HFpEF Masterclasses
In centers of expertise

FRANCE

7th November 2024 - DAY 1
8th November 2024 - DAY 2

Gilbert HABIB

Cardiac amyloidosis

How to diagnose it?

Statement of financial interest

I currently have, or have had over the last 2 years, reveiced compensation of fees or research grant with the following companies:

- Actelion
- Abbott
- Amicus
- Astra Zeneca
- Boehringer
- Novartis
- General Electric
- Pfizer
- Sanofi Genzyme
- Alnylam
- BMS

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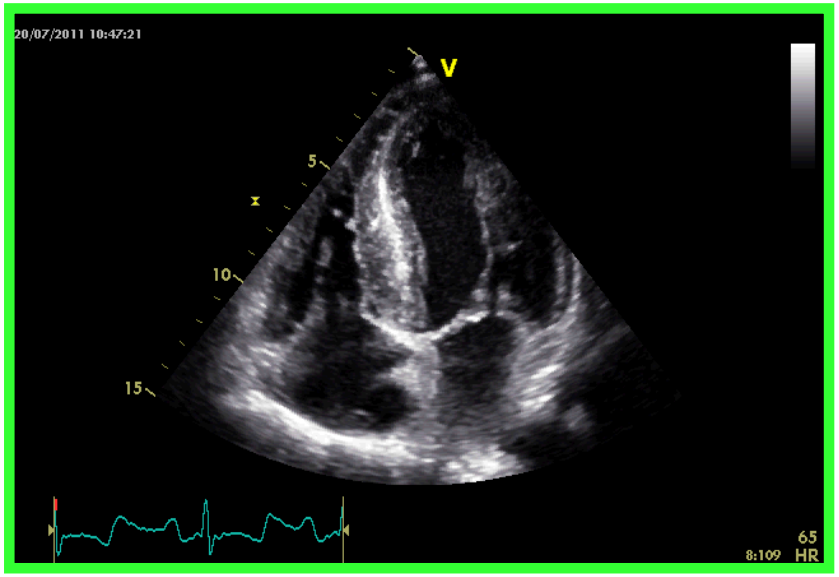
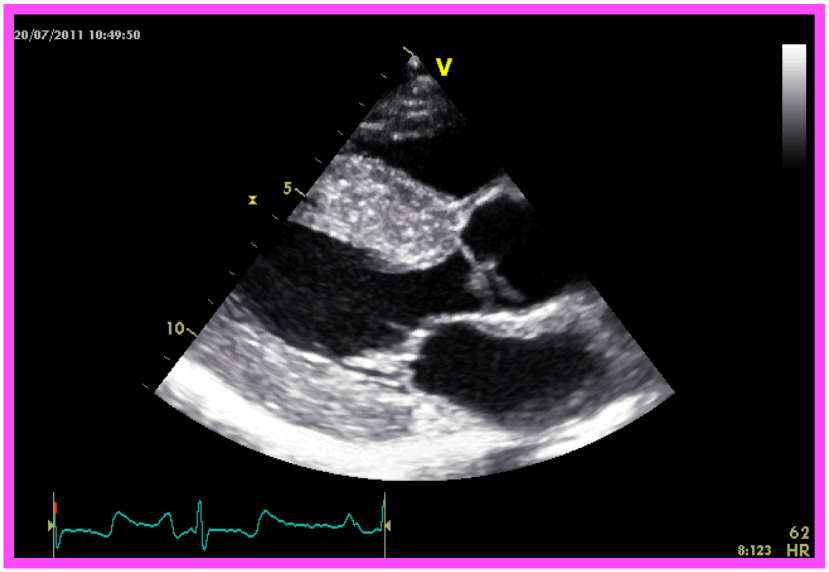
Cardiac amyloidosis

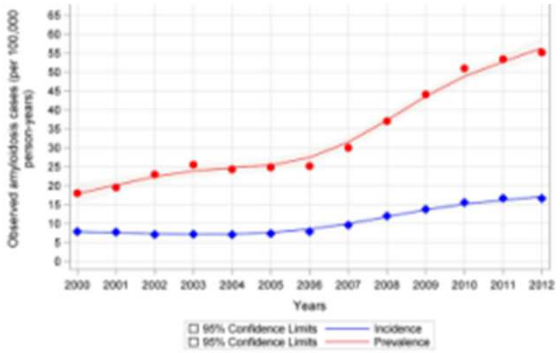
First, think about it !!!

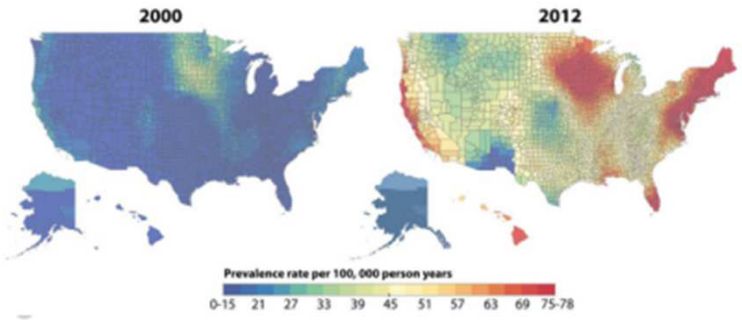
Cardiac amyloidosis: diagnosed too late ?

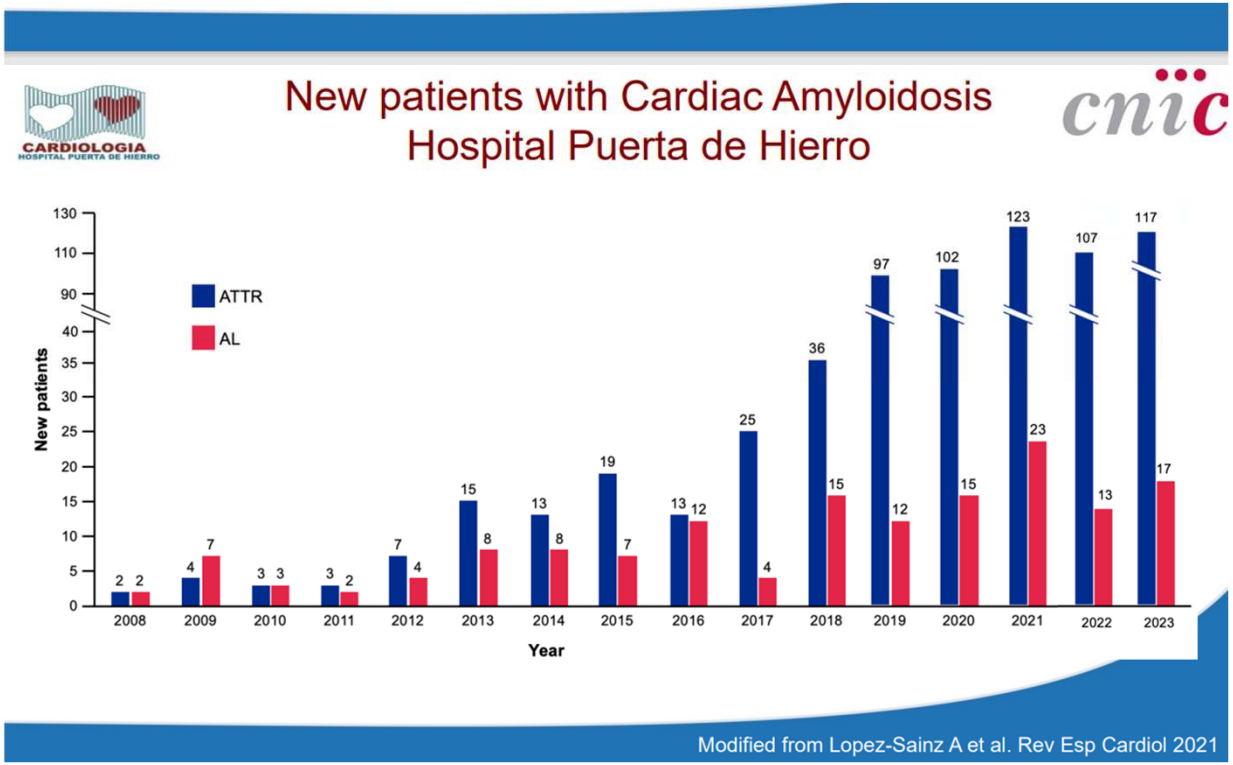




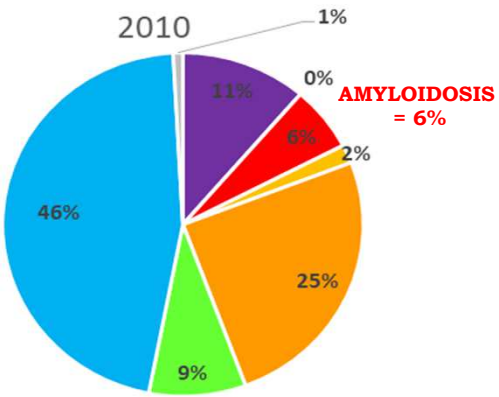
Cardiac amyloidosis is no longer a rare disease !

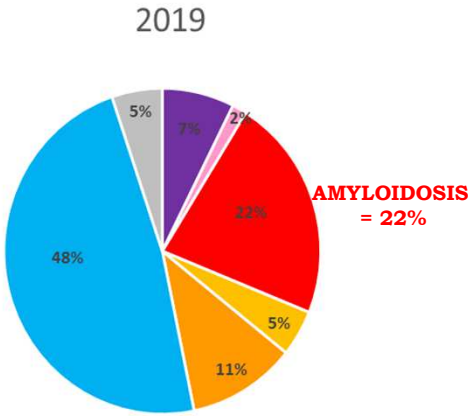






MARSEILLE REFERENCE CENTER ON CARDIOMYOPATHIES





46% HCM
25% DCM
11% LVNC
6% Amyloidosis
2% Fabry disease

48% HCM
11% DCM
7% NCVG
22% Amyloidosis
5% Fabry disease

Cardiac amyloidosis

How to diagnose it?

1. **Think about amyloidosis**
2. **Easy diagnosis in typical cases**
3. **Frequent difficult cases**
4. **Diagnostic algorithm**

Cardiac amyloidosis

How to diagnose it?

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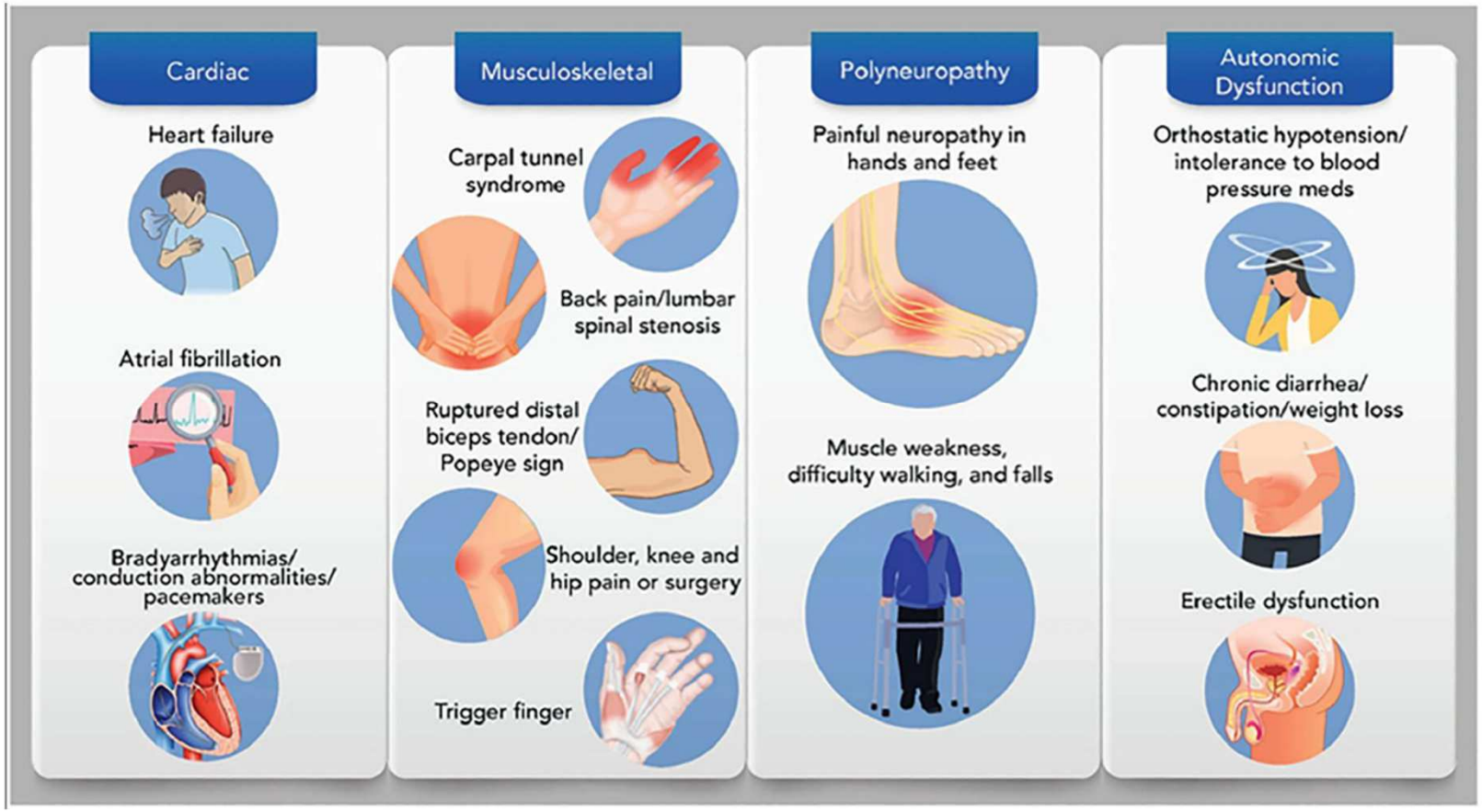
Red flags for amyloidosis suspicion

Symptoms that raise suspicion of cardiac amyloidosis

Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

Red flags for amyloidosis suspicion

Nativi-Nicolau Heart Fail Rev 2022

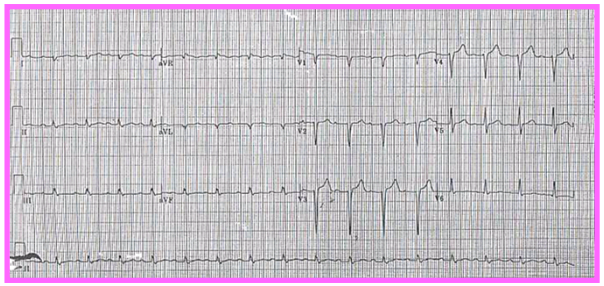


Imaging red flags

Garcia-Pavia et al Eur Heart J 2021

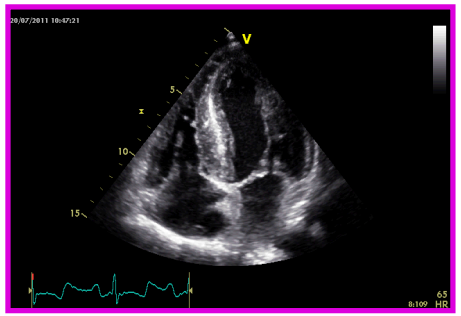
1. ECG

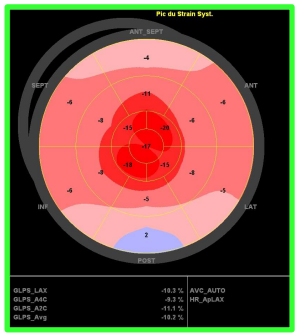
- ✓ *Decrease voltage*
- ✓ *AV conduction abnormalities*
- ✓ *Pseudo Q waves*



2. Echocardiography

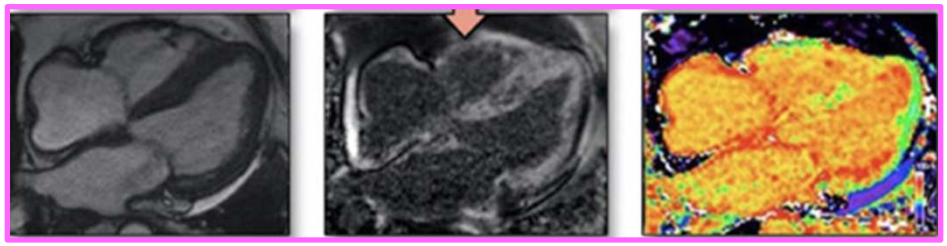
- ✓ *Biventricular hypertrophy*
- ✓ *Valvular thickening*
- ✓ *Apical sparing*





3. Cardiac MRI

- ✓ *Biventricular hypertrophy*
- ✓ *Diffuse subendocardial LGE*
- ✓ *Increase T1*



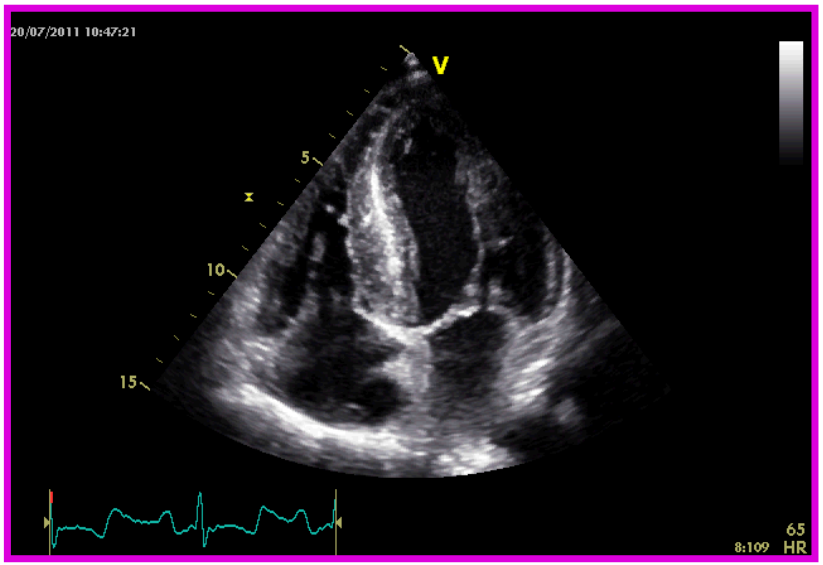
Cardiac amyloidosis

How to diagnose it?

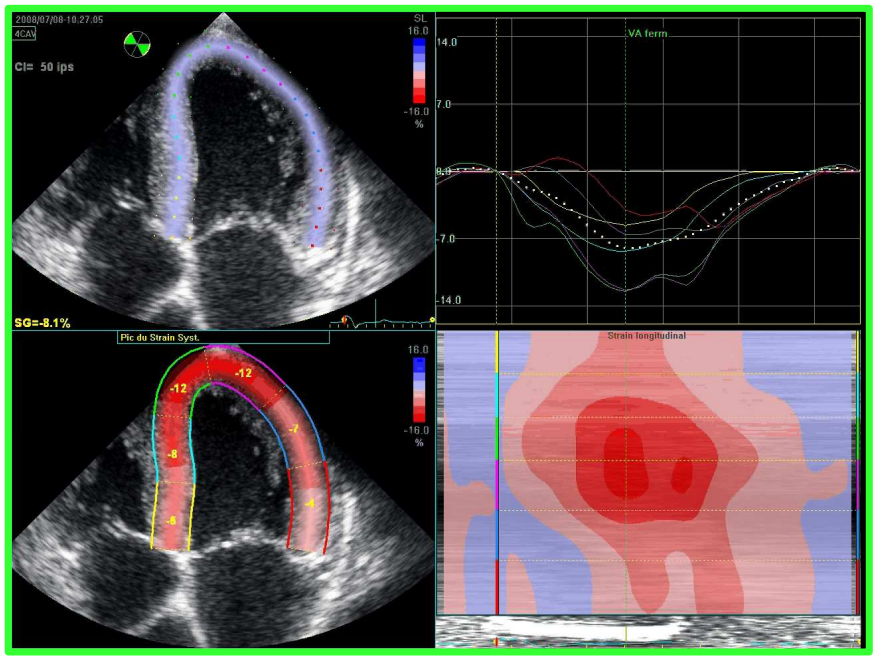
1. **Think about amyloidosis**
2. ***Easy diagnosis in typical cases***
3. **Frequent difficult cases**
4. **Diagnostic algorithm**

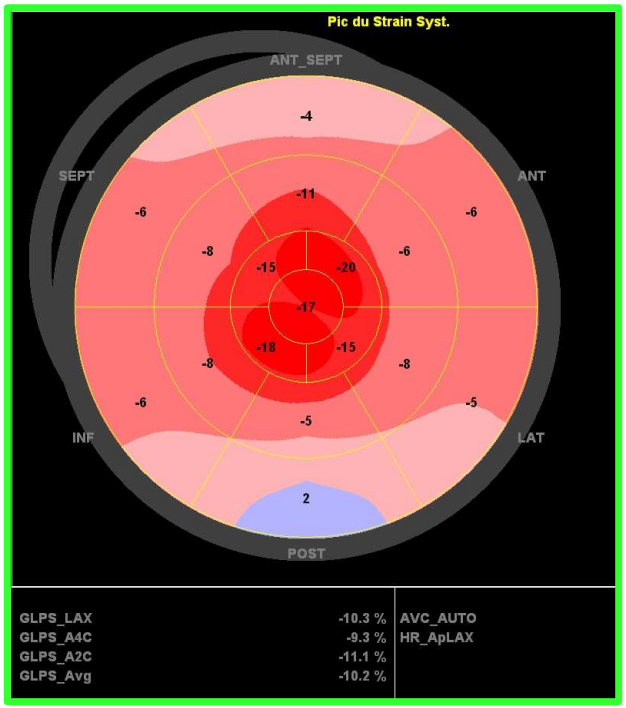
Amyloidosis: echo features

1. Concentric LV hypertrophy
2. Normal LVEF
3. Sparkling myocardial appearance
4. Atrial septal hypertrophy
5. Valvular thickening
6. Restrictive physiology (not always)



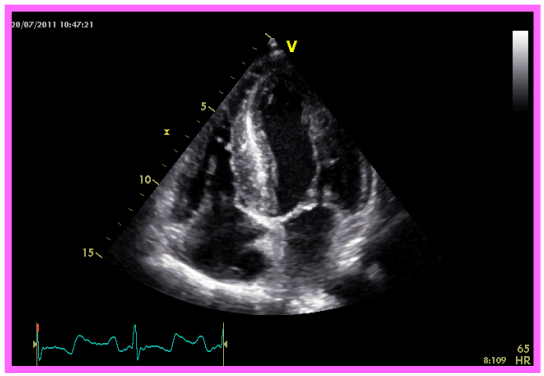
2D strain in cardiac amyloidosis

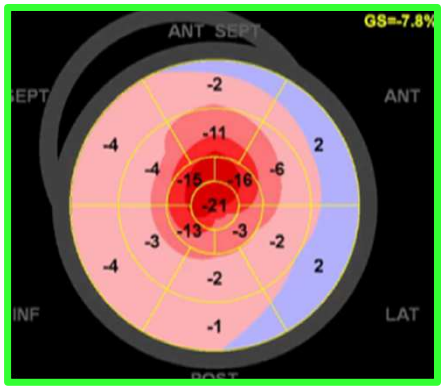


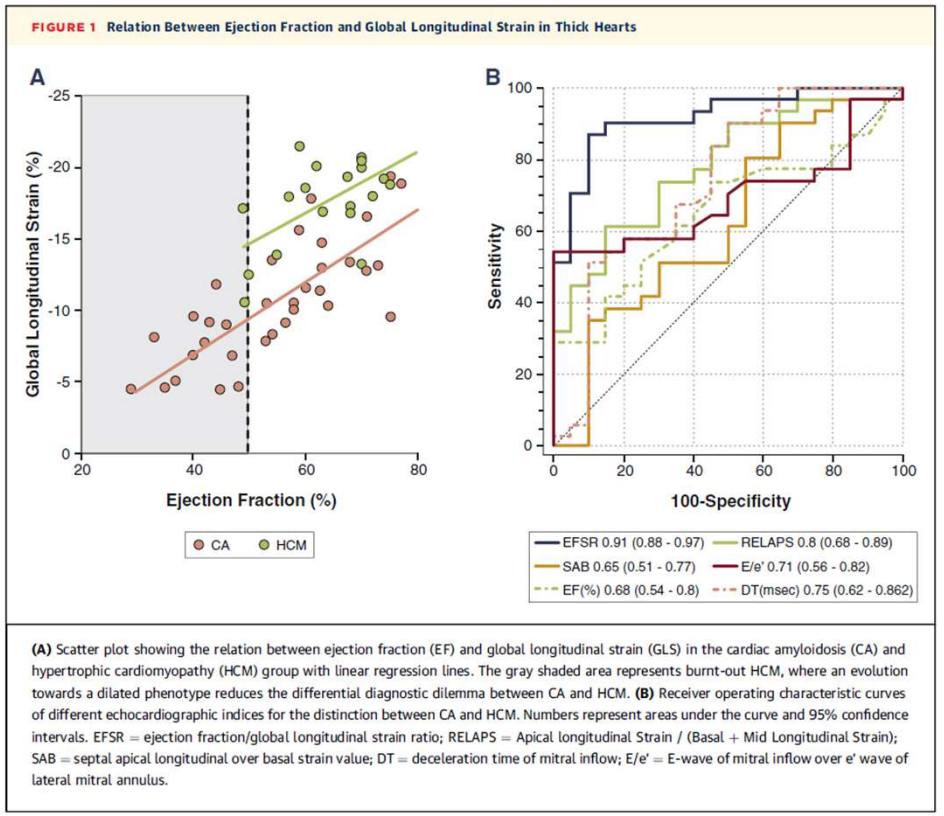


Comparison GLS vs LVEF

Pagourelias ED JACC CVI 2016





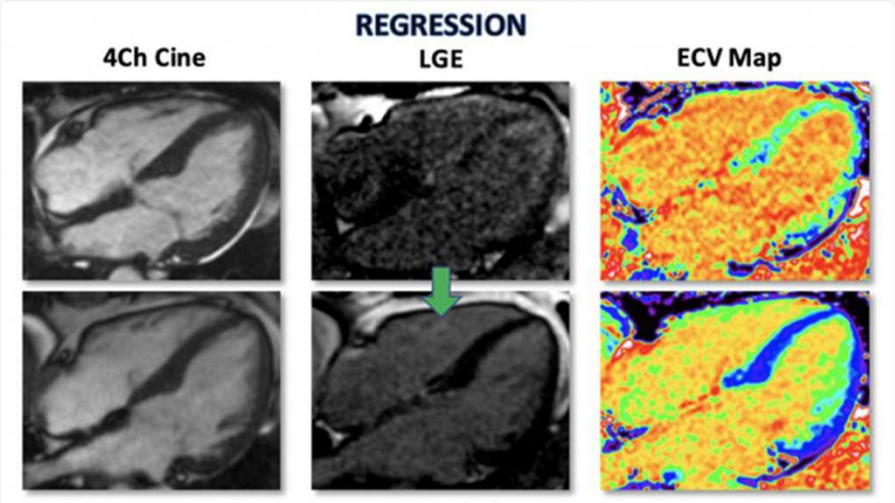


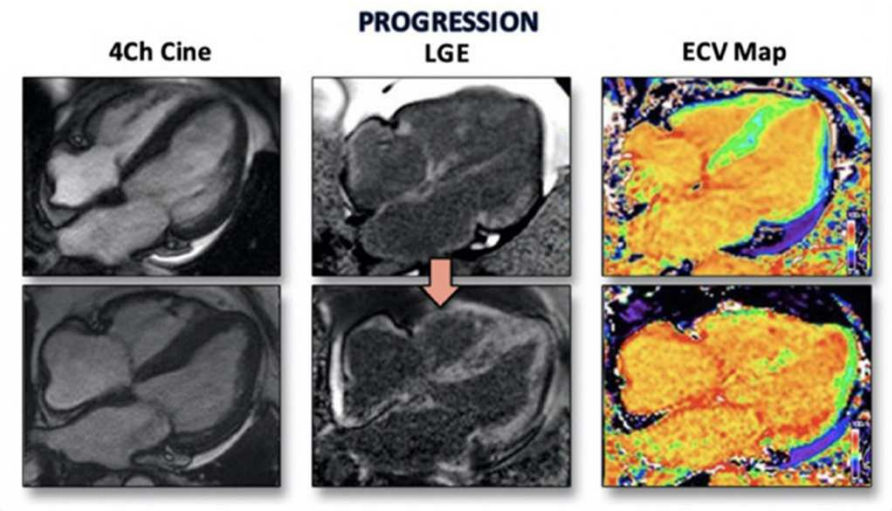
(A) Scatter plot showing the relation between ejection fraction (EF) and global longitudinal strain (GLS) in the cardiac amyloidosis (CA) and hypertrophic cardiomyopathy (HCM) group with linear regression lines. The gray shaded area represents burnt-out HCM, where an evolution towards a dilated phenotype reduces the differential diagnostic dilemma between CA and HCM. **(B)** Receiver operating characteristic curves of different echocardiographic indices for the distinction between CA and HCM. Numbers represent areas under the curve and 95% confidence intervals. EFSR = ejection fraction/global longitudinal strain ratio; RELAPS = Apical longitudinal Strain / (Basal + Mid Longitudinal Strain); SAB = septal apical longitudinal over basal strain value; DT = deceleration time of mitral inflow; E/e' = E-wave of mitral inflow over e' wave of lateral mitral annulus.

- ✓ **EFSR = EF / GLS**
- ✓ **5.7 +/- 1.7 in CA**
- ✓ **3.7 +/- 0.6 in HCM**
- ✓ **EFSR > 4.1 = threshold for amyloidosis**
- ✓ **RELAPS: average apical / average mid + basal strains**
- ✓ **RELAPS > 0.87 = threshold for amyloidosis**

Value of cardiac MRI

Razvi Y et al. . Frontiers CVMed 2020

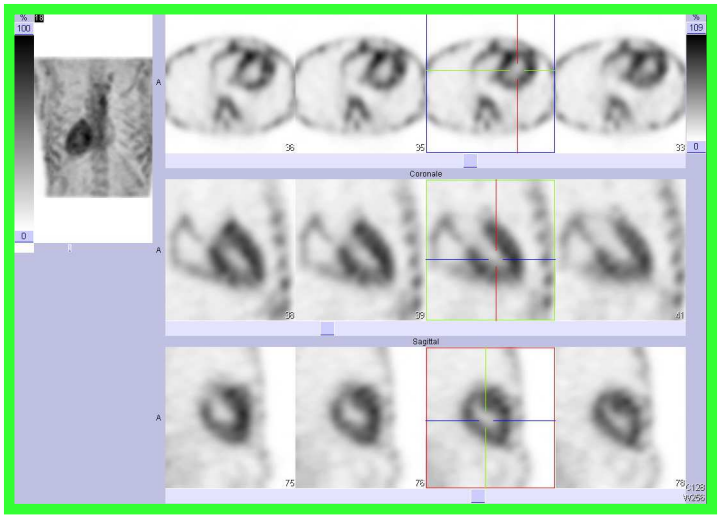


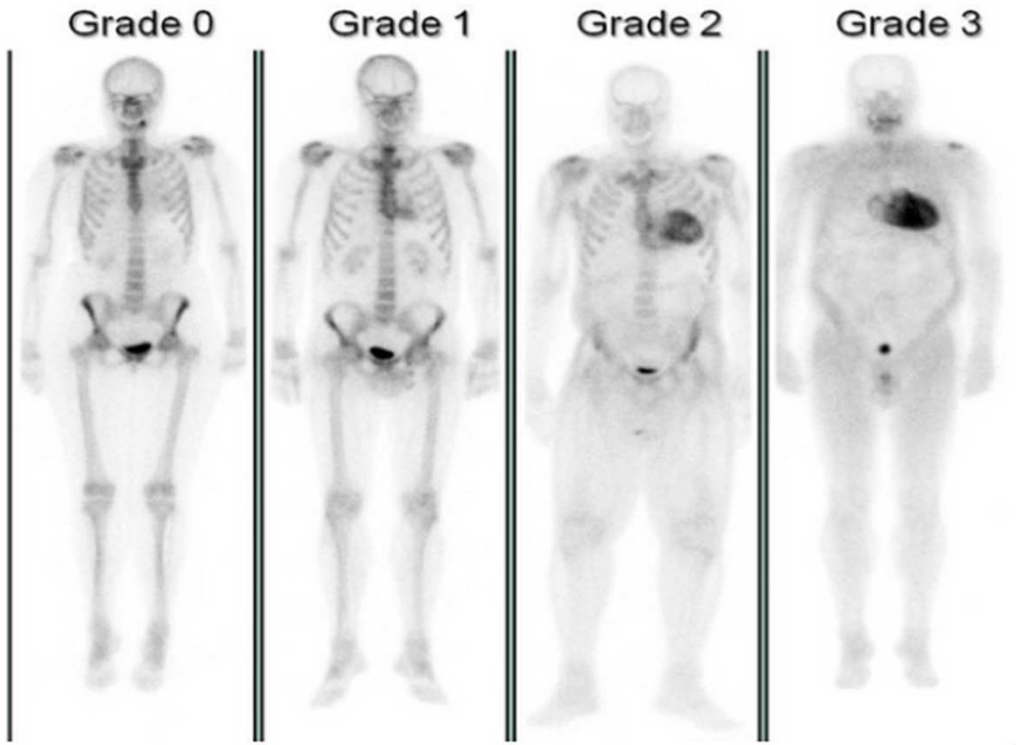


1. Concentric LV hypertrophy
2. Diffuse, transmural late gadolinium enhancement (LGE)
3. Elevated T1, increased extracellular volume (ECV)

Technetium scintigraphy

Gillmore et al. Circulation 2016





Haematologic tests

Kittleson MK – JACC 2023

1. Serum kappa/lambda free light chain ratio (abnormal if <0.26 or >1.65)
2. Serum immunofixation electrophoresis (abnormal if monoclonal protein detected)
3. Urine immunofixation electrophoresis (abnormal if monoclonal protein detected)

- ✓ **Rule out AL amyloidosis**
- ✓ **Refer immediately the patient to a reference center if positive or doubtful**

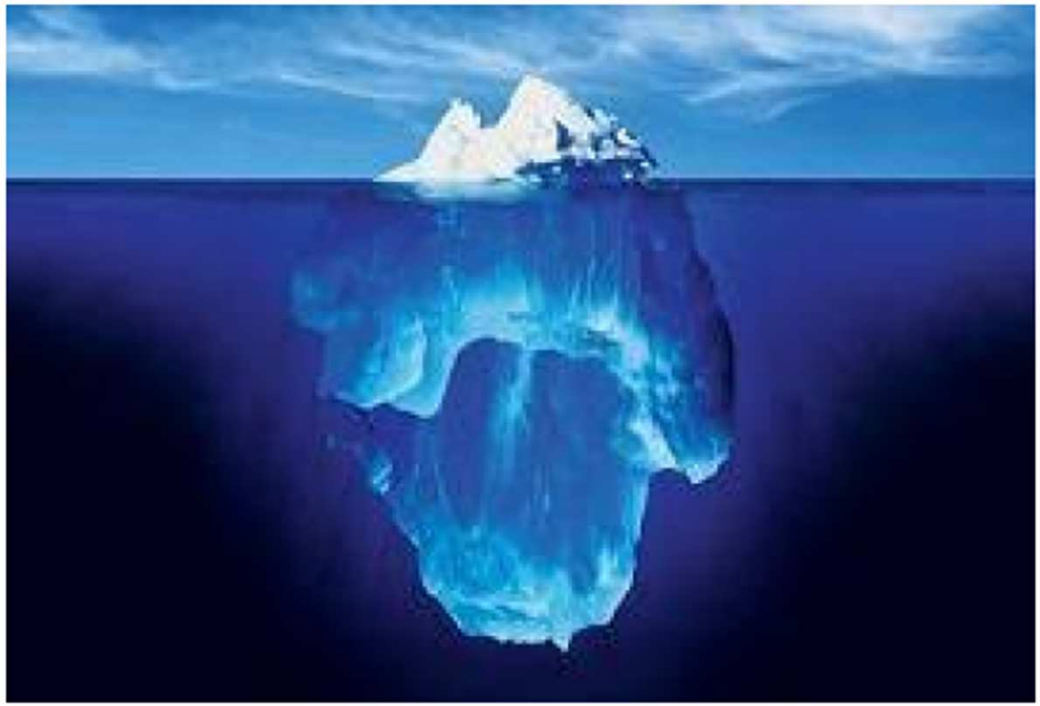
Cardiac amyloidosis

How to diagnose it?

1. **Think about amyloidosis**
2. **Easy diagnosis in typical cases**
3. ***Frequent difficult cases***
4. **Diagnostic algorithm**

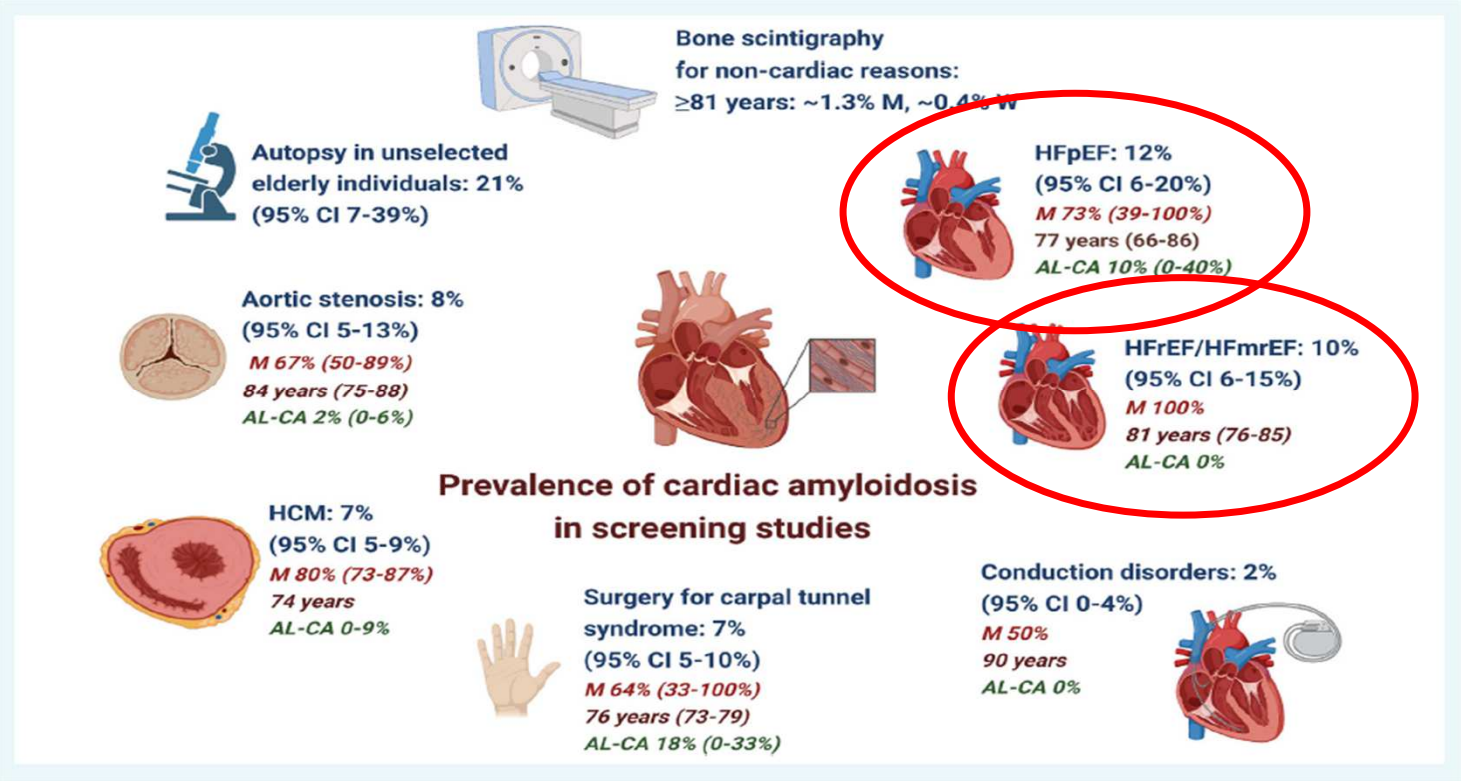
Classical picture is only the tip of the iceberg !!

Garcia-Pavia ESC 2024

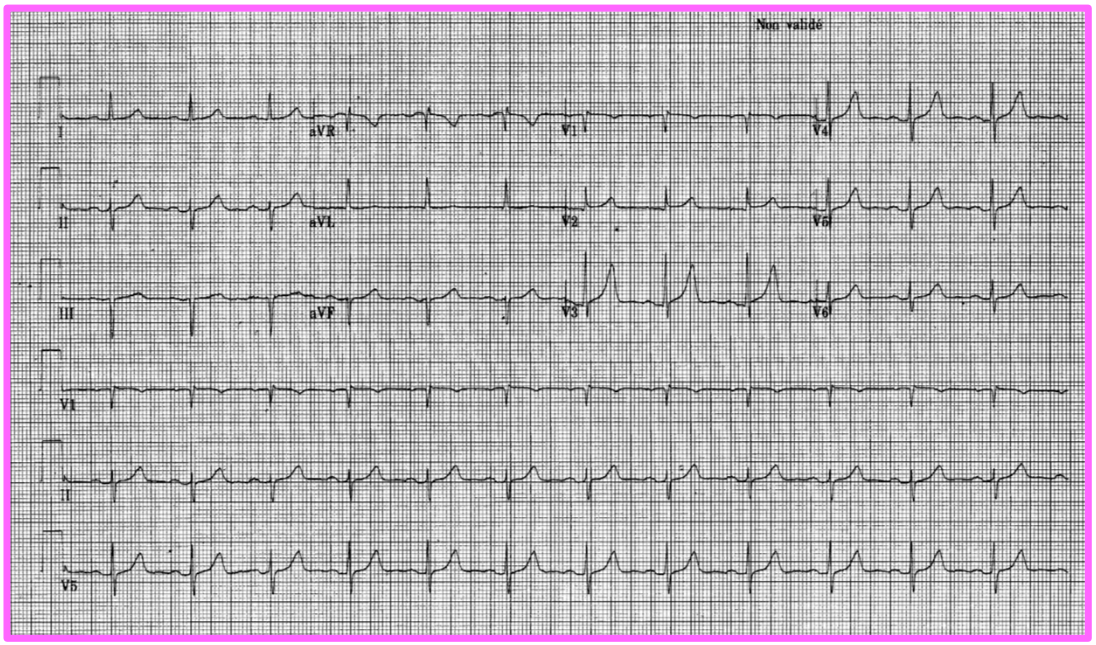


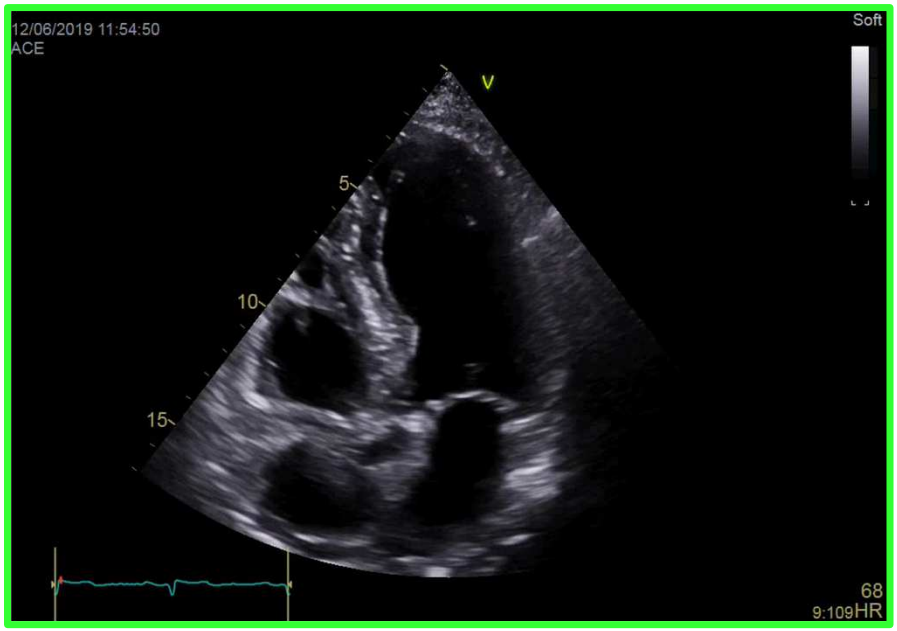
Frequently difficult diagnosis

Aimo A et al, Eur J Heart Failure 2022

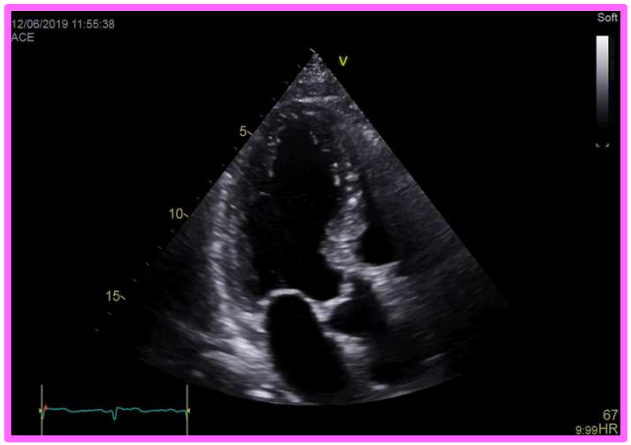


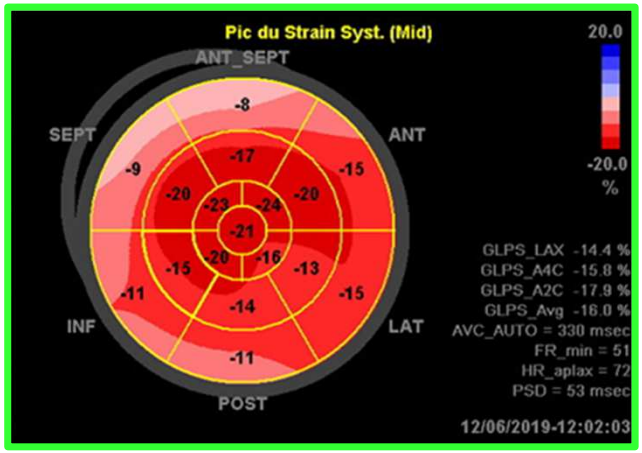
HFpEF / HPmrEF

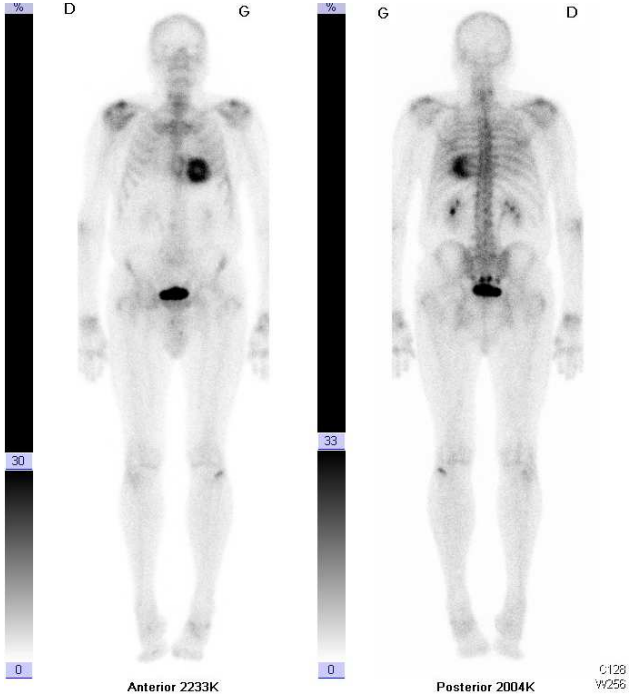




HFpEF / HPmrEF







HFpEF / HPmrEF

Gonzalez-Lopez et al – Eur Heart J 2015

European Heart Journal
doi:10.1093/eurheartj/ehv338

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

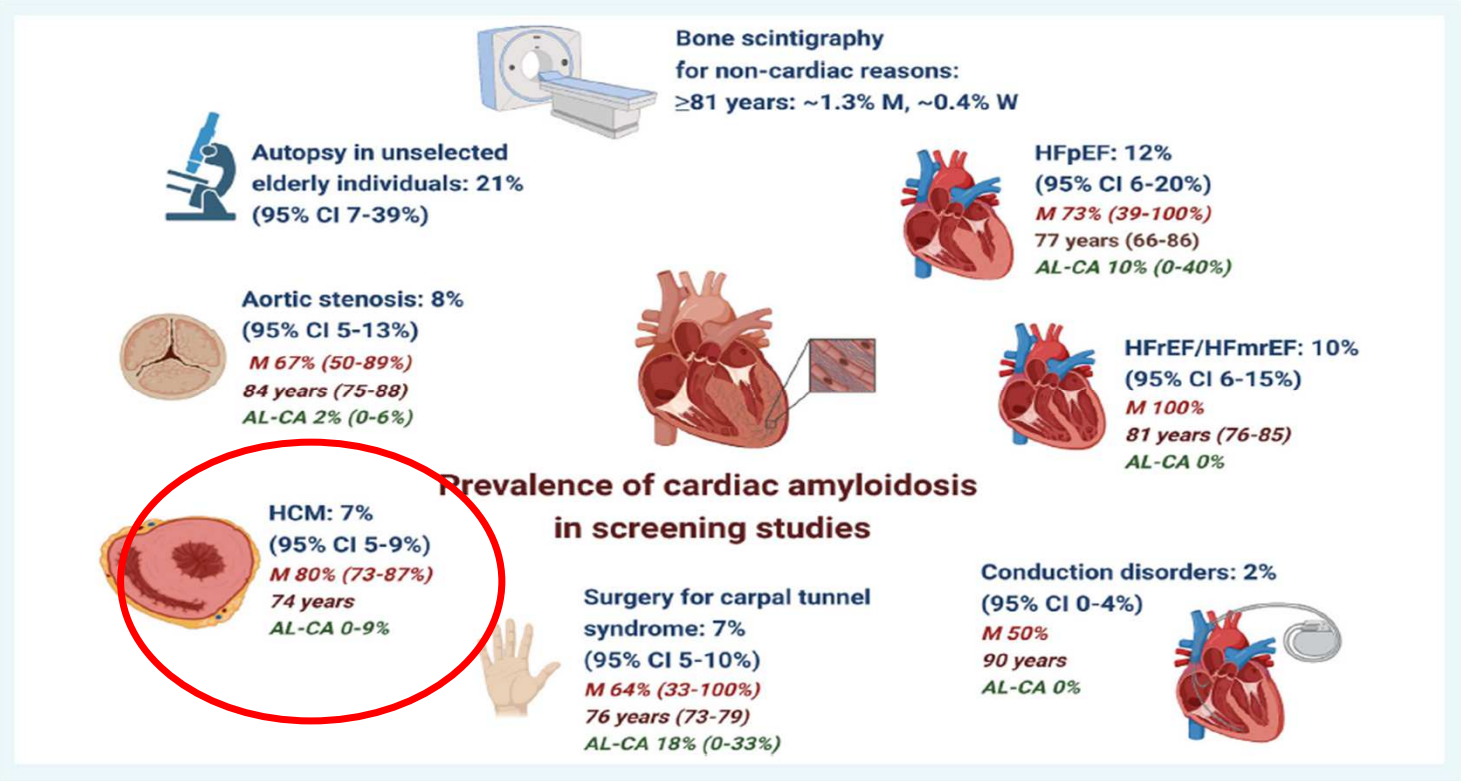
Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7*]

120 patients ≥ 60 years with HFpEF & LVH ≥ 12 mm

16 (13.3%) ATTRwt cardiomyopathy

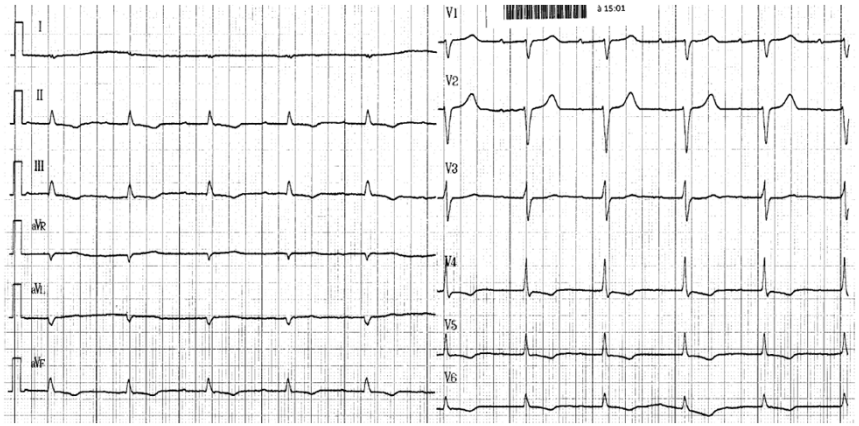
Frequently difficult diagnosis

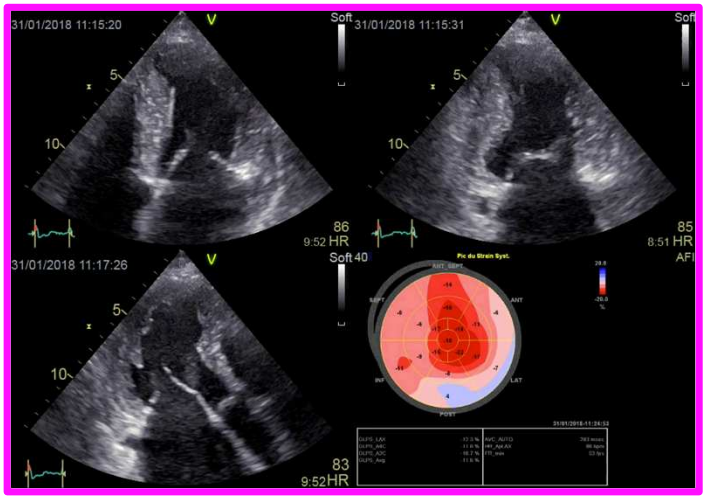
Aimo A et al, Eur J Heart Failure 2022

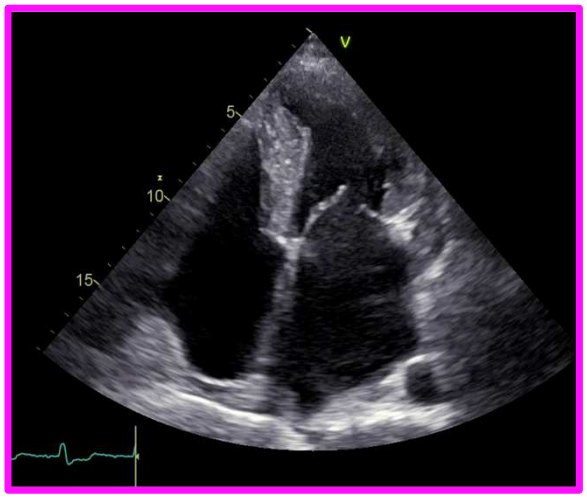


HCM + amyloidosis

- ✓ Sarcomeric HCM (MYBPC3)
- ✓ Progressive worsening HF
- ✓ New low voltage on ECG
- ✓ NT proBNP = 9200 ng/l
- ✓ TTE:
  - LVEF = 55%
  - LA dilatation
  - No obstruction
  - high LV filling pressures

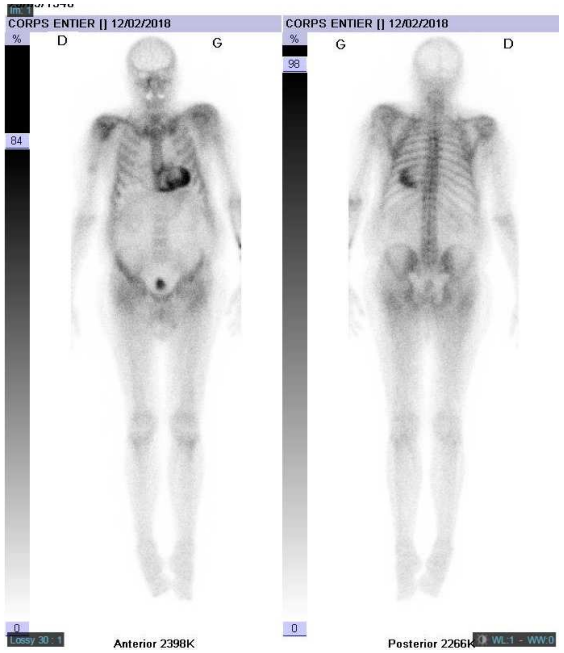






HCM + amyloidosis

- ✓ Normal haematologic tests
- ✓ Normal free-light chain level
- ✓ No Bence-Jones proteinuria



No gammapathy

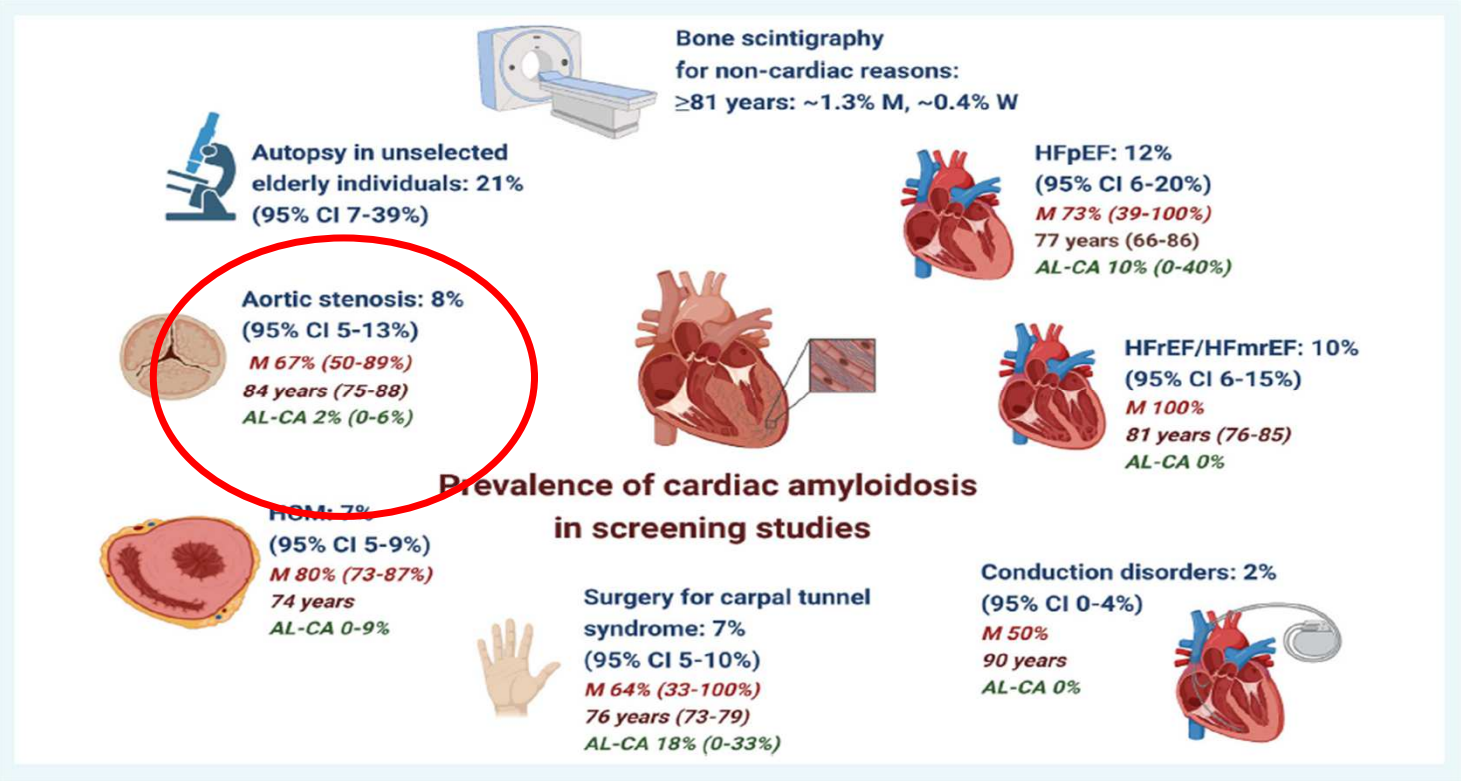
AL amyloidosis ruled out

Scintigraphy: grade 2 Peruggini

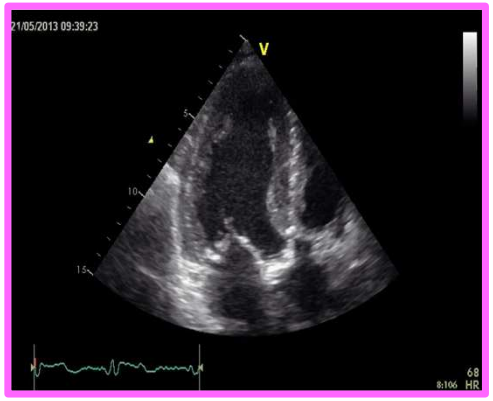
TTR amyloidosis confirmed

Frequently difficult diagnosis

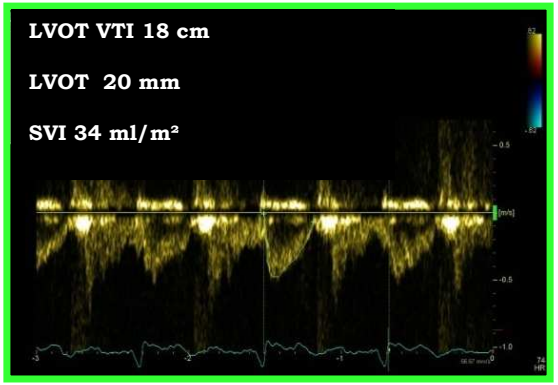
Aimo A et al, Eur J Heart Failure 2022



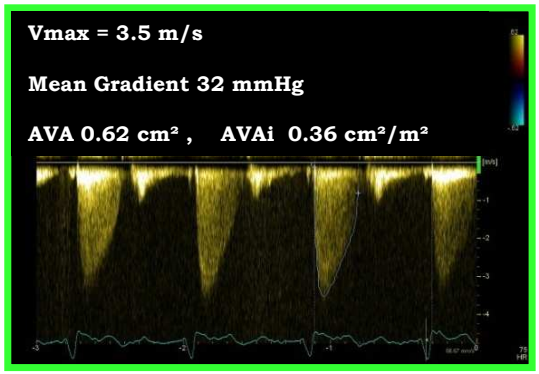
80 year-old female:LF LG aortic stenosis



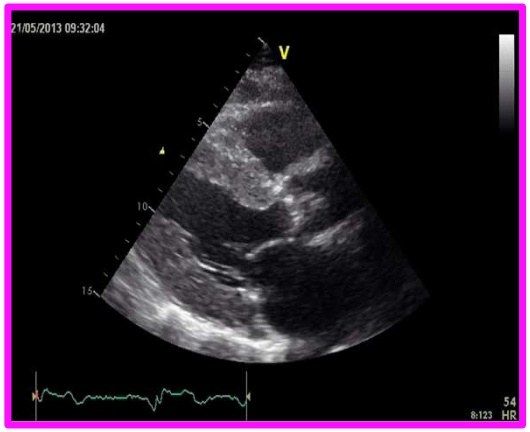
Normal LVEF

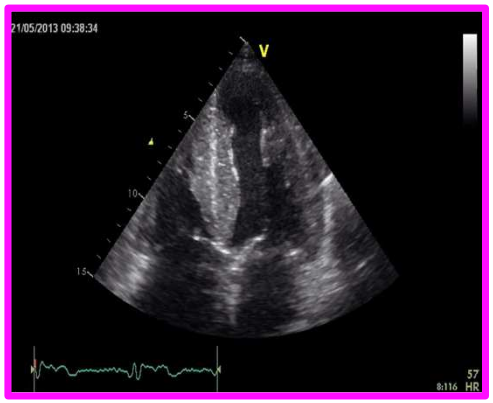


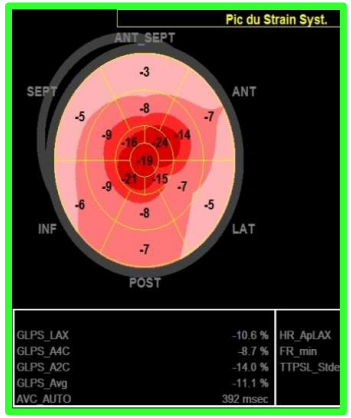
Low gradient



Low flow







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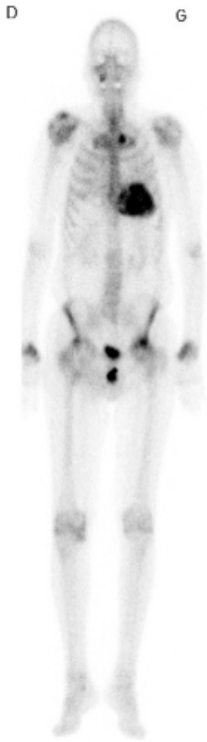
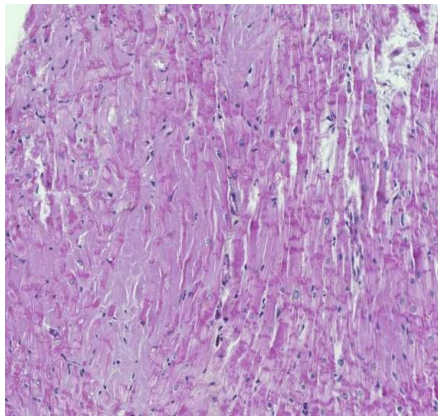


Severe cardiac uptake

Suspected amyloidosis



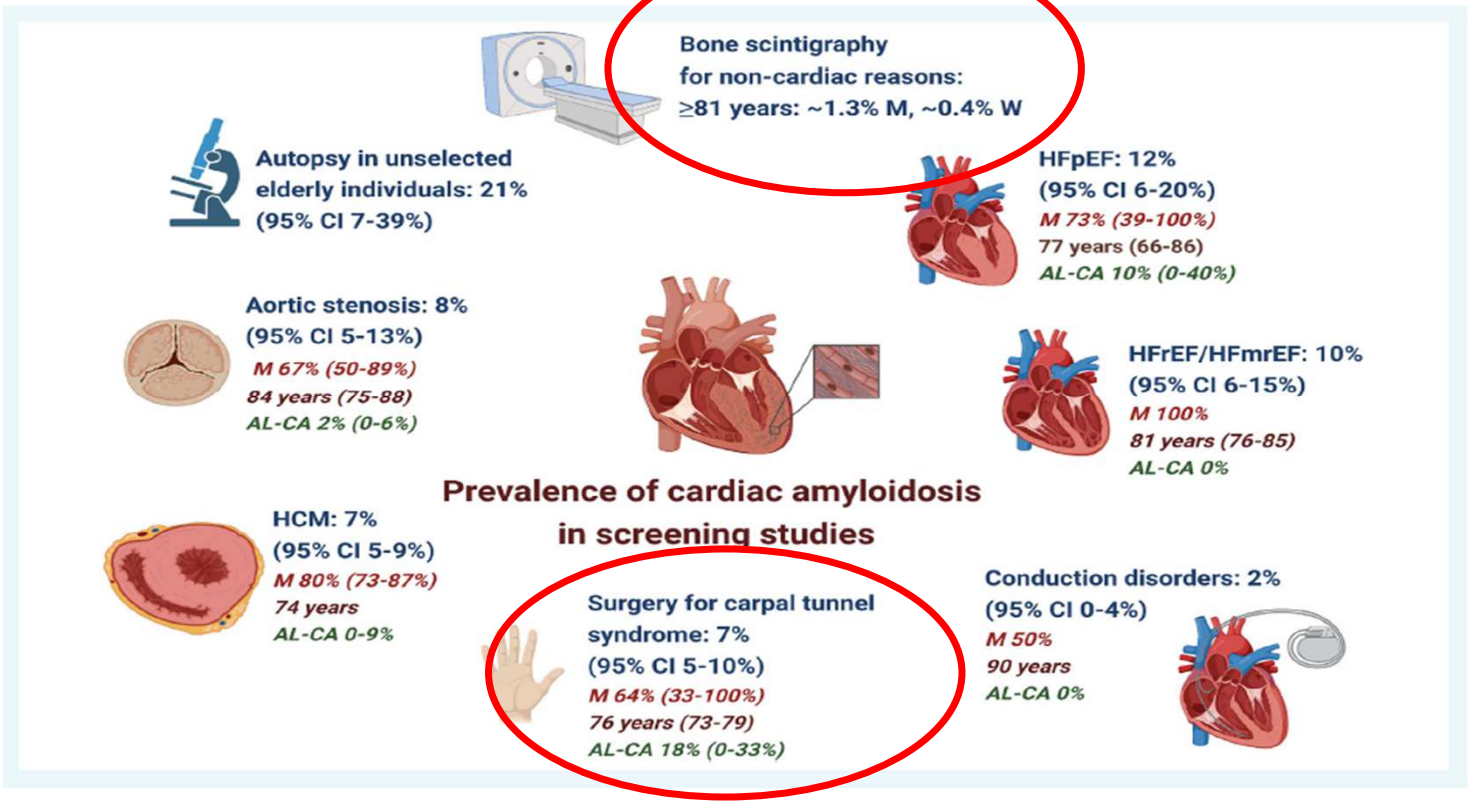
Positive for TTR amyloidosis

99mTc-HMDP scintigraphy

Endomyocardial biopsy

Frequently difficult diagnosis

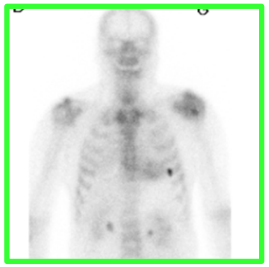
Aimo A et al, Eur J Heart Failure 2022



Diagnosis at an early stage

- 73 year-old man, carpal tunnel syndrome 2016, with histological amyloidosis
- Asymptomatic, normal BNP , normal Kappa lambda ratio

2016

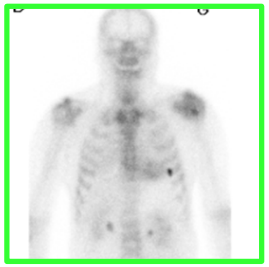


- LVEF = 65% **- GLS = -18%** **Minimal LVH – no LGE** **Perugini 1**

Diagnosis at an early stage

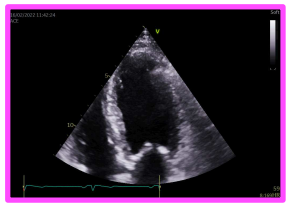
- 73 year-old man, carpal tunnel syndrome 2016, with histological amyloidosis
- Asymptomatic, normal BNP , normal Kappa lambda ratio

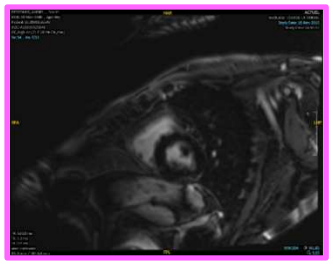
2016



- LVEF = 65% **- GLS = -18%** **Minimal LVH – no LGE** **Perugini 1**

2020





- LVEF = 65% **- GLS = -14%** **Minimal LVH – minimal LGE** **Perugini 2**

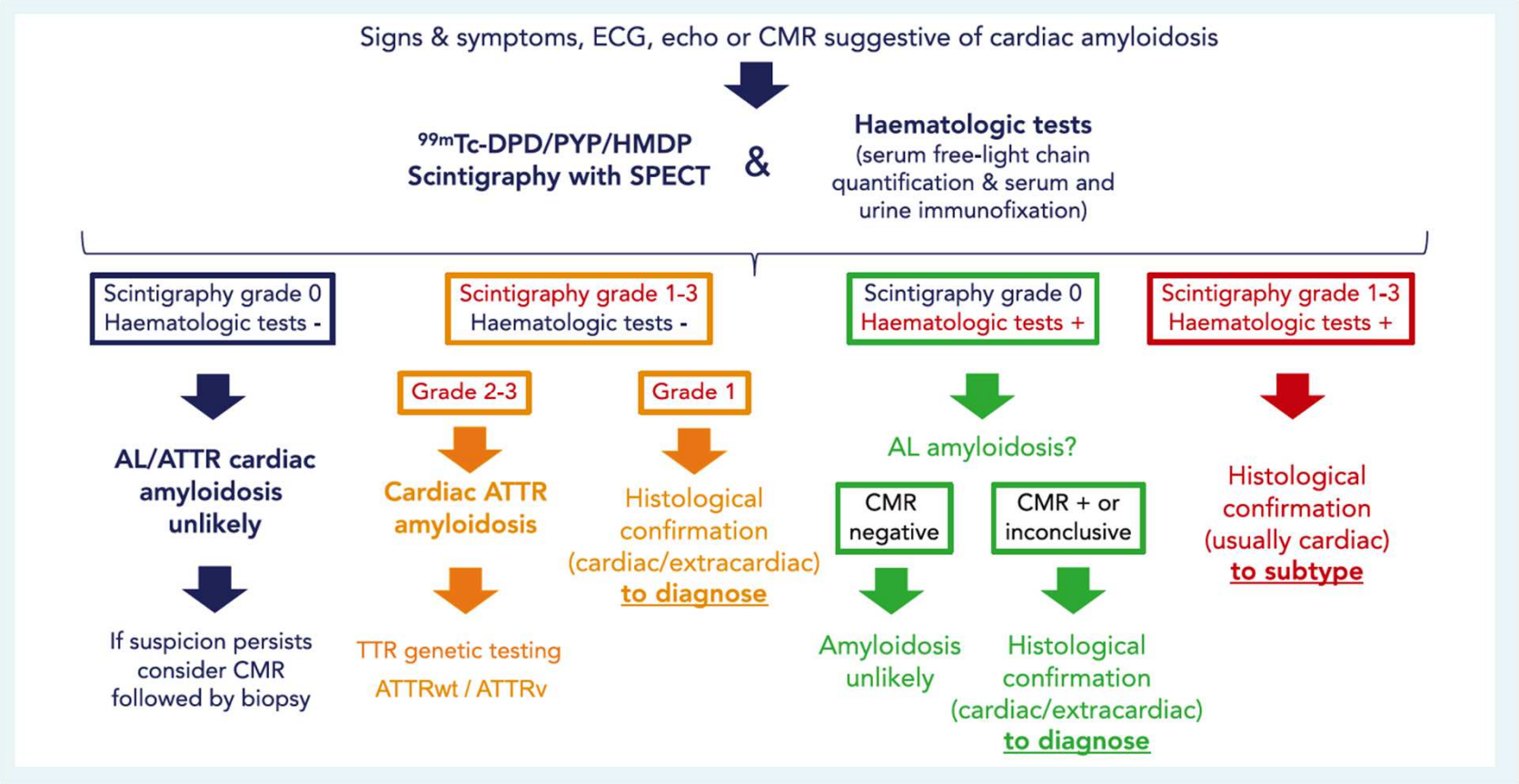
Cardiac amyloidosis

How to diagnose it?

1. **Think about amyloidosis**
2. **Easy diagnosis in typical cases**
3. **Frequent difficult cases**
4. ***Diagnostic algorithm***

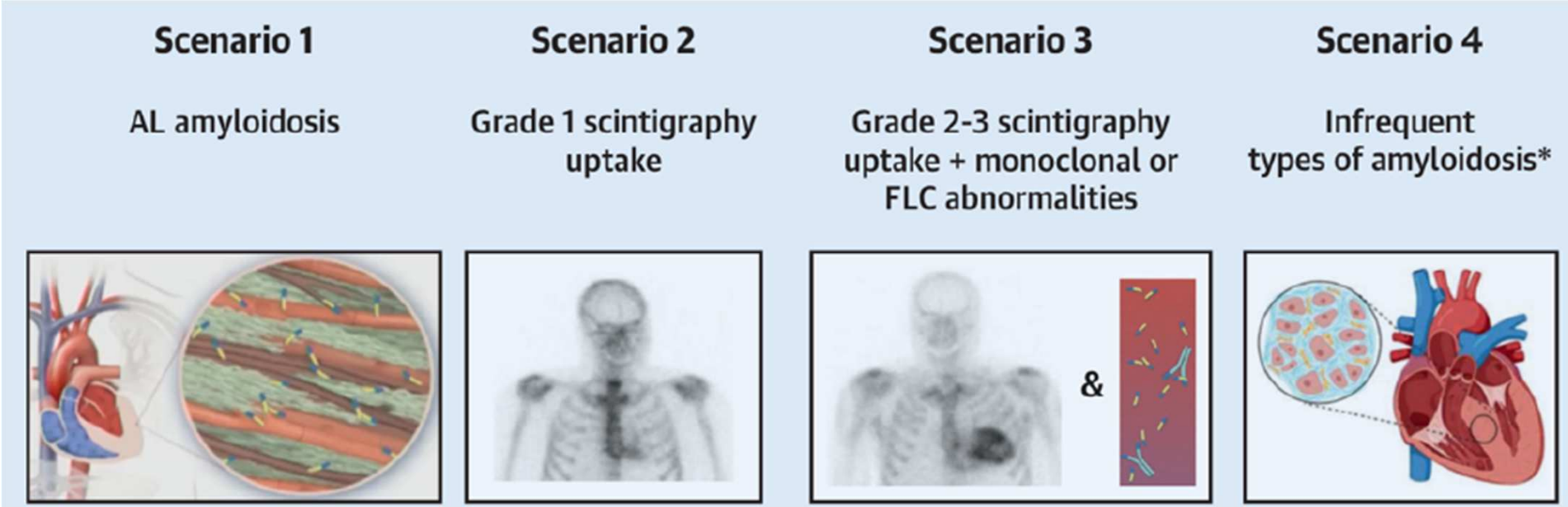
Nonbiopsy Diagnosis of Cardiac Amyloidosis

Garcia-Pavia, Position paper , Eur Heart J 2021



When is histological confirmation required ?

Gonzalo-Lopez et al. J Am Coll Cardiol 2024; 83:1085-99



Cardiac amylosidosis: how to diagnose it ?

- ✓ Think about amyloidosis
- ✓ Clinical and imaging red flags
- ✓ Confirm the diagnosis by invasive / non invasive tests
- ✓ Value of a multimodality imaging approach
- ✓ Bone scintigraphy coupled with AL blood/urine tests are the basis of amyloidosis diagnosis
- ✓ Refer patients to reference centers

La Timone Hospital; Marseille, France