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REVIEW ARTICLE

Unmasking Cardiac Amyloidosis: From Pathophysiology to Emerging Therapies

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Abstract

The spectrum of disease which is characterized by misfolded proteins that get deposited in extracellular tissues, (as an aggregate of fibrils called Amyloid fibrils) is called as Amyloidosis. Cardiac Amyloidosis, an aggregate of fibrils called Amyloid fibrils which gets deposited in heart consequently resulting into Cardiomyopathy which is “Infiltrative” Type and which is progressive in course, resulting, into wide spectrum of cardiovascular manifestations that range from Heart Failure, Arrhythmias, Ventricular arrhythmias to coronary vascular involvement. This Review Article analyzes and summarizes advancements in the field of pathology, physiology, genetics, Diagnostic modalities, Management strategies, and Novel Therapeutics. The increasing trend in diagnosis of transthyretin amyloidosis (ATTR) is due to improved diagnostic imaging and heightened clinical awareness. Development of noninvasive diagnostic tools, is playing a major role in identifying the cases in early course of disease. Endomyocardial biopsy, an invasive diagnostic approach in diagnosing the cases is a “A GOLDSTANDARD TEST”, however non-invasive tests often obviate the need for biopsy. Emerging Novel therapeutic agents like tafamidis, patisiran, vultisiran, and many more are transforming management and improving outcomes (both morbidity and mortality-related outcomes).

Keywords: Cardiac Amyloidosis, Pathophysiology, Cardiovascular manifestations, Early diagnosis, Emerging therapies, Disease-modifying Treatment, Genetic testing

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Introduction

Amyloidosis is a part of under-recognized and often underdiagnosed diseases, leading to a delay in diagnosis and management. Amyloidosis is the spectrum of clinical conditions with different etiologies, which share a characteristic microscopic appearance. The development of Amyloidosis is due "to amyloid fibrils buildup" extracellularly, which are "collections of unfathomable/insoluble, low-molecular-weight protein subunits", at specific sites based on etiology [1,3].

Cardiac Amyloidosis

Amyloidosis involving the heart, is a severely progressive ailment, due to accumulation of fibrils extracellularly. This condition is characterized by distinctive pathological findings of "*green birefringence, which is visible when examined after staining with Congo red dye examined by cross-polarized light, microscopic technique*". Amyloid fibrils, when they get deposited in the myocardial interstitium, results in increasing thickness of Ventricular wall, which leads to both systolic and diastolic Heart failure, which has a progressive clinical course and outcome [2,3].

Figure 1. Differentiating- Normal Heart and Heart with deposition of Amyloid fibrils

Cardiac Amyloidosis-Overview

- There are over 30 Amyloidogenic proteins capable of forming amyloid fibrils. Out of these "THIRTY", only NINE has been identified, which involves Heart, by accumulating in the myocardium, resulting in a wide spectrum of cardiac manifestations. Secondary cardiac amyloidosis, which is less frequent, is a consequence of chronic infections and inflammations (AA). Monoclonal Ig light chains (AL) or transthyretin (ATTR) are the leading varient of Amyloidosis involving Heart. Variants of ATTR are "ATTRv (hereditary) and ATTRwt (acquired)" [3,4].
- Deposition of monoclonal light chains, primarily affecting individuals over 50 years and involving multi-organ systems, is a characteristic finding of AL (light chain) amyloidosis. (Only 10 to 15 percent of AL is associated with Multiple Myeloma)
- Deposition of transthyretin, with forms being hereditary (ATTRv) due to mutations, as well as acquired (ATTRwt) with age, is a characteristic finding of ATTR amyloidosis. [21]
- Chronic conditions that less commonly affect the heart are linked to AA amyloidosis. [5]

Epidemiology

- AL amyloidosis predominantly affects individuals older than 40 years and is *rare* in non-white populations and those younger than 40. (Median age of diagnosis is 63years of age) [7,8]
    - Demographically men and women population is same in term of "Prevalence"
- Prevalence of Wild-type transthyretin amyloidosis (senile type) is more in elderly population.76 years is the "Median diagnostic Age" (black men are three time more susceptible than white men). This form involves the accumulation of structurally normal transthyretin (wt-TTR) leading to cardiac dysfunction. [22]
- Hereditary cardiac amyloidosis due to transthyretin gene mutation is observed more often among black individuals compared to white individuals. [23]

2.3. Pathogenesis

Protein misfolding can result from genetic mutations or aging, causing *susceptible proteins to aggregate as non-branching, cross-beta-sheet fibrils that stain with Congo red dye.*

Table 1(a). Types of Amyloid protein affecting the heart

Amyloidosis Type	***Involved Proteins***	***Inheriting Trend***	***Heart Involvement (In percentage)***
Light Chain (AL)	*Ig light chain*	*Nil*	*Around 70%*
ATTRwt	*Transthyretin*	*No*	*100%*
ATTRv	*Transthyretin*	*Yes*	*Involvement of heart varies, which depend upon type and extent of mutation. It can range from 30 to 70 percent*
amyloid A (AA)	*amyloid A*	*No*	*5%*
AFib	*Fibrinogen alpha*	*present*	*Rarely affect Heart*
AApoAI	*Apolipoprotein A-I*	*Yes*	*Rarely affect Heart (mutation dependent)*
AApoAII	*Apolipoprotein A-II*	*Yes*	*Rarely affects heart however affection of Heart depends on mutation type. Kidneys are commonly involved. [63]*
Aβ2M	*β2-microglobin*	*No*	*80%*
AGel	*Gelsolin*	*Yes*	*Percentage affection of heart(mainly conduction pathway) around 5 percent*

Table 1(b). Summarizing-Amyloid types, with Extra Cardiac manifestation, with expected Survival Duration (in untreated cases) in months

Amyloidosis Type	***Survival Duration, in Untreated Cases (expressed in months)***	***Extra cardiac manifestations***
Light Chain (AL)	*24* *(Survival duration is of 6 months only, if Patient presents in heart failure (untreated cases))*	***Renal**-Nephropathy, proteinuria (proteins in urine). [48]* ***CNS**-Autonomic dysfunction, polyneuropathy.* ***Tongue-** Macroglossia (Abnormally enlarged Tongue that protrude past the teeth) [47]*
Transthyretin (Varient-ATTRwt)	*57*	***Musculoskeletal**-Ruptured of Biceps tendon, Carpal tunnel syndrome.[46]*
Transthyretin (Varient-ATTRv)	*31 " (Val142Ile)"* *69 "(non-Val42Ile)"*	***CNS*** *"Polyneuropathy"* ***CVS**-orthostatic hypotension,[13] **Eye**-vitreous opacities.[49]*
Serum amyloid A(AA)	*133*	***Renal** -Kidney impairment (95%), proteinuria (proteins in urine) [50]* ***Hepatomegaly and other gastrointestinal** symptoms and signs*
Fibrinogen alpha (AFib)	*180*	***Renal**- Kidney impairment, proteinuria(proteins in urine)*
Apo lipoprotein A-I (AApoAI)	*No definite data*	*Primarily **involves kidneys, Liver and Spleen, adrenal glands insufficiency, laryngeal involvement** (may cause dysphonia)*
Apo lipoprotein A-II (AApoAII)	*No definite data*	***Involves Kidneys**-Causes Proteinuria (proteins in urine)*
β2-microglobin (Aβ2M)	*No definite data*	***Severe involvement of Kidneys which may require Long-term dialysis**,*

		Musculoskeletal involvement- *"Carpal Tunnel Syndrome, joint problems". [46]*
"Gelsolin" (A Gel) "Meretoja's syndrome"	*Normal life expectation*	*"Cutis laxa, Corneal lattice dystrophy, sagging/drooping eyelids, paresthesia, proteinuria (rare)".*[51]

Pathogenesis of ATTR

In ATTR, transthyretin, is produced in the Liver, and their physiological role is to act as a transporter protein for thyroxin and retinol. But when they misfolds into insoluble sheets (Beta Pleated), they get deposited as amyloid fibrils into myocardium (extracellular spaces). This center stage process of misfolding, aggregation and deposition of TTR is *due to "single point mutation" (Hereditary ATTR or hATTR).*The difference between hATTR and Wild Type variant (wtATTR) is the former variant is heritable while the later one is sporadic.[22]

Genetic mutation of gene encoding for transthyretin, results into a rare "Autosomal Dominant" inheritance, resulting into ***hATTR,*** which increases the predisposition of TTR, "monomers to misfold" and get deposited as 'collection or aggregates' of amyloid fibrils. Incomplete penetrance in respect to Genetic mutation, phenotypically manifests as Cardiomyopathy and/or polyneuropathy. [9]

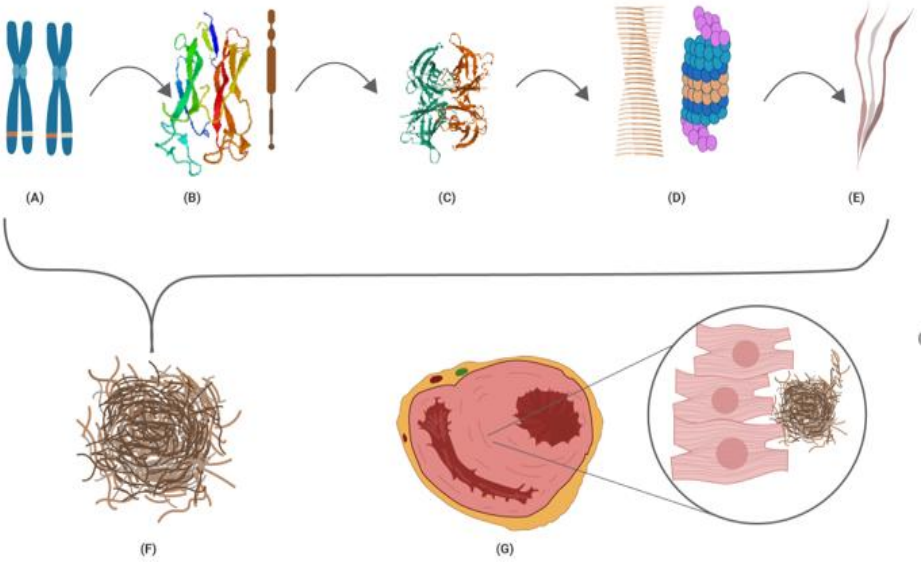

Figure 2. Amyloid formation

Description of Figure 2

(A) Genetic encoding for (TTR) proteins.
(B) Production of TTR monomer.
(C) TTR tetramer materialization.
(D) Severance of TTR tetramer as well as monomer "leads to the formation of amyloid fibril".
(E) Formation of "amyloid beta fibrils".

(F) Fibrils aggregates to form amyloids.
(G) These Fibrils aggregates gets deposition in extracellular spaces of Heart muscles (Leading to cardiomegaly)

Pathogenesis of AL

Primary AL amyloidosis occurs in those over 40 and is not sex-specific. It arises from plasma cell dyscrasia or may coexist with other plasma cell disorders.

Abnormal lambda or kappa light chains from monoclonal plasma cells misfold, become insoluble, and deposits in tissues. Lambda light chains are more common in primary AL, while kappa chains predominate in multiple myeloma.

Amyloid infiltration damages cardiac tissue through two mechanisms:

1. Direct deposition, which causes cardiomyocyte necrosis and subsequent fibrosis.
2. Circulating light chain toxicity, leading to oxidative stress damage.

A unique manifestation of AL (light chain) is, it causes oxidative stress leading to direct myotoxicity and necrosis which may lead to fibrosis of cadiomyocytes. [9]

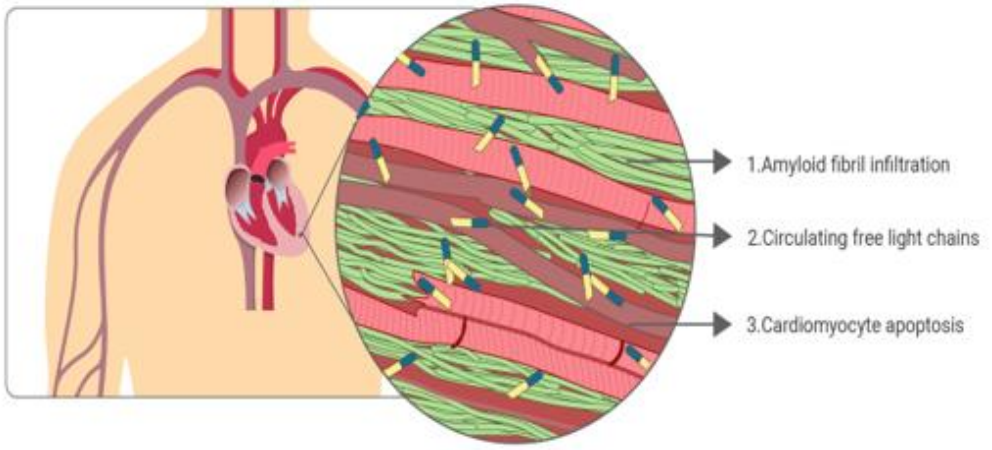

Figure 3. Pathophysiology of AL amyloidosis

1. *Amyloid fibril infiltration* leading to "Diastolic dysfunction"; 2. *Circulatory light chains* leads to dysfunction of myocardium; 3. *Cardiomyocytes apoptosis*, results from local effects of fibril infiltration.

Pathogenesis of AA amyloidosis (Causing secondary Amyloidosis)

Serum amyloid A, which is leads to inflammation and causes secondary amyloidosis, which commonly occurs due to chronic inflammatory conditions like Autoimmune diseases and infections which are chronic in nature and their sequels. *Kidneys are the primary pathological target of Secondary Amyloidosis, with rare involvement of the myocardium.*

Cardiovascular manifestations

- Clinically, it presents as heart failure with preserved ejection fraction (HFpEF). Impaired diastolic function and reduced left ventricular end-diastolic volume resulting into decreased stroke volume and persevered Ejection Fraction, which in turn leads to reduced cardiac output and clinically manifests as "*fatigue and generalized weakness"*. [64] The resulting congestion associated with heart failure leads to respiratory symptoms such as *Breathlessness on*

exertion and in later course of disease progression orthopnea. Venous congestion manifests *as increased JVP, Abdominal distention due to fluid accumulation, and congestive Liver enlargement.* [10,11]

In An Advanced Course of Disease Cardio Vascular System Examination will reveal clinically:

- The Cardiac apex is typically not displaced and is difficult to palpate.
- "The Third heart sound (S3) is appreciated by auscultation".
- "A fourth heart sound (S4) is rarely appreciated on auscultation, even in presence of restrictive cardiomyopathy". [12,16]
- *Atrial dilatation* develops because of "raised left ventricular filling pressures, due to the development of restrictive cardiomyopathy". [12,16]
- Arrhythmias associated with cardiac amyloidosis include atrial fibrillation and ventricular arrhythmias. (Commonly Arrhythmias). [65]
- Predominant signs of right heart failure include-
  - Swelling in both lower limbs (pitting in nature)
  - Increased jugular venous pressure (JVP)
  - Liver enlargement
  - Ascites.
- Acute Coronary Syndrome may be clinically presented due to "amyloid deposition in the coronary arteries" in Cardiac Amyloidosis. [24]

AL and its Cardiovascular manifestations (90%)

- AL most commonly involves cardiovascular system due to infiltration of any cardiac structure with amyloid.
- Vascular involvement leads to heart failure.
- In Diastolic dysfunction due to involvement of conducting pathways, it can manifest as a rhythm disturbance. Commonly, sinoatrial fibrosis or atrioventricular fibrosis occurs, leading to conduction defect, which can manifest clinically as various types of arrhythmias and Heart Blocks, [15,25]

ATTR and its Cardiovascular manifestation:

- ATTR and AL both clinically manifests chiefly as "Right heart failure "and "Heart Failure with Preserved Ejection Fraction" (HFpEF).
- Mutations in Val30Met transthyretin present clinically as serious involvement of conduction pathways, warranting pacemaker implantation.
- Other variants, like" Val122Ile and Thr60Ala (T60A)", affect the mechanical function of the heart but spares, conducting pathways. [49]
- Mutations in wtATTR involves mostly conducting system, leading to arrhythmia. Atrial fibrillation is the commonest arrhythmias [7,8,26].
- Wild-type ATTR is paradoxically associated with Aortic Stenosis (AS) with low flow and low gradient [27]

Extra cardiac manifestations (Table 1b)

Secondary amyloidosis

Secondary amyloidosis rarely occurs due to "chronic inflammatory conditions" (Autoimmune diseases like

'Rheumatoid Arthritis' and Chronic infections like 'Tuberculosis' and there sequels) Cardiovascular manifestations of secondary amyloidosis include progressive ventricular wall thickening which results in "Supply Demand" mismatch (Coronary artery supply mismatch with the myocardial oxygen demand, which over the period of time, if left untreated may result into " Acute coronary syndrome" which may present into "Regional Wall Motion Abnormalities". [6,8]

Diagnosis [5,7,9]

The diagnosis of cardiac amyloidosis involves a structured, stepwise approach to ensure comprehensive assessment and accurate identification of the disease markers. The following steps outline a typical diagnostic pathway:

Suspicion Phase

In the initial suspicion phase, clinicians should be vigilant for red flags [15] of cardiac amyloidosis. These include unexplained "*heart failure with preserved ejection fraction*" (HFpEF). Biochemical markers includs *elevated NT-proBNP levels*, *signs and symptoms of right heart failure*., and the presence of extracardiac symptoms such as proteinuria (due to Nephrotic Syndrome), macroglossia, skin bruises, Carpal Tunnel syndrome. Clinicians should use these clues, along with cardiac imaging findings [23], to suspect cardiac amyloidosis (Table 2).

Table: 2 Summarizing Types (Clinical or investigation hints), Red Flag, Amyloidosis Where It is Most Frequently Found (Both Cardiac and Extracardiac)

Type	**Red Flag** [15]	**Amyloidosis Where It is Most Frequently Found**
Extracardiac		
Clinical [27]	Polyneuropathy Dysautonomia Skin bruising Skin discoloration Cutis laxa Macroglossia Deafness Bilateral Carpal tunnel syndrome Ruptured biceps tendon Lumbar spinal stenosis Vitreous deposits Corneal lattice dystrophy Family history	ATTRv, AL, AA, AGel ATTR, AL AL AApoAI AGel AL ATTRwt ATTRv, ATTRwt ATTRwt ATTRwt ATTRv AGel ATTRv, AApoAI, AApoAI
Laboratory [48,50,51]	Renal insufficiency Proteinuria	ALL, AA, AApoAI, AApoAII, AApoAIV, Aβ2M, AFib, AL, AA, AApoAI, AApoAII, AFib

Type	**Red Flag** [15]	**Amyloidosis Where It is Most Frequently Found**
	Cardiac	
Clinical/ ECG [24]	Hypotension or normotensive if previous hypertensive Pseudo infarct pattern Low and decreased QRS voltage, AV conduction disease	ATTR, AL All All
Laboratory [29,31,32]	Disproportionately elevated NT-proBNP to degree of HF Persisting elevated troponin levels	All ATTR, AL
Echocardiogram [26,42]	Granular sparkling of myocardium Increased right ventricular wall thickness Increased valve thickness Pericardial effusion Reduced longitudinal strain with apical sparing pattern	All All All All All
CMR [41]	Subendocardial late gadolinium enhancement Elevated native T1 values Increased extracellular volume Abnormal gadolinium kinetics	All All All All
AA, serum amyloid A amyloidosis; AApoAI, apolipoprotein AI amyloidosis; AApoII, apolipoprotein AII amyloidosis; AApoAIV, apolipoprotein A-IV amyloidosis; AB2M, β2-microglobulin amyloidosis; AFib, fibrinogen amyloidosis; AGel, gelsolin amyloidosis; AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CTS, carpal tunnel syndrome; HF, heart failure; LSS, lumbar spinal stenosis; AV, atrio-ventricular; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.		

Initial Diagnostic Tests

Once cardiac amyloidosis is suspected, a series of non-invasive tests should be conducted to strengthen the suspicion. These include routine serum and urine tests to identify monoclonal light chains using the serum-free light chain assay, urine protein electrophoresis with immunofixation, and serum protein immunofixation. ECG may show “low-

voltage QRS complexes in the limb leads" and Echocardiography [42] may show increased "left ventricular wall thickness", hinting towards infiltration with amyloid fibrils. [19,23]

Confirmatory Phase

The confirmatory phase focuses on the definitive diagnosis and classification of the amyloid. Invasive diagnostic criteria are employed when non-invasive methods are inconclusive. "***Endomyocardial biopsy remains the gold standard for detection"***, [18] showing "apple-green birefringence under polarized light when stained with Congo red dye". Other techniques, like mass spectrometry along with immunohistochemistry, can be used to characterize the type of amyloid. In ATTR, non-invasive cardiac scintigraphy techniques, such as 99mTc-PYP, DPD, or HMDP scintigraphy, are valuable in detecting myocardial uptake and ruling out other potential causes of cardiac involvement [17,18,25].

Genetic Testing [20, 40]

Genotyping is crucial for distinguishing between wild-type and hereditary forms of ATTR amyloidosis, once ATTR is confirmed by scintigraphy or biopsy, using the step-wise diagnostic algorithm provided by the ***European Society of Cardiology*** (Figure 4).

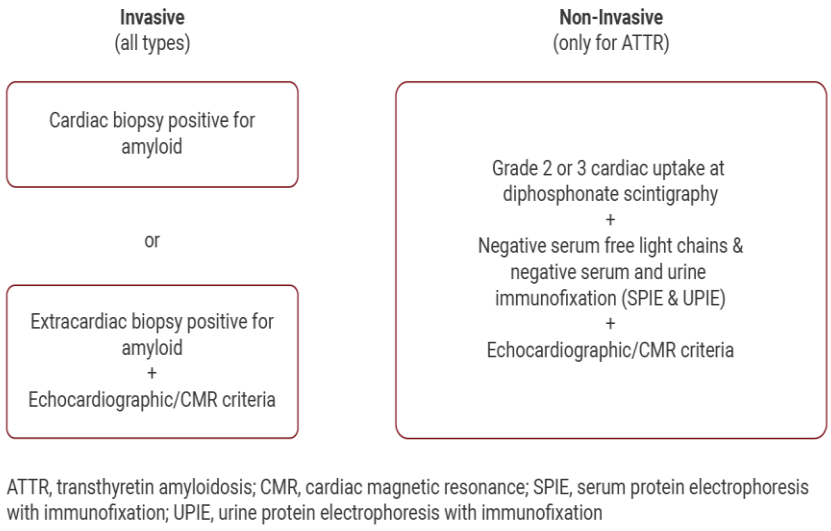

Figure 4. Algorithm showing" Approach to diagnosis of cardiac amyloidosis"

Invasive diagnostic criteria

An endomyocardial biopsy confirms amyloid deposits after Congo red staining, irrespective of the degree of left ventricular (LV) wall thickness. The classification of amyloid fibril proteins is performed after identifying amyloid using "mass spectrometry, immunohistochemistry, or immunoelectron microscopy". [17]

Diagnosis is also confirmed with amyloid deposits in an extra cardiac biopsy accompanied by characteristic features of cardiac amyloidosis, in the absence of an alternative cause for increased *LV wall*

thickness, or by characteristic features on CMR.

Proposed echocardiographic score to facilitate echocardiographic diagnosis of AL or ATTR amyloidosis in the presence of increased LV wall thickness.

- Scores>=8 points if of LV wall thickness is present
- Scores >=12 points if amyloid deposits are found in extra cardiac Biopsy.

Non-invasive diagnostic criteria

Cardiac ATTR amyloidosis is diagnosed in the absence of typical echocardiographic or CMR histological findings when 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), 99mTc-pyrophosphate (PYP), or 99mTc-hydroxymethylene diphosphonate (HMDP) scintigraphy shows Grade 2 or 3 myocardial uptake of the radiotracer (Image 1) and clonal dyscrasia is excluded by all the following tests:

- Serum-free light chain (FLC) assay
- Urine (UPIE) protein electrophoresis and Serum (SPIE) with immunofixation [19,24] (Figure 5).

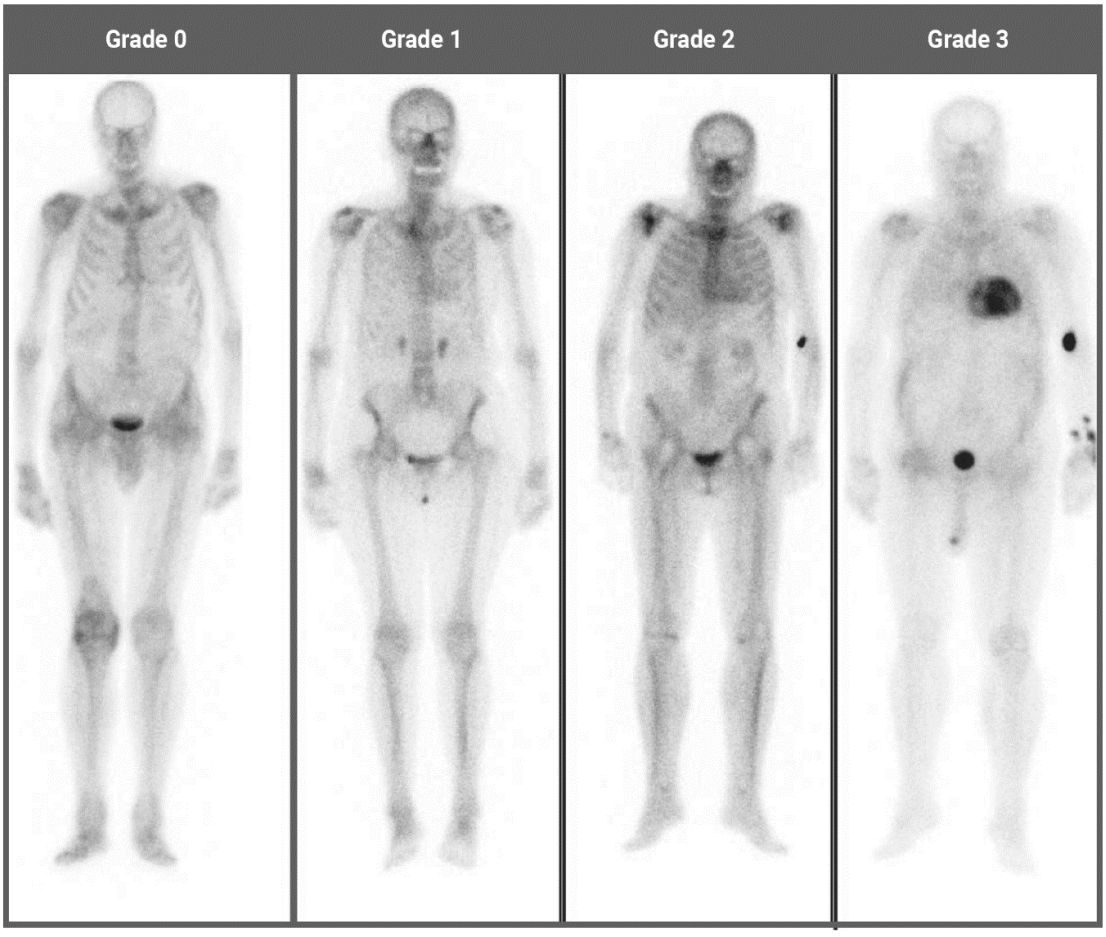

Figure 5. Showing cardiac uptake grading by bisphosphonate scintigraphy.

The combination of SPIE and UPIE quantification, *performed with immunofixation*, is used *to increase the sensitivity of the assays for detecting monoclonal proteins* (Figure 5). It is done

using cardiac uptake grading by bisphosphonate scintigraphy.

Bisphosphonate scintigraphy - cardiac uptake grading *[25]*
Grade 0: "*Normal* bone uptake"
Grade 1: "Myocardial uptake is *lower* than bone uptake"
Grade 2: "Myocardial and bone uptake are *equal*"
Grade 3: "Myocardial uptake is *more* than bone (with reduced/absent bone uptake)

Table 5. Tests to rule out light-chain amyloidosis [19]

Tests	**What Does It Detect?**	**Most Sensitive Test For:**	**Normal Range**
SPIE	Clonal immunoglobulin and/or clonal light chain	Confirming clonal immunoglobulin production	No monoclonal protein is present
UPIE	Clonal immunoglobulin and/or clonal light chain	Confirming clonal light chain production	No monoclonal protein is Present
Serum-free light-chain assay	Ratio of serum kappa: lambda light chains	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1	Free lite: 0.26–1.65[b] N Latex: 0.53–1.51

eGFR, estimated glomerular filtration rate; SPIE, serum protein electrophoresis with immunofixation; UPIE, urine
protein
electrophoresis with immunofixation.
[a]If any of these tests are abnormal, bone scintigraphy should not be used to establish the diagnosis of transthyretin amyloidosis.
bIn patients with kidney disease, mild elevations in the kappa: lambda ratio are frequently encountered. [b]In the setting of a normal SPIE/UPIE, a kappa, lambda ratio up to 2.0 in subjects with eGFR ≤45 mL/min/1.73 m^2 (up to 3.1 if in dialysis) can typically be considered normal.

Serum biomarkers
Non-specific serum biomarkers

"B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are raised in cardiac amyloidosis" (Due to direct compression of cardiomyocytes and stress caused by raised filling pressures). Serial NT-proBNP measurements and analysis are used to evaluate "post-chemotherapy prognostic outcomes". *Cardiac Troponin-T (cTnT) is a reliable predictor of cardiomyocyte death and a negative prognostic indicator in AL and ATTR cardiac amyloidosis*.

AL-specific biomarkers

"Serum and Urinary quantitative free light chain (FLC) assay" can detect monoclonal gammopathy. Another non-invasive technique that can be used is immunofixation electrophoresis (IFE). [19]

Electrocardiography (ECG) [24]

The characteristic finding of cardiac amyloidosis on the ECG is "low-voltage QRS complexes in the limb leads, accompanied by poor R-wave progression in the precordial leads". ECG signs of infarction with or without coronary obstruction result from amyloid deposition in the smaller penetrating arteries affecting the microcirculation. "Prolonged P wave voltage with morphological abnormalities" indicates inter- or intra-atrial conduction delay secondary to amyloid deposition.

Echocardiography [26, 42]

Cardiac amyloidosis causes concentric bi-ventricles (left and right ventricle)" wall thickening of more than 15 mm" (*wall thickness greater than 18 mm is more typical in ATTR than in AL*).

Cardiovascular magnetic resonance (CMR) imaging [41]

"Cardiovascular magnetic resonance imaging (CMR) in cardiac amyloidosis" [19,20] is used both as a *screening tool* and to *monitor response to treatment*. CMR findings include:

- Concentric left ventricular hypertrophy is a common form of remodeling seen in AL. [61]
- Asymmetric septal hypertrophy is seen in ATTR.
- Disproportionate biatrial enlargement with atrial septal wall thickening. [62]

As per the" European Society of Cardiology (ESC)", 2021 "echocardiographic and cardiac magnetic resonance (CMR) criteria for non-invasive and invasive diagnosis of cardiac amyloidosis" are mentioned below:

Table 5. Summarizing European Society of Cardiology (ESC)", 2021 "echocardiographic and cardiac magnetic resonance (CMR) criteria for non-invasive and invasive diagnosis of cardiac amyloidosis")

Echocardiography [42]
Unexplained LV thickness (≥12 mm) plus 1 or 2:
1. Characteristic echocardiography findings (≥2 of a, b, and c have to be present):
a. Grade 2 or worse diastolic dysfunction
b. Reduced tissue Dopplers. e and a' waves velocities (<5 cm/s)
c. Decreased global longitudinal LV strain (absolute value <-15%)
d.

2. Multipara metric echocardiographic score ≥8 points: a. Relative LV wall thickness (IVS+PWT)/LVEDD >0.6: 3 points b. Doppler Ewave/e' wave velocities >11: 1 point c. TAPSE ≤19 mm: 2 points d. LV global longitudinal strain absolute value <-13%: 1 point e. Systolic longitudinal strain apex to base ratio >2.9: 3 points
CMR [41] Characteristic CMR findings (a and b have to be present): a. Diffuse sub endocardial or transmural LGE b. Abnormal gadolinium kinetics c. ECV ≥0.40% (strongly supportive but not essential/diagnostic)

CMR, cardiac magnetic resonance; ECV, extracellular volume; IVS, interventricular septum; LGE, late gadolinium enhancement; LV,
left ventricular; LVEDD, left ventricular end-diastolic diameter; PWT, posterior wall thickness; TAPSE, tricuspid annular plane systolic excursion
Abnormal gadolinium kinetics: myocardial nulling preceding or coinciding with the blood pool

Nuclear imaging [8,23]

Technetium pyrophosphate scintigraphy (PYP scan) is a nuclear imaging study that detects cardiac transthyretin and is used to diagnose TTR amyloidosis. [19,20]

Biopsy

"Endomyocardial biopsy" [43] and" histological analysis" are the *gold standards for identifying cardiac amyloidosis.* Nevertheless, these "Biopsies" (abdominal fat pad and bone marrow) are invasive and require substantive technical expertise, posing a complication risk.

- "*Fat pad fine needle aspiration is sensitive in detecting systemic AL (84%) but low for hATTR and wtATTR*" (45% and 15%, respectively). [45]
- "*Endomyocardial biopsies sensitivity and specificity of 100*". [44]

Genetic testing [20,40]

Genotyping is recommended to differentiate between wild-type (wtATTR) and hereditary variants (hATTR) after ATTR is confirmed by positive scintigraphy or cardiac biopsy.

The Diagnostic approach (Flowchart) outlines the step-wise diagnostic algorithm for cardiac amyloidosis, as provided by the European Society of Cardiology (2021)

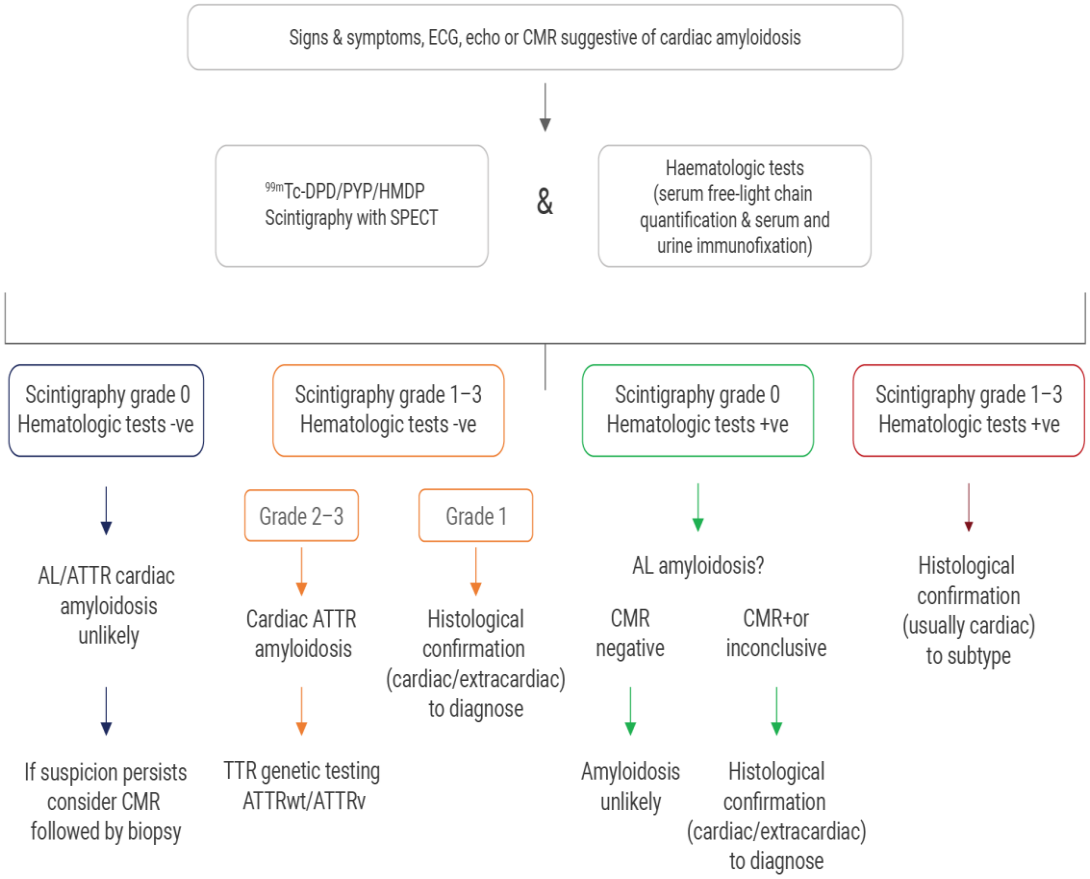

Figure 6. Diagnostic Approach

In summary, a methodical approach that combines clinical suspicion, initial screening tests, confirmatory procedures, and genetic assessment facilitates a comprehensive evaluation for effective" management of cardiac amyloidosis". [26]

Treatment

Treatment of cardiac amyloidosis and its complications focus on three areas:

- Heart failure
- Management of arrhythmias
- Initiation of disease-modifying agents.

For instance, in a patient experiencing heart failure characterized by fluid retention and generalized swelling (Anasarca), loop diuretics might be utilized to alleviate these symptoms by promoting fluid excretion. When dealing with arrhythmias, a patient presenting with atrial fibrillation would benefit from anticoagulants like warfarin to reduce the risk of stroke, other Thromboembolic Complication. Additionally, for a patient diagnosed with hereditary transthyretin amyloidosis, TTR stabilizers like diflunisal can be prescribed to slow amyloid progression and mitigate neurological deterioration. [5,9,29]

Management of heart failure [39]

- **Bioavailable loop diuretics**: Used for decongestion.
- **Aldosterone antagonists:** Used alone or in conjunction with loop diuretics in conditions with adequate blood pressure and renal function.
- **Standard guideline-directed medical therapy**: It includes angiotensin-

converting enzyme inhibitors, angiotensin receptor antagonists, angiotensin receptor blockers, and neprilysin inhibitors.

Management of arrhythmias [37]

- **Warfarin and direct oral anticoagulants**: These prevent thromboembolism and are indicated for atrial fibrillation or flutter.
- **Left atrial appendage closure devices**: Considered in patients with prohibitive bleeding risk.
- **Digoxin**: Used to control heart rate.
- **Amiodarone** is the agent of choice for both rhythm and rate control in patients where Beta-Blockade is not tolerated. Cardioversion and ablation are also recommended in a few cases.
- **Implantable cardioverter defibrillators (ICDs)**: Recommended in aborted sudden cardiac death with expected survival >1 year or significant ventricular arrhythmias. ICDs prevent sudden cardiac death.

Disease-modifying therapies for ATTR-CM [16,28]

Mechanism of Action: "Amyloid fibril aggregation occurs due to the destabilization of the TTR protein into monomers or oligomers, as seen in inherited mutations in cardiac variant transthyretin amyloidosis (ATTRv) or the aging process in wild-type disease (ATTRwt)". [52] Insoluble fibrils accumulate in the myocardium, WHICH LEADS TO restrictive cardiomyopathy, diastolic dysfunction, and congestive heart failure. [53]

Therapy targets - include several approaches: ***silencers*** reduces TTR production, therefore preventing further fibril formation; ***stabilizers*** prevent the dissociation of TTR tetramers into amyloidogenic monomers; hence helps in clearing existing amyloid fibrils from tissues.

TTR production (silencers): These protein silencers target the hepatic synthesis of TTR. Patisiran is an intravenously administered siRNA that degrades TTR mRNA, while Inotersen is a subcutaneously administered single-stranded antisense oligonucleotide that binds to TTR mRNA, leading to its degradation. [54] Vutrisiran acts by using RNA interference to trigger degradation of TTR mRNA. Vutrisiran is an effective treatment for heart failure caused by transthyretin amyloidosis Cardiomyopathy (ATTR-CM). [30]

TTR dissociation ("TTR stabilizers") binds "to the TTR tetramer" and thus preventing the "misfolding and deposition of amyloid fibrils". *NSAID diflunisal* stabilizes "TTR" in patients with ATTRv and polyneuropathy. It is associated with a reduced progression of polyneuropathy. [13]

TTR clearance from tissues (*TTR disruption*) "is the targets of clearance of amyloid fibrils from tissues". *"Doxycycline plus TUDCA (tauroursodeoxycholic acid) removes amyloid deposits"*. [60]

"Advanced heart failure therapies in ATTR-CM" [28, 39]

In ATTR-CM patients with heart failure, using an LV assist device is challenging. [55]

Heart transplantation is recommended in patients with heart failure and risk for neuropathy. [55,56]

Liver transplantation alone in ATTRv offers a prohibitive risk in the

presence of severe cardiac dysfunction and preexisting cardiac dysfunction. [57]

Targeted drug therapy for transthyretin and light-chain amyloidosis: (summary)
Transthyretin amyloidosis:

(a) <u>*TRANSTRYRATIN STABILIZERS:*</u>

1. Tafamidis: Indicated for ATTR cardiomyopathy
   Routs and frequency: PO-Daily
   NOTABLE SIDE EFFECT-GI Symptoms

2. Diflunisal: Indicated for ATTR cardiomyopathy
   Routs and frequency: PO-Twice Daily(bid)
   Notable Side Effect - Renal Dysfunctions, Increased Bleeding Tendences

(b) Transthyretin synthisis inhibiror:

1. ***Patisiran***: Indicated for Hereditary ATTR with Polyneuropathy
   Routs and frequency: IV, every Three weeks
   Notable Side Effect - Vitamin A Deficiency, infusion reaction

2. ***Inotersen:*** Indicated for Hereditary ATTR with Polyneuropathy
   Routs and frequency: Sub Cutaneous (SC). Weekly
   NOTABLE SIDE EFFECT- Thrombocytopenia, Glomerulonephritis, vitamin A Deficiency

3. ***LIGHT CHAIN AMYLOIDOSIS: (AL Amyloidosis)***

1. ***Bortezomib:***
   Routs and frequency: IV, Twice Weekly for 2 weeks per 28 days' cycle
   Notable Side Effect- Peripheral Neuropathy, Diarrhoea
   Thrombocytopenia

3. ***Cyclophosphamide***:
   Routs and frequency: PO(Orally), once weekly per 28 days' cycle
   Notable Side Effect- GI Symptoms, Pancytopenia

4. ***Daratumumab: Used for newly diagnosed AL***
   Routs and frequency: IV, once weekly (then once) per 28 days' cycle
   Notable Side Effect- Respiratory Tract infections, Diarrhoea

5. ***Doxycycline:***
   Routs and frequency: PO, bid
   Notable Side Effect- GI symptoms, Photosensitive Rash

-AL- "Light Chain Amyloidosis"
-ATTR- "Transthyretin Amyloidosis"

Complications and Comorbities in Cardiac Amyloidosis [28]
(SUMMARY OF TREATMENT)

1. ***Aortic Stenosis (AS)*** [33]
-Severe AS confers worse prognosis
-Trans catheter Aortic Valve Replacement (TAVR)

2. ***Thromboembolism*** [34, 35]
-Common complication.
-Anticoagulation Therapy specifically if AF (Atrial fibrillation is present)
(Independent on CHADS-VASc score)

3. ***Conduction defect*** [36]
-If indicated permanent Pacemaker.

-If high paced burden is expected consider Cardiac Resynchronization Therapy (CRT).

4. ***Atrial Fibrillation*** [37]
-Amiodarone is preferred anti arrhythmic agent.
-Digoxin should be used cautiously.
-Electrical Cardioversion has significant risk and should only be done after excluding any thrombi (Should be the last resort)

5. ***Ventricular Arrhythmias*** [38]
- "Implantable Cardioverter Defibrillator" (Only for Secondary prevention)
- "Trans venous Implantable Cardioverter Defibrillator (ICD)" is preferred over subcutaneous ICD (Implantable Cardioverter Defibrillator) [59]

6. ***Heart Failure*** [39]
-Control fluid intake
-Diuretics
-Avoid "*Beta Blockers, Angiotensin converting enzyme inhibitors/Angiotensin Receptor Blocker*s".
- "*Left Ventricular Assist Device*" nor indicated for most patients
- "*Heart Transplantation*" only for selected patients

OUTCOME/PROGNOSIS
LIGHT CHAIN AMYLOIDOSIS (AL)

- Median survival from onset of Heart Failure is around 6 months' in untreated cases. [58]
- As per the revised Mayo classification system, which utilises [29]
  - Troponin-T
  - NT-proBNP
  - Free light-chain levels (dFLC), - "differences between involved and uninvolved".
- These are utilised to classify THREE STAGES –With progressively worsening mortality.

Patient receive 1 POINT each for-
(a) "Troponin-T>= 0.025 ng/ml"
(b) "NT-proBNP>=1800 pg/ml"
(c) "dFLC>=18mg/dl"

- "After autologous stem cell transplantation (ASCT) – Median overall survival of patients with cardiac involvement is around 5 years". [30]

Transthyretin Cardiac Amyloidosis (Attr-Cm)

- In untreated cases of ATTR-CM median survival is 4.8 years. [31]
- Median survival often improves with targeted transthyretin therapy.

IF
  - "Troponin-T >= 0.05 ng/ml"
  - "NT-proBNP >= 3000 pg/ml"
  - "eGFR < 45ml/minute" (eGFR-Estimated Glomerular Filtration Rate)
  -

Above three prognostic parameters in cases of ATTR-CM, stratifies worse clinical outcomes. [31,32]

Statements and Declarations
Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article

Conflict of Interest

The authors declare that they do not have conflict of interest.

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