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PERSPECTIVE

Pearls from the First Gulf Cardiac Amyloidosis Summit 2021

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Abstract: These proceedings from the First Gulf Cardiac Amyloidosis Summit held in June 2021 aimed to increase awareness of cardiac amyloidosis among the wider medical community in the region. Although the clinical presentation of cardiac amyloidosis is highly variable, a number of 'red flags' have been identified to raise suspicion of the disease and prompt further investigation. Accurate diagnosis of cardiac amyloidosis is challenging and relies on the integration of clinical, imaging and laboratory investigations. Recent imaging techniques, including bone scintigraphy together with a complete serum and urine workup, allow, in the majority of patients, accurate non-invasive diagnosis without the need for confirmatory endomyocardial biopsies. Early differential diagnosis between light-chain (AL) amyloidosis and transthyretin amyloidosis (ATTR) is critical for timely delivery of appropriate therapy. AL amyloidosis is a medical emergency requiring chemotherapy and supportive care. Treatment for ATTR-amyloidosis is most effective when administered early, before development of significant symptoms or cardiac dysfunction. Optimal management of patients involves close collaboration between multidisciplinary specialists, which may include hematologists, cardiologists, and other subspecialists, ideally at a designated specialty center with interest and expertise in amyloidosis.

Keywords: Amyloidosis, Transthyretin, Diagnosis, Cardiomyopathy, Scintigraphy, Genetic testing.

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1. INTRODUCTION

The First Gulf Cardiac Amyloidosis Summit was held virtually in June 2021. The summit, sponsored by Pfizer and endorsed by the Gulf Heart Association, Emirates Cardiac Society, and New Emirates Medical Journal, aimed to raise awareness of cardiac amyloidosis, a progressive, fatal disease that is often under-recognized and misdiagnosed. The summit included presentations with a strong clinical and case-based focus, workshops and panel discussions, with a group of eminent international key opinion leaders. The attendees discussed the burden and subtypes of cardiac amyloidosis, its varied clinical presentations, evolving diagnostic pathways, including the importance of genetic testing and treatment options. The summit was an invaluable forum for in-depth interactive discussion, with an emphasis on imaging techniques that are the cornerstone of diagnosis in cardiac amyloidosis.

2. NOMENCLATURE AND EPIDEMIOLOGY OF CARDIAC AMYLOIDOSIS

Amyloidosis is a progressive, life-threatening, multisystem disorder resulting from the deposition of amyloid fibrils in the

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extracellular matrix of various organs including the heart (cardiac amyloidosis), kidneys, gastrointestinal tract, soft tissues, and peripheral and autonomic nervous systems [1, 2]. Almost 95% cases of cardiac amyloidosis are caused by misfolded amyloid transthyretin (ATTR) or amyloid light chain (AL) proteins.

AL amyloidosis is a disease caused by the accumulation of monoclonal immunoglobulin light chain fragments and more than 98% of patients have an underlying plasma cell neoplasm [3]. Approximately 60–80% of patients with AL amyloidosis will have some degree of cardiac involvement [4]; severe cardiac involvement at diagnosis often prevents patients from getting optimal therapy leading to a median survival of 6–12 months after presenting with heart failure [5]. ATTR amyloidosis has two subtypes, hereditary (ATTRv) and wild-type (ATTRwt) amyloidosis [1, 2]. In ATTR amyloidosis with cardiomyopathy (ATTR-CM), median survival if untreated is estimated at 2–3 years for ATTRv and about 3.5 years from diagnosis for ATTRwt [6].

Recent estimates suggest prevalence rates of 40.5 cases per million persons for AL amyloidosis and between 155–191 cases per million for ATTRwt, with the prevalence of ATTRv estimated to be 5.2 cases per million [2, 7]. The prevalence of ATTRwt amyloidosis increases with age and the majority of affected patients are older than 60 years [4]. In ATTRv amyloidosis, the age at onset of disease-related symptoms varies between 20–90 years, with great variations across different populations depending on gene variant, clinical penetrance and progression [4, 6, 8]. In a Finnish population-based autopsy study, ATTRwt amyloid deposits were identified in the cardiac tissue of 25% of adults over the age of 85 years [9]. Furthermore, ATTR-CM was identified in 14–16% of elderly patients referred for transcatheter aortic valve replacement and approximately 9% of patients ≥40 years of age presenting with hypertrophic cardiomyopathy [10, 11]. Cardiac amyloid deposition is also common in elderly patients with heart failure with preserved ejection fraction (HFpEF), with 32% of patients ≥75 years presenting with such deposition [12]. Among patients undergoing surgery for carpal tunnel syndrome, 10.2% were found to have amyloid deposits on tenosynovial tissue biopsy (7 ATTR, 2 AL and 1 untyped), with cardiac involvement in two of these patients (1 ATTRwt, 1 AL); carpal tunnel syndrome may precede cardiac manifestations in amyloidosis by several years [13].

ATTR amyloidosis has historically been considered a rare, untreatable disease (other than with heart and/or liver transplant) with poor prognosis. Recent advances in scintigraphy, cardiovascular magnetic resonance imaging (CMR) and echocardiography have improved the detection of ATTR amyloidosis and a number of treatment options are now available, including supportive and targeted therapies [2, 6]. In the US, hospitalizations for amyloidosis increased more than 2-fold to >60 cases per 100,000 admissions between 2005 and 2014, with an increased risk of mortality [14]. It is thought that the causes of this increasing incidence are multifaceted, with contributions from increasing rates of diagnosis and an ageing population.

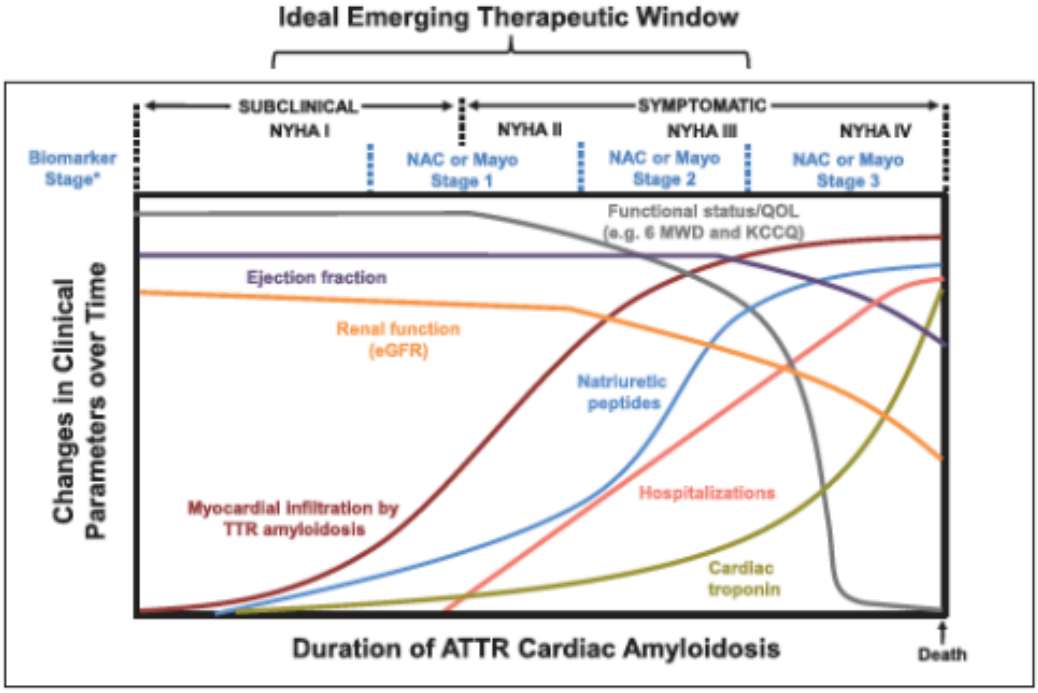


Fig. (1). Conceptual model of clinical progression over time in ATTR amyloidosis with cardiomyopathy [15]. ATTR, amyloid transthyretin; KCCQ, Kansas City Cardiomyopathy Questionnaire; 6 MWD, 6-minute walk distance; NYHA, New York Heart Association; QOL, quality of life; NAC, United Kingdom National Amyloid Center. (Reprinted from Circulation, Volume: 140, Issue: 1, Justin L. Grodin, The Truth Is Unfolding About Transthyretin Cardiac Amyloidosis, 27-30, Copyright (2019), with permission from American Heart Association, Inc.).

Table 1. Clinical 'red flags' for suspicion of cardiac amyloidosis.

Cardiac signs and symptoms	Neurologic signs and symptoms	Other signs and symptoms
• Heart failure • Arrhythmia • Orthostatic hypotension • Increase in LV mass • Discordance of QRS voltage and LV wall thickness seen on echocardiography • Marked ECV expansion, abnormal nulling time for the myocardium or subendocardial/transmural late gadolinium enhancement on CMR • Intolerance to heart failure medications • Hypertension suddenly requiring less use of hypertensives • Pericardial effusion • Atrioventricular block with increased LV wall thickness • Persistent low-level elevation in serum troponin • Disproportionately high NT-proBNP level • Pacemaker	• Neuropathy • Autonomic nervous system dysfunction; gastrointestinal complaints, unexpected weight loss, gastroparesis • Family history of polyneuropathy • Sensorineural hearing loss • Urinary retention or incontinence	• Biceps tendon rupture (Popeye sign) • Lumbar spinal stenosis • Erectile dysfunction • Hip and knee arthroplasty • Proteinuria • Macroglossia • Skin bruises • Bilateral carpal tunnel syndrome

CMR, cardiovascular magnetic resonance imaging; ECV, extracellular volume expansion; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

In Kuwait, the National Amyloid Program has successfully helped raise awareness of cardiac amyloidosis among specialists and has produced a useful algorithm to aid in its diagnosis. The program has resulted in an increased number of referrals, thus highlighting the success of the awareness campaign. Patients diagnosed with cardiac amyloidosis are often relieved that they finally have a diagnosis for the cause of their symptoms and can receive appropriate management. Furthermore, patients with ATTRv amyloidosis have responded positively to education on the importance of early diagnosis in their offspring.

ATTR-CM is a slowly progressive disease that exhibits a complex disease course with a temporal distribution of clinical scenarios (Fig. **1**). NT-proBNP varies throughout the course of the disease and two new staging systems for ATTR-CM have been proposed to reflect disease progression. One of them uses NTproBNP and eGFR to stratify patients' prognosis at diagnosis: Patients with NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min are classified as Stage I, those with NT-proBNP >3000 ng/L and eGFR <45 mL/min are classified as Stage III, and the remaining patients are classified as Stage II. The ideal therapeutic window is before significant organ dysfunction has occurred and subsequent rapid and potentially irreversible declines in functional capacity [15].

3. CLINICAL 'RED FLAGS' FOR SUSPICION OF CARDIAC AMYLOIDOSIS

One of the main challenges diagnosing ATTR amyloidosis is that it is a heterogeneous disease with various manifestations associated with the main subtypes, with worse prognosis associated with certain mutations in the *TTR* gene [16, 17]. The disease exhibits variations in age at presentation, gender, ethnicity, and prognosis and often has non-specific presenting symptoms which may include dysnpea, fatigue, and diarrhea [1,18]. While the typical patient with ATTR-CM was previously understood to be a >60-year-old male with a concentric increase in left ventricular mass, a normal ejection fraction (EF) and low voltage on ECG, only a fraction of cases actually fit this classical profile [19].

Importantly, a number of clinical 'red flags' for raising the suspicion of cardiac amyloidosis have been identified and include cardiac symptoms, neurologic manifestations, and other extra-cardiac signs and symptoms (Table **1**) [1, 6].

4. CARDIAC DYSFUNCTION AND CARDIAC AMYLOIDOSIS

4.1. Heart Failure

The predominant clinical manifestation of ATTR-CM is heart failure [1, 6, 19]. In Spain, approximately 15% of patients aged >60 years presenting with HFpEF and at least >12 mm of left ventricular hypertrophy (LVH) were found to have ATTRwt-CM [20]. Notwithstanding the strong link between ATTRwt-CM and HFpEF, a study in patients from Italy and Spain found a depressed LVEF <50% in 37% of patients with ATTRwt-CM, with 9% exhibiting an LVEF ≤30%; other centers have demonstrated similar findings [19]. In another study, 11% of patients aged ≥60 years presenting with an LVEF <50% and LVH >12 mm had ATTRwt-CM [21].

4.2. Aortic Stenosis

Five percent of patients with aortic stenosis undergoing aortic valve replacement were found to have ATTRwt-CM and 16% of patients with aortic stenosis considered for transcatheter aortic valve implantation (TAVI) had ATTR-CM [22, 23]. Patients with aortic stenosis diagnosed with ATTR-CM tend to be older, present with a higher degree of LVH, and exhibit higher values of cardiac biomarkers than those with aortic stenosis without ATTRwt-CM [10]. The RAISE score (Table **2**) has been proposed to help differentiate between patients with aortic stenosis with or without ATTR-CM and can differentiate between patients with high levels of specificity and sensitivity [24].

4.3. Hypertensive Cardiomyopathy

Hypertensive cardiomyopathy has been reported as the most frequent misdiagnosis in ATTR-CM [19]. In patients with hypertension and LVH who would often be diagnosed with hypertensive cardiomyopathy, clues for ATTR-CM include predominant right-sided heart failure, disproportionate LVH relative to history and control of hypertension, and a reduction in anti-hypertensive therapy [19]. Around 5% of patients over 55 years presenting with hypertrophic cardiomyopathy have ATTRv-CM [25].

5. IMPORTANCE OF DIAGNOSIS FOR EARLY TREATMENT OF CARDIAC AMYLOIDOSIS

The accurate diagnosis of cardiac amyloidosis continues to present a clinical challenge and relies on the integration of clinical, imaging and laboratory investigations [1]. The differential diagnosis of AL amyloidosis and ATTR-CM is essential for choosing appropriate treatment [6]. Given that AL amyloidosis is a medical emergency with an aggressive nature and poor survival, measured in weeks to months, diagnosis and treatment must be undertaken without delay [1]. Chemotherapy and stem cell transplantation have improved the prognosis for AL amyloidosis significantly [5]. Similarly, diagnosis and treatment given early in the disease course confer a greater benefit in ATTR-CM, given the progressive nature of the disease and the mechanism through which treatment with the TTR stabilizer tafamidis reduces amyloidogenesis [26]. Although rare, two different types of amyloidosis can occur in an individual patient and clinicians need to consider this possibility [27]. Given that AL amyloidosis is a hematologic malignancy with multiorgan involvement and shorter survival [6], treatment for AL amyloidosis is more clinically emergent than ATTR-CM.

5.1. AL Amyloidosis

AL amyloidosis is a plasma cell neoplasia, as is multiple myeloma, and patients with AL amyloidosis may fulfil multiple myeloma criteria despite these being different diseases. Monoclonal gammopathy of unknown significance (MGUS) is a biochemical finding of the presence of M-spike in serum; it is highly prevalent in older patients (>80 years). AL amyloidosis is characterized by the presence of light-chain amyloid identified by a complete protein study, including total protein quantification in serum and urine (24-h urine sample), serum and urine immunofixation, and the measurement of serum free light chains (FLC). FLC is important in the diagnosis of AL amyloidosis as 10–15% of patients do not exhibit large amounts of protein (M-spike) in the serum or urine. However, FLC on its own cannot result in a diagnosis of AL amyloidosis. A tissue biopsy showing AL amyloidosis is mandatory for a definitive diagnosis. Biopsy of involved organs has a higher sensitivity than non-specific biopsies of the bone marrow, lip, *etc* [2, 6].

5.2. ATTR Amyloidosis with Cardiomyopathy

Endomyocardial (cardiac) biopsy was the gold standard for definitive diagnosis but a majority of ATTR-CM cases can now be diagnosed with non-invasive imaging [1]. Echocardiography or CMR can identify patterns strongly suggestive of cardiac amyloidosis, which should be further investigated using nuclear scintigraphy with the uptake of bone-seeking radiotracers, and hematologic testing of serum FLC and serum and urine immunofixation to rule out a plasma cell disorder [1, 9]. Genotyping is essential in cases of confirmed ATTR-CM [9].

5.3. Diagnostic Algorithm

The 2021 European Society of Cardiology (ESC) has proposed a diagnostic algorithm to facilitate timely differential diagnosis between AL and ATTR when cardiac amyloidosis is suspected on ECG, echocardiography or CMR (Fig. **2**) [6]. The algorithm is based on the results of a bone scan with both planar and single-photon emission computed tomography (SPECT) imaging and hematology tests (serum FLC and serum and urine immunofixation). Bone scan limitations include false-negative results in patients with very mild disease or at early stages of disease or for some specific ATTRv genotypes; and false positive results with 1-hour *versus* 3-hour scans, or inability to differentiate blood pool. In some cases, an endomyocardial biopsy will be required for a definitive diagnosis. Diagnostic algorithms are most useful in advanced disease; symptoms on imaging may be more subtle in the early stages of the disease and an individualized approach may be necessary. Equivocal cases should be followed up in a designated specialty center or center of excellence.

Table 2. RAISE score for the discrimination of lone aortic stenosis and dual pathology aortic stenosis and cardiac amyloidosis.

Parameter	Points	
Carpal tunnel syndrome	3	
Right bundle branch block	2	
Age ≥85 years	1	
High-sensitive troponin T ≥20 mg/L	1	
Inter-ventricular septum ≥18 mm	1	
If in sinus rhythm: E/A ratio >1.4	1	
If no bundle branch block or pacemaker: Sokolow index <1.9 mV	1	
Total RAISE Score	**Specificity**	**Sensitivity**
≥6 points	100%	14.9%
≥5 points	98.9%	23.4%
≥4 points	95.0%	42.6%
≥3 points	83.6%	72.3%
≥2 points	52.1%	93.6%
≥1 point	16.7%	97.9%

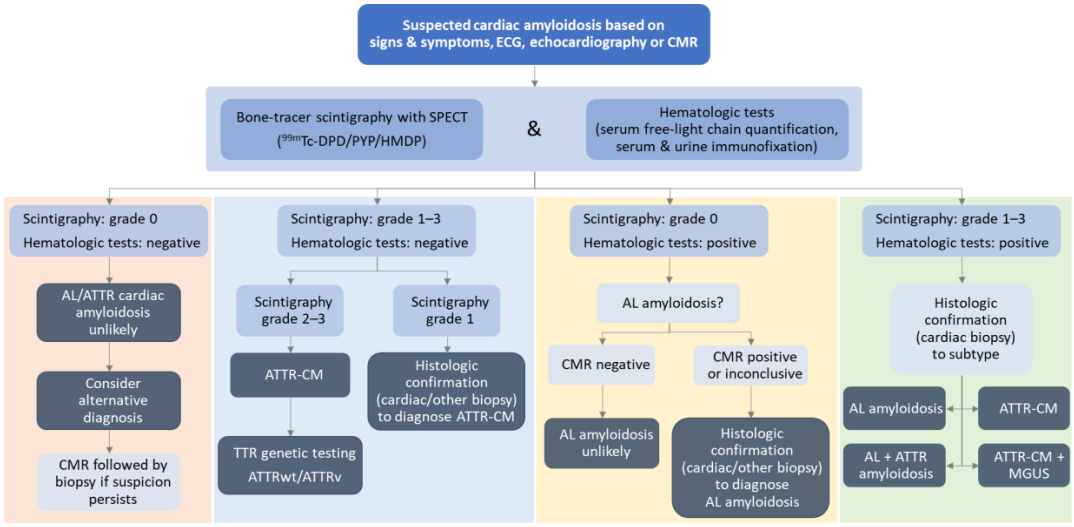
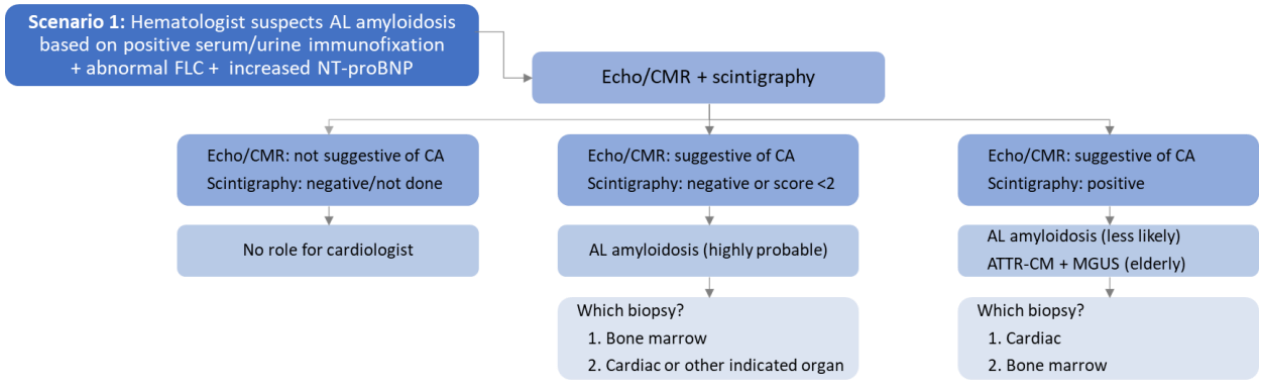


Fig. (2). Diagnostic algorithm for cardiac amyloidosis [6]. ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; AL, light-chain amyloidosis; CMR, cardiovascular magnetic resonance imaging; ECG, electrocardiogram, SPECT, single-photon emission computed tomography; TTR, transthyretin. (Reprinted from Eur J Heart Fail, Volume: 23, Issue: 4, Garcia-Pavia P, *et al*. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases).

A.



B.

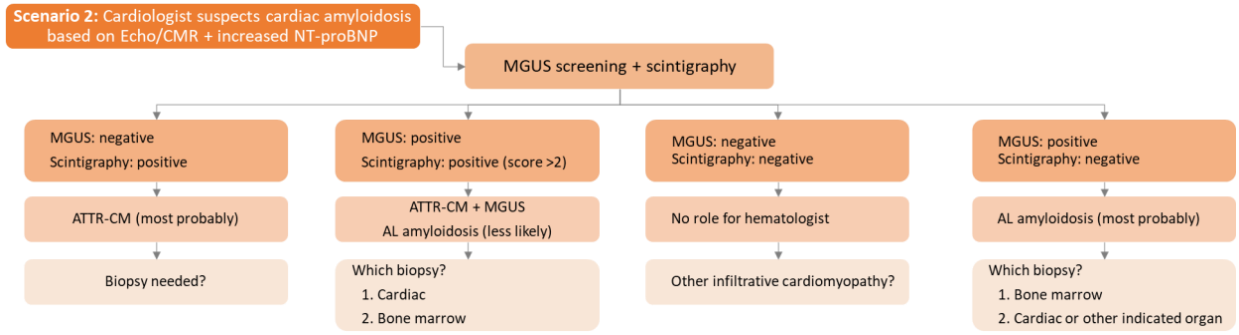


Fig. (3). Diagnostic scenario for suspected AL amyloidosis or ATTR-CM when a patient presents to the hematologist (**A**) or cardiologist (**B**). AL, amyloid light chain; ATTR-CM, amyloid transthyretin amyloidosis with cardiomyopathy; CA, cardiac amyloidosis; CMR, cardiovascular magnetic resonance imaging; Echo, echocardiography; MGUS, monoclonal gammopathy of unknown significance; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

5.3.1. Multidisciplinary Collaboration

The clinical presentation of cardiac amyloidosis is variable and patients may visit a number of specialist physicians before amyloidosis is suspected [28]. Optimal management of patients involves close collaboration between hematologists, cardiologists, and other subspecialists for both diagnosis and treatment [29]. Ideally, patients should be evaluated in a designated specialty center or center of excellence with onsite availability of a multidisciplinary care team with interest and experience in managing patients with amyloidosis and expertise in complex diagnostic techniques such as endomyocardial biopsy and mass spectrometry [6, 28, 29].

Patients with suspected cardiac amyloidosis typically present or are referred to a hematologist or cardiologist depending on their clinical signs and symptoms. Patients seen first by a hematologist likely have MGUS with increased NT-proBNP and albumin in urine, which is a `red flag' for AL amyloidosis (Fig. **3A**). Ideally, the next step is an echocardiogram or CMR and scintigraphy with planar and SPECT imaging if possible. If the findings suggest ATTR-CM, the patient should be referred to a cardiologist for treatment. If the patient presents first to the cardiologist and cardiac imaging and NT-proBNP levels suggest cardiac amyloidosis, then MGUS screening to test for AL amyloidosis and scintigraphy with planar and SPECT imaging to check for ATTR should be the next step (Fig. **3B**). MGUS screening should include serum and urine immunofixation and FLC determination. Biopsy of the bone marrow, heart, or other indicated organ may be necessary for additional diagnostic assessment in either scenario [6].

5.4. Imaging Modalities in Cardiac Amyloidosis

Choosing the most appropriate imaging modality for the suspicion and diagnosis of cardiac amyloidosis is dependent on the clinical scenario. Expert consensus recommendations for appropriate utilization of echocardiography, scintigraphy and CMR for assessment of cardiac amyloidosis in a diverse range of patient presentations have been published [30].

5.4.1. Echocardiography

Echocardiography is widely available, easy, feasible and key in the diagnosis and management of patients with cardiac amyloidosis. However, typical features seen on echocardiography present only at advanced stages of the disease and it cannot stratify the probability of cardiac amyloidosis in patients with increased LV mass. Importantly, echocardiography cannot be used alone for the diagnosis of cardiac amyloidosis, and it cannot distinguish between AL amyloidosis and ATTR-CM. ATTR-CM should be considered if there is discordance between wall thickness on echocardiogram and QRS voltage on ECG; however, this does not rule out AL amyloidosis.

Newer echocardiography modalities can assess the extent and timing of myocardial deformation, adding both sensitivity and specificity to the examination. Longitudinal global strain offers an improved technique to measure systolic function, showing apical sparing ('cherry on top' signal) and reduced values in basal and mid segments in cardiac amyloidosis. Early markers of cardiac amyloidosis include diastolic dysfunction and reduced global longitudinal strain even with a normal EF. Patients with decreased strain have a decreased survival curve [31].

5.4.1.1. Echocardiography 'Red Flags' For Cardiac Amyloidosis That are Often Missed

- Non-dilated left ventricle.
- Right and left ventricular hypertrophy.
- Atrial dilatation.
- Atrioventricular valve thickening (sometimes with mild/mild-to-moderate regurgitation).
- Interatrial septal thickening.
- Mild global pericardial effusion.
- Diastolic dysfunction (cornerstone of the disease).
- Low velocities of mitral and tricuspid tissue doppler imaging (TDI).
- Reduced stroke volume.
- Preserved ejection fraction (as the infiltration of the heart progresses, heart function will decrease).
- Disproportionate reduction in the longitudinal function compared to the radial contraction.
- Apical sparing of the longitudinal strain with reduction in the basal and mid segments.

5.4.1.2. Pneumonic For Echocardiography 'Red Flags' For TTR Cardiac Amyloidosis

T = Thick: valves, walls and septum, interventricular septum >12 mm.

T = Tissue doppler global longitudinal strain (GLS) <-14%.

R = Restriction pattern (diastolic dysfunction) with atrial dilatation.

C = Concentric left ventricular hypertrophy (80% of cases).

A = Apical sparing on strain study.

5.4.2. Scintigraphy

Nuclear scintigraphy with bone tracers is an imaging modality that has gained attention because of its high specificity and sensitivity for detecting cardiac ATTR amyloidosis in the absence of elevated light chains [6]. At many institutions, a 3-hour delay between injecting Technetium-99m pyrophosphate (Tc-99m-PYP) and imaging is standard; outside of the US, Tc-99m-diphosphono-1,2-propanodicarboxylic acid (Tc-99m-DPD) or Tc-99m-hydroxymethylene diphosphonate [Tc-99m-HMDP] may be used. Scintigraphy with bone tracers has four grades of cardiac uptake (Perugini grading system) [6, 32].

- Grade 0: Absence of tracer myocardial uptake and normal bone uptake.

● Grade 1: myocardial uptake in a lower degree than at the bone level.

● Grade 2: similar myocardial and bone uptake.

● Grade 3: myocardial uptake greater than bone with reduced/absent bone uptake.

In the absence of a detectable monoclonal protein using immunofixation in serum and urine, and/or an abnormal serum FLC ratio, the specificity of Grade 2 or 3 scintigraphy for ATTR-CM when the disease is suspected is thought to be approximately 100% [6].

Scintigraphy is an important part of the workup in patients with aortic stenosis considered for transcatheter aortic valve implantation (TAVI). It is useful to help identify patients with dual pathology and guide choice of TAVI technique based on the patient's clinical status [33]. Although routine screening of older adult patients with aortic stenosis is not feasible in routine clinical practice, screening of ATTR with scintigraphy should be considered in patients with aortic stenosis undergoing TAVI, especially patients with a low-flow low-gradient pattern and high B-type natriuretic peptide levels [24, 34].

5.4.2.1. Considerations for Bone Scintigraphy

● A heart:contralateral lung (H:CL) ratio may be calculated on anterior planar images; the region of interest (ROI) should be drawn above the diaphragm and should not include the right ventricle.

● The H:CL is considered abnormal if >1.3 at 3 hours or >1.5 at 1 hour, though 3 hours is recommended.

● The H:CL ratio should only be used for interpretation after a semi-quantitative determination of Grade 1 (or equivocal Perugini grade) has been made.

● Cardiac (blood pool activity, acute/subacute myocardial infarction, myocarditis/myopericarditis, chemotherapy/drug-associated myocardial toxicity) and non-cardiac (acute/subacute rib fracture within the heart ROI) influences can lead to false-positive results; the American Society of Nuclear Cardiology advises that planar-only cardiac PYP is no longer the standard of care and should not be used without SPECT/CT.

● Whole-body scintigraphy is not standard of practice (very low yield and time consuming) and is an optional step to view the shoulder and hip girdles which, in some cases, have activity that serves as a diagnostic sign for TTR amyloidosis (multi-organ involvement).

● Assessing the presence of monoclonal protein (*via* serum FLC and serum and urine immunofixation) to rule out the presence of AL amyloidosis is a crucial step in any imaging interpretation for ATTR-CM; AL amyloidosis can be present with any Perugini grade on bone scintigraphy from 0 to 3.

● Consultation with hematology in cases of clinical uncertainty regarding hematological markers is essential.

● Absolute quantification of tracer uptake with SPECT/CT imaging and novel PET tracers offer exciting avenues for further progress in the area of imaging for cardiac amyloidosis; it allows definitive differentiation of blood pool from myocardial uptake, which is the most common cause of a false positive ratio on planar images.

5.4.3. Cardiovascular Magnetic Resonance Imaging

CMR is one of the techniques that has transformed the approach of diagnosing cardiac amyloidosis. The diagnosis of cardiac amyloidosis may be confirmed by the presence of the following characteristic features on CMR (A and B have to be present) [6]:

A. Diffuse subendocardial or transmural late gadolinium enhancement

B. Abnormal gadolinium kinetics

C. Extracellular volume ≥0.40% (strongly supportive, but not essential for diagnosis)

CMR with T1 mapping and extracellular volume measurement can also be used to measure the cardiac amyloid load. The extracellular volume maps are useful to measure the amyloid deposits. Amyloid burden can also be measured in the liver and spleen, offering additional diagnostic information.

CMR is very sensitive for the assessment of cardiac amyloidosis of AL type, as opposed to bone scintigraphy which is positive only in a minority of patients with cardiac AL amyloidosis. However, CMR must be used together with scintigraphy to characterize ATTR amyloidosis. In ATTR amyloidosis, CMR is also important in identifying patients with mutations that are not associated with a significant cardiac uptake.

5.5. Genetic Testing in ATTR Amyloidosis

Genetic testing is recommended for relatives of patients with an inheritable form of transthyretin cardiac amyloidosis to support early diagnosis and prompt treatment [6]. The *TTR* gene is relatively small, composed of only 4 exons and localized on chromosome 18q 12.1. For genetic testing, clinicians are often keen to use automated whole exome sequencing, however, this technique has limitations, including a relatively long turnaround time, complicated bioinformatic analyses, and higher cost. In Bulgaria, *TTR* gene-targeted Sanger sequencing is used, and this is considered the gold standard (Fig. **4**). In ATTR amyloidosis, it is important to sequence the whole gene to differentiate between ATTRv and ATTRwt. Sequencing can confirm the diagnosis in clinically ambiguous cases after positive imaging and identify *TTR* gene mutations in asymptomatic subjects at risk of ATTR amyloidosis.

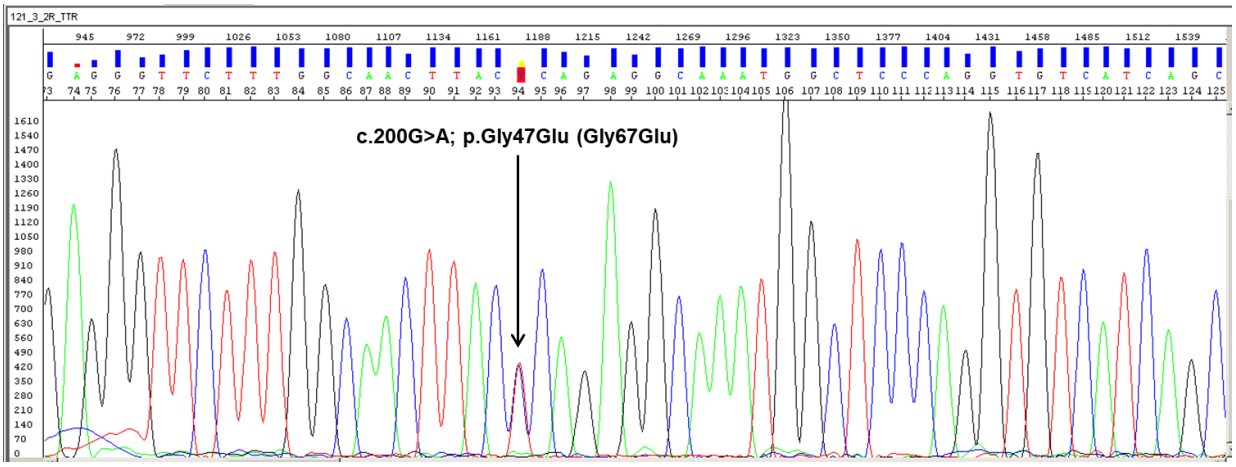


Fig. (4). Sanger sequencing, showing the profile of the mutation c.200G>A; p.Gly47Glu (Gly67Glu). Image courtesy of Albena Todorova. (Reprinted from Med Pharm Rep, Volume 94, Nakov R, Nakov V, Gospodinova M, Todorov T, Todorova A, Chamova T, Tournev I. Screening for hereditary transthyretin amyloidosis in Bulgaria. 2021. doi: 10.15386/mpr-2218. PMID: 34527899).

Table 3. Treatment of cardiac dysfunction in patients with cardiac amyloidosis.

Avoid in patients with cardiac amyloidosis	• Calcium channel blockers • Angiotensin-converting-enzyme inhibitors • Angiotensin receptor blockers
Use with caution in patients with cardiac amyloidosis[a]	• Beta blockers • Digoxin
All patients with cardiac amyloidosis	• Fluid restriction • Low salt intake
Patients with atrial fibrillation and cardiac amyloidosis	• Diuretics • Anticoagulation • Antiarrhythmic (amiodarone)
Patients with atrioventricular block and cardiac amyloidosis	• Pacemakers (some patients) • Heart transplant (some patients)

[a]Usually not well tolerated due to restrictive filling, autonomic neuropathy, and bradycardia.

Table 4. Follow-up of patients with ATTR-CM.

Every 6 months	**Every 12 months**
• ECG	• Echocardiography
• NT-proBNP and troponin laboratory tests	• 24h Holter ECG (to exclude atrial fibrillation)
• Neurological evaluation (where necessary)	• Ophthalmological evaluation (ATTRv only)
• Walking and exercise ability	• CMR

ATTR-CM, amyloid transthyretin amyloidosis with cardiomyopathy; CMR, cardiovascular magnetic resonance imaging; NT-proBNP, = N-terminal pro-B-type natriuretic peptide.

Genetic counseling is important to assist individuals to make informed choices about genetic testing. Patients should be informed that not all carriers of the *TTR* gene mutation will develop ATTR amyloidosis. It is recommended that siblings, parents and children (once aged >18 years) of identified carriers be tested. Clinical heterogeneity with regard to the age of onset, initial symptoms and survival seen between and within affected families and these differences in disease penetrance must be considered in genetic counseling, with follow-up of pre-symptomatic mutation carriers. For example, in one family with five carriers of the Gly47Glu mutation, an aggressive mutation with age of onset around 30 years has been identified, with males are more severely affected with severe motor and sensory neuropathy, severe cardiac involvement, severe gastrointestinal involvement, kidney involvement, very fast progression (within 5 years), and death before the age of 40 years.

6. SYMPTOM MANAGEMENT AND MONITORING

It is well recognized that a multidisciplinary approach is essential in the management of patients with cardiac amyloidosis. Management involves supportive care and

prevention of complications, including heart failure (volume overload or elevated intracardiac pressures), pleural effusion, and pericardial effusion (Table **3**), and specific treatment to halt or delay amyloid deposition. Management of AL amyloidosis includes supportive treatment and cytotoxic therapy to eliminate plasma cell clones [34]. Specific pharmacologic treatment using a TTR stabilizer is available for ATTR-CM [6]. Tafamidis, a TTR stabilizer, is the only approved medication for ATTR-CM [35].

Changes due to treatment can be tracked over time in patients with AL amyloidosis using ECG, echocardiography, CMR, and NT-proBNP. Amyloid progression might occur in patients with AL amyloidosis despite the presence of a good hematological response, highlighting the need for suppression of the production of amyloid throughout the disease pathway. In ATTR-CM, a preliminary study has shown the potential of CMR in tracking changes over time, but more studies are needed to confirm this finding [36].

The European Society of Cardiology Working Group on Myocardial and Pericardial Diseases have proposed a follow-up scheme for patients with ATTR-CM (Table **4**) [6].

6.1. Amyloid-Specific Therapy

The treatment of ATTR amyloidosis currently depends on the presence of cardiomyopathy or polyneuropathy. There are three potential approaches: blocking amyloid production in the liver (*via* genetic editing, genetic silencing, and liver transplantation), stabilizing the TTR molecule, and eliminating amyloid deposits [6]. Blocking TTR production by liver transplantation is an option that should be avoided. *TTR* silencers include patisiran and inotersen, which are not currently approved for ATTR-CM. Patisiran and inotersen inhibit ribonucleic acid (RNA) and antisense oligonucleotide and have shown significant and long-term TTR protein reduction over time in studies in patients with ATTRv amyloidosis with polyneuropathy [37, 38].

The TTR stabilizer, tafamidis, is the only approved medication for ATTR-CM. Tafamidis is indicated for treatment of patients with ATTRv-CM or ATTRwt-CM and is approved for the treatment of ATTR polyneuropathy across multiple countries. Findings from the ATTR-ACT study, which compared pooled data for tafamidis 80 mg and 20 mg *versus* placebo in patients with heart failure due to ATTR-CM, showed that tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life compared with placebo [26]. Tafamidis reduced the risk of all-cause mortality across all sub-groups of NYHA class I–III [26]. A higher frequency of CV-related hospitalizations was observed with tafamidis *versus* placebo in patients with more severe disease at baseline (NYHA class III) [26], which may be attributable to the lower mortality rate with tafamidis and underscores the importance of early diagnosis and treatment [35, 39]. In a long-term extension of ATTR-ACT, all-cause mortality assessment favored 80 mg of tafamidis and there were no dose-related safety concerns [40]. Thus, the FDA-approved and recommended dosage is tafamidis 80 mg, which is available in a single capsule for patient convenience as tafamidis free acid 61 mg (bioequivalent to 80 mg) [41]. As already highlighted, treatment of ATTR-CM involves management of cardiac complications, such as fluid management with diuretics for heart failure, as well as early initiation of disease-modifying therapy with tafamidis to slow disease progression [35].

CONCLUSION

The diagnosis of cardiac amyloidosis is often delayed due to low awareness of the disease among physicians and the heterogeneity of presenting symptoms. With an approved therapy now available for treatment of ATTR-CM, timely diagnosis is essential for optimal management. Physicians need to be aware of the clinical 'red flags' that raise suspicion of cardiac amyloidosis and take advantage of the non-invasive imaging techniques and diagnostic tools available to establish a diagnosis without the necessity for confirmatory endomyocardial biopsies. Managing cardiac amyloidosis and its complications requires a multidisciplinary approach and ongoing follow-up.

KEY TAKE-HOME MESSAGES

- Cardiac amyloidosis is a protein-folding disorder nearly exclusively caused by misfolded amyloid transthyretin (ATTR) and amyloid light chain (AL) proteins. Early differentiation between ATTR and AL is vital for timely delivery of appropriate treatment.
- Clinicians need to be aware of the 'red flags' that raise suspicion for cardiac amyloidosis, including heart failure, arrhythmia, and other signs and symptoms, to avoid delays in diagnosis and treatment that impact mortality and morbidity.
- Screening for ATTR may be considered in clinical scenarios in which the disease has been shown to be prevalent: aortic stenosis undergoing TAVI, HFpEF, phenocopy of hypertrophic cardiomyopathy.
- All patients with suspected amyloidosis should undergo complete serum and urine workup and scintigraphy to establish a differential diagnosis between ATTR-CM and AL amyloidosis.
- Recent imaging techniques allow accurate non-invasive diagnosis of ATTR-CM in the majority of cases without the necessity for confirmatory endomyocardial biopsies.
- Timely treatment of both AL amyloidosis and ATTR-CM is critical: AL amyloidosis is a medical emergency and treatment of ATTR-CM is most effective if administered early in the disease course.
- Management of cardiac amyloidosis and its complications requires a multidisciplinary approach with collaboration between specialties from diagnosis to follow-up.

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