KASR ALAINY
CAIRO UNIVERSITY - FACULTY OF MEDICINE

Cardiac Amyloidosis

The Unseen or The Overlooked

WALID AMMAR

PROFESSOR OF CARDIOLOGY

CAIRO UNIVERSITY

Enthusiasm about cardiac amyloidosis has grown as a result of 3 simultaneous areas of advancement:

1. Imaging techniques allow accurate noninvasive diagnosis without the need for confirmatory endomyocardial biopsies;
2. Observational studies indicate that the diagnosis of ATTR-CM may be under-recognized in a significant proportion of patients with heart failure;
3. Disease-modifying therapeutic approaches have evolved significantly, and pharmacologic therapies that slow or halt disease progression are becoming available.

ELSEVIER

Check for updates

Canadian Journal of Cardiology 36 (2020) 322–334

Society Position Statement

Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis

AHA SCIENTIFIC STATEMENT

Cardiac Amyloidosis: Evolving Diagnosis and Management

A Scientific Statement From the American Heart Association

ESC European Society of Cardiology

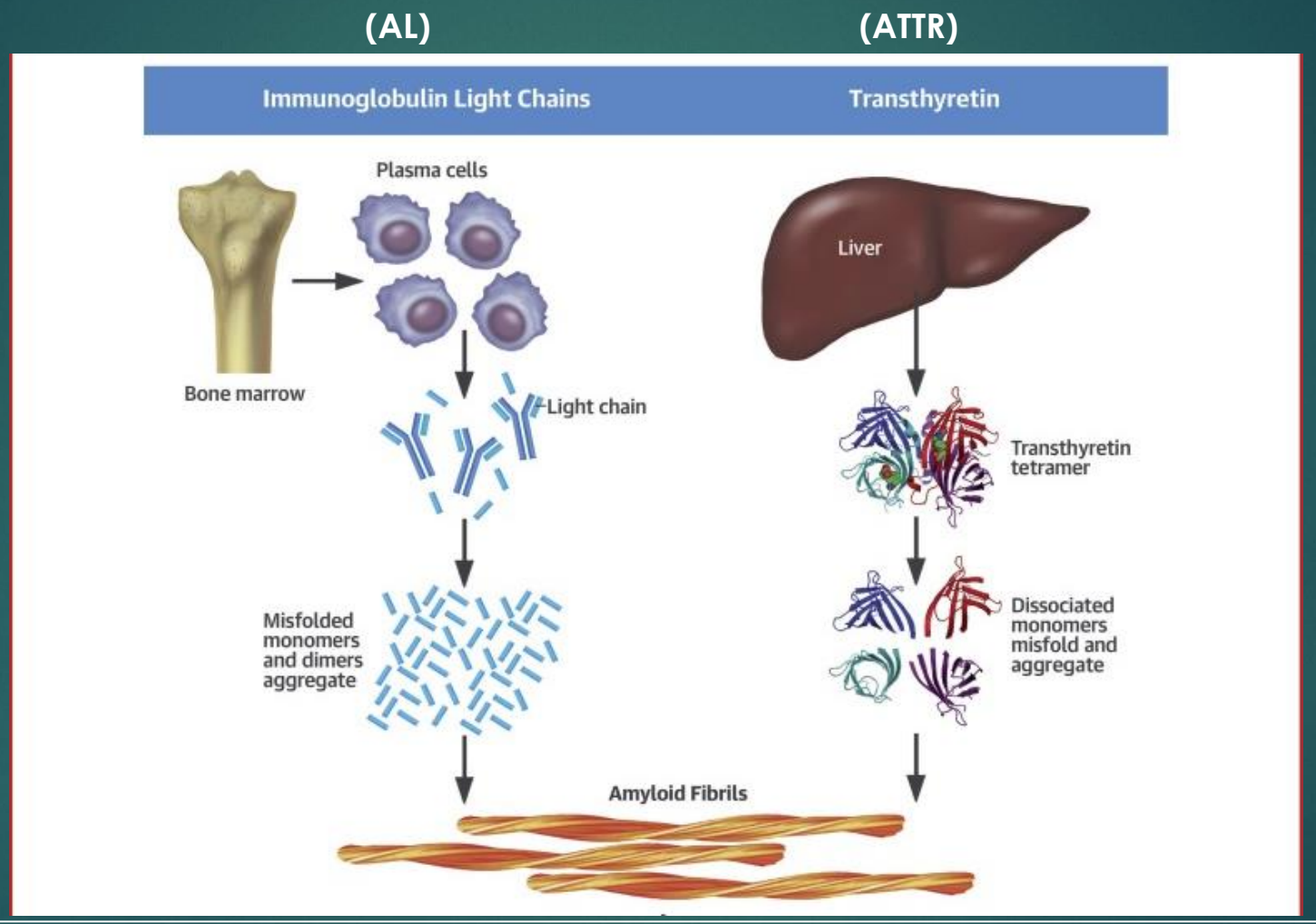
European Heart Journal (2021) **42**, 1554–1568
doi:10.1093/eurheartj/ehab072

SPECIAL ARTICLE
Heart failure and cardiomyopathies

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Rudolf Virchow 1821 - 1902

Types of Amyloidosis

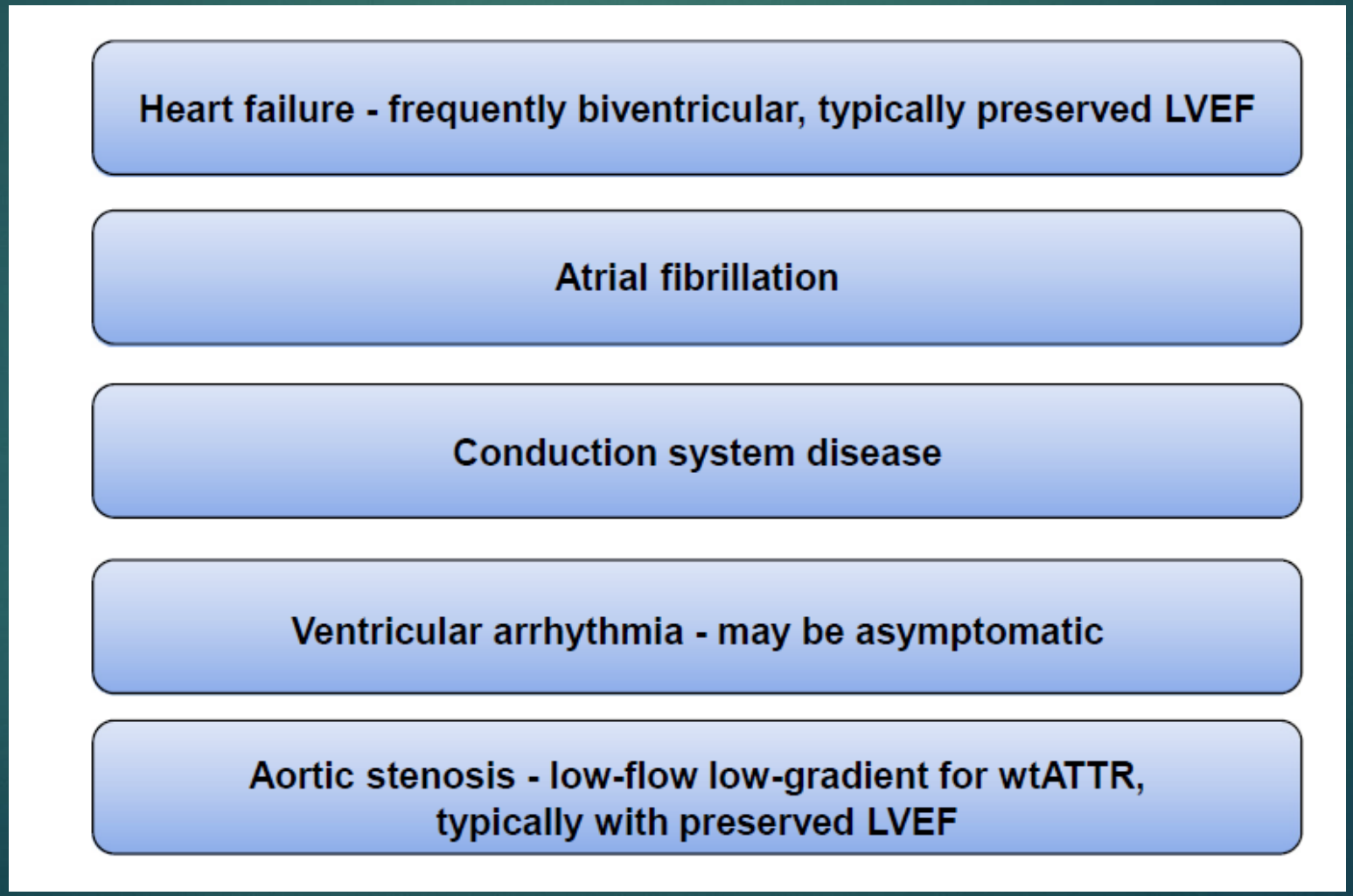


- Hereditary subtype (h ATTR) caused by a gene mutation of the ATTR protein
- An age-related wild type (wt ATTR),

Incidence & Prevalence

- The disease is believed to be underdiagnosed, particularly ATTR, for which the true incidence and prevalence are uncertain.
- In autopsy studies, myocardial ATTR deposits have been identified in up to 25% of individuals older than 80 years.
- Noninvasive methods have identified ATTR in:
  - 13% of patients with HF with preserved ejection fraction
  - 16% of patients who undergo TAVR for severe AS
  - 5% of patients with presumed hypertrophic cardiomyopathy

Cardiovascular manifestations of cardiac amyloidosis.



Cardiovascular manifestations of cardiac amyloidosis.

- Syncope and orthostatic lightheadedness.
- The need to reduce or discontinue antihypertensive therapy in patients with a previous diagnosis of hypertension, particularly agents such as b-blockers or (ACE) inhibitors, should prompt consideration of cardiac amyloidosis

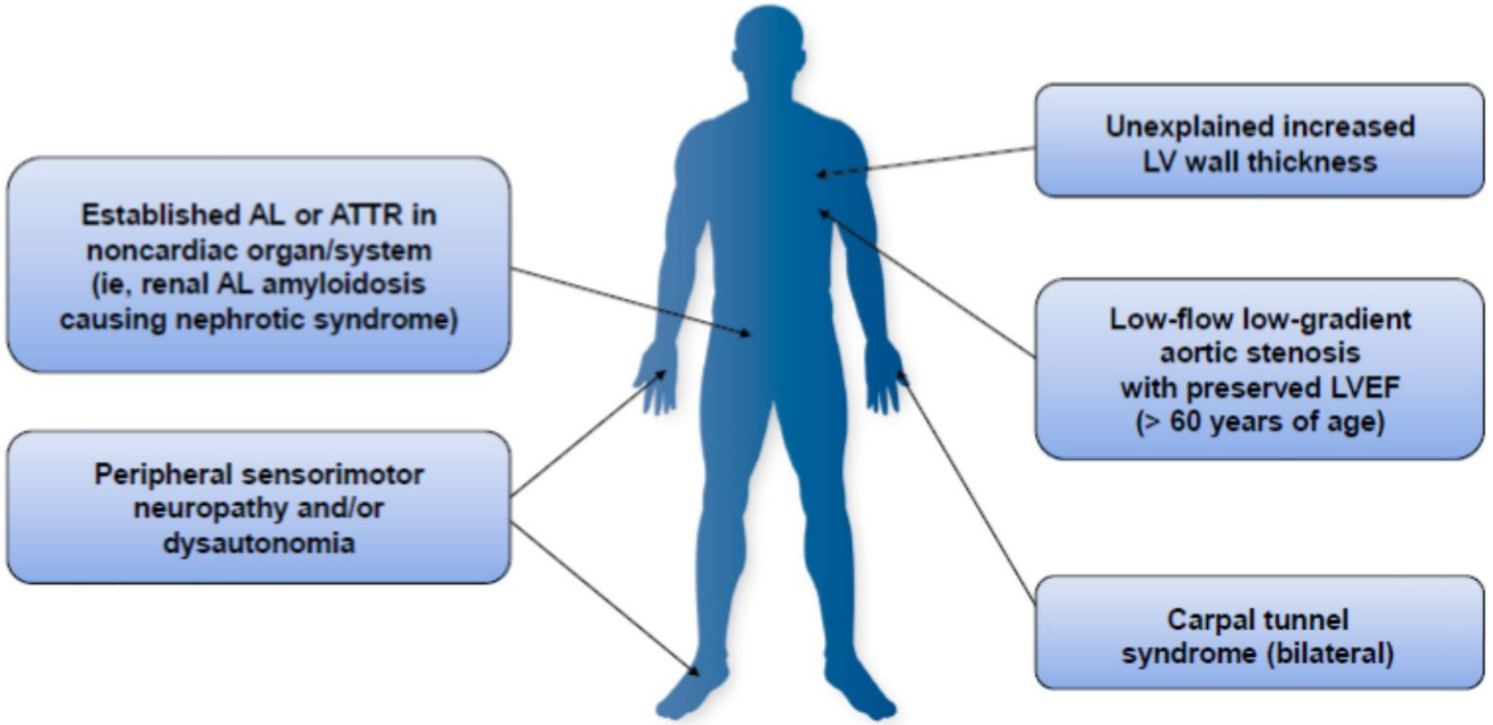
Extracardiac manifestations

Table 2. Extracardiac manifestations of common subtypes of cardiac amyloidosis

Manifestation	AL	hATTR	wtATTR
Renal	• Renal insufficiency • Nephrotic syndrome		• Milder renal insufficiency (mainly due to heart failure)
Autonomic		• Orthostatic hypotension • Gastroparesis • Sexual dysfunction • Sweating abnormalities	
Neurologic	• Peripheral sensorimotor neuropathy (might be predominant feature of hATTR, and relatively mild or absent for wtATTR)	• Carpal tunnel syndrome (bilateral)	• Spinal stenosis (predominantly lumbar)
Musculoskeletal		• Muscle weakness • Arthropathy • Fatigue • Cachexia/weight loss	
	• Pseudohypertrophy (ie, macroglossia)		• Biceps tendon rupture
Gastrointestinal	• Nausea, constipation, early satiety, abdominal bloating (gastroparesis might be secondary to dysautonomia and/or gastrointestinal involvement)	• Elevated liver enzymes	
Hematologic	• Bleeding and easy bruising (ie, periorbital)		
Ocular manifestations		• Vitreous opacities	

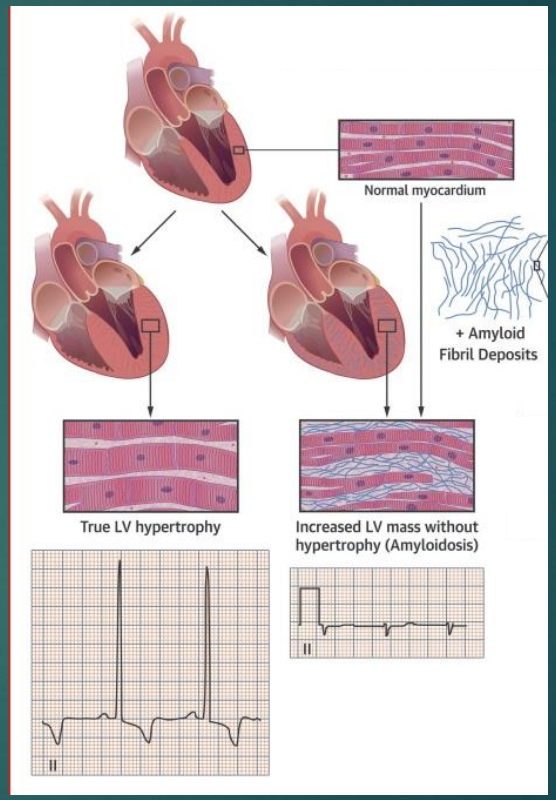
AL, light chain amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild type transthyretin amyloidosis.

SUSPECT CARDIAC AMYLOIDOSIS WHEN NEW ONSET HEART FAILURE WITH ≥ 1 OF THE FOLLOWING



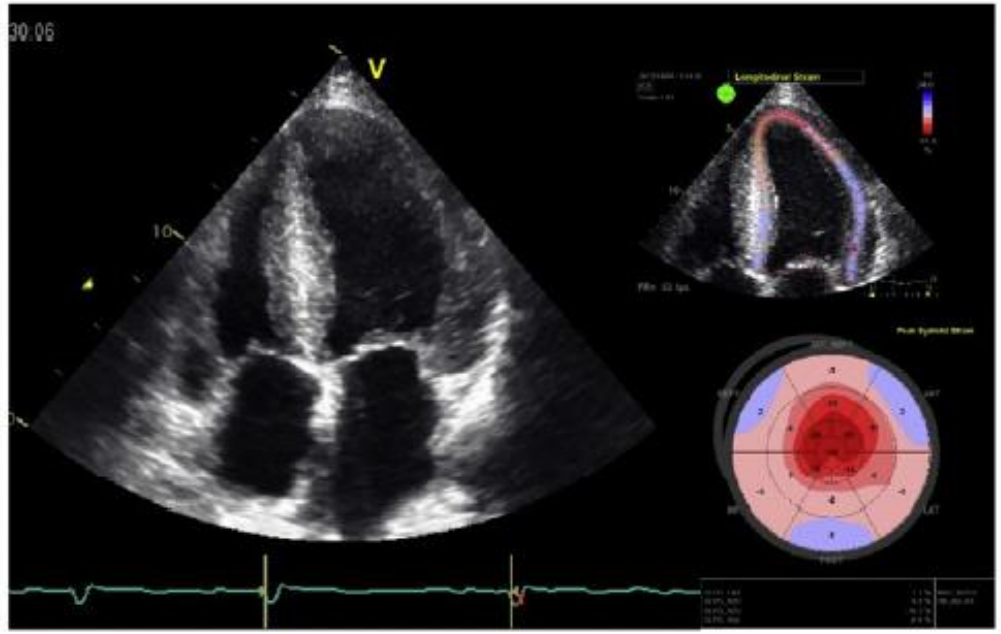
Cardiac amyloidosis: ECG findings

- Classic ECG findings include low QRS voltage, especially in the limb leads, and a pseudoinfarct pattern
- The combination of disproportionately low QRS voltage and increased LV wall thickness on cardiac imaging
- The presence of ECG criteria for LV hypertrophy does not rule out cardiac amyloidosis.



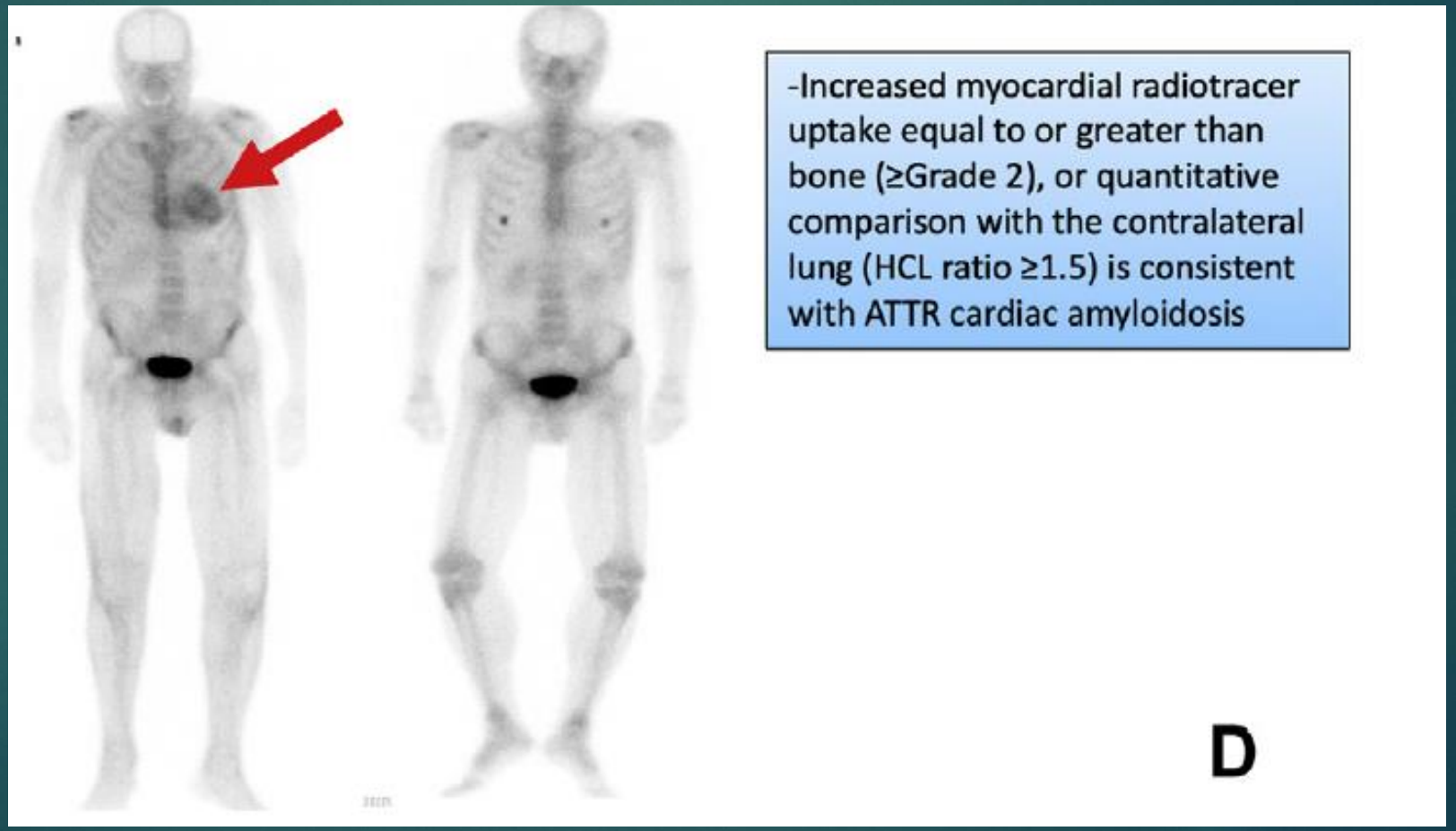
- Other nonspecific findings include AF, conduction system abnormalities, and ventricular ectopy

Cardiac amyloidosis: Echocardiographic findings



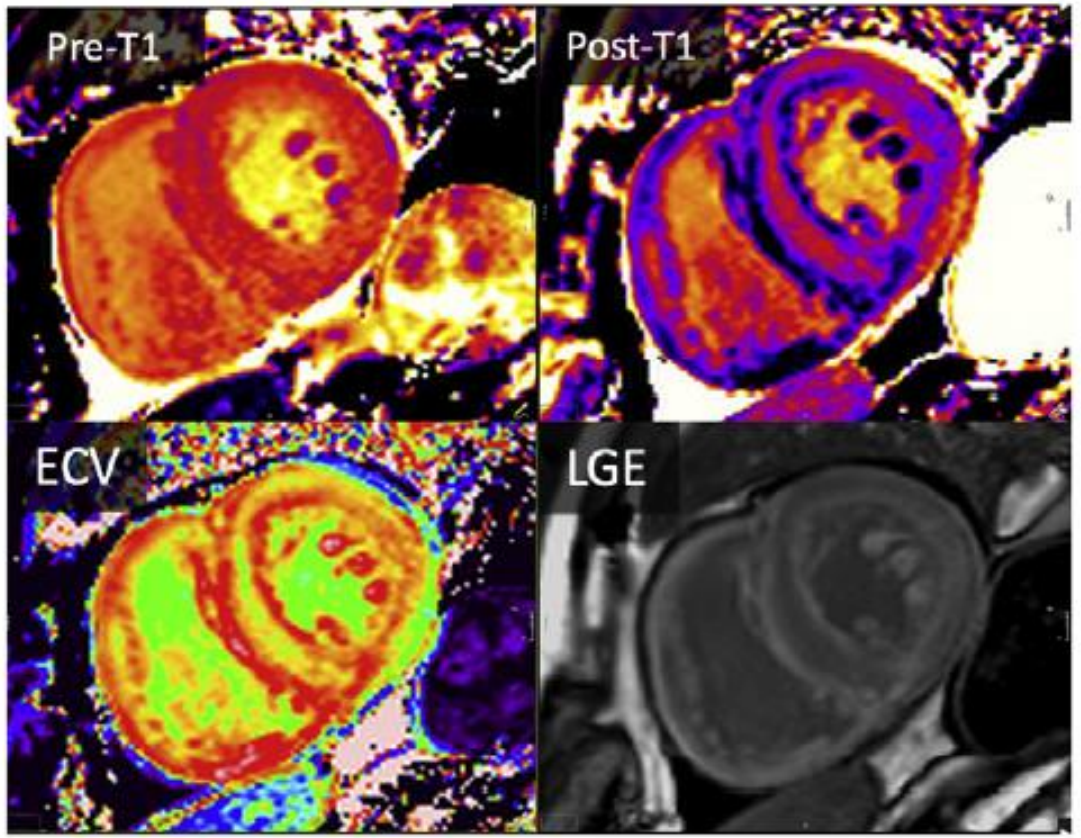
-Increased LV and RV wall thickness
-Preserved ventricular size, biatrial enlargement
-Diastolic dysfunction
-Increased valvular and interatrial septum thickness
-Small pericardial effusion
-Reduced LV GLS, preserved apical strain (basal-apical gradient)

Cardiac amyloidosis: Nuclear imaging findings

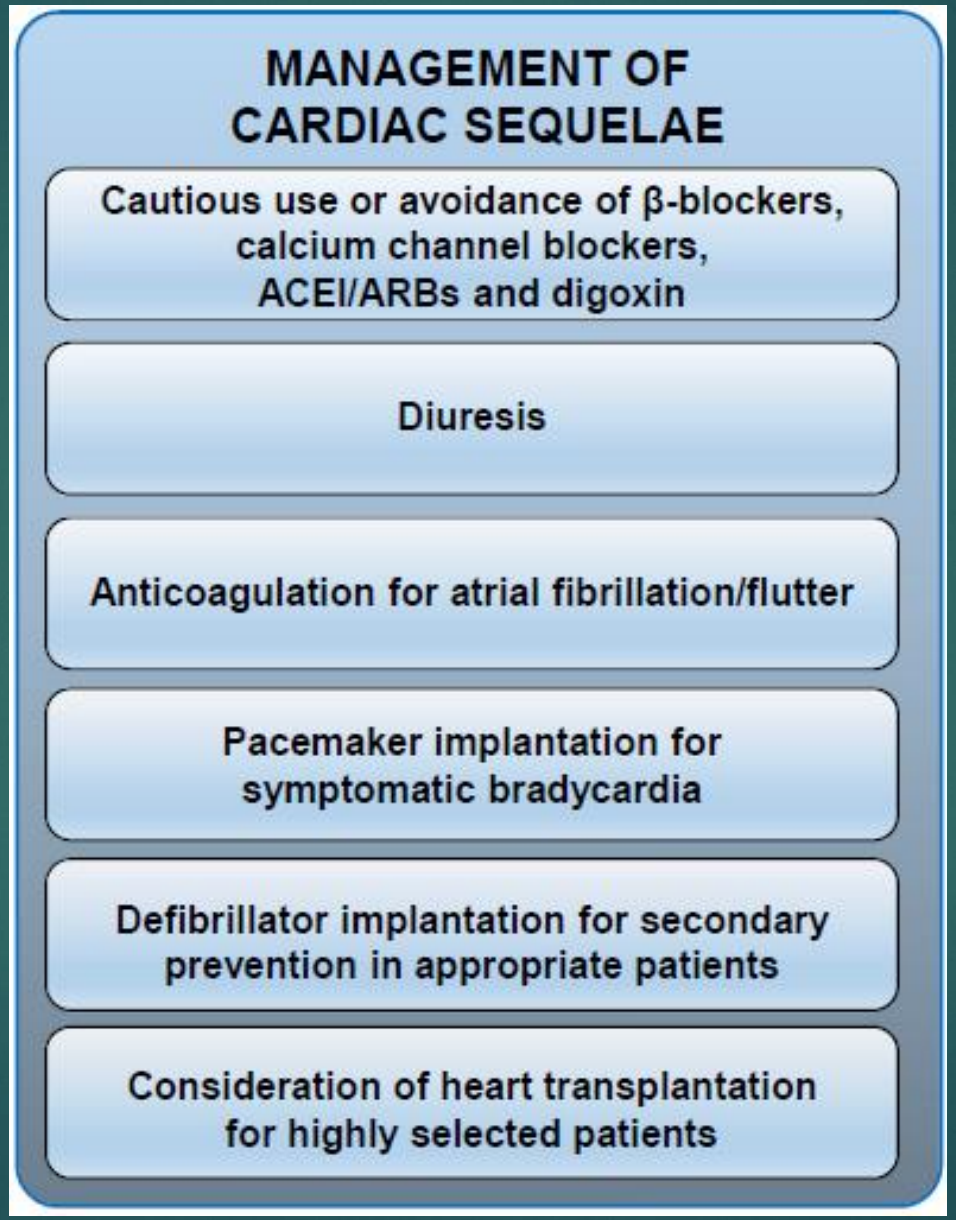


Cardiac amyloidosis: CMR findings

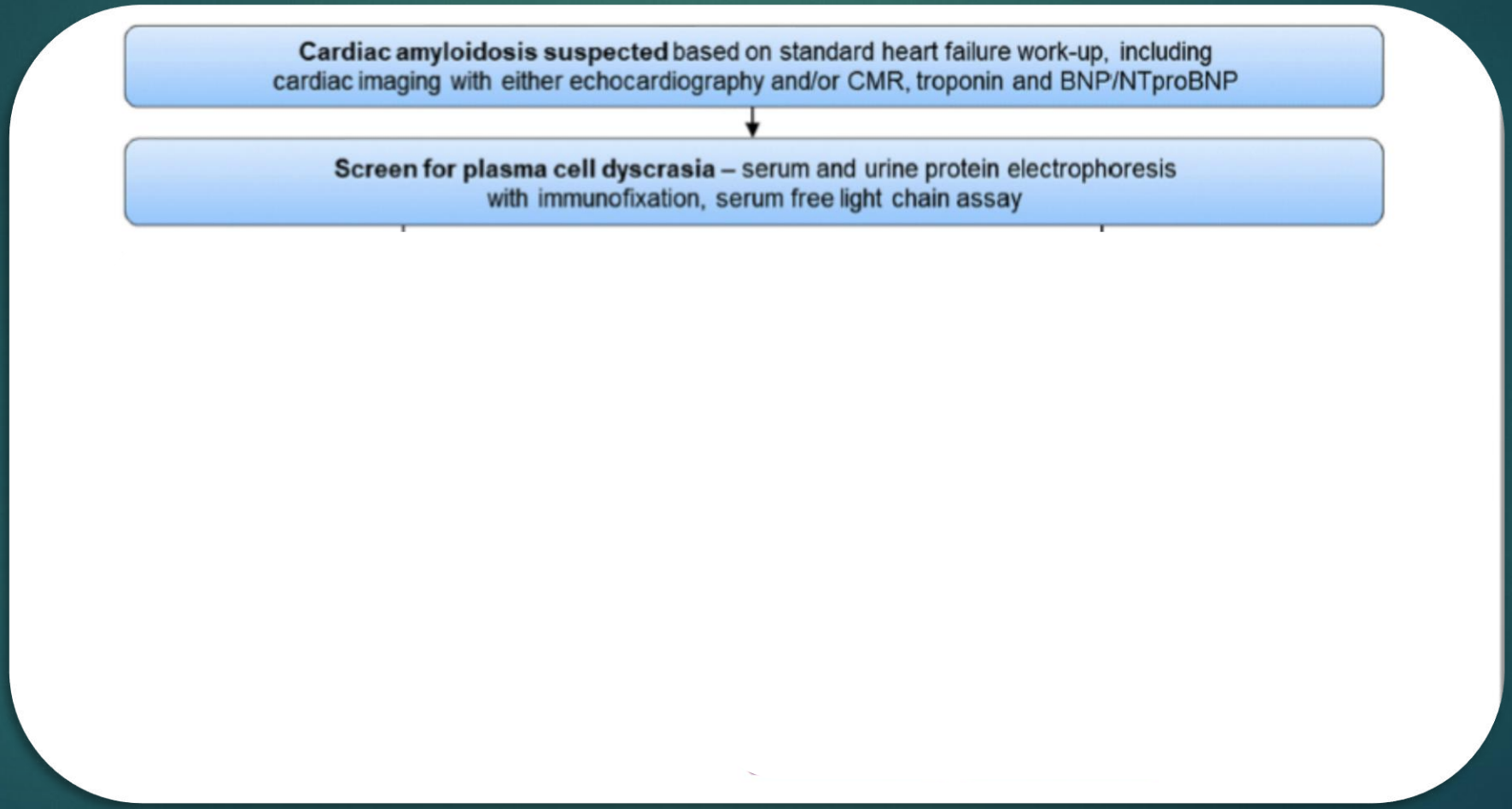
-Diffuse transmural or subendocardial pattern LGE
-Left atrial LGE
-Elevated native (non-contrast) T1 relaxation time
-Shortened post-contrast T1 relaxation time
-Elevated extracellular volume (ECV) fraction



C


MANAGEMENT OF CARDIAC SEQUELAE
Cautious use or avoidance of β-blockers, calcium channel blockers, ACEI/ARBs and digoxin
Diuresis
Anticoagulation for atrial fibrillation/flutter
Pacemaker implantation for symptomatic bradycardia
Defibrillator implantation for secondary prevention in appropriate patients
Consideration of heart transplantation for highly selected patients

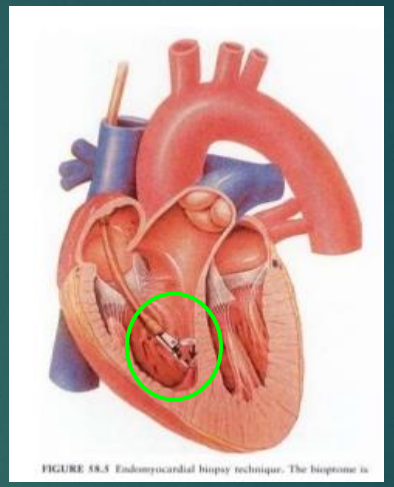
Diagnostic work-up

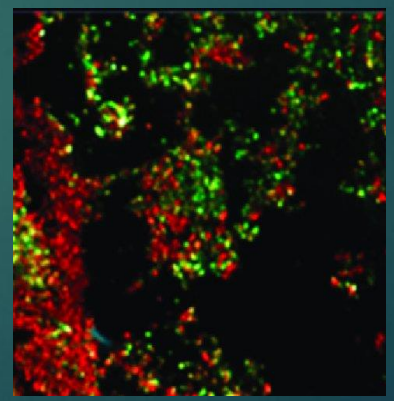


MS: mass spectrometry, IHC: immunohistochemistry,

Endomyocardial Biopsy

- EMB remains the diagnostic gold standard for all subtypes and should be performed when noninvasive evaluation yields equivocal results or clinical suspicion remains high despite a negative workup.
- Biopsy samples should be stained with Congo red, with amyloid deposits showing apple green birefringence when viewed under polarized light.
- Identification of subtype requires mass spectrometry or immunohistochemistry





Tissue Biopsy

- Bone marrow biopsy: Patients with monoclonal protein, to exclude concurrent multiple myeloma.
- Biopsy of remote sites (such as abdominal fat , rectum) have variable diagnostic yield but might obviate the need for endomyocardial biopsy when positive and combined with imaging evidence of cardiac involvement.
- Direct biopsy of a clinically involved organ has the highest sensitivity.

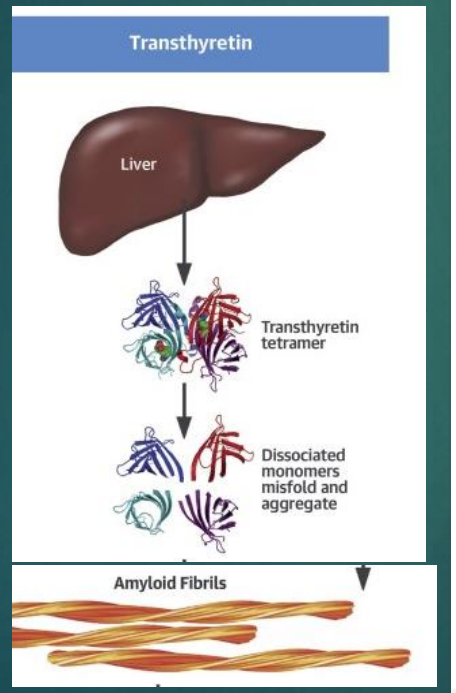
Need for Genetic Testing

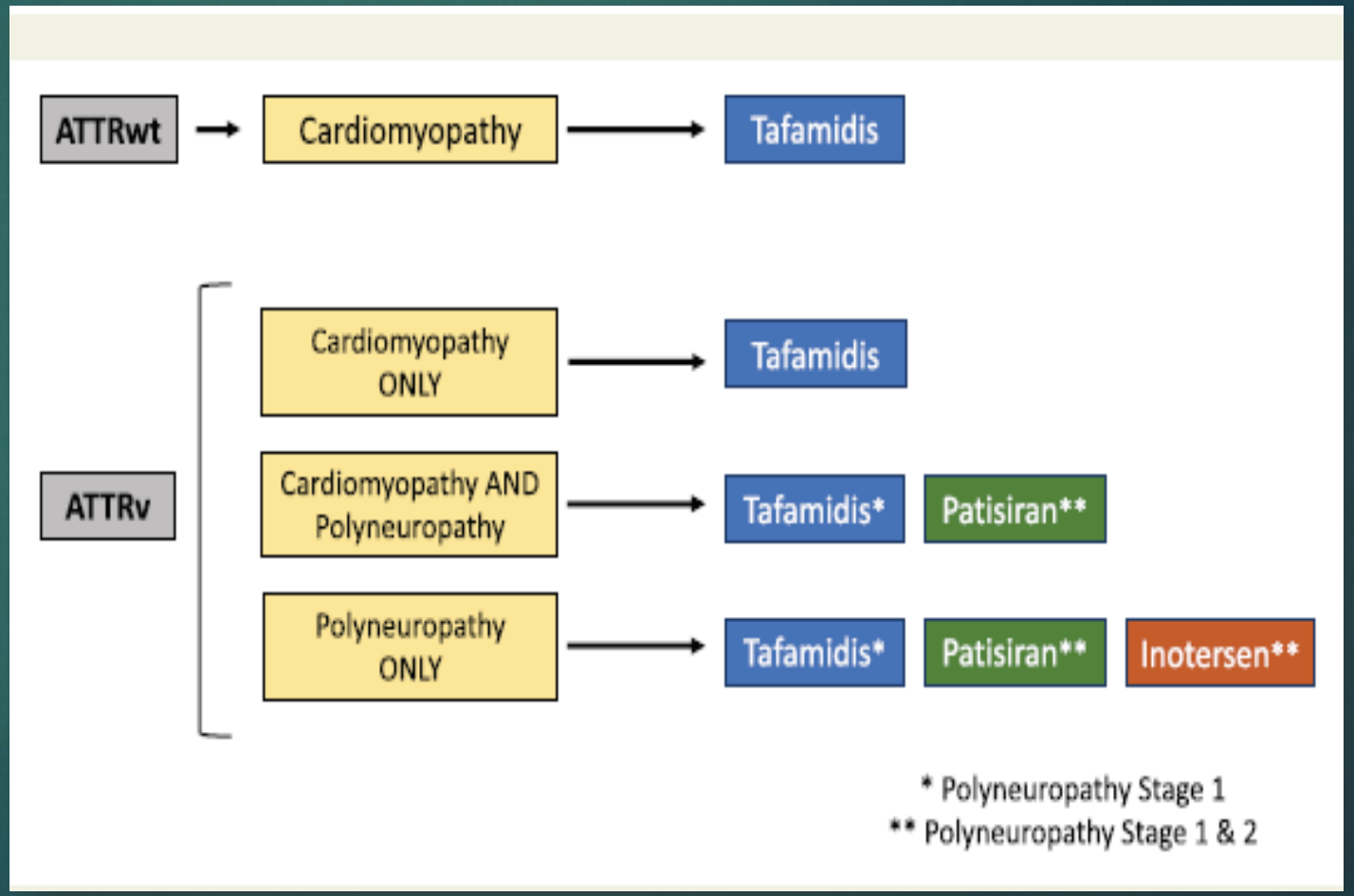
- When ATTR is confirmed, genetic testing to differentiate hATTR from wtATTR should be performed.
- This has relevance for :
  - Prognostic assessment
  - The likelihood of extracardiac involvement
  - The need for family member screening
  - The eligibility for novel ATTR-targeted therapies

When a TTR gene mutation is identified, referral for genetic counselling is recommended

Disease-modifying therapies in transthyretin amyloidosis

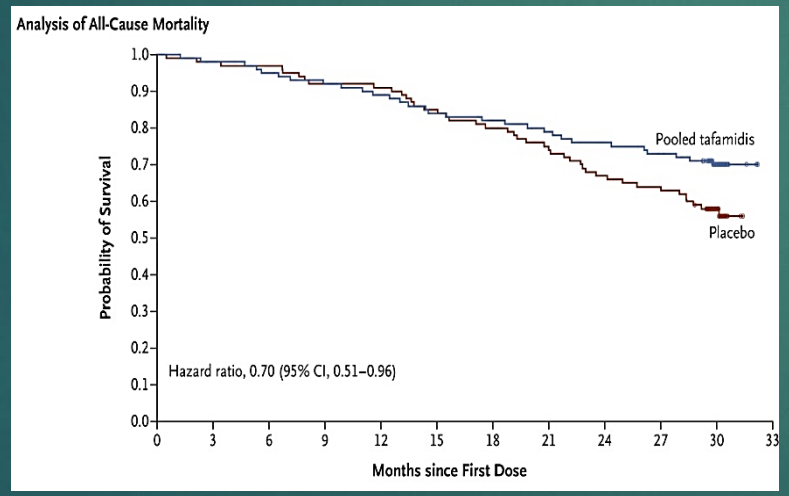
- ATTR Stabilizers
- Genetic silencers

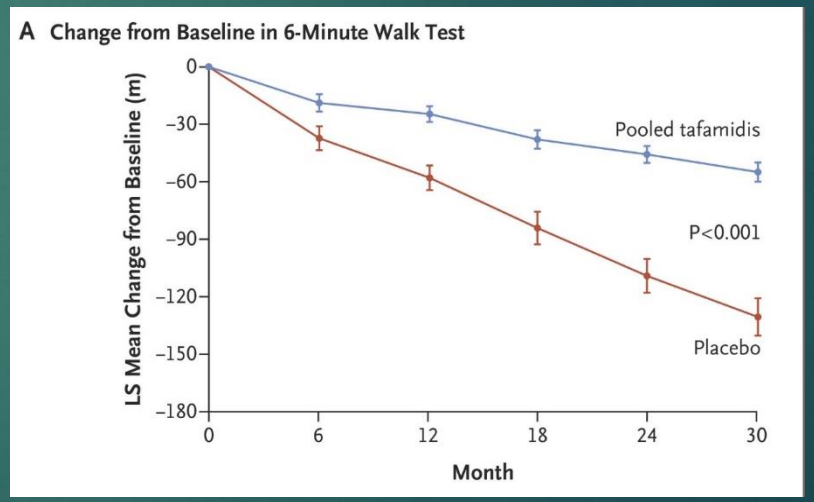




Disease-modifying therapies in transthyretin amyloidosis

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy





Take home message

- The development of effective therapy is anticipated to improve the historically poor prognosis associated with this condition
- It is increasingly important for clinicians to recognize the cardiac and extra-cardiac clinical features of amyloidosis, understand strategies for diagnosis, and be aware of important management advances.

Thank you