Cardiac Amyloidosis

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Objectives

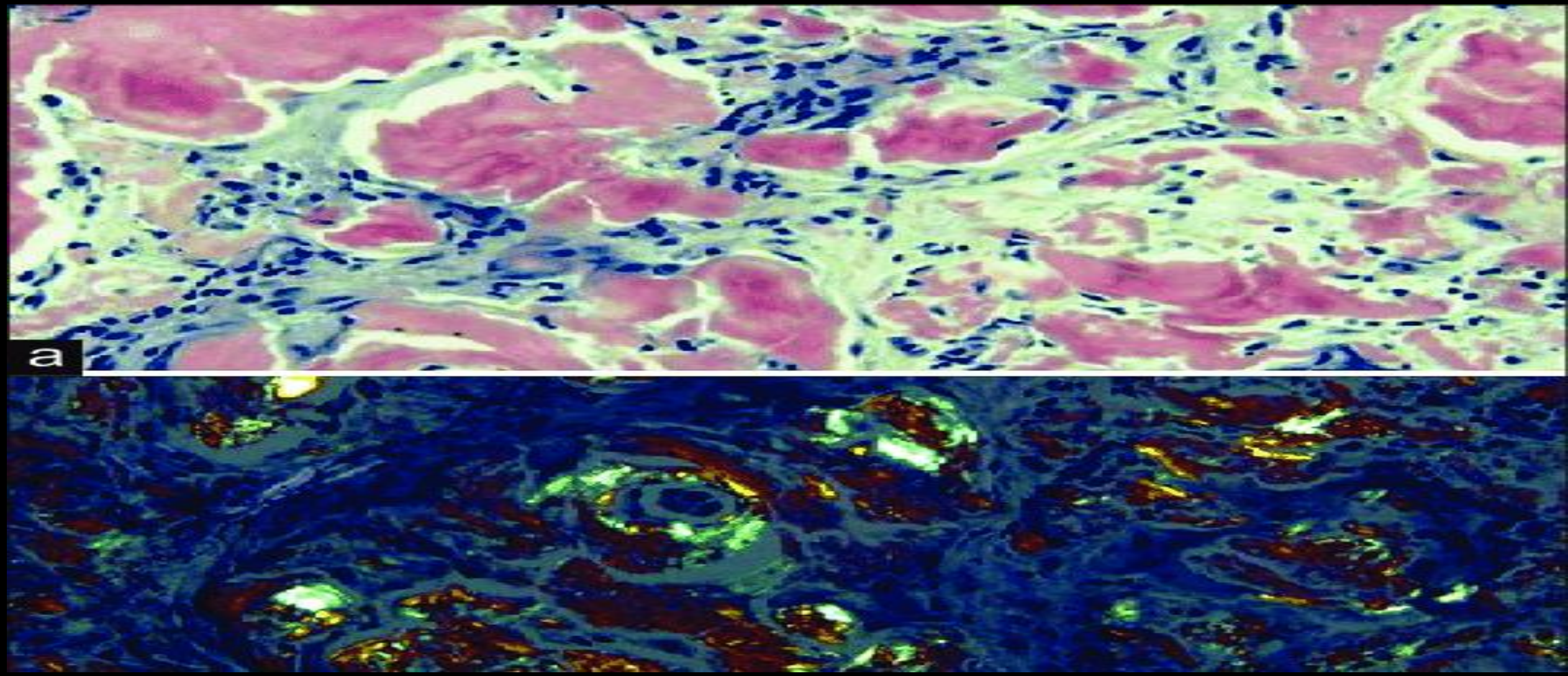
- 1. Recognize that cardiac amyloidosis is under diagnosed
- 2. Understand that the differentiation between AL and a-TTR amyloid is vital
- 3. Recognize the clinical manifestations of amyloidosis
- 4. Understand the risk factors related to amyloidogenesis
- 5. Be able to stage cardiac amyloidosis and understand the prognostic impact of early detection
- 6. Become familiar with appropriate testing
- 7. Understand management and treatment options

Disclosures: None

- Amyloid is a general term used to refer to the extracellular tissue deposition of highly ordered fibrils.

- Transthyretin/light chains

- The characteristic appearance (under polarized light microscopy) of amyloid tissue is that of an apple green color when staining with Congo red dye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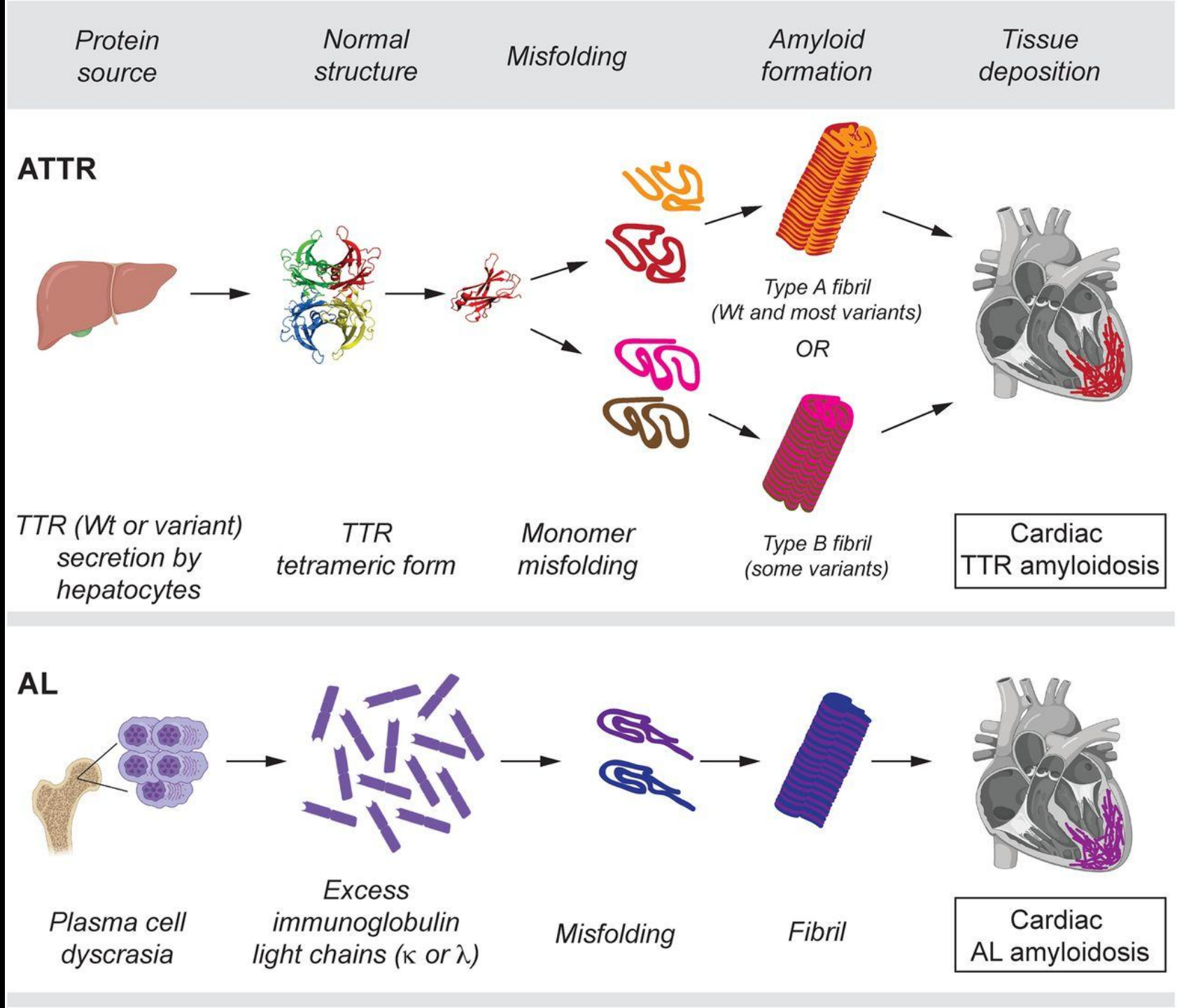
- The formation of amyloid results from misfolding of previously soluble precursor peptides (pre albumin, light chains)
- This conformational change results in mostly antiparallel beta-pleated sheets, which stack in a twisted configuration
- Genetics play a role in some cases, including the evolution of point mutations and deletions, and premature stop codons


Protein source
Normal structure
Misfolding
Amyloid formation
Tissue deposition
ATTR
Type A fibril
(Wt and most variants)
OR
Type B fibril
(some variants)
TTR (Wt or variant) secretion by hepatocytes
TTR tetrameric form
Monomer misfolding
Cardiac TTR amyloidosis
AL
Plasma cell dyscrasia
Excess immunoglobulin light chains (κ or λ)
Misfolding
Fibril
Cardiac AL amyloidosis

- 42 different human protein precursors of amyloid fibrils are known.
- Some are produced at the site of amyloid formation (localized amyloid) and some circulate in the blood to deposit in a variety of tissues and organs (systemic amyloidosis)
- There are also major contributions from non-fibrillar components found in all types of amyloids, including serum amyloid P component (SAP), apolipoprotein E, and glycosaminoglycans.

- There are 18 different types of systemic and 28 localized forms of amyloidosis. The principal systemic types seen in tertiary referral centers and inpatient medical services are the primary (immunoglobulin light chain AL) and transthyretin (ATTR) types.

- AL amyloid caused by a plasma cell dyscrasia, is due to deposition of protein derived from immunoglobulin light chain fragments. AL amyloid is a potential complication of any plasma cell dyscrasia that produces monoclonal immunoglobulin light chains. These can be subtle, but a monoclonal protein is detectable in urine and or serum in > 95% of affected patients if both serum and urine immunofixation and free light chain assays are performed.

- AL amyloid can present with a variety of symptoms or signs that include heavy proteinuria and edema, hepatosplenomegaly, unexplained heart failure and carpal tunnel syndrome. It can occur in association with multiple myeloma, non-Hodgkins lymphoma or CLL.

- ATTR amyloid may occur as a wild-type (ATTRwt) associated with aging or as mutant proteins (ATTRv or hATTR).

- Deposition of normal ATTR (wild-type) amyloid in myocardium and other sites may result in a form of amyloidosis that is now referred to as wild-type transthyretin systemic amyloidosis (superseding the previous terminology of systemic senile amyloidosis (SSA))

- The term TTR amyloid cardiomyopathy is used to describe those patients who develop cardiomegaly and clinical heart failure from infiltrative cardiomyopathy. Asymptomatic amyloid deposition in the heart is a common autopsy finding, often without clinical consequences.

- Compared with patients with cardiac involvement from AL amyloid, heart failure due to ATTR is less severe than that in AL. Those patients with ATTRwt disease survive longer (75 vs 11 months) despite having ventricular free wall and septal thickening due to the amyloid deposits.

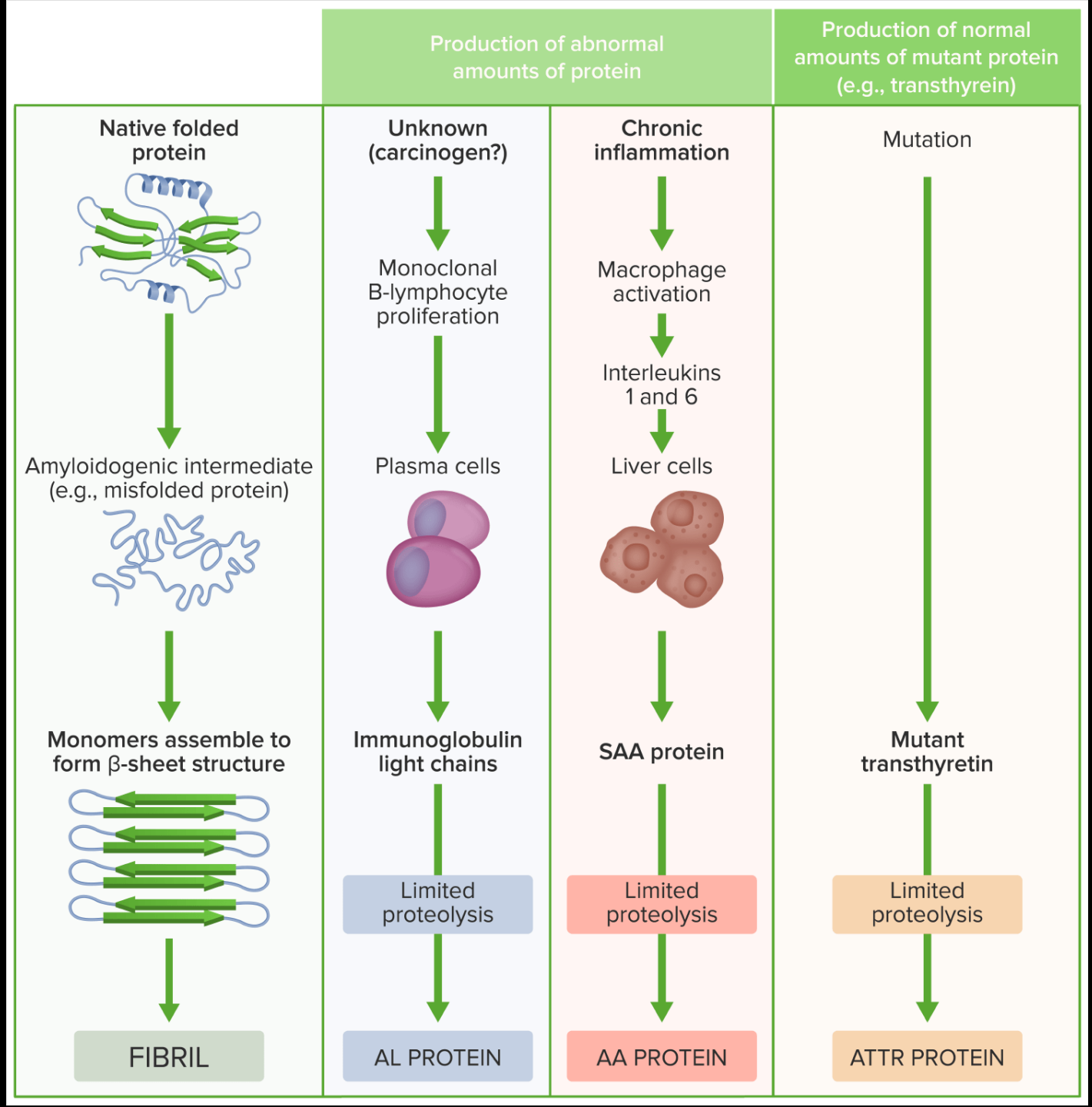
- A history of carpal tunnel syndrome is common and spinal stenosis is well recognized, but significant renal involvement is very rare in the systemic disorder.

- Differentiation of ATTR amyloidosis from cardiac AL amyloidosis is of vital importance as the treatments and prognosis are completely different.

- There may be overlap clinically between cardiac amyloidosis due to deposition of wild-type TTR and the late onset cardiomyopathy due to mutant TTR.

- Screening for informative mutations (lle 122 in African American patients) may be necessary to distinguish the two causes of restrictive cardiomyopathy.

- Serum amyloid A protein (an acute phase reactant) can also generate amyloidosis (AA amyloid). AA amyloid may complicate chronic diseases in which there is ongoing or recurring inflammation such as RA, inflammatory bowel diseases and chronic infections. It may also occur in association with neoplastic diseases.


Production of abnormal amounts of protein
Production of normal amounts of mutant protein (e.g., transthyrein)
Native folded protein
Amyloidogenic intermediate (e.g., misfolded protein)
Monomers assemble to form β-sheet structure
FIBRIL
Unknown (carcinogen?)
Monoclonal B-lymphocyte proliferation
Plasma cells
Immunoglobulin light chains
Limited proteolysis
AL PROTEIN
Chronic inflammation
Macrophage activation
Interleukins 1 and 6
Liver cells
SAA protein
Limited proteolysis
AA PROTEIN
Mutation
Mutant transthyretin
Limited proteolysis
ATTR PROTEIN

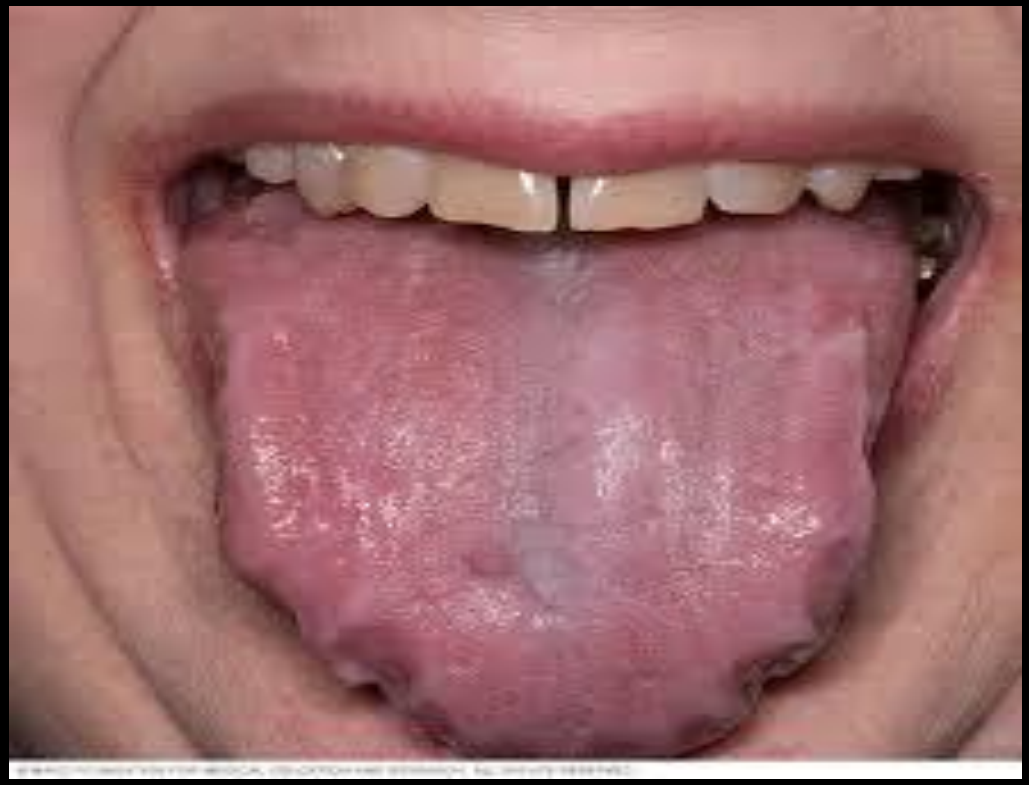
- Primary AL amyloid and ATTR amyloid are more common in developed countries whereas in developing countries, AA amyloid is more frequent. This variation is likely the result of a higher burden of chronic infections such as TB, leprosy and osteomyelitis.

Clinical manefestations

- Waxy skin
- Easy bruising
- Enlarged muscles (tongue, deltoids)
- Heart failure
- Conduction abnormalities
- Hepatomegaly
- Proteinuria
- Peripheral and autonomic neuropathy
- Fatigue
- Change in taste
- Dry mouth
- Weight loss
- Spinal stenosis and carpal tunnel syndrome, years before this condition becomes apparent
- Progressive deafness

Community based survey of 341 patients

- Fatigue
- SOB
- Edema
- Dizziness upon standing
- Fullness in the stomach
- Constipation and diarrhea
- Numbness of legs/arms
- Weight loss
- Purpura
- Enlarged tongue



Risk Factors

- Age: Most people diagnosed with amyloidosis are between ages 60 and 70, rarely under age 40
- Sex: More common in males (25-50 cases in men for every case in women)
- Other diseases: Having a chronic infectious or inflammatory disease increases the risk of AA amyloidosis
- Family history: Some types of amyloidosis are hereditary

Risk Factors…

- Dialysis (not all large proteins are removed from the blood
- Race (West African, Caribbean and Latin American descent)
- Genetic mutations (Portugal, Sweden, Japan, Finland)

Frequency

- AL amyloidosis: 4000 new cases yearly (1 case per 64,500 adults)
- Hereditary ATTR amyloidosis: 4% of West African descent. In European descent the occurrence is 1 in 100,000 people but in Portugal, 1 in 538 people
- Wild-type ATTR amyloidosis: Underdiagnosed condition and has an estimated prevalence of >10% in patients aged over 60. 10% of patients with AS may have ATTR-w
- Dialysis-related amyloidosis: 20 % of those on dialysis for 2-4 years have amyloidosis and everyone on dialysis for 13 years or more have amyloidosis

Organ involvement

- Abdominal fat
- Bone marrow
- Gut
- Heart
- Kidneys
- Liver
- Nervous system
- Skin and soft tissue
- Tongue

- Cardiac amyloidosis is most common type of restrictive CM
- Cardiac sarcoidosis
- Cardiac hemochromatosis

Typical presentation

- Rapidly progressive diastolic dysfunction in a non-dilated ventricle
- Discovered incidentally in patients with other signs of systemic amyloidosis
- Delay in diagnosis is common and may lead to a delay in treatment

Types of cardiac amyloidosis

- Primary amyloidosis (aka amyloid light chain amyloidosis)
- Secondary amyloidosis (AA amyloidosis, caused by the deposition of serum amyloid A, which is an inflammatory protein produced with chronic inflammation)
- Senile systemic amyloidosis (aka wild type transthyretin) caused by age-related amyloid made from normal transport-thyroxine-and-retinol protein. Most common type of cardiac amyloidosis

Types of amyloid…

- Familial amyloidosis (ATTR-m) caused by mutant TTR

- Isolated atrial amyloidosis (caused by deposition of amyloid made from atrial natriuretic peptide)

Pathophysiology

- Direct interstitial infiltration leads to increased ventricular wall thickness, stiffness and diastolic dysfunction
- In AL, amyloid deposits in arterioles leading to angina or MI
- Deposits in atria results in structural changes and may cause AF.
- Increases LA thrombus formation w/wo AF
- Direct injury to myocardial cells via reactive oxygen species

Cardiac amyloidosis signs and symptoms

- Dizziness
- Fainting/Syncope
- Fatigue
- Fluid retention
- Hypotension
- Dyspnea

Stages of cardiac amyloidosis

- Stage I: Normal levels of both NT-proBNP and TnT

- Stage II: Elevated level of either NP-proBNP or TnT, but not both
- (NT-proBNP level greater than 332 ng/L and TnT level greater than 0.1ng/ml)

- Stage III: Elevated levels of both NT-proBNP and TnT

Prognosis

- Stage I: 5.8 years after being diagnosed
- Stage II: 3.9 years after being diagnosed
- Stage III: 2 years after being diagnosed

Lab tests

- Tissue samples stained with Congo red, generates a green glow
- Serum and urine protein electrophoresis with immunofixation
- Light chain assay (serum and urine)

Imaging

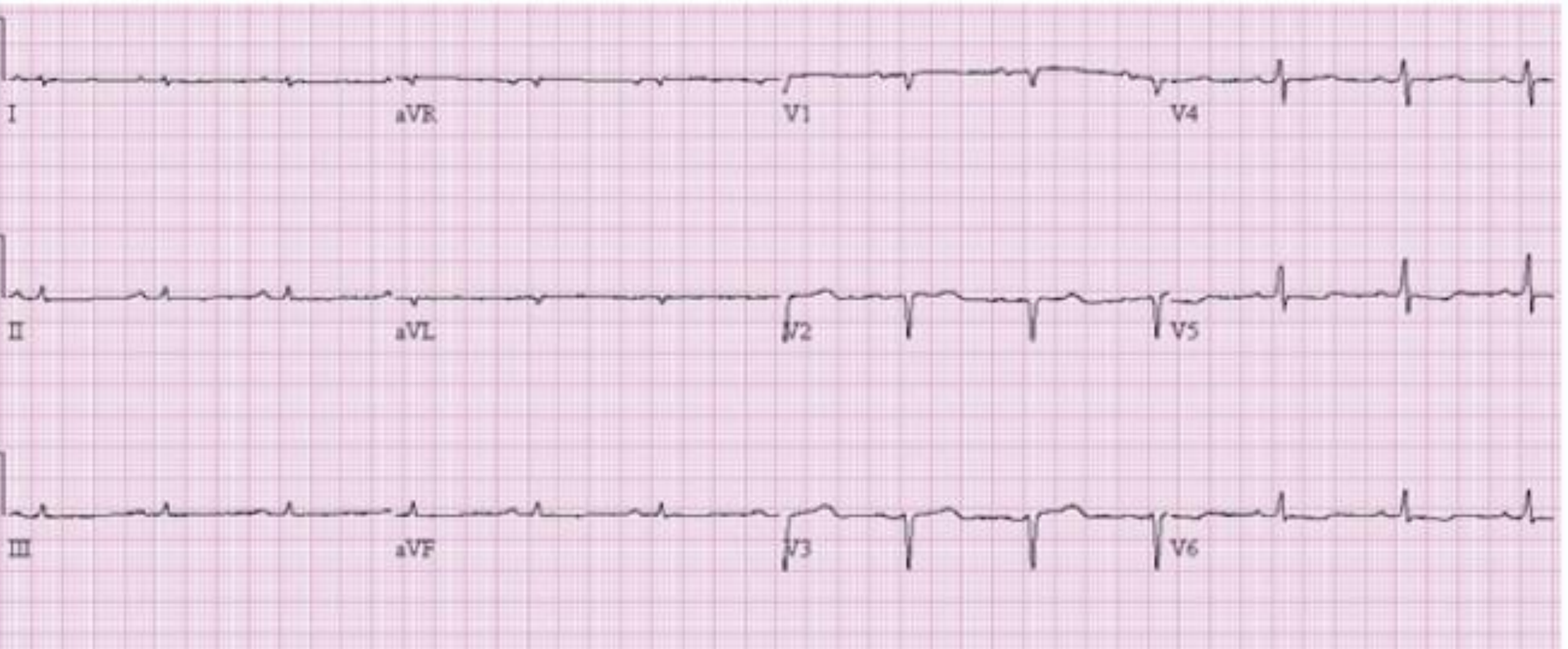
EKG

Echocardiography

Scintigraphy

MRI

Low voltage (discordance between EKG and Echo)

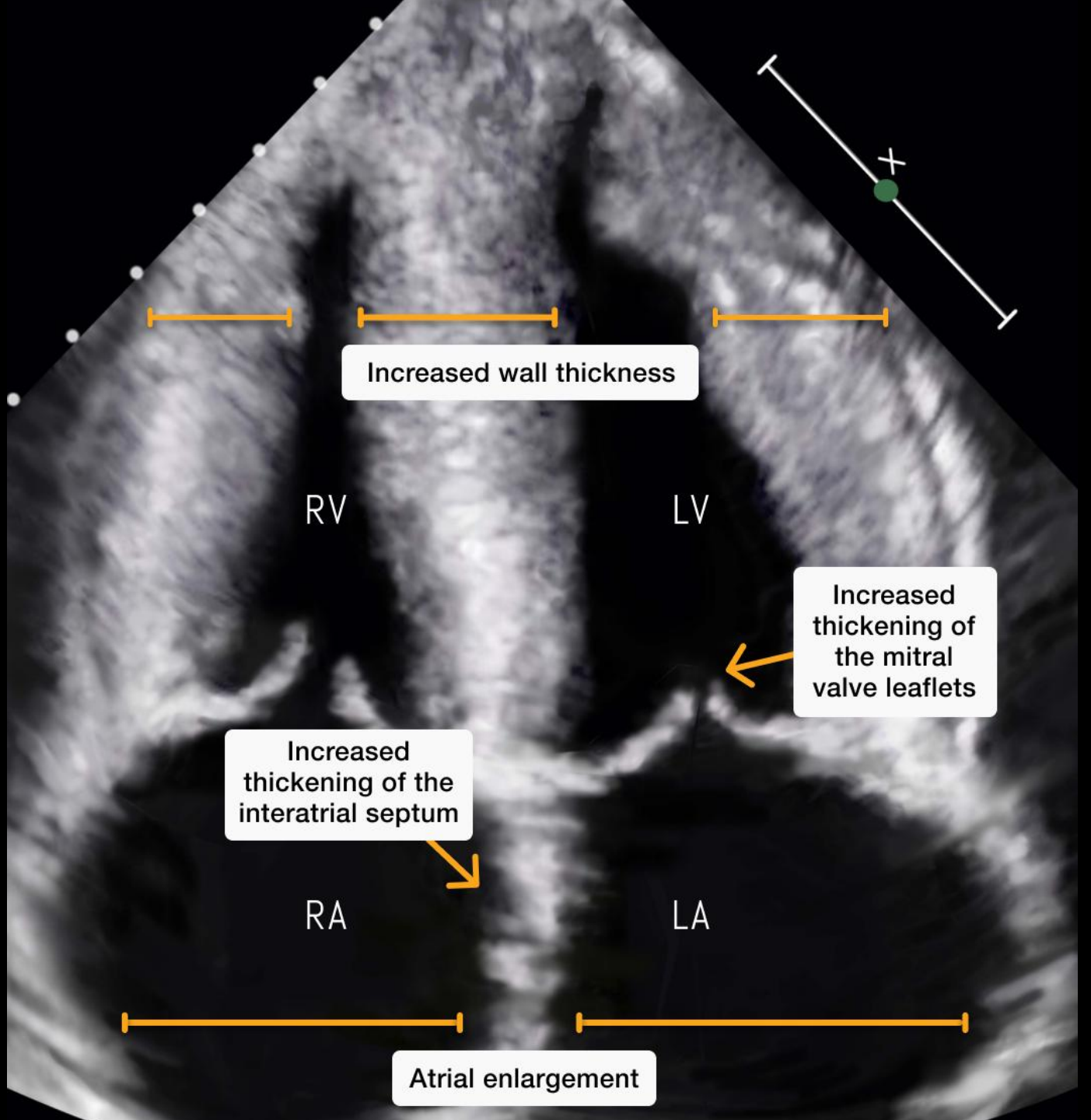


EKG…

- May also see pseudo infarct pattern
- Varying degrees of AV block (AL amyloid)
- LBBB more common in a-TTR
- AF

Echocardiography

- Increased LV and RV wall thickening
- Bi-atrial enlargement
- Increased LV wall thickness with low-voltage criteria on EKG
- Grade II or greater diastolic dysfunction with elevated filling pressures
- Severely reduced mitral annular tissue doppler velocities
- Reduced global longitudinal strain (GLS) with apical sparing
- Low-flow, low-gradient AS
- Pericardial effusion
- Increased atrial septal thickness
- Diffuse valve thickening
- Preserved EF with low stroke volume index


Increased wall thickness
RV
LV
Increased thickening of the mitral valve leaflets
Increased thickening of the interatrial septum
RA
LA
Atrial enlargement

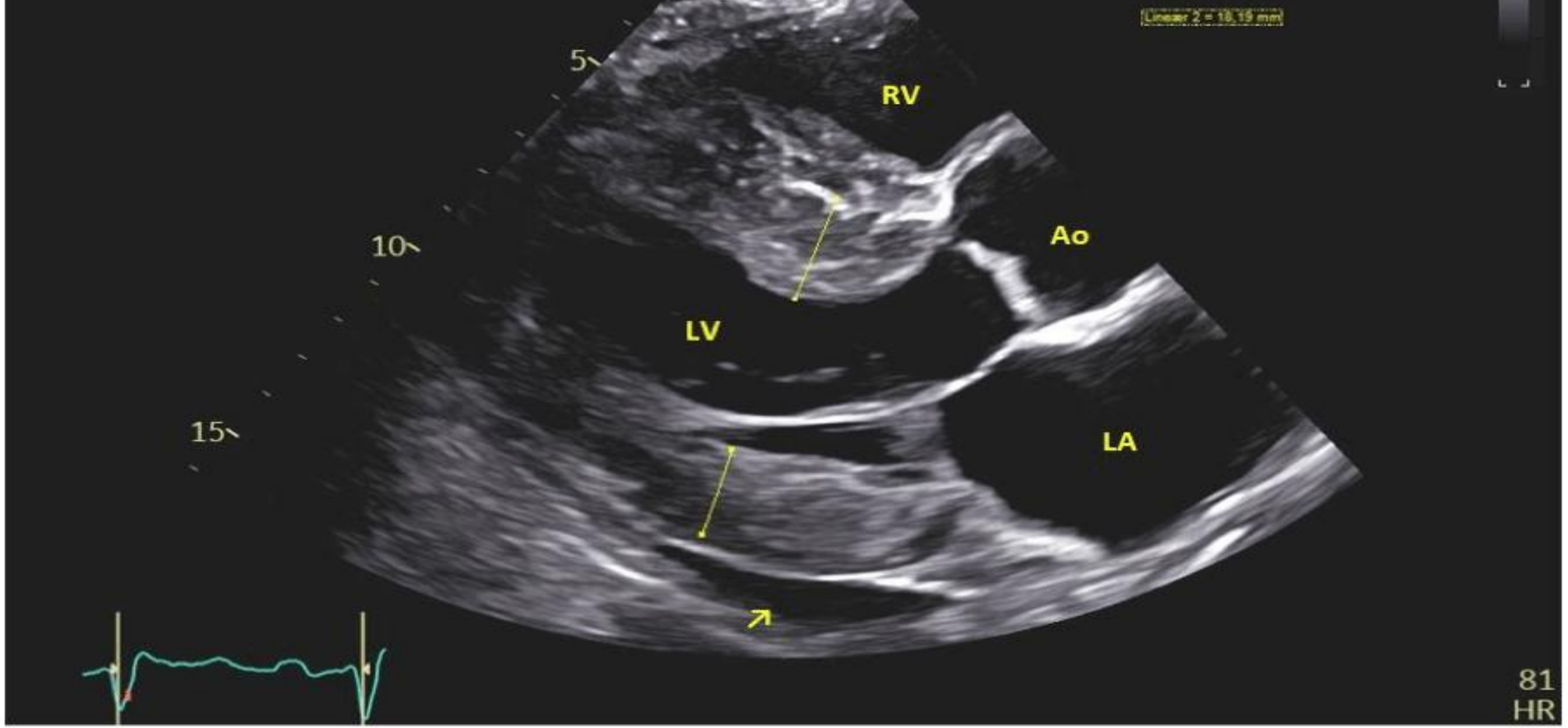


Figure 1. In the parasternal long-axis view, left ventricular wall hypertrophy is evident. Specifically, the basal septum exhibits significant thickening, measuring 22 mm (indicated by the yellow line), while the posterior wall measures 18 mm (also marked by the yellow line). Additionally, the intraventricular septum appears speckled and hyperechoic. Notably, pericardial effusion is observed behind the posterior left ventricular wall (yellow arrow). Ao, aorta; LV, Left Ventricle; RV, Right

LV strain

- Global longitudinal strain (GLS) is a unitless measure of longitudinal deformation with more negative values denoting greater deformation or more pronounced shortening.

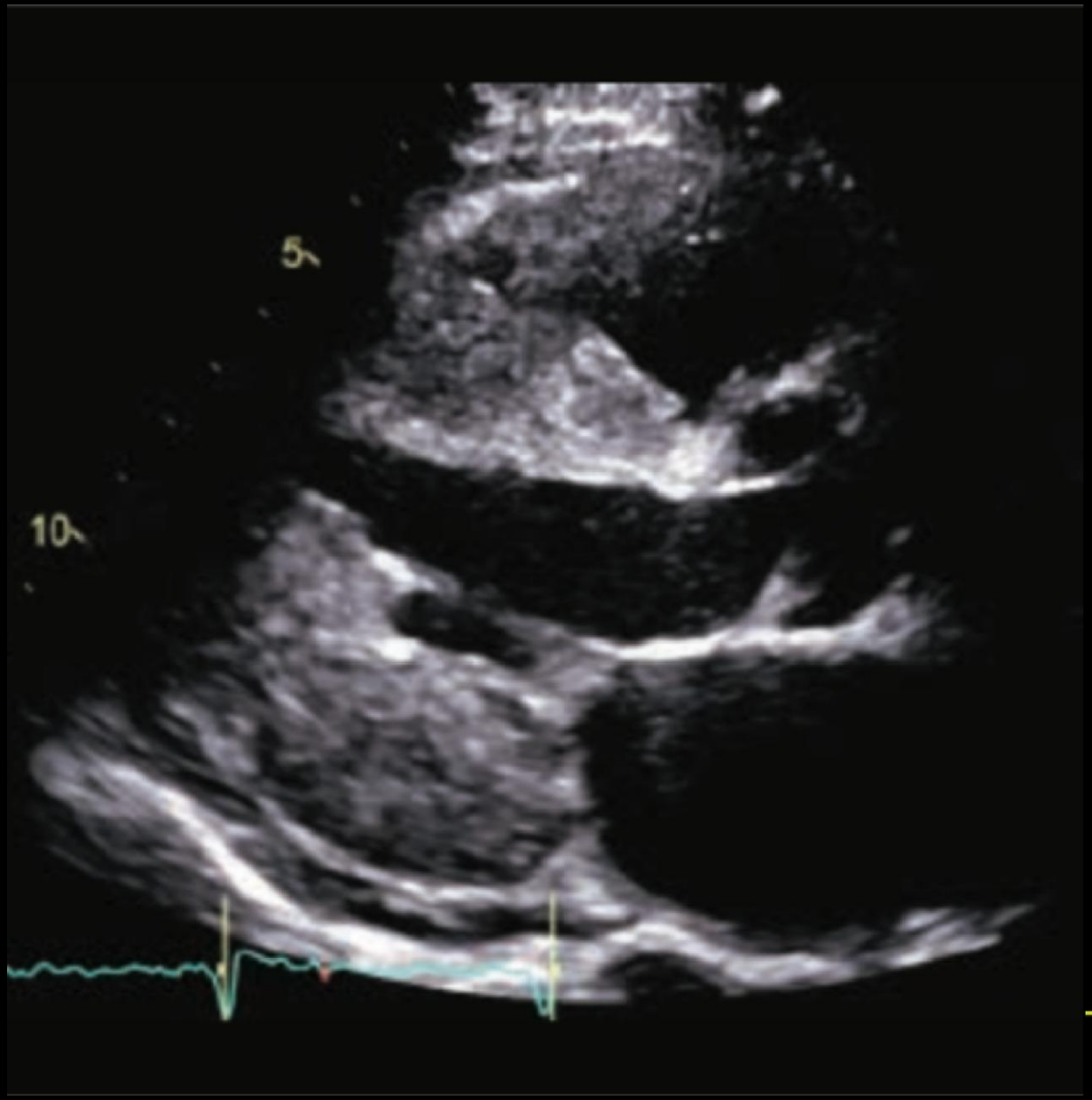
- Values nearing 0 % indicate akinesis, positive values indicate dyskinesis and negative values indicate shortening/contraction.

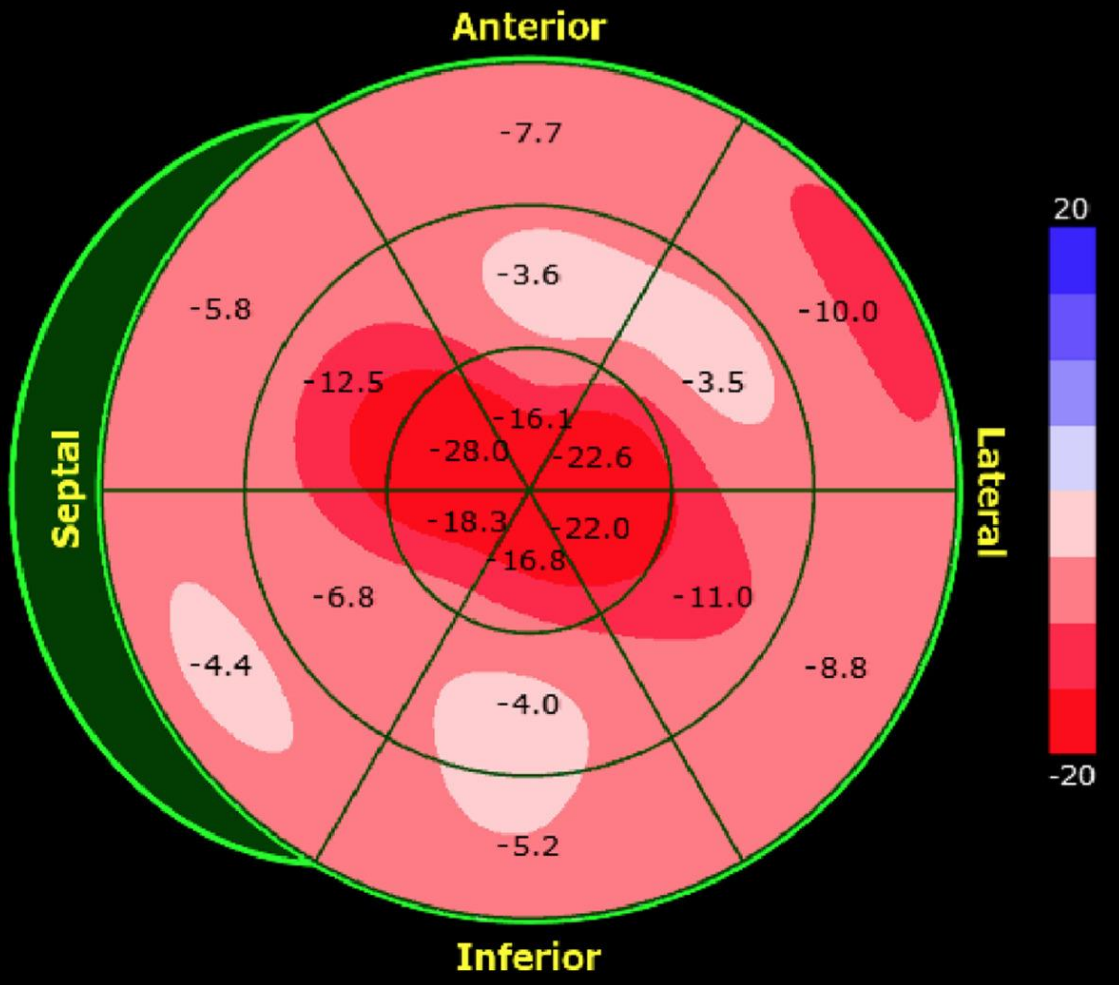
- Normal values of GLS are usually more negative than -20% (lower limit -16% to -18%)

Apical sparing

- There is a normal base to apex gradient in GLS however it is more pronounced in cardiac amyloid.

- In cardiac amyloid, the apical segmental strain values are greater than those in the basal and middle segments. When plotted on a bull’s eye map, this will generate a characteristic “apical-sparing” pattern.


5
10


Anterior
Septal
Lateral
Inferior
-7.7
-3.6
-5.8
-10.0
-12.5
-3.5
-16.1
-28.0
-22.6
-18.3
-22.0
-16.8
-6.8
-11.0
-4.4
-8.8
-4.0
-5.2
20
-20

99m Technetium-pyrophosphate imaging

- Must do with myocardial SPECT and planer imaging
- Semiquantitative visual grading of pyp uptake compared to bone(rib) uptake
- Grade 0: No uptake and normal bone uptake
- Grade 1: Uptake less than rib uptake
- Grade 2: Uptake equal to rib uptake
- Grade 3: Uptake greater than rib uptake with mild/absent rib uptake

Planar and SPECT images

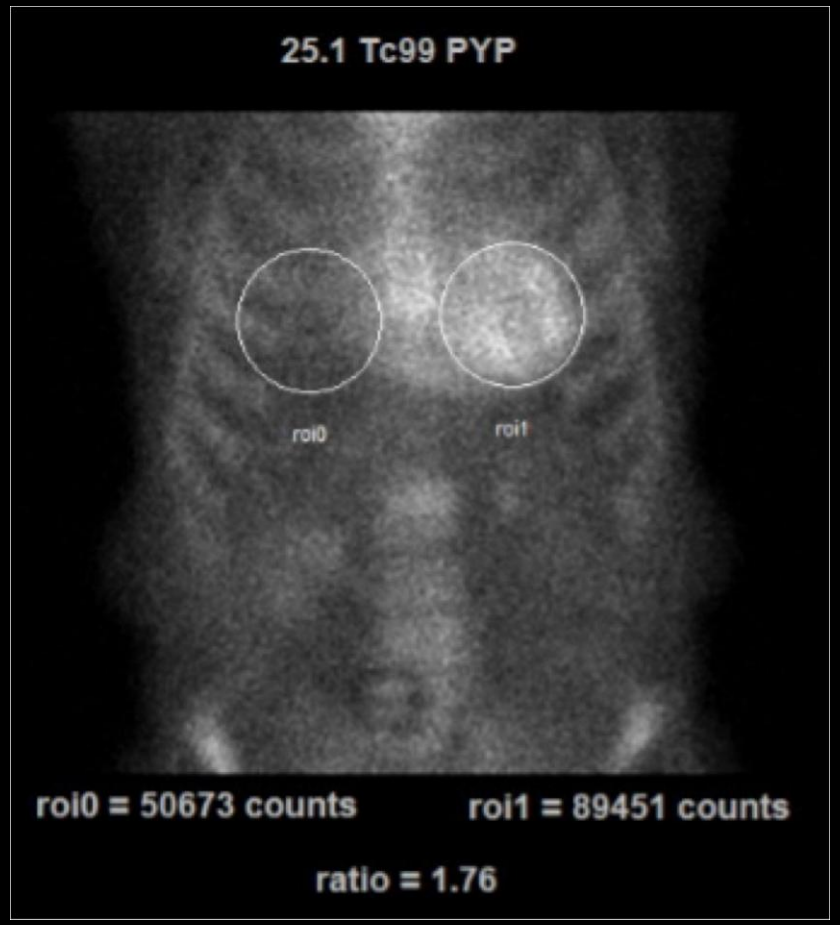
- Quantitation of cardiac PYP uptake using heart to contralateral lung ratio

- H/CL <1
- H/CL 1-1.5
- H/CL >1.5

Overall interpretation (Three categories)

- Not suggestive: Visual grade 0 or H/CL ratio <1
- Equivocal : Visual grade 1 or H/CL ratio 1-1.5
- Strongly suggestive: Visual grade 2-3 or H/CL ratio >1.5

PYP

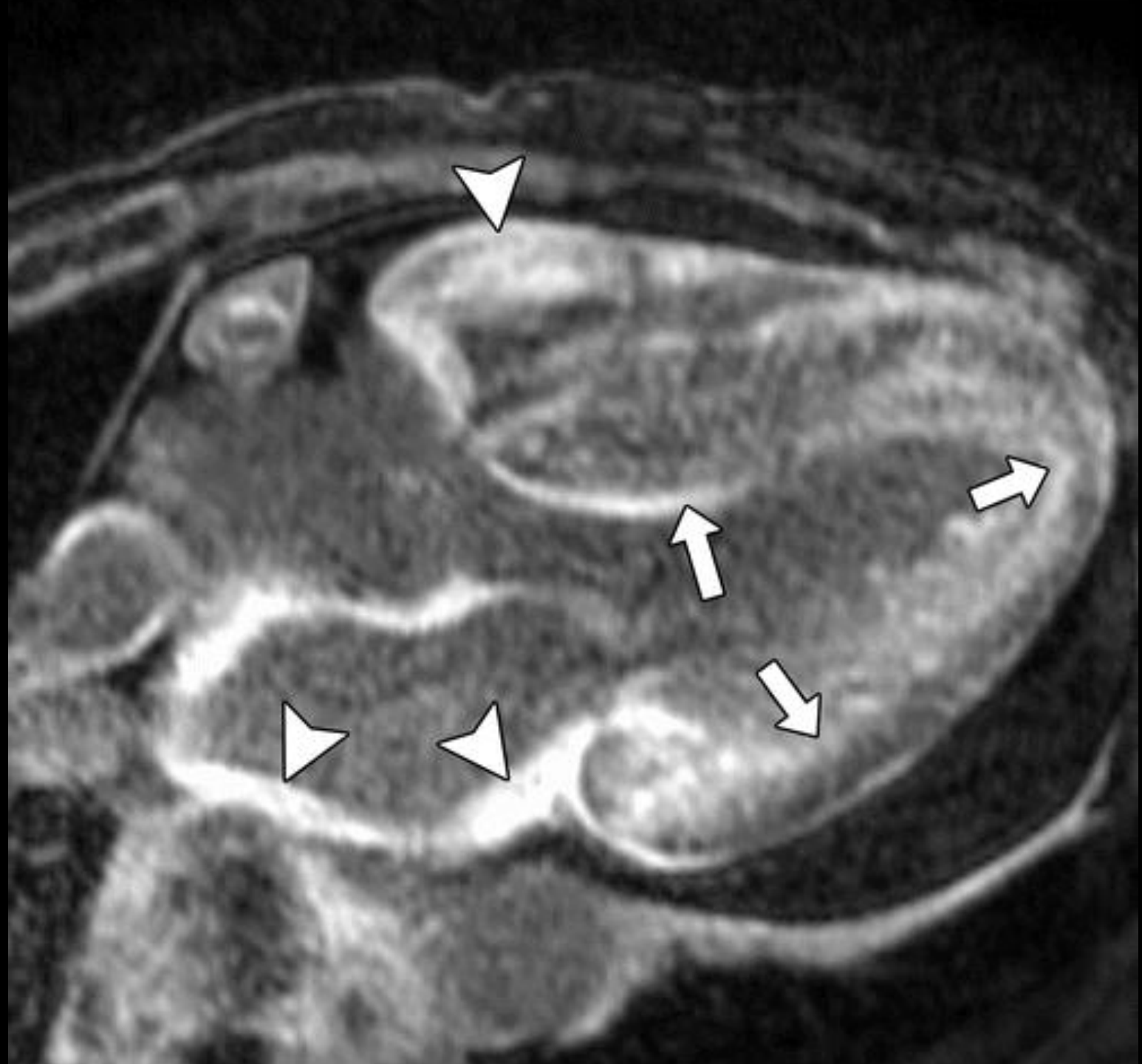

25.1 Tc99 PYP
roi0
roi1
roi0 = 50673 counts
roi1 = 89451 counts
ratio = 1.76

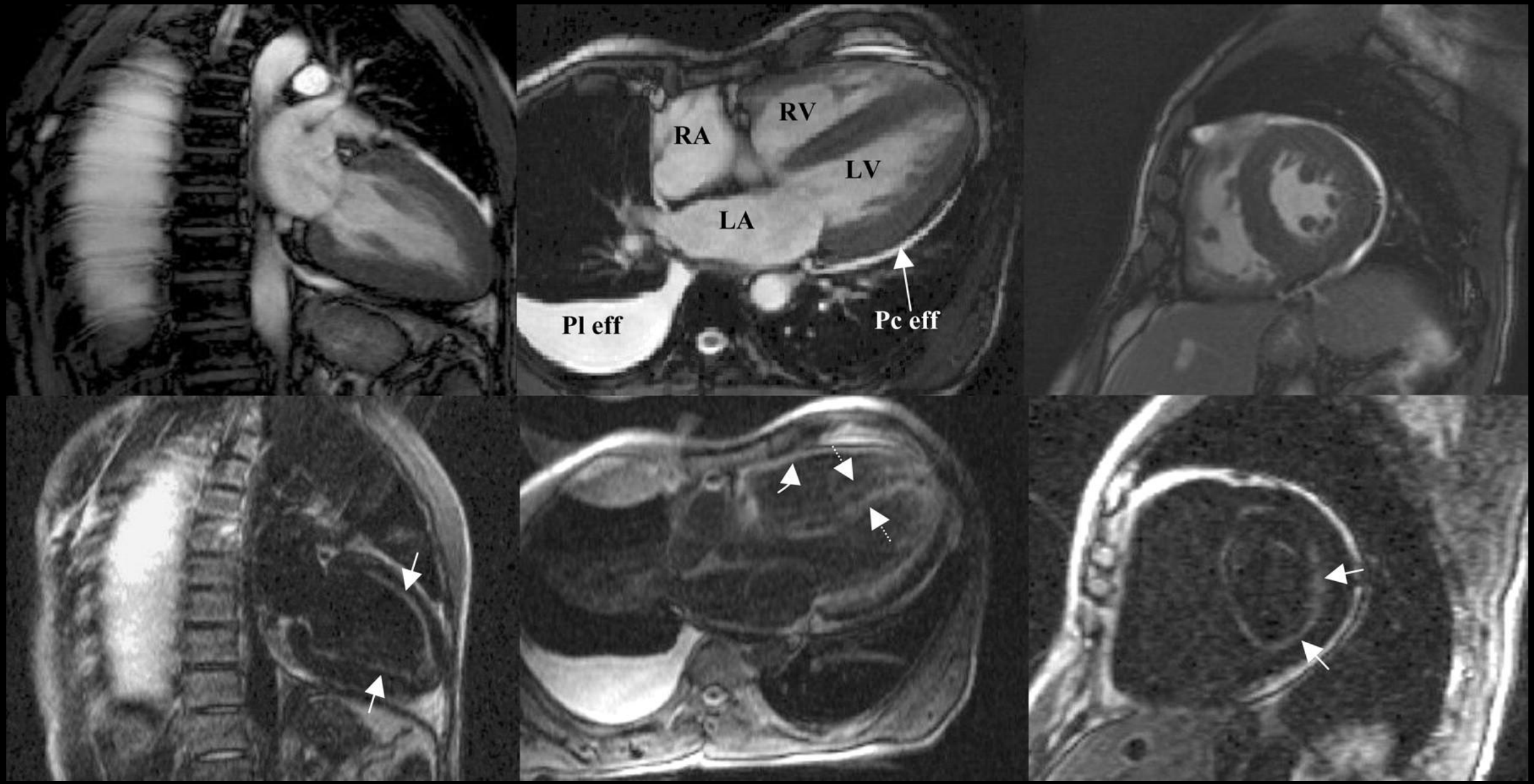
Cardiovascular magnetic resonance

- Can detect early cardiac amyloidosis before LVH develops
- Cannot distinguish cardiac AL from a-TTR amyloidosis

- Three LGE patterns correlate with the degree of myocardial infiltration (none, subendocardial and transmural)

- T1 mapping provides quantitative measures of myocardial relaxation time. T1 increases with amyloid infiltration




RA
RV
LV
LA
Pl eff
Pc eff

Cardiac amyloid features

- Monoclonal gammopathy, multiple myeloma or known extra cardiac amyloid: AL
- Unexplained heart failure with hepatomegaly, macroglossia, periorbital purpura: AL
- Heart failure and unexplained peripheral sensorimotor neuropathy: v-ATTR or AL
- Men > 50 years, with bilateral carpal tunnel syndrome/biceps tendon rupture/spinal stenosis: wt-ATTR
- Age > 60 years with low-flow, low gradient AS and increased wall thickness: wt-ATTR
- African Americans > 60 years with increased wall thickness and or unexplained heart failure: v-ATTR

- Light chain amyloidosis always requires cardiac or noncardiac tissue typing. PYP scan may be used in the proper clinical setting if AL is excluded. Carpal tunnel syndrome, especially bilateral, may be present with any type of amyloid.

Clinical suspicion*

- History: HFpEF, orthostatic hypotension, peripheral neuropathy, proteinuria, bilateral carpal tunnel syndrome
- ECG: Low-voltage QRS (disproportional to LV wall thickness)
- Echo: unexplained LV hypertrophy; abnormal LV GLS with apical sparing
- Biomarkers: persistent unexplained cTn elevation; significant NP elevation (disproportional to symptoms)
- CMR: diffuse LGE

*see Tables 1 and 2 for more details

Initial screening

Serum kappa/lamda free light chain ratio & serum/urine immunofixation electrophoresis

- *If negative:* Bone scintigraphy with Tc-99m-PYP/DPD/HMDP

Final diagnosis

Positive light chain assay/immunofixation:

- Haematological workup
- Tissue biopsy (abdominal fat, affected organs) with Congo red staining & mass spectroscopy or immunohistochemistry

Negative light chain assay/immunofixation & positive bone scintigraphy:

- TTR gene sequencing; NT-proBNP & eGFR for staging

Management and Treatment

- Most forms of cardiac amyloidosis are treatable, but cure rarely possible
- Treatment depends on the type of amyloidosis
- Early detection is key
- Without early detection and treatment, permanent damage occurs
- Only treatment for permanent damage is transplantation

Treatment…

- For AL amyloid, diuretics are the cornerstone of treatment
- Most patients do not tolerate RAAS-I (AL amyloid) but in a-TTR it is better tolerated
- Autonomic dysfunction common (can use midodrine)
- BB poorly tolerated
- Mineralocorticoid receptor antagonist and loop diuretics are vital in management of heart failure related to amyloid

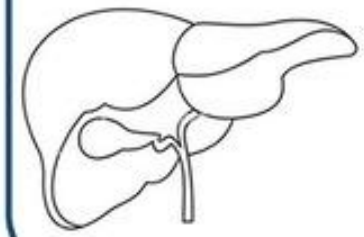
AL amyloidosis

- Chemotherapy to destroy malfunctioning plasma cells
- Stem cell transplant
- Immunotherapy

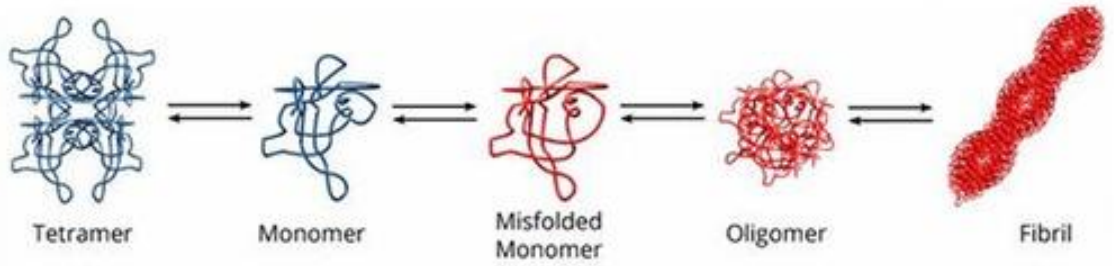
ATTR amyloidosis

- Liver transplant was once the only option (Mutant only)
- Genetic silencers: Temporarily allows liver to produce normal proteins
- Stabilizers: Prevents misfolding of TTR molecules
- Fibril inhibitors: Prevents amyloid fibril stacking

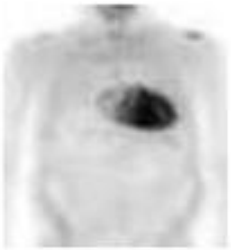
TTR production



TTR tetramer dissociation and misfolding



TTR deposits



Inhibition of TTR synthesis

- **Liver transplantation**
- **RNA silencing**

siRNA:
- Patisiran
- Revusiran
- Vutrisiran

ASO
- Inotersen
- Eplontersen

- **Gene editing**

CRISPR–Cas9:
- NTLA-2001

TTR stabilization

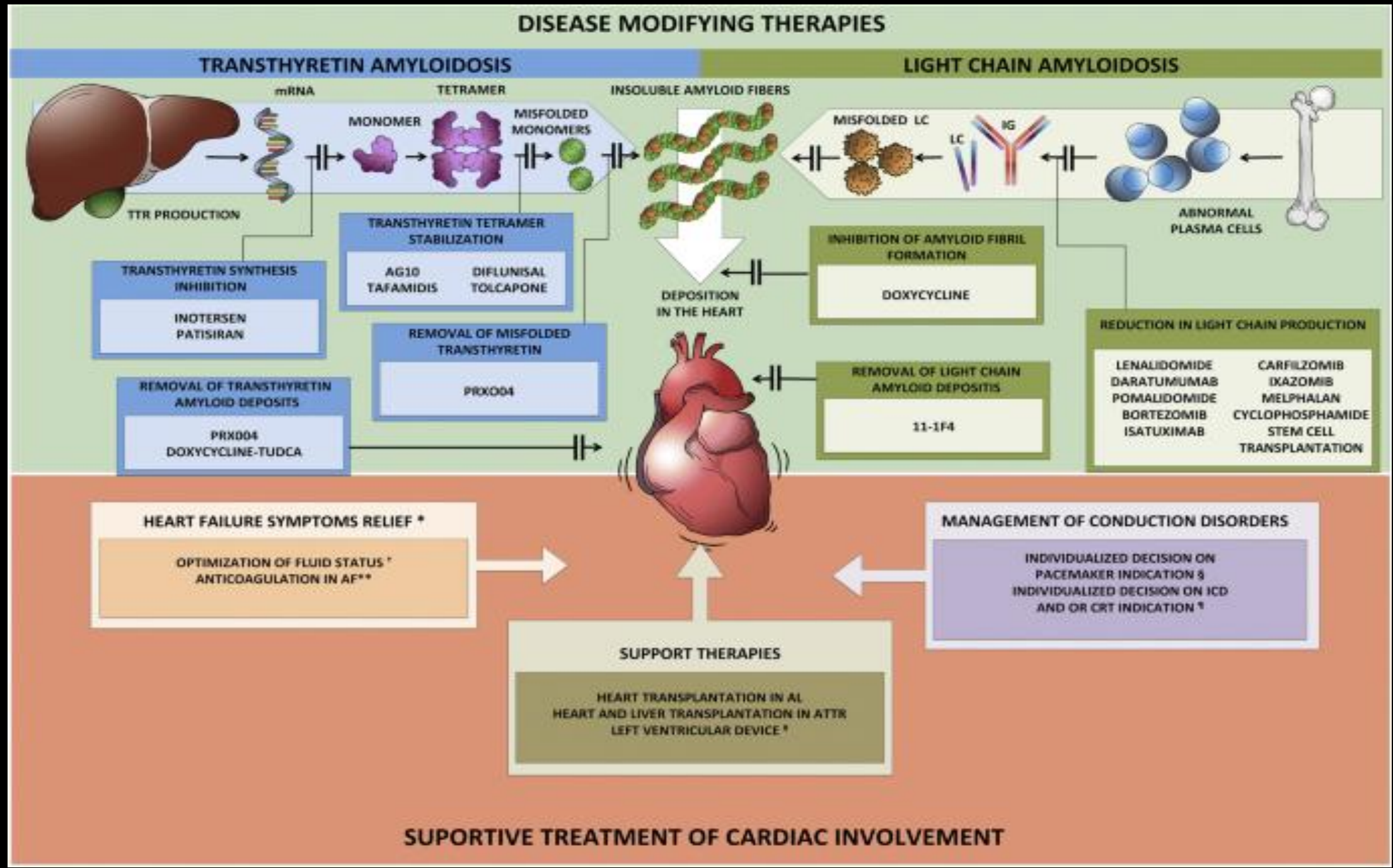
Non-selective agents
- Diflusinal

Selective agents
- Tafamidis
- Acoramidis

TTR degradation

- Doxyciclin and (T)UDCA

Monclonal Ab
- PRX004
- NI006


DISEASE MODIFYING THERAPIES
TRANSTHYRETIN AMYLOIDOSIS
LIGHT CHAIN AMYLOIDOSIS
mRNA
TETRAMER
INSOLUBLE AMYLOID FIBERS
MONOMER
MISFOLDED MONOMERS
MISFOLDED LC
LC
IG
TTR PRODUCTION
ABNORMAL PLASMA CELLS
TRANSTHYRETIN TETRAMER STABILIZATION
AG10
TAFAMIDIS
DIFLUNISAL
TOLCAPONE
TRANSTHYRETIN SYNTHESIS INHIBITION
INOTERSEN
PATISIRAN
INHIBITION OF AMYLOID FIBRIL FORMATION
DOXYCYCLINE
DEPOSITION IN THE HEART
REMOVAL OF MISFOLDED TRANSTHYRETIN
PRX004
REDUCTION IN LIGHT CHAIN PRODUCTION
LENALIDOMIDE
DARATUMUMAB
POMALIDOMIDE
BORTEZOMIB
ISATUXIMAB
CARFILZOMIB
IXAZOMIB
MELPHALAN
CYCLOPHOSPHAMIDE
STEM CELL TRANSPLANTATION
REMOVAL OF TRANSTHYRETIN AMYLOID DEPOSITS
PRX004
DOXYCYCLINE-TUDCA
REMOVAL OF LIGHT CHAIN AMYLOID DEPOSITS
11-1F4
HEART FAILURE SYMPTOMS RELIEF *
OPTIMIZATION OF FLUID STATUS *
ANTICOAGULATION IN AF**
MANAGEMENT OF CONDUCTION DISORDERS
INDIVIDUALIZED DECISION ON PACEMAKER INDICATION §
INDIVIDUALIZED DECISION ON ICD AND OR CRT INDICATION ¶
SUPPORT THERAPIES
HEART TRANSPLANTATION IN AL
HEART AND LIVER TRANSPLANTATION IN ATTR
LEFT VENTRICULAR DEVICE *
SUPORTIVE TREATMENT OF CARDIAC INVOLVEMENT

- ATTR-ACT trial
- Tafamidis compared with placebo among patients with TTR-CM
- Randomized, parallel, placebo controlled, blinded
- Tafamidis arm 264: Placebo arm 177
- 30 month follow up
- Exclusion: NYHA class IV, AL amyloid, Liver or Heart TP, Implanted cardiac devices, previous treatment with tafamidis, CKD, malnutrition

- Primary outcome of all-cause death occurred in 29.5 % of the tafamidis group compared to 42.9 % of the placebo group ($p<0.05$)
- Improved survival by 30%
- Improved HF related quality of life
- Improved 6 minute walk

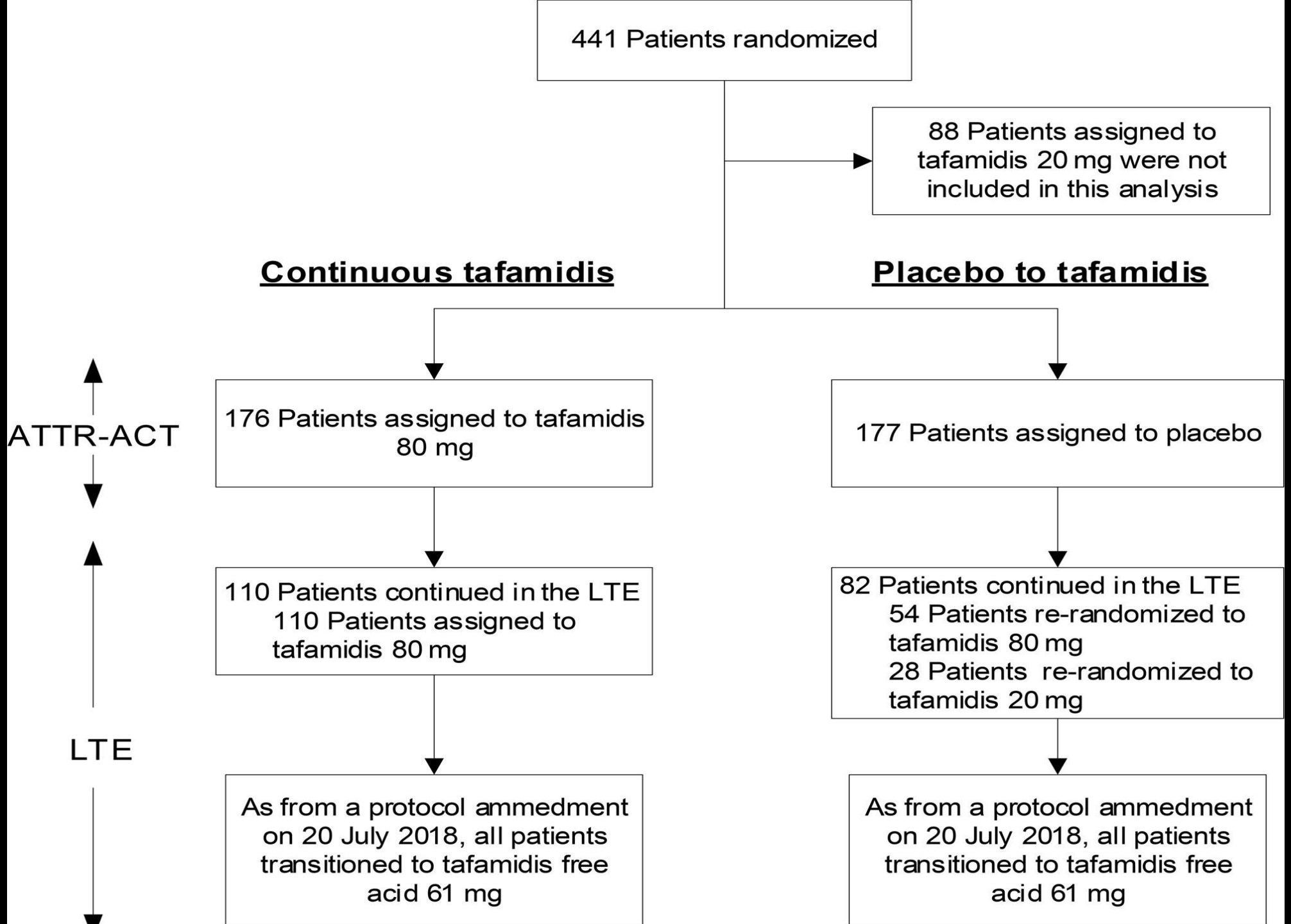
Acoramidis

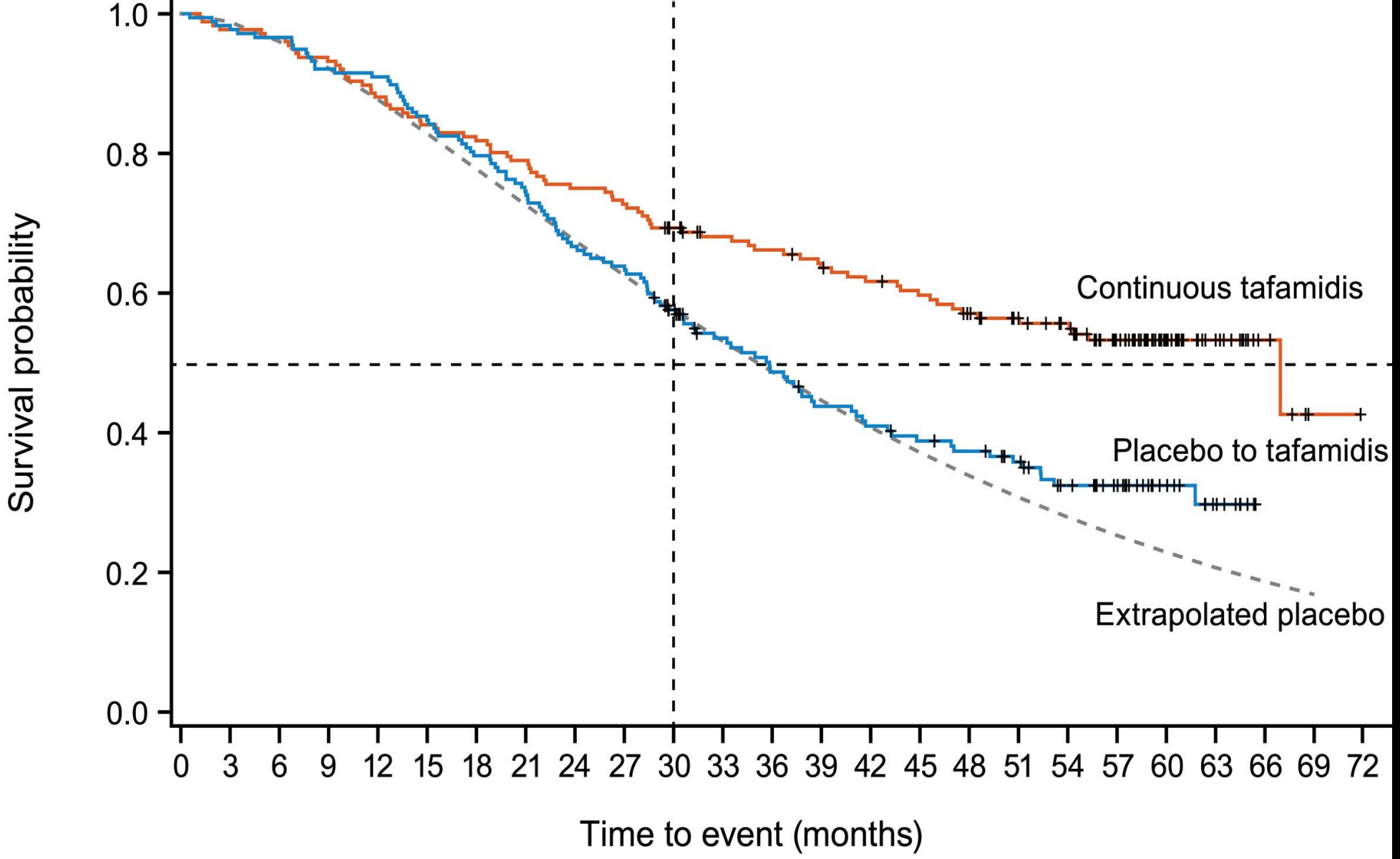
- More contemporary trial
- 632 patients followed for 30 months
- Improved endpoints of survival
- Less admissions for HF
- Improved 6-minute walk and nt-proBNP
- Similar chemical structure to T119m (super stabilizer)

- T119m (TTR variant) protects individuals from getting a-TTR amyloidosis, even if they have another pathologic gene mutation

- Individuals with T119m appear to have a lower risk of stroke, and they live longer than the general population (observational study)

Long Term Extenson Trial


441 Patients randomized
88 Patients assigned to tafamidis 20 mg were not included in this analysis
Continuous tafamidis
Placebo to tafamidis
ATTR-ACT
176 Patients assigned to tafamidis 80 mg
177 Patients assigned to placebo
110 Patients continued in the LTE
110 Patients assigned to tafamidis 80 mg
82 Patients continued in the LTE
54 Patients re-randomized to tafamidis 80 mg
28 Patients re-randomized to tafamidis 20 mg
LTE
As from a protocol ammedment on 20 July 2018, all patients transitioned to tafamidis free acid 61 mg
As from a protocol ammedment on 20 July 2018, all patients transitioned to tafamidis free acid 61 mg

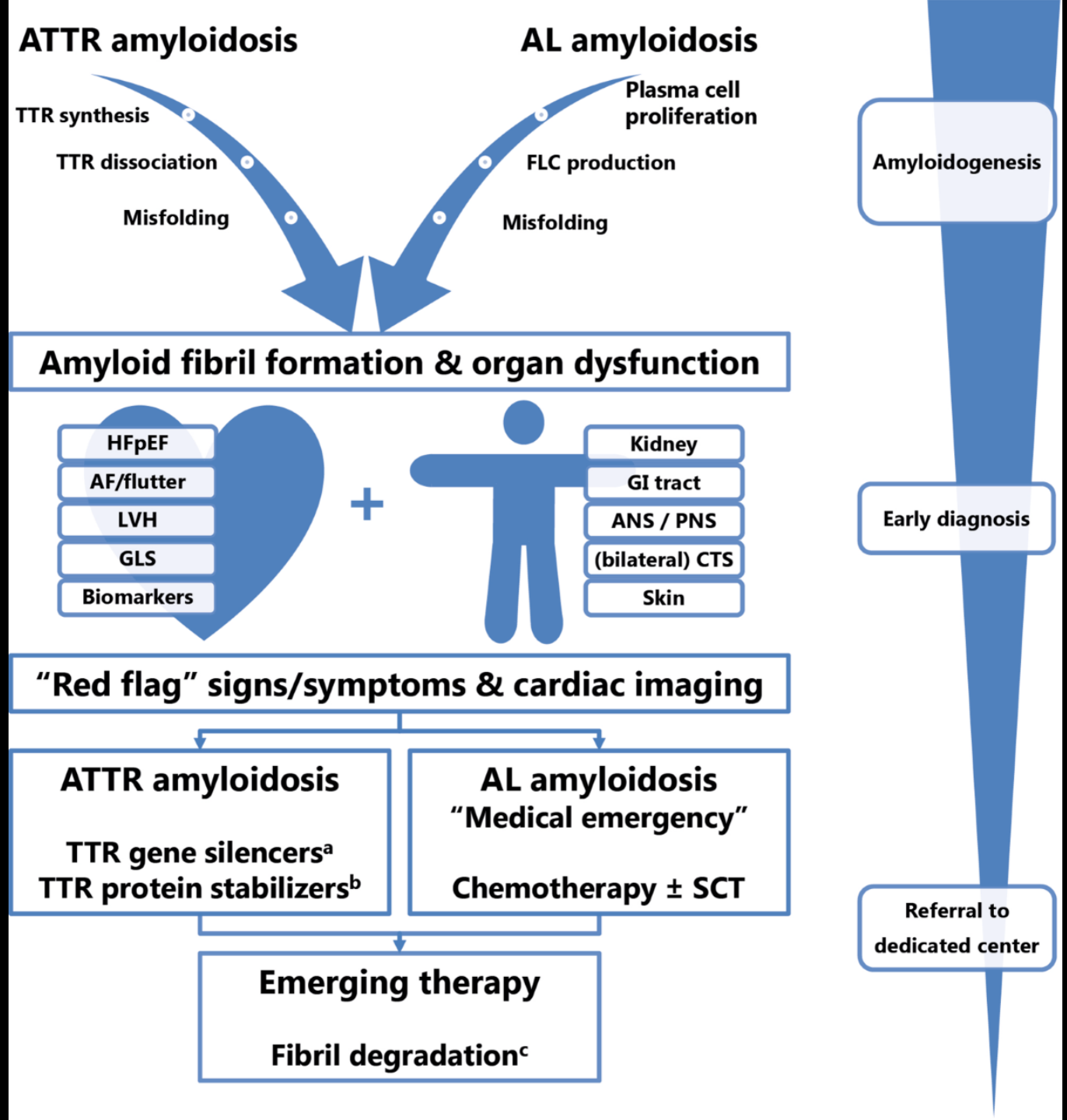


Patients remaining at risk (cumulative events)

Continuous tafamidis	176 (0)	172 (4)	170 (6)	164 (12)	155 (21)	148 (28)	144 (32)	139 (37)	132 (44)	128 (48)	117 (54)	107 (56)	104 (59)	99 (63)	95 (66)	91 (69)	85 (73)	78 (74)	72 (75)	56 (78)	30 (78)	17 (78)	6 (78)	1 (79)	0 (79)

Vutrisiran

- Approved for a-TTR amyloidosis
- HELIOS-B trial demonstrated reduced all cause mortality
- Used alone or in combination with stabilizers
- 25 mg SC q 3 months


ATTR amyloidosis
AL amyloidosis
TTR synthesis
TTR dissociation
Misfolding
Plasma cell proliferation
FLC production
Misfolding
Amyloid fibril formation & organ dysfunction
HFpEF
AF/flutter
LVH
GLS
Biomarkers
+
Kidney
GI tract
ANS / PNS
(bilateral) CTS
Skin
"Red flag" signs/symptoms & cardiac imaging
ATTR amyloidosis
TTR gene silencers[a]
TTR protein stabilizers[b]
AL amyloidosis
"Medical emergency"
Chemotherapy ± SCT
Emerging therapy
Fibril degradation[c]
Amyloidogenesis
Early diagnosis
Referral to dedicated center