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REVIEW

Navigating the emerging landscape of asymptomatic ATTR-CM: challenges, opportunities and the path ahead

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ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) has long been considered a rare and inexorably fatal condition. However, advances in noninvasive diagnosis, disease awareness, and available treatments have enabled diagnosis in asymptomatic stages, before development of clinical heart failure (HF). The emerging entity of asymptomatic ATTR-CM presents both challenges and new opportunities for improving patient care. Data remain limited, as asymptomatic patients have been excluded from clinical trials, and their management currently relies on empirical judgment. Understanding the natural history of asymptomatic ATTR-CM is essential for guiding individualized clinical decisions at the patient level and for designing future clinical trials in this population. While these patients do not exhibit overt HF, recent evidence suggests that a subset may experience disease progression and develop significant morbidity and mortality within a relatively short time. This review explores the rapidly evolving landscape of asymptomatic ATTR-CM with regard to diagnostic pathways, phenotypic variability, natural history, and prognostic stratification. It also discusses current barriers encountered in clinical practice for timely diagnosis, the clinical role of imaging and biomarkers, and potential indications for early therapeutic interventions in this under-recognized population, which is projected to exponentially increase in the coming years.

PLAIN LANGUAGE SUMMARY

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a heart disease caused by the buildup of an abnormal protein called transthyretin (TTR) in the heart muscle. This buildup makes the heart stiffer and less able to pump blood properly. In the past, most people were diagnosed only when the disease was advanced and they already had symptoms of heart failure, such as shortness of breath or swelling in the legs. Nowadays, thanks to better awareness and advances in cardiovascular imaging, ATTR-CM can be diagnosed earlier, even before symptoms appear. Some people with early signs of the disease may still face worsening of their cardiovascular condition over time. This raises important questions about how best to monitor these patients and when to begin treatment. Starting therapy early could help delay or even prevent heart failure and improve long-term outcomes

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1. Introduction

Transthyretin (TTR) amyloidosis, also called ATTR amyloidosis, is a life-threatening and often underrecognized disease caused by progressive deposition of misfolded or cleaved TTR protein in various organs [1]. The more common non-hereditary form, wild-type ATTR (ATTRwt), arises from age-related impairment of homeostatic mechanisms, whereas the hereditary form, variant ATTR (ATTRv), results from destabilizing mutations in the TTR gene and may present in younger individuals [2]. Amyloid fibril aggregation within the extracellular matrix disrupts tissue structure, integrity, and function, ultimately leading to organ dysfunction [3]. In clinical practice, ATTRwt amyloidosis typically manifests as transthyretin amyloid cardiomyopathy (ATTR-CM), while ATTRv amyloidosis is most often associated with polyneuropathy (ATTR-PN) and may also involve the heart [1].

Over the past decade, ATTR-CM has evolved from a rare, progressive, and fatal cardiomyopathy to a relatively prevalent disease with effective therapies capable of slowing or potentially halting disease progression [4,5]. The landscape of ATTR-CM has rapidly evolved following three landmark innovations: the development of a noninvasive algorithm for diagnosing ATTR-CM, the availability of disease-modifying drugs, and renewed disease awareness coupled with the identification of early clinical markers of disease [6]. These advances have led to an increasing proportion of patients diagnosed with ATTR-CM in an asymptomatic stage, with no history of HF or clinical signs of fluid overload [1,4]. However, these patients have been excluded from all clinical trials of disease-modifying treatment and their diagnosis and management currently rely solely on clinical judgment and empirical practice [7,8]. This emerging entity in clinical practice, which is projected to

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Article highlights

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is increasingly diagnosed at an asymptomatic stage thanks to improved disease awareness, noninvasive diagnostic tools, and targeted screening.
- Asymptomatic ATTR-CM represents an emerging and clinically relevant population in clinical practice, not a benign condition for all patients.
- Diagnosis of asymptomatic ATTR cardiac amyloid infiltration often occurs incidentally through suggestive cardiac imaging, incidental myocardial uptake on bone scintigraphy, ATTR proof on extracardiac biopsy, or positive TTR genetic testing.
- Bone scintigraphy remains the cornerstone for identifying cardiac amyloid infiltration and estimating disease burden in asymptomatic patients, with promising roles for cardiac magnetic resonance and PET/CT with novel amyloid tracers.
- The Perugini grade is associated with the extent of myocardial infiltration and predicts disease progression and cardiovascular outcomes in asymptomatic patients with ATTR-CM.
- A subset of asymptomatic patients – particularly those with grade 2–3 myocardial uptake – show meaningful cardiovascular morbidity and mortality within 3 years.
- Current wall thickness thresholds for raising suspicion of cardiac amyloidosis may underdiagnose disease in women, underscoring the need for sex-specific indexed criteria.
- Carpal tunnel syndrome is the earliest clinical marker of disease and a promising target for early screening strategies.
- Multimodality imaging, biomarkers, and AI-based tools may further refine early diagnosis and risk stratification.
- Identifying the optimal timing for therapeutic intervention in asymptomatic patients is crucial to improve long-term outcomes.

exponentially increase in the coming years, poses significant challenges with regard to diagnosis, prognostic stratification, and clinical management.

This review will discuss latest evidence in asymptomatic ATTR and will explore the diagnostic challenges and opportunities in this newly opened horizon in ATTR amyloidosis.

2. The emerging group of asymptomatic ATTR-CM

The diagnosis of ATTR-CM has been traditionally confirmed via direct endomyocardial biopsy in patients with clinical suspicion of the disease [9]. Most patients had overt HF when they were diagnosed, with an estimated median overall survival around 3–5 years following diagnosis, with significant differences in ATTRv amyloidosis according to the specific TTR variant [1,2,10]. In recent years, a noninvasive algorithm for confirmation of ATTR-CM has been validated combining repurposed bone tracer scintigraphy along with assessment for monoclonal proteins in serum and urine [9]. Recognition of extracardiac "red flags" – such as bilateral carpal tunnel syndrome (CTS), lumbar spinal stenosis, or biceps tendon rupture – has supported earlier suspicion and targeted screening. In particular, CTS is now recognized as the earliest clinical marker of future amyloidosis and can precede cardiac symptoms by 5–10 years [11,12]. There has been an exponential increase in the number of patients diagnosed with ATTR-CM, including those identified in an asymptomatic stage [7,13–15]. A 20-year nationwide UK study demonstrated a substantial increase in diagnoses of ATTR-CM, especially the wild-type [16], with 60% of patients being diagnosed 2017–2021 with a National Amyloidosis Centre (NAC) ATTR stage I [16]. This shift toward earlier diagnosis has broadened our understanding of disease progression and has led to a higher number of patients being identified earlier in the disease process, with a shorter duration of symptoms being associated with better preserved cardiac structure and function [4,17]. With broader implementation of early diagnostic strategies (i.e., CTS) and extended TTR genotyping allowing for identification of carriers [11,12,18,19], the number of patients with asymptomatic ATTR cardiac amyloid infiltration is projected to increase exponentially in the coming years.

However, large-scale registries have traditionally focused on symptomatic patients [15,20], and the epidemiological figure of patients with asymptomatic ATTR-CM remains unclear.

The largest study to date [13], conducted across multiple European centers for amyloidosis, has reported a steady increase in the numbers of asymptomatic patients identified in clinical practice, ranging from 26 in 2008–2011, to 60 in 2012–2015, 157 in 2016–2019, and 242 in 2020–2023 (Figure 1). In clinical practice, most of these patients are currently identified when typical abnormalities are detected on cardiac imaging during follow-up for other cardiovascular conditions, when incidental myocardial tracer uptake is observed on bone scintigraphy, or when ATTR amyloid is found on extracardiac biopsy specimens obtained for unrelated indications. Additional pathways include the identification of a pathogenic TTR variant through genetic testing performed because of a positive family history of hereditary amyloidosis or the presence of neurological symptoms suggestive of systemic involvement, often accompanied by histological confirmation of ATTR amyloid or genetic evidence of a disease-causing TTR variant [7,13,14] (Figure 2). Bone scintigraphy in these subgroups may detect the presence of an abnormal myocardial uptake, imaging amyloid deposition in their hearts and prompting further assessment [18,21–23].

A recent Italian survey on pathways leading to diagnosis of ATTRwt-CM has reported that approximately 50% of patients are now diagnosed through pathways not triggered by clinical HF [14]. Being diagnosed through an alternate pathway – such

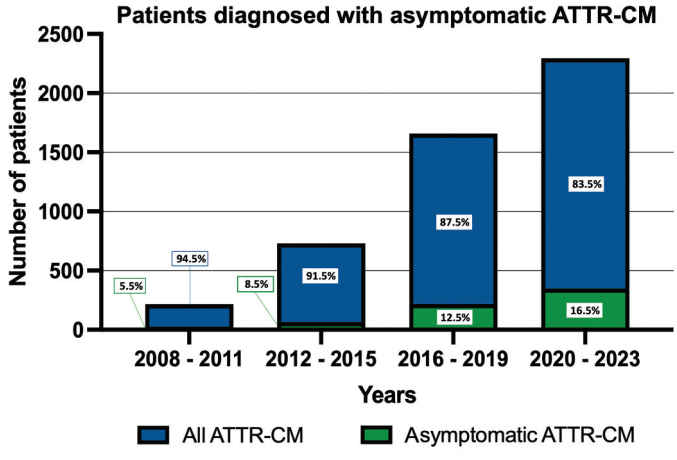

Figure 1. Increasing number of patients diagnosed with asymptomatic ATTR-CM over time in referral centers for amyloidosis.
Data from [13].

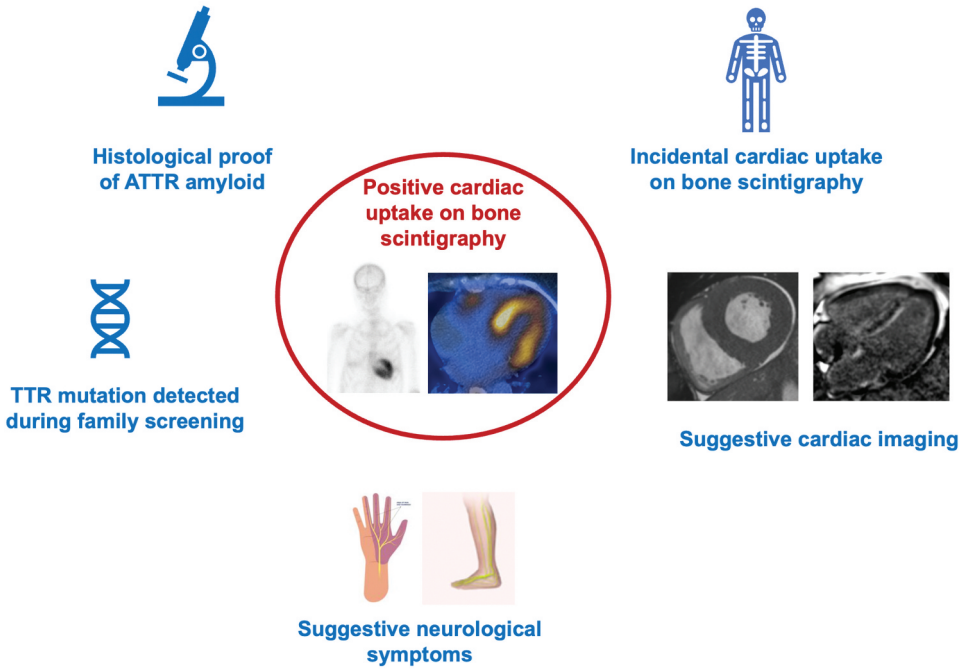

Figure 2. Common pathways for identification of asymptomatic patients with ATTR-CM in clinical practice.
Legend: ATTR, Transthyretin Amyloidosis; TTR, Transthyretin.

as the hypertrophic cardiomyopathy (HCM) pathway, incidental imaging findings (e.g., bone scintigraphy or cardiac magnetic resonance), or incidental clinical signs (e.g., CTS) – was independently associated with a more favorable prognosis compared to diagnoses triggered by the HF pathway [14]. Dedicated studies from large international registries are required to understand the prevalence of asymptomatic ATTR-CM in real-world patients.

3. Phenotype of pre-symptomatic ATTR-CM

Two recent studies have characterized the heterogeneous phenotype of ATTR-CM patients without HF. They demonstrated that asymptomatic ATTR cardiac amyloid infiltration may present with highly variable disease burden, spanning from minimal amyloid deposition without measurable structural or functional cardiac alterations to established cardiomyopathy characterized by typical HF symptoms, elevated cardiac biomarkers, and echocardiographic evidence of morphological remodeling and systolic dysfunction.

The first, conducted by Gonzalez-Lopez et al. [7] in 2022, retrospectively evaluated 118 patients with ATTR-CM (58% variant, 42% wild type), predominantly diagnosed by tissue biopsy, across 6 international centers for amyloidosis. All patients were in New York Heart Association (NYHA) class I, not receiving loop diuretic agents at initial evaluation and had a NT-proBNP <600 pg/mL (if data was available). Median age was 66 years and 80% were males. The median NT-proBNP was 308.1 pg/mL and the mean estimated glomerular filtration rate was 84 ml/min/1.73 m^2, with most patients being classified in NAC stage I or II. Median maximum left ventricular (LV) wall thickness was 15.5 mm, with preserved systolic function (mean LVEF of 61%) and impaired LV global longitudinal strain (−15.8%). Although all had no clinical HF, the spectrum of cardiac structural and functional changes ranged from structural cardiomyopathy with increased wall thickness and reduced systolic function to near-normal or mildly increased wall thickness and normal systolic function.

Bone scintigraphy is currently a key imaging modality in the noninvasive diagnostic algorithm for ATTR-CM. Beyond its established diagnostic value [9,24], the degree of myocardial uptake of bone tracers has also been shown to provide a gross estimate of the presence and extent of cardiac amyloid infiltration [25–28]. Therefore, bone scintigraphy is uniquely positioned to distinguish between cardiac amyloid deposition and overt ATTR-CM.

Building on this concept, a larger study in 2025 led by the National Amyloidosis Centre (London, UK) across 12 international centers for amyloidosis investigated the clinical phenotype of asymptomatic ATTR-CM from a different angle [13]. Similarly to the study by Gonzales et al., patients were classified as asymptomatic in the absence of HF history, HF signs and symptoms, and diuretic therapy at diagnosis. Of note, diagnosis of ATTR cardiac amyloid infiltration was based on evidence of myocardial uptake on bone scintigraphy (grade 1, 2, or 3) confirmed by single-photon emission computed tomography (SPECT)/CT imaging. In patients without biochemical evidence of a plasma cell dyscrasia (PCD), this finding was considered diagnostic, whereas in those with PCD, histological confirmation of ATTR amyloid was required [13]. The study included 485 asymptomatic patients (77% wild type, 23% hereditary), 86% males, with a mean age of 75 years, who were classified into two groups based on the Perugini grade: 116 patients (23.9%) with grade 1 myocardial uptake and 369 patients (76.1%) with grade 2 or 3 myocardial uptake. Despite similar age at diagnosis, patients with grade 1 myocardial uptake showed less abnormal cardiac structure and function,

and had normal or only mildly elevated NT-proBNP concentrations compared to patients with grade 2 and 3 myocardial uptake who exhibited typical echocardiographic features of amyloid infiltration and significantly elevated serum NT-proBNP concentrations [13]. These findings show different disease stages within the spectrum of asymptomatic ATTR cardiac amyloid infiltration, and support the use of Perugini score to estimate cardiac amyloid load in pre-symptomatic patients.

4. Clinical use of ECG and cardiovascular imaging in asymptomatic ATTR-CM

Identification of electrocardiographic (ECG) and echocardiographic red-flags is essential to raise suspicion of cardiac amyloidosis, even in asymptomatic individuals. The ECG may reveal low voltage QRS complexes, pseudoinfarct pattern with Q waves, and poor R wave progression in the precordial or limb leads [1]. Typical echocardiographic red flags include diffuse increase in wall thickness with a 'granular speckling' appearance of the myocardium, small ventricular cavity, biatrial dilatation, restrictive diastolic filling, interatrial septum or valve thickening, right ventricular wall thickening, pericardial effusion and apical sparing pattern on strain imaging [1]. However, the likelihood of detecting these abnormalities is related to the extent of cardiac amyloid infiltration [29]. Consequently, these red-flags are more commonly found in patients with increased wall thickness and significant cardiac amyloid infiltration. In patients with initial amyloid deposition, ECG and echocardiographic findings may be entirely normal despite underlying amyloid infiltration [13]. The diagnostic value of ECG and echocardiographic "red flags" has been validated primarily in patients with increased left ventricular wall thickness, while their role in individuals with normal wall thickness remains largely unknown [30,31]. Recent studies in asymptomatic carriers of pathogenic TTR variants without abnormal cardiac uptake on bone scintigraphy have shown that deformation parameters on echocardiography often remain within the normal range [32].

In the future, application of artificial intelligence may broaden the role of ECG and echocardiography in early detection and monitoring of ATTR-CM. In a recent study from the Mayo Clinic, AI-based ECG analysis successfully predicted the presence of cardiac amyloidosis more than 6 months prior to clinical diagnosis in 60% of cases [33]. Machine learning models can recognize subtle electrical or structural patterns, undetectable to the human eye, enabling identification of subclinical disease, TTR mutation carriers at risk, and potentially, tracking disease progression and treatment response.

At present, bone scintigraphy and cardiac magnetic resonance with extracellular volume (ECV) quantification are widely used in clinical practice to identify cardiac amyloid infiltration in patients with suspected cardiac amyloidosis or in asymptomatic carriers of pathogenic TTR variants [1]. Under normal condition, the myocardial extracellular space accounts for 22–28% of total myocardial volume. Amyloid deposition leads to progressive expansion of the myocardial interstitium, and, by combining pre- and post-contrast T1 maps, this signal can be isolated to obtain a surrogate quantitative measure of cardiac amyloid load: the ECV. This parameter may help identify early cardiac involvement in asymptomatic carriers of pathogenic TTR variants, as a global increase in myocardial ECV in this setting most likely reflects an increase in the amyloid burden [34,35].

Positron electron tomography (PET) imaging has recently emerged as a promising tool for detecting cardiac amyloid infiltration and potentially differentiating between ATTR and AL amyloidosis [36,37]. Cardiac uptake on PET/CT imaging has been observed in patients with confirmed ATTR amyloidosis but no clinical evidence of cardiac involvement, normal bone scintigraphy, and normal cardiac biomarkers, suggesting that PET/CT imaging may detect early amyloid deposition before changes on bone scintigraphy [38,39]. Although very promising, this imaging technique still lacks sufficient validation in clinical practice and requires further research, particularly among asymptomatic populations.

5. Natural history of pre-symptomatic ATTR-CM

Despite the absence of HF symptoms at diagnosis, asymptomatic patients with ATTR-CM experience substantial morbidity and mortality in the short term follow up [7,13]. In longitudinal cohorts, approximately one-third of patients progressed to clinical HF – defined as having been hospitalized for HF or progression to NYHA class ≥ II requiring diuretic agents – with a higher cumulative incidence observed in ATTRwt-CM compared to ATTRv-CM [7]. Atrial fibrillation and conduction abnormalities were common, with nearly 20% of patients requiring pacemaker implantation during follow-up [7].

The extent of cardiac amyloid infiltration established by myocardial uptake of bone tracer – has emerged as a key parameter to predict morbidity and mortality. In symptomatic patients, this has been demonstrated using SPECT imaging to distinguish localized from diffuse right ventricular uptake [27]. More recently, the prognostic relevance of Perugini grade 1 vs grades 2 or 3 myocardial uptake has been reported in asymptomatic ATTR-CM [13].

When assessing validated criteria of disease progression at 3 years, patients with grade 2 or 3 myocardial uptake had significantly higher rates of development of HF, greater outpatient diuretic initiation and NT-proBNP elevation, greater HF hospitalization and unplanned CV hospitalization compared to patients with grade 1 myocardial uptake [13] (Figure 3). Although all-cause mortality rates were similar between patients with grade 2 or 3 uptake vs those with grade 1 uptake (with these groups having a similar age at diagnosis), cardiovascular mortality was 5-fold higher in patients with grade 2 or 3 myocardial uptake compared with those with grade 1 uptake, in whom non-CV death was predominant [13]. These data may have significant implications for patients' management, but warrant confirmation in larger, more diverse cohorts – particularly including more women and patients with hereditary ATTR amyloidosis – to refine risk stratification and inform clinical management. Of note, proper ascertainment of true myocardial grade 1 uptake requires SPECT/CT fusion imaging to avoid misclassification of blood pool activity, which was not performed in several earlier studies on bone scintigraphy in patients with possible cardiac amyloidosis. Furthermore, the lack of significant prognostic

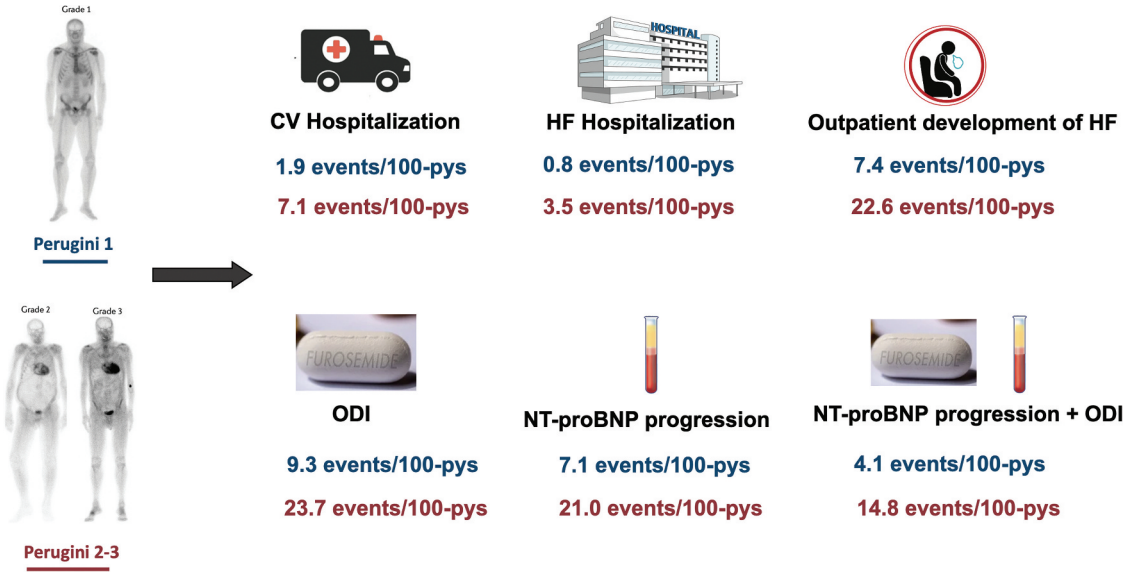

Figure 3. Event rate in asymptomatic patients with ATTR-CM according to Perugini grade at diagnosis.
Legend: CV, Cardiovascular; HF, Heart Failure; ODI, Outpatient Diuretic Intensification; pys, patient-years. Data from [13].

differences between grades 2 and 3 uptake indicates the limitations of current scintigraphic grading systems for risk stratification. Alternative or complementary approaches may be useful for refining risk stratification strategies in asymptomatic patients including quantitative SPECT/CT using standardized uptake values (SUV), ECV quantification by CMR imaging, or PET/CT imaging with novel amyloid-specific radiotracers.

6. To monitor or to treat patients with asymptomatic ATTR-CM?

Understanding the natural history of asymptomatic ATTR cardiac amyloid infiltration is essential for guiding both individualized clinical decisions at the patient level and for designing future clinical trials in this population. Although patients may present without HF symptoms, accumulating evidence indicates that the absence of overt HF does not directly indicate freedom from cardiovascular risk. The degree of myocardial uptake on bone scintigraphy can identify the subgroup of patients at higher risk of developing HF and cardiovascular death within the wider spectrum of asymptomatic ATTR cardiac amyloid infiltration, potentially warranting early intervention.

Gonzales-Lopez et al. [7] reported that treatment with TTR stabilizers in asymptomatic patients with ATTR-CM was associated with improved long-term survival, with a favorable trend toward reducing or delaying the development of clinical HF. Given the progressive and ultimately fatal nature of ATTR amyloidosis if untreated, initiating disease-modifying therapies able to prevent TTR tetramer dissociation or to suppress the production of TTR by the liver before substantial structural cardiac impairment establishes could theoretically confer greater benefit as opposed to starting treatment once the disease has already progressed. Bone scintigraphy interpreted with a clinical mind-set may be useful to personalize treatment strategies. Patients with grade 1 myocardial uptake generally show initial cardiac amyloid infiltration and predominantly non-cardiovascular mortality, resulting mostly from competing risks of death not related to amyloidosis. Initiation of disease-modifying treatment in this population may offer very limited benefit, with the exception of patients with hereditary ATTR amyloidosis with established neuropathy. In contrast, patients with grade 2 or 3 myocardial uptake have a more advanced cardiac amyloid infiltration, along with an increased risk of HF hospitalization and CV mortality, and are more likely to benefit from timely therapeutic intervention. However, current European [40] and American [41] guidelines recommend treatment with tafamidis in symptomatic patients with ATTR-CM and HF to reduce symptoms, CV hospitalizations, and mortality. Re-assessing these indications in light of emerging data is critical in upcoming guidelines, particularly for asymptomatic patients with grade 2 and 3 myocardial uptake.

In the era of earlier diagnosis, research in the field of amyloidosis is moving toward the direction of preventive studies. The ongoing placebo-controlled ACT-EARLY trial (NCT06563895) is evaluating the efficacy of acoramidis to delay or prevent development of ATTR amyloidosis – defined as cardiomyopathy and/or neuropathy – in a contemporary population of approximately 600 asymptomatic carriers of pathogenic TTR variants [42].

While awaiting these results, asymptomatic patients with evidence of cardiac structural and functional impairment, elevation in cardiac biomarkers and grade 2 and 3 myocardial uptake may potentially benefit from implementation of conventional HF medications.

Patients with ATTR-CM have similar – and possibly greater – neurohormonal activation as compared to patients with HF of different etiologies, raising the possibility of benefit from neurohormonal modulation also in this patient

population. Emerging evidence indicates a protective effect of low-dose beta-blockers (when ejection fraction is equal or below 40%, even in patients without concomitant ischemic heart disease) [43], mineral-corticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors across the spectrum of disease [44,45]. These drugs have been recently demonstrated beneficial in contemporary cohorts of ATTR-CM patients to reduce HF hospitalization, cardiovascular-related and all-cause mortality, and are therefore increasingly considered in ATTR-CM management.

7. Open challenges and actionable targets for earlier diagnosis of ATTR-CM

7.1. Diagnostic accuracy of the non-biopsy algorithm in low pretest settings

Repurposed bone scintigraphy is the cornerstone of a validated imaging-based algorithm for the noninvasive diagnosis of ATTR-CM that has enabled confirmation of disease in 70% of cases without the need for tissue biopsy. When applied in appropriate clinical scenarios, bone scintigraphy reliably differentiates cardiac amyloidosis from other cardiac conditions presenting with increased wall thickness such as hypertrophic cardiomyopathy. In the presence of suggestive clinical, echocardiography or CMR findings, a Perugini grade 2 or 3 myocardial uptake on bone scintigraphy along with the absence of monoclonal protein in serum and urine (confirmed by serum free light chain assay, serum and urine immunofixation) has been shown to yield a positive predictive value approaching 100% for ATTR-CM. In the landmark study by Gillmore et al. [9] validating the non-biopsy algorithm, the number of false positive results (positive test without evidence of any form of cardiac amyloidosis) was near to zero, but the study cohort consisted of patients at high clinical suspicion of disease. However, with heightened disease awareness and broader clinical application of this diagnostic algorithm, it is critical to evaluate its diagnostic performance in settings with lower pretest probability.

The Amylo-VIP-HF study [46] addressed this question by prospectively evaluating 104 unselected patients with HFpEF or HF with mildly reduced ejection fraction (mean age of 72 years). They were not pre-selected based on red flags or typical features of amyloidosis, and no threshold for LV wall thickness (i.e., ≥12 mm) was applied for inclusion. Bone scintigraphy demonstrated myocardial uptake in seven patients: four had grade 1 uptake (two had confirmed ATTR amyloidosis via subcutaneous fat aspirate), two with grade 2 uptake, and one with grade 3 uptake. AL amyloidosis was excluded in all cases. Ultimately, five patients (4.8%) were diagnosed with wild-type ATTR-CM. All confirmed cases had increased wall thickness, supporting its continued use as a gatekeeper for further evaluation in the setting of HF of the elderly, with a high pretest probability of wild-type ATTR amyloidosis. Notably, no cases of ATTR-CM were identified in patients with normal wall thickness, suggesting that substantial amyloid burden is required to produce detectable impairment in cardiac structure and function in ATTR-CM.

These observations align with current pathophysiological model of ATTR amyloidosis, in which the main mechanism of damage is related to progressive extracellular amyloid deposition in the organ rather than direct cardiotoxicity [4]. This is different from AL amyloidosis, where smaller amyloid burden can result in severe systolic dysfunction due to the toxic effect of circulating light chain oligomers on cardiomyocytes. Therefore, in ATTR-CM, a larger amyloid burden is typically required to produce detectable structural or functional cardiac impairment. This explains the frequent clinical observation of preserved ejection fraction despite significantly increased wall thickness and advanced cardiac amyloid infiltration [27]. Consequently, ATTR amyloidosis is unlikely to be the primary cause of HF in patients with Perugini grade 1 myocardial uptake and normal or mildly increased wall thickness. Subcutaneous fat aspiration failed to confirm the diagnosis in two patients with grade 1 myocardial uptake, consistent with its known low sensitivity in early or isolated cardiac involvement (especially in wild-type ATTR amyloidosis) [47]. Interestingly, myocardial uptake on bone scintigraphy remained stable during follow up (2 to 5 years) in these two patients, suggesting that early disease may progress slowly in wild-type ATTR amyloidosis. Altogether, these observations indicate that Perugini grade 1 myocardial uptake often reflects early, sub-clinical stages of cardiac amyloid infiltration that have not yet progressed to a cardiomyopathy or clinically relevant disease. An important exception lies in the anatomical location of amyloid deposition. Even minimal deposition in critical conduction system structures, such as the atrio-ventricular node, may result in clinically significant bradyarrhythmias or high-grade AV block [48].

Of note, none of the patients were diagnosed with hereditary ATTR-CM in the Amylo-VIP-HF study. This explains the absence of cardiac uptake in patients with normal wall thickness, which can be seen in very early stages of cardiac amyloid infiltration in hereditary ATTR amyloidosis before wall thickness increases. Therefore, the identification of ATTR-CM through the HF pathway is more likely to identify older patients with ATTRwt-CM.

To enhance diagnostic precision, minimizing both false positives and false negatives is essential. Prior studies have shown that the sensitivity of a positive technetium-labeled radionuclide bone scintigraphy for the identification of cardiac ATTR amyloid deposits is 99% when any degree of myocardial uptake is considered. However, this sensitivity declines to 70% when considering only grade 2 or 3 myocardial uptake combined with the absence of monoclonal proteins in serum and urine, even in patients with a high pretest probability of disease [9]. Therefore, the risk of false negative results may be relevant in settings at lower pretest probability, for patients with early disease or with MGUS, which is the focus of population-based screening. Dedicated studies using multimodality imaging will be required to improve sensitivity and refine diagnostic accuracy across diverse clinical scenarios.

7.2. Limitations of current wall thickness thresholds for raising suspicion of disease

A remarkable male predominance has been consistently reported in symptomatic ATTR-CM approaching >80–90% of

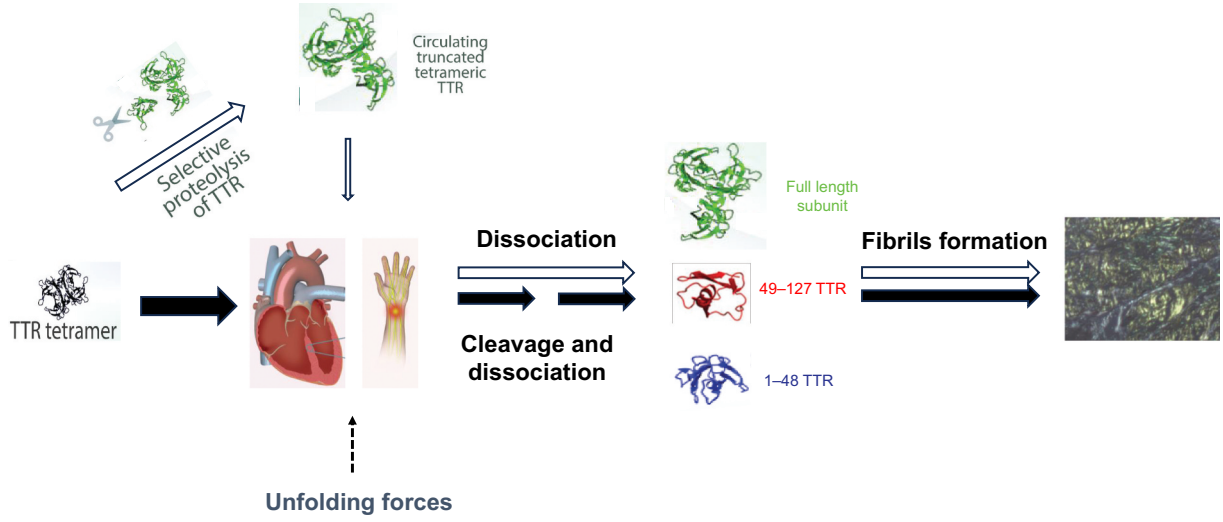

Figure 4. Mechano-enzymatic cleavage model for transthyretin amyloid formation in tissues with elevated biomechanical forces.
Legend: TTR, transthyretin. Re-used from Porcari et al. [4] under an Open Access CC-BY-NC-ND license.

cases, and exceeding this in ATTRwt-CM [49]. This finding was observed also in available studies in asymptomatic patients with ATTR-CM [7,13]. The basis for this sex imbalance remains unclear. It may reflect a true biological predisposition or result, at least to some extent, from diagnostic bias related to the criteria currently used to suspect and identify the disease.

Echocardiography is the frontline imaging modality that most frequently raises suspicion of disease. Among the recognized red flags, increased wall thickness which remains the main finding triggering further diagnostic work-up. Current European and American guidelines on cardiac amyloidosis recommend a value for non-indexed LV wall thickness of 12 mm or greater on echocardiography to prompt referral for investigation for ATTR-CM. Of note, the use of this threshold has several limitations in clinical practice. First, this cut off value for septal thickness was taken from early studies in patients with systemic immunoglobulin AL amyloidosis where it was used to confirm the presence of cardiac involvement and arbitrarily applied to ATTR-CM. This cut off value is very sensitive and minimizing missing AL-CA, as missing cardiac involvement in AL amyloidosis has detrimental consequences. In AL amyloidosis, patients are much younger and with less comorbidities as opposed to patients with ATTR-CM, and thus increased wall thickness may be more reflective of cardiac amyloid deposition than other processes such as arterial hypertension or aortic valve stenosis. Second, a universal threshold of 12 mm for LV wall thickness does not seem to perform adequately in ATTR-CM as the 12 mm cutoff is not sex-specific. Normal reference values for LV wall thickness are lower in women than in men. Therefore, using a single diagnostic threshold may lead to underdiagnosis in women and delayed disease recognition, contributing to the observed male predominance in ATTR-CM.

Third, an absolute threshold of 12 mm does not consider the anthropometric features such as body surface area or height, which are known to influence ventricular wall thickness. A recent study by the National Amyloidosis Centre suggested that using non-indexed IVS thickness values may lead to inaccurate perception of a milder clinical phenotype in women compared to men. Indexed LV wall thickness using BSA or height may potentially reflect more accurately the severity of cardiac involvement [49,50], highlighting the need to establish sex-specific thresholds to refine diagnostic criteria in both men and women. Large prospective studies are needed to determine the clinical impact of sex-specific cutoffs in patients evaluated for suspected amyloidosis, which may change the epidemiological figure of ATTR amyloidosis as we know it today.

7.3. Leveraging early clinical markers for targeted screening

With effective diagnostic approaches and timely initiation of disease-modifying therapy able to improve outcomes, population-based screening for early identification of ATTR-CM before significant organ dysfunction has ensued is becoming a clinical priority [19]. As such screening has to be effective and sustainable, identification of early and reliable clinical markers is essential to target subgroups at high pretest probability [19].

CTS has emerged as a common extracardiac site for ATTR amyloid deposition, both in wild-type and variant forms, and is the earliest clinical marker of disease known nowadays, which can precede by 5 to 10 years the future development of ATTR-CM [51,52]. CTS may occasionally occur in AL amyloidosis, but its prevalence is comparable to that of the general population. Notably, amyloid deposition in tenosynovial tissues, nearly all ATTR, has been identified in 10% to 30% of patients at the time of carpal tunnel surgery [53,54]. However, the reason for this association has not been elucidated. A plausible explanation for the preferential deposition of ATTR amyloid in anatomical sites exposed to significant mechanical stress, such as the heart and the carpal tunnel, comes from the mechano-enzymatic cleavage hypothesis [4,55]. This model suggests that biomechanical forces, particularly shear stress from physiological fluid flow, may

facilitate the enzymatic cleavage of transthyretin, thereby promoting fibrillogenesis and subsequent amyloid deposition [56] (Figure 4). While conceptually compelling, this hypothesis may not fully explain amyloid deposition in all organs affected by ATTR and additional mechanisms yet to be fully elucidated, are likely to contribute to tissue-specific amyloid tropism.

Data from the Cardiac Amyloidosis Carpal TUnnel Syndrome (CACTUS) study [11] exploring the presence of ATTR-CM in 250 patients who had undergone bilateral carpal tunnel release 5 to 15 years before enrollment, helped identify clinical phenotypes at increased risk of disease. The prevalence of ATTR-CM was 8.8% overall among men and reached 21.2% in men aged ≥70 years with a BMI < 30 kg/m^2, highlighting the potential clinical impact of systematic screening for amyloidosis in this population. In a sub-analysis of this study, measuring cardiac biomarkers after 5 to 10 years from carpal tunnel surgery has been explored as a cost-effective strategy for screening for ATTR-CM. A TnT <13 ng/L or a NT-proBNP below the age-dependent threshold were shown to effectively rule out early cardiac amyloidosis, with a negative predictive value of 99–100% [57]. Whilst reasonable as rule out strategy, the use of cardiac biomarkers in this population for rule in purposes may pose substantial challenges.

Interestingly, the presence of unexplained cardiac hypertrophy (i.e., increased wall thickness in the absence of abnormal loading conditions) by echocardiography at the time of carpal tunnel surgery has been reported to identify a subgroup of patients at elevated risk of future ATTR-CM diagnosis [12].

Altogether, these findings support the use of CTS as an early clinical marker to raise suspicion of ATTR-CM and to identify individuals at increased risk who warrant longitudinal monitoring. The feasibility of implementing systematic screening among all CTS surgery patients should be evaluated from a health-economic perspective, particularly in resource-limited settings [19,58].

8. Conclusion

With major advances in disease awareness, noninvasive diagnosis and the availability of disease-modifying treatment, the landscape of ATTR-CM is evolving rapidly [59]. Once considered a rare and fatal disease, ATTR-CM is now increasingly identified at asymptomatic stages, posing new challenges and opportunities for clinical management.

Asymptomatic ATTR-CM is not benign for all patients. A subset of patients experience meaningful cardiovascular morbidity and mortality within a relatively short time. The degree of myocardial uptake on bone scintigraphy, as graded by the Perugini score, may help identify patients with faster disease progression who could benefit from early therapeutic intervention; despite current guidelines restrict treatment to symptomatic patients with overt HF. However, our understanding of asymptomatic ATTR cardiac amyloid infiltration remains limited, with many key questions left unanswered: where is the boundary between "physiological" amyloid deposition and clinically significant disease (cardiac amyloidosis)? what is the minimal amyloid burden that justifies treatment with costly disease-modifying therapies? how can large-scale, cost-effective and sustainable screening be implemented in populations at risk for early identification of ATTR-CM? how should disease progression be monitored in asymptomatic stages, with cardiovascular imaging, biomarkers, or both? Could artificial intelligence improve diagnostic accuracy or refine risk stratification in pre-symptomatic stages?

As the population of asymptomatic ATTR-CM patients continues to grow, defining reliable strategies for early identification, disease staging, monitoring, and indications for therapeutic intervention will be essential to optimize patient outcomes and fully leverage the potential of early diagnosis.

9. Future perspective

Over the next decade, the field of ATTR-CM is expected to shift toward systematic early detection and personalized treatment strategies. Screening programs targeting high-risk populations, such as individuals with CTS, carriers of pathogenic TTR variants, and elderly patients with unexplained increases in ventricular wall thickness, will likely become more structured, accessible and cost-effective. Advances in multimodality imaging, biomarkers, and AI are anticipated to enable earlier and more accurate detection of early disease and risk stratification. In parallel, the therapeutic landscape will expand to include next-generation TTR stabilizers and gene-silencing or in-vivo editing approaches, allowing treatment initiation before the onset of clinical HF. These innovations have the potential to substantially change the natural history of the disease. Furthermore, the development of amyloid-depleting strategies using targeted antibodies may transform ATTR-CM from a late-diagnosed, progressive cardiomyopathy into a treatable, or even reversible model of cardiac disease.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Porcari A, Fontana M, Gillmore JD. Transthyretin cardiac amyloidosis. Cardiovasc Res. 2023;118(18):3517–3535. doi: 10.1093/cvr/cvac119

2. Porcari A, Razvi Y, Masi A, et al. Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy. Eur J Heart Fail. 2023;25(4):515–524. doi: 10.1002/ejhf.2776
3. Porcari A, Bussani R, Merlo M, et al. Incidence and characterization of concealed cardiac amyloidosis among unselected elderly patients undergoing post-mortem examination. Front Cardiovasc Med. 2021;8:749523. doi: 10.3389/fcvm.2021.749523
4. Porcari A, Sinagra G, Gillmore JD. Breakthrough advances enhancing care in ATTR amyloid cardiomyopathy. Eur J Intern Med. 2024;123:29–36. doi: 10.1016/j.ejim.2024.01.001
5. Aimo A, Castiglione V, Rapezzi C, et al. RNA-targeting and gene editing therapies for transthyretin amyloidosis. Nat Rev Cardiol. 2022;19(10):655–667. doi: 10.1038/s41569-022-00683-z
6. Gonzalez-Lopez E, Maurer MS, Garcia-Pavia P. Transthyretin amyloid cardiomyopathy: a paradigm for advancing precision medicine. Eur Heart J. 2025;46(11):999–1013. doi: 10.1093/eurheartj/ehae811
7. Gonzalez-Lopez E, Escobar-Lopez L, Obici L, et al. Prognosis of transthyretin cardiac amyloidosis without heart failure symptoms. JACC Cardiooncol. 2022;4(4):442–454. doi: 10.1016/j.jaccao.2022.07.007
   - **This was the first study investigating the phenotype and outcomes of patients with ATTR-CM without heart failure symptoms, reporting the potential benefit of disease-modifying treatment in this population.**
8. Law S, Bezard M, Petrie A, et al. Characteristics and natural history of early-stage cardiac transthyretin amyloidosis. Eur Heart J. 2022;43(27):2622–2632. doi: 10.1093/eurheartj/ehac259
9. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404–2412. doi: 10.1161/CIRCULATIONAHA.116.021612
10. Porcari A, Merlo M, Rapezzi C, et al. Transthyretin amyloid cardiomyopathy: an uncharted territory awaiting discovery. Eur J Intern Med. 2020;82:7–15. doi: 10.1016/j.ejim.2020.09.025
11. Westin O, Fosbøl EL, Maurer MS, et al. Screening for cardiac amyloidosis 5 to 15 years after surgery for bilateral carpal tunnel syndrome. J Am Coll Cardiol. 2022;80(10):967–977. doi: 10.1016/j.jacc.2022.06.026
12. Porcari A, Pagura L, Longo F, et al. Prognostic significance of unexplained left ventricular hypertrophy in patients undergoing carpal tunnel surgery. ESC Hear Fail. 2022;9(1):751–760. doi: 10.1002/ehf2.13606
13. Porcari A, Razvi Y, Cappelli F, et al. Clinical phenotype and prognosis of asymptomatic patients with transthyretin cardiac amyloid infiltration. JAMA Cardiol. 2025;10(5):437. doi: 10.1001/jamacardio.2024.5221
   - **This was the first study to characterise the clinical phenotype and outcomes of contemporary asymptomatic patients with ATTR cardiac amyloid infiltration and demonstrate the clinical use of the Perugini grade to refine prognostic stratification.**
14. Tini G, Milani P, Zampieri M, et al. Diagnostic pathways to wild-type transthyretin amyloid cardiomyopathy: a multicentre network study. Eur J Heart Fail. 2023;25(6):845–853. doi: 10.1002/ejhf.2823
15. Westin O, Butt JH, Gustafsson F, et al. Two decades of cardiac amyloidosis. JACC Cardiooncol. 2021;3(4):522–533. doi: 10.1016/j.jaccao.2021.05.004
16. Ioannou A, Patel RK, Razvi Y, et al. Impact of earlier diagnosis in cardiac ATTR amyloidosis over the course of 20 years. Circulation. 2022;146(22):1657–1670. doi: 10.1161/CIRCULATIONAHA.122.060852
17. Fontana M, Porcari A. Imaging in amyloidosis. JACC Cardiovasc Imag. 2024;17(11):1287–1289. doi: 10.1016/j.jcmg.2024.06.005
18. Muller SA, Peiró-Aventin B, Biagioni G, et al. Evaluation of the 2021 ESC recommendations for family screening in hereditary transthyretin cardiac amyloidosis. Eur J Heart Fail. 2024;26(9):2025–2034.
19. Porcari A, Tomasoni D. Leveraging carpal tunnel syndrome to develop screening strategies for amyloidosis. Int J Cardiol. 2025;418:132629. doi: 10.1016/j.ijcard.2024.132629
20. Gilstrap LG, Dominici F, Wang Y, et al. Epidemiology of cardiac amyloidosis–associated heart failure hospitalizations among fee-for-service Medicare beneficiaries in the United States. Circ Hear Fail. 2019;12(6). doi: 10.1161/CIRCHEARTFAILURE.118.005407
21. Fontana M, Porcari A, Hawkins PN. Standardising care and treatment of transthyretin amyloid cardiomyopathy. Glob Heart. 2023;18(1):63. doi: 10.5334/gh.1275
22. Porcari A, Rossi M, Dore F, et al. Ten questions for the cardiologist about cardiac scintigraphy with bone tracers, amyloidosis and the heart. G Ital Cardiol (Rome). 2022;23(6):424–432.
23. Porcari A, Chimenti C, Merlo M, et al. Diagnostic-therapeutic care pathways for patients with cardiac amyloidosis - SIC/ANMCO consensus document. Edited by the Italian Cardiac Amyloidosis Network (RIAC). G Ital Cardiol (Rome). 2024;25(12):900–920. doi: 10.1714/4372.43703
24. Rauf MU, Hawkins PN, Cappelli F, et al. Tc-99m labelled bone scintigraphy in suspected cardiac amyloidosis. Eur Heart J. 2023;44(24):2187–2198. doi: 10.1093/eurheartj/ehad139
25. Ioannou A, Patel RK, Razvi Y, et al. Multi-imaging characterization of cardiac phenotype in different types of amyloidosis. JACC Cardiovasc Imag. 2023;16(4):464–477. doi: 10.1016/j.jcmg.2022.07.008
26. Hutt DF, Fontana M, Burniston M, et al. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. Eur Heart J Cardiovasc Imag. 2017;18(12):1344–1350. doi: 10.1093/ehjci/jew325
27. Porcari A, Fontana M, Canepa M, et al. Clinical and prognostic implications of right ventricular uptake on bone scintigraphy in transthyretin amyloid cardiomyopathy. Circulation. 2024;149(15):1157–1168. doi: 10.1161/CIRCULATIONAHA.123.066524
28. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol. 2017;70(4):466–477. doi: 10.1016/j.jacc.2017.05.053
29. Knight DS, Zumbo G, Barcella W, et al. Cardiac structural and functional consequences of amyloid deposition by cardiac magnetic resonance and echocardiography and their prognostic roles. JACC Cardiovasc Imag. 2019;12(5):823–833. doi: 10.1016/j.jcmg.2018.02.016
30. Merlo M, Pagura L, Porcari A, et al. Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from phase 2 of the AC-TIVE study, an Italian nationwide survey. Eur J Heart Fail. 2022;24(8):1377–1386. doi: 10.1002/ejhf.2504
31. Merlo M, Porcari A, Pagura L, et al. A national survey on prevalence of possible echocardiographic red flags of amyloid cardiomyopathy in consecutive patients undergoing routine echocardiography: study design and patients characterization — the first insight from the AC-TIVE study. Eur J Prev Cardiol. 2022;29(5):e173–7. doi: 10.1093/eurjpc/zwab127
32. Fazzini L, Castrichini M, Li Y, et al. Phenotypic presentation and longitudinal characterization of hereditary ATTRv amyloidosis in previously undiagnosed family members. JACC Adv. 2025;4(8):102036. doi: 10.1016/j.jacadv.2025.102036
33. Grogan M, Lopez-Jimenez F, Cohen-Shelly M, et al. Artificial intelligence-enhanced electrocardiogram for the early detection of cardiac amyloidosis. Mayo Clin Proc. 2021;96(11):2768–2778.
34. Fontana M, Chung R, Hawkins PN, et al. Cardiovascular magnetic resonance for amyloidosis. Heart Fail Rev. 2015;20(2):133–144. doi: 10.1007/s10741-014-9470-7
35. Martinez-Naharro A, Kotecha T, Norrington K, et al. Native T1 and extracellular volume in transthyretin amyloidosis. JACC Cardiovasc Imag. 2019;12(5):810–819. doi: 10.1016/j.jcmg.2018.02.006
36. Genovesi D, Vergaro G, Giorgetti A, et al. [18F]-Florbetaben PET/CT for differential diagnosis among cardiac immunoglobulin light chain, transthyretin amyloidosis, and mimicking conditions. JACC Cardiovasc Imag. 2021;14(1):246–255. doi: 10.1016/j.jcmg.2020.05.031
37. Dorbala S, Kijewski MF. Molecular imaging of systemic and cardiac amyloidosis: recent advances and focus on the future. J Nucl Med. 2023;64(Suppl 2):20S–28S. doi: 10.2967/jnumed.122.264866

38. Wall JS, Martin EB, Lands R, et al. Cardiac amyloid detection by PET/CT imaging of iodine ((124)I) evuzamitide ((124)I-p5+14): a phase 1/2 study. JACC Cardiovasc Imag. 2023;16(11):1433–1448.
39. Smiley DA, Einstein AJ, O'Gorman KJ, et al. Early detection of transthyretin cardiac amyloidosis using (124)I-Evuzamitide positron emission tomography/computed tomography. JACC Cardiovasc Imag. 2025;18(7):799–811.
40. McDonagh TA, Metra M, Adamo M, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–3726.
41. Heidenreich PA, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation. 2022;145(18):e895–1032.
42. Soman P, Garcia-Pavia P, Gillmore JD, et al. Rationale & design of ACT-EARLY, the Acoramidis Transthyretin Amyloidosis Prevention Trial: early detection using cardiac radionuclide imaging. J Nucl Cardiol. 2024;38:38. doi: 10.1016/j.nuclcard.2024.101948
43. Ioannou A, Massa P, Patel RK, et al. Conventional heart failure therapy in cardiac ATTR amyloidosis. Eur Heart J. 2023;44(31):2893–2907. doi: 10.1093/eurheartj/ehad347
- **This landmark study was the first to demonstrate that beta-blockers and MRAs are not only well tolerated in ATTR-CM, but can also significantly improve survival in patients with heart failur.**
44. Porcari A, Cappelli F, Nitsche C, et al. SGLT2 inhibitor therapy in patients with transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2024;83(24):2411–2422. doi: 10.1016/j.jacc.2024.03.429
- **This was the first study to show that SGLT2 inhibitors are safe, well tolerated, and associated with improved clinical outcomes in patients with ATTR-CM and heart failure. Uniquely, 220 ATTR-CM patients receiving SGTL2 inhibitors were propensity-score matched to 220 untreated ATTR-CM using 16 key clinical variables, ensuring robust comparison.**
45. Porcari A, Fontana M. The changing landscape of heart failure treatment in transthyretin amyloid cardiomyopathy: is the time ripe for clinical use of sodium–glucose cotransporter 2 inhibitors? Eur J Heart Fail. 2024;26(4):948–951. doi: 10.1002/ejhf.3245
46. Tubben A, Tingen HSA, Prakken NHJ, et al. Prevalence of wild-type transthyretin amyloidosis in a prospective heart failure cohort with preserved and mildly reduced ejection fraction: results of the Amylo-VIP-HF study. Eur J Heart Fail. 2024;26(3):695–698. doi: 10.1002/ejhf.3186
47. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. Eur Heart J. 2017;38(24):1905–1908. doi: 10.1093/eurheartj/ehx047
48. Porcari A, Rossi M, Cappelli F, et al. Incidence and risk factors for pacemaker implantation in light-chain and transthyretin cardiac amyloidosis. Eur J Heart Fail. 2022;24(7):1227–1236. doi: 10.1002/ejhf.2533
49. Patel RK, Ioannou A, Razvi Y, et al. Sex differences among patients with transthyretin amyloid cardiomyopathy – from diagnosis to prognosis. Eur J Heart Fail. 2022;24(12):2355–2363. doi: 10.1002/ejhf.2646
- **This was the first study to explore sex-differences in a large cohort of patients with wilde-type and hereditary ATTR-CM and reporting diagnostic delay in women. It was also the first study to propose to adopt sex-specific cut off values to define increased wall thickness and, consequently, cardiac involvement in men and women, to reduce the diagnostic delay.**
50. Aimo A, Tomasoni D, Porcari A, et al. Left ventricular wall thickness and severity of cardiac disease in women and men with transthyretin amyloidosis. Eur J Heart Fail. 2023;25(4):510–514. doi: 10.1002/ejhf.2824
51. Milandri A, Farioli A, Gagliardi C, et al. Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies. Eur J Heart Fail. 2020;22(3):507–515. doi: 10.1002/ejhf.1742
52. Aimo A, Merlo M, Porcari A, et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. Eur J Heart Fail. 2022;24(12):2342–2351. doi: 10.1002/ejhf.2532
53. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. J Am Coll Cardiol. 2018;72(17):2040–2050. doi: 10.1016/j.jacc.2018.07.092
54. DiBenedetto M, Soong M, Hunter A, et al. Prevalence and subtypes of tenosynovial amyloid in patients undergoing carpal tunnel release. J Hand Surg Am. 2022;47(6):540–543. doi: 10.1016/j.jhsa.2022.02.013
55. Mangione PP, Porcari R, Gillmore JD, et al. Proteolytic cleavage of Ser52Pro variant transthyretin triggers its amyloid fibrillogenesis. Proc Natl Acad Sci USA. 2014;111(4):1539–1544. doi: 10.1073/pnas.1317488111
- **This landmark study was the first to describe an in-vivo pathway for amyloidogenesis in a model of Ser52Pro variant TTR protein.**
56. Marcoux J, Mangione PP, Porcari R, et al. A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis. EMBO Mol Med. 2015;7(10):1337–1349. doi: 10.15252/emmm.201505357
57. Noory N, Westin O, Fosbøl E, et al. Value of troponin and NT-proBNP to screen for cardiac amyloidosis after carpal tunnel syndrome surgery. Int J Cardiol. 2024;415:132469. doi: 10.1016/j.ijcard.2024.132469
58. Razvi Y, Ioannou A, Porcari A, et al. Early detection of transthyretin amyloid cardiomyopathy through carpal tunnel decompression biopsies - a prospective multicentre United Kingdom study. J Am Coll Cardiol. 2025;85(12):4694. doi: 10.1016/S0735-1097(25)05178-2
59. Fontana M, Aimo A, Emdin M, et al. Transthyretin amyloid cardiomyopathy: from cause to novel treatments. Eur Heart J. 2025:ehaf667. doi: 10.1093/eurheartj/ehaf667