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Table 1. Amyloidosis subtypes that affect the heart.

Amyloidosis type	Protein	Hereditary	Frequency of heart involvement	Median Survival (months)	Usual Extracardiac signs
AL	Immunoglobulin light chain	No	80%	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% Depending on the mutation	31 (Val142Ile) 69 (non-Val142Ile)	Polyneuropathy, vitreous opacities, gastrointestinal problems
AA	Serum Amyloid A	No	5%	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
Aβ2M	β2-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, paresthesia, proteinuria (rare)

CTS: Carpal tunnel syndrome; LSS: lumbar spinal stenosis.

Table 2. Cardiac and extracardiac amyloidosis Red-Flags.

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

CMR: cardiac magnetic resonance; HF: heart failure; LV: left ventricle.

Table 3. Echocardiographic and CMR criteria for diagnosis of cardiac amyloidosis in the presence of extracardiac biopsy-proven amyloidosis or Grade 2-3 diphosphonate myocardial uptake.

Echocardiography

Unexplained LV thickness (≥12 mm) plus 1 or 2:

1. Characteristic echocardiography findings (all have to be present)
    a. Grade 2 or worse diastolic dysfunction
    b. Reduced tissue Doppler s', e', and a' waves velocities
    c. Decreased global longitudinal LV 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. Global longitudinal LV strain ≤ -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*
c. ECV ≥0.40% (strongly supportive, but not essential/diagnostic)

IVS: interventricular septum; ECV: Extracellular Cardiac Volume. LGE: Late Gadolinium Enhancement; LV: Left Ventricle; LVEDD: Left ventricle end-diastolic diameter; PWT: posterior wall thickness; TAPSE: tricuspid anular plane systolic excursion; * Abnormal gadolinium kinetics: myocardial nulling preceding or coinciding with the blood pool.

Table 4. Possible false positives and false negatives of biphosponate scintigraphy for detecting ATTR cardiac amyloidosis.

	Situation	How to suspect and detect?
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.
	Aβ2M amyloidosis	Long-term dialysis (>9 years). Requires histologic confirmation.
	Blood pool	Severe cardiac dysfunction 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.
False negative	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 AI amyloidosis; AApoAII: Apolipoprotein AII amyloidosis; AApoAIV: Apolipoprotein A-IV amyloidosis; Aβ2M: β2-Microglobulin amyloidosis; AL: light-chain amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; SPIE: serum protein electrophoresis with immunofixation; UPIE: urine protein electrophoresis with immunofixation.

Table 5. Prognostic staging scores in AL and ATTR amyloidosis.

Kumar et al. J Clin Oncol 2012 **AL**		**Grogan et al. J Am Coll Cardiol 2016** **ATTRwt**		**Gillmore et al. Eur Heart J 2018** **ATTRv & ATTRwt**	
Staging parameters: FLC-diff ≥ 18 mg/dL Troponin T ≥ 0.025 ng/mL NT-ProBNP ≥ 1,800 pg/mL		**Staging parameters:** Troponin T ≥ 0.5 ng/mL NT-ProBNP ≥ 3,000 pg/mL		**Staging parameters:** eGFR < 45ml/min NT-ProBNP > 3,000 pg/mL	
Stage	**5-year Survival**	**Stage**	**4-year Survival**	**Stage**	**Median Survival**
Stage I (0 parameters)	68%	Stage I (0 parameters)	57%	Stage I (0 parameters)	69.2 months
Stage II (1 parameter)	60%	Stage II (1 parameter)	42%	Stage II (1 parameter)	46.7 months
Stage III (2 parameters)	28%	Stage III (2 parameters)	18%	Stage III (2 parameters)	24.1 months
Stage IV (3 parameters	14%				

eGFR: estimated glomerular filtration rate calculated by MDRD formula; FLC-diff: difference between involved and uninvolved free light chain.

Table 6. Proposed follow-up scheme in cardiac amyloidosis

<table>
<tr><td rowspan="4">Patient with cardiac amyloidosis</td><td>AL</td><td>ATTR</td></tr>
<tr><td>Every month (during initial hematological treatment):
Complete blood count, basic biochemistry, NT-proBNP and Troponin
Serum Free light chain quantification
Clinical evaluation by Hematology
Evaluation by Cardiology if clinically indicated.</td><td>Every 6 months:
ECG
Blood tests including NT-proBNP and Troponin
Neurological evaluation (if ATTRv).
6MWD (optional)
KCCQ (optional)</td></tr>
<tr><td>Every 3-4 months (after completing initial hematological treatment):
Complete blood count, basic biochemistry, Nt-proBNP and Troponin
Serum Free light chain quantification.
Clinical evaluation by Hematology</td><td>Every 12 months:
Echocardiography/CMR
24h Holter ECG
Ophthalmological evaluation (if ATTRv)</td></tr>
<tr><td>Every 6 months:
ECG
Echocardiography/CMR
Evaluation by Cardiology</td><td></td></tr>
<tr><td>Every 12 months:
24h Holter ECG</td><td></td></tr>
<tr><td>ATTRv asymptomatic genetic carriers*</td><td colspan="2">Yearly:
ECG
Blood tests including NT-proBNP and Troponin
Echocardiography
Neurological and Ophthalmological evaluation.
Every 2 years:
Holter ECG
Every 3 years or if any of above complementary tests is abnormal:
Scintigraphy
CMR</td></tr>
</table>

* Clinical follow-up to be started 10 years before proband's age or predicted usual onset age for the specific ATTRv mutation.

6MWD: 6-minute walking distance test; KCCQ: Kansas City cardiomyopathy questionnaire.

Table 7. Autologous Stem Cell transplantation (ASCT) eligibility criteria.

Physiological age ≤70 years old

Left ventricular ejection fraction ≥40%

ECOG/WHO Performance Score ≤ 2*

NYHA Class I-II

Increased Troponin levels

Systolic blood pressure ≥90 mmHg (preferred if ≥100 mmHg)

Creatinine Clearance ≥ 30 ml/min (unless on chronic dialysis)

*** ECOG/WHO Patient Performance Status Score:**
0: Fully active; able to carry on all predisease activities without restriction (corresponds to a Karnofsky index ≥ 90%).
1: Restricted in physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature (corresponds to a Karnofsky index of 70% to 90%).
2: Ambulatory and capable of self-care but unable to perform any work aactivities. Up and about >50% waking hours (corresponds to a Karnofsky index of 50% to 70%).
3: Capable of only limited self-care; confined to bed or chair >50% waking hours (corresponds to a Karnofsky index of 40% to 50%).
4: Completely disabled. Unable to perform any self-care. Totally confined to bed or chair. (corresponds to a Karnofsky index of <40%).
5: Dead.