



# Are we under Diagnosing Cardiac Amyloidosis in the Aged Population?

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## Abstract

Heart Failure is a common condition in the aged population with a multitude of underlying causes. Cardiac Amyloidosis (CA) is now known to play a significant role in the development of heart failure in aged patients. However, CA remains underappreciated as a cause of heart failure and continues to go undiagnosed. The clinical manifestations of CA are non-specific cardiac findings (e.g. heart failure, dyspnea, atrial arrhythmias) and potential multi-system dysfunction (liver, kidney, and/or nervous system) making a high index of suspicion crucial to CA diagnosis. Some laboratory results and electrocardiographic findings can increase suspicion of CA in aged patients. However, none of those findings are diagnostic nor can their absence rule out the disease. Several echocardiographic findings should increase suspicion for CA, but of these, depressed global longitudinal strain with relative apical sparing is the most sensitive and specific to CA and warrants further investigation. Cardiac MRI can accurately identify all types of CA, even in early-stage disease. Diffuse late gadolinium enhancement as well as increased T1 native and extracellular volume on cardiac MRI are highly sensitive and specific markers but cannot yet definitively type the off ending amyloid protein. Nuclear bone scintigraphy can diagnose one type of CA, but all other suspected cases require endomyocardial biopsy for diagnosis. Recently, several promising disease-modifying therapies have emerged that can improve outcomes in CA patients. These treatments are most effective in early-stage disease, further emphasizing the need for more frequent early-diagnosis.

## Introduction

Heart Failure (HF) is common in the aged population and has many underlying aetiologies. Until recently, the significance of Cardiac Amyloidosis (CA) as a cause of HF in older patients has been under appreciated [1]. CA is caused by the accumulation of misfolded proteins in the cardiac interstitium, resulting in the loss of normal cardiac architecture and eventually cardiac dysfunction [2]. At least 30 different proteins can form amyloid fibrils and deposit in the heart, however, most CA results from either monoclonal light-chain Amyloidosis (AL), or a transthyretin-related amyloidosis (ATTR) [3,4]. ATTRs occur exclusively in the aged population and are further separated into mutant ATTR (ATTRm) and wild-type ATTR (ATTRwt) [3]. Regardless of the protein responsible, CA plays a significant role in the development of HF in the aged population.

Due to improved diagnostic techniques and an increased disease burden associated with the aging population, diagnoses of CA in elderly patients presenting with HF have surged in the last 5 years [5-7]. In the past the prevalence of CA was estimated to be 1/100,000, but recent literature suggests these figures were significantly underestimated [6-8, 10]. New studies suggest 13% to 18% of all patients hospitalizations for HF with preserved ejection fraction (HFpEF) are attributable to ATTRwt and 30% of patients with HFpEF have cardiac amyloid deposits on autopsy [11-13]. Interestingly, 3% to 4% of African-American and Afro-Caribbean individuals also carry an ATTRm-causing mutation [14,15]. This significantly increases the risk of CA-related HF in these populations as they age [16].

Development of disease-modifying therapies is transforming CA from an incurable disease into a manageable chronic condition, especially if diagnosed early in the disease process [17]. However, a belief that CA is rare, and an incomplete understanding of how to diagnose and manage the disease continue to prevent early diagnosis [1]. This review aims to promote a high index of suspicion for CA in the context of HF in aged patients and to provide a framework for CA work-up and management.

## Clinical Diagnosis

Recent findings suggest increased suspicion of CA is warranted in hypertensive patients

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**Table 1:** The 3 Most Common Types of Cardiac Amyloidosis.

| Protein <sup>2</sup>   | Light Chain Amyloidosis (AL)  |                | Transthyretin-related Amyloidosis (ATTR)  |   |
|------------------------|---|----------------|---|---|
|                        | Monoclonal Light-chain  | Immunoglobulin | Wild-type transthyretin (ATTRwt)  | Inherited mutant transthyretin (ATTRm)  |
| Mechanism <sup>2</sup> | Plasma cell dyscrasia results in over-production of monoclonal light-chain(either kappa or lambda) which aggregate and deposit in tissues |                | Transthyretin is intrinsically unstable, has propensity to misfold, aggregate, and deposit as individuals age | Amino acid substitutions result in highly unstable transthyretin monomers prone to aggregation and deposition |

**Table 2:** Maintaining a High Index of Suspicion for CA.

| Criteria                      | AL  | ATTRwt   | ATTRm  |
|-------------------------------|---|--|--|
| Demographic                   | >60 years,<br>Men = Women,<br>Ethnicity variable <sup>19,20</sup>   | >70 years,<br>Mostly men (90-97%) <sup>3,6</sup><br>Women present later <sup>18</sup><br>Caucasian (90%) <sup>6</sup>  | >60 years,<br>Mostly men,<br>Ethnicity variable <sup>8</sup> ; most common is V122I mutation in African, Afro-Caribbean <sup>8,14-16</sup> |
| Associated signs and symptoms | Rapid onset HF, multi-system damage, macroglossia, periorbital purpura, and petechial lesions of eyelids/periorbita <sup>19-22</sup>  | Often: Insidious HF, dyspnea, and/or atrial arrhythmias <sup>6,8,23</sup><br>Occasionally: syncope, angina, and neuropathy (mostlyATTRm) <sup>6,8,23</sup><br>Ruptured distal biceps tendon <sup>8,25</sup><br>Carpal tunnel syndrome (especially bilateral) <sup>24</sup> Spinal stenosis <sup>26</sup> |  |
| Laboratory findings           | Spontaneously normalized HTN requiring medication discontinuation or Unable to tolerate standard HF medications (ACEi/ARB, Beta-blocker) <sup>18</sup><br>*Monoclonal gammopathy on serum or urine electrophoresis and immunofixation and/or increased dFLC (>50mg/L) <sup>19</sup><br>Increased NT-proBNP, cTnT disproportionate to cardiac strain <sup>9,29</sup> |  |  |
| Electrocardiogram             | Pseudo-infarction pattern (anterior leads),<br>Atrial arrhythmias,<br>AV or bundle-branch blocks <sup>18</sup><br>Low QRS; using a modified Sokolow index (cut-off<0.5mV) <sup>30,31</sup><br>Depressed global longitudinal strain with relative apical sparing <sup>33</sup>   |  |  |
| Echocardiogram                | LVH>12mm (symmetrical or asymmetrical),<br>AV-valve thickening,<br>atrial dilation <sup>18,32</sup>   |  |  |
| Cardiac MRI                   | Diffuse late gadolinium enhancement,<br>Increased T1 native and extracellular volume <sup>7,34-37</sup>   |  |  |

Difference between involved and uninvolved free light-chain (dFLC), N-terminal pro-B type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), \*AL occurs in the context of plasma cell dyscrasia, but FLC and dFLC both increase in monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma (MM). Thus, these markers cannot differentiate AL from ATTR with a concurrent MGUS/MM.

whose pressures spontaneously normalize and require medication discontinuation, and in HF patients who are unable to tolerate standard medication regimens [18].

The presentation of AL among specific ethnic groups is variable [19]. It occurs equally in male and females, and onset normally occurs after the age of 60 years old [19,20]. AL is characterized by rapidly-progressive HF and often accompanied by multi-organ dysfunction (primarily kidney, heart, liver, and nervous system) [20,21]. In the context of an aged patient with HF, findings of macroglossia, periorbital purpura, and recurrent petechial lesions on the eyelids or periorbita, are highly suggestive of AL [5,22]. Although all AL is seen in plasma cell dyscrasia, it is important to note that only 10% to 15% is concurrent with multiple myeloma [20]. Without treatment, AL is rapidly fatal following symptom onset, which highlights the importance of early diagnosis and discrimination from other types of CA [21].

In contrast, ATTR patients often present with common, non-specific findings such as insidious HF or dyspnea, atrial arrhythmias, and occasionally syncope, angina, and neuropathy [6,8,23]. Therefore, the most important factors in identifying ATTR as a cause of HF is a high index of suspicion and exploring a cardiomyopathy-sensitive history and physical exam. History of ruptured distal biceps tendon, carpal tunnel syndrome (especially if bilateral), and spinal stenosis should serve as red flags when distinguishing ATTR from other causes of HF [8,24-26].

ATTRwt specifically, presents predominantly in Caucasian males (90% to 97%) over 70 years old [3,6]. However, recent findings suggest ATTRwt is more common in woman than previously believed but develops at a later age [18,23]. ATTRm usually after the age of 60 [3]. There are many associated mutations each specific to different populations with varying degrees of penetrance, making it difficult to use family history or ethnicity as reliable diagnostic tools for ATTRm [8]. However, the most common ATTRm-causing mutation (V122I) is carried by 3% to 4% of Africans and Afro-Caribbean’s, increasing the index of suspicion for CA when faced with HF in these populations [14-16].

### Clinical Investigation

AL results from plasma cell dyscrasia, thus any suspected case of CA requires serum and urine Free Light Chain (FLC) electrophoresis and immunofixation to establish the presence of monoclonal gammopathy [19]. However, in patients with Chronic Kidney Disease (CKD), FLC can be high without monoclonal gammopathy as CKD prolongs FLC half-life [27]. Hence the most useful marker is the difference between involved and uninvolved FLC (dFLC) which determines the monoclonal component and remains unaltered in CKD [19]. Unfortunately, since FLC and dFLC both increases in Monoclonal Gammopathy of Unknown Significance (MGUS) and multiple myeloma, these markers cannot differentiate AL from ATTR with concurrent MGUS [19]. Although not diagnostic, concentrations of N-terminal pro-B type natriuretic peptide (NT-

**Table 3:** Emerging Disease-modifying Therapies for Cardiac Amyloidosis.

| Class                                      | Drug  | Mechanism   |
|--|---|---|
| Transthyretin gene silencers               | siRNA53,<br>antisense oligonucleotides50  | Suppress expression of the transthyretin gene whether mutated or wild-type                    |
| Transthyretin stabilizers                  | Diffunisal52,<br>Tafamidis51,54   | Stabilizes misfolded transthyretin monomers, preventing aggregation and deposition in tissues |
| Novel combination therapy <sup>55,56</sup> | 1) CPHPC: small molecule followed by,<br>2) Anti-SAP IgG: humanized monoclonal antibody | 1) CPHPC complexes with SAP in serum, complex is cleared by liver                             |

(R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC), Serum amyloid P component (SAP).

proBNP) and cardiac troponin T (cTnT) are both elevated in CA and are used in staging AL and ATTR [9,28]. Elevated NT-proBNP and cTnT, disproportionate to cardiac strain, in an elderly HF patient should increase suspicion of CA [9,29].

### Electrocardiograph

A pseudo-infarction pattern (anterior leads), atrial arrhythmias, AV or bundle-branch blocks, and low QRS voltages are the most common ECG abnormalities in CA, however, ECG may be normal [18]. Low QRS voltage in CA is best quantified using a modified Sokolow index (cut-off <0.5mV) but is a late-stage finding [30,31]. No ECG abnormality can reliably screen for CA, but the above findings should increase suspicion in the appropriate clinical context [18,30].

### Echocardiograph

Morphological echocardiographic findings suggestive of CA are; LV hypertrophy (LVH >12mm, symmetric in 75% of CA, asymmetric in 25%), AV-valve thickening, and atrial dilation [18,32]. Depressed global longitudinal strain with relative apical sparing is the most sensitive and specific echocardiographic finding to CA and differentiates CA from other causes of LVH [33].

### Specialized imaging

Cardiac MRI provides detailed information on cardiac morphology and function but also allows for visualization (*via* late gadolinium enhancement, LGE) and quantification (*via* T1 mapping and Extracellular volume, ECV) of amyloid infiltration [34-36]. Recently native T1, LGE and ECV have been validated as diagnostic tools capable of detecting even early-stage CA [7,37]. ECV also has prognostic value [7]. Although CMRI is a very sensitive measure of CA and results may suggest either AL or ATTR, it cannot definitively type the amyloid fibril [38]. Since treatment differs significantly between AL and ATTR, further investigations are required.

Bone scintigraphy is 99% sensitive for ATTR with false positives arising from low-grade (grade 1) radiotracer uptake in AL [39]. In the absence of MGUS, high grade (grade 2-3) up-take on scintigraphy is 100% specific to ATTR and allows for diagnosis of ATTR without histopathological confirmation [39]. Currently, <sup>99m</sup>Tc-Technetium (<sup>99m</sup>Tc)-pyrophosphate and <sup>99m</sup>Tc-3, 3-diphosphono-1,2-propanodicarboxylic are the only validated radiotracers for ATTR diagnosis but preliminary data also shows other <sup>99m</sup>Tc-labeled radiotracers may be equivalent [39-41]. These techniques remove the need for Endomyocardial Biopsy (EMB) in most cases of ATTR, thus reducing risk of procedural harm in a frail population [42].

### Biopsy

All suspected cases that cannot be definitively identified with scintigraphy require biopsy for diagnosis. In suspected AL, biopsy of an affected organ is most useful, followed by Fat Pad Fine-needle Aspiration (FPFA). FPFA is not recommended in suspected cases of ATTR due to low sensitivity and so EMB is required [43,44]. The gold-standard for tissue analysis in CA diagnosis is mass spectrometry-

based proteomic analysis identifies all amyloid fibril types more accurately than immuno-histological staining [45].

## Clinical Management

Management of HF in patients with concomitant CA is difficult due to poor tolerance of traditional HF medications (e.g. ACEi/ARB, beta-blockers) [21,46]. Symptom management is best achieved with loop diuretics +/- spironolactone [21,46]. If atrial fibrillation is present, beta-blockers for rate-control should be used cautiously and anticoagulation is indicated regardless of risk score [21,46]. Nevertheless, the most important step in managing CA-related HF is reducing further amyloid formation and deposition.

Current AL treatments aim to decrease FLC concentrations which reduce amyloid deposition and minimize cardio-toxic effects from the FLCs themselves, however, tissue involvement is not necessarily reversed [21]. Common tri-agent therapies; melphalan or cyclophosphamide, bortezomib, and dexamethasone can improve survival and, in some patients, organ function [47,48]. Response to treatment is monitored by reductions in dFLC, NT-proBNP, and cTnT to below established levels [49].

Therapies such as, Transthyretin gene silencers (siRNA, antisense oligonucleotides) and stabilizers (diflunisal, tafamidis) have demonstrated potential benefit in the treatment of ATTR, and a phase-3 clinical trial involving tafamidis is ongoing [50-54]. Therapy targeting Serum Amyloid P component (SAP), a protein essential to amyloid deposit stabilization, is also emerging. A combination therapy of (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC) followed by administration of anti-SAP IgG has shown remarkable results [55,56]. For individuals with ATTRm who meet transplant criteria, the most effective treatment may still be liver transplantation [57]. Transplant effectively removes the source of abnormal TTR; drastically slowing disease progression resulting in >50% survival at 20 years [57].

## Conclusion

The significance of CA as a cause of HF in older patients has been underappreciated. The landscape of CA management is rapidly changing. Treatments are both more effective and better tolerated by patients with early-stage disease [17]. Fortunately, new Cardiac MRI and nuclear imaging techniques allow for non-invasive identification of early-stage CA. However, the non-specific presentation and perceived rarity of CA remains an obstacle to early diagnosis. To overcome this barrier, clinicians treating elderly HF patients should maintain a high index of suspicion for CA.

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