
Cleveland Clinic
Wake Up and Look Around Cardiac
Towards Earlier Recognition Diagnosis
and Treatment of Cardiac Amyloid
David Wolinsky MD FACC MASNC
Section Head Nuclear Cardiology
Director Cardiac Amyloid Center
Cleveland Clinic Florida

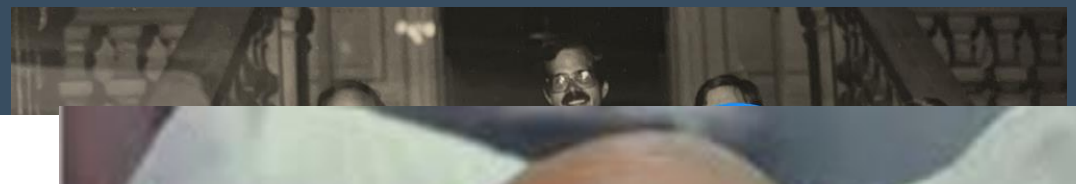
Disclosures

- Consultant – Astellas, Akcea
- Speaker– Astellas, Akcea

Learning Objectives

- 1). Understand that amyloidosis has a broad range of clinical manifestations that make recognition difficult
- 2). Identify which cardiac patients have signs or symptoms consistent with cardiac amyloidosis
- 3). Learn indications for non-invasive testing for cardiac amyloidosis and how to interpret results
- 4). Appreciate the value of early diagnosis on treatment options and prognosis

A Long Story with a Good Ending



A — Initial

Henry Masu — man, M.D., Gary Worr

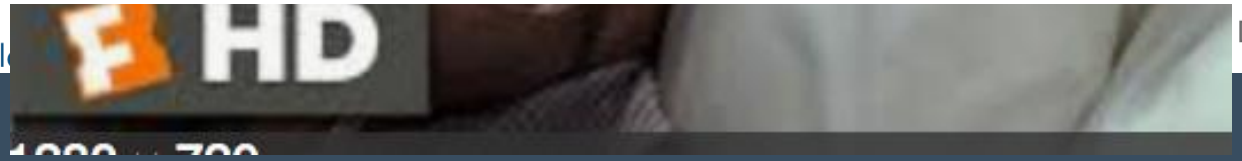
"A person living with HIV has a similar life expectancy to an HIV-negative person – providing they are diagnosed in good time, have good access to medical care, and are able to adhere to their HIV treatment."

Article

35 References 790 Citing Articl

305:1431-1438

DOI: 10.1056/NEJM198112103052402



Case WW

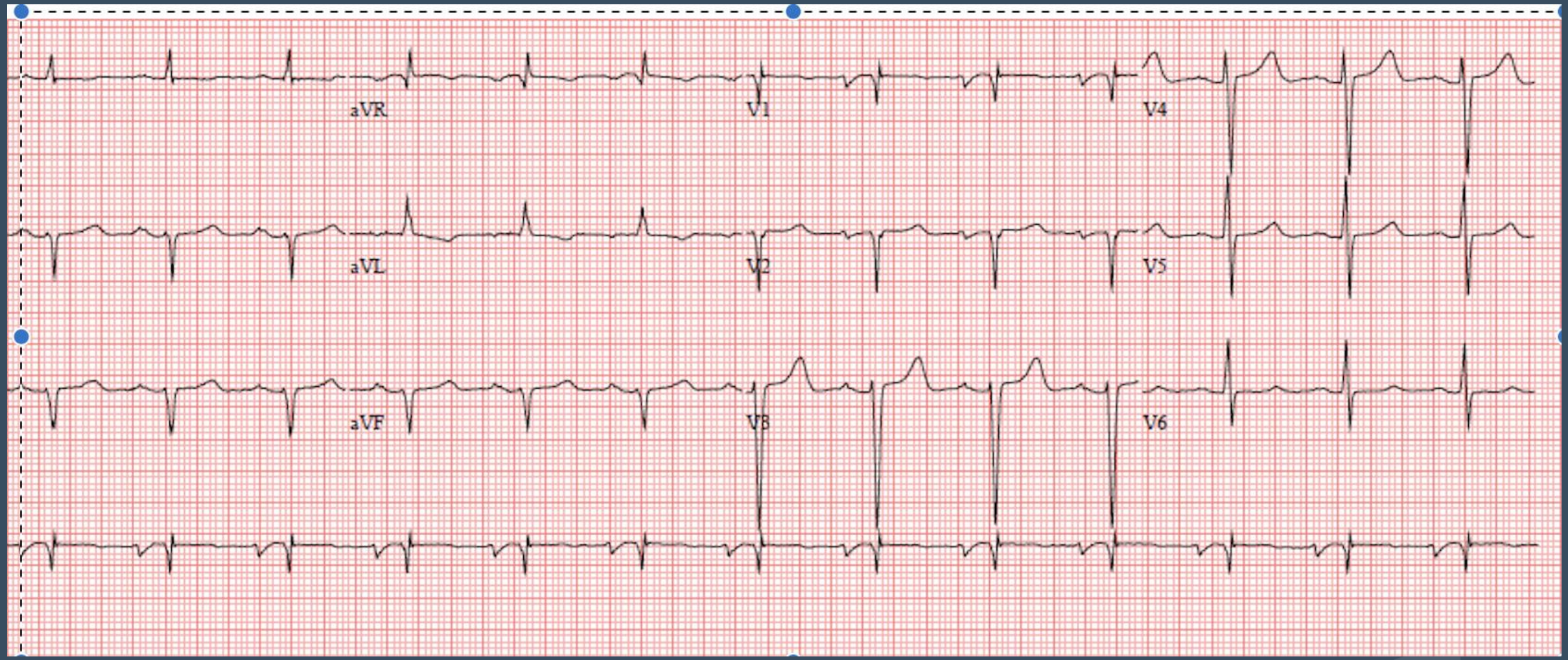
- 76 yo Afro-Caribbean male with history of pacemaker 5 yrs prior. NO hx DM, HTN, CAD
- Saw Cardiologist two months prior. “Everything was good.”
- Stress test negative
- ECHO EF 48% , Bi-atrial enlargement

  Moderate concentric LVH

WW

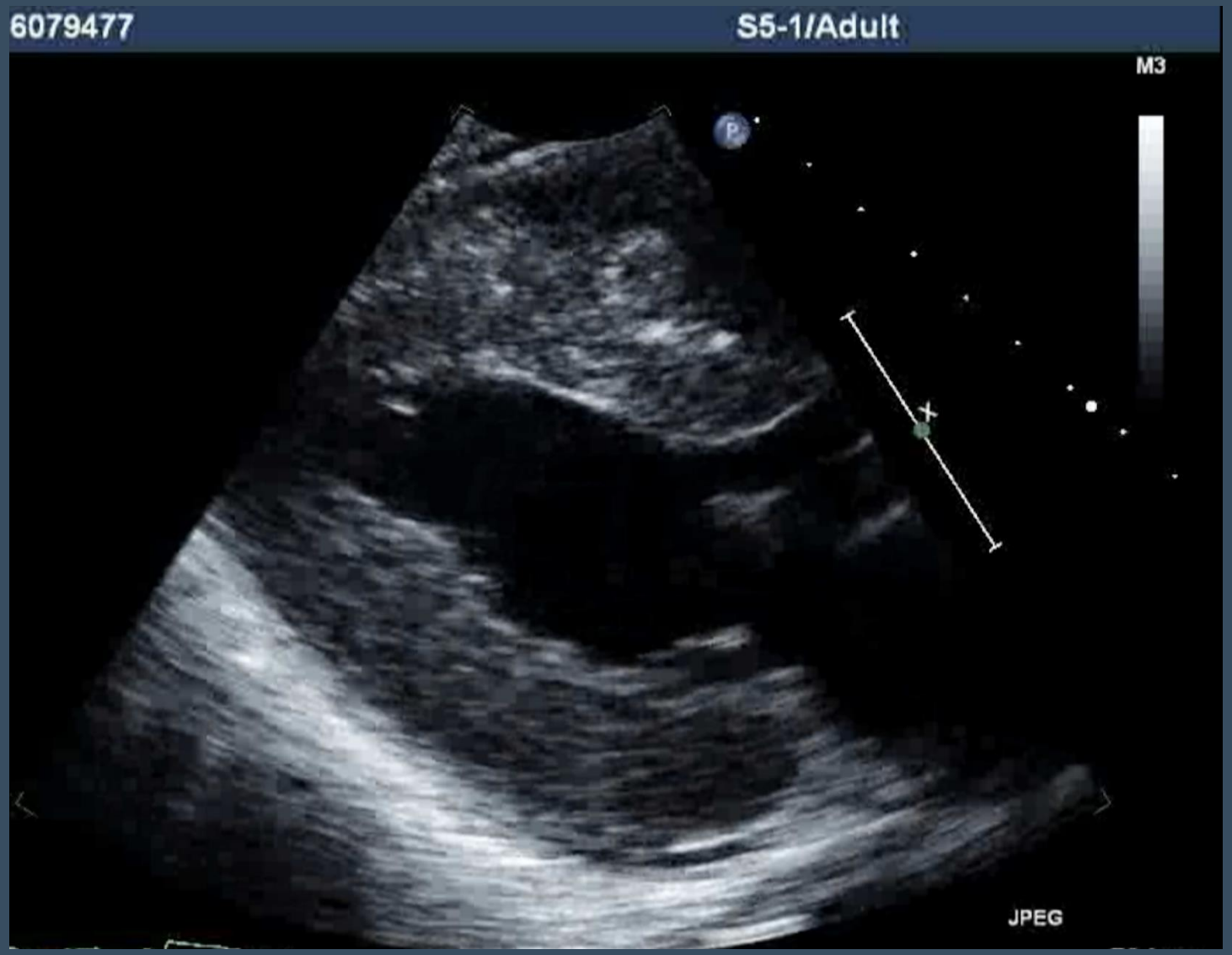
- Presented to ER abdominal pain, 20 pound weight loss , SOB, inability to walk
- Long history of numbness in hands and toes.
- Attributed to cervical and lumbar radiculopathy
- Progressive decrease in ability to walk
- BUN/CR =28/1.2 ;NtBNP=3200,Tn =0.66

ECG



ECHO

EF 38%



Clinical Impression

- Heart failure – chronic diastolic
- Profound weakness and ambulatory limitation -refer to Neurology
- Weight loss , cachexia – refer to GI
- No testing to evaluate etiology of cardiac disease
- Discharged after 36 hr

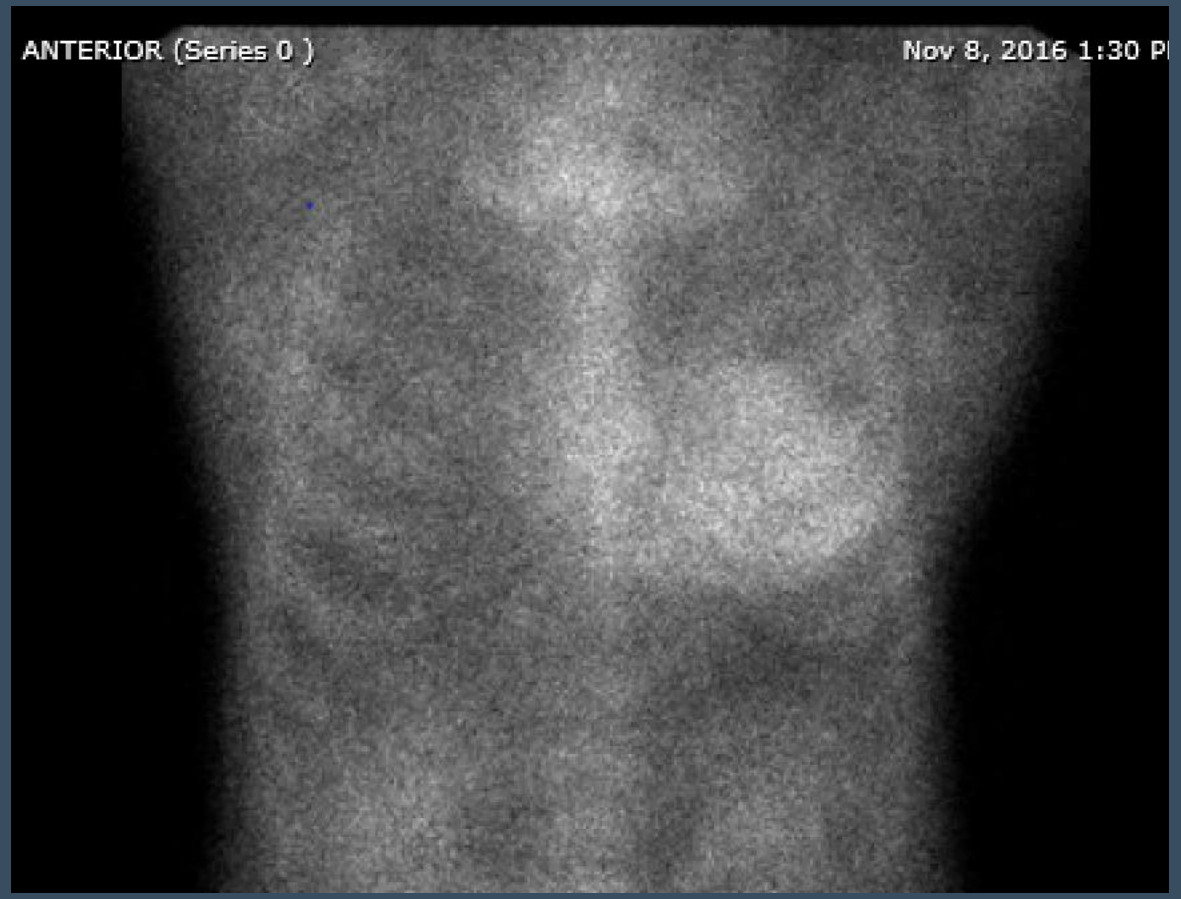
Followup

- Neurology-CTS, arm weakness , no explanation why he could not walk
- GI- cardiac cachexia due to sysrtolic heart failure
- Neurosurgery- Not an operative candidate

Finally Returned to Cardiology

- Weaker , SOB, unable to swallow , unable to walk without use of walker
- ECG = new Afib
- ECHO= EF 20%
- Imaging for Amyloid
- Genetic testing

PYP Planar



Cardiac Uptake greater than contralateral bone

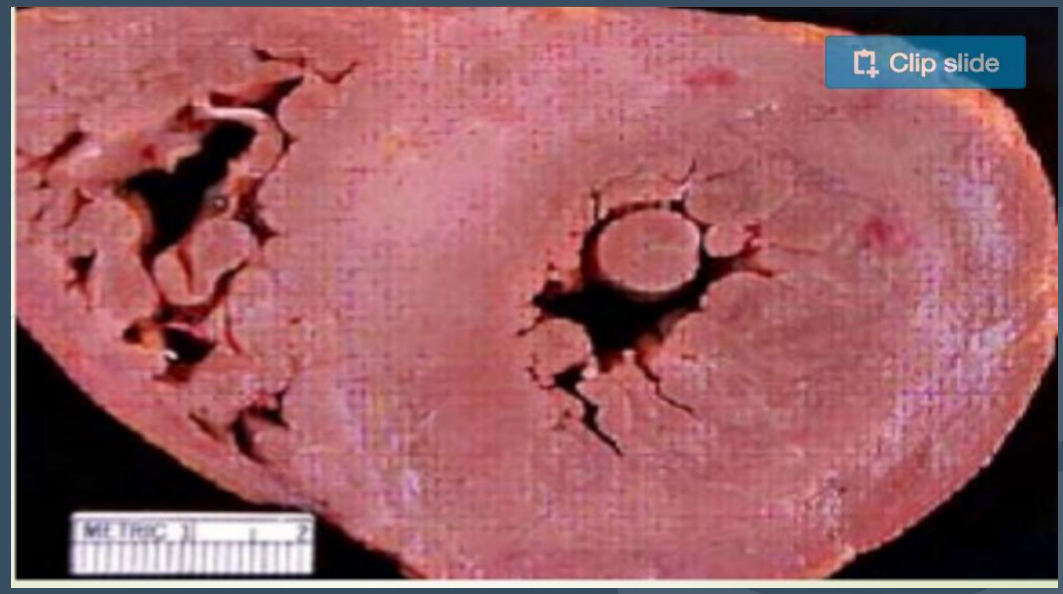
Genetic Testing= Val122Il Mutation

Summary

- Chronic Diastolic Heart Failure- Progression to systolic
- Paroxysmal Atrial Fibrillation
- Abnormal ECG- Low voltage
- Abnormal ECHO - LVH, Bi-atrial enlargement
- Peripheral Neuropathy
- Edema
- GI Symptons –
- Bilateral CTS, spinal stenosis
- Weight loss and Cachexia

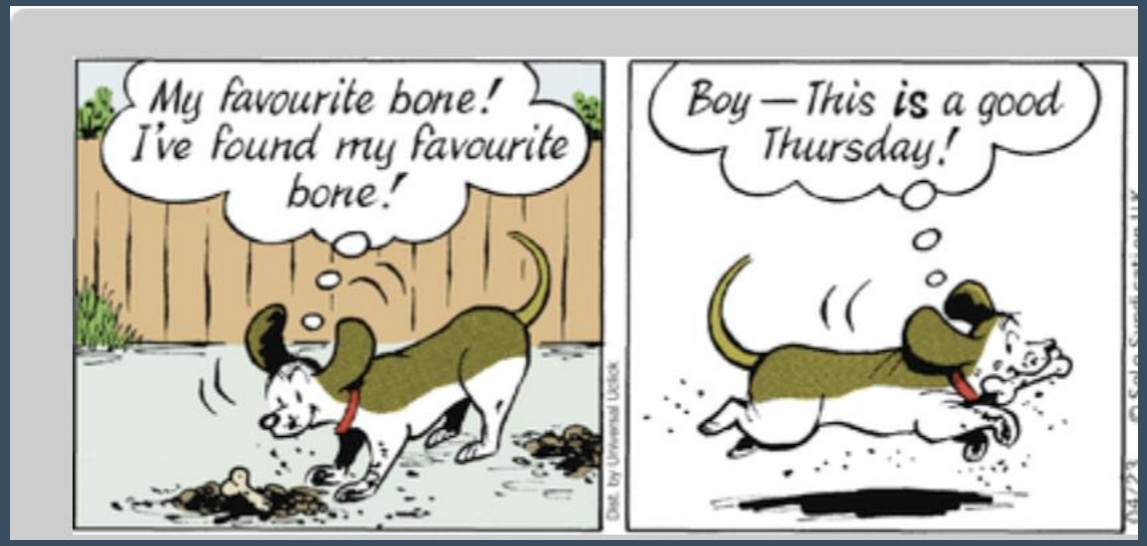
=

- Amyloidosis



Cardiac Amyloid

- If you don’t think of looking for it , you won’t find it



But if you Find it You can Help

Amyloid is a Disease of Abnormal Protein Deposition

AL

A DISEASE OF BONE MARROW

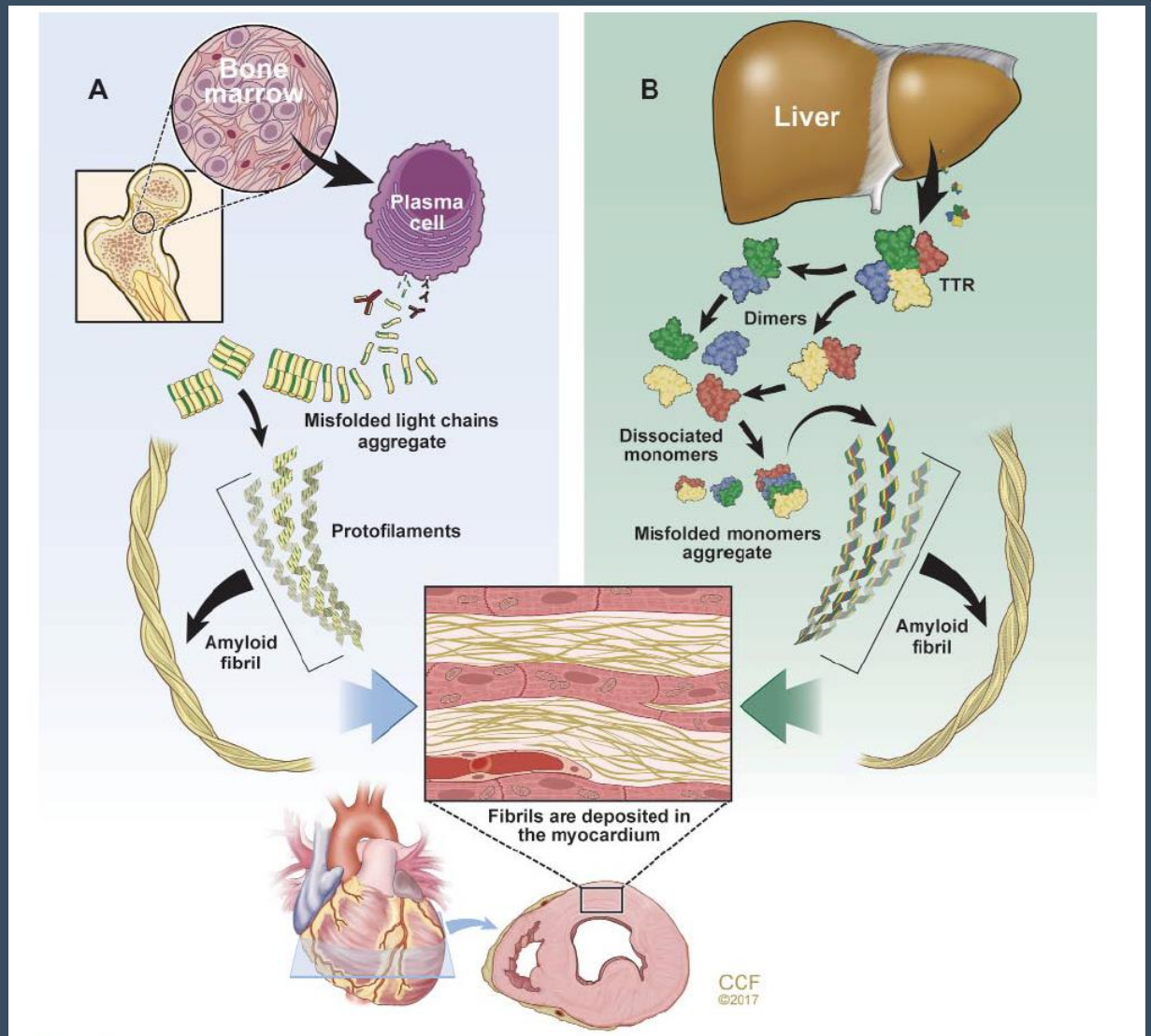


Figure 1. The 2 main types of amyloidosis that affect the heart. (A) Immunoglobulin light chain amyloidosis (AL) results from aberrant plasma cell production of monoclonal light chains that misfold. (B) Transthyretin amyloidosis (ATTR) results from transthyretin (TTR) produced by the liver that dissociates into monomers and misfolds. The misfolded proteins aggregate to form oligomers, protofilaments, and mature amyloid fibrils that deposit extracellulary in the interstitial space of the myocardium.

TTR

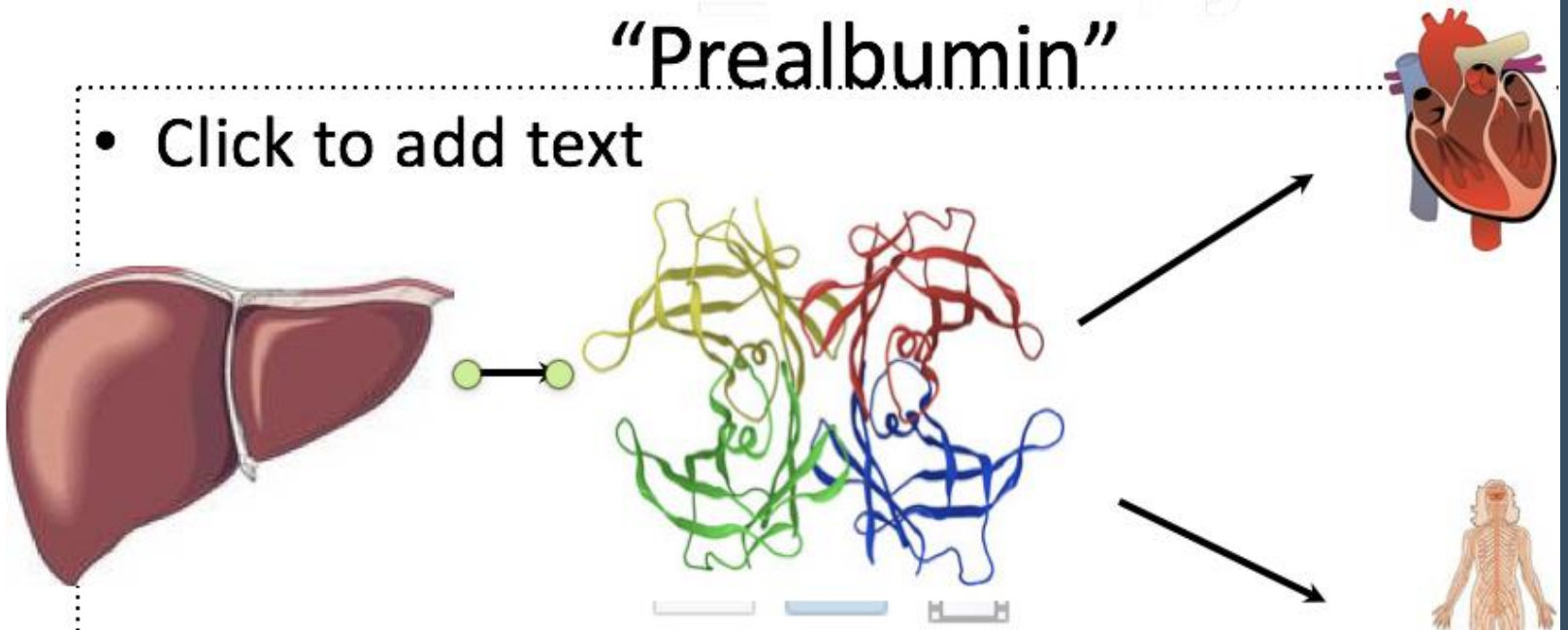
A DISEASE OF PROTEINS MADE BY THE LIVER

Donnelly Cleveland Clinic Jl Medicine 2017

Presentations of Amyloid Types

Transthyretin (TTR)
"Prealbumin"

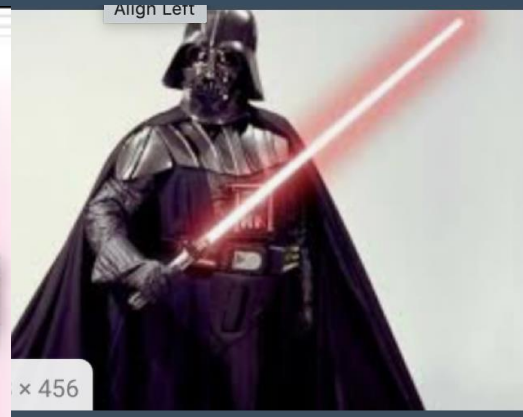
- Click to add text

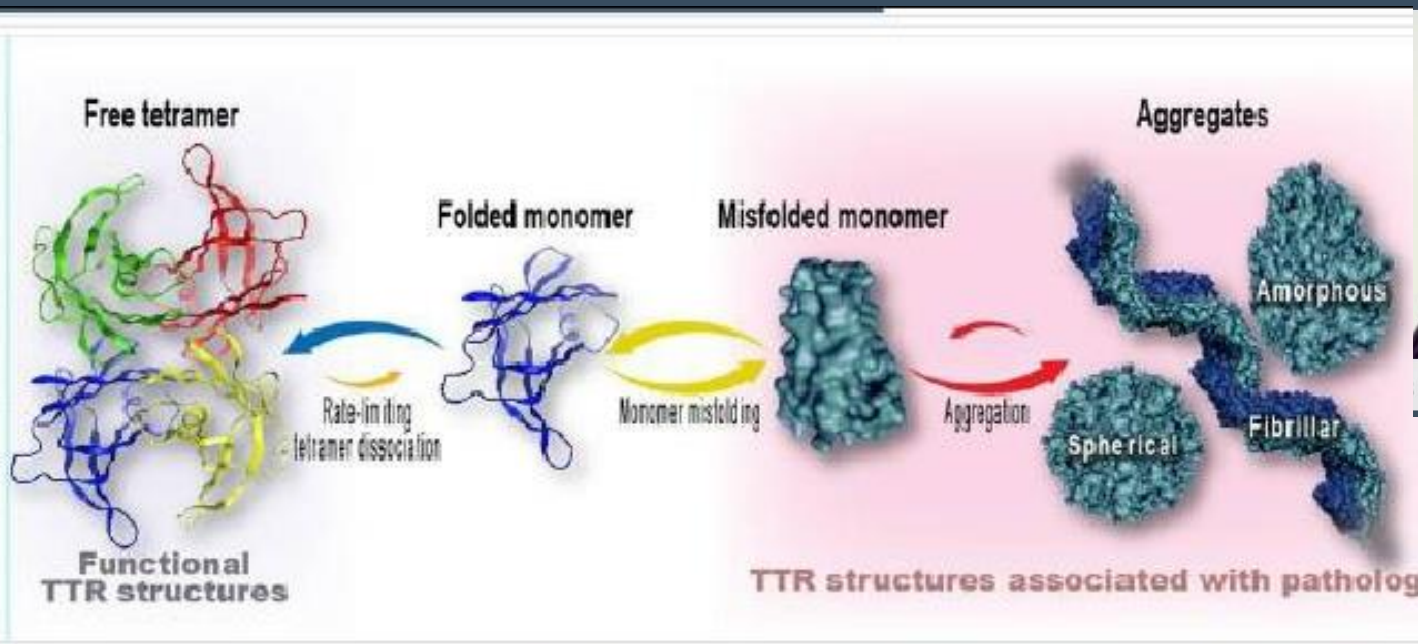


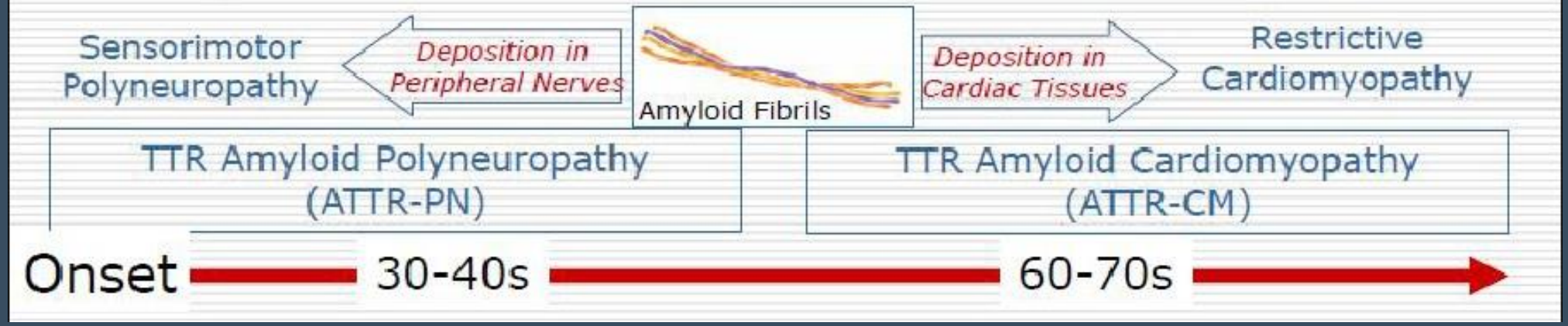
Transport protein for thyroxine and retinol
Homotetramer: 4 identical monomers 127 amino acids each
> 100 mutations described: single amino acid substiutions

Courtesy Wael Jaber MD

Pathogenesis of ATTR Amyloidosis

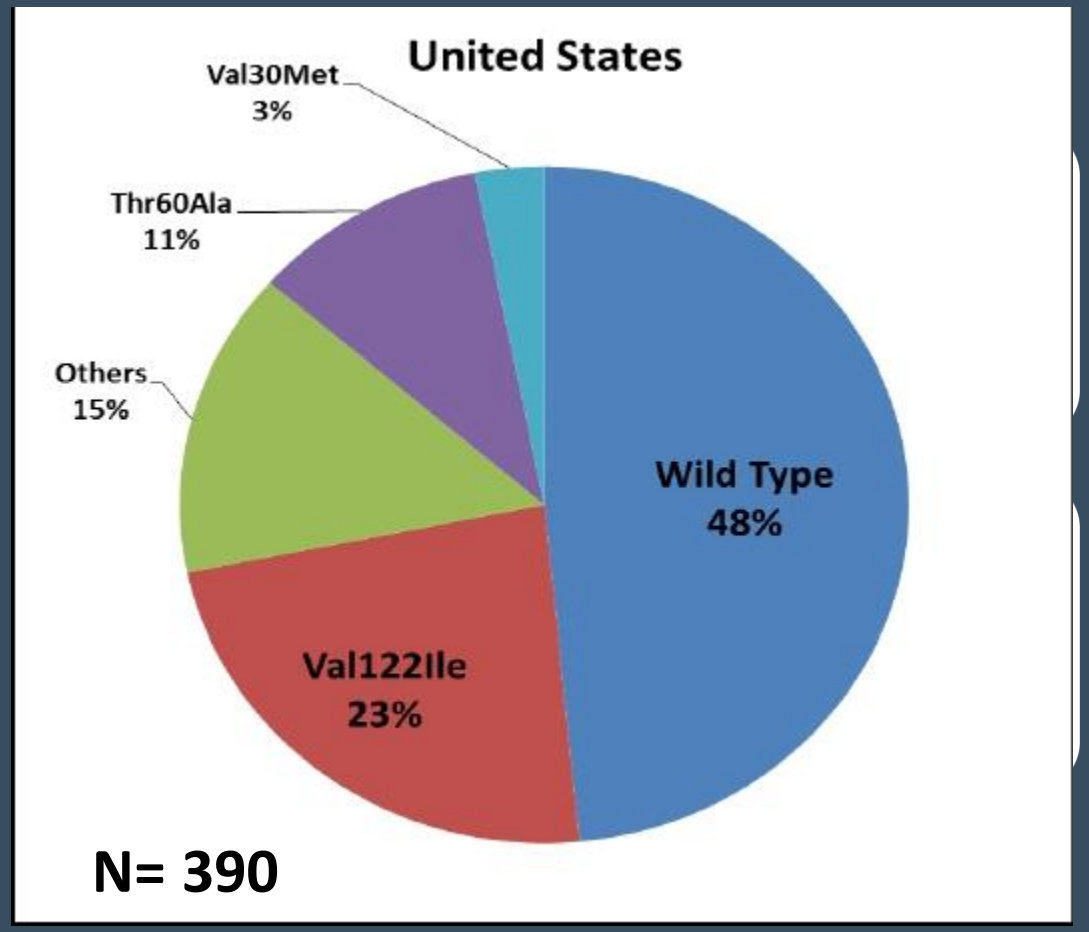






ATTR Amyloidosis in United States: THAOS Registry

- Most common type is ATTRwt
- 76±7 years
- 97% Males
- Echo;
  - IVS = 18±3 mm
  - EF = 51±12%
- Survival: 58.5% at 3 years



JACC. 2016;68(2):161-72

Eighty Percent of hATTR Patients Have Have Cardiac Involvement

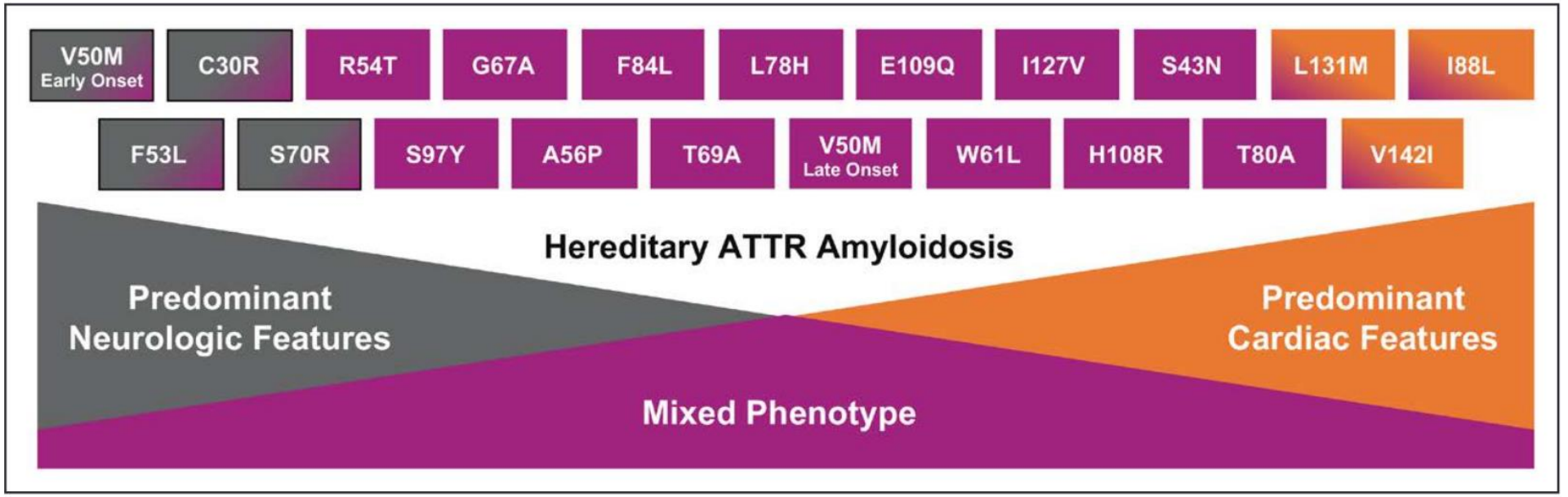


Figure 1. Genotype–phenotype correlations in mutant transthyretin amyloidosis.
ATTR, transthyretin amyloidosis. Reprinted with permission from Akcea Therapeutics.

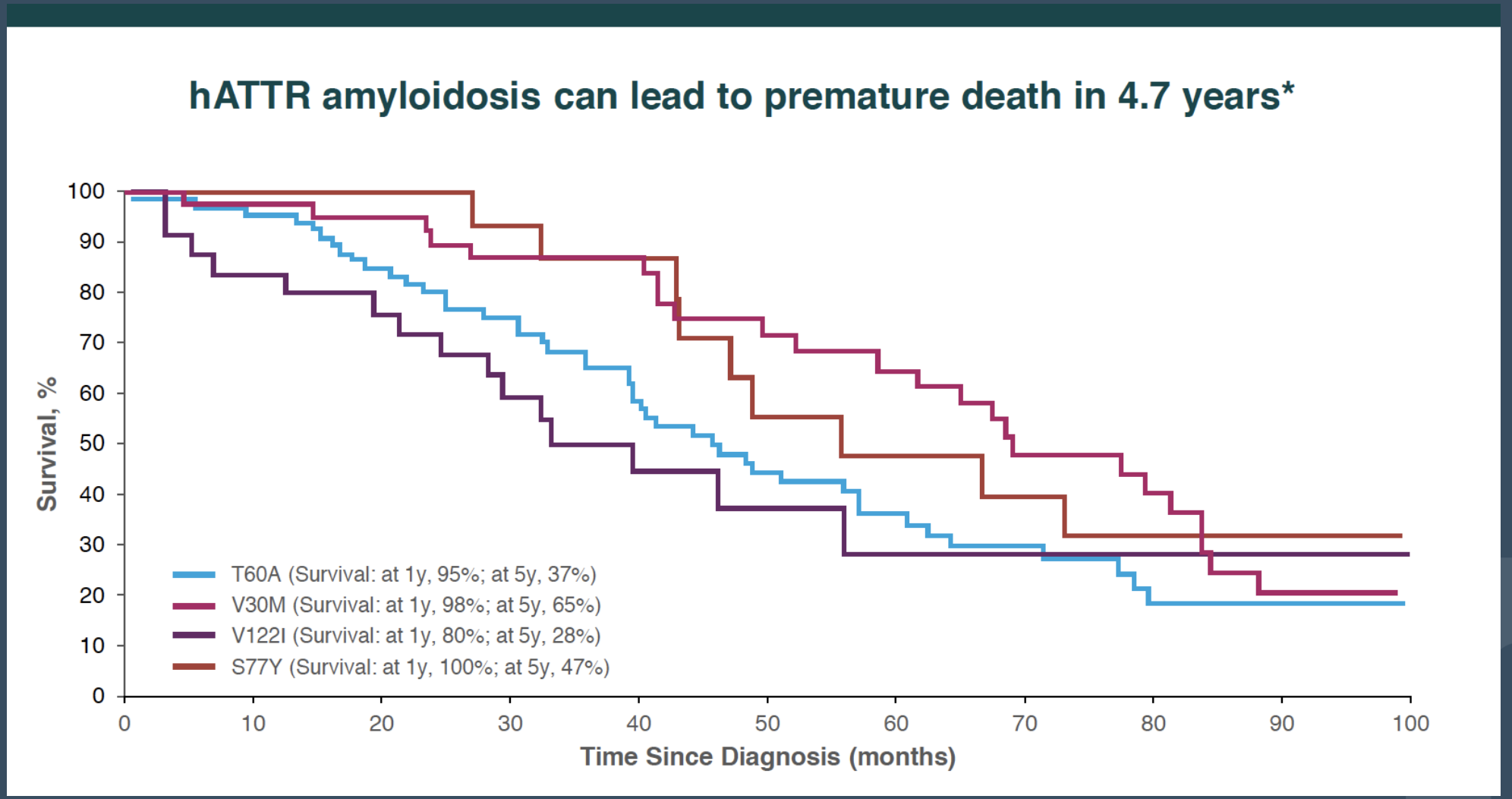
Circ Heart Fail. 2019;12:e006075. DOI: 10.1161/CIRCHEARTFAILURE.119.006075 September 2019

Therefore cardiologists are most likely to make the diagnosis

Table 2. Phenotypic Findings in AL-CA and in the Most Frequent Types of ATTR-CA

	AL[39,47]	ATTRwt[34,37,39]	Val122Ile[34]	Ile 68Leu[31]	Thr60Ala[33]
Median age at diagnosis, y	62	76	70	70	62
Males, %	66	95	75	75	70
Common ethnicity	Variable	White	African American Caribbean	White (Italy)	White (United States, Ireland)
Cardiac referral route, %	65	>80	>80	>80	30
IVS/PW (median values)	15/14	18/17	17/17	17/16	17/17
LVEF, %	56	50	50	50	53
Low QRS voltages, %	45	33	45	30	16
Peripheral sensory-motor neuropath, %	10–20	<10	15	25	54
History of carpal tunnel syndrome, %	<10	30–45	30	37	Unknown
Autonomic symptoms, %	24	12–20	10	<10	75
Median survival, y	Depends on stage	3.5	2–3	4–5	3.5
NT-pro-BNP, pg/L (median)	↑↑↑	↑↑	↑	↑	↑

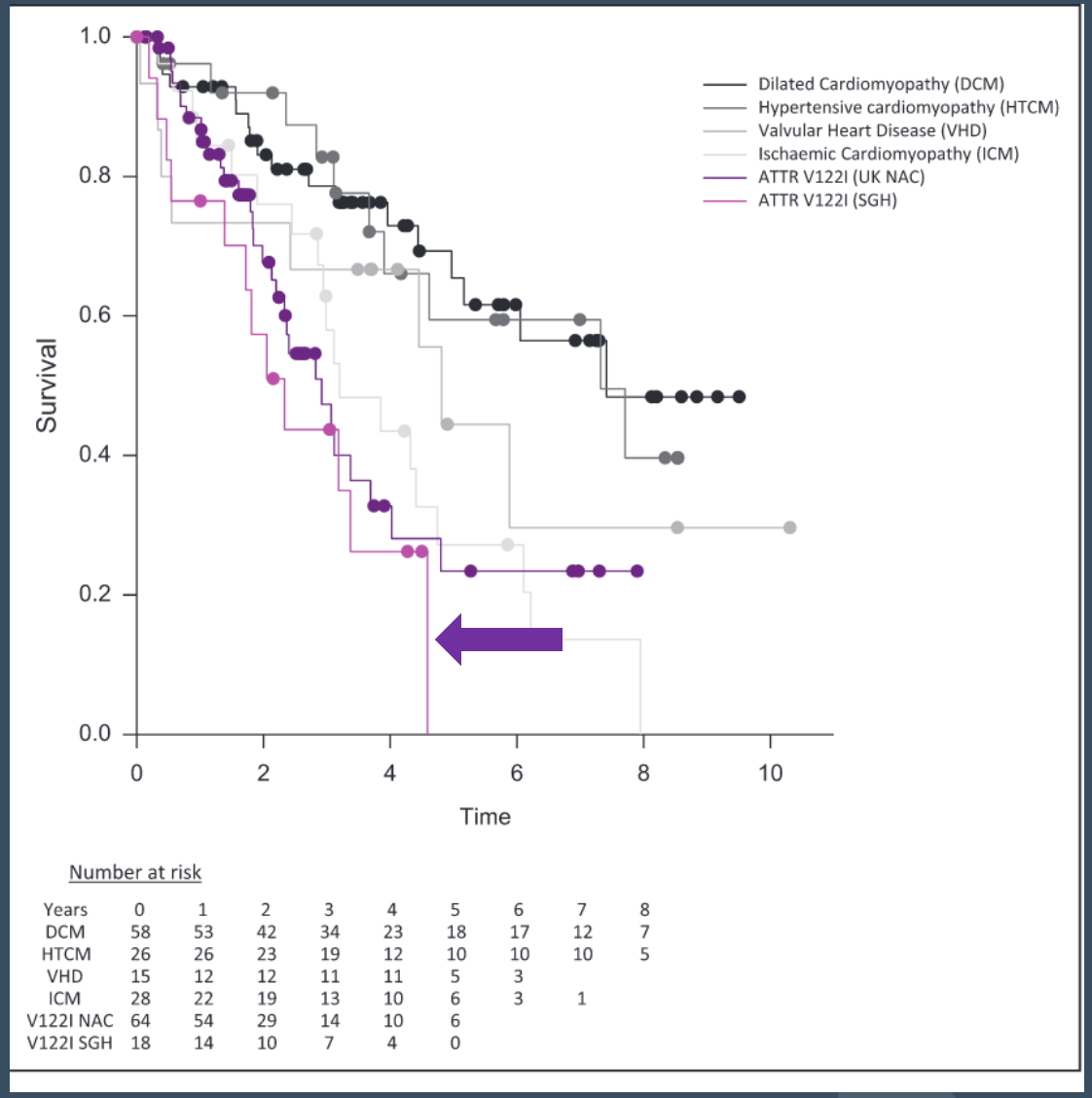
Prognosis of hATTR



Swedicki AMYLOID 2015

Prognosis: hATTR vs Other Cardiomyopathies

Prognosis is worse than other types of HFpEF in Afro Caribbeans in UK



Number at risk

Years	0	1	2	3	4	5	6	7	8
DCM	58	53	42	34	23	18	17	12	7
HTCM	26	26	23	19	12	10	10	10	5
VHD	15	12	12	11	11	5	3		
ICM	28	22	19	13	10	6	3	1	
V122I NAC	64	54	29	14	10	6			
V122I SGH	18	14	10	7	4	0			

Dungu et al Circ Heart Fail. 2016;9:e003352

Clinical Evaluation

Why is Amyloid So Hard to Diagnose?

- No Treatment
- No Noninvasive Diagnostic Test
- Multiorgan presentation
- Symptoms are not unique to amyloid:
- Hypertensive heart disease, Diabetic neuropathy, IBS
- Silos of care

GI Amyloid

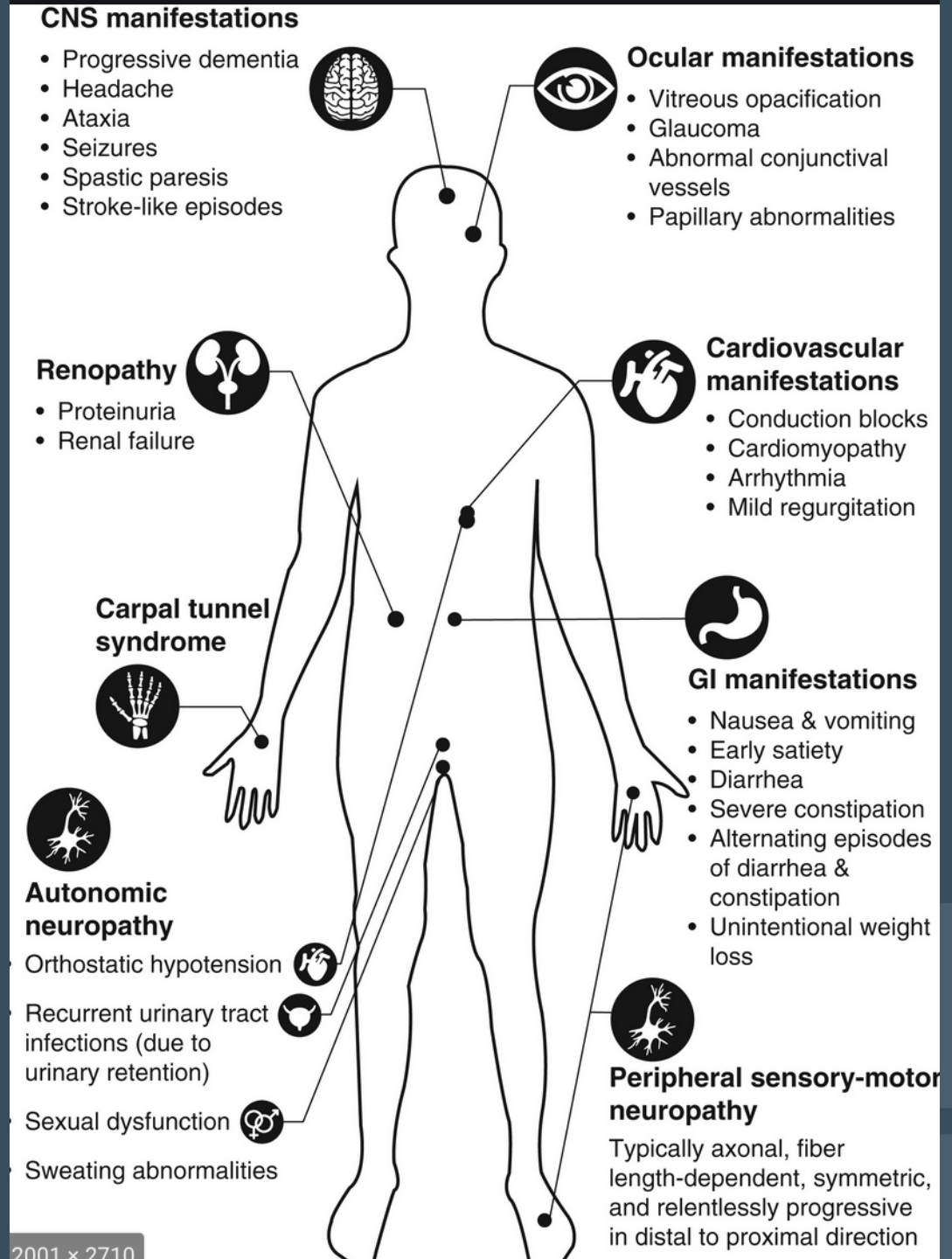
- Amyloid can deposit anywhere in the GI tract or nerves that regulate it
- Luminal GI Patterns:
  - Mucosal infiltration
  - Muscle infiltration
  - Neuropathy
  - Vascular

Symptoms

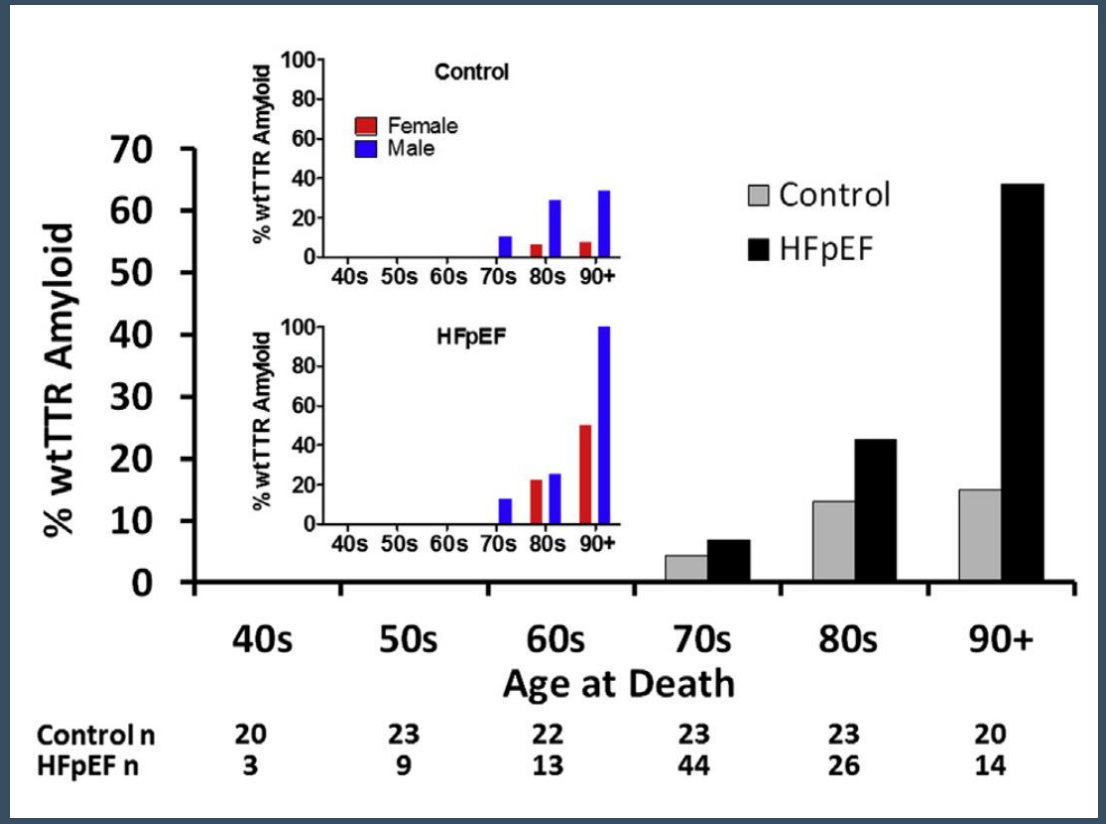
- Symptoms are linked to area of involvement & are often non-specific
  - Esophagus:
    - Reflux
    - Dysphagia
    - Food impaction
  - Stomach
    - Abdominal pain
    - Nausea
    - Vomiting
    - Distention
- Small intestine
  - Diarrhea
  - Malabsorption
  - Weight loss
  - Pseudo-obstruction
- Colon
  - Diarrhea
  - Constipation
  - Fecal incontinence

Courtesy John Clarke MD Stanford

Myriad of Symptoms in ATTR Amyloid



Heart Failure and Amyloid Increased Prevalence with Age



- The older you are the more you are likely to have it
- Does natural history change with age
- What are the right treatments for patients in their 80s and 90s

Mohammed JACC Heart Fail 113-22

What is the “typical” ECG pattern cardiac Amyloid

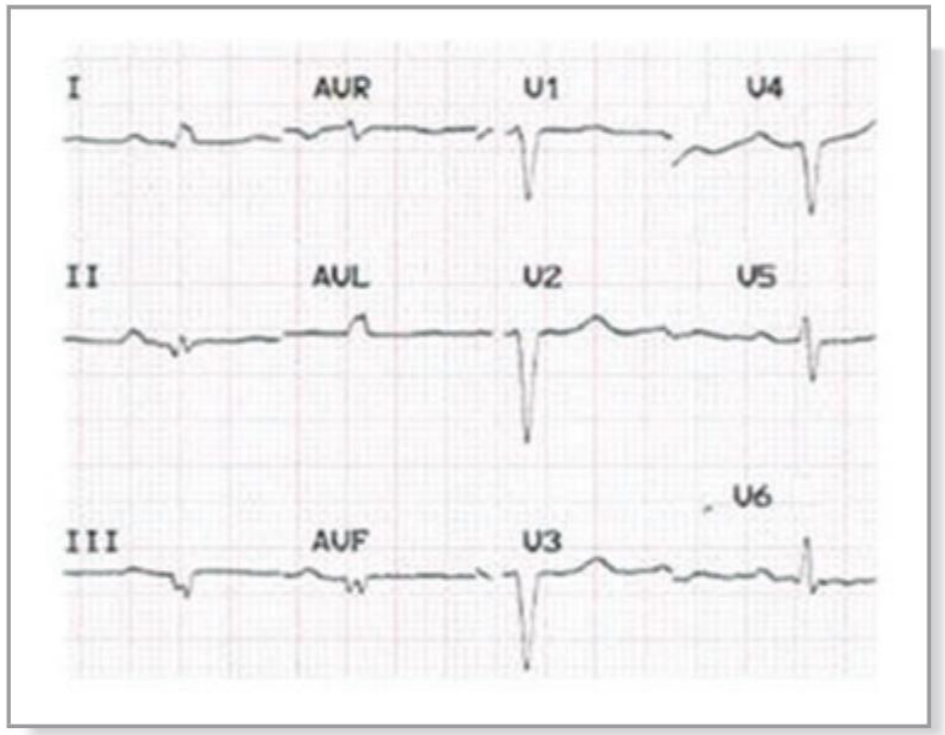
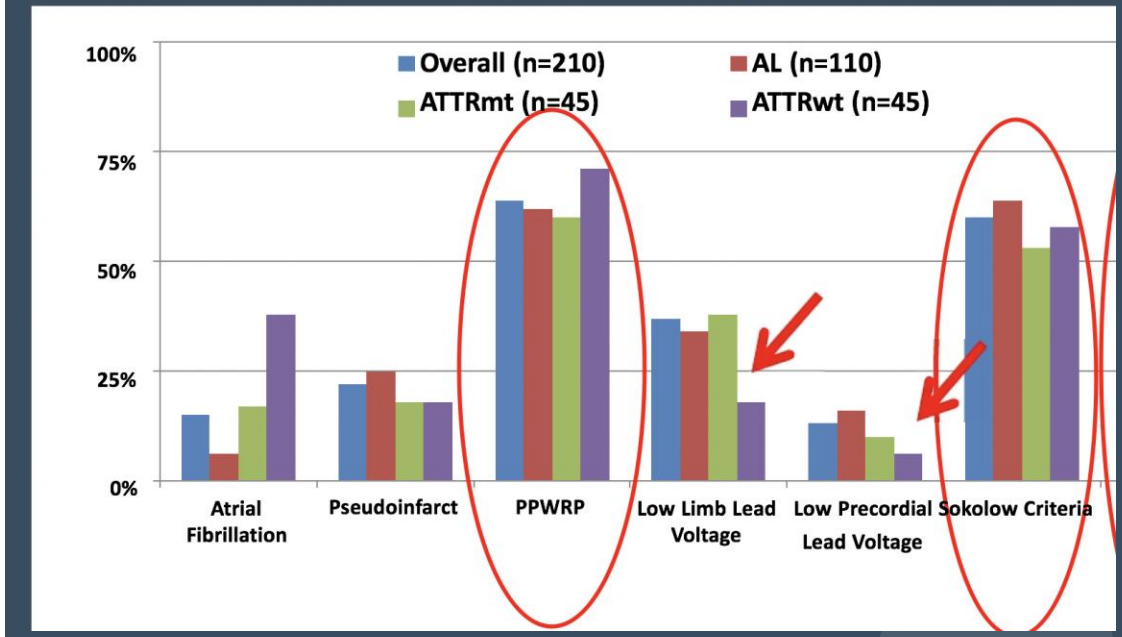
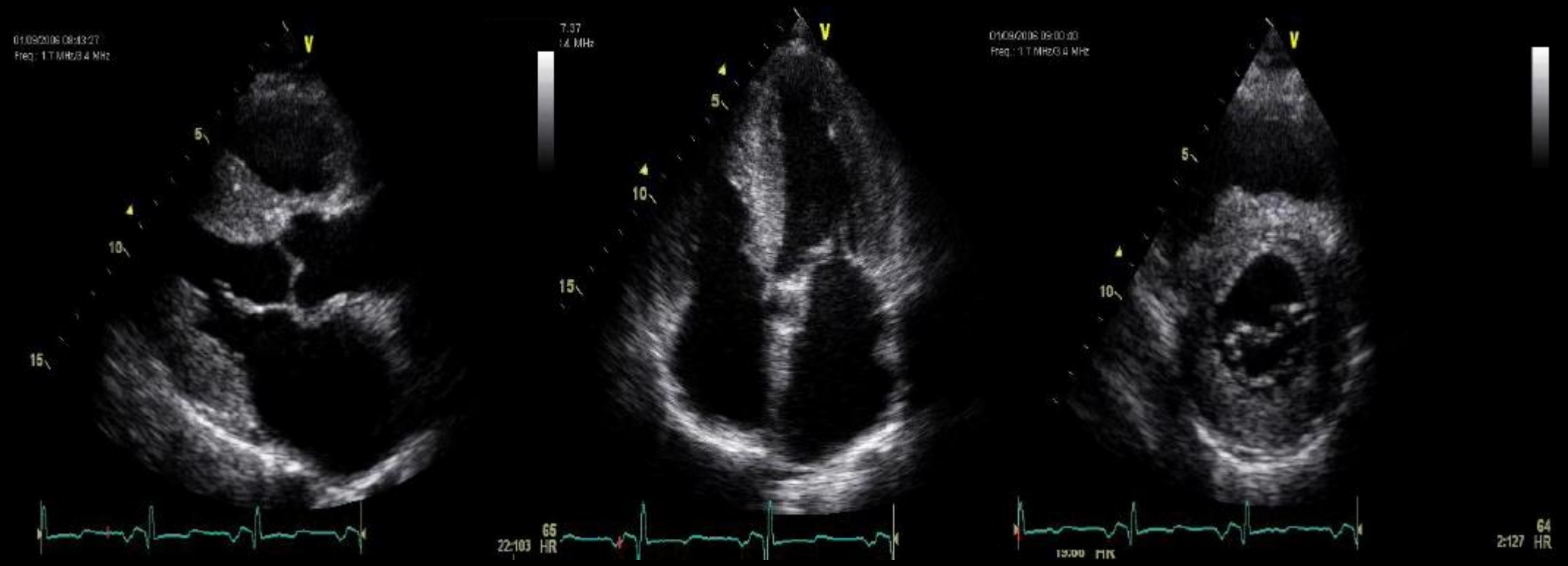


Figure 1. ECG of a patient with cardiac AL amyloidosis showing small QRS voltages (defined as ≤6 mm height), predominantly in the limb leads and pseudoinfarction pattern in the anterior leads.



Am J Cardiol. 2014;114(7):1089-93

Echocardiographic Findings

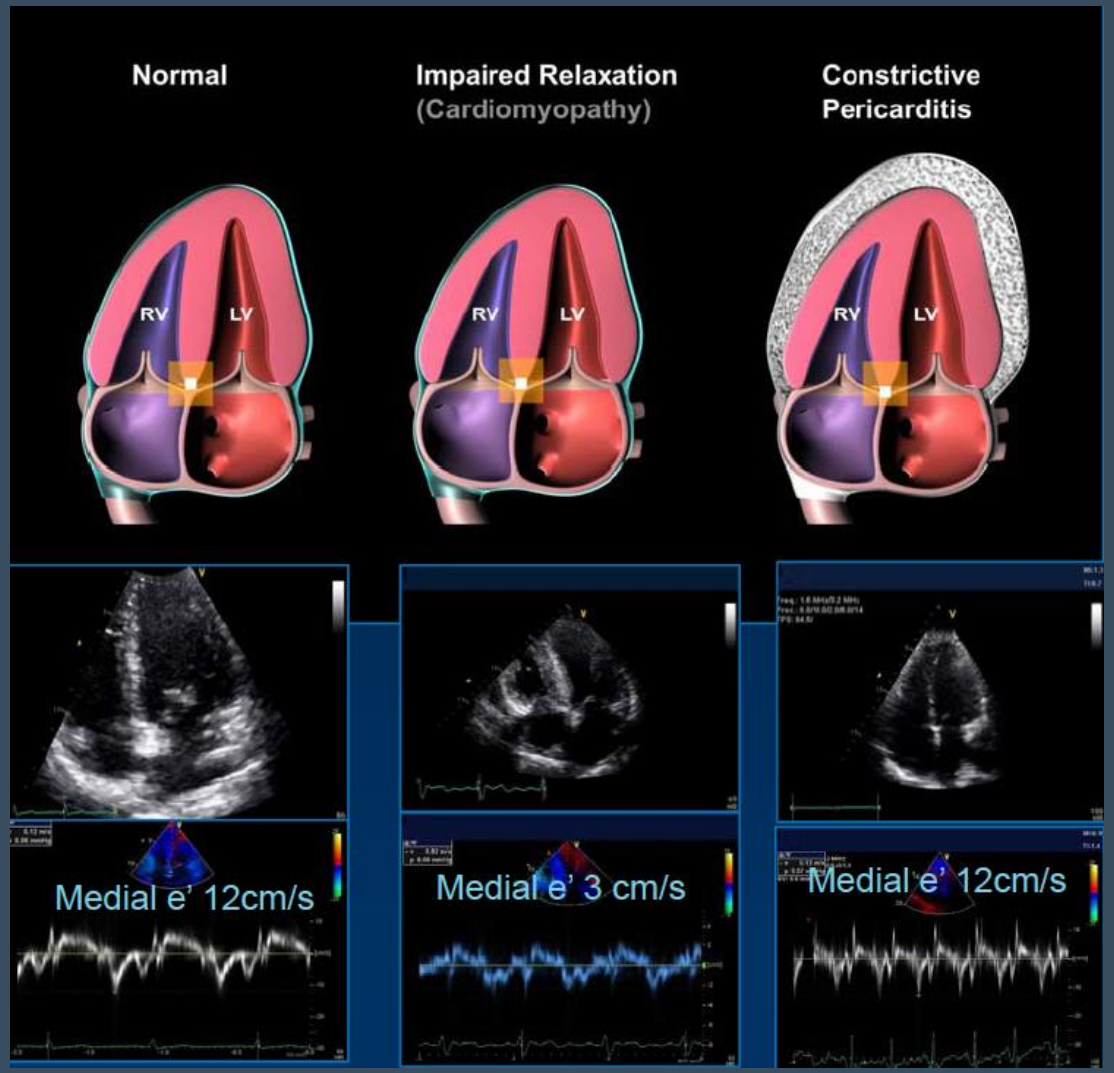


- Increased bi-ventricular wall thickness
- Thickened interatrial septum
- Valvular thickening
- Bi-atrial enlargement

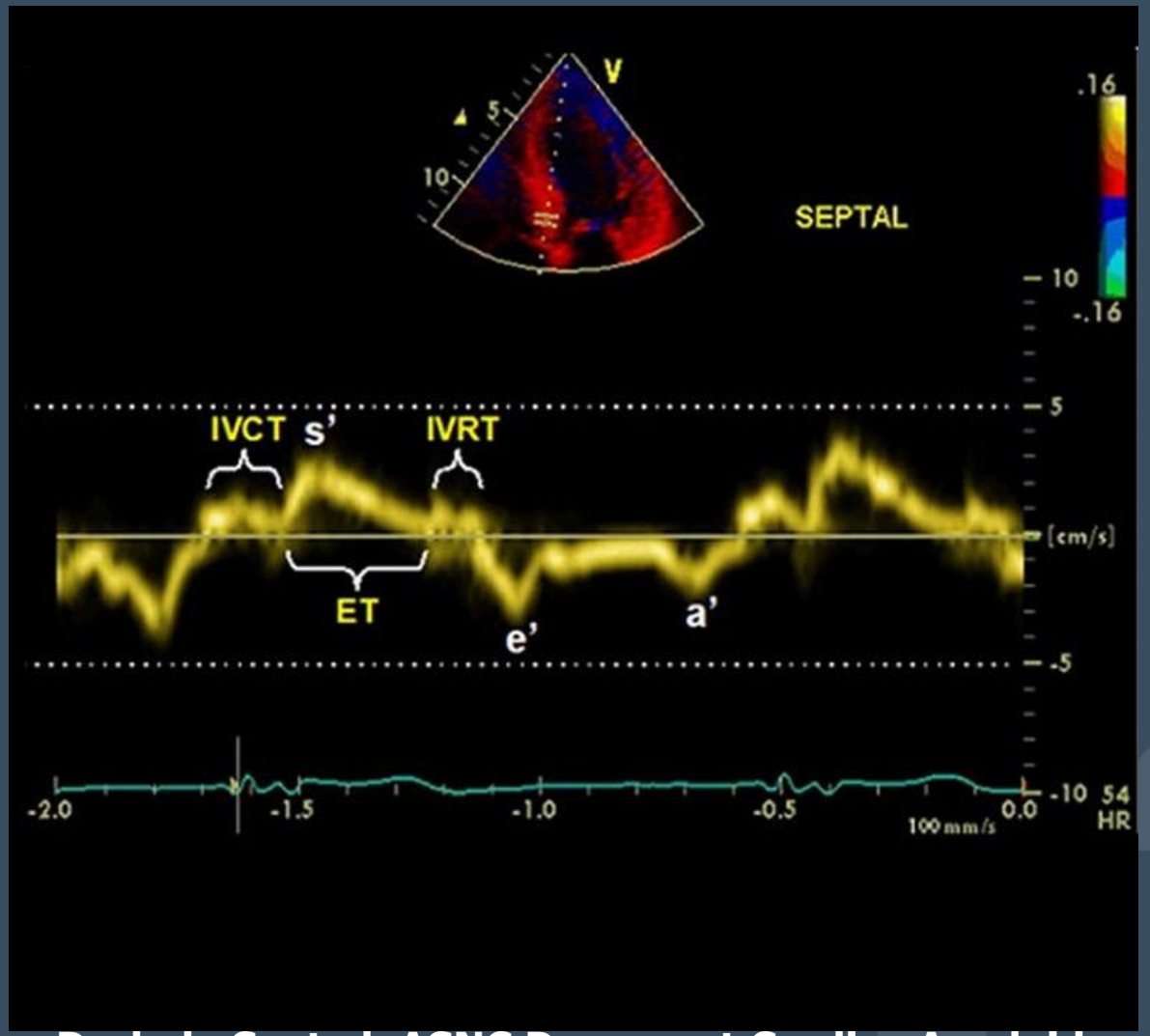
Diastolic dysfunction
Restrictive phenotype
Pericardial effusion
Preserved ejection fraction (early)
Systolic heart failure (late)

Cardiac Amyloidosis – Echo Diagnosis

"5,5,5 sign" – all TDI velocities < 5 cm/sec



Oh J K, JACC 2016;68:6891



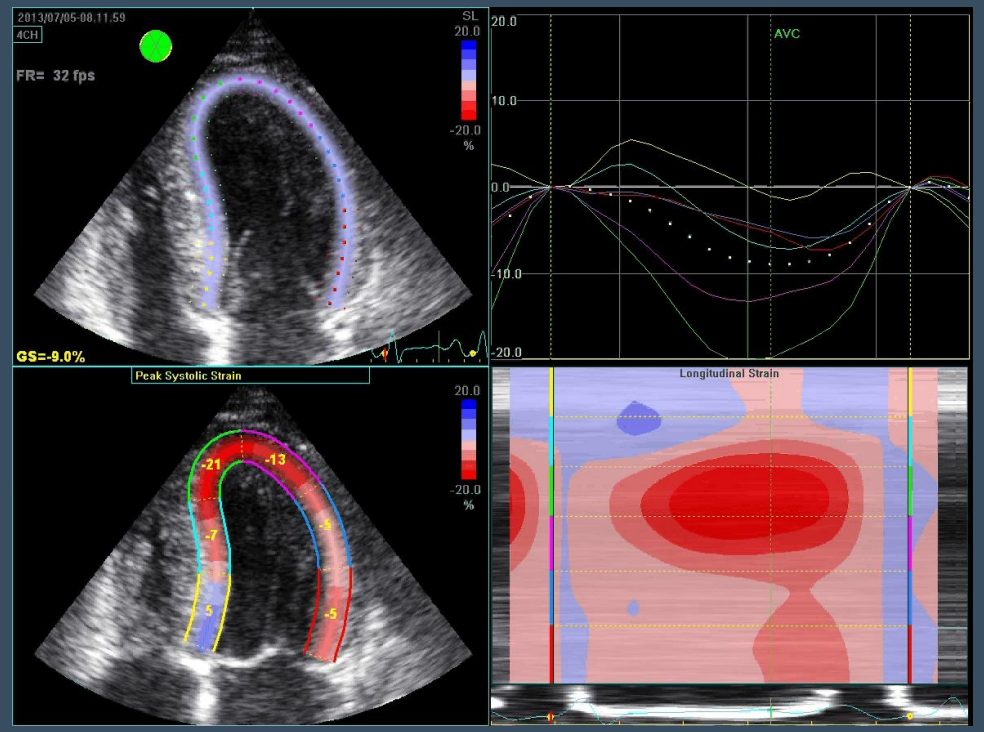
Dorbala S, et al, ASNC Document Cardiac Amyloid, J Nucl Cardiol 2019;26:2065

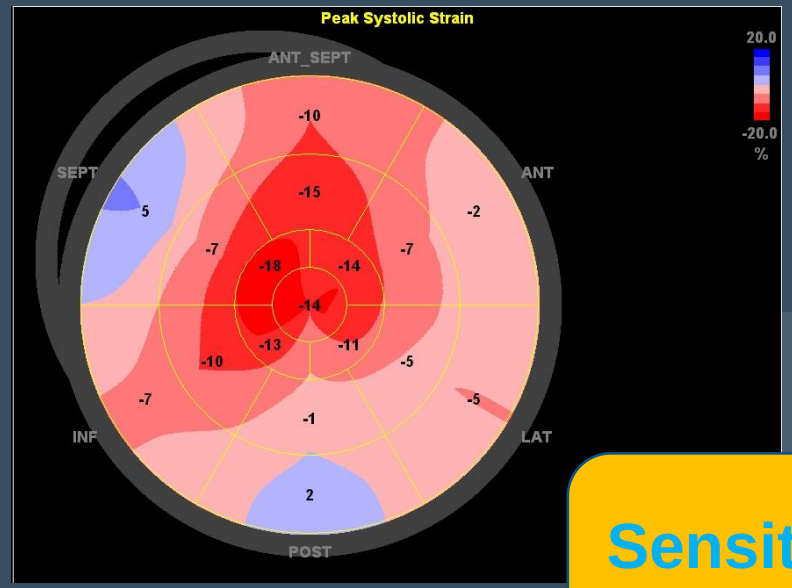
ORIGINAL ARTICLE

Heart 2012; 98: 1442

Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis

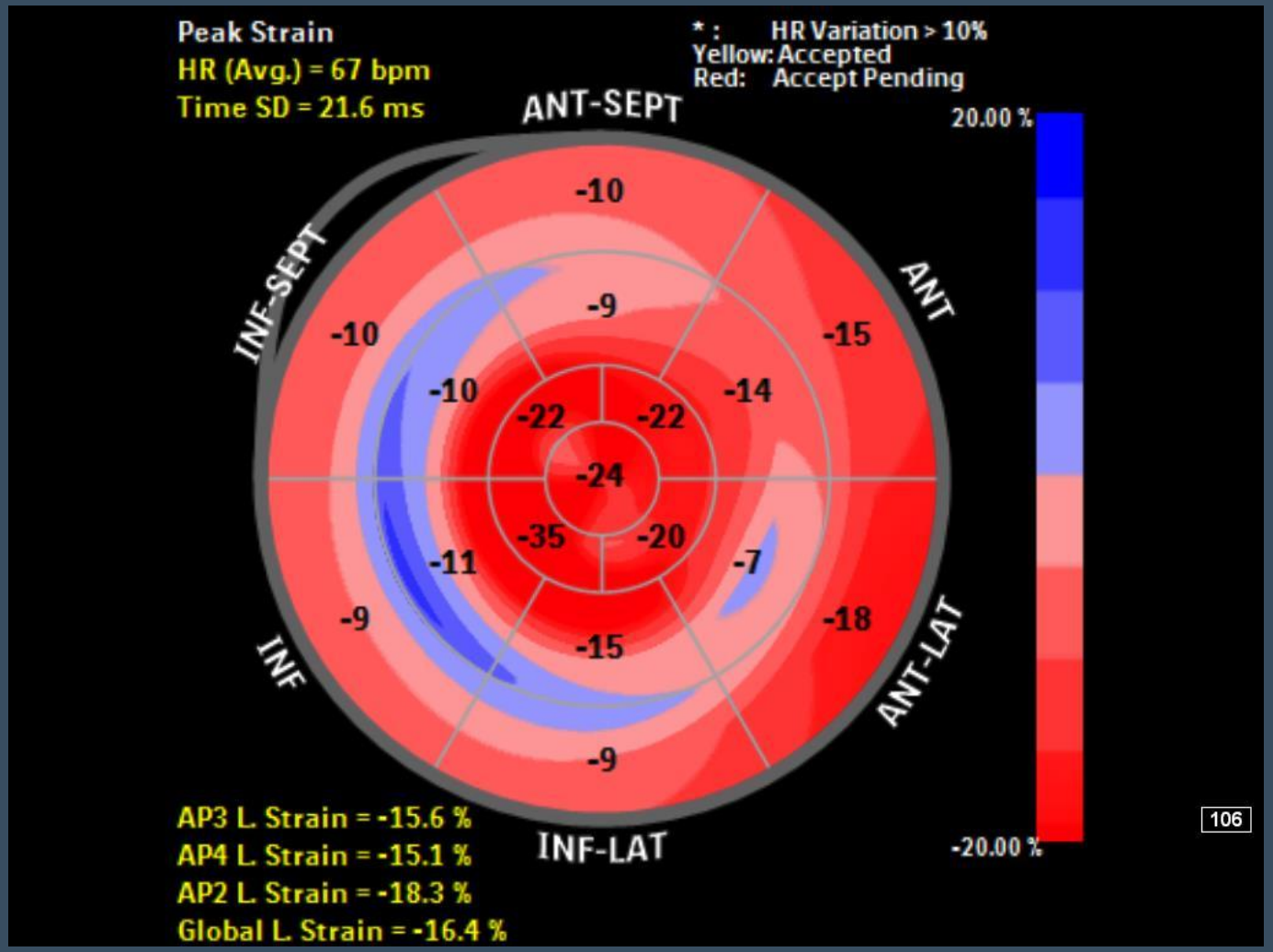
Dermot Phelan, Patrick Collier, Paaladinesh Thavendiranathan, Zoran B Popović, Mazen Hanna, Juan Carlos Plana, Thomas H Marwick, James D Thomas





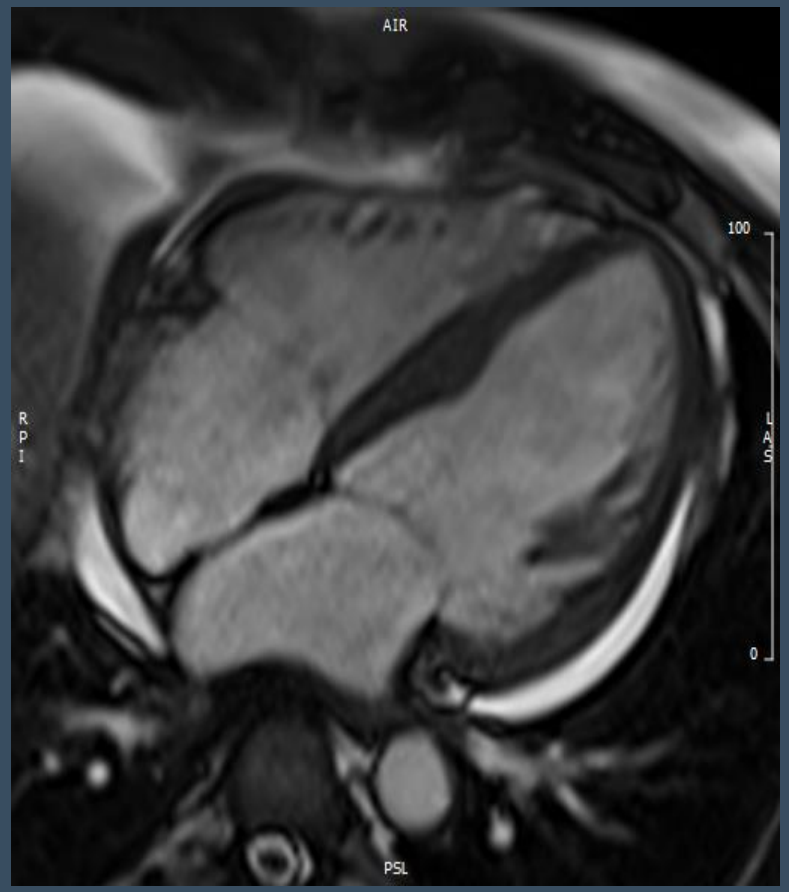
Sensitivity: 93%
Specificity 82%

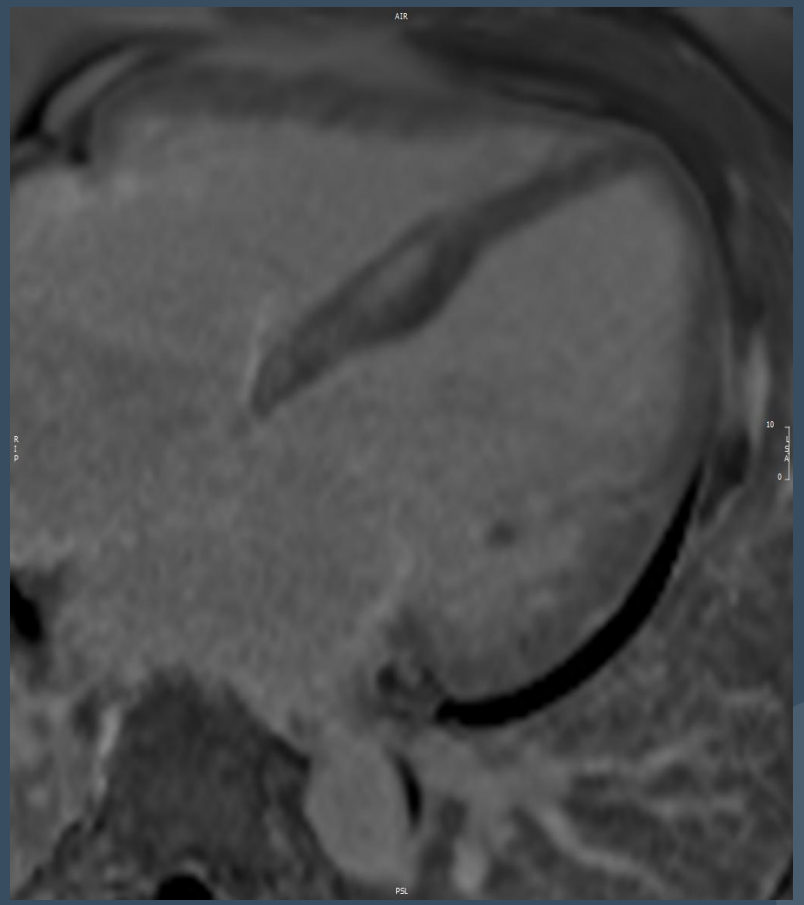
SV Apical Sparing



- Consistent with but not diagnostic of amyloid

CMR

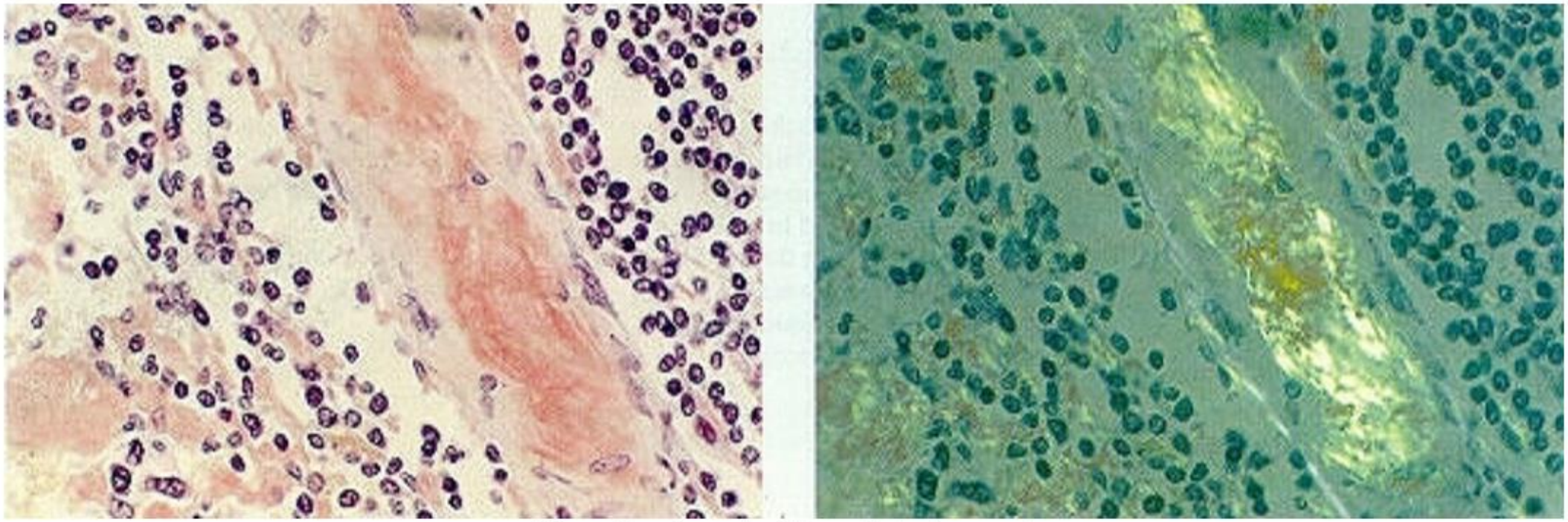




Potential Utility of CMR in Cardiac Amyloidosis

1. FINDINGS: Increase suspicion of presence of disease
   - Diffuse late enhancement that can either be subendocardial or transmural, that does not follow coronary distribution, poor myocardial signal nulling on PSIR LGE sequence
   - Marked increase in extracellular volume (>40%) or native (non-contrast) T1
   - Not diagnostic of amyloidosis, should prompt further evaluation
2. CLINICAL UTILITY:Confers prognostic value
   - Transmural or high ECV, worst prognosis
   - Absence of LGE, best prognosis
3. POTENTIAL USE: Serial imaging for response to therapy

Myocardial Biopsy



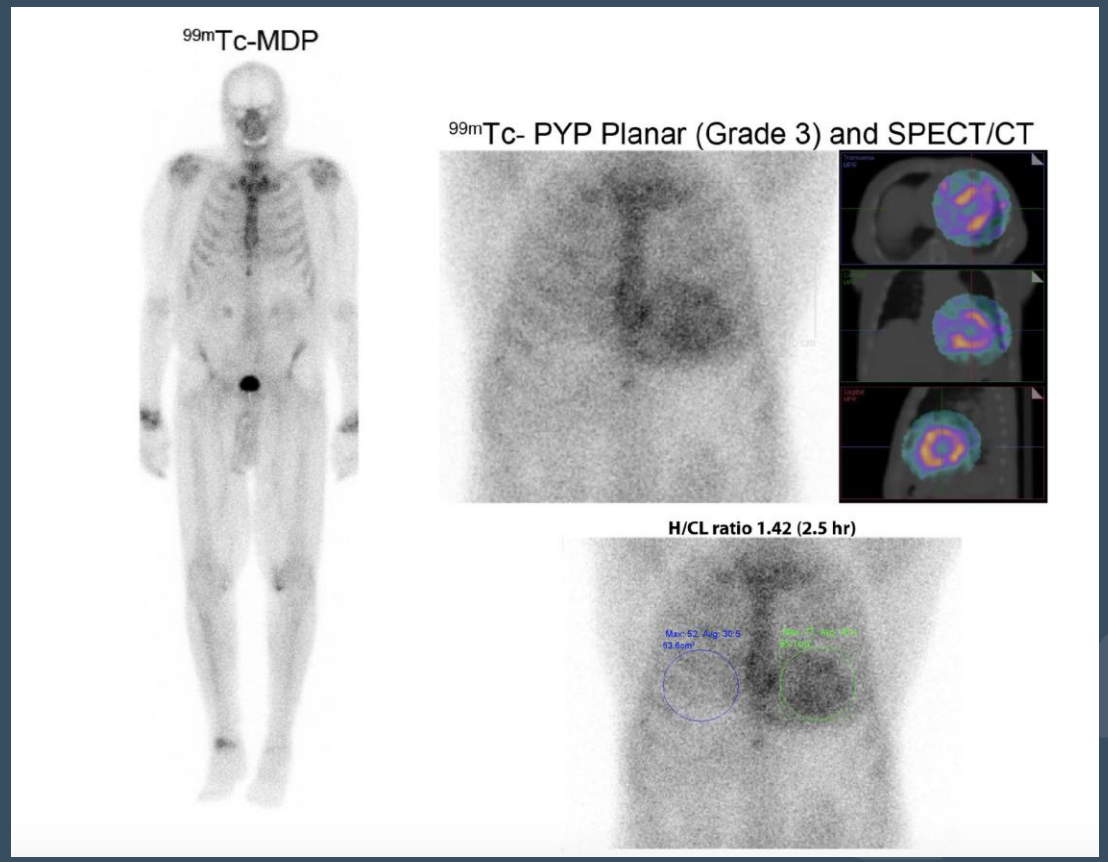
Result: Amyloid - pink to red
Amyloid under polarized light after Congo red staining - apple green

Nuclear Cardiology and TTR Amyloid

A game changer

Tc-PYP Scan

- PYP is calcium avid
- Used in bone Scan
- 1970’s used to diagnose acute myocardial infarction
- Mechanism for binding to amyloid tissue unclear



Semi-Quantitative Interpretation- Perugini

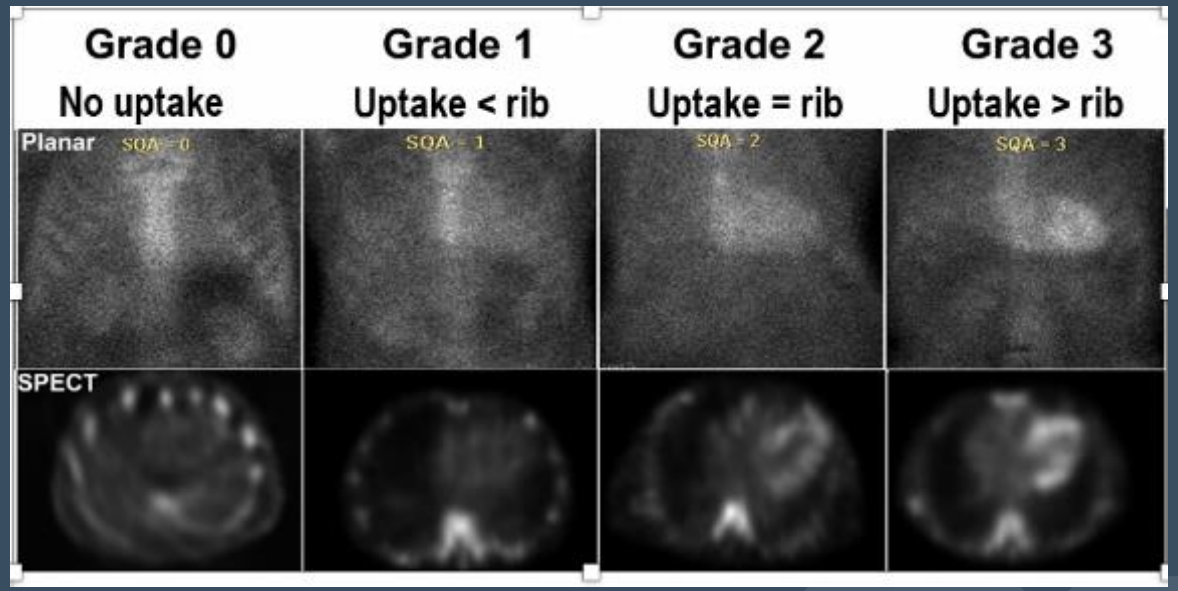
ASNC
American Society of Nuclear Cardiology

ASNC
CARDIAC AMYLOIDOSIS
PRACTICE POINTS

^{99m}Technetium-Pyrophosphate Imaging for Transthyretin Cardiac Amyloidosis

Table 2. Semi-quantitative Visual Grading of Myocardial ^{99m}Tc-PYP Uptake by Comparison to Bone(rib) Uptake

Grade	Myocardial ^{99m}Tc-PYP Uptake
Grade 0	no uptake and normal bone uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/ absent rib uptake



Grade 2 and above is consistent with a positive PYP scan for cardiac Amyloid

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

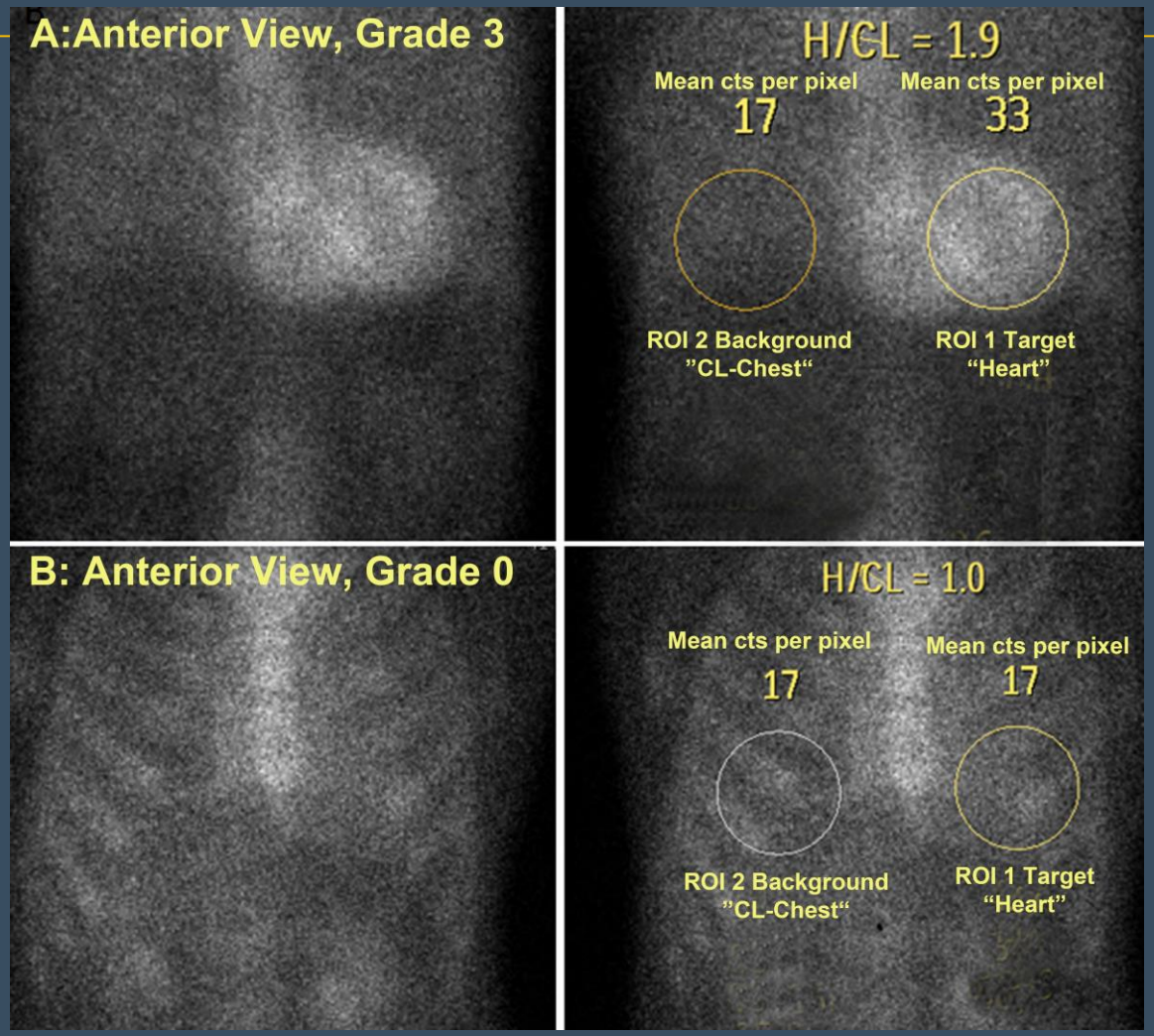
Table 2. Scintigraphic Findings in the Patient Population and Control Group

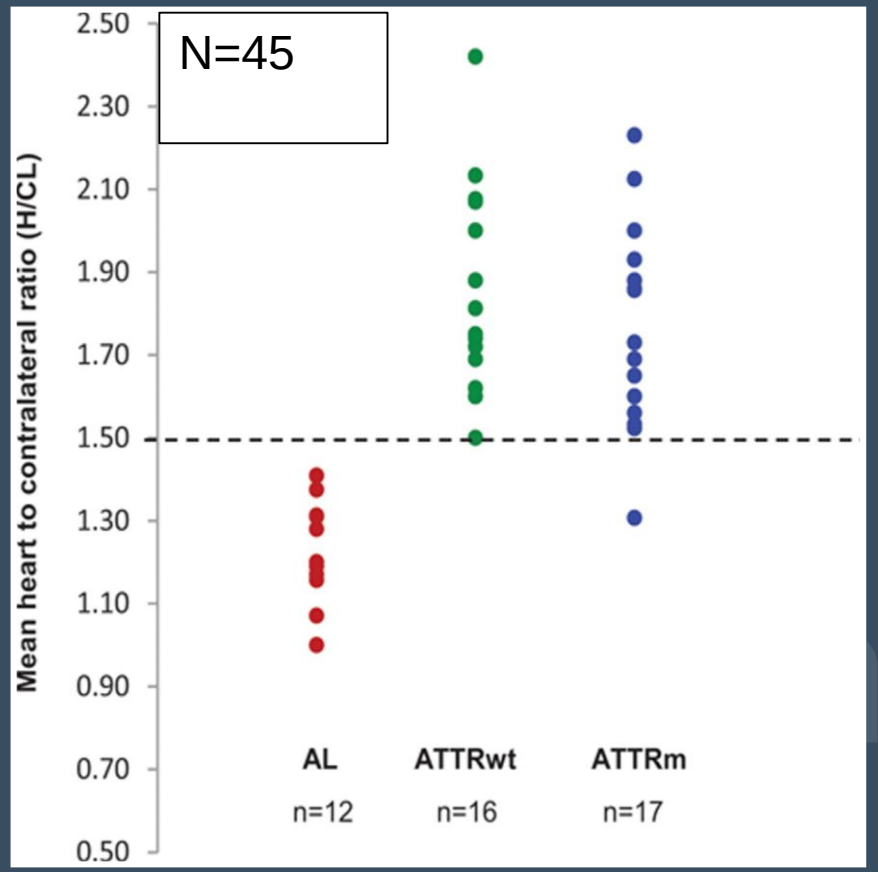
	Group A TTR-Related CA (15 Patients)	Group B AL CA (10 Patients)	Unaffected Control Patients (10 Patients)
Heart tracer retention (%)			
Median	7.3*†	3.8‡	2.9
Interquartile range	6.7–8.4	3.4–4.05	2.7–3.5
Whole-body tracer retention (%)			
Median	70.1†	67.6‡	56
Interquartile range	63.6–77.3	61.8–71.3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

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

Perugini E et al. JACC 2005;46:1076–84

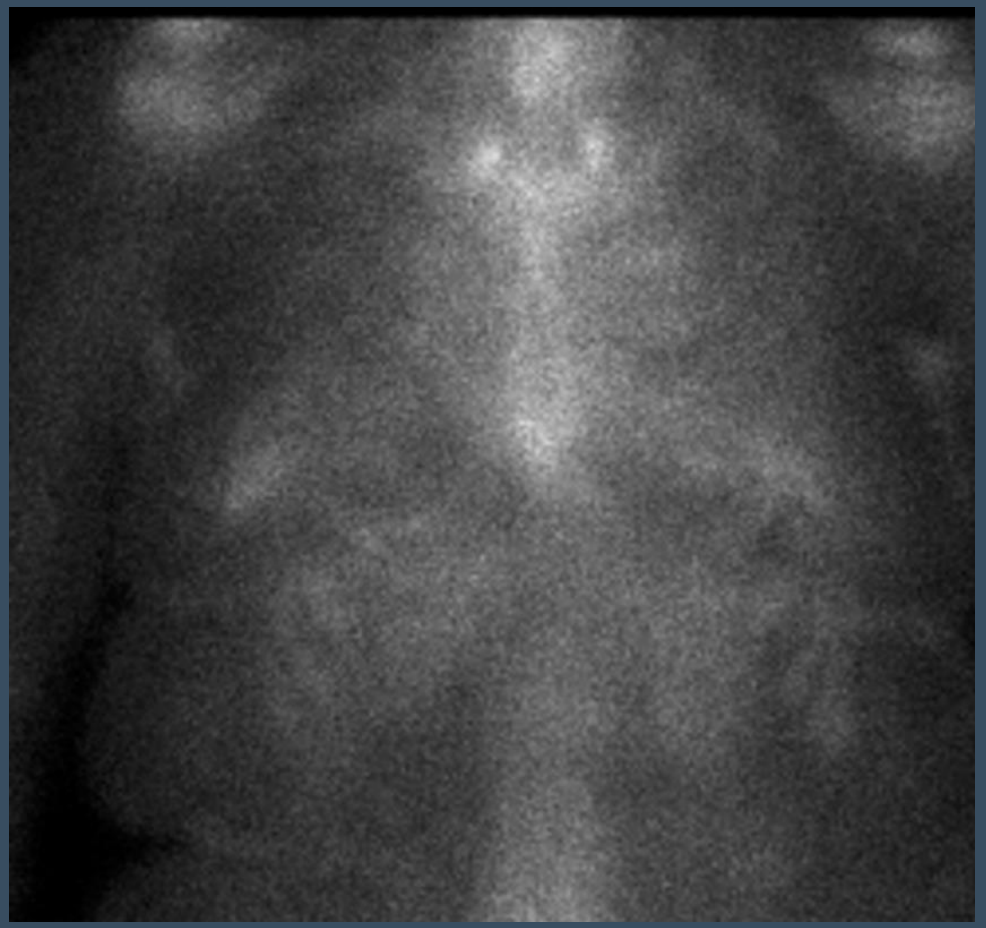
^{99m}Tc-PYP planar: Heart to contralateral ratio **Quantitation**

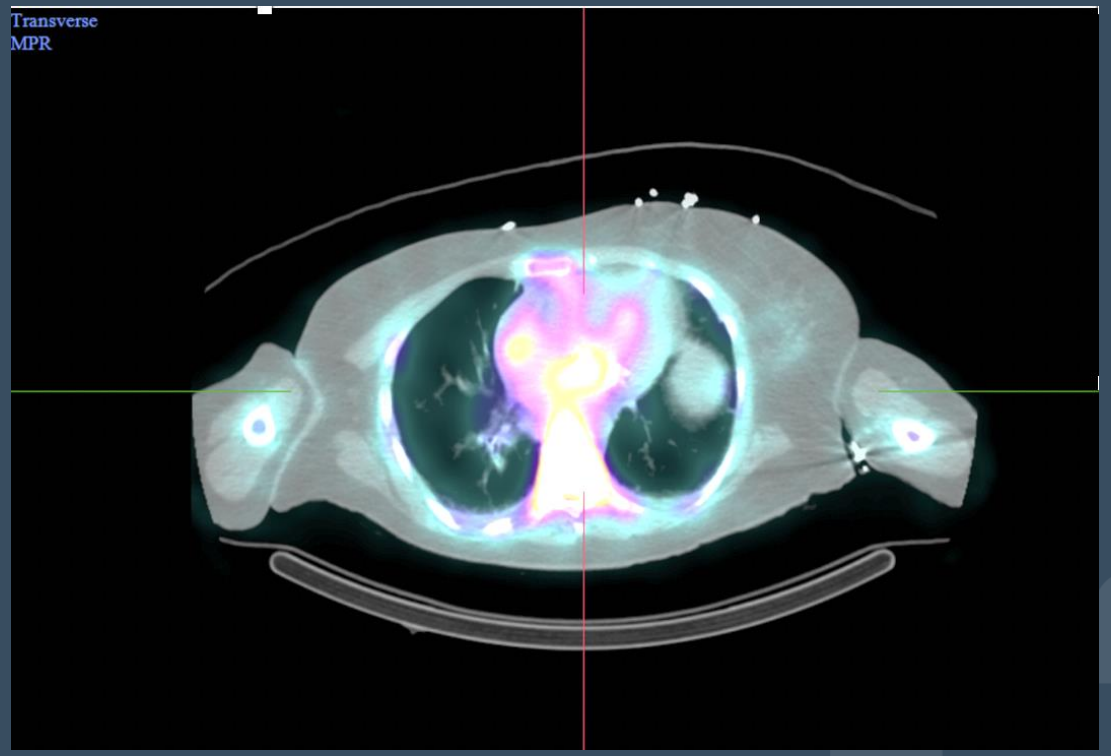




Bokhari S et al. Circ CVIM 2013;6:195-2013

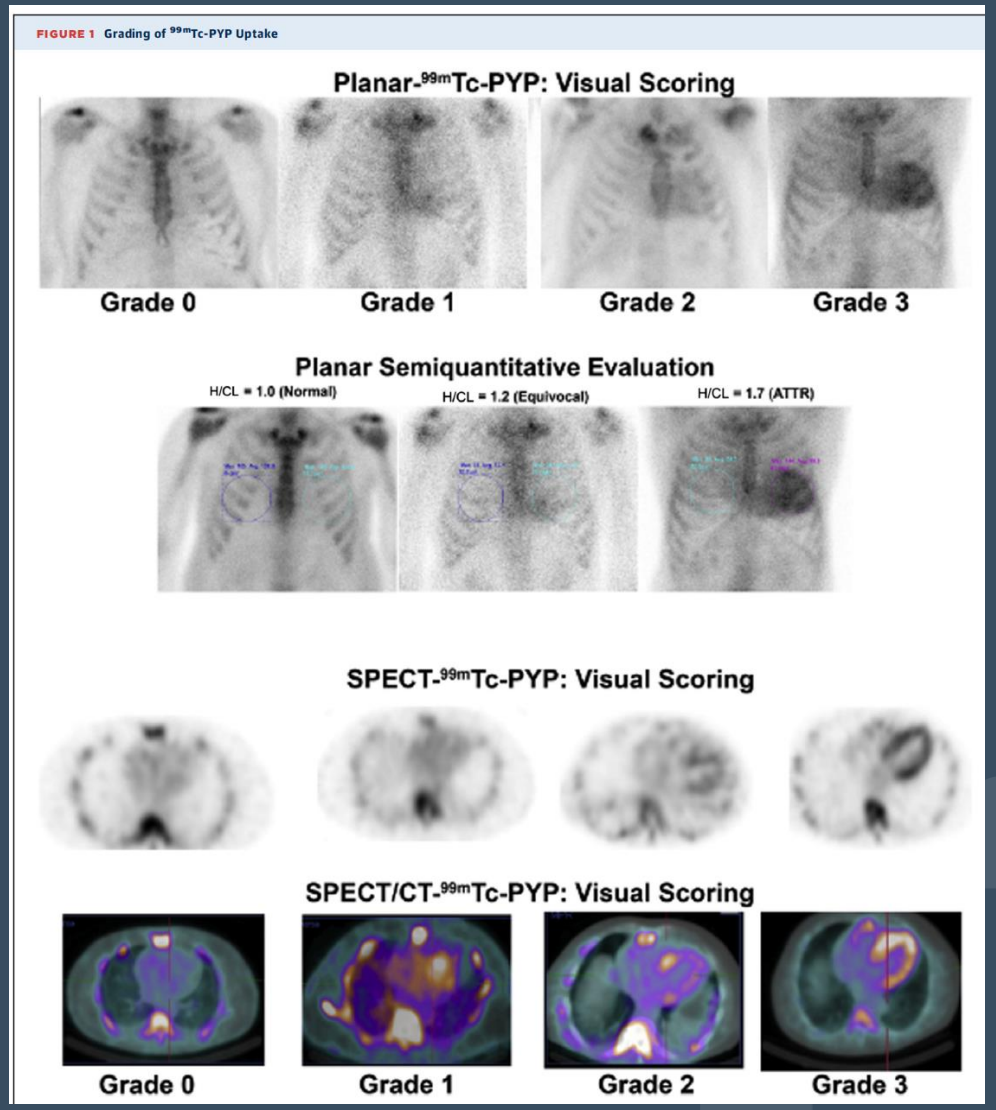
Don’t Be Confused By Blood Pool Uptake





The Role of SPECT

- Avoid overlap of lung uptake
- Distinguish blood pool from myocardial uptake
- Identify Tc-PYP uptake in septum
- Quantify uptake compared to ribs
- Assess distribution of tracer uptake (apical sparing)



Hanna M JACC 2020

Optimizing Imaging Protocol

Table 1. Accuracy of Tc-pyrophosphate scan for detecting ATTR Cardiac amyloidosis based on semiquantitative and quantitative assessments

	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Semiquantitative visual Score			
1-hour delay positive scan ≥ 2	95	79	0.938 (0.873-0.984)
3-hour delay positive scan ≥ 2	58	100	0.980 (0.932-1.000)
Combined analysis	88	88	0.945 (0.901-0.977)
Quantitative H/CL ratio			
1-hour delay positive scan ≥ 1.5	92	97	0.971 (0.949-0.992)
3-hour delay positive scan ≥ 1.3	88	86	0.935 (0.848-0.988)
Combined analysis	91	92	0.960 (0.930-0.981)

Tc-PYP, Tc pyrophosphate; *ATTR*, transthyretin amyloidosis; *AUC*, area under the curve; *CI*, confidence interval; *H/CL*, ratio = heart-to-contralateral lung ratio. Adapted from Castano et al.[25]

-One hour study less specific – More blood pool update Cutoff= 1.5

-Three Hour less sensitive Increased bone uptake Cutoff= 1.3

CCF Uses one hour - more specific

Singh JI Nuc Card 2018

Light Chain Analysis To Rule out AL- Amyloid

- Free Kappa (3.3-19.4) mg/L
- Free Lambda (5.7-26.3)
- Ratio (0.26-1.65)
- Urine IFE/Serum IFE- no monoclonal Ig

Serum Free Light Chain Assay

Test	Sensitivity
FLC κ/λ ratio	91%
Serum IFE	69%
Urine IFE	83%
FLC κ/λ ratio and urine IFE	91%
FLC κ/λ ratio and serum IFE	99%
Serum IFE and urine IFE	95%
All three tests	99%

Serum Free Light Chain Assay

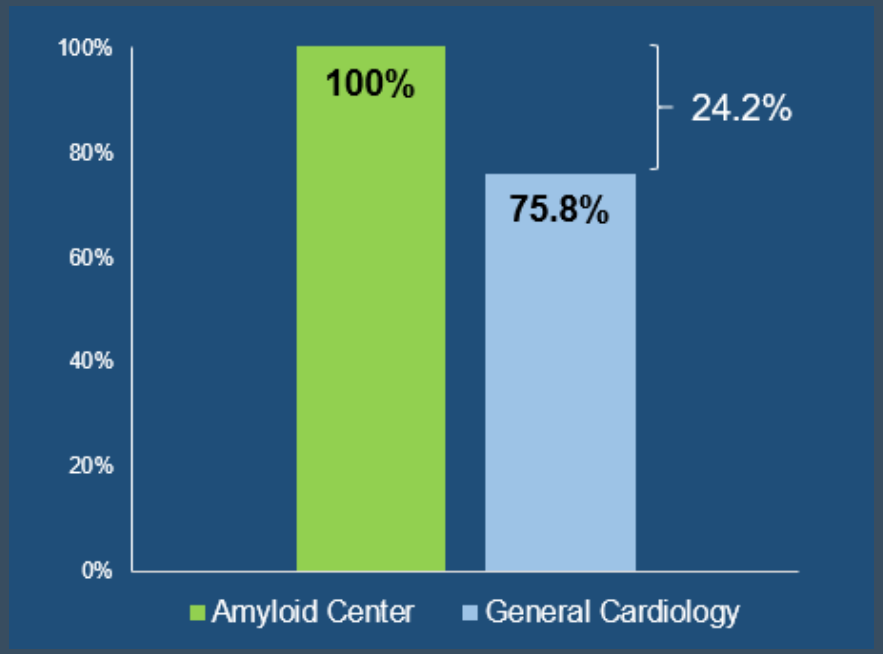
IF Positive-refer to Hematology

FLC κ/λ ratio	91%
Serum IFE	69%
Urine IFE	83%
FLC κ/λ ratio and urine IFE	91%
FLC κ/λ ratio and serum IFE	99%
Serum IFE and urine IFE	95%
All three tests	99%

Nuclear Scintigraphy Must be Coupled with Clonal Analysis

Percent of Referrals for 99mTc-PYP Scan in which Clonal Analysis was Performed

N=470



← Educational Opportunity

Nearly a quarter of patients referred for 99mTc-PYP scanning from general cardiology vs. amyloid center did not have measures for monoclonal protein (24.2% vs. 0%, $p<0.0001$)

Genetic Testing To Distinguish mutant vs Wild type ATTR

GENETIC TESTING

Genetic testing is a crucial component of the diagnostic process in determining a hATTR amyloidosis diagnosis, because it identifies the specific *TTR* mutation present.[3]

In a patient with confirmed TTR amyloid, genetic testing differentiates between hereditary and wild-type ATTR amyloidosis.[3]

Mutation in *TTR* gene sequence?

YES: hereditary ATTR (hATTR) amyloidosis

The most common *TTR* mutations include V30M and V122I worldwide, but V122I and T60A are the common mutations in the United States. More than 120 causative mutations have been identified.[3,7,8]

NO: wild-type ATTR (wtATTR amyloidosis)

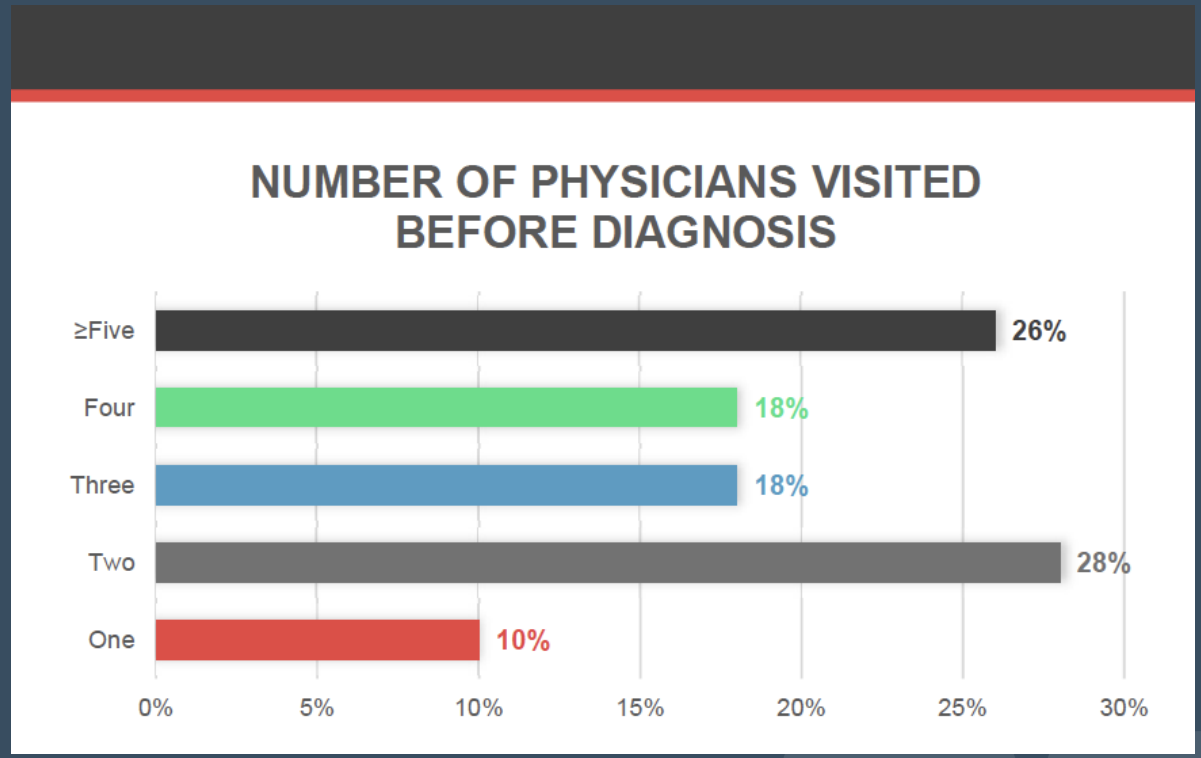
Wild-type ATTR amyloidosis is acquired and is most commonly diagnosed in men >60 years of age.[9,10]

Manifestations of hATTR and wtATTR amyloidosis can overlap significantly, but differentiation is important because[5]:

Towards Earlier Diagnosis and Treatment

Delayed Diagnosis of CA

- Time from Initial Sx → Dx is unacceptably high
  - AL-CA: 2 years, ~1/3 visited >5 physicians before Dx
  - ATTR-CA: there was a 34 month (median) delay in diagnosis (ATTR) amyloidosis.
  - Cardiologists consulted more often than other specialists but less likely to make dx



Bishop, Emily E. (2018) Amyloid, DOI: 10.1080/13506129.2018.1498782
Maurer Circulation q2017;135:1357-1377.

(Lousada et al., Adv Ther, 2015)

Carpal Tunnel and Amyloid

- CTS predates cardiac amyloid by as much as 10 years
- 50% of patients with TTR amyloid have bilateral CTS
- 10% of patients with CTS have amyloid

Other Orthopedic Findings

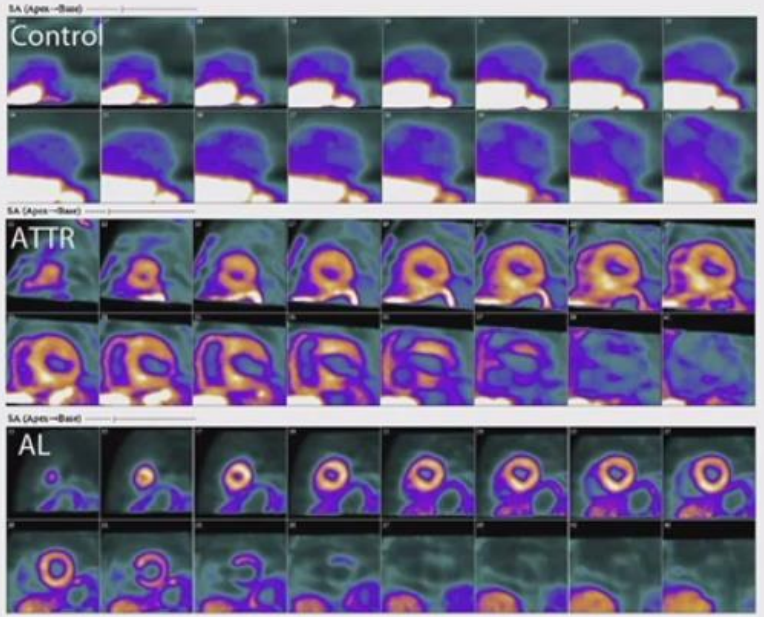
- At least 30% of lumbar stenosis tissue stains positive for amyloid
- Ruptured biceps tendons
- Cervical spine Disease

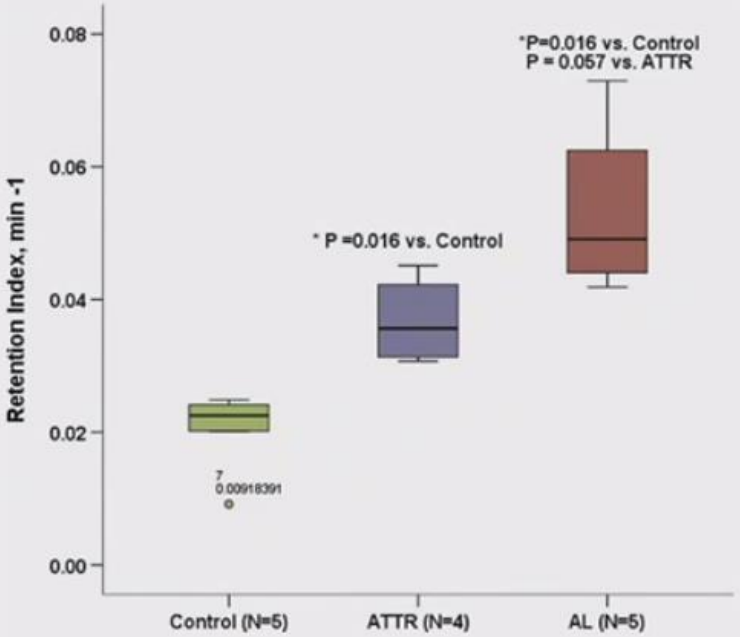
The Future of Amyloid Imaging :PET

Identifies AL and ATTR
Earlier identification

F-18 florbetapir

- approved for imaging beta amyloid in the brain
- May be novel PET tracer for both AL and ATTR





Dorbala et al, Eur J Nucl Med Mol Imaging (2014)

Dorbala et al

^{99m}Tc-PYP for Earlier Dx

ELSEVIER

JACC: Cardiovascular Imaging

Volume 10, Issue 6, June 2017, Pages 713-714

Letter to the Editor

Can ^{99m} Tc-Pyrophosphate Aid in Early Detection of Cardiac Involvement in Asymptomatic Variant TTR Amyloidosis?

Muhammad Haq MD, Sumeet Pawar MBBS, John L. Berk MD, Edward J. Miller MD, PhD, Frederick L. Ruberg MD

TABLE 1 Clinical, Genetic, Echocardiographic, and Scintigraphic Characteristics of ATTR and HFpEF

	HFpEF (n = 8)	Asymptomatic TTRm Carriers (n = 12)	Symptomatic TTRm Carriers (ATTRm) (n = 20)	p Value
Age, yrs	72 ± 8	51 ± 15*†	68 ± 9	0.003
Male	6 (75)	8 (67)	17 (80)	0.477
NYHA functional class > II	2 (25)	0 (0)	5 (25)	
TTR mutation				
V122I	0	1 (8)	8 (40)	
T60A	0	4 (33)	5 (25)	
V30M	0	1 (8)	1 (5)	
B-type natriuretic peptide, pg/ml	1,042 (484-1,263)	15 (10-37)*†	234 (128-752)	0.001
Troponin, ng/ml	0.1 (0.02-0.21)	0.008 (0.006-0.01)*†	0.09 (0.03-0.19)	<0.001
Left ventricular ejection fraction, %	59 ± 14	61 ± 8†	51 ± 14	0.04
Interventricular septal thickness, cm	1.2 ± 0.2	0.9 ± 0.3†	1.5 ± 0.3	<0.001
E/e'	18.8 ± 8.2	8 .1 ± 1.5*†	18.1 ± 8.9	<0.001
Abnormal ^{99m}Tc-PYP visual grade	4 (50)	10 (83)	20 (100)	0.04
H/CL ratio	1.2 ± 0.1	1.5 ± 0.4*†	1.8 ± 0.4	<0.001

Values are mean ± SD, n (%), or median (interquartile range). *p < 0.05 in comparison to HFpEF. †p < 0.05 in comparison to ATTRm.

ATTR = amyloid transthyretin; ATTRm = amyloid transthyretin mutation; H/CL = heart-to-contralateral ratio; HFpEF = heart failure with preserved ejection fraction; NYHA = New York Heart Association; ^{99m}Tc-PYP = 99m-technetium pyrophosphate (abnormal uptake = grade 1, 2, or 3); TTRm = transthyretin mutation.

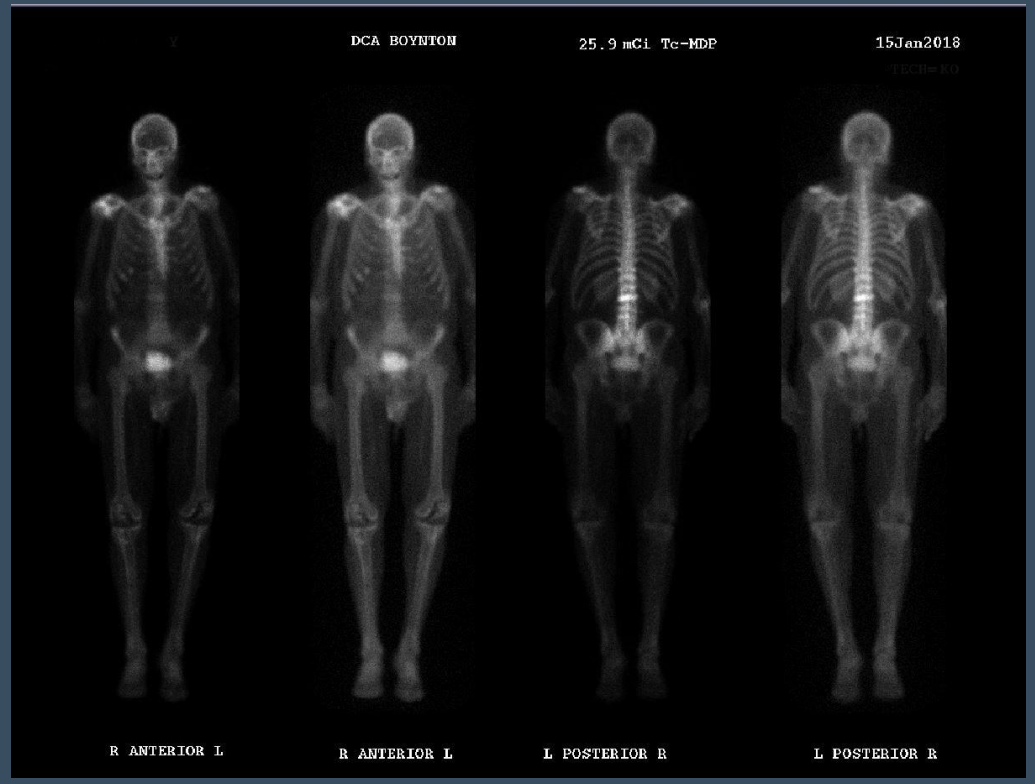
Abnormal ^{99m}Tc-PYP cardiac scans in known carriers of hATTR mutations despite asymptomatic status, normal biomarkers, and normal TTE

JA

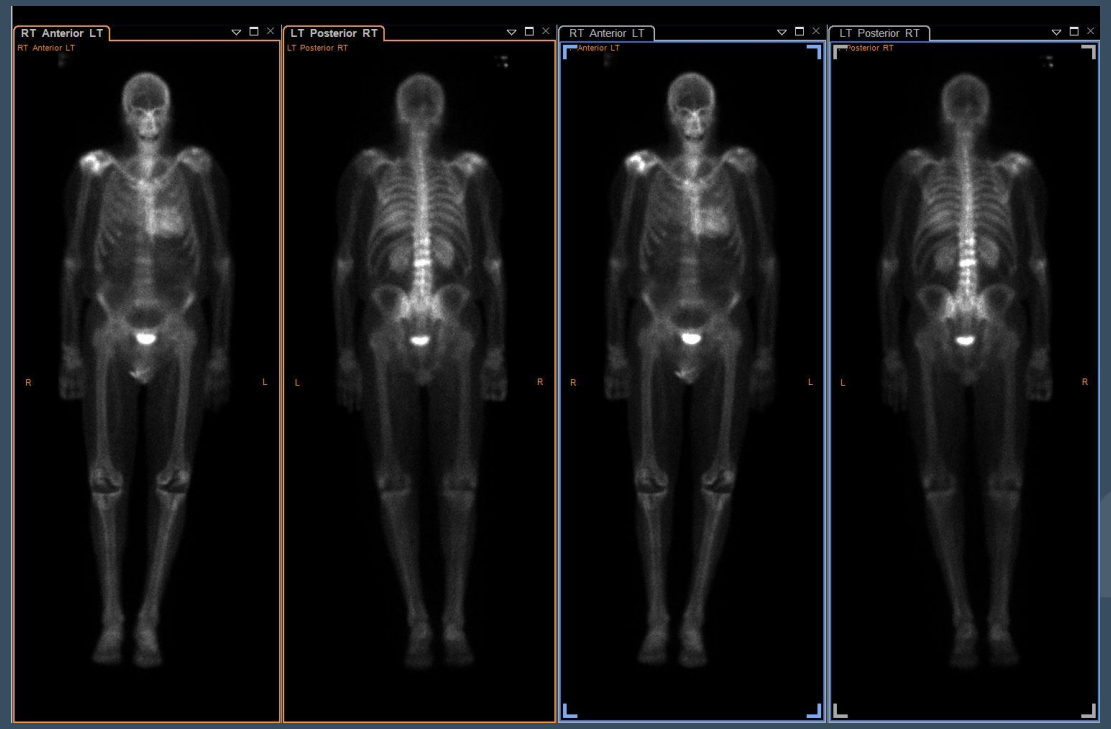
- 70 male with history of CAD and CABG radical prostatectomy June 2018. Preop MPI unremarkable Six months later followup bone scan - normal
  Well active without any cardiac or neurologic symptoms
- Another six months later referred for referred for followup bone scan (Tc-MDP)

JA

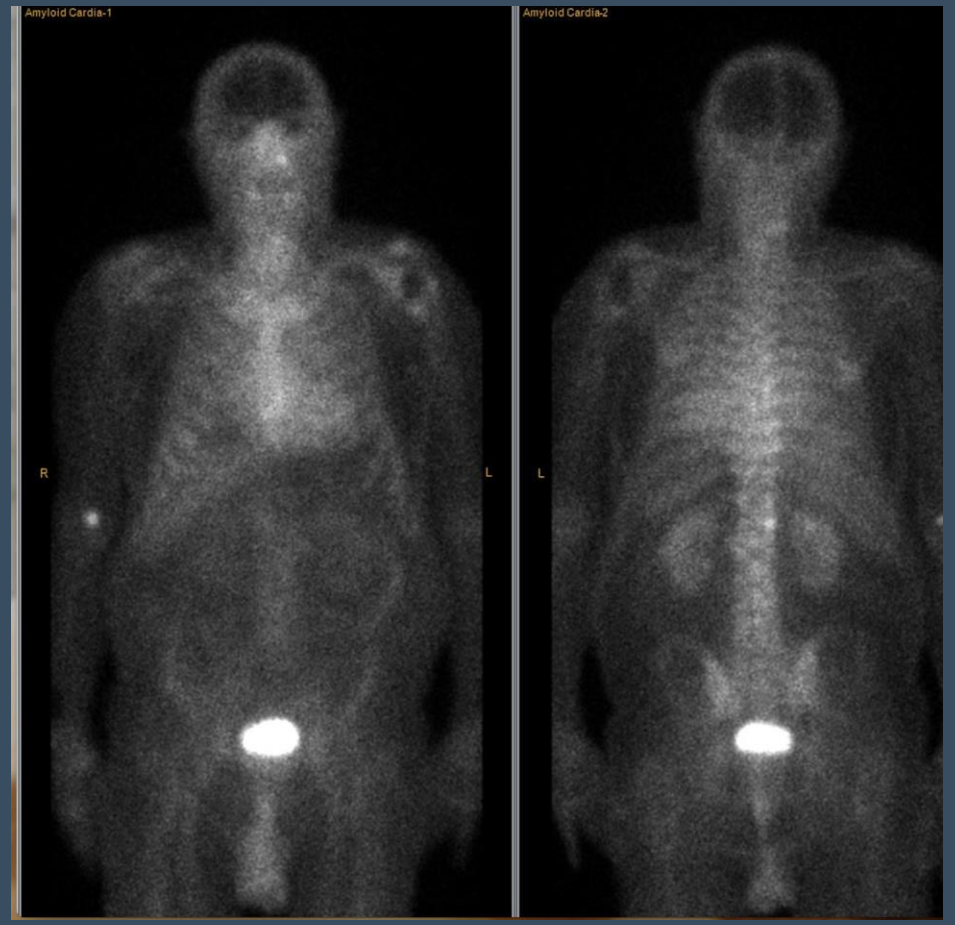
Initial Post Op Bone Scan



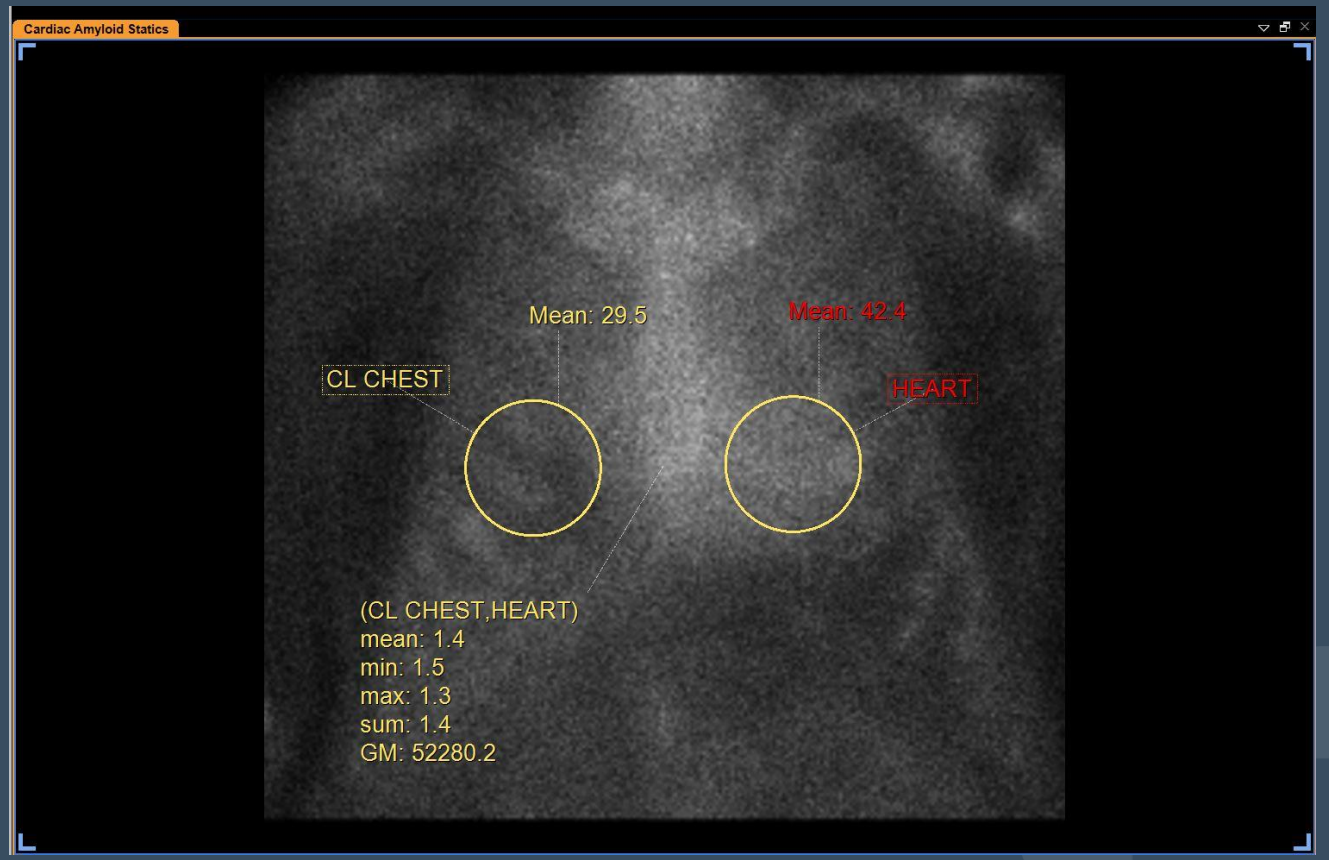
Six months later



PYP Planar



3 Hr Image



H/CL- 1.4

PYP SPECT

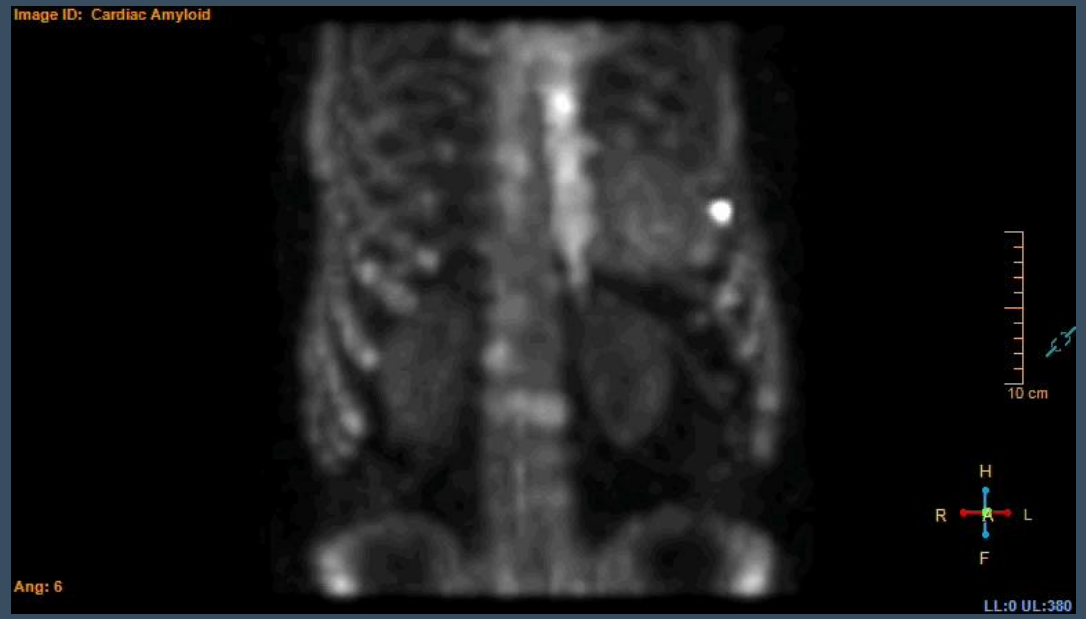
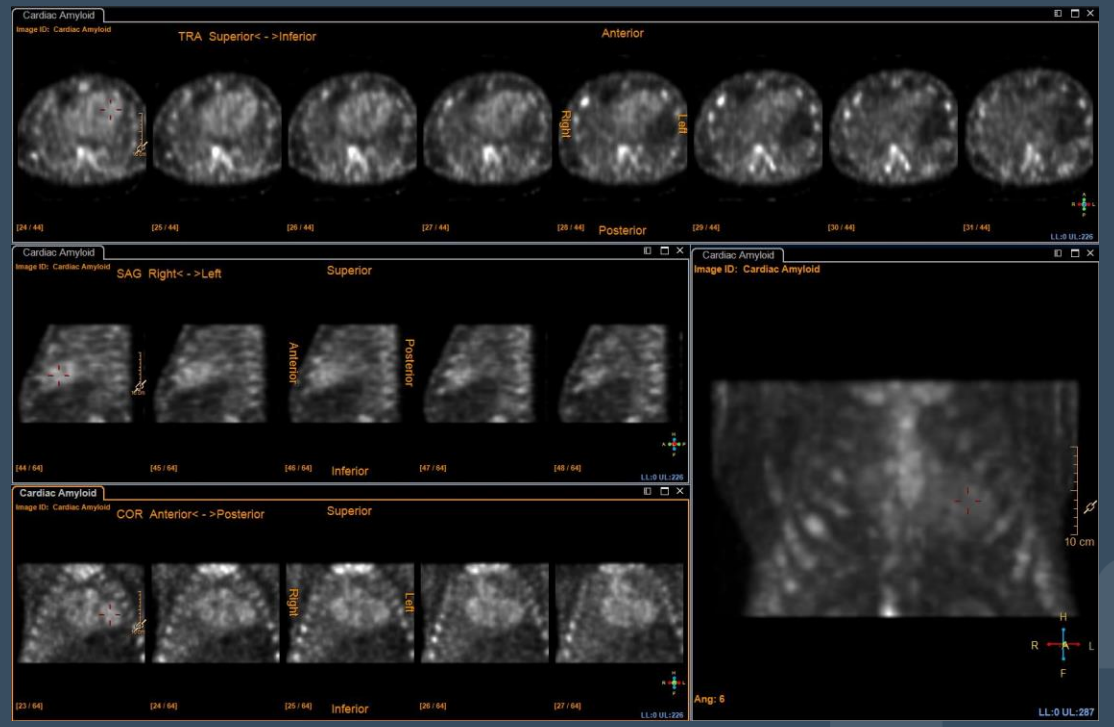


Image ID: Cardiac Amyloid
10 cm
H
R
L
F
Ang: 6
LL:0 UL:380


Cardiac Amyloid
TRA Superior< - >Inferior
Anterior
Right
Left
Posterior
Cardiac Amyloid
SAG Right< - >Left
Superior
Anterior
Posterior
Inferior
Cardiac Amyloid
COR Anterior< - >Posterior
Superior
Right
Left
Inferior
Cardiac Amyloid
Image ID: Cardiac Amyloid
10 cm
H
R
L
F
Ang: 6
LL:0 UL:287

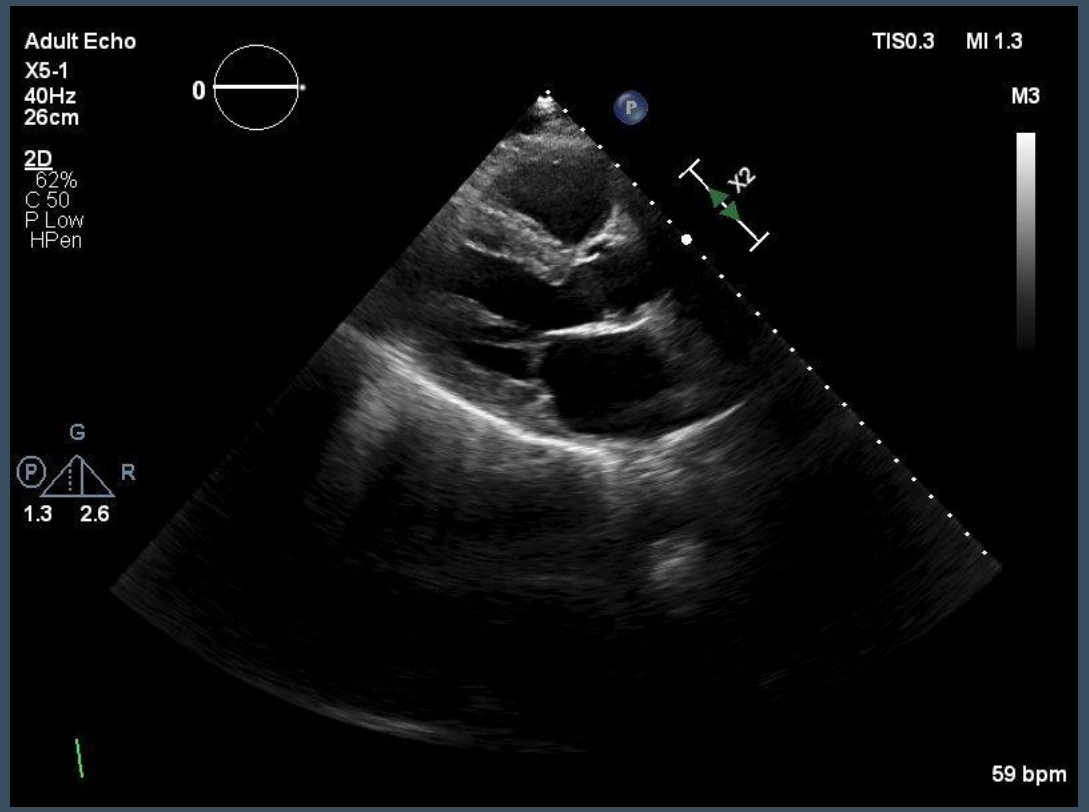
CMR

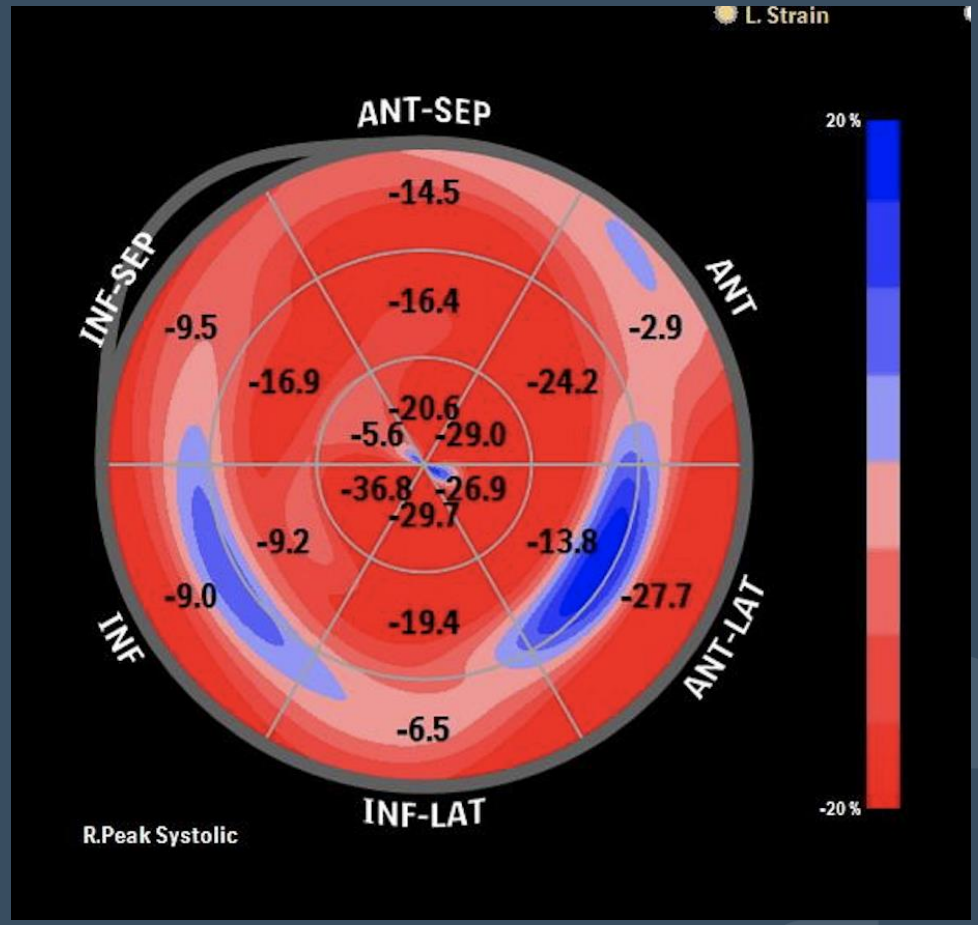
Impression

IMPRESSION:

1. Normal left ventricular size. Mild concentric left ventricular hypertrophy (max thickness = 1.4 cm). Normal/low normal left ventricular systolic function (LVEF = 57%).
2. All left ventricular walls are fully viable and without evidence of myocardial scar/infarction.
3. Mildly dilated right ventricle (based on qualitative comparison with the left ventricle). Normal right ventricular systolic function.
4. Mild biatrial dilatation. Mild mitral regurgitation.

ECHO


Adult Echo
X5-1
40Hz
26cm
2D
62%
C 50
P Low
HPen
TIS0.3
MI 1.3
M3
0
X2
G
P
R
1.3
2.6
59 bpm


L. Strain
ANT-SEP
ANT
ANT-LAT
INF-LAT
INF
INF-SEP
-14.5
-16.4
-2.9
-24.2
-9.5
-16.9
-20.6
-5.6
-29.0
-36.8
-26.9
-29.7
-9.2
-13.8
-9.0
-27.7
-19.4
-6.5
20 %
-20 %
R.Peak Systolic

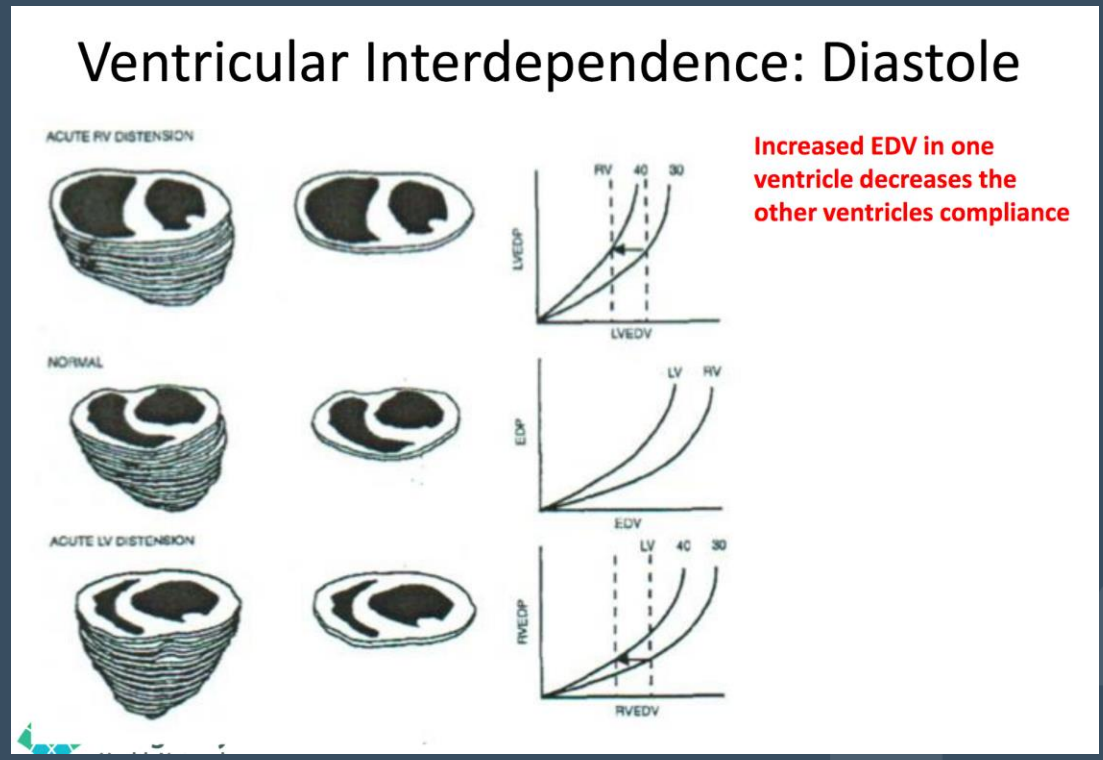
Followup

- Genetic testing negative
- 3m months later onset DOE
- ECHO – increased LV thickness
- Elevated Tn and BNP
- Started on diuretics
- Started on Tafamidis
- DX = Early TTR-wt Amyloid

Treatment Of Cardiac Amyloid

Patients are Volume Sensitive

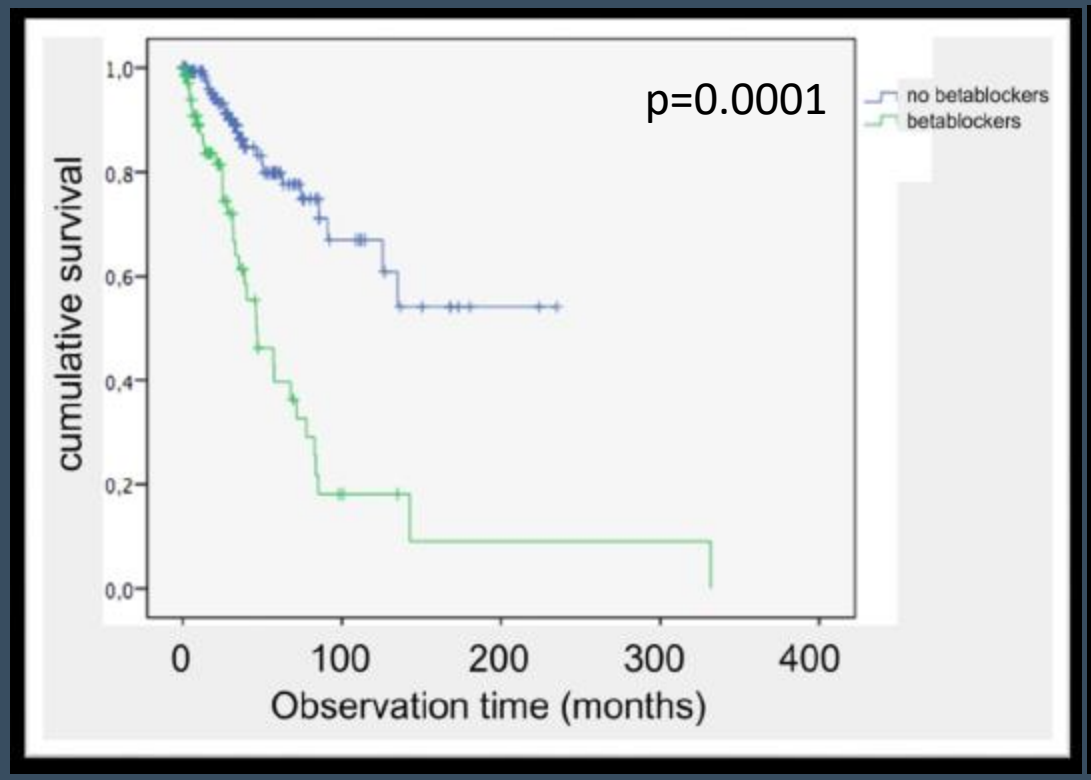
- Small LV
- Orthostatic hypotension
- Immobile with dependent legs
- Cardiorenal syndrome

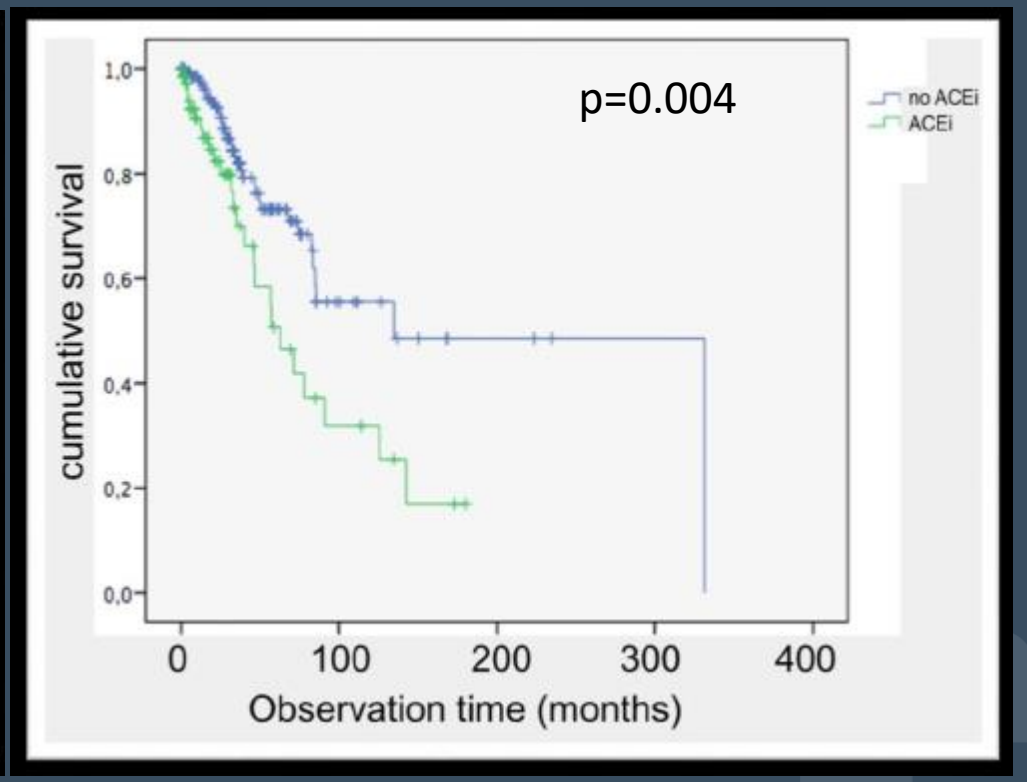


Medical Therapy for Amyloid

- Diuretic - Use Torsemide, Bumetanide, They have better intestinal absorption
- PRN metolazone- do not delay- start with 3-5 lb weight gain
- Aldactone
- Adjust diuretics based on clinical status , not BUN/Cr
- Avoid multiple clinicians ordering meds
- Avoid ACE,ARB,ARNI unless severe LV dysfunction
- Avoid CCB, Beta Blocker digoxin
- Midodrine for orthostatic hypotension

ACE/ARB and Beta Blockers in TTR Amyloid





F. aus dem Siepen, ISA 2016

Rhythm Management

- Cautious with rate controlling agents -BB, CCB, Digoxin (binds to amyloid fibrils) Need heart rate for cardiac output
- Atrial fibrillation- cardioversion
- Amiodarone- maintainace of NSR
- Anti-coagulation High thromboembolic risk- Consider 30 day or implantable loop monitor
- A-V Node ablation and pacemaker- limited experience
- ICD 30% appropriate shock

Rhythm Management

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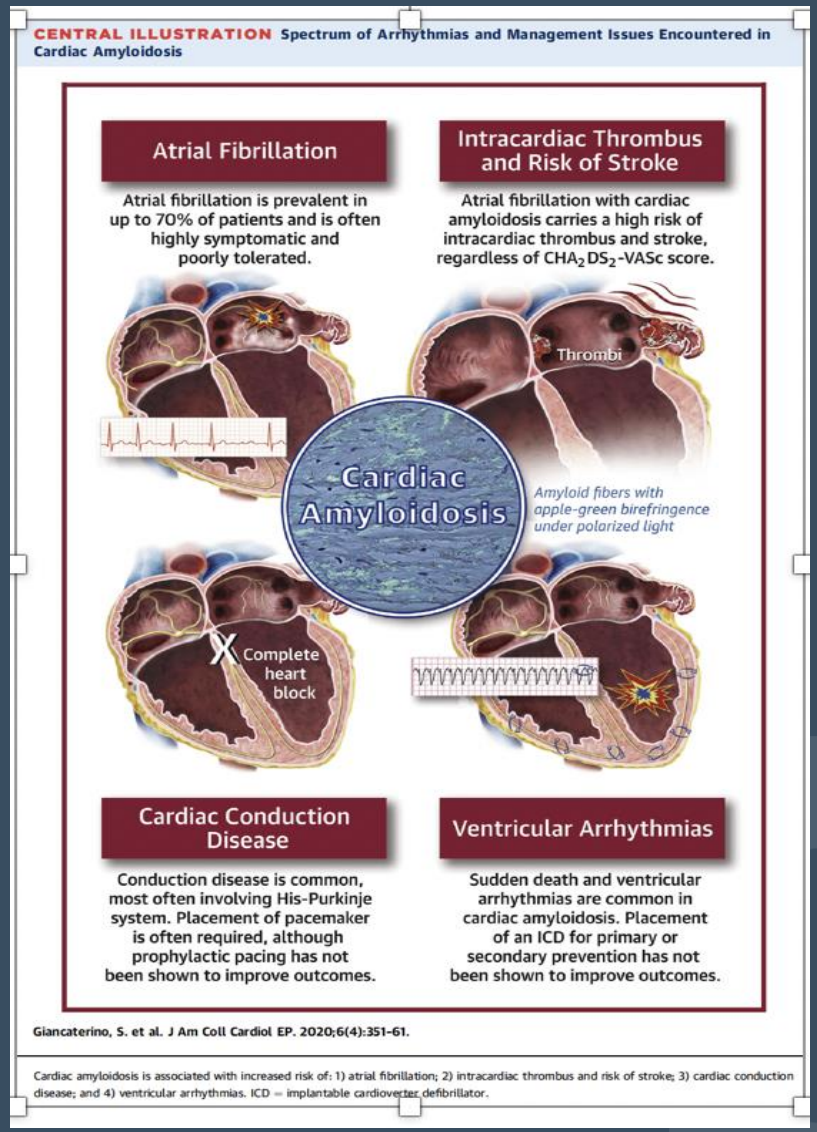


Pacemakers and Amyloid

Cardiac devices in patients with transthyretin amyloidosis: Impact on functional class, left ventricular function, mitral regurgitation, and mortality

Eoin Donnellan MD | Oussama M. Wazni MD | Walid I. Saliba MD | Bryan Baranowski MD | Mazen Hanna MD | Michael Martyn MD | Divyang Patel MD | Kevin Trulock MD | Venu Menon MD | Ayman Hussein MD | Philip Aagaard MD, PhD | Wael Jaber MD | Mohamed Kanj MD

Worsening of LV function:

-26% if RV paced <40%

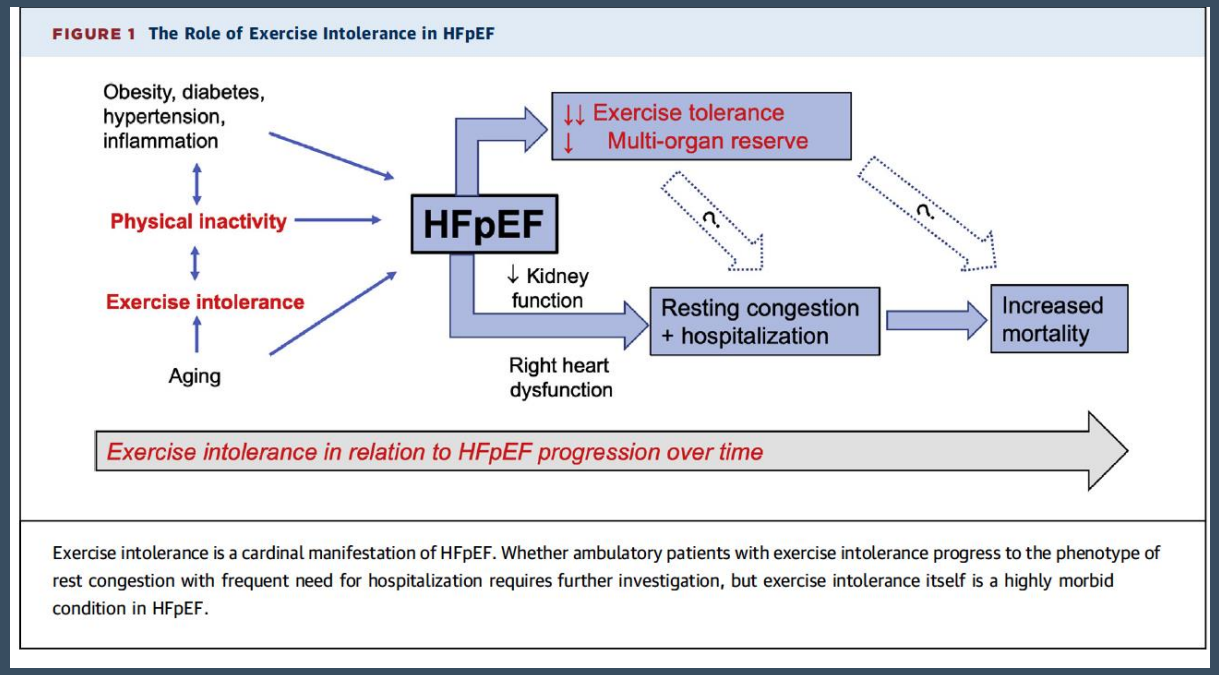
-89% if RV paced >40%

Mitral regurgitation worsened more frequently if RV paced >40%

CRT improved LVEF,NYHA class, Severity MR

Donelan Jl CV Electro Phys. Nov 2019

Exercise in HFpEF and Right Heart Failure



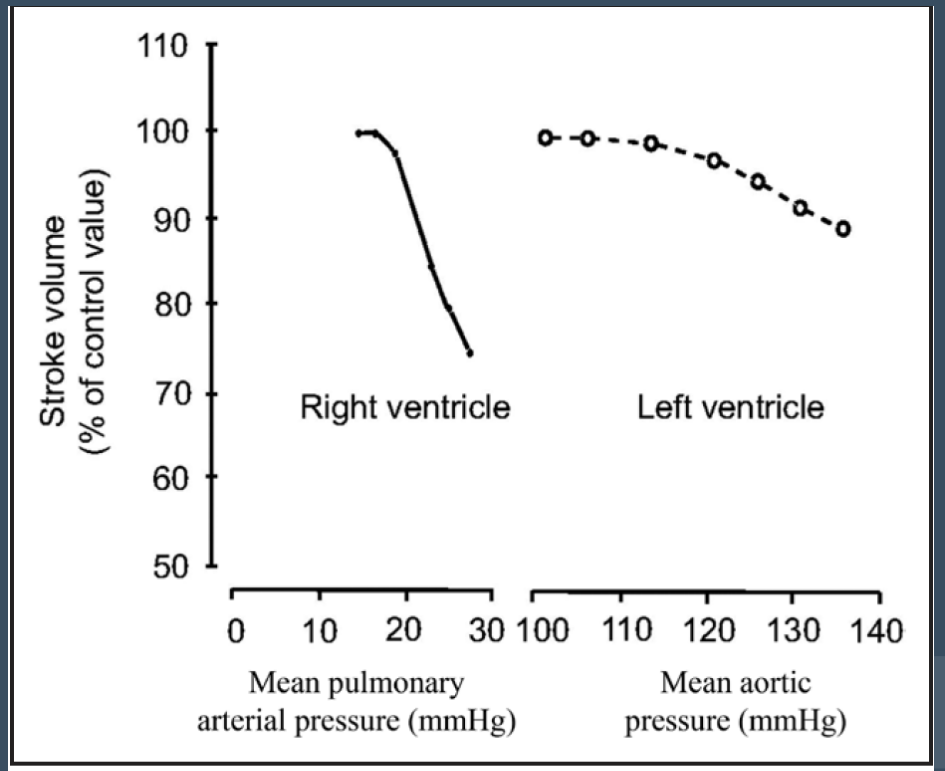
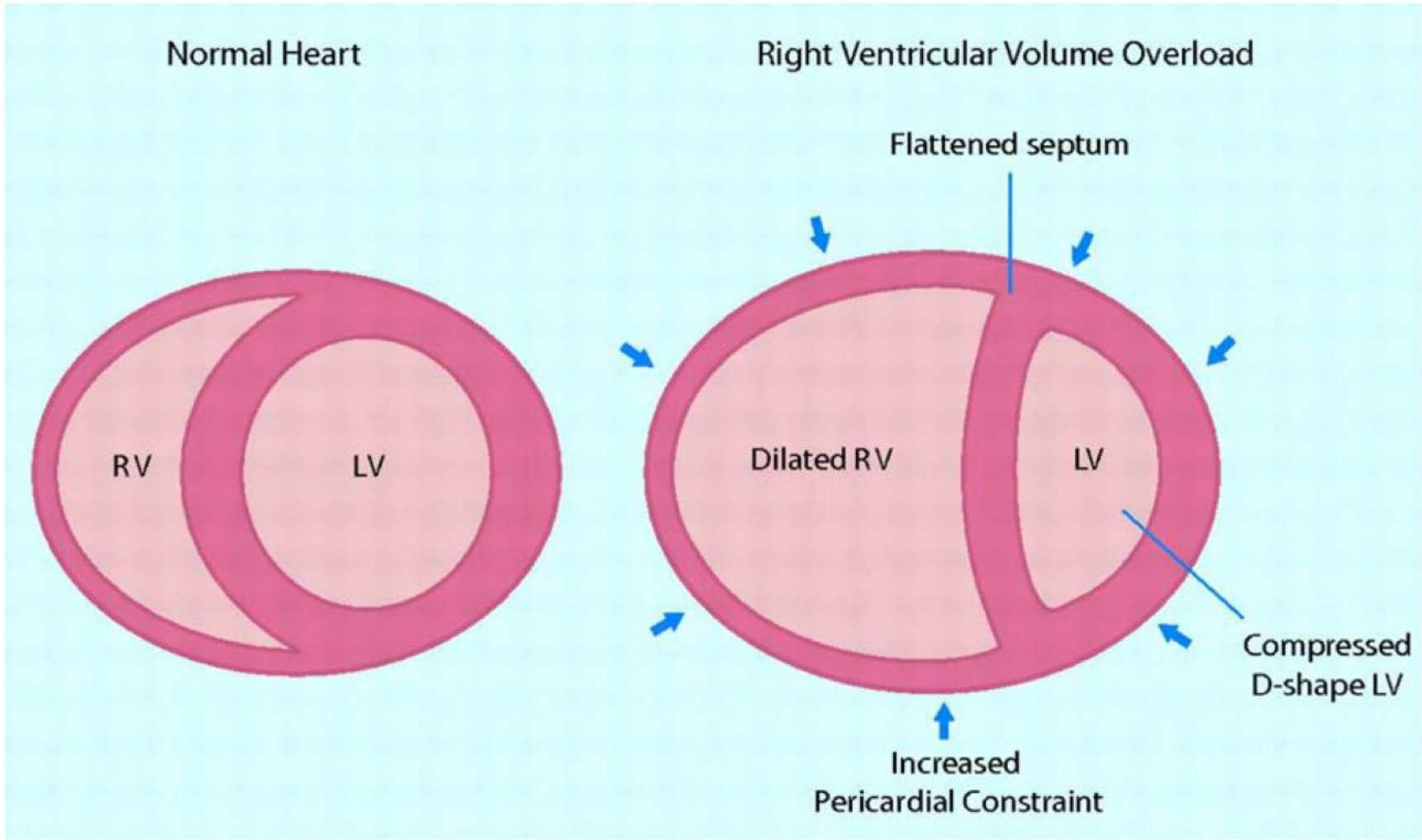


Figure 4. Relationship of right ventricular (RV) and left ventricular (LV) stroke volumes to increases in after-load.

Eur J Heart Fail. 2017 Nov;19(11):1457-1465. doi: 10.1002/ejhf.899. Epub 2017 Aug 24.

Inotropic myocard predominant feat cardiac amyloidos

Tor Skibsted Clemmensen [1], Her Andersen [3], Søren Mellemkjaer [1] Harms [2], Steen Hvitfeldt Poulser



The Role of Transplant

JACC Heart Fail. 2020 May 4. pii: S2213-1779(20)30075-5. doi: 10.1016/j.jchf.2019.12.013. [Epub ahead of print]

Outcomes in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation.

Barrett CD[1], Alexander KM[2], Zhao H[3], Haddad F[2], Cheng P[2], Liao R[2], Wheeler MT[2], Liedtke M[2], Schrier S[2], Arai S[2], Weisshaar D[3], Witteles RM[4].

Author information

Abstract

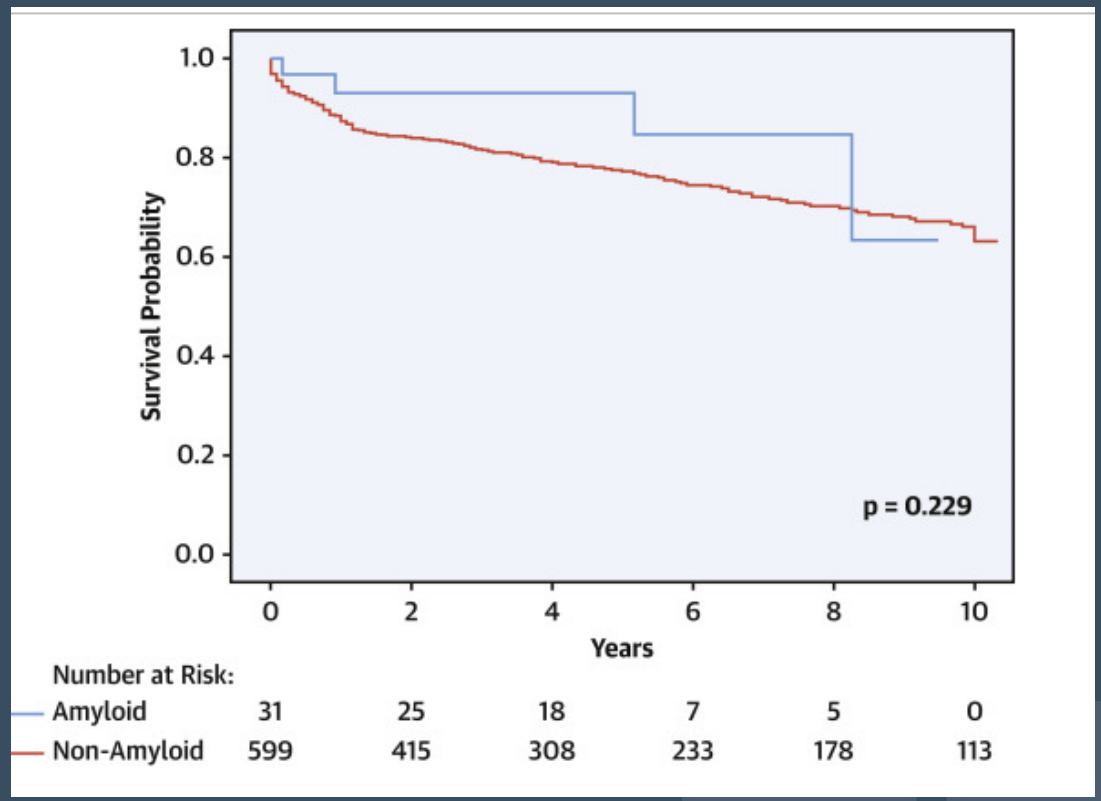
OBJECTIVES: The purpose of this study is to report outcomes after heart transplantation in patients with cardiac amyloidosis based on a large single-center experience.

BACKGROUND: Cardiac amyloidosis causes significant morbidity and mortality, often leading to restrictive cardiomyopathy, progressive heart failure, and death. Historically, heart transplantation outcomes have been worse in patients with cardiac amyloidosis compared with other heart failure populations, in part due to the systemic nature of the disease. However, several case series have suggested that transplantation outcomes may be better in the contemporary era, likely in part due to the availability of more effective light chain suppressive therapies for light chain amyloidosis.

METHODS: This study examined all patients seen between 2004 and 2017, either at the Stanford University Medical Center or the Kaiser Permanente Santa Clara Medical Center, who were diagnosed with cardiac amyloidosis and ultimately underwent heart transplantation. This study examined pre-transplantation characteristics and post-transplantation outcomes in this group compared with the overall transplantation population at our center.

RESULTS: During the study period, 31 patients (13 with light chain amyloidosis and 18 with transthyretin [ATTR] amyloidosis) underwent heart transplantation. Patients with ATTR amyloidosis were older, were more likely to be male, had worse baseline renal function, and had longer waitlist times compared with both patients with light chain amyloidosis and the overall transplantation population. Post-transplantation, there were no differences in post-operative bleeding, renal failure, infection, rejection, or malignancy. There was no significant difference in mortality between patients who underwent heart transplantation for amyloid cardiomyopathy and patients who underwent heart transplantation for all other indications.

CONCLUSIONS: In carefully selected patients with cardiac amyloidosis, heart transplantation can be an effective therapeutic option with outcomes similar to those transplanted for other causes of heart failure.

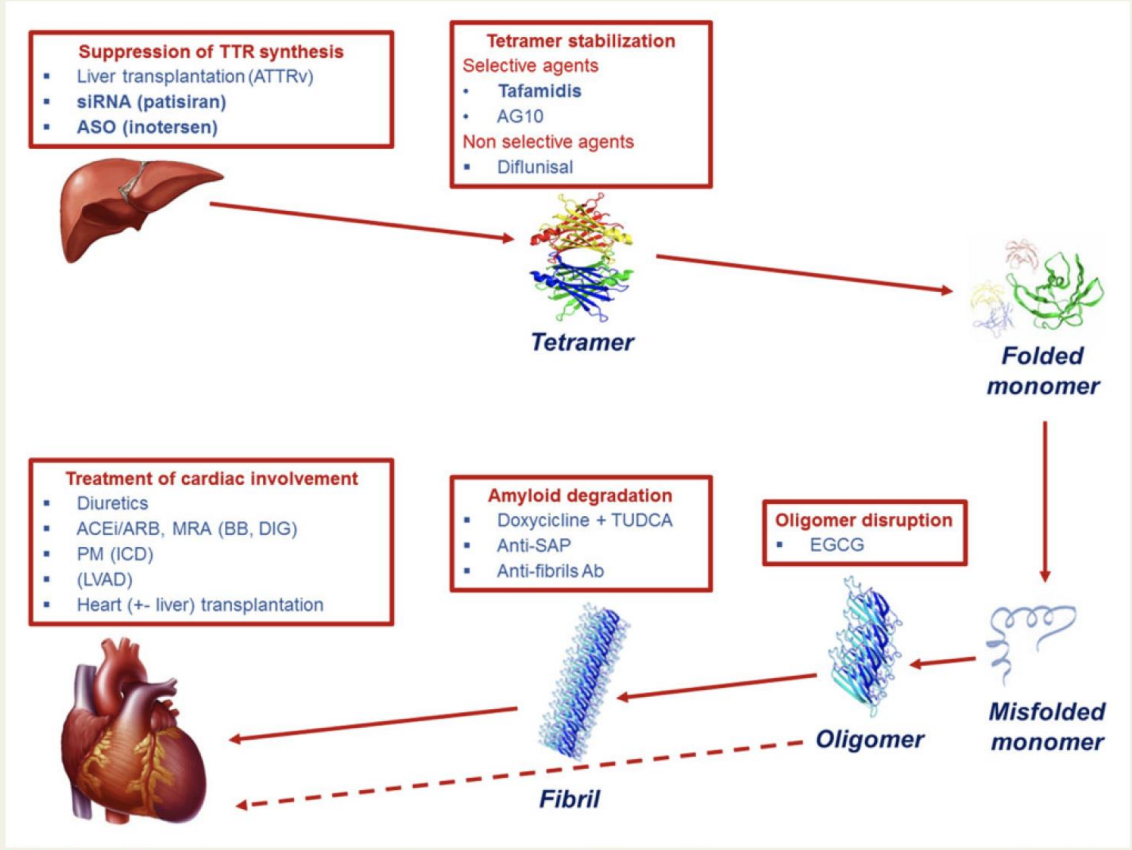


AL amyloid, with liver transplant and stem cell transplant

TTR - V122 ,Thr 60 mutations

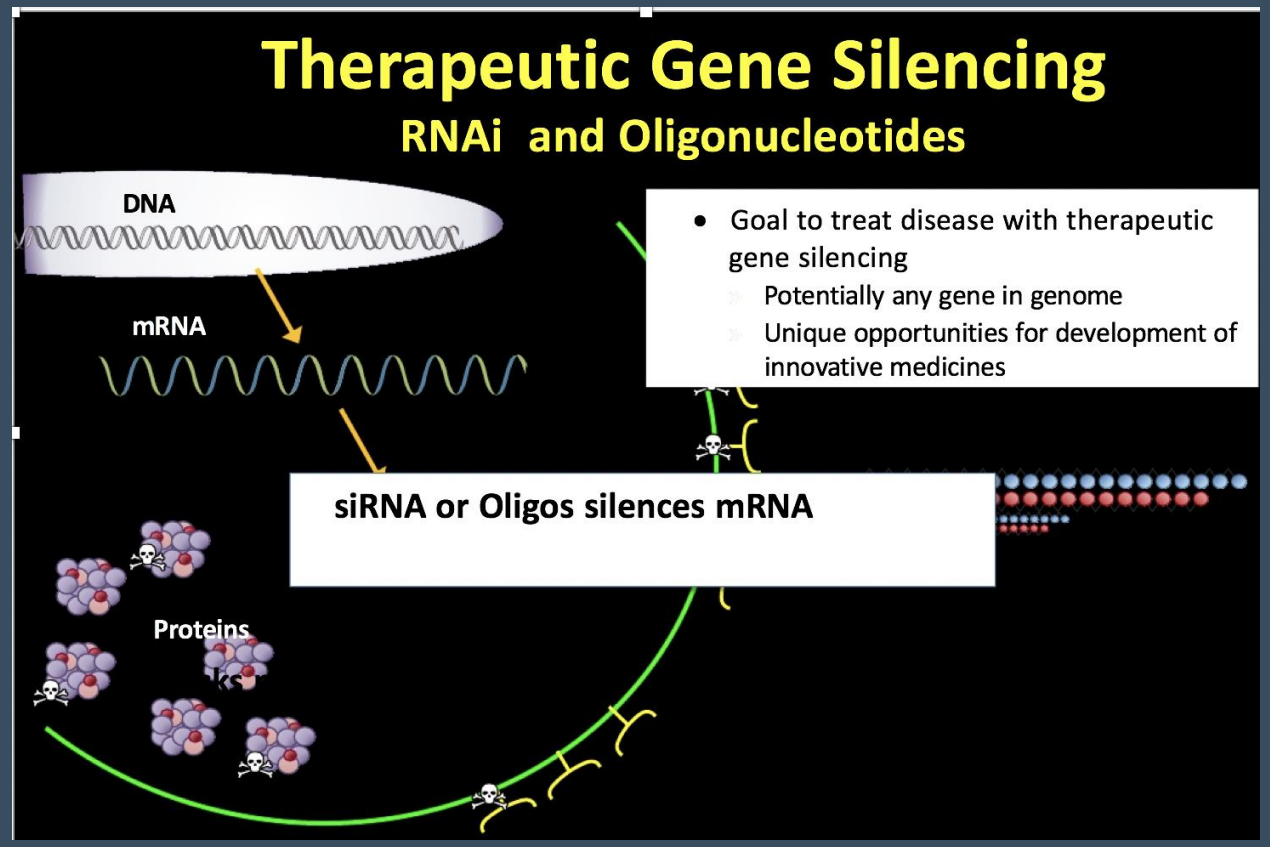
Disease Modifying Therapy for Amyloid

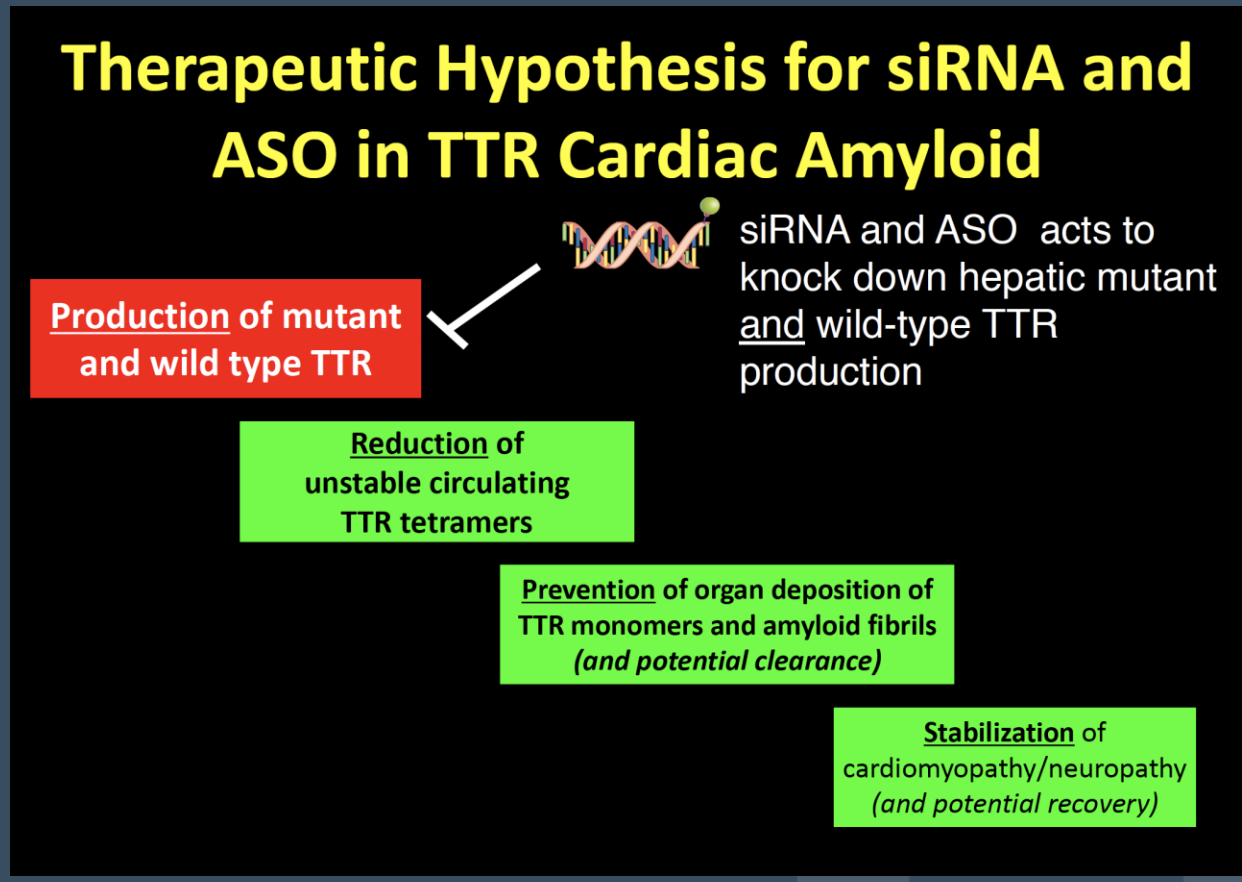
Management of Cardiac ATTR Amyloid



Take home figure The pathogenetic cascade of cardiac transthyretin (TTR) amyloidosis and proposed therapeutic approaches for each step. The more promising approaches, for which a phase 3 study is available, are evidenced in bold, while the least established options are reported in brackets. Ab, antibody; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; ASO, antisense oligonucleotide; BB, beta-blockers; EGCG, epigallocatechin gallate; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; ATTRv, variant transthyretin amyloidosis; MRA, mineralocorticoid receptor antagonists; PM, pacemaker; SAP, serum amyloid P component; siRNA, small interfering RNA; TUDCA, tauroursodeoxycholic acid.

Disease Modifying Therapy





Courtesy Mat Maurer MD

TTR Silencing with siRNA or ASO

New England Journal of Medicine

Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis

Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attariari S, Plante-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH III, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MJ, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB

New England Journal of Medicine

Inotersen treatment for patients with hereditary transthyretin amyloidosis

Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Plante-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH III, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceicao I, Schmidt HH, Vita G, Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T

Adams D, et al. *N Eng J Med.* 2018;379:11-21.
Benson MD, et al. *N Eng J Med.* 2018;379:22-31

Patisiran

- Approved for hereditary polyneuropathy
- Infusion q 3weeks 0.3mc/kg up 30mg-- Pretreat
- Infusion site reaction
- Other side effects – decreased Vitamin A
- Improved polyneuropathy

- Patisiran +small interfering ribonucleic acid (siRNA)=treatment, a class of drugs that “silences” the portion of RNA involved in causing the disease. Deliver the drug directly into the patient’s liver.
  Reduces amyloid deposit accumulation

Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Analysis of the APOLLO Study

Scott D. Solomon ✉, David Adams, Arnt Kristen, Martha Grogan, Alejandra González-Duarte, Mathew S. Maurer, Giampaolo Merlini, Thibaud Damy, Michel S. Slama, Thomas H. Brannagan III, Angela Dispenzieri, John L. Berk, Amil M. Shah, Pushkal Garg, Akshay Vaishnaw, Verena Karsten, Jihong Chen, Jared Gollob, John Vest, Ole Suhr

Originally published 14 Sep 2018 | https://doi.org/10.1161/CIRCULATIONAHA.118.035831 | Circulation. 2018;139:431–443

Conclusions:

Patisiran decreased mean left ventricular wall thickness, global longitudinal strain, *N*-terminal prohormone of brain natriuretic peptide, and adverse cardiac outcomes compared with placebo at month 18, suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis.

Prespecified Subgroups

Effects on BNP begin to be seen at 9 months on NT-BNP

Inotersen

- Anti- sense drug decreases production of Transthyretin
- Approved for mutant ATTR polyneuropathy
- Given at home by SQ injection
- Side EFFECTS –thrombocytopenia and hemorrhagic glomerulonephritis
- Markedly reduced with monitoring program
- Reduction of LV mass and improved 6 minute walk

Safety and Efficacy of a TTR Specific Antisense Oligonucleotide in Patients With Transthyretin Amyloid Cardiomyopathy

Merrill D Benson [1 2], Noel R Dasgupta [3], Stacy M Rissing [4], Jessica Smith [4], Harvey Feigenbaum [3]

Affiliations + expand

PMID: 28906150 DOI: 10.1080/13506129.2017.1374946

TTR CONCENTRATIONS REDUCED 39% TO 91%

Results: Eight patients with hereditary ATTR amyloidosis and 7 patients with wild-type ATTR amyloidosis with moderate to severely advanced restrictive cardiomyopathy showed stabilization of disease as measured by left ventricular wall thickness, left ventricular mass (LVM), 6-min walk test (6MWT), and echocardiographic global systolic strain. IONIS-TTR$_{Rx}$ was well tolerated by all 15 subjects and showed a good safety profile.

Conclusions: ASO treatment of patients with moderate to advanced ATTR cardiomyopathy shows indication of stabilization of disease progression and may therefore contribute to enhanced life expectancy.

Keywords: Amyloidosis; cardiomyopathy; heart failure; transthyretin.

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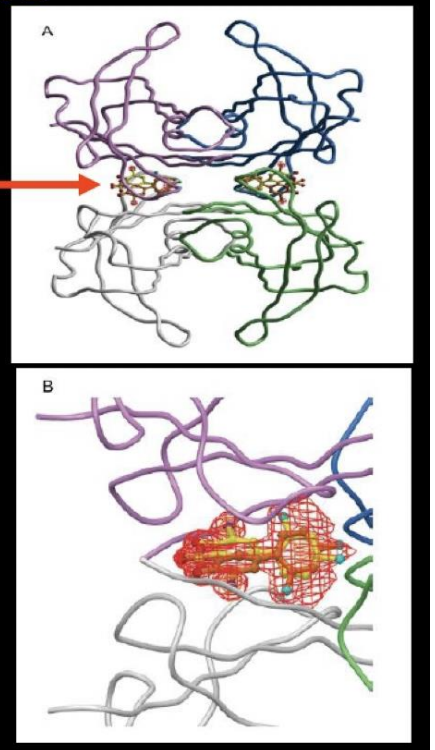
TTR Stabilizers

TTR Stabilizers

- Diflunisal
  - NSAID; Binds and stabilizes common familial TTR variants against acid-mediated fibril formation.
- Tafamidis
  - Binds to thyroxine-binding sites of the TTR tetramer, inhibiting dissociation into monomers and blocking the rate-limiting step in the TTR amyloidogenesis cascade



Amyloid. 2006 Dec;13(4):236-49

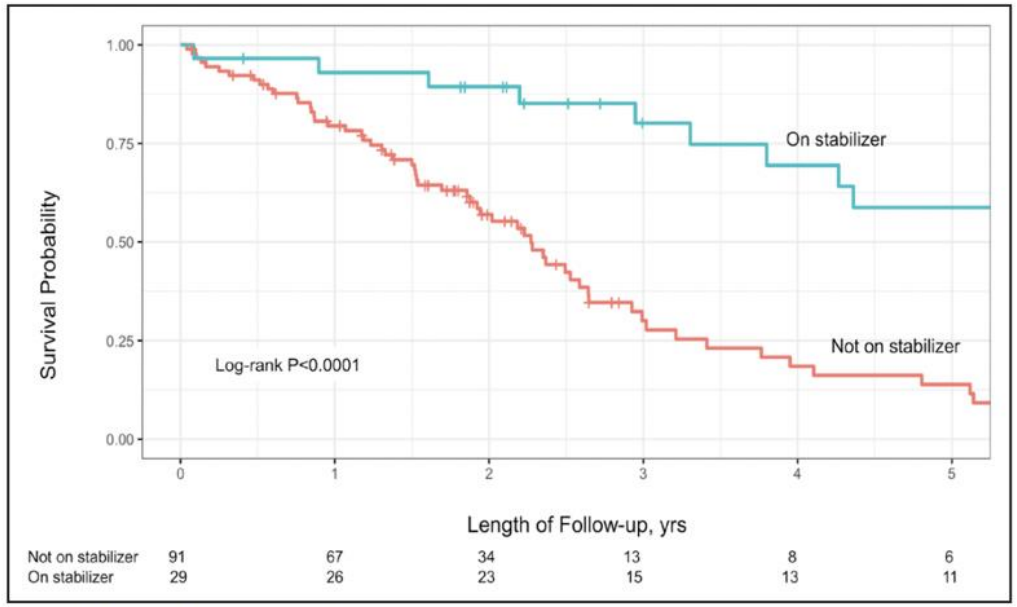
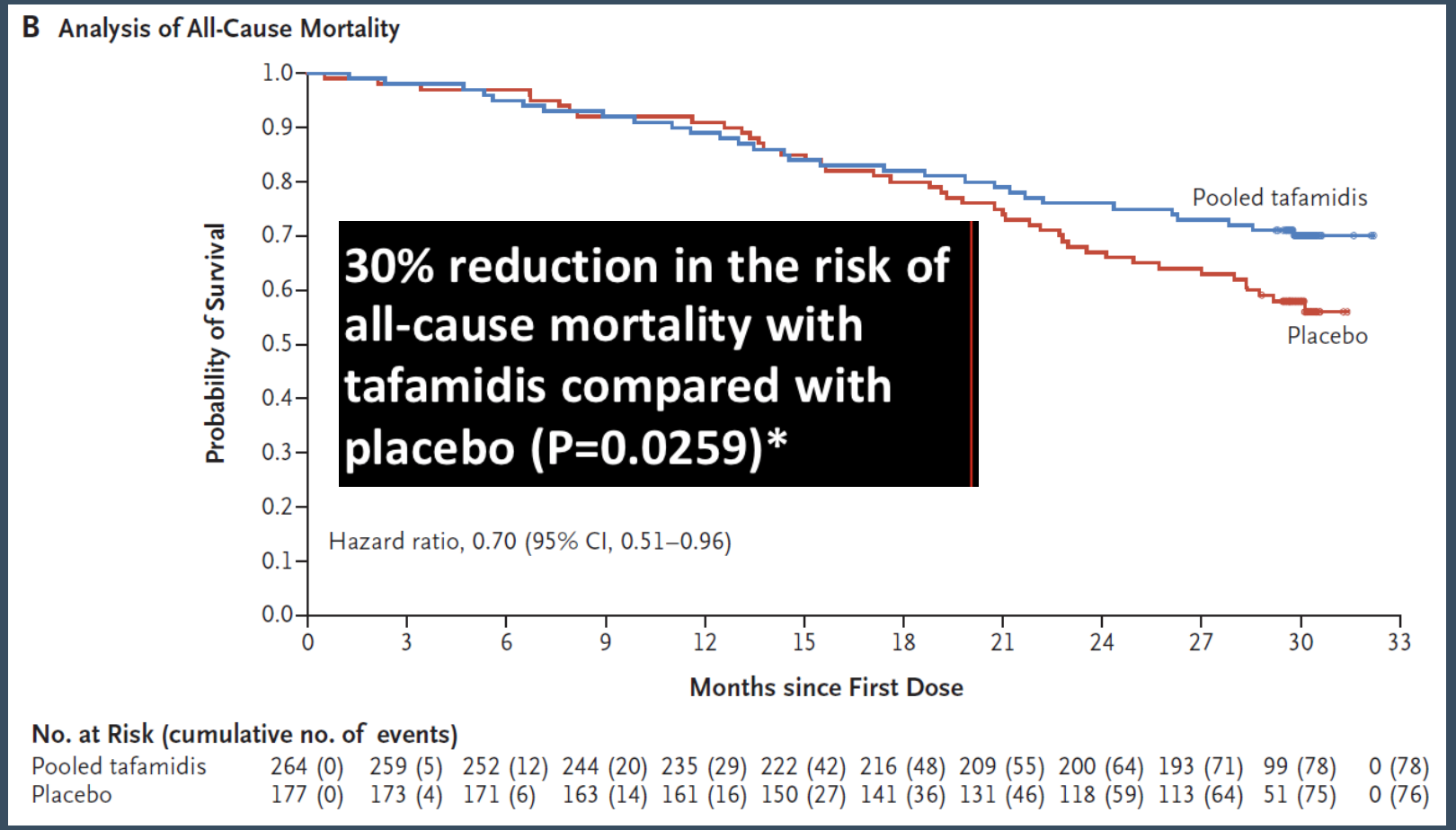


Figure 2. Kaplan–Meier analysis among 120 patients with TTR (transthyretin) cardiac amyloidosis over the 1.9-y median follow-up for the outcome of death or orthotopic heart transplant, stratified by use of stabilizer.

Rosenblum Circ Heart Fail. 2018;11:e004769. DOI: 10.1161/

Tafamidis

The NEW ENGLAND JOURNAL of MEDICINE



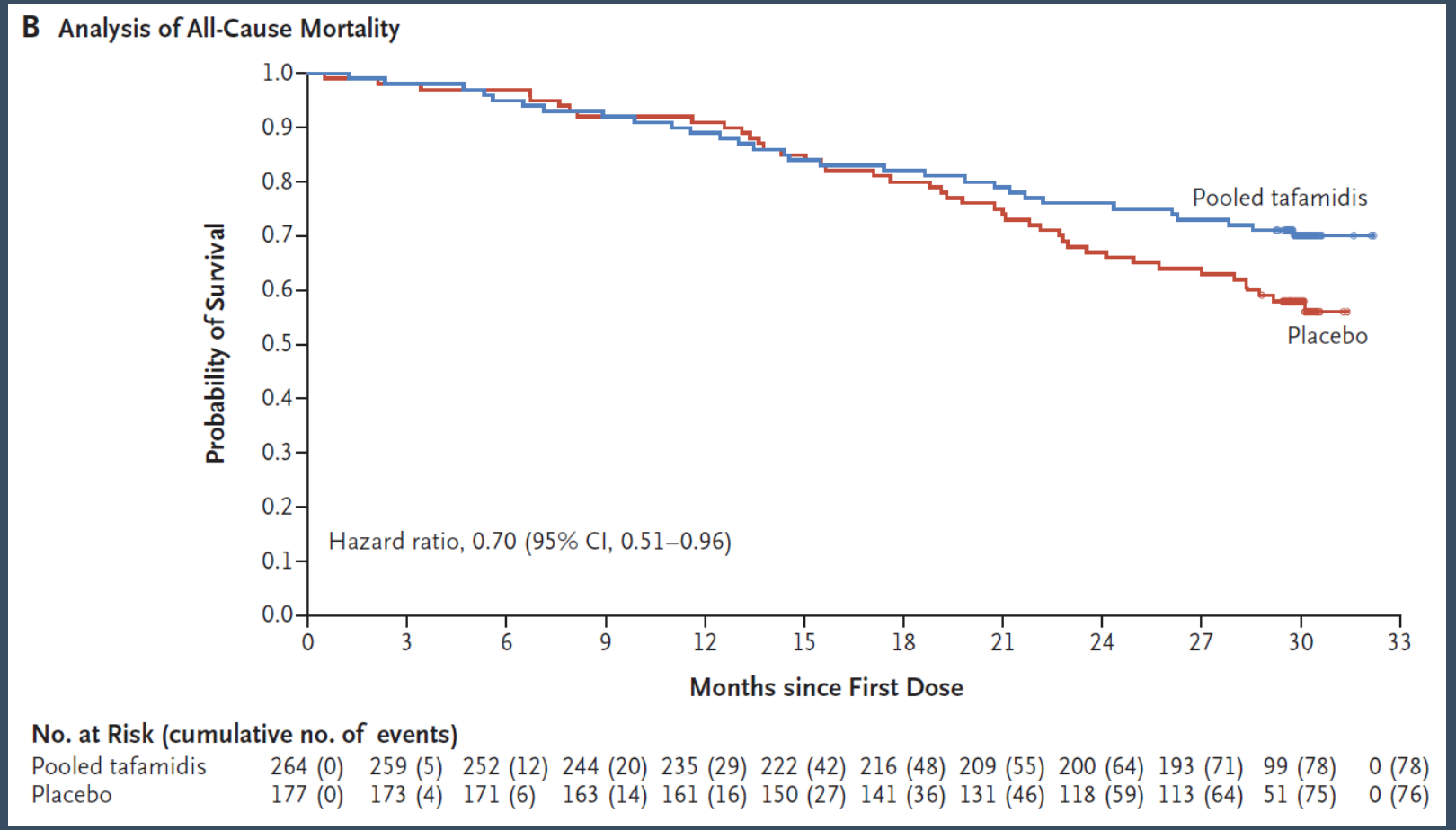
Maurer MS,.. N Engl J Med 2018;379:1007-1016

	APOLLO B Patisrian	Helios B Vutrisiran	Ionis Study Cardiotransform	AG10 ATTRibute
Dosing	IV every 3 weeks (siRNA)	SC every 3 months (RNAi therapeutic)	SC every month (inotersen-antisense)	Oral bid (Transthyretin stabilization)
Patient Population	ATTR-CM	ATTR-CM	ATTR-CM	ATTR-CM
Sample Size	300	600	750	510
Tafamadis Allowance	After 6 months if progressing (30% tafamadis arm)	After 6 months if progressing (30% tafamadis arm)	No stipulations	Not for 24 months
Treatment arms	Patisiran vs placebo	Vutrisiran vs placebo	Ionis vs placebo	AG10 vs placebo
Anticipated Start Date	Open to Enrollment	Spring 2020	Spring 2020	Open to Enrollment
Sponsor	Alnylam	Alnylam	Ionis Pharm	Eidos Therapeutics
CCFTarget	5	6	5-10	4
H				
Attractive Features	-MD screening -3 patients already identified	-MD screening -SC q 3 months for out of town patients	-MD screening -No stipulation regarding tafamidis	-MD Screening -1 patient already recruited -Patients that cant afford or get tafamidis

	Apollo B	Helios B	Cardio-TTRansform	ATTribute-CM	PRX004
Patient Population	ATTR-CM	ATTR-CM	ATTR-CM	ATTR-CM	Hereditary ATTR with polyneuropathy
Treatment Arms	Patisiran vs placebo	Vutrisiran vs placebo	ION-682884 vs placebo	AG10 vs placebo	PRX004 Open Label
Tafamadis Allowance	After 6 months if progression of cardiac symptoms	After 6 months if progression of cardiac symptoms	No stipulations	Not allowed for 24 months	If on stable dose for 6 months prior
Dosing	IV infusion every 3 weeks (siRNA)	SC injection every 3 months (RNAi therapeutic)	SC injection every month (inotersen-antisense)	Oral pill 2x daily (transthyretin stabilizer)	IV infusion every month (monoclonal antibody)
Anticipated Start Date	Open to Enrollment	Spring 2020	Spring 2020	Open to Enrollment	Open to Enrollment

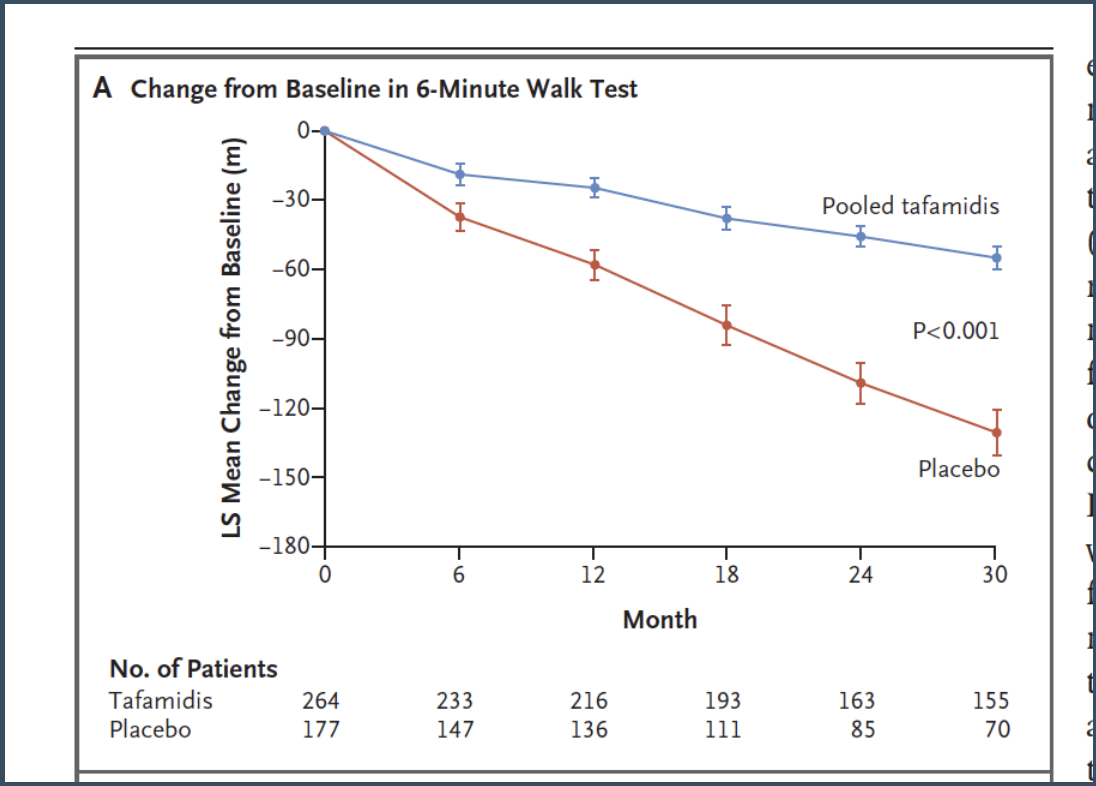
Tafamidis

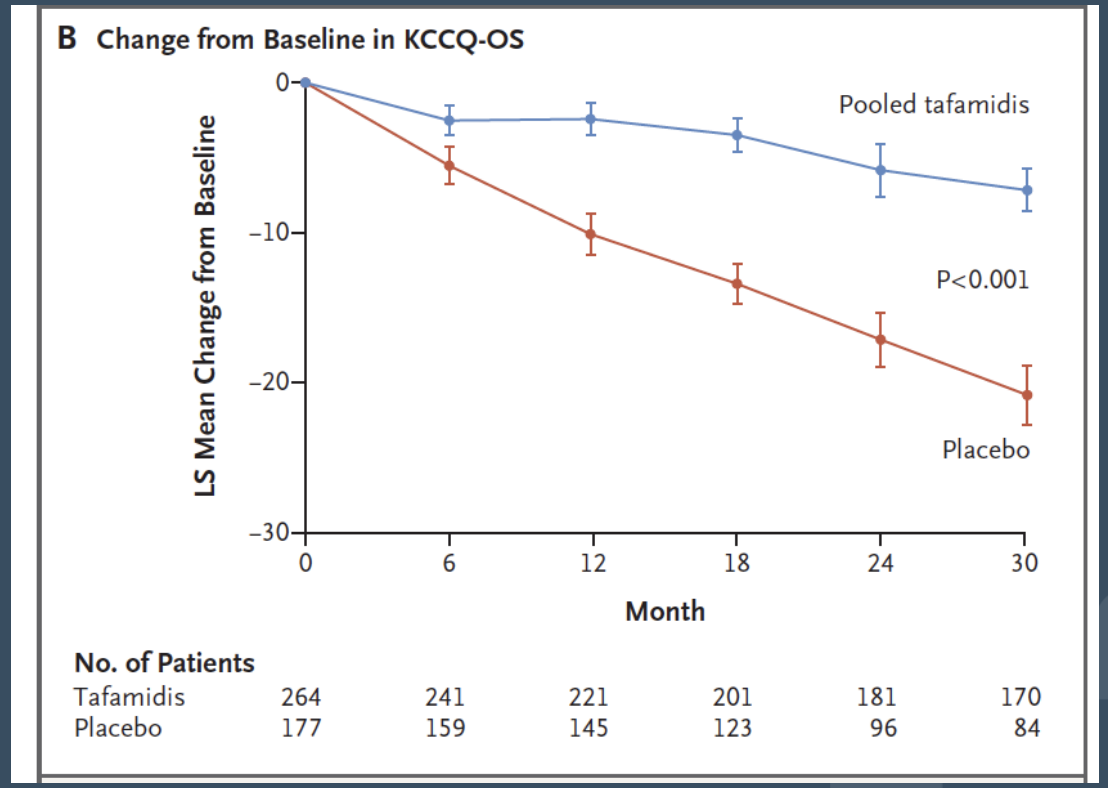
The NEW ENGLAND JOURNAL of MEDICINE



Maurer MS,.. N Engl J Med 2018;379:1007-1016

Tafamidis – Reduces Rate of Clinical Deterioration





Maurer MS,.. N Engl J Med 2018;379:1007-1016

Viewpoint

ONLINE FIRST

January 8, 2020

Tafamidis—A Pricey Therapy for a Not-So-Rare Condition

Jerry H. Gurwitz, MD[1,2]; Mathew S. Maurer, MD[3]

» Author Affiliations | Article Information

JAMA Cardiol. Published online January 8, 2020. doi:https://doi.org/10.1001/jamacardio.2019.5233

Both agents carry a high price tag with a wholesale acquisition cost (the "list" price) of $225 000 per year. While this is lower than the price of other ATTR drugs (inotersen and patisiran) approved for treating polyneuropathy in hereditary transthyretin-mediated amyloidosis (but not ATTR-CM), tafamidis meglumine and tafamidis are still the world's most expensive medications for cardiovascular disease. Annual sales are projected to exceed $1 billion by 2024, but this estimate could prove conservative as the prevalence of ATTR-CM increases because of greater awareness and higher rates of diagnosis.

Other Treatments

Green tea (EGCG) Stabilizer

Dose 750-1000 mg / day

Doxycycline plus TUDCA dissolves fibrils

Dose 100 mg bid/250 tid

Tumeric (Curcumin) 1500 mg/day

Disease Monitoring

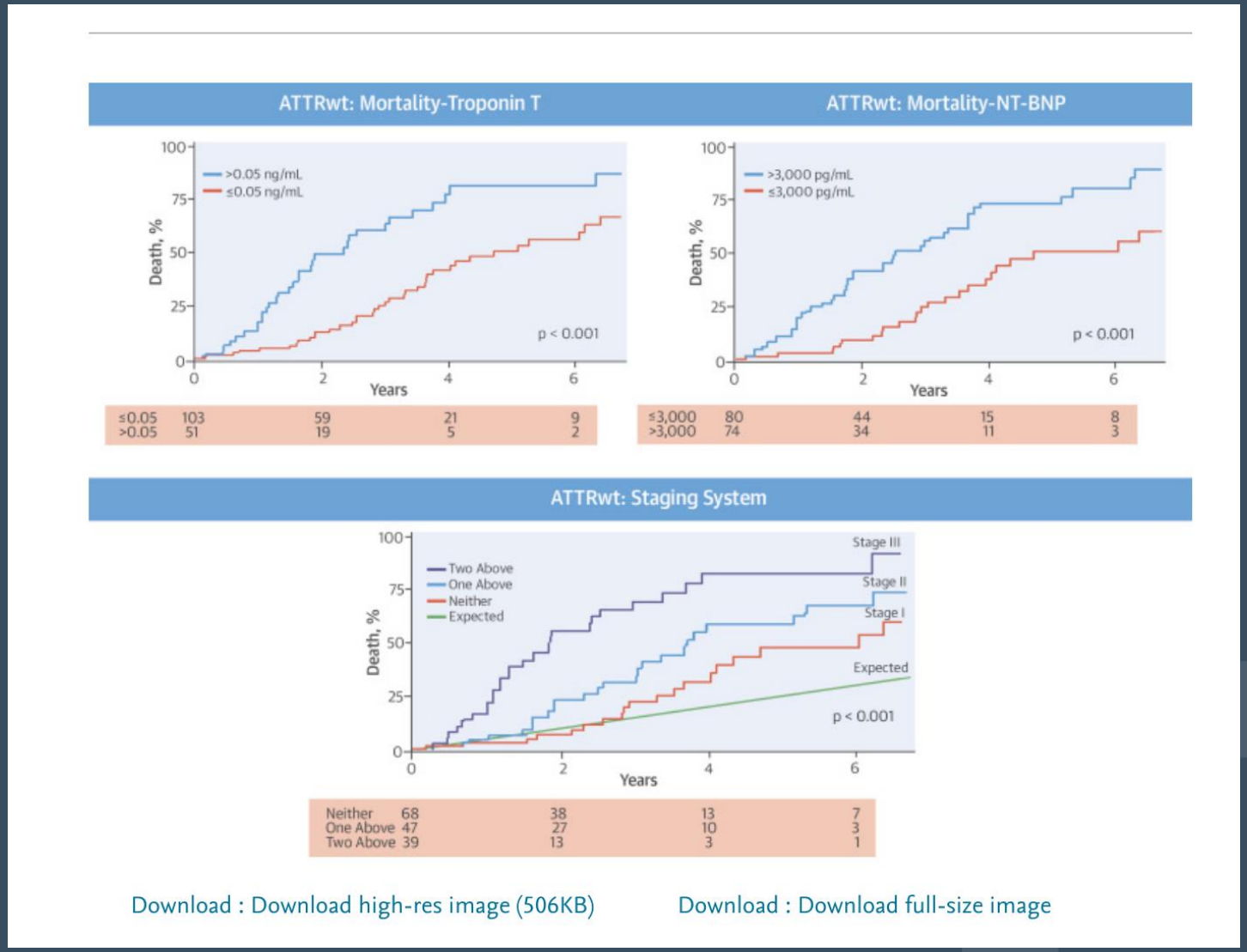
Am I getting better?

Are the medicines working?

Biomarkers-Mayo Clinic

T-BNP cutoff 3000

Tn cutoff n 0.05 ng/ml



Download : Download high-res image (506KB)

Download : Download full-size image

Grogan M.J Am Coll Cardiol 2016;68:1014–20G

Biomarkers and Prognosis

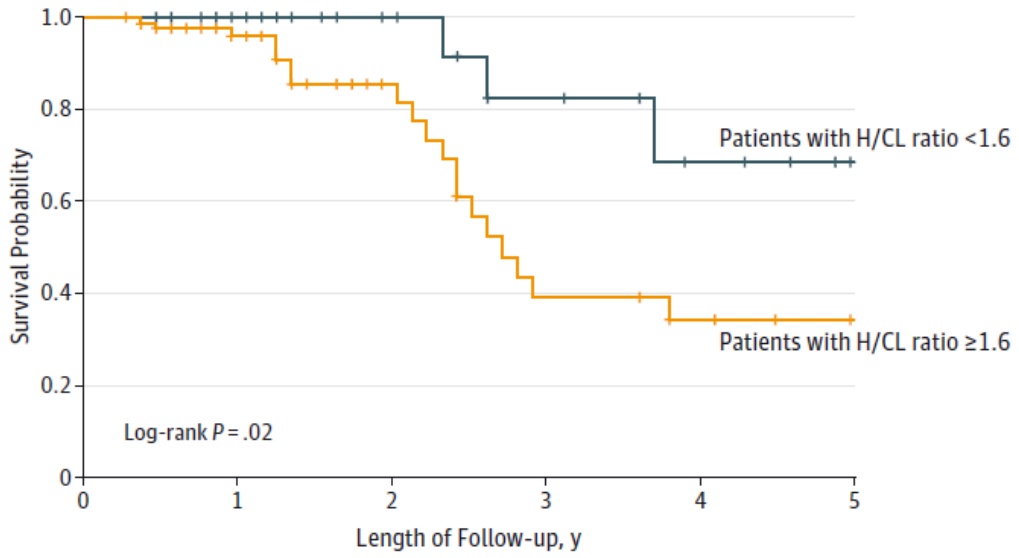
STAGE	NT_BNP	GFR	SURVIVAL (MONTHS)
I	LESS THAN 3000	GREATER THAN 45	69
II	REMAINDER	REMAINDER	46
III	GREATER THAN 3000	LESS THAN 45	24

Gillmore Eur Ht Jl 2018 39, 2799-2806

^{99m}Tc-PYP for Prognosis

High vs. Low H/CL predicted worse survival
HR 7.91 (95% CI 1.68-37.30, p=0.02)

Figure 3. Kaplan-Meier Survival Curves Among 121 Patients With ATTR Cardiac Amyloidosis Over the 5-Year Follow-up, Stratified by Heart to Contralateral (H/CL) Ratio



No. at risk						
Patients with H/CL ratio <1.6	38	18	12	7	4	0
Patients with H/CL ratio ≥1.6	83	39	19	9	3	0

Multicenter cohort
N=121 w/ ATTR-CA

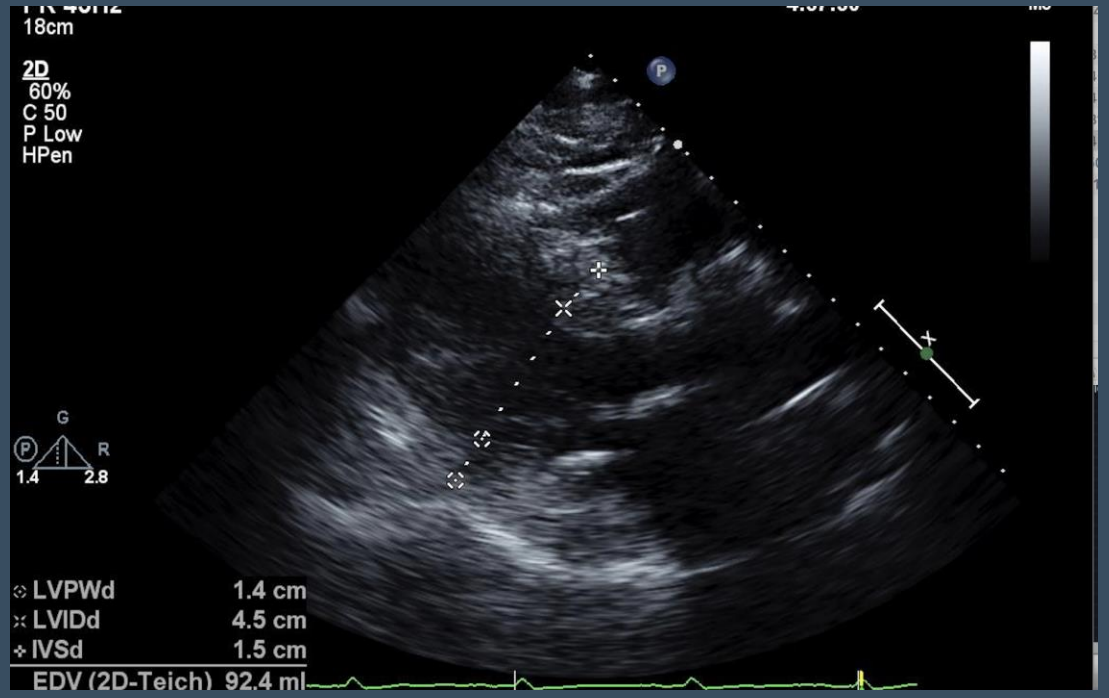
Castano et al., JAMA Cardiology, 2016

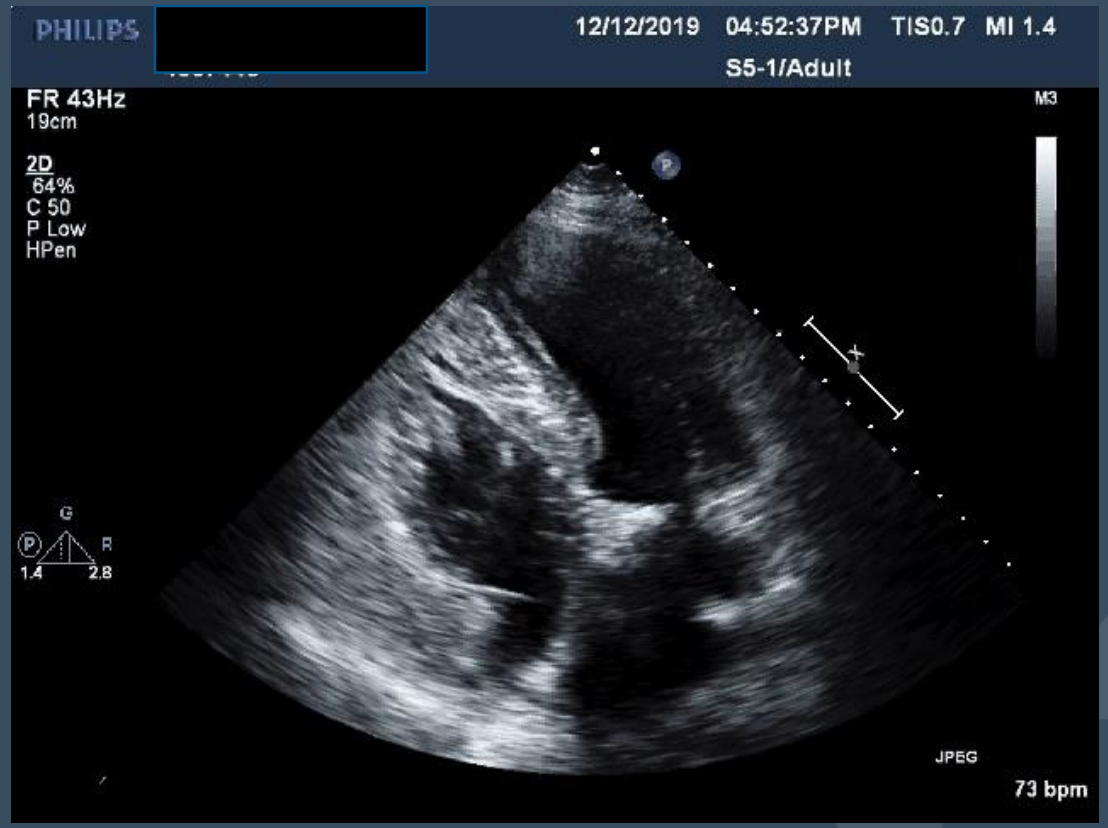
Aortic Stenosis and TTR Amyloid

AN

- 82 yo history of COPD underwent TAVR for symptomatic aortic stenosis
- Peri-procedure heart block His bundle pacing , pacemaker dependent
- Subsequent good recovery
- Unremarkable 6 month echo

ECHO


18cm
2D
60%
C 50
P Low
HPen
G
P
R
1.4
2.8
LVPWd 1.4 cm
LVIDd 4.5 cm
IVSd 1.5 cm
EDV (2D-Teich) 92.4 ml

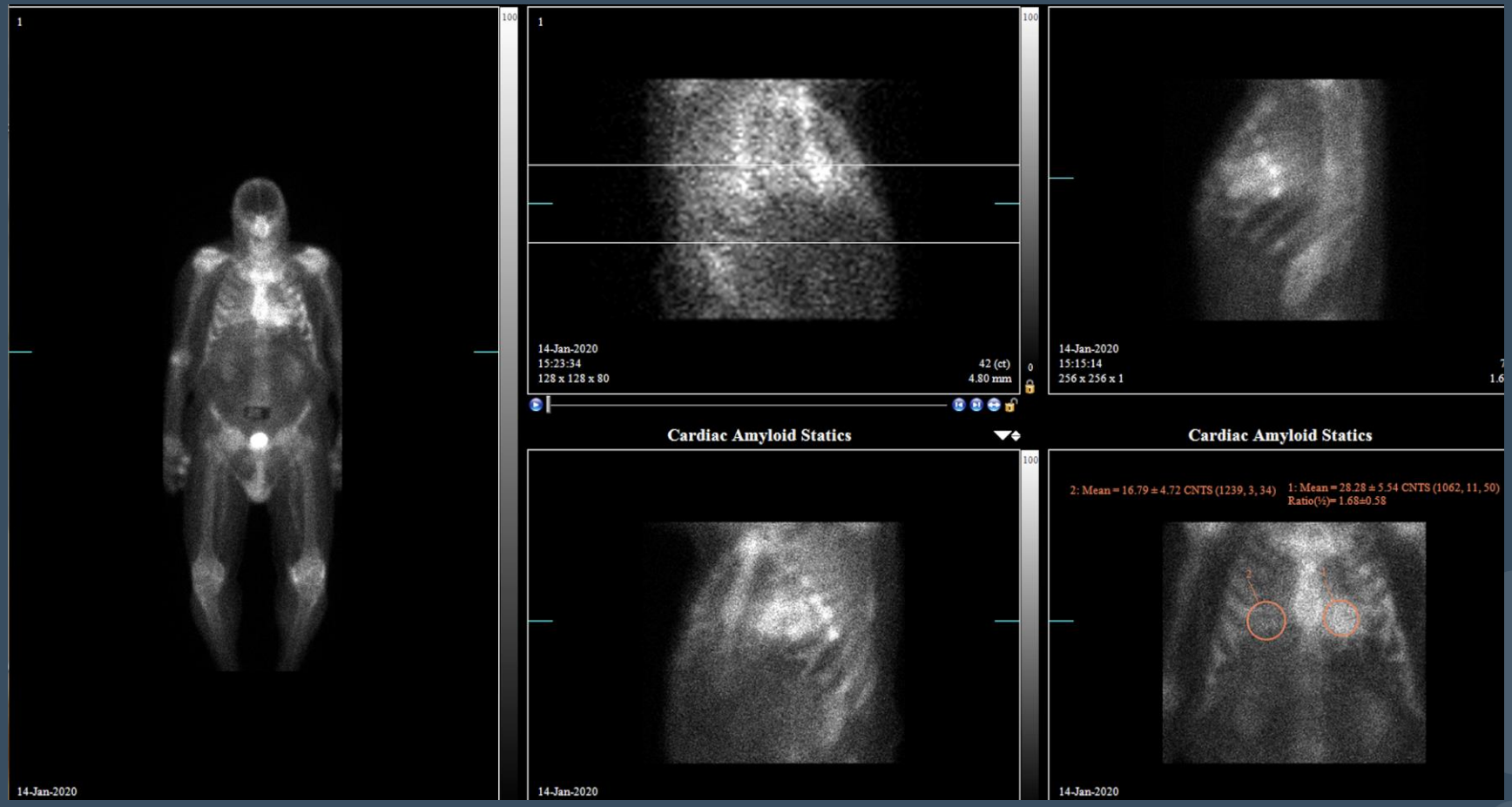

PHILIPS
12/12/2019 04:52:37PM TIS0.7 MI 1.4
S5-1/Adult
FR 43Hz
19cm
M3
2D
64%
C 50
P Low
HPen
G
P
R
1.4
2.8
JPEG
73 bpm

Two Years Later

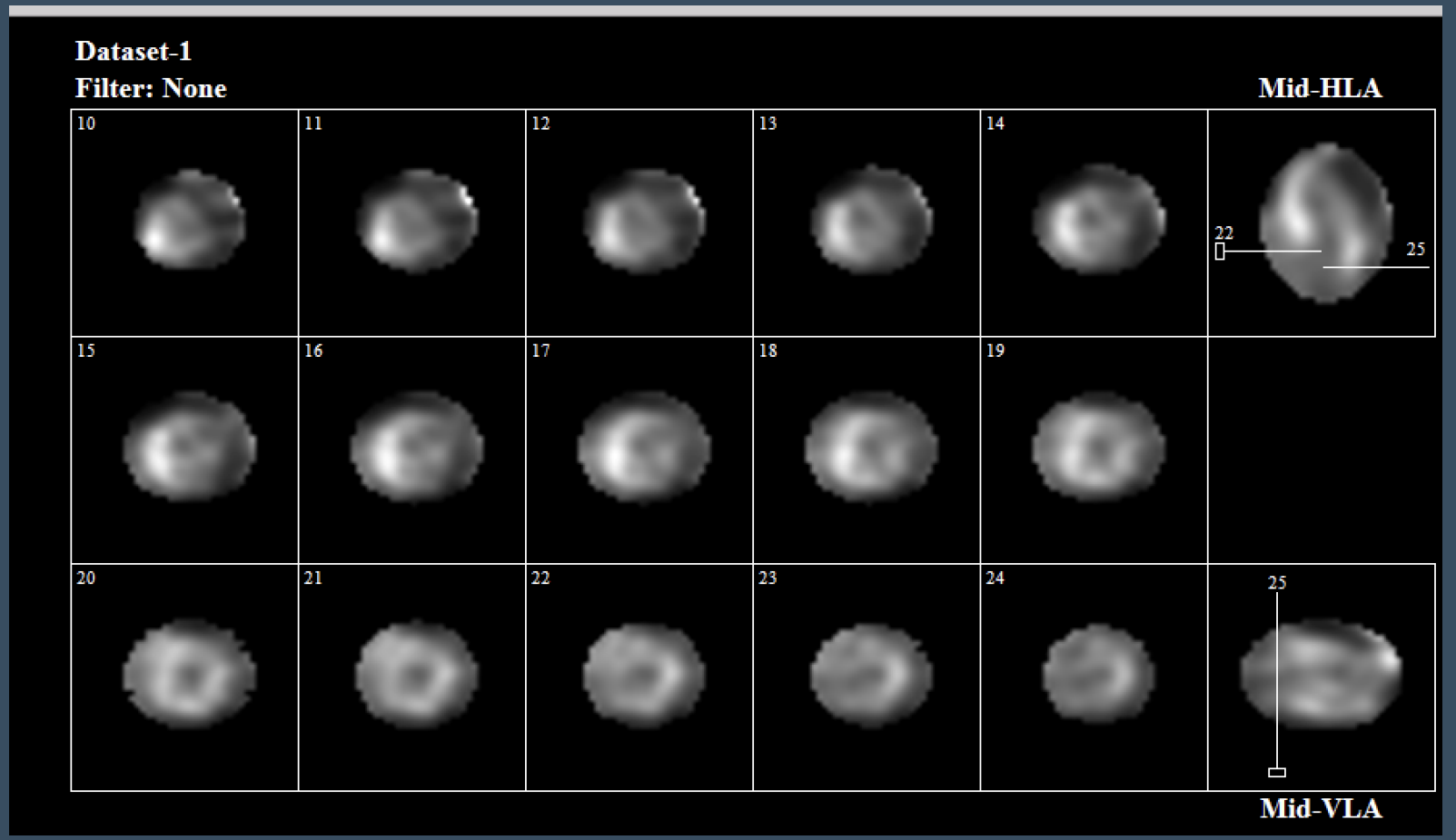
- Development of increasing SOB Weakness
- Poor appetite, poor taste, 10 # weight loss
- Labs show increase in creatinine 1.74 otherwise unremarkable
- Follow up ECHO;

No aortic stenosis, mild perivalvular aortic regurgitation RVSP=49. LVH

Tc-PYP Scan


1
14-Jan-2020
1
14-Jan-2020
15:23:34
128 x 128 x 80
42 (ct)
4.80 mm
14-Jan-2020
15:15:14
256 x 256 x 1
Cardiac Amyloid Statics
Cardiac Amyloid Statics
2: Mean = 16.79 ± 4.72 CNTS (1239, 3, 34)
1: Mean = 28.28 ± 5.54 CNTS (1062, 11, 50)
Ratio(½)= 1.68±0.58
14-Jan-2020
14-Jan-2020
14-Jan-2020

Tc-PYP Scan

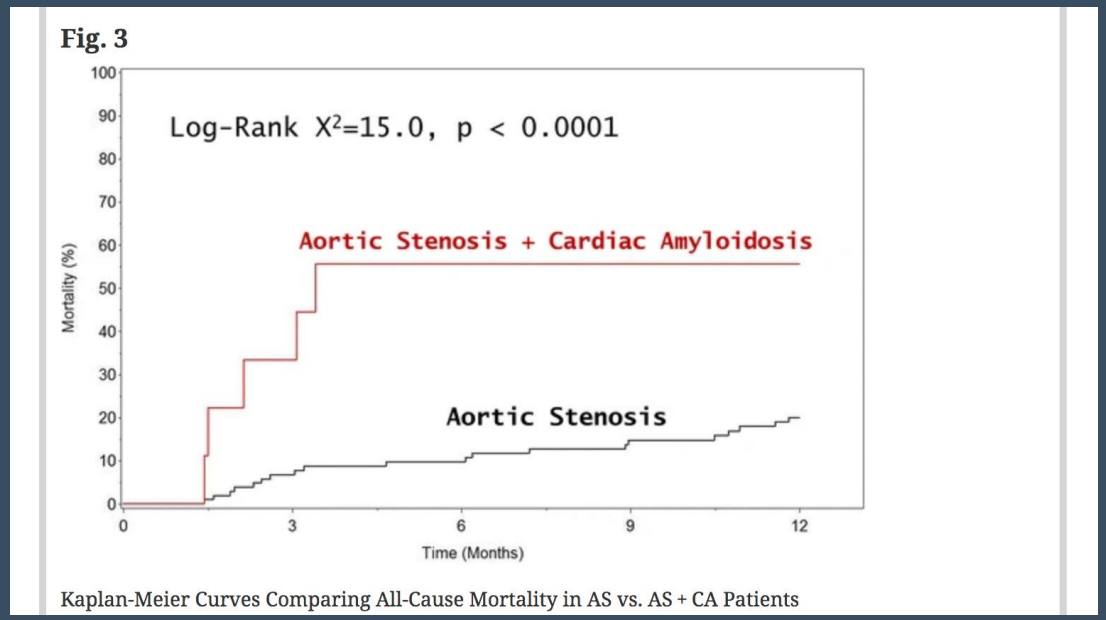

Dataset-1
Filter: None
Mid-HLA
10
11
12
13
14
22
25
15
16
17
18
19
20
21
22
23
24
25
Mid-VLA

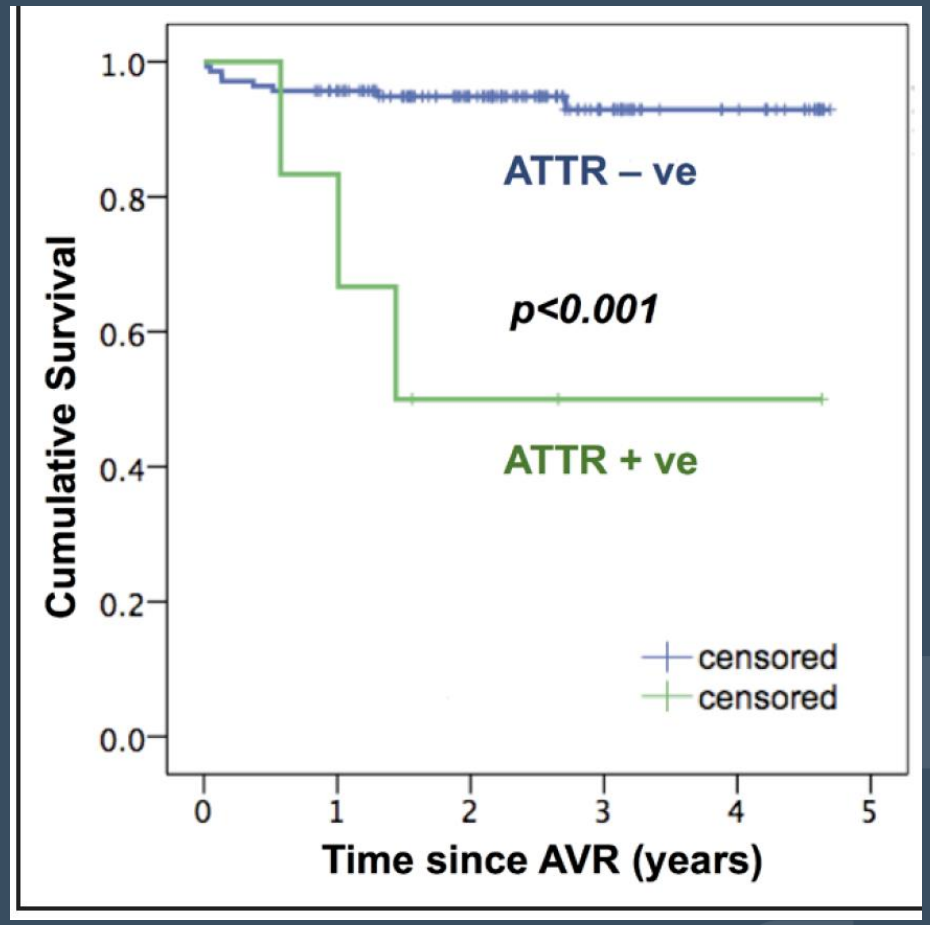
Amyloid and Aortic Stenosis

- 101 pts for TAVR-
- 13.4% (one in seven) +TTR
- AVG slightly lower
- Predominantly Perugini Grade 2 Genetics all wild type
- Two pre-TAVR deaths
- Malignant disease

Scully JACC 71, 4:2018

Prognosis of Aortic Stenosis in the Presence of Co-existent Amyloid



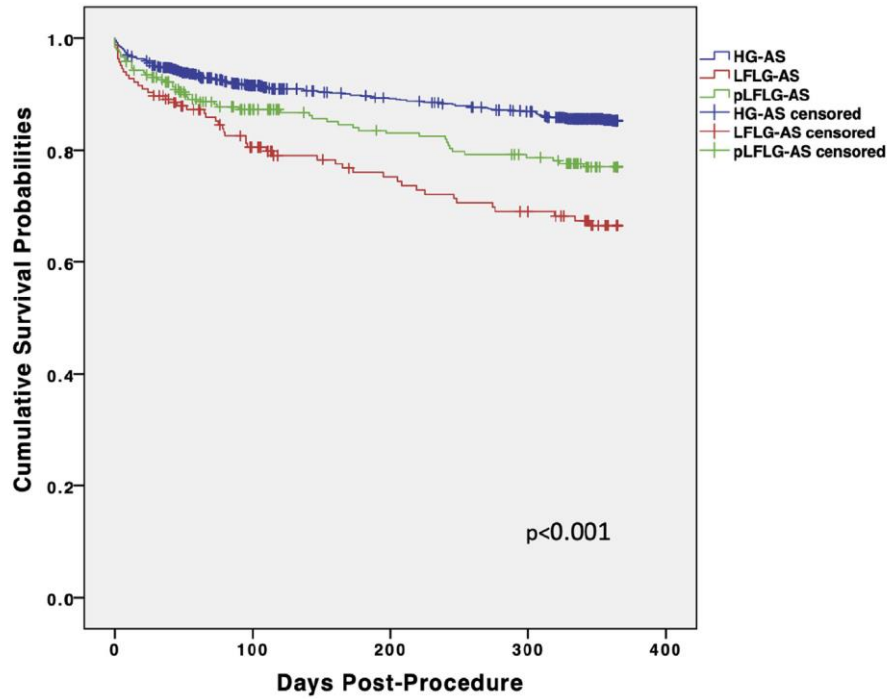


CIRCIMAGING.116.005066(1).pdf 2020-02-06 14-47-24.png

Cavalcante. Journal of Cardiovascular Magnetic Resonance **volume 19**, Article number: 98 (2017)

1-Year Survival After TAVR of Patients With Low-Flow, Low-Gradient and High-Gradient Aortic Valve Stenosis in Matched Study Populations

FIGURE 2 Survival Curves Based on All-Cause Mortality for Patients in the Overall (Unmatched) Study Population



No. at risk					
HG-AS	1052	803	722	684	501
LFLG-AS	166	115	96	89	69
pLFLG-AS	244	176	155	144	117

- Compared to High Gradient AS and Paradoxical Low flow/ low gradient preserved EF patients
- Presence of Low Flow-low gradient- lowEF patients did worse with TAVR

(Fischer-Rasogat **JACCIntv 2019;12:752–63)**

Identifying AS Patients with Amyloid Preoperatively

B Features that Should Elevate Suspicion for Cardiac Amyloidosis in Patients with Severe Symptomatic AS

Clinical & Demographic
- ✓ Older adult male
- ✓ Low-flow/low-gradient AS
- ✓ Low systolic blood pressure
- ✓ Elevated BNP

Electrocardiographic
- ✓ Low ECG voltage-to-mass ratio
- ✓ Increased QRS duration
- ✓ Presence of RBBB

Echocardiographic, Speckle-strain, & Tissue Doppler
- ✓ Heart failure mid-range ejection fraction (HFmrEF)
- ✓ Increased wall thickness
- ✓ Left atrial enlargement
- ✓ Low SV index
- ✓ Low-flow low-gradient (stage D2)
- ✓ Low myocardial contraction fraction
- ✓ Advanced diastolic dysfunction
- ✓ Impaired global longitudinal strain
- ✓ Low mitral annular tissue Doppler S' (average septal and lateral annulus)

✓ Low-flow/low-gradient AS
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Figure 4 Prevalence and phenotype of ATTR-CA among patients undergoing transcatheter aortic valve replacement at our institution. ATTR-CA, transthyretin cardiac amyloidosis.

Castano Eur Ht Jl 2017

Aortic Stenosis Plus Amyloidosis

CENTRAL ILLUSTRATION Diagnostic Confirmations and Therapeutic Managements in Severe Aortic Stenosis Patients With Cardiac Amyloidosis

Cardiac Amyloidosis

CA Red Flags

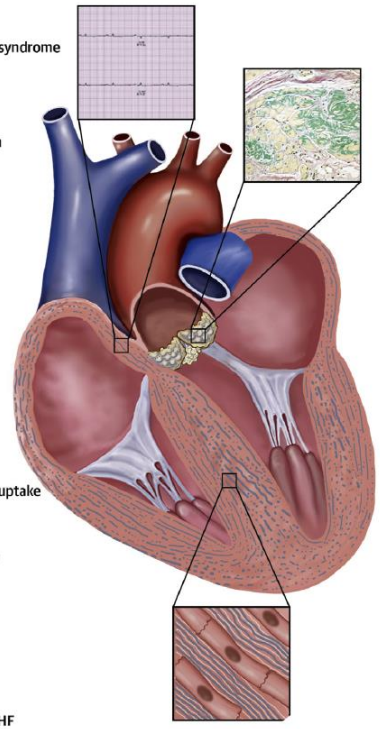
- **Clinical:** ≥65 years, Male, carpal tunnel syndrome
- **ECG:** Low-voltage despite LVH, Pseudo-infarction pattern
- **Biomarkers:** Disproportionate elevation of troponin and BNP
- **TTE:** Severe biventricular hypertrophy, Myocardial granular sparkling, Severe LV longitudinal systolic dysfunction with apical sparing
- **CMR:** Extensive LV LGE and elevated ECV values

Confirm Diagnosis of CA

- **Confirm TTR-CA:** Grade 2 or 3 cardiac uptake on bone scintigraphy with negative blood or urine monoclonal light chain
- **Exclude CA Diagnosis:** Grade 0 cardiac uptake on bone scintigraphy with negative blood or urine monoclonal light chain
- **Prevalence of TTR-CA in AS:** up to 15%

Therapeutic Management of CA

- **AL-CA:** Chemotherapy
- **TTR-CA:** TTR stabilizer in patients with HF
- **Heart Management: CHAD-STOP**



Aortic Stenosis

AS Features in Patients with CA

- High prevalence of paradoxical low-flow, low-gradient AS
- Aortic valve amyloid infiltration
- Faster AS progression?

Confirm AS Severity

- **AV Calcium Score by Non-Contrast CT**
  - ≥ 1,200 AU in women
  - ≥ 2,000 AU in men

Therapeutic Management of AS

- **Evaluation by Heart Team**
- **TAVR** in low-flow, low-gradient severe AS
- **TAVR** in high-gradient AS with depressed LV systolic function
- **SAVR or TAVR** according to surgical risk in high-gradient AS with preserved LV systolic function
- **Medical treatment** alone in patients with high risk of AVR futility

Ternacle, J. et al. J Am Coll Cardiol. 2019;74(21):2638–51.

AL = light-chain; AS = aortic stenosis; AV = aortic valve; AVR = aortic valve replacement; BNP = brain natriuretic peptide; CA = cardiac amyloidosis; CHAD-STOP = Conduction and rhythm disorders prevention, High heart rate maintenance, Anticoagulation, Diuretics, and STOP ß-receptor and calcium-channel blockers, digoxin, renin-angiotensin-aldosterone inhibitors; CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiogram; ECV = extracellular volume; GLS = global longitudinal strain; HF = heart failure; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve implantation; TTE = transthoracic echocardiography; TTR = transthyretin.

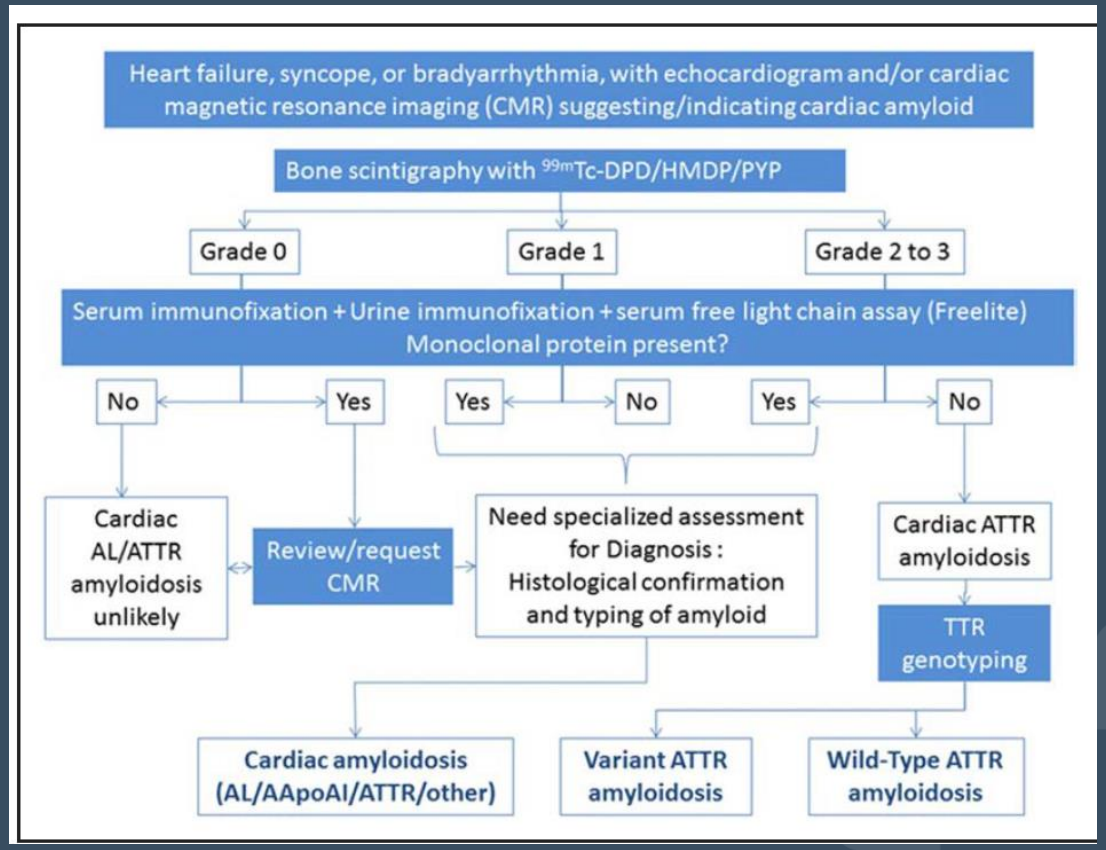
Look, Listen, and Test

Table 1. Clinical Clues From Routine Cardiac Evaluation That Should Prompt Additional Diagnostic Evaluation for ATTR-CM

Traditional Cardiac Clues	Noncardiac Clues
Intolerance to antihypertensive or heart failure medications because of symptomatic hypotension or orthostasis	Neurological: sensorimotor polyneuropathy (paresthesias and weakness), autonomic dysfunction (orthostatic hypotension, postprandial diarrhea alternating with constipation, gastroparesis, urinary retention, and incontinence)
Persistent low-level elevation in serum troponin	Orthopedic: carpal tunnel syndrome, lumbar spinal stenosis, unprovoked biceps tendon rupture, hip and knee arthroplasty
Discordance between QRS voltage on an ECG and wall thickness on imaging	Black race
Unexplained atrioventricular block or prior pacemaker implantation	Family history of polyneuropathy
Unexplained LV wall thickening, right ventricular thickening, or atrial wall thickening	
Family history of cardiomyopathy	

ATTR-CM indicates transthyretin amyloid cardiomyopathy; and LV, left ventricular.

Kittelson Circulation July 2020 e7-20



Maurer Circulation 2017

Cardiac Amyloidosis

Cleveland Clinic Florida's Cardiac Amyloidosis Center consists of a multidisciplinary specialty team that is dedicated to the diagnosis and treatment of cardiac amyloidosis (CA).

Appointments 877.463.2010

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- Cardio-Oncology
- Vascular Surgery
- Hypertrophic Cardiomyopathy Center

Resources

amyloidosis foundation

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www.amyloidosis.org

Amyloidosis Research Consortium

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AMYLOIDOSIS RESEARCH CONSORTIUM, INC.
320 NEVADA STREET, SUITE 210 NEWTON, MA 02460 USA | 617-467-5170
22 (G1) FORTH STREET, EDINBURGH, UK EH1 3LH | +44 (0) 131 550 3866
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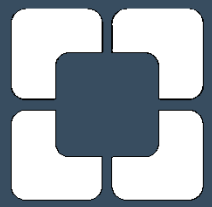
AMYLOIDOSIS SUPPORT GROUPS

You Are Not Alone

www.amyloidosissupport.org



Cleveland Clinic

Every life deserves world class care.

wolinsd@ccf.org ; dwolinsk@gmail.com; 518-365-0618; 954-659-5290