377.1 (96.3)†
KCCQ-OS score†	67.3 (21.4)	65.9 (21.7)	69.8 (21.2)	70.3 (20.7)	71.7 (19.4); (n=408)	70.5 (20.7); (n=202)	73.0 (19.4)	72.3 (19.9)
Cardiac parameters								
NT-proBNP, pg/mL*	2995.9 (1751.5 to 4861.5)	3161.0 (1864.4 to 4825.0)	2008.0 (1135.0 to 2921.0)	1813.0 (952.0 to 3079.0)	2326 (1332 to 4019)	2306 (1128 to 3754)	2021 (1138 to 3312)‡	1801 (1042 to 3082)‡
Troponin I, pg/mL*	140 (90 to 200)	140 (80 to 190)	64.0 (38.6 to 92.0)	60.2 (38.2 to 103.1)	N/A	N/A	71.9 (44.9 to 115.9)‡	65.2 (41.1 to 105.5)‡
mBMI§	1058.8 (173.8)†	1066.4 (194.4)†	1147.0 (988.4 to 1273.8)*	1134.0 (1018.7 to 259.1)*	N/A	N/A	1183.8 (1082.7 to 1306.1)‡	1210.9 (1098.5 to 1333.5)‡
Echocardiographic parameters								
Left ventricular ejection fraction, %	48.4 (10.3)†	48.6 (9.5)†	58.0 (46.0 to 66.4)*	60.3 (45.5 to 65.4)*	N/A	N/A	N/A	N/A
Global longitudinal strain, %	−9.3 (3.5)†	−9.4 (3.6)†	−10.7 (−13.2 to −8.5)*	−10.9 (−13.0 to −9.4)*	N/A	N/A	N/A	N/A
Stroke volume, mL	45.8 (16.1)†	45.1 (16.9)†	47.0 (38.2 to 57.8)*	50.7 (39.7 to 60.9)*	N/A	N/A	N/A	N/A
Interventricular wall thickness,† mm	16.7 (3.8)	16.2 (3.5)	N/A	N/A	N/A	N/A	N/A	N/A
Left atrial anterior-posterior diameter size,† mm	43.8 (7.0)	43.7 (6.1)	N/A	N/A	N/A	N/A	N/A	N/A
NYHA classification, n (%)								
Class I	24 (9.1)	13 (7.3)	10 (6)	15 (8)	51 (12.1)	17 (8.1)	49 (15)	35 (11)
Class II	162 (61.4)	101 (57.1)	156 (86)	150 (84)	293 (69.6)	162 (76.8)	250 (77)	258 (79)
Class III	78 (29.5)	63 (35.6)	15 (8)	13 (7)	77 (18.3)	32 (15.2)	27 (8)	35 (11)
Concomitant medication, n (%)								
Diuretic	175 (66.3)	123 (69.5)	168 (93)	164 (92)	N/A	N/A	N/A	N/A
High-ceiling diuretic¶	N/A	N/A	166 (92)	158 (89)	N/A	N/A	261 (80)	259 (79)
β-Blocker	76 (28.8)	53 (29.9)	73 (40)	77 (43)	N/A	N/A	N/A	N/A

(*Continued*)

Table. Continued

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ACEI, ARB, or ARNI	69 (26.1)	48 (27.1)	82 (45)	71 (40)	N/A	N/A	N/A	N/A
Mineralocorticoid receptor antagonist	N/A	N/A	92 (51)	74 (42)	N/A	N/A	N/A	N/A
SGLT2 inhibitor	N/A	N/A	8 (4)	7 (4)	N/A	N/A	10 (3)	11 (3)

6MWT indicates 6-minute walk test; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary; mBMI, modified BMI; N, number randomized; n, number treated; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SGLT2, sodium-glucose cotransporter-2.

*Median (range).

†Mean (SD).

‡Median (interquartile range).

§mBMI is calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in meters).

¶High-ceiling diuretics include azosemide, bumetanide, furosemide, and torasemide.

6MWT and KCCQ-OS data for ATTRibute-CM are derived from BridgeBio and Fontana et al.[35,36]

greater proportion of patients with New York Heart Association Class III disease. Taken together, these baseline characteristics show a marked trend toward less severe disease in patients in the APOLLO-B, ATTRibute-CM, and HELIOS-B studies, compared with those in the older ATTR-ACT trial (Figure 1). More broadly, the baseline age and proportion of males among clinical trial participants for ATTR-ACT,[13] APOLLO-B,[11] ATTRibute-CM,[12] and HELIOS-B[15] were similar across the 4 trials. The proportion of patients with wild-type ATTR was slightly higher in the 3 more recent trials, APOLLO-B, ATTRibute-CM, and HELIOS-B. ATTRibute-CM and HELIOS-B reported a slightly higher proportion of V122I-positive patients compared with APOLLO-B; the proportion of patients with the V122I variant was not reported for ATTR-ACT.

Patients in more recent trials also seem to have slower rates of disease progression compared with patients in older trials.[11–13,14] At 12 months, placebo-treated patients in the ATTR-ACT study showed greater worsening of 6MWT and KCCQ–Overall Summary scores compared with patients in the placebo arms of the more recent APOLLO-B and ATTRibute-CM trials.[11–13] Similar results were also seen at a longer follow-up of up to 30 months when comparing 6MWT and KCCQ–Overall Summary scores from placebo patients in ATTR-ACT with those in the recent HELIOS-B study.[13,14] The differences in decline of 6MWT between the placebo arms in ATTR-ACT and ATTRibute-CM were less marked at 30 months compared with 12 months, with similar scores for KCCQ–Overall Summary. There are no 30-month data available from the APOLLO-B trial for comparison. Survival rates in trials with 30-month data available (ATTR-ACT and ATTRibute-CM) and up to 42-month data from HELIOS-B highlight the improved prognosis over time in patients with ATTR-CM. In ATTR-ACT, patients receiving a placebo had a survival rate of 57.1%,[13] whereas those assigned to placebo in the more recent ATTRibute-CM and HELIOS-B trials had survival rates of 74.3% and 74%, respectively.[12,14] Comparing data for hospitalizations and biomarkers such as NT-proBNP in the placebo arms across the trials would be of interest but is not possible due to vast differences in the way data were collected and analyzed in each trial. Overall, these data support the hypothesis that the ATTR-CM clinical trial population is becoming less sick over time, with less severe disease and a better long-term prognosis. These observations are further supported by real-world clinical data. Over time in a retrospective observational study (2002–2021), the duration of symptoms before diagnosis decreased, and there was a higher proportion of patients with early-stage disease at diagnosis.[10] This was associated with more favorable echocardiographic parameters and a progressive decline in mortality during the study.

DETERMINING CLINICAL RELEVANCE OF TREATMENT EFFECTS

The slower progression rate observed in the placebo arms of modern ATTR-CM clinical trials has important implications. ATTR-CM remains a progressive and fatal disease, and the predominant objective of treatment with current therapeutics is to slow disease progression rather than to reverse the disease course. Thus, demonstrating a therapeutic effect requires deterioration in untreated patients. With patients in the placebo arms of more recent clinical trials showing slower deterioration, differences in outcomes between the investigational treatment and placebo arms have become smaller. Therefore, it is imperative to understand the clinical relevance of these treatment differences and what they mean to patients' daily lives.

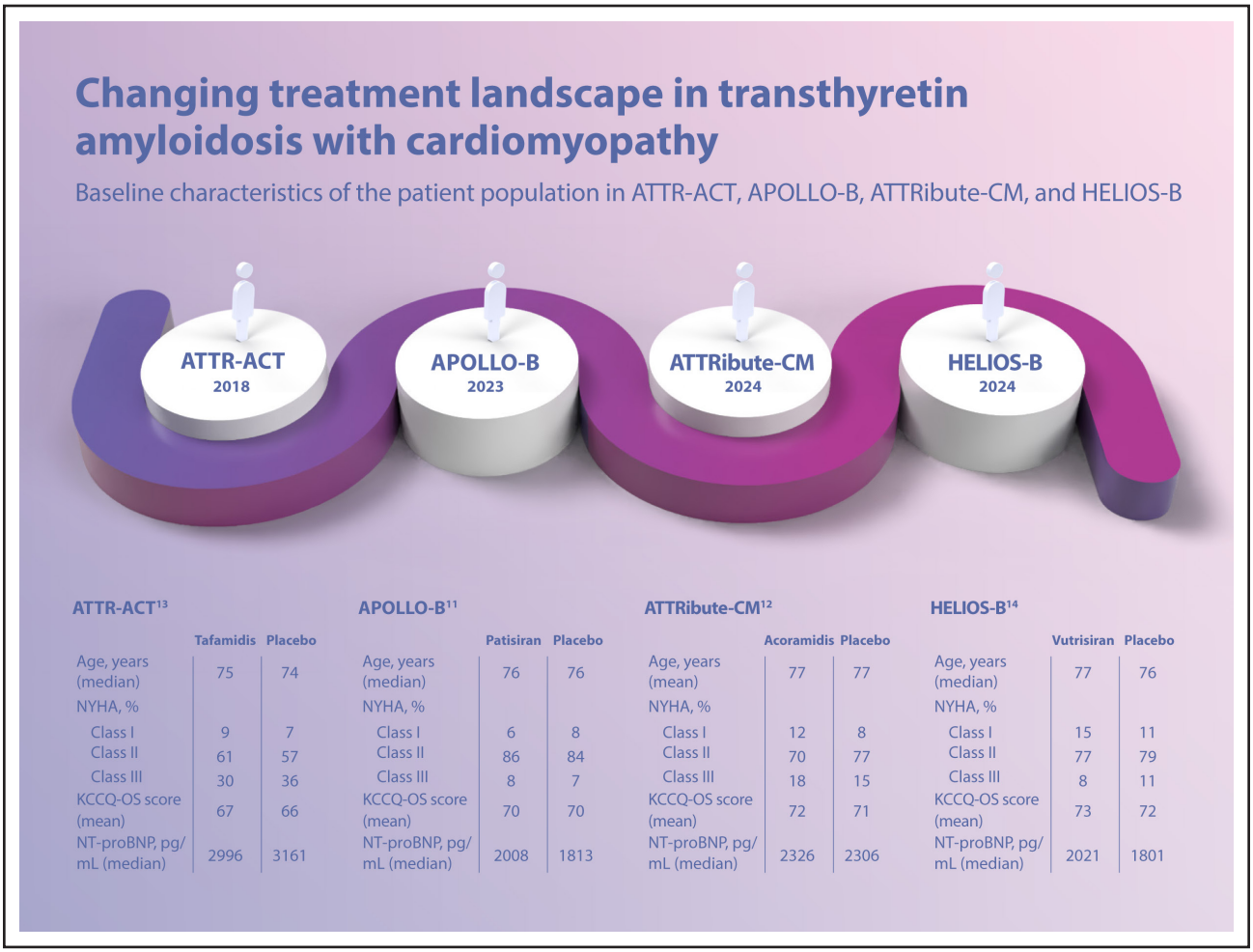

Figure 1. Changing treatment landscape in transthyretin amyloidosis with cardiomyopathy: overview.
KCCQ-OS indicates Kansas City Cardiomyopathy Questionnaire–Overall Summary, NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

Although statistical testing can provide insights into the numerical significance of differences between treatment arms in clinical trials, the clinical significance of any difference requires a more nuanced approach. The concept of the MCID was introduced in 1989, assessing patients with chronic heart and lung disease to define the smallest difference in a particular outcome measure that patients perceive as beneficial.[37] Defining an MCID for a particular end point helps translate data from clinical trials into clinical relevance. Importantly, the MCID must be disease-specific to be clinically useful. For example, the defined MCID for the 6MWT varies by cardiopulmonary diseases and patient characteristics.[38] Given the differences in patient populations (including age, which is one of the main determinants of MCID), extrapolating these cardiopulmonary disease MCID values to end points in ATTR-CM clinical trials is impractical.

Recent studies investigating the prognostic importance of different parameters in patients with ATTR-CM are providing the basis for identifying MCIDs for end points of interest. An absolute reduction of >35 m or reduction of >5% in 6MWT distance at 1 year was found to be associated with an increased risk of mortality,[39] as was the combination of an increase in NT-proBNP (>700 ng/L and >30%) and outpatient diuretic intensification (any postdiagnosis initiation or increment in the dose of loop diuretic [furosemide equivalent]).[40] In patients with ATTR-CM, a 15 m decline in 6MWT distance has been shown to be associated with a reduced ability to perform activities of daily living, as measured by the KCCQ Physical Limitation domain.[41] Other studies have looked at assessing imaging biomarkers in patients with ATTR-CM. For echocardiographic parameters, worsening of mitral and tricuspid regurgitation were independently associated with mortality.[8] Cardiac magnetic resonance imaging studies have indicated that higher native T1 time and extracellular volume and lower myocardial-to-skeletal-T2 ratio were associated with higher mortality.[42] Evidence also suggests that cardiac magnetic resonance imaging–derived extracellular volume may be a useful monitoring tool for assessing changes in cardiac amyloid load in

patients receiving treatment although further evidence is needed to verify these preliminary results.[43]

Further studies are needed to optimize which end points and MCIDs are relevant to incorporate into future clinical trials.

CURRENT CLINICIAN AND PATIENT EXPECTATIONS AND GOALS IN ATTR-CM MANAGEMENT

Even with advances in diagnosis and treatment, ATTR-CM remains a severe, progressive, and fatal disease. Although there are several expert consensus recommendations[6,15,17,18,44] and heart failure guidelines,[45] including ATTR-CM, there are currently no best-practice clinical guidelines specifically for the disease. Mineralocorticoid receptor antagonists[34] and low-dose beta-blockers, in patients with left ventricular ejection fraction ≤40%, have been associated with prognostic benefit in patients with ATTR-CM[33]; however, standard cardiomyopathy β-blocker dosing can be poorly tolerated in patients with this condition, and discontinuation of this therapeutic class is common in patients with chronotropic incompetence and advanced stages of ATTR-CM. Other treatment options include sodium-glucose cotransporter-2 inhibitors for symptomatic heart failure[46] (although data from randomized controlled trials in ATTR-CM are currently lacking), anticoagulants for arrhythmia, and pacemakers for conduction disturbances and bradyarrhythmia.[18,47]

Patients with ATTR-CM have severely reduced functional capacity and QOL; therefore, improvements in or stabilization of measures such as the 6MWT, KCCQ, and other patient-reported outcomes are frequently a priority for patients. The KCCQ is a clinical outcome assessment tool used to determine the impact of heart failure on patients' lives.[48] KCCQ subdomains encompassing symptoms, functional limitation, and QOL provide more granular information on what is most affecting a patient's health status, and specific subdomains may be more relevant to different patients, depending on their lifestyle.

The main goals of ATTR-CM management should be to improve cardiovascular-related mortality, heart failure (both hospitalizations and heart failure worsening in the outpatient setting, as assessed by metrics such as outpatient diuretic intensification), patient QOL, and functional capacity (as measured by the 6MWT, KCCQ, or other patient-reported outcomes; Figure 2). Response to treatment can be determined by measuring specific pathways, for example, amyloid deposits with imaging, blood biomarkers such as NT-proBNP, troponin, TTR, neurofilament light chain, and structural and functional changes by echocardiogram. One recent group recommendation included monitoring for disease progression between 6 and 12 months using criteria across 3 domains: clinical and functional; laboratory biomarker; and imaging and ECG.[17] However, these recommendations are not yet supported by robust clinical evidence; evidence-based guidelines remain an unmet need in the monitoring of ATTR-CM.

CURRENT UNMET NEEDS AND FUTURE EXPECTATIONS

The past decade has seen great improvements in clinical outcomes for patients with ATTR-CM; however, there remain unmet needs in the treatment and management of this progressive and debilitating disease. Future treatment developments include the availability of compounds that target the disease pathways at different levels with different mechanisms of action; understanding the role of combination treatment; identifying which treatments to select for specific patients; and how to initiate second- and third-line therapies (Figure 2). In terms of monitoring response to treatment, robust evidence is lacking, and more data are needed to provide clear definitions and thresholds of disease progression, for example, functional tests, QOL, patient-reported outcomes, NT-proBNP, and signs of heart failure worsening to assess clinical progression, as well as assessment of biomarkers. To use these potential markers of disease status in clinical practice, more evidence is needed to determine the magnitude of improvement or decline that would be considered a sign of progression or an inadequate response to prompt a change in treatment of a patient. Another clear unmet need is the lack of information from the patients' perspective. Understanding what matters most to patients in terms of their disease symptomatology and management will also help to inform clinical decision-making (Figure 2).

CONCLUSIONS

Due to earlier diagnoses and the availability of new therapeutics, today's patients with ATTR-CM are healthier than their counterparts from a decade ago. This is clearly demonstrated by the milder baseline disease characteristics of patients enrolled in the APOLLO-B, ATTRibute-CM, and HELIOS-B clinical trials compared with patients in the ATTR-ACT trial. In addition, the less rapid disease progression evidenced by the placebo groups in the more recent trials impacts trial design and MCID determinations. Notably, caution should be used when making comparisons across the 3 trials due to the different trial designs and some differences in assessment time points. This evolution in the patient population poses a new challenge for clinicians when assessing treatment responses because the differences observed between placebo and active treatment will be smaller, given the improved prognosis of the untreated patients. In the clinic, this is compounded by a lack of evidence-based guidelines on

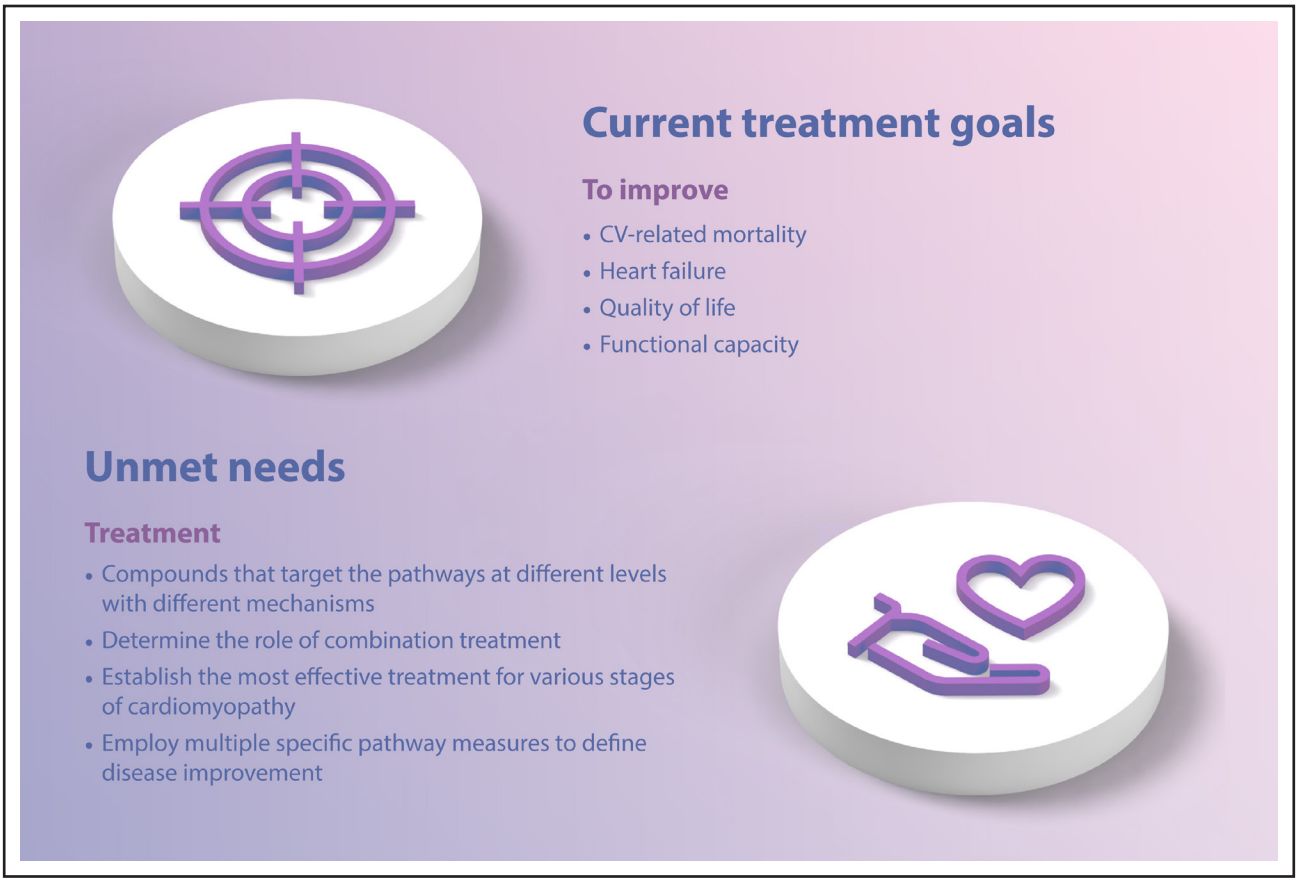

Figure 2. Changing treatment landscape in transthyretin amyloidosis with cardiomyopathy: unmet needs.
CV indicates cardiovascular.

treatment goals or MCID thresholds for key outcomes. Importantly, unmet needs remain to further improve the lives of patients with ATTR-CM and, in particular, to reduce hospitalizations and deaths. Robust data to help clinicians monitor different disease pathways and treatment effects, and determine biomarker thresholds for disease progression, are all needed.

ARTICLE INFORMATION

Received June 12, 2024; accepted March 4, 2025.

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Acknowledgments

Medical writing assistance was provided by Kerrie O'Rourke, PhD, of Adelphi Communications (Bollington, UK), in line with Good Publication Practice Guidelines.

Sources of Funding

This work was supported by Alnylam Pharmaceuticals (Cambridge, MA).

Disclosures

Dr Fontana reports consultancy/advisory boards for Alexion/Caelum Biosciences, Alnylam, AstraZeneca, Attralus, Bayer, BridgeBio/Eidos, Cardior, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Mycardium, Novo Nordisk, Pfizer, and Prothena; research grants from Alnylam, AstraZeneca, BridgeBio, and Pfizer; salary from the British Heart Foundation Intermediate Fellowship; share options in Lexeo Therapeutics; and shares in Mycardium. Dr Berk reports advisory boards for AstraZeneca, BridgeBio, Intellia, and Ionis Pharmaceuticals; consulting for Alnylam Pharmaceutical; and institutional research support from Alnylam, Alexion, Ionis Pharmaceutical, and Intellia. Dr Drachman reports advisory boards for Pfizer and consulting fees from Alnylam Pharmaceuticals. Dr Garcia-Pavia reports speaking fees from Alnylam, AstraZeneca, BridgeBio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; consulting fees from Alexion, Alnylam, AstraZeneca, ATTRalus, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Pfizer, Neuroimmune, and Novo Nordisk; and research/educational support to his institution from Alnylam, AstraZeneca, BridgeBio, Intellia, Novo Nordisk, and Pfizer. Dr Hanna reports consultancy/advisory boards for Alexion, Alnylam, AstraZeneca, Attralus, BridgeBio, Ionis Pharmaceuticals, and Pfizer. Dr Lairez reports consultancy/advisory boards for Alnylam, Amicus Therapeutics, AstraZeneca, Neurimmune, and Pfizer. Dr Witteles reports consulting fees from Alexion, Alnylam, AstraZeneca, BridgeBio, Janssen, Novo Nordisk, and Pfizer. The other authors report no conflicts.

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