Cardiac Amyloidosis

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History

“Amylum” (in Latin), “Amylon” (in Greek)

Amyloid = starch like

First described by Rokitansky

- in 1842

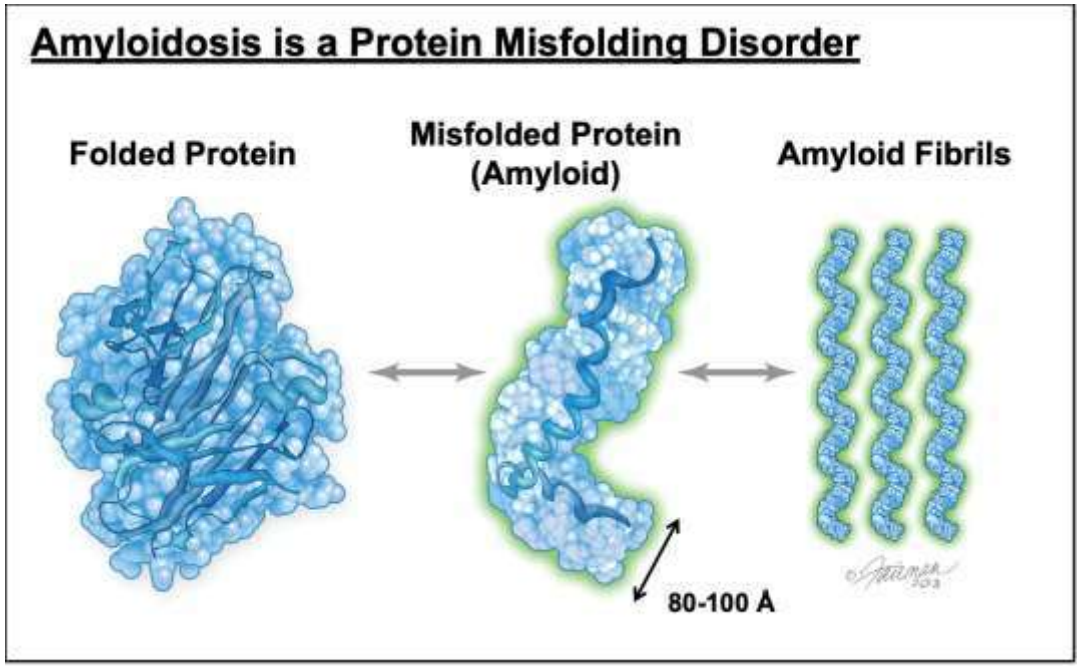
- Term first used by Rudolf Virchow in 1854 based on the color after staining it with crude iodine-staining techniques.

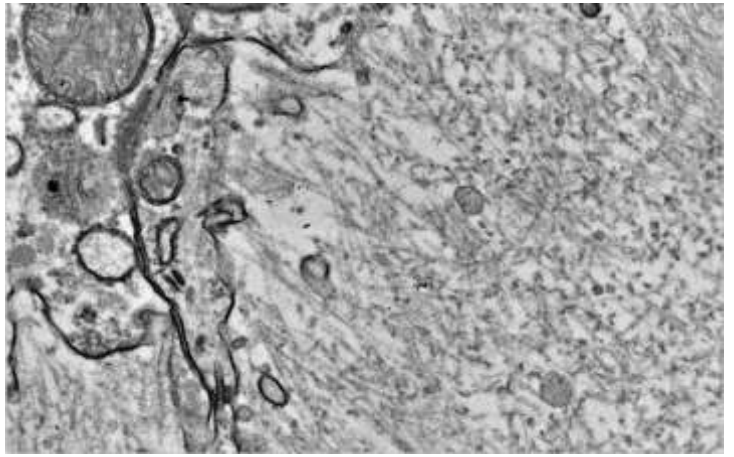
- Later recognized as Protein by Friedreich and Kekule 5 years later.

R.Virchow

AMYLOİDOSİS

Definition: Amyloid refers to insoluble, abnormal protein fibrils, accumulate in tissue and organs. This condition of deposition of amyloid in tissue is known as ***Amyloidosis***





Electron microscopy of amyloid fibrils

leopard print amyloid deposits (in an iodine solution)

AMYLOİDOSİS

- Group of protein-folding **disorders in which >1 organ is infiltrated by** proteinaceous deposits known as amyloid
- The deposits are derived from 1 of several amyloidogenic precursor proteins, and the **prognosis of the disease is determined both by involved the organ(s)** and the **type of amyloid**
- Amyloid involvement of the heart (cardiac amyloidosis) carries the **worst prognosis** of any involved organ, and **light-chain (AL) amyloidosis is the most serious form of the disease**

AMYLOIDOSIS IN HEART

- More than 30 proteins can form amyloid material

- 5 amyloidogenic proteins cause myocardial involvement (AL, ATTR, AA, ApoA-I, AH)

- Most cases (> 98%) correspond to:

-Immunoglobulin light chain- AL-CA

-Transthyretin amyloidosis- ATTR-CA

Hereditary (ATTRv)

Acquired (ATTR wt)

DOI: https://doi.org/10.3949/ccjm.84.s3.02

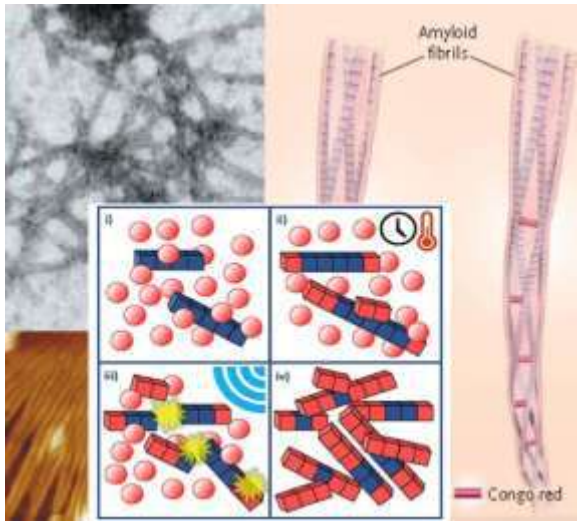
Table 1 Amyloidosis subtypes that affect the heart

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% Depending on the mutation	31 (Val142Ile) 69 (non-Val142Ile)	Polyneuropathy, orthostatic hypotension, 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, paresthaesia, proteinuria (rare)

AA, serum amyloid A amyloidosis; AApoAI, apolipoprotein AI amyloidosis; AApoAII, apolipoprotein AII 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; CTS, carpal tunnel syndrome; HF, heart failure; LSS, lumbar spinal stenosis.

DEFINITION AND PHYSIOPATHOLOGY

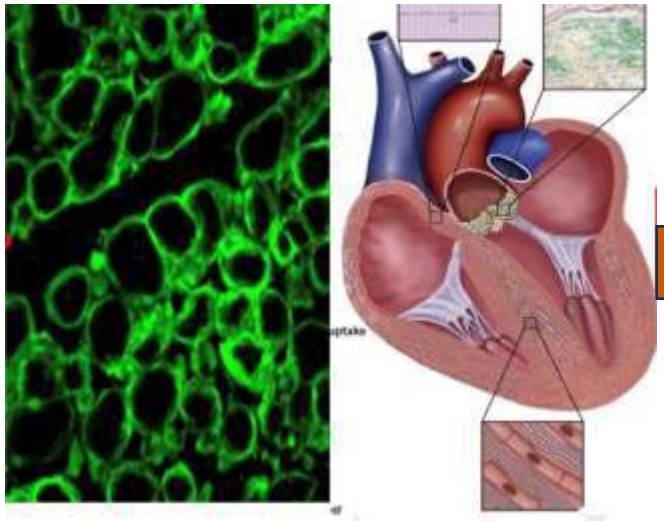
Amyloid Fibrills



Amyloid fibrills: > 30 Proteins
Non Immunogenic +++
Associated with Aging Process

Dynamic Progress+++

Organs Infiltration

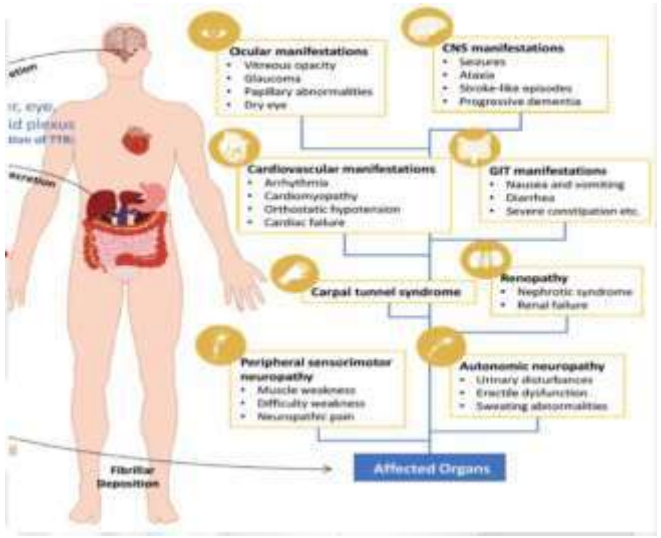


Extracellular infiltration

Cellular Death
Stiffness: CMR
Thickness:LVH

Stroke volume
Cardiac Output

Human Disease



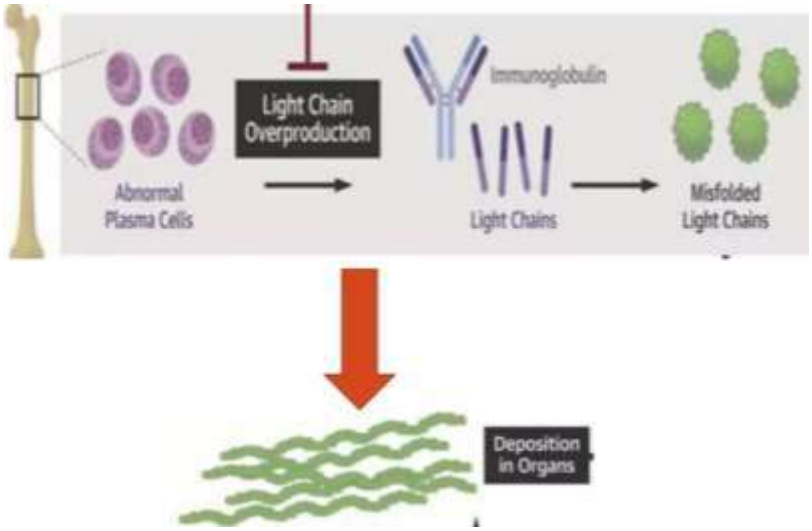
Extracardiac SD

Heart Failure
Conduction D
Rhythm D
Death

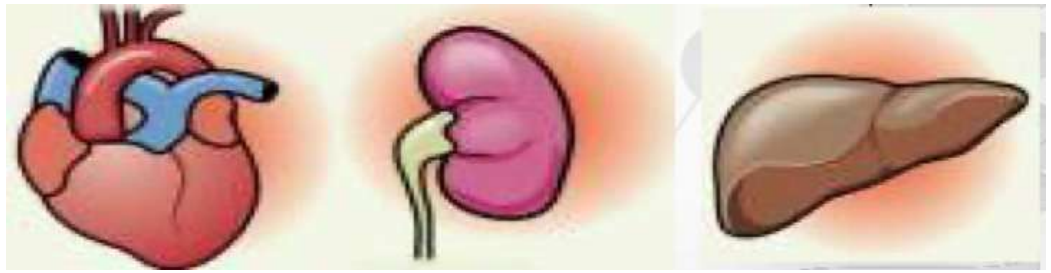
Merlini, NEJM 2003 Ternacle J, JACC 2019

AL- AMYLOIDOSIS

- AL-Amyloidosis: Over production of one type of light chain (Lambda>Kappa) by Lymphocytes
- AL-CA with HF symptoms without treatment = DEATH in 6months
- AL-CA = EMERGENCY!
- PROGNOS = MAYO STAGING

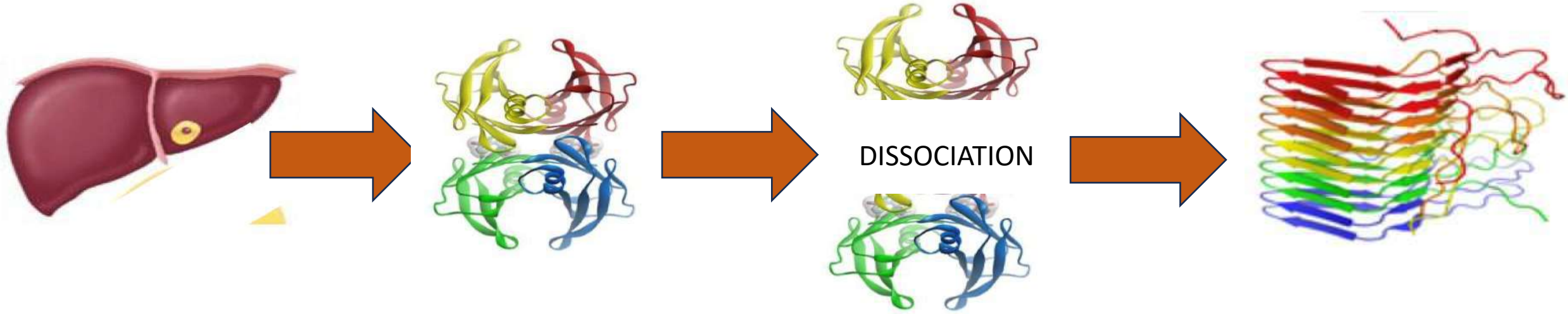


65% 75% 17%



https://www.nejm.org/doi/pdf/10.1056/NEJMoa054494

TRANSTHYRETIN- CA



HEREDITARY –ATTRv (VARIANT)

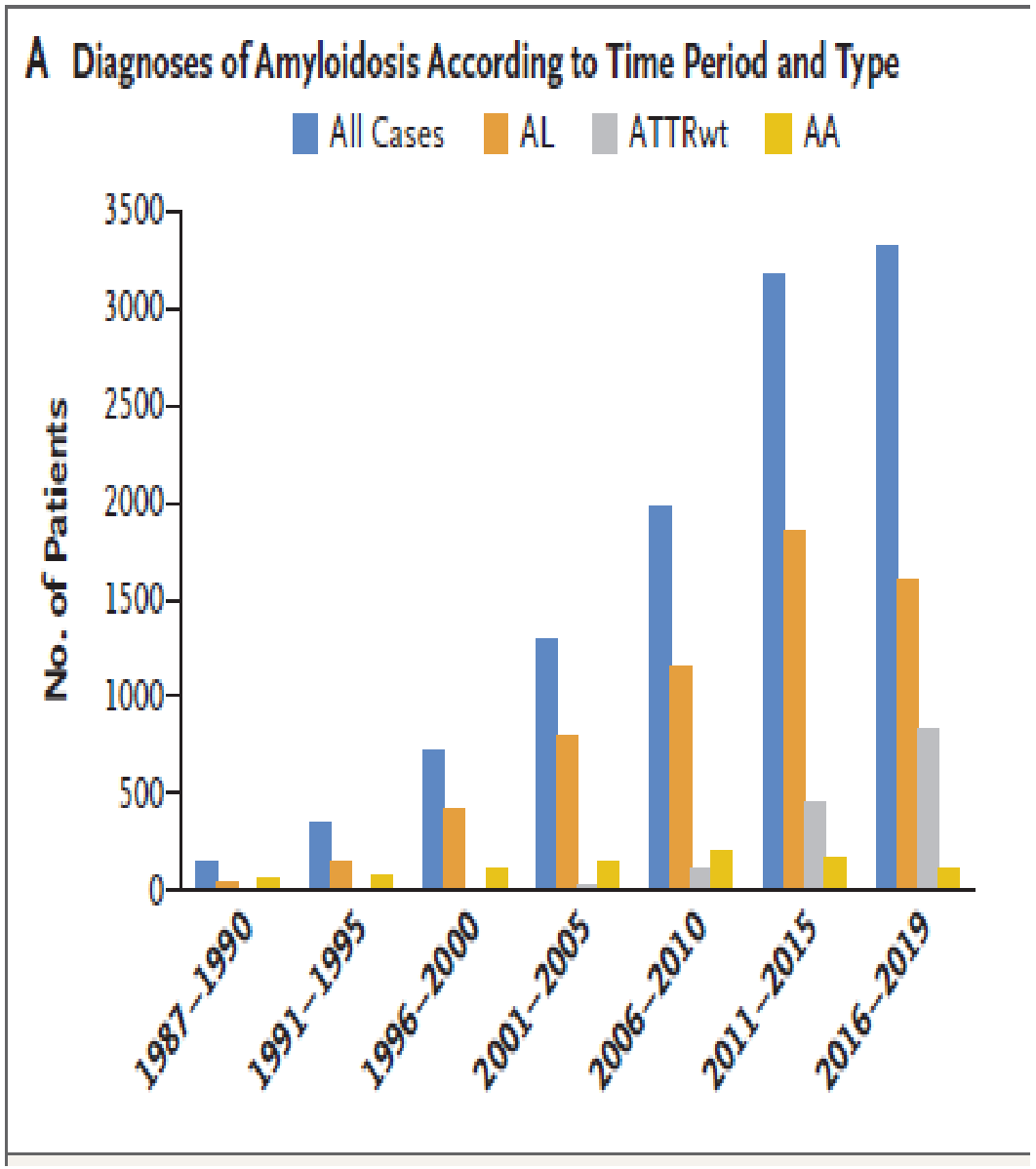
- Autosomal dominant
- 120 mutations
- HEART>>>nerve
- ≈ 75 y.o

SENIL TYPE-ATTRwt

- “Cardiac Alzheimer”
- 1/4 of 80 y.o TTR amyloid involve the heart
- ≈83 y.o

Is Cardiac Amyloidosis Rare?

- AL-CA 8-12/ per million
- ≈3000 newly diagnosed cases of AL amyloid per year in USA
- 30% to 50% have symptomatic cardiac involvement
- The population prevalence of ATTR-CA remains uncertain.
- It is often overlooked as a cause of common cardiovascular conditions in older adults, such as HFpEF, low-flow aortic stenosis, and atrial fibrillation.



https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.116.024438

In whom should one consider Cardiac Amyloidosis?

IF YOU DON'T THINK OF IT YOU WON'T DIAGNOSE IT

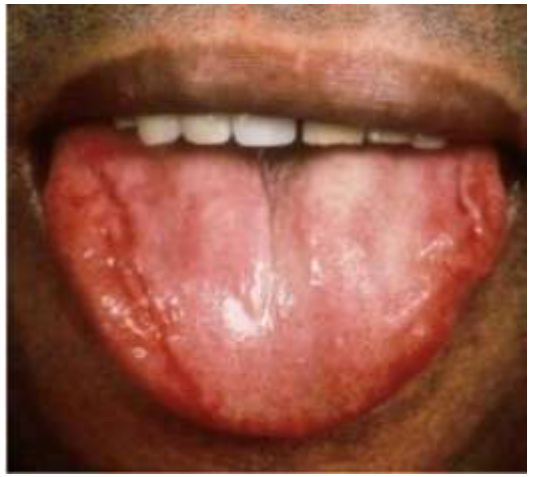
Table 5 Cardiac and extracardiac amyloidosis red flags

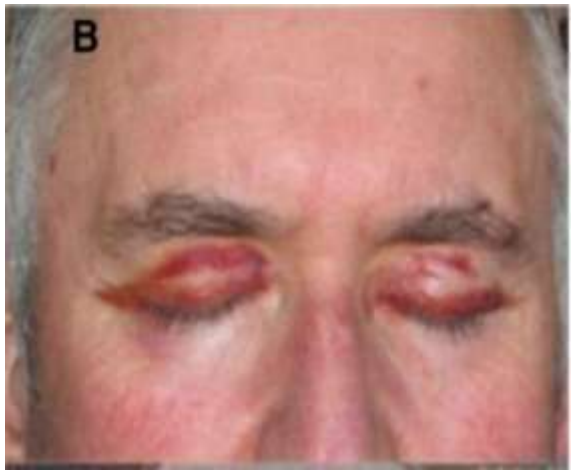
Extracardiac/cardiac	Type	Red flag	Amyloidosis where it is most frequently found
Extracardiac	Clinical	Polyneuropathy	ATTRv, AL, AA, AGel
		Dysautonomia	ATTR, AL
		Skin bruising	AL
		Skin discoloration	AApoAI
		Cutis laxa	AGel
		Macroglossia	AL
		Deafness	ATTRwt
		Bilateral carpal tunnel syndrome	ATTRv, ATTRwt
		Ruptured biceps tendon	ATTRwt
		Lumbar spinal stenosis	ATTRwt
		Vitreous deposits	ATTRv
		Corneal lattice dystrophy	AGel
		Family history	ATTRv, AApoAI, AApoAII
	Laboratory	Renal insufficiency	AL, AA, AApoAI, AApoAII, AApoAIV, Aβ2M, AFib
		Proteinuria	AL, AA, AApoAI, AApoAII, AFib

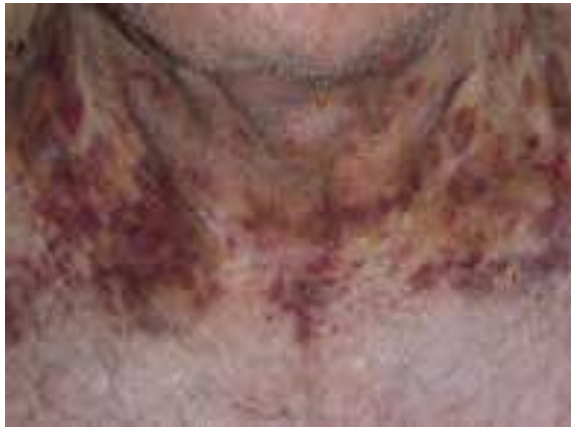
IF YOU DON'T THINK OF IT YOU WON'T DIAGNOSE IT

RED FLAGS FOR AL

- HfpEF+Nephrotic Syndrome
- Macroglossia and/or periorbital purpura
- Orthostatic Hypotension
- Peripheral Neuropathy





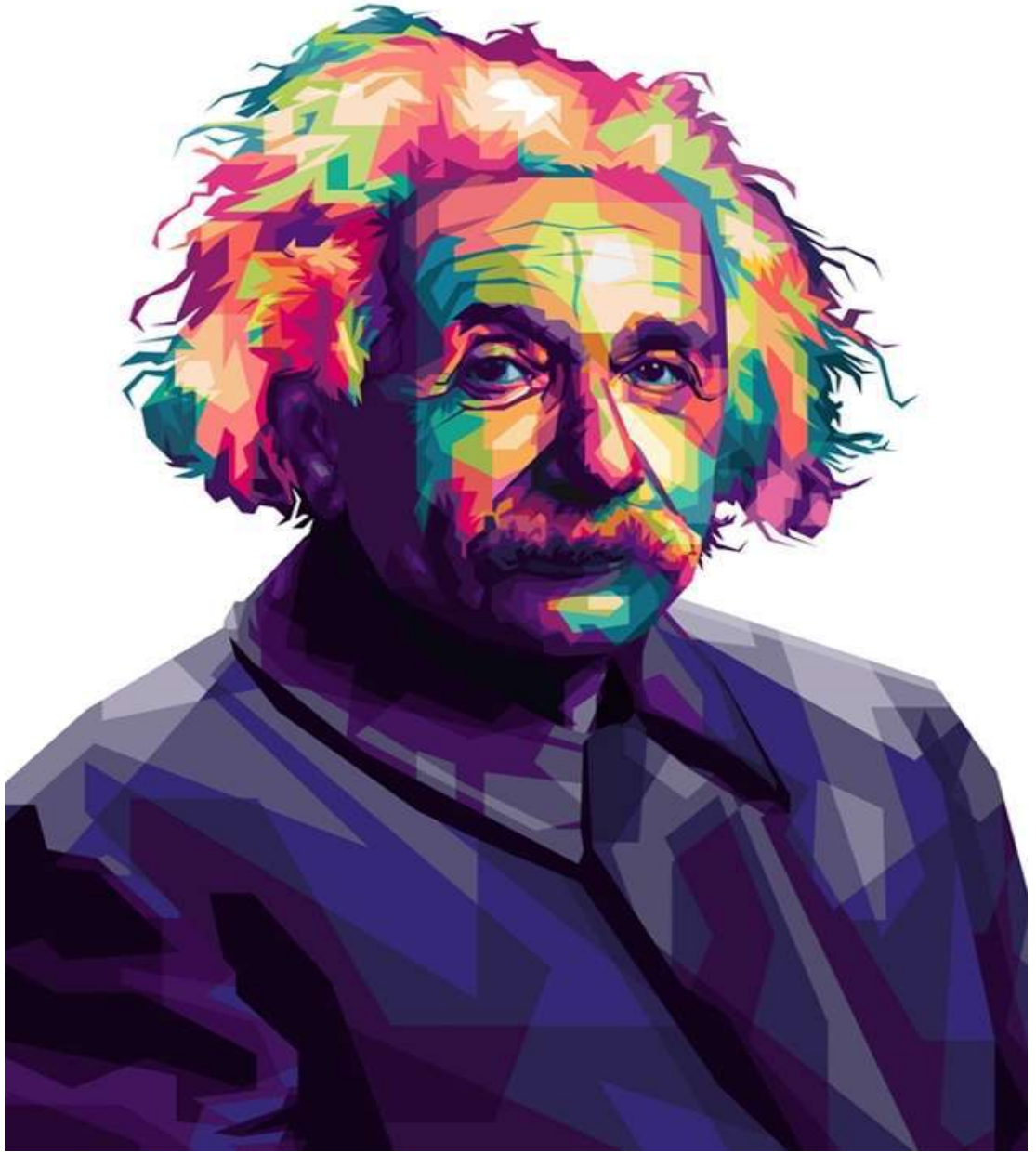


RED FLAGS FOR ATTR

- White male age>60 with HFpEF + carpal tunnel syndrome and or/spinal stenosis
- African American age>60 with HFpEF without history of HTN
- New diagnosis of hypertrophic cardiomyopathy in an elderly patient
- New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
- Family history of ATTR amyloidosis

Amyloidosis Diagnosis

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




SUSPECT
CONFİRM /RULE OT
IDENTİFY THE TYPE
START TREATMENT

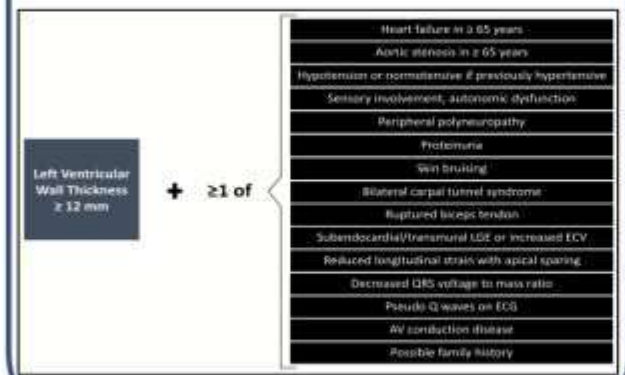
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & **Haematologic tests** (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

I STEP: SUSPECT

Left Ventricular Wall Thickness ≥ 12 mm

+ ≥1 of

- Heart failure in ≥ 65 years
- Aortic stenosis in ≥ 65 years
- Hypotension or normotensive if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history

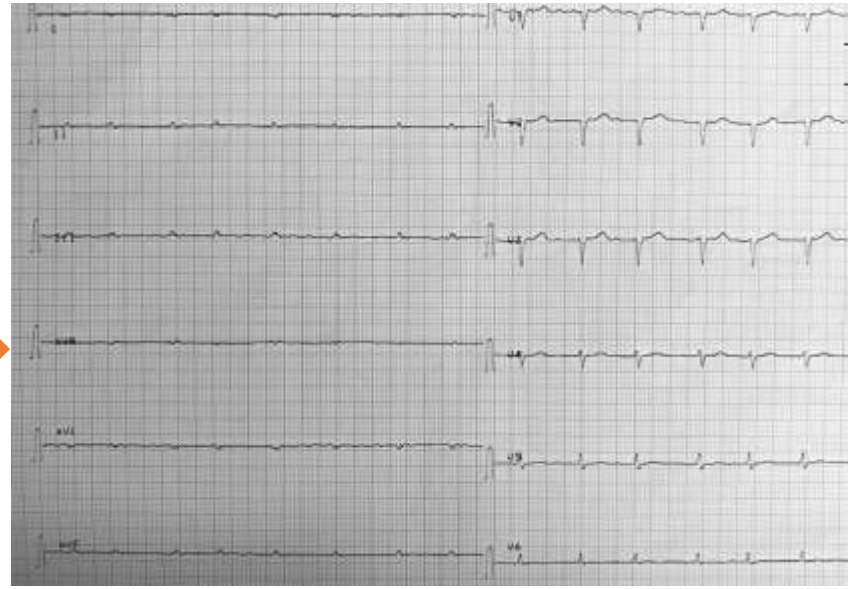
II step:

ECG
ECHO
CHEST RADIOGRAPHY
LABORATORY MARKERS

IS THE ECG USEFUL FOR IDENTİFYİNG CA?

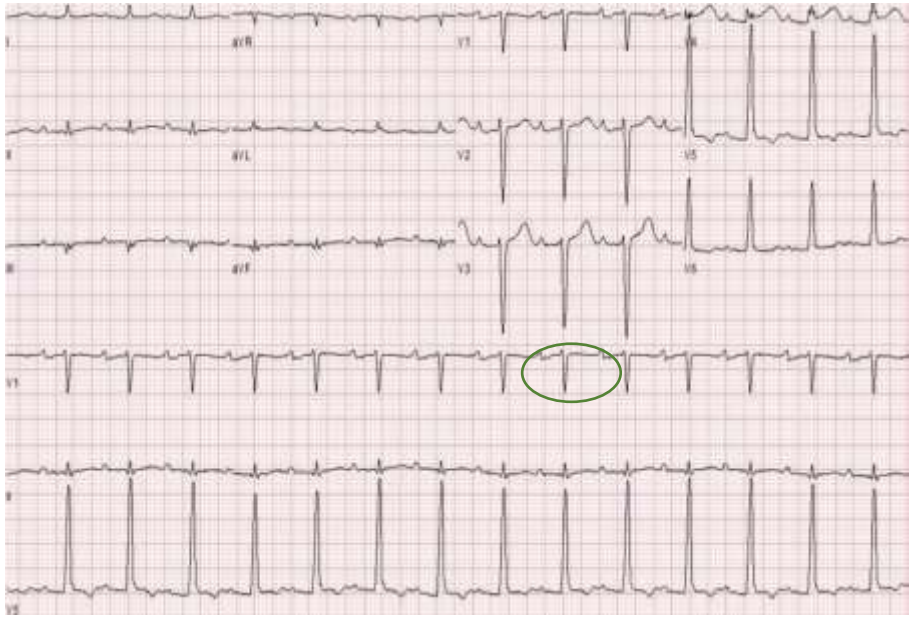
- Low QRS voltage - in s.d
- Pseudoinfarction patterns
- AV block
- AF

AF
Low voltage



Low voltage

AV block I d.



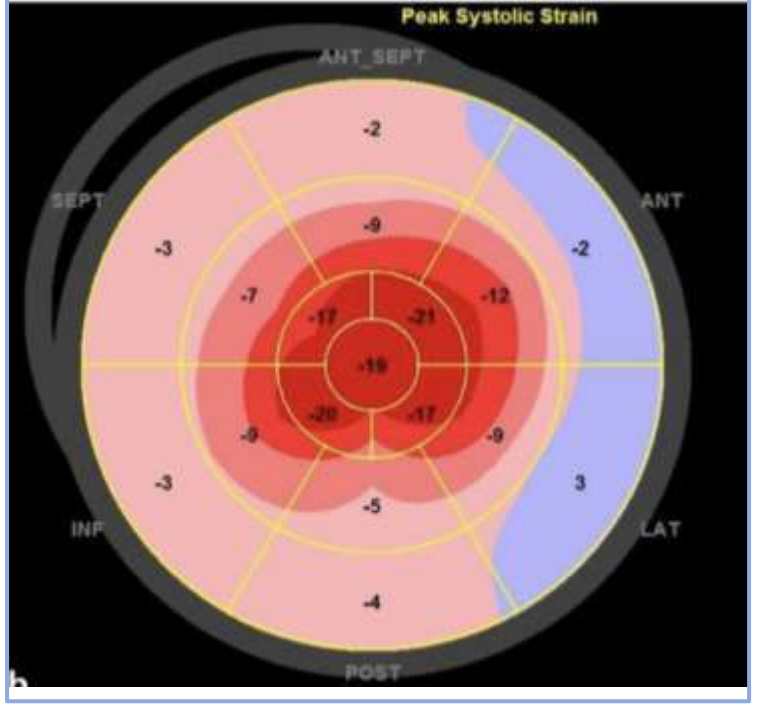
- Low voltage varies with ethiology (AL 60%, ATTR 20%)
- Abcense of Low QRS- does not exclude disease
- ATTR-(30% patients LV hypertrophy+ LBBB)

LV hypertrophy+ older patient+AV block--→
-→ CA should always be considered

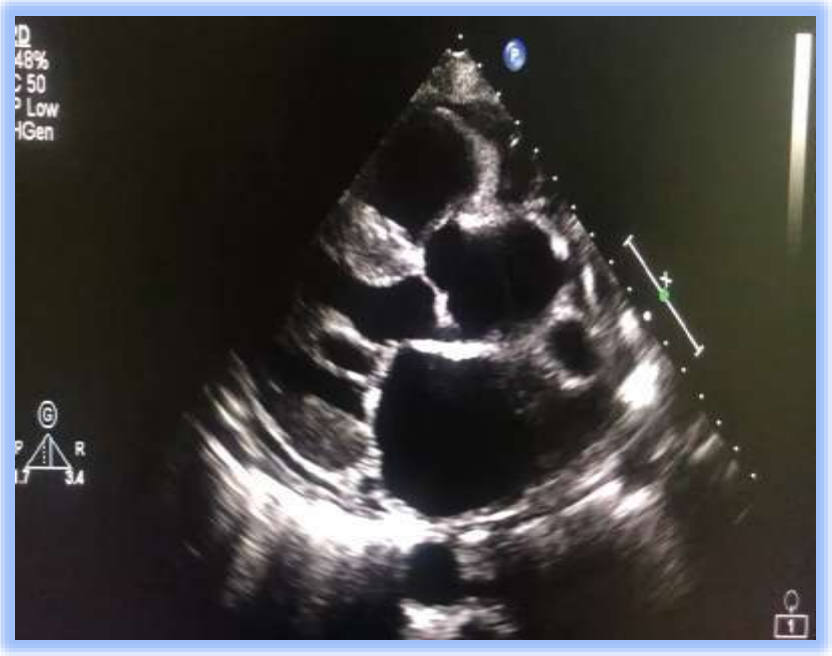
ECHOCARDİOGRAPHY

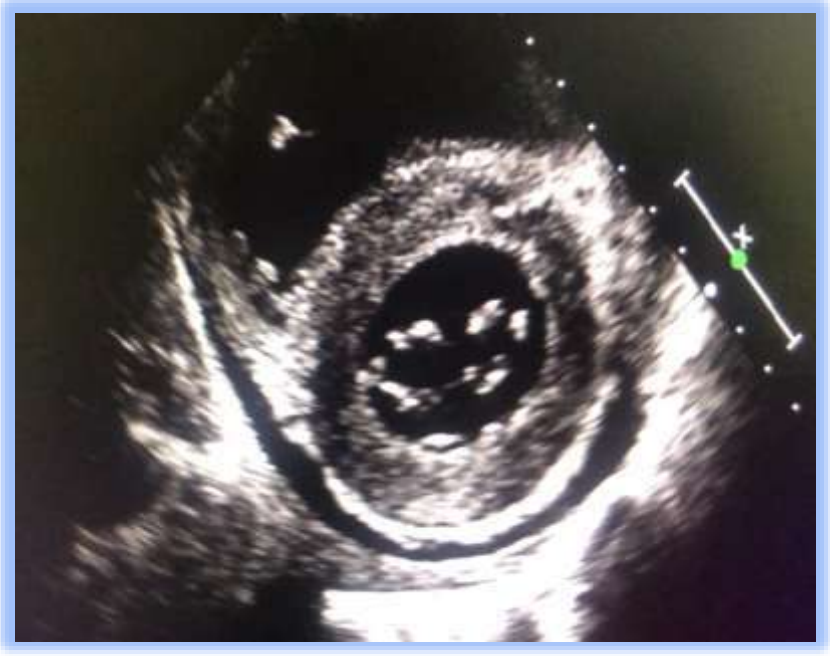
- Preserved EF
- Pericardial effusion
- LV/RV Hypertrophy ,
- ”granular sparkling”
- Diastolic disfunction
- Atrial dilatation

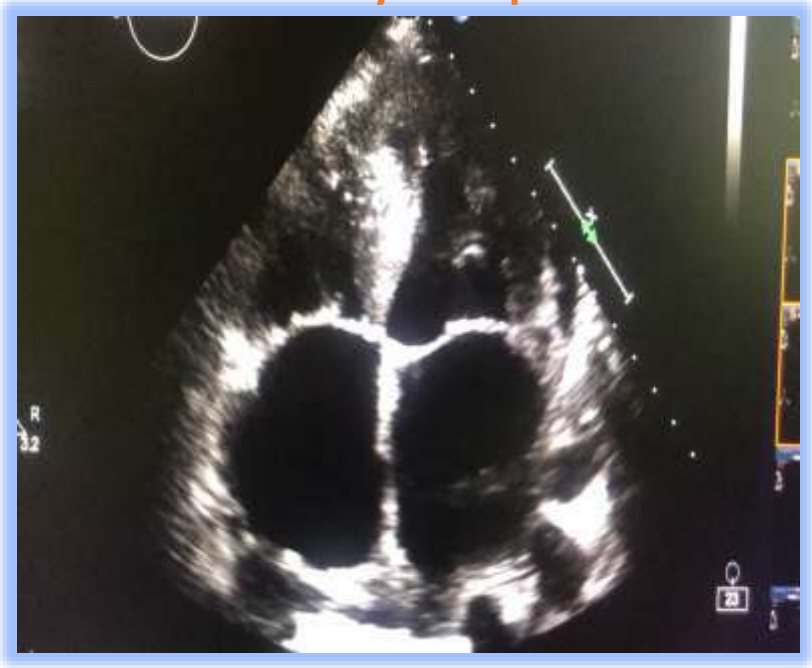
reduced strain in the basal and mid segments
relatively preserved in the apical region
Especiaaly in the early stages of disease



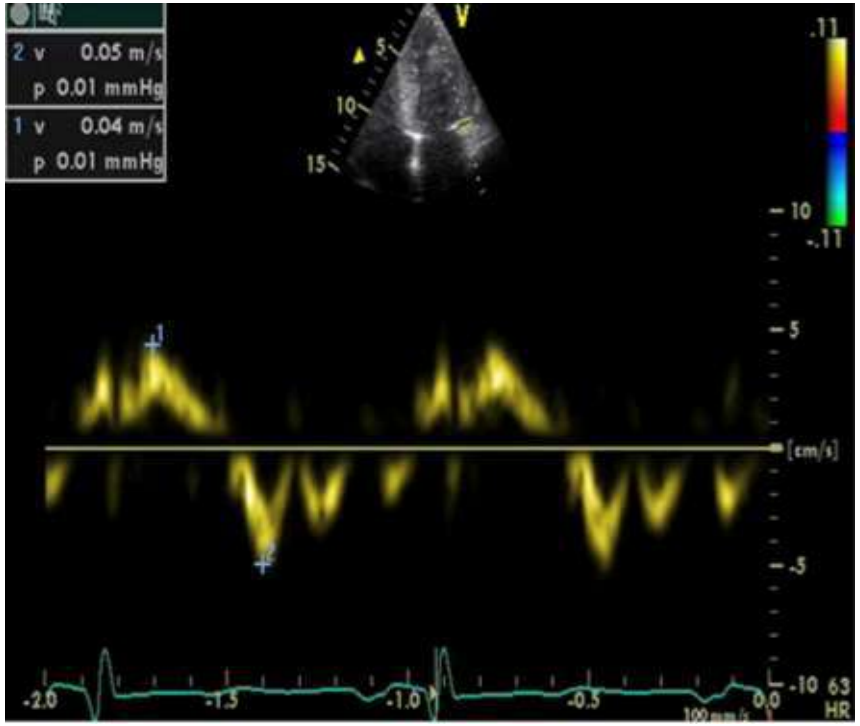
“cherry on top”







ECHO



- Increasing E/A ratio
- Normal E wave velocity
- Reduction A wave velocity

Reduction of mitral annular TD velocities

- Diastolic disfunction progresses from relaxation impairment to restrictive pattern
- Advance DD, impact on ventricular performance
- Although normal LVEF, reduction DF
  AL-CA tend to more restrictive, ATTR-CA tend to greater LV thickness

Apical sparing pattern …

- Apical sparing alone was not found highly sensitive neither specific imaging biomarkers
- Present 1/3 of non-CA patients
- 1/10 of healthy subjects

- *CKD*
- *Dannon disease*
- *Aortic Stenosis without CA-*

Lower specifity of apical sparing conditions

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2024) 25, 754–761
https://doi.org/10.1093/ehjci/jeae021
ORIGINAL PAPER

Limitations of apical sparing pattern in cardiac amyloidosis: a multicentre echocardiographic study

JASE
JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY

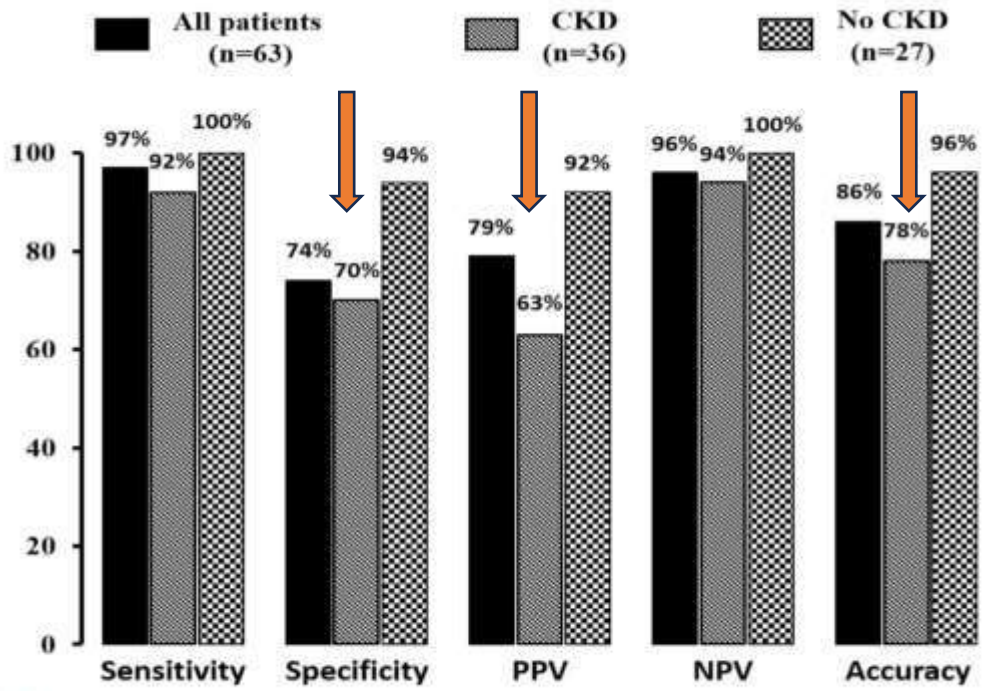
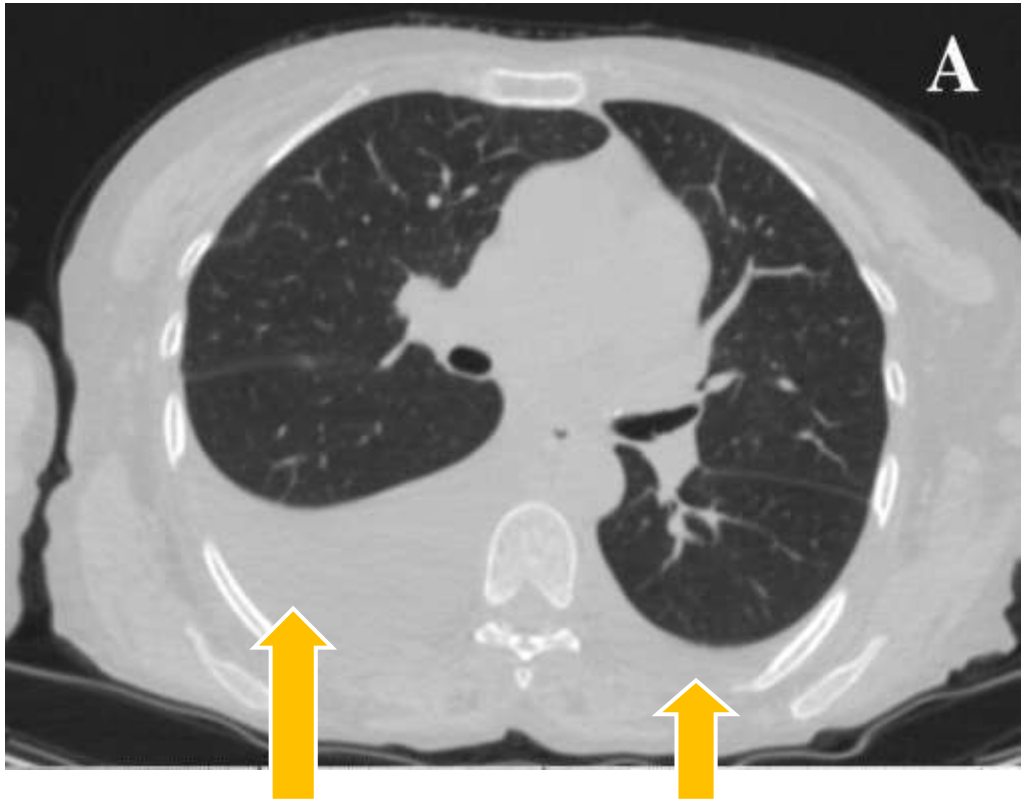


Figure 1 Bar graph depicting statistical measures of performance of an ASP for diagnosis of CA. *NPV*, Negative predictive value; *PPV*, positive predictive value.

Journal of the American Society of Echocardiography
Volume 33 Number 7

Chest Radiography

- Pleural effusion (bilateral)



Labortary tests

- Creatinin ↑
- UA – protein+
- Troponin I ↑ (apoptotic effect)
- ↑↑ NT – pro BNP (direct toxic effect)

NT-pro-BNP

- biomarker of clinical response
- Progression of illness
- Response to therapy

Richards DB, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, et al. Therapeutic clearance of amyloid by antibodies to serum amyloid P component. N Engl J Med 2015;373:1106- 14

Do Laboratory tests pedict Prognosis?

- NT-pro-BNP
- Cardiac troponin T
- sFLC

AL-CA prognosis

+++ point

NT-pro BNP≥ $1800 pg/mL$
Troponin ≥ 0.025ng/mL
FLC difference- ≥18mg/dL

Median survival is 3.5-4.1month

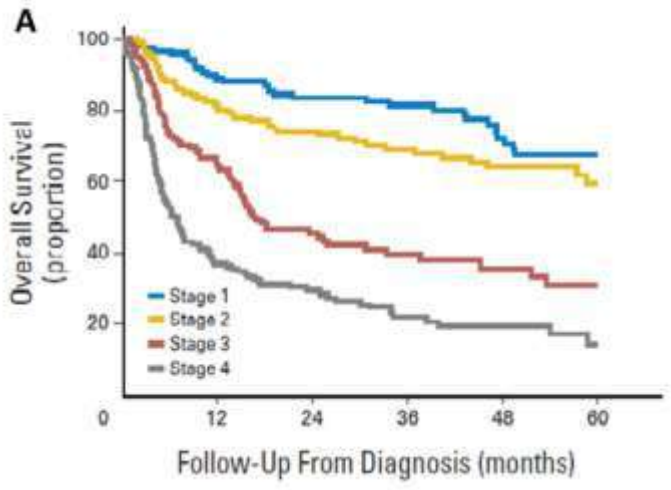
AL-CA and Mayo Clinic Staging System

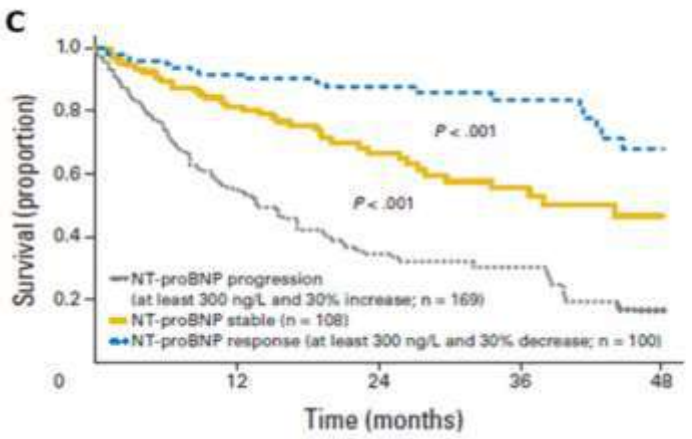
Table 4 Prognostic staging scores in AL and ATTR amyloidosis

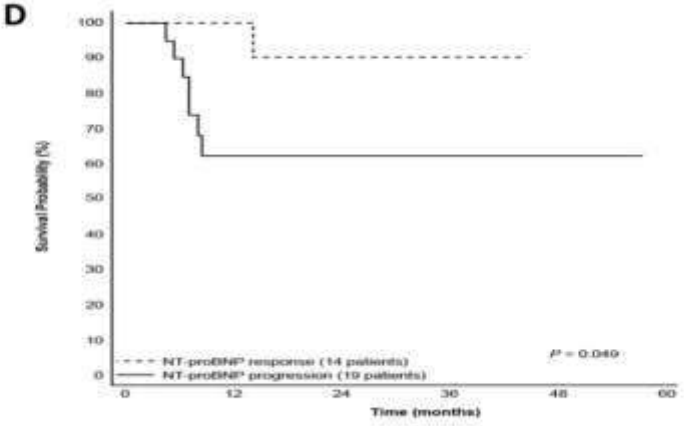
Kumar et al.[11] (Mayo) AL	Lilleness et al.[16] (BU) AL	Gregan et al.[17] (Mayo) ATTRwt	Gilmore et al.[18] (NAC) ATTRv & ATTRwt	Cheng et al.[19] ATTRv & ATTRwt
Staging parameters: FLC-diff ≥18 mg/dL Troponin T ≥0.025 ng/mL NT-proBNP ≥1800 pg/mL	**Staging parameters:** Troponin I >0.1 ng/mL NP >81 pg/mL	**Staging parameters:** Troponin T >0.05 ng/mL NT-proBNP >3000 pg/mL	**Staging parameters:** eGFR <45 mL/min/1.73 m² NT-proBNP >3000 pg/mL	**Scoring parameters:** 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)

Stage	5-year survival	Stage	Median survival	Stage	4-year survival/ median survival	Stage	Median survival	Score	Median survival
Stage I (0 parameters)	68%	Stage I (0 parameters)	Not reached	Stage I (0 parameters)	57% 66 months	Stage I (0 parameters)	69.2 months	Score 1–3	90.5 months
Stage II (1 parameter)	60%	Stage II (1 parameter)	112.8 months	Stage II (1 parameter)	42% 40 months	Stage II (1 parameter)	46.7 months	Score 4–6	38.5 months (Mayo) 36 months (NAC)
Stage III (2 parameters)	28%	Stage III (2 parameters)	51.6 months	Stage III (2 parameters)	18% 20 months	Stage III (2 parameters)	24.1 months	Score 7–9	20.3 months (Mayo) 19.8 months (NAC)
Stage IV (3 parameters)	14%	Stage IIIb (2 parameters and BNP >700 pg/mL)	12 months						

AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BNP, B-type natriuretic peptide; 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.



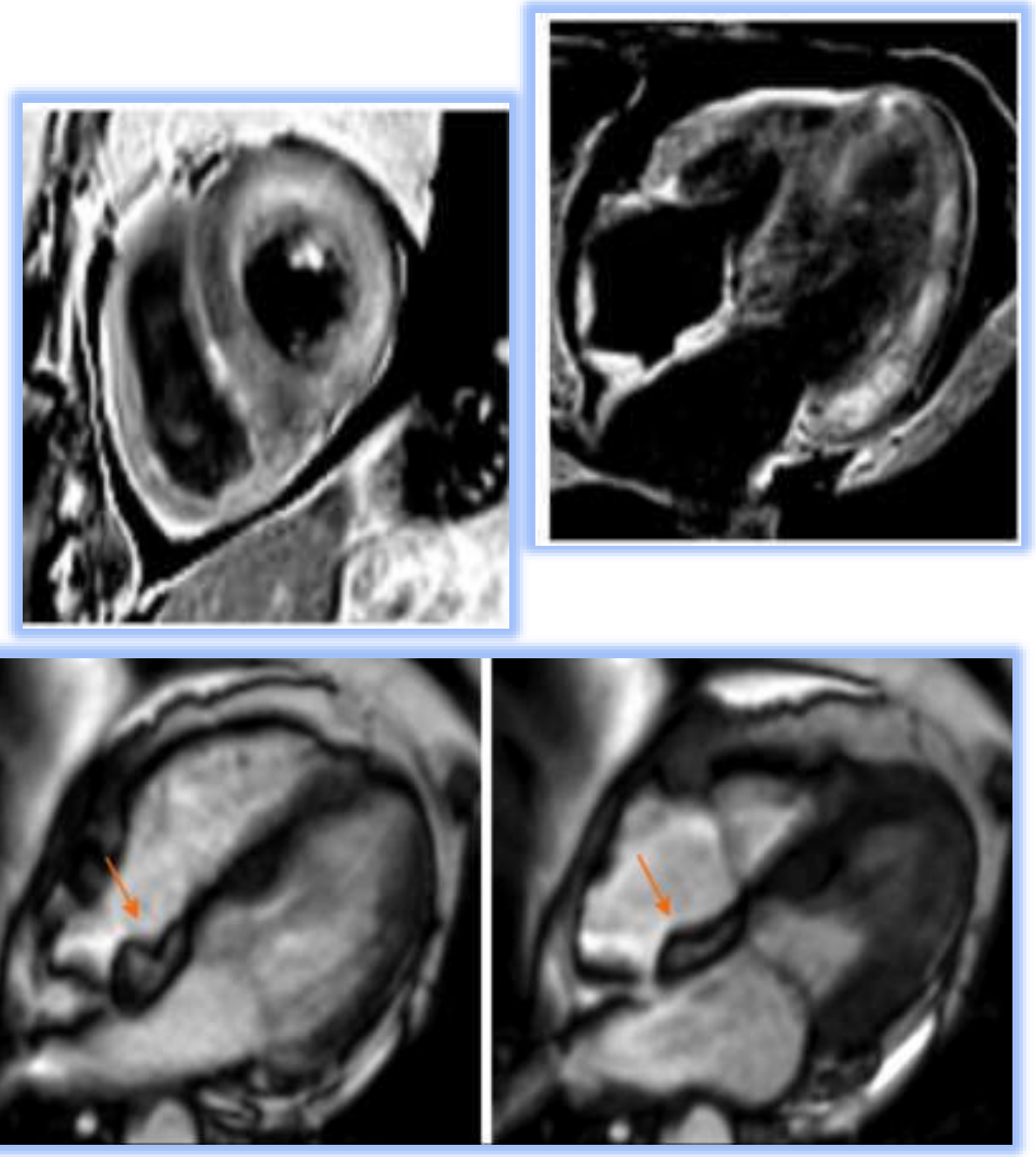


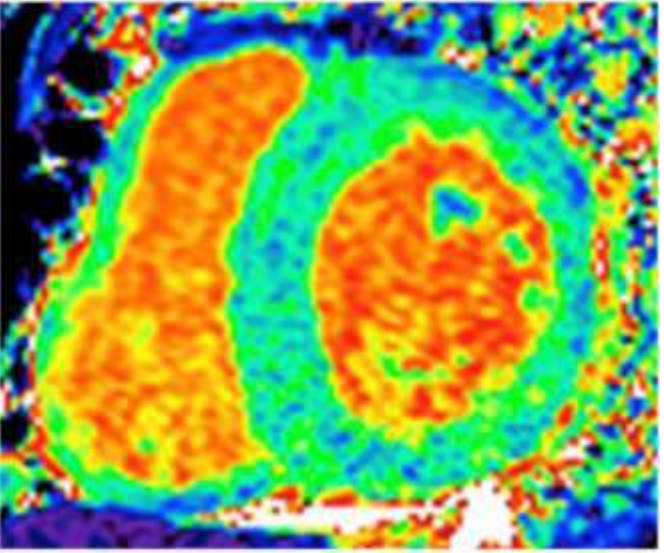


J Clin Oncol. 2012;30(9):989-995.doi:10.1200/JCO.2011.38.5724

CMR-III STEP

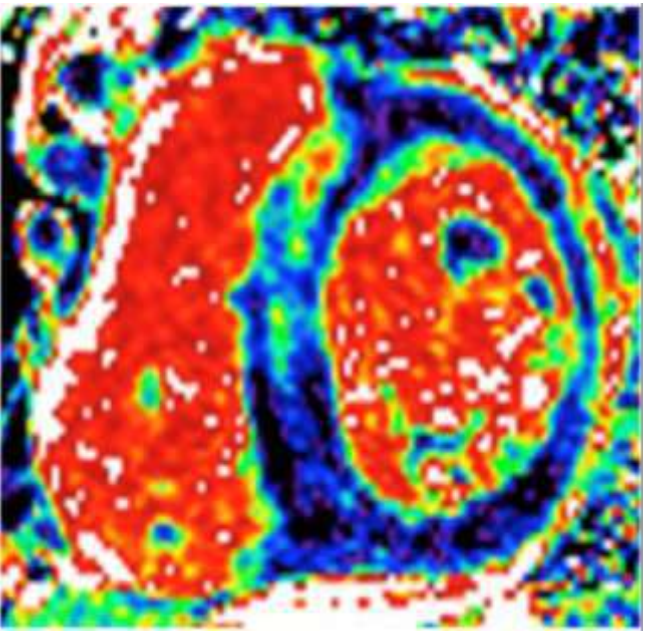
- LV/RV hypertrophy
- Biatrial dilatation
- Atrial septal hiperyophy (>6mm-20% cases)
- Pericardial and pleural effusion
- **Subendocardial/transmural fibrosis**
- **High T1 values and extracellular fibrosis (T1, ECV)!!!!**





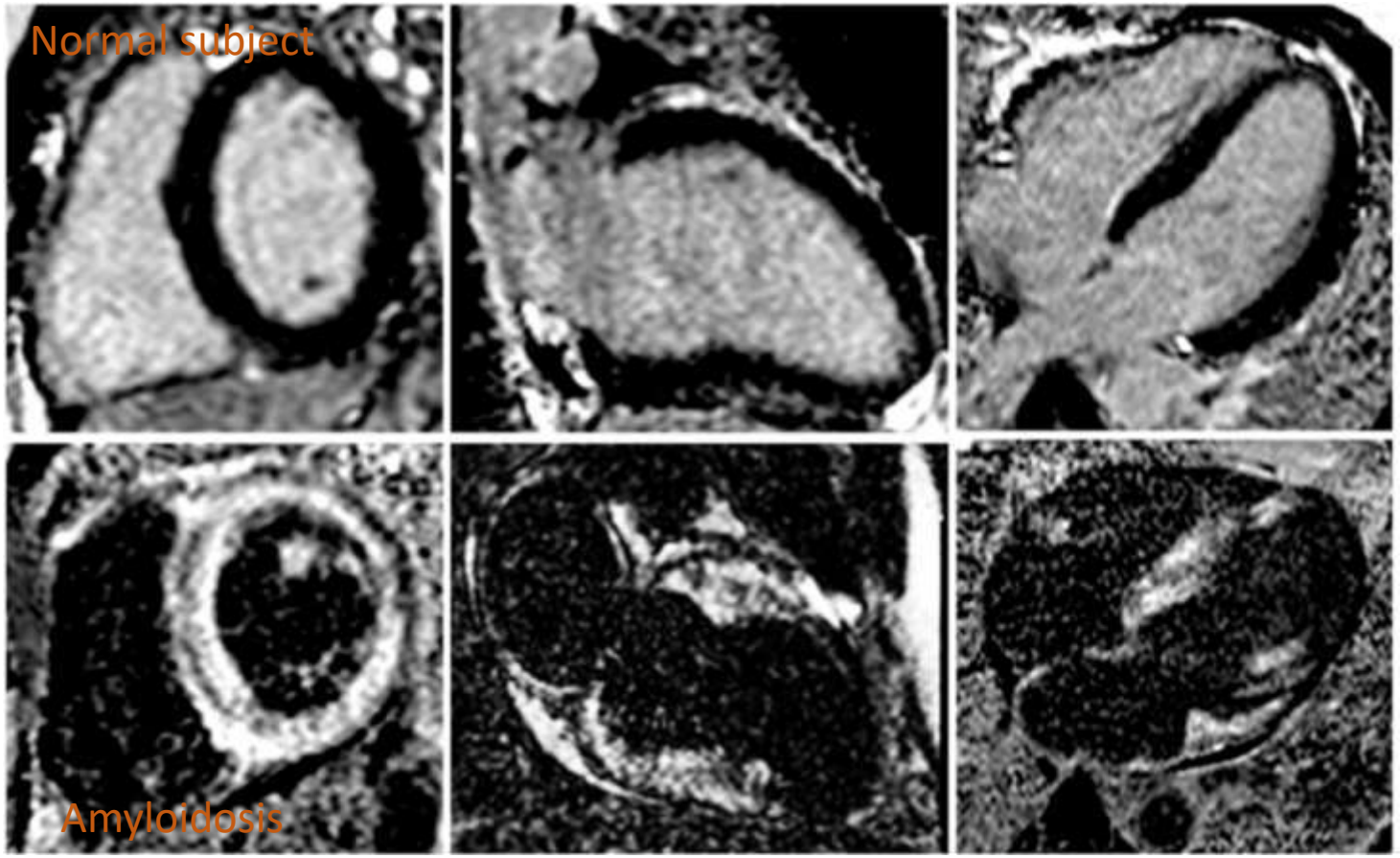
Nativ TI

ECV



Post contrast TI

Increased both native TI (1260msn) and ECV (76%)
Even in the absence of LGE informative
>44% prognostic for mortality



Late Gadolinium Images

Sensitvity 85%, Specifity 92%
Transmural, circumferential LGE+ apical sparring

TI scout images

AL-type amyloidosis

Normal health subject

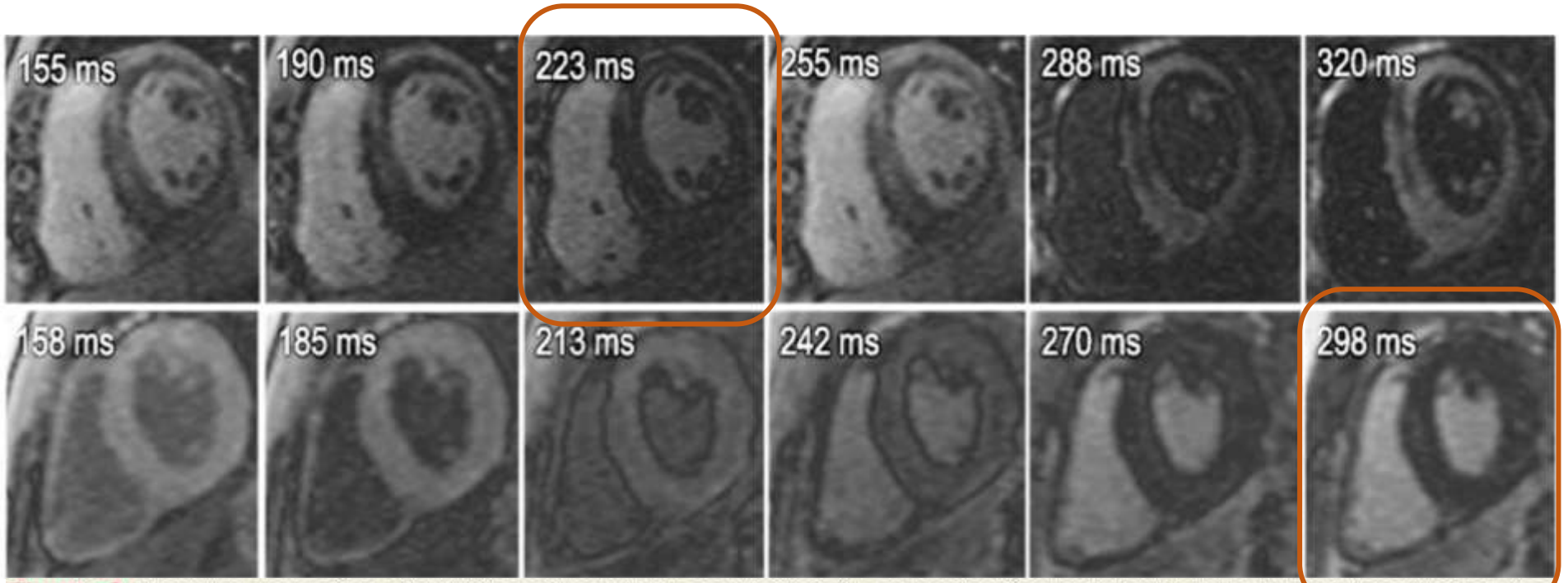


Figure 8 TI scout sequences in a patient with confirmed AL-type amyloidosis (upper row) and in a normal subject (lower row). In amyloidosis, the myocardium contains more GBCA than the blood pool, and thus it reaches the null point earlier than the blood pool, at around 223 ms. On contrary, in the case of the healthy subject, blood pool becomes black first, and then, the myocardium reaches the null point at 298 ms. Inspection of the TI scout pattern is always useful for the CMR diagnosis of cardiac amyloidosis by identifying abnormal Gadolinium kinetics.

- TI scout pattern always useful for diagnosing of CA by identifying abnormal gadolinium kinetics
- Myocardium contains GBCA, reaches null point earlier

European Heart Journal - Cardiovascular Imaging (2020) 21, 833–844
doi:10.1093/ehjci/jeaa063

Testing for monoclonal protein

ATTR-no blood tests for TTR identifying
AL-serum/urine immunofixation (99% sensitivity)

IV STEP:

sFLC-

- Alone is not specific for AL
- Increased in Renal failure

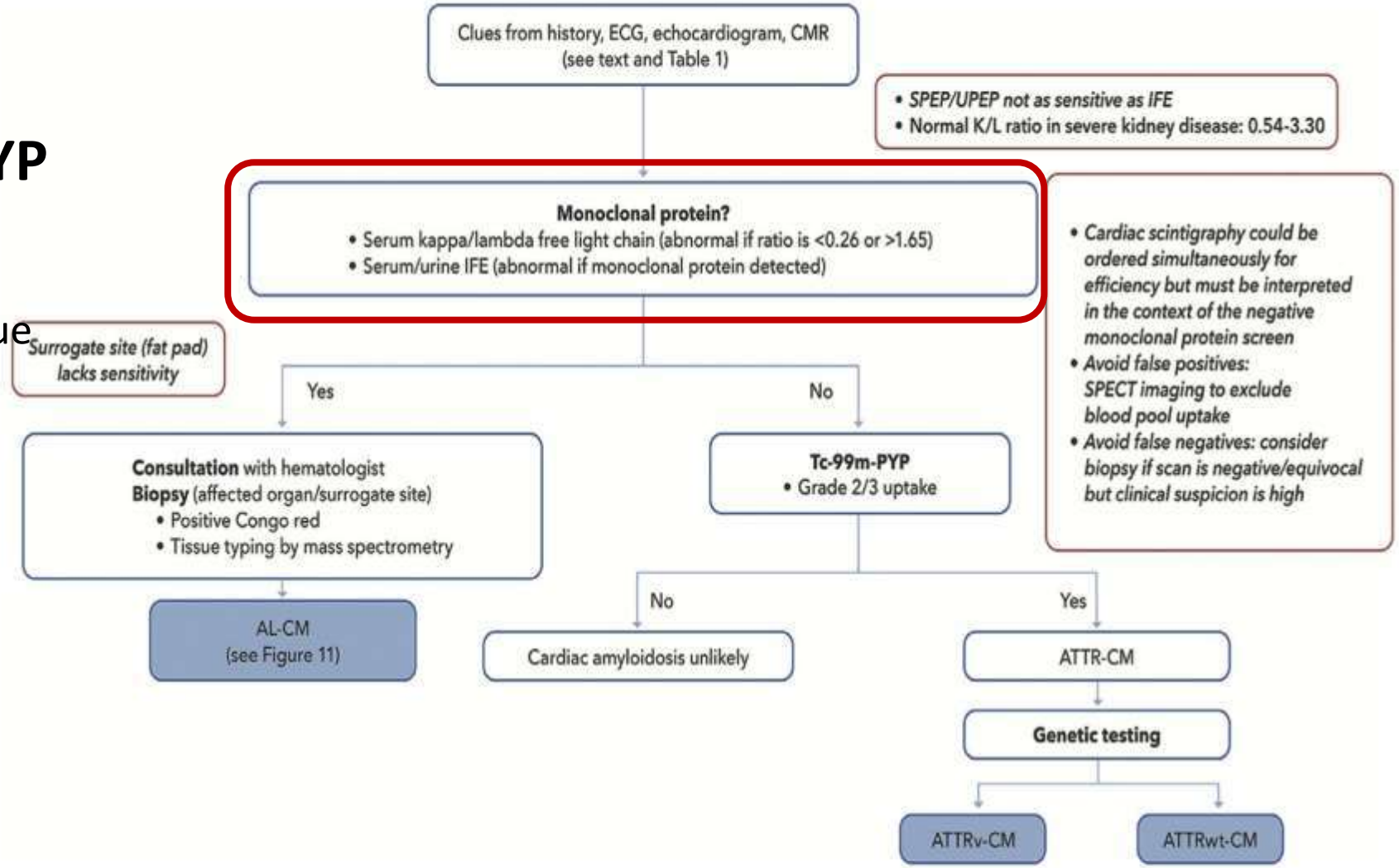
Table 3 Serum and urine tests to rule out AL amyloidosis

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.
[a]If any of these tests are abnormal, bone scintigraphy should not be used to establish the diagnosis of transthyretin amyloidosis.
[b]In 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 m^2 (up to 3.1 if in dialysis) can typically be considered normal. This correction is not applicable to Siemens N Latex assay.

- **False positives in the PYP**
  - Light Chain Amyloidosis (AL)
  - Hydroxychloroquine Toxicity
  - Suboptimal Scintigraphy Technique

FIGURE 3 Diagnostic Algorithm for Cardiac Amyloidosis



AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM = amyloid transthyretin cardiomyopathy; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; CMR = cardiac magnetic resonance; ECG = electrocardiogram; IFE = immunofixation electrophoresis; K/L = kappa/lambda; PYP = pyrophosphate; SPECT = single-photon emission computed tomography; SPEP/UPEP = serum/urine protein electrophoresis.

Who gets referred to PYP(pyrophosphate) imaging?

- Suspicious echo
- Suspicious CMR
- Aortic stenosis
- Relatives of ATTRv types
- Extra cardiac TTR- tendon rupture

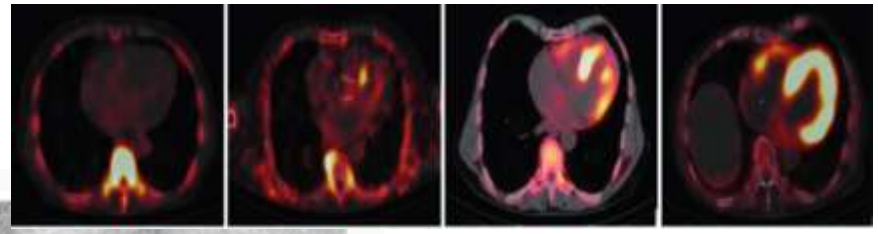
ATTR

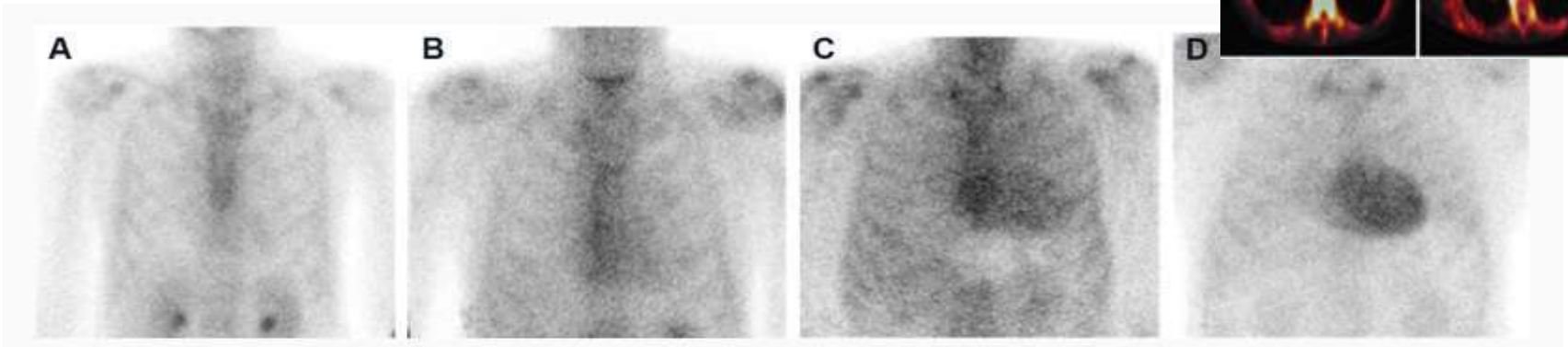
=

+ ve PYP

+

-ve serum/ urine





Technetium-99m pyrophosphate bone scan at 1 h: (A) visual score 0; (B) visual score 1; (C) visual score 2; and (D) visual score 3.

- ATTR++++
- AL-/or mild+
- Grade II and III — that is, uptake equal to or greater than bone tissue — are diagnostic for ATTR-CA.
- Sensitivity and specificity are 100%."

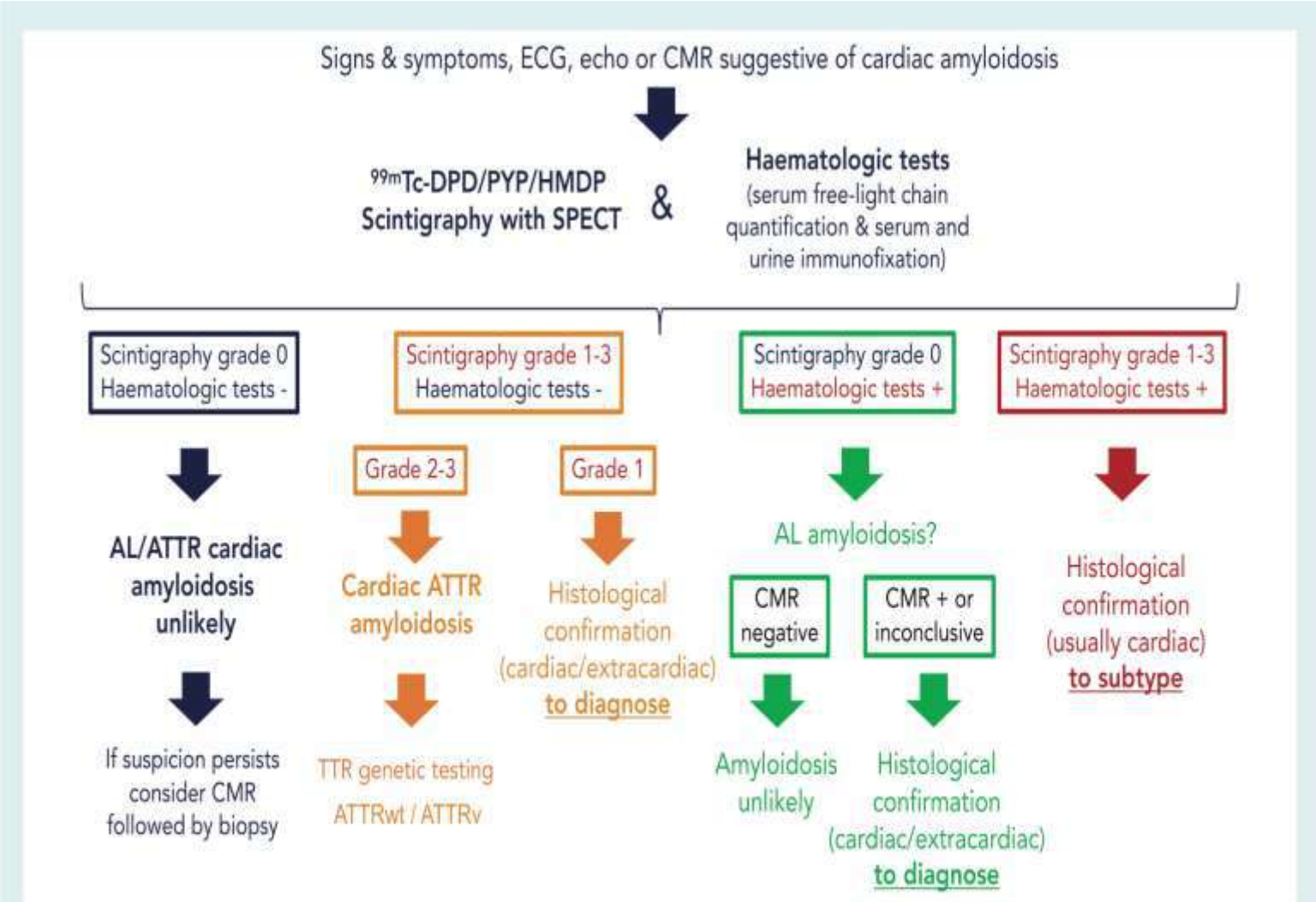


Figure 4 Diagnostic algorithm for cardiac amyloidosis. ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; AL, light-chain amyloidosis; CMR, cardiac magnetic resonance; ECG, electrocardiogram; SPECT, single photon emission computed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

European Heart Journal – Cardiovascular Imaging (2014) **15**, 1307–1315
doi:10.1093/ehjci/jeu158

Cardiac biopsy always the referenace standard?

Challenge 1

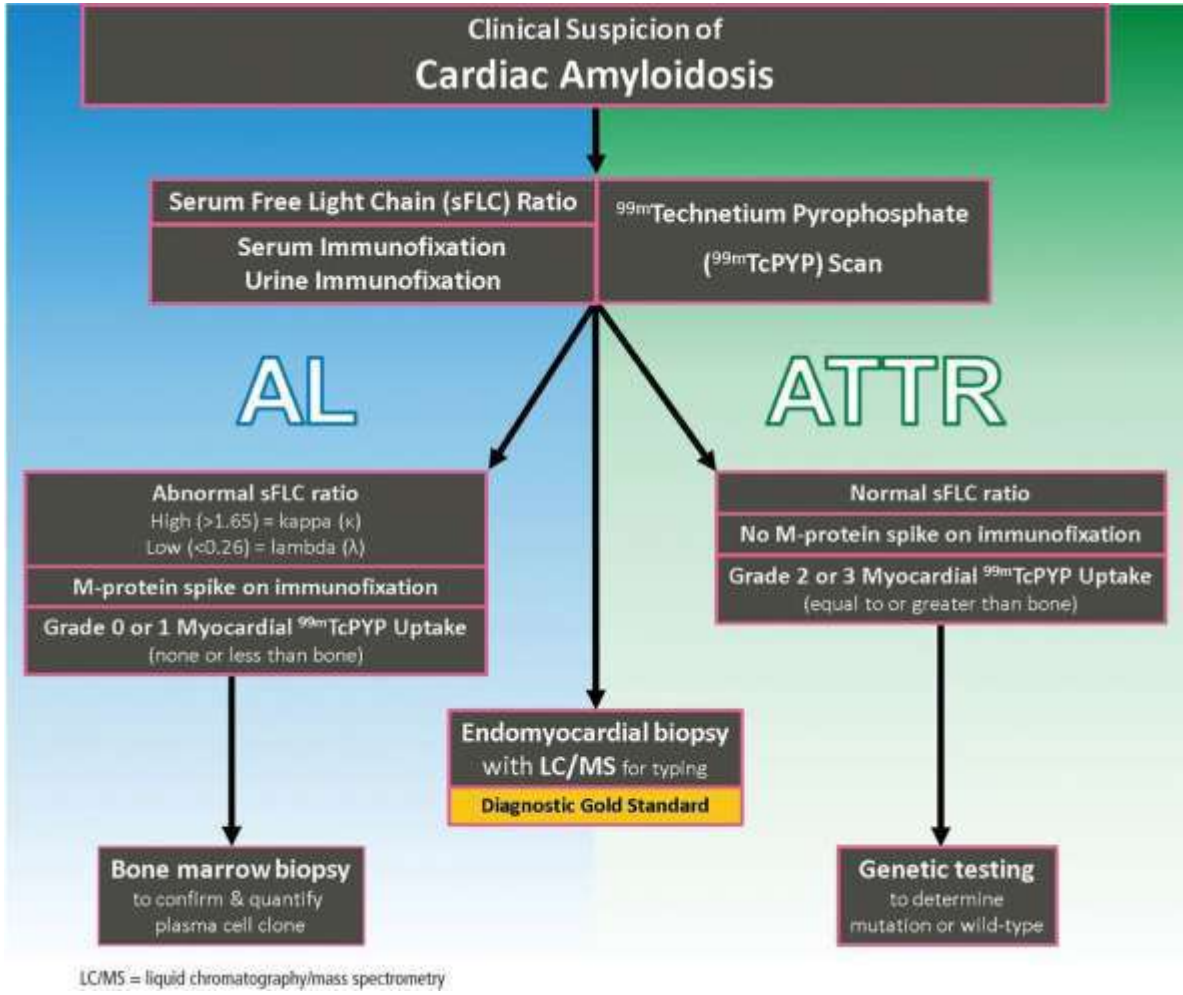
- Renal biopsy-+++
- Heart biopsy-has high risk, expensive and rarely performed
- Rectal biopsy-more invasive, not sensitive
- Abdominal fat aspiration-highly variable sensitivity (60-80% AL, 65-85% ATTR)

Challenge 2

- congo red does not identify the type
- Not the only step in the diagnosis

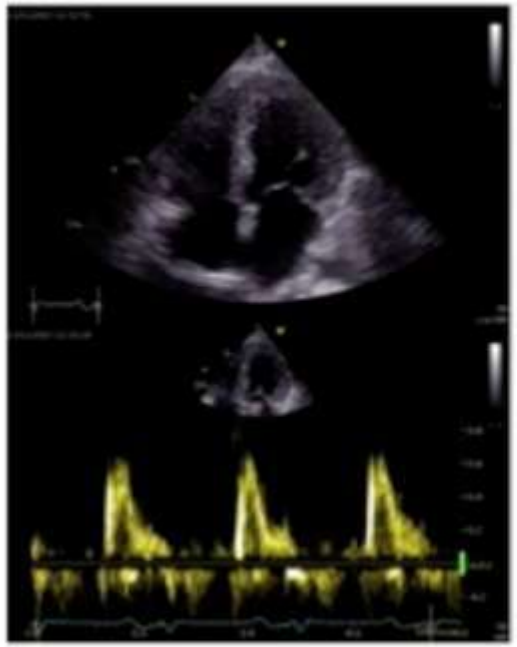
NEGATIVE BİOPSY DOES NOT RULE OUT CA!!

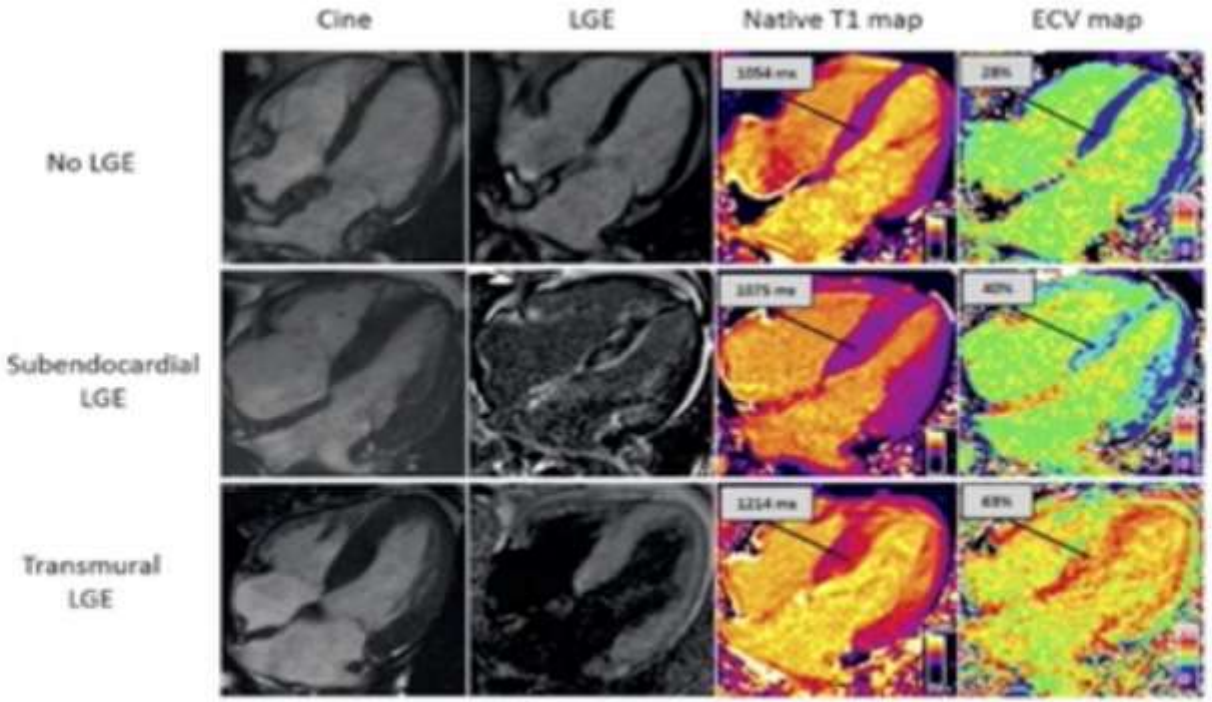
Depends on operator, pathologist and how much tissue removed



Cleveland Clinic Journal of Medicine December 2017, 84 (12 suppl 3) 12-26; DOI: https://doi.org/10.3949/ccjm.84.s3.02

What is the best imaging modality?





The most useful and appropriate method varies at each step of the patient pathway

What is the best imaging modality?

Multimodality imaging

- Multimodality approach beyond the structure and function….
- Information on tissue composition

Table I **Role of various imaging techniques in the different steps of cardiac amyloidosis diagnosis and management (modified after[61])**

Phase of workup	Echocardiography	Cardiac MR[a]	Bone tracers scintigraphy[b]
Diagnostic suspicion	+++	++	+
Definite diagnosis	++	++	+++
Early diagnosis	+	+	+++
Functional evaluation	+++	+++	-
Prognostic stratification	+	+++	+
Amyloidosis burden	+	+++	+
Response to therapy	+	++	?

-, not useful; +, possibly useful; ++, useful, to be considered; +++, very useful, recommended; ?, unknown; ATTR, transthyretin-related amyloidosis; MR, magnetic resonance.
[a]Late gadolinium enhancement and native T1 mapping.
[b]For ATTR amyloidosis.

European Heart Journal - Cardiovascular Imaging (2020) 21, 833–844
doi:10.1093/ehjci/jeaa063

Treatment Approaches

Treatment of Cardiac Complications and Comorbidities in Cardiac Amyloidosis

Aortic Stenosis

- Severe AS confers worse prognosis.
- Concomitant ATTRwt risk factor for periprocedural AV block.
- TAVR improves outcome in amyloid-AS.

Thromboembolism

- High risk, common.
- Anticoagulate if AF, consider in selected cases in SR.
- Anticoagulate independent of CHA_2DS_2-VASc score.

Conduction disorders

- PPM according to standard indications.
- Consider CRT if high paced burden expected.

Heart failure

- Control fluid.
- Diuretics.
- Deprescribe B-Blockers.
- Avoid ACEI/ARB.
- LVAD not suitable for most patients.
- Heart transplant for selected cases.

Atrial Fibrillation

- Amiodarone, preferred AA.
- Use digoxin cautiously.
- Electrical CV has significant risk of complications and AF recurrence is frequent.
- Exclude thrombi before electrical CV.
- AF ablation data scarce and controversial.

Ventricular arrhythmias

- ICD for secondary prevention.
- ICD in primary prevention usually not recommended.
- Transvenous ICD preferred over subcutaneous ICD.

European Journal of Heart Failure (2021) 23, 512–526 doi:10.1002/ejhf.2140

HF treatment in Amyloidosis

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
HF setting					
Loop or thiazide diuretics	Recommended	Recommended	Recommended	Recommended, but avoid underfilling and worsening renal function from restrictive physiology	Recommended
Nitrates or carperitide (AHF)	No recommendation	No recommendation	No recommendation	No recommendation	Might be considered
Catecholamines, PDE inhibitor (AHF)	No recommendation	No recommendation	No recommendation	No recommendation	Might be considered
Beta-blockers	Not recommended, deprescribe (should be avoided)	Avoid or very cautious use	Avoid or very cautious use	No data for benefit; may not be tolerated given fixed stroke volume (should be avoided)	Tolerated dosing might be considered
ACE inhibitor/ARB	Not recommended (should be avoided)	Avoid or very cautious use	Avoid or very cautious use	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction (should be avoided)	Tolerated dosing might be considered
Sacubitril/valsartan	No recommendation	No recommendation	No recommendation	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction (should be avoided)	No recommendation
MRA	No recommendation	No recommendation	Recommended	Might be considered in conjunction with loop diuretics if adequate blood pressure and renal function	Tolerated dosing might be considered

Rapezzi et al. J Am Coll Cardiol 2022;79:1288–1303

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
AF/flutter/tachycardia setting					
Digoxin	Might be considered[b]	Avoid or very cautious use[b]	Avoid or very cautious use[b]	Might be considered; use cautiously[b]	Not recommended (should be avoided)[a]
Amiodarone	Might be considered (first choice)[a]	No recommendation	Might be considered (first choice)[a]	Might be considered (first choice)[a]	No recommendation
Beta-blockers	Not recommended (should be avoided)[a]	Avoid or very cautious use[a]	Avoid or very cautious use[a]	Might be considered[a]	Case-by-case decision (may be considered)[a]
Non-DHP CCB: ATTR-CA, preserved LV function	No recommendation	Avoid or very cautious use[a]	Avoid or very cautious use[a]	Avoid whenever possible[a]	Case-by-case decision (may be considered)[a]
Non-DHP CCB: ATTR-CA, reduced LV function					Not recommended (should be avoided)[a]
Non-DHP CCB: AL-CA				Not recommended (should be avoided)[a]	Not recommended (should be avoided)[a]
Anticoagulation regardless of CHA_2DS_2-VASc score?	Yes (recommended)[a]	No recommendation	Yes (recommended)[a]	Yes (recommended)[a]	No recommendation
Anticoagulation in SR?	Might be considered[a]	No recommendation	No recommendation	Might be considered[a]	No recommendation

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Treatment

TABLE 2
Amyloid-specific pharmacotherapies

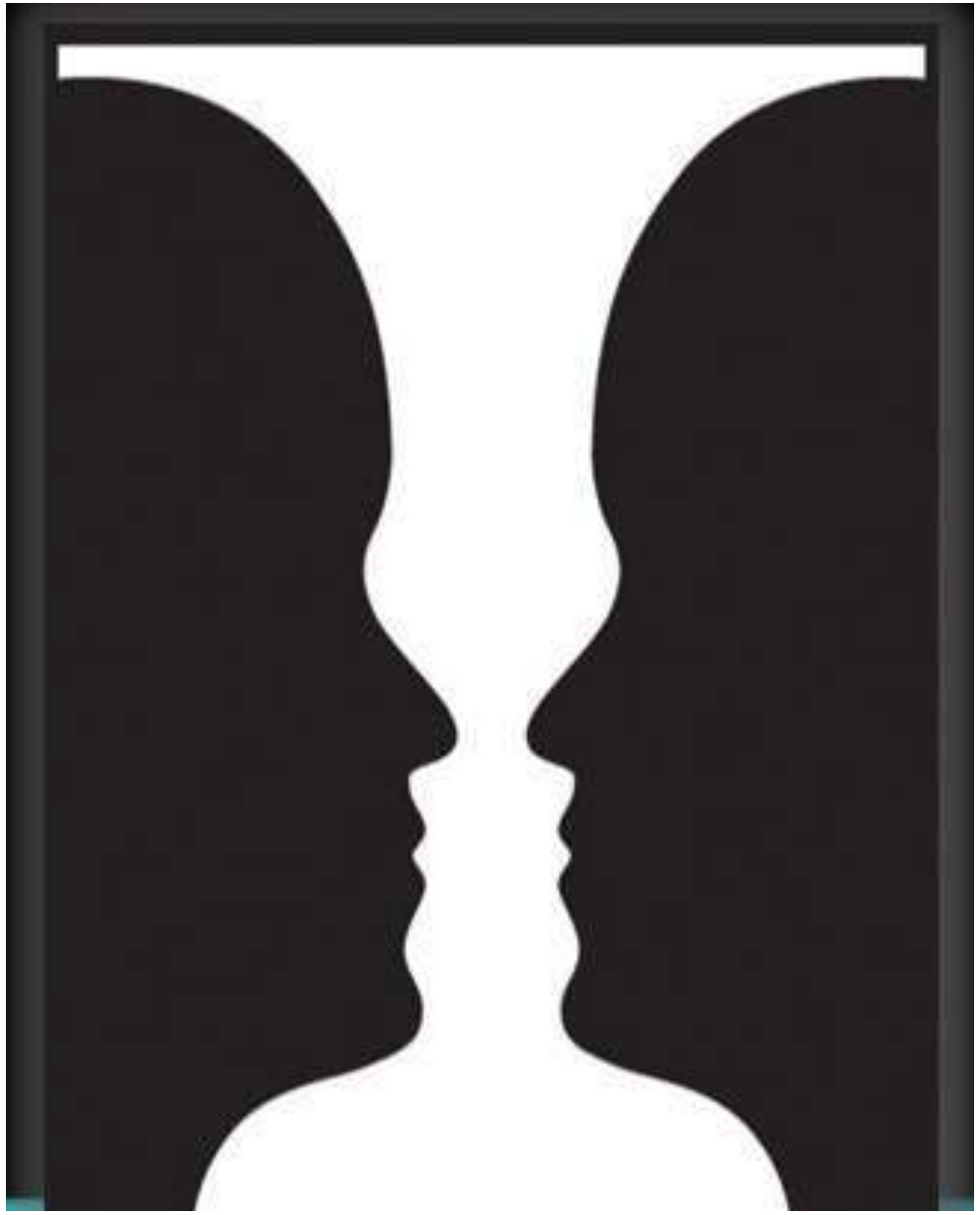
AL			ATTR		
Anti-plasma cell therapies	*Alkylating agents*	Melphalan	TTR silencers	*siRNA*	Patisiran
		Cyclophosphamide		*ASO*	Inotersen (IONIS-TTR$_{Rx}$)
	Proteasome inhibitors	Bortezomib	TTR stabilizers	Diflunisal	
		Ixazomib		Tafamidis	
	Immunomodulators	Pomalidomide		Tolcapone	
	Anti-CD38 monoclonal antibody	Daratumumab		AG10	
Anti-amyloid antibody	NEOD001		Fibril disruptors	Doxycycline + TUDCA	
				Green tea extract	
				Curcumin	
				Anti-amyloid antibody	PRX004
Ubiquitous Anti-Amyloid Fibril Antibody					
Monoclonal IgG1 anti-SAP antibody					

AL = immunoglobulin (Ig) light chain amyloidosis; ASO = antisense oligonucleotide; ATTR = transthyretin amyloidosis; SAP = serum amyloid P component; siRNA = small interfering RNA; TTR = transthyretin protein; TUDCA = tauroursodeoxycholic acid

Cleveland Clinic Journal of Medicine December 2017, 84 (12 suppl 3) 12-26; DOI: https://doi.org/10.3949/ccjm.84.s3.02

CONCLUSION

- Amyloidosis is a multisystemic disease, clinical presentation depending on the pattern of organ involvement
- ECG and Echo findings often not typical
- Biopsies, considered the reference standard, high FP and FN rates
- Structure and function is not enough, information on the tissue composition important
- Multimodality imaging approach should be considered



" The truth and hidden beauty often await just beyond a shift in perspective."

THANK YOU FOR ATTENTION!