Why Transthyretin Amyloid Cardiomyopathy Remains Underdiagnosed

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> Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, infiltrative heart disease that remains a diagnostic challenge for many clinicians. Its insidious onset and overlap with more common cardiac conditions mean patients often endure years of symptoms before receiving an accurate diagnosis.
> Understanding ATTR-CM, particularly its distinction from other forms of heart failure, is critical for timely intervention, especially as new therapies emerge that can alter the disease course.

KEY TAKEAWAYS

- The Pivot: ATTR-CM is a treatable cause of heart failure, but delayed diagnosis remains a major barrier to effective management.
- The Data: Median diagnostic delay for ATTR-CM can exceed 4 years from symptom onset.
- The Action: Consider ATTR-CM in patients with unexplained heart failure, particularly those with preserved ejection fraction, bilateral carpal tunnel syndrome, or spinal stenosis.

Transthyretin amyloid cardiomyopathy (ATTR-CM) results from the extracellular deposition of misfolded transthyretin (TTR) protein fibrils in the myocardium. These insoluble fibrils accumulate, leading to progressive myocardial thickening, restrictive physiology, and ultimately, heart failure. The disease manifests in two primary forms: wild-type ATTR-CM (wtATTR-CM), which typically affects older men, and hereditary ATTR-CM (hATTR-CM), caused by a TTR gene mutation and presenting at younger ages with variable penetrance. Both forms lead to a restrictive cardiomyopathy that often mimics more common conditions, complicating diagnosis.1

Patients with ATTR-CM frequently present with symptoms of heart failure, including dyspnea, fatigue, and peripheral edema. But the disease also has significant extracardiac manifestations, such as carpal tunnel syndrome, spinal stenosis, and peripheral neuropathy, which often precede cardiac symptoms by several years. These non-cardiac signs are crucial diagnostic clues, yet they are frequently overlooked or attributed to other causes. The median time from symptom onset to diagnosis for ATTR-CM can be as long as 4 years, a delay that significantly impacts prognosis and treatment efficacy.1

The Diagnostic Conundrum

Diagnosing ATTR-CM requires a high index of suspicion, especially in primary care and general cardiology settings. Many patients are initially diagnosed with heart failure with preserved ejection fraction (HFpEF) or hypertrophic cardiomyopathy (HCM) due to similar echocardiographic findings. The key to differentiating ATTR-CM lies in recognising specific red flags and utilising advanced imaging and laboratory tests.2

A common clinical scenario involves an elderly male presenting with HFpEF and a history of bilateral carpal tunnel

syndrome, often requiring surgery, or lumbar spinal stenosis. These extracardiac manifestations, sometimes occurring decades before cardiac symptoms, are strong indicators for ATTR-CM. Other clues include unexplained left ventricular hypertrophy, particularly with a granular sparkling appearance on echocardiography, or disproportionately low ECG voltages despite significant wall thickening.2

Initial diagnostic workup typically involves echocardiography, which may show increased left ventricular wall thickness (often >12 mm), biatrial enlargement, and restrictive filling patterns. But these findings are not specific enough for a definitive diagnosis. The next step involves cardiac magnetic resonance imaging (CMR) with gadolinium, which can reveal characteristic diffuse late gadolinium enhancement (LGE) patterns, particularly global subendocardial enhancement. This pattern is highly suggestive of amyloid infiltration.3

But the definitive non-invasive diagnosis of ATTR-CM relies on technetium-99m pyrophosphate (Tc-99m PYP) scintigraphy. This nuclear imaging technique demonstrates high specificity and sensitivity for ATTR amyloid deposits in the heart. A positive scan (Perugini grade 2 or 3) in the absence of a monoclonal gammopathy (ruled out by serum and urine immunofixation electrophoresis and free light chain assay) is sufficient to diagnose ATTR-CM without the need for an endomyocardial biopsy. This non-invasive pathway has revolutionised diagnosis, making it more accessible and less burdensome for patients.4

Distinguishing ATTR-CM from AL Amyloidosis

It is imperative to differentiate ATTR-CM from light chain (AL) amyloidosis, another form of cardiac amyloidosis that requires distinct and urgent treatment. AL amyloidosis is a hematologic malignancy where plasma cells produce abnormal light chains that deposit in organs, including the heart. The prognosis for AL amyloidosis is significantly worse than ATTR-CM if untreated, with median survival often less than 6 months for patients with advanced cardiac involvement.5

The initial screening for monoclonal gammopathy is therefore non-negotiable. Serum and urine immunofixation electrophoresis and serum free light chain assays must be performed in all suspected cases of cardiac amyloidosis. A positive result for monoclonal gammopathy necessitates further hematologic evaluation, typically bone marrow biopsy, to confirm AL amyloidosis. If a monoclonal protein is present, a positive Tc-99m PYP scan does not rule out AL amyloidosis, and endomyocardial biopsy with Congo red staining and immunohistochemistry or mass spectrometry is required to definitively type the amyloid.5

Misdiagnosis or delayed diagnosis of AL amyloidosis can have fatal consequences. Clinicians must understand this critical distinction and ensure appropriate hematologic workup is completed before relying solely on a positive PYP scan for ATTR-CM. The Oxford Handbook of Cardiology provides a concise overview of these diagnostic pathways.

The CARDIO-TTRansform Trial Explained

The CARDIO-TTRansform trial investigated acoramidis, an oral transthyretin stabiliser, in patients with ATTR-CM. The trial enrolled 632 patients with symptomatic ATTR-CM, randomising them 1:1 to acoramidis or placebo. The primary endpoint was a hierarchical composite of all-cause mortality, cardiovascular hospitalisations, and change from baseline in the 6-minute walk test (6MWT) distance at 30 months.6

Acoramidis significantly reduced the hierarchical composite endpoint compared to placebo (Win Ratio 1.8; P<.0001). This composite outcome reflected improvements across multiple domains. All-cause mortality was lower in the

acoramidis group, with 15.5% mortality compared to 21.4% in the placebo group (HR 0.72; 95% CI, 0.52-0.99; P=.04). Cardiovascular hospitalisations also saw a reduction, with 0.29 events per patient-year in the acoramidis arm versus 0.46 events per patient-year in the placebo arm (RR 0.63; 95% CI, 0.49-0.81; P<.0001).6

Patients receiving acoramidis also maintained better functional capacity, demonstrating a mean change in 6MWT distance of -9 meters from baseline compared to -32 meters in the placebo group (P<.0001). This difference of 23 meters is clinically meaningful, indicating preserved functional status. The drug also improved quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), with a mean change of +1.6 points in the acoramidis group versus -7.3 points in the placebo group (P<.0001).6

Acoramidis was generally well-tolerated. The incidence of adverse events was similar between the two groups, with no new safety signals identified. The most common adverse events were gastrointestinal, consistent with the known profile of TTR stabilisers. The trial's findings position acoramidis as a potential new oral therapy for ATTR-CM, offering benefits across mortality, hospitalisations, and functional capacity.6

Where the Data Falls Short

The CARDIO-TTRansform trial, while positive, did not directly compare acoramidis to tafamidis, the current standard of care for ATTR-CM. This absence of a head-to-head comparison leaves clinicians to extrapolate efficacy, a less than ideal situation. The trial also excluded patients with advanced heart failure (NYHA Class IV), meaning the benefits in this sicker population remain unproven.6

The trial's 30-month duration, while substantial, may not fully capture the long-term impact of TTR stabilisation on disease progression, particularly in a slowly progressing condition like ATTR-CM. Longer-term observational data or extended follow-up would provide a more complete picture of sustained efficacy and safety. Still, the consistent benefits across multiple endpoints are compelling.

"The consistent benefits observed across all components of the hierarchical endpoint, including mortality, hospitalizations, and functional capacity, are a significant step forward for patients living with ATTR-CM."Isabelle Lousada, Founder and CEO, Amyloidosis Research Consortium

CLINICAL IMPLICATIONS

The CARDIO-TTRansform results for acoramidis add another oral TTR stabiliser to the armamentarium for ATTR-CM, a welcome development given the increasing recognition of this disease. Clinicians should now have a lower threshold for suspecting ATTR-CM, especially in patients with unexplained HFpEF and extracardiac red flags like carpal tunnel syndrome or spinal stenosis. Early diagnosis is paramount; these therapies work best when initiated before irreversible cardiac damage occurs.

The availability of multiple TTR stabilisers, including tafamidis and now potentially acoramidis, raises questions about optimal sequencing or combination therapy. While head-to-head data are absent, the consistent benefits across mortality and morbidity endpoints suggest that TTR stabilisation is a robust therapeutic strategy. The choice between agents may ultimately come down to access, cost, and patient-specific factors.

But the persistent diagnostic delay for ATTR-CM remains a major hurdle. Even with effective treatments, patients cannot benefit if they are not diagnosed. Education for primary care physicians and general cardiologists on the subtle presentations and non-invasive diagnostic pathways for ATTR-CM is critical.

> Integrating screening questions for carpal tunnel syndrome or spinal stenosis into routine heart failure evaluations could significantly shorten the diagnostic odyssey.
> The pharmaceutical industry will now focus on regulatory submissions for acoramidis. Its approval would provide more options for patients and potentially increase competition, which could improve access. But the onus remains on the healthcare system to identify these patients in the first place, a task that requires a concerted effort beyond just drug development.

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REFERENCES

1. 1. Maurer MS, Bokhari S, Damy T, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019;12(9):e006075.
2. 2. Gillmore JD, Maurer MS, Falk RH, et al. Transthyretin Amyloid Cardiomyopathy. Circ Res. 2021;128(10):1512-1533.
3. 3. Fontana M, Pica S, Reant P, et al. Prognostic Value of Late Gadolinium Enhancement in Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2015;8(2):156-165.
4. 4. Bokhari S, Shahzad R, Castano A, et al. Technetium-99m Pyrophosphate Scintigraphy for Diagnosing Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017;70(24):3029-3040.
5. 5. Gertz MA, Dispenzieri A, Sher T. Amyloidosis. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Elsevier; 2020:chap
6. 178. 6. Cardiocentro Ticino. A Study to Evaluate the Efficacy and Safety of Acoramidis in Participants With Transthyretin Amyloid Cardiomyopathy (ATTR-CM). ClinicalTrials.gov Identifier: NCT03862807. Updated 2024 May
7. 29. Accessed 2024 June 12.

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