Chronic Dyspnea

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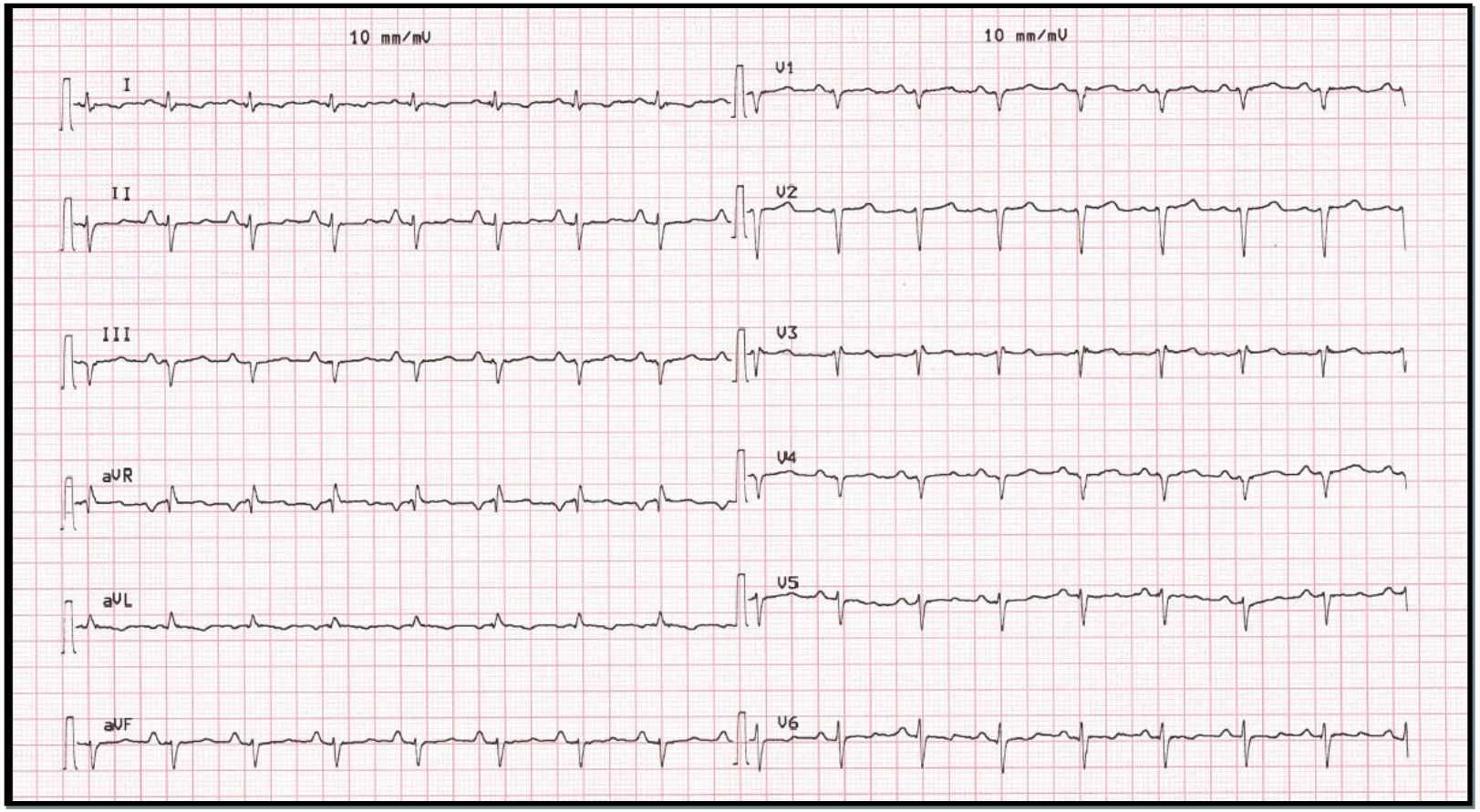
Disclosures

- I have no conflicts of interest to declare

Mrs M. 1949: 1st admission November 2014

Past medical history	• Retired music teacher • Fibromyalgia diagnosed in 2000 • No other comorbities, no regular medications
History of present illness	• Progressive dyspnea, currently NYHA class III, onset during Summer 2014 • Slight chest oppression • Swollen legs for 2 weeks
Risk factors	• Active smoker (40 pack-years) • Overweight (BMI = 27.6 kg/m^2) • « Social drinker»: ½ pastis (anise-flavored spirit) before lunch, 1 glass whisky in the evening
Physical exam	• BP 105/82 mmHg. HR 92 bpm. SaO_2: 93% on room air • JVP NA. Non-displaced apex beat. Mild pedal oedema. Bibasilar pulmonary rales • S1/ S2 hardly audible, ∅ S3/S4, 2/6 systolic murmur at left sternal border

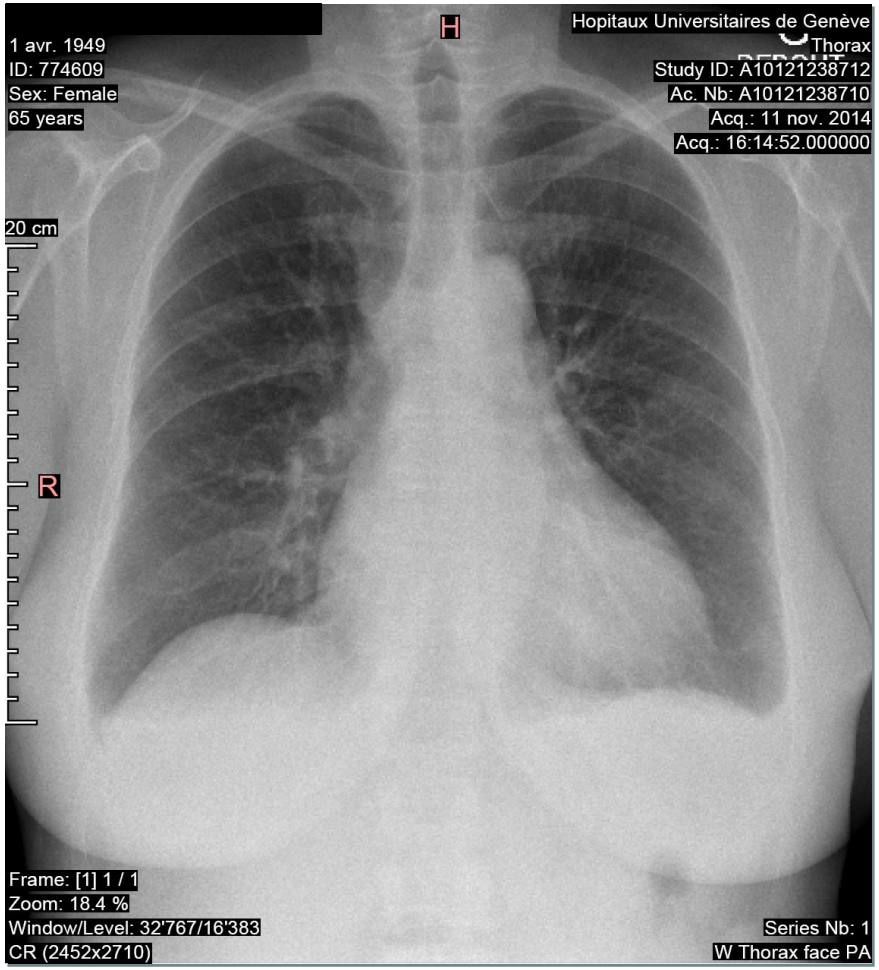
Mrs M. 1949: ECG

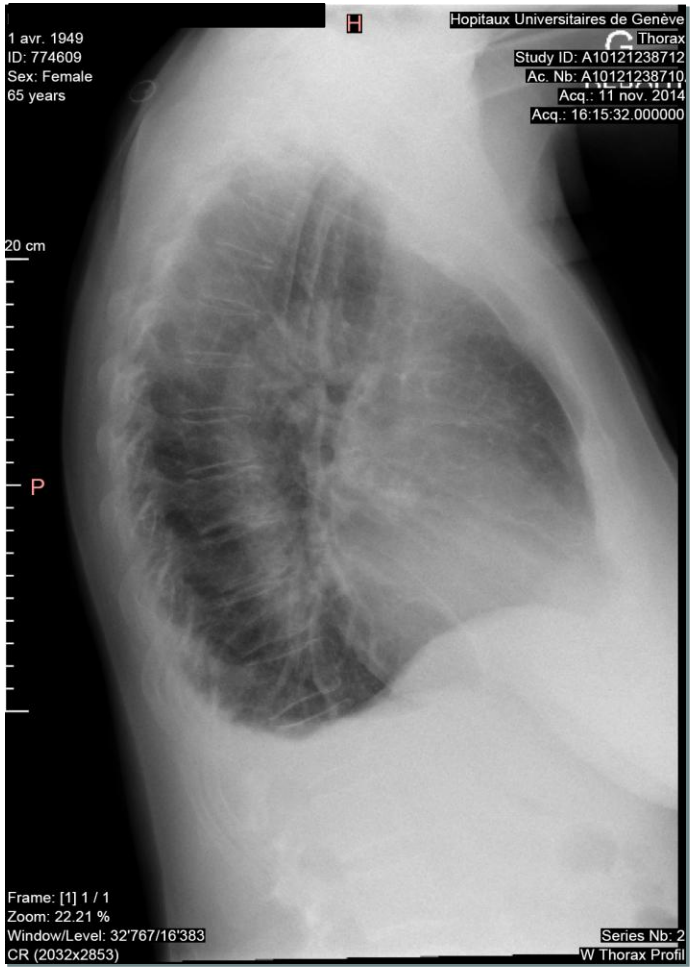


Mrs M. 1949: laboratory tests

- Normal blood count
- INR 1.24 (TP 62%)
- Creatinine: 92 µmol/l, GFR (CKD-EPI) 56 ml/min/1.73 m^2
- GGT 47 U/l
- Troponin I: 0.166 µg/L (>0.090); BNP: 517 ng/L
- D-dimer: 720 µg/L

Mrs M. 1949: chest x-ray





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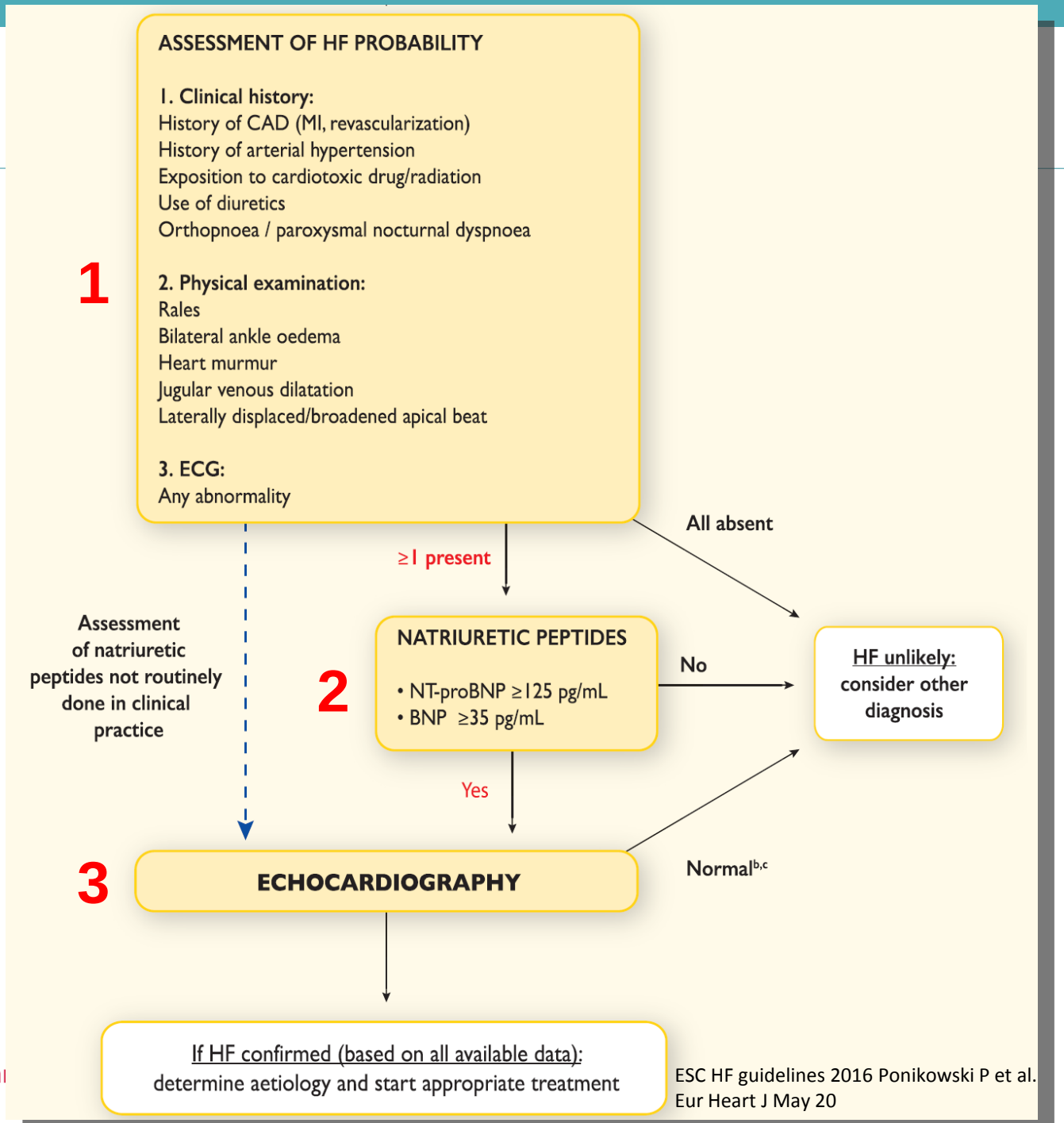
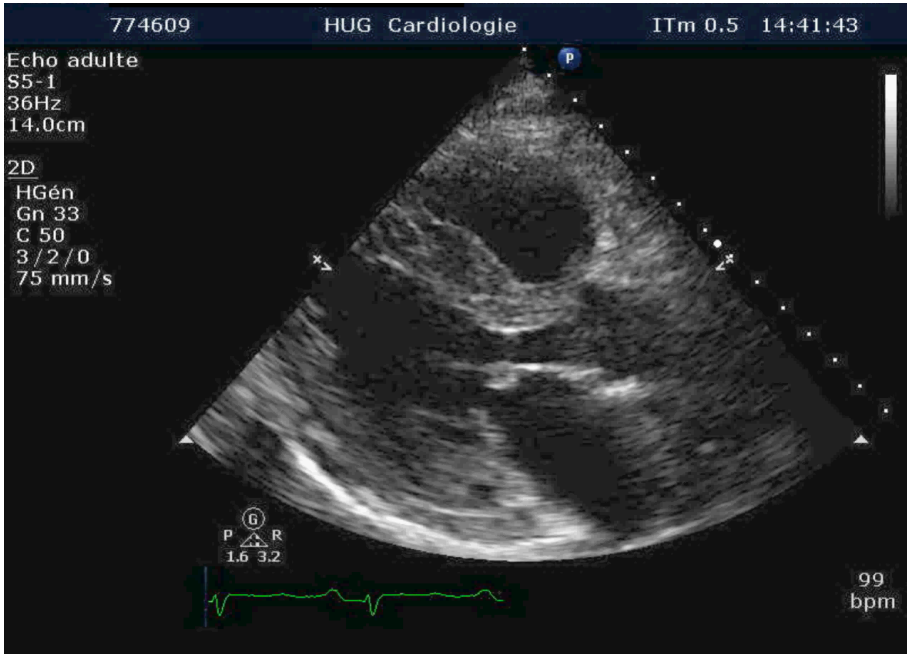
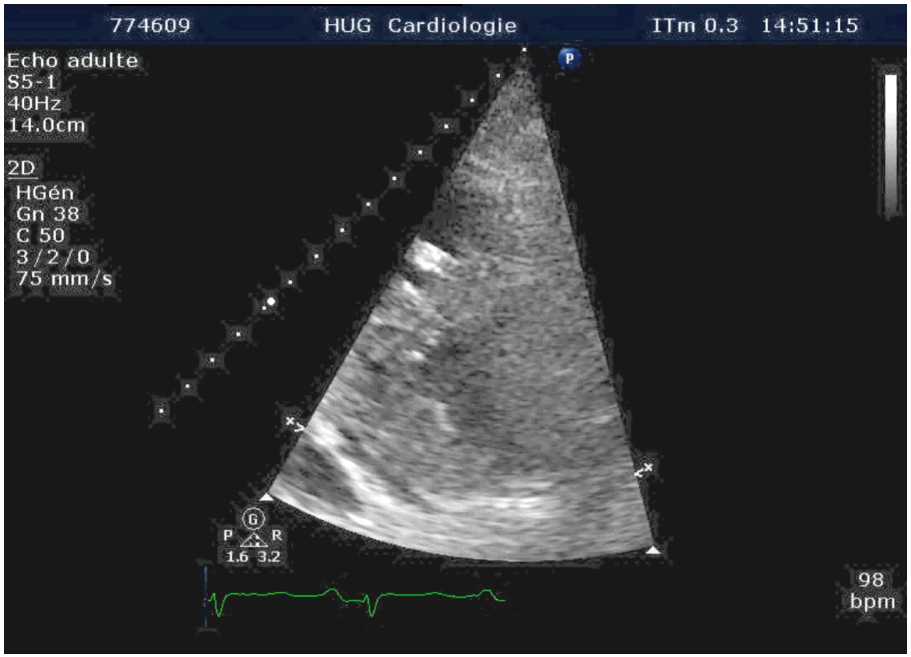
Is it



ESC HF guidelines 2016 Ponikowski P et al. Eur Heart J May 20

Mrs M. 1949: TTE at admission (portable device)





- Non dilated LV
- Increased wall thickness (IVS 12 mm)

- Mild pericardial and pleural effusions

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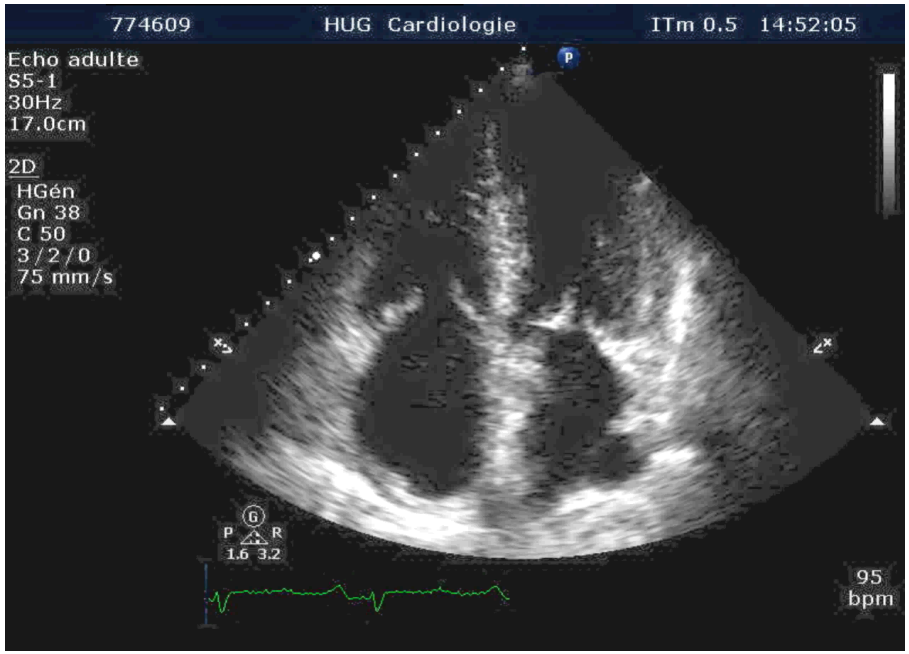
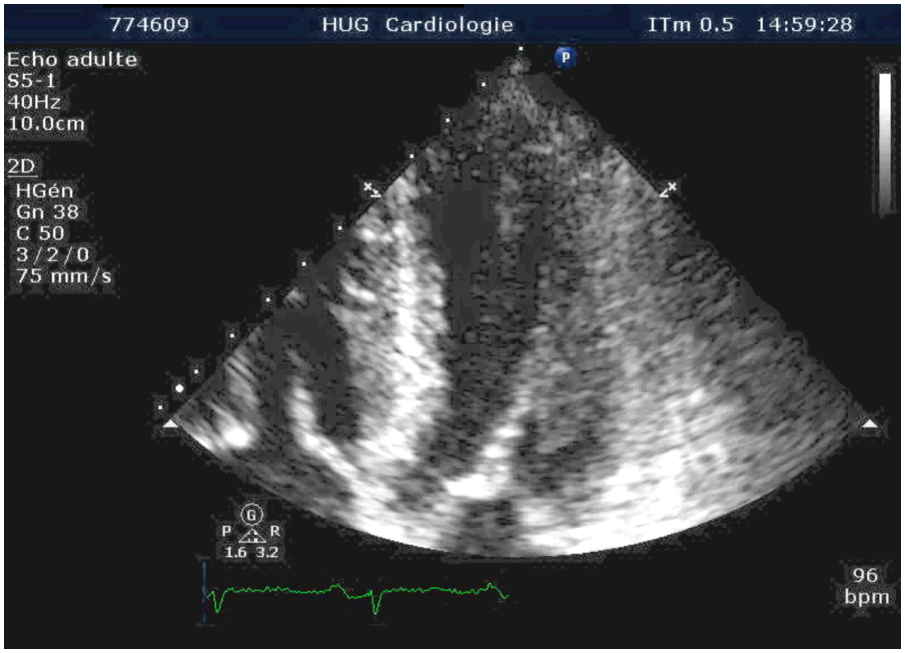
Mrs M. 1949: TTE





- Bi-atrial enlargement
- LVEF estimated at 65%

Pulmonary function tests

Conclusions:

- **No obstructive defect**
  - FEV1/FVC = 76% predicted
  - FEV1 = 82% predicted
- **No restrictive defect** (TLC 90% predicted)
- **Normal CO diffusing capacity** (80% predicted)

Qu. 3: What is the most likely diagnosis?

1	Anginal equivalent	
2	HFpEF	
3	COPD	
4	Pulmonary embolism	
5	Deconditioning	

Qu. 3: What is the most likely diagnosis?

1	Anginal equivalent	
2	HFpEF	✔
3	COPD	
4	Pulmonary embolism	
5	Deconditioning	

All conditions are met for HFpEF diagnosis

HFrEF
Symptoms ± Signs[a]
LVEF <40%

Heart failure with reduced ejection fraction (EF)

HFmrEF
Symptoms ± Signs[a]
LVEF 40–49%
1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Heart failure with mid-range EF

HFpEF
Symptoms ± Signs[a]
LVEF ≥50%
1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction (for details see Section 4.3.2).

Heart failure with preserved EF

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ESC HF guidelines 2016 Ponikowski P et al. Eur Heart J May 20

What

DISEASED MYOCARDIUM		
Ischaemic heart disease	Myocardial scar	
	Myocardial stunning/hibernation	
	Epicardial coronary artery disease	
	Abnormal coronary microcirculation	
	Endothelial dysfunction	
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-Inflammatory drugs, anaesthetics.
	Radiation	
Immune-mediated and inflammatory damage	Related to infection	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).
	Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss).
Infiltration	Related to malignancy	Direct infiltrations and metastases.
	Not related to malignancy	Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease).
Metabolic derangements	Hormonal	Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.
	Nutritional	Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity.
Genetic abnormalities	Diverse forms	HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies.
ABNORMAL LOADING CONDITIONS		
Hypertension		
Valve and myocardium structural defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve diseases.
	Congenital	Atrial and ventricular septum defects and others (for details see a respective expert document).
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis Pericardial effusion
	Endomyocardial	HES, EMF, endocardial fibroelastosis.
High output states		Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.
Volume overload		Renal failure, iatrogenic fluid overload.
ARRHYTHMIAS		
Tachyarrhythmias		Atrial, ventricular arrhythmias.
Bradyarrhythmias		Sinus node dysfunctions, conduction disorders.

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Ponikowski P et al.
Eur Heart J May 20

Myocardial ischemia ruled out by PET-CT

Discharge diagnosis:
Heart failure with preserved ejection fraction due to hypertensive heart disease

Discharge medications:
- Torasemide 15 mg od
- Spironolactone 12.5 mg od
- Carvedilol 3.125 mg bid
- Lisinopril 5 mg od

		expert documents), muscular dystrophies and laminopathies.
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ESC HF guidelines 2016
Ponikowski P et al.
Eur Heart J May 20

Mrs M. 1949: February 2015: worsening HF

- Actually the patient never had high blood pressure…
- Recurrence of dyspnea and leg edema
- NT-pro-BNP 3769 ng/L
- Creatinine 119 µmol/l, GFR (CKD-EPI) 40 ml/min/1.73 m^2

Qu. 4: What would be your next diagnostic step?

1	Repeat echocardiography	
2	MRI	
3	Endomyocardial biopsy	
4	Coronary angiogram	
5	Psychiatry consult	

Qu. 4: What would be your next diagnostic step?

1	Repeat echocardiography	✔
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3	Endomyocardial biopsy	
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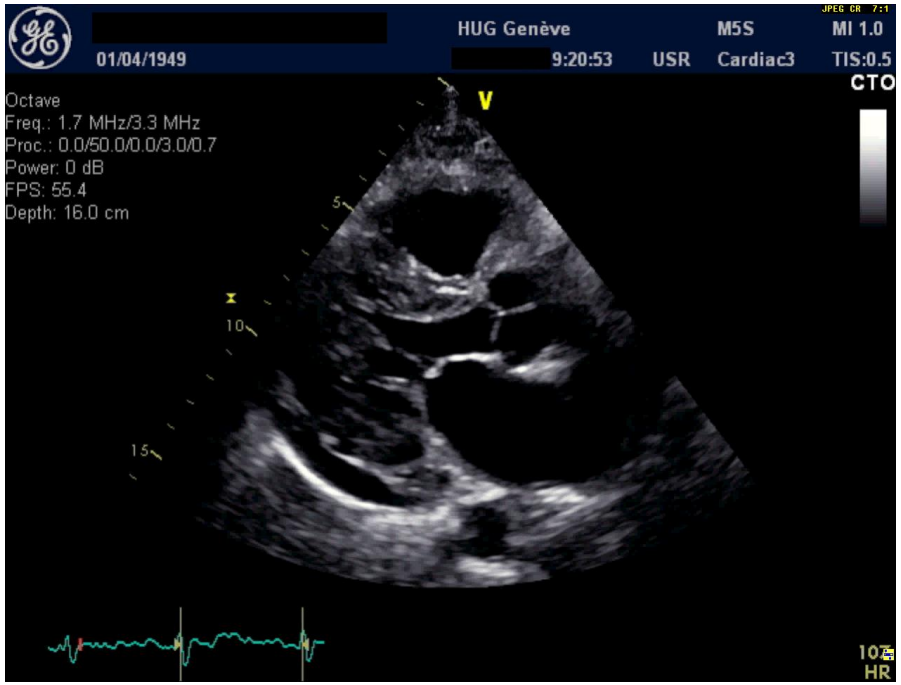
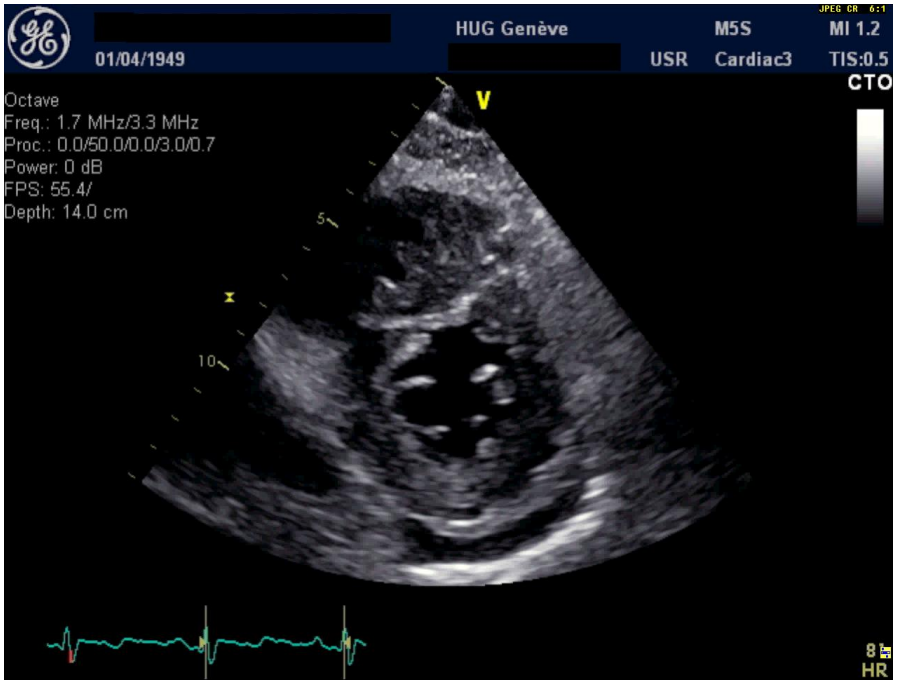
5	Psychiatry consult	

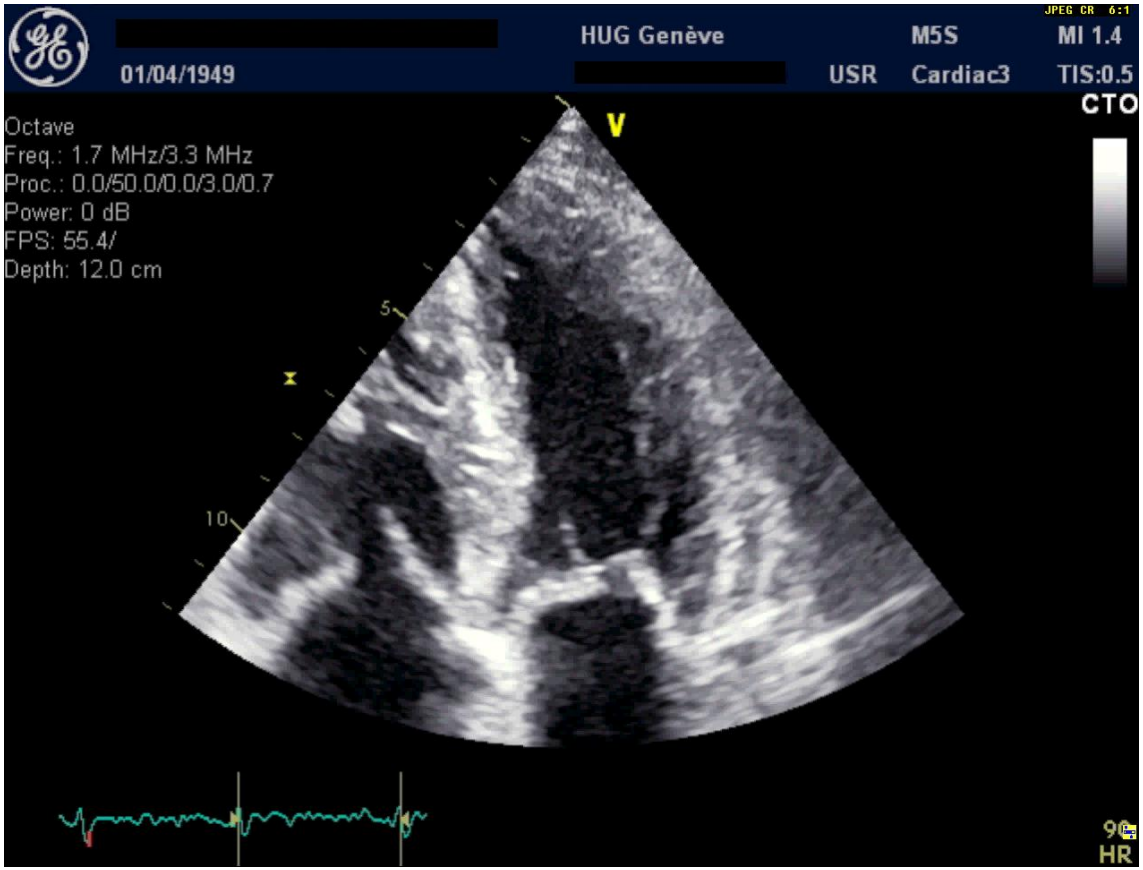
TTE (2): parasternal views





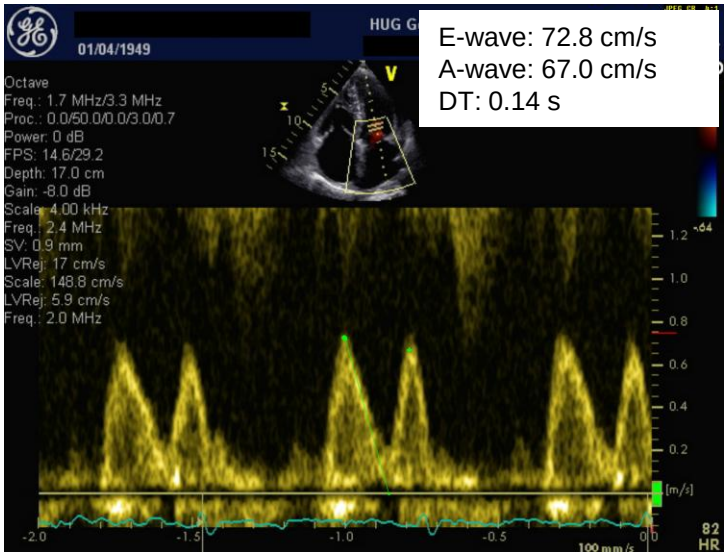
- Increased LV wall thickness (IVS 13 mm)
- Slight progression of pericardial effusion

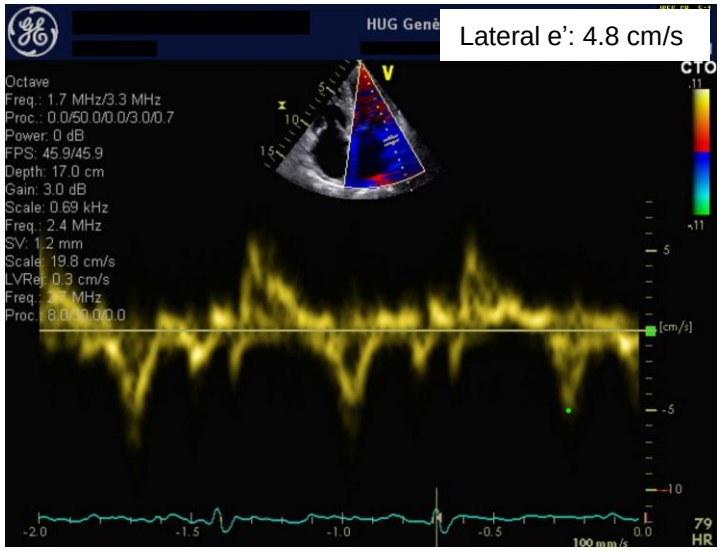
TTE (2): apical view

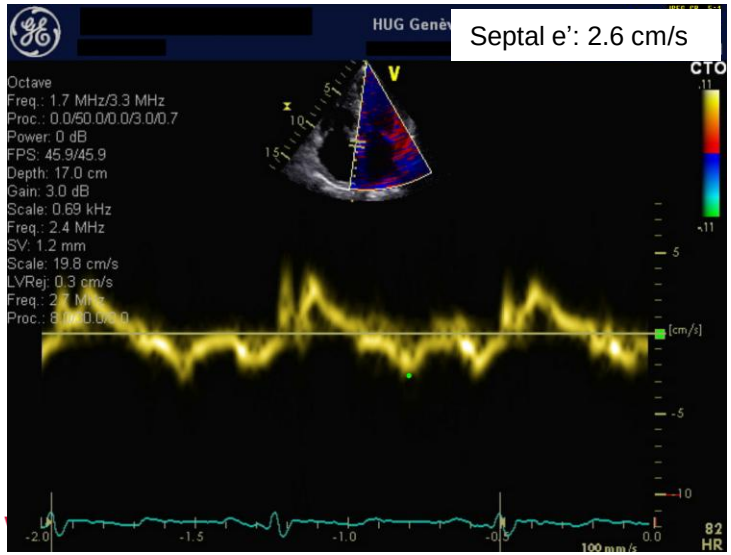


- Normal LVEF calculated at 56% (modified 2D Simpson's rule)
- AV valve thickening

TTE (2): diastolic function







- Grade II diastolic dysfunction (pseudonormalisation)
- E/e' mean ratio: 21.3 (indicating increased LVEDP)

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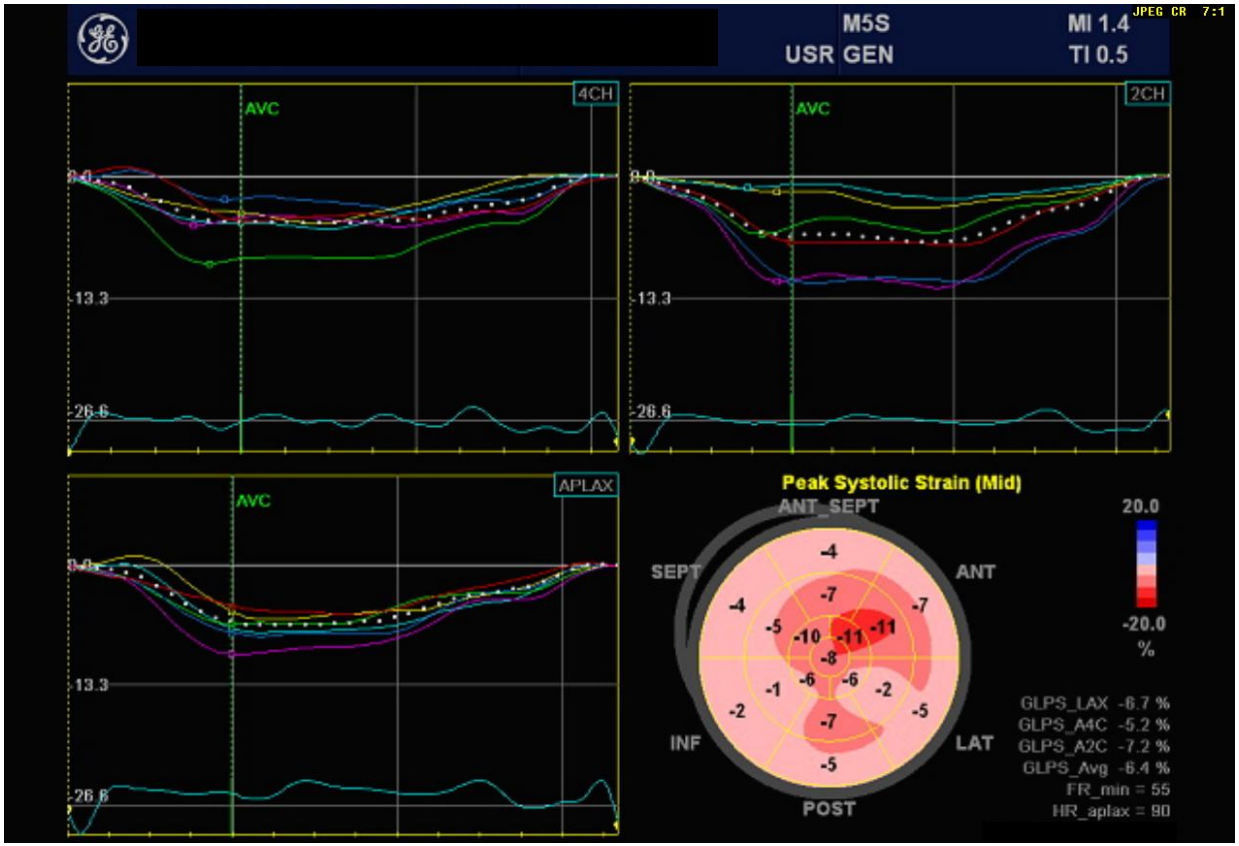
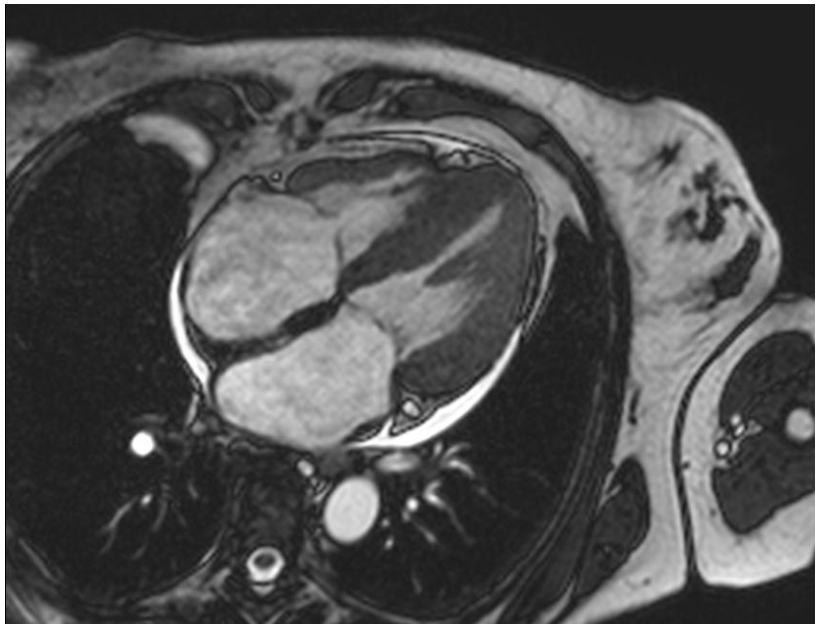
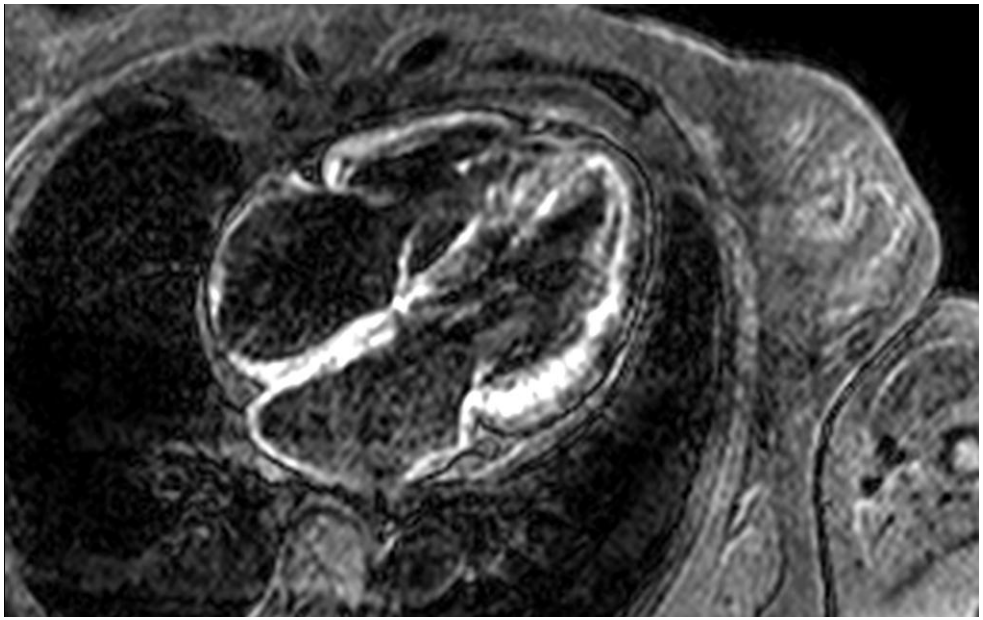
TTE (2): longitudinal strain



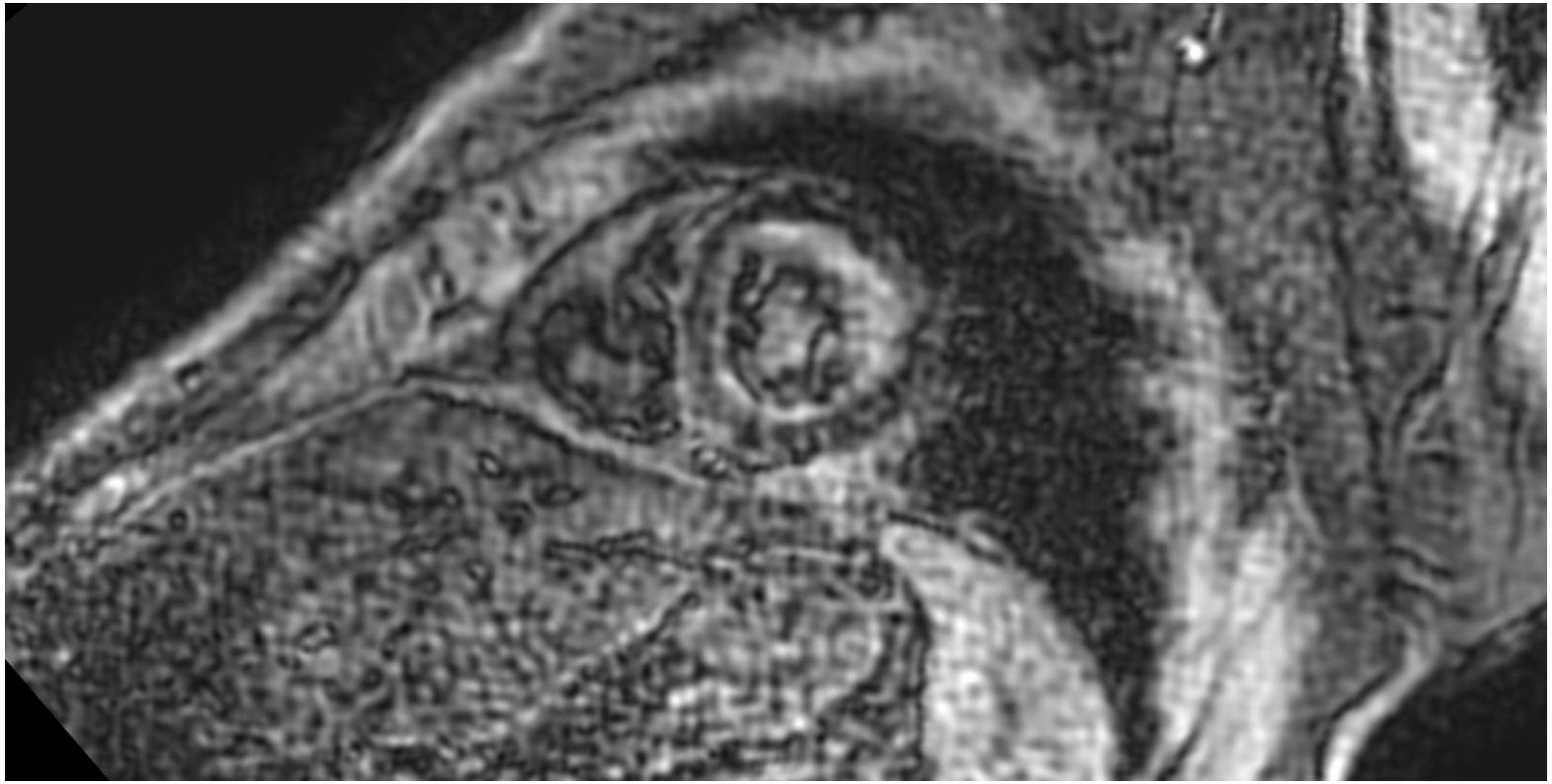
- Severely reduced global longitudinal strain -6.5% (normal value = -21%)
- More pronounced reduction in the basal segments

Mrs M. 1949: cardiac MRI





Mrs M. 1949: cardiac MRI



Typical subendocardial ring of enhancement after gadolinium injection

Qu. 5: What is now the most likely diagnosis?

1	Ischemic heart disease	
2	Familial HCM	
3	Cardiac amyloidosis	
4	Fabry’s disease	
5	Sarcoidosis	

Qu. 5: What is now the most likely diagnosis?

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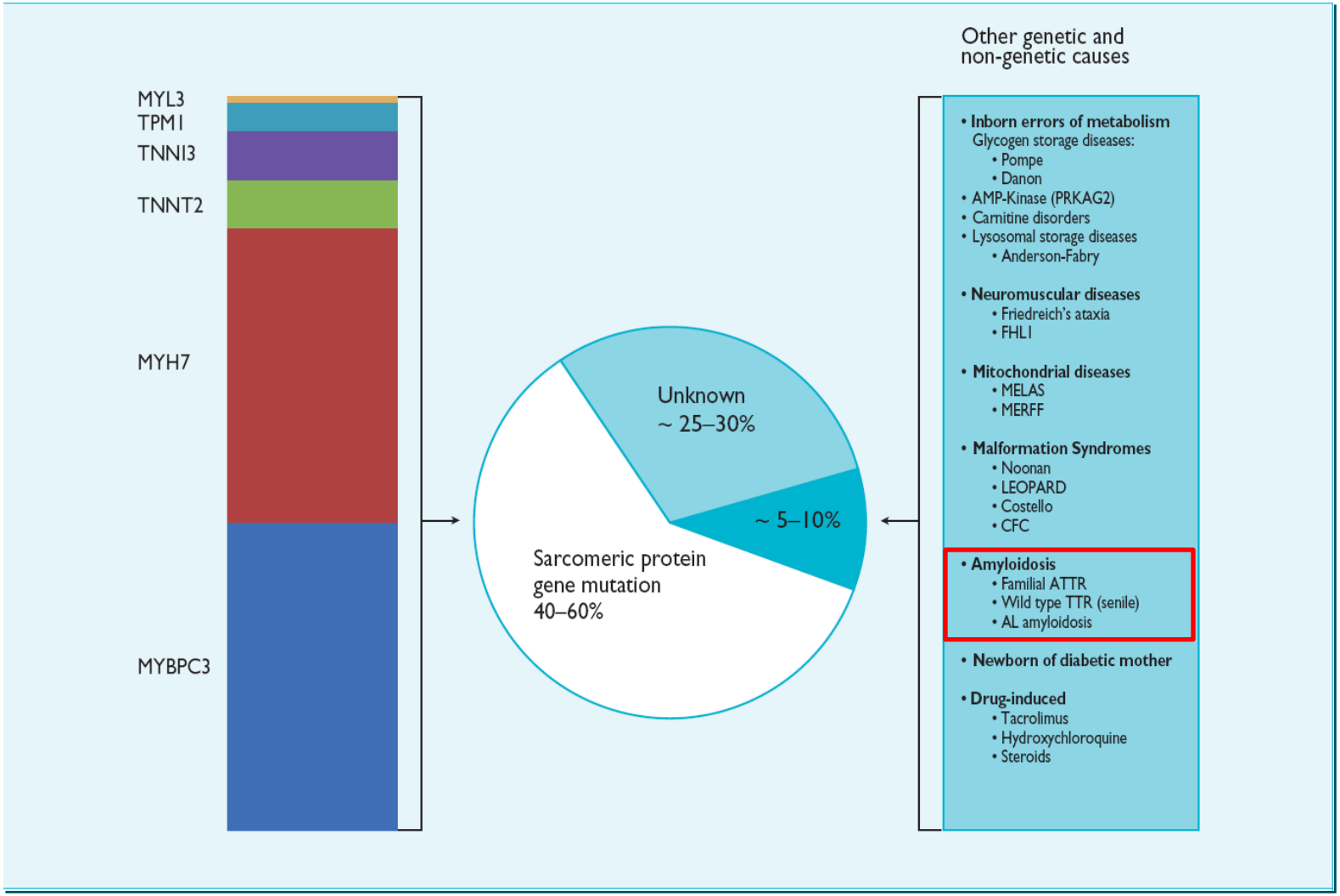
Concentric LVH in the absence of HTN or aortic valve stenosis: differential diagnosis



ESC guidelines hypertrophic cardiomyopathy Eur Heart J 2015.

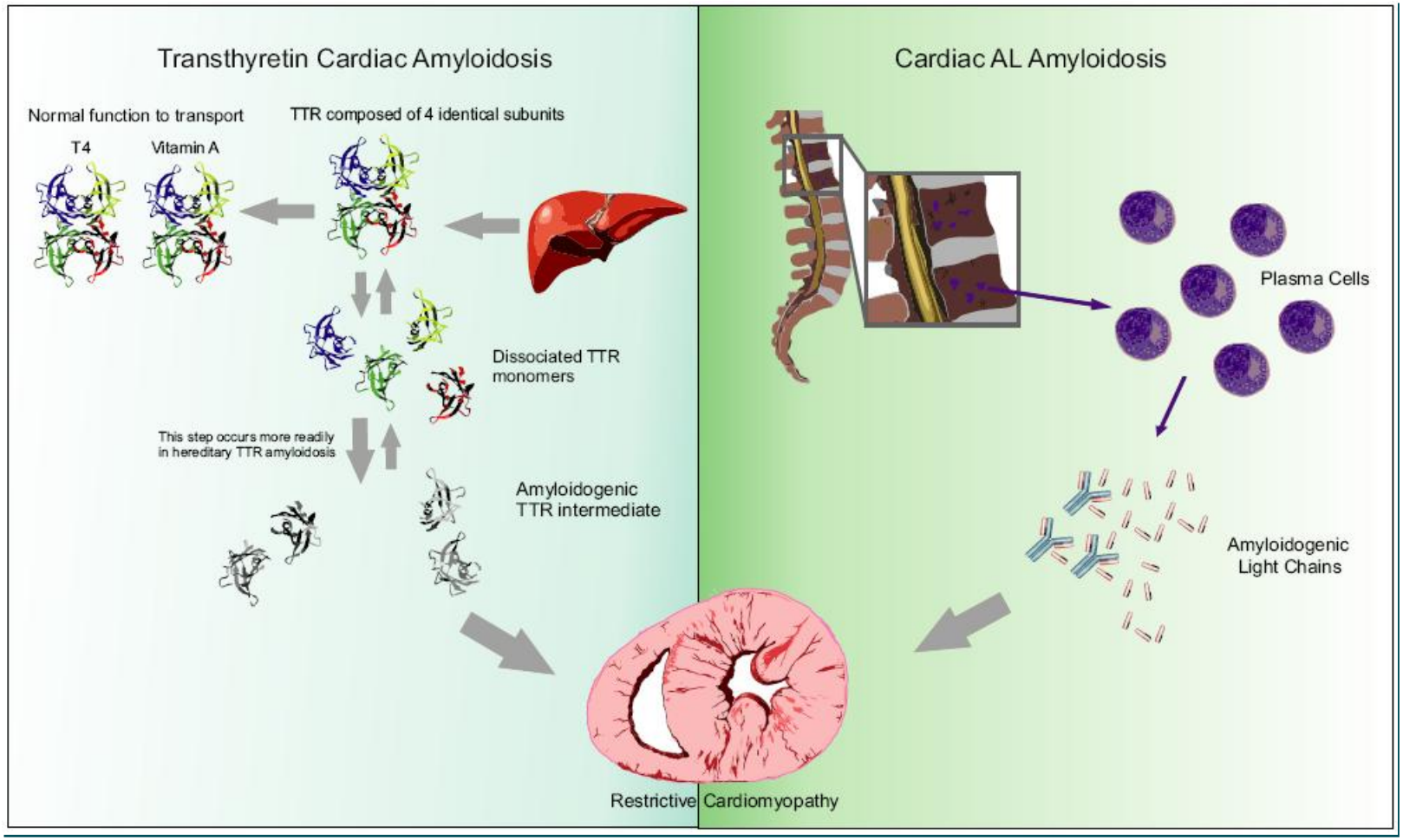
What is cardiac amyloidosis?

Table 1 *The commonly diagnosed types of cardiac amyloidosis*

	Primary (AL)	ATTRwt (SCA)	ATTR V122I	ATTR T60A	ATTR V30M
Precursor/ amyloidogenic protein	Monoclonal immunoglobulin light chain	Wild-type transthyretin	Variant transthyretin	Variant transthyretin	Variant transthyretin
Average age at presentation	60–70 years	70–80 years	≥60 years	≥60 years	30–40 or 50–60 years
Common ethnicity	Any	Caucasian	African/ Caribbean	Caucasian (Irish)	Any (Portuguese, Swedish, Japanese)
Frequency of cardiac involvement	40–50%	Almost 100%	Almost 100%	Detectable in at least 90%	Uncommon
Other systemic involvement	Kidney, liver, soft tissue, nerves, spleen	Carpal tunnel (bladder, spine)	Carpal tunnel	Nerves	Nerves
Treatment	ASCT or chemotherapy. Consider cardiac transplantation followed by ASCT	Supportive	Supportive. Cardiac transplantation in young patients	Supportive	Liver transplantation (+cardiac transplantation) in select cases
Prognosis/median survival from diagnosis	Generally poor but variable	3–5 years	2–3 years	2.5–5.5 years	Good with liver transplantation but variable

Patel KS et al. J Intern Med 2015; 278: 126–144.

What is cardiac amyloidosis?



Patel KS et al. J Intern Med 2015; 278: 126–144.

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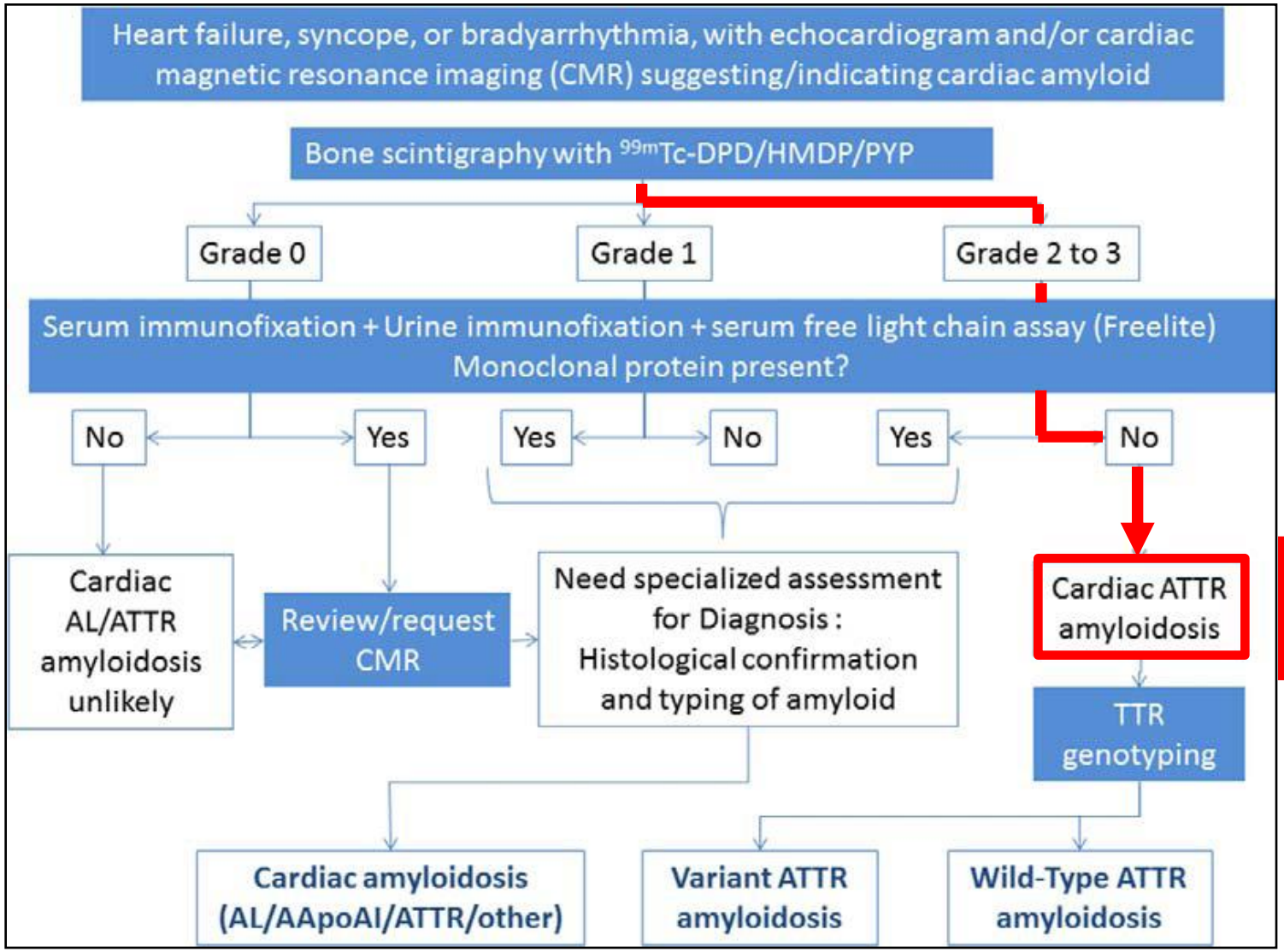
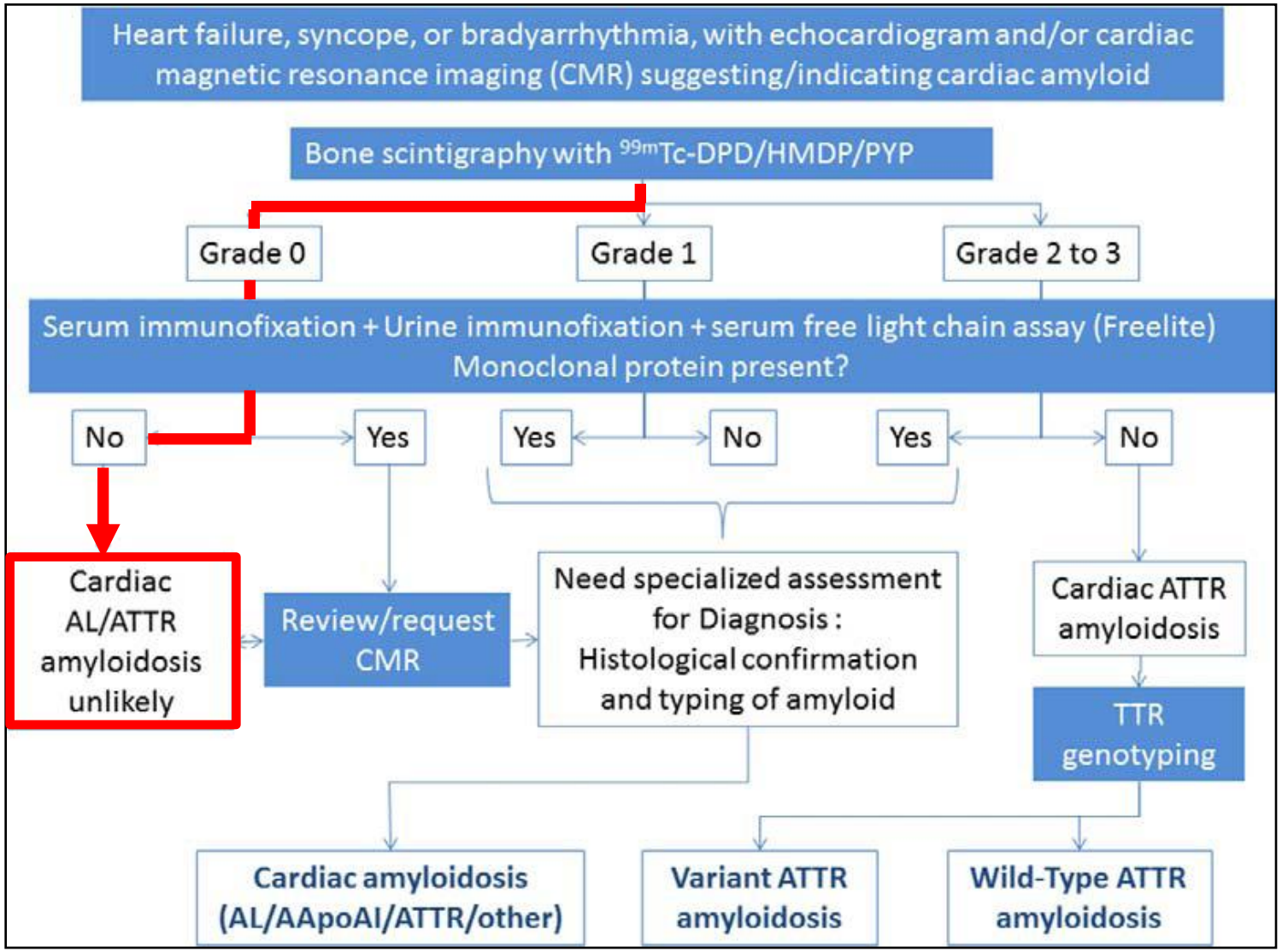
Diagnostic algorithm of cardiac amyloidosis



specificity and PPV = 100%!

Gillmore JD et al. Circulation. 2016;133:2404-2412.

Diagnostic algorithm of cardiac amyloidosis



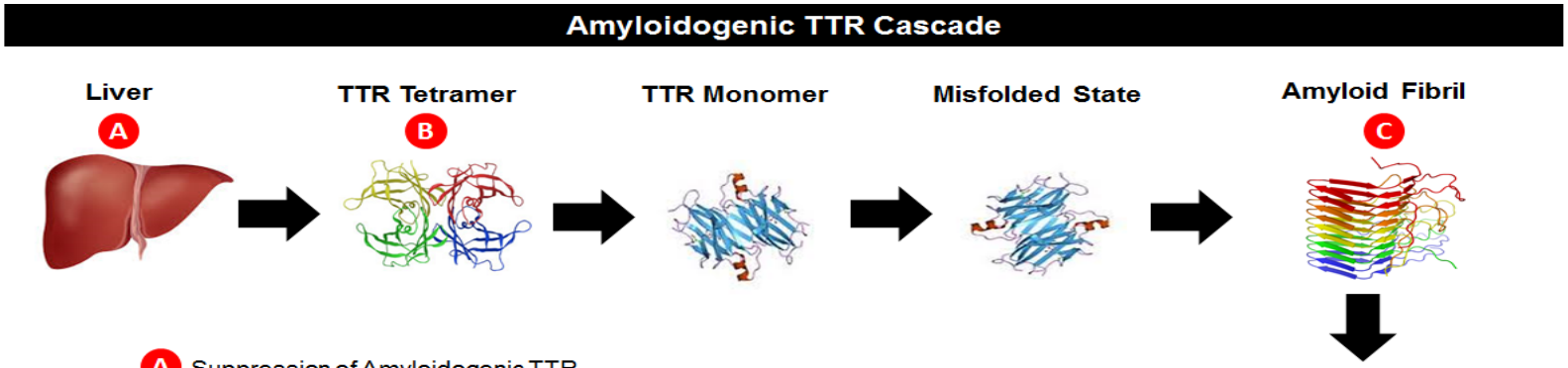
Gillmore JD et al. Circulation. 2016;133:2404-2412.

Indications for endomyocardial biopsy

- In cases of **suspected AL cardiac amyloidosis** if:
  - Skin fat aspirate/biopsy negative
  - Bone marrow aspirate negative

- In very rare cases of **suspected ATTR cardiac amyloidosis** and inconclusive bone scans (grade 1)

Specific treatment perspectives



TTR THERAPEUTIC DRUG CLASS / DRUG	MECHANISM OF ACTION	POTENTIAL RISKS	PIPELINE STAGE	ROUTE	DOSING	DRUG COMPANY
SILENCERS	A					
ASO	Suppresses hepatic TTR mRNA and serum TTR levels.	Injection site reaction	Phase 3	IV/SQ	300 mg	ISIS
siRNA	Small interfering RNA bound to the RNA-induced silencing complex mediates the cleavage of target messenger RNA. Delivery agents includes lipid nanoparticles (ALN-TTR01, ALNTTR02) and GalNAC conjugation (ALN-TTRSC).	Injection site reaction; LFT changes; Monocytosis	Phase 3	IV/SQ	5 or 7.5 mg/kg QD x5 days, QWK x5 weeks	Alnylam
STABILIZERS	B					
Tafamidis	Binds to thyroxine-binding sites of the TTR tetramer, inhibiting dissociation into monomers and blocking the rate-limiting step in the TTR amyloidogenesis cascade.	Urinary tract infection, diarrhea, abdominal pain	Phase 3	Oral	20 mg QD	Pfizer
Diflunisal	NSAID; Binds and stabilizes common familial TTR variants against acid-mediated fibril formation.	COX enzyme- related volume overload, GI bleeding, renal dysfunction	Phase 3	Oral	250 mg BID	Merck
DEGRADERS	C					
Doxycycline-TUDCA	Removes already-deposited amyloid.	Under investigation	Phase 2	Oral	100 mg BID/ 250 mg TID	West-Ward
Monoclonal anti-SAP Antibodies	Antibody against a normal non-fibrillar glycoprotein SAP promotes a giant cell reaction that removes visceral amyloid deposits.	Infusion site reaction	Phase 1	IV	To be determined	GSK

Back to Mrs M. 1949

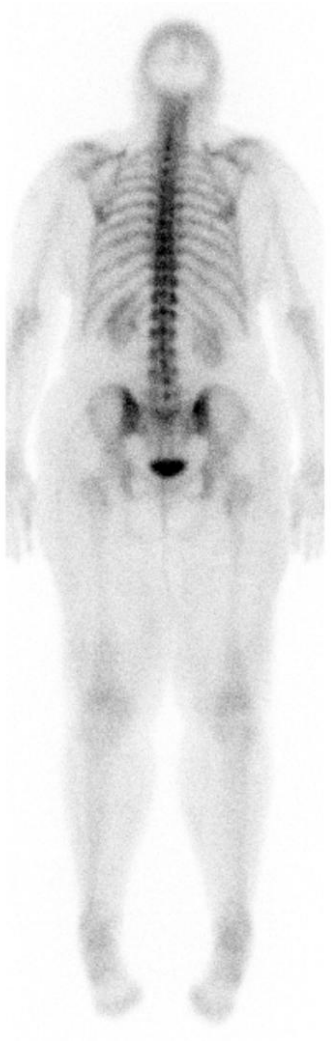
- **Protein electrophoresis**:
  - Paraprotein IgM lambda
  - Free lambda light chains 623 g/l (5.7-26.3)
  - No Bence Jones protein in the urine
- Beta-2 microglobulin: 2.6 mg/l (0.8-2.2)

- **=> High suspicion of AL amyloidosis**

- Skin fat biopsy: negative. Second biopsy: negative

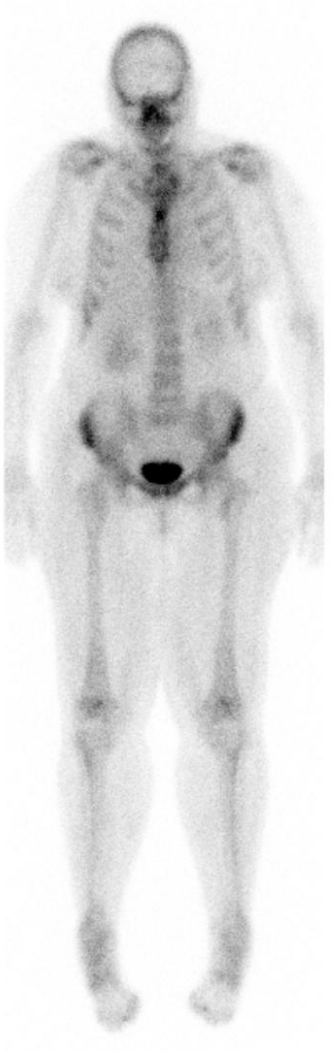
- Bone marrow aspiration: monoclonal plasmocytosis lambda 10% but no amyloid deposits

Mrs M. 1949: ^{99}mTc-DPD (bone) scintigraphy

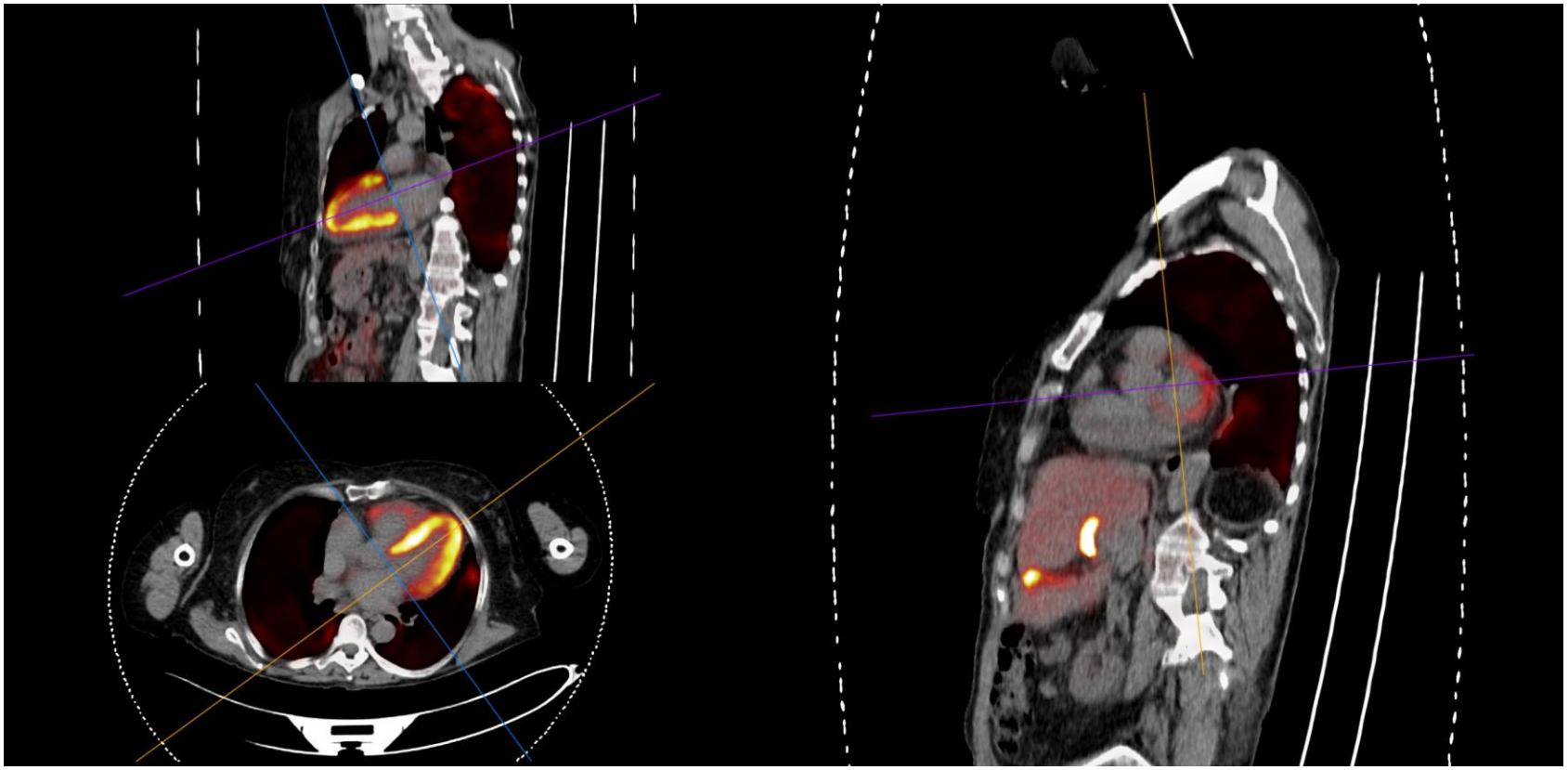


No cardiac uptake

(highly sensitive for ATTR amyloid deposits)



Mrs M. 1949: PET-CT (F18-Florbetapir)*



Radiotracer uptake in the LV, RV and atria walls

Highly suggestive of AL amyloïdosis

*experimental protocol

Mrs M. 1949

- **Protein electrophoresis**:
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- **=> High suspicion of AL amyloidosis**

- Skin fat biopsy: negative. Second biopsy: negative

- Bone marrow aspiration: monoclonal plasmocytosis lambda 10% but no amyloid deposits

- **Third skin fat biopsy: positive for amyloid AL!**

Evolution

- **March 31st 2015**: First cycle of chemotherapy (cyclophosphamide, bortezomibe and dexamethasone)
- **April 30th**: sepsis due to acute diverticulitis treated conservatively by antibiotics
- **May**: not considered for HTx because of age and poor immediate prognosis
- **June 12th**: sudden death at night

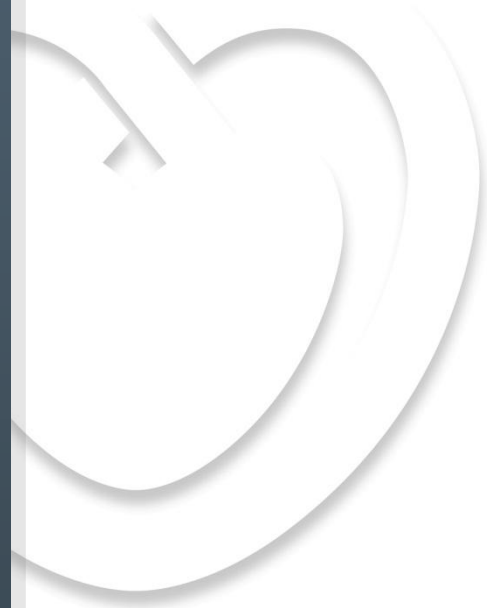
Take home messages

Cardiac amyloidosis should be suspected in any patient with HFPEF without a clear history of HTN

The diagnosis is complex and often requires a multidisciplinary approach including new imaging modalities

An accurate diagnosis is crucial since specific therapies targeting the different types of cardiac amyloidosis are or will be available soon

Thank you!



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