Diagnostic Approach to Cardiac Amyloidosis – The Great Masquerader

Sabahat Bokhari, MD
Professor of Medicine
Director of Advanced Cardiac Imaging
Director of Amyloidosis and Cardiomyopathy Center
Rutgers Robert Wood Johnson Medical School
Robert Wood Johnson University Hospital

Disclosure Information

Consultant/advisory board:

- *Pfizer*
- *Alnylam*

- **Speakers bureau:**

- *Pfizer*
- *Astellas*
- *Alnylam*

Main Types of Cardiac Amyloidosis

Immunoglobulin light chain amyloidosis (AL)[1-3]

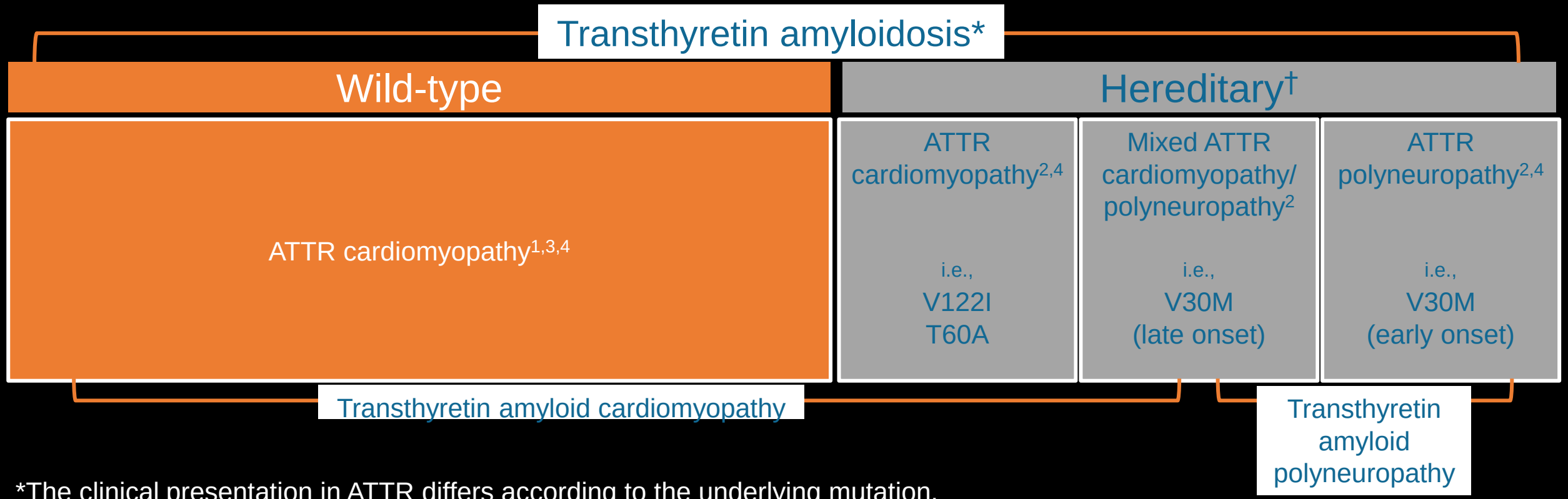
Transthyretin amyloidosis (ATTR)[1-4]

Others including[1,3]
Serum amyloid A
Apolipoprotein A1 (AApoA1)
Immunoglobulin heavy chain
Fibrinogen alpha chain
Gelsolin

Account for more than 95% of all cardiac amyloidosis diagnoses[1]

1. Donnelly J, Hanna M. *Cleve Clin J Med.* 2017;84(12 suppl 3):12-26. 2. Siddiqi OK, Ruberg FL. *Trends Cardiovasc Med*. 2018;28:10-21. 3. Kholová I, Niessen HW. *J Clin Pathol.* 2005;58:125-133.
4. Adams D, et al. *Curr Opin Neurol*. 2016;29(suppl 1):S14-S26.

ATTR-CM Has 2 Subtypes: Wild-Type and Hereditary[1,2]



*The clinical presentation in ATTR differs according to the underlying mutation.

†The mutations shown above are the most common mutations in ATTR.[5]

1. Nativi-Nicolau J, et al. *Curr Opin Cardiol*. 2018;33:571-579. 2. Rapezzi C, et al. *Eur Heart J.* 2013;34:520-528. 3. Maurer MS, et al. *J Am Coll Cardiol.* 2016;63:161-172.
4. González-López E, et al. *Rev Esp Cardiol*. 2017;70:991-1004.

Raising Clinical Suspicion

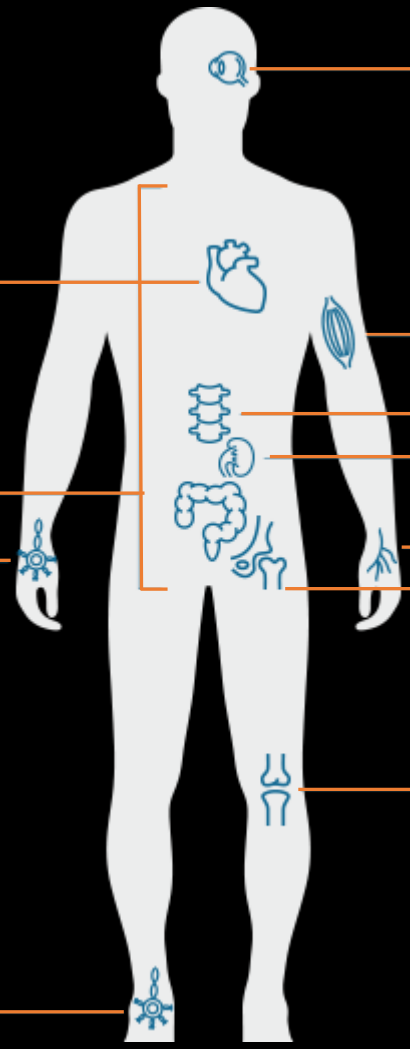
- Clinical Presentation
- Biomarkers
- Electrocardiogram (ECG)
- Transthoracic Echocardiography (TTE)
- Cardiac MRI

Clinical Presentation

Signs and Symptoms That May Present in Patients With ATTR-CM[1-13]

Cardiovascular
- Heart failure
- Intolerance to standard HF therapies
- Low voltage relative to LV thickness
- Echocardiography showing increased LV wall thickness
- Cardiac arrhythmia
- Aortic stenosis

Nervous System
- Autonomic
  - Autonomic neuropathy
  - Gastrointestinal complaints
  - Unexplained weight loss
  - Orthostatic hypotension
  - Sexual impotence
- Peripheral
  - Peripheral sensory motor dysfunction
  - Peripheral neuropathy



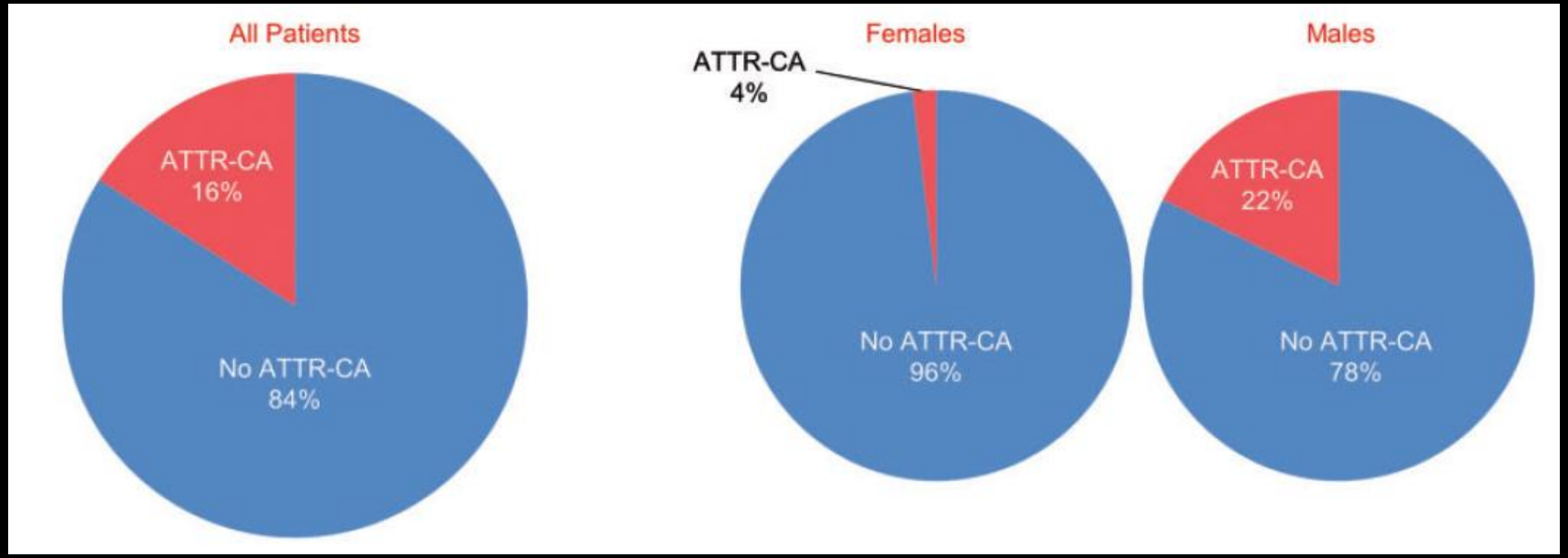
Ocular
- Vitreous opacity
- Glaucoma

Musculoskeletal/Orthopedic
- Biceps tendon rupture
- Lumbar spinal stenosis
- Carpal tunnel syndrome
- Hip/knee arthroplasty

Renal
- Renal impairment
- Cardiorenal syndrome

1. Nativi-Nicolau J, et al. *Curr Opin Cardiol*. 2018;33:571-579. 2. Narotsky DL, et al. *Can J Cardiol*. 2016;32:1166.e1-e10. 3. Maurer MS, et al. *Circulation*. 2017;135:1357-1377. 4. Brunjes DL, et al. *J Card Fail*. 2016;22:996-1003. 5. Siddiqi OK, Ruberg FL. *Trends Cardiovasc Med*. 2018;28:10-21. 6. Maurer MS, et al. *J Am Coll Cardiol*. 2016;63:161-172. 7. González-López E, et al. *Rev Esp Cardiol*. 2017;70:991-1004. 8. Reynolds MM, et al. *Am J Ophthalmol*. 2017;183:156-162. 9. Rubin J, et al. *Amyloid*. 2017;24:224-228. 10. Dang J, et al. *Mayo Clin Proc*. 2019;94:961-975. 11. Castano A, et al. *Eur Heart J.* 2017;38:2879-2887. 12. Gillmore JD, et al. *Eur Heart J*. 2018;39:2799-2806. 13. Treibel TA, et al. *Circ Cardiovasc Imaging.* 2016;9:54-63.

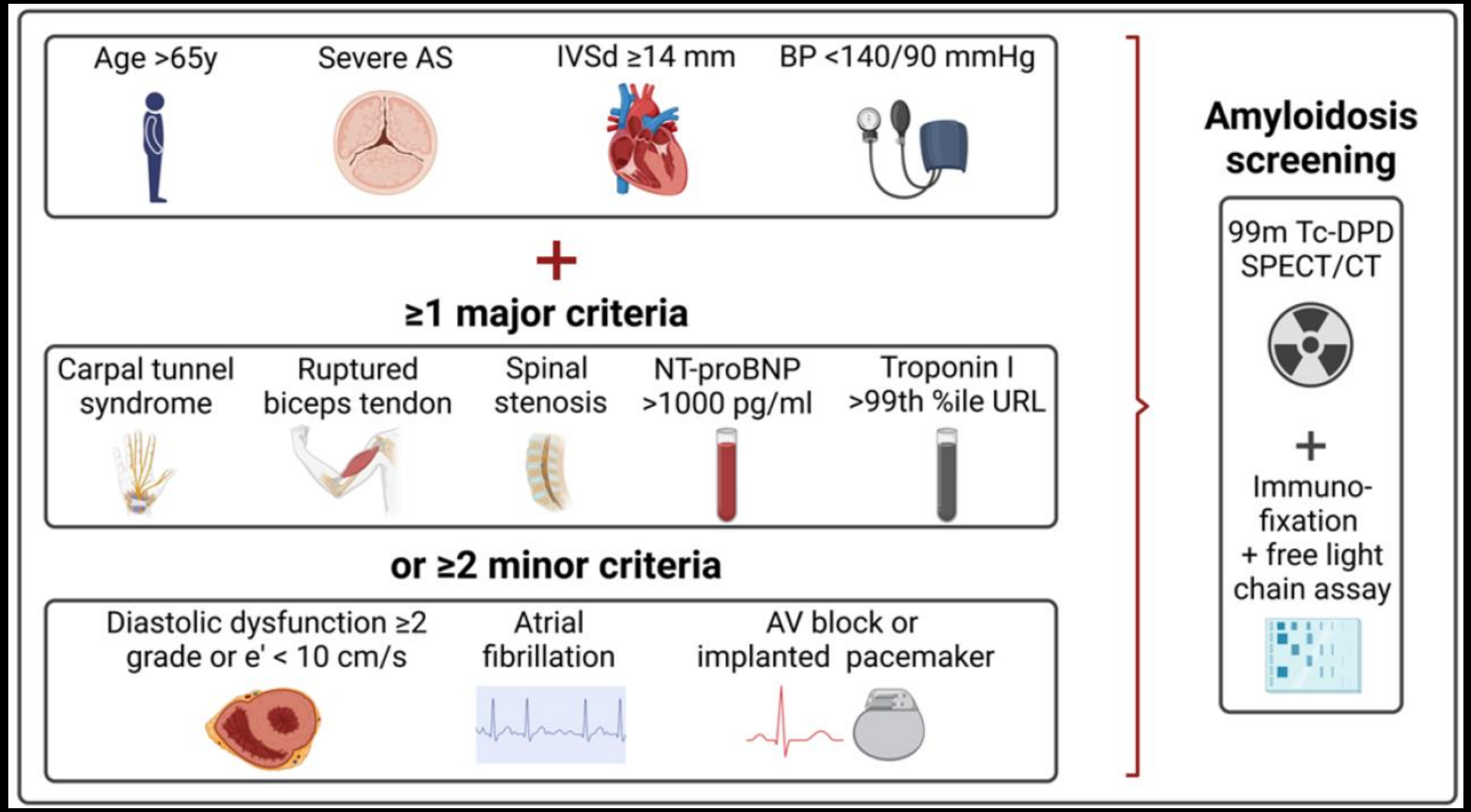
Prevalence of wtATTR-CA among patients with severe AS undergoing TAVR



16% undergoing TAVR
6% undergoing SAVR

Castano et al. European Heart J. 2017.
Treibel et al. Circulation CV Imaging. 2016.

Cardiac Amyloid Screening Pre TAVR



Biomarkers

Laboratory/Biomarker Clues[1-3]

Cardiac biomarkers

- Low-grade persistent troponin elevation
- NT-proBNP level elevation
- Prealbumin & Albumin (mBMI)
- eGFR

Laboratory tests
(to rule out AL amyloidosis)

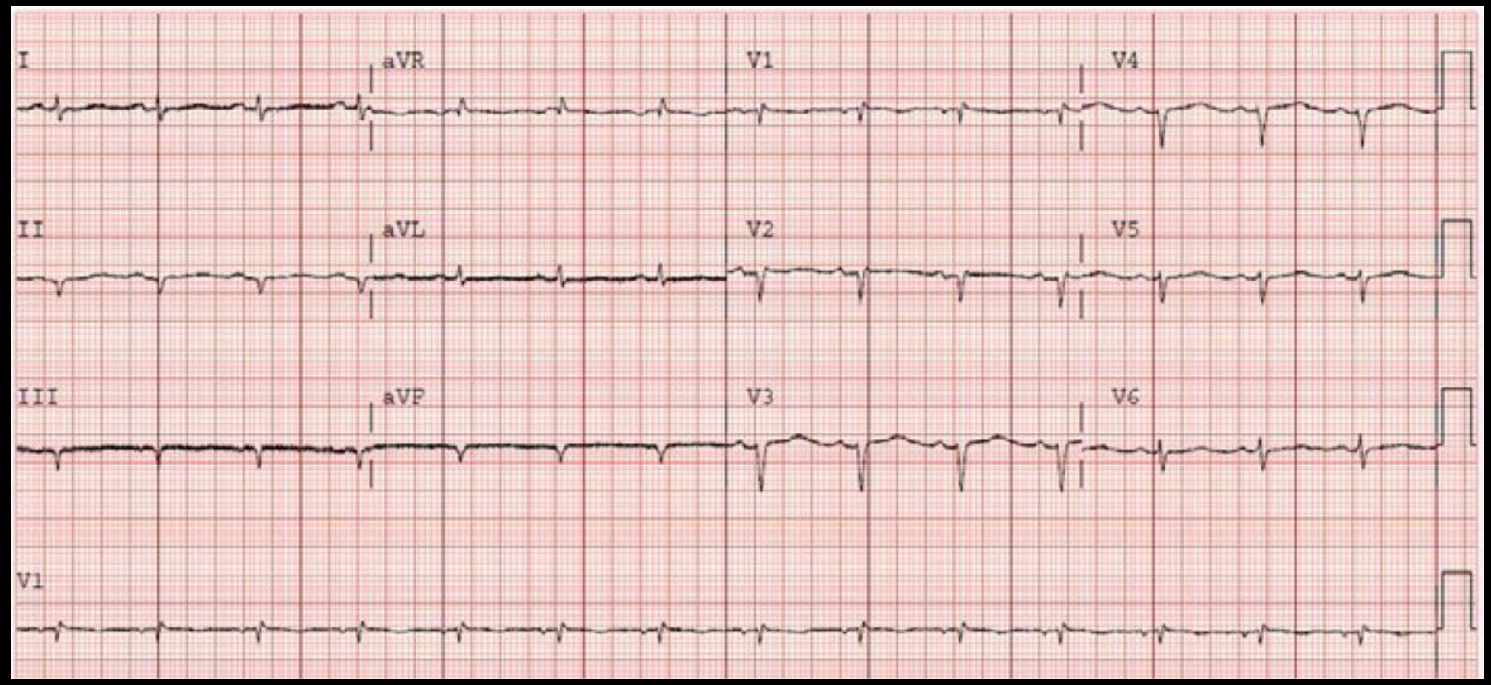
- Abnormal free light-chain ratio
- Abnormal clone by serum + urine immunofixation (not SPEP)

1. Donnelly JP, Hanna M. *Cleve Clin J Med*. 2017;84(12 suppl 3):12-26. 2. Nativi-Nicolau J, Maurer MS. *Curr Opin Cardiol*. 2018;33:571-579. 3. Ruberg FL, Berk JL. *Circulation*. 2012;126:1286-1300.

Electrocardiogram

Electrocardiogram (ECG)[1-4]

- Discordance between LV wall thickness and QRS voltage
- Pseudoinfarct patterns in up to 70% of cases
- Conduction disease
- Atrioventricular block in up to 22% of cases
- Atrial fibrillation



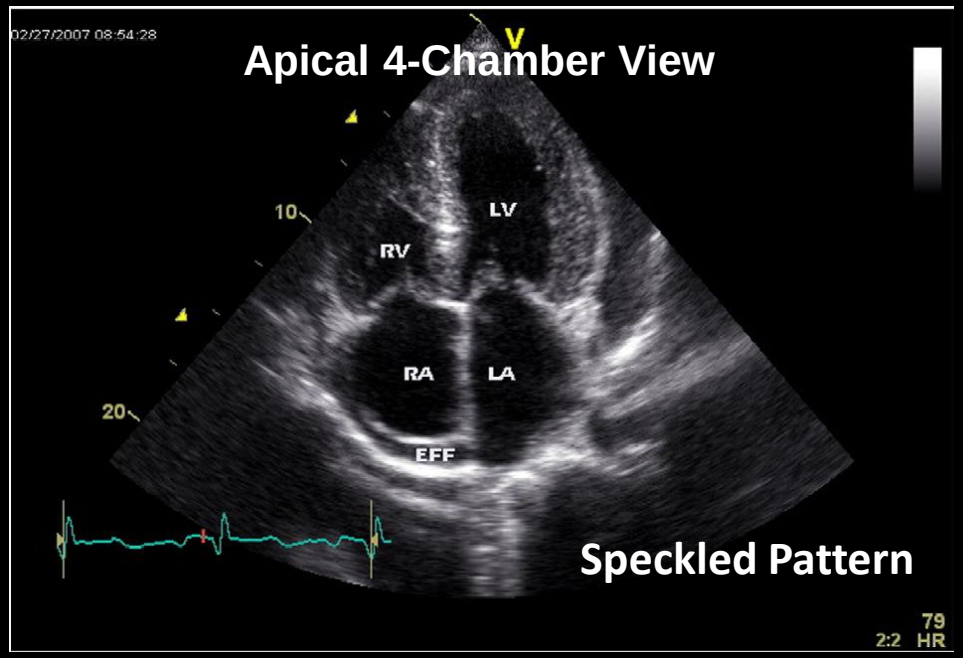
ECG showing low voltage throughout, pseudoinfarcts in the anterior and inferior leads, and poor R-wave progression.
Figure used with permission from Edwards et al.[4]

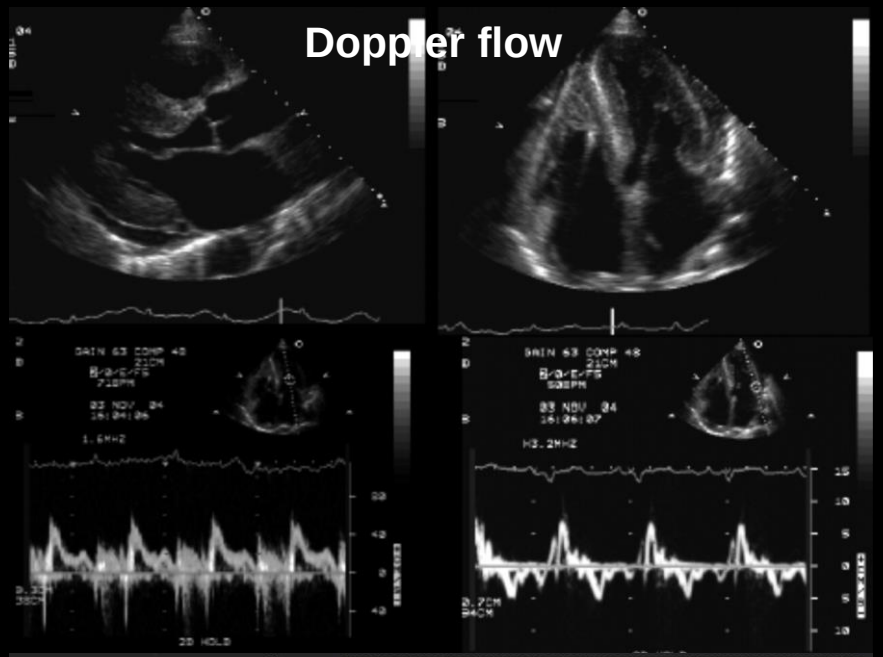
Prevalence of low QRS voltage varies: ATTR-CM (20%) and AL amyloidosis (60%)

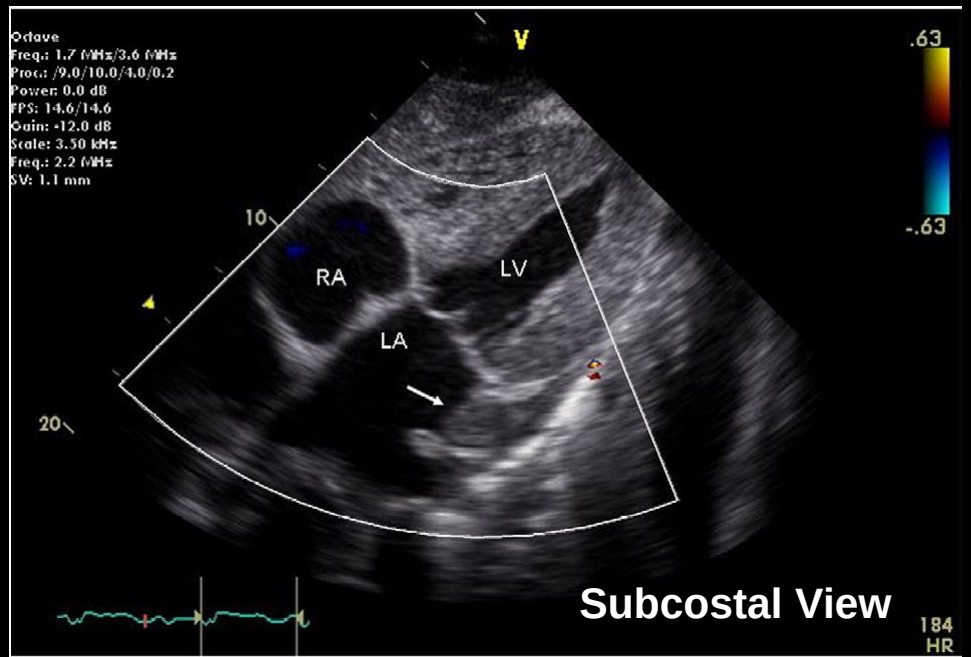
1. Siddiqi OK, Ruberg FL. *Trends Cardiovasc Med*. 2018;28:10-21. 2. Maurer MS, et al. *Circulation*. 2017;135:1357-1377. 3. Donnelly J, Hanna M. *Cleve Clin J Med*. 2017;84(12 suppl 3):12-26. 4. Edwards A, et al. *J Integr Cardiol*. 2015;1:40-45.

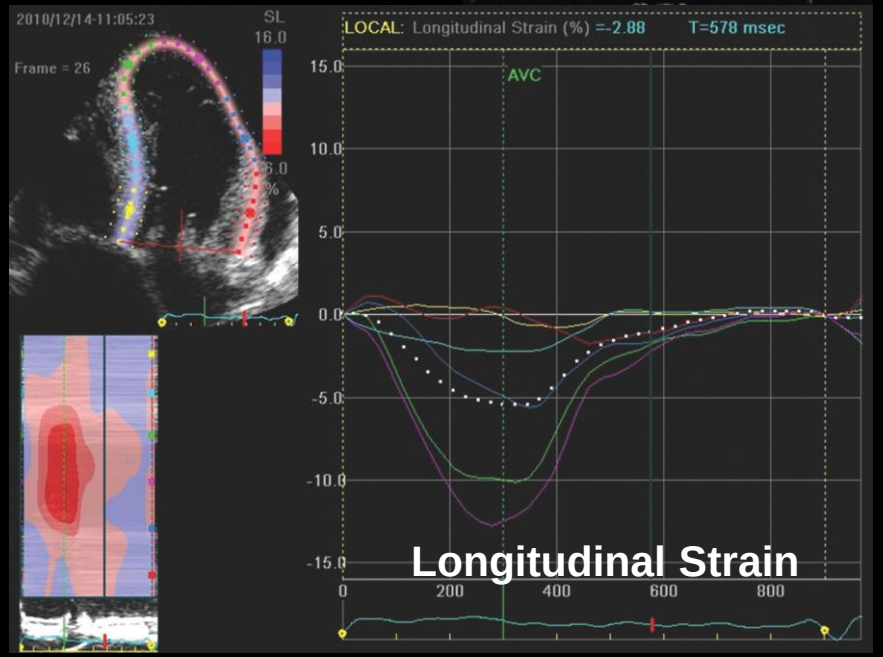
Echocardiogram

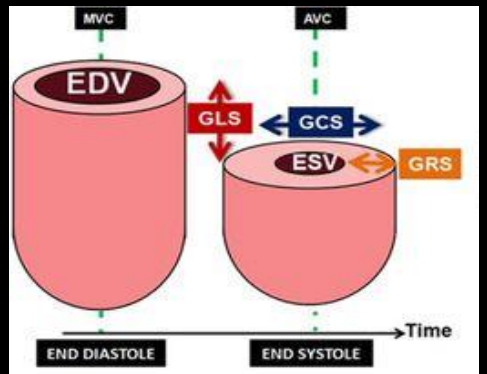
Echocardiographic Images in Cardiac Amyloidosis

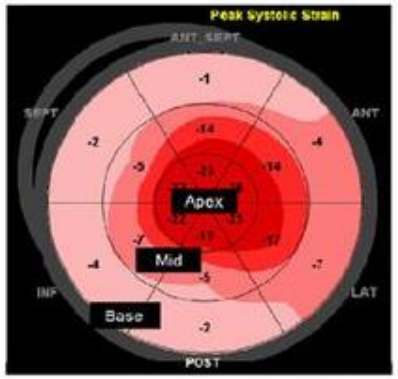




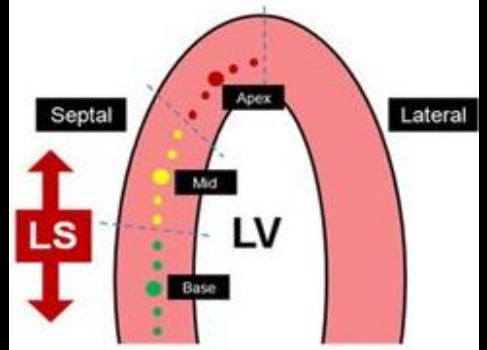








$$\text{RELAPS} = \frac{\text{Average Apical LS}}{\text{Sum of the average Basal and Mid LS}}$$



$$\text{SAB} = \frac{\text{Apical septal LS}}{\text{Basal septal LS}}$$

CMR

Cardiac amyloidosis unlikely

Sensitivity 98% (97%-99%)
Specificity 19% (15%-24%)

135 patients (15%)
<2 points

CMR

Perform additional tests

Sensitivity 61% (57%-66%)
Specificity 27% (22%-32%)

498 patients (54%)
2 - 7 points

Cardiac amyloidosis → Clonal dyscrasia
DPD/HMDP
Scintigraphy

Sensitivity 46% (42%-50%)
Specificity 98% (95%-99%)

290 patients (31%)
≥8 points

n = 923

IWT Score

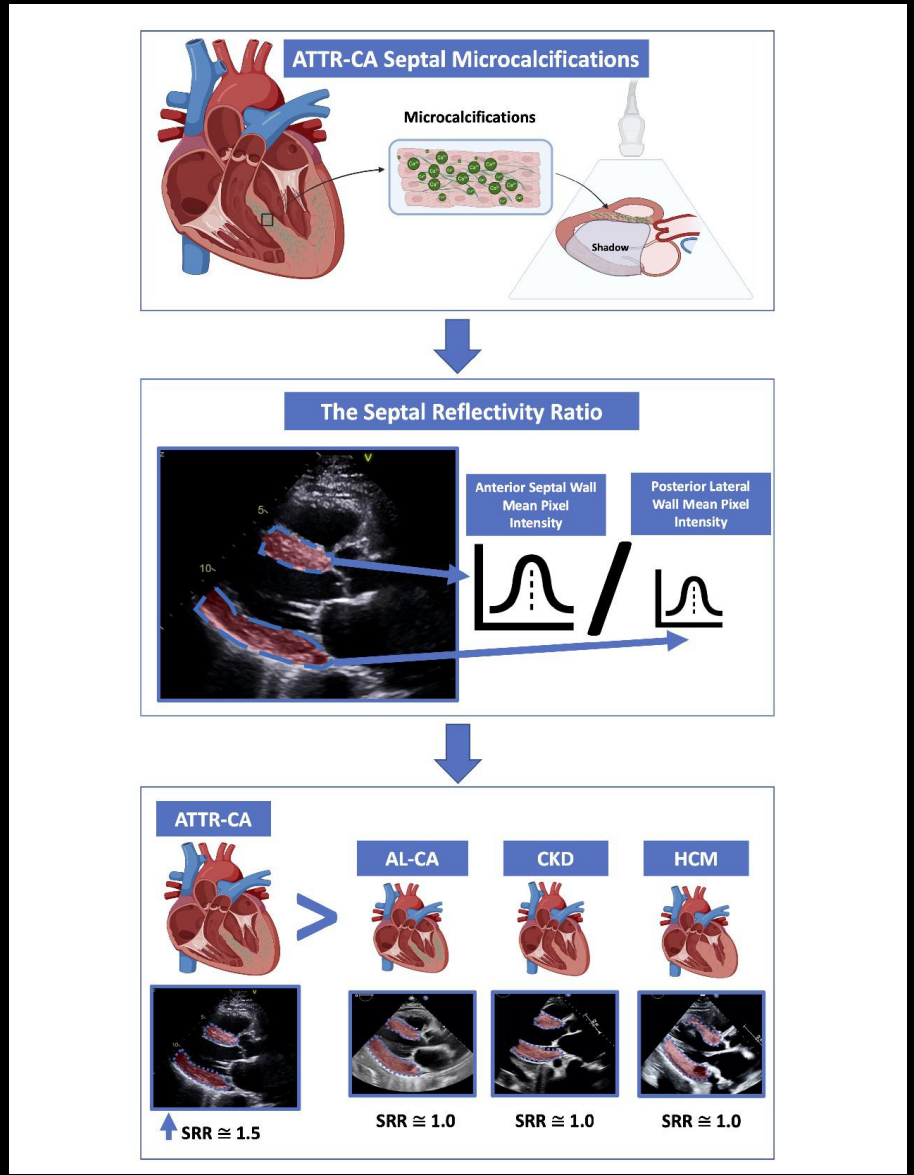
AUC = 0.87
(95% CI: 0.85-0.90)

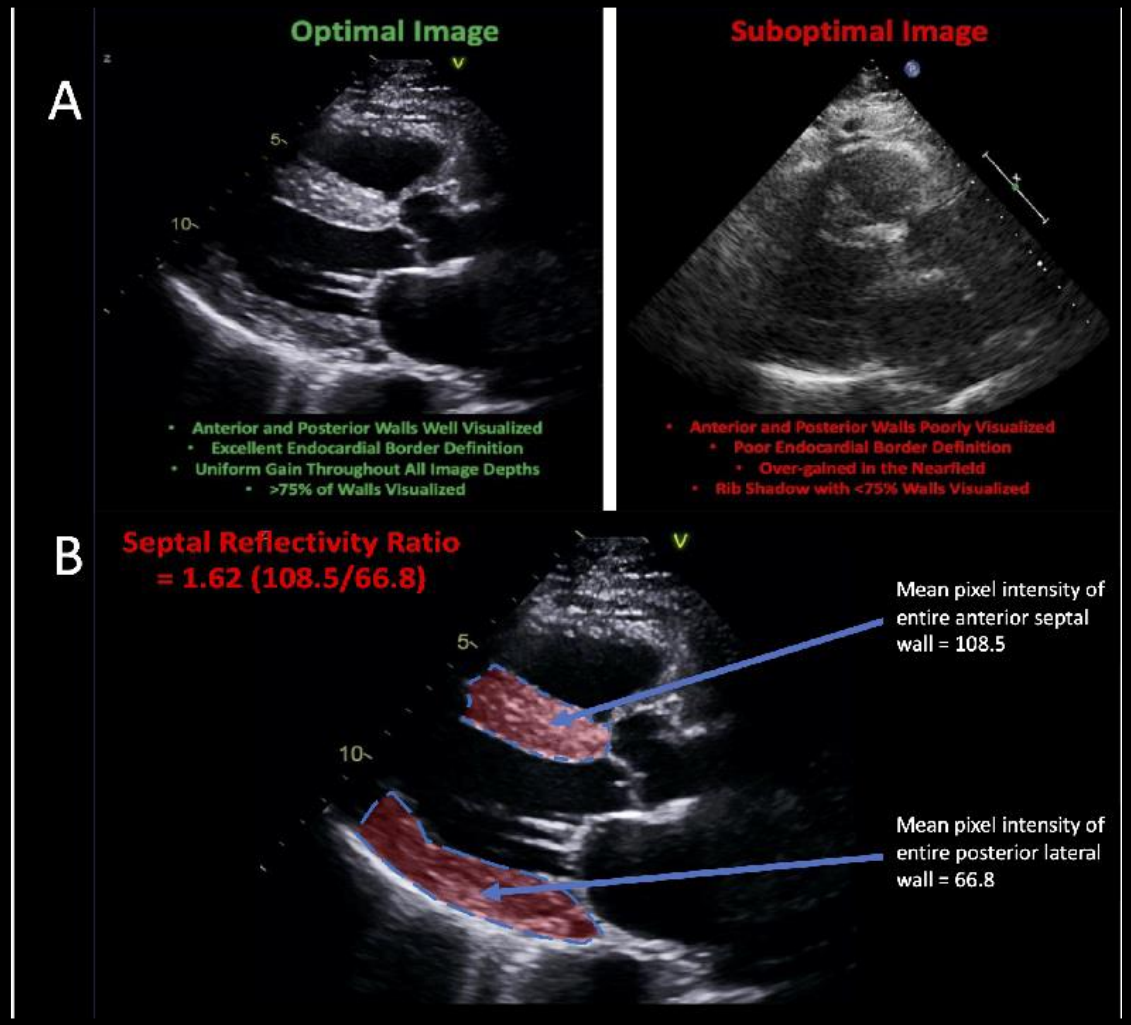
PARAMETERS		
	RWT >0.6	3 points
	E/e' >11	1 point
	TAPSE ≤19 mm	2 points
	LS ≥ -13%	1 point
	SAB> 2.9	3 points

Increased Wall Thickness Score for the diagnosis of TTR-CM

Boldrini, M. et al. J Am Coll Cardiol Img. 2020;13(4):909

The septal reflectivity ratio



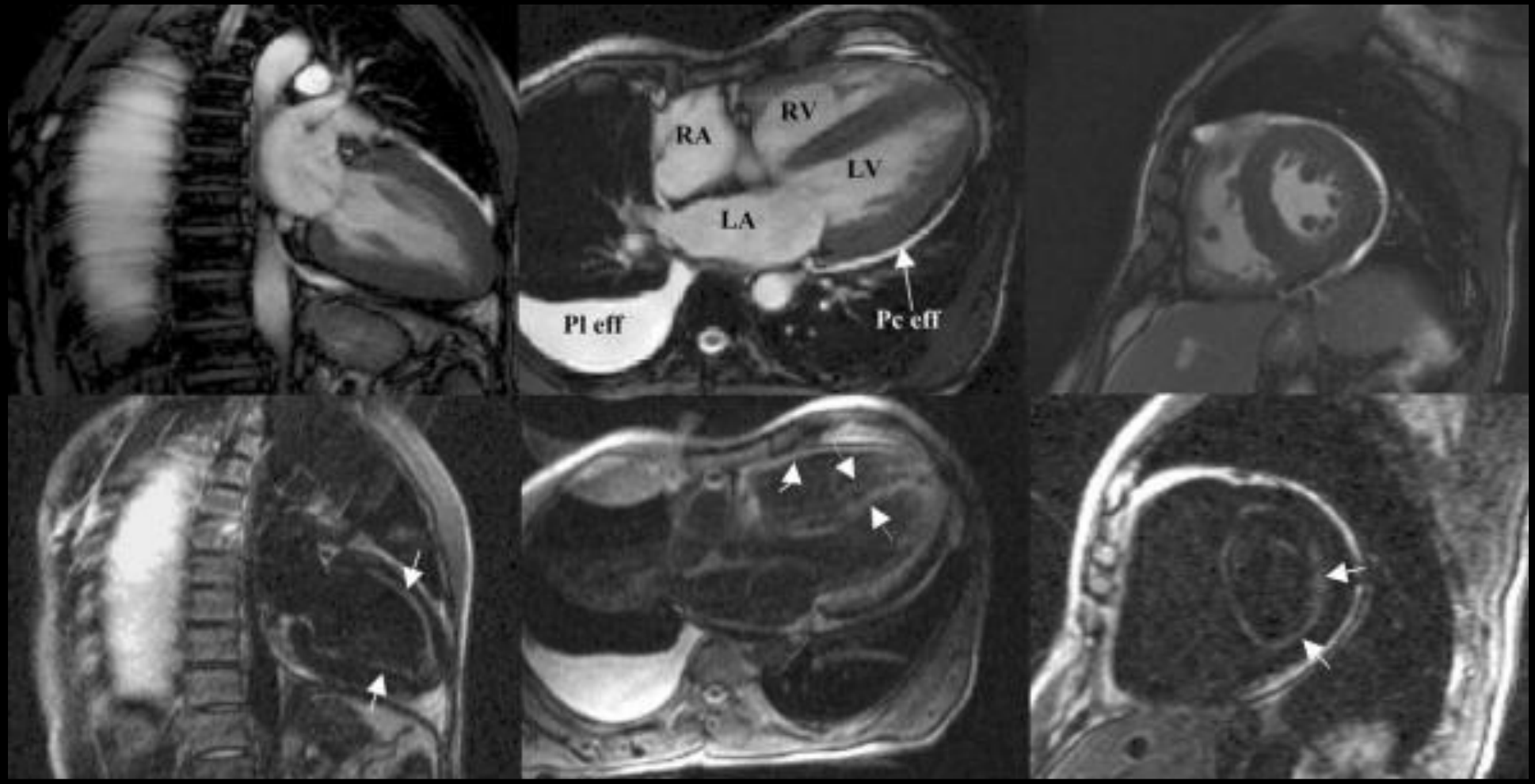


Cardiac MRI

Magnetic Resonance Imaging in Cardiac Amyloidosis

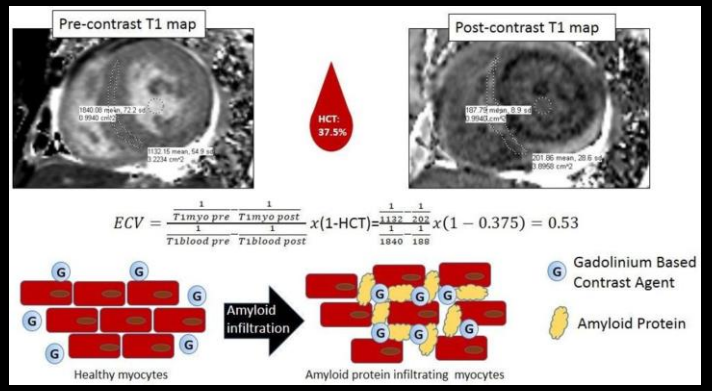
Cine

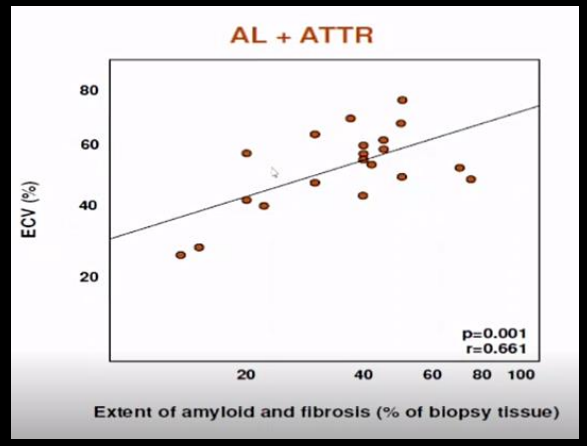
LGE

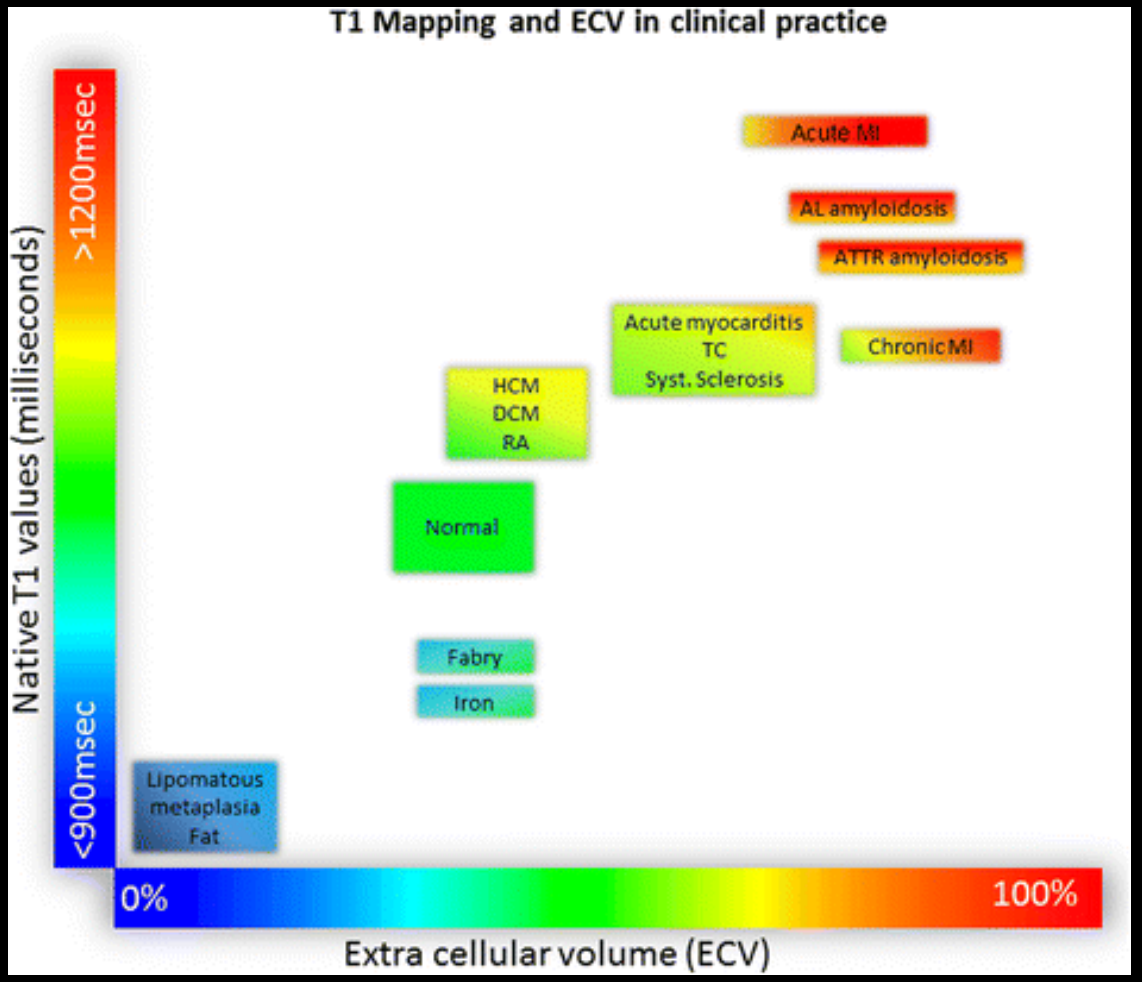


Maceria A. *Circulation* 2005

Extracellular volume fraction in amyloidosis







Clinical Applications of ^{99m}Tc-PYP Imaging in Suspected Cardiac Amyloidosis

Nuclear Imaging Modalities

Bone Seeking Tracers

- ^{99m}Tc-pyrophosphate (PYP)
- ^{99m}Tc-hydroxymethylene diphosphonate (HMDP)
- ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD)
- PET tracers: ^{18}F-NaF

Sympathetic Innervation

- ^{123}I-*m*IBG

Amyloid Deposits

- ^{99m}Tc-aprotinin and ^{123}I-*SAP*
- PET tracers: ^{18}F-florbetapir , ^{18}F-florbetaben, F-18 flutemetamol and ^{11} C-PIB (Pittsburgh Compound B)

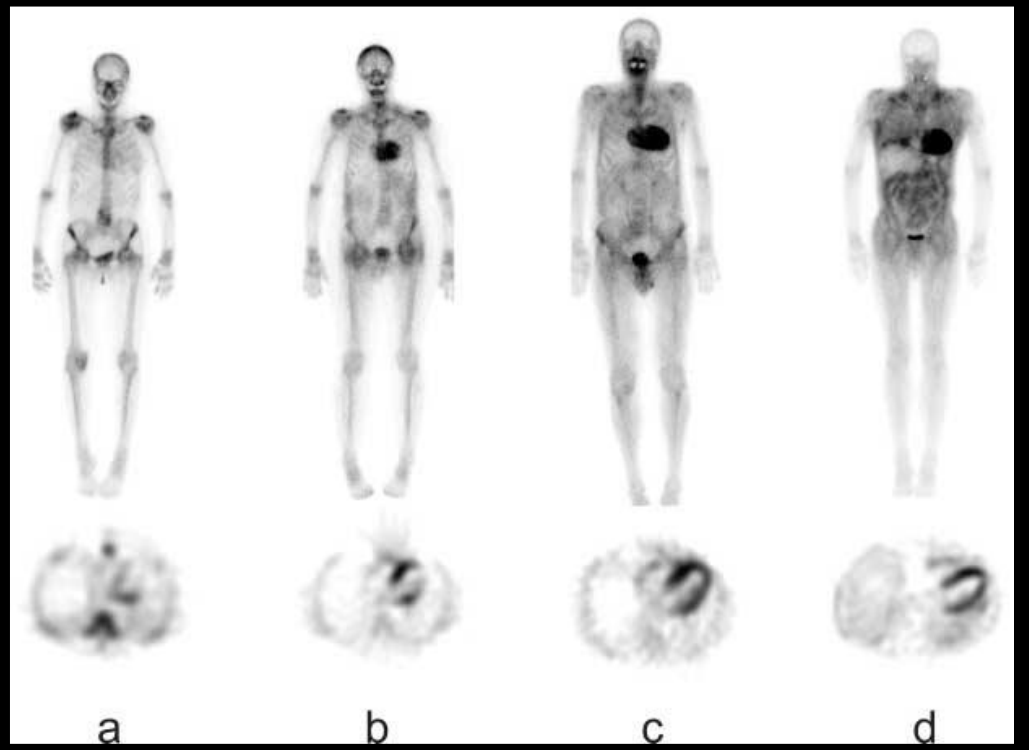
Other Tracers

- ^{68}Ga, ^{111}In-antimyosin, ^{11}C-choline

Bokhari S, et al: *J Nucl Cardiol.* 2014;21:175-184.

^{99m}Tc-DPD Scintigraphy in Transthyretin-Related Familial Amyloidotic Polyneuropathy (FAP)

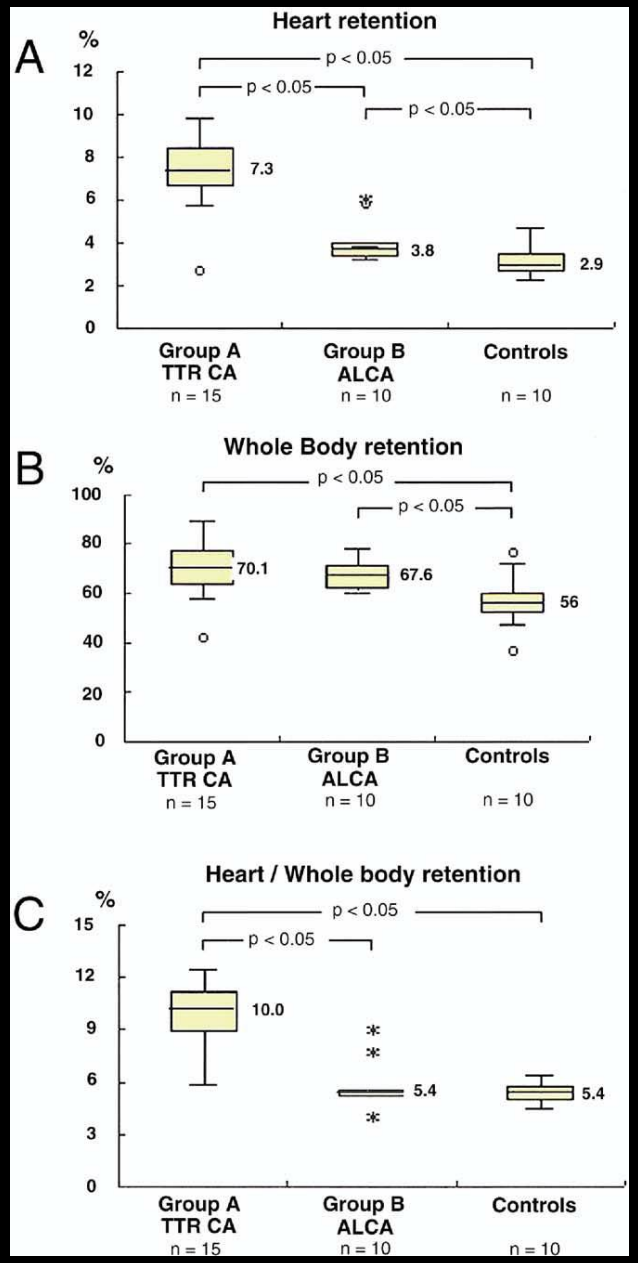
- *8 pts with ATTR-FAP (4 M, mean 54 +/- 8 years) and 10 control oncological out-pts*
- *WB tracer retention at 3 hour and heart-to-whole body uptake ratio*
- *The 3 FAP patients with highest uptake had CM & arrhythmia*

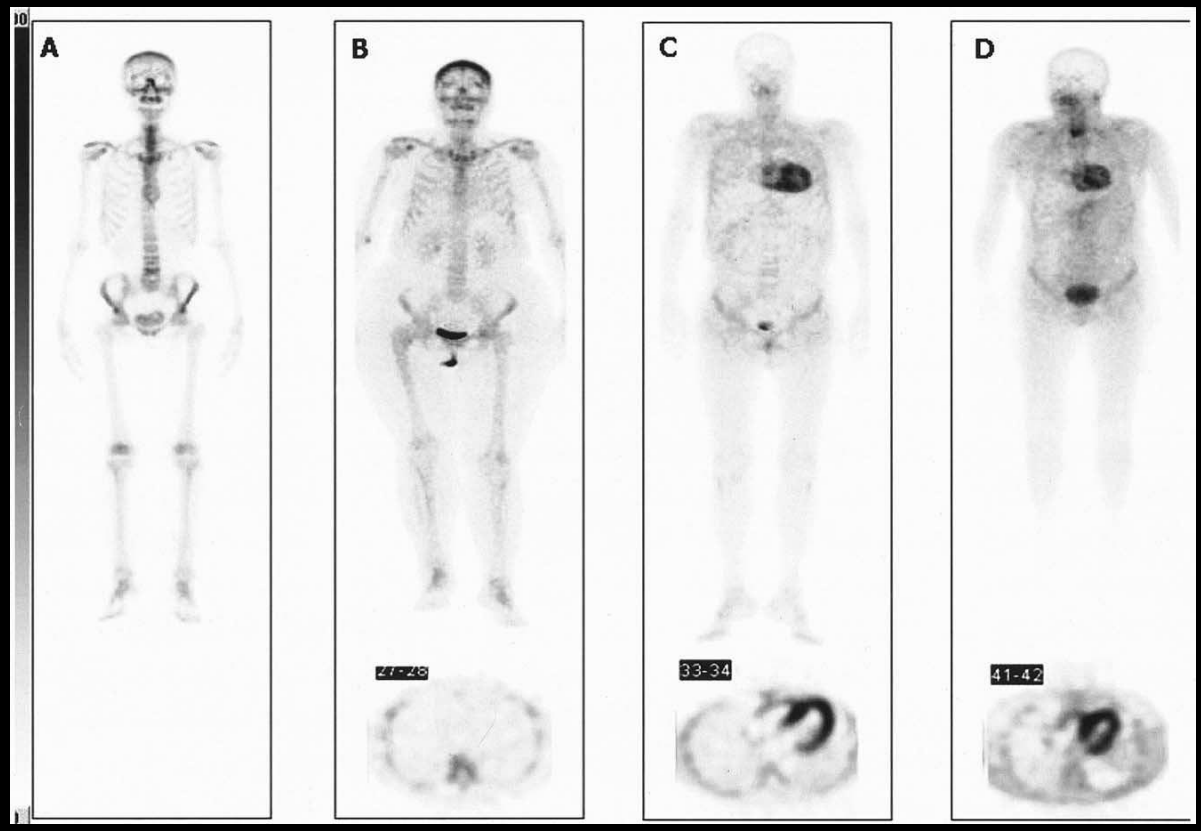


^{99m}Tc-DPD scintigraphy is proposed as a simple and valuable diagnostic aid to evaluate the severity of the disease and the risk of concomitant heart problems

Puille M, et al. *Eur J Nucl Med Mol Imaging.* 2002;29:376-379.

Diagnostic Value of ^{99m}Tc-DPD

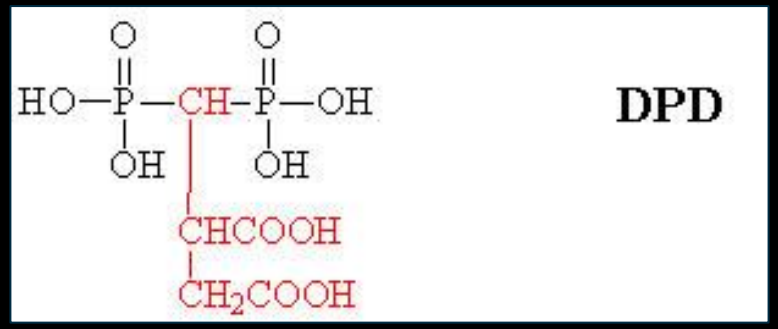


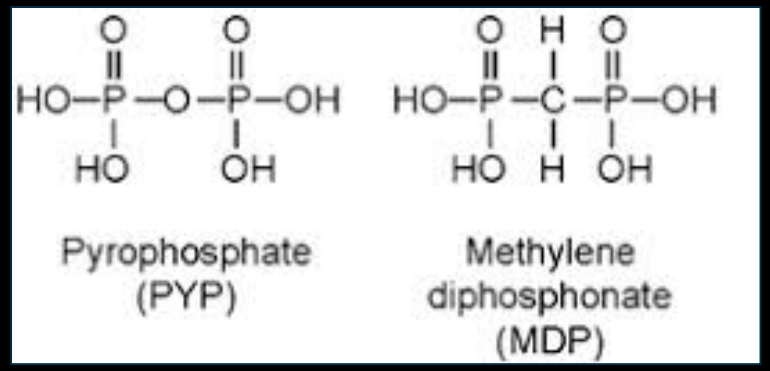


Perugini E, et al: *J Am Coll Cardiol.* 2005;46:1076-1084.

Resurrecting ^{99m}Tc-PYP

An old test gains new purpose

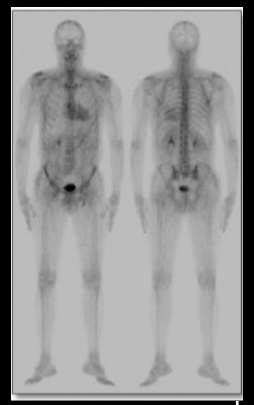




PYP is readily available in US and approved for the following indications:

- Blood pool imaging
  - *GI bleed*
  - *Gated blood pool studies*
- Cardiac imaging
  - *Detection of acute MI*
- Bone imaging

Comparison of ^{99m}Tc-DPD and ^{99m}Tc-PYP Scan Timelines



^{99m}Tc-DPD 25-30 mCi

Study Time: 220 min

Imaging Time: 64 min

Inject

WB scan

WB scan SPECT

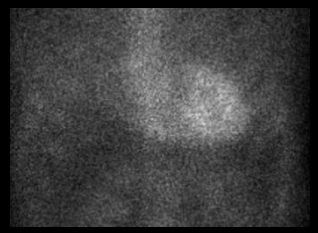
min

0 5 15 30 45 60 75 90 105 120 135 150 165 180 195 210 220

Planar SPECT

Planar SPECT

Inject



^{99m}Tc-PYP 10 mCi

Study Time: 60 to 80 min

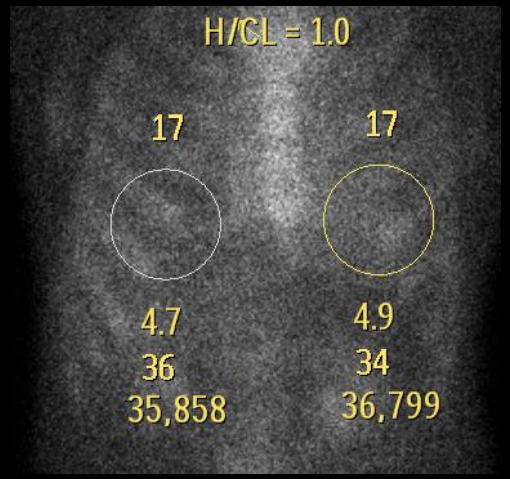
Imaging Time: 5 to 20 min

Bokhari et al: *Circ Cardiovasc Imag.* 2013;6:195-201.

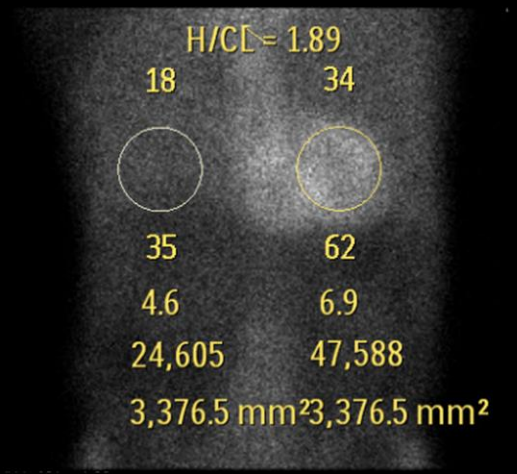
Bokhari et al. *J Nucl Cardiol*. 2018;25:181-190.

Quantitative Score

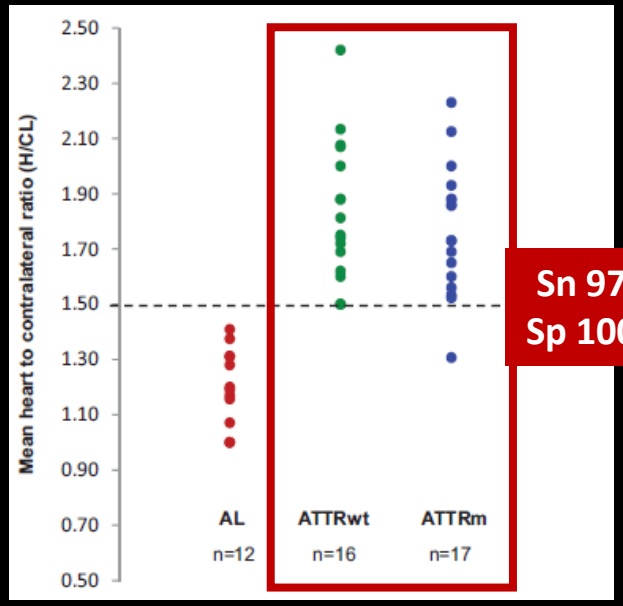
- Circular ROI over heart, copied, mirrored CL chest
- Mean counts/pixel corrected for background counts
- Heart-to-contralateral ratio (H/CL)



AL



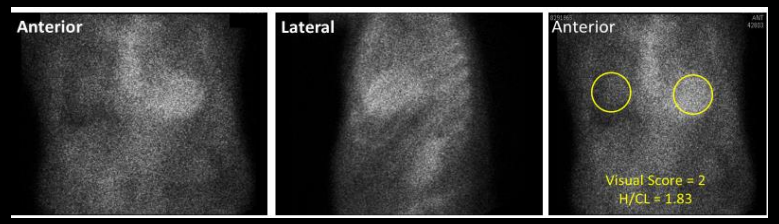
ATTR

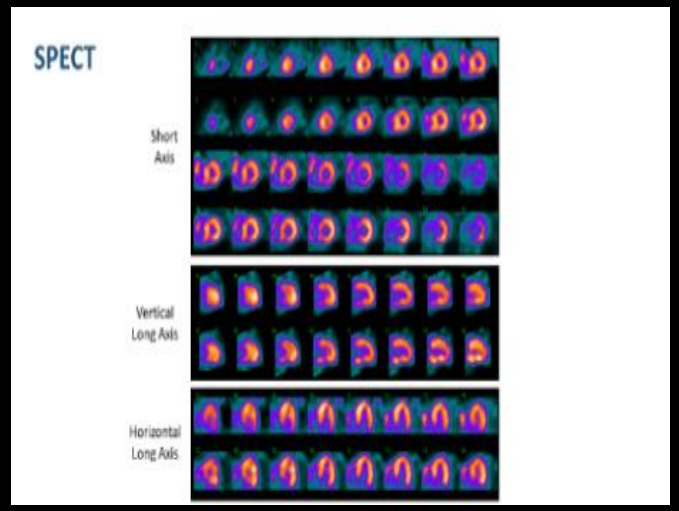


Bokhari et al: *Circ Cardiovasc Imag.* 2013;6:195-201.

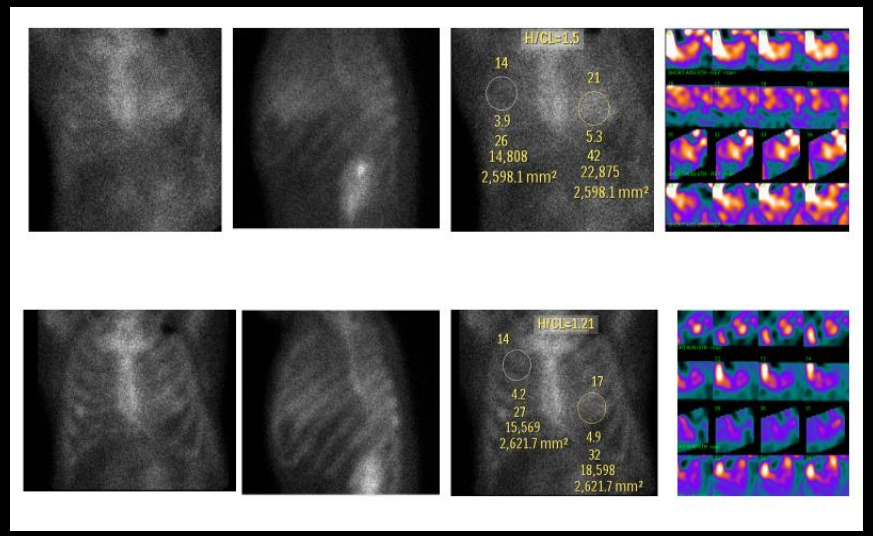
Both Planar and SPECT Imaging should be reviewed and Interpreted using visual and quantitative approaches

SPECT imaging is necessary for studies that show planar cardiac uptake because it can help differentiate myocardial uptake from blood pool

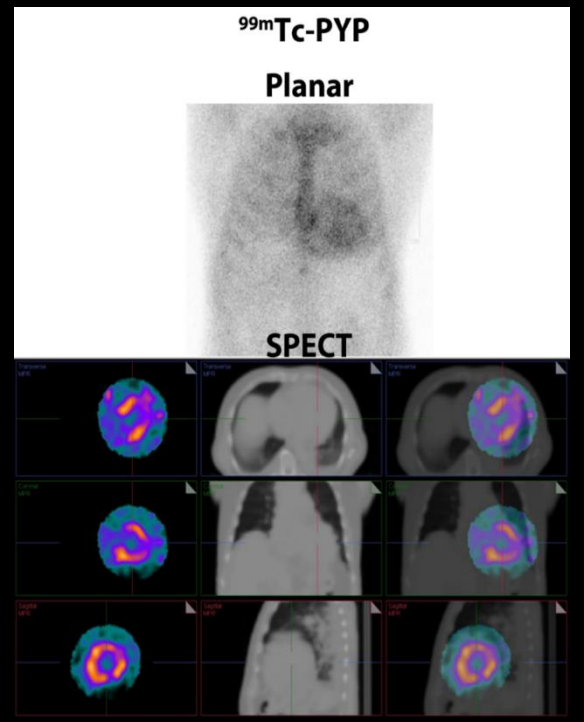




Positive SPECT with no blood pool

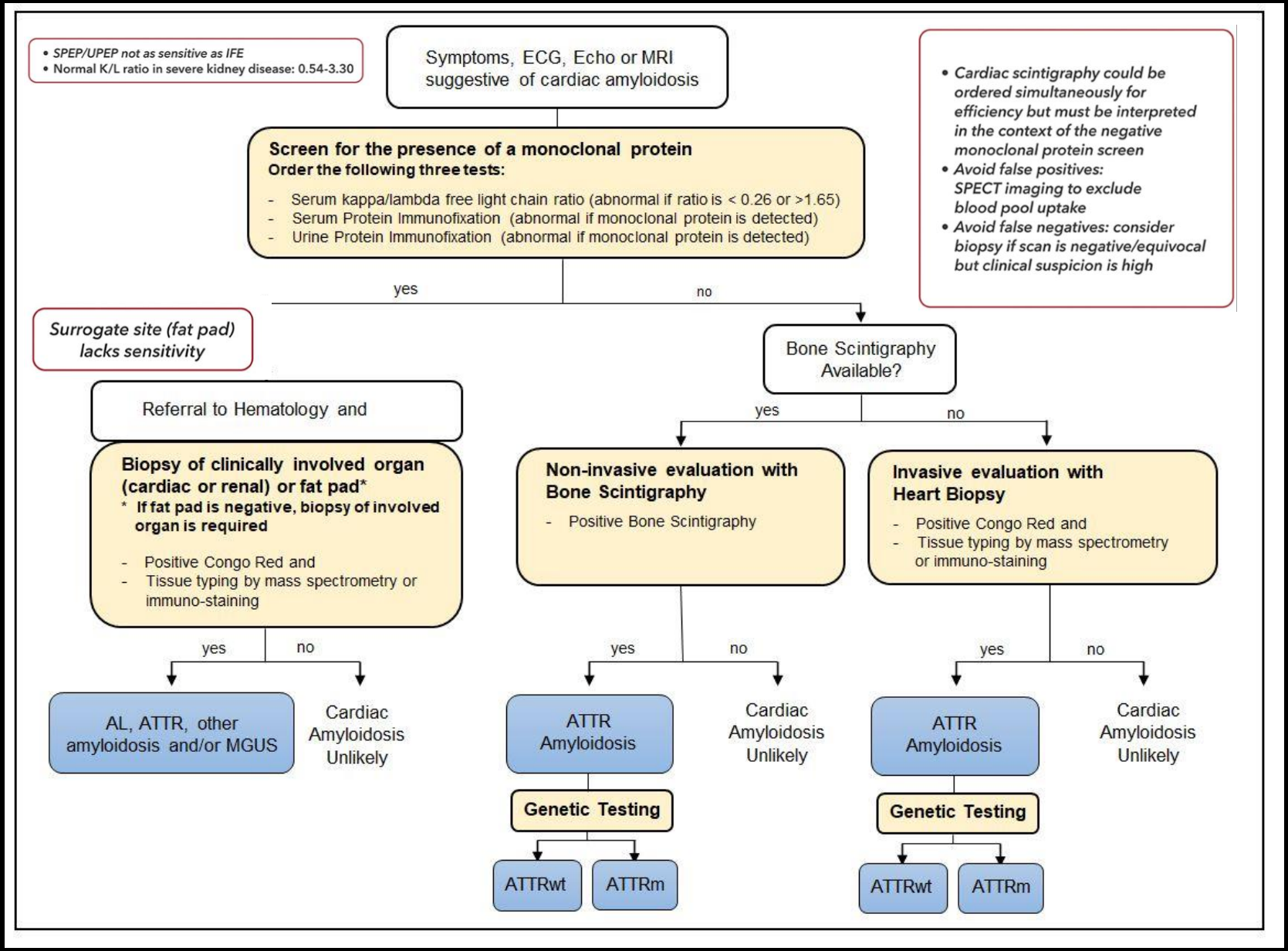


Top row is 1 hour incubation, SPECT revealing blood pool. Bottom row is 3- hour delayed imaging revealing clearance of blood pool



SPECT/CT fusion images reveal myocardial uptake and no blood pool

Expert Consensus Recommendations for the Suspicion and Diagnosis of ATTR-CM

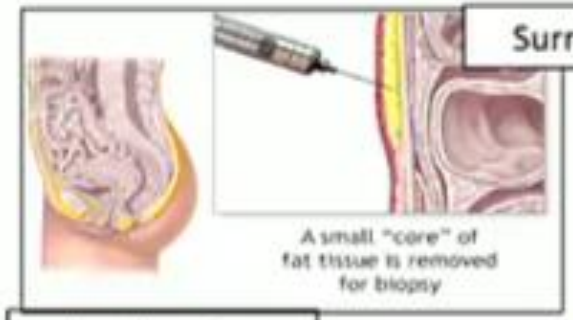


Maurer, Bokhari et al; *Circulation Heart Failure*, 2019.

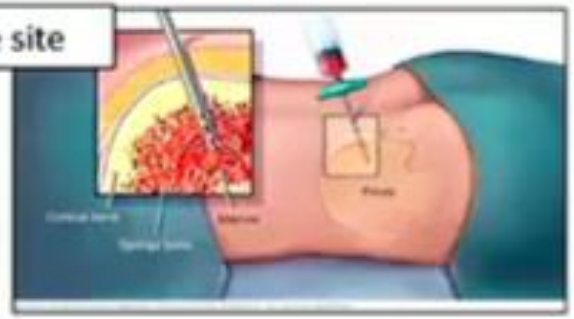
GENETIC TESTING AND COUNSELING ARE RECOMMENDED TO DISTINGUISH BETWEEN HEREDITARY AND WILD-TYPE ATTR-CM

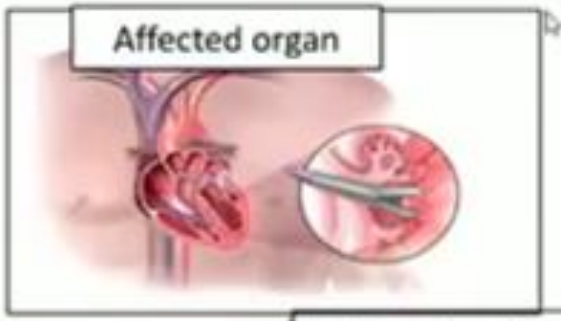
- wtATTR-CM and hATTR cannot be distinguished by clinical profile alone
- Genetic counseling and *TTR* gene sequencing are both recommended in all forms of confirmed ATTR-CM
- In healthy relatives of patients with hATTR, pre- and post-genetic test counseling may be offered

Biopsy: *Where* should you biopsy?



Surrogate site





Affected organ

Less Invasive

Less Accurate

More Invasive

More Accurate

Sensitivity	ATTR-CM		AL-CM
	ATTRwt-CM	ATTRv-CM	
Abdominal fat pad	14-16%	45-67%	73-84%
Bone marrow	30-38%	41-47%	60%
Endomyocardial biopsy	100%	100%	100%

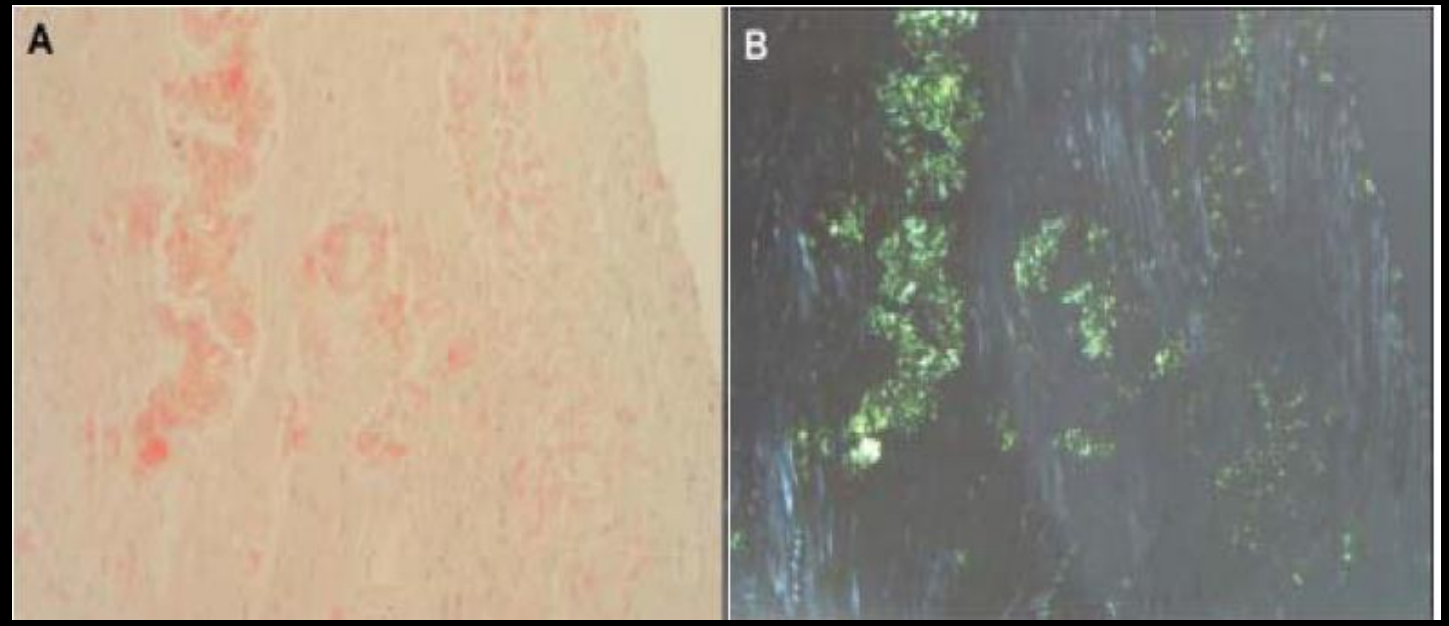
Cohen OC et al. Eur J Haematol. 2020 Sep;105(3):352-356.

Quarta CC et al. Eur Heart J. 2017 Jun 21;38(24):1905-1908.

Fine NM et al. Am J Cardiol. 2014 May 15;113(10):1723-7.

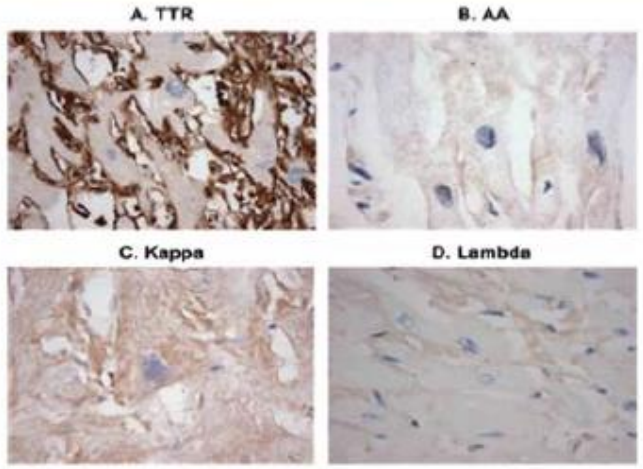
CARDIAC TISSUE BIOPSY IS AN INVASIVE TECHNIQUE USED TO HELP DIAGNOSE ATTR-CM

- Documents the extent of amyloid infiltration
- Provides definitive etiologic classification of the amyloidogenic protein
- Achieves a definitive classification to help rule out AL amyloidosis



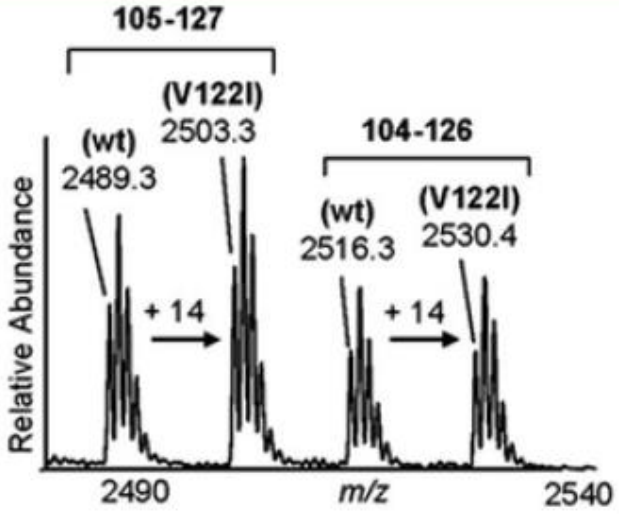
TISSUE TYPING AFTER BIOPSY CAN PROVIDE ETIOLOGIC CLASSIFICATION OF THE AMYLOIDOGENIC PROTEIN

IMMUNOHISTOCHEMISTRY[3]



Technetium pyrophosphate myocardial uptake and peripheral neuropathy in a rare variant of familial transthyretin (TTR) amyloidosis (Ser23Asn): A case report and literature review, Castaño A, et al. *Amyloid*, 2012, Taylor & Francis Ltd, reprinted by permission of Taylor & Francis Ltd.

MASS SPECTROMETRY[4,5]



This research was originally published in *Molecular and Cellular Proteomics*. Lavatelli F, et al. Amyloidogenic and Associated Proteins in Systemic Amyloidosis Proteome of Adipose Tissue. *Mol Cell Proteomics*. 2008;7:1570-1583.

A negative biopsy may not necessarily rule out cardiac amyloidosis[6]

The sensitivity of the biopsy depends on tissue location, pathologist tissue sample technique, tissue staining technique, and the varied distribution of amyloid deposits in the organ biopsied[2,6]

A Simple Score to Predict ATTR- CM

Clinical Variable	Value	Points
Age (years)	60-69	2
	or 70-79	3
	or ≥ 80	4
Sex	Male	2
Ejection Fraction	< 60%	1
Posterior Wall Thickness	≥ 12 mm	1
Relative Wall Thickness	> 0.57	2
Hypertension Hx	Present	-1

	ATTR-CM Prevalence	AUC	Score ≥ 6 Sensitivity	Score ≥ 6 Specificity	Score ≥ 6 PPV	Score ≥ 6 NPV
Derivation	45%	0.89 (0.86-0.92)	93%	62%	67%	91%
Validation Referral	48%	0.84 (0.79-0.89)	89%	56%	65%	85%
Validation Community	6%	0.85 (0.75-0.94)	83%	72%	17%	98%

Davies et al, JACC 2021

Thank you for listening!