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Amyloidosis:
Diagnosis and (Finally) Treatment

Sanjiv J. Shah, MD, FASE

Stone Professor of Medicine
Director of Research, Bluhm Cardiovascular Institute
Director, Northwestern HFpEF Program
Division of Cardiology, Department of Medicine
Northwestern University Feinberg School of Medicine
sanjiv.shah@northwestern.edu • http://www.hfpef.org • Twitter: @HFpEF

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

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Case #1

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Case presentation

70-year-old woman with HTN, T2DM, a-fib, hospitalized with acute decompensated HF

PEX: BP 92/50, HR 114, RR 16
JVP 12 cm, bibasilar crackles, tachy, regular, +ectopy, normal S1 S2, +S3, 2+ LE edema

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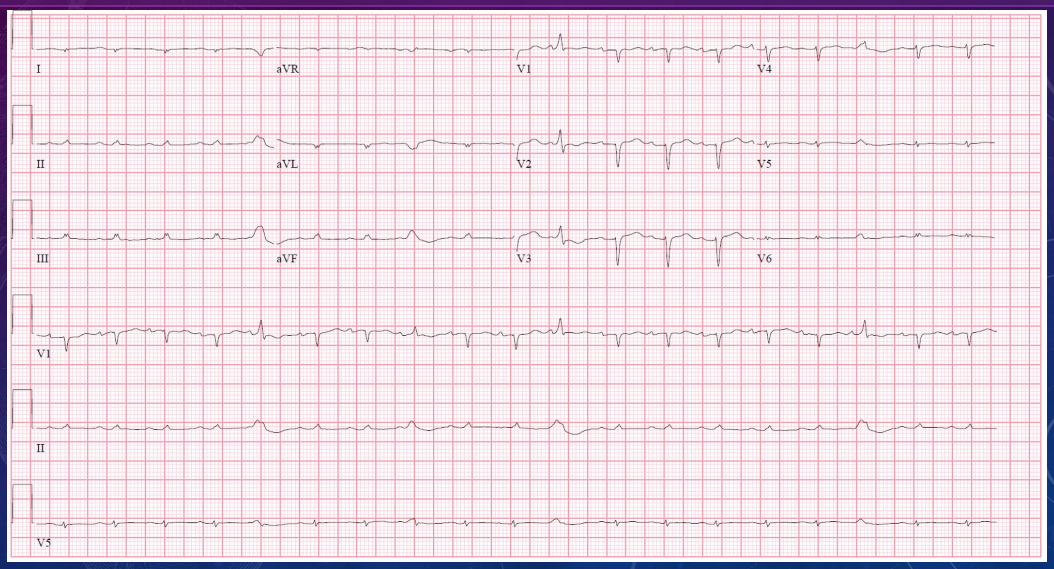
12-lead ECG on admission



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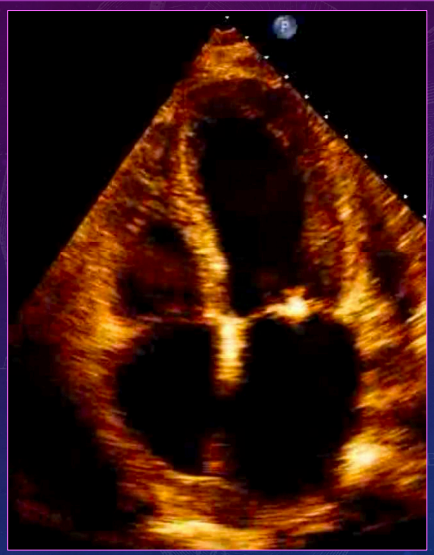
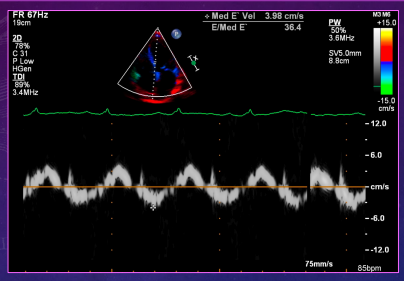
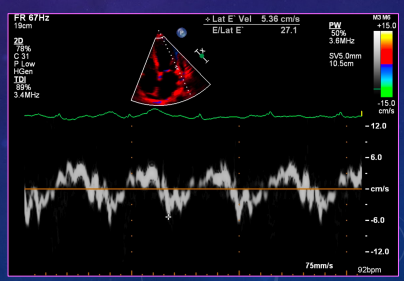
Echocardiogram on admission







- **LVEF 32%**
- **Sparkling texture of the myocardium**
- **↑LV wall thickness**
- **↓↓Tissue Doppler s', e', and a' velocities**

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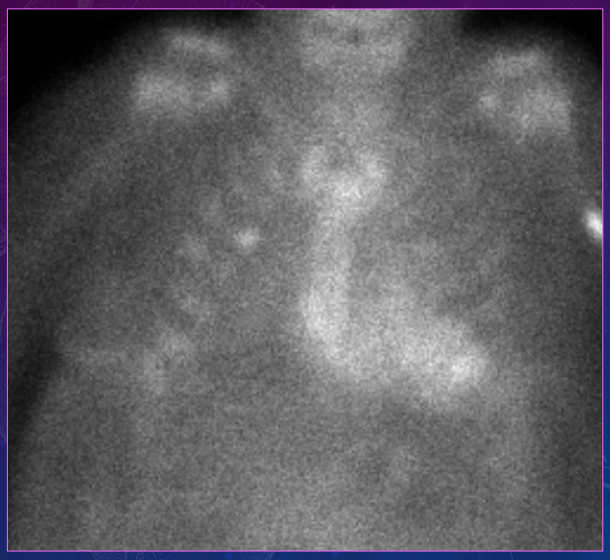
Technitium pyrophosphate scan



- AL labs showed no evidence of a plasma cell dyscrasia
- PYP scan shows heart-to-contralateral lung ratio = 1.5, qualitative grade 3 uptake
- Here is the planar image (myocardial uptake corroborated on SPECT)

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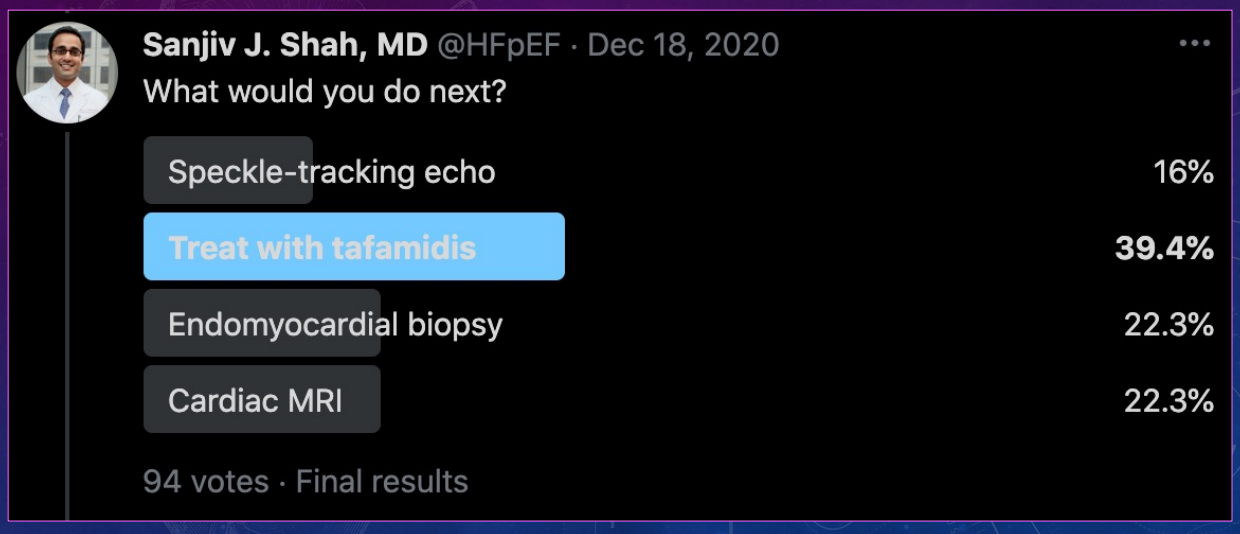
What would you do next?



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Case resolution

- What to do next? ***Endomyocardial biopsy***
- Recent MI was the cause of false positive PYP scan
- Given very +PYP uptake, would want to definitively rule out ATTR-CM so biopsy needed
- Wall motion was tip-off to exclude MI
- CMR would help but would still not answer the question about ATTR-CM definitively
- Endomyocardial biopsy: +cardiomyocyte hypertrophy and interstitial fibrosis; no evidence of amyloid

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Case #2

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Case presentation

58-year-old woman with CAD, NSTEMI, HTN, pacemaker for heart block, mixed connective tissue disease, HFpEF, presents with evidence of restrictive cardiomyopathy and progressive right-sided heart failure, now with cirrhosis

Liver biopsy: sinusoidal dilation, consistent with post-hepatic (e.g., cardiac) cause of cirrhosis

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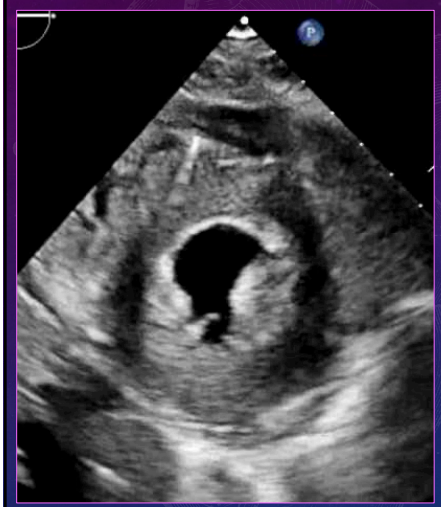
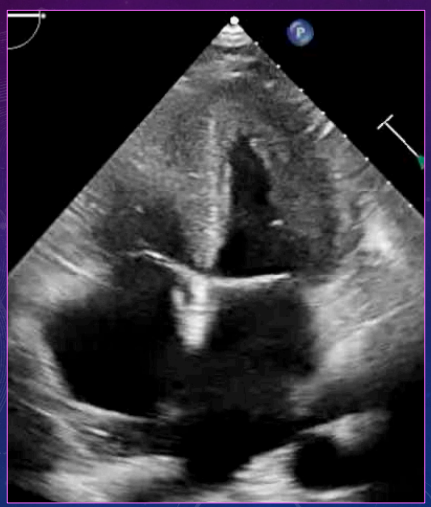
Echocardiogram





- **LVEF 60%**
- **Sparkling texture of the myocardium**
- **↑LV wall thickness**
- **↓↓Tissue Doppler s', e', and a' velocities**

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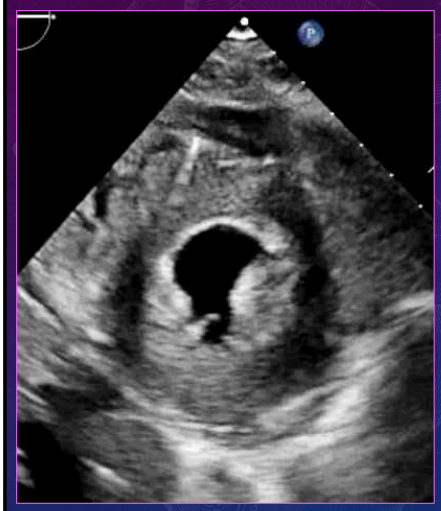
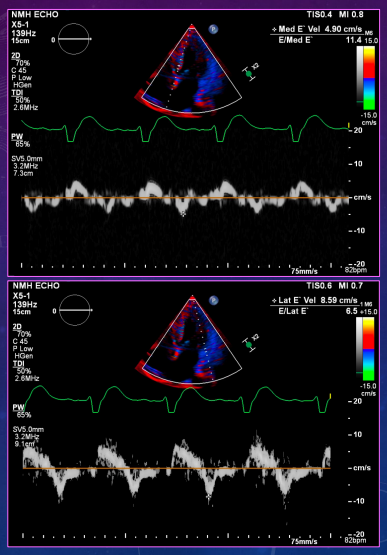
Echocardiogram





- LVEF 60%
- Sparkling texture of the myocardium
- ↑LV wall thickness
- ↓↓Tissue Doppler s', e', and a' velocities

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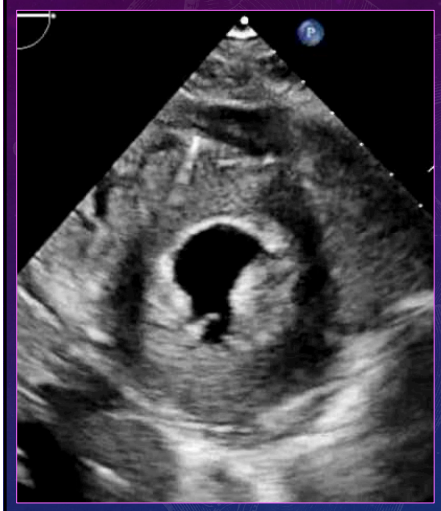
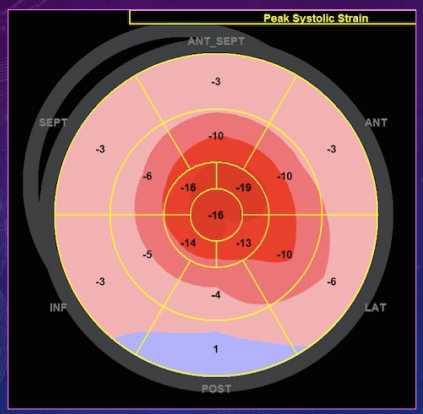
Echocardiogram





- LVEF 60%
- Sparkling texture of the myocardium
- ↑LV wall thickness
- ↓↓Tissue Doppler s', e', and a' velocities
- Relative apical sparing on LV longitudinal strain bullseye map

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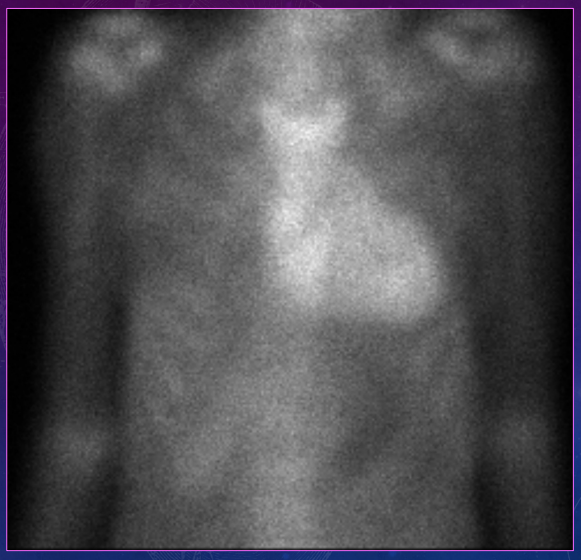
Technitium pyrophosphate scan



- She had progressive worsening of symptoms, so right heart catheterization was done:
- RA 22 mmHg, RV 42/22 mmHg, PA 44/25 mmHg, PCWP 24 mmHg, PA sat 55%, CI 1.6 L/min/m^2
- Tc-PYP scan showed ↑↑H/CL ratio 1.56, grade 3 uptake, confirmed on SPECT to be myocardial uptake
- AL amyloid work-up was negative

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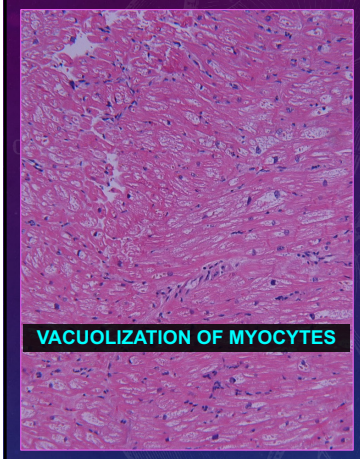
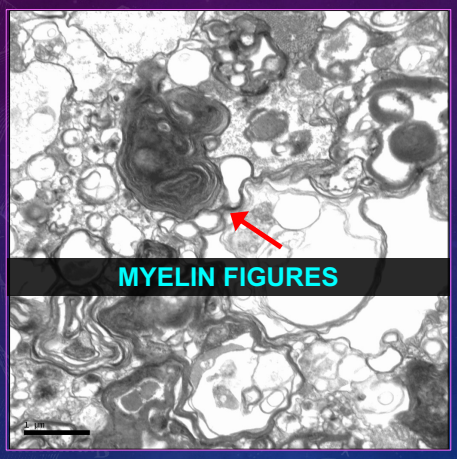
Endomyocardial biopsy





- This patient was on hydroxychloroquine for 29 years
- Endomyocardial biopsy showed intense vacuolization of cardiomyocytes on H&E and myelin figures on EM, consistent with hydroxychloroquine cardiotoxicity

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Case #3

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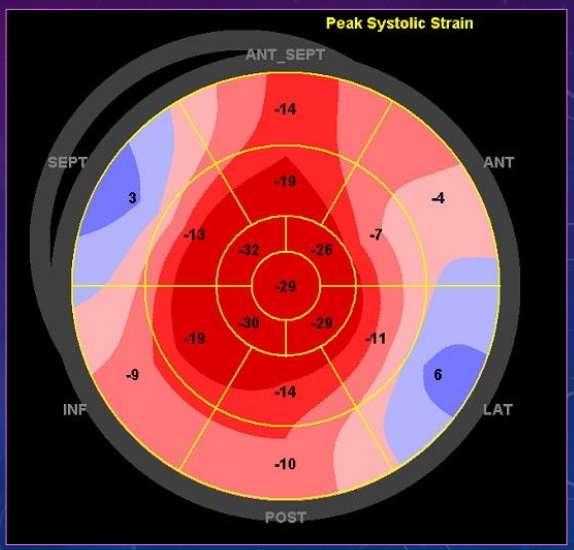
Case presentation

A woman in her late 60s with a history of limited cutaneous systemic sclerosis, HTN, DM2, DVT, TIA, hypothyroid, ILD, OSA, and GERD presents to ER with leg swelling.

What's the diagnosis?



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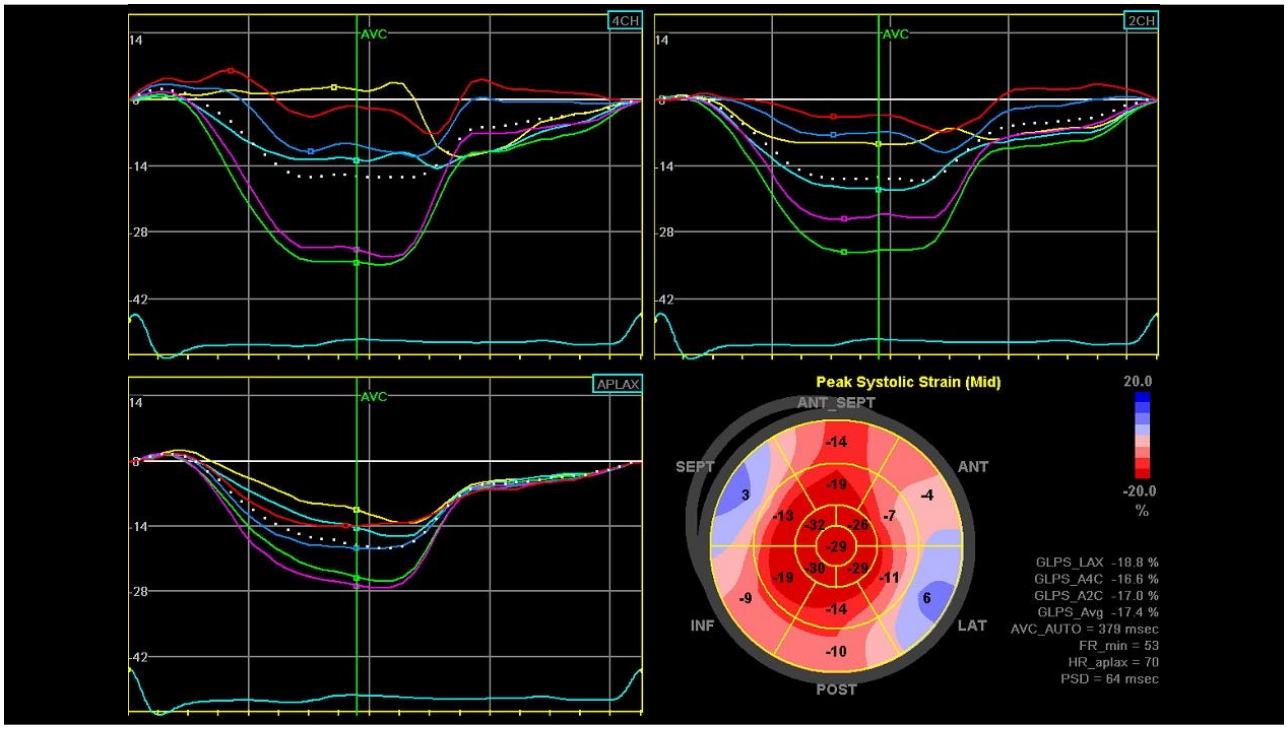
4CH
AVC
2CH
AVC
APLAX
AVC
Peak Systolic Strain (Mid)
ANT_SEPT
SEPT
ANT
INF
LAT
POST
20.0
-20.0
%
GLPS_LAX -18.8 %
GLPS_A4C -16.6 %
GLPS_A2C -17.0 %
GLPS_Avg -17.4 %
AVC_AUTO = 379 msec
FR_min = 53
HR_aplax = 70
PSD = 64 msec

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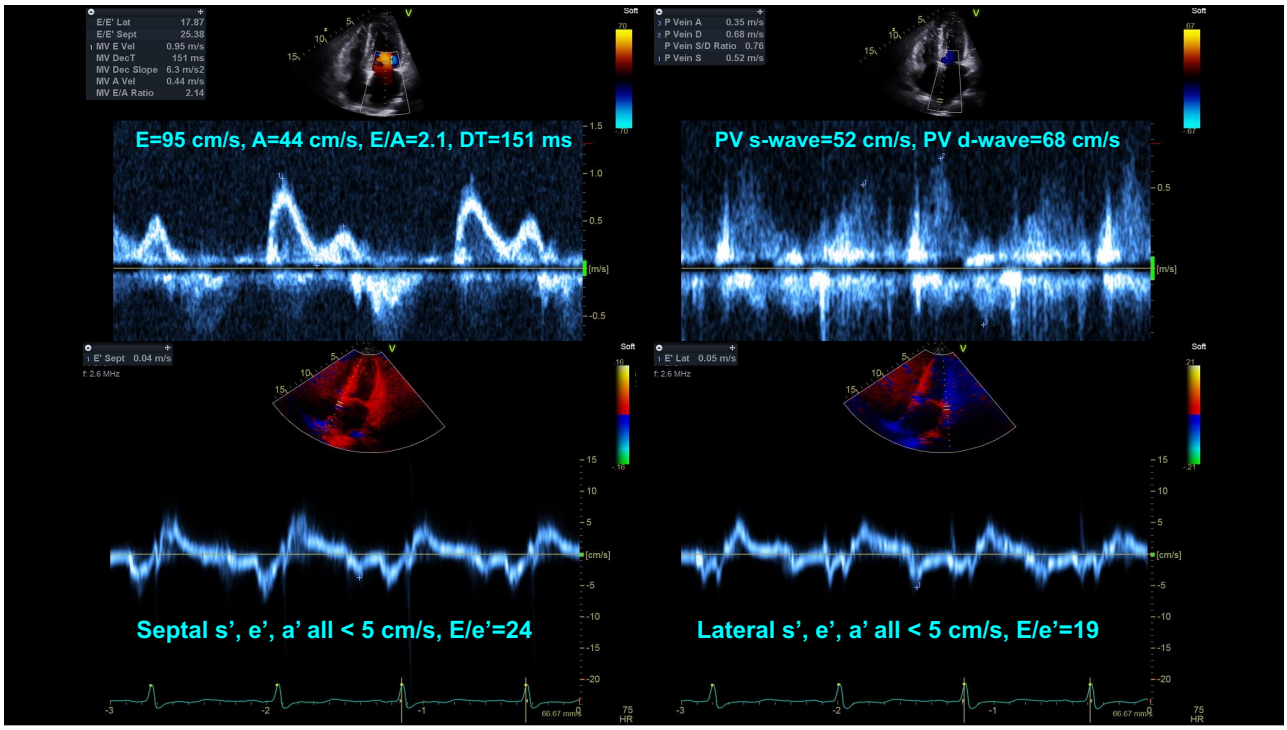
E=95 cm/s, A=44 cm/s, E/A=2.1, DT=151 ms
PV s-wave=52 cm/s, PV d-wave=68 cm/s
Septal s', e', a' all < 5 cm/s, E/e'=24
Lateral s', e', a' all < 5 cm/s, E/e'=19

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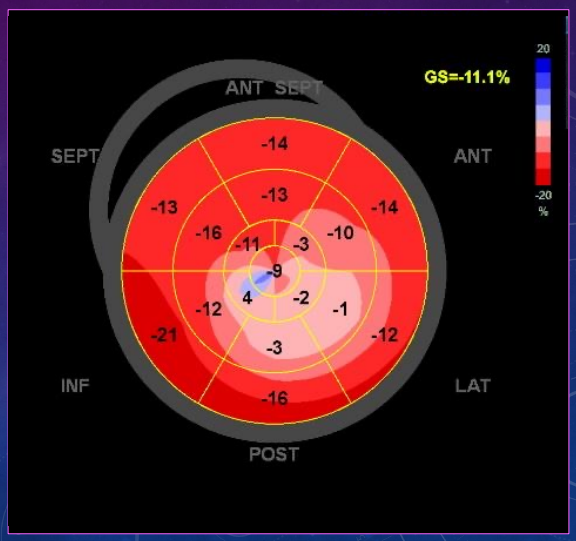
3 months later…

- Work-up for cardiac amyloidosis (PYP scan, AL amyloid labs: negative)
- Stable symptoms
- Echo repeated due to persistent shortness of breath

Now what's the diagnosis?



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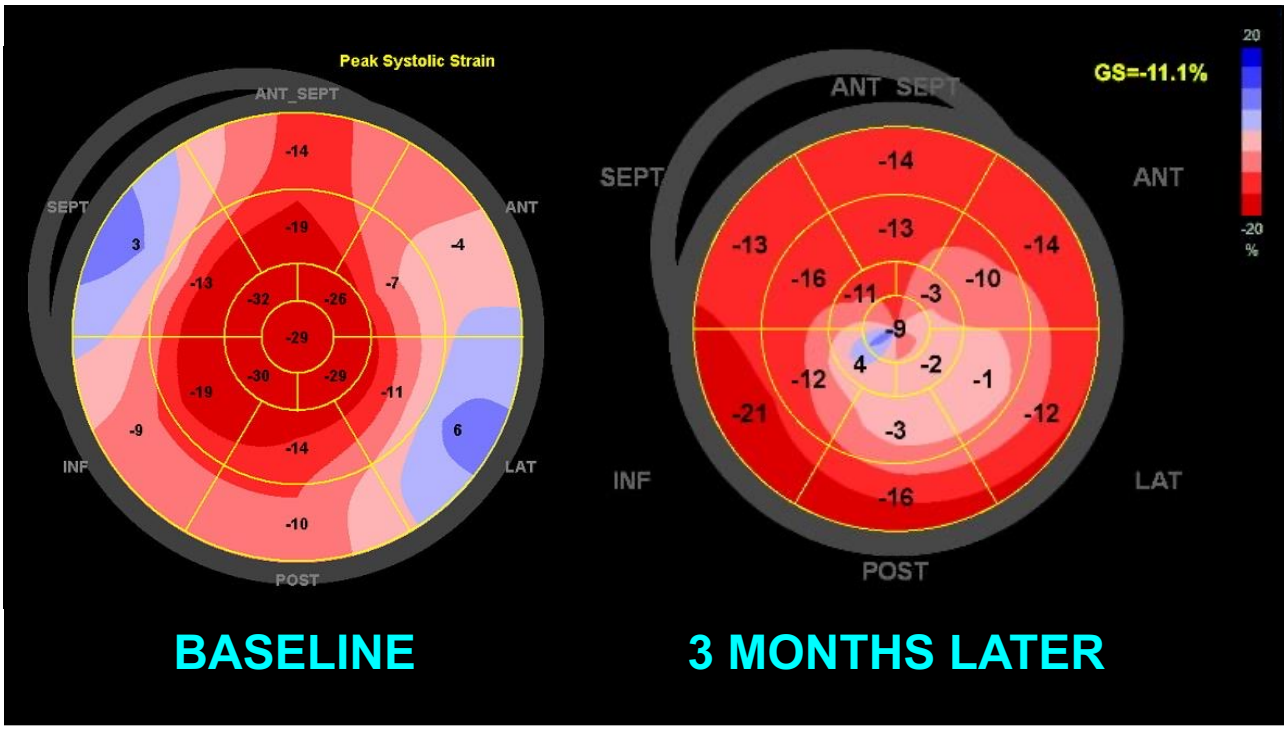

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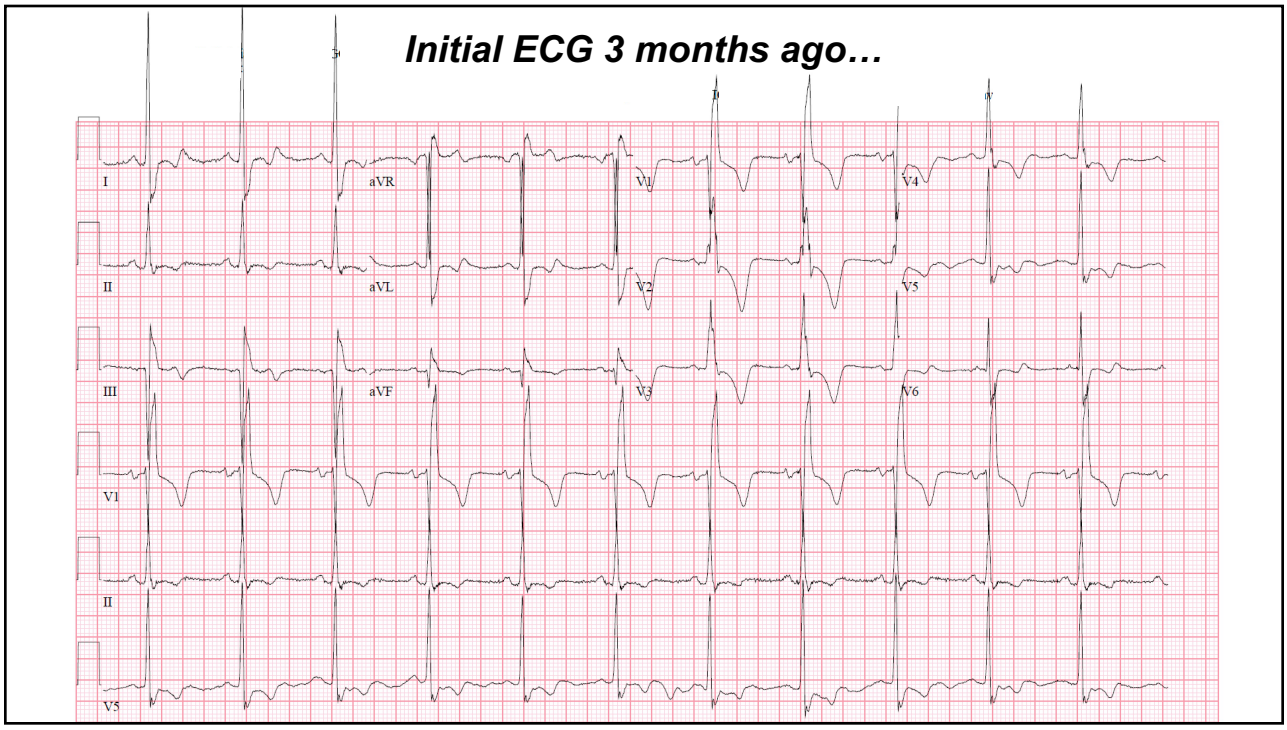
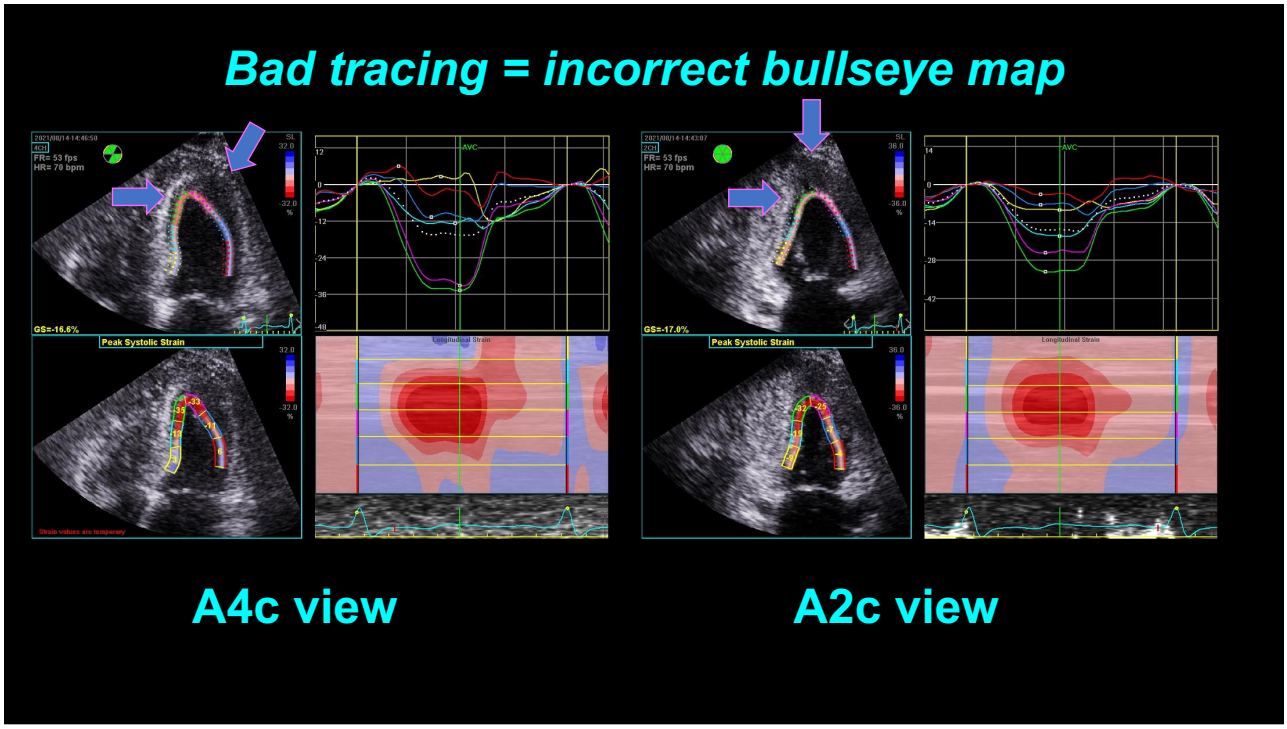

Initial ECG 3 months ago…
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5

23


Bad tracing = incorrect bullseye map
FR= 53 fps
HR= 70 bpm
GS=-16.6%
Peak Systolic Strain
FR= 53 fps
HR= 70 bpm
GS=-17.0%
Peak Systolic Strain
A4c view
A2c view

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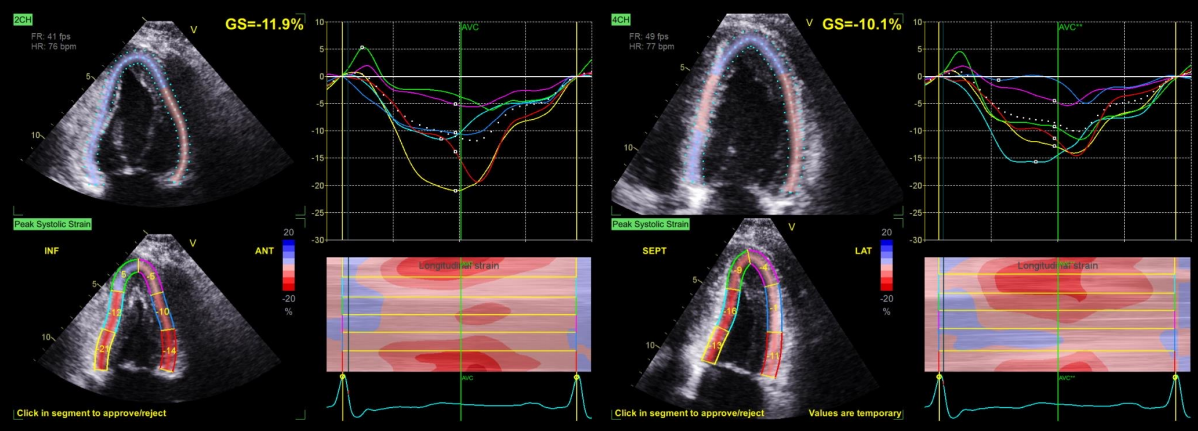
Correct tracing



A4c view

A2c view

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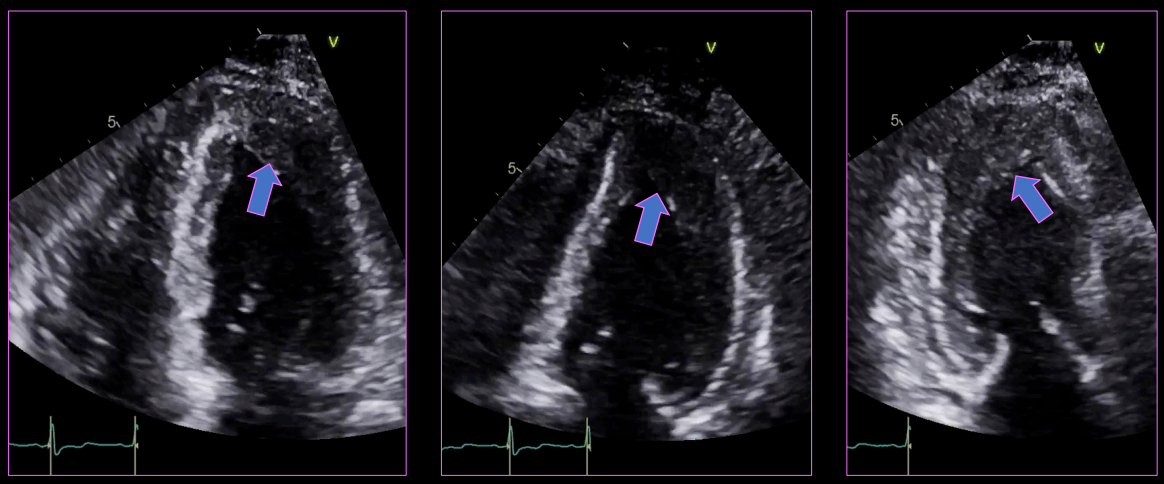
Final diagnosis (confirmed by cardiac MRI)



Apical hypertrophic cardiomyopathy

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The high cost of a misdiagnosis…

Circulation

ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Tafamidis Therapy for Transthyretin Amyloid Cardiomyopathy

Assuming a threshold of $100,000 per quality-adjusted life-year gained and current drug price, tafamidis was cost-effective in 0% of 10,000 probabilistic simulations. A 92.6% price reduction from $225,000 to $16,563 would be necessary to make tafamidis cost-effective at $100,000/quality-adjusted life-year.

Kazi D… Shah SJ *Circulation* 2020

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What is amyloidosis?

- Group of disorders characterized by extra-cellular deposition of fibrillar protein
- Deposits composed of amyloid fibrils → progressive end-organ dysfunction
- > 20 proteins form amyloid fibrils *in vivo*
- 2 predominant types involve the heart:
  - ✓ Transthyretin (TTR)-associated: hereditary and wild-type
  - ✓ AL: typically associated with plasma cell dyscrasia

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When to suspect cardiac amyloidosis

Red flags for cardiac amyloidosis	Low voltage ECG + thick LV, thickening of RV, valves, atria
	Intolerance to beta-blockers, ACE-I/ARB, sacubitril/valsartan
	Low BP in patients with prior history of HTN
	History of bilateral carpal tunnel syndrome, lumbar spinal stenosis, or biceps tendon rupture
Clues to ATTR amyloid	HFpEF with carpal tunnel or spinal stenosis
	HFpEF without a history of HTN
	New diagnosis of HCM in older pt
	New dx of low-flow, low-gradient AS in an older pt
	Family history of ATTR amyloid
Clues to AL amyloid	HFpEF + nephrotic syndrome
	Macroglossia, periorbital purpura
	Peripheral neuropathy
	Orthostatic hypotension

Adapted from:
Donnelly JP, Hanna M.
CCJM 2017

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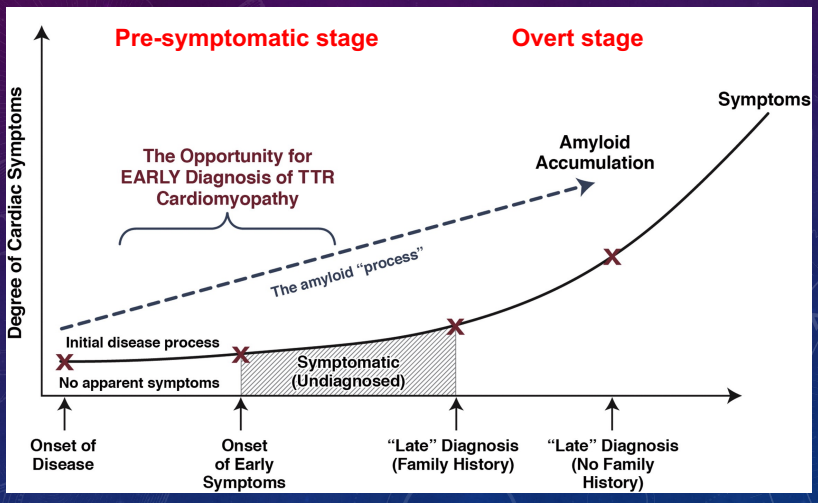
Early diagnosis is critical in amyloid



Arbustini G, Merlini G. *JACC Cardiovasc Imaging*. 2014;7:511–4.

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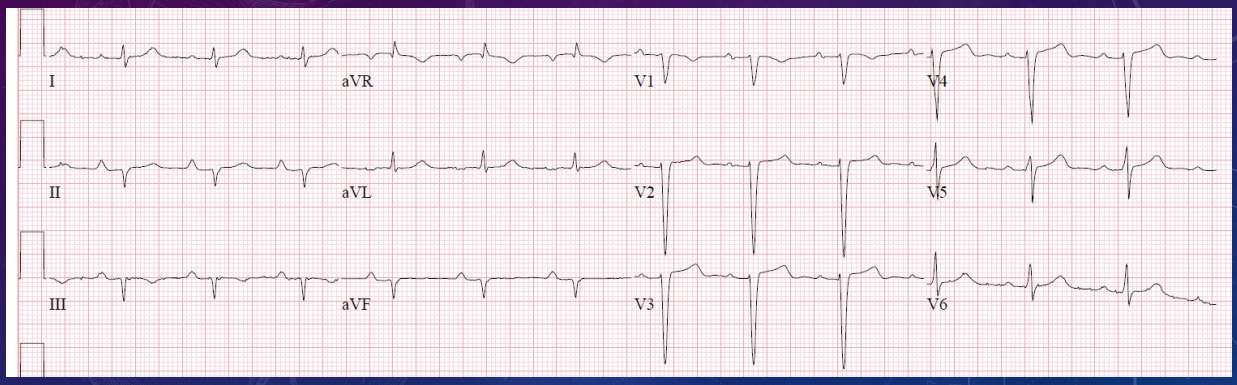
Cardiac amyloid: typical ECG findings



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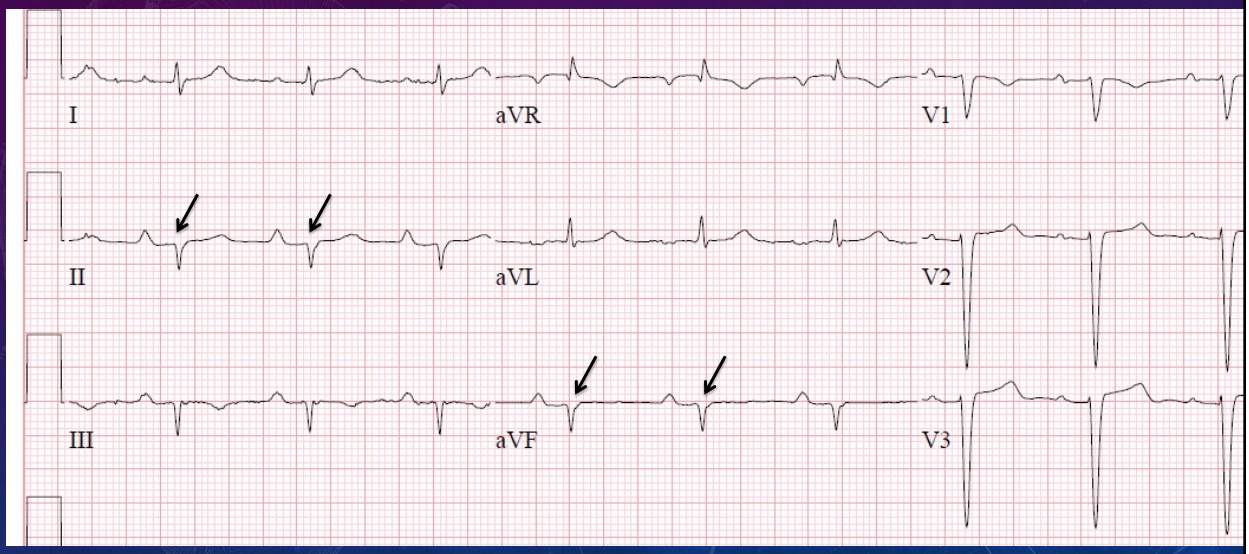
Cardiac amyloid: typical ECG findings



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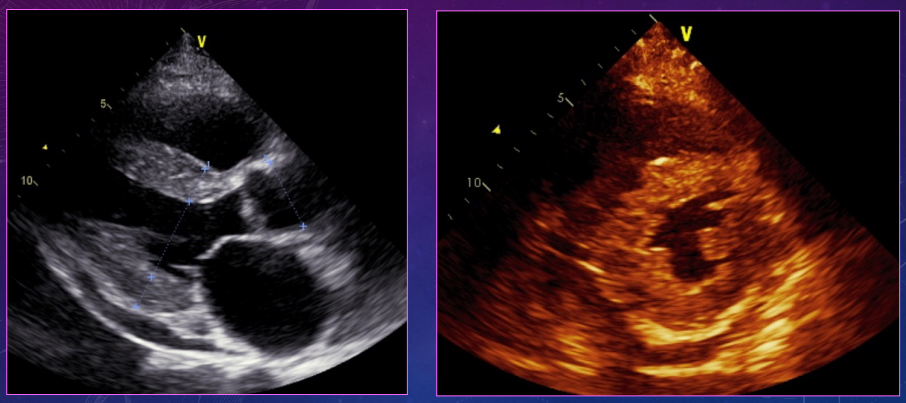
Cardiac amyloid: typical echo findings



Thick walls, sparkling myocardium, pericardial effusion

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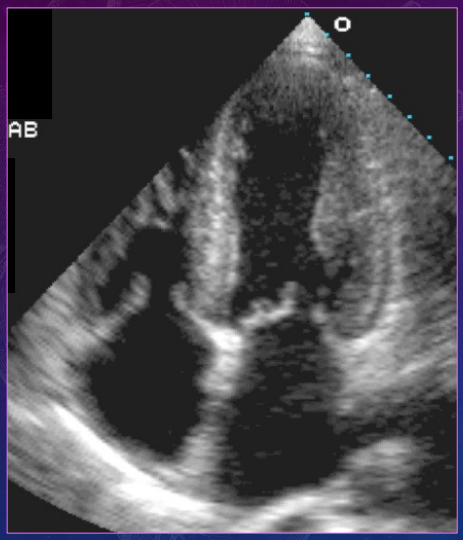
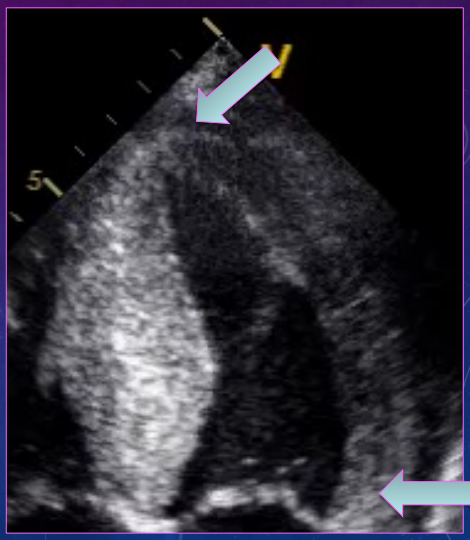
Cardiac amyloid: typical echo findings





Loss of longitudinal cardiac function

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Typical echo findings

Severely reduced longitudinal tissue velocities

"5-5-5 sign"

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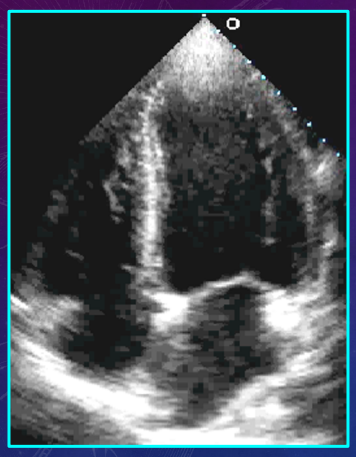
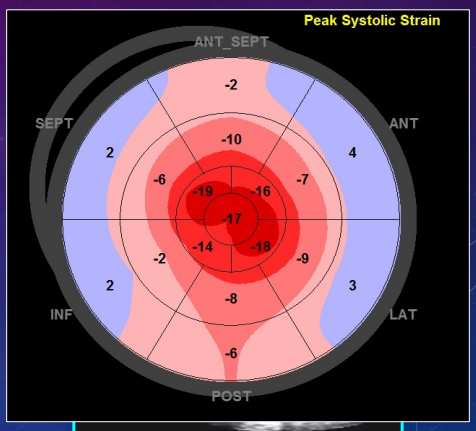
Echo diagnosis of cardiac amyloid



"Garden-variety" HFpEF



"Cherry on the top" sign on speckle-tracking echo bullseye map of LV global longitudinal strain

Cardiac amyloidosis

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Echo diagnosis of cardiac amyloid

Table 4. Bootstrapped ROC Curve Characteristics and Cut-Off Points of Deformation Echo Parameters for Differential Diagnosis of Amyloidosis

Variable	AUC	95% CI	*P* Value	Cutoff	95% CI	Sens, %	95% CI	Spec, %	95% CI	+LR	95% CI	–LR	95% CI
GLS, %	0.85	0.77–0.89	<0.0001	>–15.1	>–16.7 to >–13.1	87.5	73–96	71.7	59–83	3.09	2–4.7	0.17	0.08–0.4
GCS, %	0.83	0.73–0.90	<0.0001	<–18.3	>–22.2 to >–17.4	86.2	68.3–96.1	57.1	43.2–70.3	2.01	1.4–2.8	0.24	0.09–0.6
GRS, %	0.82	0.72–0.90	<0.0001	≤9.01	≤5.33 to ≤9.78	65.5	45.7–82.1	89.3	78–96	6.1	2.7–13.6	0.39	0.2–0.6
EFSR	0.95	0.89–0.984	<0.0001	>4.1	>3.6 to >4.1	89.7	75.8–97.1	91.7	81.6–97.2	10.8	4.6–25.1	0.11	0.04–0.3
RELAPS	0.78	0.68–0.86	<0.0001	>0.87	>0.79 to >1	62.5	43.8–77.3	85	73.4–92.9	4.17	2.2–8	0.44	0.3–0.7
				>1.0*	…	37.5	22.7–54.2	93.3	83.8–98.2	5.63	2–15.7	0.67	0.5–0.9
SAB	0.67	0.57–0.76	0.0024	>3.1	>1.7 to >3.7	47.5	31.5–63.9	86.7	75.4–94.1	3.56	1.7–7.3	0.61	0.4–0.8
				>2.1*	…	65	48.3–79.4	53	41.6–67.9	1.44	1–2.1	0.64	0.4–1.0

+LR indicates positive likelihood ratio; –LR, negative likelihood ratio; AUC, area under curve; Cutoff, values that distinguish best in our data set; CI, confidence intervals; EFSR, ejection fraction strain ratio; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; RELAPS, relative apical sparing (ratio of apical longitudinal /sum of base and mid longitudinal strain); ROC, receiver operator characteristic; SAB, septal apical to base longitudinal strain; Sens, sensitivity; and Spec, specificity.

- EFSR = LVEF/GLS ratio, cut-off >4.1 for cardiac amyloid (LR+ 10.8, LR- 0.11)

Pagourelias E, et al. *Circ CV Imaging* 2017

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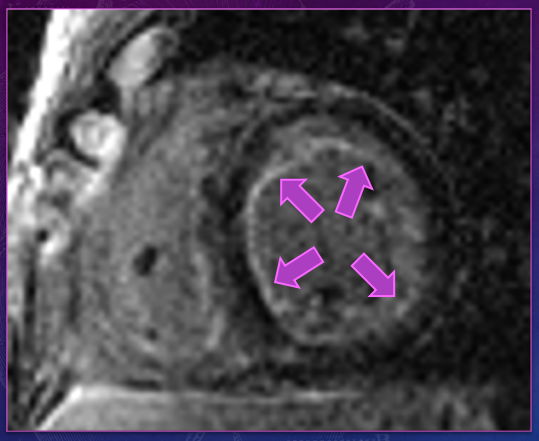
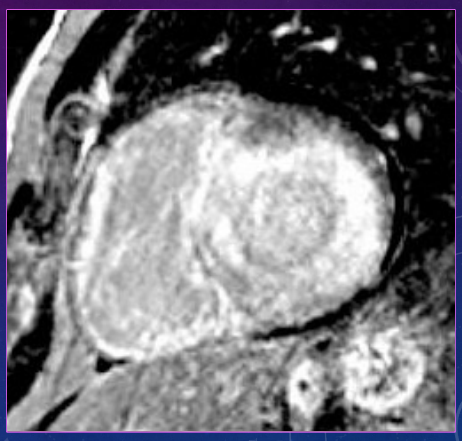
Typical cardiac MRI findings



Diffuse subendocardial delayed enhancement



Difficulty nulling the myocardium

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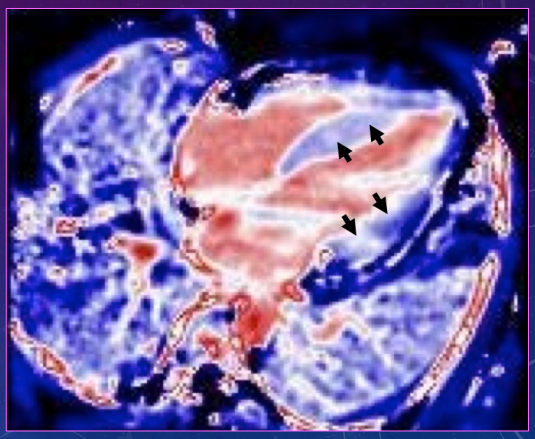
Typical cardiac MRI findings

Extracellular volume (ECV; % of myocardium)	
4-chamber	43.8%
Short axis (base)	40.4%
Short axis (mid)	37.8%
Normal	< 25%



Increased ECV on T1 mapping in a patient with AL amyloidosis

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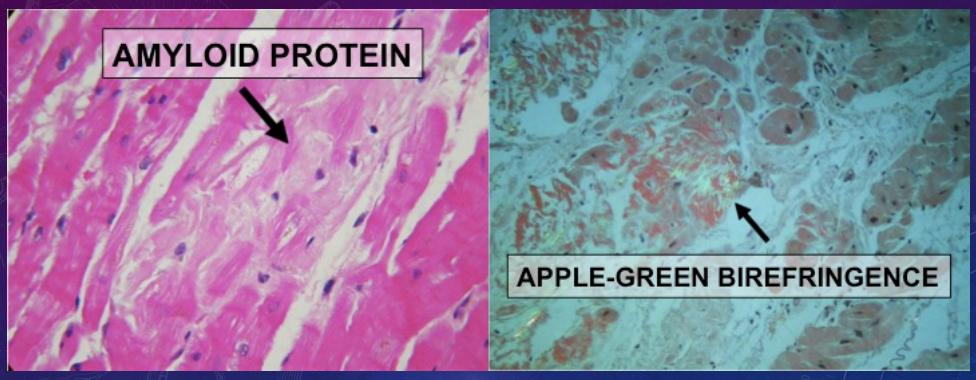
Endomyocardial biopsy findings



Mass-spectrometry: amyloid fibrils composed of abnormal transthyretin (TTR)
Genotyping: V122I *TTR* variant

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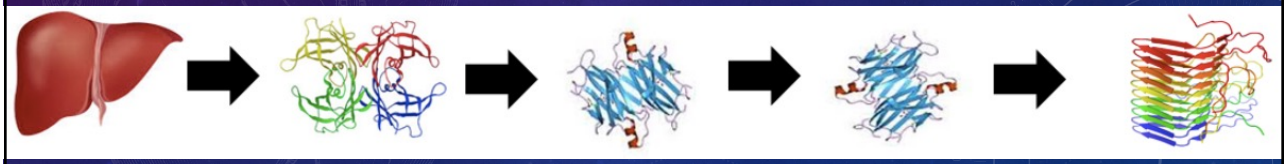
ATTR-cardiomyopathy (ATTR-CM)

- Transthyretin (TTR [=prealbumin]):
  - ✓ Primarily made by the liver, abundant in serum
  - ✓ Transports thyroxine and retinol binding protein
  - ✓ Normally tightly folded and forms a stable tetramer



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History of ATTR-CM

- TTR amyloid cardiomyopathy (ATTR-CM):
  - ✓ Recognized as distinct form of cardiac amyloid in 1980s
  - ✓ 2 types: hereditary and wild-type (senile)
  - ✓ Biopsy required to make the diagnosis
  - ✓ Thought to be a rare cause of heart failure
  - ✓ Often diagnosed late, high morbidity + mortality
  - ✓ Only treatment = heart tx or heart+liver tx
  - ✓ TTR tetramer dissociation: rate-limiting step in TTR amyloid fibril formation

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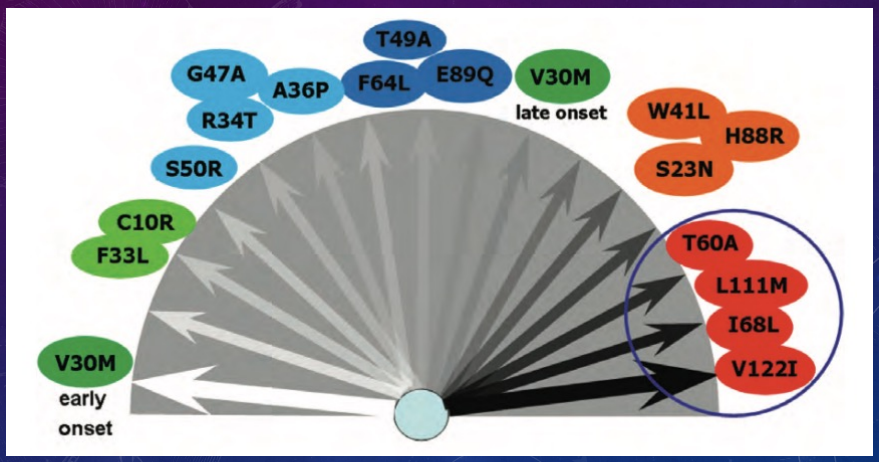
Spectrum of hereditary ATTR phenotypes



NEUROLOGIC CARDIAC

Rapezzi C, et al. *Eur Heart J* 2013

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ATTR-CM is not rare…

- ATTR-CM is common in older HFpEF patients:
  - ✓ 13% of hospitalized HFpEF pts age > 60 with LV wall thickness > 1.2 cm
  - ✓ 14% of HFpEF patients undergoing cardiac biopsy
  - ✓ 15% of patients age > 80 undergoing TAVR
- Imaging techniques for non-biopsy diagnosis:
  - ✓ Echo with speckle-tracking, cardiac MRI with T1 mapping, bone scintigraphy (e.g., Tc-PYP scanning)

Gonzalez-Lopez E, et al. *Eur Heart J* 2015; Hahn V, et al. *JACC Heart Fail* 2020; Castano A, et al. *Eur Heart J* 2017

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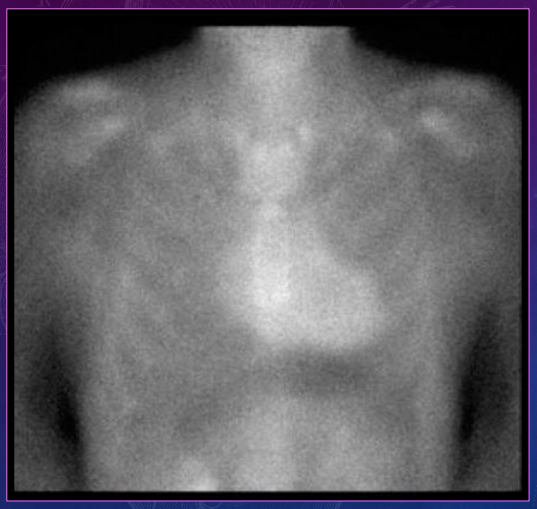
Bone scintigraphy (^{99m}Tc-PYP)



- TTR amyloid fibrils are Ca^{2+} avid
- Bone scintigraphy (e.g., Tc-PYP) differentiates TTR from AL cardiac amyloid*
- Heart/contralateral lung ratio:
  - > 1.5 diagnostic*, < 1.0 ruled out
  - > 1.6 → poor prognosis

***MUST FIRST RULE OUT AL AMYLOIDOSIS WITH SERUM, URINE TESTING**

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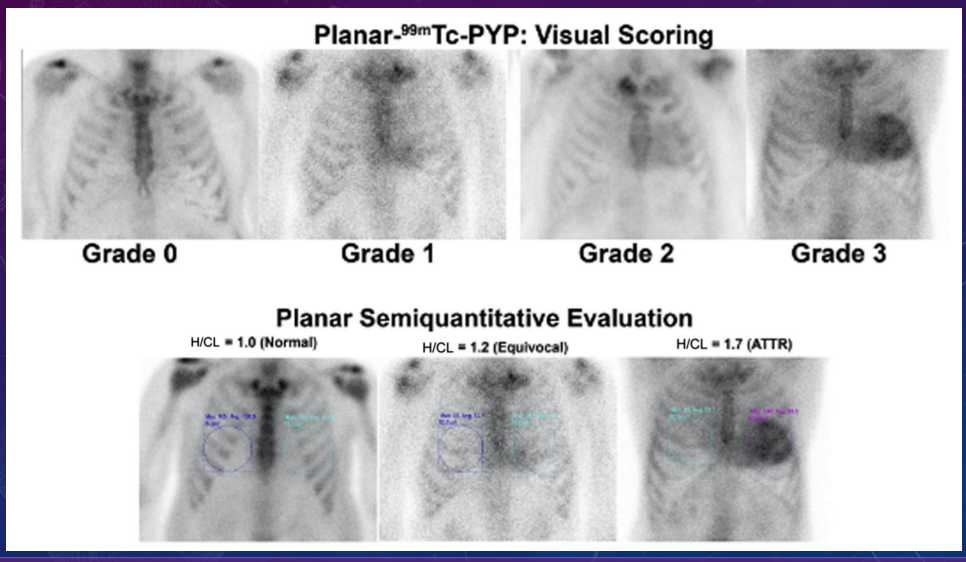
^{99m}Tc-PYP: Planar images



Hanna M, et al. *JACC* 2020

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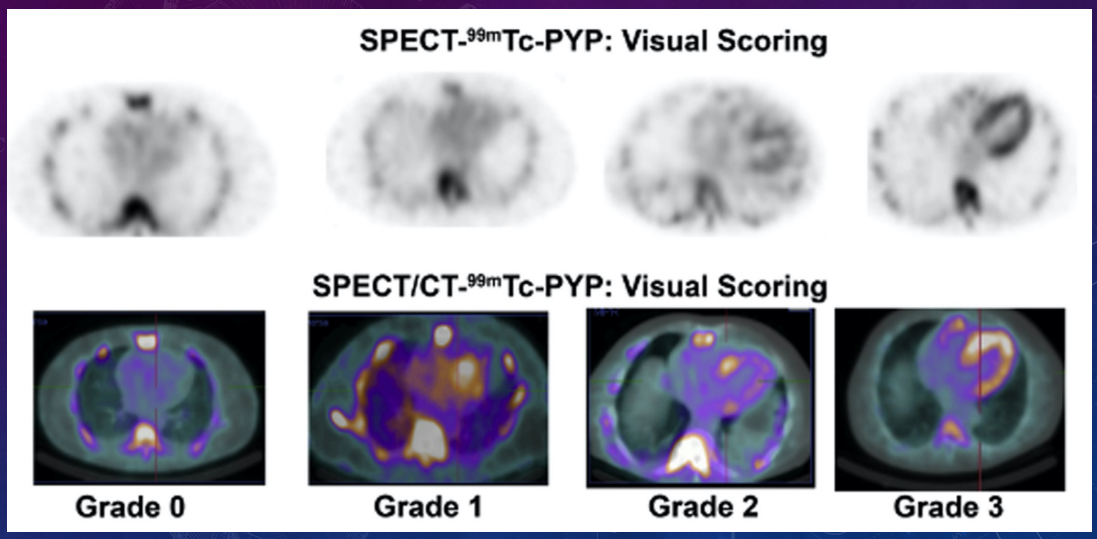
^{99m}Tc-PYP: SPECT images



Hanna M, et al.
JACC 2020

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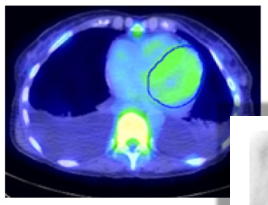
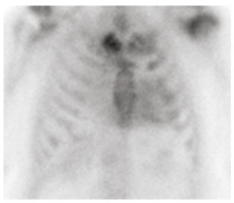
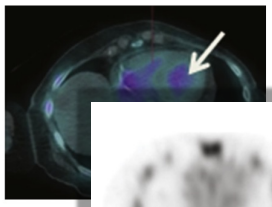
^{99m}Tc-PYP: Don't get burned…



Positive PYP ≠ ATTR; Diagnc

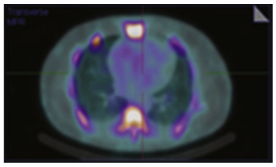
❖ Always screen for





Positive PYP = blood pool upta

❖ Always perform S



Negative PYP, Clinical suspicion persists

Cardiac biopsy: Diagnosis = ATTRv

❖ Perform biopsy if strong clinical suspicion

Hanna M, et al.
JACC 2020

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^{99m}Tc-PYP: False positives/negatives

- False positives:
  - ✓ AL amyloidosis
  - ✓ Blood pool uptake
  - ✓ Rib fracture
  - ✓ Recent MI
  - ✓ Hydroxychloroquine cardiotoxicity
  - ✓ Other rare forms of cardiac amyloidosis
- False negatives:
  - ✓ Early disease
  - ✓ Val30Met *TTR* mutation
  - ✓ Phe64Leu *TTR* mutation

Hanna M, et al. *JACC* 2020

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Rx landscape for ATTR-CM

TTR stabilizers	**Tafamidis (FDA-approved)**	
	Diflunisal	
	AG10	
	Tolcapone	
TTR silencers	***siRNA***	**Patisiran**
	ASO	**Inotersen**
	Gene editing	**NTLA-2001**
Fibril disruptors	**Doxycycline + TUDCA**	
	Green tea extract	
	Anti-amyloid antibody	

Adapted from Donnelly JP, Hanna M. *CCJM* 2017

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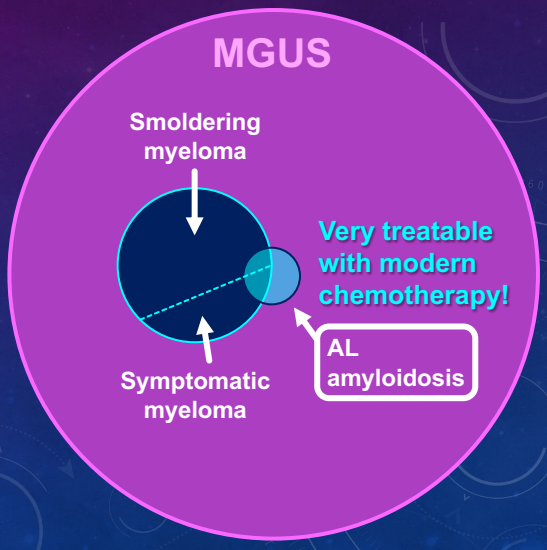
AL amyloidosis: Major advances in Rx

- Plasma cell dyscrasias:
  - ✓ Plasma cell clones in bone marrow produce monoclonal antibody and excess light chains
- 3 possible outcomes:
  1. Only small % of marrow, circulating light chains don't deposit → MGUS
  2. Large % of marrow involved → multiple myeloma
  3. **Circulating light chains deposit in tissue → AL amyloidosis**



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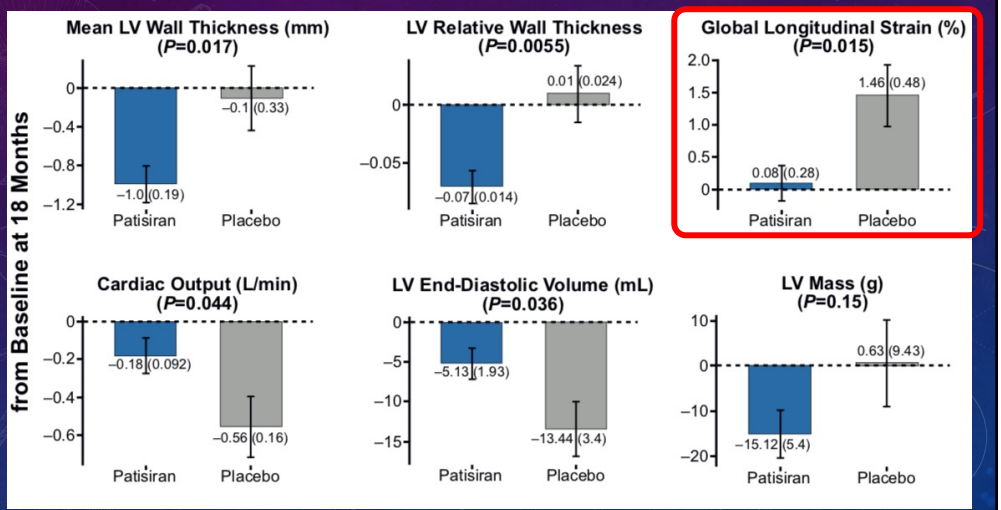
Can Rx of cardiac amyloid improve strain?

APOLLO RCT: TTR silencer patisiran (RNAi) for hereditary TTR peripheral neuropathy

Cardiac subgroup = LVH + no HTN



Solomon SD et al. *Circulation* 2019

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Can Rx of cardiac amyloid improve strain?

ATTR-ACT RCT: TTR stabilizer tafamidis for TTR cardiac amyloidosis (included hereditary and wild-type)

No change in wall thickness or LVEF but ↑SV, ↑circ strain, ↑radial strain (LV GLS slight improvement)

Echocardiography Measure	Pooled Tafamidis (N = 264)	Placebo (N = 177)	Difference (tafamidis – placebo)	
			LS Mean	95% CI
Left ventricular ejection fraction — %				
Baseline, mean (SD)	48.4 (10.3)	48.6 (9.5)		
Change from baseline at 30 months, LS mean (SE)	-2.82 (0.85)	-4.34 (1.10)	1.51 (1.06)	-0.57 to 3.60
Left ventricular stroke volume — ml			SV	
Baseline, mean (SD)	45.8 (16.1)	45.1 (16.9)		
Change from baseline at 30 months, LS mean (SE)	-5.38 (0.99)	-11.66 (2.09)	6.28 (2.20)	1.96 to 10.59
Circumferential mid global strain — %			circ. strain	
Baseline, mean (SD)	-16.4 (8.6)	-16.8 (9.6)		
Change from baseline at 30 months, LS mean (SE)	-0.77 (0.65)	1.91 (0.65)	-2.67 (0.78)	-4.20 to -1.15
Radial mid global strain — %			rad. strain	
Baseline, mean (SD)	17.8 (11.0)	17.6 (10.4)		
Change from baseline at 30 months, LS mean (SE)	0.25 (0.77)	-3.28 (1.18)	3.53 (1.29)	1.00 to 6.06
Global longitudinal strain — %			GLS	
Baseline, mean (SD)	-9.3 (3.5)	-9.4 (3.6)		
Change from baseline at 30 months, LS mean (SE)	1.46 (0.28)	2.16 (0.33)	-0.70 (0.37)	-1.43 to 0.02

LS denotes least square, SD standard deviation, and SE standard error.

Maurer M, et al. *N Engl J Med* 2018

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Cardiac amyloidosis: SEARCH mnemonic

- **S**olidified the Dx? When in doubt: biopsy
- **E**tiology of amyloid: is it being treated?
- **A**utonomic dysfunction: evaluate and treat
- **R**hythm abnormalities: diagnose and treat
- **C**VA prophylaxis: consider even in sinus rhythm
- **H**eart failure: maintain euvolemia, and typical GDMT may be contraindicated

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Take home points

- There are several mimickers of cardiac amyloidosis… know the whole spectrum of echo findings of amyloid: don't get fooled by simply looking at bullseye map and nothing else!
- Know the causes of false positive and false negative bone scintigraphy (e.g., Tc-PYP) imaging
- Both ATTR cardiomyopathy and AL amyloidosis are treatable… not a death sentence anymore!
- Tafamidis is very expensive, so we should not treat patients who do not have ATTR cardiomyopathy!

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