



9th **CHALLENGES in** **CARDIOLOGY**

JUNE 28th - 29th 2019
Palace Hotel Monte Real

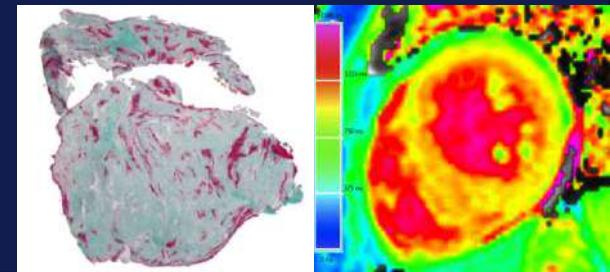


Transthyretin Cardiac Amyloidosis

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Department of Internal Medicine II, Division of Cardiology

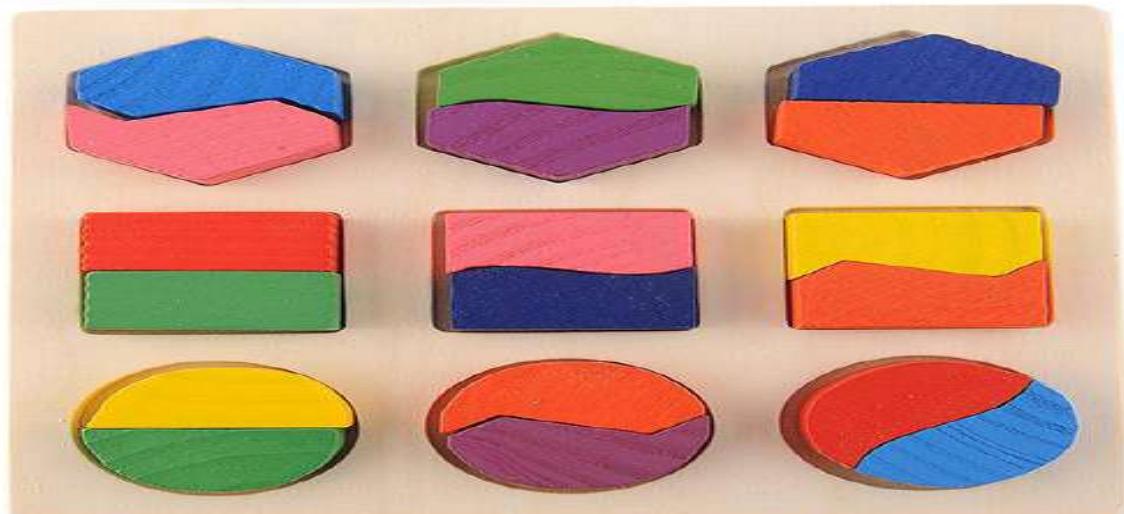
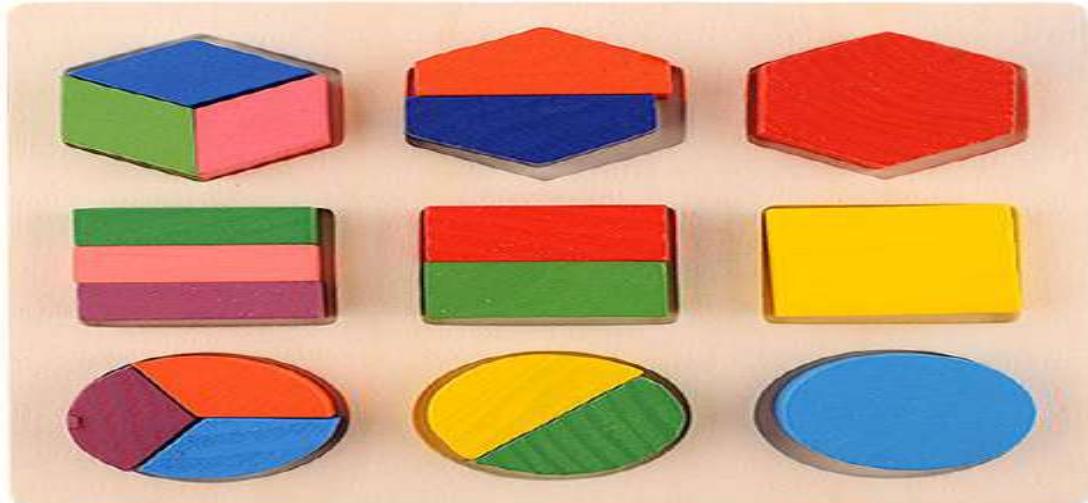


Disclosures

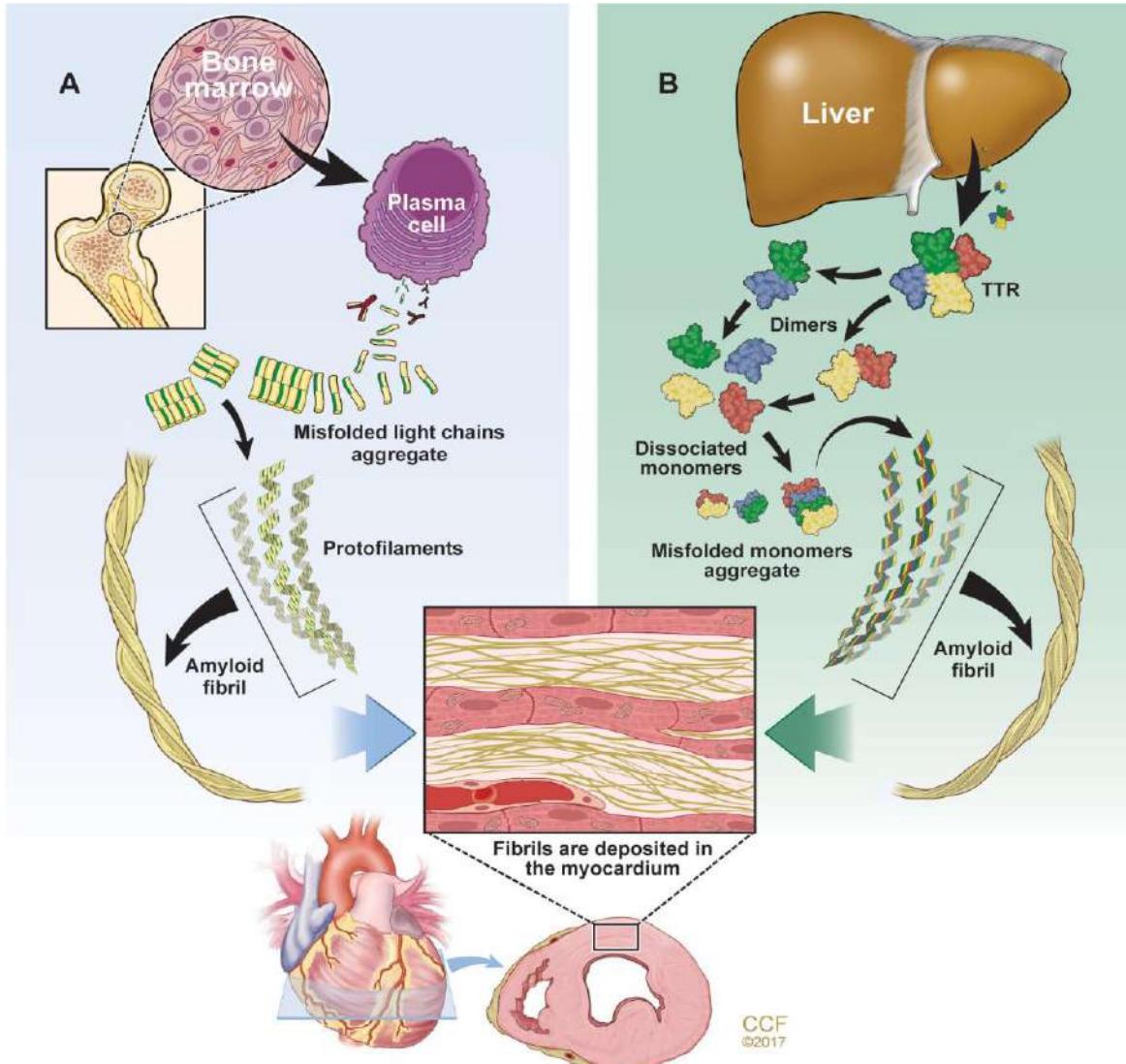
- Speaker fees and congress supports from Bayer, Novartis, Anylam, Pfizer, AOP.
- Research grants from the Austrian Society of Cardiology and Pfizer.



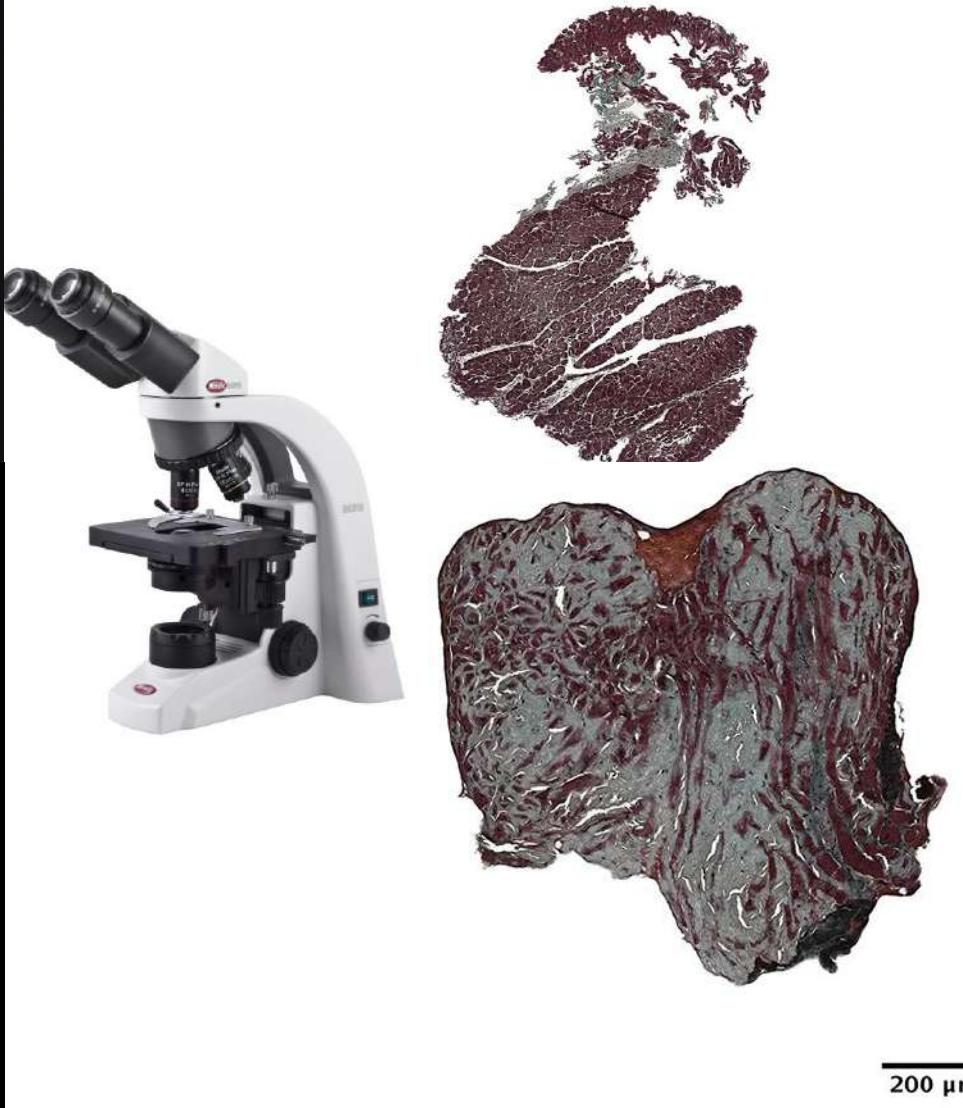
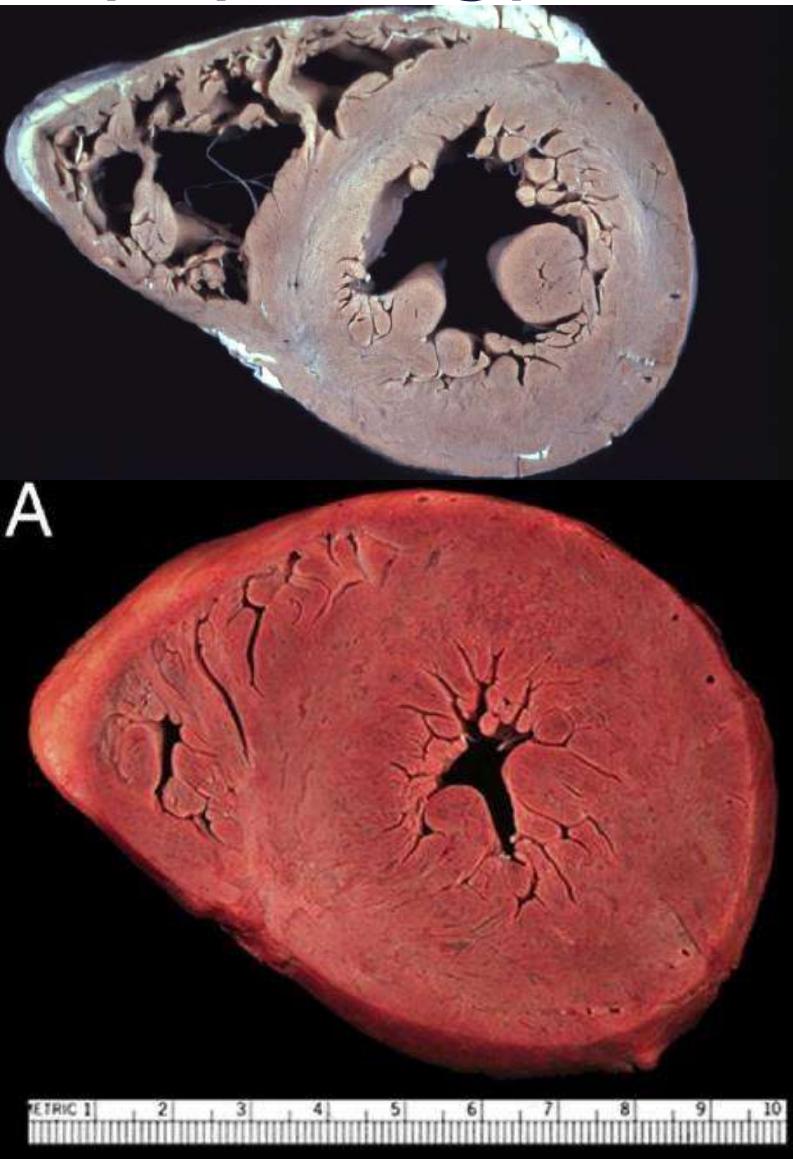
Amyloidosis- What's that?



Pathophysiology



Pathophysiology



Duca F et al. Eur J Heart Fail. 2017; Seward JB JACC 2010; University of Ottawa Department of Pathology and Laboratory Medicine
(<http://www.med.uottawa.ca/patho/eng/Public/cardio/nheartshort.gif>)

Signs and symptoms

- Dyspnea
- Chest pain
- Dizziness/Syncope
- Rhythm disorders (atrial fibrillation/flutter, ventricular tachycardia)
- **Heart failure medication not tolerated (e.g BB)**
- **Bilateral carpal tunnel syndrome**
- Polyneuropathy
- Orthostatic hypotension
- Erectile Dysfunction
- Obstipation/Diarrhea
- Weight loss



Signs and Symptoms



How to diagnose cardiac amyloidosis?

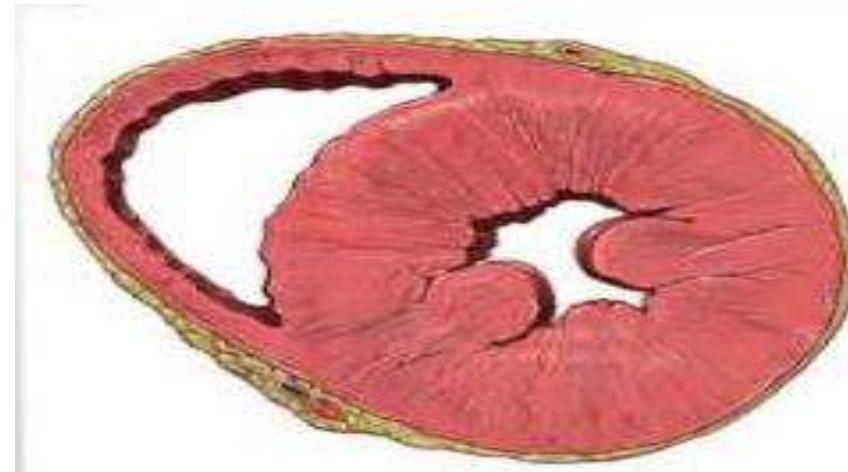
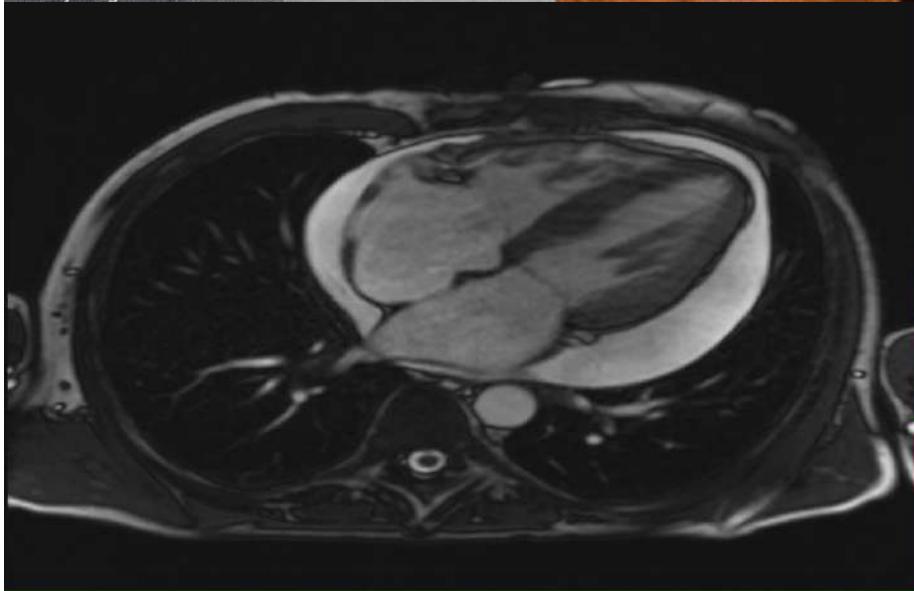


Think About It

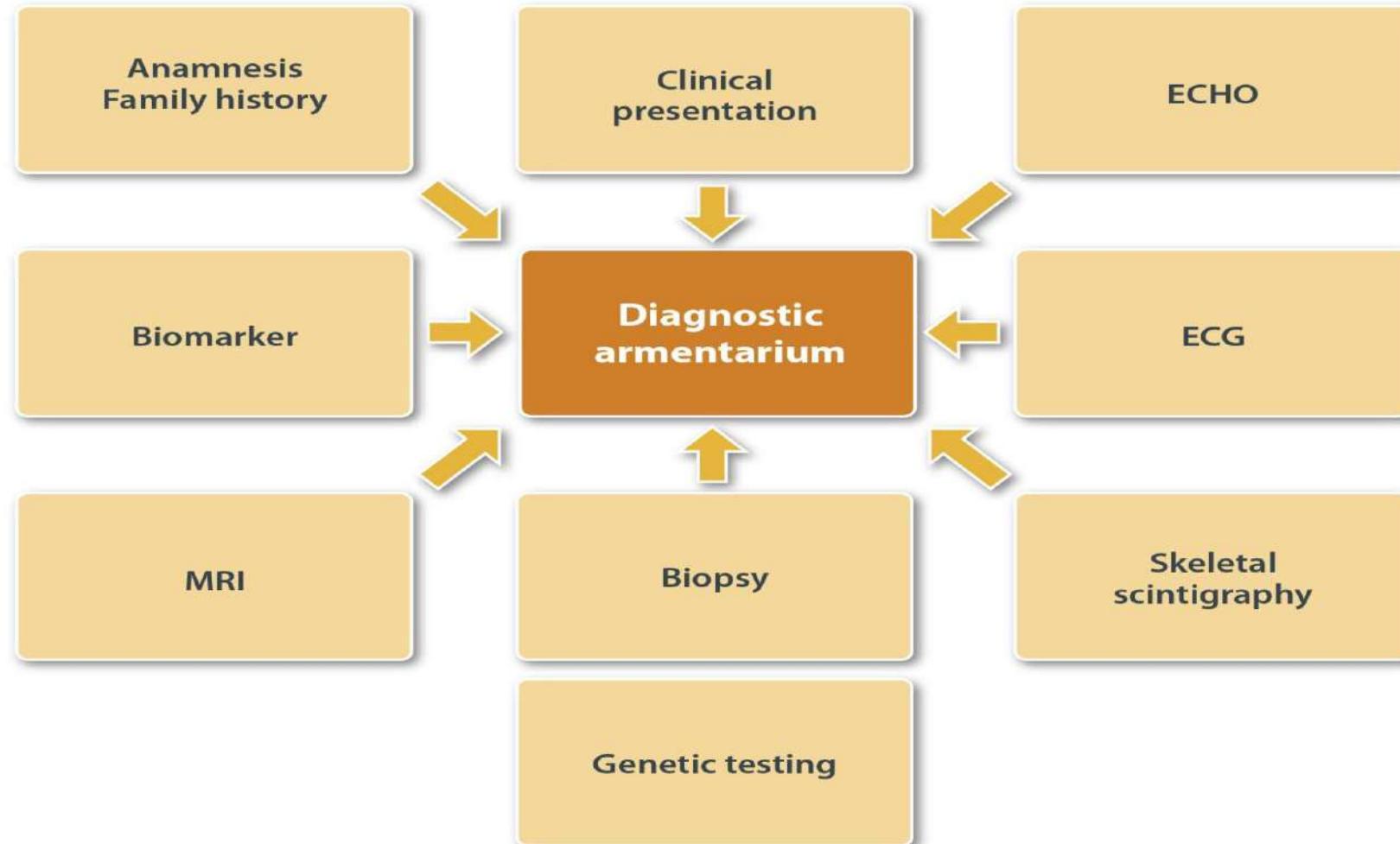
The classic ATTRwt phenotype



© Getty Images / Patrik Giardino



Diagnostic armamentarium



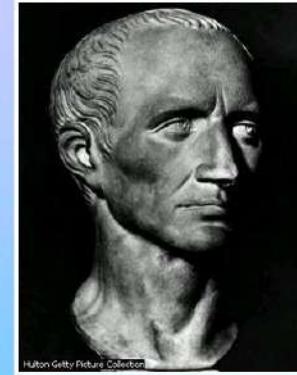
Diagnostic tools

- Biopsy is considered as the gold standard
 - HOWEVER, a negative biopsy does not exclude amyloidosis
-> aim for the affected organ.

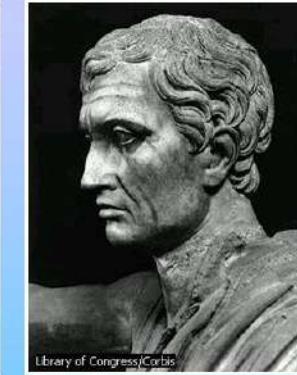
The histological

1. Triumvirat von 60–53 v. Chr.

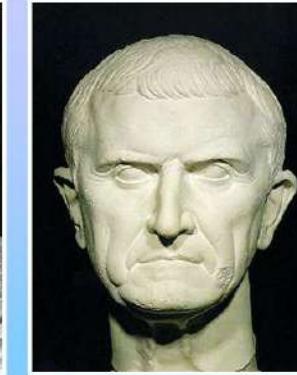
Gaius Julius Caesar



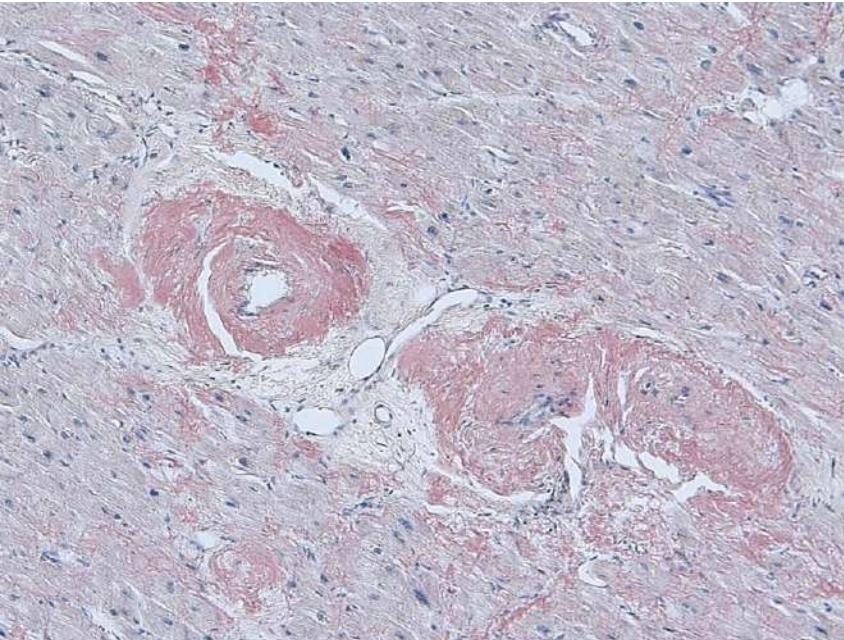
Gnaeus Pompeius



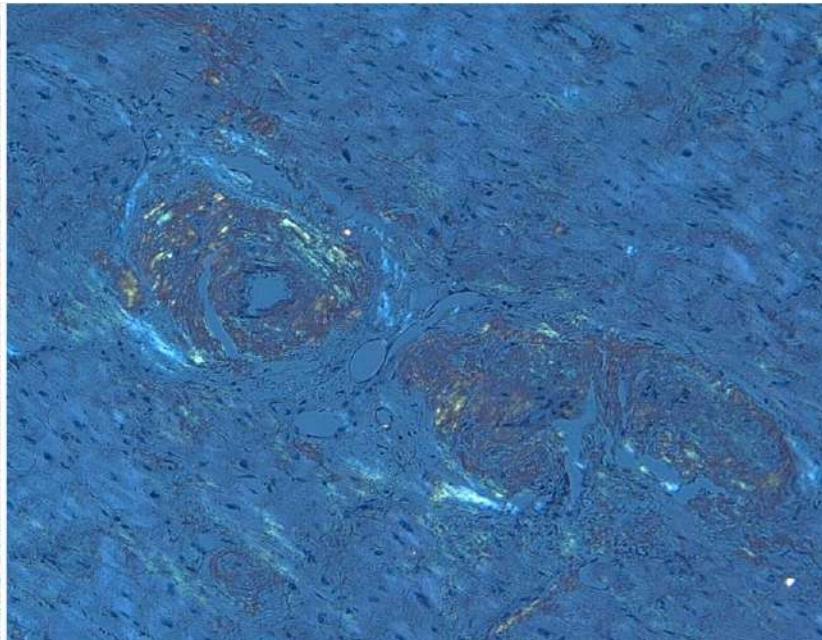
Marcus Licinius Crassus



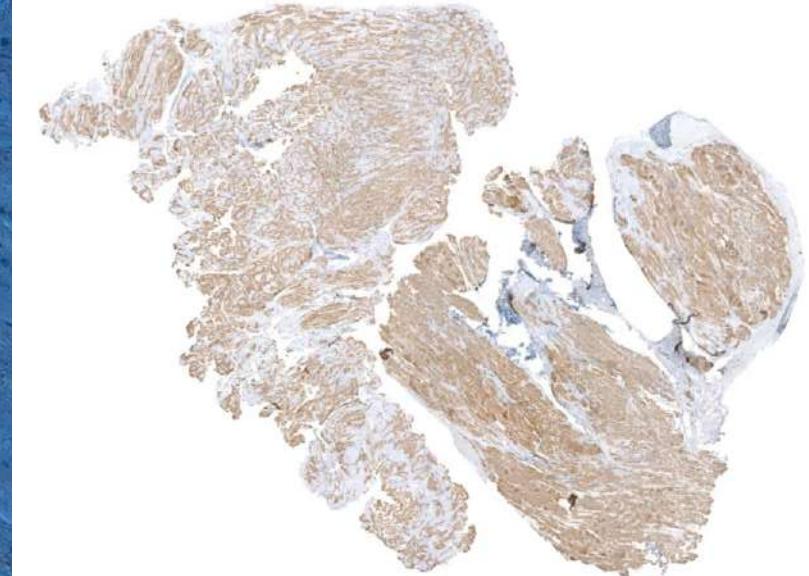
Congo red



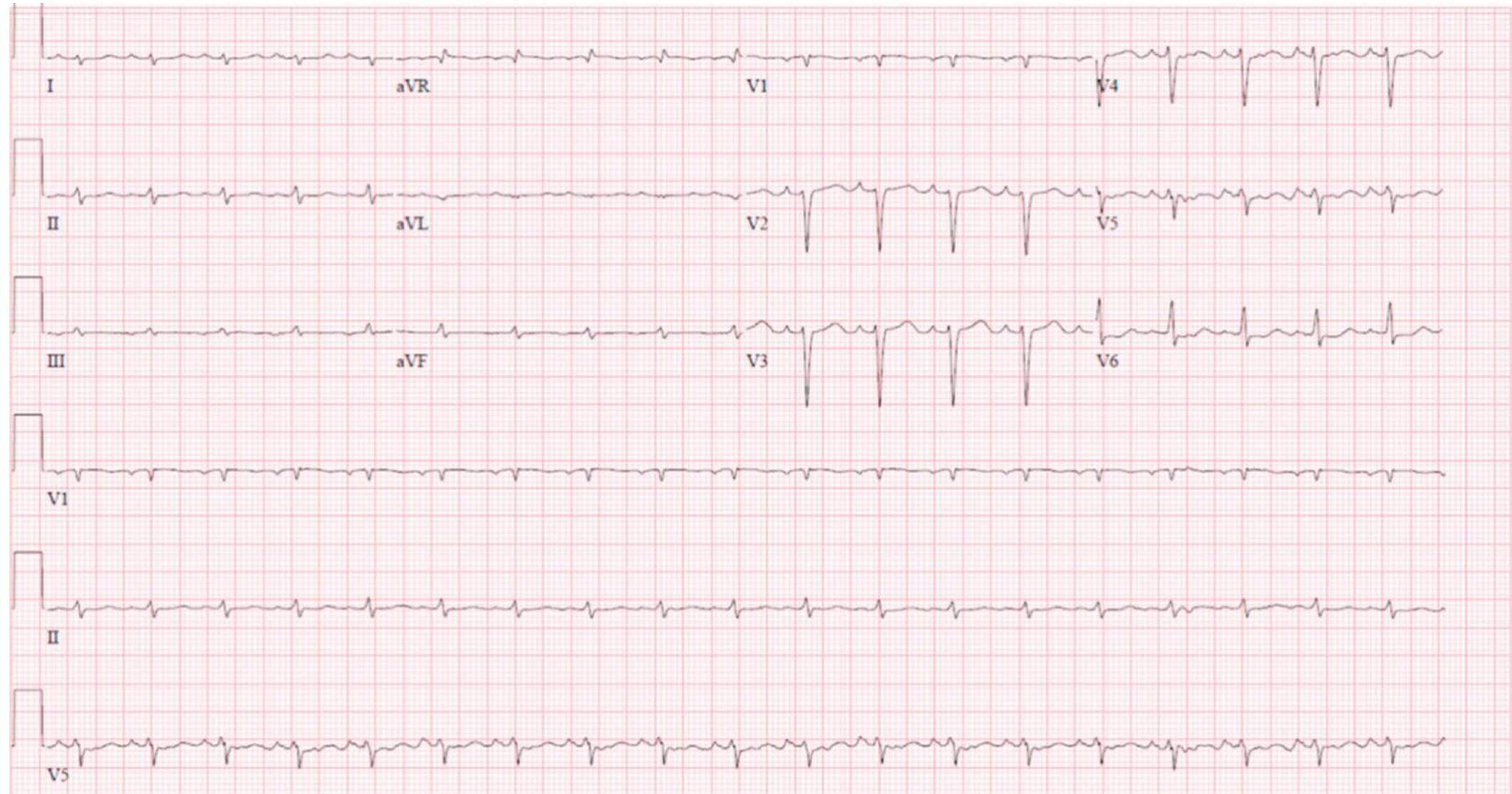
Apple green birefringence



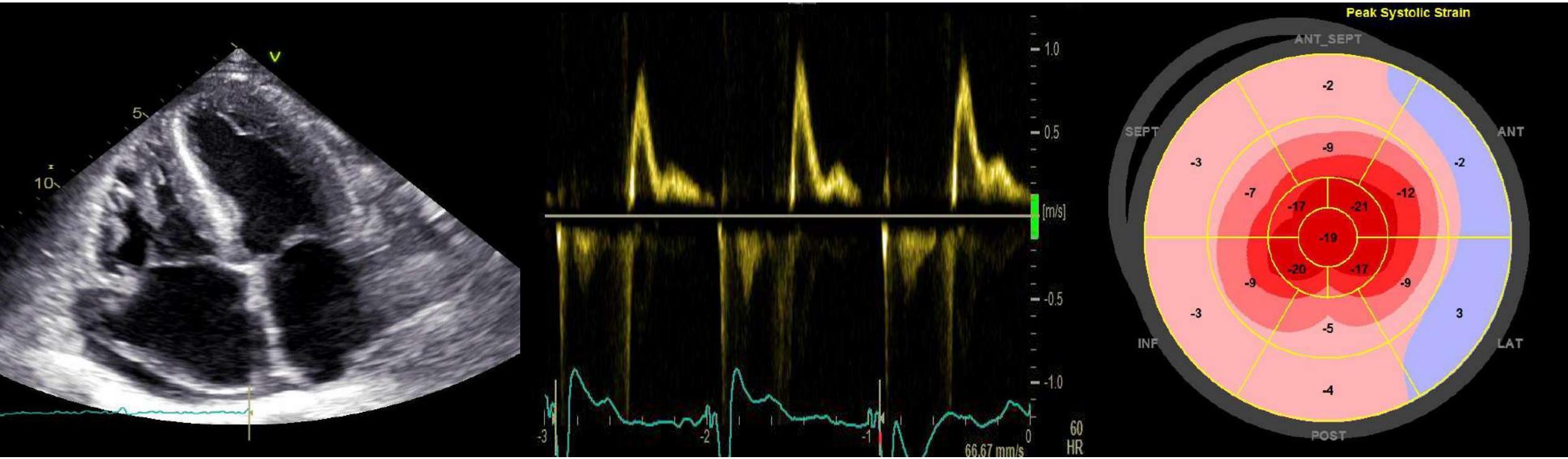
Immunohistochemistry



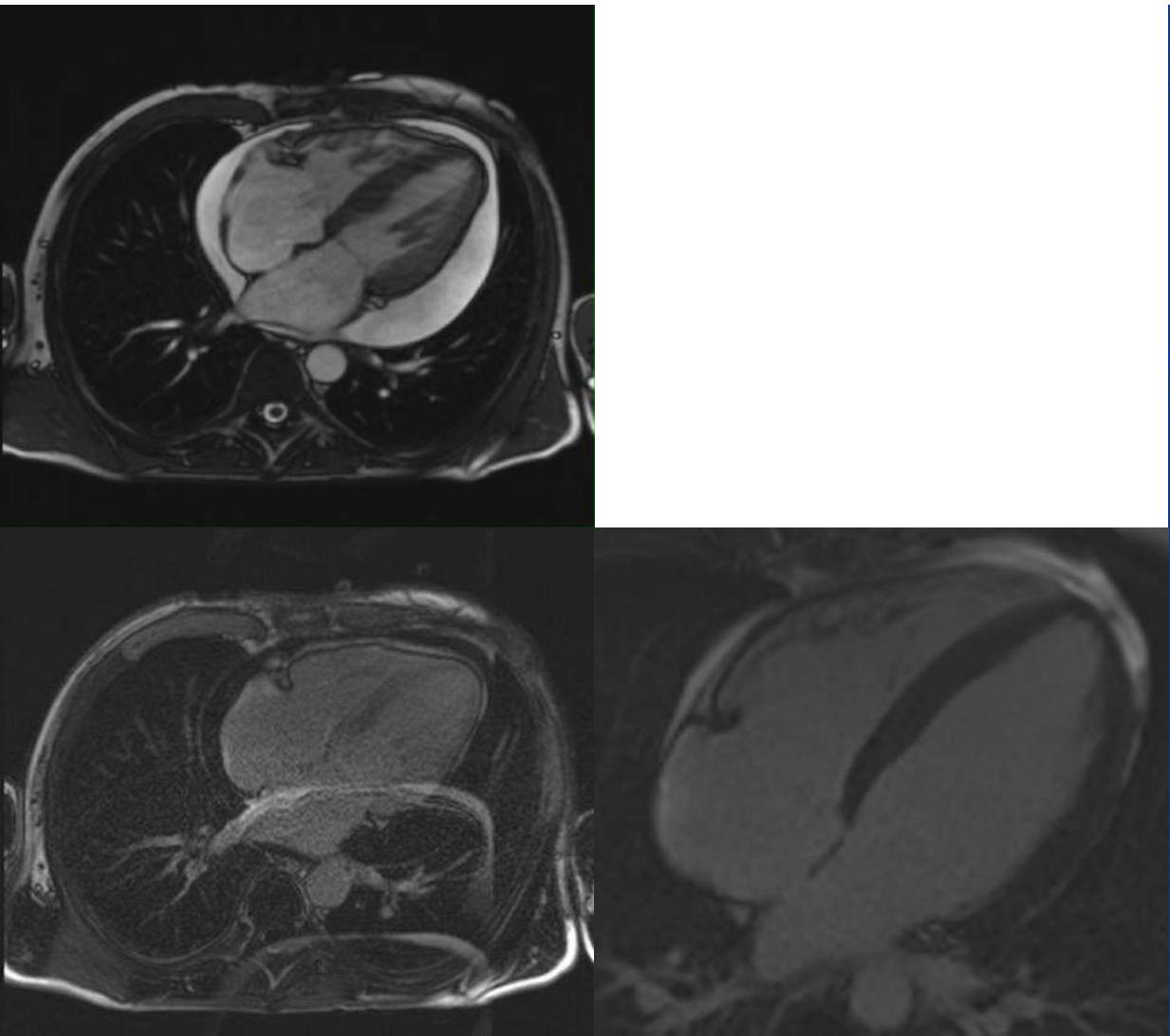
Electrocardiogram

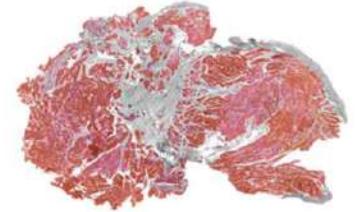
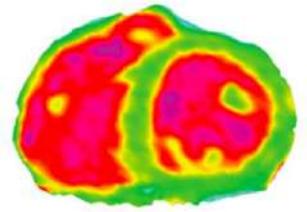
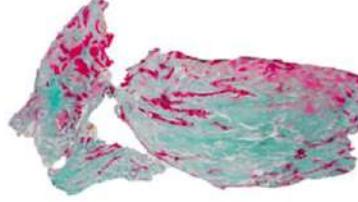
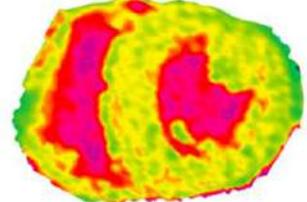


Echocardiography



Cardiac magnetic resonance imaging - T1 mapping



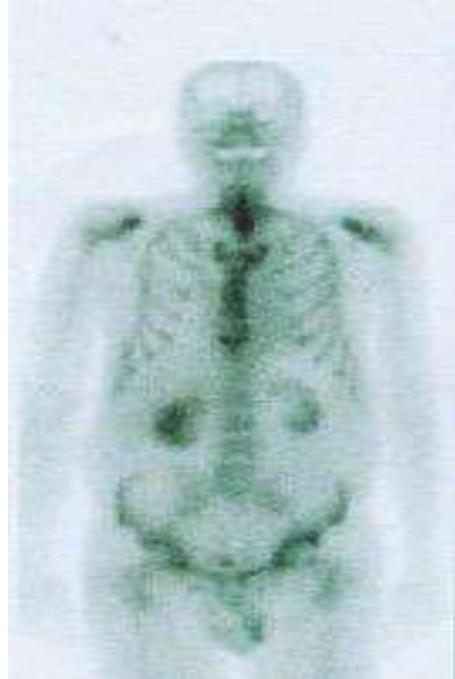
Histo-ECV	Immunohisto-ECV	MOLLI-ECV
Patient with cardiac light-chain amyloidosis and low amyloid load		
		
Extracellular volume: 36.4%	Light-chain amyloid: 27.6%	Extracellular volume: 35.4%
Patient with transthyretin cardiac amyloidosis and high amyloid load		
		
Extracellular volume: 70.9%	Transthyretin amyloid: 64.0%	Extracellular volume: 72.6%
Pros <ul style="list-style-type: none">- Gold standard method for amyloid detection- Broad availability Cons <ul style="list-style-type: none">- Procedural risk- Risk of sampling error- Overestimates myocardial amyloid content	Pros <ul style="list-style-type: none">- Gold standard method for amyloid classification and amyloid content quantification. Cons <ul style="list-style-type: none">- Procedural risk- Risk of sampling error- Not broadly available	Pros <ul style="list-style-type: none">- Excellent agreement with histology- No procedural risk Cons <ul style="list-style-type: none">- Not specific for amyloid- Not broadly available- Overestimates myocardial amyloid content



Bone scintigraphy



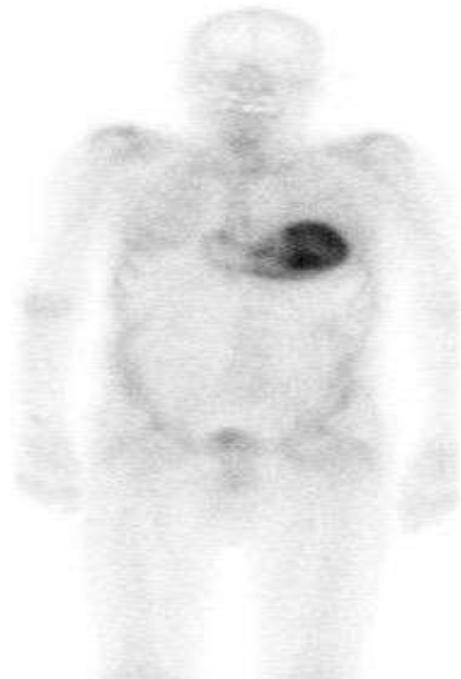
Grade 0



Grade I

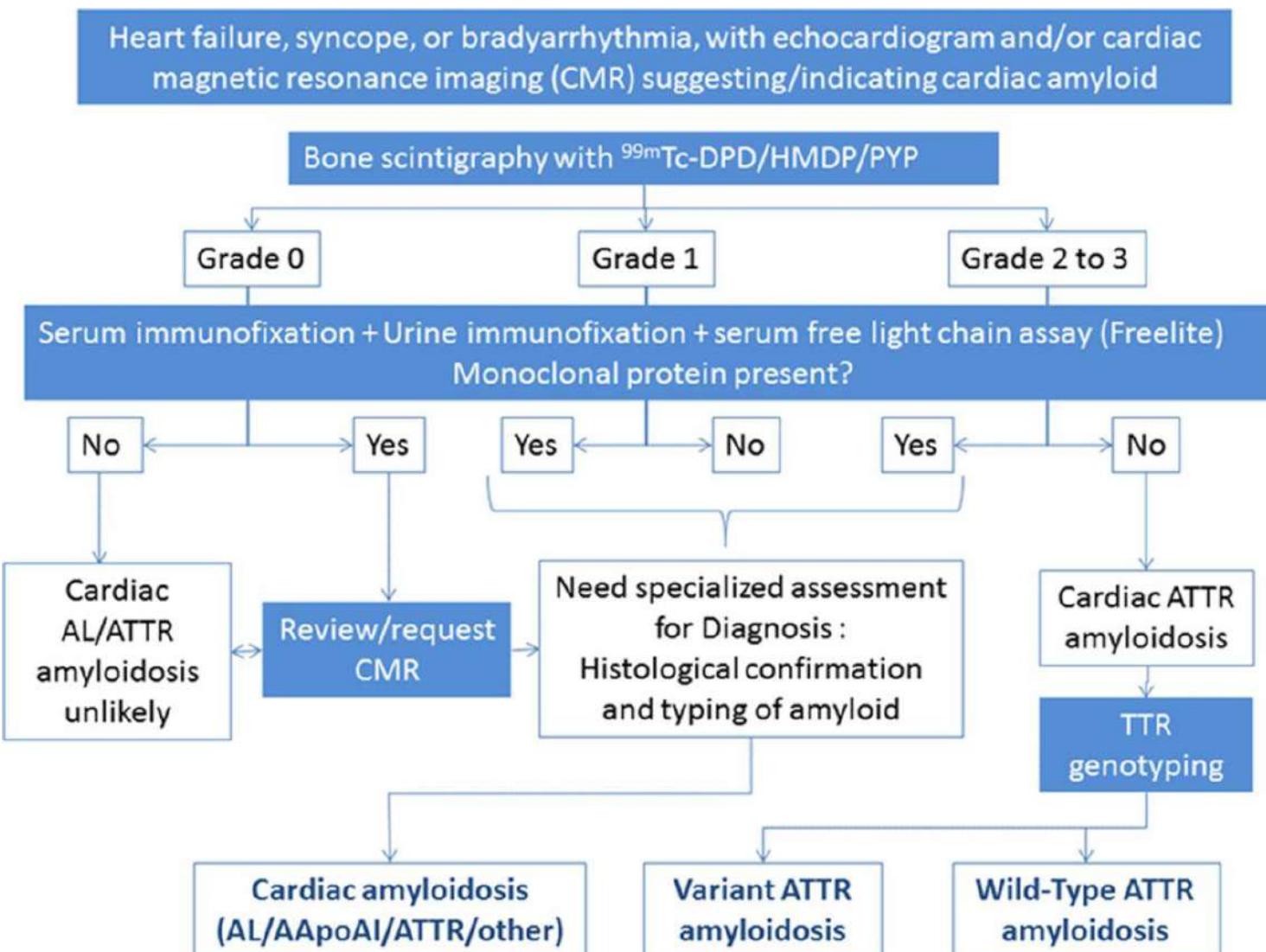


Grade II



Grade III

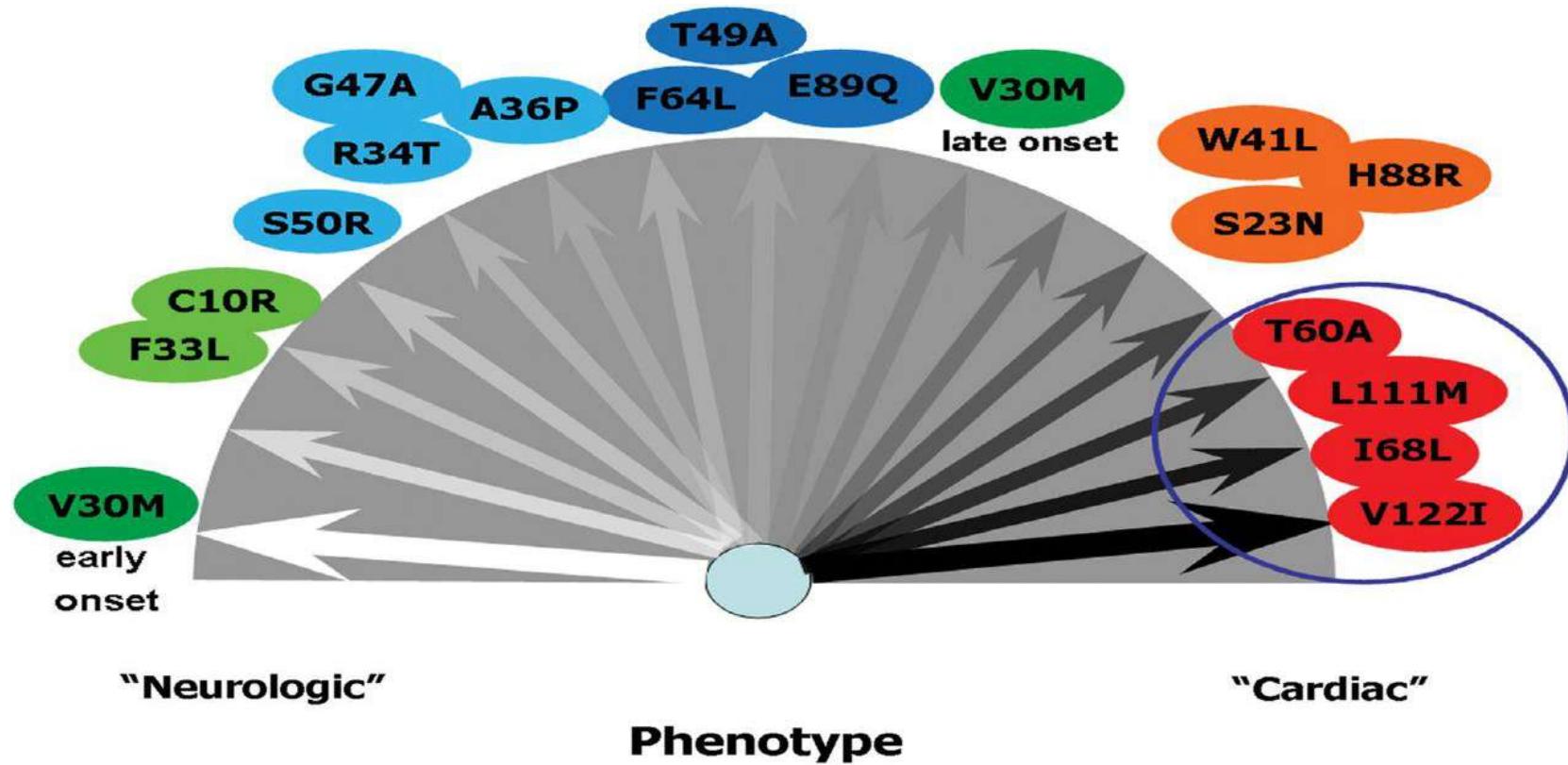
Diagnostic algorithm

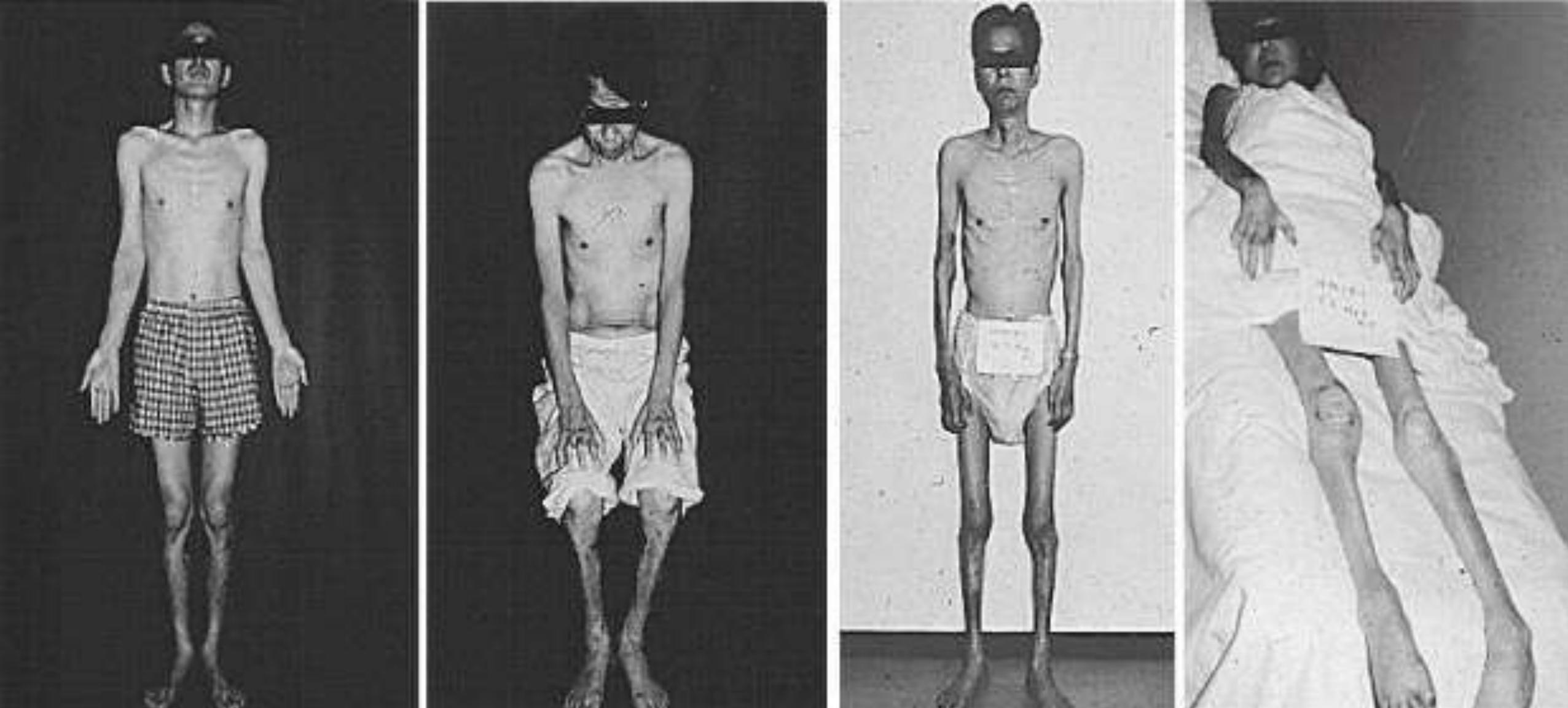


Genetics

- >140 mutations of the TTR gene
 - Most common: Val50Met (Portuguese mutation)
 - Austria: His180Arg
- Autosomal dominant inheritance
 - Variable penetrance
 - Anticipation (mother/son > father/daughter)
 - Variable phenotype (even within one family)

Genotype - Phenotype





stage 1

stage 2

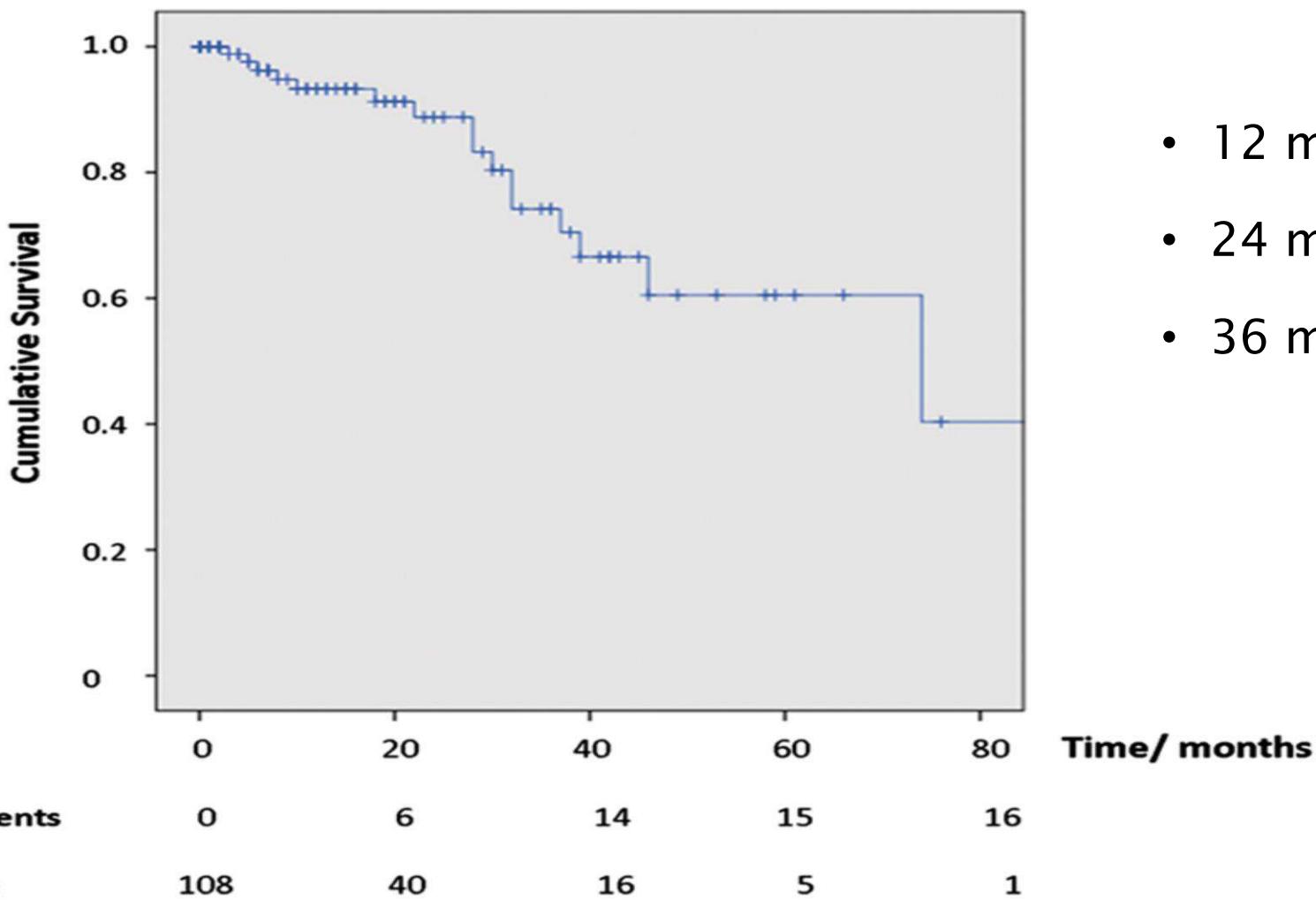
stage 3

stage 4

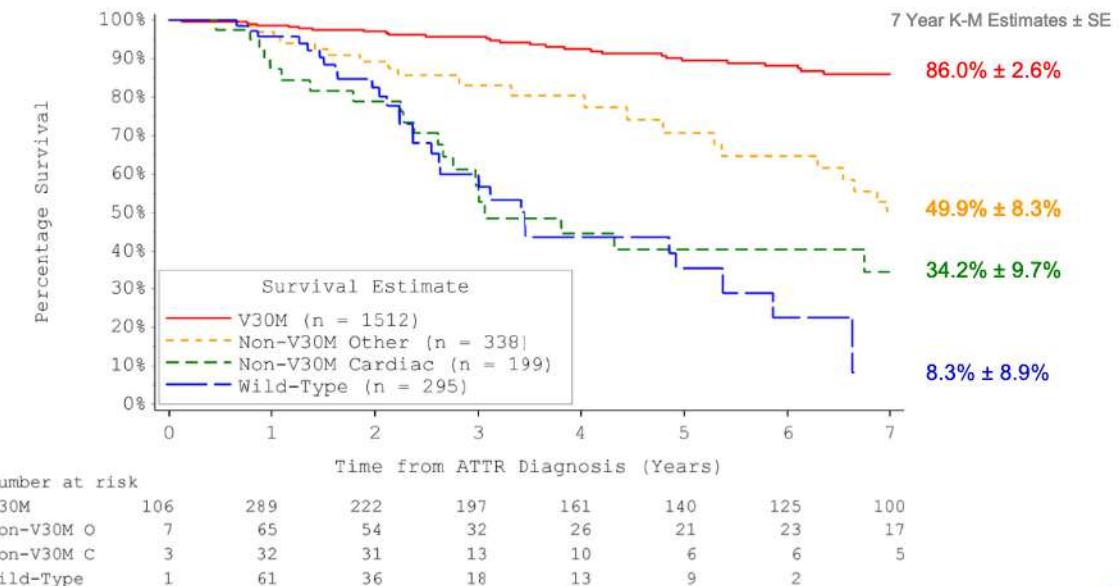
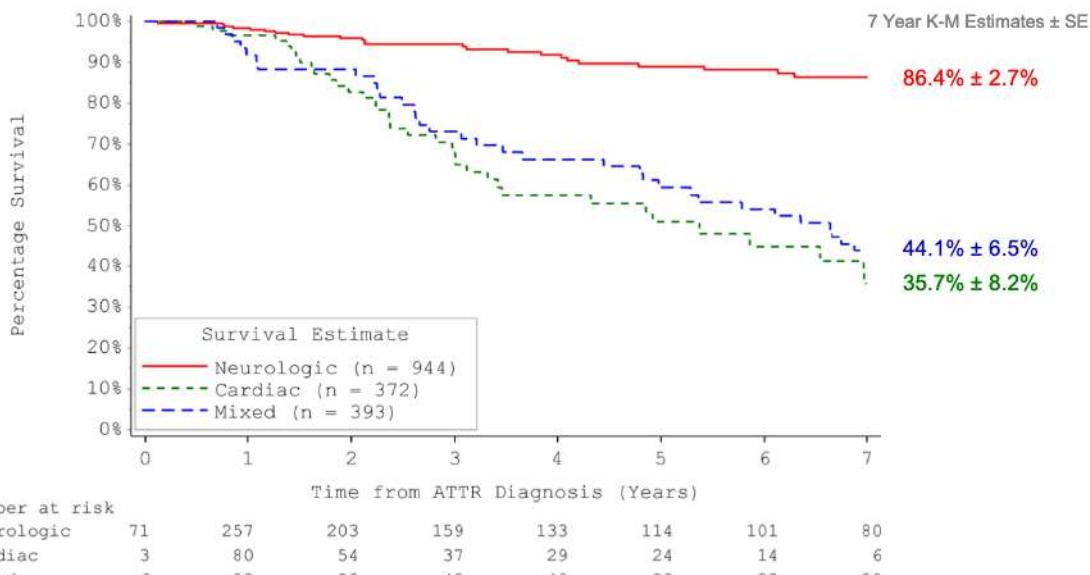
Pre-symptomatic testing

- Only after extensive information about possible consequences
- Country specific legislation
- Structured monitoring of mutation carriers during the pre-symptomatic phase

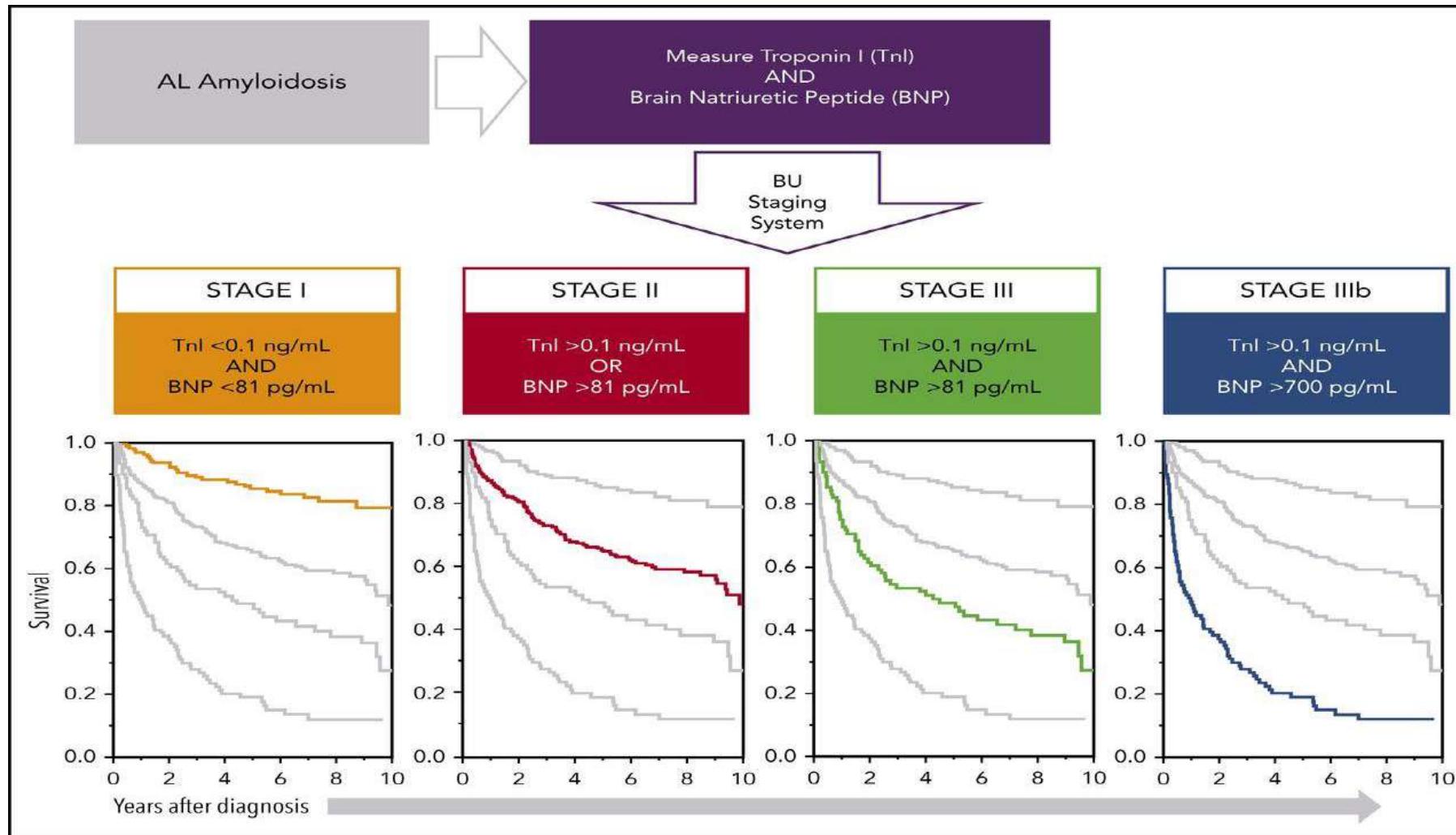
Prognosis



Prognosis



Prognosis



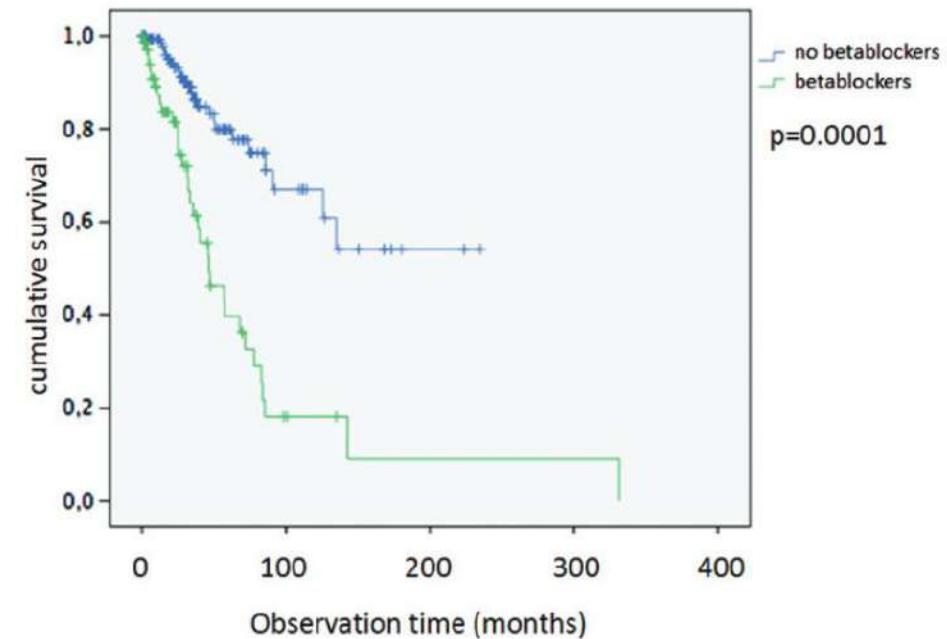
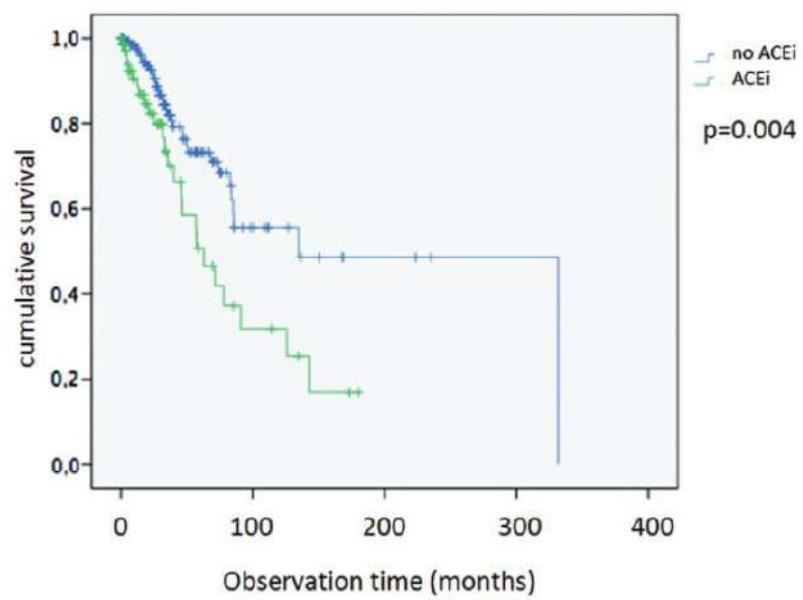
The Gretchen question:

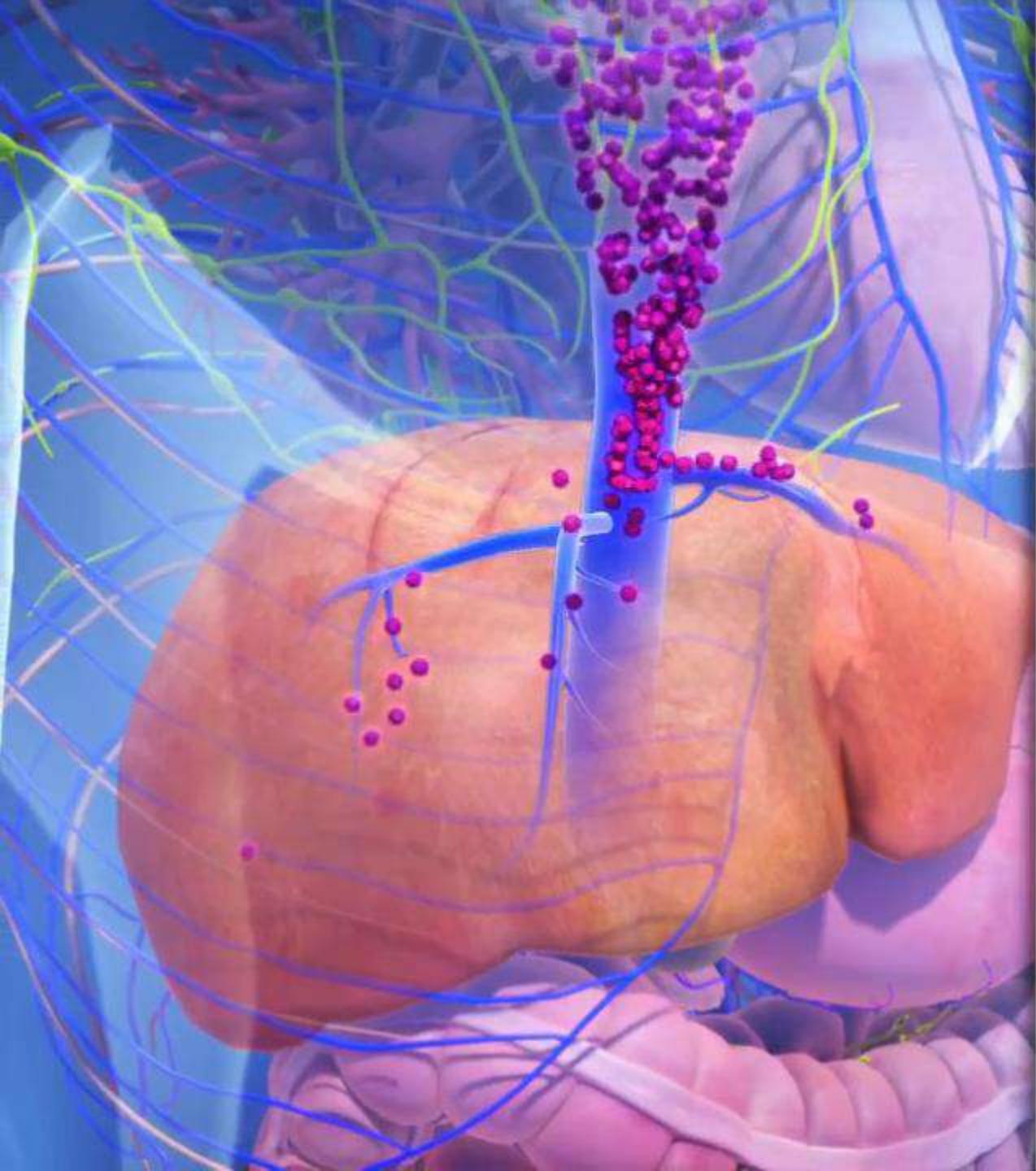


Therapies?

Supportive therapies

- Diuretics (cave: cardiac output)





Specific therapies

- TTR stabilizer
 - Tafamidis (approved only for mTTR-PNP)
- Reduction of TTR production
 - [Livertransplantation (junger patients, Val50Met)]
 - Onpattro (approved only for mTTR-PNP)
 - Inotersen (approved only for mTTR-PNP)
- Elimination of deposited amyloid

Summary

- “Orphan disease” – Think about it
- Cardiomyopathy and (or) polyneuropathy
- Specific treatments finally on the horizon

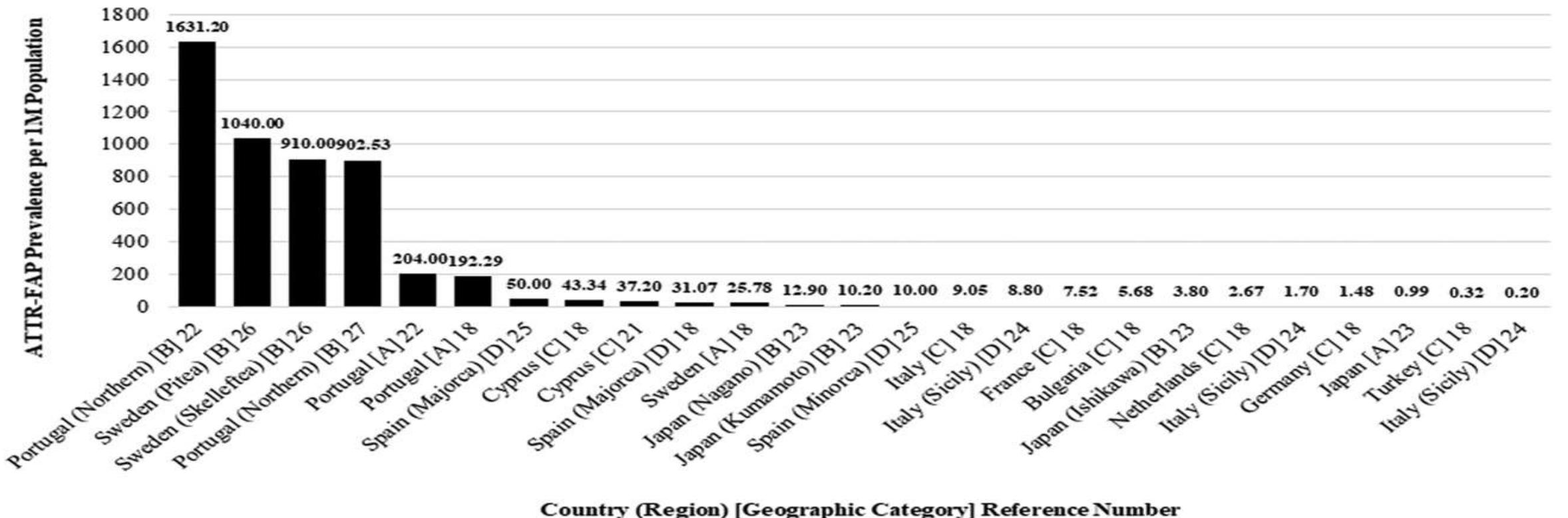
Thank you for your attention!

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Epidemiology

- Orphan disease
- Endemic areas: Portugal, Sweden, Japan.
- Prevalence: 10186 (5526 – 38468)

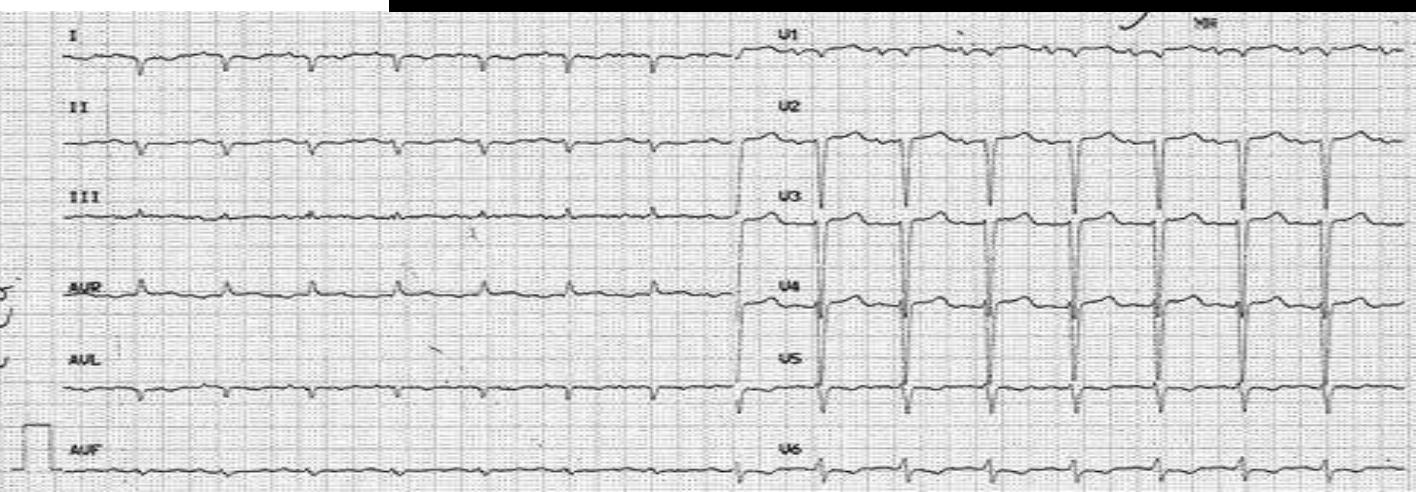


Worst case report



Case presentation

- NYHA: I
- CCS: I
- Lab:
 - NT-proBNP 1027pg/ml
- Lungfunction:
 - Normal
- Diagnosis: **LV hypertrophy due to AH**
 - Start: ACE-Inhibitor

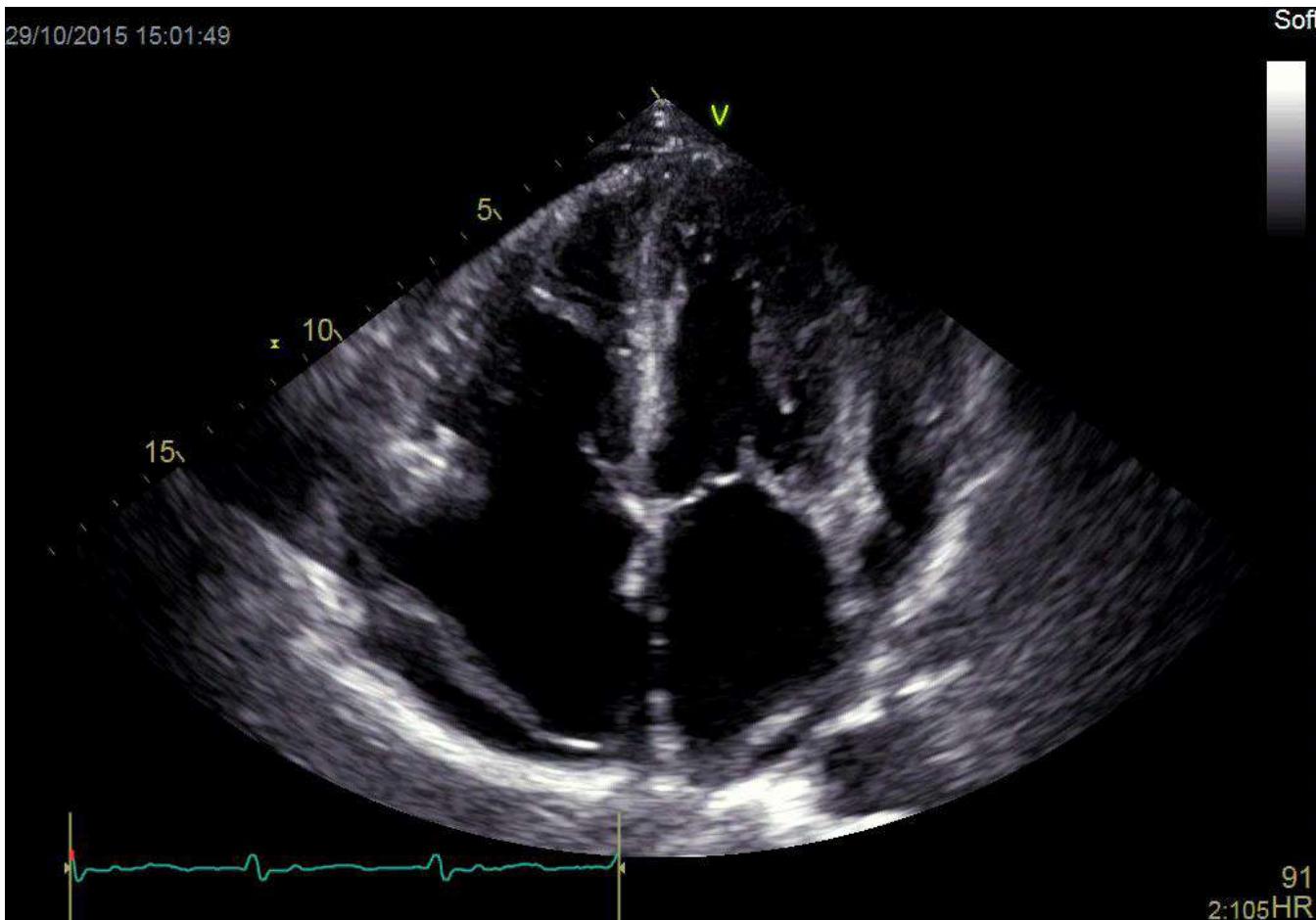


1 year later....

- Sinustachycardia 115 bpm in Ruhe.
 - Start: Beta-Blocker
- Cardiac decompensation:
 - NYHA IV
 - NT-proBNP: 17275 pg/ml
 - Inpatient treatment for iv. diuresis

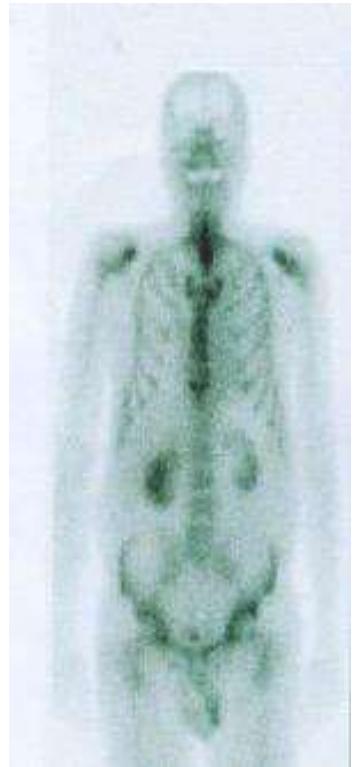
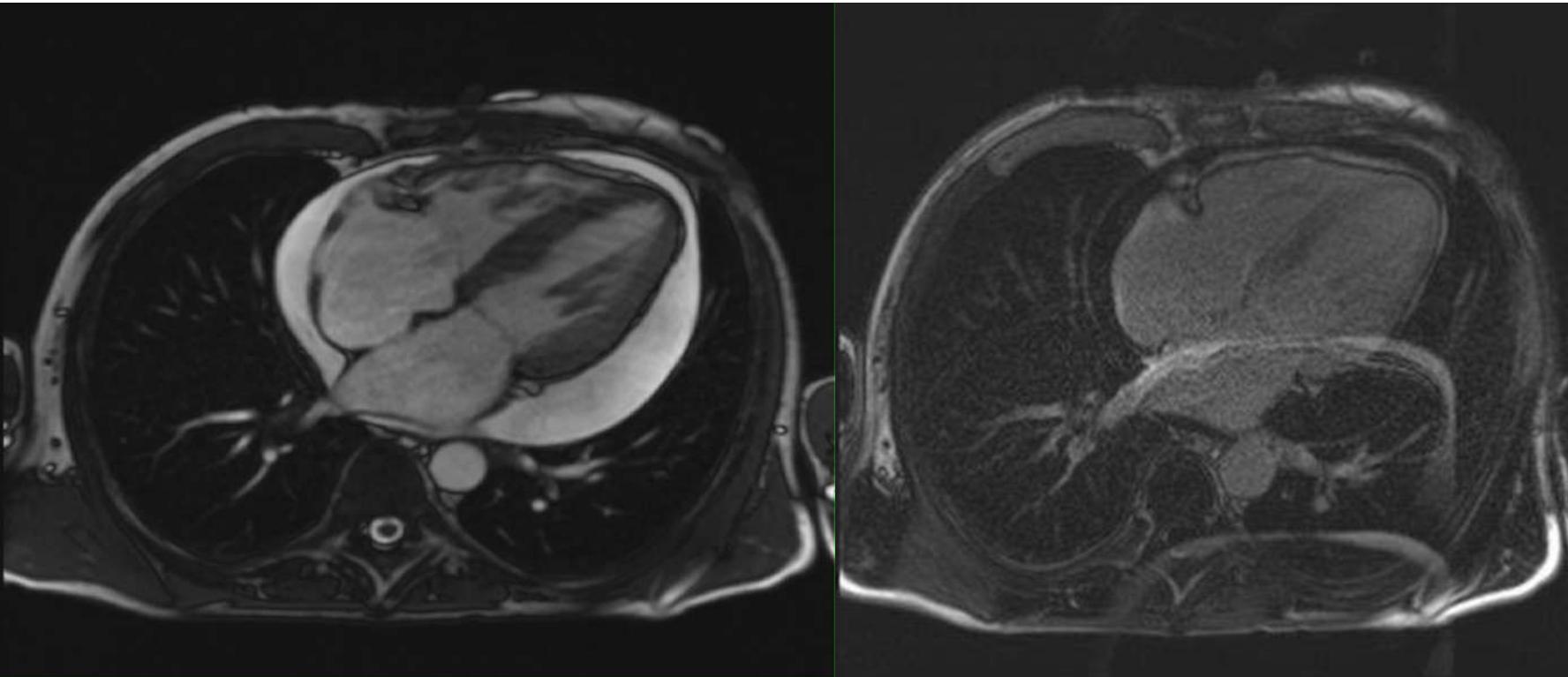
1 year later....

- Report: amyloidosis possible



1 year later....

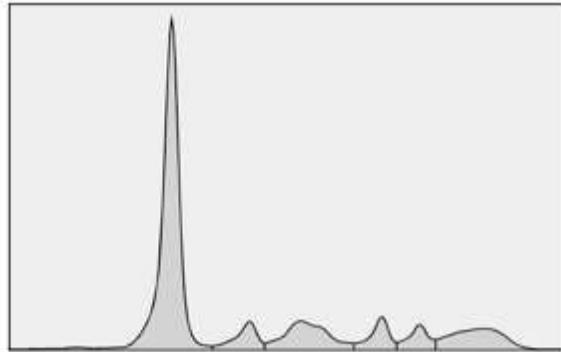
- MRI:
- DPD:



1 year later....

- Lab values:

Serum Amyloid A	↑	19.70	0 - 6.4	mg/L
Freie Kappa Leichtketten Sie.		9.55	6.7 - 22.4	mg/L
Freie Lambda Leichtketten Sie.	↑	297.00	8.3 - 27	mg/L
Freie Leichtketten				
Kappa/Lambda Ratio Sie.	↓	0.03	0.31 - 1.56	



Immun-Fixation

- Bone marrow biopsy:

- **AL amyloidosis**

1 year later....

- Recurrent cardiac decompensations
- Immunotherapy with Darzalex® (Daratumomab, CD38 Antibody)
- Stemcell harvesting
- Listing for HTx Aug. 2017
- HTx: 11.2017
- Bone Marrow transplant: planned 2019