ATTR-CM: Then and Now

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Introduction

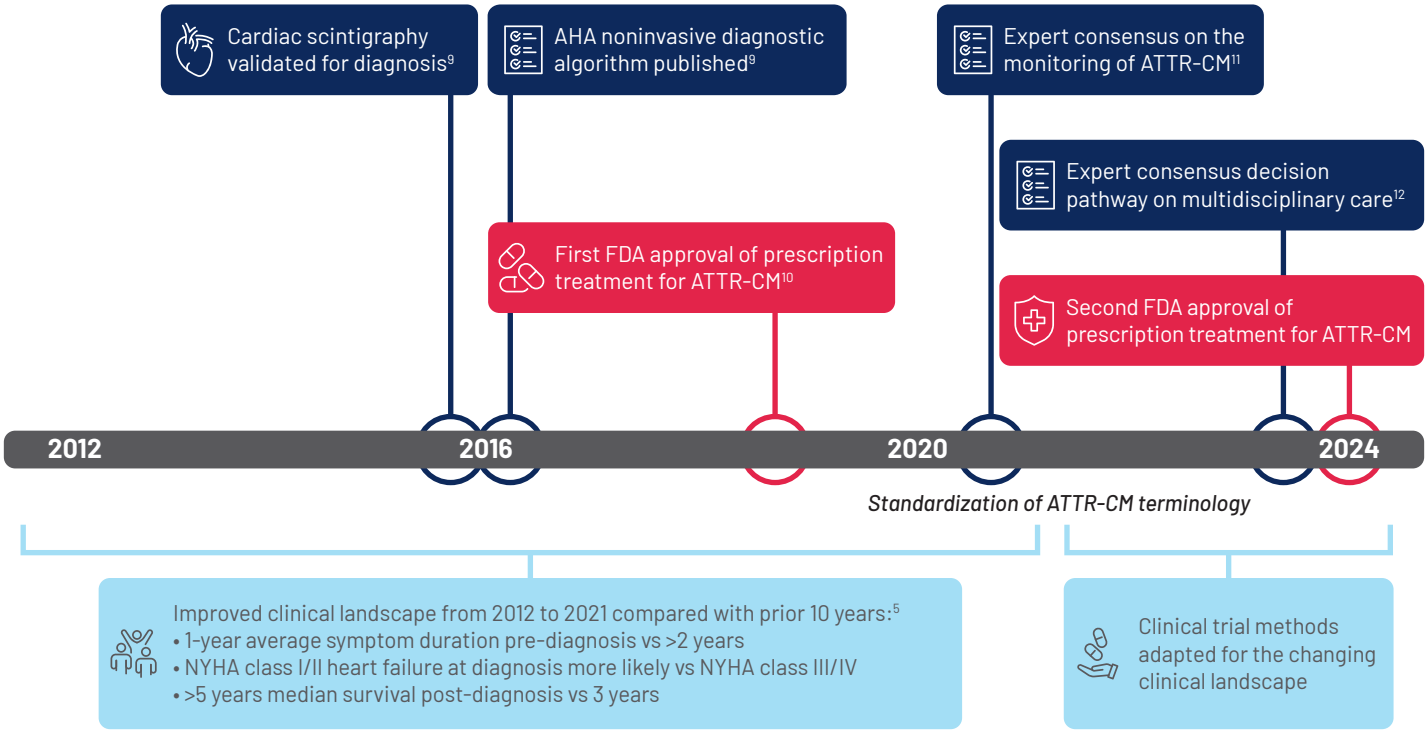
Transthyretin amyloid cardiomyopathy (ATTR-CM), historically thought to be a rare and underrecognized form of heart failure, is now considered to be more prevalent than previously believed.[1,2] There has been an exponential increase in the number of patients diagnosed with ATTR-CM over the last decade due to enhanced awareness of clinical red flags and the development of a noninvasive diagnostic algorithm.[3,4] Earlier diagnosis and advances in standard of care have improved patient outcomes—compared with 10 years ago, today's patients have less severe cardiac symptoms and better functional capacity at diagnosis, despite an increase in mean age at diagnosis.[5] Despite these developments, misdiagnosis remains common, and uptake of noninvasive diagnostic technologies has been slow.[6] Continued awareness of the evolving clinical landscape is crucial to optimizing patient management.

Improvements in ATTR-CM Diagnosis

Whereas in the past, diagnosis of ATTR-CM required endomyocardial biopsy, an invasive procedure requiring high technical expertise and carrying a risk of serious complications, advances in cardiac imaging have made noninvasive diagnosis standard.[4] Cardiac scintigraphy is widely available and has become a cornerstone of the ATTR-CM diagnostic algorithm.[4,7] Coupled with serum free light chain concentration (sFLC) and serum and urine immunofixation electrophoresis (SIFE/UIFE), ATTR-CM can be distinguished from amyloid light chain cardiomyopathy with very high specificity and relative ease.[4] Furthermore, transthyretin (TTR) gene sequencing is now included in many cardiomyopathy gene panels, enabling differentiation of hereditary from wild-type disease—an important distinction, as hereditary ATTR-CM tends to be more aggressive than wild-type and requires closer follow-up.[3,4]

These advances have allowed patients to receive a diagnosis at increasingly early stages of disease. In the past (2002–2011), patients at diagnosis had typically experienced ATTR-CM symptoms for an average of >2 years, had New York Heart Association (NYHA) class III/IV heart failure, and were faced with a median 3-year survival post-diagnosis.[5] In more recent years (2012–2021), pre-diagnosis symptom duration has been cut in half, NYHA class I/II heart failure has become more common than class III/IV, and median survival post-diagnosis has increased fivefold.[5] The importance of earlier detection cannot be overstated, as treatment of ATTR-CM is most effective before the development of significant cardiac dysfunction.[6,8]

Recent advances in ATTR-CM diagnosis and management.



ATTR-CM, transthyretin amyloid cardiomyopathy; FDA, US Food and Drug Administration; NDA, New Drug Application; NYHA, New York Heart Association.

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Evolution of ATTR-CM Management

Treating ATTR-CM

Prior to 2019, management of ATTR-CM was primarily limited to symptomatic heart failure treatments.[13] Liver or heart transplantation was the only disease-modifying option and was not feasible for most patients.[13] In 2019, the first disease-modifying pharmacotherapy for ATTR-CM, a TTR stabilizer, was approved by the US Food and Drug Administration (FDA).[10] As a number of additional disease-modifying treatments advance through late-stage clinical development, the repertoire of FDA-approved options is expected to expand rapidly over the next few years.[14–17]

With the shift toward diagnosing patients at earlier stages of disease, treatment goals have diversified, as evidenced by an expanded perspective around which endpoints should be considered clinically meaningful in clinical trials. Early clinical trials primarily focused on treatment effects in prolonging survival and reducing cardiovascular hospitalization (CVH).[18] However, as opportunities for earlier intervention have grown, more recent trials have placed increasing focus on preserving independence and functional capacity, maintaining quality of life (QoL), and stabilizing or improving levels of prognostic biomarkers.[19–21]

Monitoring ATTR-CM Progression

Significant advancements have been made in defining best practices for monitoring ATTR-CM disease progression, with the first expert consensus on this topic published in 2021.[11] These guidelines define criteria for disease progression in patients with ATTR-CM based on clinical and functional parameters (CVH, NYHA Class, QoL instruments, 6-minute walk distance), clinically relevant laboratory values (NT-proBNP, troponin, eGFR), and imaging and electrocardiography (left ventricular wall thickness, diastolic dysfunction grade, systolic measurement, new onset conduction disturbance), reflecting the varied impact of the disease.[11] Baseline serum TTR is also emerging as a potential prognostic indicator and surrogate measure of TTR tetramer stability.[22] An analysis of a recent study showed that increases in serum TTR from baseline due to treatment with a stabilizer are associated with a reduced risk of first CVH and a reduced risk of cardiovascular mortality.[23,24]

Although advances have been made in defining disease progression, precisely how changes in the above-mentioned variables translate to patient outcomes is not yet fully understood. Data from placebo groups in clinical trials help provide insight into the natural history of the disease and are expected to clarify these relationships in the future further.[25] As the therapeutic armamentarium expands, health care professionals may soon have multiple approved pharmacotherapy options, and validated methods for response monitoring will become essential.

Conclusion

In the last 10 years, heightened awareness of ATTR-CM and the introduction of noninvasive testing have facilitated earlier diagnosis of people affected by the condition. The growing capacity to intervene early, before significant cardiac dysfunction has occurred, and the potential for future treatment options are rapidly evolving patient management and providing opportunities to better understand the disease. As awareness, diagnostic tools, and treatment algorithms continue to improve, there is a bright future ahead for managing what has historically been an inexorably progressive and fatal disease.

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