Imaging in Cardiac Amyloidosis

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Disclosures

I have no actual or potential conflict of interest in relation to this presentation.

Objectives

Review epidemiology and workup of cardiac amyloidosis

Systemic manifestations

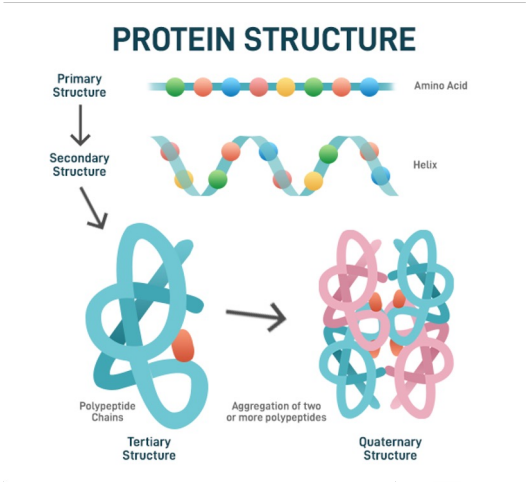
Common misconceptions

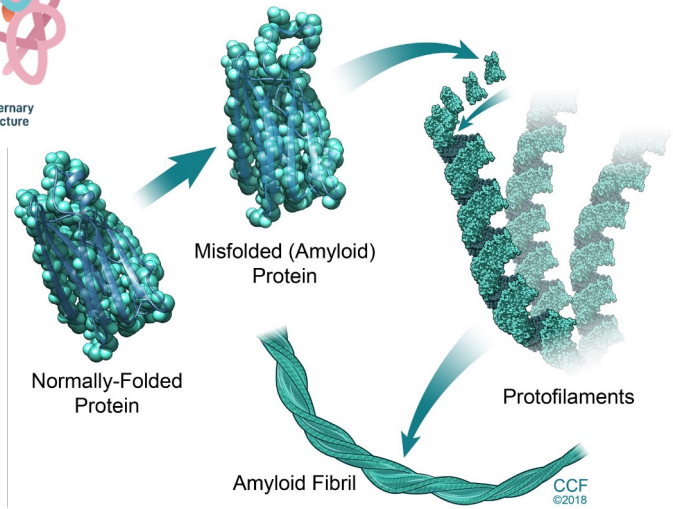
Role of multimodality imaging

Novel treatment strategies in ATTR amyloidosis

Amyloidosis

Protein misfolding disorder.





First described by Rudolf Virchow in 1858 describing the reaction of tissue deposits with iodine and sulfuric acid.

Donnelly and Hanna; Cleveland Clinical Journal of Medicine; Dec 2017

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Table 1 Main protein types causing amyloidosis with the emphasis on cardiovascular system involvement

Amyloid protein	Precursor	Distribution	Syndrome
AL	**Immunoglobulin light chain**	Systemic/localised	Primary/myeloma associated
AH	**Immunoglobulin heavy chain**	Systemic/localised	Primary/myeloma associated
AA	**Serum amyloid A**	Systemic	Secondary
Aβ_2 Microglobulin	**β_2 Microglobulin**	Systemic	Secondary
ATTR	**Transthyretin**	Systemic	Senile systemic/familial
AANF	**Atrial natriuretic factor**	Localised	Atrial isolated
AApoA-I	**Apolipoprotein A-I**	Localised/systemic	Aortic/familial
AApoA-II	Apolipoprotein A-II	Systemic	Familial
Amed	**Lactadherin**	Localised	Aortic
Agel	Gelsolin	Systemic	Familial
Alys	Lysozyme	Systemic	Familial
Afib	Fibrinogen α chain	Systemic	Familial
Acys	Cystatin C	Systemic	Familial
Aβ	Aβ Protein precursor	Localised	Alzheimer's disease, aging
AprP	Prion protein	Localised	Spongiform encephalopathies
Abri	ABri protein precursor	Localised	Familial dementia
Acal	(Pro)calcitonin	Localised	Thyroid tumours derived from C cells
AIAPP	Islet amyloid polypeptide	Localised	Langerhans islets, insulinomas
Apro	Prolactin	Localised	Prolactinomas, pituitary in elderly
Ains	Insulin	Localised	Iatrogenic
Aker	Kerato-epithelin	Localised	Familial, cornea
Alac	Lactoferrin	Localised	Familial, cornea

Proteins involved in the cardiovascular system are in bold.

Types of Cardiac Amyloidosis

AL **95%**

ATTR(wt, m, v)

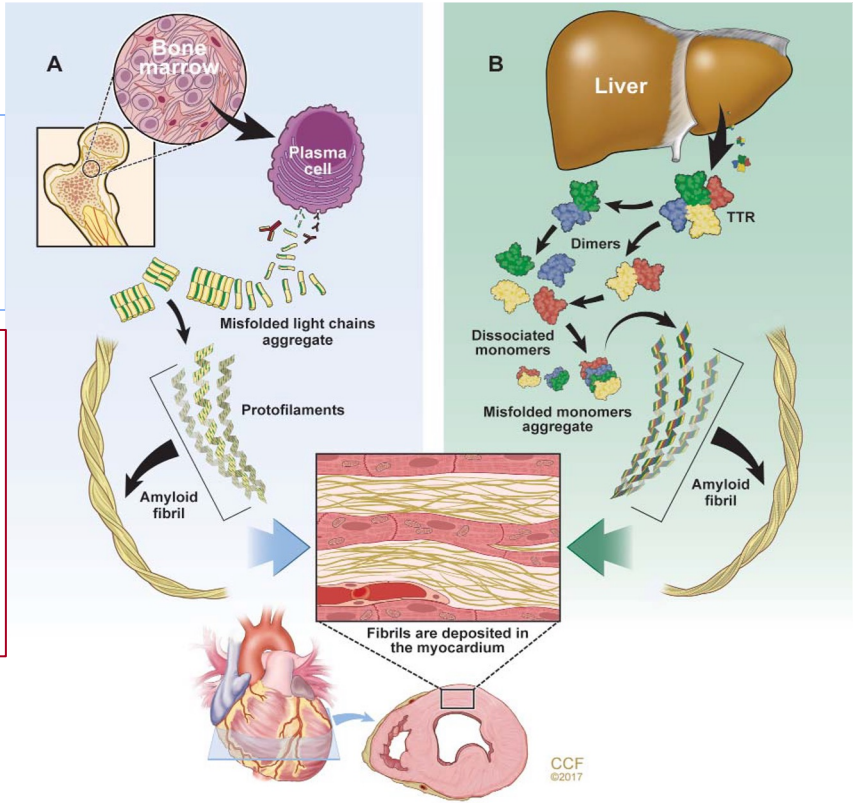
AA

AApoA1

AH **5%**

AANF

Aβ2m



Why do you need to tell the amyloid subtype?

Different treatments

Different prognosis

Genetic component; different phenotypes and implications for screening family.

Donnelly and Hanna; Cleveland Clinical Journal of Medicine; Dec 2017

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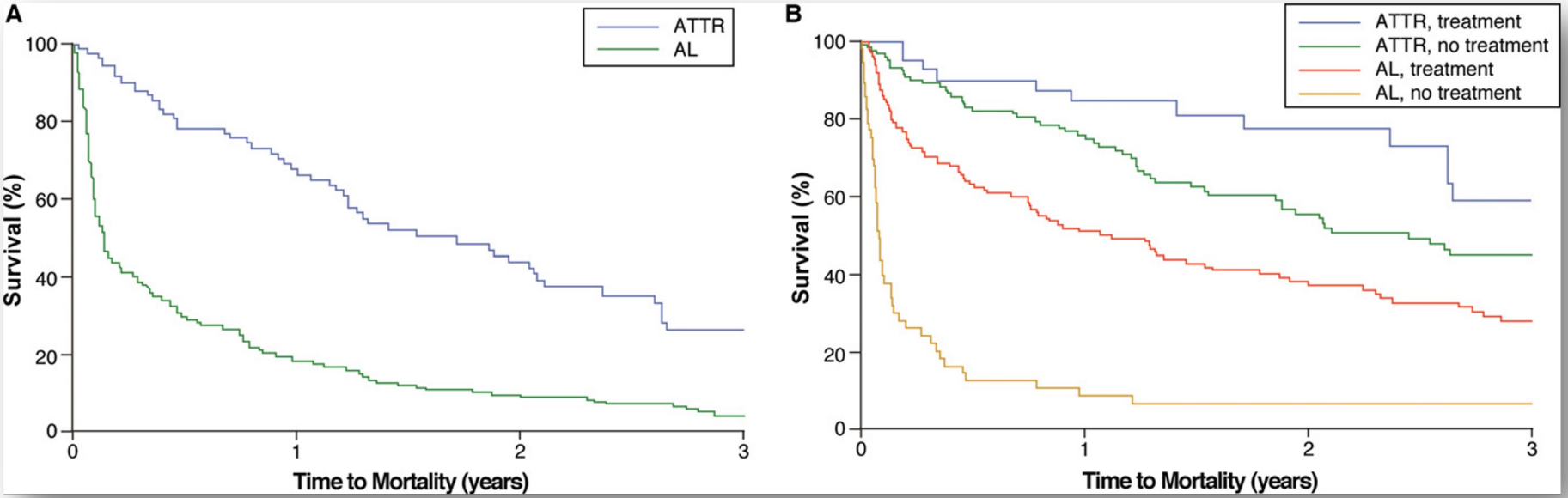
Prognosis in Cardiac Amyloidosis



Sperry et al; Subtype-Specific Prognosis in Cardiac Amyloidosis - *J Am Heart Association* - 2016

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Pathology

Both AL/TTR cause diffuse amyloid deposition (both ventricles); pattern **AL (subendo, diffuse)** vs **TTR (patchy and transmural)**

Increase in LV mass without dilatation **(ASH in TTR ?HCM)**

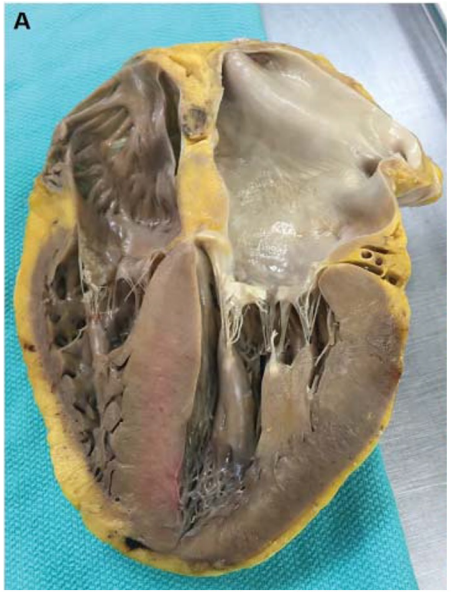
Atrial changes: Atrial infiltration is universal impairing atrial contraction; interatrial septal thickening and AFib (TTR>AL)

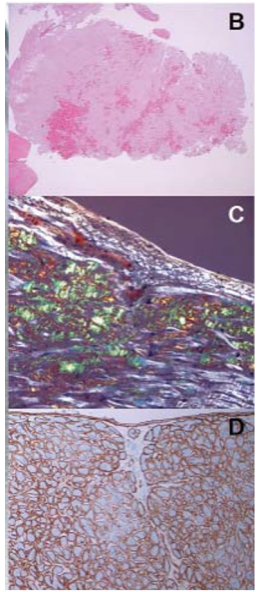
Conduction system (AVB, BBB TTR>AL)

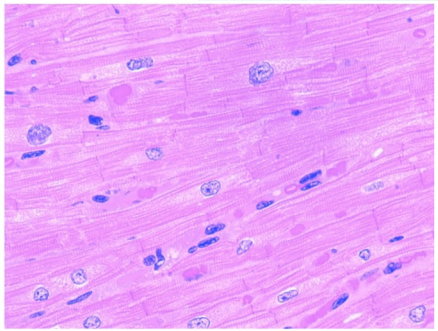
Valves: Thickened, mild to mod regurgitation.

Microvascular ischemia (deposition in small intramural coronaries; angina AL>TTR)

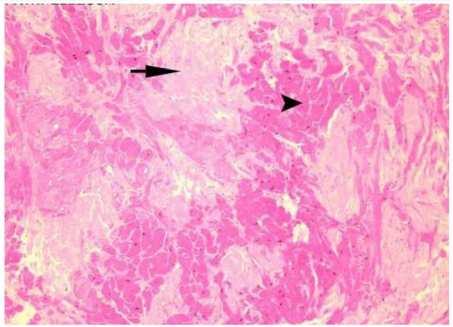
Pericardial involvement (effusion, usually mild)







Normal heart



Cardiac amyloid

Donnelly and Hanna; Cleveland Clinical Journal of Medicine; Dec 2017

Clinical manifestations

Heart failure: Diastolic heart failure >> Systolic HF; (L&R HF)

Lightheadedness and syncope (Brady arrhythmias, AV block, Atrial fibrillation, and autonomic dysfunction)

Fatigue and weakness (low CO; ?? aging)

Afib or embolic stroke as a first presentation (TTRwt)

Cardiogenic shock (diffuse ischemia)

Low flow low gradient aortic stenosis (preserved EF and low SVI)

AL - Plasma cell dyscrasia

Age 40s-70s

Men = women

Macroglossia, periorbital purpura, petechiae

Renal failure/Proteinuria

Bilateral Carpal tunnel syndrome

Orthostatic hypotension!

GI involvement (diarrhea) or alternating constipation; weight loss

ATTR

Age 60s-80s

Men > women (3:1)

African Americans (Val122I mutation)

HFpEF, Low-flow low-gradient AS

Bilateral carpal tunnel syndrome

Spinal stenosis (ligamentum flavum)

Peripheral neuropathy (in some variants)

Spontaneous biceps tendon rupture.

An elderly patient with a new diagnosis of HCM

Normalization or low blood pressure in a previously hypertensive patient.

Misconceptions

1. Cardiac Amyloidosis is a rare disease.

The Changing Landscape of Cardiac Amyloidosis

The prevalence of AL-CA has remained stable (~8 cases per million; ~3000 cases per year).

Recent data shows substantially higher prevalence in the HFpEF population.

TTR-CA remains a largely underdiagnosed disease;

More emphasis on early diagnosis is critical to afford the best efficacy of therapies.

Median survival is lower than most malignancies in advanced stages.

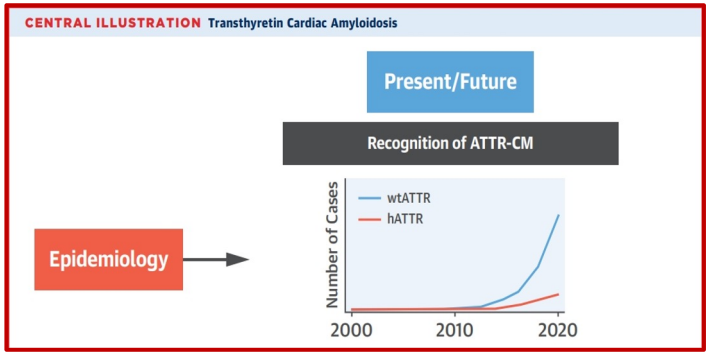


TABLE 1 Disease Course and Prognosis of Hereditary and Wild-Type ATTR-CM

	Hereditary (hATTR-CM)	Wild-Type (wtATTR-CM)
Age of onset	Variable (30–80 yrs) dependent on the mutation	Average 75 yrs, usually >60 yrs
TTR genotype	Abnormal, single nucleotide mutation	Normal
Heritability	Autosomal dominant (50% chance of passage to offspring)	Not known to be heritable
Predominant countries of origin	Val122Ile: U.S., U.K., Western Africa Thr60Ala (Appalachian mutation): U.S., U.K. (predominately Northern part of Republic of Ireland) Val30Met: Sweden, Portugal, Japan Leu111Met: Denmark Ile68Leu: Italy	No known geographic disparities
Prevalence	Val122Ile genotype: 3.4% of African Americans (7) Thr60Ala genotype: ~1% of Northern part of Republic of Ireland (37)	Up to 25% with wtATTR deposits at autopsy 13% in hospitalized HFpEF with wall thickness >12 mm 6%–16% of patients undergoing AVR possibly 1%–3% >75 yrs of age
Median survival after diagnosis without treatment	~2.5 yrs* (Val122Ile)	~3.5 yrs*

*Can be further risk stratified with cardiac biomarker staging systems.

ATTR-CM = transthyretin amyloid cardiomyopathy; AVR = aortic valve replacement; HFpEF = heart failure with preserved ejection fraction.

Ruberg et al. JACC Vol.73, No 22; 2019; Transthyretin Amyloid Cardiomyopathy

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Misconceptions

It is no longer a rare disease:

- **Under-appreciated and under-recognized**

- **13%** of patients admitted with HFpEF and septal thickness >12mm
- **16%** of patients undergoing TAVR (22% of men undergoing TAVR)
- **30%** of patients with LFLG AS with LVEF <50%
- **12%** of patients with bilateral carpal tunnel syndrome undergoing carpal tunnel release (among men ≥ 50 and women ≥ 60 years)
- The most common ATTRv in the US is **Val 122 Ile (3.4% of African Americans; 1.5 million allele carriers)**

EHJ (2015) 36, 2585-2594; Castano et al EHJ 2017; Treibel et al Circ Imaging 2016; Sperry et al JACC 2018

Misconceptions

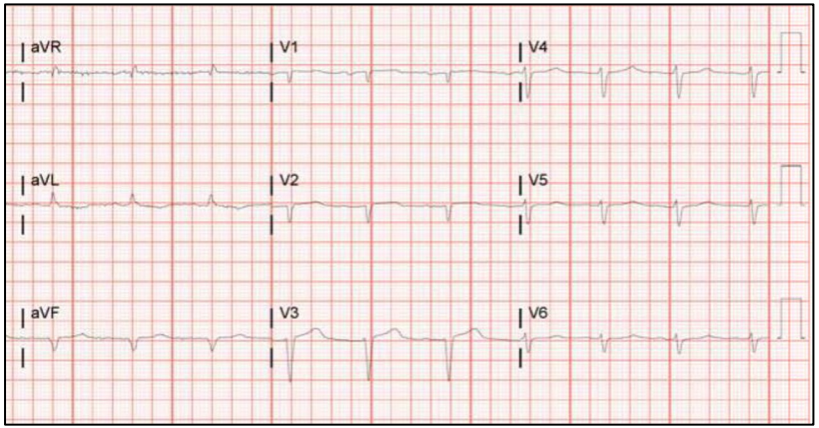
1. Cardiac Amyloidosis is a rare disease.
2. Low voltage on ECG is a good screening test

EKG in Cardiac Amyloidosis

a. **Low voltage complex** (limb>>precordial)

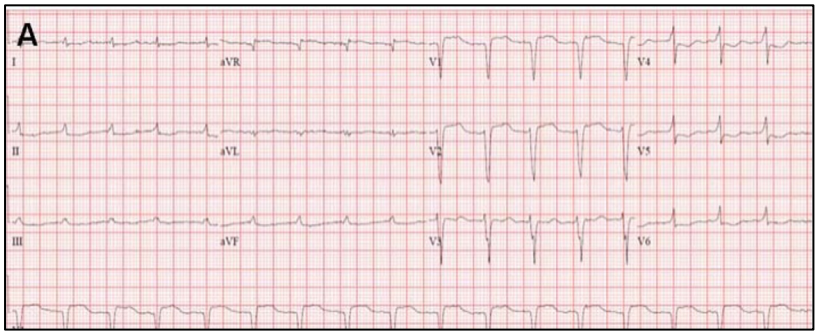
b. **Pseudoinfarct pattern** (qS pattern in 2 consecutive leads)

c. **Voltage to mass ratio** (whenever there is a disconnect, think of infiltrative process; poor prognosis)



Wide QRS complexes - TTR

Limb lead voltages are low (AL)



Remember: **> 50% of patients do not have any typical EKG changes.**

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Misconceptions

1. Cardiac amyloidosis is a rare disease.
2. Low voltage on ECG is a good screening test.
3. Fat pad biopsy has high sensitivity.

Diagnostic sensitivity of fat pad fine needle aspiration in different cardiac amyloidoses

Amyloid type	*n*	Number positive by Congo red staining	Diagnostic sensitivity (CI)
Systemic AL amyloidosis	216	181	84% (78–88%)
ATTRm	113	51	45% (36–54%)
Val122Ile	69	23	33%
Thr60Ala	21	14	67%
ATTRwt	271	42	15% (11–20%)

Misconceptions

1. Cardiac amyloidosis is a rare disease.
2. Low voltage on ECG is a good screening test.
3. Fat pad biopsy has high sensitivity.
4. Need invasive and risky endomyocardial biopsy for diagnosis.

Non invasive diagnosis with bone scintigraphy (Tc99mPYP) alone is enough to diagnose TTR-CA, in the absence of monoclonal proteins.

For AL amyloidosis, will need some tissue diagnosis; non cardiac options = **bone marrow, fat pad, skin lesion, kidney or any organ of involvement.**

Misconceptions

1. Cardiac amyloidosis is a rare disease - **X**
2. Low voltage on ECG is a good screening test - **X**
3. Fat pad biopsy has high sensitivity - **X**
4. Need invasive and risky endomyocardial biopsy for diagnosis - **X**
5. Everyone dies, so it is not worth diagnosing.

Treatments

AL cardiac amyloidosis

Bortezomib + cyclophosphamide + dexamethasone (CyBorD)
Daratumumab
CyBorD+ Daratumumab
High dose melphalan + ASCT considered in patients with less cardiac involvement
Doxycycline, turmeric/curcumin
Advanced therapies

ATTR cardiac amyloidosis

Tafamidis(oral) for ATTRwt and hATTRcardiomyopathy
Patisiran(IV infusion) or Inotersen(SQ injection) for ATTRm neuropathy
Vutrisiran(SQ injection, once in 3 months) – ATTRm neuropathy
Green tea extract (EGCG 600-800mg/day), doxycycline/TUDCA, turmeric (curcumin)
Several ongoing Clinical trials
Advanced therapies (**Vutrisiran**, **Akcea-TTR-LRx(newer version of inotersen)**

“The only way to diagnose Cardiac Amyloidosis is to consider the diagnosis”

Echocardiogram in Cardiac Amyloidosis

1. Increased wall thickness >12 mm in the absence of hypertension; usually symmetrical; rarely LVOTO.
Remember – “both LV and RV thickening”
Average septal thickness: 15 mm (AL); 18 mm (TTR)

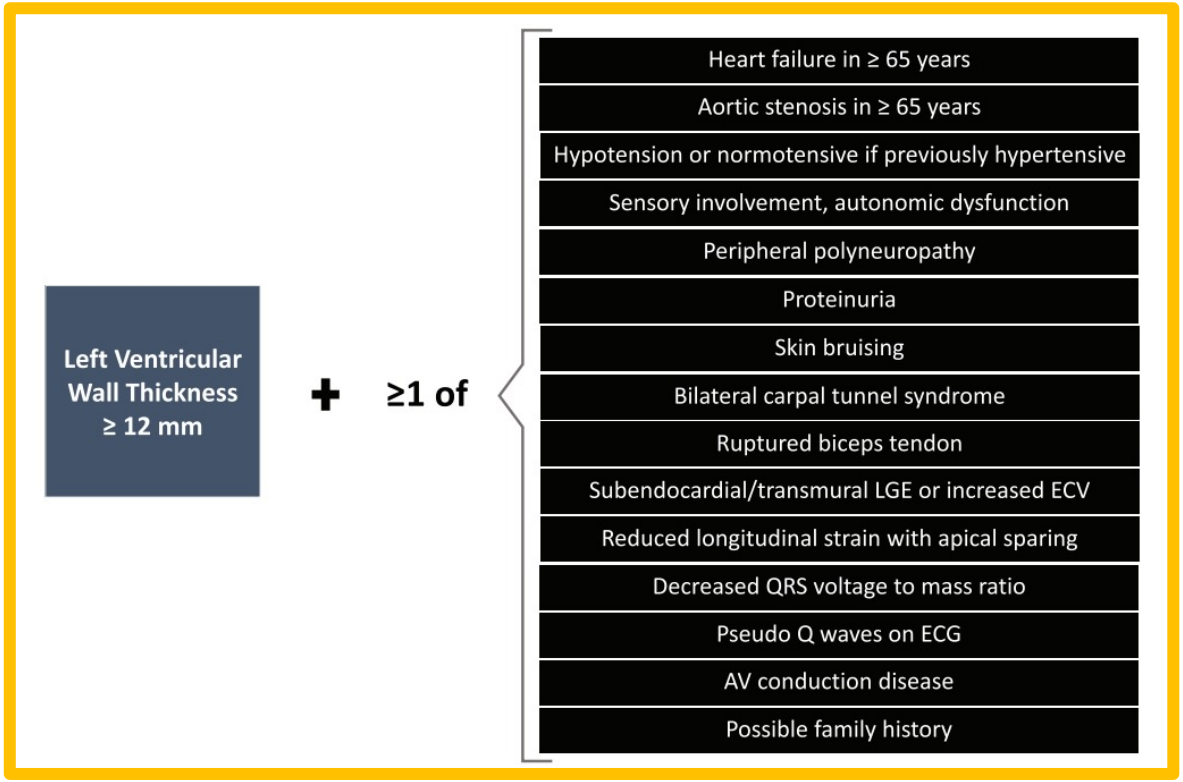
2. Sparkling, granular (speckling) **texture** of myocardium.

Look at renal function:
If no severe CKD or ESRD, sparkling appearance (especially with severely decreased longitudinal function), **think infiltrative**, most commonly amyloid.

Echocardiogram in Cardiac Amyloidosis

Differentials:

Hypertension
HCM
Fabry's disease (XL-R)
LV Non-compaction
Danon disease (XL-D; LAMP2 gene)



ESC:

Proposed Screening for Amyloidosis

P Garcia-Pavia et al; EJHF April 7, 2021. Diagnosis and treatment of cardiac amyloidosis. A position statement of the ESC Working Group on Myocardial and Pericardial Diseases

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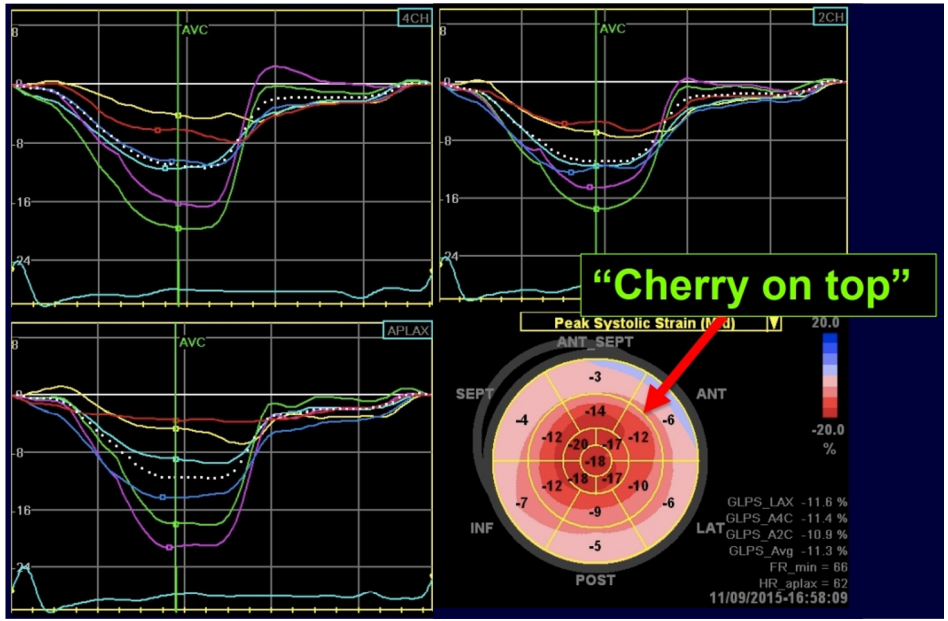
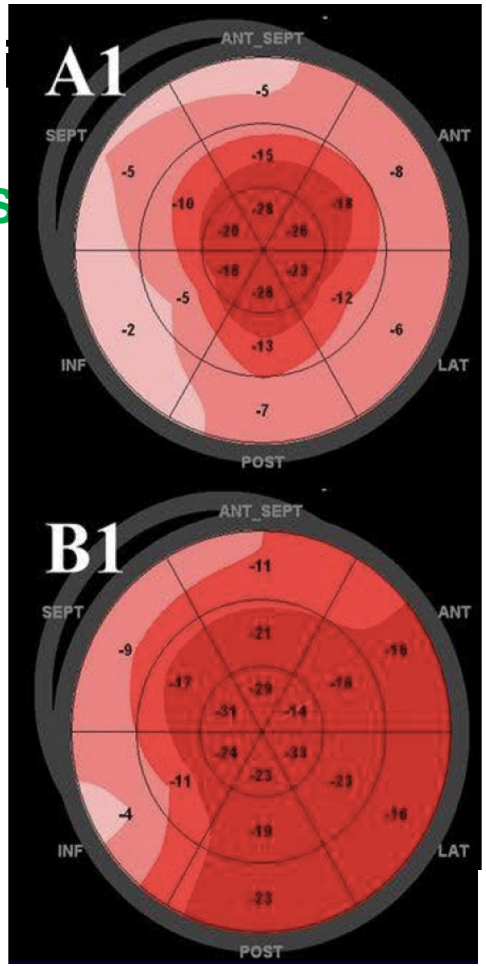
Echocardiogram in Cardiac Amyloi

Apical sparing LV strain pattern and the GLS





Relative Strain

$$\frac{\text{Apical}}{\text{Basal}} > 2$$

$$\frac{\text{Apical}}{\text{Basal + mid}} > 1.0$$

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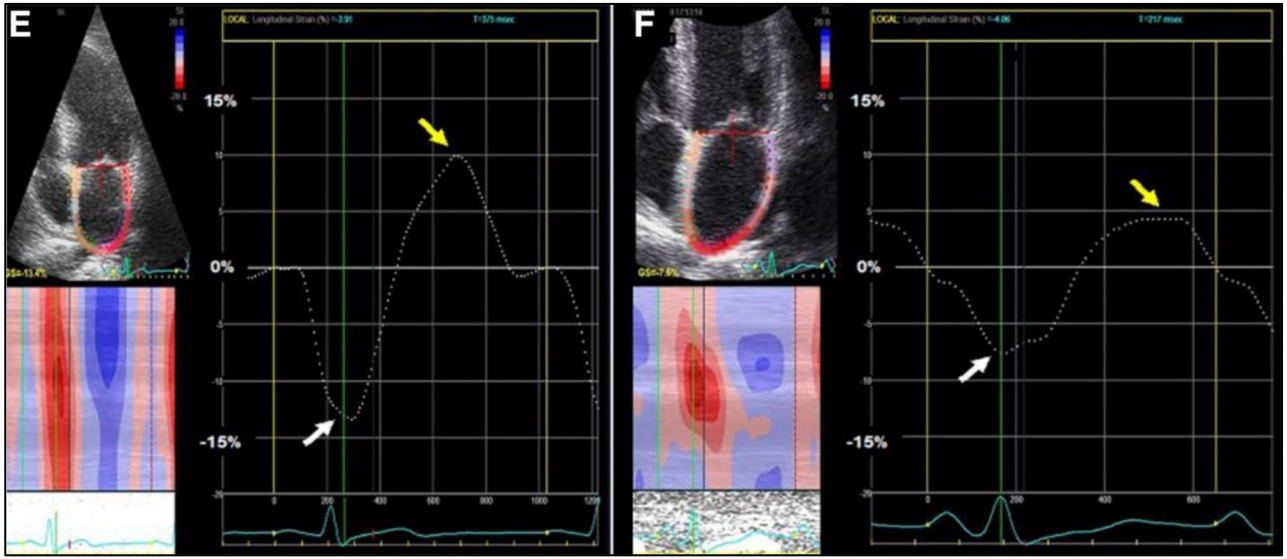
Left atrial strain and strain rate.

Like LV Strain, RA strain is to look for a highly reproducible pattern of impaired reservoir function



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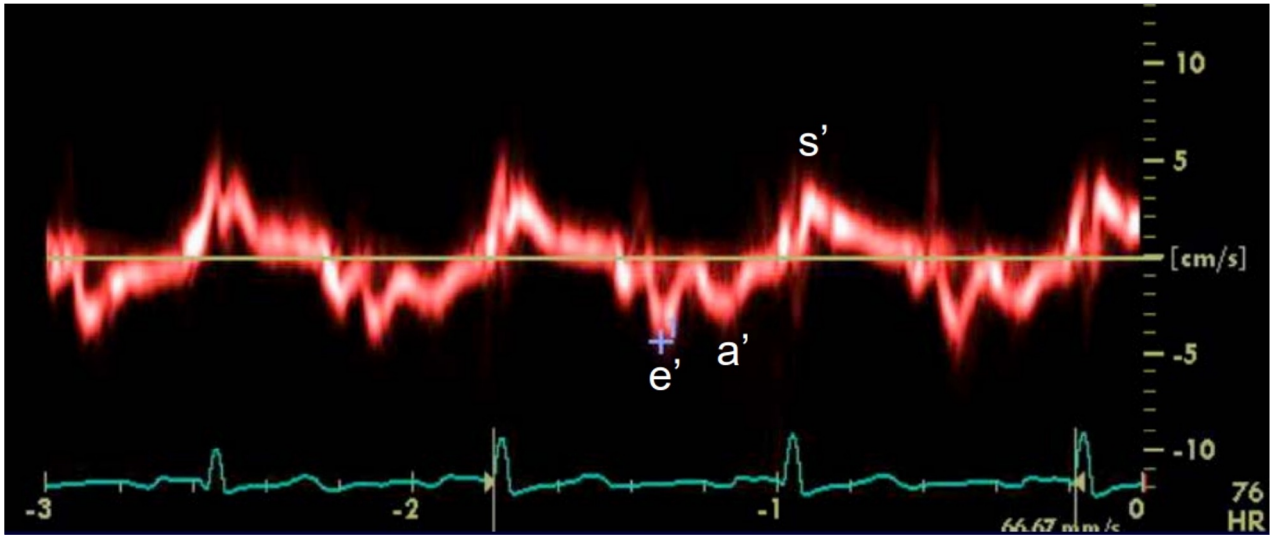
Echocardiogram in Cardiac Amyloidosis

Severely reduced Longitudinal tissue doppler velocities
The **“5-5-5”** sign



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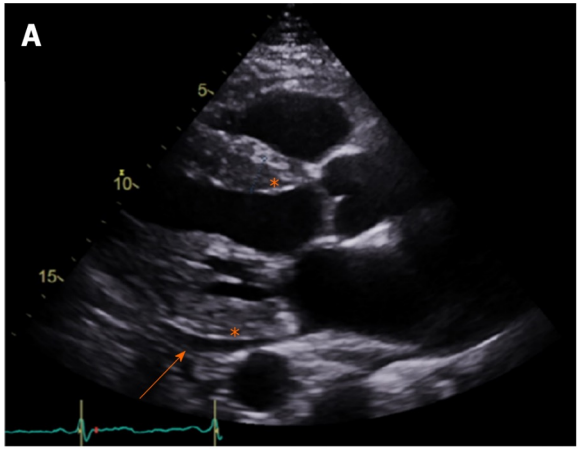

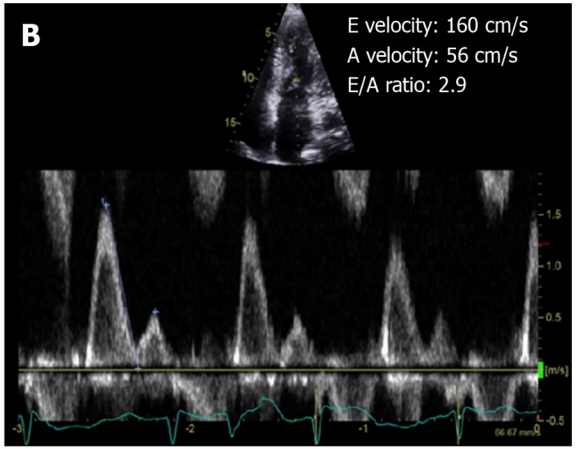

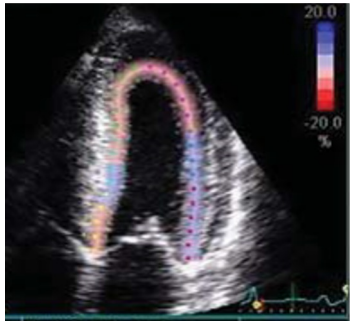

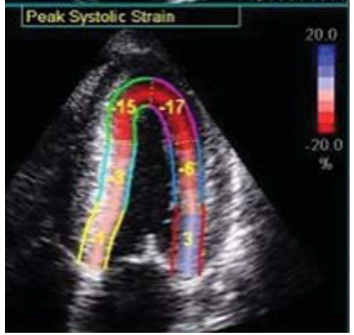

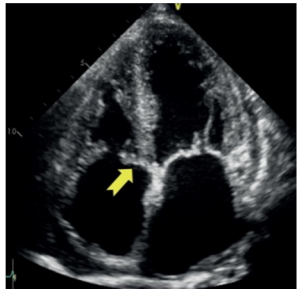

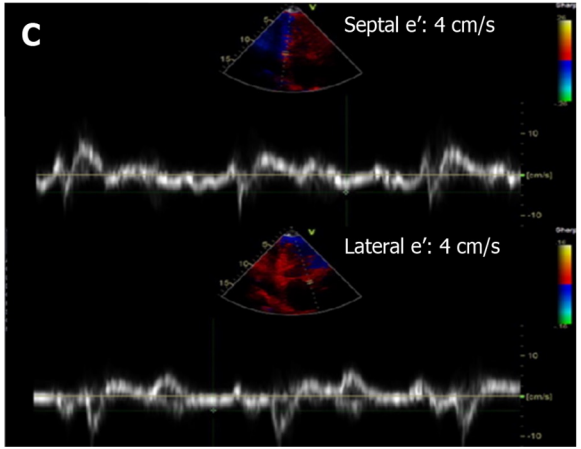

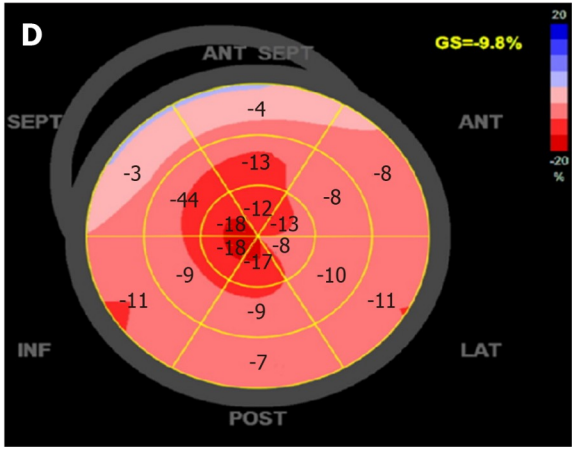

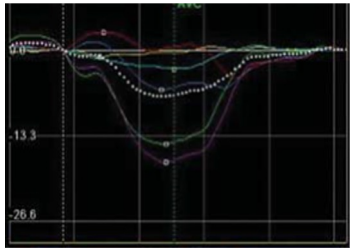

Wang TKM *et al.* Multi-modality imaging of cardiac amyloidosis. W J of Radiology June 2020

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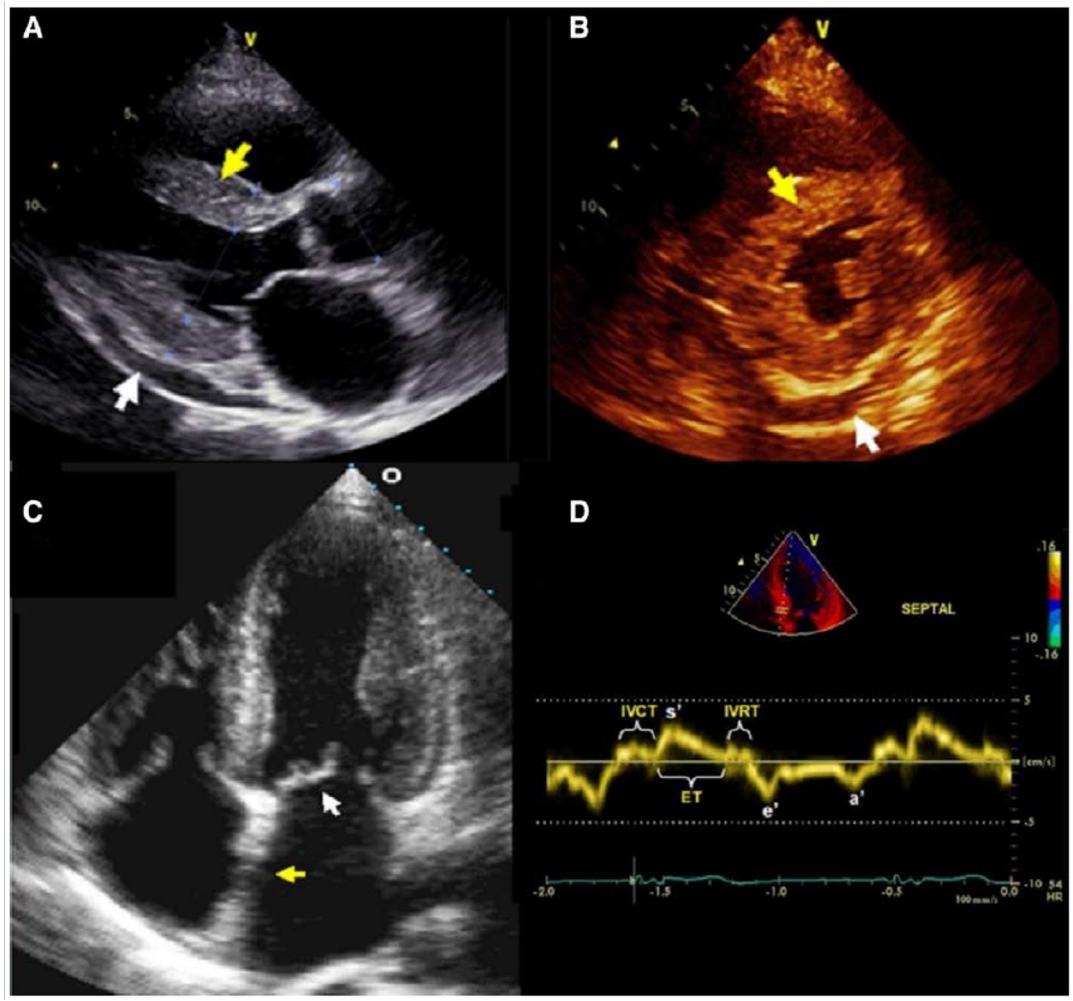

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Echocardiogram in Cardiac Amyloidosis – contd.

- Increased LV wall thickness
- Atrial involvement
- Atrial septal involvement (0.5mm)
- Pericardial effusion – late manifestation, and poor prognosis
- Diastolic dysfunction
- Elevated RAP and PASP
- Abnormalities in Tissue doppler velocities
- Longitudinal LV strain rate
- Longitudinal strain map (Bull’s eye)

Guidelines

Circulation: Cardiovascular Imaging
Volume 14, Issue 7, July 2021; Page e000029
https://doi.org/10.1161/HCI.0000000000000029

American Heart Association.

EXPERT CONSENSUS RECOMMENDATIONS

ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging

American College of Cardiology | Kentucky CHAPTER

Table 1. Standardized Acquisition, Interpretation, and Reporting of Echocardiography for Cardiac Amyloidosis

Parameter for Acquisition and Reporting	Abnormal Parameter	Notes	Recommendations for Reporting
2D, Color, and Spectral Doppler Imaging			Required
LV wall thickness	Increased LV wall thickness (>1.2 cm) and increased relative wall thickness (>0.42)	Increased LV wall thickness relative to ECG QRS voltage is particularly suggestive	Required
Myocardial echogenicity	Increased echogenicity of the myocardium (sparkling, hyper-refractile "texture" of the myocardium)	Not highly specific (differential diagnosis includes ESRD or other infiltrative cardiomyopathies). However, this finding in conjunction with severely reduced longitudinal function of the LV is highly suggestive.	Required
Atrial size and function	Atrial enlargement and dysfunction	Non-specific but important finding to support the diagnosis and potentially provide insight into risk for stroke or arterial embolism	Required
Interatrial septum and valves	Thickening of the interatrial septum and valves (>0.5 cm)	Non-specific but suggestive of the diagnosis	Required
Pericardial effusion	Pericardial effusion	Non-specific, but when coupled with other echo signs is suggestive of the diagnosis	Required
Diastolic function	Grade 2 or worse diastolic dysfunction with high E/A ratio (>1.5) and reduced E deceleration time (<150 ms)	Doppler diastolic function is helpful in determining prognosis. Severely reduced A wave velocity can be due to LA failure, which can be helpful in determining risk of stroke.	Required
Estimated PA systolic and right atrial pressure	Increased pressures (>35mmHg for PA, ≥10mmHg for RA)	These are important parameters to estimate volume status and optimize diuretic dosing.	Required
Tissue Doppler Imaging			Required
Tissue Doppler velocities	Reduced tissue Doppler s', e', and a' velocities (all <5 cm/s)	If present, the "5-5-5" sign (all TDI velocities <5 cm/s) can be useful and is typically highly suggestive of the diagnosis but may not be sensitive for the diagnosis in early forms of the disease	Required
Strain Imaging			Recommended
Longitudinal LV strain	Decreased global longitudinal LV strain (absolute value less than −15%)	2D and STE shows characteristic appearance of myocardial deformation in patients with cardiac amyloidosis	Recommended
Longitudinal LV strain bullseye map	"Cherry-on-the-top" sign on STE longitudinal strain bullseye map (preservation of apical longitudinal strain with severely abnormal basal and mid-LV longitudinal strain)	Characteristic bullseye pattern is likely the most specific sign to rule in the diagnosis of cardiac amyloidosis (but still does not differentiate ATTR vs. AL amyloidosis)	Recommended
Reporting			
An overall interpretation of the echo findings into categories of: 1. **Not suggestive:** Normal LV wall thickness, normal LV mass normal atrial size, septal or lateral tissue Doppler e' velocity >10 cm/s 2. **Strongly suggestive:** Increased LV wall thickness, increased LV mass, typical LV longitudinal strain pattern, mitral annular TDI <5 cm/s, biatrial enlargement, small A wave in sinus rhythm, small pericardial and or pleural effusions 3. **Equivocal:** Findings not described above			Required
Interpret the echo results in the context of prior evaluation.			Recommended
Provide follow-up recommendations: Strongly suggestive echocardiographic findings cannot distinguish AL from TTR cardiac amyloidosis. Endomyocardial biopsy is not always indicated in patients with strongly suggestive echo findings. Please see Part 2, Table 1 "Expert Consensus Recommendations for Diagnosis of Cardiac Amyloidosis" for indications for endomyocardial biopsy. Consider evaluation (1) to exclude AL amyloidosis, evaluate for plasma cell dyscrasia (serum and urine immunofixation, serum FLC assay) and (2) to exclude ATTR cardiac amyloidosis, consider imaging with ^{99m}Tc-PYP/DPD/HMDP.			Recommended

Circulation: Cardiovascular Imaging
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https://doi.org/10.1161/HCI.0000000000000029

EXPERT CONSENSUS RECOMMENDATIONS

Reporting: An overall interpretation of the echo findings into 3 categories.

1. **Not suggestive**: Normal LV wall thickness, normal LV mass, normal atrial size, septal or lateral tissue Doppler e' velocity >10 cm/s.

2. **Strongly suggestive**: Increased LV wall thickness, increased LV mass, typical LV longitudinal strain pattern, mitral annular TDI <5cm/s, biatrial enlargement, small A wave in sinus rhythm, small pericardial and or pleural effusions

3. **Equivocal**: Findings not described above.

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“The only way to diagnose Cardiac Amyloidosis is to consider the diagnosis”

Biochemical markers

Non-Specific:

1. **NT-pro BNP.**
2. **Troponin T or I.**

Specific:

1. **Serum-free light chains (sFLC).**
2. **Serum Protein Immunofixation Electrophoresis (SPIE)**
3. **Urine Protein Immunofixation Electrophoresis (UPIE**

Clinical Suspicion of
Cardiac Amyloidosis

Serum Free Light Chain (sFLC) Ratio
Serum Immunofixation
Urine Immunofixation

^{99m}Technetium Pyrophosphate
(^{99m}TcPYP) Scan

AL

Abnormal sFLC ratio
High (>1.65) = kappa (κ)
Low (<0.26) = lambda (λ)

M-protein spike on immunofixation

Grade 0 or 1 Myocardial ^{99m}TcPYP Uptake
(none or less than bone)

ATTR

Normal sFLC ratio

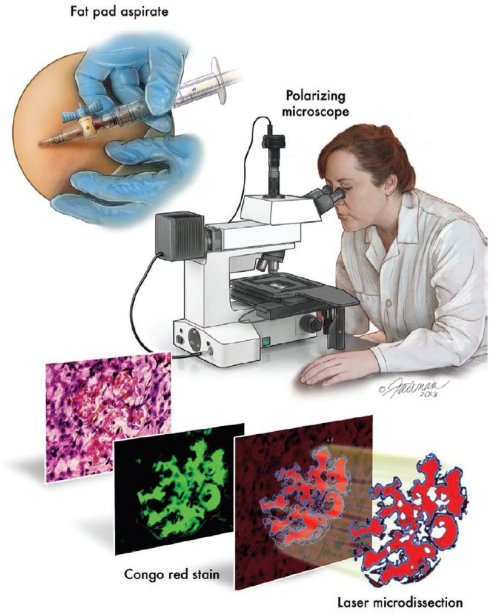
No M-protein spike on immunofixation

Grade 2 or 3 Myocardial ^{99m}TcPYP Uptake
(equal to or greater than bone)

Endomyocardial biopsy
with **LC/MS** for typing
Diagnostic Gold Standard

Bone marrow biopsy
to confirm & quantify
plasma cell clone

Genetic testing
to determine
mutation or wild-type



Diagnostic Gold Standard

Donnelly and Hanna; Cleveland Clinical Journal of Medicine; Dec 2017

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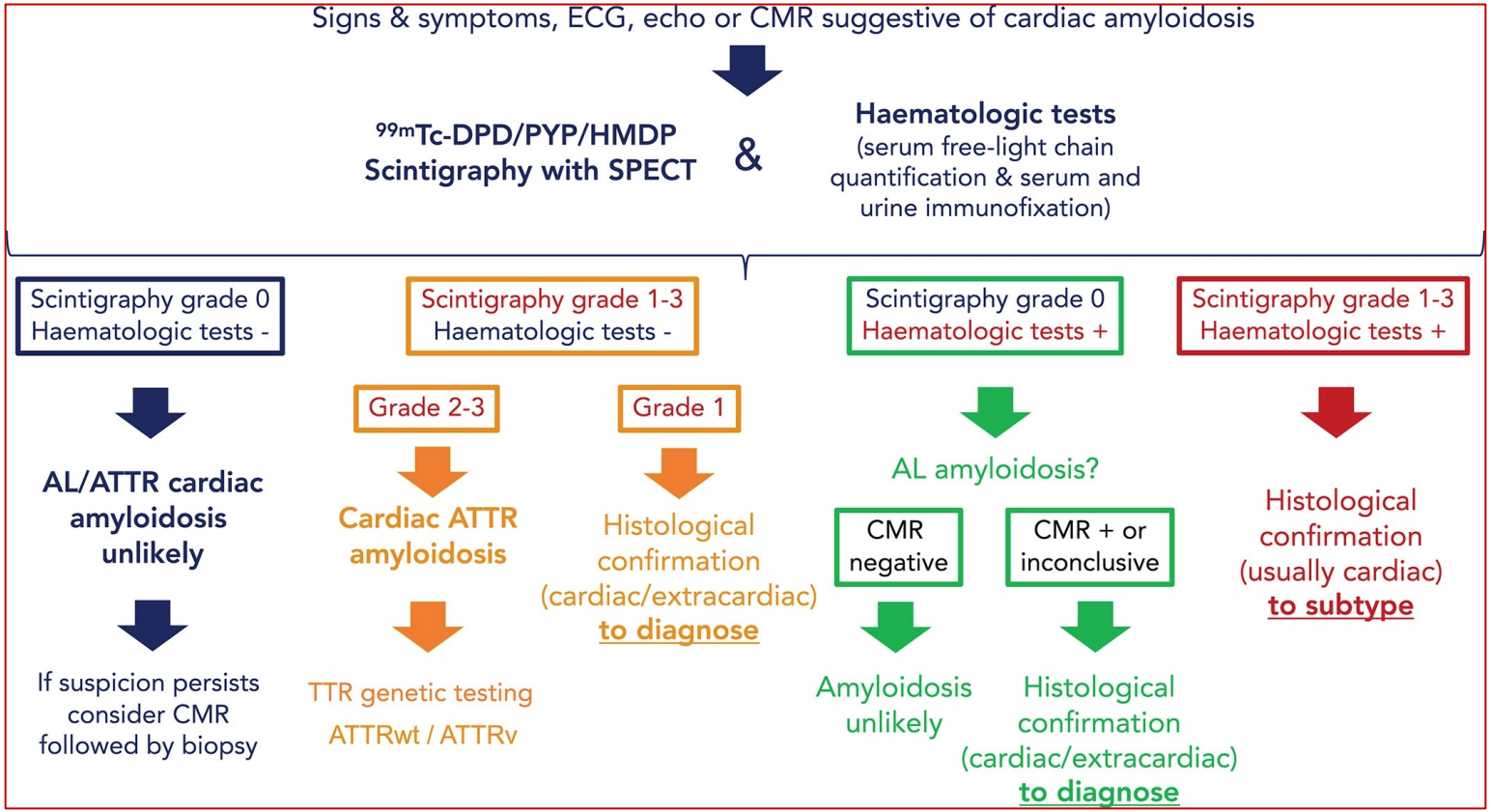
European Journal of Heart Failure



Pablo Garcia-Pavia; EJHF **April 7, 2021**. Diagnosis and treatment of cardiac amyloidosis. A position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Free kappa+lambda light chains serum

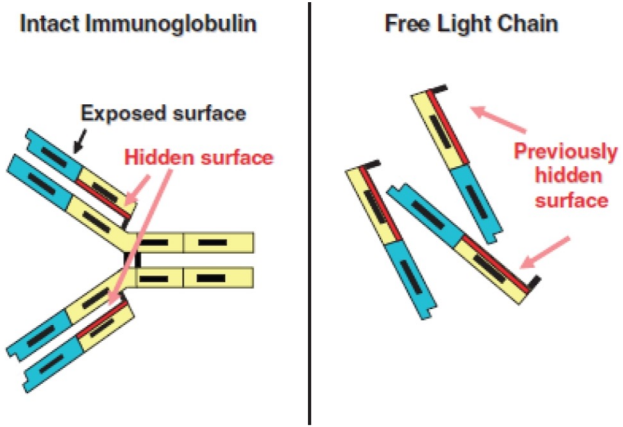
Serum immunofixation

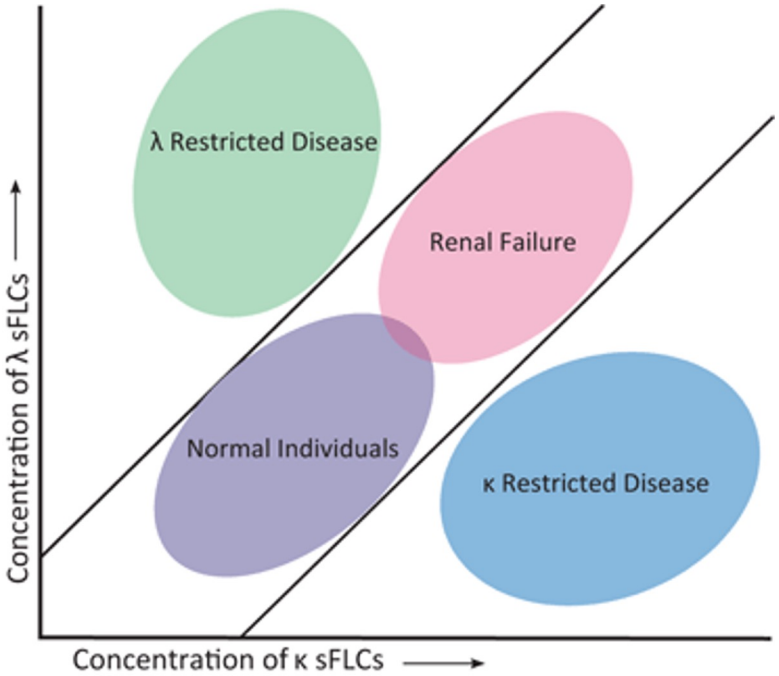
Urine immunofixation

99%

Kappa Free, Serum	3.30 - 19.40 mg/L	34.3 (H)
Lambda Free, Serum	5.7 - 26.3 mg/L	475.0 (H)
K/L Ratio, Serum	0.26 - 1.65	0.07 (L)

Principle





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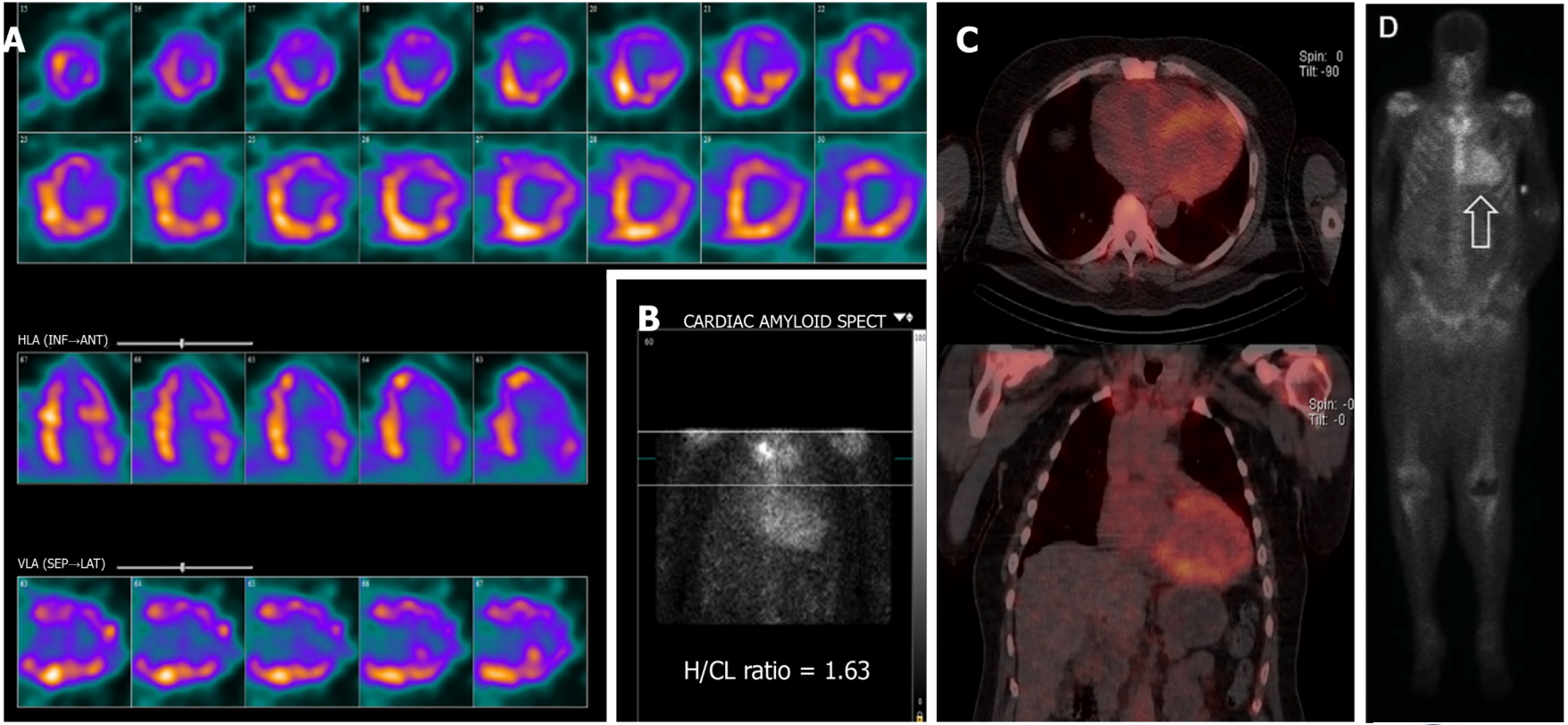
99m-Tc-PYP or PYP Scan (SPECT-CT)

Bone tracer

No specific preparation.

No fasting is required.

Rest Scan (1h or 3h)



Wang TKM *et al.* Multi-modality imaging of cardiac amyloidosis. W J of Radiology June 2020

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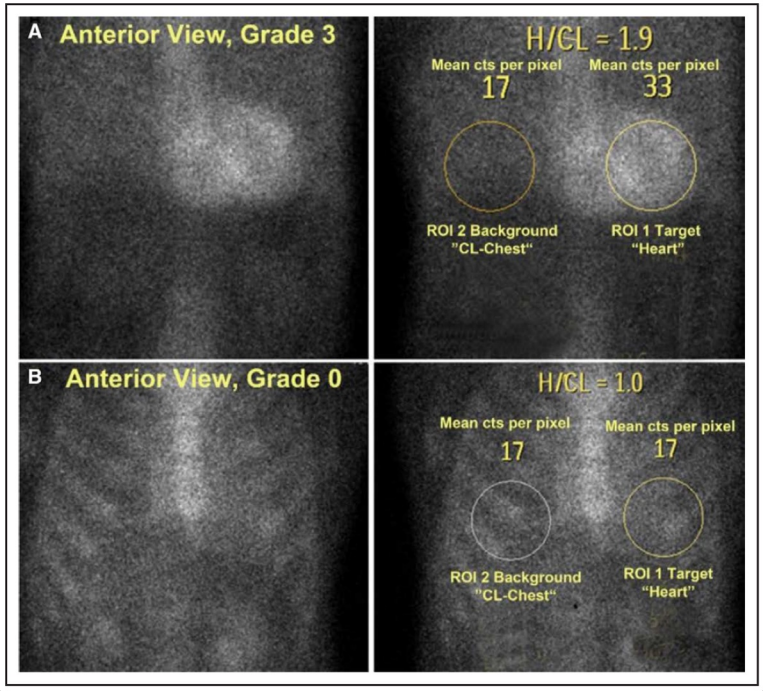
Table 5. Recommendations for Interpretation of ^{99m}Tc-PYP/DPD/HMDP for Cardiac Amyloidosis

Step 1: Visual interpretation
Evaluate planar and SPECT images to confirm diffuse radiotracer uptake in the myocardium.
Differentiate myocardial radiotracer uptake from residual blood pool activity, focal myocardial infarct, and overlapping bone (eg, from rib hot spots from fractures) on SPECT images. If excess blood-pool activity is noted, recommend repeat SPECT imaging at 3 h.
If myocardial tracer uptake is visually present on SPECT, proceed to step 2, semi-quantitative visual grading. If no myocardial tracer uptake is present on SPECT, the visual grade is 0.
Step 2: Semi-quantitative grading to distinguish AL from ATTR cardiac amyloidosis (1- or 3-hour approach)
Examine planar and SPECT images for relative tracer uptake in the myocardium relative to ribs and grade using the following scale:

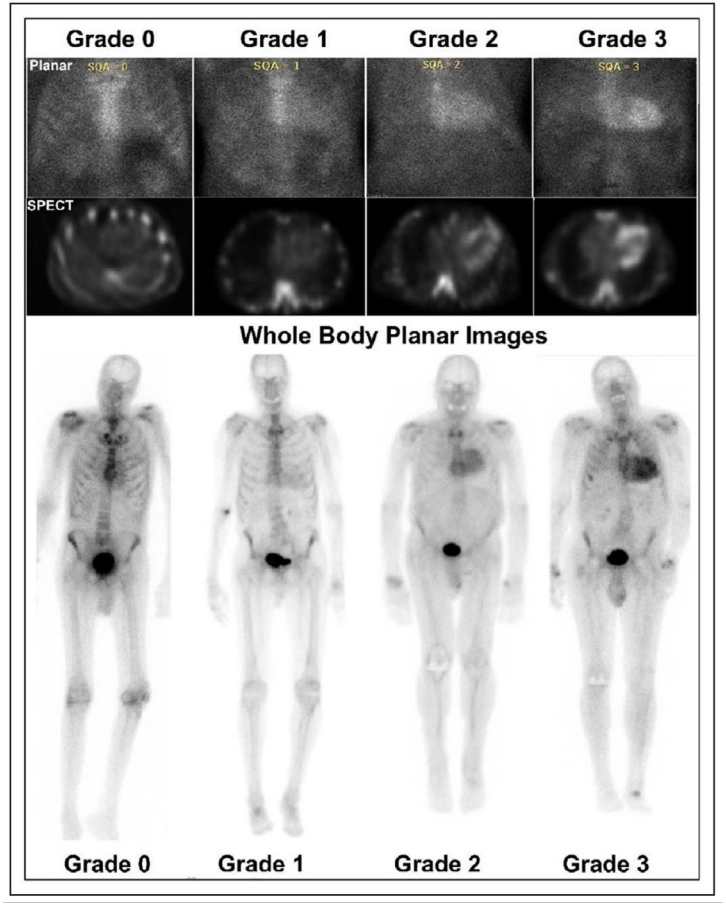
Grade 0	No myocardial uptake and normal bone uptake
Grade 1	Myocardial uptake less than rib uptake
Grade 2	Myocardial uptake equal to rib uptake
Grade 3	Myocardial uptake greater than rib uptake with mild/absent rib uptake

Step 3: Heart/contralateral lung uptake ratio assessment (when applicable)
A circular ROI should be drawn over the heart on the anterior planar images with care to avoid sternal overlap and with size adjusted to maximize coverage of the heart without inclusion of adjacent lung. This ROI (same size) should be mirrored over the contralateral chest without inclusion of the right ventricle, to adjust for background and rib uptake (see Fig. 6*). The heart and contralateral ROIs should be drawn above the diaphragm.
An H/CL ratio is calculated as the fraction of heart ROI mean counts to contralateral lung ROI mean counts.
H/CL ratios of ≥1.5 at 1 h can accurately identify ATTR cardiac amyloidosis if myocardial PYP uptake is visually confirmed on SPECT and systemic AL amyloidosis is excluded.[114] An H/CL ratio of ≥1.3 at 3 h can identify ATTR cardiac amyloidosis.
NOTE: Diagnosis of ATTR cardiac amyloidosis cannot be made solely based on H/CL ratio alone with PYP. H/CL ratio is not recommended if there is absence of myocardial uptake on SPECT. Additionally, if the visual grade is 2 or 3, diagnosis is confirmed and H/CL ratio assessment is not necessary. H/CL ratio is typically concordant with visual grade. If discordant or the visual grade is equivocal, H/CL ratio may be helpful to classify equivocal visual grade 1 vs 2 as positive or negative.
See Fig. 7.* Grade 2 or Grade 3 uptake is consistent with ATTR cardiac amyloidosis if a monoclonal plasma cell dyscrasia is excluded, as this degree of uptake can be seen in >20% of patients with AL cardiac amyloidosis.[3] Grade 0 and Grade 1 uptake may be observed in AL cardiac amyloidosis and warrants further evaluation to exclude AL amyloidosis.[3] The writing group would like to emphasize the importance of excluding a monoclonal process with serum/urine immunofixation and a serum-free light-chains assay in all patients with suspected amyloidosis.
Of note: ^{99m}Tc-PYP/DPD/HMDP uptake could be seen in other causes of myocardial injury, including pericarditis, myocardial infarction (regional uptake), and chemotherapy or drug-associated myocardial toxicity.

PYP - Planar and SPECT/CT



Perugini Score



PYP Scan - Standardized Reporting

Table 6. Recommendations for Standardized Reporting of ^{99m}Tc-PYP/DPD/HMDP Imaging for Cardiac Amyloidosis

Parameters	Elements
Demographics	Patient name, age, sex, reason for the test, date of study, prior imaging procedures, biopsy results if available (Required)
Methods	Imaging technique, radiotracer dose and mode of administration, interval between injection and scan, scan technique (planar and SPECT) (Required)
Findings	Image quality Visual scan interpretation (Required) Semi-quantitative interpretation in relation to rib uptake (Required) Quantitative findings H/CL lung ratio (Optional; recommended for positive scans)
Ancillary findings	Whole-body imaging if planar whole-body images are acquired (Optional) Interpret CT for attenuation correction if SPECT/CT scanners are used (Recommended)
Conclusions	1. An overall interpretation of the findings into categories of (1) not suggestive of ATTR cardiac amyloidosis; (2) strongly suggestive of ATTR cardiac amyloidosis; or (3) equivocal for ATTR cardiac amyloidosis after exclusion of a systemic plasma cell dyscrasia (Required) a. Not suggestive: A semi-quantitative visual grade of 0. b. Equivocal: If diffuse myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP is visually confirmed and the semi-quantitative visual grade is 1 or there is interpretive uncertainty of grade 1 versus grade 2 on visual grading. c. Strongly suggestive: If diffuse myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP is visually confirmed, a semi-quantitative visual grade of 2 or 3. 2. Statement that evaluation for AL amyloidosis by serum FLCs, serum, and urine immunofixation is recommended in all patients undergoing ^{99m}Tc-PYP/DPD/HMDP scans for cardiac amyloidosis. (Required) 3. Statement that results should be interpreted in the context of prior evaluation and referral to a hematologist or amyloidosis expert is recommended if either: a. Recommended echo/CMR is strongly suggestive of cardiac amyloidosis and ^{99m}Tc- PYP/DPD/HMDP is not suggestive or equivocal and/or b. FLCs are abnormal or equivocal. (Recommended)

False positives and negatives in PYP Scintigraphy

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.
	Aβ2M amyloidosis	Long-term dialysis (>9 years). Requires histologic confirmation.
	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.
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.

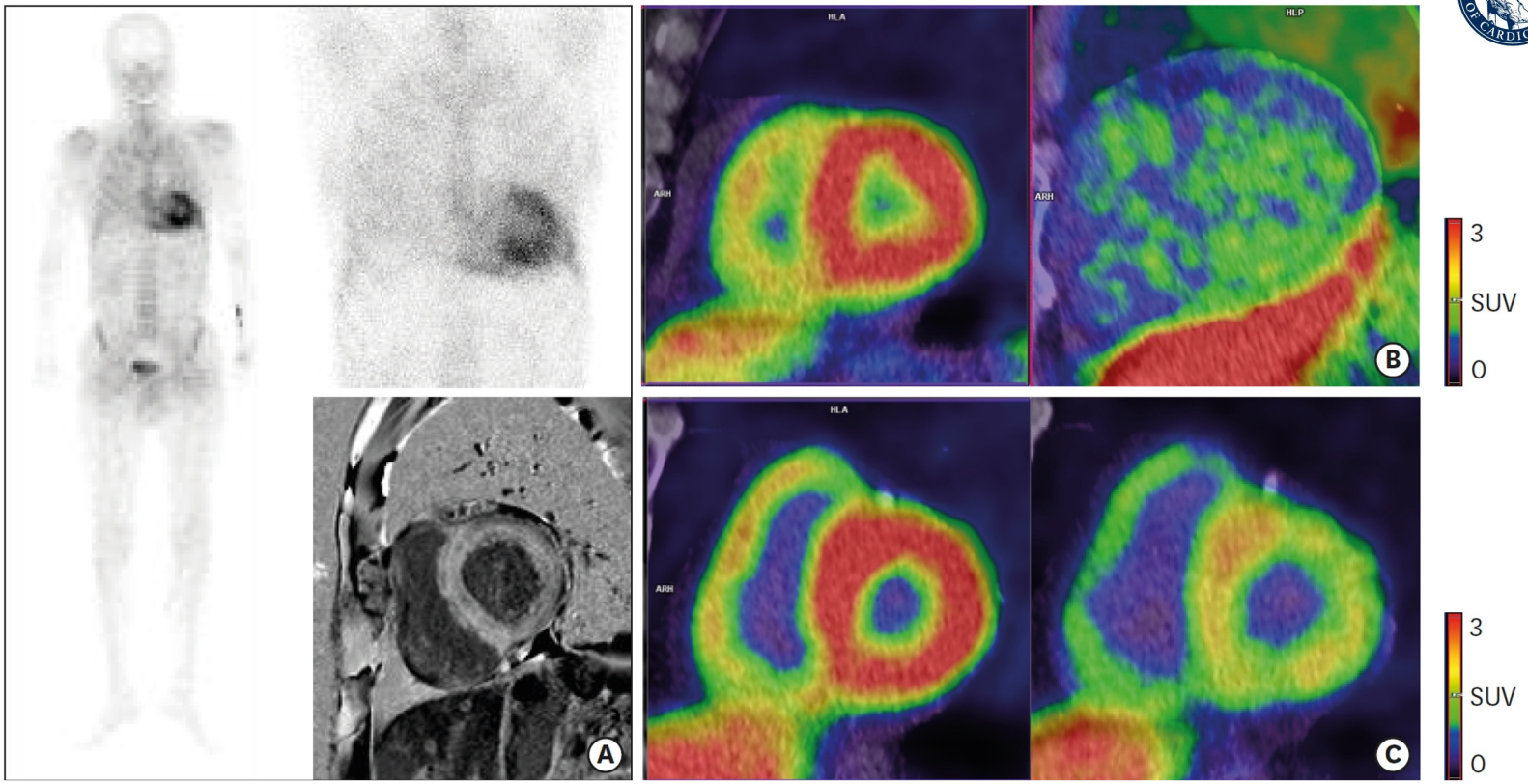


Figure 4. Nuclear imaging in diagnosis of cardiac amyloidosis and follow-up. (**A**) A representative image of ^{99m}Tc-DPD SPECT in an ATTR cardiac amyloidosis patient. Evident uptake of ^{99m}Tc-DPD in the myocardium is noted and is supported by suboptimal nulling on CMR. (**B**) Uptake of ^{11}C-Pittsburgh B (PiB) compound in a patient with biopsy-proven cardiac amyloidosis (left panel). This compound is specific for amyloid deposits as no ^{11}C-PiB is noted in healthy volunteers (right panel). (**C**) A significant decrease of ^{11}C-PiB uptake in a patient with cardiac amyloidosis 12 months after chemotherapy and autologous stem cell transplantation (left panel; before chemotherapy, right panel).

Cardiac MRI in Cardiac Amyloidosis

1. LV function and morphology; tissue characterization.

2. Amyloid imaging - LGE imaging; myocardial signal suppression pattern

3. Amyloid quantification - Native T1 mapping & Post-contrast T1 (ECV)

Table 3. Recommendations for Standardized Interpretation and Reporting of CMR for Cardiac Amyloidosis

Parameter for Acquisition and Reporting	Criteria	Notes	Recommendations for Reporting
LV function and morphology			
LV function	Biventricular long-axis impairment with relative apical functional sparing	Although LV ejection fraction is typically preserved in cardiac amyloidosis, a reduced LV ejection fraction may be seen in advanced cases	Required
LV wall thickness	Increased LV wall thickness: >laboratory ULN for sex on SSFP cine CMR[205] and increased relative wall thickness >0.42 cm	Increased LV wall thickness is suggestive in the presence of normal or low QRS voltage on ECG and/or concomitant increased right ventricular wall thickness While increased LV wall thickness is typically concentric, it can be asymmetric in ATTR cardiac amyloidosis[172]	Required
Stroke volume index	LV stroke volume index (<35 mL/m^2)	A low stroke volume index is non-specific but suggestive of cardiac amyloidosis	Required
LV mass	LV mass ≥91 g/m^2 for men and ≥78 g/m^2 for women (with papillary muscle included as part of LV mass measurement)[206]	To quantify myocardial and amyloid mass	Required
Atrial size and function (based on Simpson's method)	Increased left atrial volume >163 mL for men and >131 mL for women[206] Increased right atrial volume >85 mL/m^2[206] Reduced atrial function: <29% for men and <35% for women.[206]	Non-specific but important finding to support the diagnosis and potentially provide insight into risk for stroke or arterial embolism	Required
Pericardial effusion	Pericardial effusion	Non-specific, but when coupled with other CMR signs is suggestive of the diagnosis, especially in the setting of normal LV ejection fraction	Required
Amyloid Imaging			
LGE imaging	Abnormal LGE Pattern Diffuse LGE Subendocardial LGE Patchy LGE Difficulty in achieving myocardial nulling over a range of inversion times Dark blood pool signal	Standard mag-IR LGE imaging is not recommended given difficulty in selecting the optimal inversion time (TI). Phase-sensitive reconstruction is preferred Data acquisition should be obtained in every other RR interval Quantification of LGE is challenging in amyloidosis and is not recommended for routine clinical practice.	Required
Myocardial signal suppression pattern	Abnormal myocardial signal suppression pattern Myocardium nulls before blood pool on Look Locker, Cine IR, or TI scout sequences		Recommended
Amyloid quantitation			
Native T1 mapping (pre-contrast)	Abnormal T1 mapping (criteria may vary based on the sequence used [MOLLI, ShMOLLI] and the field strength of the magnet)	Assess interstitial amyloid accumulation without gadolinium Reference range should be based on a site's local calibrated values on specific field strengths.	Recommended
T1 mapping post-contrast (ECV estimation)	ECV >0.40 is highly suggestive of cardiac amyloidosis	Assess expansion of ECV from interstitial amyloid accumulation A. 1 pre- and 1 post- contrast measurement (15-min post-contrast injection) B. 1 pre- and 3 post- contrast measurements (5-, 15-, and 25-min post contrast injection)	A. Recommended B. Optional

Circulation: Cardiovascular Imaging
Volume 14, Issue 7, July 2021; Page e000029
https://doi.org/10.1161/HCI.0000000000000029

EXPERT CONSENSUS RECOMMENDATIONS

American Heart Association.

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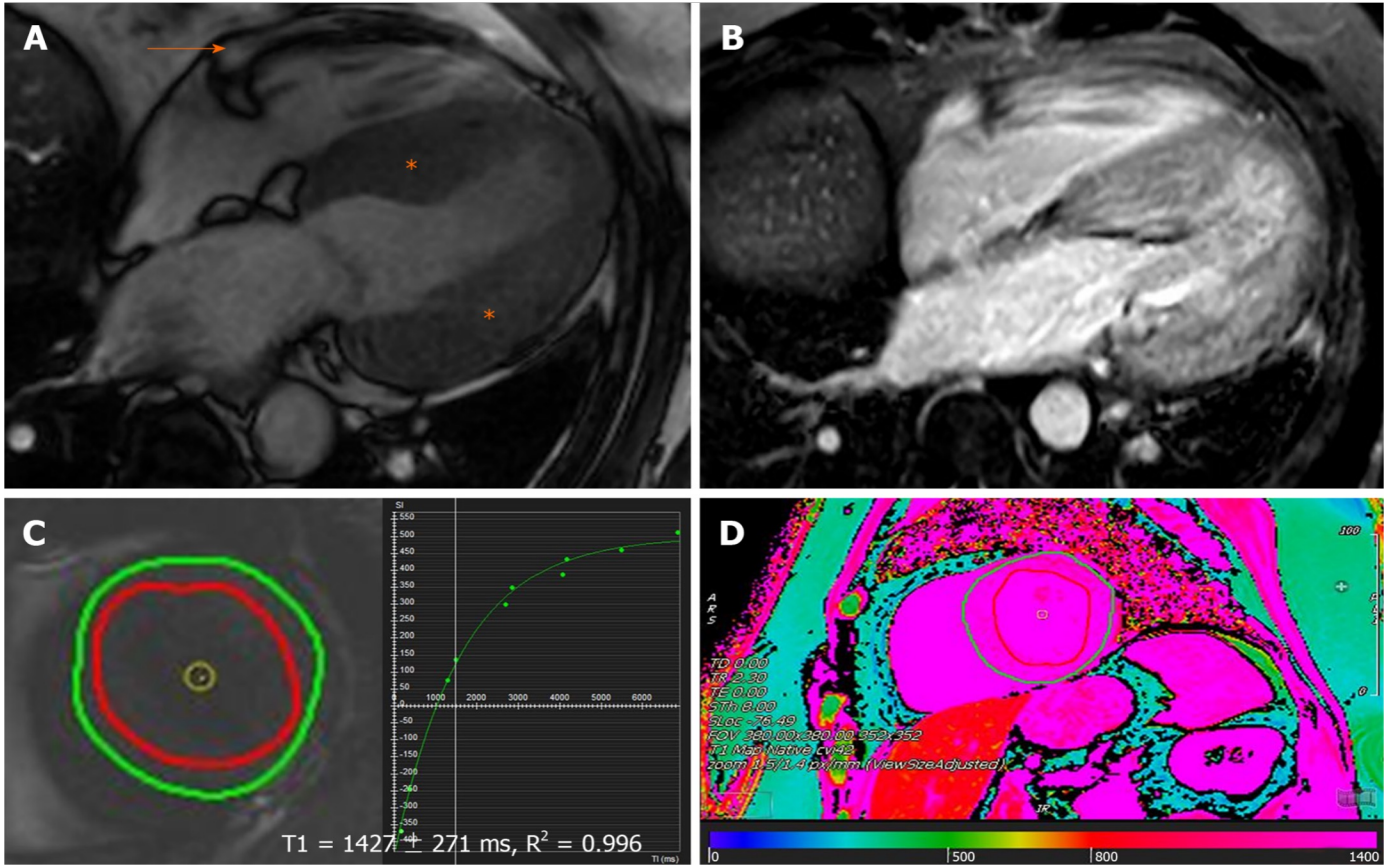

Wang TKM *et al.* Multi-modality imaging of cardiac amyloidosis. W J of Radiology June 2020

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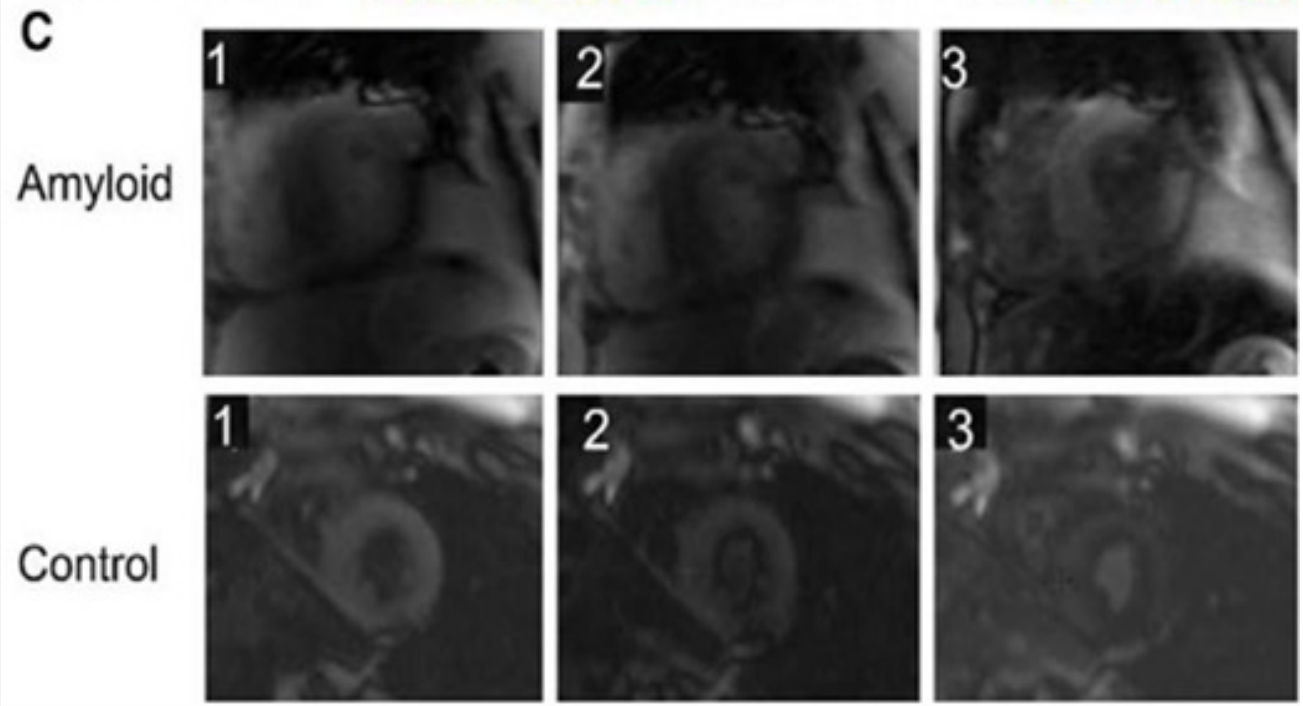
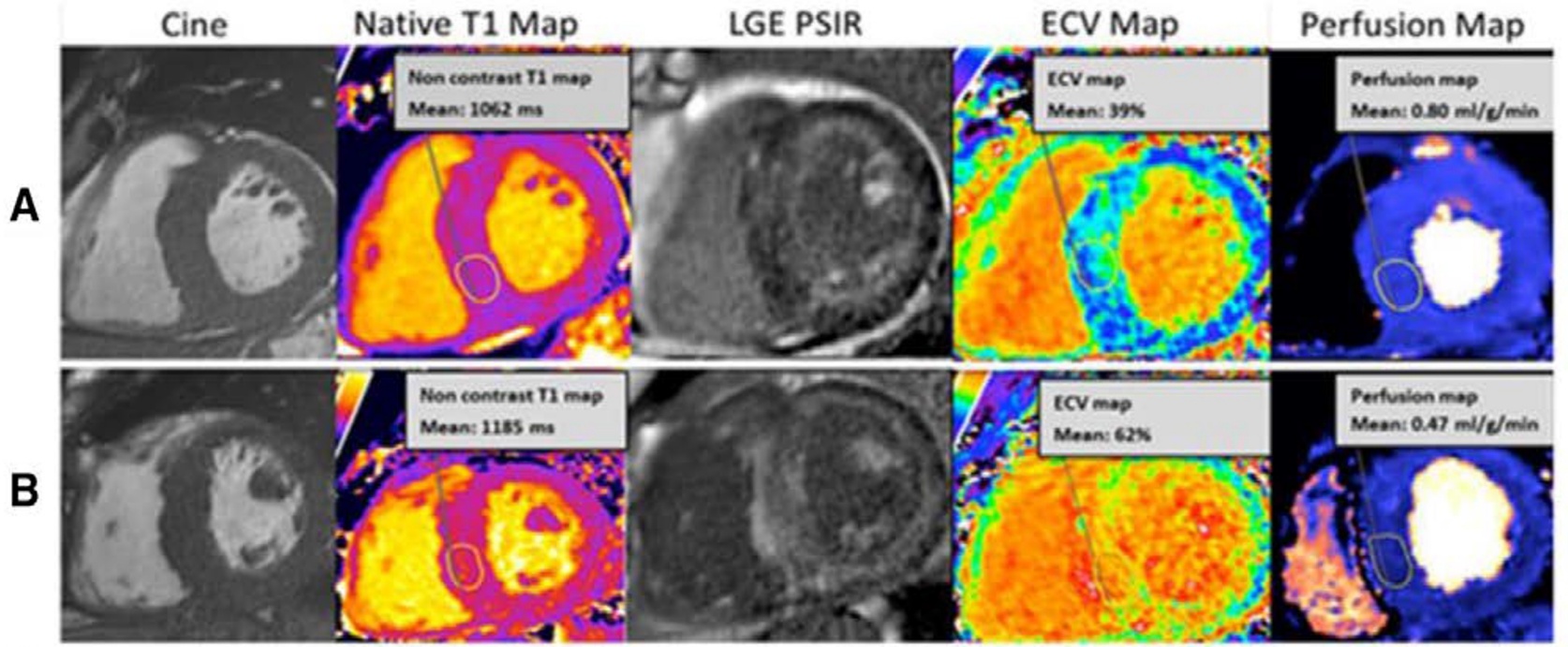


Inversion scout images in two patients, upper row amyloid, lower row nonamyloid control.

Dorbala *et al*. Circulation Cardiovascular Imaging 2021. Multimodality Imaging in Cardiac Amyloidosis, Part 1: Evidence Base and Standardized Methods.



Dorbala *et al*. Circulation Cardiovascular Imaging 2021. Multimodality Imaging in Cardiac Amyloidosis, Part 1: Evidence Base and Standardized Methods.

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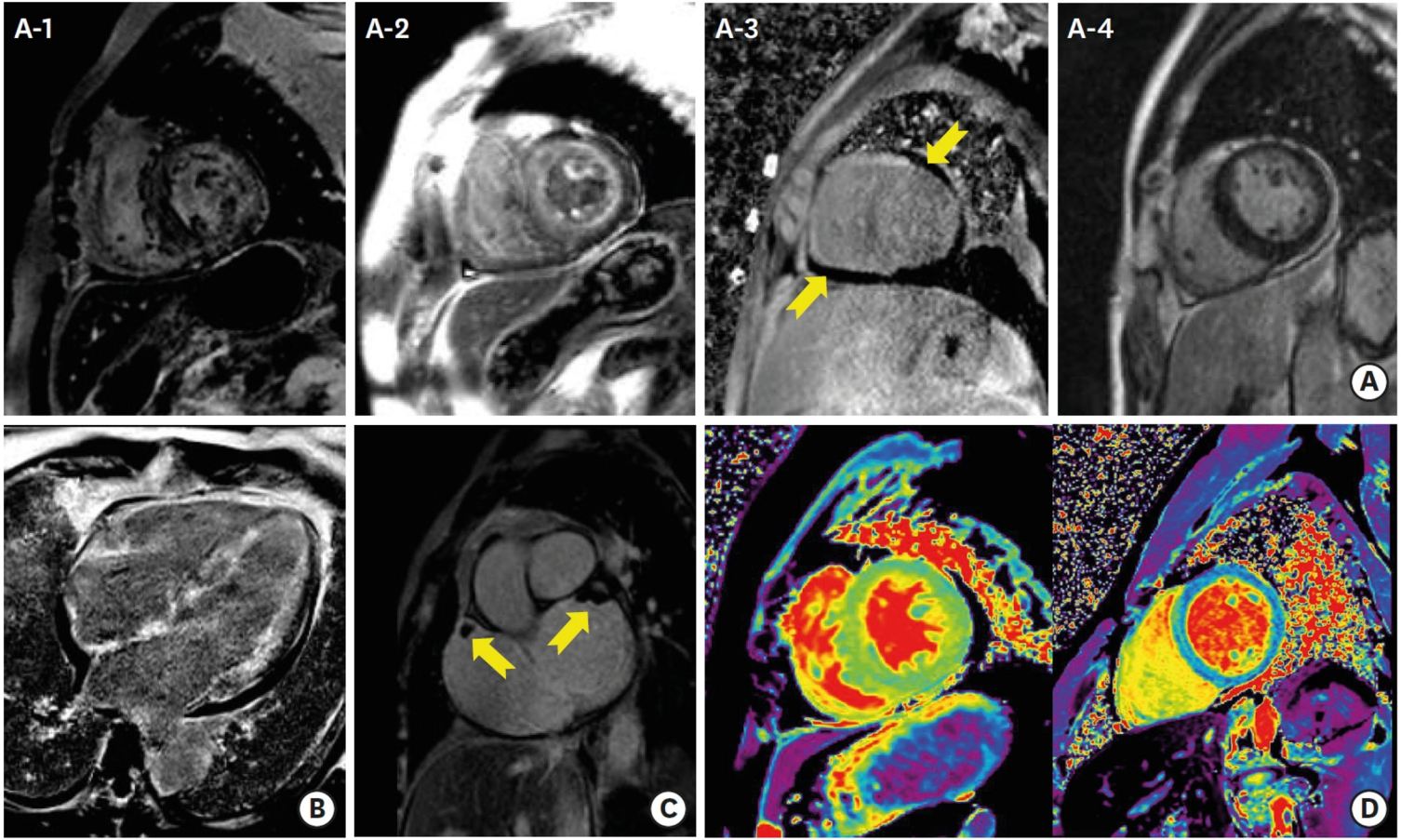
Journal of Cardiovascular Imaging JCVI



Seung-Pyo Lee; Contemporary Imaging Diagnosis of Cardiac Amyloidosis; JCVI. Dec 2018

Circulation: Cardiovascular Imaging
Volume 14, Issue 7, July 2021; Page e000029
https://doi.org/10.1161/HCI.0000000000000029

EXPERT CONSENSUS RECOMMENDATIONS

An overall interpretation of the CMR findings into categories of: **Not suggestive:** Normal LV wall thickness, normal LV mass, no ventricular LGE, normal atrial size **Strongly suggestive:** Increase LV wall thickness, increased LV mass, biatrial enlargement, typical diffuse or global LGE pattern, difficulty in achieving myocardial nulling, significantly increased ECV (>0.40), small pericardial and or pleural effusions **Equivocal:** Findings not described above.	Required
Interpret the CMR results in the context of prior evaluation.	Recommended
Provide follow-up recommendations: Strongly suggestive CMR findings cannot distinguish AL from ATTR cardiac amyloidosis. Endomyocardial biopsy is frequently unnecessary in patients with strongly suggestive CMR findings and histologically defined systemic amyloidosis or diagnostic ^{99m}Tc-PYP/DPD/HMDP imaging. Consider evaluation (1) to exclude AL amyloidosis, evaluate for plasma cell dyscrasia (serum and urine immunofixation, serum FLC assay) and (2) to exclude ATTR cardiac amyloidosis, consider imaging with ^{99m}Tc-PYP/DPD/HMDP.	Recommended

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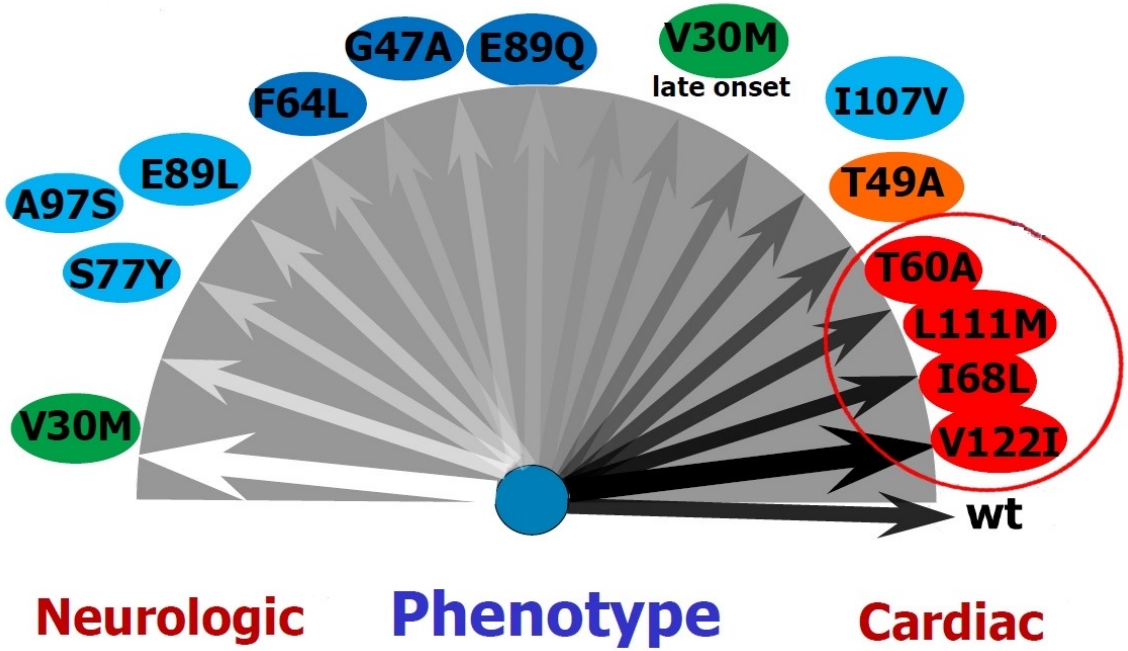
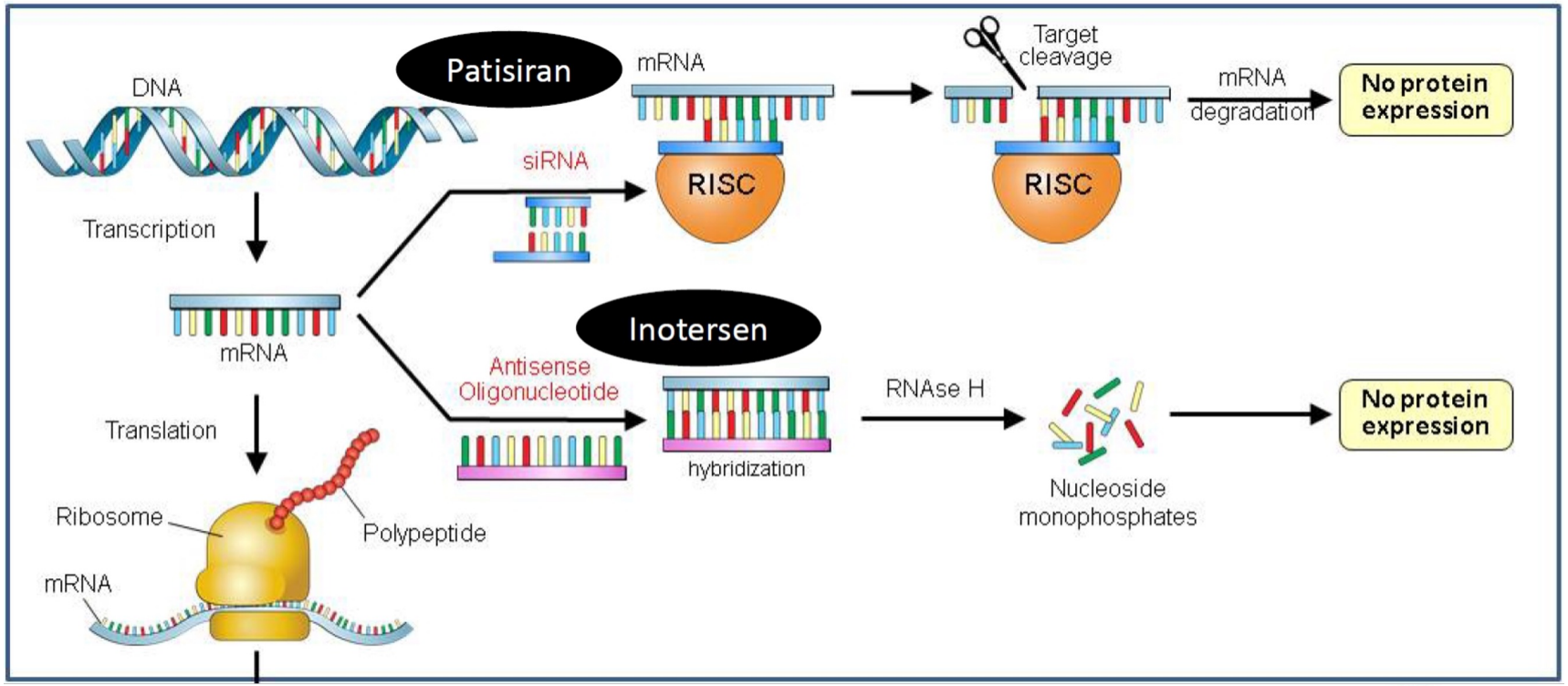
Mutations in Hereditary TTR Amyloidosis





Sperry et al; Subtype-Specific Prognosis in Cardiac Amyloidosis - *J Am Heart Association* - 2016

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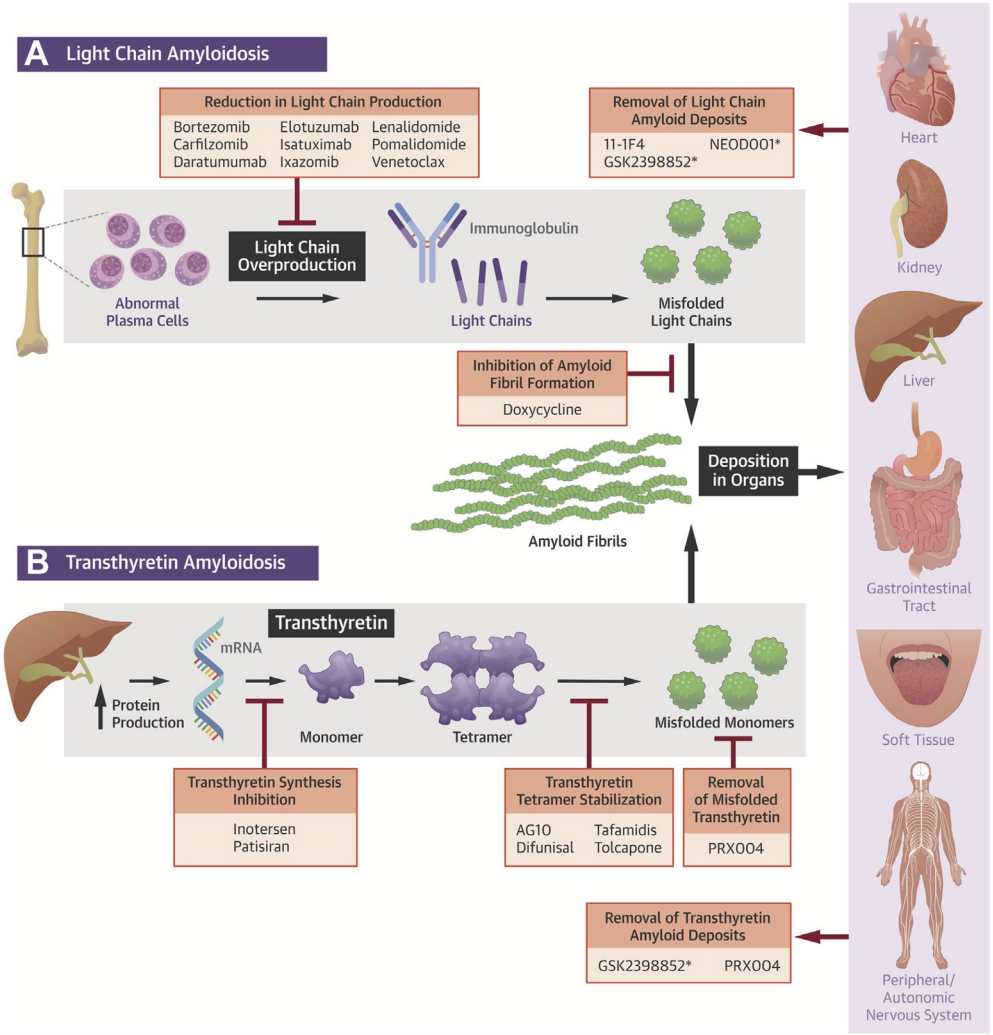

FDA Approval

Patisiran: Aug 10, 2018
Inotersen Oct 8, 2018
Tafamidis: May 6, 2019

Zhang, K. W. et al. J Am Coll Cardiology Basic Trans Science. 2019: Emerging therapeutics in Amyloidosis

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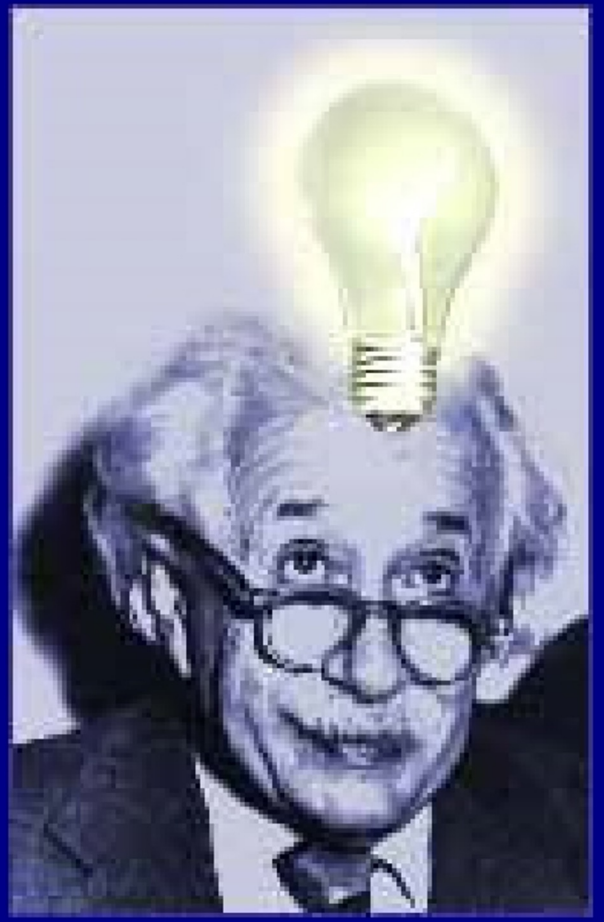
"The only way to diagnose amyloidosis is to consider the diagnosis."



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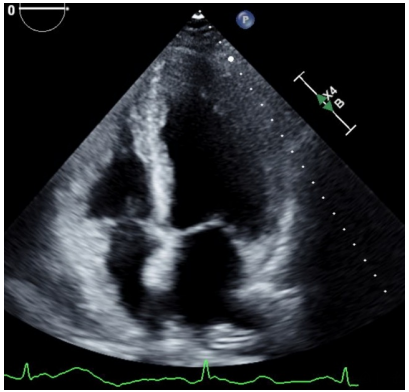
2. Sperry *et al*; Subtype-Specific Prognosis in Cardiac Amyloidosis - *J Am Heart Association* – 2016
3. Donnelly and Hanna; Cleveland Clinical Journal of Medicine; Dec 2017
4. Ruberg *et al*. JACC Vol.73, No 22; 2019; Transthyretin Amyloid Cardiomyopathy
5. Ruberg *et al*. JACC Vol.73, No 22; 2019; Transthyretin Amyloid Cardiomyopathy
6. P Garcia-Pavia *et al*; EJHF April 7, 2021. Diagnosis and treatment of cardiac amyloidosis. A position statement of the ESC Working Group on Myocardial and Pericardial Diseases
7. Wang TKM *et al.* Multi-modality imaging of cardiac amyloidosis. W Journal of Radiology June 2020

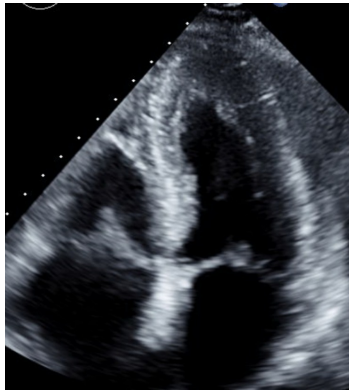
Recent Case

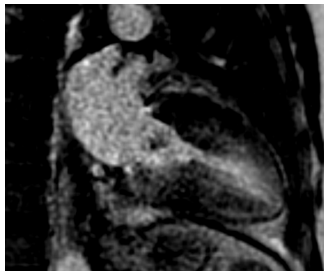
- Late 2021

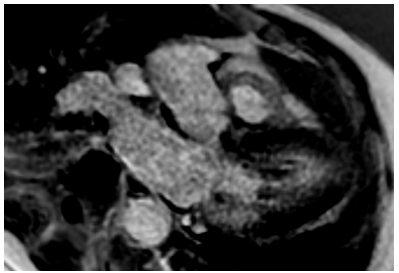
66-year-old male, dizziness and chest pain, recently started on **midodrine**, due to **orthostatic hypotension**.

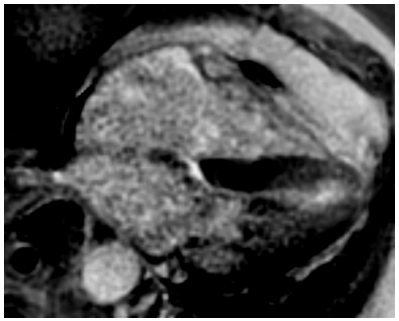
- 2014 - **left foot drop**, diagnosed as L5 radiculopathy
- 2015 - s/p spinal surgery, he had no relief
- 2017 - Mononeuritis multiplex. IgM spike (on SPEP); K/L ratio 0.26,
  BM bx- lymphoplasmacytic lymphoma,
  Confirmed as Waldenstrom macroglobu. (MYD88+ve/L265P mutation), s/p rituximab, improved IgM
- 2018 - IgM spike again; s/p Ibrutinib; developed side effects (diarrhoea, COP, and Afib)
- 2019 - Started diltiazem (for afib)
- 2020 - Zabrutinib
- 2021 - **>7 g proteinuria**; Oncology suspected AL amyloidosis with cardiac and neurologic; echo and cardiology referral (echo had findings)
- 2022 - We sent for **PYP negative**
- 2022 - MRI: EF 70%, **mild LVH (1.27cm),** pre-contrast **T1 1072 ms** (950-1050ms), T2 mildly elevated (edema/toxic), difficulty in nulling, **ECV increased**, diffuse subendocardial enhancement, becoming near transmural in the basal inferior, inferolateral and anterolateral segments – infiltrative cardiomyopathy.

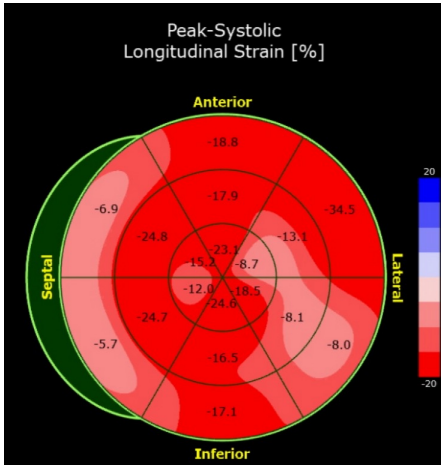


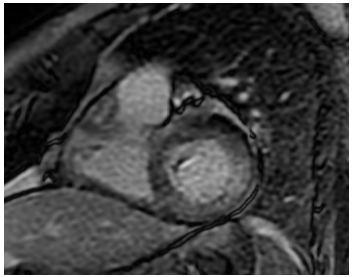


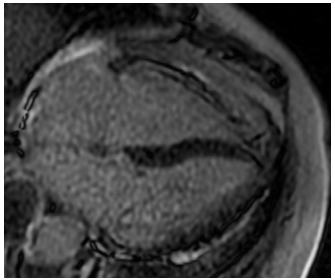


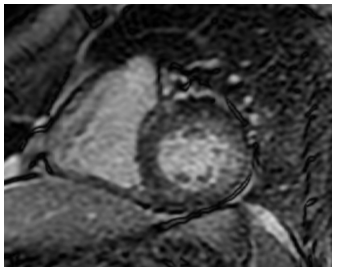












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