REVIEW

Unmasking the Hidden Culprit: Advances in Diagnosis and Treatment of Transthyretin Amyloid Cardiomyopathy

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Abstract. Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized but historically underdiagnosed cause of heart failure, particularly in elderly populations. ATTR-CM results from extracellular deposition of misfolded transthyretin protein, which exists in either a hereditary (ATTRv) or wild-type (ATTRwt) form. Alongside light-chain (AL) amyloidosis, it constitutes an important cause of heart failure. The disease often presents as restrictive cardiomyopathy with preserved ejection fraction, left ventricular hypertrophy, arrhythmias, and conduction disturbances, frequently accompanied by systemic features such as bilateral carpal tunnel syndrome or autonomic dysfunction. Electrocardiography, echocardiography, and cardiac magnetic resonance imaging are the main diagnostic tools. However, medical advances—particularly in cardiac imaging and bone scintigraphy—have facilitated earlier, non-invasive detection and differentiation between ATTR and AL amyloidosis, which is critical given their divergent therapeutic strategies. Tafamidis, a transthyretin stabilizer, is the first disease-modifying treatment shown to reduce mortality and hospitalizations in early-stage ATTR-CM. Other emerging therapies, including TTR gene silencers and stabilizers like acoramidis, are under investigation. Standard heart failure therapies are often poorly tolerated, and careful symptom management remains essential. Early diagnosis, accurate subtype identification, and timely intervention are vital for improving outcomes in patients with ATTR-CM.

Keywords: *cardiac amyloidosis, transthiretin, wild type*

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INTRODUCTION

Amyloidosis refers to the extracellular accumulation of amyloid fibrils in otherwise normal organs. The two most frequently involved proteins in cardiac amyloidosis (CA) are transthyretin (TTR-CA) and immunoglobulin light chains (AL-CA). Senile systemic amyloidosis (SSA), also known as wild-type ATTR (ATTRwt), is the most common form of ATTR amyloidosis. It typically presents after the seventh decade of life, with increasing prevalence with aging and a strong male predominance, with a male-to-female ratio between 25:1 and 50:1 — in contrast to hereditary ATTR amyloidosis, which shows an approximately equal distribution between sexes [1,2].

Additionally, prevalence is higher in developed countries where there is access to emerging diagnostic tools, including cardiovascular magnetic resonance imaging and technetium-labeled scintigraphy[3].

TTR is not the only protein capable of forming amyloid deposits in the heart. Another major form of cardiac amyloidosis involves monoclonal immunoglobulin light chains, known as AL cardiac amyloidosis (AL-CM). In this condition, a clonal

population of plasma cells infiltrates the bone marrow and secretes monoclonal light chains that can deposit in various tissues, including the heart in roughly half of the cases. AL amyloidosis is a rare hematologic disorder with systemic manifestations and an incidence of approximately 10–12 cases per million people annually. Although both AL-CM and ATTR-CM may involve multiple organ systems, it is the extent of cardiac involvement that most critically influences the patient's prognosis. Despite being a systemic disease, the heart is generally the only clinically involved organ.

PATHOPHYSIOLOGY

In transthyretin amyloidosis (ATTR) the amyloid fibrils (A) originate from transthyretin (TTR), a tetrameric transport protein primarily produced in the liver, as well as in the choroid plexus and retinal pigment epithelial cells. Under certain conditions, TTR can become unstable, misfold, and accumulate as insoluble fibrils in the extracellular space of various tissues and organs. Hereditary transthyretin amyloidosis is an autosomal dominant disorder caused by over 120 mutations in the TTR gene, located on chromosome 18. When this deposition occurs in the heart, it leads to cardiac amyloidosis, which frequently manifests as restrictive cardiomyopathy [3,4]. Wild-type ATTR-CM is typically diagnosed at 60 to 65 years of age, although its prevalence increases with age, and it affects predominantly males [5].

Amyloid deposition in the heart can infiltrate any cardiovascular structure. Myocardial and valvular infiltration is common and often serves as a "red flag" raising suspicion of cardiac amyloidosis. Infiltration of the left ventricular myocardium by amyloid typically progresses from the base toward the apex and leads to increased thickness and stiffness of the biventricular walls, ultimately resulting in a restrictive hypertrophic cardiomyopathy, with severe impairment of diastolic function and longitudinal systolic function of the left ventricle. The most common type of heart failure associated with cardiac amyloidosis is diastolic heart failure with preserved left ventricular ejection fraction, although nearly one-third of patients present with reduced ejection fraction [6,7].

CLINICAL PRESENTATION AND DIAGNOSIS

The prevalence of transthyretin amyloid cardiomyopathy increased over the past decade. This shift is primarily attributed to advancements in non-invasive cardiac imaging and diagnostic methods. However, the diagnosis of cardiac amyloidosis is

often delayed, which leads to postponement in initiating specific treatment and a poor prognosis for these patients—the average survival after diagnosis being between 2 and 3.5 years. Suspicion of cardiac amyloidosis arises when left ventricular wall thickening greater than 12 mm is observed in association with heart failure in an elderly patient (over 65 years in men, over 70 in women) [1]. Clinically, it often presents with cardiac arrhythmias, such as atrial fibrillation. In the presence of left ventricular hypertrophy, the probability of diagnosis increases in the context of alarm signs related to cardiac infiltration, such as heart failure with preserved ejection fraction, especially when poorly responsive to standard treatment, severe aortic stenosis requiring replacement, atrioventricular conduction abnormalities, infiltration of the nervous system manifesting as sensory disturbances, autonomic dysfunction such as diarrhea or constipation, hypotension or normal blood pressure (particularly in patients previously known to be hypertensive), erectile dysfunction, peripheral polyneuropathy, and lumbar canal stenosis. Renal involvement may be indicated by proteinuria, while connective tissue infiltration may present with skin lesions, rupture of the biceps tendon (up to 33%), or bilateral carpal tunnel syndrome (46–49% coexisting with cardiac amyloidosis). Less common clinical signs include ocular manifestations such as glaucoma or vitreous opacities [2,5].

From a paraclinical perspective, diagnostic orientation arises from the discordance between the echocardiographically visible thickness of the left ventricular wall and the low amplitude of the QRS complex on ECG. However, low voltage identified on ECG is more frequently seen in AL amyloidosis than in ATTR (60% versus 20%). ECG findings also include pseudoinfarction patterns (up to 70% of cases), as well as other rhythm or conduction disturbances.

Echocardiographic red flags include a restrictive cardiomyopathy pattern with concentric hypertrophy and left ventricular wall thickness of at least 12 mm, atrial dilation, longitudinal systolic dysfunction with reduced longitudinal strain from base to apex with characteristic apical sparing, thickened cardiac valves, and a “sparkling” appearance of the myocardium [8-11].On cardiac MRI, a pathognomonic pattern of diffuse subendocardial gadolinium distribution not following a coronary territory may be observed. Transmural late gadolinium enhancement with unfavorable prognosis has also been described. Cardiac MRI can also reveal an estimated extracellular volume of at least 40%. [5,10]

Differential diagnosis between AL and ATTR amyloidosis is often difficult. Hematologic consultation is necessary, including measurement of the kappa/lambda free light chain ratio or serum/urine immunofixation electrophoresis. The presence of monoclonal proteins indicates AL amyloidosis. However, incidental clonal plasma cell dyscrasia is present in up to one-quarter of patients with wild-type ATTR amyloidosis, often due to age, increasing the possibility of misdiagnosing ATTR as AL. Thus, scintigraphy plays an important role in distinguishing between the two main types of amyloidosis, with the key difference being ATTR’s specific avidity for bisphosphonates, which is less present in AL amyloidosis. Accurately assessing the level of radiotracer uptake in the heart is a crucial step in diagnosing transthyretin amyloid cardiomyopathy (ATTR-CM) through bone scintigraphy. Perugini et al. developed a straightforward visual grading system based on delayed (3-hour) planar imaging:

- Grade 0 indicates no cardiac uptake;
- Grade 1 signifies mild uptake (less than that of bone);
- Grade 2 reflects cardiac uptake equal in intensity to rib bone uptake;
- Grade 3 represents strong cardiac uptake with minimal or absent signal in the surrounding bone.

In the absence of a tissue biopsy, ATTR-CM can be confidently diagnosed when a patient exhibits a clinical profile suggestive of amyloidosis, imaging findings on echocardiography or cardiac MRI consistent with the disease, grade 2 or 3 cardiac tracer uptake on bone scintigraphy, and no evidence of monoclonal immunoglobulins in serum or urine as determined by highly sensitive assays. If the diagnosis remains unclear, a cardiac or extracardiac biopsy (rectum or subcutaneous fat are preferred sites) and histological examination with Congo red staining or apple-green birefringence under polarized light is often necessary to reach a definitive diagnosis [8].

Confirmation of ATTR amyloidosis diagnosis

ATTR amyloidosis is confirmed by at least one of the following: a positive bisphosphonate scintigraphy showing myocardial uptake of grade 2 or 3, biopsy of tissue where amyloid can be identified or genetic testing with TTR gene sequencing to determine whether the amyloidosis is hereditary or wild type.

Therapeutic options

Therapeutic management includes two main steps: symptomatic therapy and administration of specific agents depending on the type of amyloid. Supportive care also plays a key role in improving quality of life. Treating HF in these patients is complex, as many standard HF medications are either ineffective or potentially harmful. Diuretics are essential for managing congestion but must be used cautiously to avoid hypotension, especially in patients with autonomic dysfunction. Beta-blockers and calcium channel blockers are poorly tolerated, and ACE inhibitors, ARBs, and sacubitril/valsartan are generally avoided due to hypotension risk. Although traditionally contraindicated, digoxin can be used in small doses for atrial fibrillation (AF) rate control. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) showed promising results but need further study in this patient population [12]. Atrial arrhythmias, particularly AF, are common and challenging to manage due to limited drug options. Amiodarone is commonly used, and catheter ablation may be effective if performed early. Anticoagulation is often necessary even in sinus rhythm due to high thromboembolic risk, but standard scoring tools like CHA_2DS_2-VA may not be reliable indicators [13,14]. Pacemakers are frequently required due to conduction disturbances, and biventricular pacing is preferred to minimize HF progression. The role of ICDs for primary prevention of sudden cardiac death is still unclear and varies by guideline.

Supportive therapies such as valve repair and, in selected cases, advanced HF interventions like heart transplantation or left ventricular assist devices may be considered. However, extracardiac involvement and frailty are important factors that may limit transplant eligibility. In hereditary ATTR (ATTRv), combined heart-liver transplantation was once standard, but post-transplant use of disease-modifying therapies now offers an alternative.

Autologous stem cell transplantation or chemotherapy (melphalan, dexamethasone, bortezomib, immunomodulatory agents) are treatment options for patients with AL amyloidosis. Orthotopic heart transplantation is associated with a low survival rate and is difficult to perform in the context of multiple organ infiltration by amyloid or potential involvement of the transplanted heart. Advances in understanding the pathobiology of amyloid transthyretin ATTR amyloidosis have paved the way for the development of several TTR-targeted therapies for ATTR cardiomyopathy. In 2011, the European Union approved the administration of tafamidis, a transthyretin tetramer stabilizer, for patients with familial ATTR polyneuropathy [1,15]. Recent studies confirm that tafamidis reduces the risk of death and all-cause hospitalizations in

patients with ATTR amyloidosis compared to placebo. The landmark ATTR-ACT trial demonstrated that tafamidis significantly reduced mortality, hospitalizations, and functional decline. The 80 mg dose showed superior long-term survival benefits. Tafamidis does not reverse existing amyloid deposits but slows disease progression. It is indicated for NYHA class I–III patients, especially earlier stages. Treatment eligibility may depend on functional status, survival expectancy, frailty, and renal function. Accessibility and high cost remain significant barriers globally.

Other Stabilizers:

- *Acoramidis (AG10)* was recently approved by the US Food and Drug Administration (FDA) and shows promising results in increasing TTR levels [16,20].
- In the phase 3 HELIOS-B trial, the TTR silencer *vutrisiran* improved cardiovascular outcomes, including survival, function, and quality of life, both in the overall population and in the monotherapy group that was not on tafamidis at baseline.
- *Diflunisal*, a nonsteroidal anti-inflammatory drug, also stabilizes TTR. It may benefit cardiac structure and survival but carries risks like GI bleeding and renal issues and is not yet approved for ATTR [17].

Patisiran, an IV small interfering RNA (siRNA), reduces production of both wild-type and mutant TTR in the liver. Approved for ATTRv with polyneuropathy, it showed efficacy in improving neurological symptoms in the APOLLO trial [18].

Prognosis and Disease Monitoring

N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (cTnT-HS) serve as key diagnostic and prognostic biomarkers in assessing the extent of cardiac involvement in patients with transthyretin amyloid cardiomyopathy (ATTR-CM), and they are integral components of disease staging systems. Elevated levels of these markers correlate with more advanced cardiac impairment and a worse prognosis. Notably, NT-proBNP levels are often disproportionately elevated relative to the severity of heart failure symptoms in all forms of cardiac amyloidosis, which—along with increased cTnT-HS—acts as a clinical 'red flag' for the disease [19]. Regardless of the diagnostic and therapeutic methods listed above, the prognosis of cardiac amyloidosis remains very poor, resulting in death in about six months after the onset of congestive heart failure. Only 5% of the patients with primary amyloidosis survive beyond 10 years, making this a critically fatal condition that underscores the urgent need for further research into earlier diagnosis, more effective treatments, and potential curative therapies.

CONCLUSIONS

ATTR-CM has gained increased recognition as a significant contributor to heart failure, particularly among older adults. This growing awareness is largely due to improvements in diagnostic imaging, such as cardiac MRI and technetium-labeled scintigraphy, which have enhanced detection rates of both wild-type and hereditary ATTR. Despite these advancements, ATTR-CM continues to be underdiagnosed due to its variable and often subtle clinical features. Early recognition is essential, especially in patients over 65 who present with heart failure with preserved ejection fraction, unexplained left ventricular hypertrophy, conduction system disease, or associated systemic signs such as bilateral carpal tunnel syndrome, lumbar stenosis, or signs of autonomic dysfunction. Differentiating ATTR from AL amyloidosis is critical, as each requires a different treatment approach. Bone scintigraphy, in

combination with serum and urine testing for monoclonal proteins, now enables a non-invasive diagnosis of ATTR-CM in most patients, reducing the reliance on invasive biopsies. Treatment has advanced significantly recently. Tafamidis, the first approved disease-modifying therapy, stabilizes transthyretin and has been shown to reduce mortality and hospitalization in patients with early-stage ATTR-CM. Other investigational agents, such as acoramidis and gene-silencing therapies like patisiran, offer additional therapeutic promise. While supportive care remains important, especially diuretic therapy for volume management, conventional heart failure medications are often poorly tolerated and require careful adjustment. Management of arrhythmias and conduction disturbances is a common challenge and may necessitate pacemaker implantation or rhythm control strategies.

In summary, ATTR-CM is an increasingly recognized cause of heart failure in the elderly, and early identification is key to improving prognosis. With the availability of advanced diagnostic tools and evolving therapeutic options, clinicians are now better equipped to diagnose and manage this once-overlooked disease. Continued research and improved access to therapies will be essential to further enhance care for patients with this complex condition.

Author Contributions

M.M.P. and A.M.M. conducted the research, selected the relevant articles, and drafted the initial version of the manuscript. C.C.D. revised and refined the draft, contributing additional content to strengthen and finalize the review. M.M.P. originated the concept, designed the review structure, and supervised both the editorial process and the preparation of the final manuscript. All authors contributed equally to data interpretation, final editing, and approved the final version.

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