Why cardiac amyloidosis diagnoses are surging and what it means for GPs

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> Heart failure remains a pervasive clinical challenge, often presenting with a constellation of non-specific symptoms that complicate timely diagnosis. For years, a significant subset of these patients likely suffered from an insidious, often fatal, infiltrative cardiomyopathy that clinicians simply missed. That is changing now, with a notable uptick in cardiac amyloidosis diagnoses across Europe.

KEY TAKEAWAYS

- The Pivot: Advanced imaging techniques and heightened clinical suspicion are driving a significant increase in cardiac amyloidosis diagnoses.
- The Data: Prevalence estimates for ATTR-CM in heart failure with preserved ejection fraction (HFpEF) now range from 10% to 15% in some cohorts.
- The Action: GPs should consider cardiac amyloidosis in older patients with unexplained heart failure, particularly those with preserved ejection fraction, carpal tunnel syndrome, or spinal stenosis.

Cardiac amyloidosis, a restrictive cardiomyopathy caused by the extracellular deposition of misfolded proteins, has historically been considered a rare disease. Its protean manifestations, often mimicking more common cardiovascular conditions, contributed to diagnostic delays and underrecognition. Patients frequently presented with symptoms of heart failure, arrhythmias, or conduction disturbances, leading to diagnoses of idiopathic dilated cardiomyopathy or hypertensive heart disease, often without further investigation into the underlying cause. This diagnostic inertia meant many patients progressed to advanced stages of the disease before a correct diagnosis, limiting therapeutic options and worsening prognosis.

The two most prevalent forms affecting the heart are light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis. AL amyloidosis, a plasma cell dyscrasia, involves the deposition of misfolded immunoglobulin light chains. It is a rapidly progressive, systemic disease requiring urgent chemotherapy. ATTR amyloidosis stems from the misfolding of transthyretin protein, which can be hereditary (hATTR) due to a genetic mutation or wild-type (wtATTR), previously known as senile systemic amyloidosis, occurring spontaneously in older individuals. Wild-type ATTR amyloidosis is increasingly recognised as a significant cause of heart failure, particularly in the elderly population. Understanding these distinctions is paramount for guiding appropriate management, as treatments differ substantially between types.

The Diagnostic Revolution

The surge in cardiac amyloidosis diagnoses is not due to an increase in disease incidence, but rather a revolution in diagnostic capabilities and a heightened awareness among clinicians. For decades, the gold standard for diagnosis was

endomyocardial biopsy, an invasive procedure with inherent risks and limited availability. This barrier significantly hampered early and widespread detection. But the landscape shifted dramatically with the advent of non-invasive imaging techniques. Cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement (LGE) emerged as a powerful tool, demonstrating characteristic patterns of diffuse subendocardial or transmural LGE that are highly suggestive of amyloid infiltration. CMR offers detailed tissue characterisation, allowing for differentiation from other causes of ventricular hypertrophy.

But the real game-changer arrived with technetium-99m pyrophosphate (Tc-99m PYP) scintigraphy, a bone scintigraphy agent that binds specifically to transthyretin amyloid deposits in the heart. This nuclear imaging technique offers excellent sensitivity and specificity for ATTR cardiac amyloidosis, often obviating the need for biopsy in patients with a negative serum and urine monoclonal protein screen. A Perugini score of 2 or 3 on Tc-99m PYP scan, in the absence of a monoclonal gammopathy, is diagnostic of ATTR cardiac amyloidosis. This non-invasive approach has democratised diagnosis, making it accessible to a broader patient population and significantly reducing diagnostic delays. The simplicity and high diagnostic yield of PYP scans have made them a cornerstone of modern cardiac amyloidosis work-up, allowing for earlier intervention and improved patient outcomes.

But the imaging advancements alone do not fully explain the diagnostic surge. Increased clinical suspicion among cardiologists and general practitioners plays an equally vital role. Clinicians are now more attuned to the 'red flags' that should prompt investigation for cardiac amyloidosis. These include unexplained left ventricular hypertrophy, particularly in the absence of severe hypertension or aortic stenosis, and disproportionately low voltage on electrocardiogram despite ventricular thickening. Other extracardiac manifestations, such as carpal tunnel syndrome, spinal stenosis, biceps tendon rupture, and peripheral neuropathy, often precede cardiac involvement by several years. Recognising these seemingly disparate symptoms as potential harbingers of systemic amyloidosis is crucial for early detection. The Oxford Handbook of Cardiology provides a concise overview of these diagnostic pathways.

The Clinical Picture and Subtypes

Wild-type ATTR cardiac amyloidosis (wtATTR-CM) predominantly affects older men, typically over the age of 60, and is increasingly recognised as a cause of heart failure with preserved ejection fraction (HFpEF). Its prevalence in HFpEF cohorts is substantial, with some studies reporting it in 10% to 15% of patients. These patients often present with progressive dyspnoea, fatigue, and peripheral oedema. The infiltrative nature of amyloid deposits leads to stiffening of the ventricular walls, impairing diastolic filling and increasing filling pressures, even with normal systolic function. This makes wtATTR-CM a critical consideration in the differential diagnosis of HFpEF, a syndrome for which effective treatments have historically been limited.

Hereditary ATTR cardiac amyloidosis (hATTR-CM) results from one of over 130 known mutations in the TTR gene. The most common mutation, V122I, is prevalent in individuals of African or African-Caribbean descent, affecting approximately 3% to 4% of this population. This form often presents with a mixed phenotype, involving both cardiac and neurological manifestations, such as peripheral neuropathy and autonomic dysfunction. The age of onset and severity of symptoms can vary widely even within families, reflecting incomplete penetrance and variable expressivity of the genetic mutations. Genetic counselling and testing are essential for affected individuals and their at-risk relatives, allowing for early diagnosis and intervention.

AL cardiac amyloidosis, while less common than wtATTR-CM, carries a graver prognosis due to its rapid progression

and systemic nature. It can affect individuals of any age, though it is more frequent in those over 50. The cardiac involvement in AL amyloidosis is often more severe, leading to rapid deterioration of cardiac function and a median survival of less than 6 months if left untreated. Prompt diagnosis and initiation of chemotherapy are critical to halt amyloid deposition and improve outcomes. The presence of a monoclonal gammopathy, detected through serum and urine protein electrophoresis and immunofixation, is the key to distinguishing AL from ATTR amyloidosis. Bone marrow biopsy confirms the underlying plasma cell dyscrasia.

Therapeutic Advances and Future Directions

The increased diagnostic yield has coincided with, and indeed spurred, the development of disease-modifying therapies for ATTR cardiac amyloidosis. For wtATTR-CM and hATTR-CM, tafamidis, an oral transthyretin stabiliser, has demonstrated significant clinical benefits. The ATTR-ACT trial showed that tafamidis reduced all-cause mortality by 30% (HR 0.70; 95% CI, 0.51-0.96; P=.016) and cardiovascular-related hospitalisations by 32% (RR 0.68; 95% CI, 0.56-0.81; P<.001) over 30 months compared to placebo. Patients receiving tafamidis also experienced less decline in functional capacity, as measured by the 6-minute walk test, and improved quality of life. This was a landmark trial, providing the first approved therapy to alter the natural history of ATTR-CM. The drug stabilises the transthyretin tetramer, preventing its dissociation into monomers that misfold and deposit as amyloid fibrils.

For hATTR amyloidosis with polyneuropathy, RNA interference (RNAi) therapies like patisiran and inotersen, and antisense oligonucleotides like vutrisiran, have shown efficacy in reducing TTR protein production. These agents target the mRNA responsible for TTR synthesis, effectively silencing the gene and reducing the circulating levels of both wild-type and mutant TTR protein. While initially approved for polyneuropathy, these therapies also demonstrate cardiac benefits, particularly in early-stage disease. The APOLLO trial, for instance, showed that patisiran improved neurological function and quality of life, with secondary analyses suggesting favourable cardiac outcomes. These therapies represent a paradigm shift, moving beyond symptomatic management to address the root cause of the disease.

Still, challenges remain. Early diagnosis is paramount, as therapies are most effective when initiated before irreversible organ damage occurs. The average diagnostic delay for cardiac amyloidosis still ranges from 2 to 4 years from symptom onset, a period during which significant cardiac remodelling and dysfunction can occur. This highlights the ongoing need for greater awareness among primary care physicians and specialists alike. The cost of these novel therapies is also substantial, raising questions about equitable access and healthcare resource allocation across different European health systems. Furthermore, while these drugs halt disease progression, they do not reverse established amyloid deposits, underscoring the importance of early detection.

The open-label design of some early studies is an obvious caveat, but the robust data from large, randomised, placebo-controlled trials like ATTR-ACT provide strong evidence for the efficacy of TTR stabilisers. The trial was not powered to detect differences in specific genetic subtypes of hATTR-CM, and that gap matters for understanding the full spectrum of therapeutic benefit. Tafamidis was tested only in patients with ATTR-CM; whether benefits extend to other forms of amyloidosis remains unclear. The long-term effects of these therapies, particularly on cardiac remodelling and regression of amyloid burden, require further investigation through ongoing registries and post-marketing surveillance.

The field also awaits more effective therapies for AL cardiac amyloidosis, where current chemotherapy regimens, while improving outcomes, still leave significant unmet needs. The development of novel immunotherapies and amyloid-degrading agents for AL amyloidosis is an active area of research.

CLINICAL IMPLICATIONS

The rising tide of cardiac amyloidosis diagnoses presents a clear call to action for general practitioners. No longer a medical curiosity, this condition is a treatable cause of heart failure, particularly in older patients. GPs must integrate a higher index of suspicion into their routine assessments, especially for those presenting with unexplained heart failure, carpal tunnel syndrome, or spinal stenosis.

The availability of non-invasive diagnostic tools, primarily Tc-99m PYP scintigraphy, means that a definitive

> diagnosis is now within reach for many more patients. Referring appropriate cases for cardiac imaging or a cardiology consultation is no longer an academic exercise; it directly impacts patient prognosis. Early diagnosis allows for timely initiation of disease-modifying therapies like tafamidis, which demonstrably improves survival and reduces hospitalisations.
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> But the diagnostic pathway still requires careful navigation. Distinguishing AL from ATTR amyloidosis is critical, as misdiagnosis can lead to inappropriate and potentially harmful treatments. GPs should ensure that patients undergo comprehensive screening for monoclonal gammopathy before proceeding with ATTR-specific imaging. This initial work-up is a fundamental step that prevents diagnostic errors and guides subsequent management.
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> The financial implications of these advanced therapies are substantial, and health systems will need to grapple with how to ensure equitable access. For now, the focus must remain on identifying patients who stand to benefit most from early intervention. The era of cardiac amyloidosis as an untreatable, obscure disease is over; clinicians now have the tools to make a difference, provided they look for it.

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