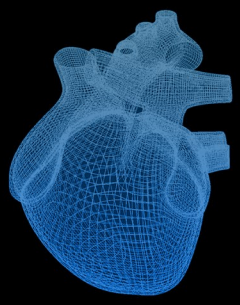
Overview of
Cardiac Amyloidosis



Cardiac amyloidosis is a disorder caused by the extracellular deposition of misfolded amyloid fibrils in the myocardium, leading to restrictive cardiomyopathy.

TYPES OF CARDIAC AMYLOIDOSIS

Amyloidosis can result from different precursor proteins, but the two main types affecting the heart are:

AL (Light-Chain) amyloidosis
Caused by the deposition of misfolded immunoglobulin light chains, which are produced in excess by clonal plasma cells. This form is typically associated with systemic amyloidosis and rapid progression to cardiac failure.

ATTR amyloidosis
Caused by misfolded transthyretin (TTR) protein, a transport protein for retinol and thyroxine.

ATTR has two subtypes:

ATTRwt
This non-genetic form occurs due to age-related TTR misfolding. Typically affects older males.

hATTR
Due to mutations in the TTR gene, this form is passed down genetically.

CLINICAL PRESENTATION AND IMPACT ON CARDIAC FUNCTION

It causes restrictive cardiomyopathy, where amyloid deposits stiffen the myocardium, impairing both diastolic and systolic function. Key clinical manifestations include:

Heart failure with preserved ejection fraction:
Progressive diastolic dysfunction is often seen in both AL and ATTR amyloidosis.

Arrhythmias:
Conduction system involvement leads to atrial fibrillation, atrioventricular block and other rhythm disturbances.

Conduction abnormalities:
Amyloid infiltration can lead to heart blocks and may require pacemaker implantation.

Systemic Involvement (particularly in AL amyloidosis) includes: Renal dysfunction and Neuropathy.

DIAGNOSTIC CHALLENGES

Symptoms overlap and delay diagnosis. The table below shows the prevalence of cardiac amyloidosis in different settings.

Condition/Symptom:	Percentage:
Heart failure with preserved ejection fraction	12%
Heart failure with reduced ejection fraction	10%
Aortic stenosis	8%
Hypertrophic cardiomyopathy	7%
Carpal tunnel syndrome	7%
Conduction disorder	2%

Source: Aimo A et al. Eur J Heart Fail. 2022;24(12):2342.

PREVALENCE

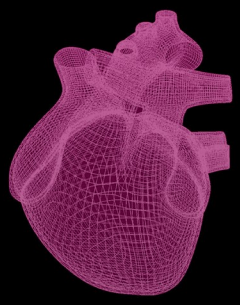
- AL Amyloidosis: Rare but rapidly progressive with a poor prognosis if untreated (median survival <12 months).
- ATTR Amyloidosis: Increasingly recognised in elderly populations, particularly men with heart failure with preserved ejection fraction and arrhythmias.
- The prevalence of cardiac amyloidosis was reported to be higher among men (70 per 100,000 person-years) compared with women (44 per 100,000 person-years).

Source: Gilstrap LG et al. Circ Heart Fail. 2019;12(6):e005407.

This programme is supported by an unrestricted educational grant from AstraZeneca.

Note: All information is true at the time of writing (October 2024). Please check authentic sources for the latest updates.
AL, Light-Chain Amyloidosis; ATTR, Transthyretin Amyloidosis; ATTRwt, Wild-type Transthyretin Amyloidosis; hATTR, Hereditary Transthyretin Amyloidosis; HFpEF, Heart Failure with Preserved Ejection Fraction; TTR, Transthyretin.

Management of Hereditary Transthyretin Amyloidosis (hATTR)



MULTIDISCIPLINARY CARE

Multidisciplinary team:
- hATTR amyloidosis is a systemic disease; hence, there is a need for multidisciplinary management.
- hATTR amyloidosis requires coordinated care between cardiology, neurology and genetics teams to manage the systemic nature of the disease.

Symptom management:
- **Cardiac:** Manage heart failure, arrhythmias and conduction system disease (pacemakers). Cardiology is a central player as over 75% of patients are represented with cardiomyopathy.
- **Neurological:** Address peripheral neuropathy and autonomic dysfunction.

Genetic counselling:
- Family screening for hereditary transmission.

NON-PHARMACOLOGICAL TREATMENT

Atrial fibrillation, intracardiac thrombus and risk of stroke, cardiac disease reduction and ventricular arrhythmias are the significant issues in the management of hATTR amyloidosis.

The ESC gives a Class IIa, Level of Evidence: C, for ICD implantation in secondary prevention, recommending consideration for those with either AL or hATTR cardiac amyloidosis and ventricular arrhythmia causing hemodynamic instability who are expected to survive >1 year with good functional status.

As we anticipate the introduction of new therapies aimed at managing hATTR amyloidosis more effectively, it is essential to recognise that these advances are likely to bring about significant changes in patient prognosis. Given the evolving landscape of treatment options, conducting further studies is critical.

PHARMACOLOGICAL TREATMENT

TTR stabilisers:
- **Tafamidis:** Prevents TTR tetramer dissociation, reducing amyloid deposition. Approved for cardiac and mixed phenotypes.
- **Acoramidis:** Investigational agent designed to mimic the action of the naturally occurring T119M mutation, which stabilises the TTR tetramer better than wild-type ATTR.
- **Diflunisal:** Stabilises TTR but is limited by side effects.

TTR gene silencers:
- **Patisiran:** Decreases TTR production, improving both neurological and cardiac outcomes. Approved for neuropathy.
- **Vutrisiran:** New-generation RNAi agent, showing promise in treating both neurological and cardiac phenotypes.
- **Inotersen:** Reduces TTR production, primarily beneficial for neuropathy with some cardiac impact. Due to risks of severe thrombocytopenia and glomerulonephritis, it is available only through the TEGSEDI REMS programme.
- **Eplontersen:** Approved by the FDA for hATTR-PN. It is the first self-administered therapy that reduces TTR protein production and improves neuropathy symptoms and quality of life. This is being evaluated for ATTR-CM.

RECENT/ONGOING CLINICAL TRIALS (PH 3)

Trial name/NCT ID	Title
APOLLO-B (NCT03997383)	Testing patisiran in patients with ATTR cardiomyopathy
HELIOS-A (NCT03759379)	Evaluating vutrisiran vs patisiran in hATTR amyloidosis
HELIOS-B (NCT04153149)	Investigating vutrisiran in patients with ATTR cardiomyopathy
NCT05071300	Long-term safety and efficacy of eplontersen in patients with hereditary transthyretin-mediated amyloid polyneuropathy
CARDIO-TTRansform (NCT04136171)	Evaluating the efficacy of eplontersen in treating ATTR cardiomyopathy, a systemic, progressive condition leading to heart failure
MAGNITUDE (NCT06128629)	Evaluating NTLA-2001, a CRISPR-based gene-editing therapy, in patients with transthyretin amyloidosis with cardiomyopathy
ACT-EARLY (NCT06563895)	Exploring acoramidis for pre-symptomatic treatment in carriers of pathogenic TTR variants

Source: ongoing clinical trials from the ClinicalTrials.gov repository.

FUTURE DIRECTIONS

Gene-Silencing Therapies: The ongoing CARDIO-TTRansform trial is testing eplontersen, a ligand-conjugated antisense oligonucleotide, in 1400 patients with ATTR-CM – the largest placebo-controlled trial to date in this population. Already approved for ATTR-vPN, it received FDA fast track designation for an extension to ATTR-CM patients.

Gene-Editing (CRISPR-Cas9): The MAGNITUDE trial is studying NTLA-2001, which could offer a one-time curative option by permanently editing the TTR gene.

Personalised Medicine: Early genetic screening and tailored treatment plans are crucial for improving outcomes, as exemplified by the ACT-EARLY trial focusing on preventive strategies.

Self-Administration Therapies: Eplontersen represents a major advancement as the first therapy that can be self-administered with an auto-injector, improving patient convenience and adherence.

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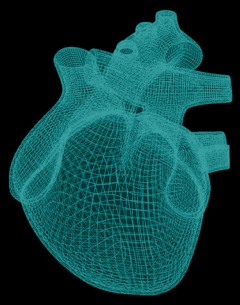
ATTR-CM, Transthyretin Amyloid Cardiomyopathy; ESC, European Society of Cardiology; hATTR, Hereditary Transthyretin Amyloidosis; ICD, Implantable Cardioverter Defibrillator; NSAID, Non-Steroidal Anti-Inflammatory Drug; PN, polyneuropathy; REMS, Risk Evaluation and Mitigation Strategy; RNAi, RNA Interference; TTR, Transthyretin.

Cardiac Amyloidosis
Imaging and Diagnosis



ROLE OF IMAGING MODALITIES

SCINTIGRAPHY

- **99mTc-DPD/PYP scintigraphy:** This imaging technique is considered the non-invasive gold standard for diagnosing transthyretin amyloid cardiomyopathy. It employs the Perugini Grading system to assess and quantify cardiac uptake of the tracer, with grades ranging from 0 to 3.
  - **Grade 0:** Indicates the absence of any tracer uptake in the heart.
  - **Grade 1:** Reflects mild tracer uptake in the heart, notably lower than that observed in the bone.
  - **Grade 2:** Represents a level of uptake in the heart that is equivalent to that seen in the bone.
  - **Grade 3:** Signifies a strong cardiac uptake with minimal to no uptake in the bone tissue.

ECHOCARDIOGRAPHY

Key Features:
- **LV wall thickening:** Caused by amyloid deposits, this results in thickening of the left ventricle walls.
- **Apical sparing pattern:** Identified through Global Longitudinal Strain, this pattern indicates amyloidosis, where the heart's apex remains relatively unaffected.
- **Biatrial enlargement and restrictive diastolic dysfunction:** This leads to the enlargement of both atria and indicates difficulty in heart filling during relaxation.

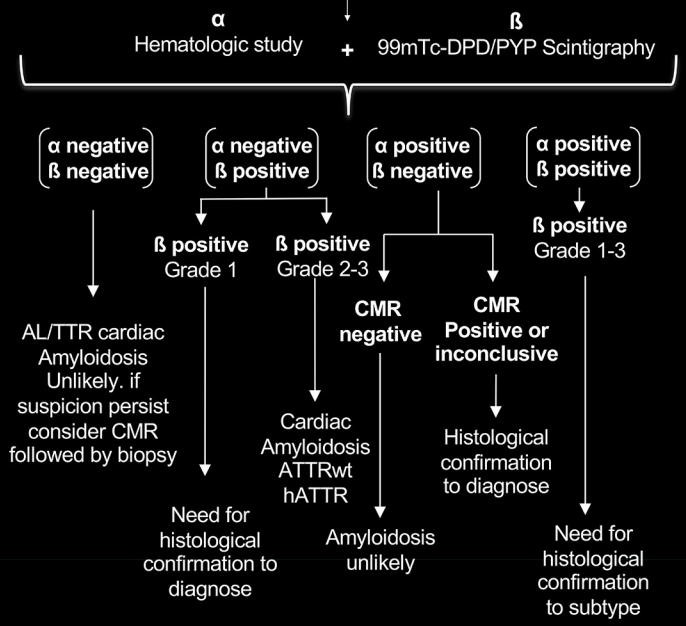
Warning signs: Low voltage readings on an ECG, alongside thickened LV walls, suggest possible amyloid infiltration.

CARDIAC MAGNETIC RESONANCE IMAGING

- **Late gadolinium enhancement:** This imaging technique is particularly indicative of amyloid deposition, characterised by a diffuse subendocardial enhancement pattern that highlights the presence of amyloid in the heart's tissue.
- **Extracellular volume mapping:** This method allows for the quantification of amyloid burden within the heart. An extracellular volume fraction greater than 40% typically suggests a significant involvement of amyloid, indicating its potential impact on cardiac function.
- **Cardiac MRI:** provides essential prognostic information, as higher levels of extracellular volume and more extensive late gadolinium enhancements are associated with worse clinical outcomes.

DIAGNOSTIC ALGORITHM

Heart failure, syncope, or bradyarrhythmia, with echocardiogram and / or cardiac magnetic resonance imaging indicating cardiac amyloid



Source: Garcia-Pavia P et al. Eur Heart J. 2021; 42(16): 1554.

DIAGNOSTIC INTEGRATION

- **Scintigraphy:** Best for confirming ATTR amyloidosis diagnosis.
- **Echocardiography:** Excellent for assessing heart structure, function and monitoring disease progression.
- **CMR:** Provides detailed tissue characterisation and is useful for quantifying amyloid load early.

KEY TAKEAWAYS

- **Non-invasive diagnosis:** Scintigraphy confirms ATTR amyloidosis, reducing the need for biopsy in most cases.
- **Imaging importance:** Echo and MRI offer detailed insights into myocardial involvement, helping guide treatment strategies and monitor disease progression.

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