21η Διημερίδα «Εξελίξεις στην Καρδιαγγειακή Απεικόνιση 2024»

Καρδιακή Αμυλοείδωση
Διαγνωστικές & θεραπευτικές προσεγγίσεις

9/2/2024

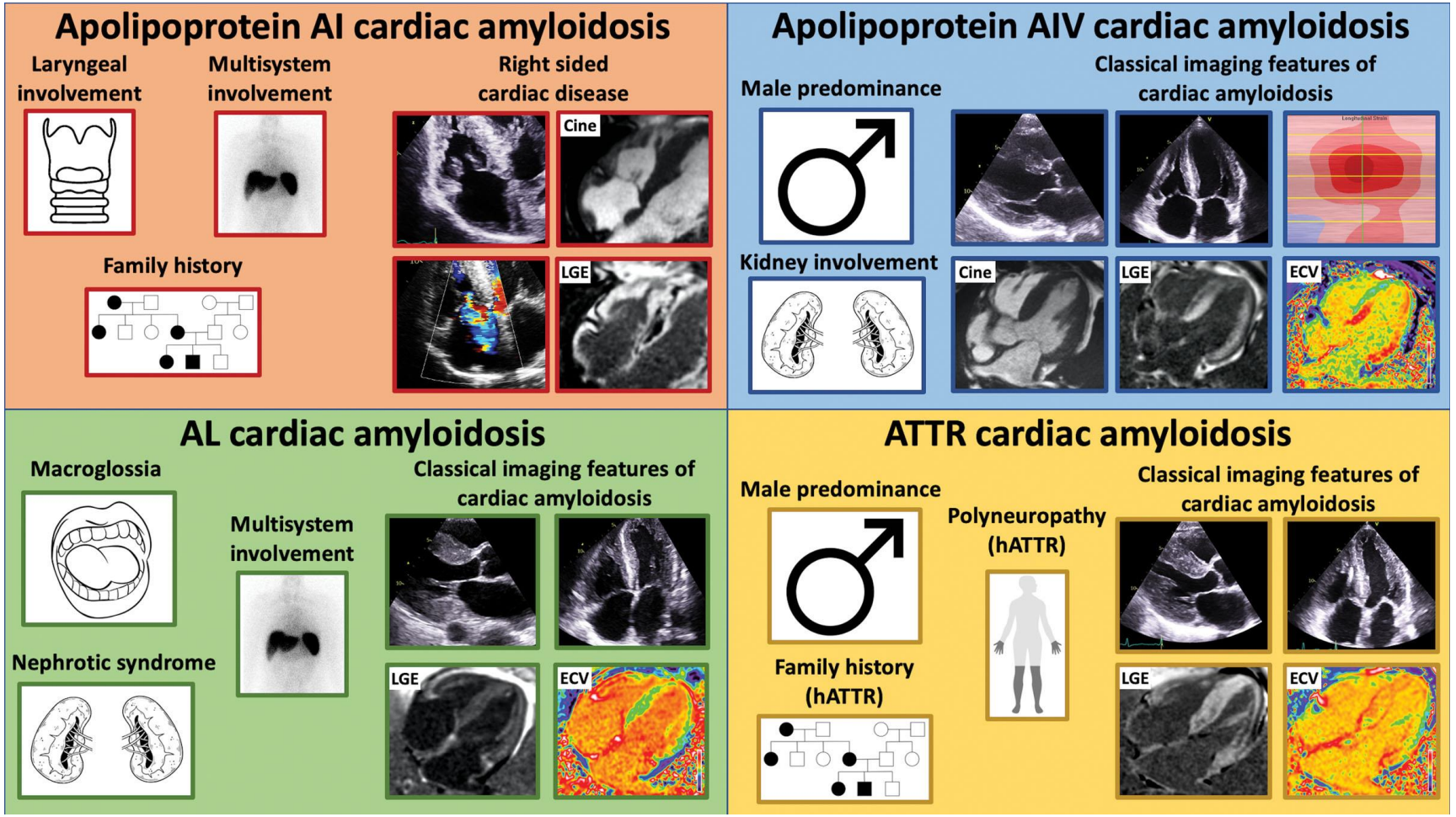
Αλέξιος Αντωνόπουλος MD PhD

Unit of Inherited and Rare Cardiovascular Diseases, 1st Cardiology Dpt, National and Kapodistrian University of Athens

DISCLOSURES

Honoraria from Genesis Pharma, Pfizer
Competitive Research Grant Award - Global ASPIRE ATTR Amyloidosis (Pfizer Global Medical)
Research collaboration with Pfizer's Center for Digital Innovation (CDI)
Consultant fees and shareholder (family member) in Caristo Diagnostics, a CT imaging company

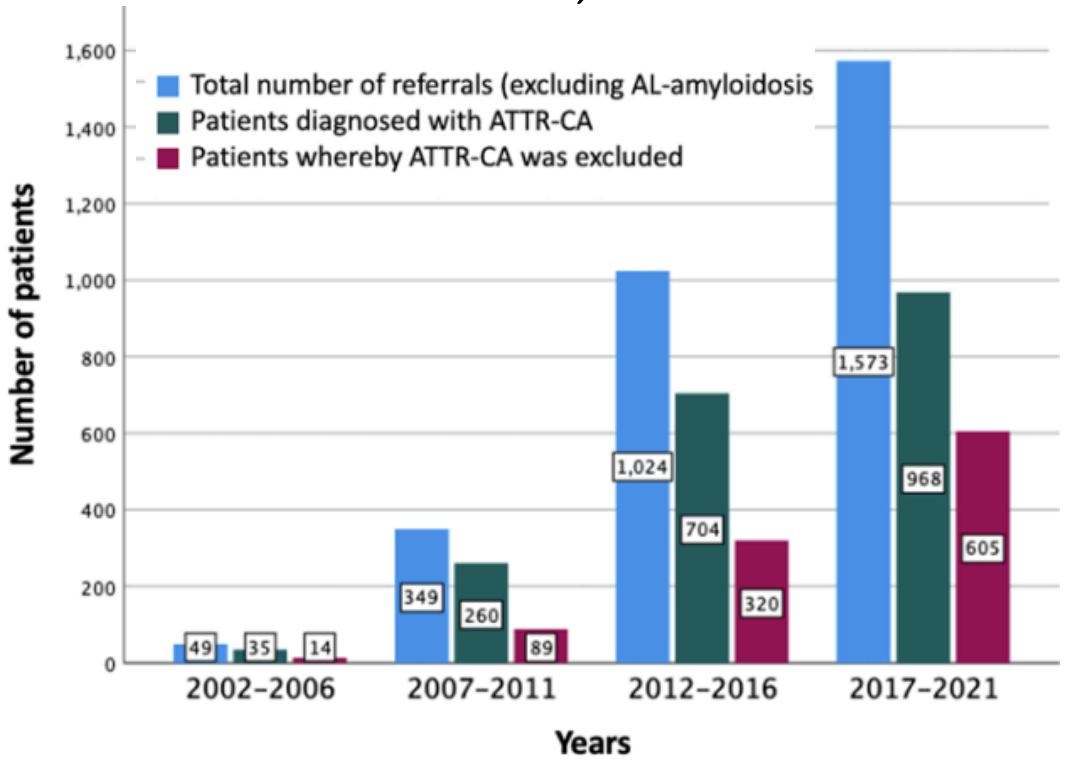
Different clinical phenotypes among CA subtypes



Ioannou et al, Circulation: Cardiovascular Imaging 2023

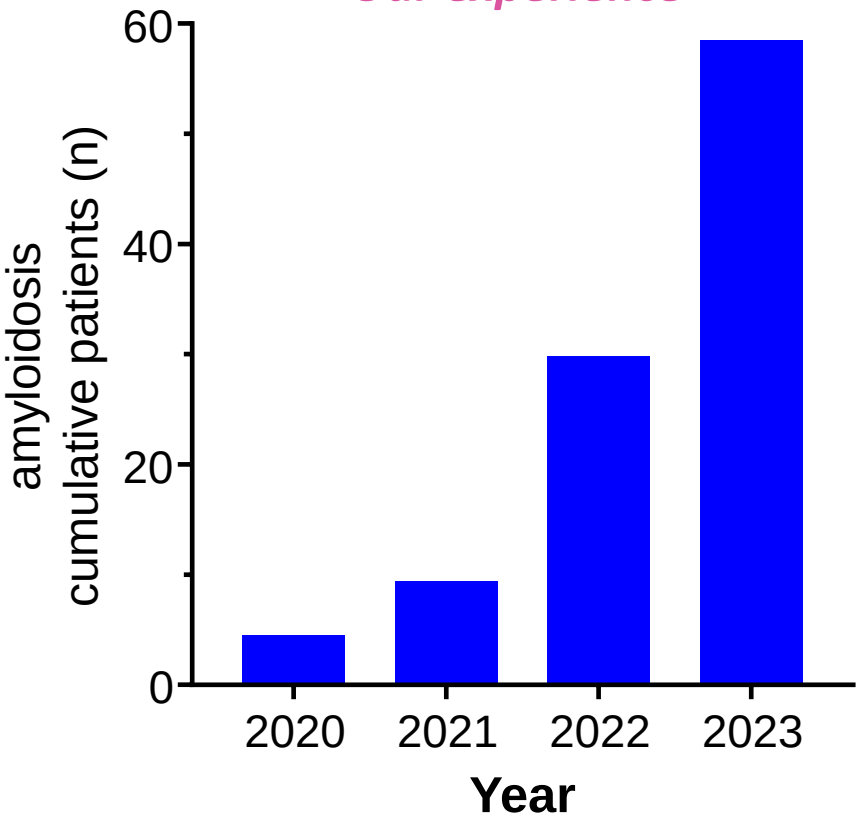
Increasing awareness for cardiac amyloidosis

NAC, UK



Ioannou et al. Circulation 2022;146:1657–1670

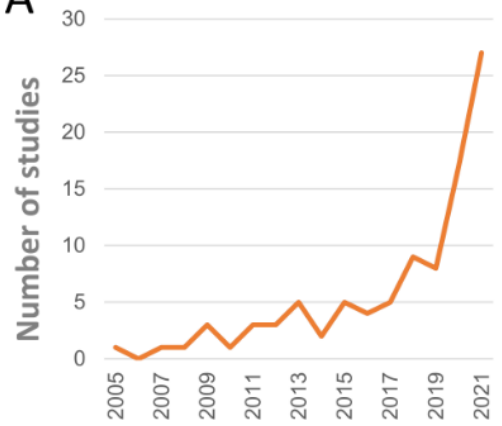
Our experience



EKKAN archive

Prognosis of ATTR-CM at a global level

A

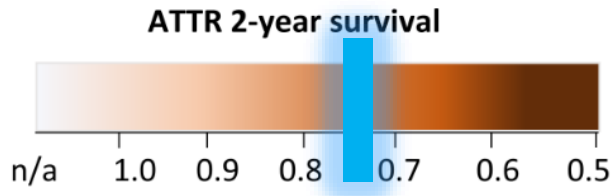


B

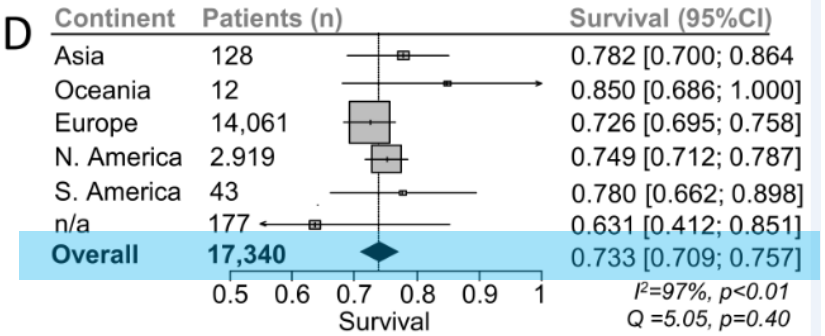
Country	Survival (95%CI)	(n)
UK	0.73 (0.70-0.76)	9204
USA	0.75 (0.71-0.79)	2919
France	0.65 (0.60-0.73)	2293
Sweden	0.62 (0.58-0.72)	994
Germany	0.84 (0.79-0.89)	564
Italy	0.73 (0.63-0.84)	555
Spain	0.80 (0.64-0.96)	332
Austria	0.83 (0.74-0.93)	112
Japan	0.75 (0.59-0.92)	58
Israel	0.82 (0.72-0.92)	47
Brazil	0.78 (0.66-0.90)	43
China	0.61 (0.35-0.87)	23
Australia	0.85 (0.69-1.00)	12
Denmark	0.71 (0.31-1.00)	7
n/a	0.63 (0.41-0.85)	441

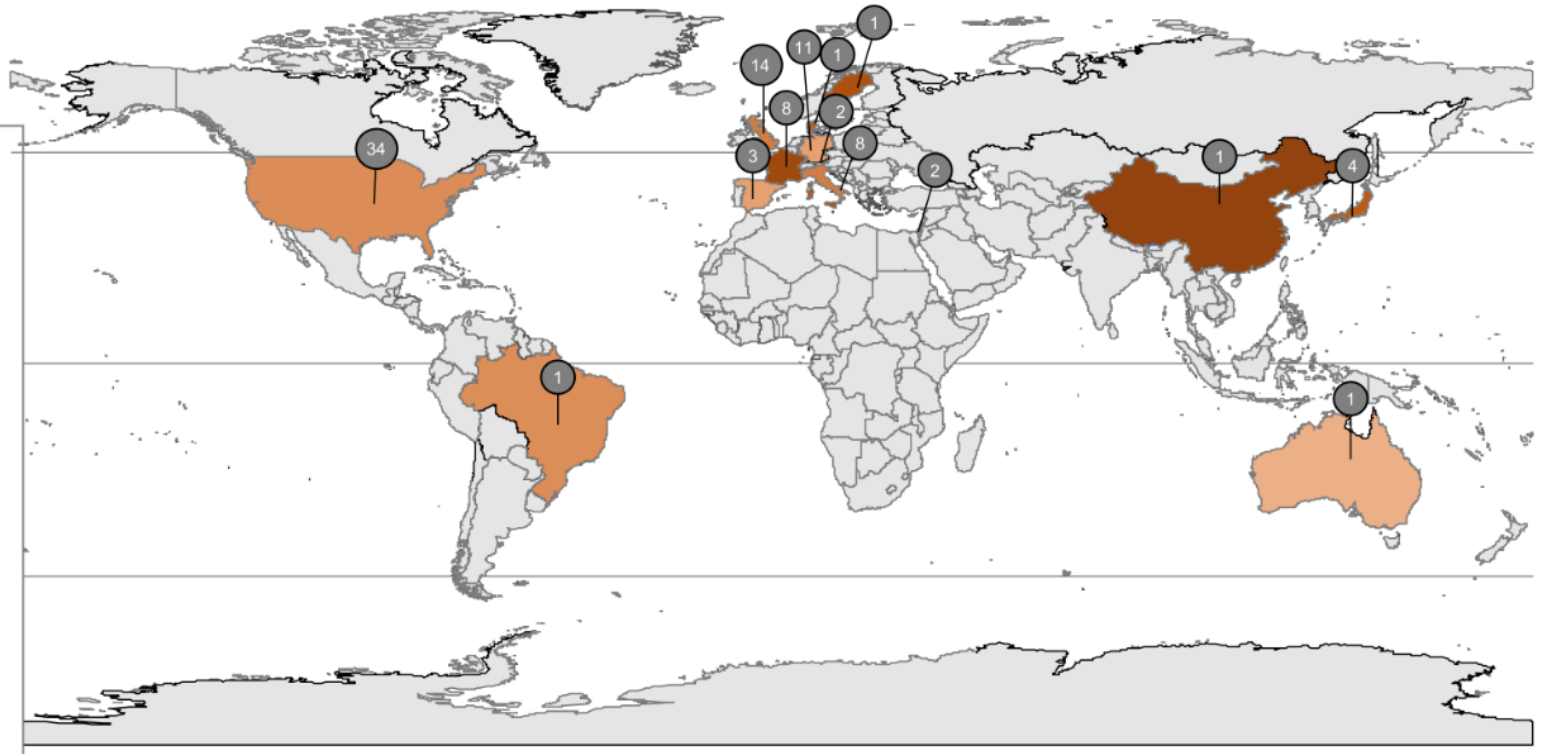
Between countries: Q=67.8, p=4.8x10^{-9}

C



D

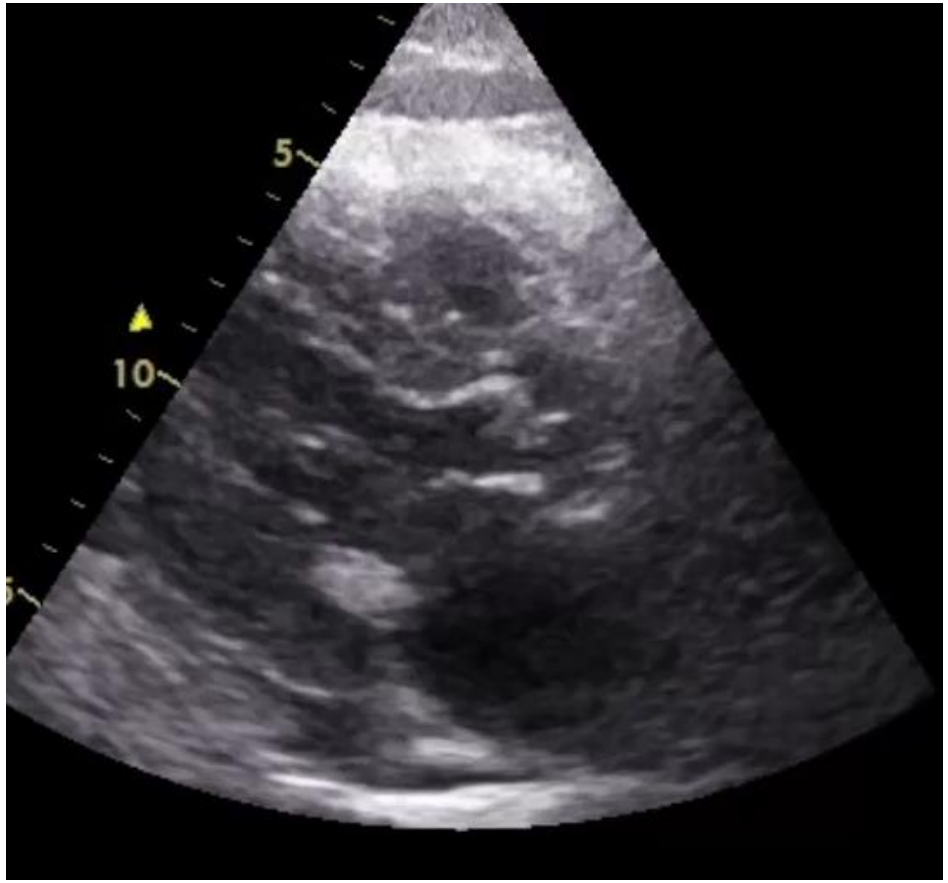




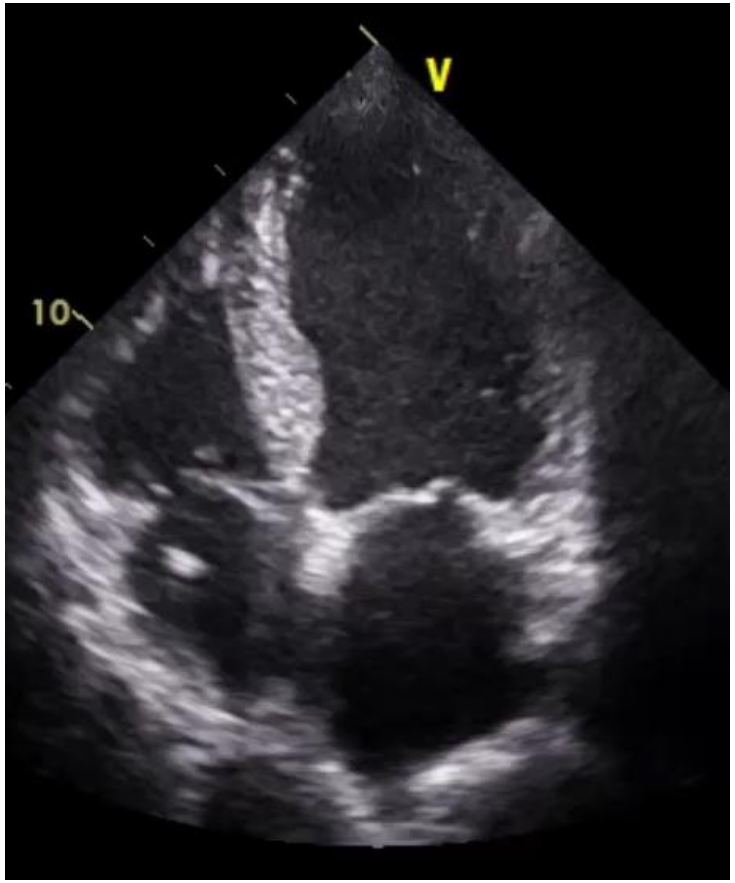
Antonopoulos AS et al Eur J Heart Fail. 2022 Sep;24(9):1677-1696

ATTR-CM: diverse phenotypes

Typical ATTR



Non-typical ATTR



EKKAN archive

Prevalence of cardiac amyloidosis in various subgroups

ESC European Society of Cardiology
European Journal of Heart Failure (2022)
doi:10.1002/ejhf.2589
RESEARCH ARTICLE

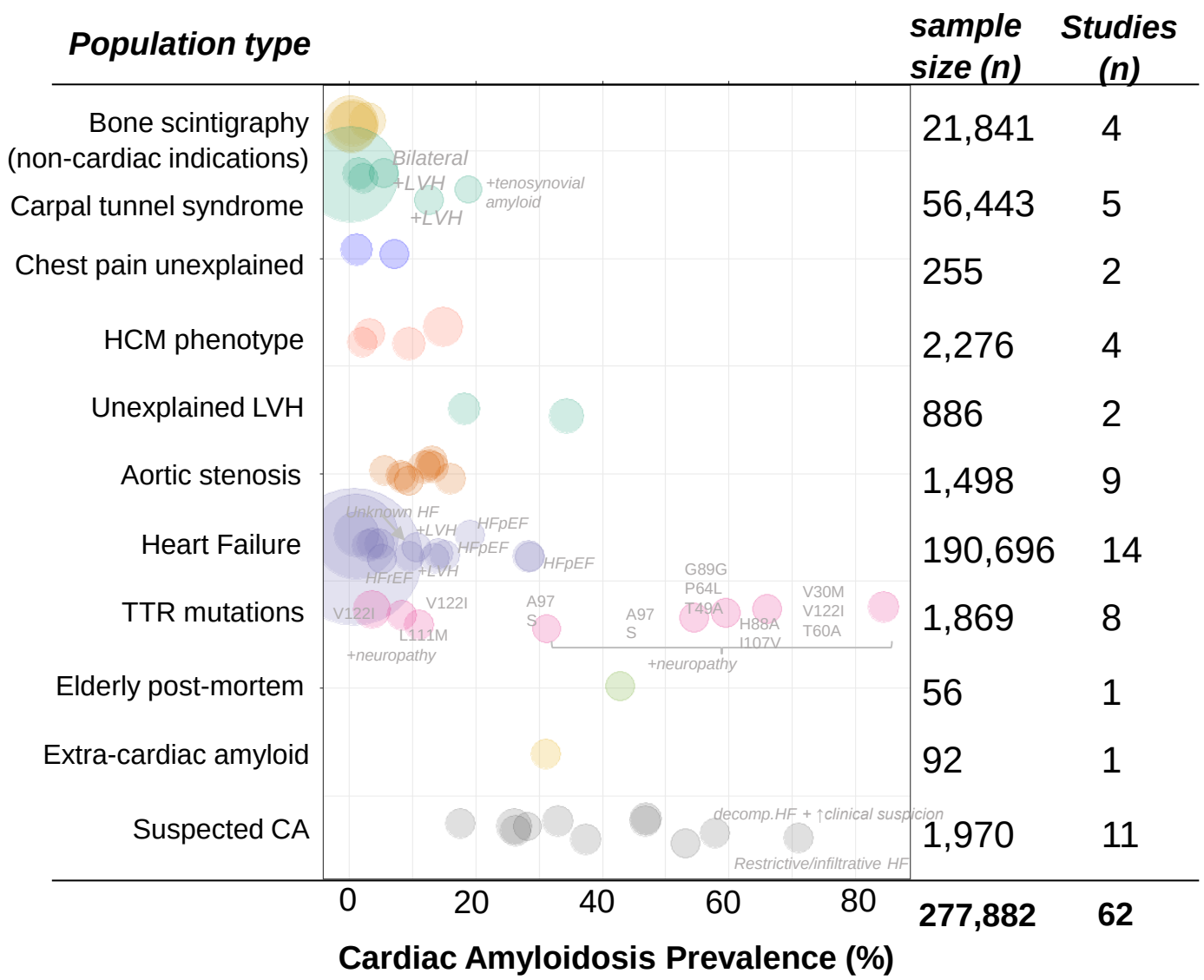
Prevalence and clinical outcomes of transthyretin amyloidosis: a systematic review and meta-analysis

Alexios S. Antonopoulos[1], Ioannis Panagiotopoulos[1], Alexandrina Kouroutzoglou[1], Georgios Koutsis[2], Pantelis Toskas[1], Georgios Lazaros[1], Konstantinos Toutouzas[1], Dimitris Tousoulis[1], Konstantinos Tsioufis[1], and Charalambos Vlachopoulos[1]*

[1]1st Cardiology Department, National and Kapodistrian University of Athens, Hippokration University Hospital, Athens, Greece; and [2]Neurogenetics Unit, 1st Department of Neurology, National and Kapodistrian University of Athens, Eginition University Hospital, Athens, Greece

Received 9 November 2021; revised 10 June 2022; accepted 18 June 2022

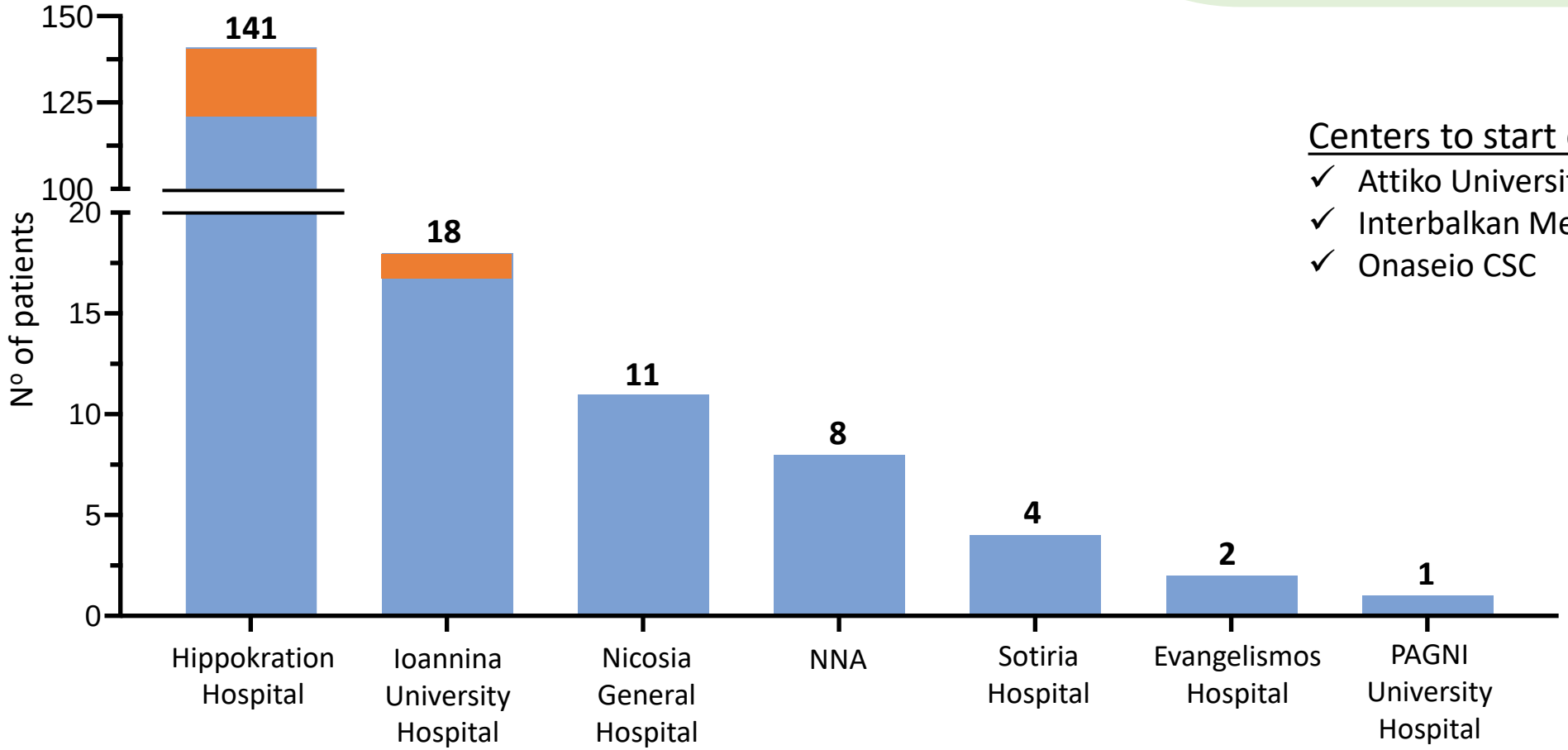
Antonopoulos AS et al Eur J Heart Fail. 2022 Sep;24(9):1677-1696



Greek REgistry for Cardiac Amyloidosis in TAVI patients: GRECA-TAVI

January 2024 Report

Total AS patients enrolled: **185**
ATTR positive patients: **22**



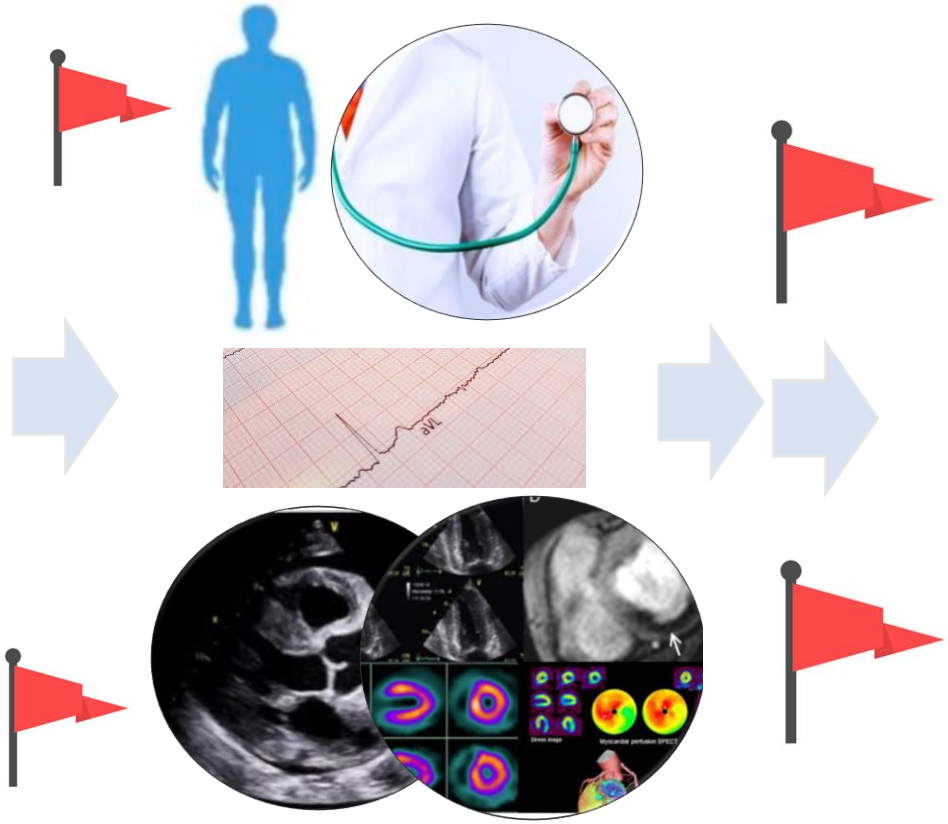
Centers to start enrollment soon

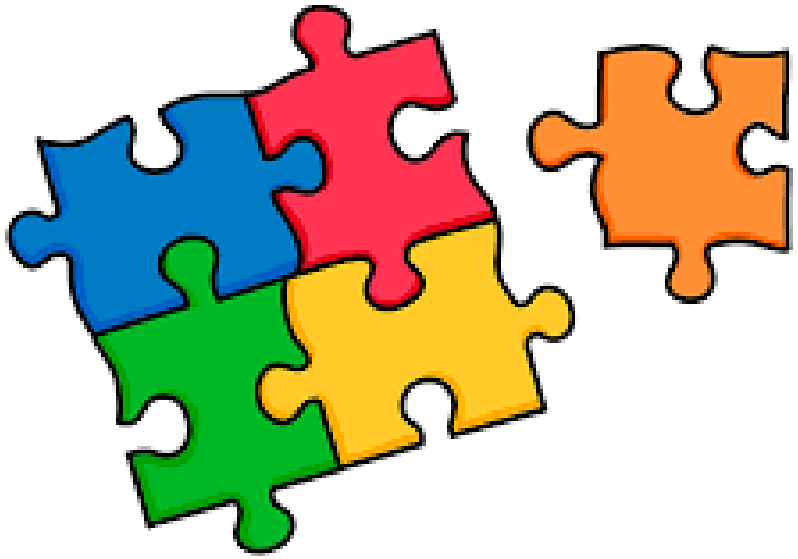
- ✓ Attiko University Hospital
- ✓ Interbalkan Medical Center
- ✓ Onaseio CSC

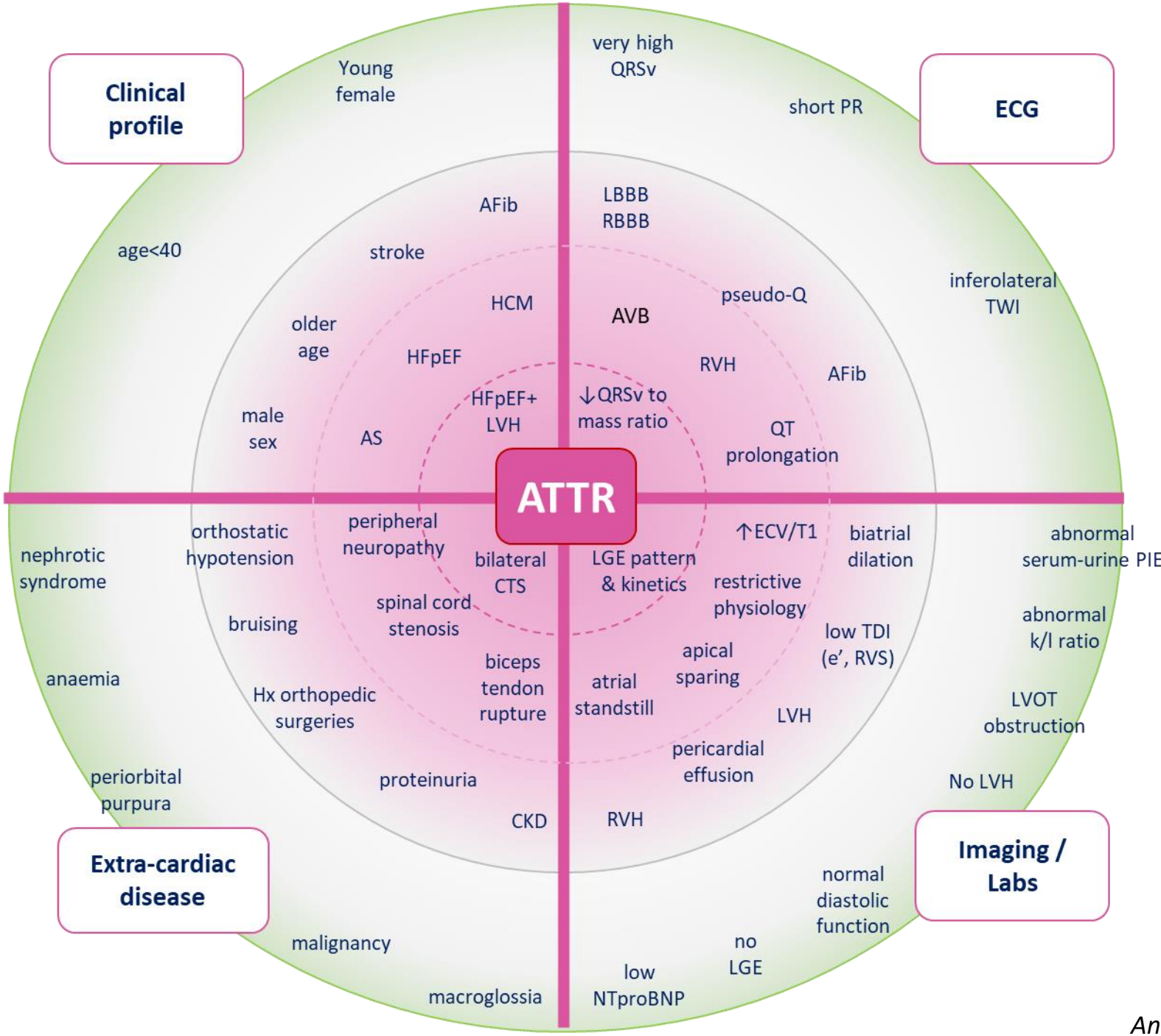
A cardiomyopathy mindset (for ATTR)

Patient clinical characteristics

Clinical work-up





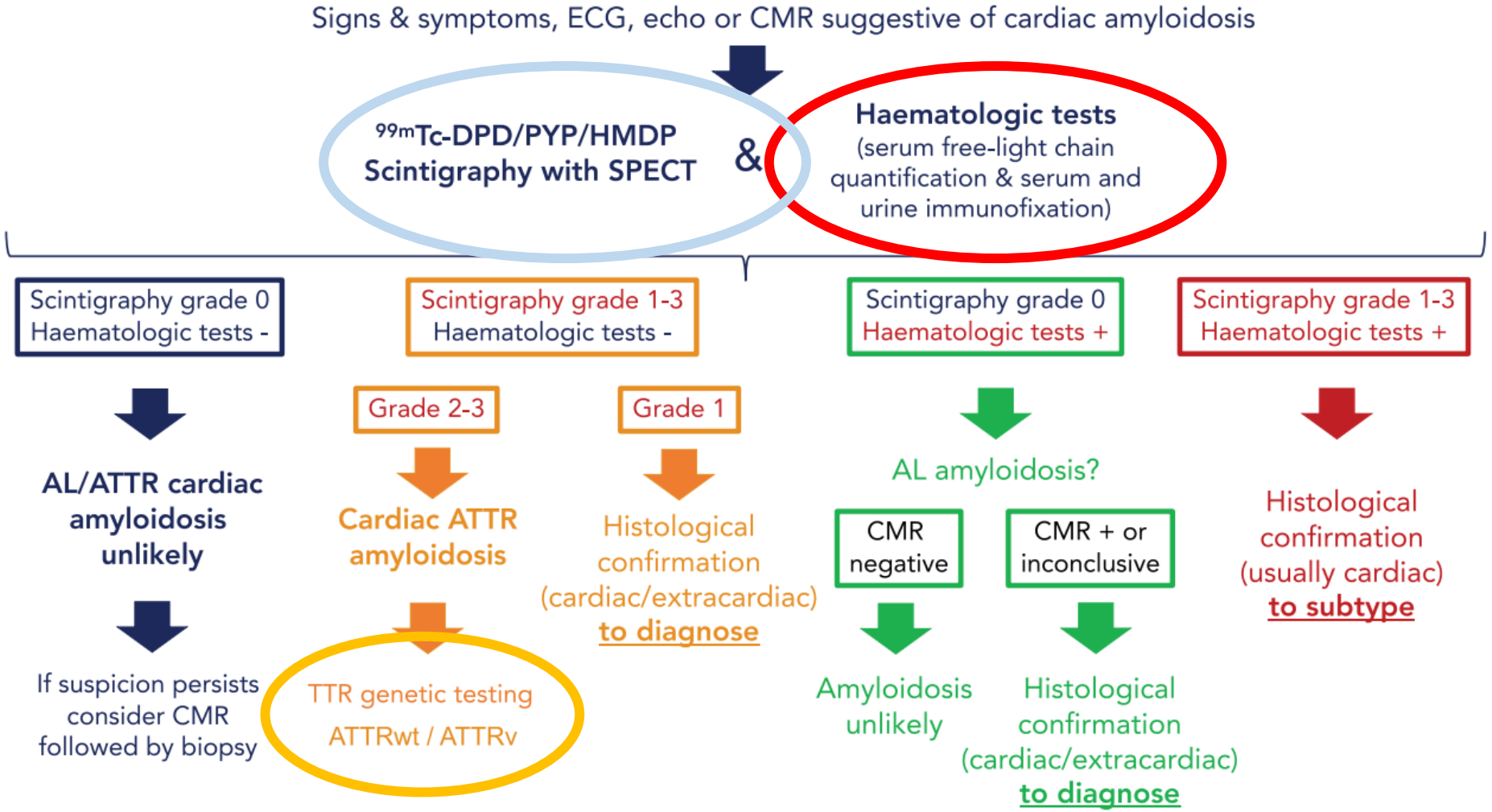


Antonopoulos AS et al (submitted)

Diagnostic approaches for cardiac amyloidosis

Unit of Inherited and Rare Cardiovascular Diseases, 1st Cardiology Dpt, National and Kapodistrian University of Athens

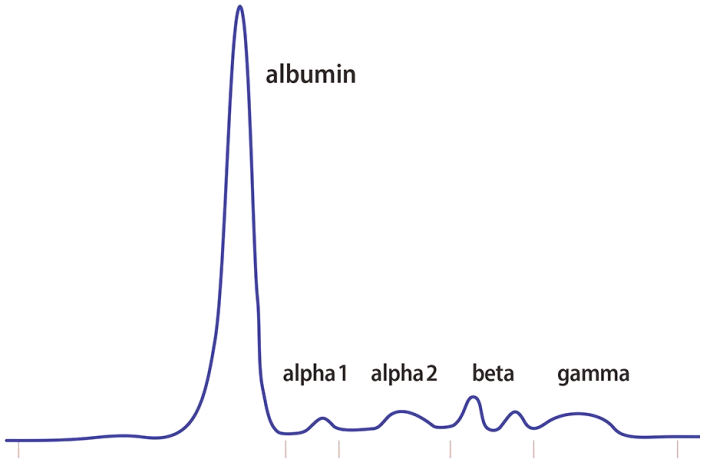
Diagnostic algorithm for cardiac amyloidosis



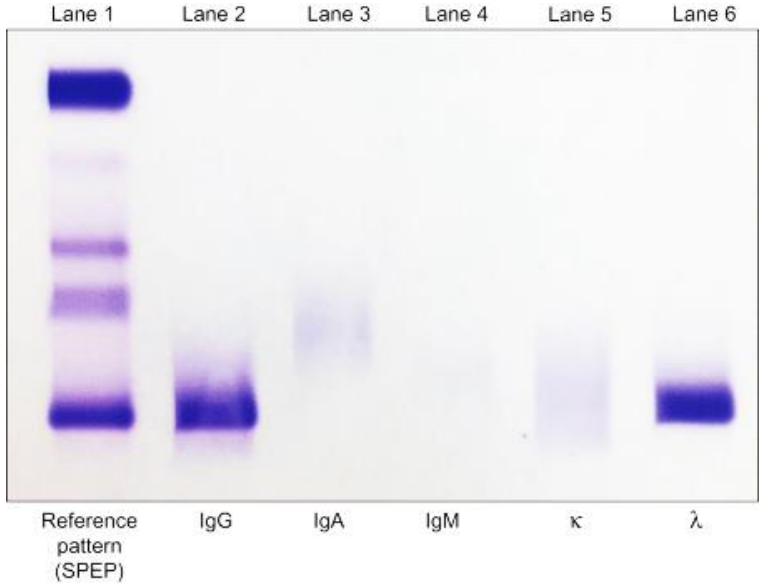
Diagnostic interpretation of hematological tests in CKD

Serum and urine

Protein Electrophoresis



Protein Immunofixation

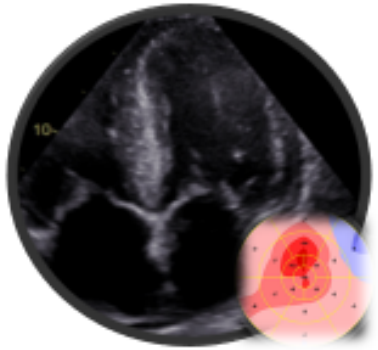
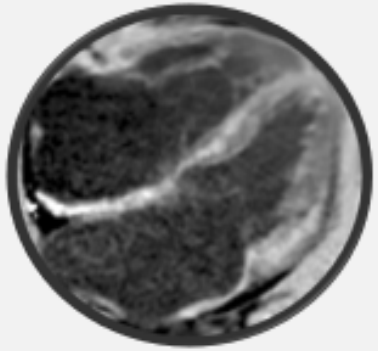
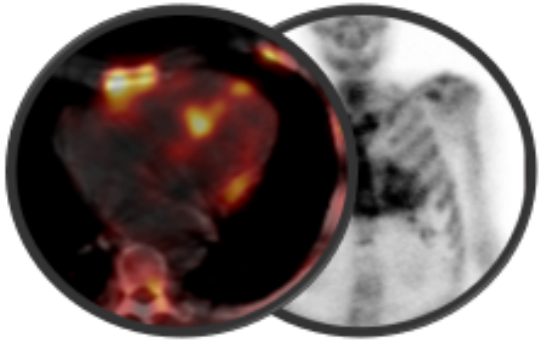
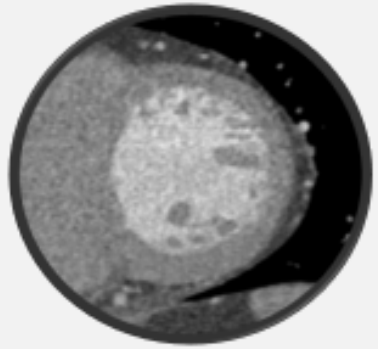


Free light chains (FLC)

kappa / lamba ratio

If all negative >99% NPV for AL amyloidosis

Multimodality imaging of cardiac amyloidosis

Echocardiography	CMR	Nuclear	Cardiac CT
			
• Concentric LVH with sparkling appearance • Biatrial dilation • IAS or cardiac valve thickening • Normal or low LVEF • Restrictive filling pattern • Impaired longitudinal function with apical sparring ("cherry-on-top" pattern) • Pericardial effusion	• Increased LV mass • Normal or low LVEF • RVH and IAS thickening • Increased native T1 (typically >1135ms) • Highly raised ECV (typically >40%) • Diffuse LGE (typically subendocardial to transmural) • Abnormal gadolinium kinetics (myocardium nulls earlier than blood pool) • Reduced myocardial perfusion reserve on stress imaging • Pleural effusions • Pericardial effusion	• Increased myocardium uptake of 99mTc-PYP, 99mTc-DPD, 99mTc-HMDP (typical for ATTR but AL cannot be excluded if low grade uptake) • Increased uptake on planar bone scintigraphy to confirmed by SPECT or SPECT/CT (to exclude false positive from blood pool uptake)	• LV subendocardial hypodensity • Increased ECV (by dynamic equilibrium CT) • Pleural effusions • Pericardial effusion

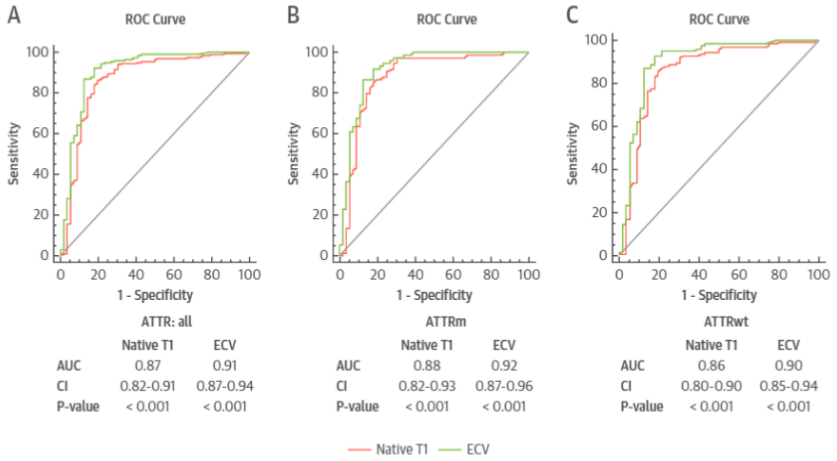
Antonopoulos AS et al Hellenic J Cardiol 2020

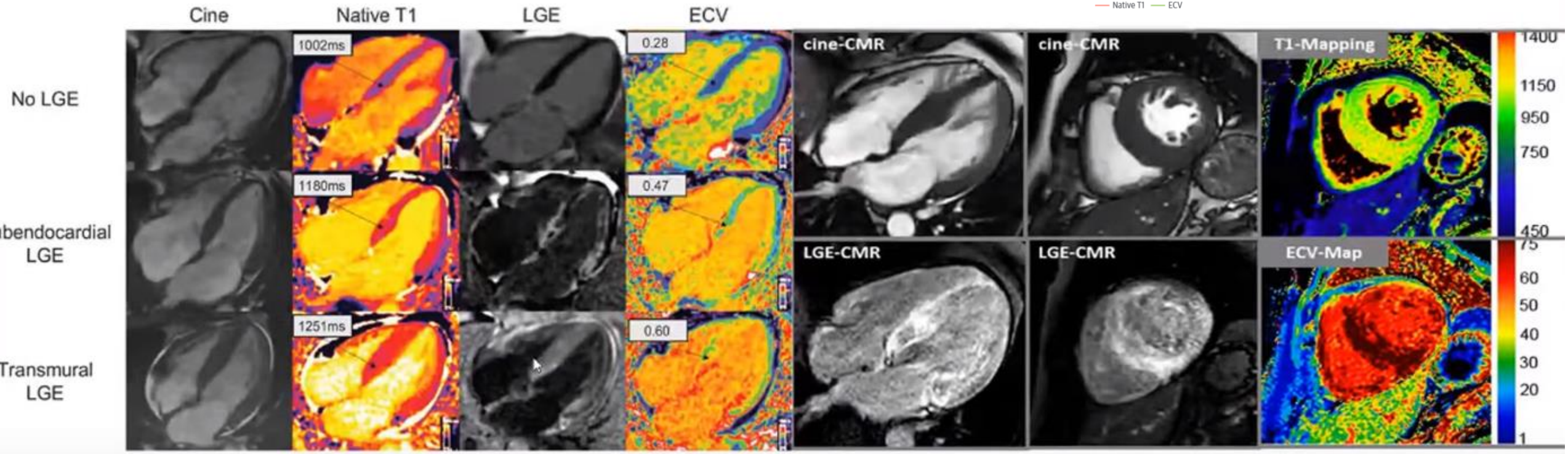
CMR for cardiac amyloidosis diagnosis

ORIGINAL RESEARCH

Native T1 and Extracellular Volume in Transthyretin Amyloidosis

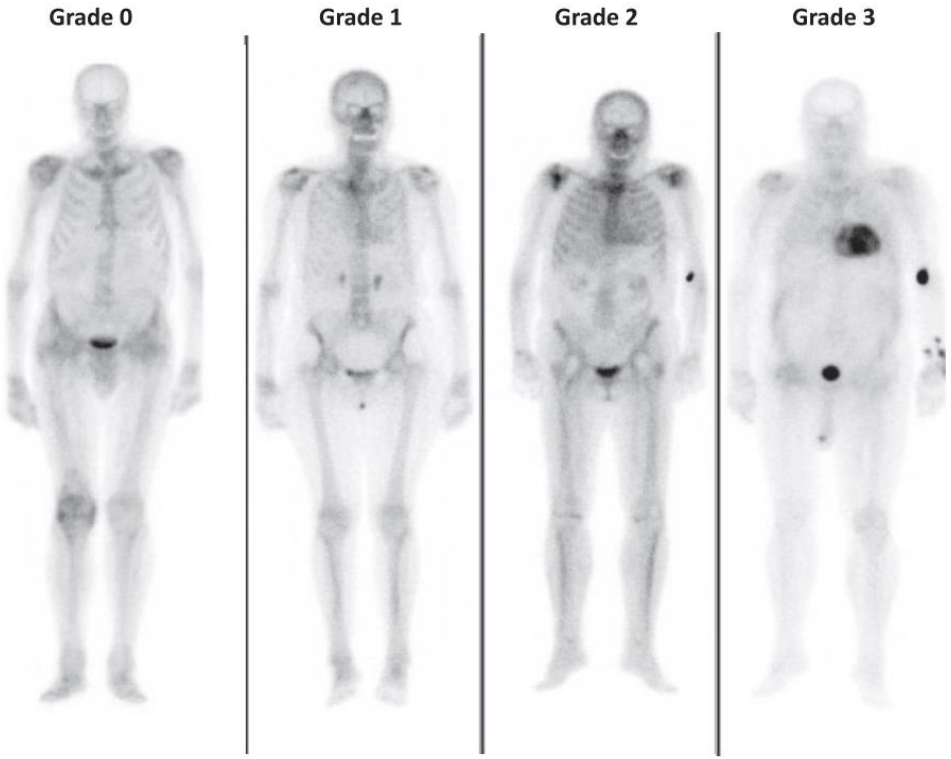
Ana Martinez-Naharro, MD,[a,*] Tushar Kotecha, MBChB,[a,b,*] Karl Norrington, MBBS,[a] Michele Boldrini, MD,[a] Tamer Rezk, MBBS,[a] Candida Quarta, MD, PhD,[a] Thomas A. Treibel, PhD,[b,c] Carol J. Whelan, MD,[a] Daniel S. Knight, MD,[a] Peter Kellman, PhD,[d] Frederick L. Ruberg, MD,[e] Julian D. Gillmore, MD, PhD,[a] James C. Moon, MD,[b,c] Philip N. Hawkins, PhD,[a] Marianna Fontana, MD, PhD[a]



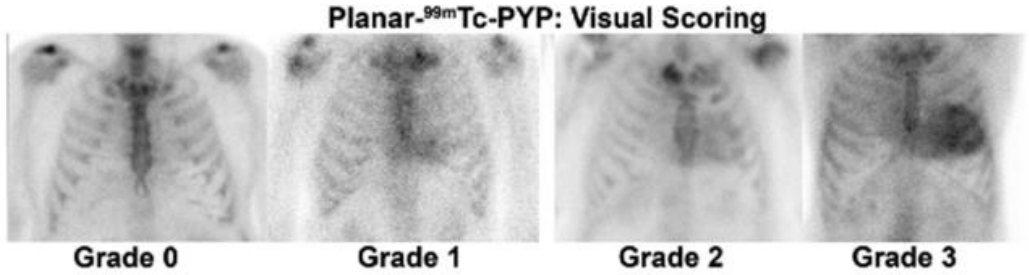


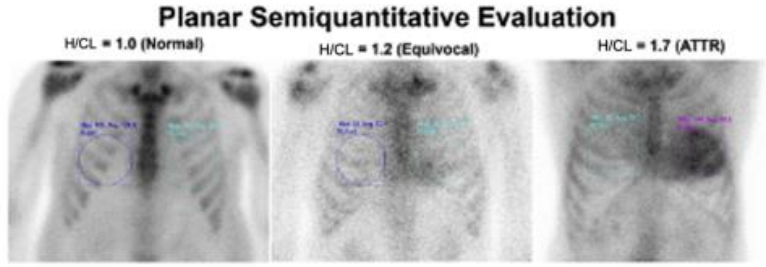
Bone scintigraphy for ATTR diagnosis

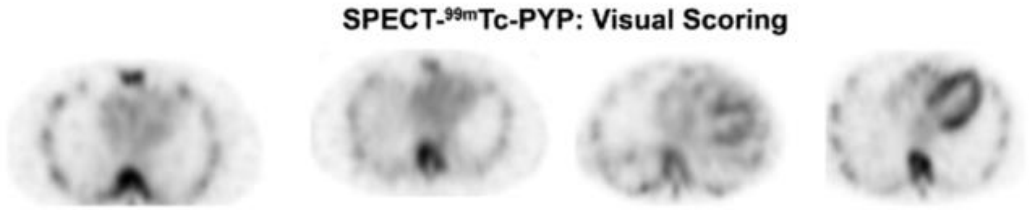
Perugini scale

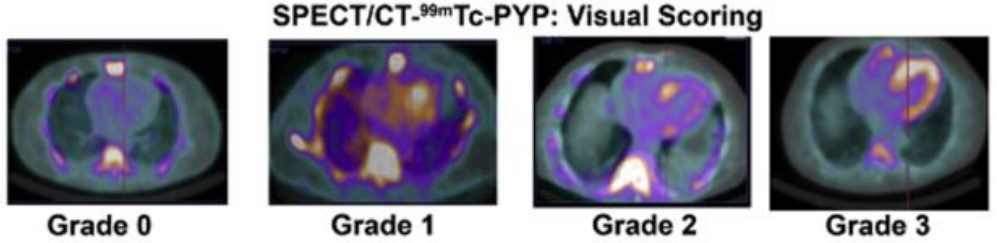


Hanna et al J Am Coll Cardiol 2020;75:2851–620





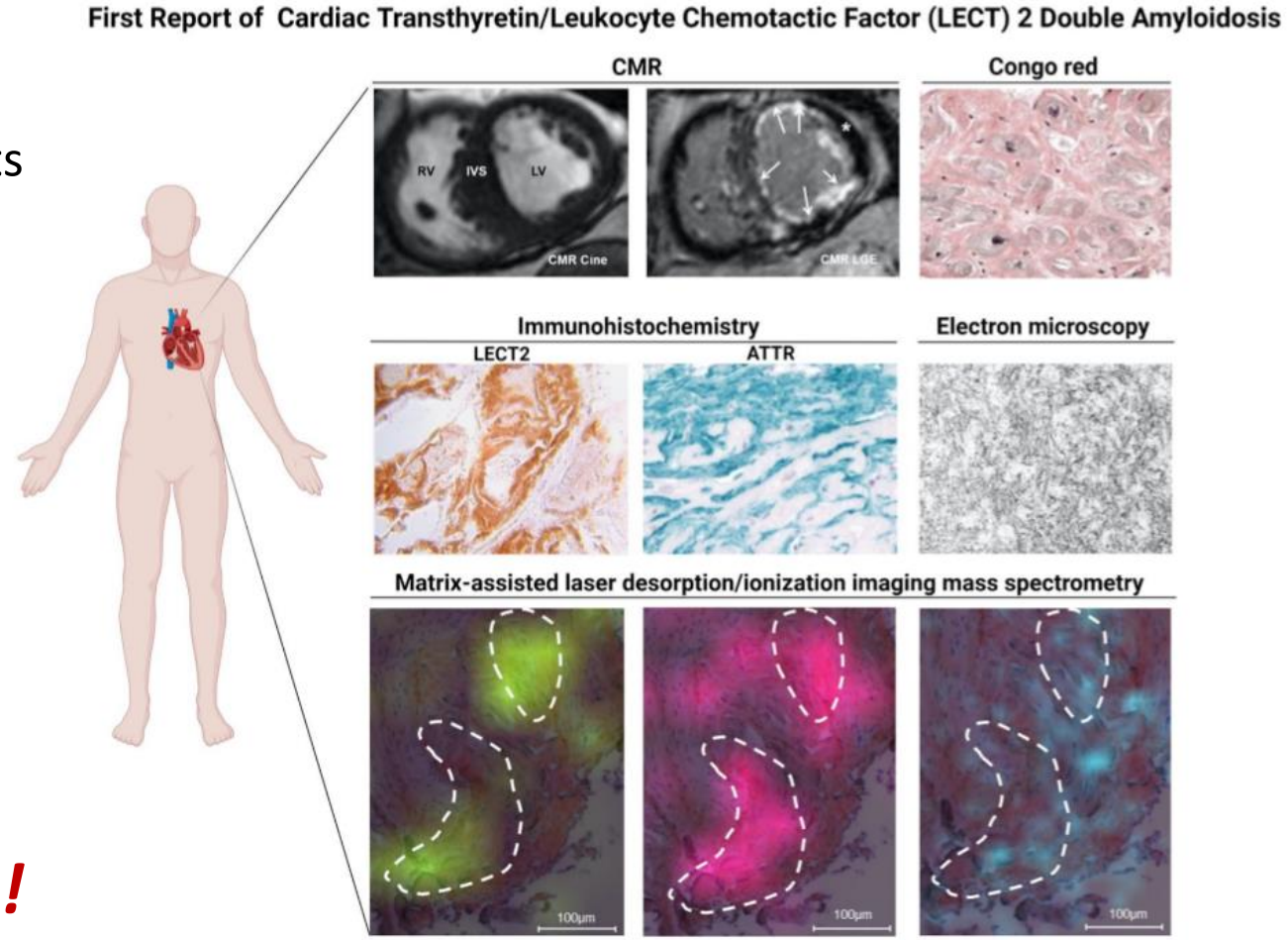




Endomyocardial biopsy for cardiac amyloidosis

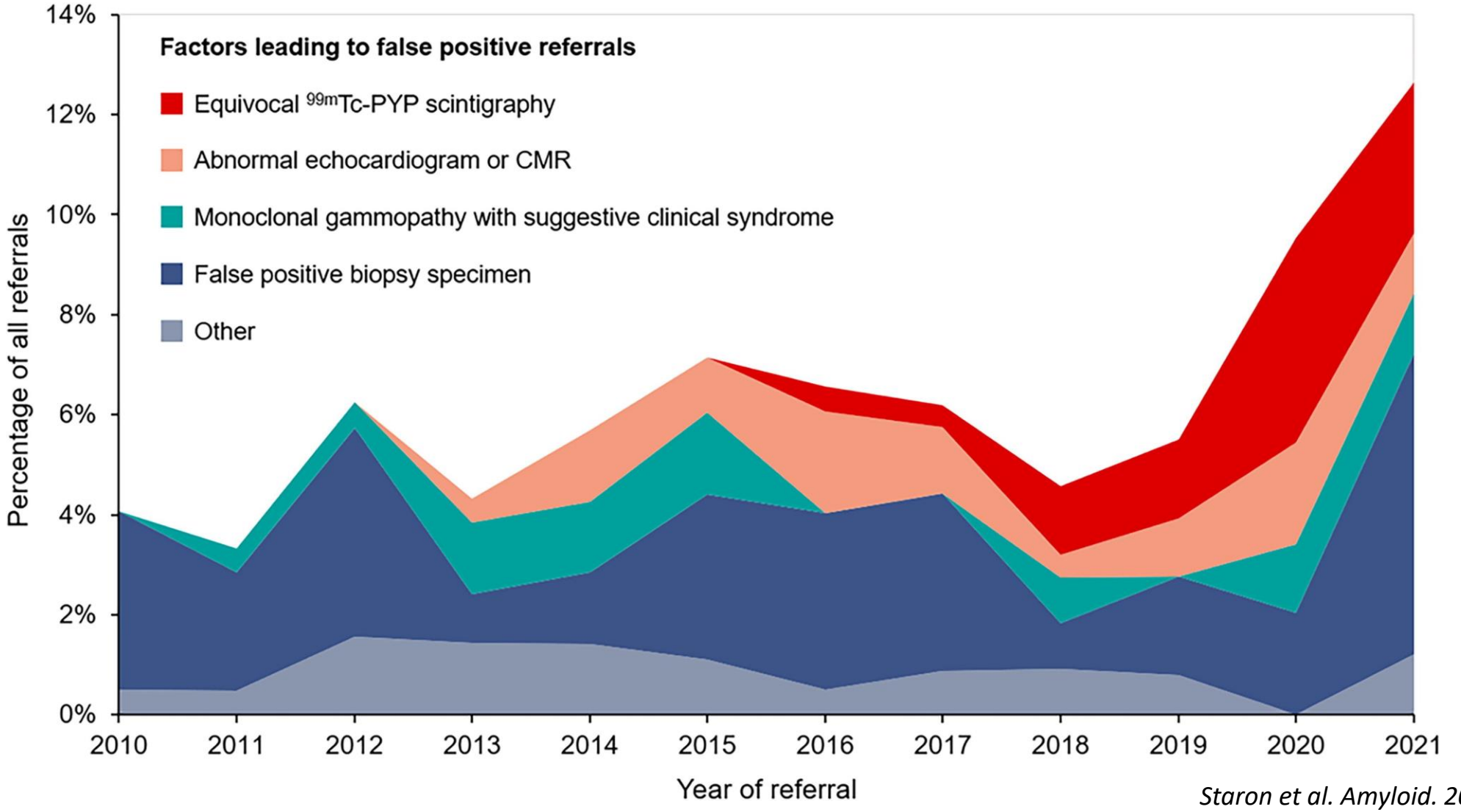
- Equivocal imaging findings
- High clinical suspicion
- Presence of abnormal hematological tests
- Non-TTR amyloidosis

ALECT2
Common form of renal amyloidosis
In Egyptians
Purjabi, Sudanese, Chinese
Native American
Greulich S et al. Clinical Research in Cardiology



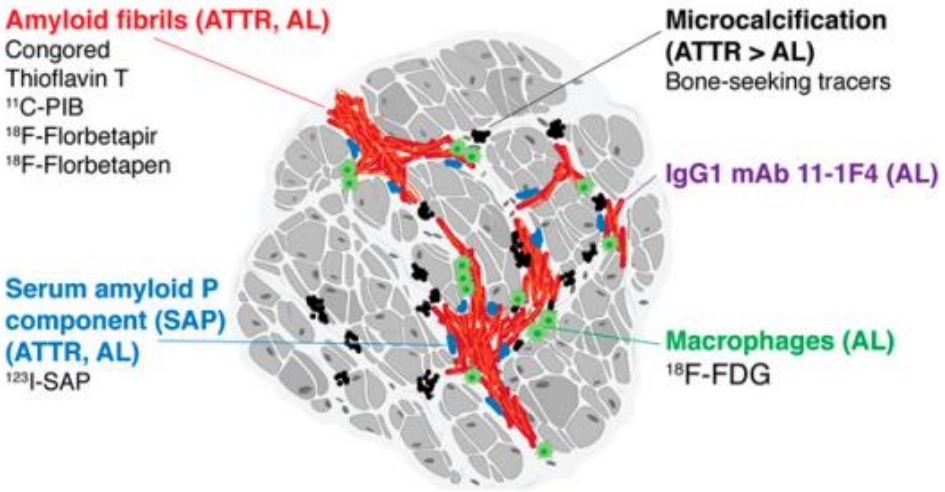
Biopsy: Target the target organ!

False positive referrals for cardiac amyloidosis



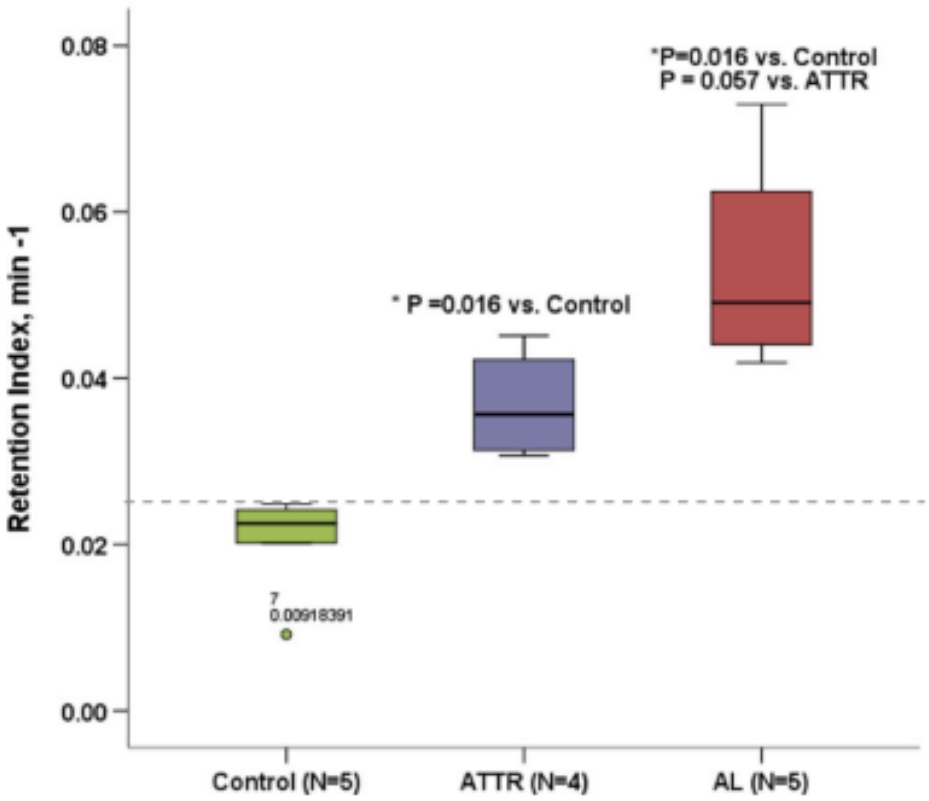
Staron et al. Amyloid. 2023 Jan 31;1-6.

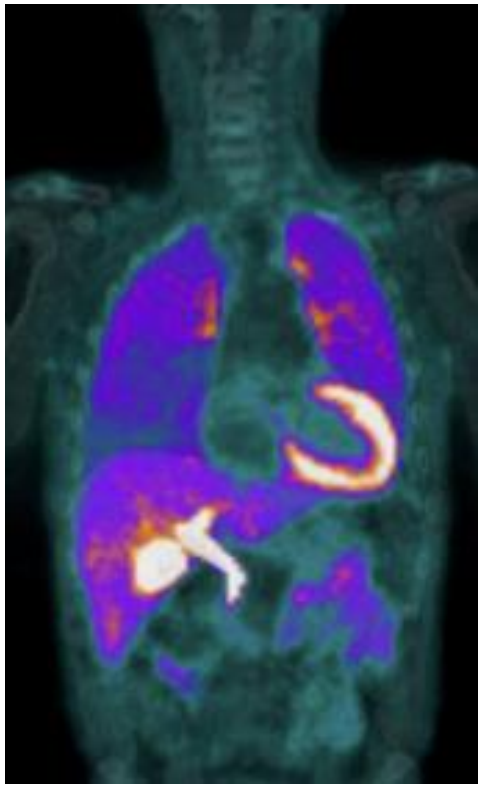
18F-florbetapir PET/CT for AL cardiac amyloidosis



Radionuclide Tracers for Imaging of Amyloidosis

Tracer	Molecular target	Disease target
SPECT tracers		
Bone-seeking radiotracers	Phosphate binders	ATTR
^{99m}Tc-pyrophosphate		
^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid		
^{99m}Tc-hydroxymethylene diphosphonate		
Other radiotracers		
^{123}I-serum amyloid protein	Serum amyloid P	All amyloidoses
^{123}I-aprotinin	Serum protease inhibitor, amyloid binder	All amyloidoses
PET tracers		
Thioflavin-T derivatives	All amyloid fibrils (β-structure and side chains)	AL and ATTR
^{18}F-florbetapir		
^{18}F-florbetaben		
^{18}F-flutemetamol		
^{11}C-Pittsburgh compound B		
^{18}F-sodium fluoride	Microcalcification	ATTR
^{124}I-m11-1F4 monoclonal antibody	Immunoglobulin ALs	AL





Masri et al. J Nucl Med 2020; 61:965–970
Ehman et al. J Nucl Med 2019; 60:1234–1239
Dorbala et al. Eur J Nucl Med Mol Imaging 2014;**41**, 1652–1662

CT Radiomics for cardiac amyloidosis diagnosis and prognosis

CTAs of patients undergoing TAVI

Heart segmentation

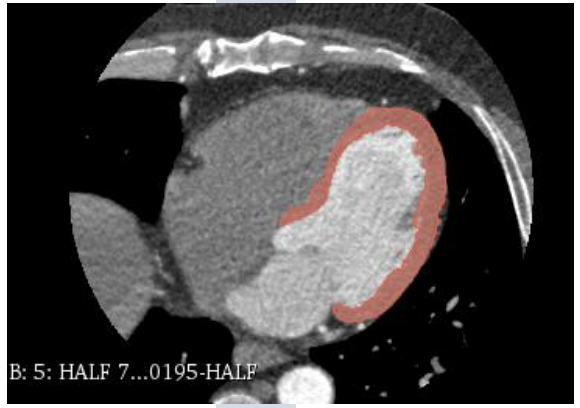
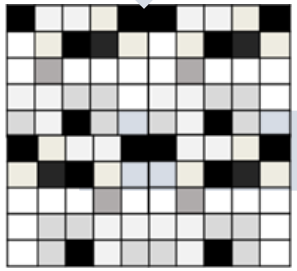
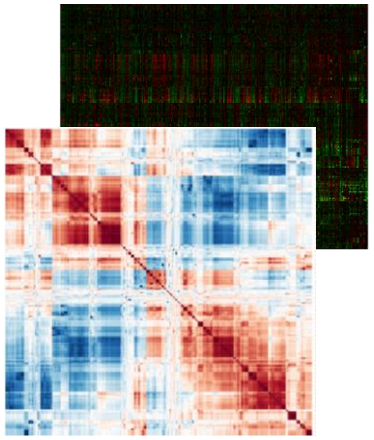


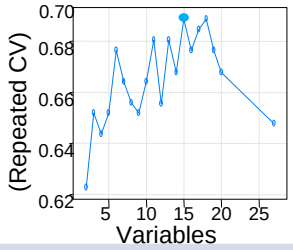
Image discretization

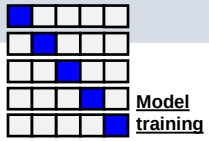


Myocardial CT radiomics features' extraction

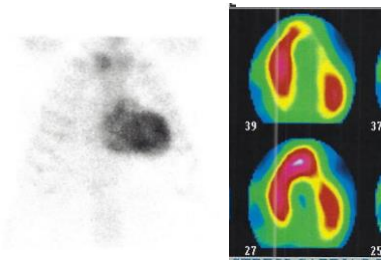


Linked clinical outcomes





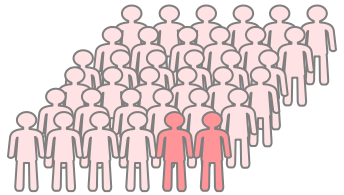
Bone scintigraphy Tc99m-PYP scan



Gold standard for ATTR-CM diagnosis

Diagnose ATTR-CM from a single CT scan

CCTA scans of low-risk patients

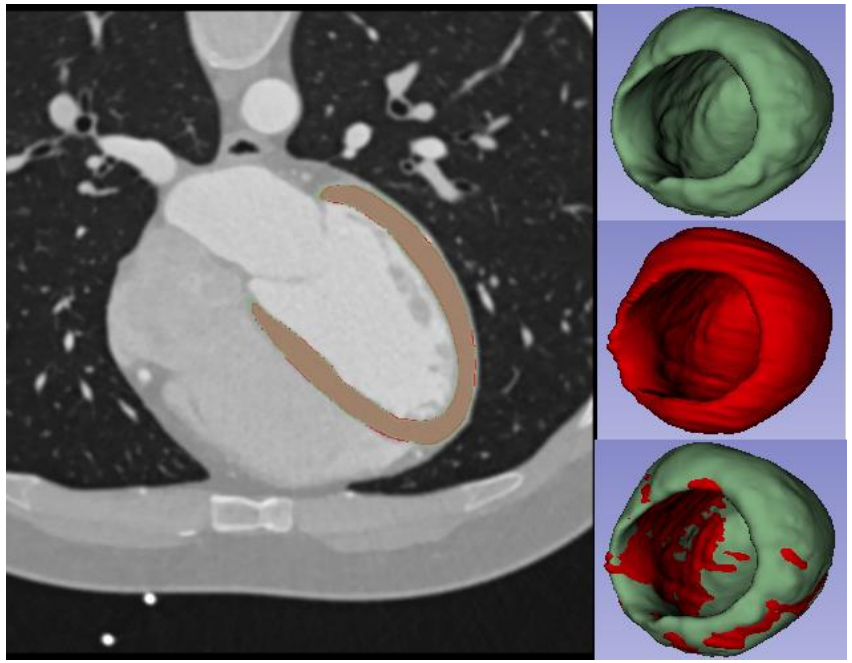


Junior ASPIRE ATTR-CM Research Grant (#67570577)

Development of novel AI tools for myocardial disease phenotyping

Collaboration with Pfizer Hub for Digital Innovation

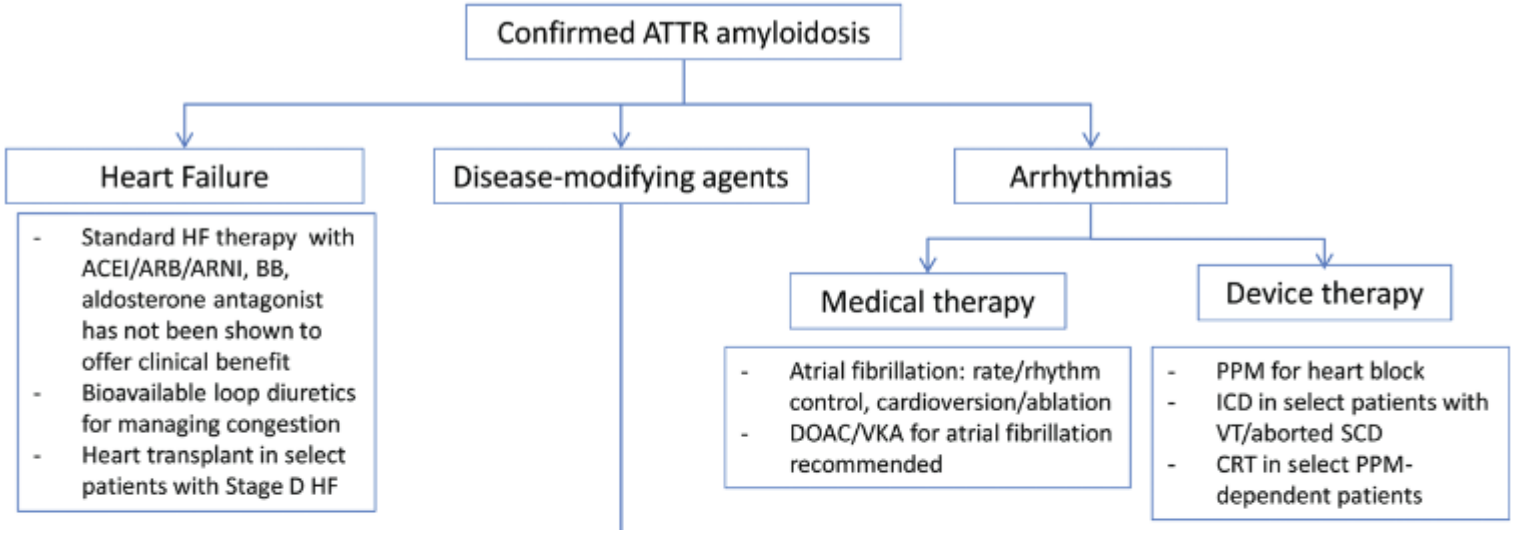
- ✓ Development of an automatic AI algorithm for myocardial tissue segmentation
- ✓ Aim: Recognition of diseased vs healthy myocardial tissue through radiomic feature extraction



Therapeutic approaches for cardiac amyloidosis

Unit of Inherited and Rare Cardiovascular Diseases, 1st Cardiology Dpt, National and Kapodistrian University of Athens

Treatment options for ATTR



Kittleson et al. Circulation. 2020;142:e7–e22.

Treatment options for ATTR

Suppression of TTR

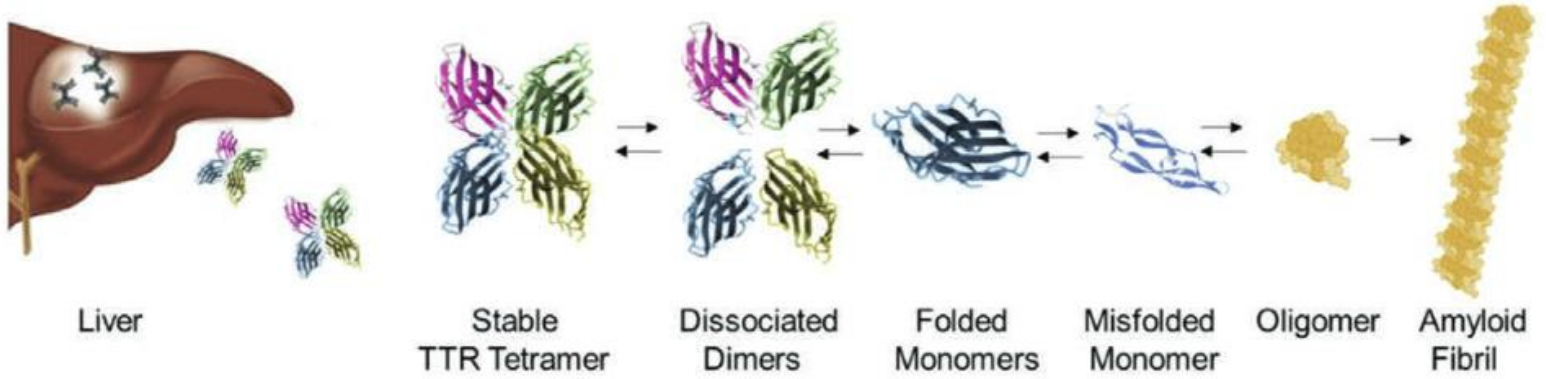
- Liver Transplantation
- TTR Gene silencers (Patisiran/Inotersen)

TTR Stabilization

- Tafamidis
- Diflunisal
- Green Tea
- AG10

TTR disruption/resorption

- Doxycycline/TUDCA
- Monoclonal antibodies



CRISPR-Cas9

Recombinant-Ab anti-TTR

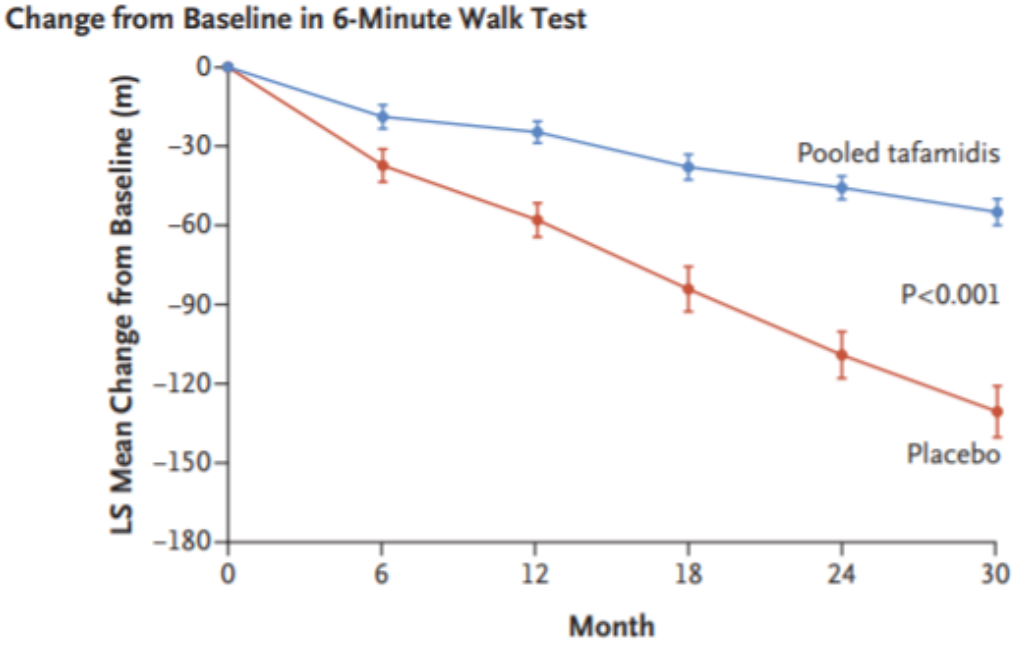
Kittleson et al. Circulation. 2020;142:e7–e22.

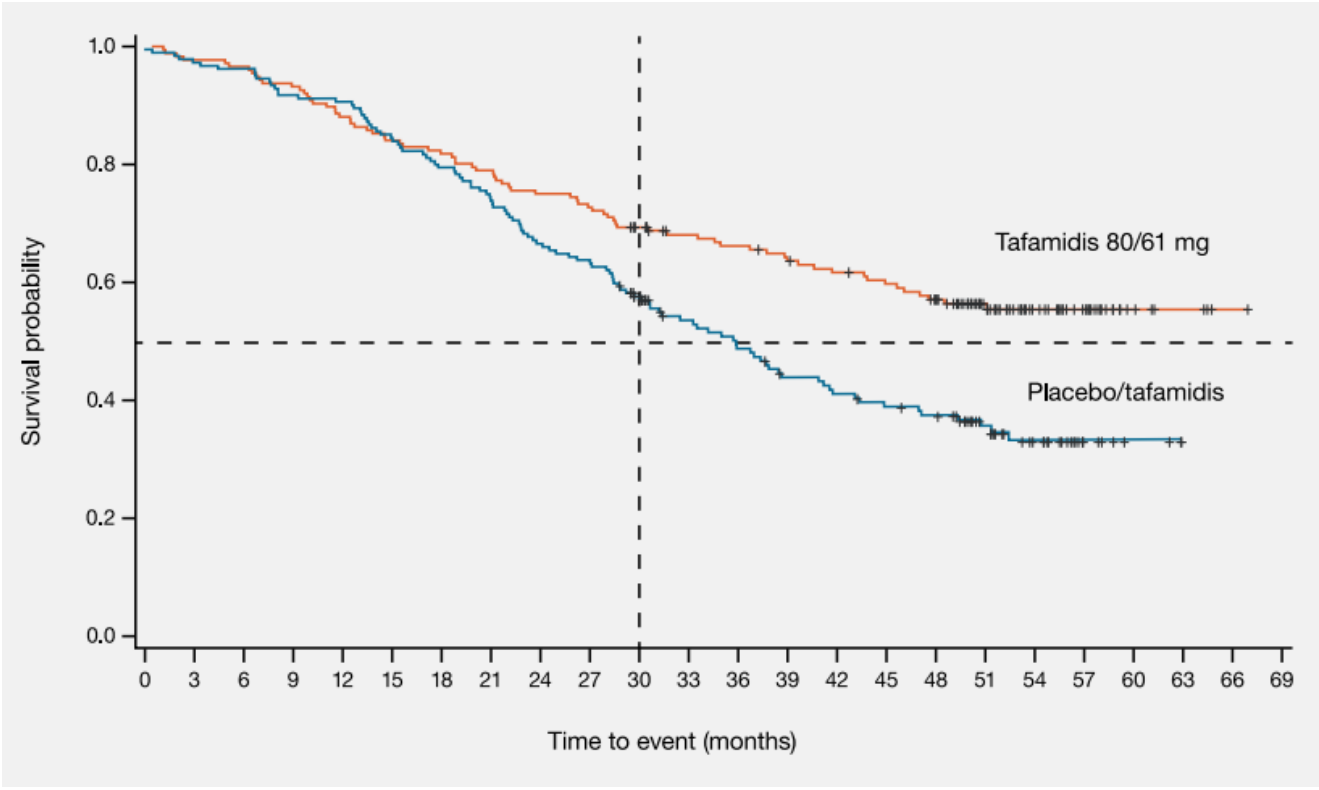
Tafamidis for ATTR (ATTR-ACT)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

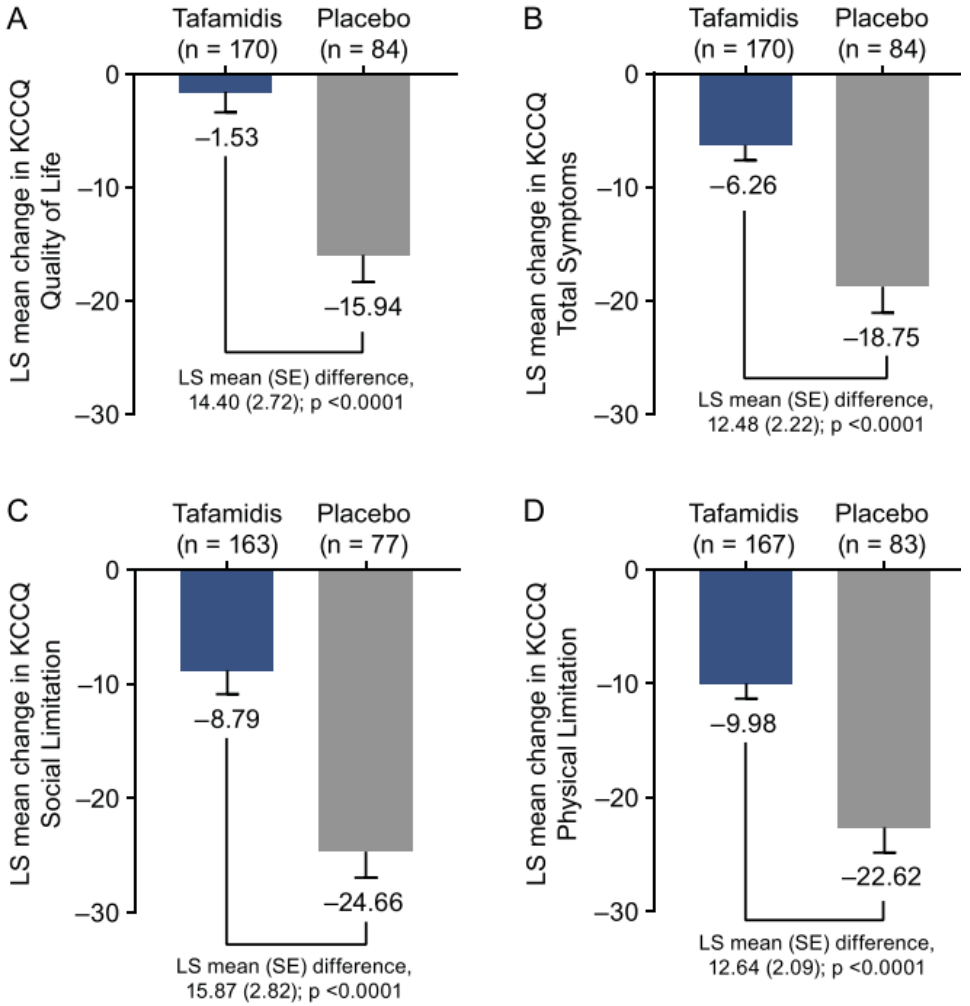
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy





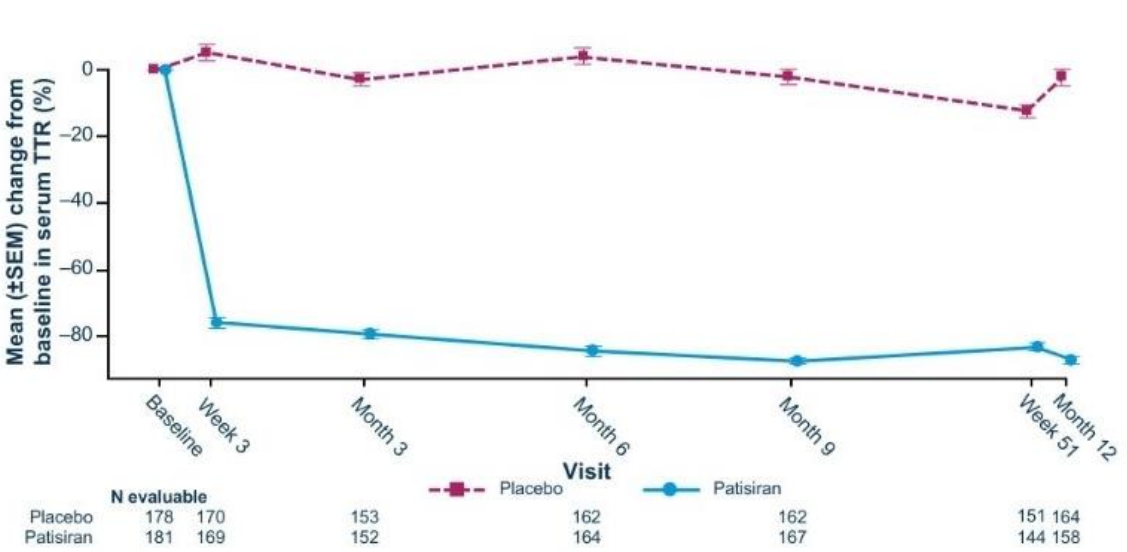
Maurer et al NEJM 2018:379;11

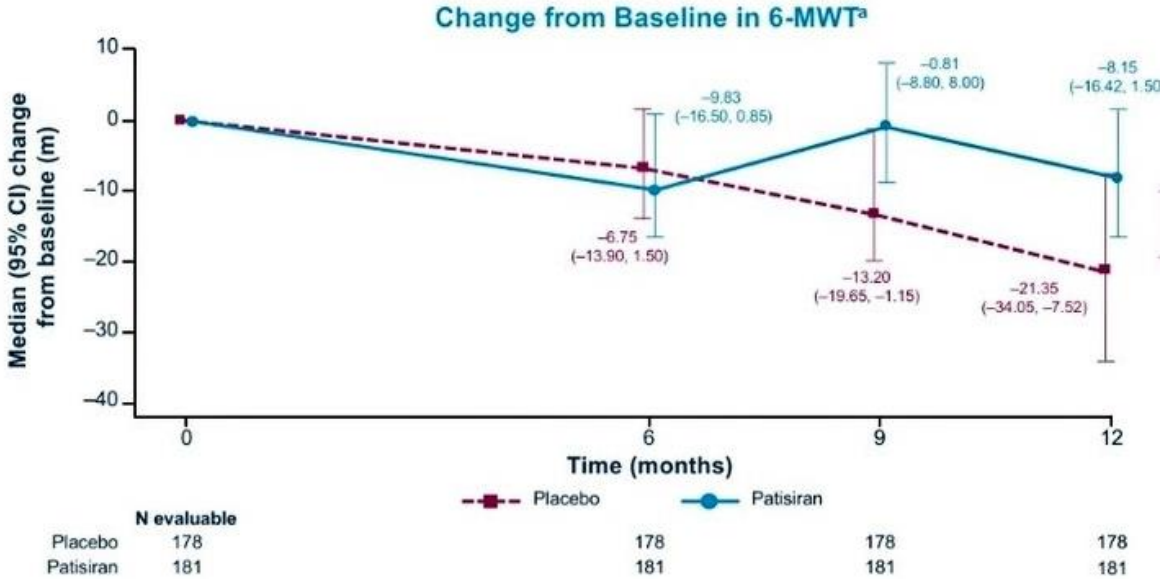
Tafamidis for ATTR (ATTR-ACT) – Quality of life

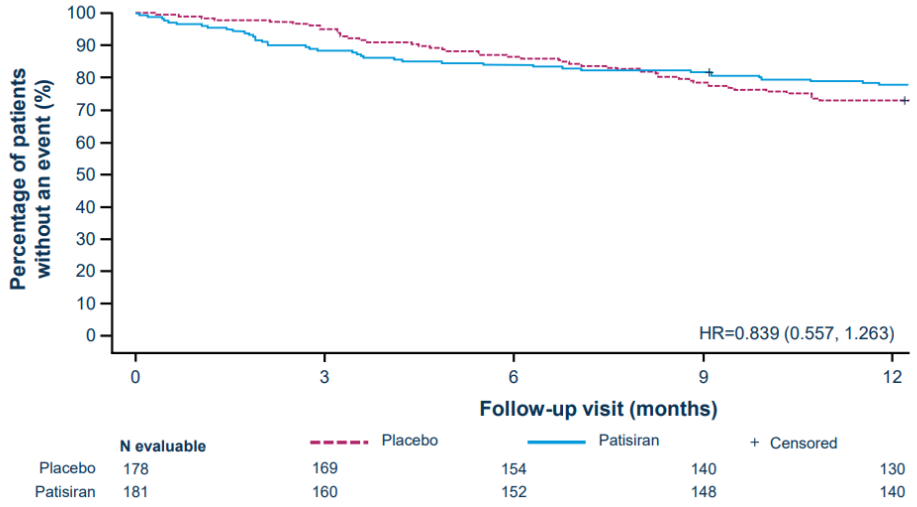


Hanna et al Am J Cardiol 2021;141:98−105

APOLLO-B: Patisiran siRNA for hATTR treatment

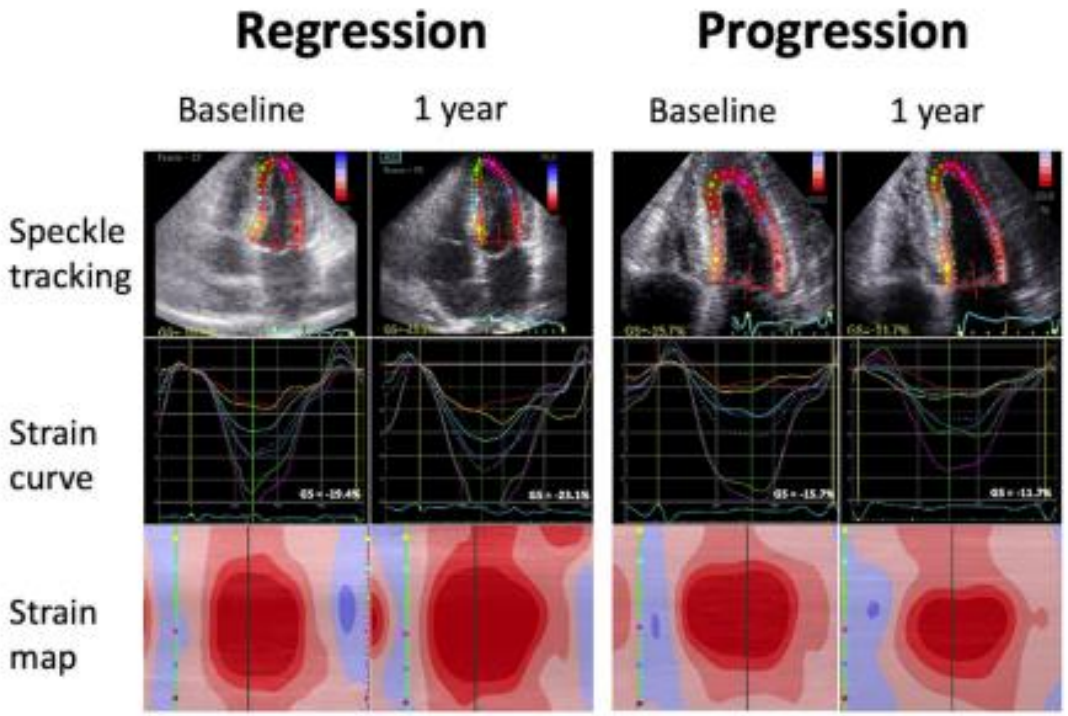


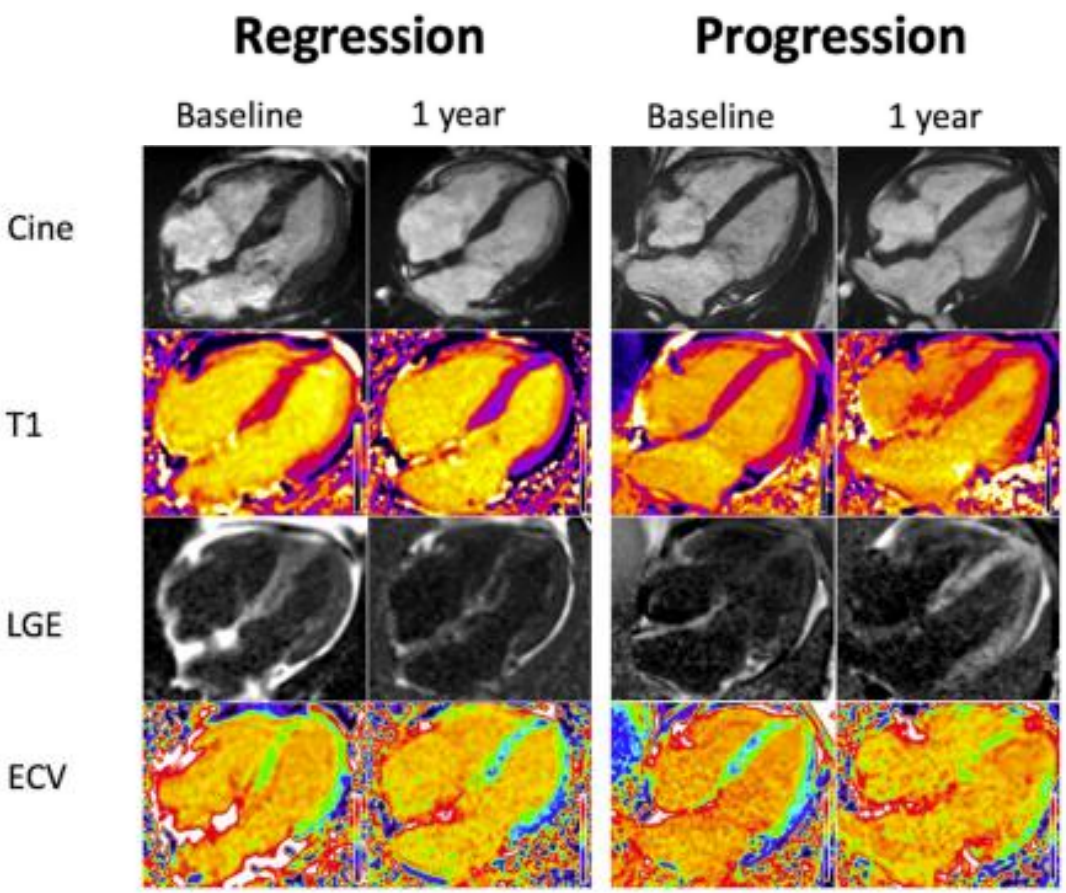




Maurer et al ISA 2022, Heidelberg

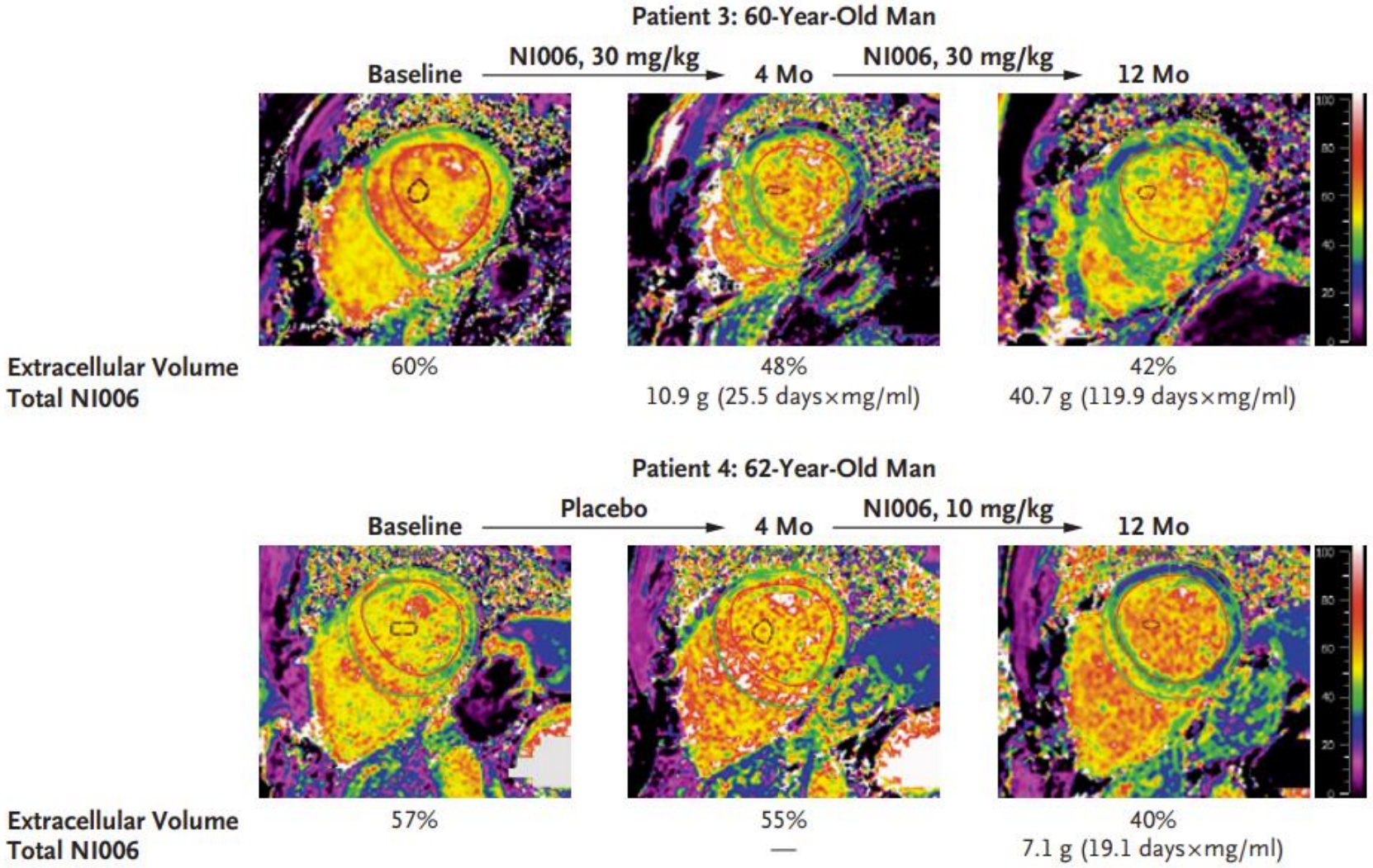
Imaging to monitor treatment effects and disease status





Ioannou et al. Current Cardiology Reports (2022) 24:839–850

NI006 recombinant antibody against TTR



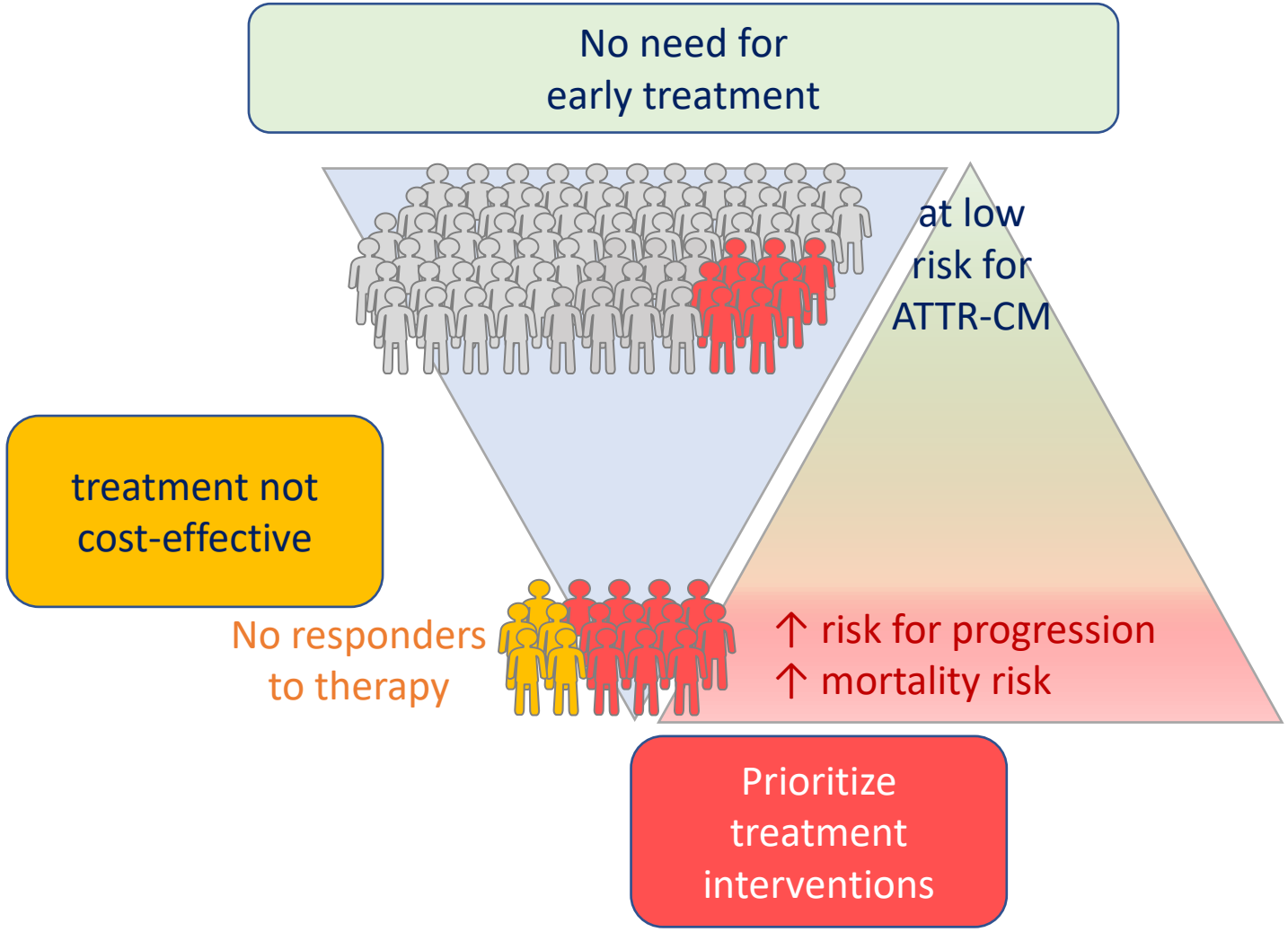
recombinant human anti-ATTR monoclonal IgG1 antibody t

Selectively binds amyloid conformations of both wild-type and variant TTR

inducing Ab-mediated phagocytosis of ATTR fibrils and removal of ATTR deposits from tissues.

Garcia Pavia et al. NEJM 2023

How to deploy high cost TTR-therapeutics?



Conclusions

Facts on ATTR

- Much more common than previously thought
- Significantly underdiagnosed & undertreated
- Males >> Females at risk
- HFpEF + LVH, elderly with AS, HCM
- HF with red flags (Hx musculoskeletal problems etc)
- Natural course of the disease survival 1/4 at 2y
- htATTR heterogeneous disease
- Newer TTR therapeutics alter the natural course of the disease and reduce mortality

Challenges

- Important gaps exist in ATTR epidemiological research at global level, with large parts of the world being unrepresented in available clinical cohorts

- Need to set-up national registries
- Country-tailored screening programs for ATTR

- Better understand pathophysiology of disease
- Risk factors for ATTR development - progression
- How early to treat and how late is too late?

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