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Diagnosis and Management of Cardiac Amyloidosis: The Role of Multimodal Imaging—A Mini Review

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Abstract

Cardiac amyloidosis is a disease characterized by the deposition of misfolded proteins in the myocardium, leading to restrictive cardiomyopathy. It comprises two subtypes: immunoglobulin light chain cardiac amyloidosis (AL) and transthyretin cardiac amyloidosis (ATTR). ATTR is classified as wild-type (wtATTR) and hereditary (hATTR), depending on the presence or absence of a transthyretin (TTR) genetic mutation. The diagnosis of cardiac amyloidosis is challenging due to nonspecific symptoms with other cardiac conditions, often resulting in misdiagnosis. This mini review provides an in-depth analysis of cardiac amyloidosis, focusing on its subtypes, clinical manifestations, diagnostic multimodal imaging, and recent therapeutic advancements.

Keywords

Amyloid, Echocardiography, Diastolic Dysfunction, Cardiac Infiltration

1. Introduction

Cardiac amyloidosis (CA) is a disease characterized by the myocardial infiltration of unregulated amyloid fibrils, which are a type of misfolded proteins deposited

in the extracellular matrix in diverse tissues causing organ dysfunction. This misfolding results in the production of oligomers and aggregates of folded β-sheets that upon deposition can lead to restrictive cardiomyopathy with heart failure [1]. CA has two subtypes, immunoglobulin light chain cardiac amyloidosis (AL) and transthyretin cardiac amyloidosis (ATTR) [2]. Transthyretin (TTR) also known as prealbumin, is a protein synthesized mainly by the liver, with some production by the choroid plexus and retinal pigmented epithelial cells of the eye [3]. The function of TTR is to transport thyroxine and holoretinol binding protein. However, when it misfolds, it can aggregate and contribute to the pathology of cardiac amyloidosis [4].

CA has emerged in recent years as a more prevalent diagnosis, particularly among elderly individuals presenting with heart failure with preserved ejection fraction (HFpEF). The importance of early and precise detection cannot be overstated, given the markedly poor prognosis in untreated cases with survival rates averaging less than six months for patients with AL amyloidosis, and approximately three to five years for those with ATTR forms, contingent upon the disease stage at the time of diagnosis.

Advancements in imaging modalities have significantly transformed the setting of ATTR diagnosis, leading to a substantial rise in case detection. These developments in non-invasive imaging techniques, including speckle-tracking echocardiography, cardiac magnetic resonance imaging (CMR), and bone-avid radiotracer-based nuclear scintigraphy, have substantially refined the diagnostic pathway [5].

The widespread adoption of techniques has enabled earlier identification of disease, a factor closely associated with improved and reduced mortality. These modalities facilitate early identification and enable accurate differentiation of CA without necessitating endomyocardial biopsy, thereby expediting therapeutic decision-making and potentially improving patient outcomes. Beyond enhancing diagnostic precision, the integration of multimodal imaging has deepened our understanding of disease pathophysiology, refined risk stratification, and strengthened the ability to monitor therapeutic efficacy. Collectively, these innovations represent a pivotal advancement in the clinical management of ATTR, offering the potential to significantly improve patient outcomes in this progressive and life-threatening condition, ultimately contributing to more favorable clinical outcomes in individuals affected by this progressive condition [5] [6].

2. Subtypes

Immunoglobulin light chain amyloidosis (AL) is the most common subtype, in more than half of the patients, it is distinguished by alterations in plasma cells which causes an excessive production of a quantity of abnormal antibody proteins [7]. It affects primarily men, with a mean age of 65 years at the moment of diagnosis, over 75% of the patients with this subtype will develop cardiac affection [7] [8]. According to the genetic aspect, ATTR has two subtypes, a wild-type (wtATTR) or hereditary (hATTR) depending on the absence or presence of the

TTR genetic mutation. wtATTR was previously known as senile systemic amyloidosis. wtATTR is more common in male patients with a mean age of 75 years during diagnosis [8]. On the other hand, hATTR has a variable onset age and is associated with more than 130 mutations in the ATTR gene, thus, it can have clinical variability and can also cause a cardiomyopathic, neuropathic, or mixed phenotype. AL can impact the kidney in 30% of patients, peripheral and autonomic fibers in 12% - 17%, the gastrointestinal tract in 1%, and infrequently the liver. The Val112Ile is the most frequent variant reported, with a prevalence of 3.4% in the African American population [9] [10].

Accurate distinction between AL amyloidosis and ATTR amyloidosis is essential, given their divergent therapeutic approaches and prognostic implications. Both clinical presentation and imaging characteristics are fundamental in facilitating the differentiation between these two forms of the disease [11].

Clinically, AL amyloidosis often presents with more rapid progression and severe symptoms, typically involves multiple organ systems, presenting with unexplained heart failure, nephrotic syndrome, peripheral neuropathy, and hepatomegaly. Conversely, ATTR follows a more indolent course, predominantly affecting elderly male patients, and typically manifests as HFpEF of unknown etiology. Clinical signs often reflect features of restrictive cardiomyopathy, such as exertional dyspnea, peripheral edema and a distinct absence of ischemic symptoms. Additionally, several extracardiac clinical indicators may raise suspicion for amyloidosis, including autonomic or peripheral neuropathy, bilateral carpal tunnel syndrome, lumbar spinal stenosis, and spontaneous rupture of the biceps tendon [11] [12].

CMR facilitates comprehensive myocardial tissue characterization, playing a critical role in the precise differentiation of amyloidosis subtypes. Furthermore, the incorporation of advanced imaging modalities provides incremental diagnostic value, offering supplementary parameters that enhance the specificity and accuracy of subtype distinction [13] [14].

Tc-99m bone scintigraphy represents a highly informative diagnostic modality in the identification of ATTR amyloidosis. In cases where monoclonal protein studies yield negative results, the observation of marked myocardial radiotracer uptake on Tc-99m imaging, in conjunction with the exclusion of an underlying monoclonal gammopathy, serves as a robust indicator in favor of an ATTR-related etiology [11] [15].

A comprehensive diagnostic strategy encompassing CMR, Tc-99m bone scintigraphy, clinical evaluation, and laboratory testing for monoclonal proteins is indispensable for the accurate differentiation of amyloidosis subtypes. Collectively, these modalities not only enhance diagnostic precision but also play a critical role in guiding the selection of the most appropriate therapeutic interventions [16].

3. Pathophysiology

The understanding of the pathophysiology of the disease is fundamental for the development of novel directed treatment. Transthyretin or prealbumin, is a liver-

synthesized tetrameric protein that transports thyroid hormone and retinol. Aging or destabilizing mutations can cause the tetramer to break down into smaller units, which may misfold and aggregate into amyloid fibrils. In AL-CA, excess monoclonal immunoglobulin light chains from bone marrow plasma cells undergo misfolding and infiltrate the myocardium [9]. The myocardial deposition of insoluble amyloid occurs in a transmural pattern leading to concentric remodeling and thickening of the ventricles, resulting in wall hypertrophy [8]. As such, ventricles will present stiffness, noncompliance and elevated diastolic filling pressures. However, the ejection fraction is initially preserved, showing a significant decrease as the disease progresses. Atrial amyloid deposition occurs simultaneously, leading to impairment of the conduction system causing atrioventricular (AV) blocks or increased risk of arrhythmias such as atrial fibrillation [8].

4. Clinical Presentation

The clinical phenotype will depend on the underlying TTR variant, nevertheless clinical presentation of most of the patients with CA will be nonspecific presenting as diverse clinical syndromes. AL amyloidosis has a rapid and progressive clinical course. Certain characteristics of the light chain variable region genes increase the risk of affecting specific organs [1]. The involved organs determine the classification and severity of amyloidosis, as certain forms of amyloidosis are localized while others are systemic [7].

In the initial stages of amyloidosis, clinical presentation is frequently characterized by nonspecific and subtle symptoms, including fatigue, unintentional weight loss, and peripheral edema. These generalized manifestations often contribute to diagnostic delays, as they lack specificity and overlap with a broad range of differential diagnoses. Subsequently, more organ-specific signs emerge, facilitating the clinical suspicion of systemic amyloidosis [17].

Cardiac symptoms are decompensated heart failure, with classical findings such as dyspnea on exertion, peripheral edema and jugular venous distension. Cardiac infiltration often remains undetected because the patient's ejection fraction is within normal limits [18]. However, amyloid deposition can cause extracardiac manifestations that occur simultaneously or precede cardiac amyloidosis. Gene IGLV1-44 has been identified as a higher risk of cardiac affection.

Liver involvement leads to cholestasis and hepatomegaly. In cases where the liver is affected, hyperbilirubinemia may develop as a final stage. The IGKV1-33 germline mutation affects the liver [1]. Amyloid deposition in the kidney can affect renal interstitial or vascular cells can cause nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia and edema. The IGLV6-57 gene has been linked to an increased occurrence of renal manifestations [1].

Deposition in the flexor retinaculum causes nerve entrapment of the median nerve, manifesting as carpal tunnel syndrome. This syndrome occurs in half the patients with wtATTR and is often the earliest presenting symptom, usually preceding cardiac manifestations by several years [3]. Deposition in the ligamentum

flavum can cause spinal stenosis, usually in wtATTR. Also, one third of the patients with wtATTR present spontaneous rupture of the distal biceps tendon.

In contrast, hATTR manifests in various ways, usually at a younger age and present cardiomyopathy, peripheral or autonomic neuropathy, and vitreous opacities. Autonomic neuropathy can cause postural hypotension, erectile dysfunction and altered bowel movements (diarrhea or constipation), dry eyes, early satiety, neurogenic bladder [19]. Additionally, ATTR affects the heart's electrical system and can lead to arrhythmias such as atrial fibrillation, flutter, or AV blocks (**Figure 1**).

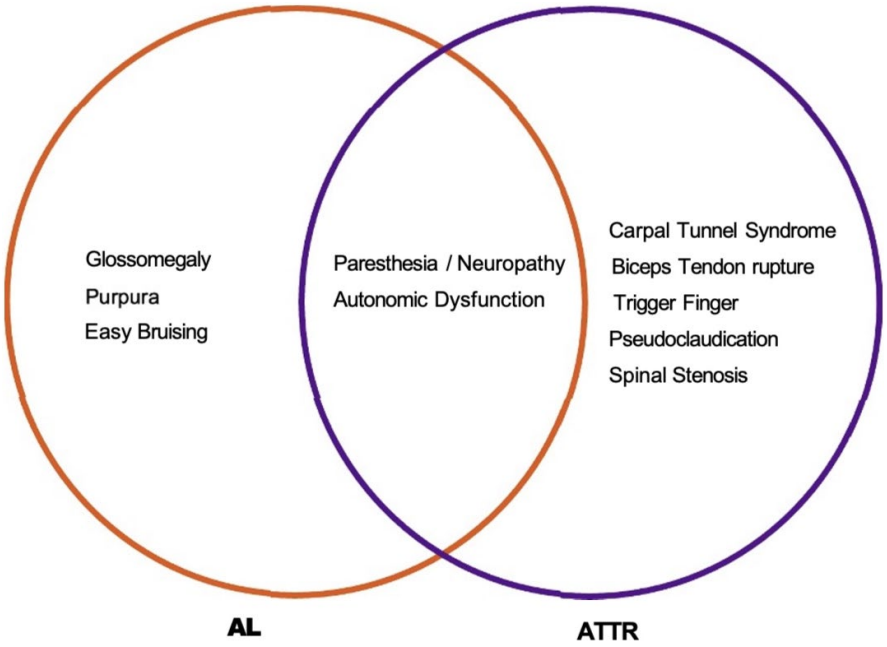

Figure 1. Clinical Presentation. Signs and symptoms associated with AL and ATTR Cardiac Amyloidosis.

A considerable degree of phenotypic overlap exists between AL and transthyretin ATTR amyloidosis, particularly in their clinical, radiological, and electrocardiographic profiles. Nonetheless, distinct extracardiac findings aid in subtype differentiation. AL amyloidosis is commonly associated with pathognomonic features such as periorbital purpura, a consequence of increased capillary fragility acquired factor X deficiency, and macroglossia or submandibular gland enlargement secondary to amyloid deposition in soft tissues [17].

Conversely, ATTR amyloidosis is more frequently linked to musculoskeletal involvement, manifesting as spontaneous rupture of the biceps tendon, lumbar spinal stenosis, and carpal tunnel syndrome, the latter often preceding cardiac manifestations by several years [17].

Both subtypes frequently involve multiple organ systems, with cardiac dysfunction, peripheral and autonomic neuropathy, and gastrointestinal manifestations representing common clinical features. Notably, ATTR tends to follow a protracted and indolent course, contrasting with the often-rapid progression observed in AL. This slow evolution of ATTR frequently contributes to its under-recognition, par-

ticularly in older adults, underscoring the necessity of heightened clinical vigilance and the implementation of non-invasive diagnostic algorithms [17].

5. Diagnosis

Clinical diagnosis remains challenging in ATTR as it is frequently misdiagnosed with entities that share similar signs or symptoms such as, hypertensive cardiomyopathy, hypertrophic cardiomyopathy, ischaemic heart disease, HFpEF and aortic stenosis. About 13% of patients initially diagnosed with diastolic heart failure, had cardiac amyloidosis. Therefore, maintaining a high clinical suspicion for CA is essential to prevent delays in diagnosis. A patient with heart failure (HF) that has a history of carpal tunnel syndrome, lumbar spinal stenosis, spontaneous biceps tendon rupture, sensorimotor neuropathy should raise suspicion of cardiac amyloidosis and require further assessment [20].

5.1. Biopsy

The gold-standard for the diagnosis is an endomyocardial biopsy, where multiple sites specimens are collected and visualized with Congo red staining with apple-green birefringence under polarized light [21]. Fat and bone marrow biopsies can also be performed to identify amyloid deposits. Fat deposits are positive in 70 to 75% of patients, nevertheless their absence does not exclude illness [7]. However, this is an invasive study.

5.2. Electrocardiogram

An electrocardiogram with a low voltage QRS (less than 5 mm in limb leads and less than 10 mm in precordial leads) should raise suspicion of cardiac amyloidosis [7]. However, the prevalence of low voltage QRS in ATTR is about 27%, therefore, in the absence of low voltage QRS, cardiac amyloidosis cannot be excluded [3]. Other features that can be seen in this study are pseudo-infarct pattern with Q waves in precordial limb leads, poor R wave progression and atrial arrhythmias such as atrial fibrillation [22] (**Figure 2**).

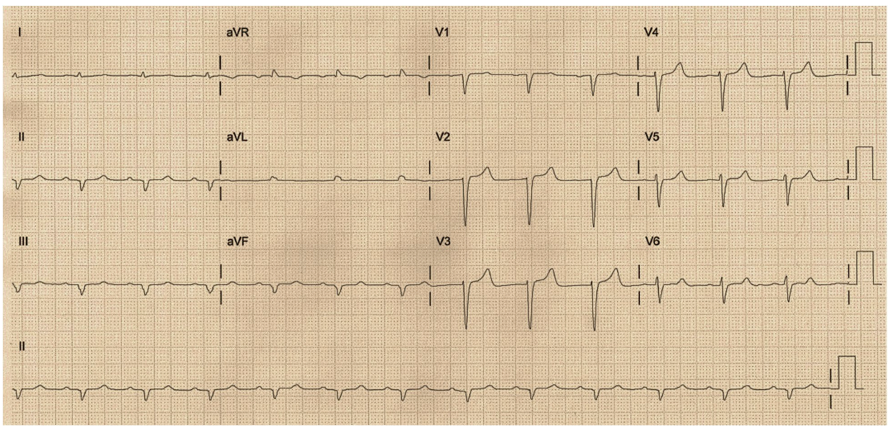

Figure 2. Electrocardiogram. Electrocardiogram in sinus rhythm, with right heart rotation, Q waves in the inferior and septal walls and low voltage QRS complexes.

5.3. Echocardiography

Echocardiography plays an important role in the initial assessment of ATTR due to its accessibility and cost-effectiveness. Characteristic findings include restrictive cardiomyopathy with left ventricular wall thickening, usually more than 12 mm, small left ventricle cavity, speckled appearance of the myocardium, often reported as "granular sparkling", also pericardial effusion can be present [23] (Video 1, Video 2).

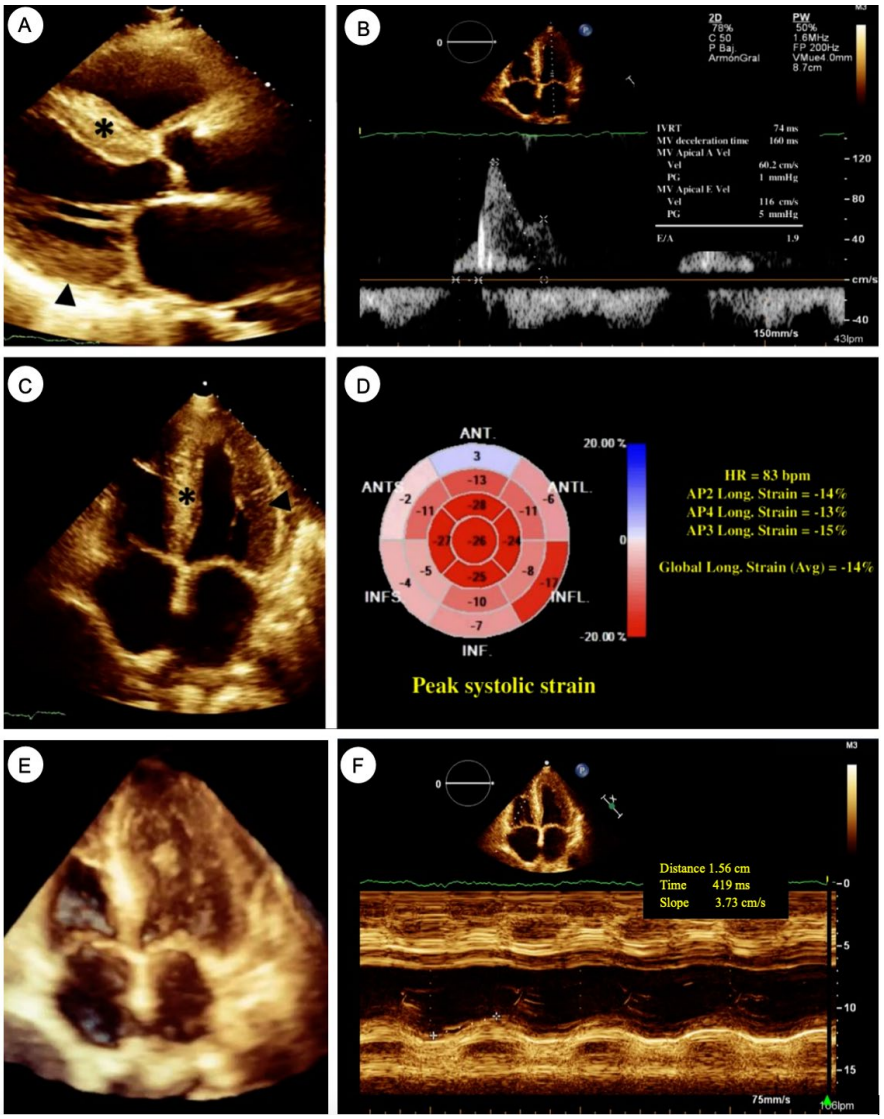

Figure 3. 2D and 3D transthoracic echocardiography. 2D and 3D transthoracic echocardiography. A) Parasternal long axis view revealing increased thickening of LV wall > 12 mm (*interventricular septum). B) Apical 4-chamber view with type III diastolic dysfunction. C) Four chamber view showing increased thickening of the LV walls with sparkling appearance of the interventricular septum. D) Peak systolic strain (speckle tracking) with a decreased global longitudinal strain and "apical sparing". E) 3D four chamber view demonstrating increased thickening of the atrioventricular valve leaflets and interatrial septum. F) RV systolic dysfunction with decreased displacement of the systolic plane of the tricuspid annulus (TAPSE). Abbreviations: Left ventricle (LV); Right ventricle; Systolic plane of the tricuspid annulus (TAPSE).

Enlargement of the left atrium, reduced mitral annular plane systolic excursion, valve, and septal thickening are also findings, along with simultaneous decreases in cardiac output and blood pressure [9] (**Table 1**, Video 3, Video 4).

Strain has emerged as a useful tool to assess ATTR amyloidosis, as cardiac amyloidosis affects longitudinal function in anticipation of radial function, significantly a left ventricular ejection fraction-to-strain ratio greater than 4 and a reduction in the apical-to-basal strain ratio of more than 2.1, in conjunction with clinical findings, increases the suspicion of this disease [24]. In comparison to ATTR-CA, AL-CA shows higher strain values for a specific wall thickness [5] [18]. Therefore, ejection fraction can be preserved until late stages of this disease, systolic and diastolic dysfunction can also be present, identified by steep deceleration time, reduced tissue Doppler velocity at the mitral annulus or E1 < 8 cm/s, and an elevated E/e1 ratio > 14 [9] [23]. Speckle tracking imaging can help differentiate between causes of myocardium wall thickening (hypertension and hypertrophic

Table 1. Imaging findings in ATTR cardiac amyloidosis.

	Echocardiography
Parasternal long axis view	Increased LV wall thickness (>12 mm) and increased relative wall thickness (>0.42) Speckled appearance of the myocardium or "granular sparkling" Thickened mitral and aortic valve Hyperechogenicity of septum Atrial enlargement
Parasternal short axis view	Abnormal movement of the mid-segment and base with preserved apex function
Subcostal view	Presence of pericardial effusion
Tissue Doppler	Reduced tissue Doppler s′, e′, and a′ velocities (all <5 cm/s) Low MAPSE values less than 10 mm indicating loss of longitudinal function
Strain (Speckle tracking)	Decreased global longitudinal LV strain (absolute value less than 16%) **"Cherry-on-the-top"** sign on STE longitudinal strain bull's eye map (preservation of apical longitudinal strain with severely abnormal basal and mid-LV longitudinal strain)
	Cardiac Magnetic Resonance
Increased LV wall thickness: > laboratory ULN for sex on SSFP cine CMR and increased relative wall thickness >0.42 cm LV stroke volume index (<35 mL/m^2) Abnormal LGE pattern • Diffuse LGE • Subendocardial LGE • Patchy LGE • Difficulty in achieving myocardial nulling over a range of inversion times • Dark blood pool signal	
Radionuclide Imaging (99mTc-PYP/99mTc-DPD/99mTc-HMDP	
Diffuse myocardial uptake of 99mTc-PYP/99mTc-DPD/99mTc-HMDP visually confirmed, a semiquantitative visual grade of 2 or 3.	

Imaging findings in ATTR cardiac amyloidosis Cardiac magnetic resonance (CMR); Late gadolinium enhancement (LGE); Left ventricle (LV); Mitral Annular Plane Systolic Excursion. (MAPSE); Speckle-tracking echocardiography (STE); Steady-state free-precession (SSFP); Upper limit of normal (ULN).

cardiomyopathy) revealing involvement of the basal and mid-segment causing a diminished global longitudinal strain, however there is a characteristic "apical sparing" pattern, resembling a cherry on top in the bull's eye mapping [25] (**Figure 1**). Also, in atrial amyloid infiltration, atrial strain can be affected in its 3 phases: reservoir, conduct and contraction (**Figure 3**).

5.4. Cardiac Magnetic Resonance

Another non-invasive imaging method that can accurately diagnose cardiac amyloidosis is CMR, which provides detailed findings such as cardiac anatomy, it can also help to determine the presence of wall thickness which is directly related to cardiac fiber infiltration, initially amyloid deposition is limited to sub-endocardium and small cardiac segments which becomes diffuse with the progression of the disease [18] [26]. Late gadolinium enhancement of the left ventricle and atria is a characteristic of CA, often detectable before changes are seen on echocardiography. CMR can also detect extracellular volume (ECV) which is increased in CA and is valuable for predicting survival outcomes [9] [27]. CMR parameters of T1, T2, and T2* produce signals that can distinguish the structural characteristics of the myocardium and provide tissue details, including myocyte and extracellular volume. T1 mapping is a useful technique when gadolinium is not recommended, high native T1 values are present in CA. In contrast, T2 mapping is used to detect edema [5] [22] (**Figure 4**).

CMR allows detailed assessment of heart tissue to differentiate between amyloidosis subtypes. AL amyloidosis typically shows diffuse subendocardial late gadolinium enhancement (LGE), while ATTR is associated with widespread transmural LGE and increased left ventricular mass. Advanced techniques like T1 and T2 mapping aid this distinction, with T2 mapping showing elevated values in AL amyloidosis. Additionally, extracellular volume (ECV) assessment reveals that AL usually has higher ECV measurements than ATTR, making it a valuable parameter for differentiation [13] [14].

5.5. Nuclear Scintigraphy

Similarly, another useful image technique is nuclear scintigraphy with the use of bone-avid radiotracers. There are three main phosphonate tracers labeled with 99mTc that are routinely used for CA evaluation: 3,3-diphosphono1, 2-propanodicarboxylic acid (DPD), hydroxymethylene diphosphonate (HMDP), and pyrophosphate (PYP) [28] [29]. These radiotracers have a higher sensitivity and specificity for ATTR amyloidosis [30]. If there's a positive radiotracer scan with an immunoglobulin abnormality, tissue must be obtained for mass spectroscopic analysis, this is currently considered as the most effective, with a sensitivity of 88% and a specificity of 96% [1] [18].

Tc-99m bone scintigraphy proves particularly valuable for identifying ATTR. When monoclonal proteins are absent, and there is marked myocardial radiotracer accumulation, the likelihood of ATTR is high. Although low-grade uptake

can sporadically occur in AL amyloidosis, it tends to be less intense and diagnostically nonspecific. Therefore, the presence of significant myocardial uptake on Tc-99m imaging, coupled with the exclusion of monoclonal gammopathy, reliably favors a diagnosis of ATTR [11] [15] (**Table 2**).

5.6. Biomarkers

The evaluation of cardiac biomarkers constitutes an essential component in the diagnostic framework of CA, particularly during the initial stages of clinical assessment. In the setting of ATTR, serum concentrations of biomarkers tend to be

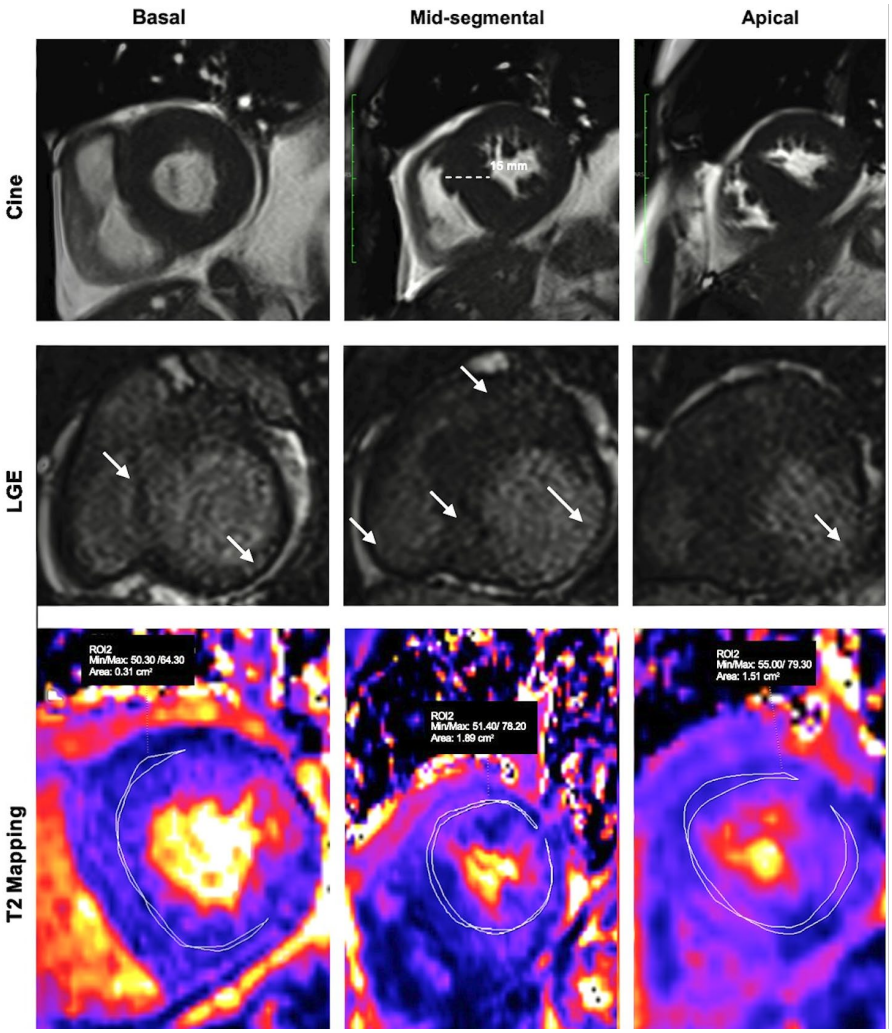

Figure 4. Cardiac magnetic resonance findings of cardiac amyloidosis. Cardiac magnetic resonance (CMR) findings of cardiac amyloidosis. Cine, late gadolinium enhancement (LGE), and T2 mapping in basal/mid-segmental/apical segments. Cine-Short axes view demonstrating LV concentric hypertrophy with an anteroseptal diameter of 15 mm. Late gadolinium enhancement (LGE)—images showing diffuse transmural nonischemic late enhancement patterns in LV and RV free wall (white arrows). T2 mapping—with increased relaxation time and reactive edema suggestive of amyloid infiltration. Abbreviations: Cardiac magnetic resonance (CMR); late gadolinium enhancement (LGE); left ventricle (LV); right ventricle (RV).

Table 2. Comparative table of imaging modalities summarizing their key features.

	Imaging Modalities
Cardiac Magnetic Resonance (CMR)	• Late gadolinium enhancement (LGE) is highlighted as a critical diagnostic marker CMR imaging. • For cardiac AL amyloidosis, diffuse septal subendocardial LGE demonstrates: Sensitivity of 88% and Specificity of 100%. • Non-invasive imaging modality. • Allows for precise quantification and localization of myocardial infiltration. • Effective in assessing the extent of cardiac involvement in amyloidosis. • Reduced capacity to differentiate between amyloidosis subtypes (AL vs. ATTR). • Higher cost and limited availability in certain clinical settings, which may restrict widespread use compared to other imaging techniques. [39]
Single Photon Emission Computed Tomography (SPECT)	• Particularly when combined with bone-avid technetium-labeled radiotracers, is highly effective in the evaluation of ATTR. (With Tc-HMDP sensitivity reaches up to 99%, and Tc-PYP specificity can be as high as 95%). • SPECT imaging has significantly advanced the non-invasive diagnosis of ATTR. • Currently considered a standard and validated component of the diagnostic algorithm for ATTR-CA. • Limited diagnostic utility for AL amyloidosis, as bone-seeking tracers do not typically accumulate in AL-related deposits. • Dependence on availability of specific radiotracers, which may limit its accessibility in certain healthcare settings. [40] [41]
Positron Emission Tomography (PET)	• Imaging with amyloid-specific radiotracers demonstrates sensitivity of 95% and specificity of 98%. • Capable of detecting both ATTR and AL. • Provides quantitative evaluation of myocardial amyloid burden. • Useful for monitoring disease progression and response to therapy in research settings. • Not yet broadly approved for routine clinical use in the diagnosis of cardiac amyloidosis. • High cost and limited access restrict its widespread implementation in standard diagnostic workflows. [42]
Echocardiography	• Identifies structural changes associated with amyloid infiltration. • Non-invasive and widely accessible, making it suitable for initial evaluation and offers real-time assessment of cardiac anatomy and function. • Speckle-tracking echocardiography (STE) enhances diagnostic precision by measuring longitudinal systolic strain and detecting early myocardial dysfunction. • Limited specificity due to overlap with other conditions such as hypertrophic cardiomyopathy or hypertensive heart disease. • May fail to detect subtle or early-stage amyloid infiltration. • • Reported diagnostic metrics vary: Sensitivity approximately 74.6% and Specificity approximately 62.5% [43]-[46].

Comparative table of imaging modalities summarizing their key features in advantages, disadvantages, sensitivity, specificity and limitations of imaging.

markedly elevated in wATTR compared to variant forms. This disparity is primarily attributed to the advanced age and frequent renal impairment observed

among patients with the wild-type phenotype [31].

Natriuretic peptides and troponin levels have been extensively studied in patients with CA. High levels of Troponin, brain natriuretic peptide (BNP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are associated with a worse prognosis [32]. In the context of CA, measurement in serum and urine of serum-free light chains (FLC) and detection of monoclonal proteins through immunofixation and electrophoresis have high sensitivity reaching 99% for identifying AL-CA. Natriuretic peptides are disproportionately elevated relative to left ventricular systolic function. Specifically, NT-proBNP levels tend to be higher in patients with AL-CA compared to those with ATTR. NT-proBNP serves not only as a marker for cardiac involvement but also as a prognostic indicator in AL-CA. Furthermore, both troponin T and troponin I serve as a specific marker of cardiac injury, elevated levels in AL have been associated with poor survival outcomes [22].

In contrast, among individuals with hATTR, biomarker levels may exhibit considerable heterogeneity, influenced by both the specific genotypic mutation and the degree of cardiac infiltration. Of clinical relevance, the presence of low circulating biomarker levels in this subgroup has been proposed as a negative predictive marker, potentially allowing for the safe exclusion of significant cardiac involvement and thus avoiding unnecessary invasive or high-cost diagnostic procedures [31].

Accurate subtype differentiation is crucial in diagnosing cardiac amyloidosis (CA), as approximately 95% of cases are due to AL or ATTR forms. Early identification of AL amyloidosis is particularly important due to its rapid progression and potential response to targeted therapies. The initial diagnostic protocol should include tests for monoclonal immunoglobulin components, essential for diagnosing AL-type amyloid deposits. Recommended tests are Serum Protein Electrophoresis with Immunofixation (SPIE), Urine Protein Electrophoresis with Immunofixation (UPIE), and serum free light chain (FLC) quantification with kappa-to-lambda ratio calculation [31].

A negative result for monoclonal protein in both serum and urine, alongside a normal kappa/lambda ratio, effectively excludes AL amyloidosis, allowing a focus on ATTR amyloidosis. If tests are abnormal, an early referral to a hematology specialist is needed for evaluation of potential clonal plasma cell disorders, such as multiple myeloma. Despite the effectiveness of this triad of tests, many patients with suspected CA do not receive complete laboratory evaluation, posing a barrier to timely diagnosis and management [31].

Consequently, the systematic implementation of standardized diagnostic algorithms anchored in laboratory, imaging, and clinical data integration is essential to ensure accurate classification and facilitate evidence-based treatment strategies for patients with cardiac amyloidosis. To optimize diagnostic precision and minimize delays in detection, current recommendations advocate for the systematic integration of biomarker profiling with clinical judgment and multimodal imag-

ing techniques. This composite diagnostic strategy is especially pertinent in the early phases of the diagnostic algorithm for systemic amyloidosis, facilitating informed therapeutic decision-making and improving the overall efficiency of the diagnostic process [31].

6. Management

The management of ATTR, has witnessed significant advancements in recent years. Early and accurate diagnosis is crucial and highly associated with improving morbidity and mortality, and once identified, patients can benefit from a multidisciplinary approach that combines conventional heart failure management with novel targeted therapies.

6.1. TTR Stabilizers

Tafamidis is the primary TTR stabilizer approved for treating ATTR, it binds to the thyroxine-binding sites of TTR, stabilizing the tetramer and preventing dissociation into misfolded monomers that form amyloid fibrils [11]. By preventing the dissociation of TTR tetramers and the subsequent misfolding of TTR protein to monomers, tafamidis can slow the progression of the disease by decreasing amyloid deposits, leading to improved cardiac function. However, this medication does not remove infiltrated amyloid fibers [33]. Clinical trials have shown reductions in mortality and hospitalizations by approximately 30%. Tafamidis has demonstrated a reduction in cardiovascular-related hospitalizations, particularly in patients with New York Heart Association (NYHA) Classes I and II, and enhances survival rates for patients with Classes I–III, with the greatest benefit observed in those within Classes I and II [33]. However, it does not reverse existing amyloid deposits and is most effective when given early in the disease [11].

6.2. Gene Silencing Therapies

Patisiran and inotersen are RNA interference (RNAi) therapies that are double-stranded RNA molecules that target the expression of TTR gene causing hence interfering and degradation. These therapies have shown remarkable efficacy in both cardiac and neurological aspects of hereditary ATTR (hATTR) amyloidosis [2]. Patisiran and inotersen reduce the production of abnormal TTR protein, thereby slowing disease progression. Patisiran is a small interfering RNA (siRNA), while inotersen is an antisense oligonucleotide (ASO). Both therapies have demonstrated effectiveness in decreasing TTR levels and improving neuropathy and quality of life for patients with hATTR amyloidosis. Furthermore, Patisiran has shown potential in enhancing cardiac outcomes in patients with ATTR-CM, as evidenced by the APOLLO-B trial, however, it has not yet received FDA approval for this use [34]. Furthermore, patisiran also has shown a reduction of wall thickening, improved longitudinal strain and increased left ventricle (LV) diastolic function, among the adverse effects that may occur are abdominal pain, nausea, back pain and flushing. Although Inotersen has not been shown to have an

impact on echocardiogram parameters, it has demonstrated decreasing LV mass and improving 6-minute walk test, substantially mild to moderate adverse events were identified as fever, headache, thrombocytopenia and nausea [35]. While these therapies are generally well-tolerated, they do require regular administration, which may pose challenges for patient compliance and increase the treatment burden [34].

6.3 Emerging Therapies

CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing techniques hold potential for directly correcting genetic mutations underlying hATTR [2]. This therapy is considered a promising option treatment for gene-mediated diseases, because it regulates TTR production through gene silencing. As a result, it prevents the development of pathogenic ATTR amyloid fibrils. However, the most common side effects include nausea, headache, and rhinorrhea [35]. Monoclonal antibodies, such as PRX004, are being investigated as potential treatments to target and bind misfolded TTR amyloid and disrupt their pathogenicity [36]. This gene editing technology offers a new way to directly target and reduce the expression of the TTR gene. The CRISPR-Cas9-based therapy is currently in early stage clinical development. It has the potential to be a one-time treatment that could provide long-lasting benefits by permanently decreasing TTR production. However, the long-term safety and effectiveness of this approach have yet to be fully established [37] [38].

7. Conclusion

In conclusion, the introduction of new therapeutic drugs and regimens, along with early diagnosis, has led to an improvement in patient survival rates. The management of ATTR amyloidosis has improved with the use of targeted therapies like tafamidis, gene silencing, and emerging treatments such as gene editing and monoclonal antibodies. Continued research and innovation remain essential to further improving the patient outcomes. In the realm of imaging modalities employed for cardiac amyloidosis, various therapeutic interventions can significantly influence diagnostic performance metrics by potentially altering the disease trajectory and the amyloid burden, as evidenced in imaging findings. For instance, effective stabilization or silencing of TTR may result in observable modifications in myocardial structure and function through imaging techniques. Nonetheless, the cost-effectiveness of these therapies, particularly gene editing, warrants careful consideration due to the substantial expenses associated with advanced biotechnological interventions. Consequently, the selection of therapy should be personalized to align with the patient's disease stage, individual characteristics, and the resources available.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sanchorawala, V. (2024) Systemic Light Chain Amyloidosis. *New England Journal of Medicine*, **390**, 2295-2307. https://doi.org/10.1056/nejmra2304088

[2] Raval, M., Siddiq, S., Sharma, K., Sanghvi, L., Jain, A., Patel, S., *et al.* (2023) A Review of Recent Advances in the Diagnosis of Cardiac Amyloidosis, Treatment of Its Cardiac Complications, and Disease-Modifying Therapies. *F1000Research*, **12**, Article 192. https://doi.org/10.12688/f1000research.130285.1

[3] Porcari, A., Fontana, M. and Gillmore, J.D. (2022) Transthyretin Cardiac Amyloidosis. *Cardiovascular Research*, **118**, 3517-3535. https://doi.org/10.1093/cvr/cvac119

[4] Ruberg, F.L., Grogan, M., Hanna, M., Kelly, J.W. and Maurer, M.S. (2019) Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*, **73**, 2872-2891. https://doi.org/10.1016/j.jacc.2019.04.003

[5] Dorbala, S., Cuddy, S. and Falk, R.H. (2020) How to Image Cardiac Amyloidosis: A Practical Approach. *JACC*: *Cardiovascular Imaging*, **13**, 1368-1383. https://doi.org/10.1016/j.jcmg.2019.07.015

[6] Ioannou, A., Patel, R.K., Razvi, Y., Porcari, A., Sinagra, G., Venneri, L., *et al.* (2022) Impact of Earlier Diagnosis in Cardiac ATTR Amyloidosis over the Course of 20 Years. *Circulation*, **146**, 1657-1670. https://doi.org/10.1161/circulationaha.122.060852

[7] Allegra, A., Mirabile, G., Tonacci, A., Genovese, S., Pioggia, G. and Gangemi, S. (2023) Machine Learning Approaches in Diagnosis, Prognosis and Treatment Selection of Cardiac Amyloidosis. *International Journal of Molecular Sciences*, **24**, Article 5680. https://doi.org/10.3390/ijms24065680

[8] Bukhari, S. (2023) Cardiac Amyloidosis: State-of-the-Art Review. *Journal of Geriatric Cardiology*, **20**, 361-375. https://doi.org/10.26599/1671-5411.2023.05.006

[9] Rubin, J. and Maurer, M.S. (2020) Cardiac Amyloidosis: Overlooked, Underappreciated, and Treatable. *Annual Review of Medicine*, **71**, 203-219. https://doi.org/10.1146/annurev-med-052918-020140

[10] Kittleson, M.M., Maurer, M.S., Ambardekar, A.V., Bullock-Palmer, R.P., Chang, P.P., Eisen, H.J., *et al.* (2020) Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement from the American Heart Association. *Circulation*, **142**, e7-e22. https://doi.org/10.1161/cir.0000000000000792

[11] Heidenreich, P.A., Bozkurt, B., Aguilar, D., Allen, L.A., Byun, J.J., Colvin, M.M., *et al.* (2022) 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. *Journal of the American College of Cardiology*, **79**, e263-e421.

[12] Tziomalos, G., Zegkos, T., Baltagianni, E., Bazmpani, M., Exadaktylou, P., Parcharidou, D., *et al.* (2025) Transthyretin Amyloid Cardiomyopathy: Current Diagnostic Approach and Risk Stratification with Multimodality Imaging. *Journal of Clinical Medicine*, **14**, Article 2014. https://doi.org/10.3390/jcm14062014

[13] Kravchenko, D., Isaak, A., Zimmer, S., Öztürk, C., Mesropyan, N., Bischoff, L.M., *et al.* (2024) Parametric Mapping Using Cardiovascular Magnetic Resonance for the Differentiation of Light Chain Amyloidosis and Transthyretin-Related Amyloidosis. *European Heart Journal-Cardiovascular Imaging*, **25**, 1451-1461. https://doi.org/10.1093/ehjci/jeae154

[14] Martinez-Naharro, A., Treibel, T.A., Abdel-Gadir, A., Bulluck, H., Zumbo, G., Knight, D.S., *et al.* (2017) Magnetic Resonance in Transthyretin Cardiac Amyloidosis. *Journal of the American College of Cardiology*, **70**, 466-477. https://doi.org/10.1016/j.jacc.2017.05.053

[15] Fontana, M., Ćorović, A., Scully, P. and Moon, J.C. (2019) Myocardial Amyloidosis. *JACC*: *Cardiovascular Imaging*, **12**, 2345-2356. https://doi.org/10.1016/j.jcmg.2019.06.023

[16] Ioannou, A., Patel, R.K., Razvi, Y., Porcari, A., Knight, D., Martinez-Naharro, A., *et al.* (2023) Multi-Imaging Characterization of Cardiac Phenotype in Different Types of Amyloidosis. *JACC*: *Cardiovascular Imaging*, **16**, 464-477. https://doi.org/10.1016/j.jcmg.2022.07.008

[17] Ahammed, M.R. and Ananya, F.N. (2024) Cardiac Amyloidosis: A Comprehensive Review of Pathophysiology, Diagnostic Approach, Applications of Artificial Intelligence, and Management Strategies. *Cureus*, **16**, e63673. https://doi.org/10.7759/cureus.63673

[18] Gertz, M.A. (2023) Immunoglobulin Light Chain Amyloidosis: 2024 Update on Diagnosis, Prognosis, and Treatment. *American Journal of Hematology*, **99**, 309-324. https://doi.org/10.1002/ajh.27177

[19] Muchtar, E., Dispenzieri, A., Magen, H., Grogan, M., Mauermann, M., McPhail, E.D., *et al.* (2020) Systemic Amyloidosis from a (AA) to T (ATTR): A Review. *Journal of Internal Medicine*, **289**, 268-292. https://doi.org/10.1111/joim.13169

[20] Adams, D., Ando, Y., Beirão, J.M., Coelho, T., Gertz, M.A., Gillmore, J.D., *et al.* (2021) Expert Consensus Recommendations to Improve Diagnosis of ATTR Amyloidosis with Polyneuropathy. *Journal of Neurology*, **268**, 2109-2122. https://doi.org/10.1007/s00415-019-09688-0

[21] Yamamoto, H. and Yokochi, T. (2019) Transthyretin Cardiac Amyloidosis: An Update on Diagnosis and Treatment. *ESC Heart Failure*, **6**, 1128-1139. https://doi.org/10.1002/ehf2.12518

[22] Jung, M., Chang, S., Han, E.J. and Youn, J. (2022) Multimodal Imaging and Biomarkers in Cardiac Amyloidosis. *Diagnostics*, **12**, Article 627. https://doi.org/10.3390/diagnostics12030627

[23] Chacko, L., Martone, R., Cappelli, F. and Fontana, M. (2019) Cardiac Amyloidosis: Updates in Imaging. *Current Cardiology Reports*, **21**, Article No. 108. https://doi.org/10.1007/s11886-019-1180-2

[24] Liang, S., Liu, Z., Li, Q., He, W. and Huang, H. (2023) Advance of Echocardiography in Cardiac Amyloidosis. *Heart Failure Reviews*, **28**, 1345-1356. https://doi.org/10.1007/s10741-023-10332-3

[25] Korosoglou, G., Giusca, S., André, F., aus dem Siepen, F., Nunninger, P., Kristen, A.V., *et al.* (2021) Diagnostic Work-Up of Cardiac Amyloidosis Using Cardiovascular Imaging: Current Standards and Practical Algorithms. *Vascular Health and Risk Management*, **17**, 661-673. https://doi.org/10.2147/vhrm.s295376

[26] Starr, N., Ioannou, A. and Martinez-Naharro, A. (2024) Monitoring Cardiac Amyloidosis with Multimodality Imaging. *Revista Española de Cardiología* (*English Edition*), **77**, 79-87. https://doi.org/10.1016/j.rec.2023.06.014

[27] Gertz, M.A. (2022) Cardiac Amyloidosis. *Heart Failure Clinics*, **18**, 479-488. https://doi.org/10.1016/j.hfc.2022.02.005

[28] Scheel, P.J., Mukherjee, M., Hays, A.G. and Vaishnav, J. (2022) Multimodality Imag-

ing in the Evaluation and Prognostication of Cardiac Amyloidosis. *Frontiers in Cardiovascular Medicine*, **9**, Article 787618. https://doi.org/10.3389/fcvm.2022.787618

[29] Hanna, M., Ruberg, F.L., Maurer, M.S., Dispenzieri, A., Dorbala, S., Falk, R.H., *et al.* (2020) Cardiac Scintigraphy with Technetium-99m-Labeled Bone-Seeking Tracers for Suspected Amyloidosis: JACC Review Topic of the Week. *Journal of the American College of Cardiology*, **75**, 2851-2862. https://doi.org/10.1016/j.jacc.2020.04.022

[30] Wang, T.K.M., Hassan, O.K.A., Jaber, W. and Xu, B. (2020) Multi-Modality Imaging of Cardiac Amyloidosis: Contemporary Update. *World Journal of Radiology*, **12**, 87-100. https://doi.org/10.4329/wjr.v12.i6.87

[31] Briasoulis, A., Bampatsias, D., Papamichail, A., Kuno, T., Skoularigis, J., Xanthopoulos, A., *et al.* (2023) Invasive and Non-Invasive Diagnostic Pathways in the Diagnosis of Cardiac Amyloidosis. *Journal of Cardiovascular Development and Disease*, **10**, Article 256. https://doi.org/10.3390/jcdd10060256

[32] Castiglione, V., Franzini, M., Aimo, A., Carecci, A., Lombardi, C.M., Passino, C., *et al.* (2021) Use of Biomarkers to Diagnose and Manage Cardiac Amyloidosis. *European Journal of Heart Failure*, **23**, 217-230. https://doi.org/10.1002/ejhf.2113

[33] Ogieuhi, I.J., Ugiomoh, O.M., Muzofa, K., Callender, K., Ayodeji, J.D., Nnekachi, N.P., *et al.* (2024) Tafamidis Therapy in Transthyretin Amyloid Cardiomyopathy: A Narrative Review from Clinical Trials and Real-World Evidence. *The Egyptian Heart Journal*, **76**, Article No. 90. https://doi.org/10.1186/s43044-024-00517-y

[34] Dohrn, M.F., Ihne, S., Hegenbart, U., Medina, J., Züchner, S.L., Coelho, T., *et al.* (2020) Targeting Transthyretin-Mechanism-Based Treatment Approaches and Future Perspectives in Hereditary Amyloidosis. *Journal of Neurochemistry*, **156**, 802-818. https://doi.org/10.1111/jnc.15233

[35] Ioannou, A., Fontana, M. and Gillmore, J.D. (2023) RNA Targeting and Gene Editing Strategies for Transthyretin Amyloidosis. *BioDrugs*, **37**, 127-142. https://doi.org/10.1007/s40259-023-00577-7

[36] Griffin, J.M., Rosenthal, J.L., Grodin, J.L., Maurer, M.S., Grogan, M. and Cheng, R.K. (2021) ATTR Amyloidosis: Current and Emerging Management Strategies: JACC: CardioOncology State-of-the-Art Review. *JACC*: *CardioOncology*, **3**, 488-505. https://doi.org/10.1016/j.jaccao.2021.06.006

[37] Maurer, M.S. (2022) Overview of Current and Emerging Therapies for Amyloid Transthyretin Cardiomyopathy. *The American Journal of Cardiology*, **185**, S23-S34. https://doi.org/10.1016/j.amjcard.2022.10.014

[38] Bampatsias, D., Wardhere, A. and Maurer, M.S. (2024) Treatment of Transthyretin Cardiac Amyloidosis. *Current Opinion in Cardiology*, **39**, 407-416. https://doi.org/10.1097/hco.0000000000001156

[39] Dohy, Z., Szabo, L., Pozsonyi, Z., Csecs, I., Toth, A., Suhai, F.I., *et al.* (2022) Potential Clinical Relevance of Cardiac Magnetic Resonance to Diagnose Cardiac Light Chain Amyloidosis. *PLOS ONE*, **17**, e0269807. https://doi.org/10.1371/journal.pone.0269807

[40] Wu, Z. and Yu, C. (2021) Diagnostic Performance of CMR, SPECT, and PET Imaging for the Detection of Cardiac Amyloidosis: A Meta-Analysis. *BMC Cardiovascular Disorders*, **21**, Article No. 482. https://doi.org/10.1186/s12872-021-02292-z

[41] Clerc, O.F., Vijayakumar, S. and Dorbala, S. (2024) Radionuclide Imaging of Cardiac Amyloidosis: An Update and Future Aspects. *Seminars in Nuclear Medicine*,

54, 717-732. https://doi.org/10.1053/j.semnuclmed.2024.05.012

[42] Kim, Y.J., Ha, S. and Kim, Y. (2020) Cardiac Amyloidosis Imaging with Amyloid Positron Emission Tomography: A Systematic Review and Meta-Analysis. *Journal of Nuclear Cardiology*, **27**, 123-132. https://doi.org/10.1007/s12350-018-1365-x

[43] Bozkurt, B., Colvin, M., Cook, J., Cooper, L.T., Deswal, A., Fonarow, G.C., *et al.* (2016) Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement from the American Heart Association. *Circulation*, **134**, e579-e646. https://doi.org/10.1161/cir.0000000000000455

[44] Dorbala, S., Ando, Y., Bokhari, S., Dispenzieri, A., Falk, R.H., Ferrari, V.A., *et al.* (2021) ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging. *Circulation*: *Cardiovascular Imaging*, **14**, e000029. https://doi.org/10.1161/hci.0000000000000029

[45] De Carli, G., Mandoli, G.E., Salvatici, C., Biagioni, G., Marallo, C., Turchini, F., *et al.* (2023) Speckle Tracking Echocardiography in Plasma Cell Disorders: The Role of Advanced Imaging in the Early Diagnosis of AL Systemic Cardiac Amyloidosis. *International Journal of Cardiology*, **389**, Article 131599. https://doi.org/10.1016/j.ijcard.2023.131599

[46] del Carmen Mallón Araujo, M., Casas, E.A.J., Casas, C.A.J., Monzonis, M.A.M., Morell, Á.R. and Núñez, V.P. (2024) Cardiac Scintigraphy and Echocardiography Assessment in the Diagnosis of Transthyretin Cardiac Amyloidosis. *The International Journal of Cardiovascular Imaging*, **40**, 415-424. https://doi.org/10.1007/s10554-023-02987-8

Abbreviations

CA	Cardiac amyloidosis
AL	Immunoglobulin light chain cardiac amyloidosis
ATTR	Transthyretin cardiac amyloidosis
TTR	Transthyretin
HFpEF	Ejection fraction heart failure
CMR	Cardiac magnetic resonance
AL	Immunoglobulin light chain amyloidosis
wtATTR	Wild-type
hATTR	Hereditary
AV	Atrioventricular
HF	Heart failure
ECV	extracellular volume
DPD	3,3-diphosphono1, 2-propanodicarboxylic acid
HMDP	Hydroxymethylene diphosphonate
PYP	Pyrophosphate
BNP	Brain natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
FLC	Free light chains
NYHA	New York Heart Association
RNAi	RNA interference
LV	Increased left ventricle
CRISPR-Cas9	Clustered Regularly Interspaced Short Palindromic Repeats