CARDIOCONNECT
DE LA VILLE À L'HÔPITAL
6ème édition
SAMEDI, 2 DECEMBRE 2023
SALONS VARENNE, NOISY-LE-GRAND

Améliorer le diagnostic des amyloses cardiaques : de la clinique à l'imagerie

Dr A. **Zaroui** (Mondor)

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Améliorer le diagnostic des AC de la clinique à l'imagerie

SESSION : AMYLOSE CARDIAQUE

AUTHEUR: Dr Amira Zaroui

Heterogeneous group of misfolded proteins/ various organs /Extensive extracellular

The recent development of effective treatment options

Need for better and earlier detection

largely under-diagnosed

Timely diagnosis of cardiac amyloidosis is challenging

Improve with emergence of newer non-invasive imaging techniques

HOW ??

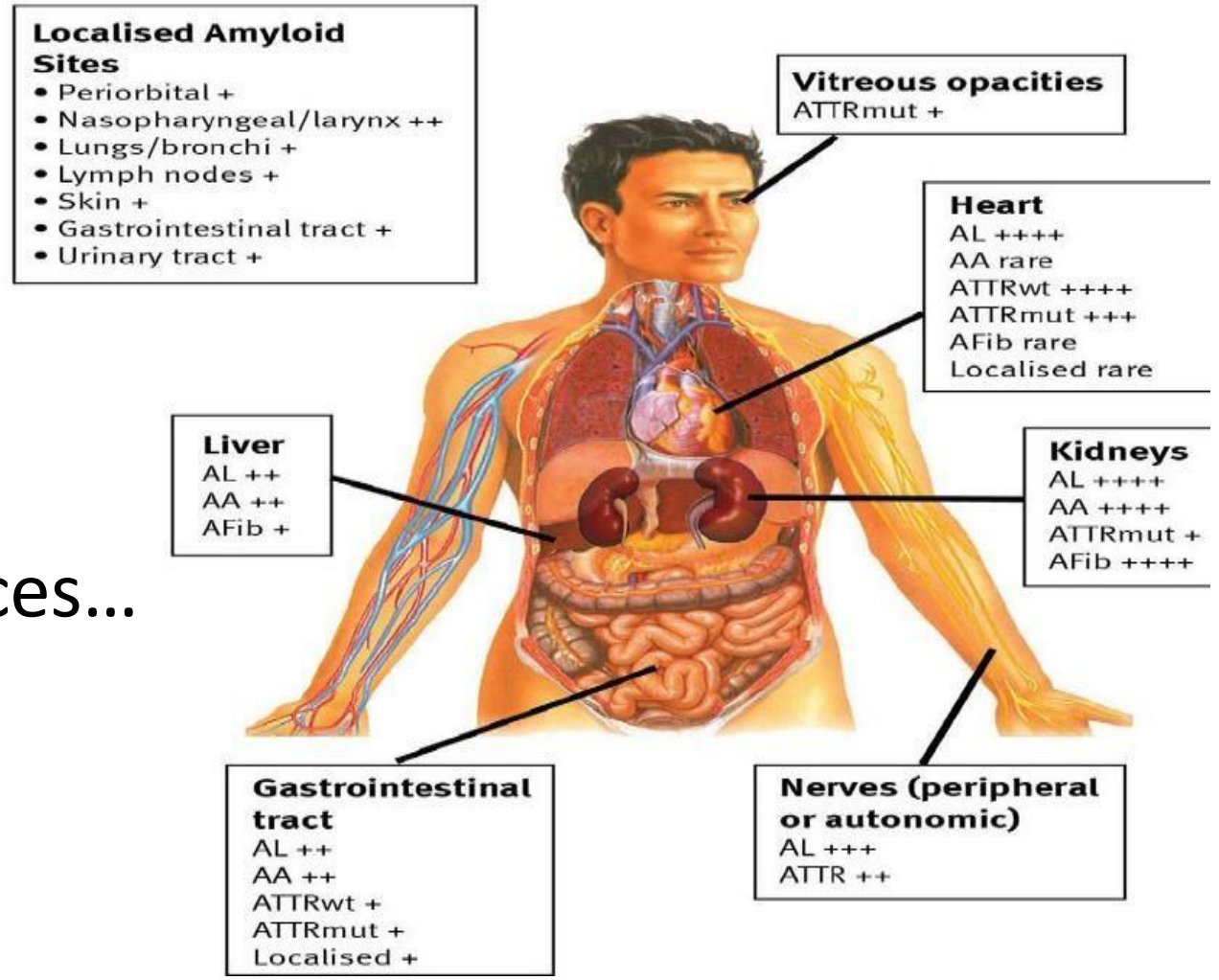
1 Better knowledge of physiology

2 Better Knowledge of the natural history

3To have a detective attitude for sceening Overview of CA and discuss the role of imaging modalities in cardiac amyloidosis 4- Explore future directions for imaging in cardiac amyloidosis.

Physiopatholy and natural history

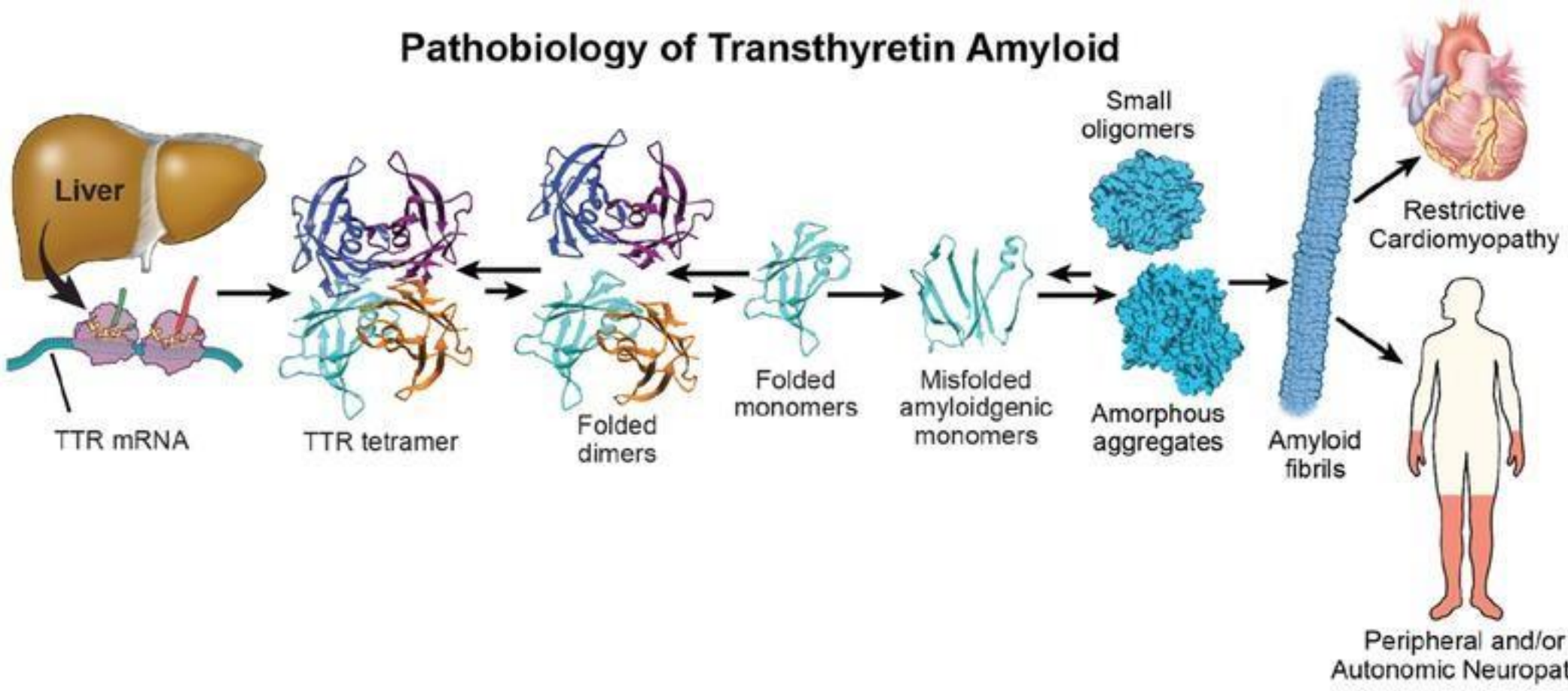
Organs involvement



Organs consequences…

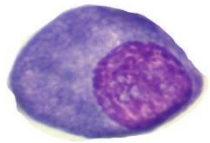
- ↗ Stifness
- ↗ Increase
- ↗Cellular death

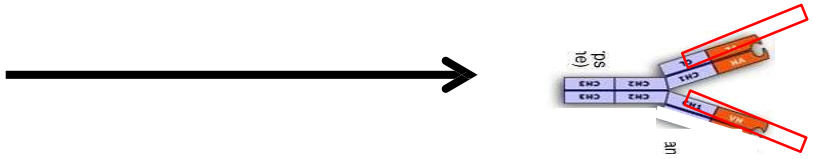
Mollee et al Journal Medecine Interne 2014

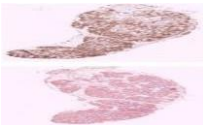


Frederick L. Ruberg, et al. J Am Coll Cardiol. 2019 June 11; 73(22): 2872–2891.

AL-CA: Gammopathy and myeloma





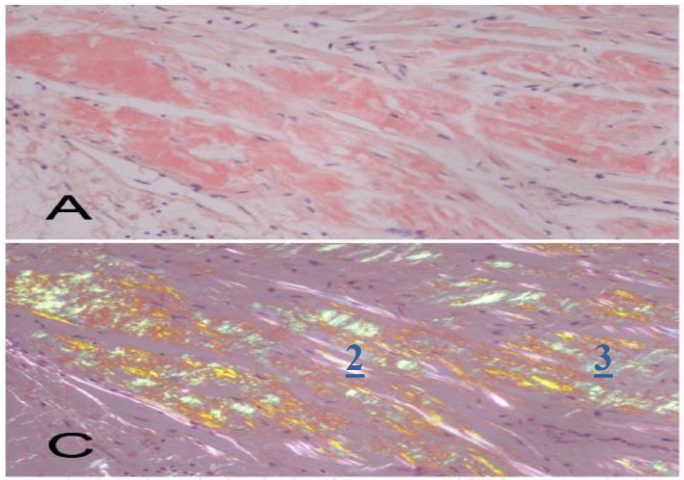


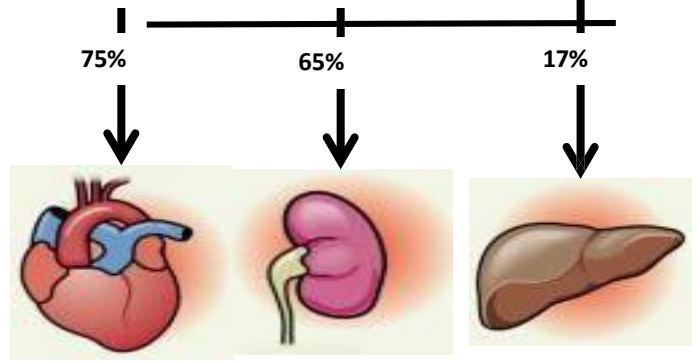
Lymphocyte

CLL

Lambda>kappa

Fibrilles amyloïdes



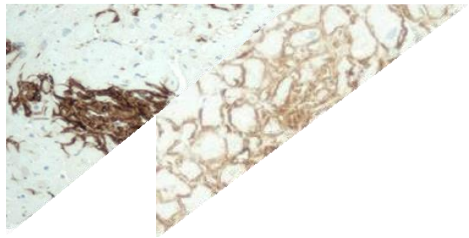


- AL-Amyloidosis: Over production of one type of light chain (Lambda>Kappa) by Lymphocytes
- AL-CA with HF symptoms without treatment = DEATH in 6months
- AL-CA = EMERGENCY! ; PROGNOSTIC = MAYO STAGING

Prevalence of Monoclonal Gammopathy of Undetermined Significance RA. Kyle et al New Engl J Med 2006

Cardiac infiltation and consequences for the heart

Myocardial

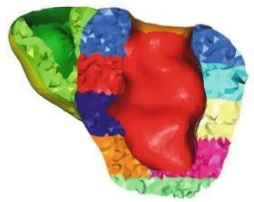


↗ Wall thickness
↗ Stifness
Diastolic dysfunction
Systolic dysfunction
Thrombosis : PE, Stroke
Cellular death: ↗ Troponin

Endocardium

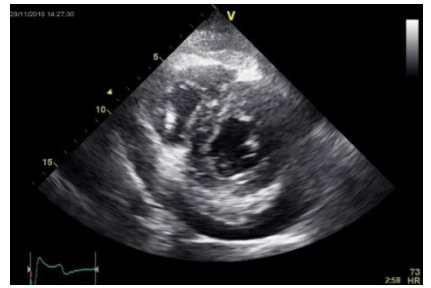
Valvular disease
Aortic Stenosis= 6 à 16%

Vascular



Ischemia
Necrosis

Pericardium



Pericarditis
Tamponnade

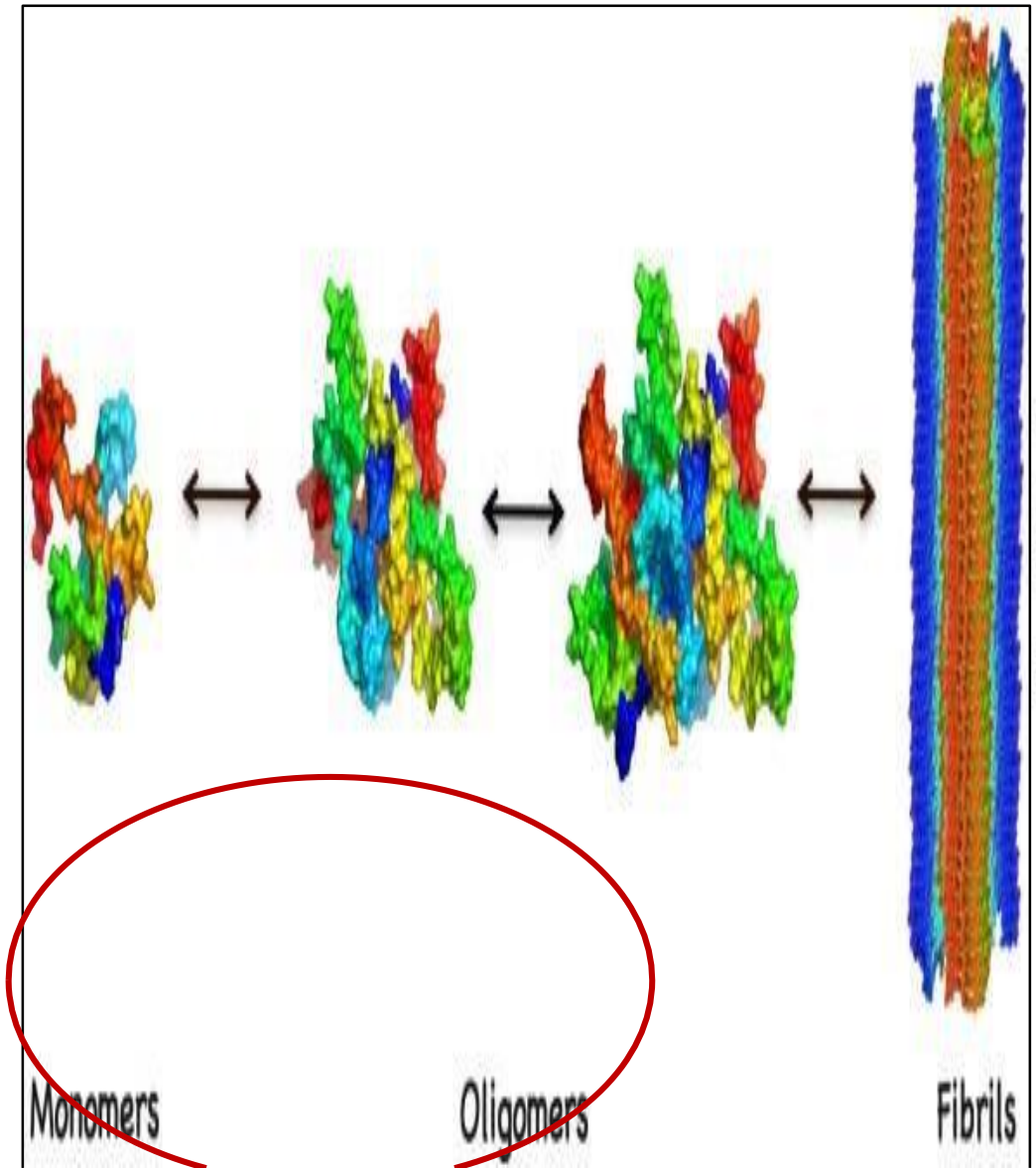
Electric cell

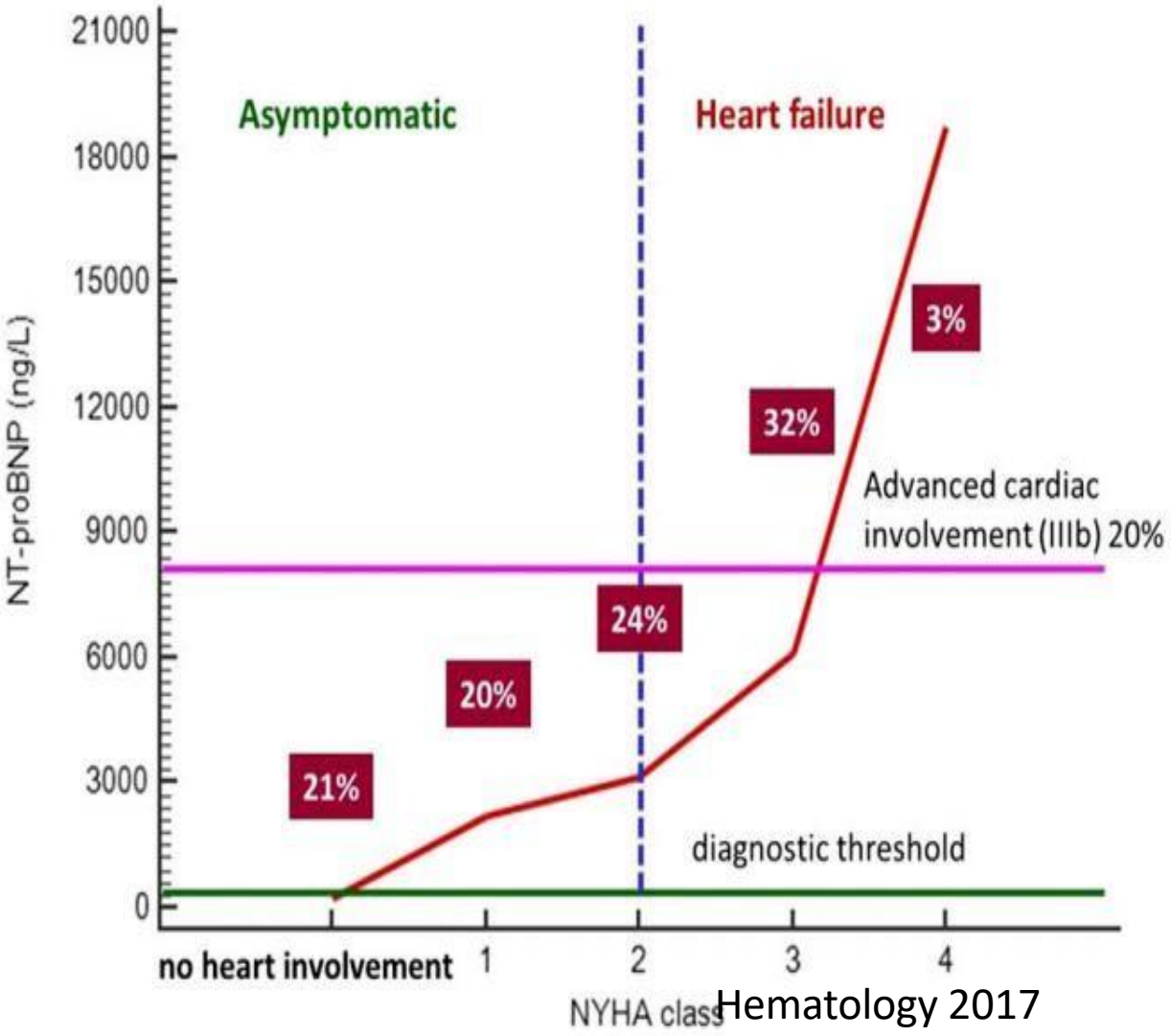
Conduction and Rhythm disorders:
AV Block, Atrial fibrilation Flutter

Autonomic system

↘ Heart rate
Hypotension
Chronotropic incompetence

Misdiagnosis , too later





Hematology 2017

ECHOGRAPHY MRI

Non specific symptoms

- New onset HF/LVH

+

- Malaise
- Weight loss
- Proteinuria
- Skin bruising
- Macroglossia
- Peripheral neuropathy
- Autonomic dysfunction
- GI disturbances
- GU disturbances

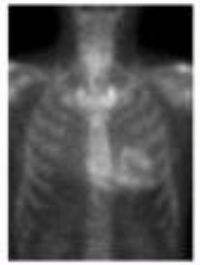
Serum and urine immunofixation

&

S-FLC kappa
S-FLC lambda
FLC kappa/lambda

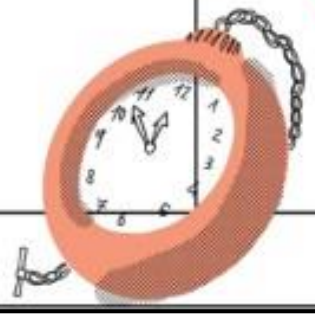
+

Bone scintigraphy



↓

Diagnostic algorithm



A TIMELY DIAGNOSIS IS KEY

AL amyloidosis

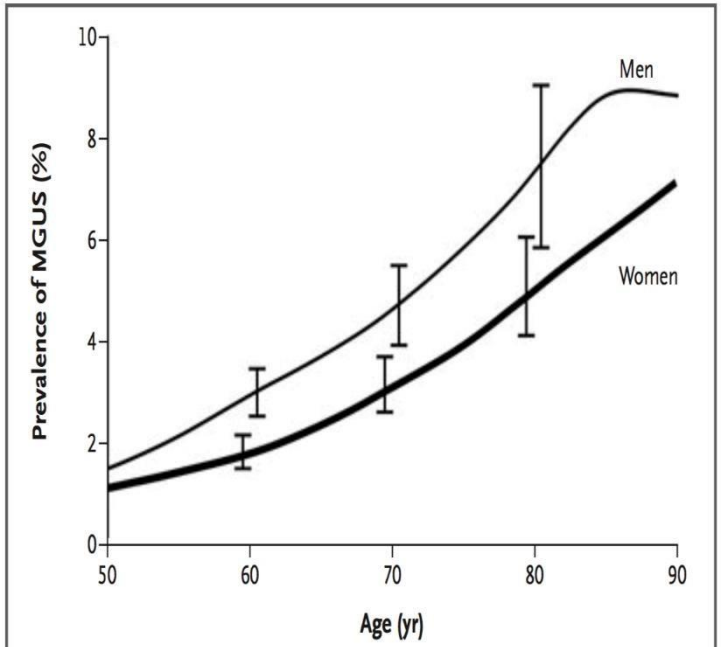


Figure 1. Prevalence of MGUS According to Age.

The I bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.

Screening MGUS ++++

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

6ème édition

European Heart Journal (2021)

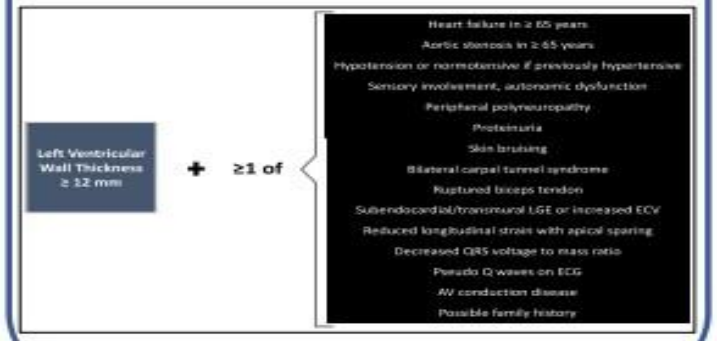
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & **Haematologic tests** (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

1st step

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT &

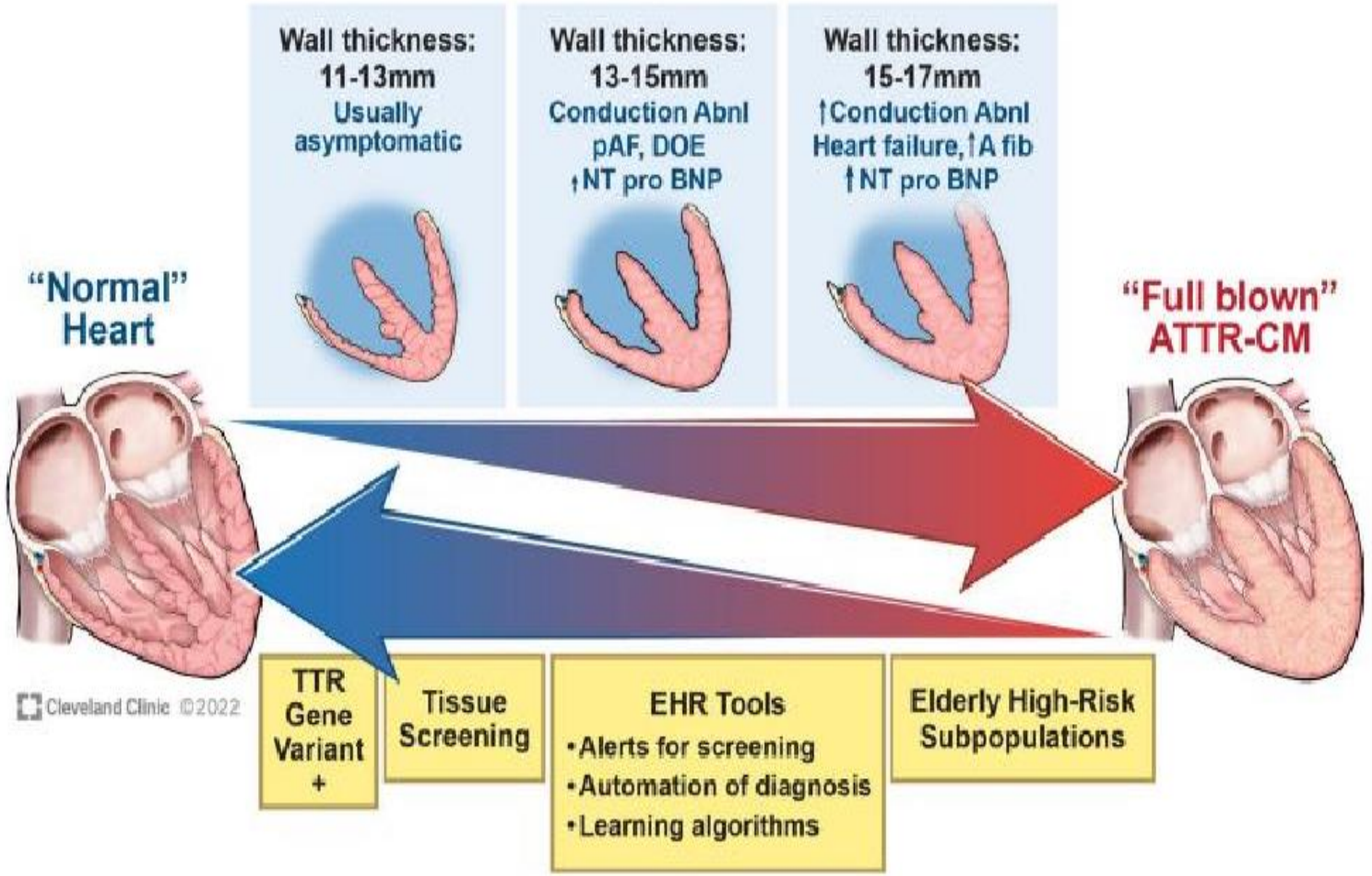
Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Scintigraphy grade 0 Haematologic tests -	Scintigraphy grade 1-3 Haematologic tests -		Scintigraphy grade 0 Haematologic tests +	Scintigraphy grade 1-3 Haematologic tests +
AL/ATTR cardiac amyloidosis unlikely	Grade 2-3	Grade 1	AL amyloidosis?	
	Cardiac ATTR amyloidosis	Histological confirmation (cardiac/extracardiac) **to diagnose**	CMR negative	CMR + or inconclusive
If suspicion persists consider CMR followed by biopsy	TTR genetic testing ATTRwt / ATTRv		Amyloidosis unlikely	Histological confirmation (cardiac/extracardiac) **to diagnose**

problematic step

Histological confirmation (usually cardiac) **to subtype**

Opportunities for Early Detection of ATTR-CM



Pertinent History for Cardiac Amyloid

Orthopedic

- Carpal tunnel syndrome
- Spinal stenosis
- Biceps tendon rupture
- Trigger finger
- Rotator cuff tear
- Hip/knee/shoulder replacement

Neuropathic

- Numbness in lower extremities
- Orthostatic symptoms
- Erectile dysfunction
- Diarrhea

Eye

- Periorbital purpura
- Vitreous opacities/vitrectomy

Cardiac

- History of pacemaker
- History of atrial fibrillation/ ablation

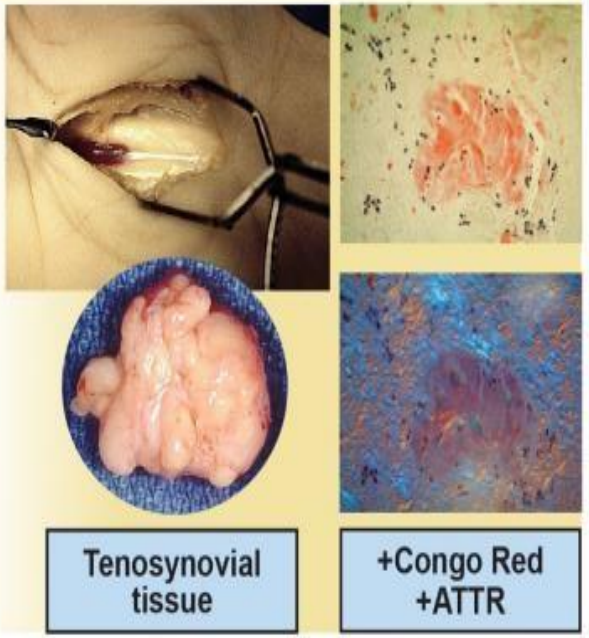
Opportunities for Earlier Diagnosis and Treatment of Cardiac Amyloidosis

- HFpEF and other cardiac conditions, including atrial fibrillation, arrhythmia and atrioventricular block
- Intolerance to standard heart failure therapies (e.g., angiotensin converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers)
- Discordance of QRS voltage and left ventricular wall thickness seen on echocardiography
- Diagnosis of carpal tunnel syndrome, biceps tendon rupture or lumbar spinal stenosis

- Echocardiography showing increased left ventricular wall thickness and/or low-flow gradient aortic stenosis and additional echocardiography parameters
- Nervous system—autonomic nervous system dysfunction
- including gastrointestinal complaints
- unexplained weight loss

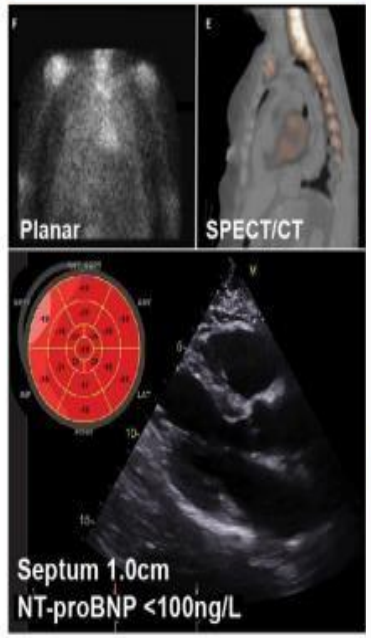
2016 → 2020 → Start Rx with Tafamidis

Carpal tunnel release surgery



^{99m}Tc-PYP scan Grade 0 uptake

^{99m}Tc-PYP scan Grade 3 diffuse uptake



Amyloidosis Algorithm for Biopsy During Carpal Tunnel Release

Tier 1

- Male age ≥ 50 years old
- Female age ≥ 60 years old
- Bilateral carpal tunnel symptoms

Tier 2

- Spinal stenosis
- Biceps tendon rupture
- Atrial fibrillation or flutter (active or previous history)
- Pacemaker
- Congestive heart failure
- Family history of ATTR amyloidosis

TWO characteristics from **Tier 1**

OR

ONE characteristic from **Tier 1** *PLUS* any **ONE** from **Tier 2**

Tenosynovial and/or TCL tissue biopsy with Congo red (or Thioflavin-S) staining

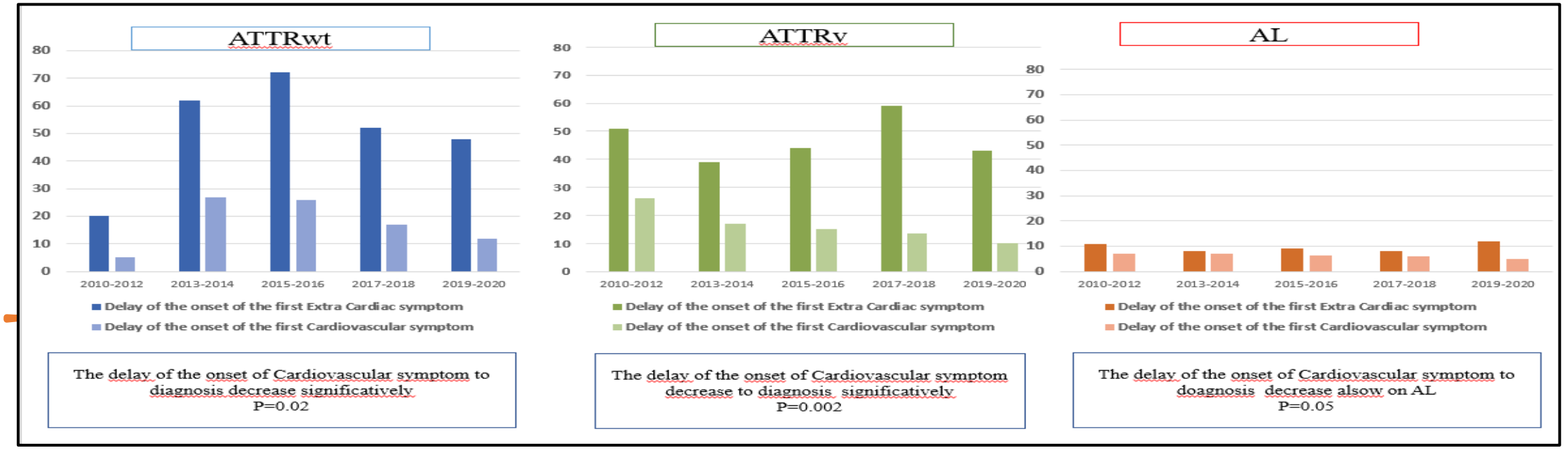
Amyloid Typing
(mass spectrometry)

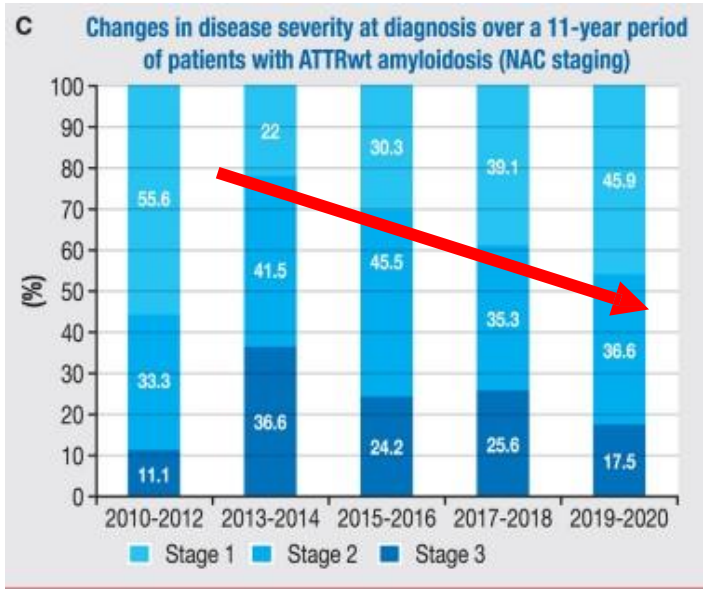
Amyloid (+)

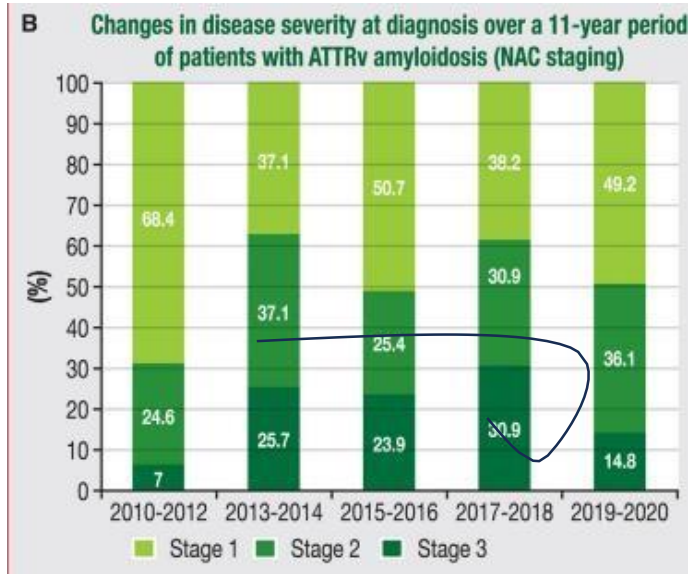
Referral to amyloid expert

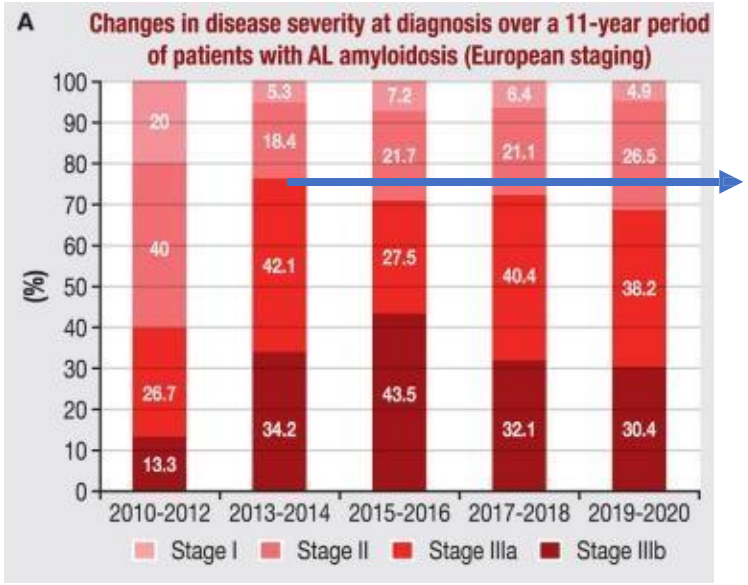
On the real life ?

Changes in amyloidosis phenotype over 11 years in a cardiac amyloidosis referral centre cohort in France

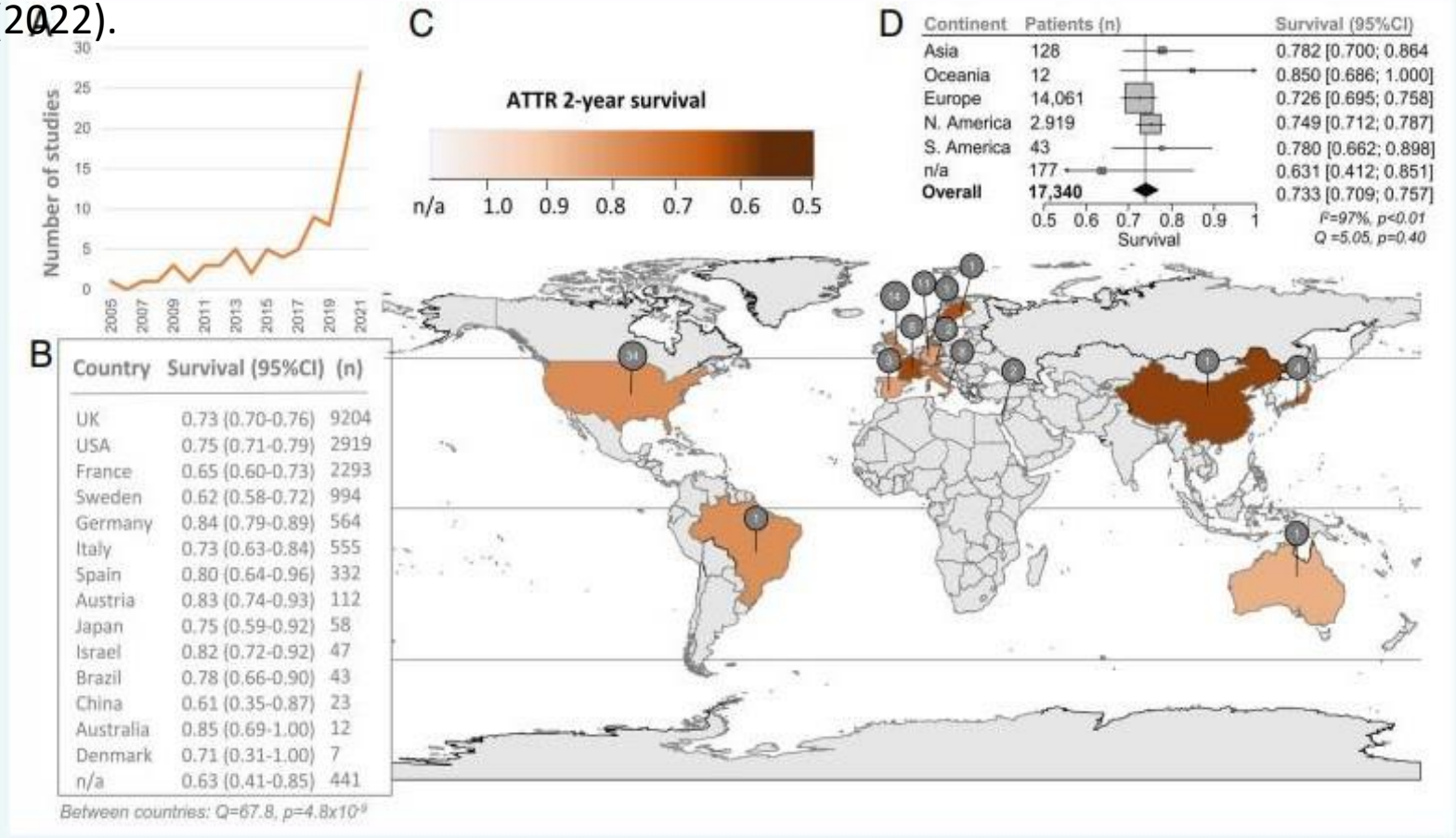


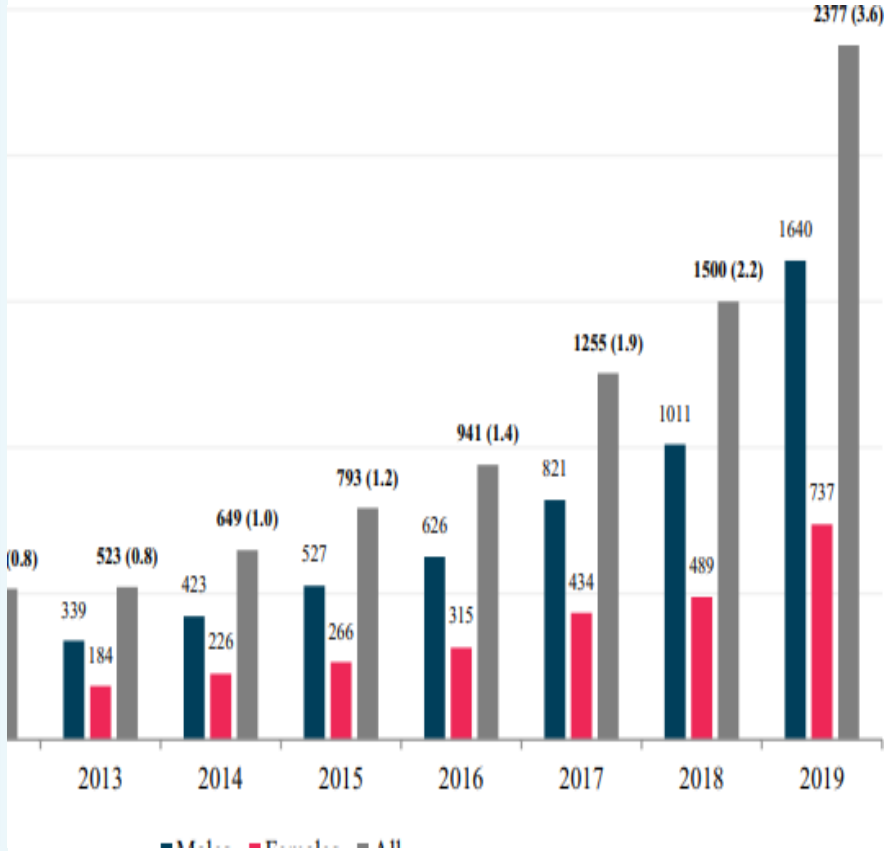






A.S. Antonopoulos et alEuropean Journal of Heart Failure (2022).





(A) Annual number of studies on transthyretin amyloidosis (ATTR) over the period 1987–2021. (B) Country-specific studies on the clinical outcome of ATTR; the survival estimates, and 95% confidence intervals (CI) are derived from random-effects meta-analysis. Studies with non subtyped forms of cardiac amyloidosis have been excluded. (C) World map demonstrates the 2-year survival rates of ATTR in the different countries. Bubbles with numbers represent the number of published studies/cohorts for each country. (D) Forest plot for ATTR 2-year survival by continent subgroup.

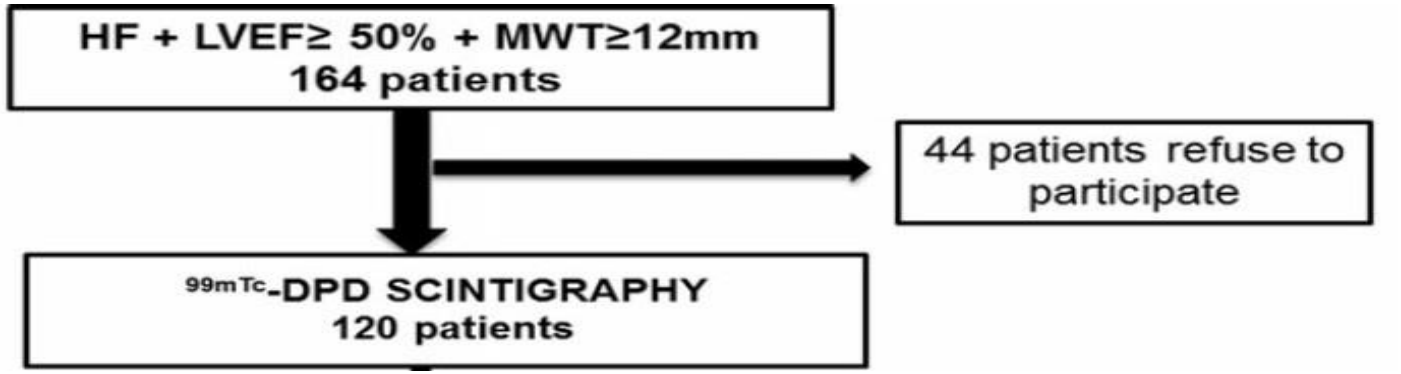
Role of Multimodality cardiac Tools

European Heart Journal (2015) **36**, 2585–2594
doi:10.1093/eurheartj/ehv338

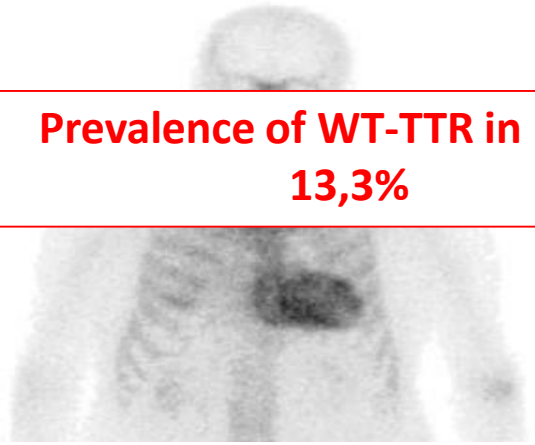
CLINICAL RESEARCH
Heart failure/cardiomyopathy

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*



Prevalence of WT-TTR in HFPEF
13,3%



Age (years)	82 ± 8
Male gender, *n* (%)	49 (41)
Median length of stay (days)	8 (IQR 6–15)
Comorbidities	
Hypertension, *n* (%)	101 (84)
Diabetes mellitus, *n* (%)	45 (37)
CAD, *n* (%)	11 (9)
Clinical features	
Systolic blood pressure (mmHg)	135 ± 26
Diastolic blood pressure (mmHg)	78 ± 21

Gonzales-Lopez et al EHJ 2015

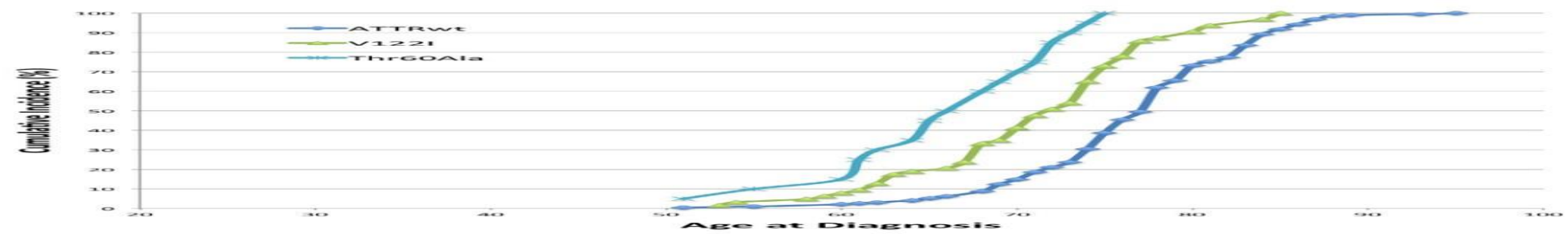


FIGURE 1 Age at diagnosis of wild-type transthyretin cardiac amyloidosis (ATTRwt) and hereditary transthyretin cardiac amyloidosis (ATTRh) including both V122I and Thr60Ala mutations, in a single center cohort (N = 300)

- Autopsy LV specimens : 109 HFPEF without known Amyloidosis; 131 control subjects.

Age (years)	82 ± 8
Male gender, *n* (%)	49 (41)
Median length of stay (days)	8 (IQR 6–15)
Comorbidities	
Hypertension, *n* (%)	101 (84)
Diabetes mellitus, *n* (%)	45 (37)
CAD, *n* (%)	11 (9)
Clinical features	
Systolic blood pressure (mmHg)	135 ± 26
Diastolic blood pressure (mmHg)	78 ± 21

	Regression coefficient	SE	p value
Percent Fibrosis (WFDM)			
Age at death (per 10 yrs)	0.5%	0.3%	0.09
HFpEF (vs Control)	2.1%	0.4%	<0.001
wtTTR present (vs absent)	2.0%	0.7%	0.005
Percent Expected Heart Weight			
HFpEF (vs Control)	32.2%	2.5%	<0.001
wtTTR present (vs absent)	−8.2%	4.0%	0.04

JACC Heart Fail. 2014 April

WT-TTR and HFpEF after 65 year-old

Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy

52 patients > 65 year-old with HFpEF

→ **29% cardiac amyloidosis with 1/3 AL amyloidosis and 2/3 WT-TTR**

Left Ventricular Amyloid Deposition in Patients with Heart Failure and Preserved Ejection Fraction

Selma F. Mohammed, MBBS*, Sultan A. Mirzoyev*, William D. Edwards, MD, Ahmet Dogan, MD, PhD, Donna R Grogan, MD, Shannon M Dunlay, MD, Veronique L. Roger, MD, Morie A Gertz, MD, Angela Dispenzieri, MD, Steven R Zeldenrust, MD, PhD, and Margaret M. Redfield, MD

Bennani Smires et al., Int J Cardiovasc Imaging 2016;32:1403-1413

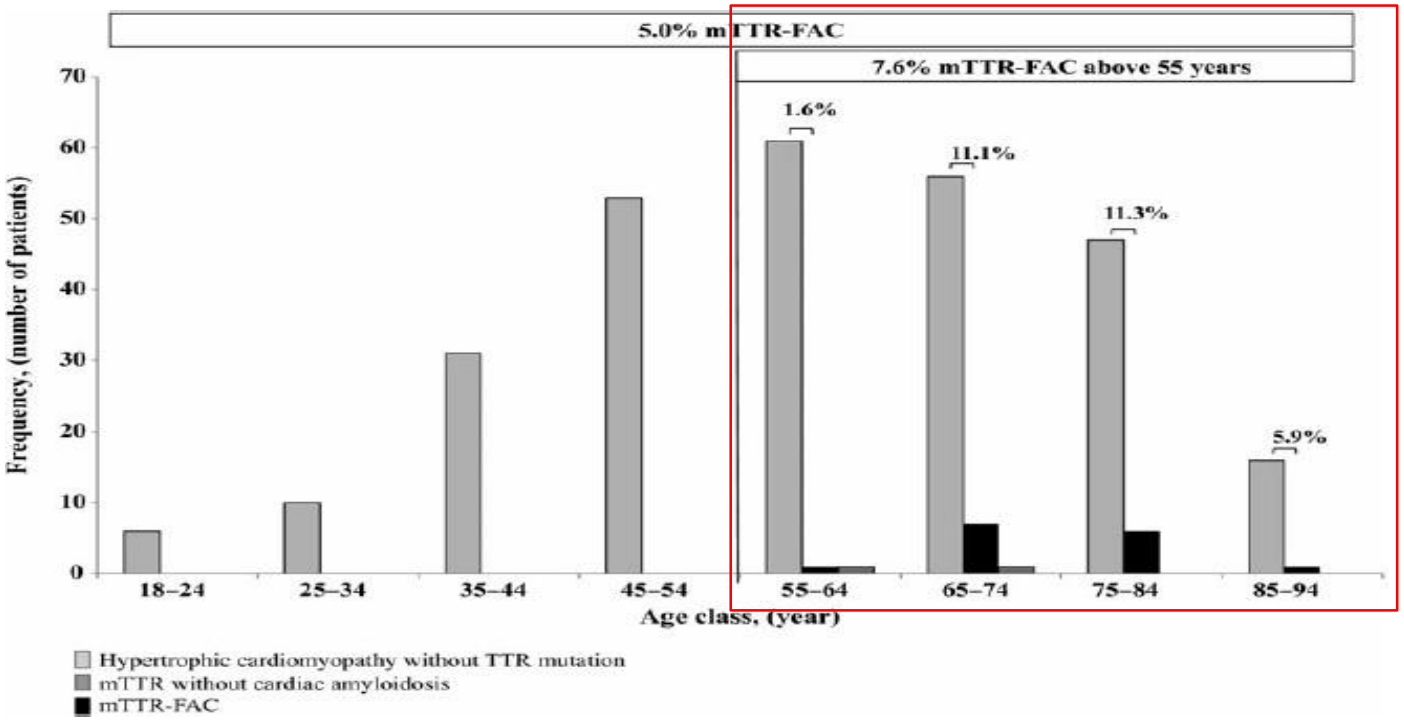
European Heart Journal
doi:10.1093/eurheartj/ehv583

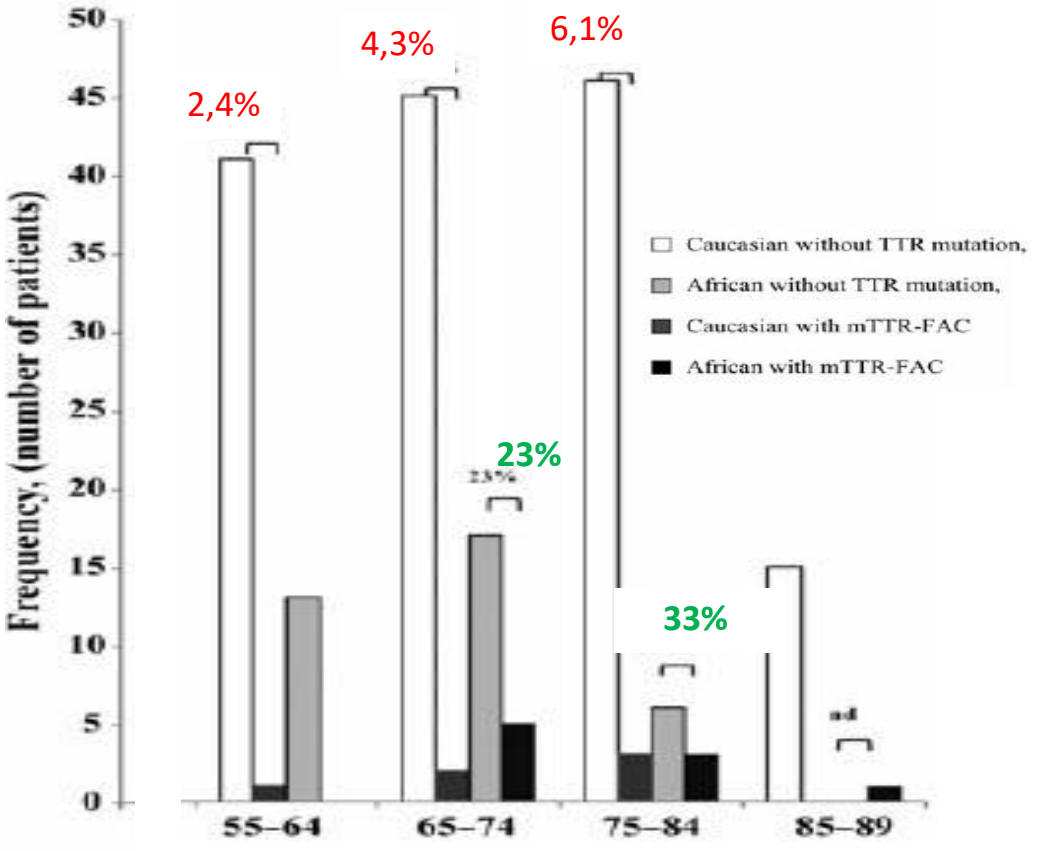
Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness

17 with ATTR mutation

15 with ATTR mutation and CARDIAC AMYLOIDOSIS

Prevalence of ATTR+CA in HCM = 5,0%
7.6% >55yrs old





Damy et al HEJ (2016) 37, 1826–1834

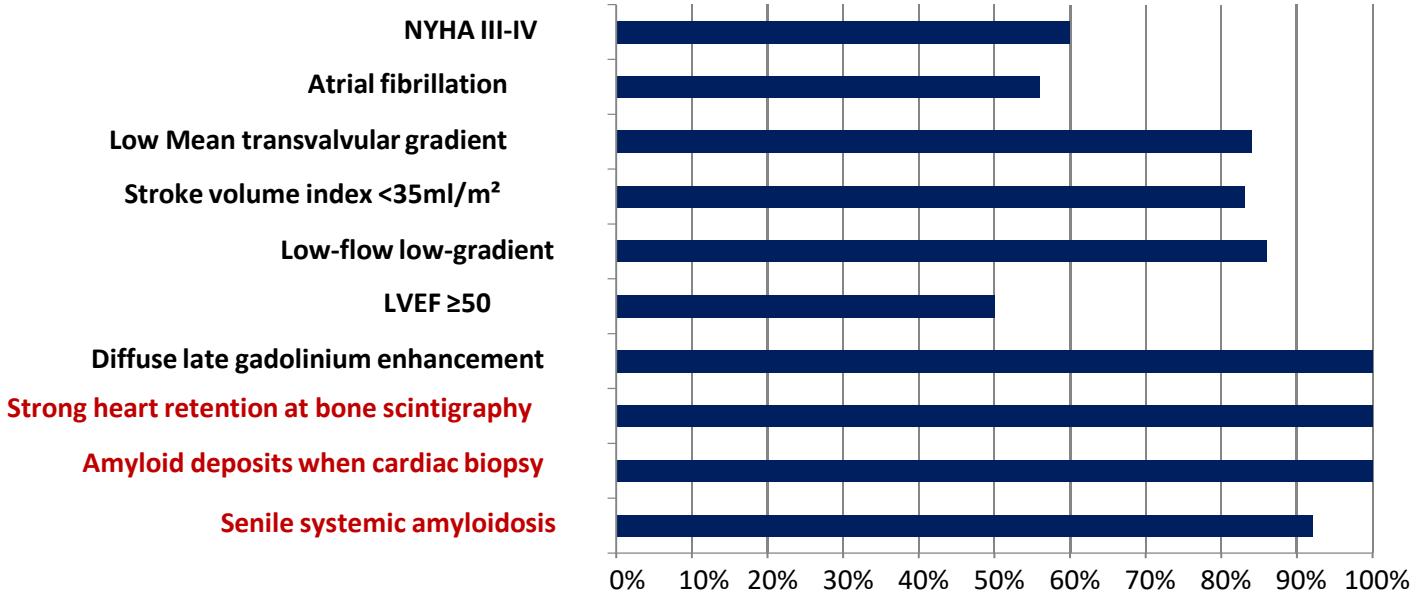
ClinicalTrials.gov Identifier: NCT01623245

Conditions	Any CA	ATTRwt	ATTRv
HFpEF	13-17%	17% ATTR deposits (autopsy); 5% moderate to severe deposits; > 80 y 40%, male predominant; < 65 y 0%	Varying levels of cardiac involvement by different TTR variants
HF	11.4% in Afro-Caribbean patients, UK		8.5% (V122I) in Afro-Caribbean patients, UK
Severe AS for surgical valve replacement	6-12%		
TAVR	8-16%		
Degenerative AS	16%		
Low-flow, low-gradient pattern AS	30%		
HCM			5%, France

Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg?

Arnault Galat[1,2,3,4,5], Aziz Guellich[1,2,3,4,5], Diane Bodez[1,2,3,4,5], Michel Slama[6], Marina Dijos[7], David Messika Zeitoun[8], Olivier Milleron[8], David Attias[9], Jean-Luc Dubois-Randé[1,2,3,4,5], Dania Mohty[10], Etienne Audureau[1,2,4,5,11,12], Emmanuel Teiger[1,2,3,4,5], Jean Rosso[1,2,13], Jean-Luc Monin[1,2,3,4,5], and Thibaud Damy[1,2,3,4,5]*

Aims : report cases of patients with both TTR-CA and AS in order to describe their specific phenotype, management and outcomes.

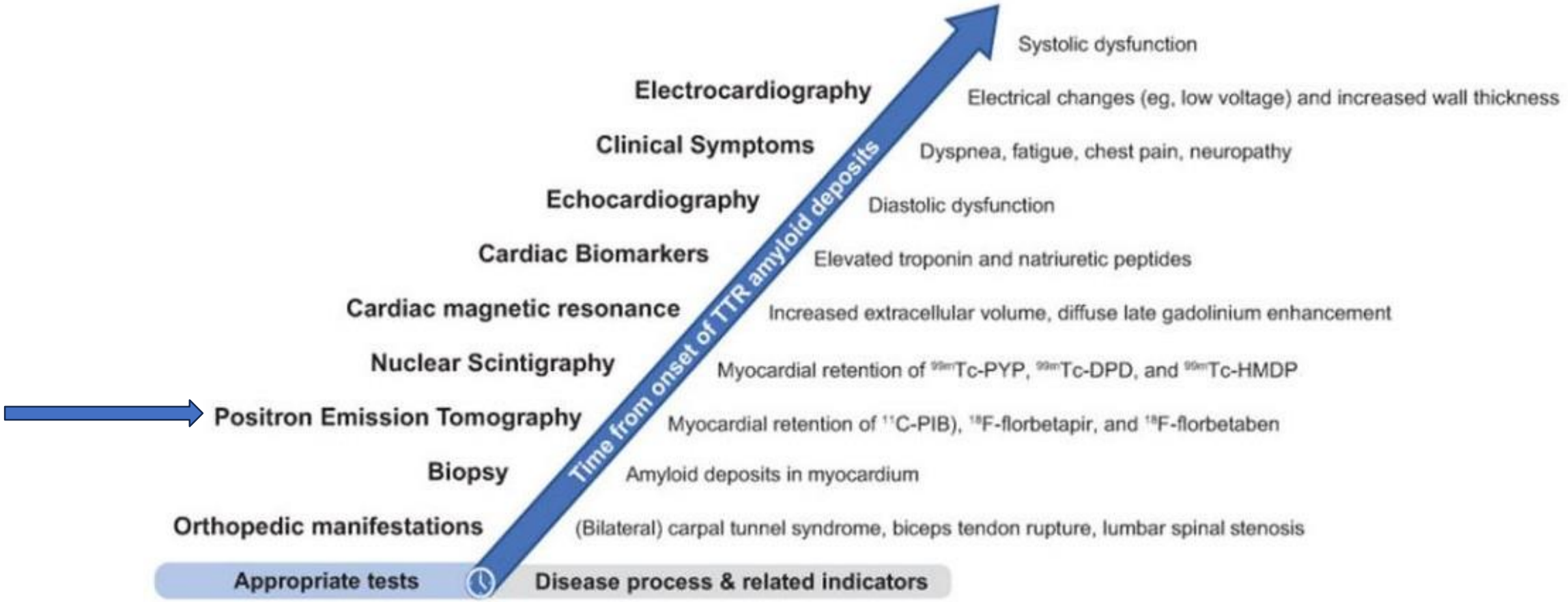


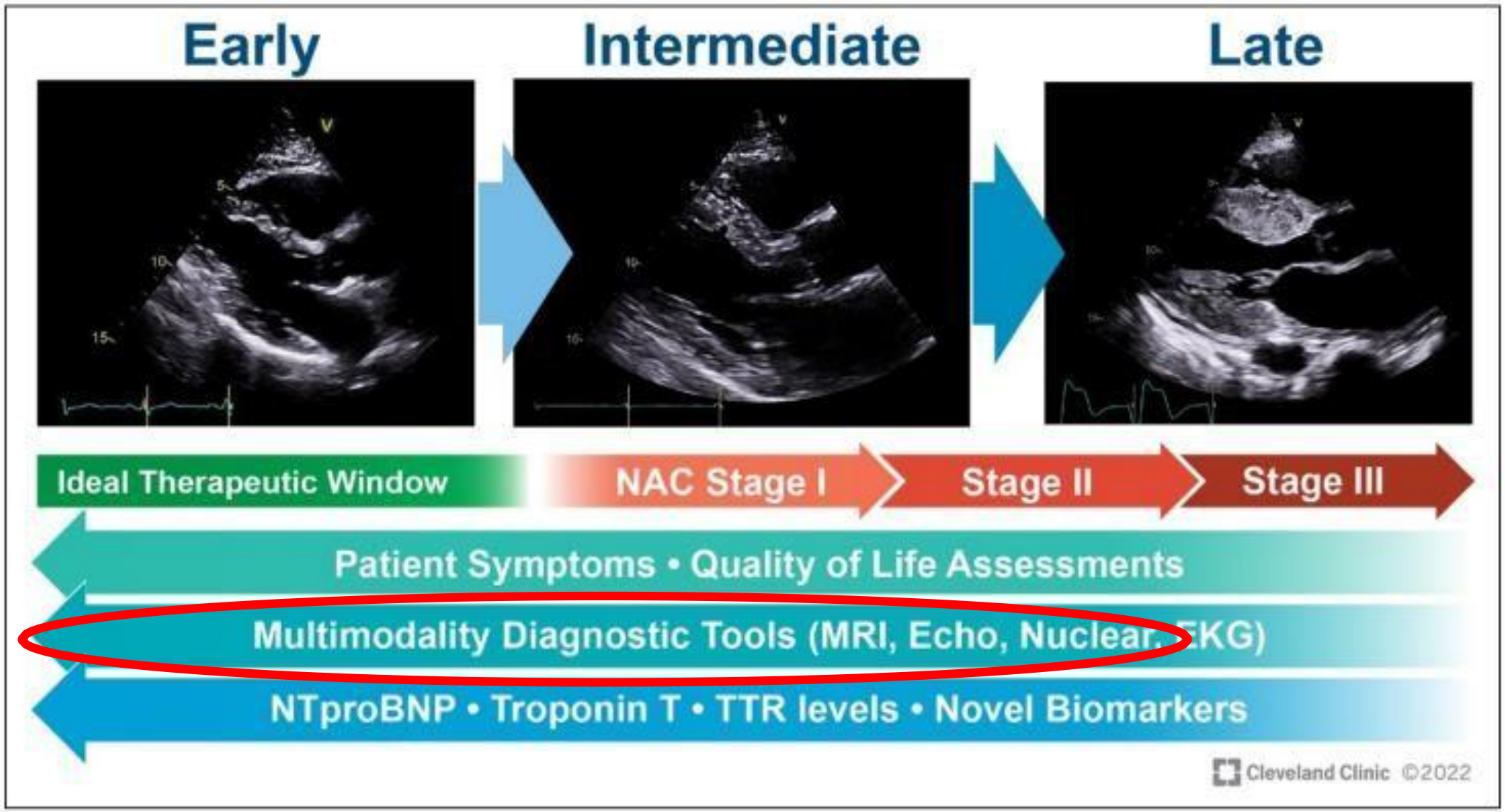
- Valve replacement was surgical in 63% and via transcatheter in 13%.
- Median follow-up in survivors was 33 (16;65) months.
- Mortality was of 44% (n=7).

Combination of AS and TTR-CA may occur in elderly patients particularly those with a low-flow low-gradient AS pattern and carries bad prognosis. Diagnosis of TTR-CA in AS is relevant to discuss specific treatment and management

Galat A et al, European Heart Journal 2016

Proposed timeline of appropriate diagnostic tests based on typical disease process




Early
Intermediate
Late
Ideal Therapeutic Window
NAC Stage I
Stage II
Stage III
Patient Symptoms • Quality of Life Assessments
Multimodality Diagnostic Tools (MRI, Echo, Nuclear, EKG)
NTproBNP • Troponin T • TTR levels • Novel Biomarkers
Cleveland Clinic ©2022

Role of cardiac imaging

Echocardiography, CMR and radionuclide tracer imaging (Single Photon Emission Tomography, SPECT, and Positron Emission Tomography, PET)

1) Diagnose cardiac amyloidosis

2) Prognosis

3)Confirm cardiac involvement in patients with known systemic amyloidosis

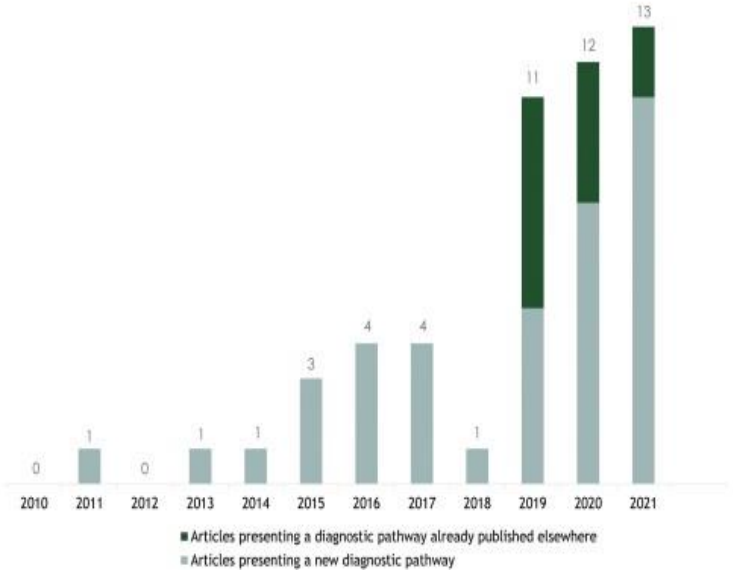
4) Monitor response to systemic therapy

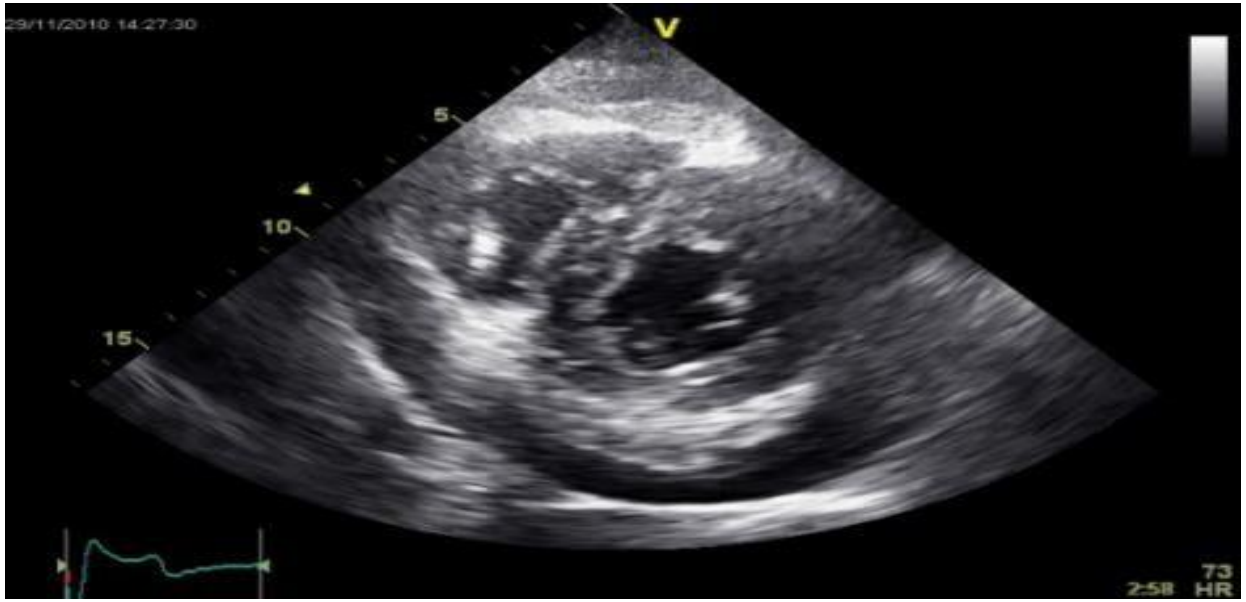
Suspicion, screening, and diagnosis of wild-type transthyretin amyloid cardiomyopathy: a systematic literature review

Katrine Bay[1,2], Finn Gustafsson[3], Michael Maiborg[4], Anne Bagger-Bahnsen[2], Anne Mette Strand[2], Trine Pilgaard[2] and Steen Hvitfeldt Poulsen[5]*

ECHO findings	
Ventricular wall thickening	44
Apical sparing global longitudinal strain pattern	36
Small pericardial effusion	28
Reduced global longitudinal strain	28
Biatrial enlargement/dilatation	27
Granular sparkling appearance of myocardium	25
Aortic stenosis	23
CMR findings	
Late gadolinium enhancement	43
Increased extracellular volume	36
Elevated native T1 mapping sequences	33
Diffuse subendocardial or transmural late gadolinium enhancement	30

Figure 3 Number of articles published between 2010 and November 2020 presenting a diagnostic pathway for wild-type transthyretin amyloid cardiomyopathy. Please note that the numbers of articles add up to 51 because the article by Dorbala *et al*. is divided into two publications.[47,48]





Multimodality Imaging : Finding, Stenghts and Limitations

Imaging modality	Findings in cardiac amyloidosis	Strengths	Limitations
Echocardiography	LVH	Readily available	No differentiation between CA subtypes
	Small LV cavity	Cheap	Variable image quality
	Large atria	High temporal resolution	Early findings in CA non-specific
	RV/LV systolic dysfunction	Identify other causes of LVH (AS, HCM, etc.)	
	Abnormal LV diastolic function	No radiation	
	Abnormal strain	Patient ease	
	Pericardial/pleural effusion		
Magnetic resonance imaging (MRI)	Similar morphologic findings to echocardiography (**Figure 2**)	Reproducible	Expensive
	Late gadolinium enhancement in atria and ventricles	Direct tissue characterization	Limited availability
	Pericardial/pleural effusion	No radiation	Special expertise required
	Atria dysfunction	Identify other causes of LVH (HCM, infiltrating disease)	Multiple patient specific exclusions (implants, claustrophobia, etc.)
	Interatrial septum thickening	Higher spatial resolution and multi-dimensional strain	
	Abnormal strain		
Cardiac scintigraphy (PYP, DPD, and HDMP)	Increased radiotracer uptake	Cheap	Radiation
	Increased H/CL ratio	Widely available	Mostly qualitative
		Ease of interpretation	Genetic variant uptake variability
		Differentiate amyloid subtype	
PET imaging	Increased radiotracer uptake	Quantitative assessment	Radiation
		Differentiate amyloid subtype	Expensive

AS, aortic stenosis; H/CL, heart/contralateral; HCM, hypertrophic cardiomyopathy; LV, left ventricle; LVH, left ventricular hypertrophy; PET, positron-emission tomography.

EXPERT CONSENSUS RECOMMENDATIONS

ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/ SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis Part 1 of 2—Evidence Base and Standardized Methods of Imaging

Parameter for Acquisition and Reporting	Abnormal Parameter	Notes	Recommendations for Reporting
2D, Color, and Spectral Doppler Imaging			Required
LV wall thickness	Increased LV wall thickness (>1.2 cm) and increased relative wall thickness (>0.42)	Increased LV wall thickness relative to ECG QRS voltage is particularly suggestive	Required
Myocardial echogenicity	Increased echogenicity of the myocardium (sparkling, hyper-refractile "texture" of the myocardium)	Not highly specific (differential diagnosis includes ESRD or other infiltrative cardiomyopathies). However, this finding in conjunction with severely reduced longitudinal function of the LV is highly suggestive.	Required
Atrial size and function	Atrial enlargement and dysfunction	Non-specific but important finding to support the diagnosis and potentially provide insight into risk for stroke or arterial embolism	Required
Interatrial septum and valves	Thickening of the interatrial septum and valves (>0.5 cm)	Non-specific but suggestive of the diagnosis	Required
Pericardial effusion	Pericardial effusion	Non-specific, but when coupled with other echo signs is suggestive of the diagnosis	Required
Diastolic function	Grade 2 or wo high E/A ratio (eration time (<	elpful in determining A wave velocity can be e helpful in determining	Required
Estimated PA systolic and right atrial pressure	Increased pres ≥10mmHg for	rs to estimate volume osing.	Required
Tissue Doppler Imaging			Required
Tissue Doppler velocities	Reduced tissue ties (all <5 cm/	l TDI velocities <5 cm/s) ighly suggestive of the sitive for the diagnosis in	Required
Strain Imaging			Recommended
Longitudinal LV strain	Decreased glo solute value les	istic appearance of ients with cardiac amy-	Recommended
Longitudinal LV strain bulls-eye map	"Cherry-on-the- strain bullseye longitudinal str basal and mid-	n is likely the most gnosis of cardiac amy- erentiate ATTR vs. AL	Recommended

An overall interpretation of the echo findings into categories of:

- ❑ **Not suggestive: Normal LV wall thickness, <u>normal LV mass</u> normal atrial size, septal or lateral tissue Doppler e' velocity >10 cm/s**
- ❑ **Strongly suggestive: Increased LV wall thickness, increased LV mass, typical LV longitudinal strain pattern, mitral annular TDI**

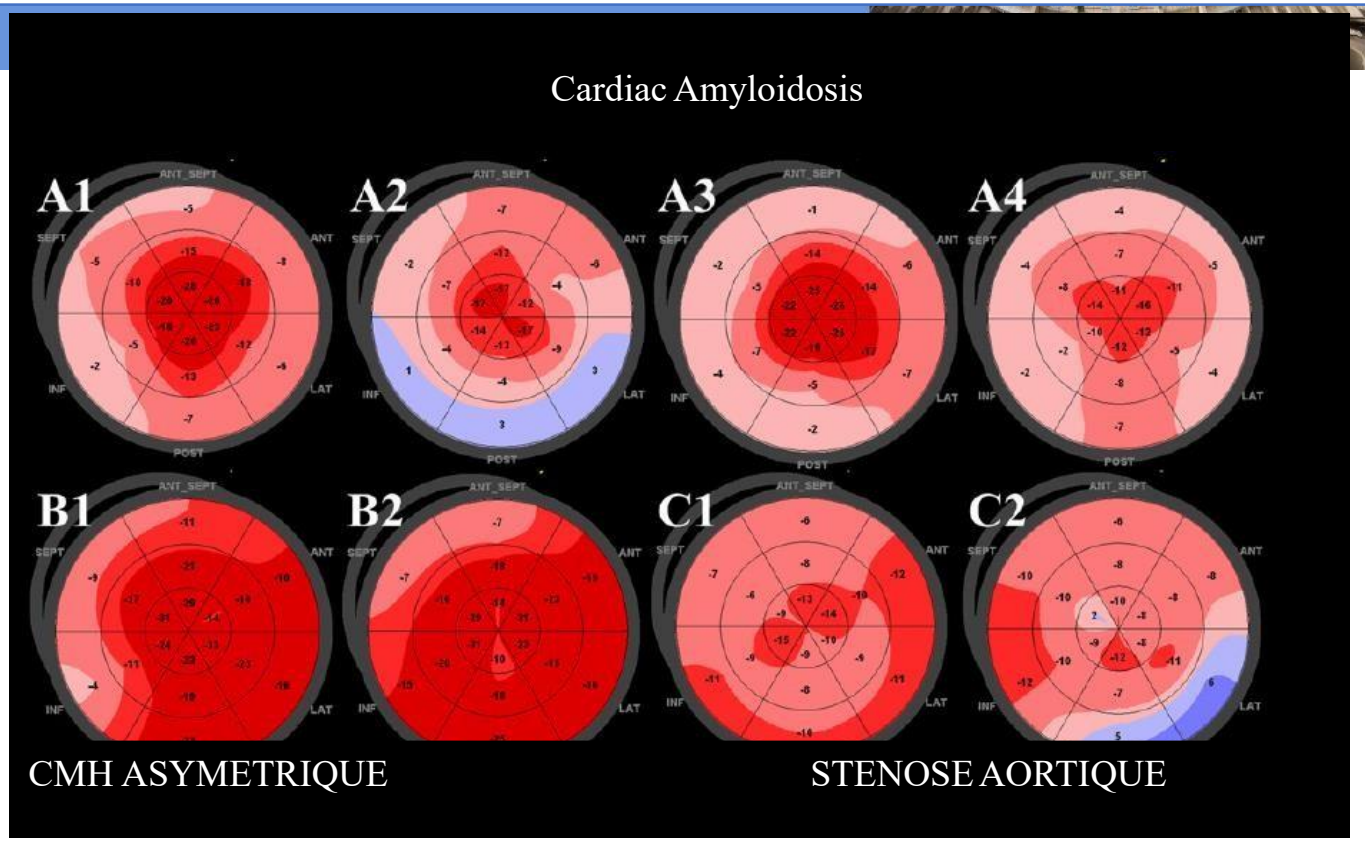
Amylodosis and longitudinal strain

CA vs HCM vs AS

Variable	CA	HCM	AS	P	LVH	P
Echo Parameters:						
Ejection Fraction (%)	47 ± 12	63 ± 5*	48 ± 14	<0.001	55 ± 13	0.003
MWT (mm)	16.9 ± 2.8	15.8 ± 3.6	15.7 ± 1.7	0.21	15.8 ± 2.7	0.07
LMVI (g/m²)	149 ± 41	131 ± 46	160 ± 45	0.16	145 ± 47	0.70
LAVI (ml/m²)	39.3 ± 10.1	40.0 ± 14.2	45.5 ± 13.3	0.053	42.2 ± 13.9	0.32
E (m/s)	0.86 ± 0.26	0.86 ± 0.27	1.0 ± 0.26	0.13	0.94 ± 0.27	0.20
A (m/s)	0.49 ± 0.27	0.94 ± 0.29*	0.70 ± 0.24*	<0.001	0.84 ± 0.29	<0.001
E/A	2.20 ± 1.1	0.95 ± 0.3*	1.56 ± 0.8	<0.001	1.22 ± 0.65	<0.001
Average e' (m/s)	4.2 ± 1.7	5.9 ± 1.7*	5.7 ± 2.0*	<0.001	5.8 ± 1.8	<0.001
E/e'	24.1 ± 12.7	15.3 ± 5.9*	20.3 ± 9.9	0.02	17.8 ± 8.4	0.008
DT m/s	183 ± 45	244 ± 64*	206 ± 65	0.001	226 ± 66	0.003
Global LS	-8.9 ± 3.7	-17.5 ± 3.4*	-12.4 ± 3.8*	<0.001	-14.9 ± 4.4	<0.001

No difference between LVH/ LVEF

Diastolic Function + GLS more altered If CA



« APICAL Sparing » Longitudinal strain

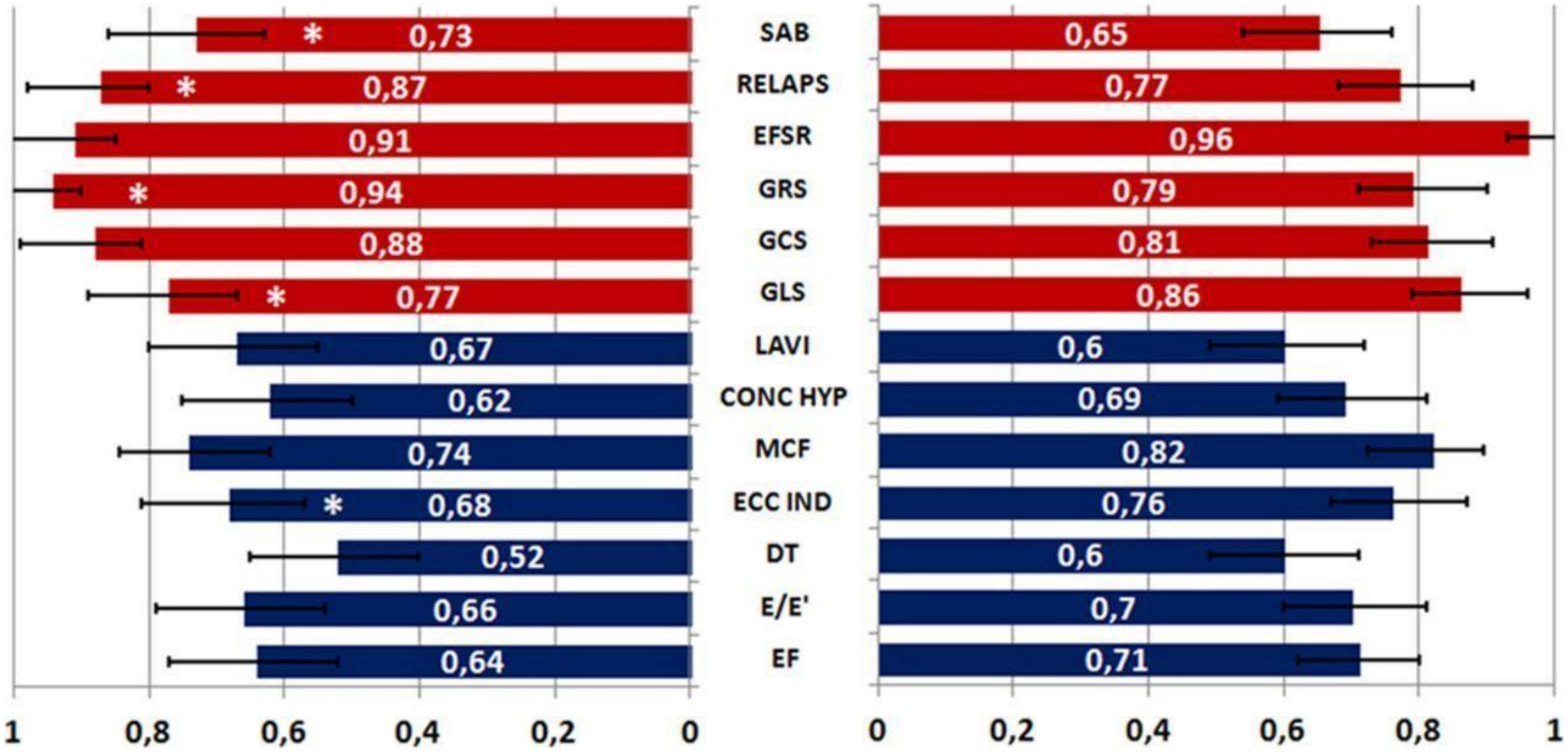
Ratio : $\frac{\text{Apical Strain}}{\text{Strain L basal + médian}}$

>1 = Cardiac Amyloidosis

Se : 93% Sp: 82%.

Phelan et al, Heart 2012

Amylodosis and longitudinal strain



CA, n=40
HMC, n=40
HBP, n=20

AUC ROC :
SAB : strain LVS apical / basal
RELAPS : ratio apical/basal
EFSR : LVEF/GLS
GRS : radial
SG GCS : circonferential
SG GLS : GLS
LAVI : LA volume
CONC HYP : concentric LVH
MCF : Myocardial contraction Fraction
DT : Deceleration Time
ECC IND : (LVS/Pw)

Ratio LVEF / GLS > 4.1 (Se 90% ; Sp 92%)
THE BEST ECHOCARDIOGRAPHIC INDEX ?

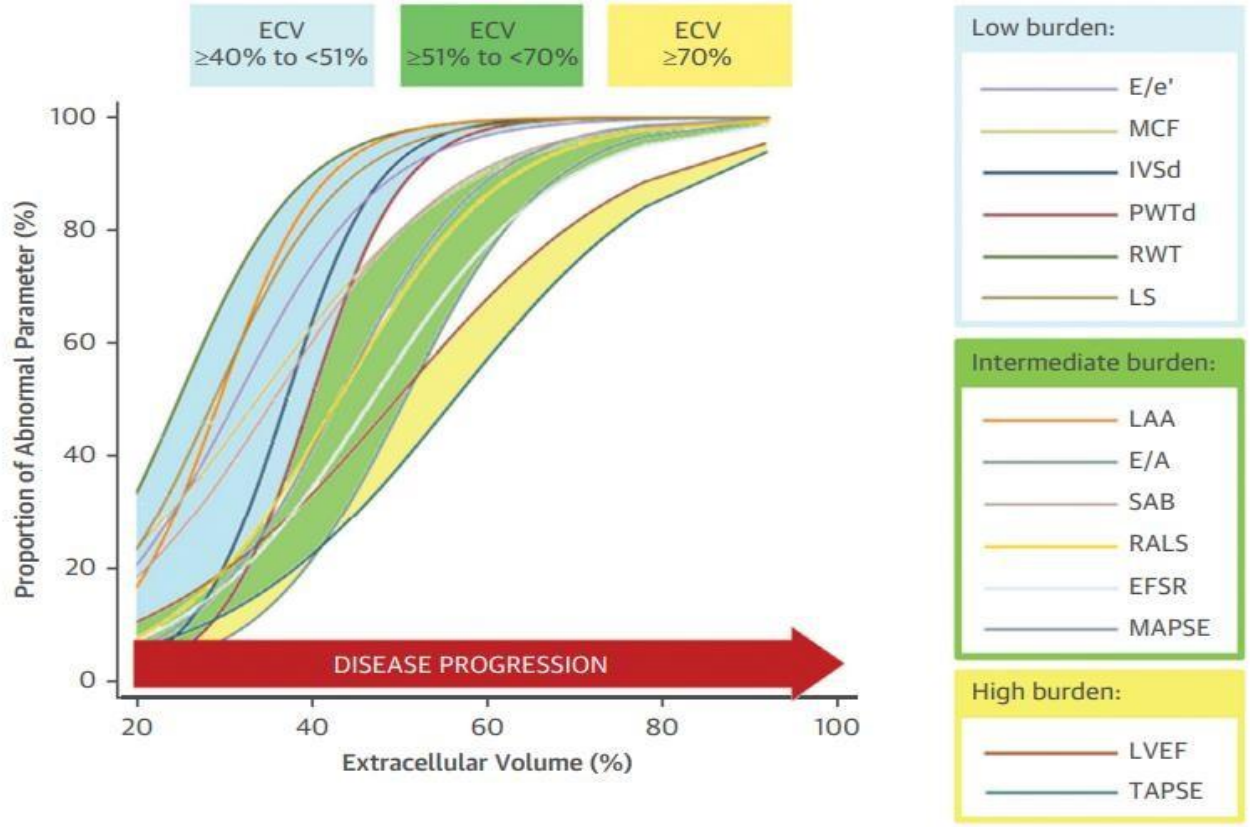
Pagourelias ED, Circ Cardiovasc Imaging, 2017

Echocardiography : Multi-Parametric Scores

- Aimo and colleagues developed a simpler echocardiographic score to maximize specificity of the diagnosis.
- The Amyloidosis Index (AMYLI) score equals RWT × E/e'
- limitation: exclusion of patients in atrial fibrillation during echocardiogram.
- A cutoff >2.36 in patients with systemic AL amyloidosis and <2.22 in unexplained LVH excluded CA

Multiparametric Echocardiography Scores for the Diagnosis of Cardiac Amyloidosis

FIGURE 1 Abnormal Echocardiographic Parameters According to ECV Values

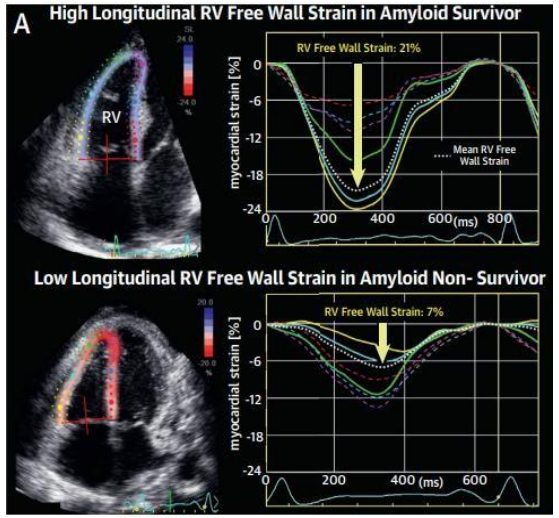


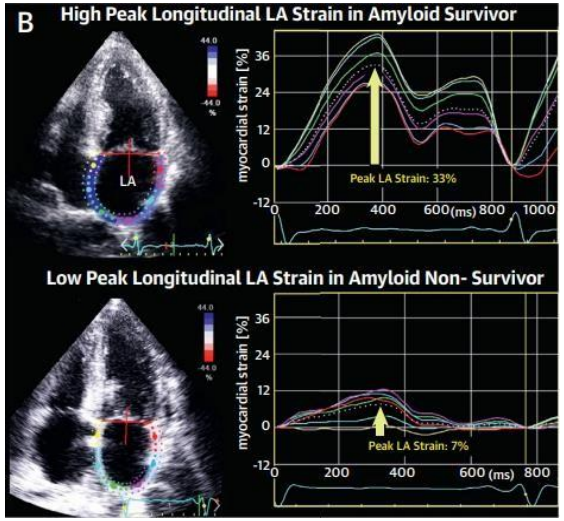
- The probability of cardiac structural and functional variables being abnormal across the spectrum of cardiac amyloid burden (as defined by ECV).
- Variables can be categorized into 3 groups according to their likelihood of being abnormal: either predominantly at low, intermediate, or high burden of amyloid infiltration.

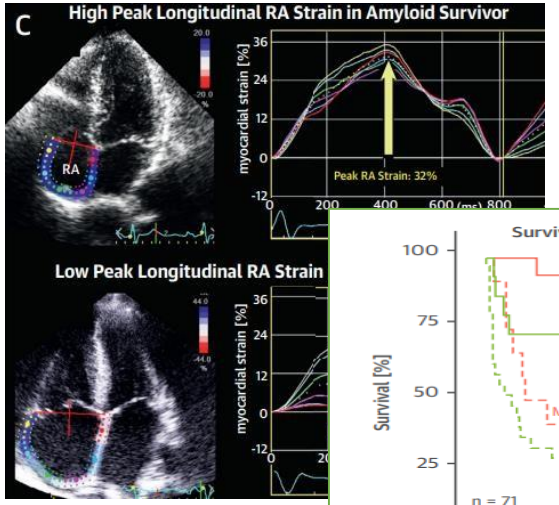
SGLS 10.4%

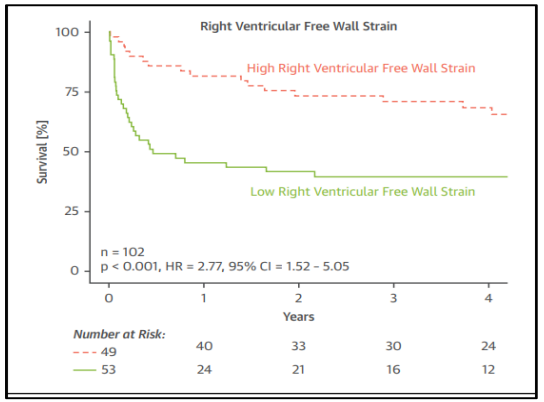
Prognostic Utility of Echocardiographic Atrial and Ventricular Strain Imaging in Patients With Cardiac Amyloidosis

Peter R. Huntjens, PhD,[a] Kathleen W. Zhang, MD,[a] Yuko Soyama, MD, PhD,[a] Maria Karmpalioti, MD,[a] Daniel J. Lenihan, MD,[a] John Gorcsan III, MD[b]

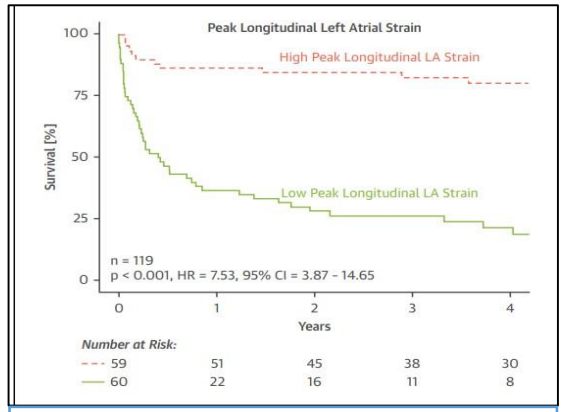




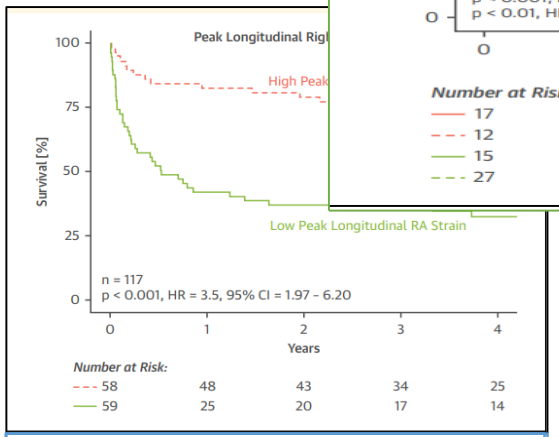




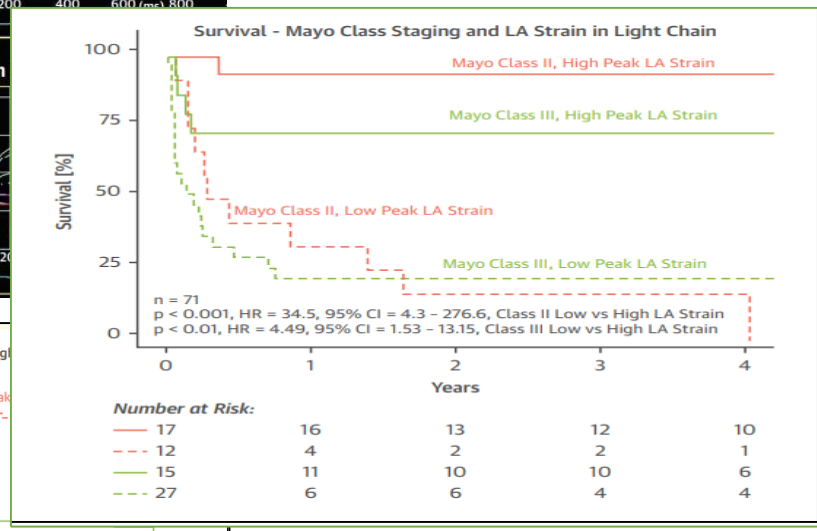
RV St 17%



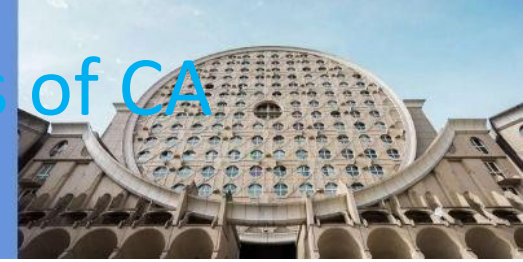
LAS 13%



RAS 12.4%



JACC: CARDIOVASCULAR IMAGING, VOL. 14, NO. 8, 2021
AUGUST 2021:1508–19



summary of Diagnosis and prognostic parameters of CA

Index	CA possibility	Sensitivity	Sensitivity	Reference
Possible diagnosis of CA				
Apical sparing	Possible CA	93%	82%	[40]
LVEF/GLS > 4.95	Possible CA	75%	66%	[44]
GLS ≤ 16.10%	Possible CA	92.9%	93.7%	[45]
GAS ≤ 32.95%	Possible CA	81%	53.1%	
GLS ≤ 16.09%	Possible CA in AL	94.23%	87.5%	[46]
GAS ≤ 36.54%	Possible CA in AL	86.54%	80%	
GRS ≤ 31.90%	Possible CA in AL	80.8%	47.5	
GAS < 19.4%	Possible CA	67.70%	75%	[47]
RV apical ratios > 0.8	Differentiating AL-CA and ATTR-CA	97.80%	90%	[51]
GWE < 86.5%	Differentiating AL-CA and ATTR-CA	80%	66.7%	[57]
Poor prognosis of CA				
GAS < −19%	HR = 1.23	–	–	[47]
Basal longitudinal strain ≤ 13.07%	HR = 0.812 (0.675–0.976)	–	–	[48]
LVMWI < 1039 mmHg%	HR = 6.4 (2.4–17.1)	–	–	[58]
LVMWE < 89%	AUC = 0.689 (0.597–0.771)	65%	48%	[60]
MCF < 25%	HR = 5.369 (2.4–1.817–15.86)	–	–	[62]

AL-CA light-chain cardiac amyloidosis, *ATTR-CA* transthyretin-related cardiac amyloidosis, *CA* cardiac amyloidosis, *GLS* global longitudinal strain, *GAS* global area strain, *GRS* global radical strain, *GWE* global work efficiency, *LVEF* left ventricular ejection fraction, *LVMWI* left ventricular myocardial work index, *LVMWE* left ventricular myocardial work efficiency, *MCF* myocardial contraction fraction

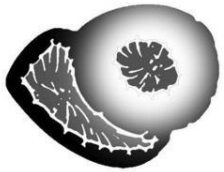
Advance of echocardiography in cardiac amyloidosis Shichu Liang1 · Zhiyue Liu1 · Qian Li1 · Wenfeng He1 · He Huang

CMR & cardiomyopathy

ESC Cardiomyopathy Guidelines 2023

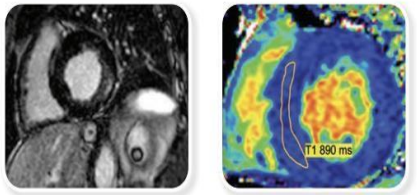
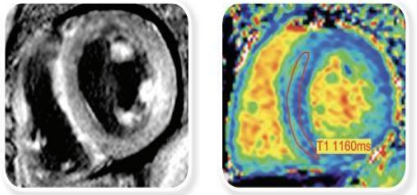
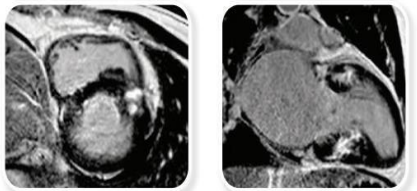
Recommendation Table 5 — Recommendations for cardiac magnetic resonance indication in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
Contrast-enhanced CMR is recommended in patients with cardiomyopathy at initial evaluation.[10,90,116,119–143]	I	B



Transmural LGE
- Amyloidosis

Global Subendocardial LGE
- Amyloidosis
-Systemic Sclerosis
- Post Heart Transplantation

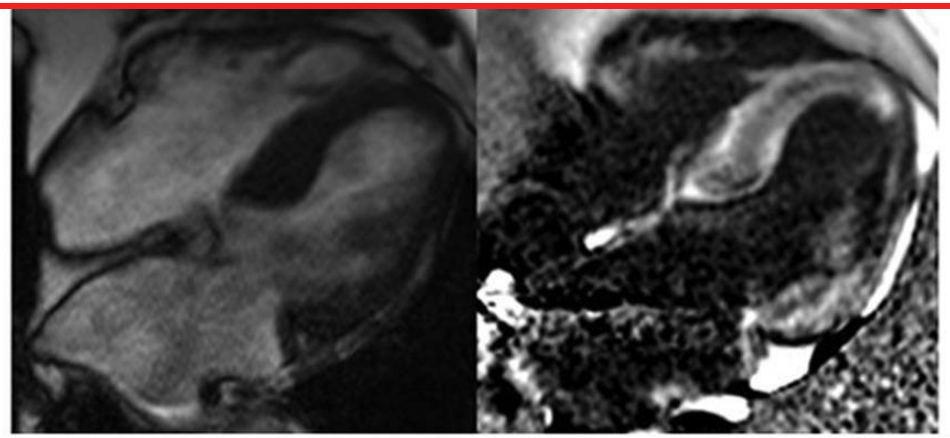
Cardiomyopathy phenotype	Finding	Cardiac CMR examples	Specific diseases to be considered
HCM	Posterolateral LGE and concentric LVH Low native T1		Anderson–Fabry disease
	Diffuse subendocardial LGE, high native T1		Amyloidosis
	Patchy mid-wall in hypertrophied areas		Sarcomeric HCM

Always specify for LGE + T1/T2 + ECV !

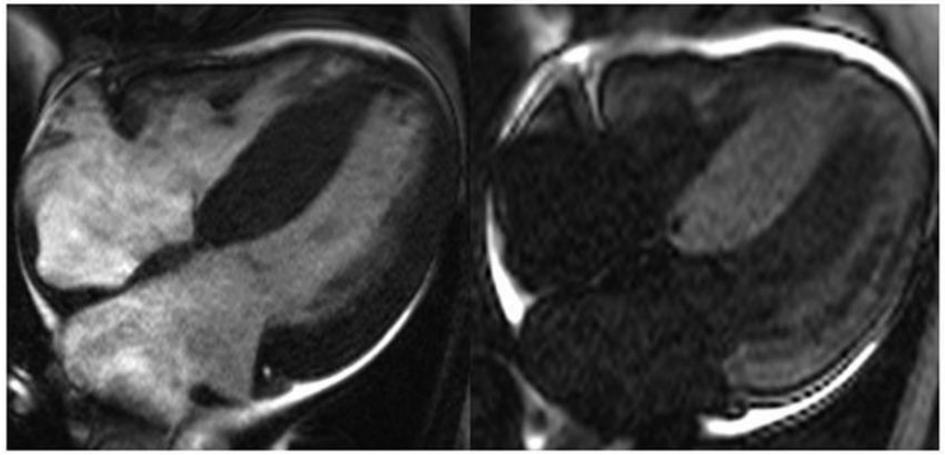
CMR: morphological analysis

Cine-CMR: morphological analysis > patterns of left ventricule hypertrophy

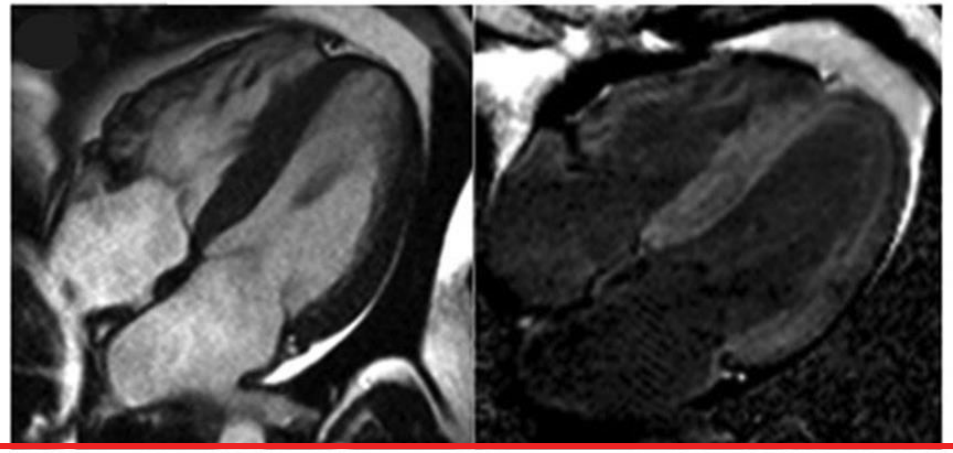
Asymmetric hypertrophy. Sigmoid septal contour (55%)



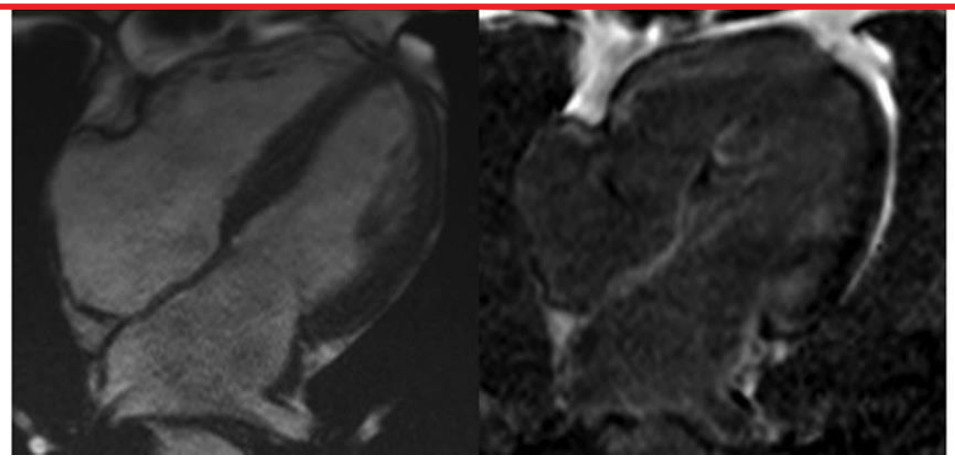
Asymmetric hypertrophy. Reverse septal contour (24%)



Symmetric hypertrophy (18%)



No LVH (3%)

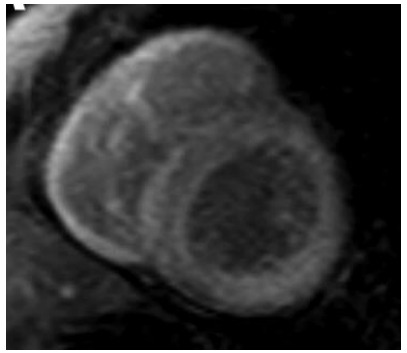


Ana Martinez Naharro, JACC, 2017

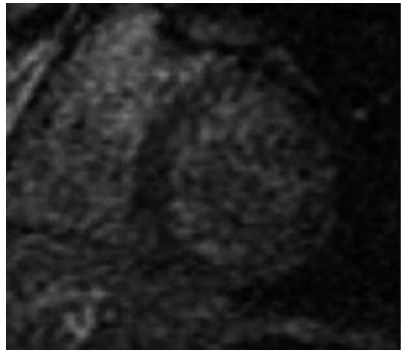
CMR: late gadolinium enhancement

Diffuse enhancement 49 %

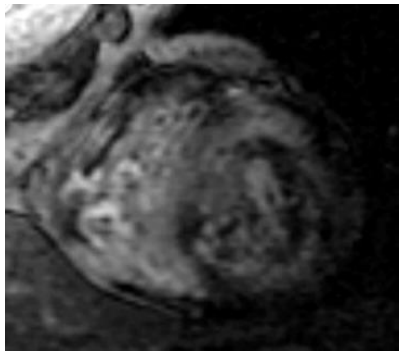
Transmural & homogenous



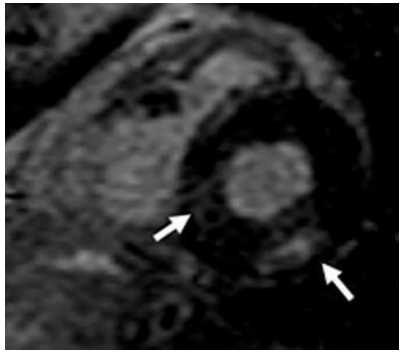
Suboptimal myocardial nulling (16%)



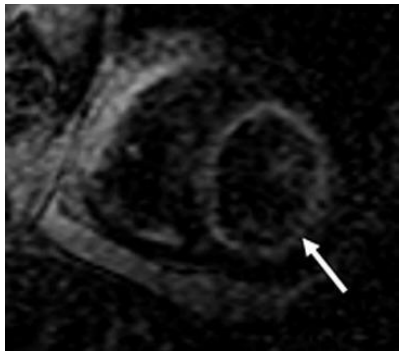
Transmural & heterogeneous



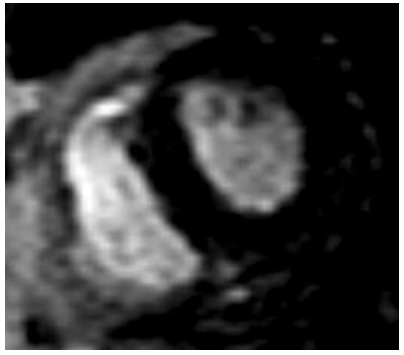
Patchy focal 14% (posterior/basal+++)



Subepicardial

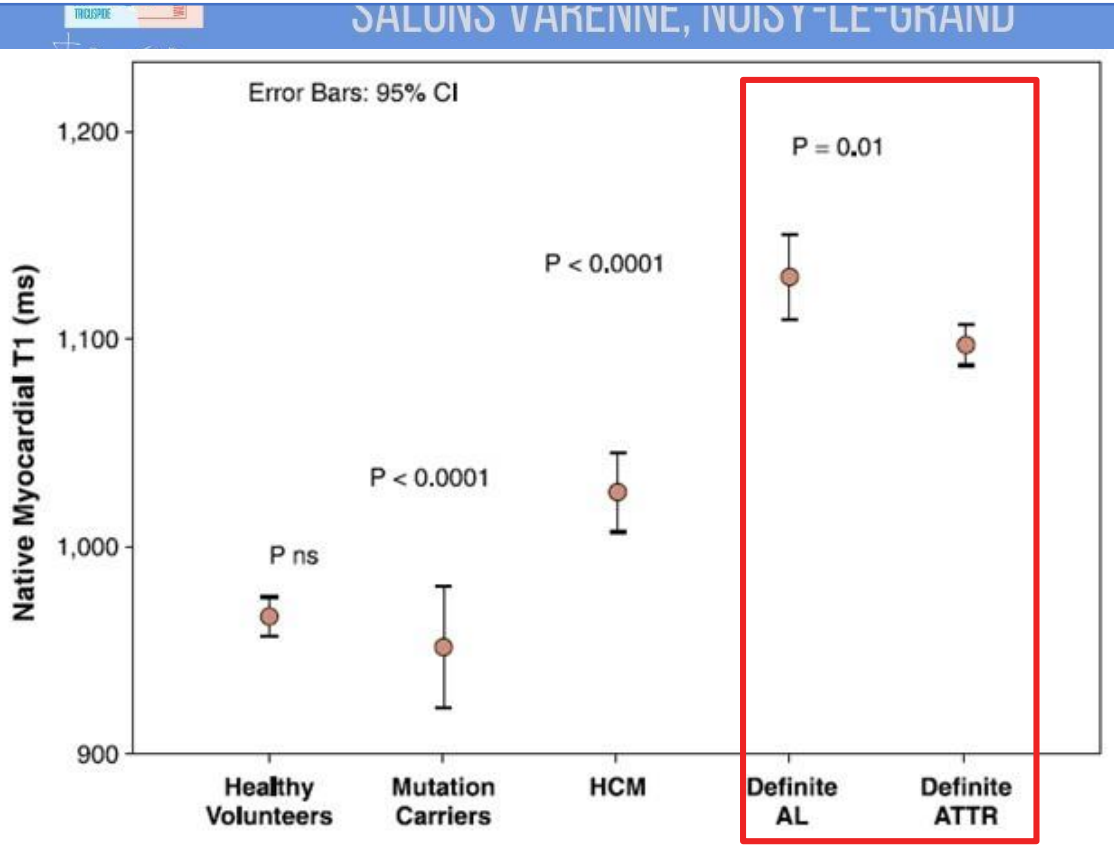


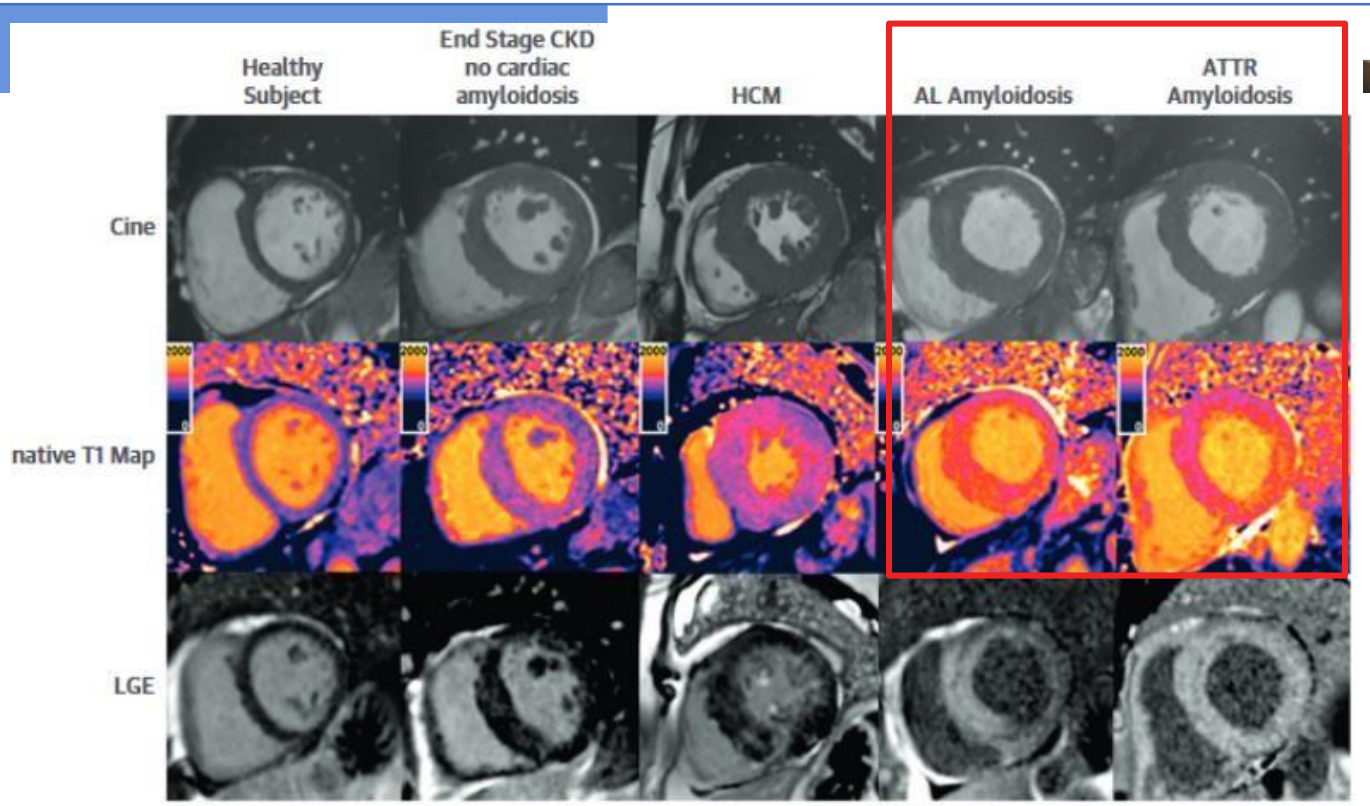
None 21%



Syred IS, JACC CV Imaging, 2010

CMR: Native T1 mapping (before gadolinium)





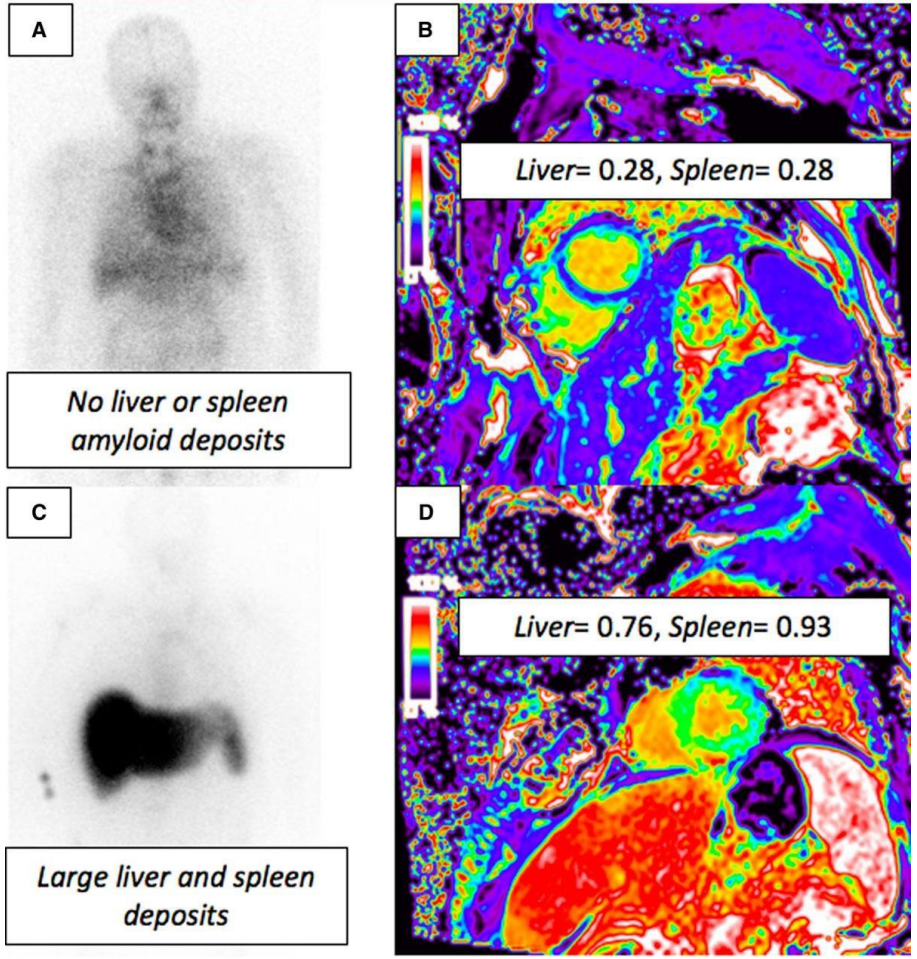
- **Native T1 is higher in cardiac amyloidosis (AL > ATTR-CA) then others HCM**
- **<u>Example cut-off values to diagnose CA:</u>**
  - **1,048 ms (Se 80%-Sp 83%)**
  - **< 1,036 (98% NPV) ; > 1,164 (98% PPV)**

<u>Limits:</u> T1 depends of vendor, type of gadolinium, HR, magnetic field, eGFR …
<u>Advantage:</u> no gadolinium!

Fontana M et al, JACC Imaging, 2014

Baggiano A, JACC Imaging, 2020

Extracardiac amyloidosis and MRI



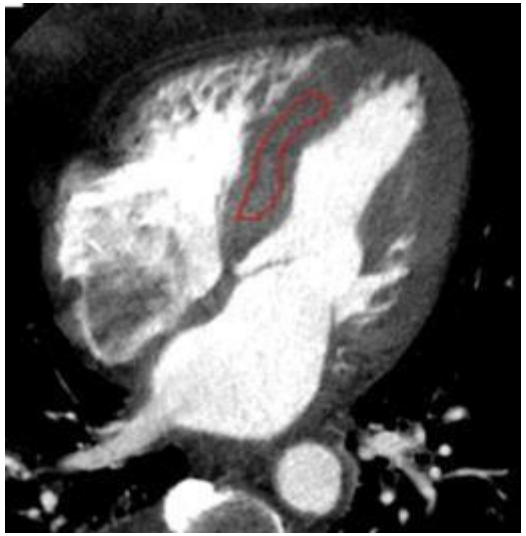
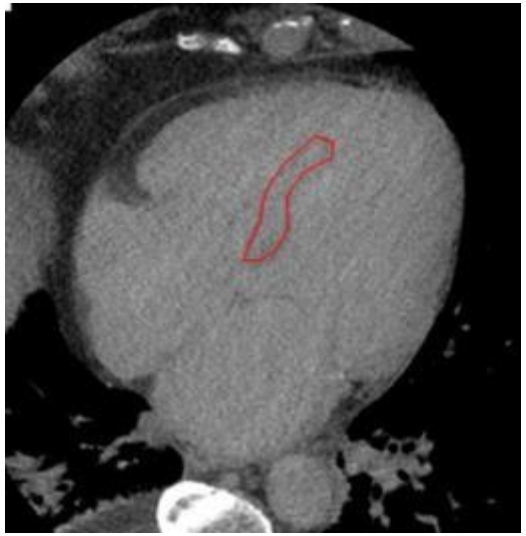
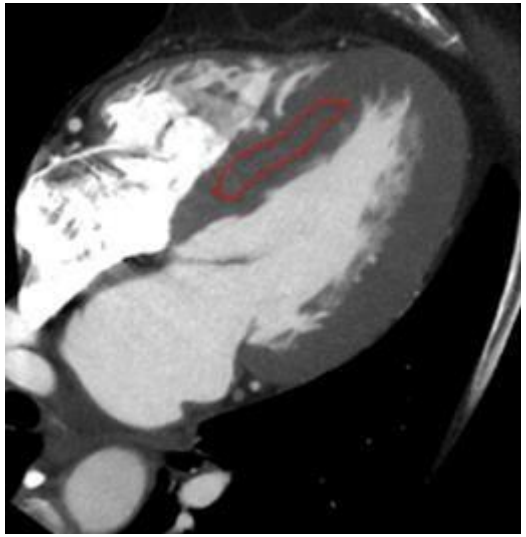
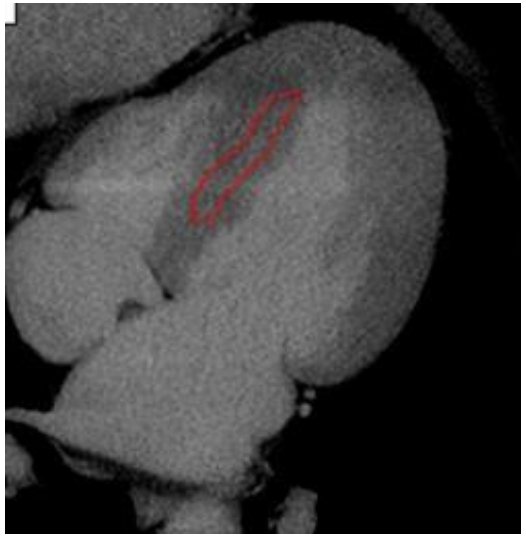
- **Spleen & Liver ECV mapping is possible on CMR**
- **ECV can detects splenic & hepatic amyloidosis.**

Liver ECV cutoff, 0.395; Se 90.7%; Sp, 77.7%; *P*<0.001;
Spleen ECV cutoff, 0.385; Se, 93.6%; Sp, 87.5%; *P*<0.001).

Chacko L, Circulation CV Imaging, 2021

Computed tomography scan

CT scan

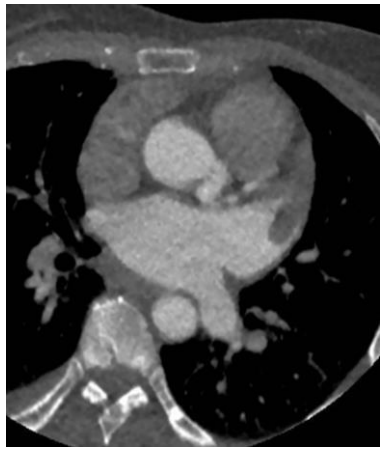
	Arterial	Late (5 min)
Cardiac amyloidosis		
Hypertensive heart disease		

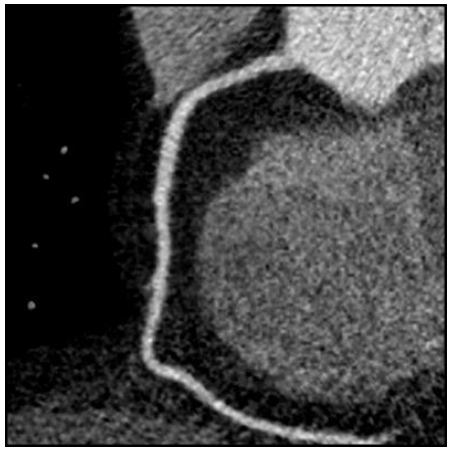
Morphological analysis (id CMR/TTE)

Late iodine enhancement / ECV (id CMR)

Atrial thrombus ?

Coronary heart disease ?





Chevance V, Eur Radio, 2018

Nuclear imaging

Recommendations	Class[a]	Level[b]
DPD/PYP/HMDP bone-tracer scintigraphy is recommended in patients with suspected ATTR-related cardiac amyloidosis to aid diagnosis.[166–168]	I	B

Bone scintigraphy

ESC Cardiomyopathy Guidelines 2023

Late phase of DPD/HMDP scan for diagnosis

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)	p Value (Kruskal-Wallis Test/ Contigency Tables)
Heart tracer retention (%)				
Median	7.3*†	3.8‡	2.9	0.0001
Interquartile range	6.7–8.4	3.4–4.05	2.7–3.5	
Whole-body tracer retention (%)				
Median	70.1†	67.6‡	56	0.010
Interquartile range	63.6–77.3	61.8–71.3	52–60	
Heart/whole-body ratio				
Median	10.0*†	5.4	5.4	0.0001
Interquartile range	8.9–11.2	5.2–5.5	5.0–5.7	
Visual cardiac score				
0	0 (0%)	10 (100%)	10 (100%)	0.0001
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.

DPD scan seemed to discriminate TTR-CA from AL-CA with perfect accuracy … ?

Perugini E, JACC, 2005

Late phase of DPD/HMDP scan for diagnosis

Amyloid type (*n*)	Cardiac ^{99m}Tc-DPD uptake			
	Grade of myocardial uptake *n* (%)			
	0	1	2	3
$ATTR_{wt}$ *n* = 94	1 (1)	5 (5·5)	81 (86)	7 (7·5)
ATTR-Val122Ile *n* = 38	0	0	23 (61)	15 (39)
$ATTR_{mt}$ (total) *n* = 46	6 (13)	7 (15)	26 (57)	7 (15)
Val30Met *n* = 12	6 (50)	1 (8)	5 (42)	0
AL *n* = 44	26 (59)	17 (39)	1 (2)	0
AA *n* = 3	2 (67)	1 (33)	0	0
ApoA1 *n* = 5	1 (20)	4 (80)	0	0
AFib *n* = 2	2 (100)	0	0	0
ALys *n* = 1	1	0	0	0
Unknown *n* = 2	1 (50)	1 (50)	0	0

HMDP	AL (N = 26)	TTR (N = 39)	LVH (N = 20)
Perugini score			
Score 0	24 (92%)	0	20 (100%)
Score 1	2 (8%)	3 (7%)	0
Score 2	0	16 (41%)	0
Score 3	0	20(52%)	0

HMDP

All with CA	AL	m-TTR	wt-TTR
N	14	26	21
Visual cardiac score			
Score 0, *n* (%)	13 (93)	2 (8)	0 (0)
Score 1, *n* (%)	1 (7)	5 (19)	1 (5)
Score 2, *n* (%)	0 (0)	14 (54)	16 (76)
Score 3, *n* (%)	0 (0)	5 (19)	4 (19)

- **Diffuse heart uptake = cardiac amyloidosis.**
- **Mild uptake (Score 1) = AL / ATTR-CA ? AL > 7-41% of AL CA have a positive scan.**
- **Moderate to strong uptake (Score 2/3) = ATTR-CA >> AL (if no clone).**

Hutt DF, EHJ CV imaging, 2014

Galat A, Amyloid, 2015

Capelli F, JNC, 2017

Nonbiopsy diagnosis of TTR-CA

Table 5. Combined Radionuclide 'Bone' Scintigraphy and Monoclonal Protein Studies Compared With Amyloid Histology

Grade 2 or 3 Radionuclide Scan+Absence of Clone vs ATTR Amyloid Deposits on Histology From Any Organ (n=1217)				
	Grade 2/3 Scan+No Clone, n	Grade 0/1 Scan or Clone, n	Sensitivity and Specificity (CI), %	PPV and NPV (CI), %
Cardiac ATTR amyloid	391	139	74 (70–77) sensitive*	NPV, 83 (80–86)
No cardiac ATTR amyloid	0	687	100 (99–100) specific	PPV, 100 (99–100)

Visual score ≥2 DPD/HMDP scan & no clone = ATTR cardiac amyloidosis (PPV 100% ; Se 74%)

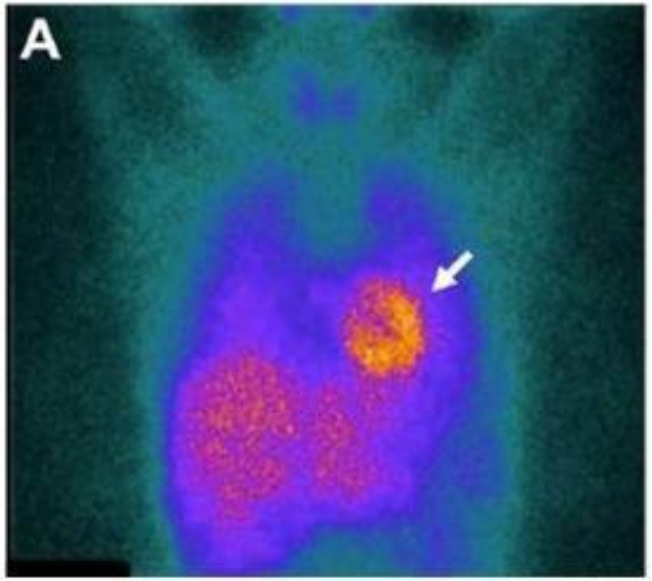
Histology is not mandatory anymore to diagnose ATTR-CA

Gillmore JD, Circulation, 2016

Others radiotracers

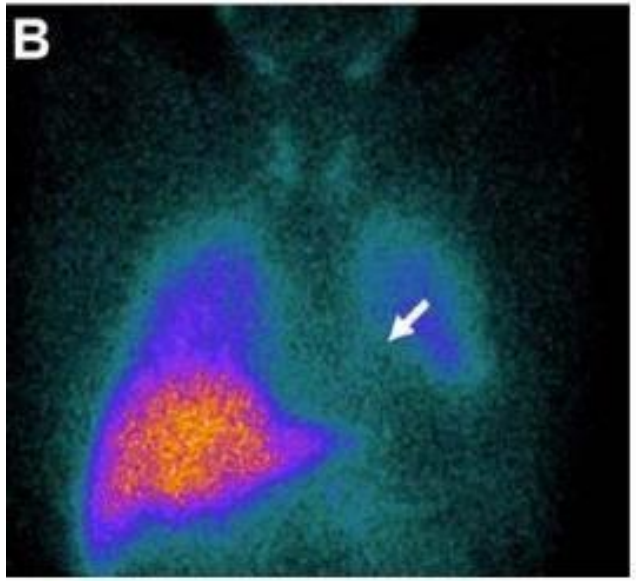
MIBG

- Cardiac sympathetic denervation is a useful prognostic marker in hTTR V30M
- Could be abnormal in early stage of CA in TTR mutated carriers

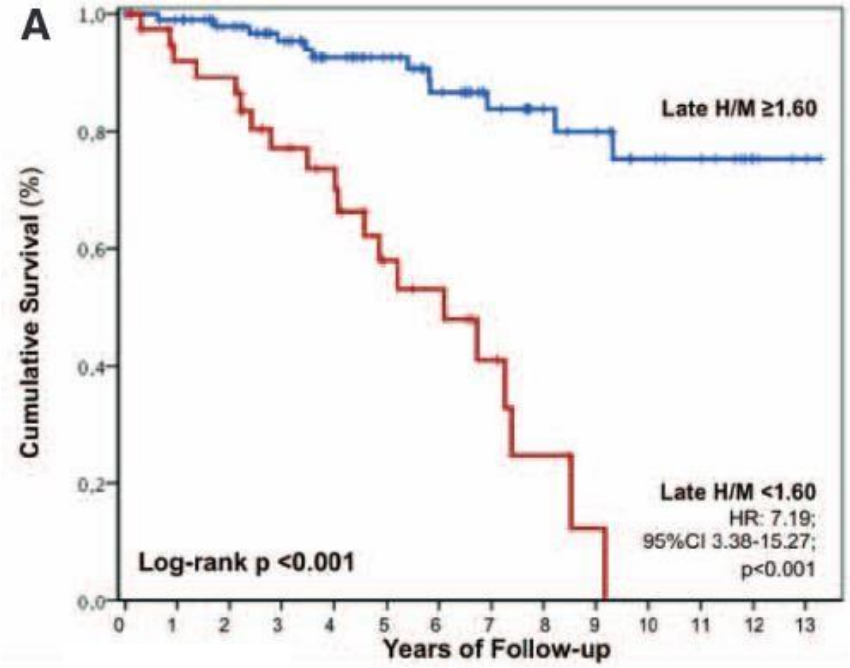


TTR V30M asymptomatic carrier
H/M = 2,5

Piekarski, EJNMMI, 2018



TTR V30M
H/M = 1,2

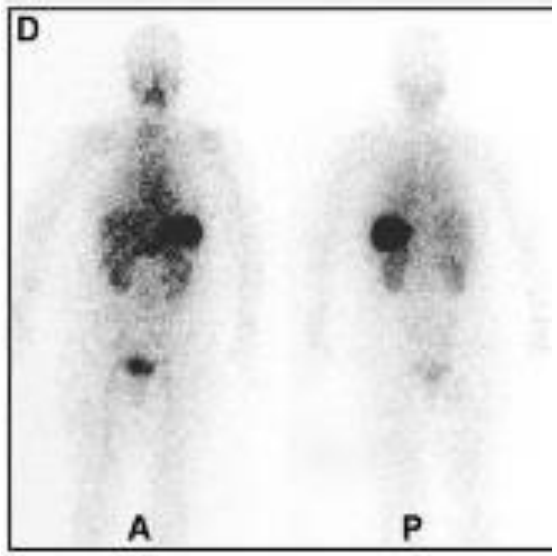


Coutinho MC, Circ Cardiovasc Imaging, 2013

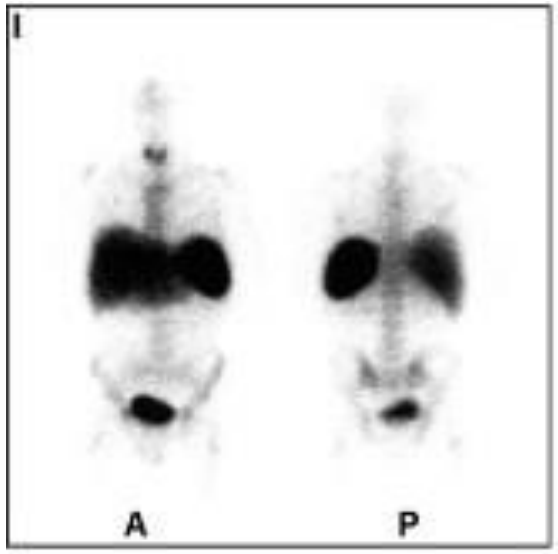
Others radiotracers

123I-labeled serum amyloid P component (SAP)

- Show extra-cardiac involvement of amyloidosis.
- Sensitive to diagnose AA and AL amyloidosis. Less sensitive for TTR.



Spleen and kidney uptake (AA)



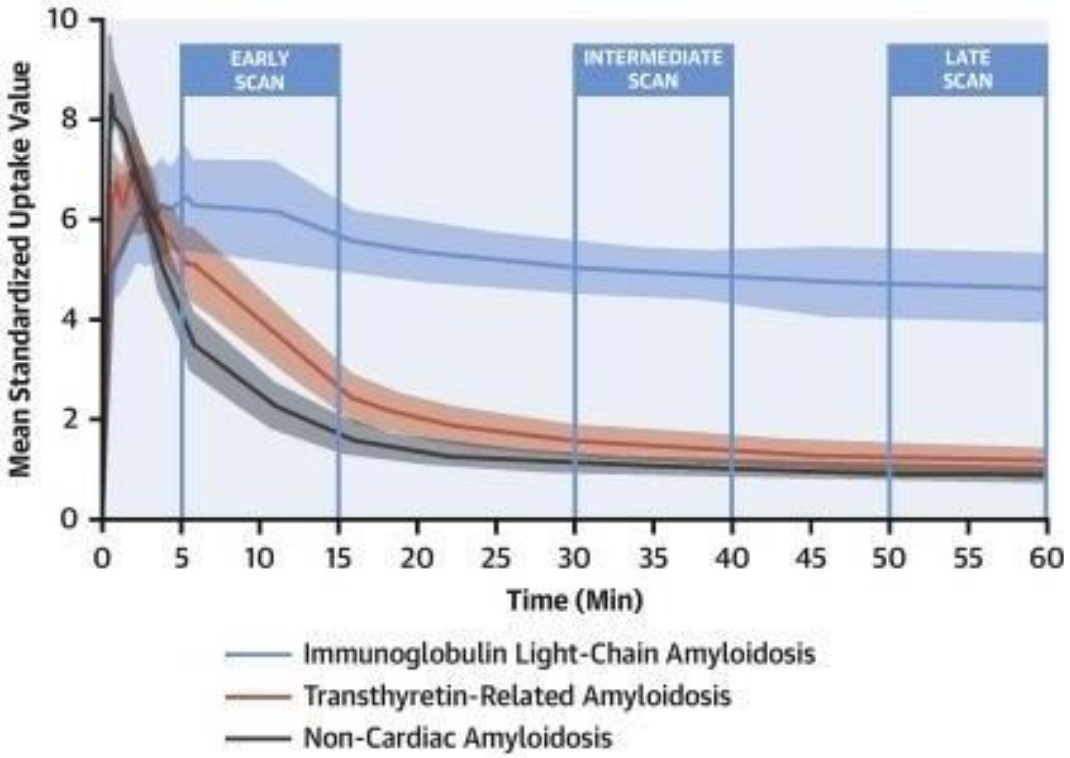
Spleen, liver, and bone marrow (AL)

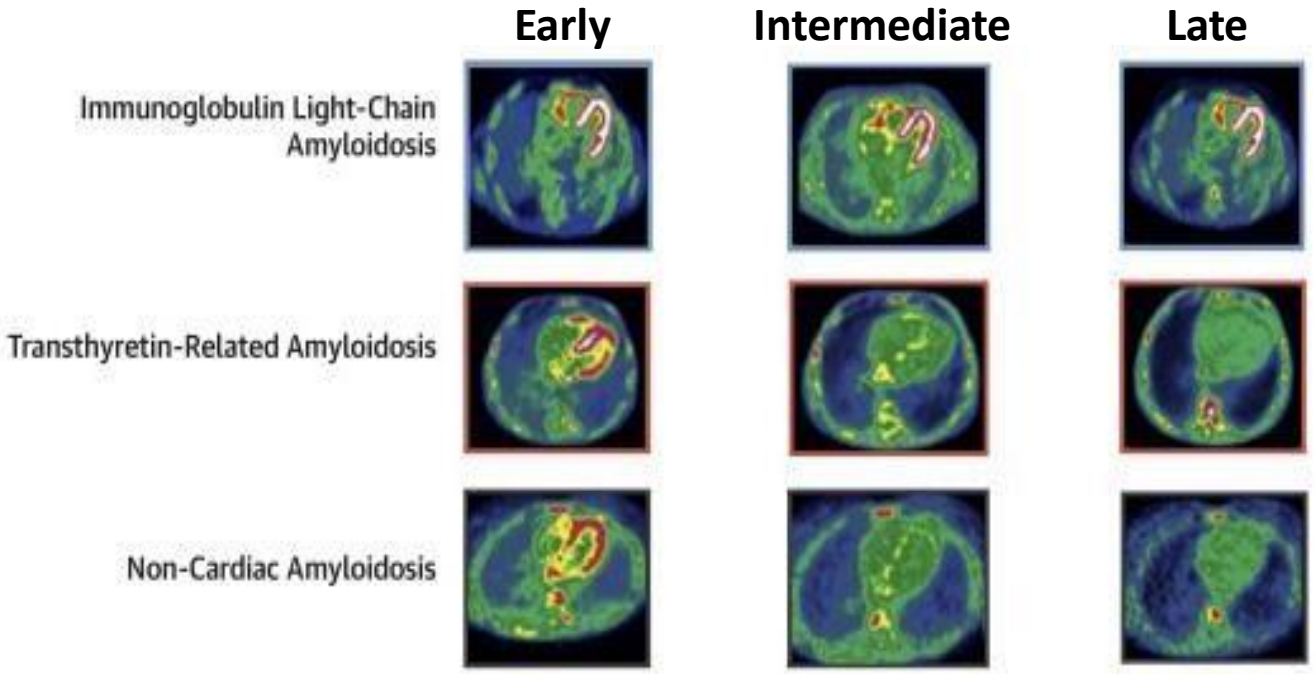
Dorbala, S, Eur J Nucl Med Mol Imaging, 2014

Thioflavin-T and Stilbene Derivatives

- PET tracer developed for Alzheimer's disease. Bind to b-pleated motif of amyloid fibrils (AL and ATTR-CA).
- Tracers : C–Pittsburgh compound-B ; 18F–florbetaben ; 18F–florbetapir …

18F–florbetaben Scan : delayed cardiac uptake may discriminate AL-CA vs TTR-CA



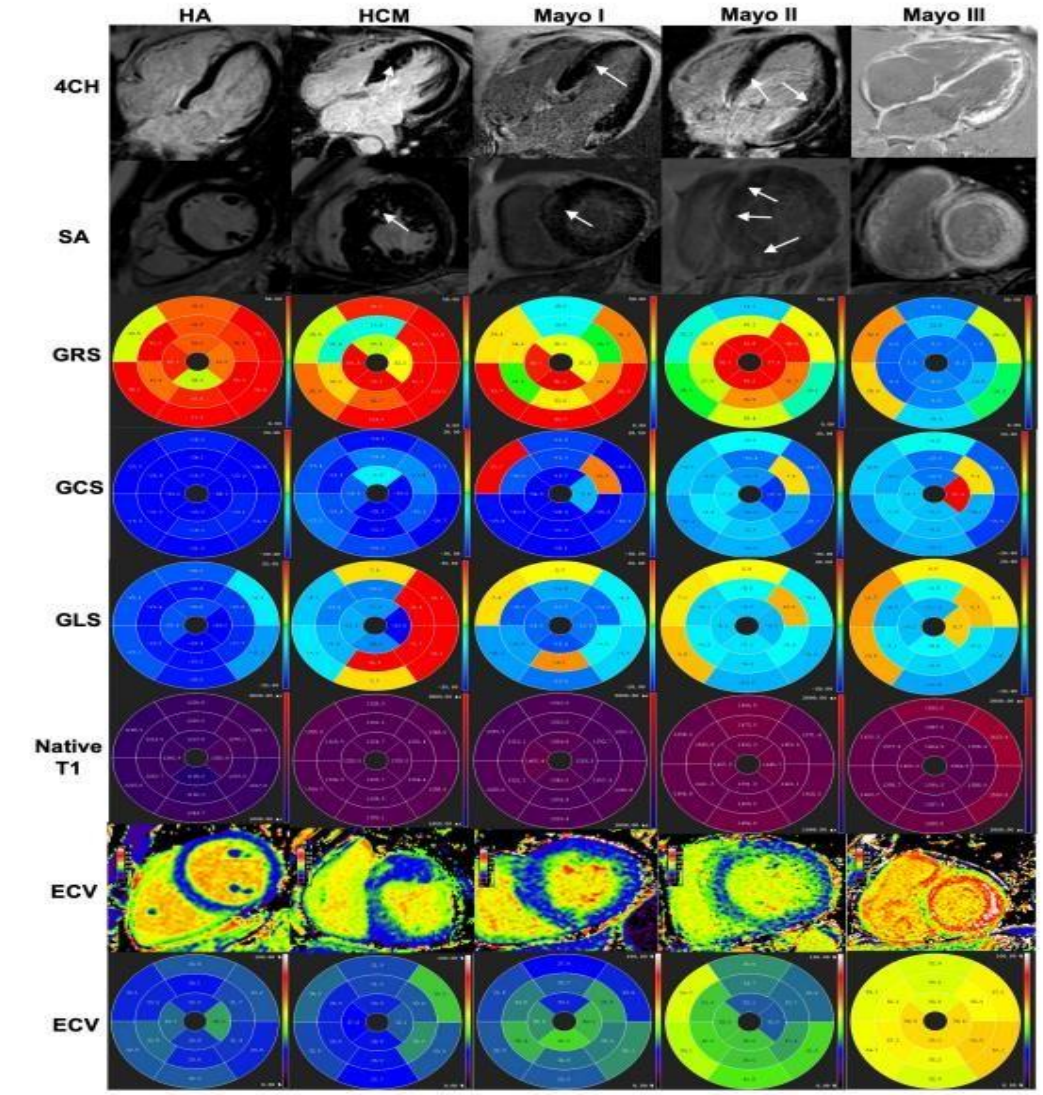


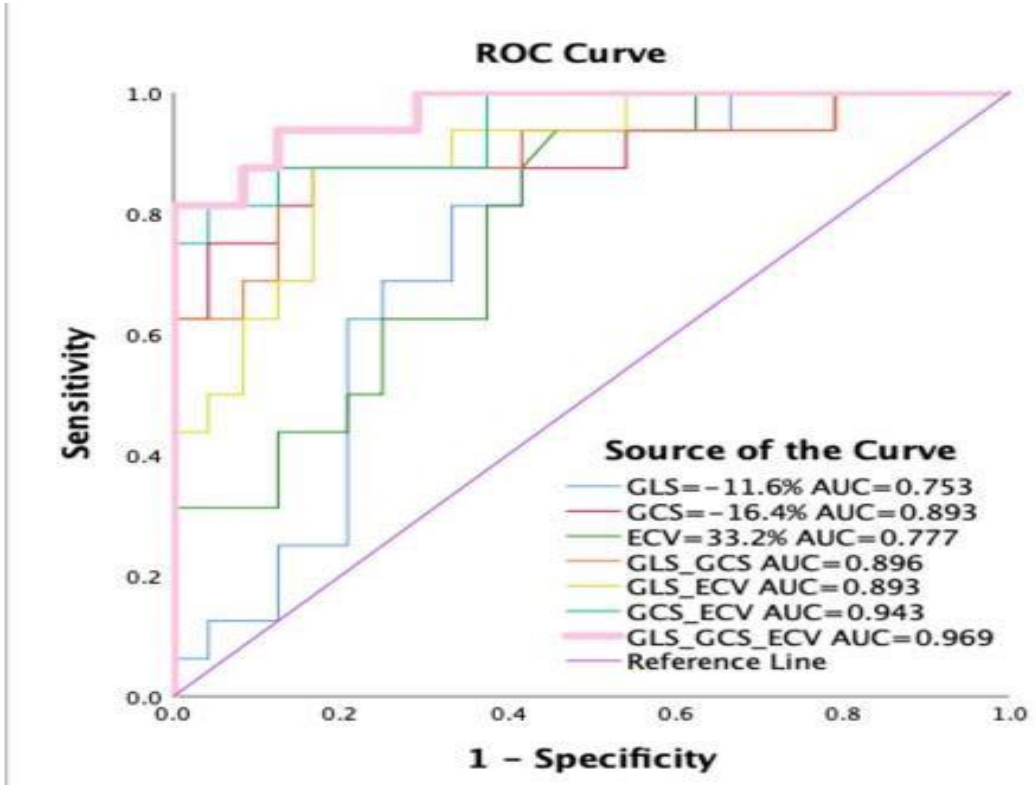
Genovesi D, JACC CV Imaging, 2021

Dorbala, S, Eur J Nucl Med Mol Imaging, 2014

The diagnostic value of multiparameter cardiovascular magnetic resonance for early detection of light-chain amyloidosis from hypertrophic cardiomyopathy patients

Xiuzheng Yue[1†], Lili Yang[2†], Rui Wang[2], Queenie Chan[3], Yanbing Yang[2], Xiaohong Wu[2], Xiaowei Ruan[2], Zhen Zhang[2], Yuping Wei[4] and Fang Wang[2*†]





Yue et al.

Deep Learning on Bone Scintigraphy to Detect Abnormal Cardiac Uptake at Risk of Cardiac Amyloidosis

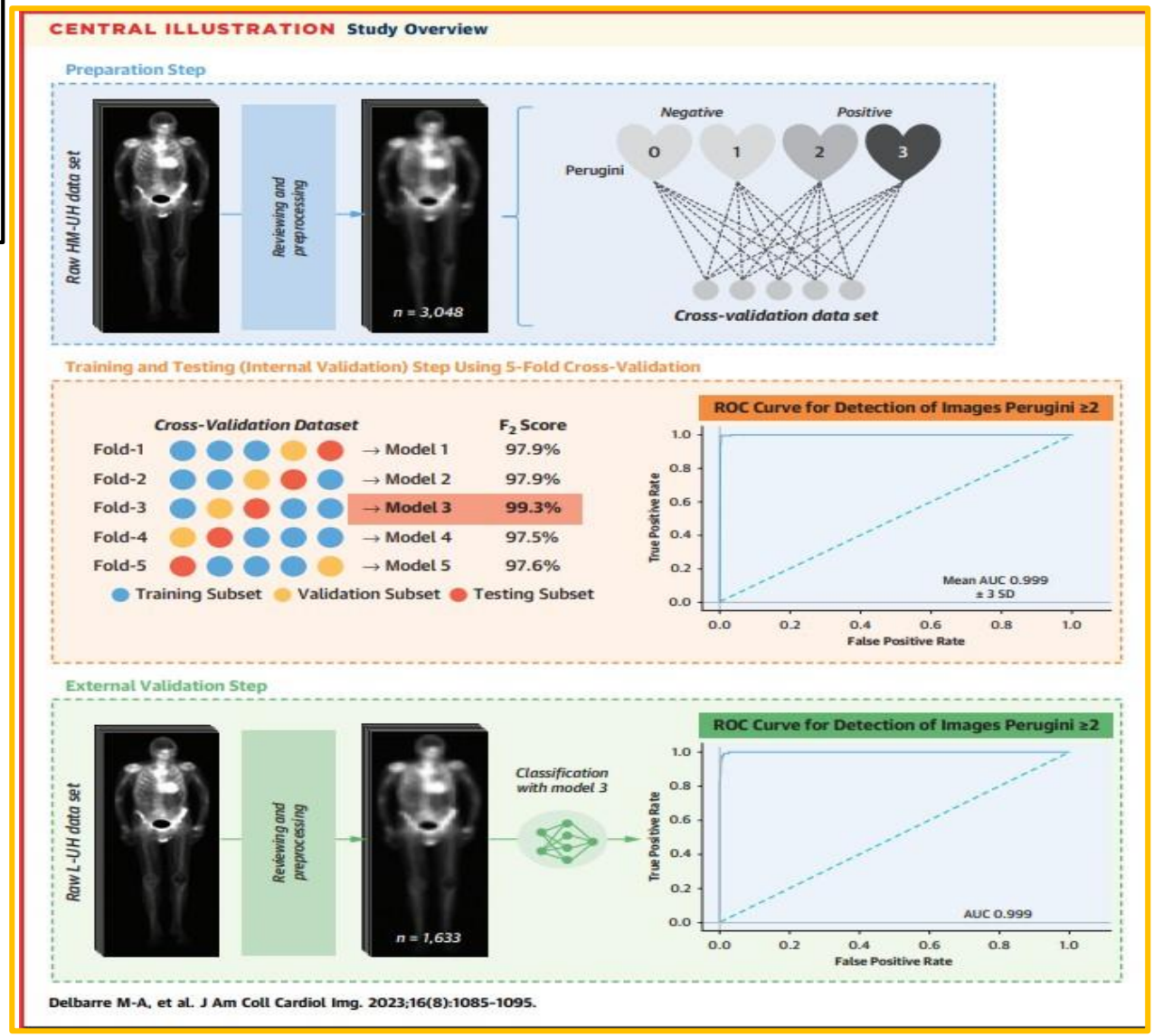
Marc-Antoine Delbarre, MD, MSc,[a,b] François Girardon, MSc,[c] Lucien Roquette, MSc,[c]

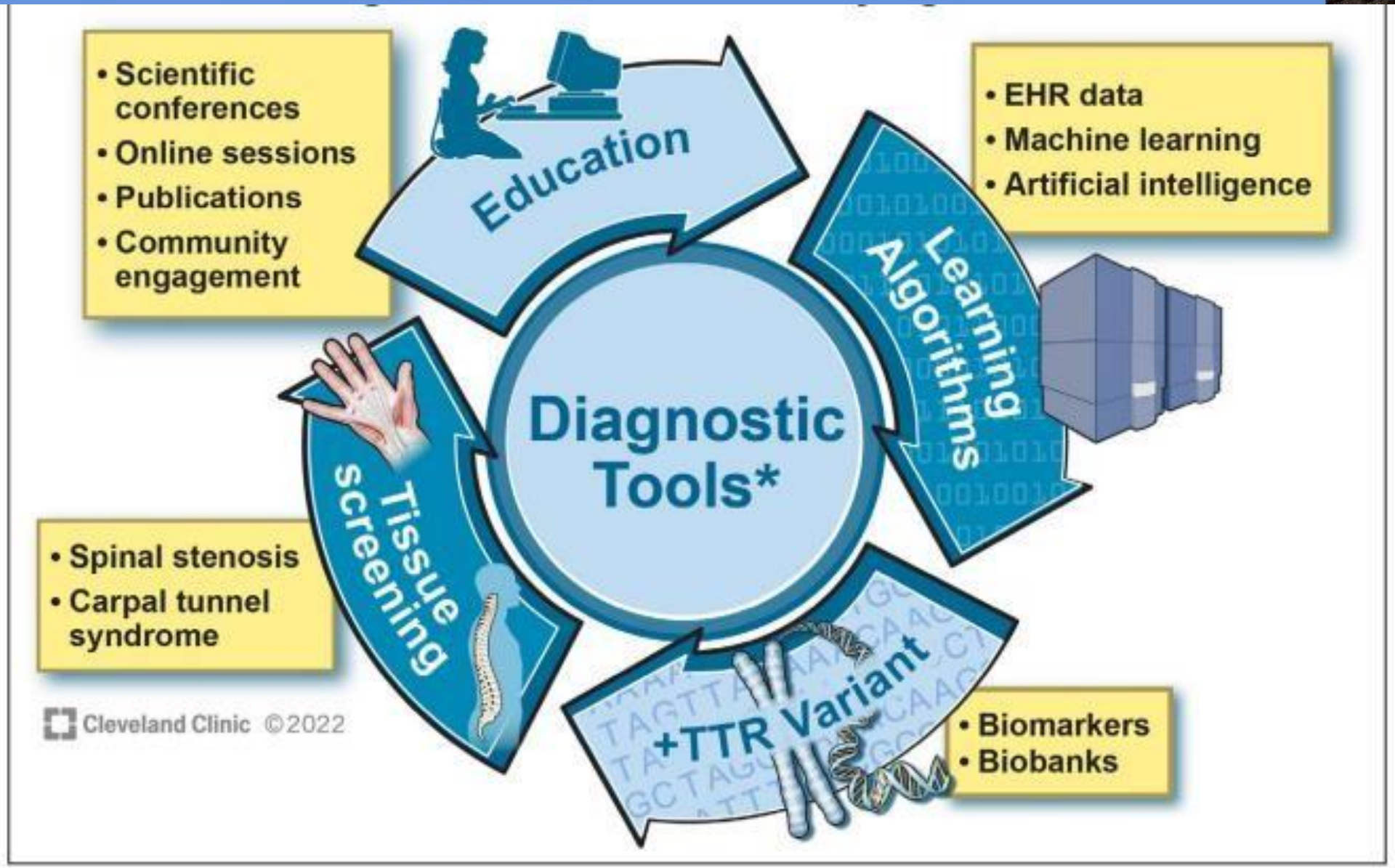
-The training data set consisted of 3,048 images: 281 positives (Perugini grade $2) and 2,767 negatives.

-External validation data set consisted of 1,633 images: 102 p and 1,531 n.

-Performance of the 5-fold cross-validation and external validation : 98.9% (1.0) and 96.1% for sen, 99.5% (0.4) and 99.5% for spe.

- AUC= 0.999 of the receiver-operating characteristic curves.

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