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Diagnosing and managing transthyretin amyloid cardiomyopathy
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Abbreviations used in this review:

AAN = Australian Amyloidosis Network;
ACE = angiotensin-converting enzyme; **AL** = amyloid light chain;
ARB = angiotensin receptor blocker;
ATTR-CM = transthyretin amyloid cardiomyopathy;
ATTRv-CM = hereditary ATTR-CM; **ATTRwt-CM** = wild-type ATTR-CM;
CHADS2 VaSc = congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category;
DPD = 3,3-diphosphono-1,2-propanodicarboxylic acid;
EGCG = epigallocatechin gallate; **HF** = heart failure;
HFpEF = heart failure with preserved ejection fraction; **LV** = left ventricular;
MGUS = monoclonal gammopathy of undetermined significance;
NYHA = New York Heart Association; **PYP** = pyrophosphate;
RNA = ribonucleic acid;
SPECT = single photon emission computed tomography; **Tc** = technetium;
TTR = transthyretin; **TUDCA** = tauroursodeoxycholic acid.

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This educational review provides an overview of the clinical management of transthyretin amyloid cardiomyopathy, including its diagnosis and management. This publication was sponsored by Pfizer Australia Pty Ltd.

Introduction

Transthyretin (TTR), or prealbumin, is a thyroxine and retinol (vitamin A) transport protein.[1] Although the liver is principally responsible for generating circulating TTR, it is also produced by the choroid plexus and retinal pigmented epithelium.[1] Transthyretin amyloid cardiomyopathy (ATTR-CM) is a chronic progressive disease caused by the accumulation of misfolded TTR amyloid protein that deposits in the heart.[2,3] The amyloid deposits accumulate in the extracellular 'interstitial' space of the myocardium, leading to increased left ventricular (LV) wall thickness, with a consequent stiffening of the heart muscle, impairing its ability to relax and fill adequately to pump blood efficiently.[4] This results most commonly in heart failure with preserved ejection fraction (HFpEF), arrhythmias (irregular heart rhythms), conduction abnormalities, and low flow low gradient aortic stenosis.[4]

There are two main forms of ATTR-CM:[2,3,5]

- **Wild-type ATTR-CM (ATTRwt-CM)**: In this form, misfolded normal (wild-type) protein makes up the amyloid deposits.[1] ATTRwt-CM often typically affects older individuals.[2] It is the most common form of cardiac amyloidosis worldwide.[2]
- **Hereditary ATTR-CM (ATTRv-CM)**: This form of ATTR-CM is caused by genetic mutations in the *TTR* gene, producing abnormal TTR protein.[1] ATTRv-CM can be inherited in an autosomal dominant manner.[1]

The estimated prevalence of systemic amyloidosis is 12 cases per million persons per year.[5] However, this does not account for ATTR-CM, which has historically been underdiagnosed.[3,5] Poor disease awareness contributes to misdiagnosis and diagnostic delays, negatively impacting treatment outcomes.[1,6–8] One study reported a median treatment delay of 92.2 months for ATTRwt-CM.[9] The mental and physical burden of untreated ATTR-CM felt by people with ATTR-CM and their caregivers worsens with the progression of disease severity.[8] On average, patients with ATTR-CM have an approximate survival of 3 to 5 years from diagnosis, with the median survival in ATTRwt-CM ranging from 43–67 months from diagnosis and 73 months from symptom onset.[10]

Signs and symptoms

Heart failure (HF) is the most common presentation of ATTR-CM, and LV function is typically preserved, though in advanced stages progresses to HF with reduced ejection fraction.[10] **Table 1** outlines the additional cardiac and extracardiac manifestations listed in the American College of Cardiology Expert Consensus.[1] The Australian and European guidelines also recognise these 'red flag' symptoms.[2,5] ATTR-CM should be suspected in men ≥65 years or women ≥70 years who have an unexplained case of increased LV wall thickness, presenting with either HF or 'red flag' signs/symptoms (**Table 1**).[2,5,10] People with ATTR-CM also often report peripheral neuropathy symptoms and problems walking, and many find it challenging to participate in social, leisure, or household activities.[8]

Table 1. 'Red flag' signs and symptoms of ATTR-CM.[1]

Cardiac manifestations

Clinical	Electrical	Imaging	Laboratories
• Fatigue • HF symptoms • Family history of HF	• Conduction system disease with pacemaker • Arrhythmias, the commonest being atrial fibrillation • Pseudoinfarct pattern on ECG • Discordant QRS voltage for the degree of increased LV wall thickness on imaging	• Increased LV wall thickness • Grade 2 or worse diastolic function • Abnormal global longitudinal strain despite preserved ejection fraction, with apical sparing pattern • Diffuse subendocardial or transmural late gadolinium enhancement with poor 'nulling' on CMR imaging. • High native T1 time and increased extracellular volume fraction	• Persistent low-level troponin elevation • Elevated B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide

Extracardiac manifestations

Musculoskeletal	Neurologic	
• Bilateral carpal tunnel syndrome • Lumbar/cervical spinal stenosis • Spontaneous biceps tendon rupture	• Peripheral neuropathy • Family history of neuropathy • Autonomic dysfunction • Orthostatic hypotension	• Gastroparesis • Urinary incontinence • Erectile dysfunction

CMR = cardiac magnetic resonance; **ECG** = echocardiogram; **HF** = heart failure; **LV** = left ventricular.

Testing and diagnosis

The diagnostic algorithm proposed by the European Society of Cardiology in their 2023 guidelines [2] is summarised in **Figure 1**. There may be variations in local practice.

The diagnostic process begins with clinical history/examination, electrocardiogram, and transthoracic echocardiogram.[1,2,5] Due to considerable overlap in clinical, imaging, and electrocardiographic features, cardiac manifestations alone are insufficient to distinguish ATTR-CM from other forms of amyloidosis conclusively.[1] However, musculoskeletal manifestations, such as spontaneous biceps tendon rupture, carpal tunnel syndrome, and spinal stenosis, are unique to ATTR-CM.[1] The non-invasive approaches outlined below can be used to diagnose ATTR-CM definitively.[1,2,5]

Bone scintigraphy

Bone scintigraphy is a highly sensitive imaging technique used to evaluate the distribution of active bone formation in the body.[10] Scintigraphy with technetium (Tc)-labelled bisphosphonates localises to TTR cardiac amyloid deposits, although the molecular basis for this remains unknown.[11] ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), ^{99m}Tc-labeled pyrophosphate (PYP), and ^{99m}Tc-labeled hydroxymethylene diphosphonate (HMDP) have all shown high sensitivity and specificity for imaging cardiac TTR amyloid.[11] A recent study showed an increase in the prevalence of 99mTc-DPD over time with incremental referrals under the indication of cardiomyopathy workup.[12] Myocardial uptake of DPD and PYP is highly specific (up to ~99%) for diagnosing cardiac amyloidosis, while the specificity was 86% in a large international study with more than 1,200 individuals.[11] However, it is a diagnostic pitfall to interpret a cardiac scintigraphy scan without a concomitant monoclonal gammopathy screen.[1] Moreover, in addition to planar imaging, single photon emission computed tomography (SPECT) imaging should be obtained to improve the accuracy of myocardial uptake.[13] A scintigraphy scan alone is neither appropriate nor valid for distinguishing ATTR-CM from light chain (AL) amyloidosis.[1]

Ruling out AL amyloidosis

AL amyloidosis is the other main type of cardiac amyloidosis that arises from the overproduction and misfolding of monoclonal immunoglobulin light chains.[1–3] For patients with AL amyloidosis, untreated survival can be less than six months, making the timely exclusion of this disease a clinical priority.[10] This can be accomplished through performing a monoclonal gammopathy screen with serum, urine protein electrophoresis, immunofixation electrophoresis, and quantifying serum-free light chains.[1,2,510] The combined use of these tests has a high sensitivity of 99% for identifying AL amyloidosis.[10] If no monoclonal protein or abnormal serum-free light chain ratio is detected, bone scintigraphy (planar and SPECT scanning) becomes ~100% specific for diagnosing ATTR-CM.[10]

Biopsy

Traditionally, amyloidosis diagnosis relied on Congo red-stained tissue biopsies, which displayed characteristic green birefringence under polarised light.[2,10] While endomyocardial biopsy was the historical gold standard for cardiac amyloidosis, its invasiveness and associated risks have limited its use.[5,10] Extracardiac biopsies, like abdominal fat pads, may yield a diagnosis, but their accuracy is notably lower in ATTR-CM due to a higher false-negative rate.[1,10]

However, histological confirmation remains necessary in cases where bone scintigraphy and monoclonal gammopathy tests suggest possible AL amyloidosis.[1,10] This confirmation involves immunohistochemistry or mass spectrometry to identify and classify amyloid deposits.[1,10] Tandem mass spectrometry is recommended as the preferred method for amyloid subtyping, as immunohistochemistry findings can be subtle and can be prone to misinterpretation in the absence of extensive expertise.[1,5,10]

Genetic testing

Clinical and histological methods and bone scintigraphy cannot be used to reliably differentiate between ATTRv-CM and ATTRwt-CM.[2,10] Thus, *TTR* gene sequencing should be performed as the definitive diagnostic approach in all confirmed cases of ATTR-CM, regardless of the specific form.[1,2,5,10]

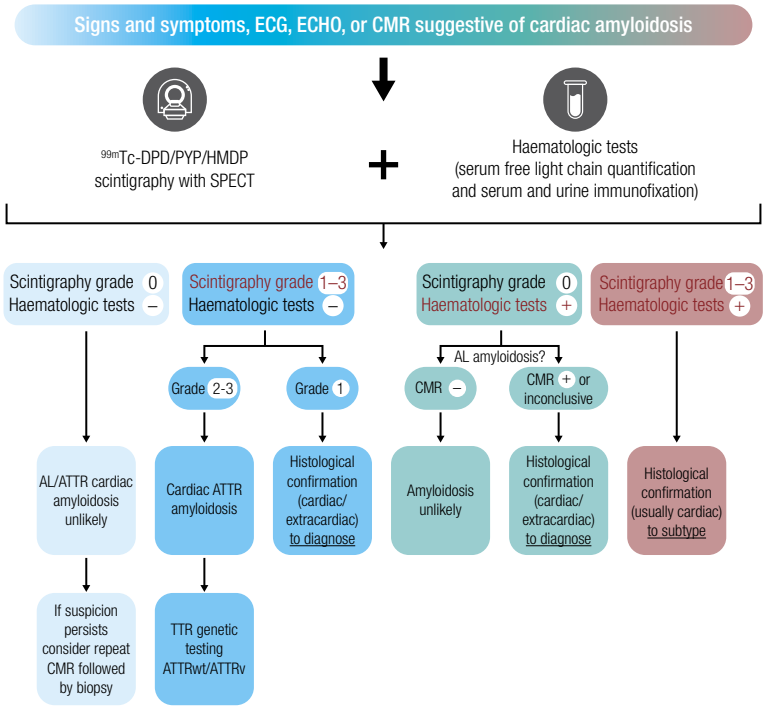

Figure 1. Diagnostic algorithm for cardiac amyloidosis proposed by the European Society of Cardiology.[1] Variations may be present in local practice.
AL = amyloid light chain; **ATTR** = transthyretin amyloidosis; **ATTRv** = variant transthyretin amyloidosis; **ATTRwt** = wild-type transthyretin amyloidosis; **CMR** = cardiac magnetic resonance; **DPD** = 3,3-diphosphono-1,2-propanodicarboxylic acid; **ECG** = electrocardiogram; **ECHO** = echocardiogram; **HMDP** = hydroxymethylene diphosphonate; **PYP** = pyrophosphate; **SPECT** = single photon emission computed tomography; **TTR** = transthyretin.

Treating ATTR-CM

Early diagnosis and intervention are crucial in managing the condition and improving the patient's quality of life.[3] However, medical management of ATTR-CM remains a significant unmet need, and historically, treatments for ATTR-CM have been limited.[10] Implementing a multidisciplinary approach to management, which integrates relevant medical specialties, allied health professionals, and specialised nursing staff, is highly recommended.[1,5] Current treatment of ATTR-CM comprises disease-modifying therapies, including TTR synthesis suppressors, TTR stabilisers and fibril disruptors, and supportive management of the cardiac and neurological disease.[2,5]

Novel TTR synthesis suppressors

Inotersen, which uses antisense oligonucleotide technology, and patisiran, which relies on mRNA inference, are innovative therapies designed to suppress the synthesis of TTR.[5] These agents can substantially reduce peripheral blood TTR levels by 70–90%.[5] Clinical studies have demonstrated that patisiran and antisense oligonucleotide technologies can stabilise peripheral neuropathy and improve the overall quality of life in patients with ATTRv-CM, compared with the placebo.[5] Ongoing clinical trials are investigating the potential benefits of these agents in the context of ATTRwt-CM.[5]

Tafamidis (VYNDAMAX®)

Tafamidis (VYNDAMAX®) is an orally administered selective TTR stabiliser.[14] It binds to two thyroxine binding sites on the native tetrameric structure of TTR, inhibiting its dissociation into amyloidogenic monomers.[14] Tafamidis will soon be available in Australia to treat ATTRwt-CM and ATTRv-CM in adults in NYHA classes 1 and 2.[14] It is available in the form of soft capsules.[14] The recommended daily dosage is 61 mg, equivalent to one capsule.[14] In a phase 3 randomised controlled trial, tafamidis demonstrated significant benefits compared with the placebo.[15] Tafamidis was associated with reductions in all-cause mortality and hospitalisations related to cardiovascular issues.[15] Furthermore, it mitigated the decline in functional capacity and the overall quality of life in treated individuals.[15] It is well-tolerated by patients.[5] However, in a placebo-controlled study of ATTRv patients with polyneuropathy, although tafamidis demonstrated a reduction in neurological deterioration, the study failed its primary endpoints.[16,17] Please refer to the Product Information for comprehensive prescribing information. Please note that tafamidis is not indicated for ATTR amyloidosis polyneuropathy.

Diflunisal

Diflunisal is an oral, nonsteroidal anti-inflammatory drug that is a nonselective TTR stabiliser.[5] A retrospective study suggests that diflunisal is associated with reduced death and orthotopic heart transplants, similar to tafamidis.[18] In a randomised trial of ATTRv amyloidosis, diflunisal slowed the deterioration of neuropathy and quality of life.[19] Care must be taken to monitor renal function (checked every six months) after this stabiliser is commenced, and a proton pump inhibitor to prevent gastric ulceration is also recommended.[5,20] The recommended dose is 250 mg bi-daily, equivalent to half a tablet morning and night, taken after food.[20] It should be noted that diflunisal is available in Australia through the Special Access Scheme and has been accessible through specialist amyloidosis centres.

Liver transplantation

This is no longer recommended for patients with ATTR-CM.[5]

Expert comments

Prof. Liza Thomas

ATTR amyloidosis is an underdiagnosed cause of HFpEF. However, increased awareness of this condition and non-invasive methods for diagnosis (i.e., bone scintigraphy) have led to an increased recognition of ATTR amyloidosis. Treatment was previously limited to supportive therapy and fibril disruptors (e.g., green tea extract, TUDCA, and doxycycline), and the non-selective TTR stabiliser, diflunisal, which is available through the Special Access Scheme in Australia. However, now, an increasing range of specific therapeutic options are becoming available for ATTR-CM. Notable among these is the specific TTR stabiliser, tafamidis, which will soon be available for patients with ATTR-CM, and patisaran which reduces hepatic ATTR synthesis by RNA interference.

Supportive therapy in ATTR amyloidosis is also important as standard heart failure measures are not employed. Neurohormonal agents (i.e., ACE inhibitors and ARBs) are poorly tolerated. Beta-blockers need to be used carefully as they may precipitate profound bradycardia or other conduction abnormalities. Calcium channel blockers are avoided and digoxin used judiciously as they may have increased concentration by binding to amyloid fibrils. Another important aspect is anticoagulation in atrial fibrillation which must be commenced irrespective of the CHADS2 VaSc score due to amyloid infiltration of the atria as well.

Dr. Hasib Sidiqi

ATTR-CM is increasingly becoming recognised as a significant cause of heart failure with preserved ejection fraction. One of the critical steps in the management of patients with amyloidosis is accurate subtyping. Traditionally, this has relied on either immunohistochemistry or mass spectrometry on tissue samples demonstrating Congo red avid amyloid deposits. Bone scintigraphy has a high sensitivity and specificity for diagnosing ATTR-CM in patients who do not have a monoclonal gammopathy, obviating the need for tissue biopsy. However, patients with monoclonal gammopathy of undetermined significance (MGUS), AL amyloidosis and ATTR-CM have a shared demographic of peak incidence, with some studies showing over 20% of ATTR-CM patients having a coexisting MGUS.[21,22] In these patients' tissue biopsy with definitive subtyping using immunohistochemistry or mass spectrometry should be considered. Treatment options for ATTR-CM have traditionally been limited. The addition of tafamidis, an effective agent in treating ATTR-CM, further highlights the importance of accurate diagnosis and subtyping.

Take-home messages

- ATTR-CM carries a substantial burden due to protracted time to diagnoses or misdiagnoses that delay the implementation of appropriate management strategies.
- Given the low levels of disease awareness coupled with the heterogeneity of clinical manifestations, healthcare providers must be educated on recognising patients with ATTR-CM.
- Given the diagnostic precision of bone scintigraphy in the absence of a monoclonal gammopathy, traditional invasive diagnostic methods are now largely unnecessary to achieve a definitive diagnosis of ATTR-CM.
- Multidisciplinary collaborations are crucial to increase diagnostic yield and provide patients with ATTR-CM with the best possible care.
- Although treatments for ATTR-CM have been limited historically, patients diagnosed in a timely manner can now benefit from supportive treatments and specific treatments such as diflunisal and tafamidis.

Experts' concluding comments

Prof. Liza Thomas

ATTR-CM is a progressive and debilitating condition. Early diagnosis and accurate identification of amyloid subtypes are crucial to patient management. Typical cardiac and extra cardiac 'red flags' need to be recognised; non-invasive methods have improved diagnostic yield. There are specialist amyloidosis multidisciplinary clinics for advanced testing and therapy, open for patient referral. The increasing number of specific therapeutic options (TTR stabilisers, fibril disruptors, and suppressors of TTR synthesis) and, in the future, gene therapy for ATTRv will significantly improve patient outcomes.

Dr. Hasib Sidiqi

A multidisciplinary approach is needed in managing patients with amyloidosis. This involves coordination of care between multiple specialists and allied health professionals. The improving therapeutic landscape in ATTR-CM with the addition of tafamidis makes this multidisciplinary approach critical in the appropriate choice of therapy and management of patients. The AAN has several dedicated AAN centres around Australia, providing a multidisciplinary approach to diagnosing and managing patients with amyloidosis. Further details on the referral pathway to these centres and physician and patient resources can be found at www.aan.org.au.

A number of novel TTR silencers and stabilisers are currently undergoing clinical trials for the treatment of ATTR-CM. The therapeutic landscape is likely to change significantly over the next decade. With this, we hope to see a change in the natural history of ATTR-CM with improved survival and quality of life for patients.

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