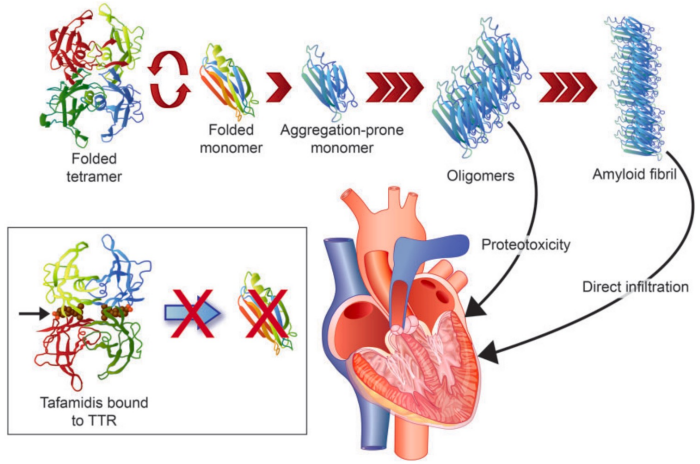
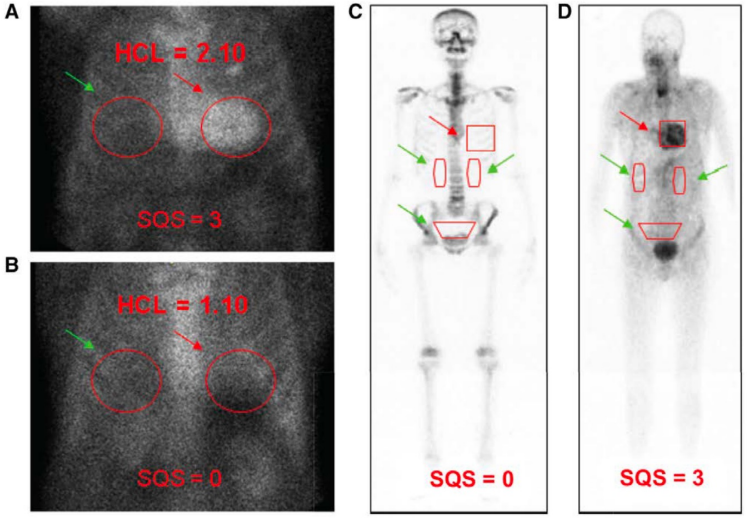
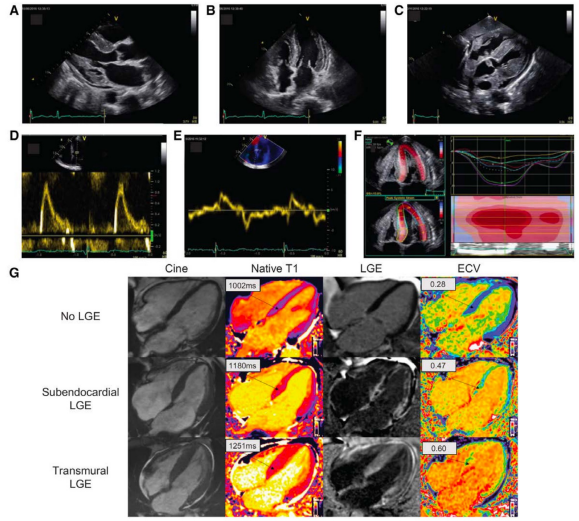
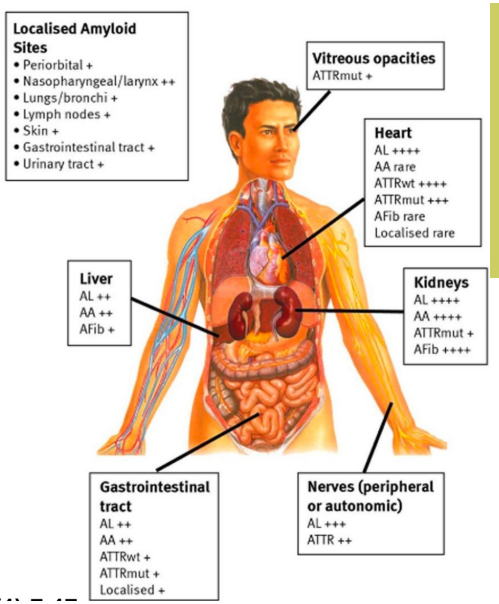








CARDIAC AMYLOIDOSIS IN 2023

Steven Droogmans

03 juni 2023

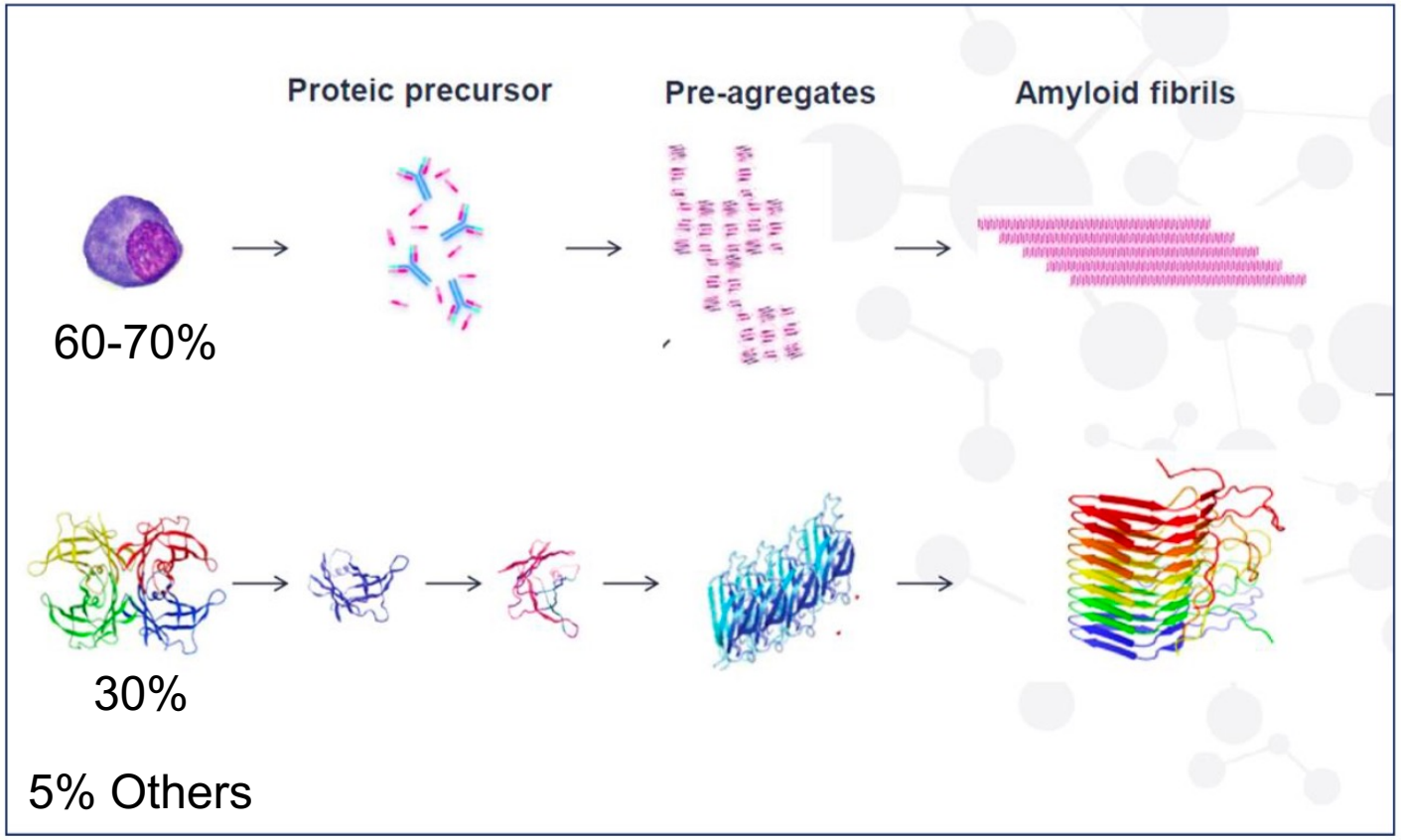
Universitair Ziekenhuis Brussel

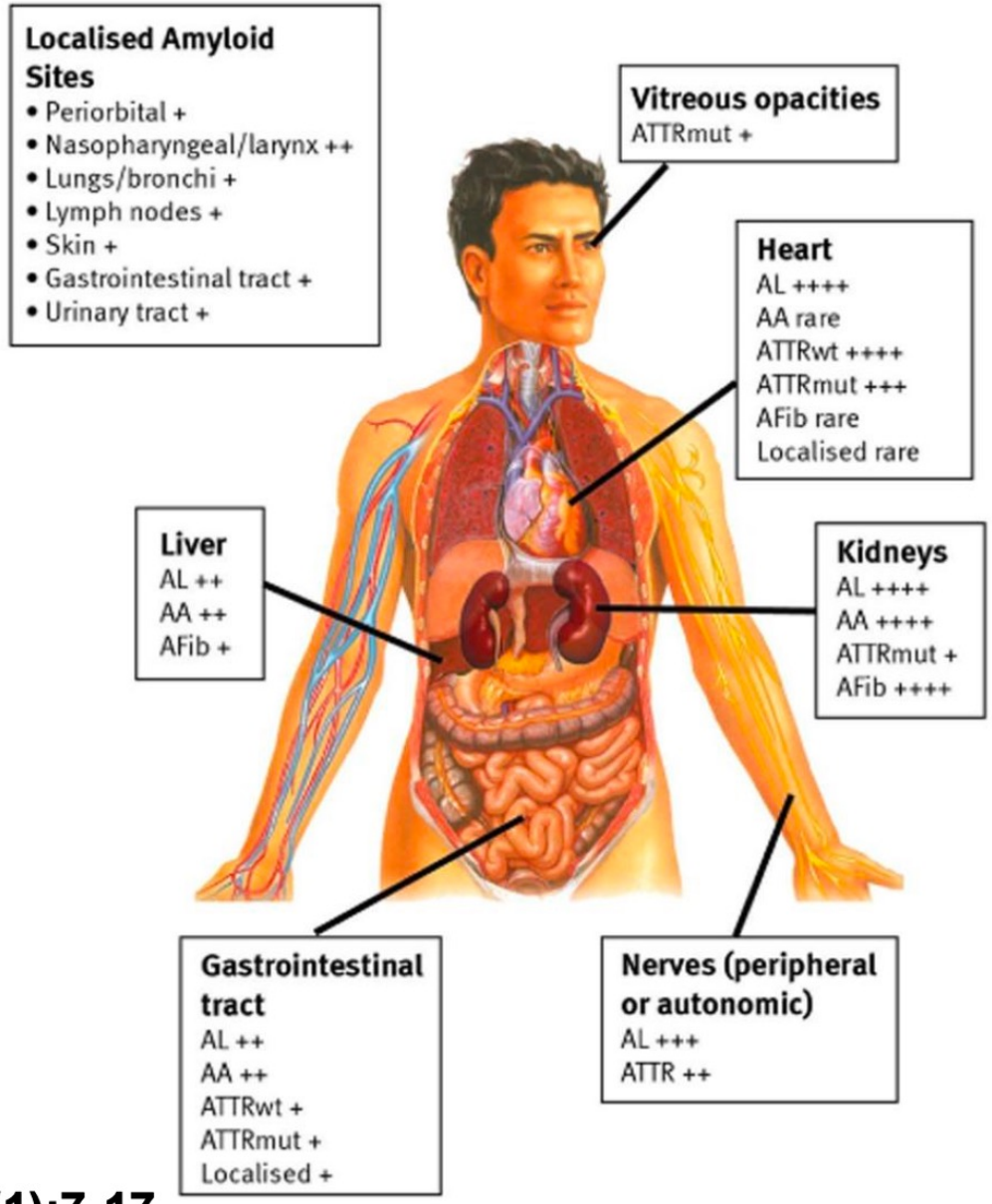
Centrum voor Hart- en Vaatziekten

DISCLOSURES

- Pfizer, Alnylam

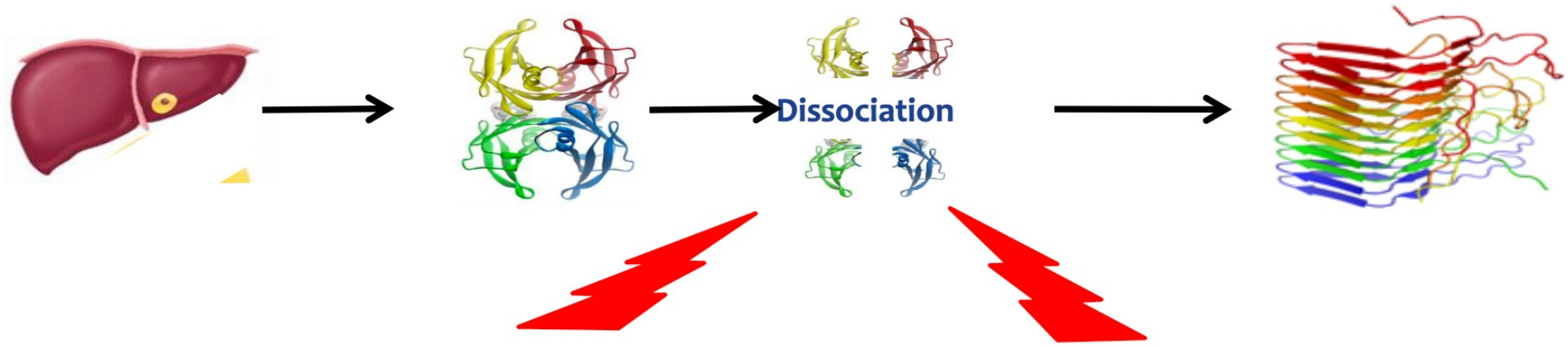
AMYLOIDOSIS IS A SYSTEMIC DISEASE
Deposition of amyloid





Mollee et al, Intern Med J 2014 Jan;44(1):7-17

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)



Hereditary : **hTTR**

Autosomal dominant

120 mutations

HEART>>>nerve

Senescence or Wild-Type : **wtTTR**

« **Cardiac Alzheimer** »

¼ of 80yrs old with TTR amyloid deposits in the heart

References

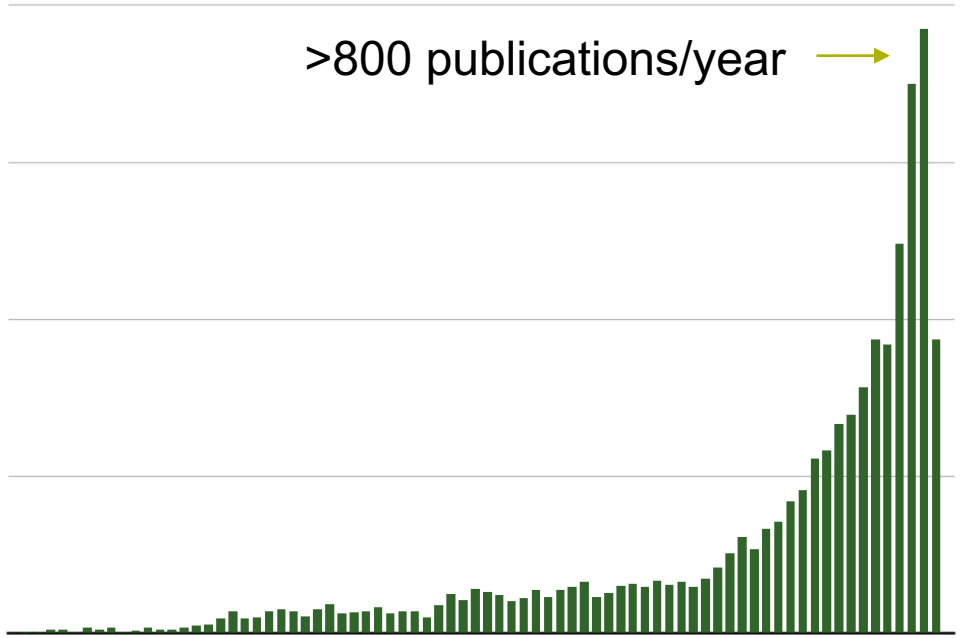
1.) Donnelly JP, et al. *Cleve Clin J Med*. 2017;84(12 Suppl 3):12–26. 2.)Siddiqi OK, et al. *Trends Cardiovasc Med.* 2018;28:10–21. 3.) Kholova I, Niessen HWM. *J Clin Pathol.* 2005;58(2):125–133. 4.) González-López E, et al. *Rev Esp Cardiol.* 2017;70:991–1004.

MOST IMPORTANT MESSAGE CARDIAC AMYLOIDOSIS

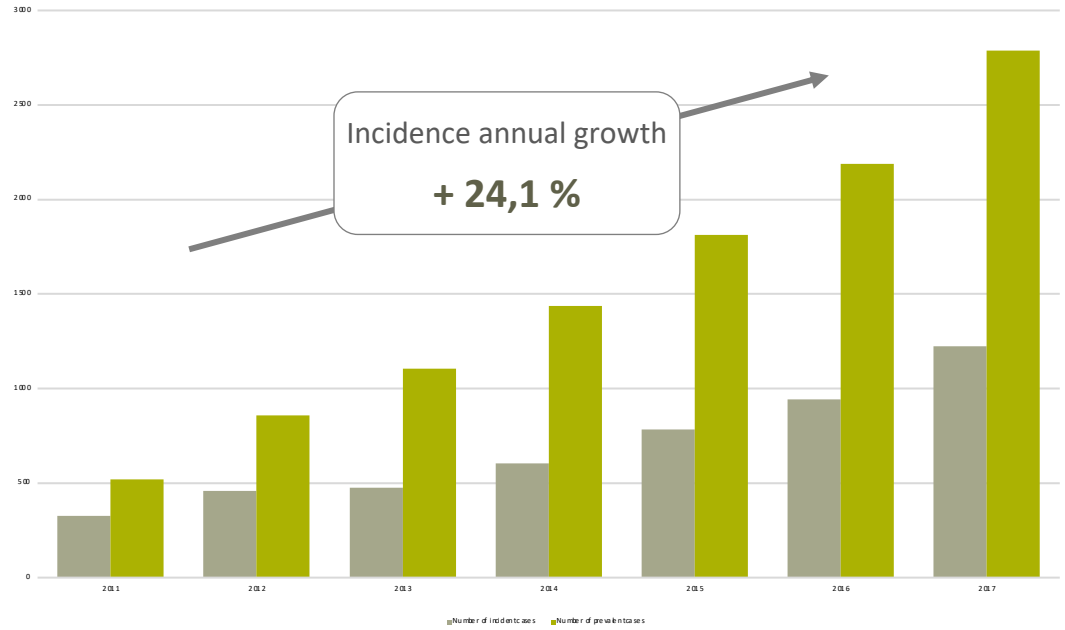
Think about it!

WHY WE NEED TO THINK ABOUT CARDIAC AMYLOIDOSIS

Because it is more frequent than previously thought



Pubmed Search ”Cardiac Amyloidosis” 1950-2022



ATTR-CM annual incidence
and prevalence in France
2011-2017 (total 4900 patients)

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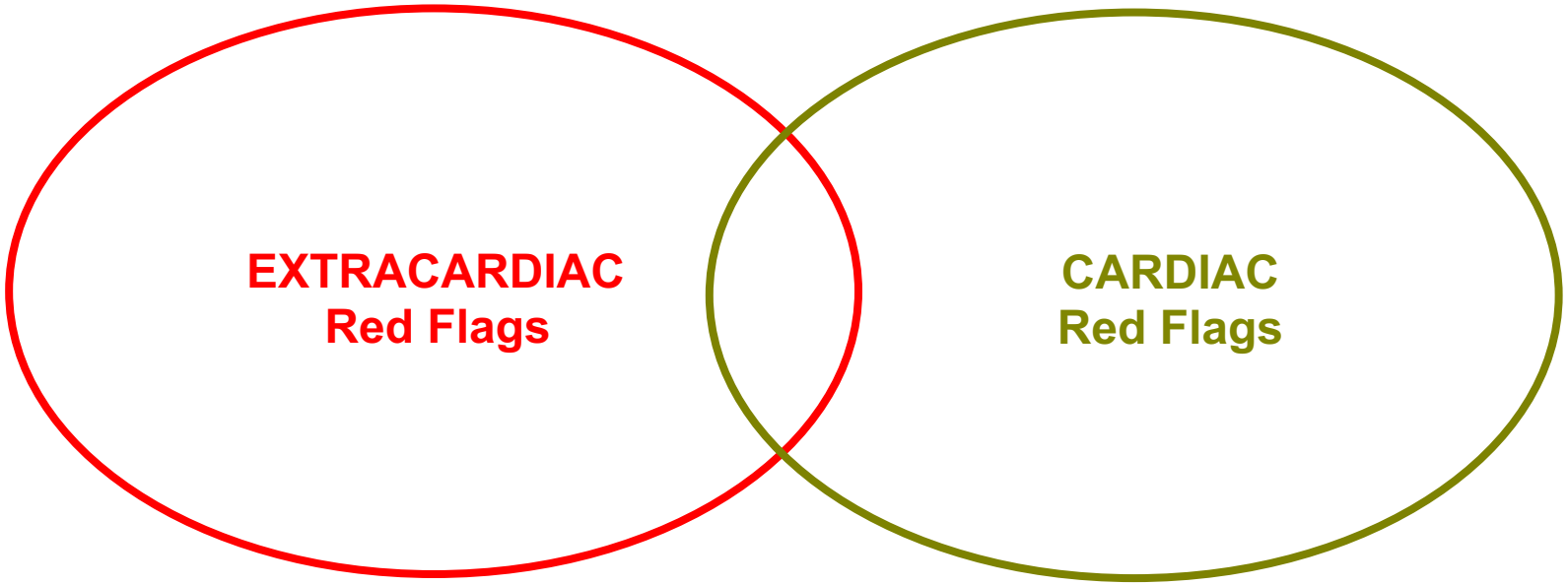
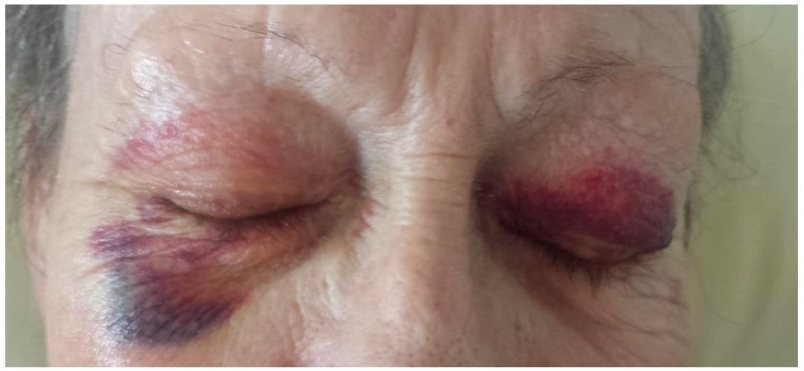
PRESENTATION OF CARDIAC AMYLOIDOSIS

Systemic disease

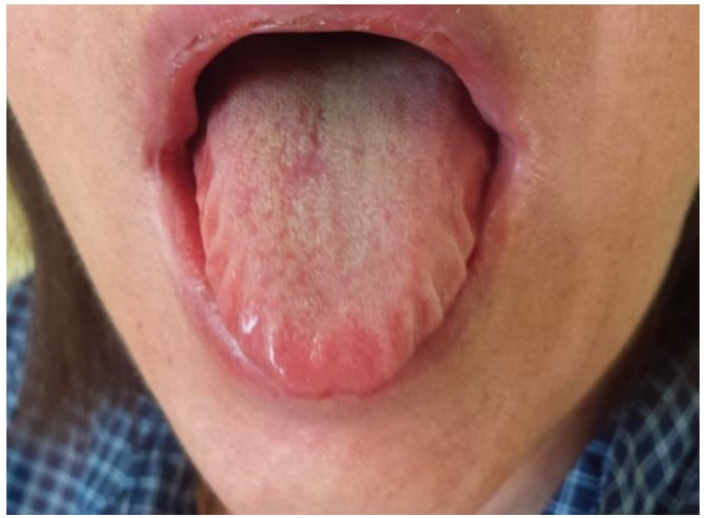


TRANSTHYRETIN AMYLOID CARDIOMYOPATHY
FREQUENT NON-CARDIAC MANIFESTIONS (RED FLAGS)

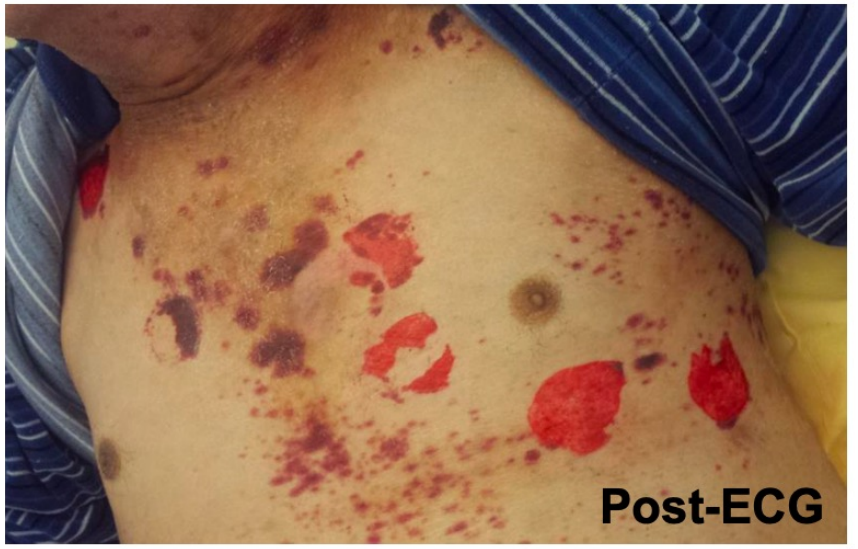
Peri-orbital purpura



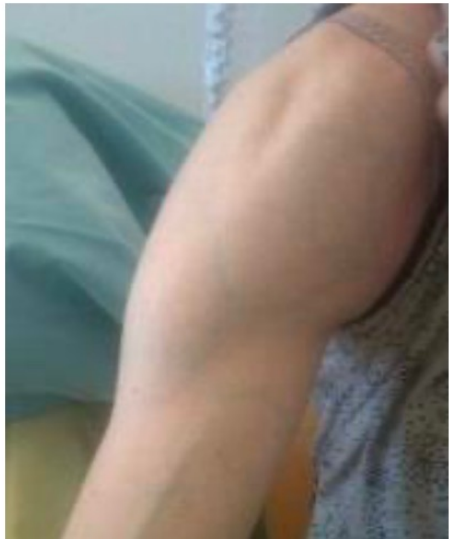
Macroglossia



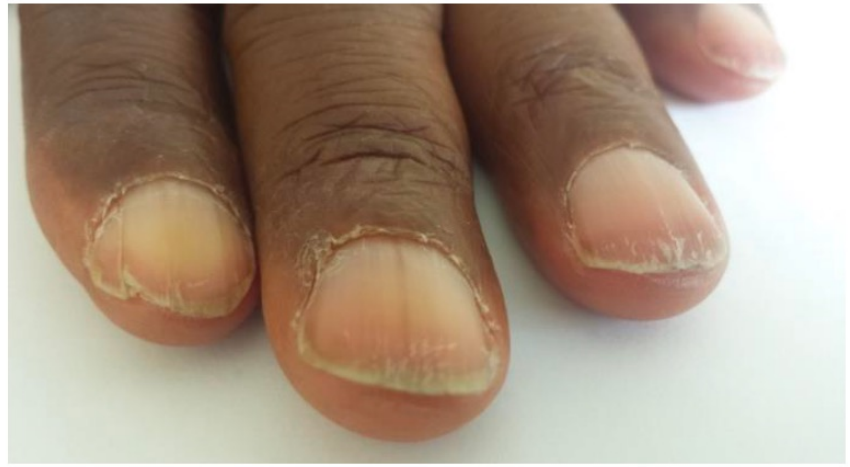
Cutaneous fragility



Pseudo-athletic appearence

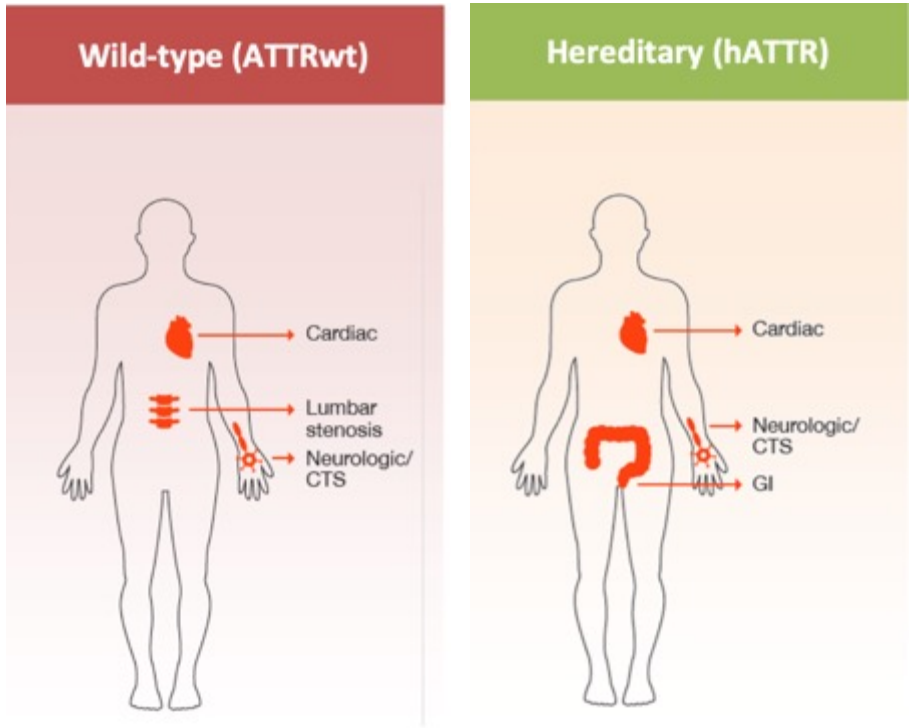


Ungual abnormalities



TRANSTHYRETIN AMYLOID CARDIOMYOPATHY FREQUENT NON-CARDIAC MANIFESTIONS (RED FLAGS)

Soft tissue	• **Lumbar stenosis** • **Ruptured distal biceps tendon**
Gastro-intestinal (GI)	• Diarrhea • Constipation • Nausea • Early satiety
Neurologic	• **Carpal Tunnel syndrome (CTS)** • Peripheral neuropathy • **Orthosasis** • Weakness

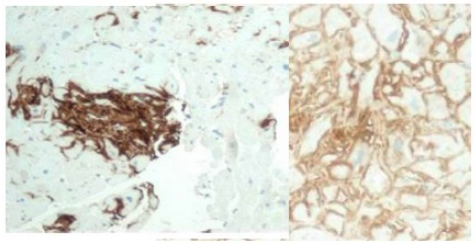


ATTR-CM : Transthyretin amyloidosis cardiomyopathy

1. Connors LH, et al.;Circulation 2016: 282-290. 2. Pinney JH , et al J. Am Heart Assoc 2013;2;(2):e000098 3. Maurer et al.; J Am Coll Cardiol 2016;68(2) :161-172 4. Nativi-Nicolau J , Maurer MS Curr opin Cardiol 2018 ;33 (5) :571-579 , 5. Geller HI et al.; JAMA 2017;318(10) :962-963 6. Westermark P et al.; Ups J Med Sci 2014;119(3):223-228 7. Yanagisawa A, et al Mod Pathol 2015;28(2) :201-207

ANATOMICAL AND PATHOPHYSIOLOGICAL CONSEQUENCES OF AMYLOID DEPOSITION

Myocardium

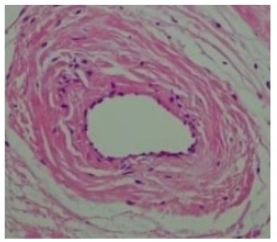


↗ Stiffness
↗ Thickness
Diastolic Dysfunction
Systolic Dysfunction
Thrombosis: (PE/STROKE)
Cell Death : ↗ Troponin

Endocardium

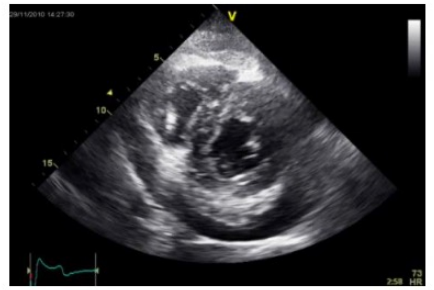
TR /MR
Aortic Stenosis
= 6 à 16%

Vascular



Ischemia
Necrosis

Pericardium



Pericardial Effusion
Tamponade

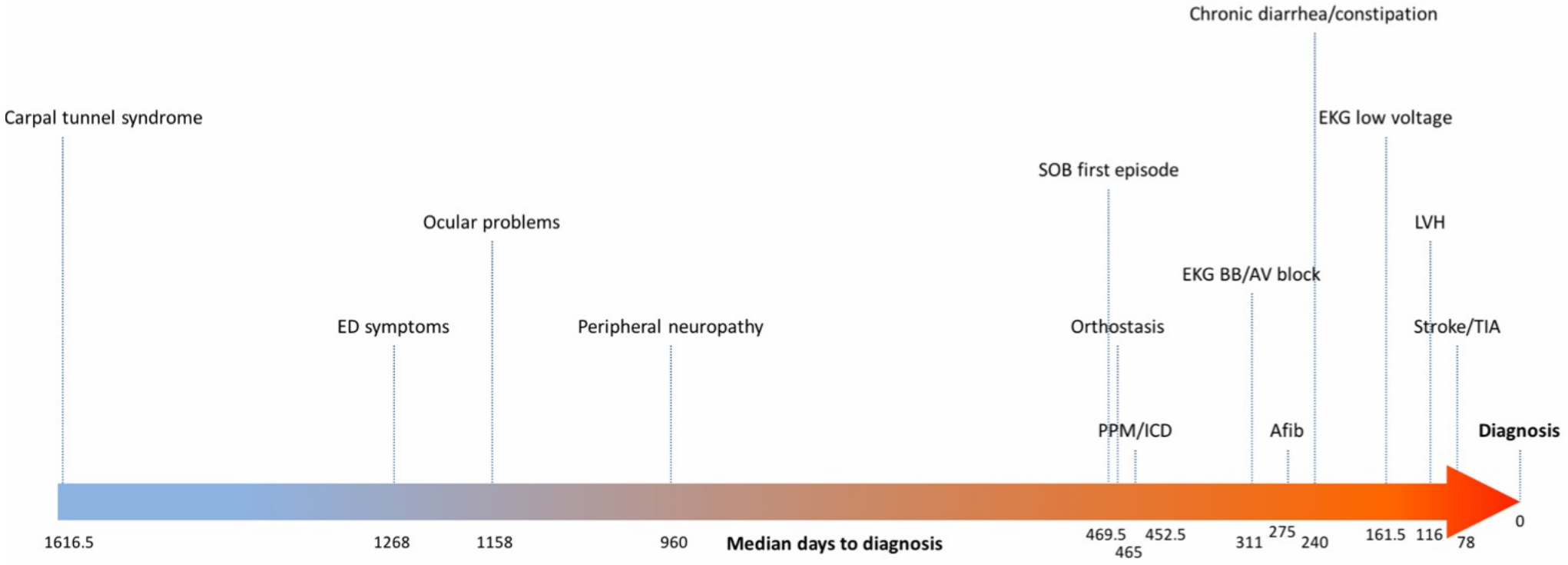
"Electrical" Cell

Rhythm disorder: Arrythmia, AF, Flutter
Conduction Disorders : AV block 1-2-3

Autonomic Nervous System

↘ Heart Rate
Chronotropic Insufficiency
Orthostatic Hypotension

WT-ATTR: DELAY FROM SYMPTOMS TO DIAGNOSIS IS LONG



J Card Fail. 2018 Feb;24(2):131-133.

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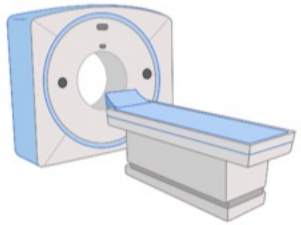
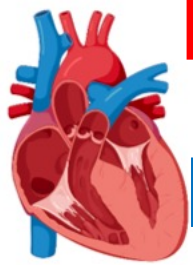
Prevalence of CA in screening studies

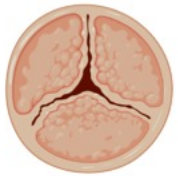


Bone scintigraphy
for non-cardiac reasons:
≥81 years: ~1.3% M, ~0.4% W

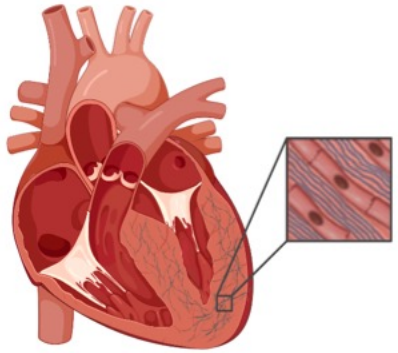
Autopsy in unselected
elderly individuals: 21%
(95% CI 7-39%)

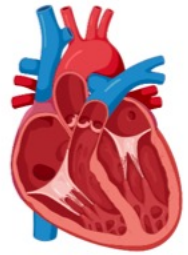


HFpEF: 12%
(95% CI 6-20%)
M 73% (39-100%)
77 years (66-86)
AL-CA 10% (0-40%)

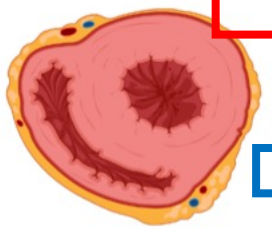


Aortic stenosis: 8%
(95% CI 5-13%)
M 67% (50-89%)
84 years (75-88)
AL-CA 2% (0-6%)





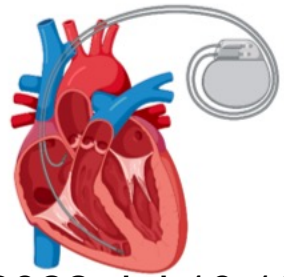
HFrEF/HFmrEF: 10%
(95% CI 6-15%)
M 100%
81 years (76-85)
AL-CA 0%



HCM: 7%
(95% CI 5-9%)
M 80% (73-87%)
74 years
AL-CA 0-9%

Surgery for carpal tunnel
syndrome: 7%
(95% CI 5-10%)
M 64% (33-100%)
76 years (73-79)
AL-CA 18% (0-33%)

Conduction disorders: 2%
(95% CI 0-4%)
M 50%
90 years
AL-CA 0%



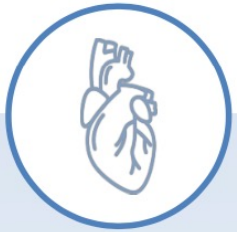
Aimo et al. Eur Heart J HF 2022 doi:10.1002/ejhf.2532

OTHER FEATURES OF CARDIAC AMYLOIDOSIS

- 81% man (20% female)
- Only 22% low voltage QRS, but pseudo-infarct (qS) pattern anterior wall 63%
- 1/3 has LVEF <50% !
- 69% have atrial fibrillation
- Asymmetric left ventricular hypertrophy in23%
- Increased troponins
- High NT-pro BNP in relation to heart failure symptoms

BUILDING UP YOUR CASE FOR ATTR CARDIAC AMYLOIDOSIS

ATTR -CM



Heart failure with preserved ejection fraction in patients typically over 60[1–4]

Intolerance to standard HF therapies (ACEi, ARBs and beta blockers)[5–7]

Discordance between QRS voltage on ECG and left ventricular (LV) wall thickness seen on echo[8–10]

Diagnosis of **carpal tunnel syndrome** or **lumbar spinal stenosis**[1,6,11–17]

Echo showing **increased LV wall thickness**
3,10,11,18,19

Autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss
3,10,11,18,19

ACEi = Angiotensin-converting enzyme inhibitors; ARBs=angiotensin receptor blockers; ECG=electrocardiography; Echo=echocardiography.

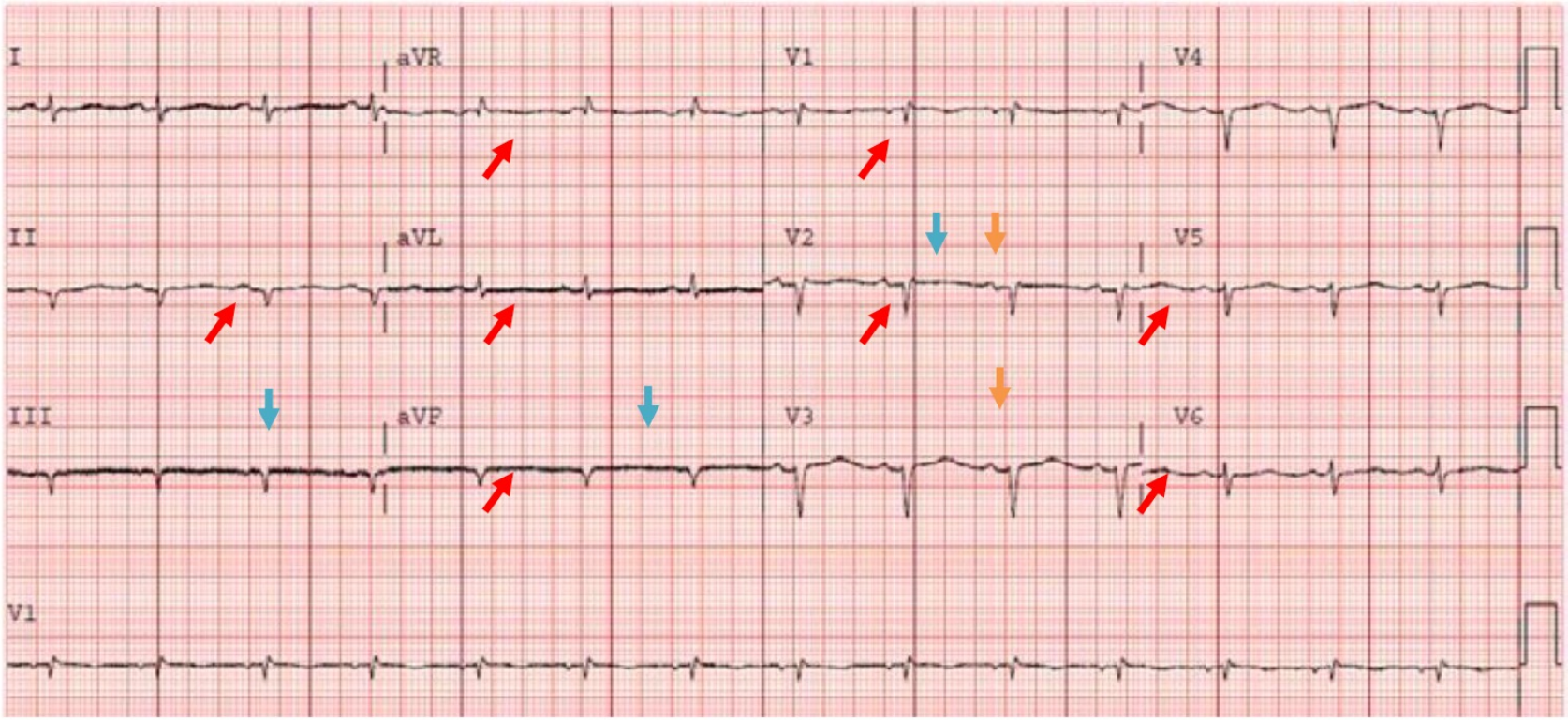
1. Connors LH, et al. *Circulation* 2016;133(3):282–290. 2. Mohammed SF, et al. *JACC Heart Fail* 2014;2(2):113–122. 3. Maurer MS, et al. *J Am Coll Cardiol* 2016;68(2):161–172. 4. González-López E, et al. *Eur Heart J* 2015;36(38):2585–2594. 5. Narotsky DL, et al. *Can J Cardiol* 2016;32(9):1166.e1–1166.e10. 6. Brunjes DL, et al. *J Card Fail* 2016;22(12):996–1003. 7. Castaño A, et al. *Heart Fail Rev* 2015;20(2): 163–178. 8. Carroll JD, et al. *Am J Cardiol* 1982;49:9–13. 9. Cyrille NB, et al. *Am J Cardiol* 2014;114(7):1089–1093. 10. Quarta CC, et al. *Circulation* 2014;129(18):1840–1849. 11. Rapezzi C, et al. *Circulation* 2009;120(13):1203–1212. 12. Nakagawa M, et al. *Amyloid* 2016;23(1):58–63. 13. Westermark P, et al. *Ups J Med Sci* 2014;119(3):223–228. 14. Yanagisawa A, et al. *Mod Pathol* 2015;28(2):201–207. 15. Connors LH, et al. *Am Heart J* 2009;158(4):607–614. 16. Sperry BW, et al. *J Am Coll Cardiol* 2018;72(17):2040–2050. 17. Sueyoshi T, et al. *Hum Pathol* 2011;42(9):1259–1264. 18. Phelan D, et al. *Heart* 2012;98(19): 1442–1448; 19. Ternacle J, et al. *JACC Cardiovasc Imaging* 2016;9(2):126–138. 20. Swiecicki PL, et al. *Amyloid.* 2015;22(2):123–131. 21. Coelho T, et al. *Curr Med Res Opin* 2013;29(1):63–76.

WHY SHOULD WE IMPROVE TIMELY DIAGNOSIS?

- Latent for years, underdiagnosed
- High mortality rate when end-stage disease
- Tailored HF therapy, different from usual recommendations
- Disease modifying drugs more effective in early stage

ELECTROCARDIOGRAM

Discordance between the LV Wall Thickness and QRS Voltage[1,2]



ECG showing low voltage throughout, pseudoinfarct pattern in the anterior and inferior leads, poor R-wave progression.

Reprinted with permission from: Edwards A, et al. Cardiac amyloidosis: A case review series. J Integr Cardiol. 2015;1(2):40–45. Copyright © 2015.

1. Siddiqi OK, Ruberg FL. *Trends Cardiovasc Med.* 2018;28(1):10–21; 2. Maurer MS, et al. *Circulation.* 2017;135(14):1357–1377; 3. Edwards A, et al. *J Integr Cardiol*. 2015;1(2):40–45.

ECHOCARDIOGRAPHIC AND CMR CRITERIA

Echocardiography

Unexplained LV thickness (≥12 mm) plus 1 or 2:

1. Characteristic echocardiography findings (≥ 2 of a, b, and c have to be present):
   a. Grade 2 or worse diastolic dysfunction
   b. Reduced tissue Doppler s′, e′, and a′ waves velocities (<5 cm/s)
   c. Decreased global longitudinal LV strain (absolute value < -15%).

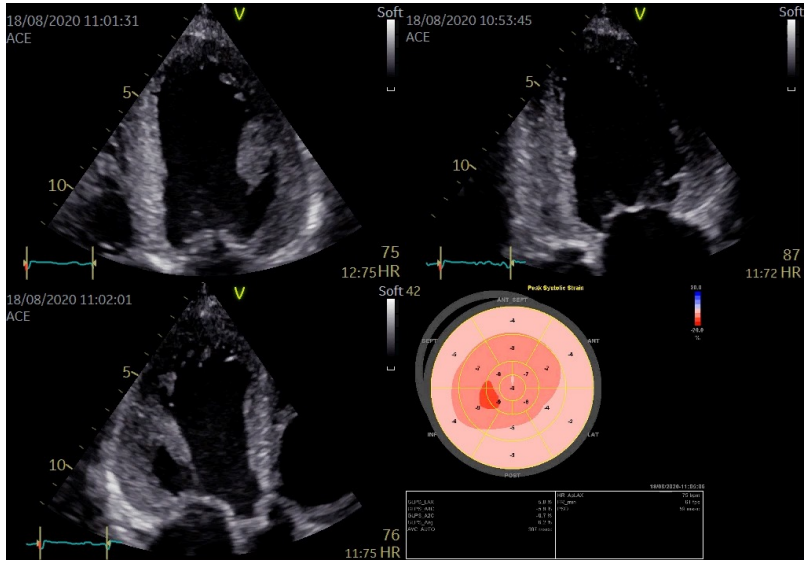
2. Multiparametric echocardiographic score ≥8 points:
   a. Relative LV wall thickness (IVS+PWT)/LVEDD >0.6
      3 points
   b. Doppler E wave/e′ wave velocities >11
      1 point
   c. TAPSE ≤ 19 mm
      2 points
   d. LV global longitudinal strain absolute value ≤ -13%
      1 point
   e. Systolic longitudinal strain apex to base ratio > 2.9
      3 points

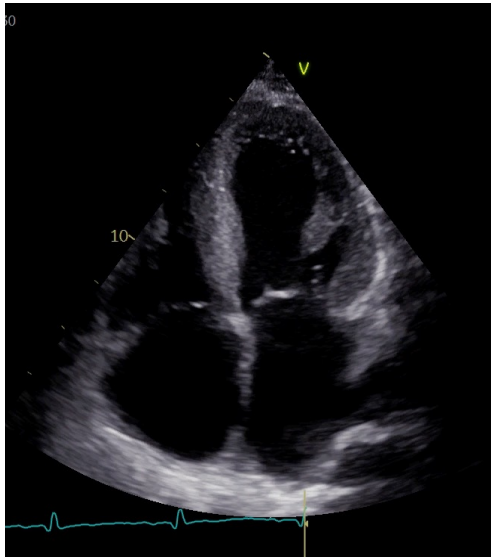
CMR

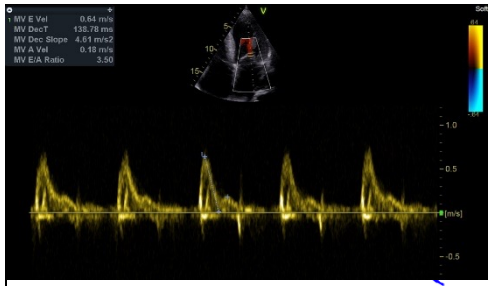
Characteristic CMR findings (a and b have to be present):

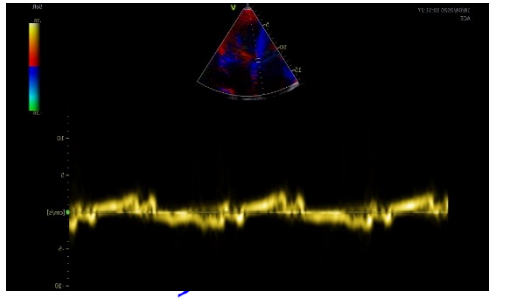
a. Diffuse subendocardial or transmural LGE
b. Abnormal gadolinium kinetics[a]
c. ECV ≥0.40% (strongly supportive, but not essential/diagnostic)

Pablo Garcia-Pavia et al -European Heart Journal, Volume 42, Issue 16, 21 April 2021, Pages 1554–1568,



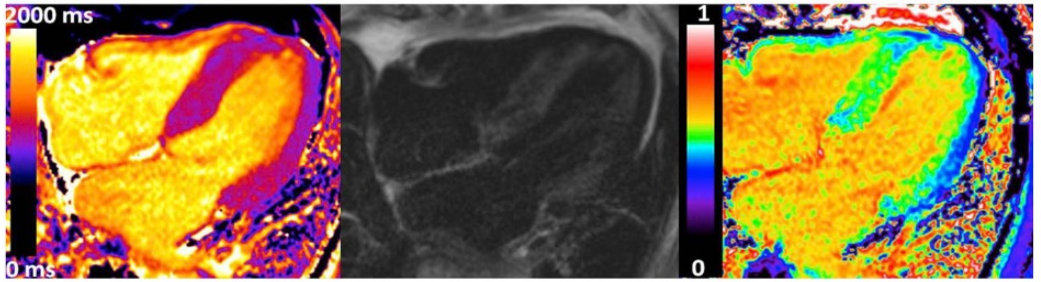






Precontrast T1 **LGE** **ECV**

Maurer Ms et al Circ Heart Fail. 2019;12:e006075. DOI: 10.1161/CIRCHEARTFAILURE.119.006075 or Fontana M heart failure Rev 2015:20(2) 133-144



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^{99m}Tc-PYP/DPD/HMDP:
Visual score accurate to diagnose TTR-CMP

Figure 1. Grading of Myocardial ^{99m}Tc-DPD/HMDP Uptake

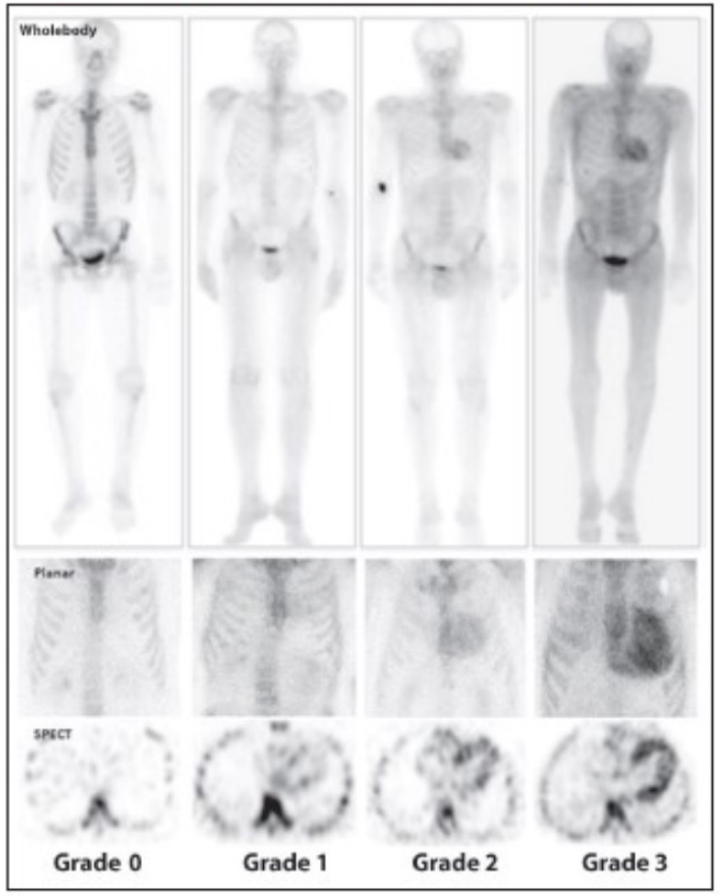


Table 2. Scintigraphic Findings in the Patient Population and Control Group

	Group A TTR-Related CA (15 Patients)	Group B AL CA (10 Patients)	Unaffected Control Patients (10 Patients)
Heart tracer retention (%)			
Median	7.3*†	3.8‡	2.9
Interquartile range	6.7–8.4	3.4–4.05	2.7–3.5
Whole-body tracer retention (%)			
Median	70.1†	67.6‡	56
Interquartile range	63.6–77.3	61.8–71.3	52–60
Heart/whole-body ratio			
Median	10.0*†	5.4	5.4
Interquartile range	8.9–11.2	5.2–5.5	5.0–5.7
Visual cardiac score			
0	0 (0%)	10 (100%)	10 (100%)
1	0 (0%)	0 (0%)	0 (0%)
2	3 (20%)	0 (0%)	0 (0%)
3	12 (80%)	0 (0%)	0 (0%)

*$p < 0.05$ group A vs. B. †$p < 0.05$ group A vs. control group. ‡$p < 0.05$ group B vs. control group.
CA = cardiac amyloidosis; TTR = transthyretin.

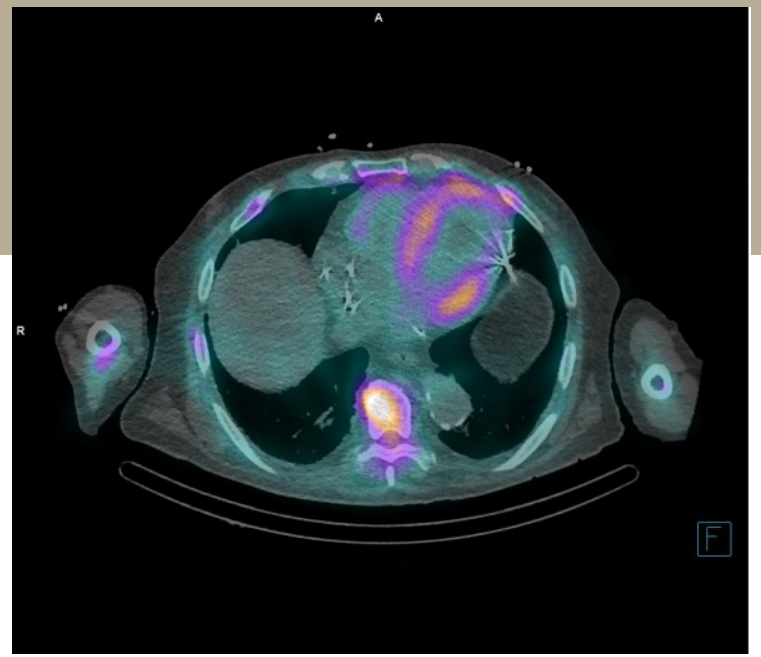
Perugini-score

BONE-SCAN: PITFALLS

False positive uptake:

- AL Amyloidosis: up-to 10% -> score 1-2 -> diagnostic algorithm
- Blood Pool uptake
- Rib Fracture
- Myocardial infarction
- Hydroxychlorquine toxicity
- Rare forms of CA

Use always concomitant SPECT-imaging (on top of Planar imaging) to confirm myocardial uptake: discuss imaging protocol with nuclear medicine

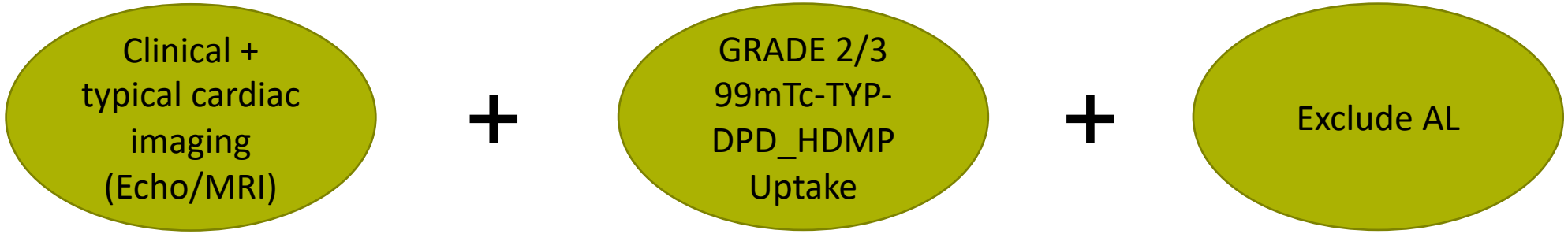


False negative uptake:

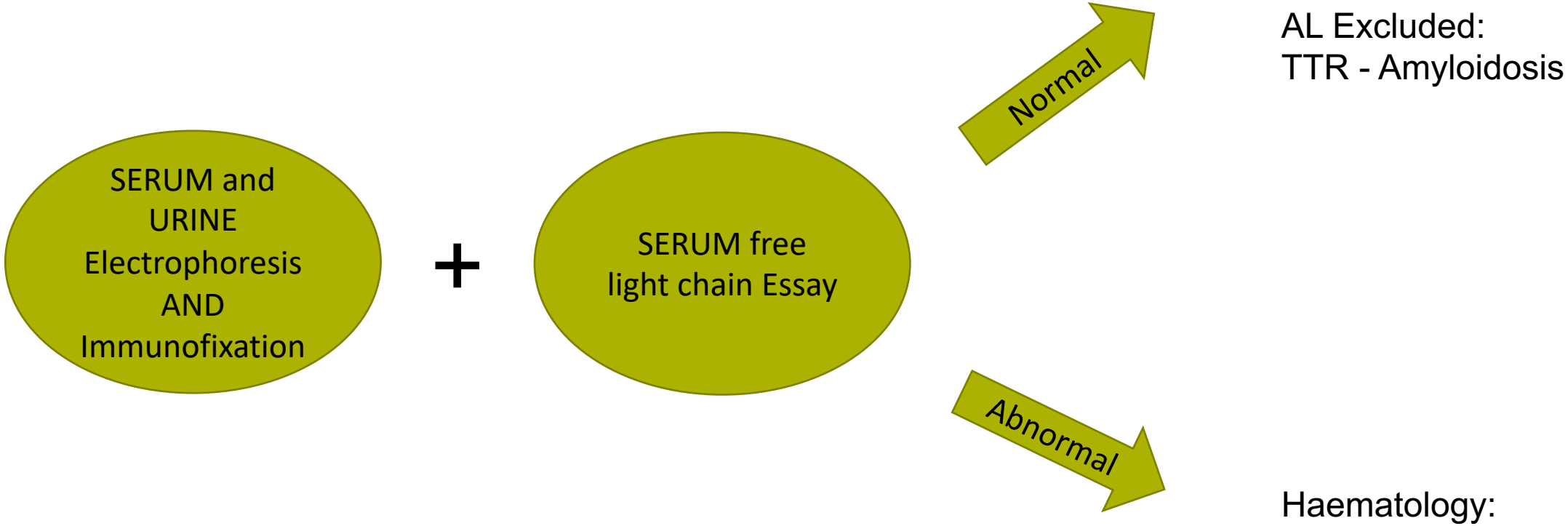
Some hTTR mutation might have negative uptake

AL: light-chain amyloidosis hATTR : hereditary transthyretin amyloidosis , SPECT : single photon emission computed tomography

DIAGNOSIS WITHOUT BIOPSY: TTR – CA

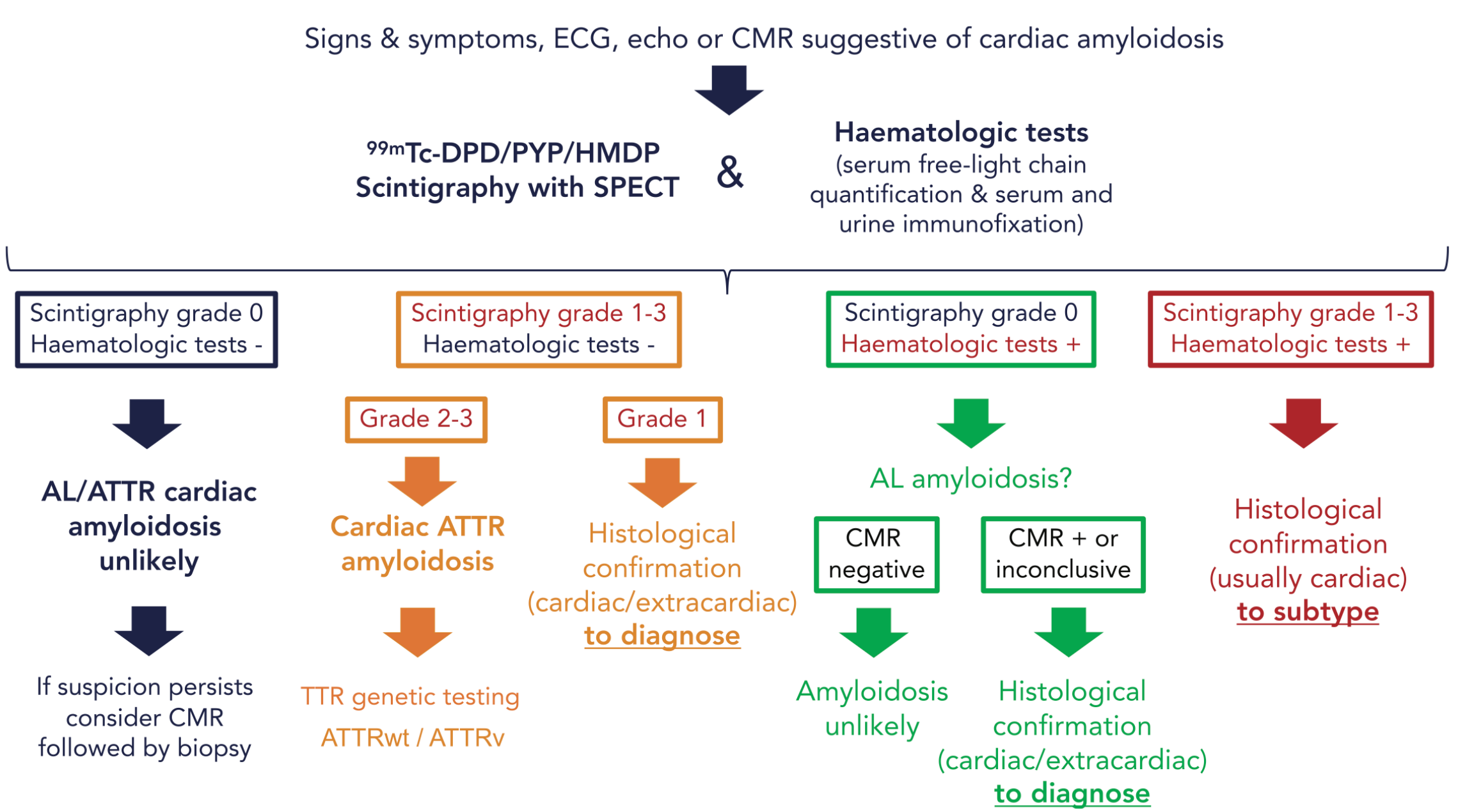


HOW TO EXCLUDE MONOCLONAL PROCESS?



AL Excluded:
TTR - Amyloidosis

Haematology:
MGUS or SM or
Multiple Myeloma?



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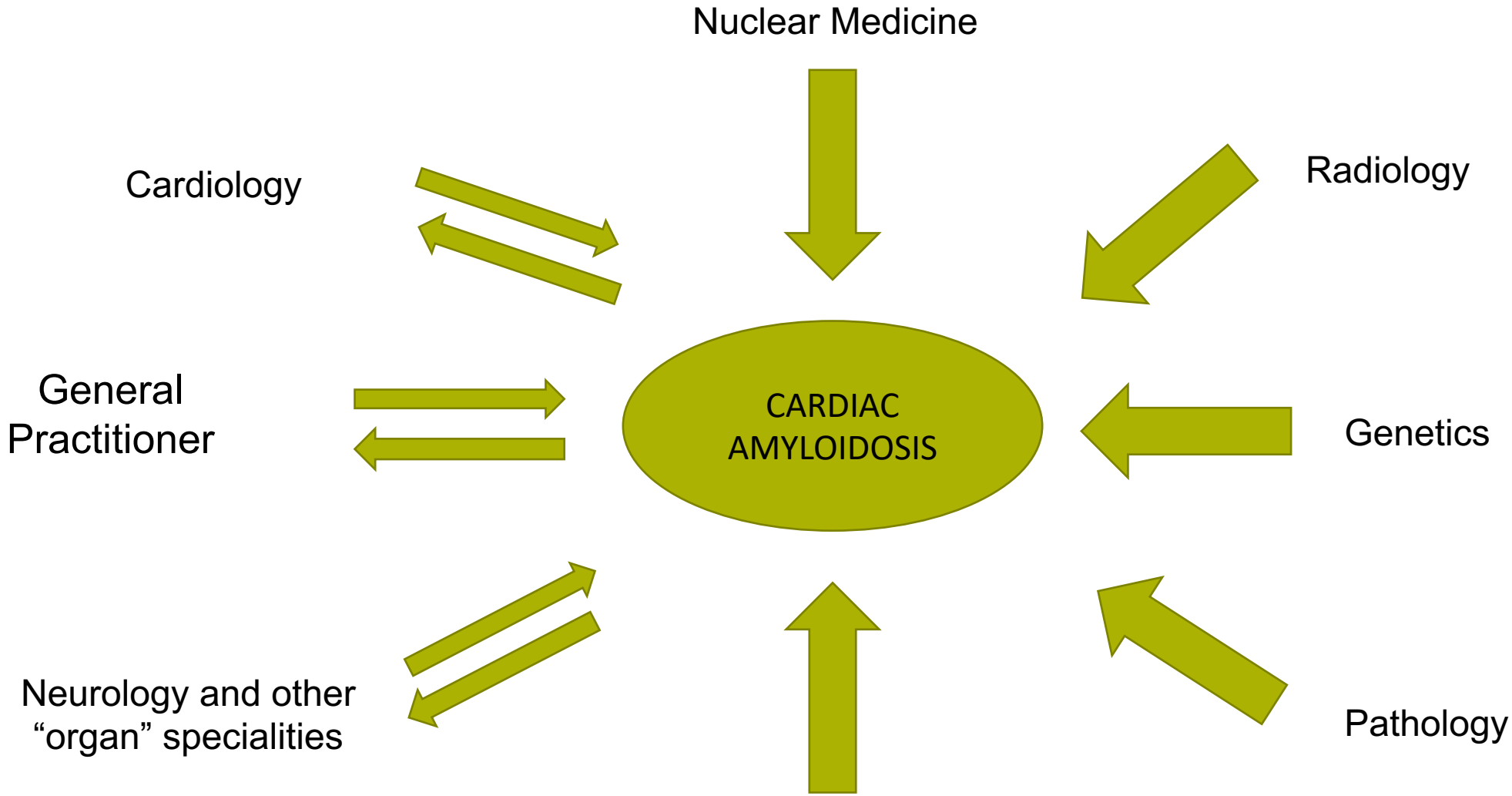
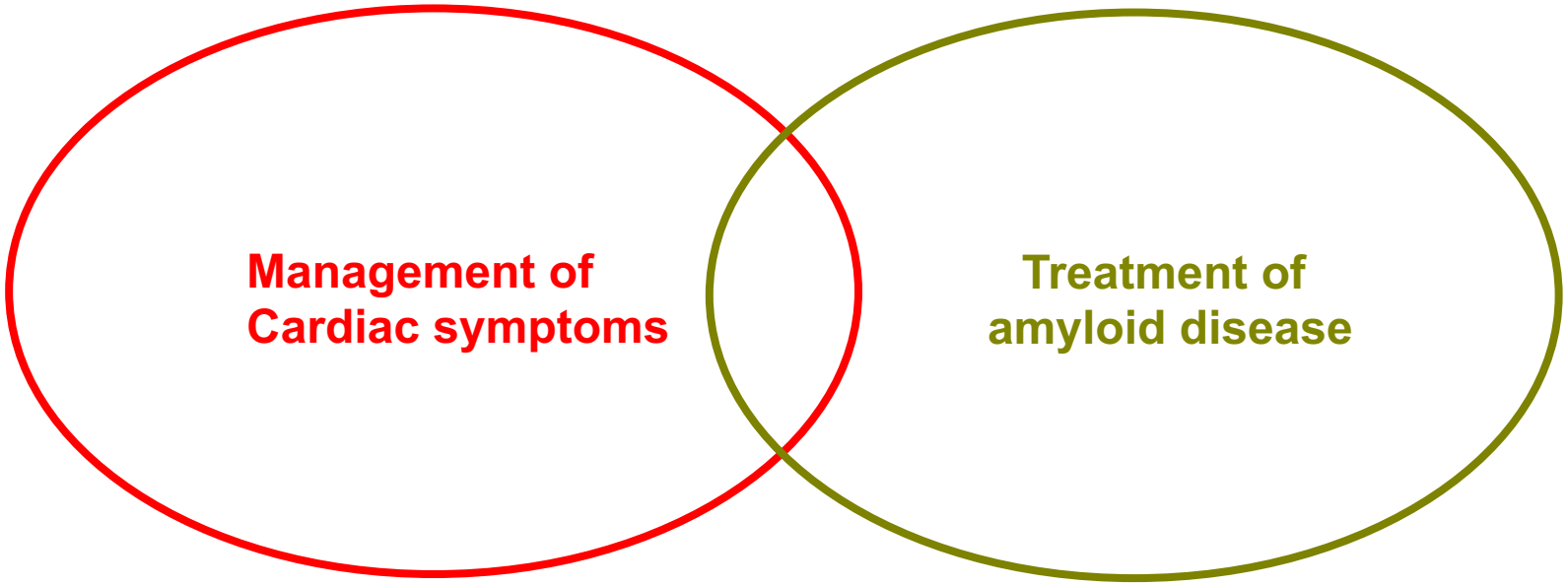
MULTI-DISCIPLINARY APPROACH: POTENTIAL SPECIALITIES INVOLVED



CARDIAC AMYLOIDOSIS: THERAPY



Treatment of Cardiac Complications and Comorbidities in Cardiac Amyloidosis

Aortic Stenosis

- Severe AS confers worse prognosis.
- Concomitant ATTRwt risk factor for periprocedural AV block.
- TAVR improves outcome in amyloid-AS.

Thromboembolism

- High risk, common.
- Anticoagulate if AF, consider in selected cases in SR.
- Anticoagulate independent of CHADS-VASC score.

Conduction disorders

- PPM according to standard indications.
- Consider CRT if high paced burden expected.

Heart failure

- Control fluid.
- Diuretics.
- Deprescribe B-Blockers.
- Avoid ACEI/ARB.
- LVAD not suitable for most patients.
- Heart transplant for selected cases.

Atrial Fibrillation

- Amiodarone, preferred AA.
- Use digoxin cautiously.
- Electrical CV has significant risk of complications and AF recurrence is frequent.
- Exclude thrombi before electrical CV.
- AF ablation data scarce and controversial.

Ventricular arrhythmias

- ICD for secondary prevention.
- ICD in primary prevention usually not recommended.
- Transvenous ICD preferred over subcutaneous ICD.

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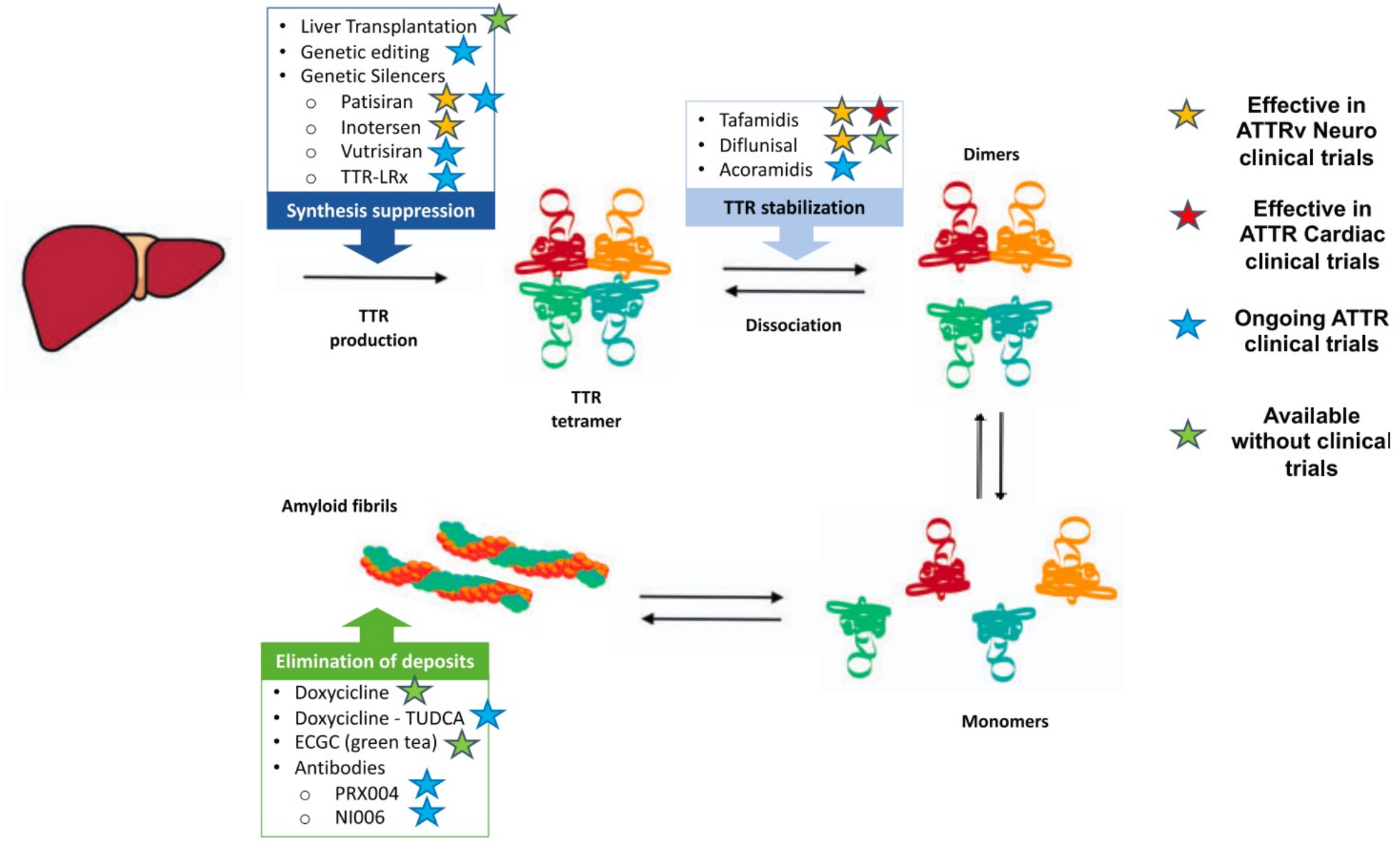
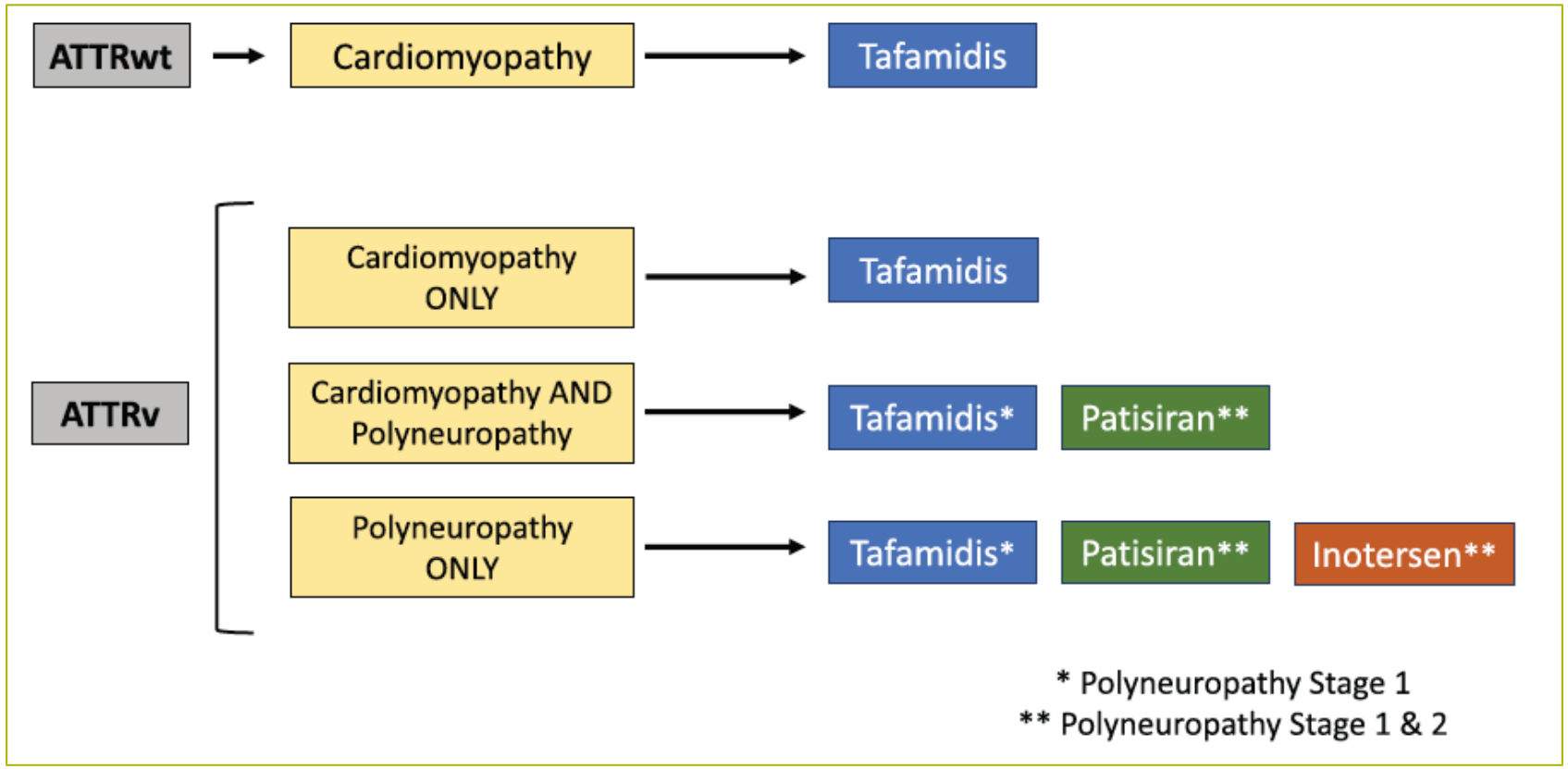
CARDIAC AMYLOIDOSIS: DISEASE-MODIFYING DRUGS



European Heart Journal (2021) 00, 1–15 doi:10.1093/eurheartj/ehab072

CARDIAC AMYLOIDOSIS: THERAPEUTIC OPTIONS



Garcia-Pavia, P et al. Eur Heart J 2021; 42: 1554–1568

POSSIBLE CLINICAL SCENARIOS OF ATTR-CM REFERRAL

- **Unexpected bone-scan myocardial tracer uptake**, i.e. staging prostate carcinoma
- Work-up **left ventricular hypertrophy**
- **Elevated trp and NT-pro-BNP without a clear cause**
- Heart failure evolves despite treatment of **aortic valve stenosis**
- **Lumbar spinal stenosis, carpal tunnel syndrome, autonomic neuropathy, biceps tendon rupture… heart failure in elderly men**
- Black/Portuguese patient with heart failure (vTTR)

KEY MESSAGES: CLINICAL FEATURES

- **Systemic disease** with cardiac and extracardiac manifestations
- Cardiac amyloidosis is an **underrecognized** cause of infiltrative CMP and heart failure
- **High Mortality rate**: long time delay to diagnosis
- AL and transthyretin amyloid (ATTR) are most frequent causes of cardiac amyloidosis
- ATTR can be hereditary (hATTR) or acquired (mATTR)

DIAGNOSTIC AND THERAPEUTIC CHALLENGES

- **Bone scintigraphy** plays important role, but low uptake possible in AL
- **Always exclude AL amyloidosis** – blood and urine (IF and sFLC)
- In doubt, tissue biopsy necessary
- Unclear how to monitor therapeutic response
- Identify patients that benefit from new disease modifying drugs

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