

Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

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Received 19 February 2021; accepted 19 February 2021

Cardiac amyloidosis is a serious and progressive infiltrative disease that is caused by the deposition of amyloid fibrils at the cardiac level. It can be due to rare genetic variants in the hereditary forms or as a consequence of acquired conditions. Thanks to advances in imaging techniques and the possibility of achieving a non-invasive diagnosis, we now know that cardiac amyloidosis is a more frequent disease than traditionally considered. In this position paper the Working Group on Myocardial and Pericardial Disease proposes an invasive and non-invasive definition of cardiac amyloidosis, addresses clinical scenarios and situations to suspect the condition and proposes a diagnostic algorithm to aid diagnosis. Furthermore, we also review how to monitor and treat cardiac amyloidosis, in an attempt to bridge the gap between the latest advances in the field and clinical practice.

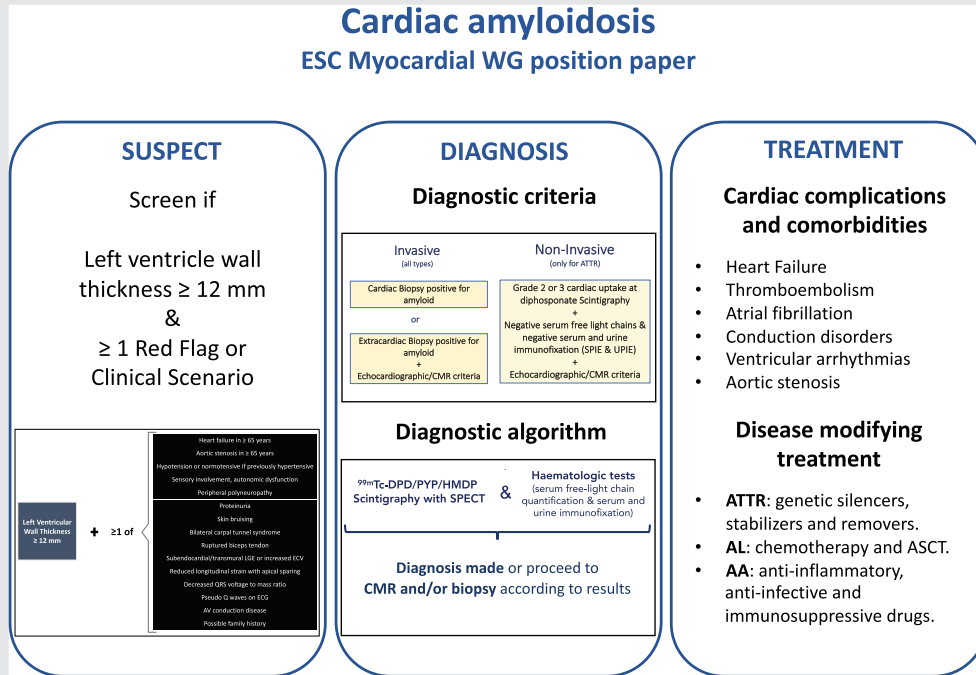
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These articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.

Graphical Abstract



Diagnosis and treatment of cardiac amyloidosis.

Introduction

Cardiac amyloidosis is characterized by the extracellular deposition of misfolded proteins in the heart with the pathognomonic histological property of green birefringence when viewed under cross polarized light after staining with Congo red.¹

Although considered a rare disease, recent data suggest that cardiac amyloidosis is underappreciated as a cause of common cardiac diseases or syndromes.² Recent advances in cardiac imaging, diagnostic strategies and therapies have improved the recognition and treatment of cardiac amyloidosis.^{1,2}

The aim of this position paper by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases is to help cardiologists and other physicians in recognizing, diagnosing and treating patients with cardiac amyloidosis.

Definitions and classifications

Types of cardiac amyloidosis

While more than 30 proteins are known to be capable of aggregating as amyloid *in vivo*, only nine amyloidogenic proteins accumulate in the myocardium to cause significant cardiac disease.³

Nevertheless, some forms (AApoAI, AApoAII, AApoAIV, A β 2M, AFib, AGel) are very rare and cardiac amyloidosis secondary to chronic inflammatory and infectious diseases (AA), although

still encountered, is now much less frequent. Accordingly, >98% of currently diagnosed cardiac amyloidosis results from fibrils composed of monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR), either in its hereditary (ATTRv) or acquired (ATTRwt) form. *Table 1* describes the main characteristics of each type of cardiac amyloidosis.

Definition of cardiac amyloidosis. Diagnostic criteria

Cardiac amyloidosis is diagnosed when amyloid fibrils are found within cardiac tissue. Both invasive and non-invasive diagnostic criteria have been proposed. Invasive diagnostic criteria apply to all forms of cardiac amyloidosis whereas non-invasive criteria are accepted only for ATTR (*Figure 1*).

Invasive diagnostic criteria

Cardiac amyloidosis is confirmed when an endomyocardial biopsy demonstrates amyloid deposits after Congo red staining irrespective of the degree of left ventricular (LV) wall thickness. Identification of amyloid should be followed by classification of the amyloid fibril protein. Although the gold standard for defining the type of amyloid remains mass spectrometry, immunohistochemistry or immunoelectron microscopy are routinely employed for amyloid typing in specialized centres.⁴

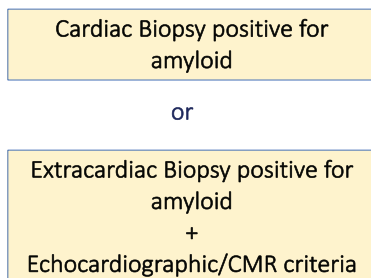
Table 1 Amyloidosis subtypes that affect the heart

Amyloidosis type	Protein	Hereditary	Frequency of heart involvement	Median survival from diagnosis (months)	Usual extracardiac signs
AL	Immunoglobulin light chain	No	70%	24 6 (if HF at diagnosis and not treated)	Nephropathy, proteinuria, autonomic dysfunction, polyneuropathy, macroglossia, spontaneous bruising, liver involvement
ATTRwt	Transthyretin	No	100%	57	CTS, LSS, ruptured biceps tendon
ATTRv	Transthyretin	Yes	30–100%	31 (Val142Ile)	Polyneuropathy, orthostatic hypotension, vitreous opacities, gastrointestinal problems
AA	Serum amyloid A	No	Depending on the mutation 5%	69 (non-Val142Ile) 133	Renal impairment (95%), proteinuria, hepatomegaly, gastrointestinal problems
AFib	Fibrinogen α	Yes	Rare	180	Renal impairment, proteinuria
AApoAI	Apolipoprotein A-I	Yes	Rare Depending on the mutation	No data. Probably >120	Primarily renal impairment, proteinuria, hepatosplenomegaly, adrenal insufficiency, dysphonia due to laryngeal involvement
AApoAII	Apolipoprotein A-II	Yes	Rare Depending on the mutation	No data	Primarily renal impairment, proteinuria
AApoAIV	Apolipoprotein A-IV	No	Unknown	79	Primarily renal impairment
A β 2M	β 2-microglobulin	No	80%	No data	Long-term dialysis, CTS, joint problems
AGel	Gelsolin	Yes	5% Primarily conduction disease	Near-normal life expectancy	Corneal lattice dystrophy, cutis laxa, drooping eyelids, paraesthesia, proteinuria (rare)

AA, serum amyloid A amyloidosis; AApoAI, apolipoprotein A-I amyloidosis; AApoAII, apolipoprotein A-II amyloidosis; AApoAIV, apolipoprotein A-IV amyloidosis; A β 2M, β 2-microglobulin amyloidosis; AFib, fibrinogen amyloidosis; AGel, gelsolin amyloidosis; AL, light-chain amyloidosis; ATTRwt, hereditary transthyretin amyloidosis; ATTRv, wild-type transthyretin amyloidosis; CTS, carpal tunnel syndrome; HF, heart failure; LSS, lumbar spinal stenosis.

Diagnosis of Cardiac Amyloidosis

Invasive (all types)



Non-Invasive (only for ATTR)

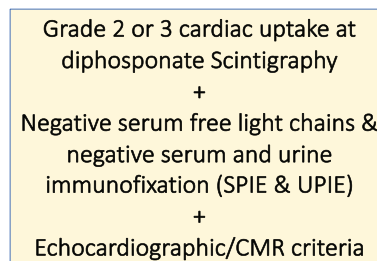


Figure 1 Invasive and non-invasive diagnosis of cardiac amyloidosis. ATTR, transthyretin amyloidosis; CMR, cardiac magnetic resonance; SPIE, serum protein electrophoresis with immunofixation; UPIE, urine protein electrophoresis with immunofixation.

Diagnosis is also confirmed if amyloid deposits within an extracardiac biopsy are accompanied either by characteristic features of cardiac amyloidosis by echocardiography, in the absence of an alternative cause for increased LV wall thickness, or by characteristic features on cardiac magnetic resonance (CMR) (Table 2).

A recent multicentre study has proposed an echocardiographic score to facilitate echocardiographic diagnosis of AL or ATTR amyloidosis in the presence of increased LV wall thickness.⁵ Although not yet externally validated, a score ≥ 8 points in the presence of LV wall thickness ≥ 12 mm in combination with amyloid deposits in an extra-cardiac biopsy could also be considered diagnostic of cardiac amyloidosis (Table 2).

Non-invasive diagnostic criteria

Cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings when ^{99m}Tc-pyrophosphate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) scintigraphy shows grade 2 or 3 myocardial uptake of radiotracer (Figure 2) and clonal dyscrasia is excluded by all the following tests: serum free light chain (FLC) assay, serum (SPIE) and urine (UPIE) protein electrophoresis with immunofixation.⁶ The combination of SPIE, UPIE and quantification of serum FLC has a sensitivity of 99% for identifying abnormal pro-amyloidotic precursor in AL

Table 2 Echocardiographic and cardiac magnetic resonance criteria for non-invasive and invasive (with extracardiac biopsy-proven amyloidosis) diagnosis of cardiac amyloidosis

Echocardiography

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 Doppler s' , e' , and a' wave velocities (< 5 cm/s)
 - c. Decreased LV global longitudinal strain (absolute value $< -15\%$).
2. Multiparametric echocardiographic score ≥ 8 points:
 - a. Relative LV wall thickness (IVS + PWT)/LVEDD > 0.6
3 points
 - b. Doppler E wave/ e' wave velocities > 11
1 point
 - c. TAPSE ≤ 19 mm
2 points
 - d. LV global longitudinal strain absolute value $\leq -13\%$
1 point
 - e. Systolic longitudinal strain apex to base ratio > 2.9
3 points

CMR

Characteristic CMR findings (a and b have to be present):

- a. Diffuse subendocardial or transmural LGE
- b. Abnormal gadolinium kinetics^a
- c. ECV $\geq 0.40\%$ (strongly supportive, but not essential/diagnostic)

CMR, cardiac magnetic resonance; ECV, extracellular cardiac volume; IVS, inter-ventricular septum; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; PWT, posterior wall thickness; TAPSE, tricuspid annular plane systolic excursion.

^aAbnormal gadolinium kinetics: myocardial nulling preceding or coinciding with the blood pool.

amyloidosis.⁷ It is important to stress that serum and urine protein electrophoresis should always be performed with immunofixation to increase the sensitivity of the assays for detecting monoclonal proteins (Table 3). Interpretation of low-level monoclonal protein or mild elevations in the kappa:lambda ratio (FLC ratio) could be challenging. These findings can be encountered in patients with chronic kidney disease (CKD) or with monoclonal gammopathy of undetermined significance (MGUS). In patients with CKD, as the glomerular filtration rate (GFR) declines, the renal clearance of polyclonal FLC decreases and serum concentrations rise.⁸ The FLC ratio also varies as the GFR declines, but this depends on the FLC assay available [Freelite assay (Binding Site, Birmingham, UK) or N Latex assay (Siemens, Marburg, Germany)].⁸ With the N Latex assay, the FLC ratio decreases as GFR declines but no reference range in CKD has yet been proposed. By contrast, with the most frequently used Freelite assay, FLC ratio increases as GFR declines and a ratio of 0.37 to 3.1 has been proposed to be

normal in patients with CKD. No reference values are available according to the severity of CKD, but in patients with moderate CKD (estimated GFR < 45 mL/min/1.73 m² by CKD-EPI formula) in the setting of a normal SPIE/UIPE, a FLC ratio up to 2.0 (or 3.1 if in dialysis) can typically be considered normal (Table 3). Otherwise, consultation with a haematologist is warranted.

In the absence of a detectable monoclonal protein and/or an abnormal serum FLC ratio, the specificity of grade 2 or 3 bone scintigraphy for cardiac ATTR when the disease is suspected has been proposed to be almost 100%.⁶ Please note, however, that scintigraphy should always include single photon emission computed tomography to confirm that cardiac uptake corresponds to myocardium uptake and not from cardiac chambers (Table 4). Nevertheless, recent reports have shown that rare situations can also lead to positive cardiac uptake.⁹ These situations should always be considered when interpreting scintigraphy results (Table 4).

Once cardiac ATTR amyloidosis is confirmed, genetic counselling and testing should be performed to assess for the presence of *TTR* mutations in order to differentiate between ATTRwt and ATTRv. Genetic testing should be performed even in elderly patients, as a significant number can have *TTR* mutations.¹⁰

Essential concepts

- Although nine types of cardiac amyloidosis are known, AL and ATTR currently account for the vast majority of cardiac amyloidosis.
- Both invasive and non-invasive diagnostic criteria are accepted to diagnose cardiac amyloidosis. While invasive diagnostic criteria apply to all forms of cardiac amyloidosis, non-invasive criteria are accepted only for ATTR.

Diagnosis of cardiac amyloidosis

Diagnosis of cardiac amyloidosis includes two critical phases: (i) *suspicious phase*, and (ii) *definite diagnosis phase*. The latter phase also includes appropriate typing of the amyloid, which is critical to guide specific treatment.

When to suspect cardiac amyloidosis

Red flags

Cardiac amyloidosis typically appears within a constellation of extracardiac signs and symptoms that are extremely useful to suspect the disease in the presence of compatible cardiac imaging findings. These signs and symptoms are termed 'red flags' and include proteinuria (even mild), macroglossia, skin bruises and carpal tunnel syndrome, among others (Table 5). There are also various red flags at the cardiac level, such as heart failure [including disproportionately high N-terminal pro B-type natriuretic peptide (NT-proBNP)] that appears to be in disproportion to 'objective' findings on echocardiogram, 'unexplained' right heart failure in the

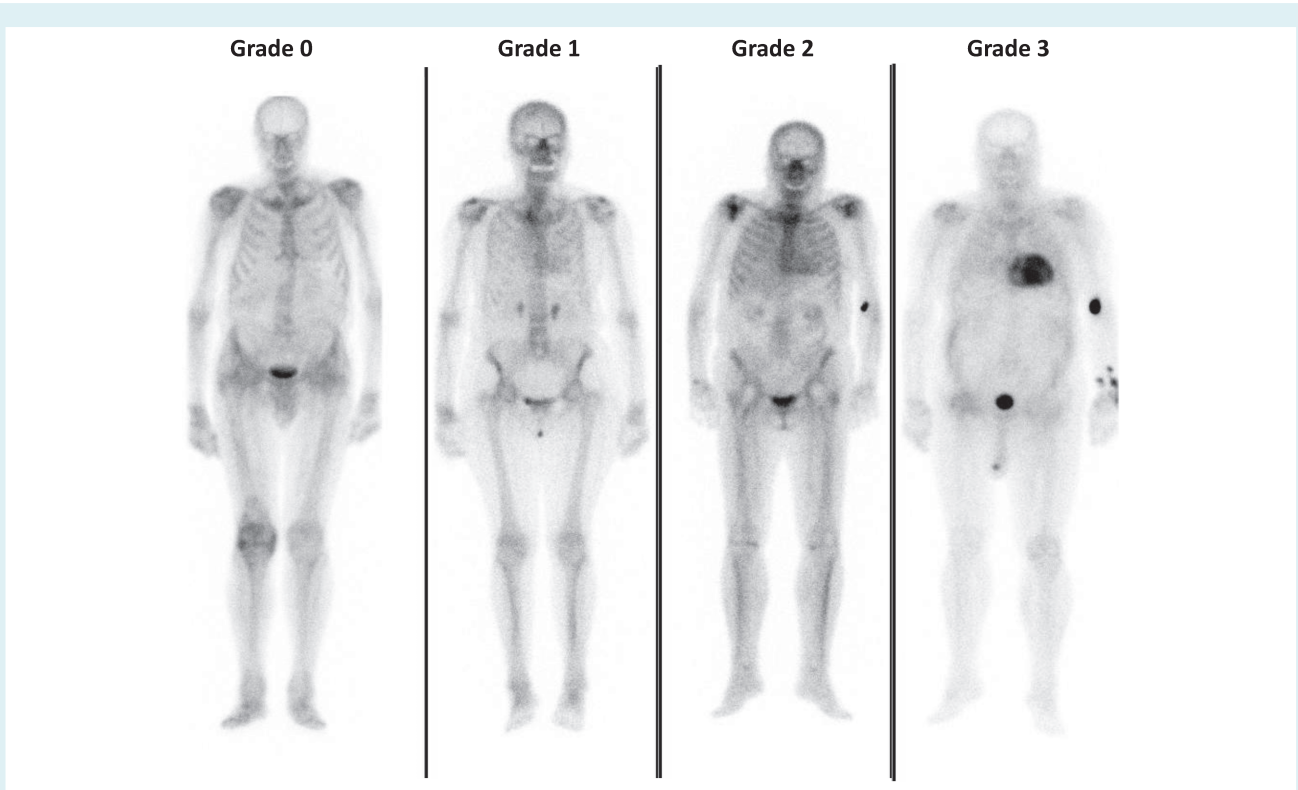


Figure 2 Cardiac uptake grading in bisphosphonate scintigraphy. Grade 0: absence of tracer myocardial uptake and normal bone uptake; Grade 1: myocardial uptake in a lower degree than at bone level; Grade 2: similar myocardial and bone uptake; Grade 3: myocardial uptake greater than bone with reduced/absent bone uptake.

Table 3 Serum and urine tests to rule out AL amyloidosis

Tests ^a	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 present
UPIE	Clonal immunoglobulin and/or clonal light chain	Confirming clonal light chain production	No monoclonal protein 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	Freelite: 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.

^aIf 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. 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 m² (up to 3.1 if in dialysis) can typically be considered normal. This correction is not applicable to Siemens N Latex assay.

presence of ostensibly ‘normal’ ventricular and valvular function, or ‘idiopathic’ pericardial effusion. Persistent troponin elevation, disproportionately low QRS voltage or early conduction system disease are also signs that could evoke cardiac amyloidosis (Table 5).

Clinical scenarios

In addition to cardiac and extracardiac findings fostering the suspicion, there are several clinical situations in which cardiac amyloidosis should always be considered.

Cardiac disease in the presence of a typical systemic condition such as plasma cell dyscrasia, nephrotic syndrome, peripheral neuropathy or a chronic systemic inflammatory condition should prompt consideration of amyloidosis, particularly if compatible cardiac imaging findings are present.

Increased wall thickness in a non-dilated left ventricle is a prominent characteristic of cardiac amyloidosis and should trigger further evaluation when found in elderly patients with common cardiac syndromes like heart failure with preserved ejection fraction, hypertrophic cardiomyopathy or severe aortic stenosis,

Table 4 Possible false positives and false negatives of bisphosphonate scintigraphy for detecting transthyretin cardiac amyloidosis

	Situation	How to suspect and confirm?
False positive	AL amyloidosis	Abnormal SPIE, UPIE or serum free light ratio. Requires histologic confirmation.
	Hydroxychloroquine cardiac toxicity	Interrogation. Requires histologic confirmation.
	AApoAI and AApoAII amyloidosis	Concomitant kidney disease present. Genetic testing.
	ApoAIV amyloidosis	Concomitant kidney disease present. Requires histologic confirmation.
	A β 2M amyloidosis	Long-term dialysis (>9 years). Requires histologic confirmation.
False negative	Blood pool	Cardiac dysfunction could be present. Use SPECT to detect uptake in myocardium. Delay acquisition.
	Rib fractures, valvular/annular calcifications	Use SPECT to detect uptake in myocardium.
	Recent myocardial infarction (<4 weeks)	Interrogation. Use SPECT to detect diffuse uptake in myocardium.
	Phe84Leu ATTRv, Ser97Tyr ATTRv	Concomitant neuropathy. Familial disease. Genetic testing.
	Very mild disease	Requires histologic confirmation
	Delayed acquisition	Shorter acquisition time interval
	Premature acquisition	Prolong acquisition time interval

AApoAI, apolipoprotein A-I amyloidosis; AApoAII, apolipoprotein A-II amyloidosis; AApoAIV, apolipoprotein A-IV amyloidosis; A β 2M, β 2-microglobulin amyloidosis; AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; SPIE, serum protein electrophoresis with immunofixation; SPECT, single photon emission computed tomography; UPIE, urine protein electrophoresis with immunofixation.

particularly among those undergoing transcatheter aortic valve replacement.^{11–13}

As ATTR has been found in a significant number of patients (up to 7% to 19%) in the abovementioned clinical scenarios, and with the possibility of non-invasive diagnosis, we recommend ascertainment of cardiac amyloidosis in individuals with increased wall thickness with either heart failure, aortic stenosis or red flag signs/symptoms, particularly if older than 65 years (Figure 3).

Diagnostic algorithm

Once cardiac amyloidosis is suspected, a timely, definitive diagnosis should be obtained as patient outcomes depend largely on early initiation of therapy (particularly in AL).

As the large majority of cases of cardiac amyloidosis are AL and ATTR, we propose a diagnostic algorithm focusing on identifying these subtypes by the initial use of ^{99m}Tc-PYP, DPD or HMDP scintigraphy coupled to assessment for monoclonal proteins by SPIE, UPIE and quantification of serum FLC (Figure 4).

The results of these tests could lead to four scenarios:

1. *Scintigraphy does not show cardiac uptake and assessments for monoclonal proteins are negative.* There is a very low probability of cardiac amyloidosis, and ATTR and AL amyloidosis are unlikely. An alternative diagnosis should be considered. Nevertheless, if suspicion persists, consider CMR followed by cardiac or extracardiac biopsy as bone scintigraphy could be negative in some ATTRv mutations (tracer uptake depends on TTR fibril composition) and in rare subtypes of cardiac amyloidosis (Table 5).
2. *Scintigraphy shows cardiac uptake and assessments for monoclonal proteins are negative.* If cardiac uptake is grade 2 or 3, ATTR cardiac amyloidosis can be diagnosed. Proceed with genetic

testing to differentiate between ATTRv and ATTRwt forms. In the case that cardiac uptake is grade 1, non-invasive diagnosis is not possible and histological confirmation of amyloid deposits (could be extracardiac) is required.

3. *Scintigraphy does not show cardiac uptake and at least one of the monoclonal protein tests is abnormal.* AL amyloidosis has to be ruled out promptly and CMR can be used to confirm cardiac involvement. If CMR findings do not support cardiac amyloidosis, the diagnosis is very unlikely. In the case that CMR findings are supportive or inconclusive, cardiac or extracardiac histological demonstration of amyloid deposits is required to diagnose AL cardiac amyloidosis. Cardiac or other clinically-affected organ biopsy is recommended to avoid time delay to diagnosis and consultation with a haematologist is warranted.¹⁴ If CMR cannot be performed promptly, consider performing biopsy directly.
4. *Scintigraphy shows cardiac uptake and at least one of the monoclonal protein tests is abnormal.* ATTR amyloidosis with concomitant MGUS (or any haematological disorder that produces FLC), AL amyloidosis or coexistence of both AL and ATTR amyloidosis are possible in this scenario. Diagnosis of cardiac amyloidosis in this case requires histology with amyloid typing, usually via endomyocardial biopsy.

Essential concepts

- Cardiac amyloidosis should be considered in patients with increased wall thickness in the presence of cardiac or extracardiac red flags and/or in specific clinical situations.

Table 5 Cardiac and extracardiac amyloidosis red flags

Extracardiac/cardiac	Type	Red flag	Amyloidosis where it is most frequently found
Extracardiac	Clinical	Polyneuropathy	ATTRv, AL, AA, AGel
		Dysautonomia	ATTR, AL
		Skin bruising	AL
		Skin discoloration	AApoAI
		Cutis laxa	AGel
		Macroglossia	AL
		Deafness	ATTRwt
		Bilateral carpal tunnel syndrome	ATTRv, ATTRwt
		Ruptured biceps tendon	ATTRwt
		Lumbar spinal stenosis	ATTRwt
		Vitreous deposits	ATTRv
		Corneal lattice dystrophy	AGel
		Family history	ATTRv, AApoAI, AApoAll
		Renal insufficiency	AL, AA, AApoAI, AApoAll, AApoAIV, Aβ2M, AFib
Cardiac	Clinical	Proteinuria	AL, AA, AApoAI, AApoAll, AFib
		Hypotension or normotensive if previous hypertensive	ATTR, AL
	ECG	Pseudoinfarct pattern	all
		Low/decreased QRS voltage to degree of LV thickness	all
	Laboratory	AV conduction disease	all
		Disproportionally elevated NT-proBNP to degree of HF	all
	Echocardiogram	Persisting elevated troponin levels	ATTR, AL
		Granular sparkling of myocardium	all
		Increased right ventricular wall thickness	all
		Increased valve thickness	all
		Pericardial effusion	all
	CMR	Reduced longitudinal strain with apical sparing pattern	all
		Subendocardial late gadolinium enhancement	all
		Elevated native T1 values	all
Increased extracellular volume		all	
Abnormal gadolinium kinetics		all	

AA, serum amyloid A amyloidosis; AApoAI, apolipoprotein A-I amyloidosis; AApoAll, apolipoprotein A-II amyloidosis; AApoAIV, apolipoprotein A-IV amyloidosis; Aβ2M, β2-microglobulin amyloidosis; AFib, fibrinogen amyloidosis; AGel, gelsolin amyloidosis; AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; AV, atrio-ventricular; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide..

- A diagnostic algorithm based initially on the use of bone scintigraphy coupled to assessment for monoclonal proteins allows appropriate diagnosis in patients with suggestive signs/symptoms.

systems have been developed for AL and ATTR cardiac amyloidosis (Table 6).^{15–19}

Available scoring systems have been constructed using parameters obtained 'at presentation' and provide an initial prognostic stratification. The prognostic impact of any change of the scores during follow-up has not yet been validated, even though recent studies have shown promising results.²⁰

Outcome and prognosis

Prognosis in cardiac amyloidosis

Although different methods to prognosticate in cardiac amyloidosis have been proposed, the focus has moved to multiparametric biomarker-based prognostic scores, and biomarker-based staging

Progression of cardiac amyloidosis

While there have been multiple studies delineating baseline risk factors associated with adverse outcomes (principally mortality) in AL and ATTR, and data are emerging from the placebo arm of therapeutic trials,²¹ there is a dearth of published data on longitudinal aspects of disease progression and none that are

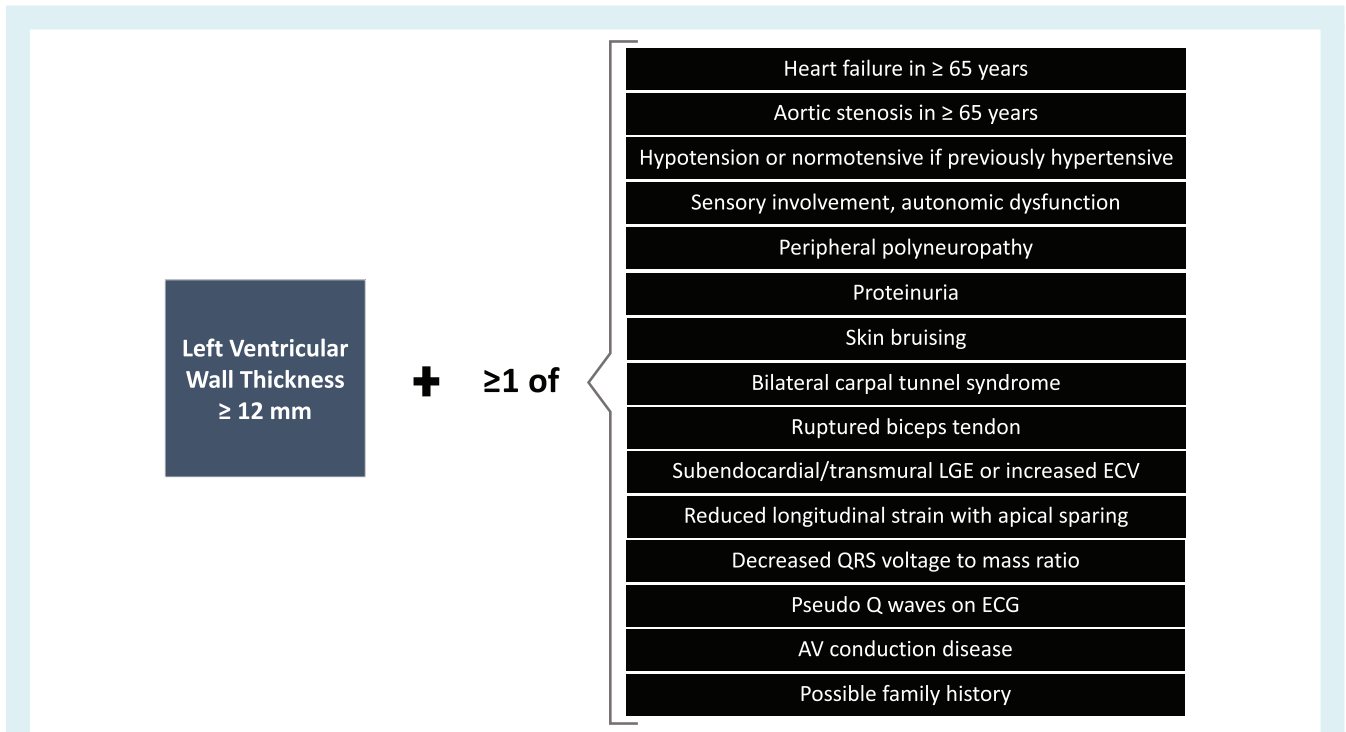


Figure 3 Screening for cardiac amyloidosis. AV, atrio-ventricular; ECG, electrocardiogram; ECV, extracellular volume; LGE, late gadolinium enhancement.

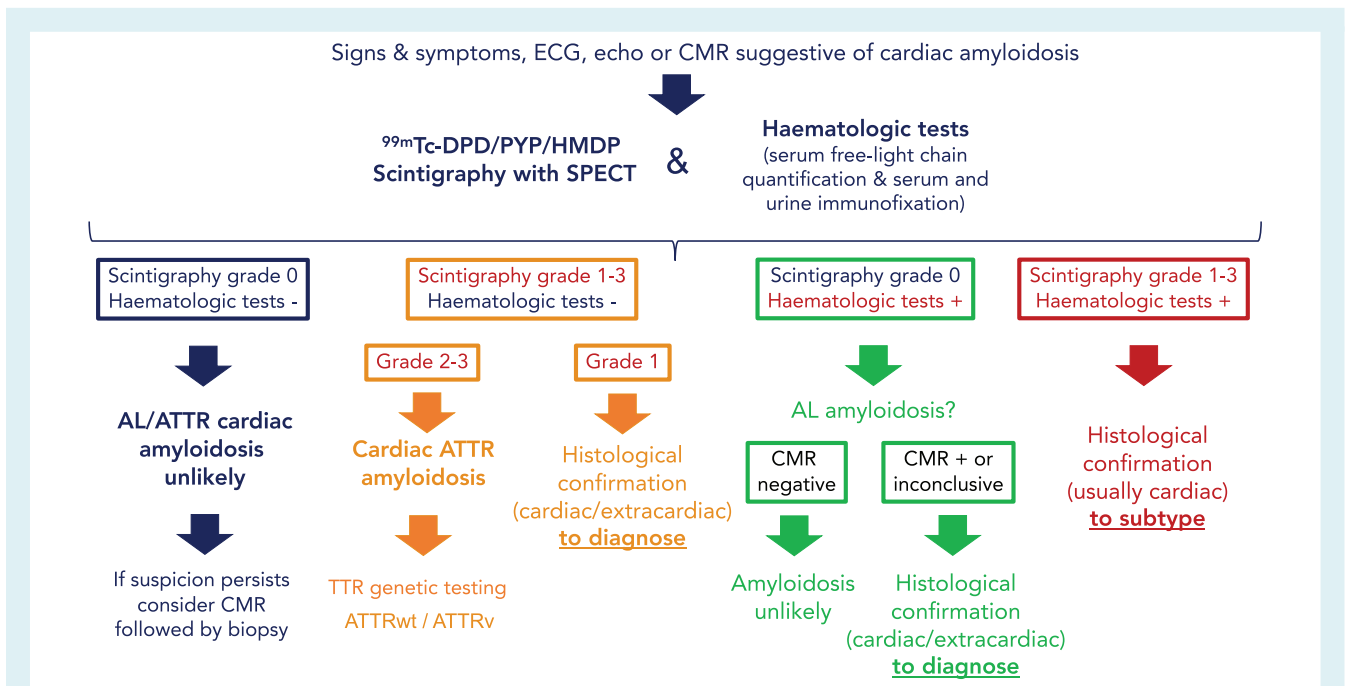


Figure 4 Diagnostic algorithm for cardiac amyloidosis. ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; AL, light-chain amyloidosis; CMR, cardiac magnetic resonance; ECG, electrocardiogram; SPECT, single photon emission computed tomography; TTR, transthyretin.

Table 6 Prognostic staging scores in AL and ATTR amyloidosis

	Kumar et al.¹⁵ (Mayo) AL	Lillenes et al.¹⁶ (BU) AL	Grogan et al.¹⁷ (Mayo) ATTRwt	Gillmore et al.¹⁸ (NAC) ATTRv & ATTRwt	Cheng et al.¹⁹ ATTRv & ATTRwt
Staging parameters:	FLC-diff ≥ 18 mg/dL Troponin T ≥ 0.025 ng/mL NT-proBNP ≥ 1800 pg/mL	Troponin I > 0.1 ng/mL BNP > 81 pg/mL	Troponin T > 0.05 ng/mL NT-proBNP > 3000 pg/mL	eGFR < 45 mL/min/1.73 m ² NT-proBNP > 3000 pg/mL	Mayo or NAC score (0 to 2 points) Daily dose of Furosemide or equivalent: 0 mg/kg (0 points), $> 0-0.5$ mg/kg (1 point), $> 0.5-1$ mg/kg (2 points), and > 1 mg/kg (3 points) NYHA class I-IV (1 to 4 points)
5-year survival	68%				
Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IIIb (2 parameters and BNP > 700 pg/mL)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9
4-year survival/median survival			57% 66 months 42% 40 months 18% 20 months	69.2 months 46.7 months 24.1 months	Score 1-3 Score 4-6 Score 7-9
Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9
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Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9
5-year survival	68%				
Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9
4-year survival/median survival			57% 66 months 42% 40 months 18% 20 months	69.2 months 46.7 months 24.1 months	Score 1-3 Score 4-6 Score 7-9
Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9
5-year survival	68%				
Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9
4-year survival/median survival			57% 66 months 42% 40 months 18% 20 months	69.2 months 46.7 months 24.1 months	Score 1-3 Score 4-6 Score 7-9
Stage	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters) Stage IV (3 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Stage I (0 parameters) Stage II (1 parameter) Stage III (2 parameters)	Score 1-3 Score 4-6 Score 7-9

AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BU, Boston University School of Medicine; eGFR, estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula; FLC-diff, difference between involved and uninvolved free light chain; NAC, UK National Amyloidosis Centre; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

Table 7 Proposed follow-up scheme in cardiac amyloidosis

	AL	ATTR
Patient with cardiac amyloidosis	<p>Every month (during initial haematological treatment):</p> <ul style="list-style-type: none"> • Complete blood count, basic biochemistry, NT-proBNP and troponin • Serum free light chain quantification • Clinical evaluation by Haematology • Evaluation by Cardiology if clinically indicated <p>Every 3–4 months (after completing initial haematological treatment):</p> <ul style="list-style-type: none"> • Complete blood count, basic biochemistry, NT-proBNP and troponin • Serum free light chain quantification • Clinical evaluation by Haematology <p>Every 6 months:</p> <ul style="list-style-type: none"> • ECG • Echocardiography/CMR • Evaluation by Cardiology <p>Every 12 months:</p> <ul style="list-style-type: none"> • 24 h Holter ECG 	<p>Every 6 months:</p> <ul style="list-style-type: none"> • ECG • Blood tests including NT-proBNP and troponin • Neurological evaluation (if ATTRv) • 6MWD (optional) • KCCQ (optional) <p>Every 12 months:</p> <ul style="list-style-type: none"> • Echocardiography/CMR • 24 h Holter ECG • Ophthalmological evaluation (if ATTRv)
ATTRv asymptomatic genetic carriers^a		<p>Yearly:</p> <ul style="list-style-type: none"> • ECG • Blood tests including NT-proBNP and troponin • Echocardiography • Neurological and ophthalmological evaluation <p>Every 2 years:</p> <ul style="list-style-type: none"> • Holter ECG <p>Every 3 years or if any of above complementary test is abnormal:</p> <ul style="list-style-type: none"> • Scintigraphy • CMR

6MWD, 6-min walking distance; AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; CMR, cardiac magnetic resonance; ECG, electrocardiogram; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide.

^aClinical follow-up to be started 10 years before the age of disease onset of affected relatives or predicted usual onset age for the specific ATTRv mutation.

population-based without referral and ascertainment biases. In the era of emerging effective therapies, this is a major unmet need.

Follow-up of patients with cardiac amyloidosis

Although no studies have yet addressed the optimal follow-up scheme in patients with cardiac amyloidosis, a common scheme consists of 6-month visits with electrocardiogram (ECG) and complete blood tests (including NT-proBNP and troponin) and yearly echocardiogram and 24 h Holter ECG. A summary of recommended follow-up tests can be found in *Table 7*.

Follow-up of mutation carriers and genetic counselling

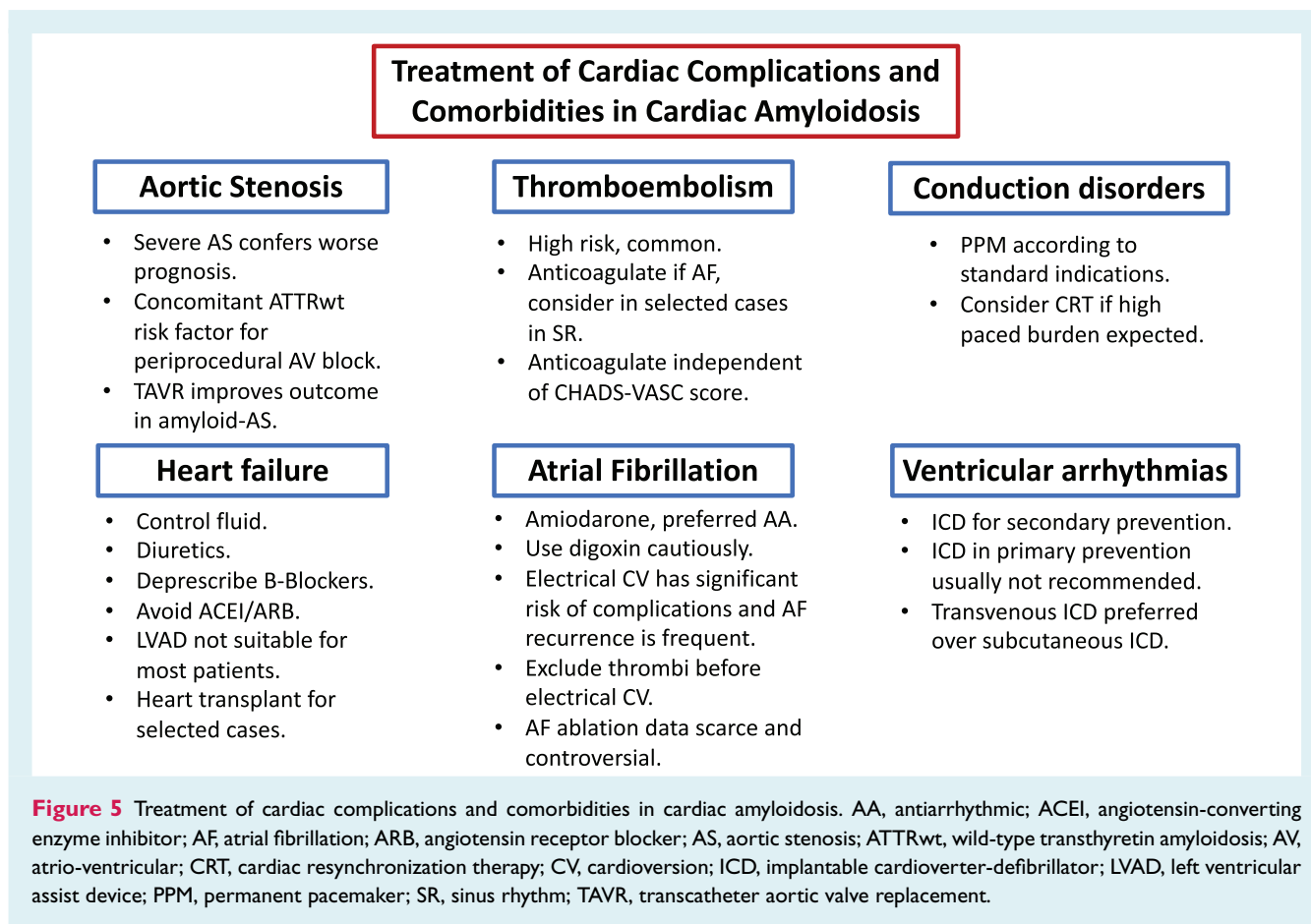
Genetic testing is recommended for relatives of patients with an inheritable form of cardiac amyloidosis. Such testing should occur along with genetic counselling of patients and their families. As

all hereditary amyloidoses have an adult onset, genetic testing of minors is discouraged. Genetic testing could be offered during young adulthood if genetic information would seem useful to guide professional choices or for reproductive planning.

As age of onset, clinical penetrance, and progression depend upon the variant, assessment of penetrance in allele carriers is generally recommended to start ~10 years prior to the age of disease onset in affected members of the family (or other individuals with the same mutation), or as soon as symptoms compatible with amyloidosis develop (*Table 7*).²²

Essential concepts

- While several staging systems are available to facilitate prognosis, there are limited data on how to assess progression. In the era of emerging effective specific therapies, this is a major unmet need.



- Follow-up of patients with cardiac amyloidosis and mutation carriers should be conducted following a structured protocol.

Treatment

Treatment of cardiac amyloidosis involves two areas: (i) treatment and prevention of complications; and (ii) stopping or delaying amyloid deposition by specific treatment.

Treatment of complications and comorbidities

Supportive care of patients with cardiac amyloidosis encompasses different clinical aspects including treatment of heart failure, arrhythmias, conduction disturbances, thromboembolism and concomitant presence of severe aortic stenosis (Figure 5).^{23–25}

Specific (disease-modifying) treatment

Treating the process of amyloid deposition should target the production of amyloid precursor protein or the assembly of amyloid fibrils.

AL amyloidosis

Specific treatment in cardiac AL amyloidosis should be undertaken by multidisciplinary teams involving oncohaematology and cardiology specialists and, whenever possible, patients should be referred to specialised centres.²⁶

Patients with AL amyloidosis not only have a haematologic malignancy, but also their multiorgan involvement makes them particularly fragile and susceptible to treatment toxicity. Therapeutic approaches depend on risk assessment that are defined in many circumstances by the degree of cardiac involvement (online supplementary Figure S1) and cardiac response depends also on haematological response (online supplementary Table S1).^{23,24} The role of the cardiologist in the specific treatment includes: (i) cardiac assessment for initial haematologic strategies, including consideration of autologous stem cell transplantation (online supplementary Table S2), (ii) heart transplant evaluation, and (iii) cardiac monitoring during chemotherapy.

ATTR amyloidosis

There is an increasing availability of novel, effective, targeted therapeutic options for ATTRwt and ATTRv. A prompt diagnosis is essential to enable the timely treatment of neurological, cardiac and other systemic manifestations, as therapy is more effective

in the early stages of the disease.^{27–29} Effective therapies reduce the production of mutated (liver transplantation) and overall TTR (genetic silencers) or stabilize circulating TTR molecule (stabilizers), preventing their dissociation or cleavage into amyloidogenic fragments (Figure 6). Several new compounds are under investigation, including agents directed to remove amyloid fibrils (online supplementary material).

Current therapeutic alternatives distinguish between ATTRv and ATTRwt and, in the case of ATTRv, according to the presence of cardiomyopathy, polyneuropathy or both (Figure 7). A detailed description of ATTR therapies that are either available or are being tested in phase III trials can be found in online supplementary material. Tafamidis should be generally considered the agent of choice in ATTR cardiac patients with reasonable expected survival while patisiran could be considered in ATTRv patients with cardiac involvement in whom gene silencers are prescribed due to symptomatic neurological disease.

Essential concepts

- Management of cardiac amyloidosis involves treatment and prevention of complications, and halting or delaying amyloid deposition by specific treatments.
- Specific pharmacologic treatments available for ATTR amyloidosis include stabilizing molecules (tafamidis) and genetic silencers (patisiran and inotersen).
- Tafamidis is currently the only drug that has shown efficacy in a randomized trial in patients with ATTRwt and ATTRv with cardiomyopathy, and should be considered in patients with reasonable expected survival.

Organization of patient care

Collaboration between centres remains essential because not all centres can perform complex diagnostic techniques (such as endomyocardial biopsy and mass spectrometry) or prescribe disease-modifying therapies, and interaction between cardiologists, haematologists, transplant surgeons, neurologists, and other specialists could be needed. The best strategy for the management of patients with amyloidosis is not the 'hub-and-spoke' model, but rather a network where centres can do at least some parts of the diagnostic workup, exchange opinions and information, and refer patients to regional or national referral centres for selected procedures or particularly complex decisions.

Summary and future directions

As knowledge evolves and new therapeutic alternatives to treat cardiac amyloidosis emerge, new areas of research and unsolved questions arise. Some of the grey zones and areas of active research are summarized in Table 8.

Table 8 Areas of investigation and uncertainty in cardiac amyloidosis

Pathophysiology

Amyloidogenesis

- Mechanism for tissue tropism
- Role of enzymatic cleavage
- Role of mechanical stress at tissue level

Determinants of phenotypic heterogeneity

- Gender
- Modifier genes
- Epigenetics
- Fibre composition

Diagnosis

Populations to screen for cardiac amyloidosis and optimal screening method

Widespread genetic testing

Identification of a plasma biomarkers of unfolded TTR

Artificial intelligence tools to facilitate diagnosis (imaging, ECG, etc.)

Identification of the target of bone tracers within amyloid deposits

Validation of PET tracers for diagnosis of cardiac amyloidosis, differential diagnosis of ATTR vs. AL, and evaluation of amyloid burden

Natural history

Disease trajectories among carriers of different mutations

Definition and measurement of disease progression

- Ventricular thickness, mass, function
- Exercise capacity
- Biomarkers including monitoring of prealbumin
- TTR stability, kinetics, ligands as monitors of disease progression

Treatment of complications

Initiation of anticoagulation in patients without atrial fibrillation

Efficacy of heart failure drugs in patients with different degrees of heart failure

Efficacy of beta-blockers. Identification of patients who could benefit

Role of invasive heart failure monitoring devices

Identification of patients that benefit from prophylactic pacemaker

Identification of subgroups that can benefit from ICD and CRT

Disease-modifying treatments

New antiplasma cell therapy in AL

New stabilizers in ATTR

New gene silencers in ATTR

Early initiation of therapy:

- ATTRv mutation carriers without phenotype
- ATTR cardiac amyloidosis without heart failure

Comparison between diverse disease-modifying drugs in ATTR

Definition of disease progression despite therapy in ATTR

Criteria for switching from one drug to another

Early identification of responders/non-responders to specific therapies

Role of combined therapy

Antibodies to induce removal of tissue amyloid deposits

Genetic editing treatments

AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; PET, positron emission tomography; TTR, transthyretin.

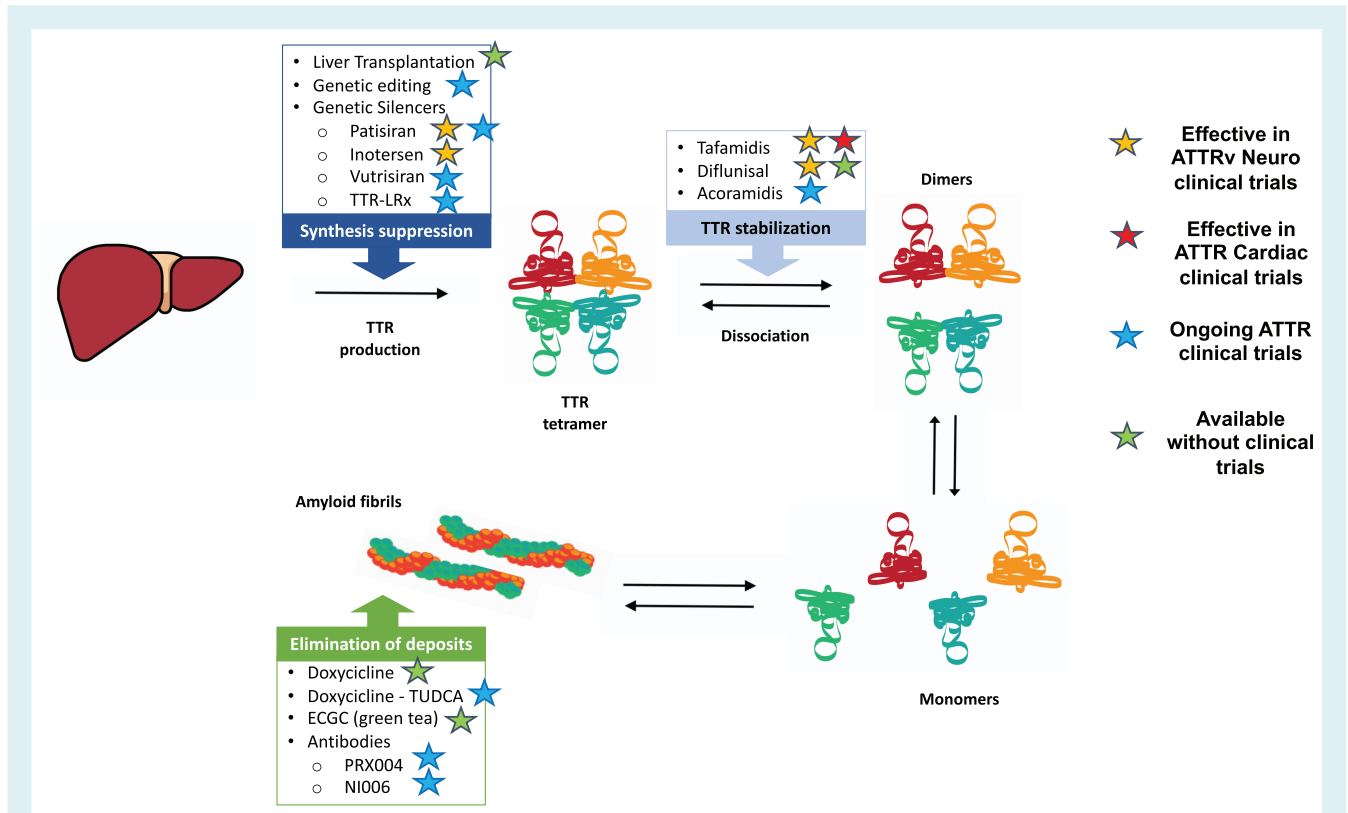


Figure 6 Available and future disease modifying therapies in transthyretin amyloidosis. ATTRv, hereditary transthyretin amyloidosis; TTR, transthyretin.

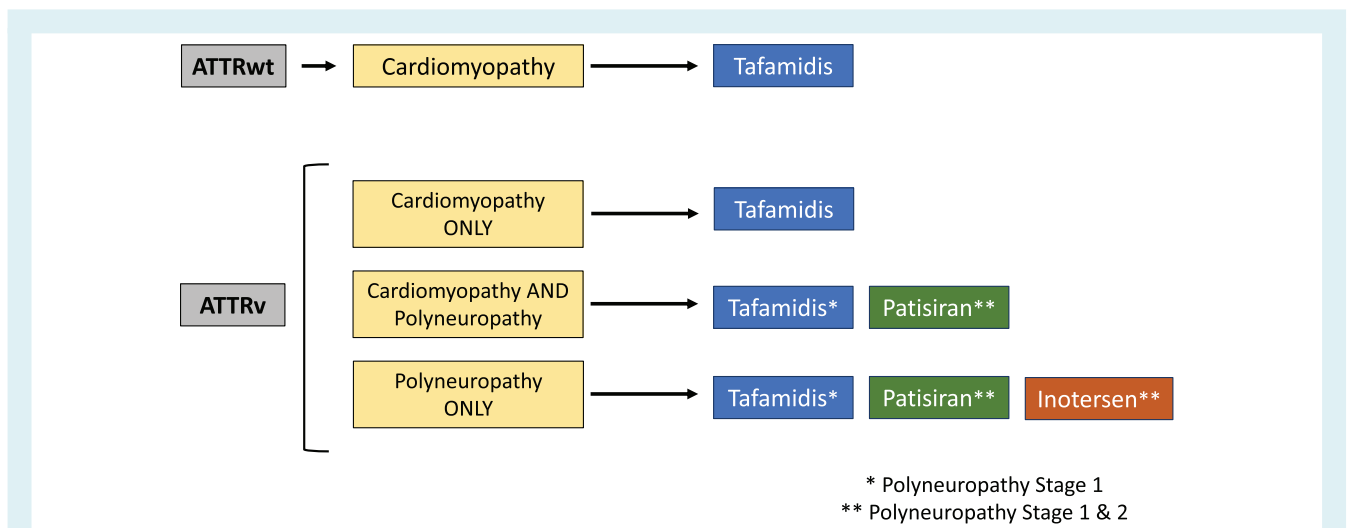


Figure 7 Proposed therapeutic alternatives in transthyretin amyloidosis patients. ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis.

It is expected that advances in the field will change the way we diagnose, prognosticate and treat cardiac amyloidosis in the next few years. Meanwhile, in this paper the Working Group on Myocardial and Pericardial Diseases proposes an invasive and non-invasive definition of cardiac amyloidosis, addresses clinical scenarios and

situations to suspect the condition and proposes a diagnostic algorithm to aid diagnosis (graphical abstract). Furthermore, we also review how to monitor and treat cardiac amyloidosis, in an attempt to bridge the gap between the latest advances in the field and clinical practice.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: P.G.P. reports grant support from Instituto de Salud Carlos III (PI20/01379); speaking fees from Pfizer, Eidos, Alnylam, and Akcea; consulting fees from Pfizer, Eidos, Neuroimmune, Alnylam, Prothena and Akcea; research support to his institution from Pfizer, Eidos and Alnylam. C.R. reports speaking fees from Pfizer, Alnylam, and Akcea; consulting fees from Pfizer, Alnylam, Prothena and Akcea; institutional research grants from Pfizer. M.A. reports receiving an advisory board fee and a research grant from Pfizer and from Sanofi Genzyme. U.E. reports consulting fees and grant support from Pfizer and Sanofi; institutional grants from Pfizer. M.F. is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/21/33447) and reports consulting fees from Pfizer, Akcea, Ionis, Alnylam, Alexion, Sanofi and research grant from Pfizer. J.D.G. reports consulting and speaking fees from Pfizer, Akcea, Alnylam, and Eidos. E.G.L. reports grant support from Instituto de Salud Carlos III (PI18/0765); speaking fees from Pfizer and Alnylam; consulting fees from Pfizer and Proclara; research support to her institution from Pfizer, Eidos and Alnylam. M.G. reports grant/clinical trial support from Alnylam, Eidos, Prothena, and Pfizer. I.K. reports speaking fees from Akcea Therapeutics Germany and Pfizer; consulting fees from Akcea Therapeutics Germany. A.V.K. reports consulting fees from Pfizer, Akcea, Alnylam, and Neurimmune and speaking fees from Pfizer, Akcea, and Alnylam. M.S.M. reports grant support from National Institutes of Health [R01HL139671-01], [R21AG058348] and [K24AG036778], consulting income from Pfizer, GSK, Eidos, Prothena, Akcea and Alnylam, and institution received clinical trial funding from Pfizer, Prothena, Eidos and Alnylam. A.G.R. reports honoraria for presentations from AstraZeneca. A.L. reports speaking fees from Pfizer; consulting fees from Pfizer, Alnylam. All other authors have nothing to disclose.

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