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ATTR Epidemiology, Genetics, and Prognostic Factors

REVIEW

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ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed disease and an underestimated cause of both heart failure and conduction abnormalities. It is characterized by pathologic accumulation of extracellular protein arising from unstable transthyretin (TTR) tetramers, which dissociate into monomers that misfold, aggregate, and form insoluble fibrils that are resistant to proteolysis. Cardiac amyloidosis appears in two distinct forms: hereditary and wild-type. There is considerable heterogeneity in the clinical presentation of ATTR, ranging from primarily cardiac, primarily neuropathic, or mixed cardiac and neuropathic disease. Pathogenic variants in the *TTR* gene that predominantly involve the heart include Val122Ile, Leu111Met, and Ile68Leu. The wild-type form of ATTR is also predominantly cardiac. Phenotypic heterogeneity is linked to differences among specific pathogenic *TTR* variants, geography, and the subtype of endemic versus nonendemic disease. Factors contributing to wild-type ATTR are largely unknown, but similar factors likely influence the penetrance of hereditary ATTR. Recognition of ATTR-CM is improving due to the increased use of cardiac scintigraphy as a noninvasive diagnostic tool, and early recognition of cardiac infiltration is crucial to optimize long-term prognosis.

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INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) is characterized by pathologic accumulation of unstable extracellular tertiary structures that misfold, aggregate, and form insoluble fibrils in blood vessels, bones, and major organs.[1,2] Transthyretin (TTR) misfolding and subsequent deposition in tissues are facilitated by TTR mutations that decrease the stability of the normally folded protein.[3]

ATTR occurring in heart muscle (ATTR-CM) is an underdiagnosed disease and underestimated cause of heart failure (HF), conduction abnormalities, and cardiac arrhythmias.[4] TTR misfolding can lead to two distinct forms of cardiac amyloidosis: hereditary (ATTRv) and wild-type (ATTRwt).[5] In ATTRv, an amyloidogenic mutation in the *TTR* gene facilitates the dissociation of its tetramer into monomers and promotes subsequent misfolding.[6] Amyloid formation also occurs in the absence of pathogenic variants in *TTR*, when dissociated TTR monomers misfold and aggregate into amyloid fibrils in the presence of favorable conditions, such as aging and oxidative stress in ATTRwt.[7,8] Misfolded TTR oligomers in circulation cause progressive interstitial infiltration, leading to increased oxidative stress and mitochondrial damage, increased cardiac wall thickness, and diastolic dysfunction.[9-11] This may accelerate the progression of ATTR-CM since worsening HF amplifies conditions that may lead to additional TTR misfolding and deposition.

EPIDEMIOLOGY AND DISTRIBUTION OF ATTR AMYLOIDOSIS

The true incidence and prevalence of ATTR-CM are currently unknown.[12,13] Historically, ATTR-CM has been considered a rare disease that mainly affects the elderly.[14] This perception is partly due to the phenotypic heterogeneity of the disease, ranging from exclusively neurologic involvement to cardiac-restricted disease.[15] This variability results from differential effects of various *TTR* mutations, their occurrence in an endemic versus nonendemic location, genetic and demographic factors such as age and sex, and probably other environmental factors that are currently unknown.[15] However, recognition of ATTR epidemiology is evolving due to the increased use of cardiac scintigraphy as a noninvasive diagnostic tool.[1] For example, using cardiac scintigraphy, Castaño et al. discovered that roughly 13% of patients admitted for HF with preserved ejection fraction (HFpEF) and a wall thickness > 12 mm may have ATTRwt, and approximately 16% of patients with severe calcific aortic stenosis (AS) undergoing percutaneous transcatheter aortic valve implantation have ATTR-CM.[16] Furthermore, carpal tunnel syndrome, which affects 3% to 6% of the general population, may precede a diagnosis of ATTR-CM by approximately 6 years.[17] This raises the question of whether ATTR-CM should be considered a common condition despite poor recognition.[13]

The US Congress, through the Rare Disease Act of 2002, defines rare disease as fewer than 200,000 affected individuals in the United States, whereas the Public Health section of the European Commission defines rare disease as affecting fewer than 1 in 2,000 people in Europe. The prevalence of ATTR-CM may be substantially higher than these numbers,[18] especially given that the prevalence of HF in the US is around 6.2 million per the Centers for Disease Control and Prevention.[19] Approximately 50% of people with HF have a preserved EF (HFpEF), and transthyretin deposition is found on autopsy in about 25% of those over 80 years of age with HFpEF. In a cohort of 109 individuals with an antemortem diagnosis of HFpEF without known amyloid who underwent autopsy, 5% had robust ATTR deposition in their hearts, while 12% had more mild cardiac deposition.[20] This suggests that at least 155,000 people (5% of estimated HFpEF prevalence) have ATTR, but milder deposition is probably playing a role in many others with HFpEF. Additionally, several studies indicate disparity in the racial prevalence of HF,[21] suggesting that the prevalence of ATTR among non-Whites with HFpEF may be higher than among Whites.

GENETICS

Transthyretin is a tetrameric serum transport protein encoded by the *TTR* gene on chromosome 18q12.1, and it spans 4 exons.[22] Traditional numbering of *TTR* codons came from early amino acid sequence analysis of the circulating protein, which lacks an N-terminal signal peptide of 20 residues.[23] Later analysis of the DNA sequence helped to determine the full-length proprotein.[24] Based on proper nomenclature by the Human Gene Organization (HUGO), codon numbering should begin with methionine—which adds 20 residues to the traditional numbering that arose from early serum protein analysis—as well as three-letter abbreviations for amino acids. This manuscript follows the majority of published literature on ATTR, using the traditional numbering and three-letter abbreviations for amino acids. However, clinical genetic laboratories typically use HUGO-based nomenclature. For example, a common pathogenic variant in *TTR* may be designated as V30M or Val30Met by traditional annotation, or p.Val50Met by HUGO-based nomenclature.

More than 130 pathogenic variants in *TTR* related to familial ATTR have been reported.[25] Heterozygosity is enough to prompt disease manifestations, although

reduced penetrance and variable expression make family history an unreliable factor in recognizing ATTRv except among individuals and families with early-onset ATTRh.[26] These mutations tend to cluster into geographic or ethnic groups with an autosomal-dominant pattern of inheritance.[10] In the US, the most common *TTR* mutations are Val122Ile, Thr60Ala, and Val30Met, whereas the most common *TTR* mutations worldwide are Val30Met, Val122Ile, and Glu89Gln.[6,27] Val30Met may be the most commonly recognized mutation worldwide, mostly found in regions of Portugal, Spain, France, Japan, Sweden, South America, and some nonendemic parts of Africa.[6] On the other hand, Val122Ile originated in West Africa and is found in approximately 3% to 4% of African Americans, with cardiac manifestations occurring in later stages of life.[28] Although the worldwide prevalence of the Val122Ile variant may exceed that of the Val30Met variant, the penetrance of Val30Met appears higher than for Val122Ile, and the incidence of ATTRv related to Val30Met may be highest.[6,29] Leu111Met and Ile68Leu are mutations mostly reported in Denmark and Italy, respectively, and cause severe cardiomyopathy in relatively early ages.[30] The Thr60Ala variant is the second most-common TTR variant in the US and the most common in the UK and Ireland, affecting approximately 1% of the population of north-western Ireland.[31,32] Val122Ile is known to be the most common cause of late-onset ATTR-CM in the US.[33] Other common causes of ATTRv-CM include Thr60Ala (early-onset phenotype), Ile68Leu (late-onset phenotype) in Italy, and Leu111Met (early-onset phenotype) in Denmark.[13,34]

Worldwide distribution of most common ATTRv genotypes by country/region is shown in ***Figure 1***.

There is heterogeneity in disease phenotypes, ranging from predominantly neuropathic (familial amyloid polyneuropathy, or TTR-FAP), predominantly cardiac (TTR amyloidosis cardiomyopathy, or ATTR-CM), or a mixed phenotype.[4] In addition, an oculoleptomeningeal type with symptoms predominantly involving the central nervous system has been reported with some rare mutations.[35] According to an international registry, Transthyretin Amyloidosis Outcomes Survey (THAOS), most patients enrolled from the US are elderly men with wtATTR-CM and a cardiac-predominant phenotype compared with patients enrolled in this registry from Europe.[27] ATTRwt tends to produce a predominantly cardiac phenotype. The predominant phenotype in patients with hereditary ATTR varies based on the underlying mutation. Both Val122Ile and Leu111Met typically cause cardiomyopathy. However, there also can be a substantial component of neuropathy in patients with Val122Ile, with almost 60% of these individuals in the THAOS survey reporting sensory neuropathy.[27] In another study with a mixed population of self-reported White and Black individuals with Val122Ile, 20% to 27% reported neuropathy.[36] Early-onset Val30Met predominantly causes polyneuropathy, but late onset often has cardiac involvement.[6] Glu89Gln has a mixed phenotype of polyneuropathy and cardiomyopathy.[6,36]

Heterogeneity in disease penetrance also occurs across different geographic regions. For example, age of disease onset related to Val30Met is much later in Sweden than

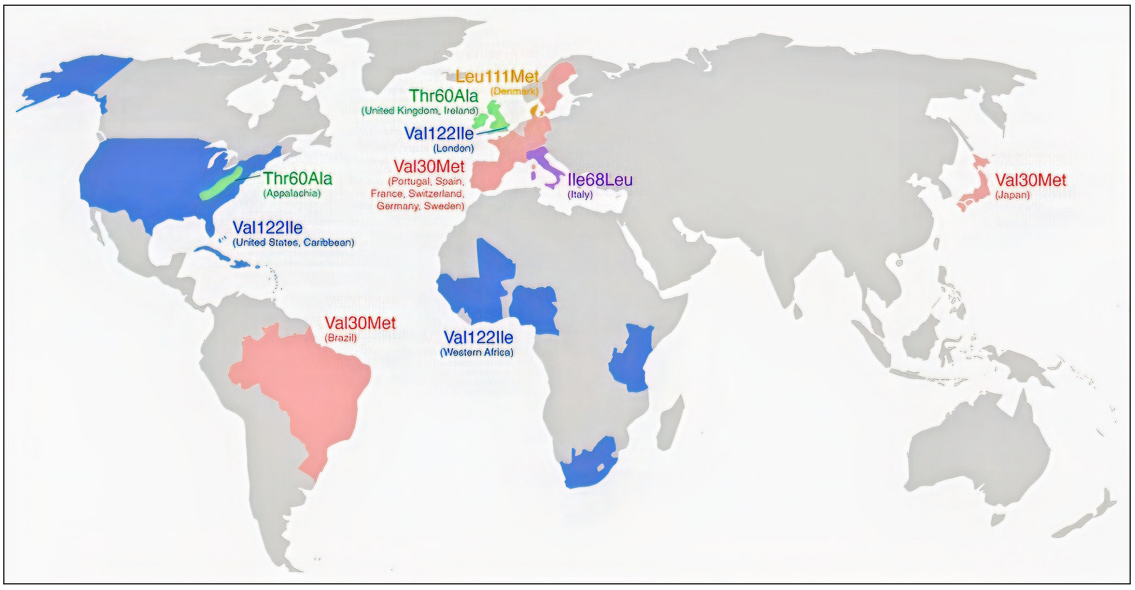

Figure 1 Worldwide distribution of most common ATTRv genotypes by country/region. Countries and regions with relatively high levels of *TTR* pathogenic variants noted in the text are represented by different colors. Each *TTR* variant is designated by its traditional nomenclature. Most *TTR* variants have even more regional heterogeneity in these countries and regions. ATTRv: hereditary transthyretin amyloid; TTR: transthyretin

in Portugal and Japan, and the Portuguese population has 80% higher penetrance of the Val30Met mutation during mid-age (50 years) compared with the French population.[37] In one study evaluating a potential parent-of-origin effect, the authors compared age of onset of TTR-FAP among French and Portuguese families with the Val30Met pathogenic variant. Out of 33 Portuguese families, the transmitting parent was found to be the mother in 153 individuals and the father in 138.[38] In comparison, out of 48 French families, the transmitting parent was the mother in 216 individuals and the father in 219. In the Portuguese families, phenotypic manifestations were earlier when the pathogenic TTR variant was inherited from the mother instead of the father ($P < .002$). The age of onset of TTR-FAP was not significantly different in the French families when comparing maternal and paternal transmission of the *TTR* mutation.

Variability among patients in terms of age of disease onset also may depend on the phenotype.[39] Traditionally, TTR-FAP and ATTRv-CM were considered two distinct disorders, although ATTR is now considered to be a single disease with a spectrum of manifestations, including nearly exclusively neuropathy or cardiomyopathy, or (more commonly) a combination of these and other manifestations. In prototypical TTR-FAP, signs and symptoms develop most commonly in the third to fifth decade of life but can be noticed from the second decade of life. Penetrance is variable and disease is usually present as a progressive sensory motor neuropathy with autonomic manifestations.[40] Without treatment, the disease is usually progressive and fatal about 10 to 13 years after the onset of symptoms. Men and women are equally affected.[41] On the other hand, prototypical hATTR-CM usually has a later onset than TTR-FAP, with symptoms occurring mostly after age 60.[42] It manifests as unexplained left ventricular hypertrophy leading to restrictive cardiomyopathy, HF, atrial fibrillation, and conduction abnormalities.[43-45]

SPECIFIC TTR PATHOGENIC VARIANTS

VAL30MET

Discovered in the 1950s, Val30Met was the first TTR variant, initially identified in Portugal and later in Sweden and Japan. It typically causes FAP, resulting from a point mutation causing substitution of methionine for valine at position 30 of the mature protein.[46] Family history is usually positive in endemic areas because inheritance is autosomal dominant.[10] Val30Met can manifest as early- or late-onset disease and, as a result of this heterogeneity, may be difficult to diagnose.[10,46] Although cardiac involvement is late among those with endemic disease, it tends to be more prominent in nonendemic areas and can lead to conduction abnormalities.[7] Late-onset Val30Met manifests as ATTRv-CM as the disease progresses.[47] The Val30Met variant is the most common mutation in several regions around the world; the largest group of individuals carrying this TTR variant may be found in northern Sweden with a prevalence of 4%,[48,49] with a gene carrier frequency of 1:538 in northern Portugal.[50] The usual age of disease onset in Portugal, Brazil, and Japan is in the third and fourth decade of life. In Portugal and Japan, more than 90% of TTR Val30Met gene carriers are symptomatic. In endemic areas of Portugal, the penetrance is high, with approximately 80% developing disease by age 50 years.[51,52] Despite the high frequency of the Val30Met mutation in the endemic areas of Sweden (4%), there is relatively low penetrance: 11% by age 50, with older age of onset and a slower disease progression than in Portugal.[37] Female gender seems to provide some protection from myocardial involvement, at least before the onset of menopause.[53]

VAL122ILE

Val122Ile is the most common *TTR* mutation in the US, resulting from a valine-to-isoleucine substitution at position 122 of the mature protein.[27,28] It has a prevalence of approximately 3.4% among African Americans, with a low penetrance that is as yet undefined. It presents with a cardiac phenotype, usually earlier than ATTRwt, typically during or after the sixth decade of life, and this variant is associated with more neurologic symptoms than ATTRwt. The Val122Ile mutation has been found in 10% of African Americans over the age of 65 years who have severe HF.[28] The mutation ultimately leads to misfolding of free TTR monomers, with an age-dependent phenotypic penetrance. After age 70, carriers show a higher frequency of HF and increased mortality.[22,28]

THR60ALA

Thr60Ala is the most common variant in the British and Irish populations, presenting with a mixed phenotype of HF and polyneuropathy, including severe autonomic neuropathy.[31,32] Neurologic manifestations are more prevalent at an earlier stage, while cardiac involvement is usually present on diagnosis and is a major determinant of its poor prognosis. In the US, carriers of this pathogenic variant are more commonly in the Appalachian region with Irish ancestry, likely due to a common founder effect.

THR119MET

Thr119Met is a variant known to stabilize the transthyretin tetramer and has been associated with more favorable outcomes.[5] This rare coding sequence is kinetically very stable and has been reported to be associated with increased longevity in a large Danish population study.[54,55]

When it occurs in trans with the Val30Met mutation, it counteracts the destabilizing effect and delays or prevents ATTR.[55]

PROGNOSIS OF ATTR-CM

With advancements in diagnostic imaging and the emergence of novel TTR-targeted therapies, the prognosis of ATTR-CM is improving. However, for those who remain undiagnosed or cannot access novel treatments, there remains significant morbidity and mortality.

STAGING SYSTEMS

To help prognosticate at the time of diagnosis, two staging systems are widely used for patients with ATTR-CM, one from Mayo Clinic and one from the UK National Amyloidosis Centre.[14,56] It should be pointed out, however, that these were developed prior to the more widespread use of disease-modifying therapies, which are associated with notable improvements in survival.

For the Mayo risk model,[14] a cohort of ATTRwt patients were classified into three prognostic stages based on elevations of troponin T (> 0.05 ng/mL) and N-terminal proB-type natriuretic peptide (NT-proBNP) (> 3,000 pg/mL) biomarkers. Stage I included patients with no elevated biomarkers, Stage II with elevation in one biomarker, and Stage III with elevations in both biomarkers. Patients classified in Stage III had significantly worse median survival compared with those classified in Stage I. Median survival for patients classified in Stages I, II, and III was 66, 40, and 20 months, respectively.

For the UK risk model,[56] the study cohort included both wild-type and hereditary ATTR variants, including the more common Val122Ile variant. Again, three prognostic stages were defined based on renal dysfunction (eGFR threshold of < 45 mL/min/1.73 m^2) and elevations in NT-proBNP (> 3,000 pg/mL). Stage I included patients with no elevation in NT-proBNP and eGFR above or equal to the threshold, Stage III with elevation in NT-proBNP and eGFR below the threshold, and Stage II included the remainder of the cohort (either elevated NT-proBNP or low eGFR alone). Outcomes were significantly worse with higher stages. Median survival for patients classified in Stage I, II, and III was 69.2, 46.7, and 24.1 months, respectively. This finding remained significant even after controlling for different genotypes and was further validated in a separate cohort of ATTR-CM patients.

More recently, a group from Columbia University evaluated the additive prognostic value of diuretic dose and New York Heart Association (NYHA) functional class to these preexisting risk staging systems.[57] Daily diuretic dosing was categorized into furosemide equivalents and assigned to a point system, with 0 points for 0 mg/kg, 1 point for > 0 to 0.5 mg/kg, 2 points for > 0.5 to 1 mg/kg, and 3 points for > 1 mg/kg. A similar point system was used for NYHA functional class with 1 point per class ranging from 1 to 4 points. The addition of these variables significantly improved the accuracy of the preexisting risk staging systems, increasing the area under the curve for the Mayo risk model from 0.693 to 0.798 and the UK risk model from 0.711 to 0.813 for all-cause mortality.

It should be noted that while these biomarkers tend to be readily available and should be considered during the initial evaluation for all patients with ATTR-CM, analogous blood tests—including high-sensitivity troponin assays and B-type natriuretic peptide (BNP)—circulate at different concentrations in plasma. A separate biologically active hormone from NT-proBNP, BNP has a shorter half-life and can be affected by use of the angiotensin receptor-neprilysin inhibitor (ARNI) class of HF therapeutics.[58] As such, high-sensitivity troponin and BNP concentrations are not interchangeable biomarkers for the previously described staging systems.

HIGH RISK CLINICAL FEATURES

Clinical features in patients with ATTR-CM, including functional status, certain comorbid conditions, and specific genotypes, have been independently associated with increased mortality. Worsening survival among those with ATTRwt-CM has been observed with declining NYHA functional classes.[59] Additionally, NYHA functional class III or IV was identified as an independent risk factor for adverse cardiovascular outcomes that include the development of conduction disease, HF hospitalization, and stroke.[60,61] Results from the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) indicated diminished benefit from the TTR stabilizing agent, tafamidis, in patients with NYHA functional class III compared to those with NYHA class I or II disease, highlighting the need for early detection of ATTR-CM.[62]

Atrial fibrillation is more common in ATTRwt compared with ATTRv and is present in up to 70% of ATTRwt patients.[63] The presence of atrial fibrillation, atrial flutter, or atrioventricular block is associated with worse prognosis. Although not independently associated with worse mortality compared to those with sinus rhythm, ATTR-CM patients with atrial fibrillation were more likely to have severe HF symptoms (NYHA class III or IV) and a higher frequency of renal dysfunction.[64,65] Furthermore, ATTR-CM patients are at increased risk for thromboembolism,[66] with one study examining cardioversion outcomes for atrial arrhythmias, noting a significantly high procedural cancellation rate mainly due to the presence of intracardiac thrombus (up to 30%) despite adequate anticoagulation.[67]

Another study of patients with ATTR-CM and atrial fibrillation noted no association between CHA2DS2-VASc score and the presence of left atrial appendage thrombus.[68]

Conduction system disease often develops in patients with ATTR-CM, and requirement of a pacemaker has been associated with worse survival.[59] In a recent study examining ATTR-CM patients with implantable cardiac devices, those with a higher RV pacing burden (> 40%) experienced worsening HF, left ventricular ejection fraction (LVEF), and mitral regurgitation severity.[69] In contrast, those with biventricular pacing noted improvements in LVEF, NYHA class, and severity of mitral regurgitation. These findings suggest that biventricular pacing should be used in patients with ATTR-CM and an indication for pacing.[70] Ventricular arrhythmias are common in ATTR-CM, most commonly nonsustained ventricular tachycardia (up to 74%). However, placement of an implantable cardioverter defibrillator (ICD) for primary or secondary prevention has not been shown to improve survival.[71] Currently, ICD implantation is of unclear benefit in this population and will need prospective studies to determine their utility as medical therapies for ATTR-CM that may improve survival and alter disease course.

Finally, specific genotypes have been identified as carrying a worse prognosis compared with other familial variants and ATTRwt. In a large ATTR-CM cohort, patients with the Val122Ile variant had significantly worse median survival compared to those with non-Val122Ile variants or wild-type disease.[72]

MORBIDITY

While not associated with survival, neuropathic involvement and functional decline in patients with ATTR-CM can add significant morbidity. This is best illustrated by studies of TTR-targeted therapies and their respective improvements in neuropathic impairment scores, functional assessments, and quality of life questionnaires. The early studies on the clinical applications of tafamidis indicated its ability to stabilize the TTR tetramer and delay peripheral neurologic impairment.[8,73] Furthermore, results from the ATTR-ACT trial noted significant improvement in several key secondary end points, including distance walked during the 6-minute walk test and KCCQ-OS score, a measure of quality of life, with differences first observed at 6 months.[62] Results from the APOLLO study—a phase 3 trial for patients with familial amyloid polyneuropathy randomized to placebo versus patisiran, a small-interfering RNA-based drug targeting hepatic synthesis of TTR—noted significant improvements in neuropathy impairment scores, 10-meter walk test, and quality of life.[74] Treatment with another TTR "silencer," inotersen, led to similar outcomes, although inotersen use was complicated by serious adverse events with glomerulonephritis (3%) and severe thrombocytopenia (3%) in this trial.[75] Both patisiran and inotersen are approved by the US Food and Drug Administration for TTR-FAP but not indicated for ATTRwt or ATTRv-CM without neuropathy. The CARDIO-TTRansform trial is currently randomizing participants with ATTR-CM to receive placebo versus eplontersen, a ligand-conjugated investigational antisense medicine designed to reduce the production of transthyretin. The HELIOS-B study is a phase 3 trial of vutrisiran, an investigational therapeutic for patients with ATTR-CM similarly designed to reduce production of transthyretin with a longer acting effect.

In summary, long-term prognostic data are limited in the era of TTR-targeted therapeutics for patients with ATTR-CM. Current staging systems were published prior to the development and more widespread use of these novel agents. As such, studies indicate that in patients with ATTR-CM, those receiving treatment have significantly improved morbidity and mortality, especially if diagnosed at an early stage of disease.

METHODS

Two online databases were explored, Google Scholar and PubMed, to retrieve relevant articles and published studies, and different keywords and search terms were used to find those most relevant. These keywords were "amyloidosis," "transthyretin amyloidosis," "epidemiology of ATTR amyloidosis," "genetics of ATTR amyloidosis," "prognosis of ATTR amyloidosis," "TTR variants," and "ATTR amyloidosis AND treatments."

Exclusion and inclusion criteria were applied to the complete contents of searched articles to identify the most relevant studies. Only randomized controlled trials, meta-analyses, observational studies with controls, case series, review articles, and reports were included. Cross references of retrieved articles were also explored to find the relevant articles. Articles from non-peer review journals, editorials, conference papers, abstracts, and letters were excluded.

CONCLUSION

Our recognition of the epidemiology of ATTR-CM, a disease that was once considered rare, is significantly changing due to increased awareness among healthcare providers and broader use of cardiac scintigraphy. There is considerable heterogeneity in the clinical presentation, and phenotypic heterogeneity is dependent on both genetic and environmental factors. Early diagnoses, recognition of the early stages of cardiac infiltration, and initiation of treatment are essential to optimize long-term prognosis.

KEY POINTS

- Phenotypic heterogeneity is linked to specific pathogenic variants in transthyretin, geography, and type of disease (endemic versus nonendemic).
- Early diagnosis is essential for effective treatment and favorable prognosis.
- Patients receiving treatment for transthyretin amyloid cardiomyopathy have significantly improved morbidity and mortality compared with historical data on patients without disease-modifying therapies.

COMPETING INTERESTS

Dr. Judge is a consultant for ADRx Pharma, Cytokinetics, Pfizer, and Tenaya Therapeutics, and the Medical University of South Carolina receives funding for ATTR clinical trials from Eidos, Ionis, and Pfizer. No other disclosures were reported.

AUTHOR CONTRIBUTIONS

Drs. Griffin and Judge contributed equally to this manuscript.

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