

MHIF FEATURED STUDY: ATTR CM

OPEN and ENROLLING: EPIC message to Research MHIF Patient Referral

CONDITION: Transthyretin-Mediated Amyloid Cardiomyopathy	PI: Mosi Bennett, MD	RESEARCH CONTACTS: Sarah Schwager Sarah.Schwager@allina.com 612-863-6257 Jane Fox Jane.Fox@allina.com 612-863-6289	SPONSOR: Ionis Pharmaceuticals
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DESCRIPTION: A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion

- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

Exclusion

- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker

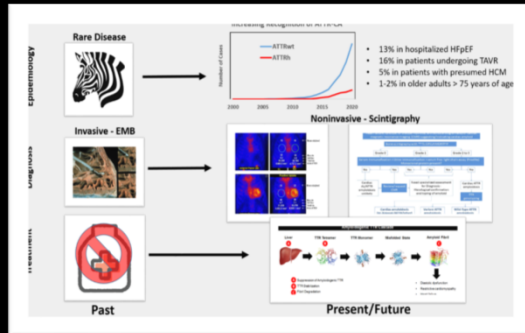
HOPE
DISCOVERED HERE™

 **Minneapolis
Heart Institute
Foundation**
Creating a world without heart and vascular disease

2021 Howard B. Burchell Memorial Lecture

Transthyretin Cardiac Amyloidosis:

Transition from a rare,
underdiagnosed and untreatable to
increasingly and easily recognized and
treatable disorder



Mat Maurer, MD

Arnold and Arlene Goldstein Professor of Cardiology
Professor of Medicine

Columbia University Irving Medical Center

April 12th 2021

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Disclosures

- I am excited about the emergence of effective therapies for ATTR amyloidosis but disappointed at the cost of such therapies which pose a significant obstacle to adoption.
- I have research support from several pharmaceutical companies :
 - NIH/NIA/NHLBI
 - GSK
 - Akcea, Inc
 - Alnylam, Inc
 - Eidos
 - Prothena
 - Ionis Pharmaceuticals
 - Pfizer, Inc.

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Objectives

At the conclusion of this seminar, learners will be able to:

1. Identify the phenotype of cardiac amyloidosis in order to facilitate early diagnosis
2. Distinguish underlying causes of cardiac amyloidosis given differences in prevalence, genetics, prognosis and treatment
3. Enumerate three strategies to address TTR cardiac amyloidosis

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Case

- 62 year old white male with progressive shortness of breath for 2 years
- Had a previous ECG which revealed a “silent MI”
- Initially had atrial fibrillation which was paroxysmal but became persistent.
- Cardiac catheterization (2 years ago): 50% - first diagonal, 40% RCA, normal EF, LVEDP = 19 mm Hg

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Case (continued)

- Treated with diuretics and ACE/Beta Blockers (intolerant)
- Worsening cardiac status; Echo shows EF=71%, LVH
- Right pleural effusion tapped – ~400 ml, negative cytology and thought secondary to heart failure
- Repeat echo 2 years after initial presentation shows LVEF=30%, had AV node ablation and BiV pacemaker

Referred for evaluation

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HFpEF vs. DHF

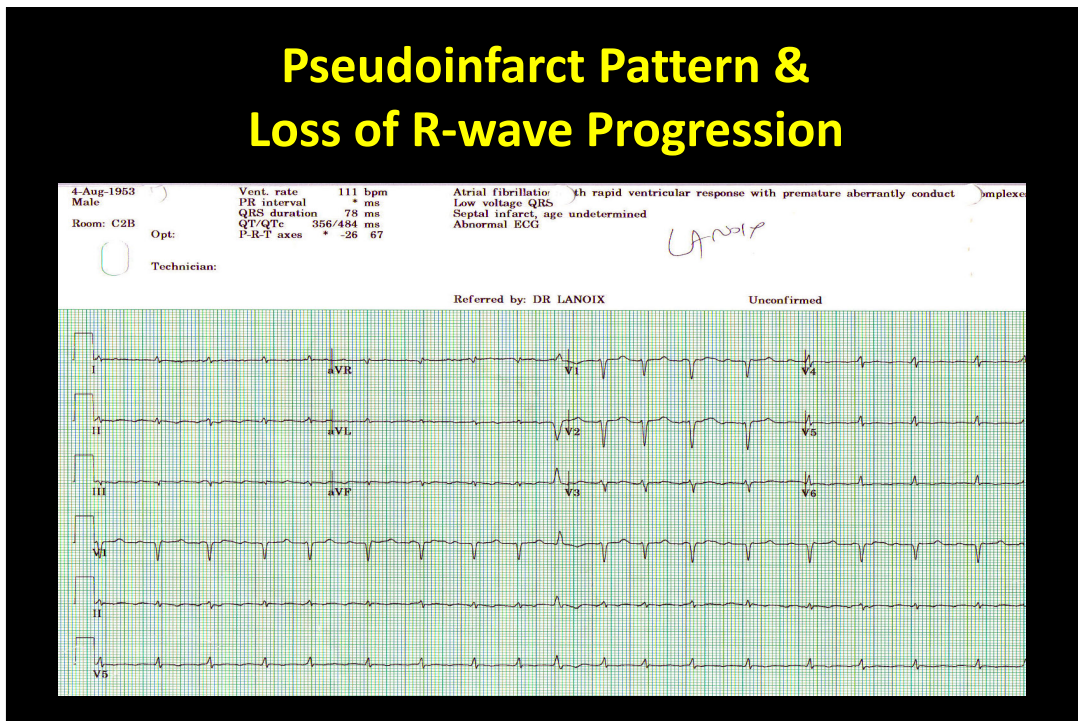
HFNEF

Age	Older Adults
Gender	Female Predominance
Blood Pressure	High

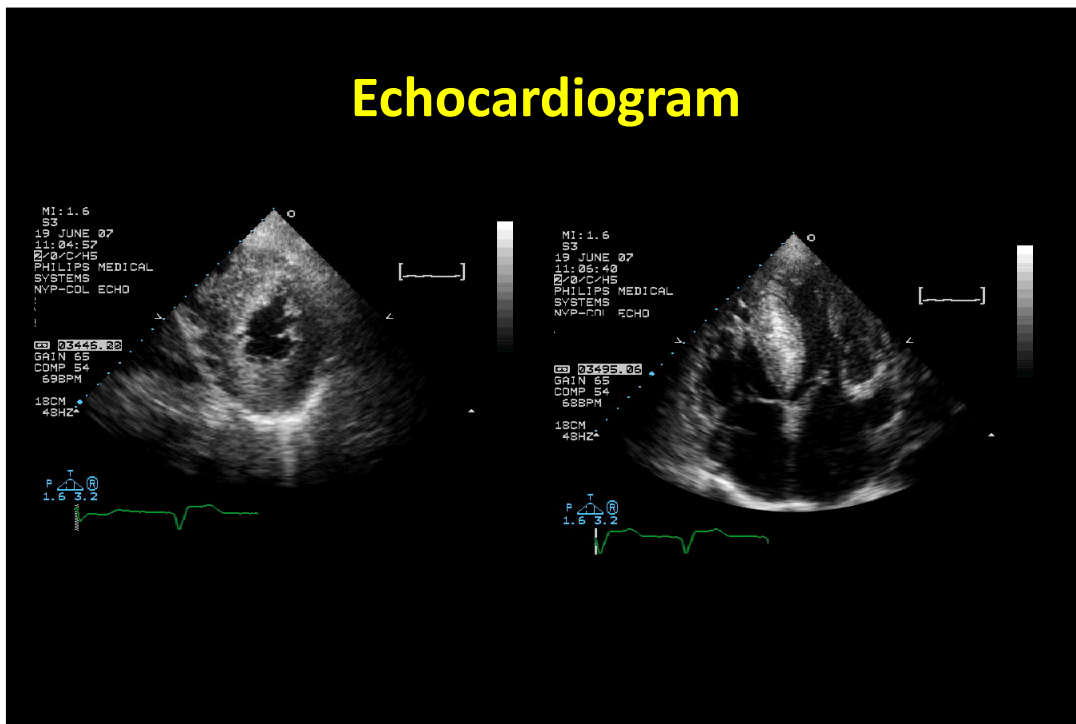
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	HFNEF	DHF (e.g. Amyloid)
Age	Older Adults	Middle Aged
Gender	Female Predominance	Male
Blood Pressure	High	Low

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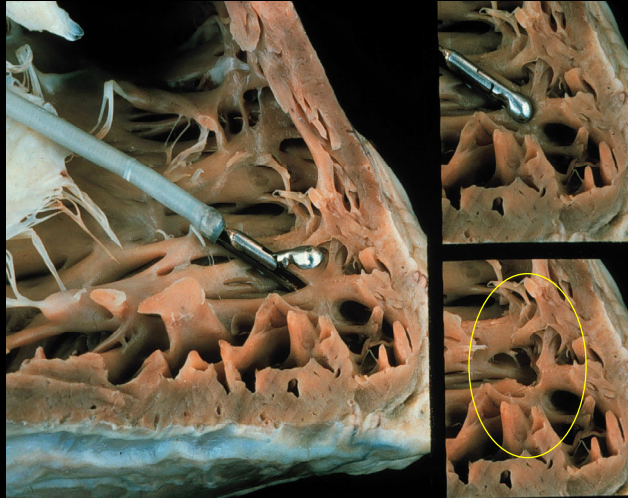
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Catheterization

- Right atrium = 15 mm Hg
- Right ventricle = 44/9 mm Hg
- Pulmonary artery = 45/23/31, saturation of 52%
- Pulmonary capillary wedge pressure = 30 mm Hg
- Cardiac output = 1.99 l/min, Cardiac index = 0.97 ml/min/m²
- Left ventricle = 83/26 mm Hg
- Aortic Pressure = 85/60 mm Hg, saturation of 95%

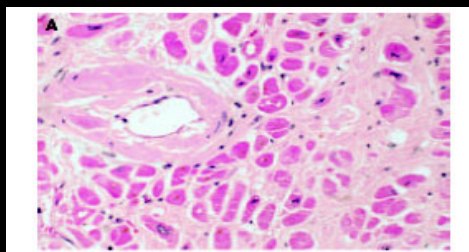
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Endomyocardial Biopsy

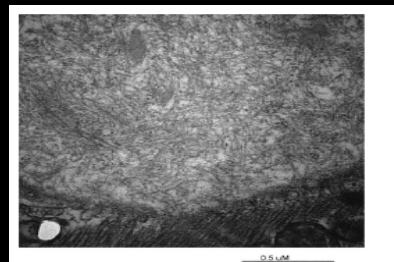
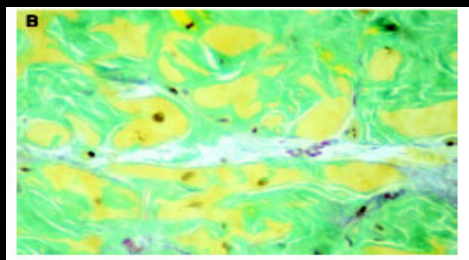
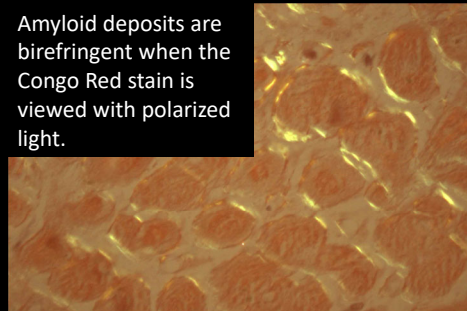


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Endomyocardial Biopsy



Amyloid deposits are birefringent when the Congo Red stain is viewed with polarized light.



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Misdiagnosis and Delayed Diagnosis of Cardiac Amyloidosis

- 75% saw > 3 physicians before diagnosis made
- 63% > 6 months to diagnosis
- 44% received an incorrect diagnosis first
- 31% required air travel to establish diagnosis
- Only 18% of these patients with cardiac AL had the correct diagnosis made by a cardiologist
- Cardiologists are the most common subspecialists to make a misdiagnosis – most commonly - hypertrophic cardiomyopathy

Lousada et al, European Hematology Association (EHA) 22nd Annual Congress 2017; June 22–25, 2017

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Systemic Amyloidosis

- Characterized by extra-cellular deposition of a fibrillar protein
- Deposits progressively interfere with the structure / function of affected organs throughout the body
- Two dozen proteins known to form amyloid fibrils in vivo
- Two predominant types involve the heart:
 1. AL – typically associated with plasma cell dyscrasia
 2. TTR Associated – transthyretin (TTR)
 - a. mutation or
 - b. wild type (SCA)

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Types of cardiac amyloidosis

Features	AL	ATTR	
Precursor protein	Light chain	Mutant TTR	TTR
Average age (range)	55 (30-75)	50 (30-70)	75 (60-100)
Gender (% male)	60%	80%	95%
Cardiac involvement (%)	~60%	Variable	All
Fat pad biopsy	50-80%	<50%	<30%
Primary Referral Route	Hematology, Cardiology, Nephrology	Neurology & Cardiology	Cardiology
Extra-cardiac manifestations	<ul style="list-style-type: none"> • Nephrotic syndrome / renal failure • Autonomic dysfunction • Purpura • Carpal tunnel 	<ul style="list-style-type: none"> • Autonomic dysfunction • Carpal tunnel 	<ul style="list-style-type: none"> • Carpal Tunnel • Neuropathy?
Median survival	12-36 months (4-6 with HF)	70	75

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Reasons for Missing Diagnosis of Cardiac Amyloidosis

1. It is thought to be rare.
 - It is an under-appreciated cause of HFpEF and low flow AS.
2. Misconceptions about diagnosis
 - EKG is a good screening test.
 - Fat pad analysis has high sensitivity
3. Cardiac amyloid is a great masquerader
 - There are clues for the prepared clinician
4. Necessity of endomyocardial biopsy
 - Non-invasive techniques can diagnose TTR cardiac amyloidosis.
5. It is thought to be untreatable
 - Treatment exists and are very effective if diagnosed early

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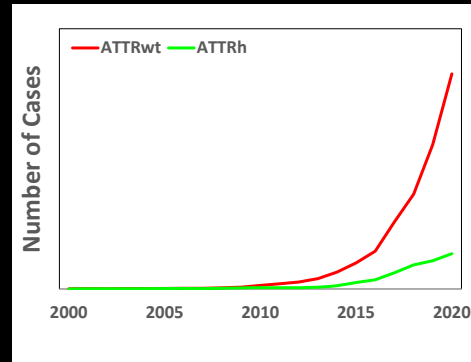
Cardiac Amyloid: A Rare Condition? Incidence/Prevalence

Type	Incidence/Prevalence
1° AL Amyloid	~2500 Cases per year Rare 50% have cardiac involvement
ATTRmutant	4% of African Americans are carriers Not so Rare 25,000-120,000 US patients
ATTRwt (SCA)	~10-25% of adults >80 years Not Rare >200,000 US patients

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Increasing Recognition of ATTR-CA

- 16% in patients undergoing TAVR
- 13% in hospitalized HFpEF
- 5% in patients with presumed HCM (25% in those > 60 years)
- 1-2% in older adults > 75 years of age



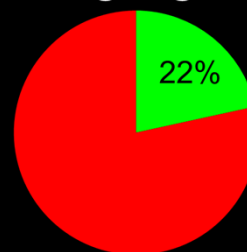
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UNVEIL Study

Using Nuclear & Echocardiographic Vehicles to Expose Inherent Loads of Amyloid

- 151 patients with severe AS.
- ^{99m}Tc-PYP planar imaging.
- Uptake in 16% (n=24), 22 of which were men.
- Phenotype of severe concentric LVH and low flow AS
 - Men (92%)
 - Elevated BNP 522 [302-1,023] vs 275 [124-722] pg/ml, p=0.041
 - Increased LV mass (130 vs 98 g/m², p=0.002)
 - Low SVI (30±11 vs 36±10 ml/m², p=0.009)
 - RBBB (38% vs 16%, p=0.023) .

ATTRwt in Males Undergoing TAVR

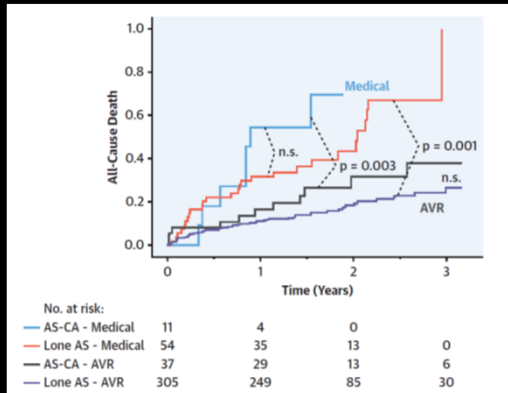


■ ATTRwt ■ Non-Amyloid

Eur Heart J. 2017 Oct 7;38(38):2879-2887

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Outcomes after TAVR in ATTR-CA compared to Non-Cardiac Amyloid AS Subjects



	Overall (N=204)	No ATTR-CA (N=177)	ATTR-CA (N=27)	P-value
Primary outcome				
Death, N (%)	63 (31%)	54 (31%)	9 (33%)	0.9423
Secondary outcomes				
First HF hospitalization, N (%)	39 (19%)	32 (18%)	7 (26%)	0.482
Recurrent HF Hospitalizations				
1 year HF Hospitalization rate, N/person years	0.149	0.114	0.372	0.004
3 year HF Hospitalization rate, N/person years	0.123	0.199	0.111	0.087

J Am Coll Cardiol 2021;77:128–39
 Eur J Heart Fail. 2020 Jul 30. doi: 10.1002/ejhf.1974

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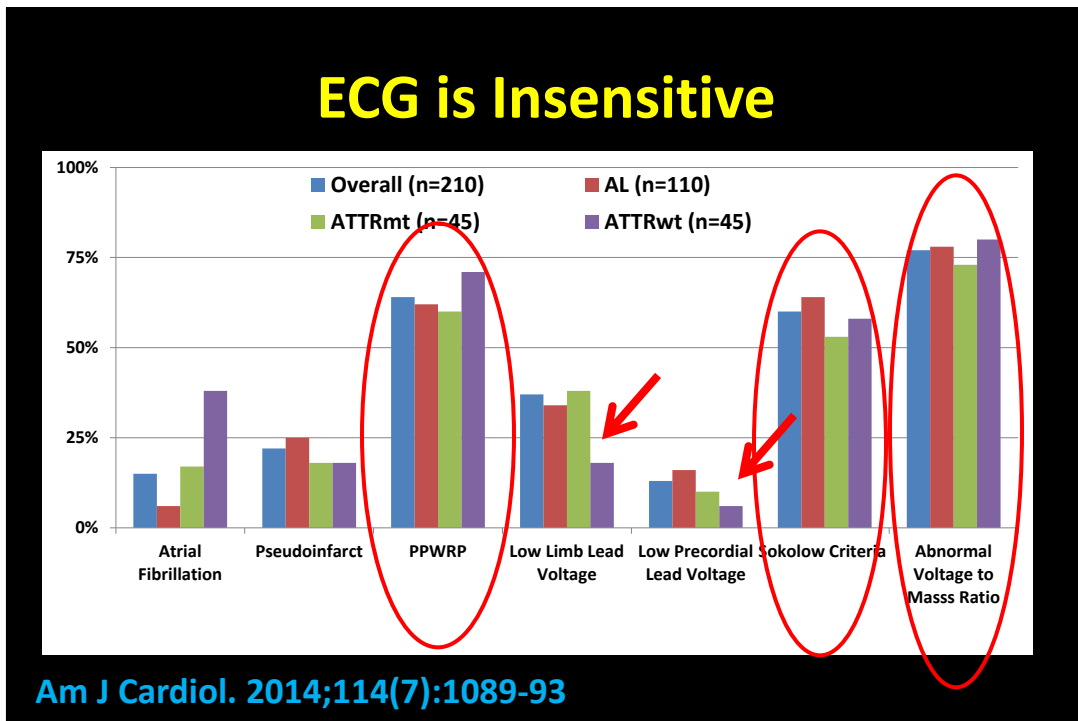
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Which patient has Cardiac Amyloidosis?

Both of them

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Discordance Between Voltage /Wall Thickness

Males

	LQV	Symm. LVH	tQRS / (LVWT / h ^{2.7})
Sens	44%	91%	78%
Spec	93%	27%	81%
LR+	6.6	1.3	3.6
LR-	0.6	0.3	0.2

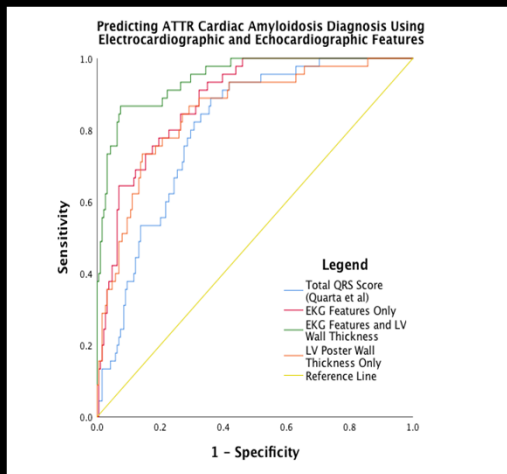
Females

	LQV	Symm. LVH	tQRS / LVWT
Sens	52%	91%	76%
Spec	91%	23%	81%
LR+	5.7	1.2	3.3
LR-	0.5	0.4	0.3

Total QRS/LVWT: Males, cutoff 8.4; Females, cutoff 7.7
 Total QRS/LVWT/h^{2.7}: Males, cutoff 36.4; Female, cutoff 27.3

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Total Electrical Activity on EKG and Wall Thickness Predict PYP Positivity



Model	AUC (95% CI)	P value
Total QRS Score (Quarta et al)	0.80 (0.74-0.87)	0.000
EKG Features Only	0.88 (0.84-0.93)	0.000
EKG Features + LV Thickness	0.945 (0.91-0.98)	0.000
LV Poster Wall Thickness Only	0.85 (0.79-0.91)	0.000

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Fat Pad Aspirate

- Sensitivity for AL amyloid of 70 % at best
- Positive in < 50 % of subjects with TTR cardiac amyloid



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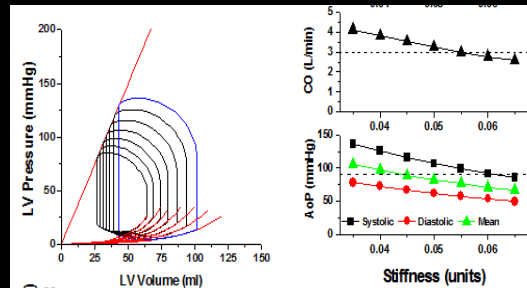
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You've Got to Think of IT to Diagnose IT!!!

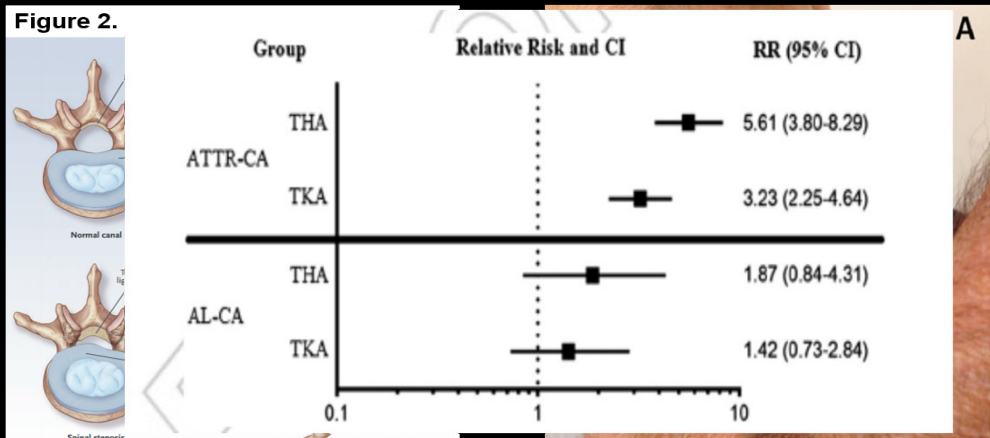
History/Exam Clues

- **HFPEF without hypertension**, particularly in **men (for TTR)**
- Evidence of **right-sided** heart failure (e.g. hepatomegaly, ascites, and lower extremity edema)
- **Intolerance** of ACE, Beta-blockers.
- **AL – Periorbital purpura**
- **TTR**
 - Bilateral carpal tunnel syndrome
 - Lumbar Spinal Stenosis
 - Biceps tendon rupture



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Orthopedic Clues to TTR Amyloidosis



Ups J Med Sci 2014;119:223-8, Mod Pathol 2015;28:201-7; JAMA. 2017 Sep 12;318(10):962-963; Amyloid. 2017 Dec;24(4):226-230.

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You've Got to Think of IT to Diagnose IT!!!

History/ Exam Clues

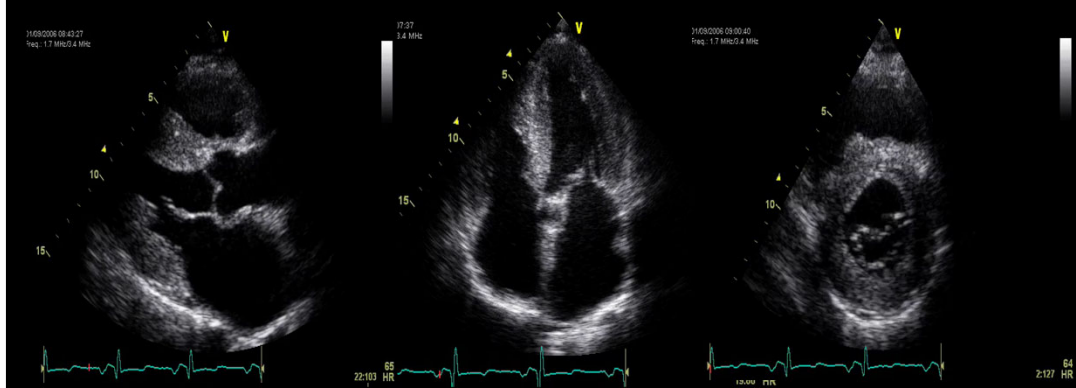
- **HFPEF without hypertension**, particularly in **men**
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- **Intolerance** of ACE, Beta-blockers.
- **Bilateral carpal tunnel syndrome**
- **Lumbar Spinal Stenosis**

Imaging Clues

- **Low voltage to mass ratio**
- **Diffuse delayed enhancement** on cardiac MRI
- **Apical sparring** on strain rate imaging
- **Low myocardial contraction fraction**
- **Myocardial Uptake on PYP Scintigraphy**

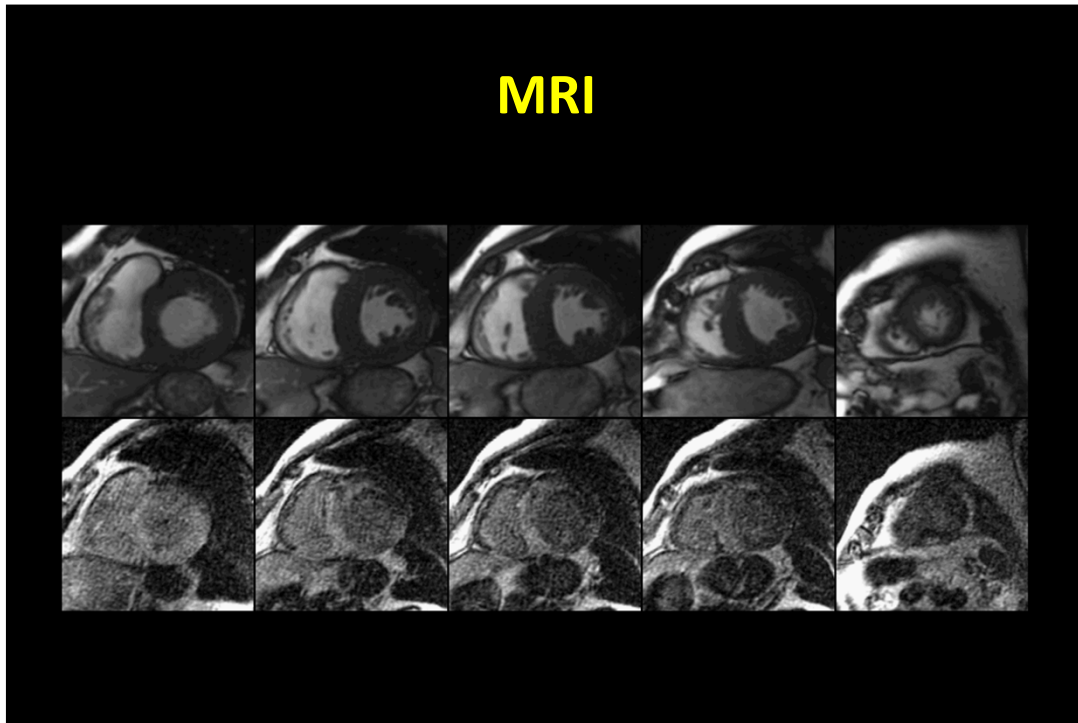
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Echocardiographic Clues

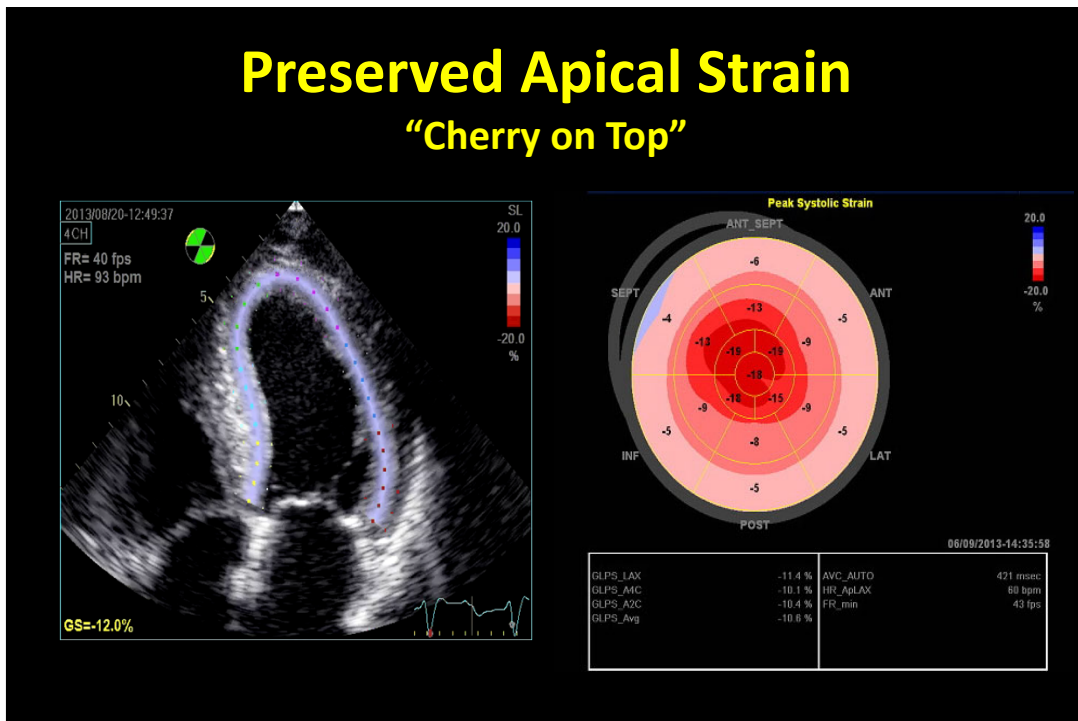


- Increased bi-ventricular wall thickness
 - Thickened interatrial septum
 - Valvular thickening
 - Bi-atrial enlargement
- Diastolic dysfunction**
Restrictive phenotype
Pericardial effusion
Preserved ejection fraction (early)
Systolic heart failure (late)

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Definition of Myocardial Contraction Fraction (MCF)

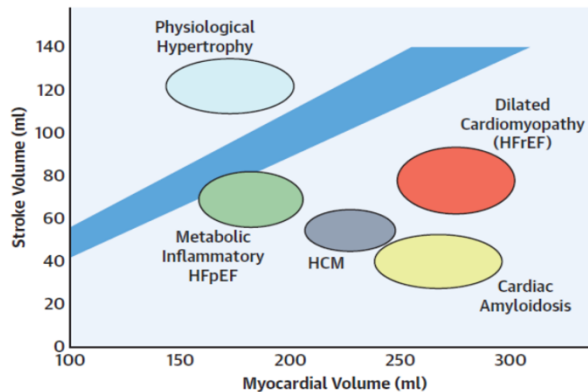
- Defined as:
 - $MCF = \text{Stroke Volume} / \text{Myocardial volume}$
- Myocardial volume is constant from end diastole to end systole.
- Epicardial and endocardial SV are equal.
- Thus indexing stroke volume to myocardial volume is a novel index of myocardial function that delineates a volumetric index of myocardial shortening.

J Am Coll Cardiol 2002;40:325–9

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Myocardial Contraction Fraction (MCF): A Volumetric Measure of Myocardial Shortening

CENTRAL ILLUSTRATION Ratio of Stroke Volume to Myocardial Volume (Myocardial Contraction Fraction) in Healthy People and in Various States of Physiological and Pathophysiological Changes in the Heart



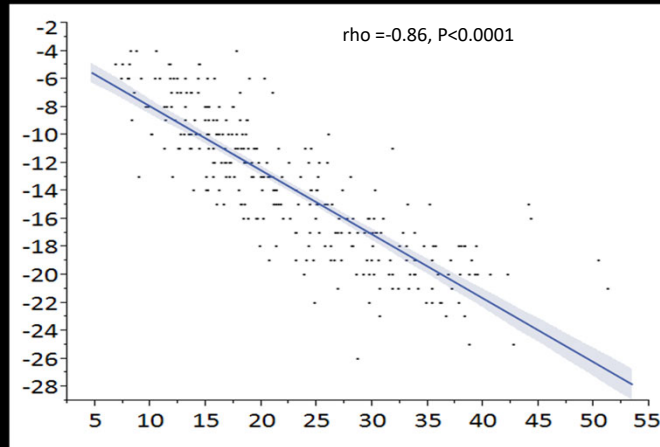
Maurer, M.S. et al. J Am Coll Cardiol Img. 2020;13(3):873-8.

Maurer, M.S. et al. J Am Coll Cardiol Img. 2020;13(3):873–8.

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MCF: Highly Correlated with Strain

Correlation between LV strain and MCF



Circ Cardiovasc Imaging. 2018 May;11(5):e006588.

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Myocardial Contraction Fraction Versus Ejection Fraction in RCM/HCM Phenotypes

Cohort	EF	MCF
Amyloid		
-TTR	60±7	30±14
-TAVR	45±18	28±11
-OHT	49±13	13±6
-AL	65±5	21±7
HCM		
-2DE	70±8	26±11

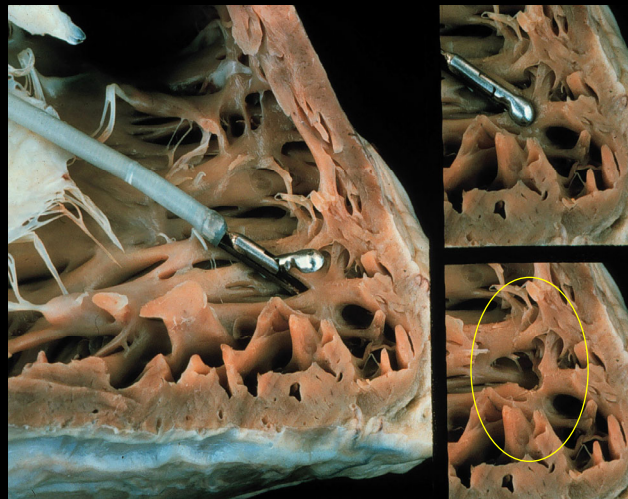
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Reasons for Missing Diagnosis of Cardiac Amyloidosis

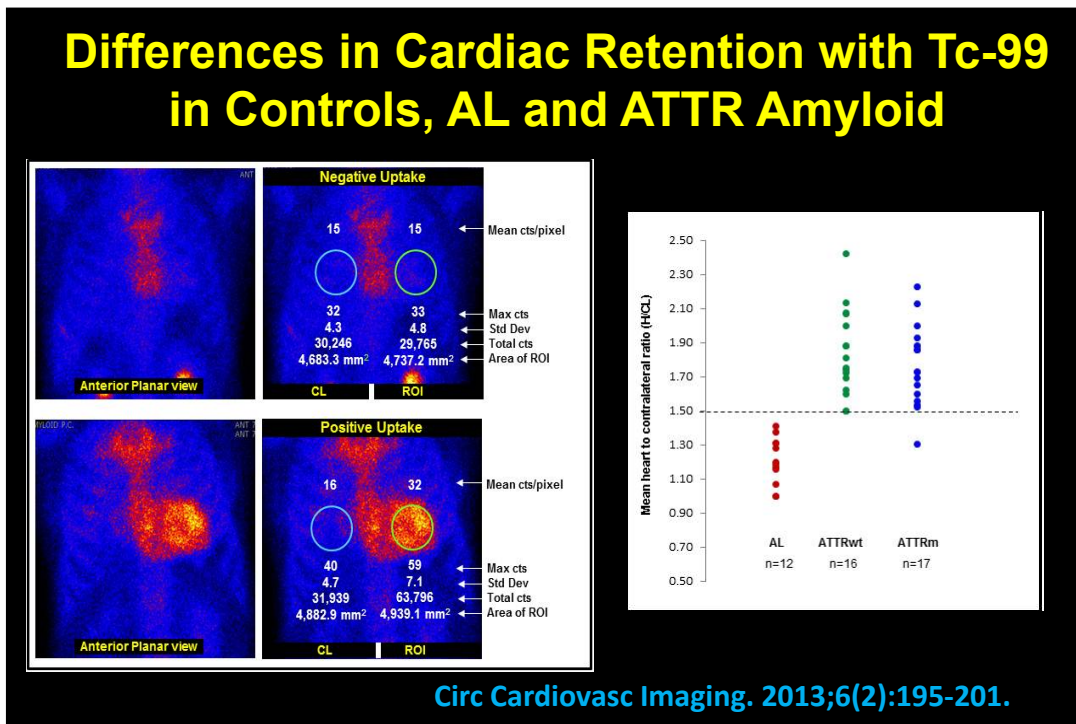
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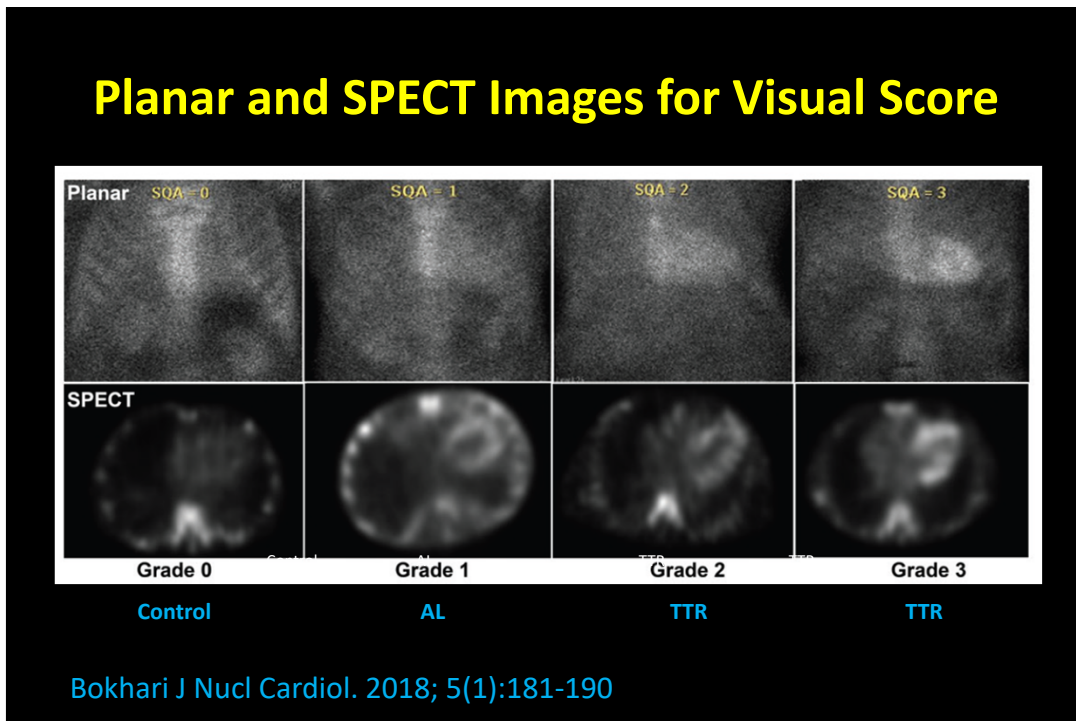
Endomyocardial Biopsy



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Accepted Non-Invasive Diagnosis of ATTR-CM

- Currently the accepted definition of a noninvasive diagnosis of ATTR-CM requires all of the following:
 1. Unexplained heart failure or carrier status of a pathogenic TTR mutation
 2. Echocardiographic and/or cardiac MRI findings suggestive of cardiac amyloidosis
 3. **The absence of a monoclonal gammopathy by serum free light chain assay and serum and urine Immunofixation**
 4. The presence of \geq grade 2 uptake on (^{99m}Tc -PYP, ^{99m}Tc -DPD, ^{99m}Tc -HDMP) ***that is confirmed by SPECT imaging***

J Nucl Cardiol. 2019 Dec;26(6):2065-2123

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Key Causes of Misdiagnosis of ATTR Cardiac Amyloidosis with PYP Scanning

Positive PYP \neq ATTR; Diagnosis = AL
✦ Always screen for AL

Positive PYP = blood pool uptake, no amyloid
✦ Always perform SPECT

- ✓ Heart Failure with typical echo and/or CMR
- ✓ Negative sFLC, serum/urine IFE
- ✓ Positive PYP with SPECT

Accurate Diagnosis = ATTR-CM
Perform TTR DNA sequence

Negative PYP, Clinical suspicion persists
Cardiac biopsy: Diagnosis = ATTRv
✦ Perform biopsy if strong clinical suspicion

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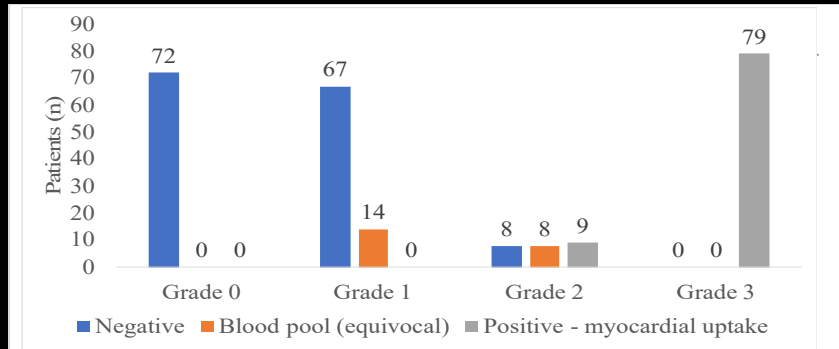
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J Am Coll Cardiol. 2020 Jun 9;75(22):2851-2862.

Poturecha T, Elias P, et. al. JACC Cardiovascular Imaging, 2020 Nov 12

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Essential Role of SPECT for Clarifying Results of Planar Imaging

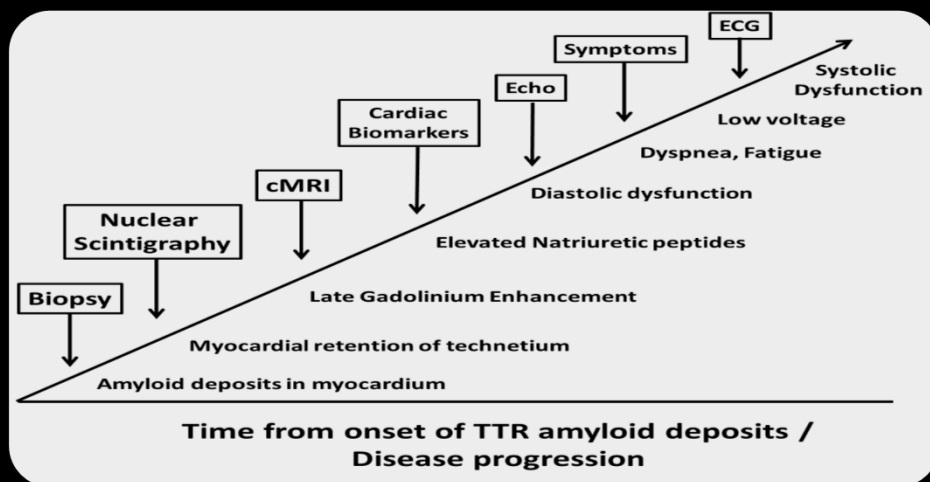


- Among Grade 2 scans (n=25) 16 or **64% were false positives.**
- The false positive rate in the entire cohort is **9.5%**

Poturecha T, Elias P, et. al. JACC Cardiovascular Imaging, 2020 Nov 12

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TTR Amyloid Cascade



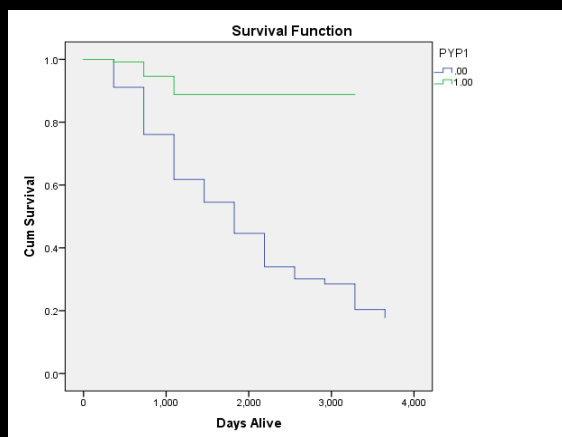
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PYP enables earlier diagnosis!

Parameter	PYP (n=126)	EMB (n=149)	P value
NYHA class (median)	2	3	0.0051
Total QRS voltage (mv)	76±52	57±33	0.0291
Systolic blood pressure (mm Hg)	119±17	113±13	0.0069
BNP (pg/ml)	354±290	691±552	<0.0001
EF (%)	48±14	42±16	0.0008
IVS thickness (mm)	1.5±0.4	1.7±0.6	0.0097
LV mass (grams)	278±100	333±199	0.0058

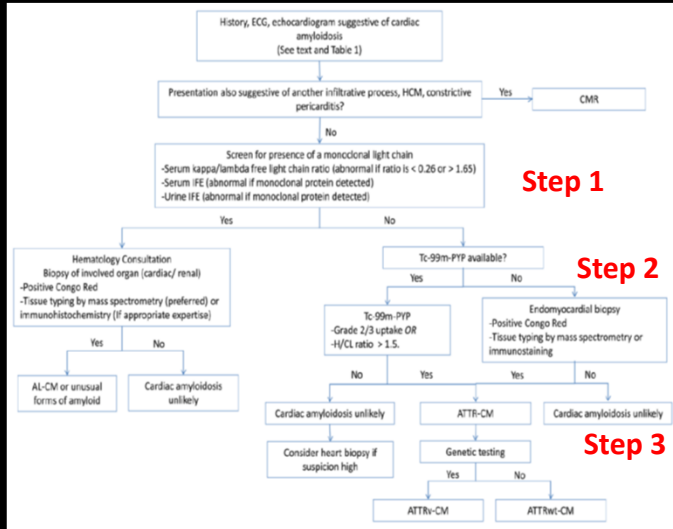
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Scintigraphy is associated with improved survival!!



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Algorithm for Non-Invasive Diagnosis of TTR Cardiac Amyloidosis



Circulation. 2020 Jul 7;142(1):e7-e22.

Three Simple Steps:

1. Check for monoclonal proteins
2. PYP scan
3. Genetic Testing

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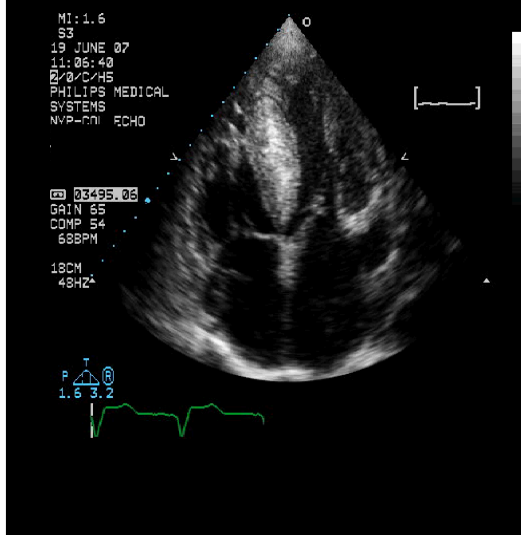
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General Treatment for Amyloid Cardiomyopathy

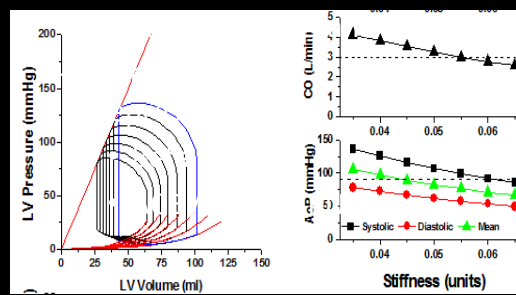
- Diuretics and Salt Restriction – Mainstay of therapy
 - Aldosterone Antagonists and Bioavailable Loop Diuretics
- Calcium channel blockers and ?digoxin - contraindicated
- ACE, ARBs and Beta Blockers – often intolerant and potentially associated with worse outcomes
- Anticoagulation in atrial fibrillation irrespective of CHADs-Vasc Score
- Hypotension – compression stockings and midodrine.
- AICD / pacer – more of a role for pacing

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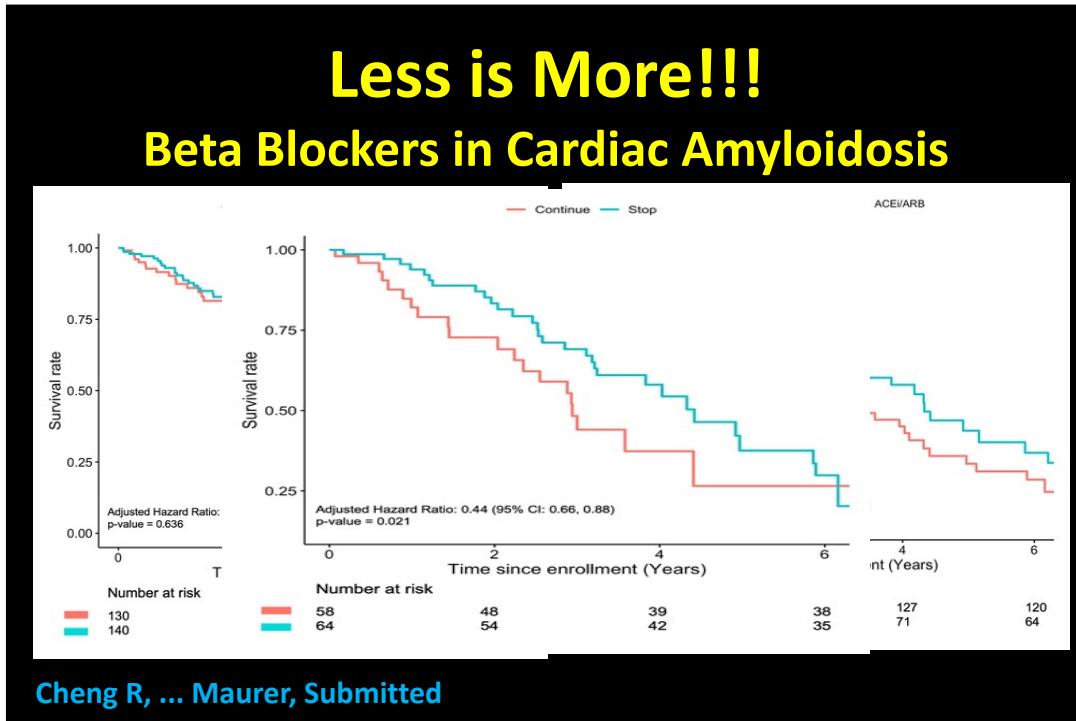
ATTR Cardiac Amyloidosis: The Quintessential form of Diastolic Heart Failure



- Restrictive cardiomyopathy
 - Progressive diastolic dysfunction
 - Reduced LV capacitance – upward and leftward shifts in EDPVR



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Atrial Fibrillation:

Nearly Universal in ATTR Cardiac Amyloidosis Over Time

- Prevalence
 - At least 1/3 in large series ^{1,2,3}
 - 53% in the ATTR-ACT study
- Incidence
 - ~90% develop AF over time
- Anticoagulation in atrial fibrillation irrespective of CHADs-Vasc Score

Event Rate Per 100 Person Years			
Outcome	NOAC (n=116)	Warfarin (n=78)	P value
Stroke	3.5	2.9	0.73
Bleed	5.2	3.7	0.45

¹Circulation. 2009;120(13):1203-12. ²Amyloid. 2019;26(3):128-138. ³ESC Heart Fail. 2018 Oct;5(5):772-779

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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%

55

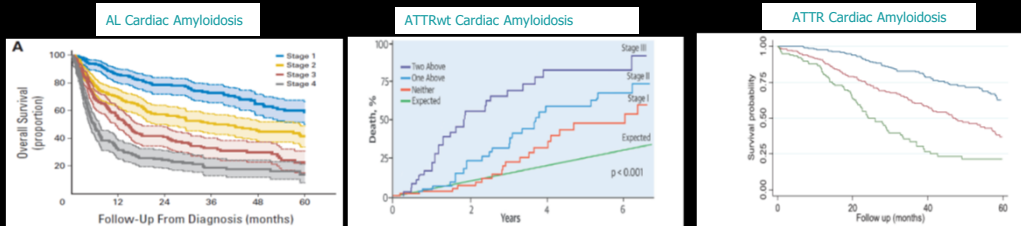
Six routine tests to get on every patient with suspected cardiac amyloidosis

Assess for presence of monoclonal protein by:

1. Abnormal serum kappa / lambda free light chain ratio
2. Immunofixation of serum
3. Immunofixation of urine

Obtain biomarkers for staging including:

4. NTproBNP
5. Troponin T
6. eGFR

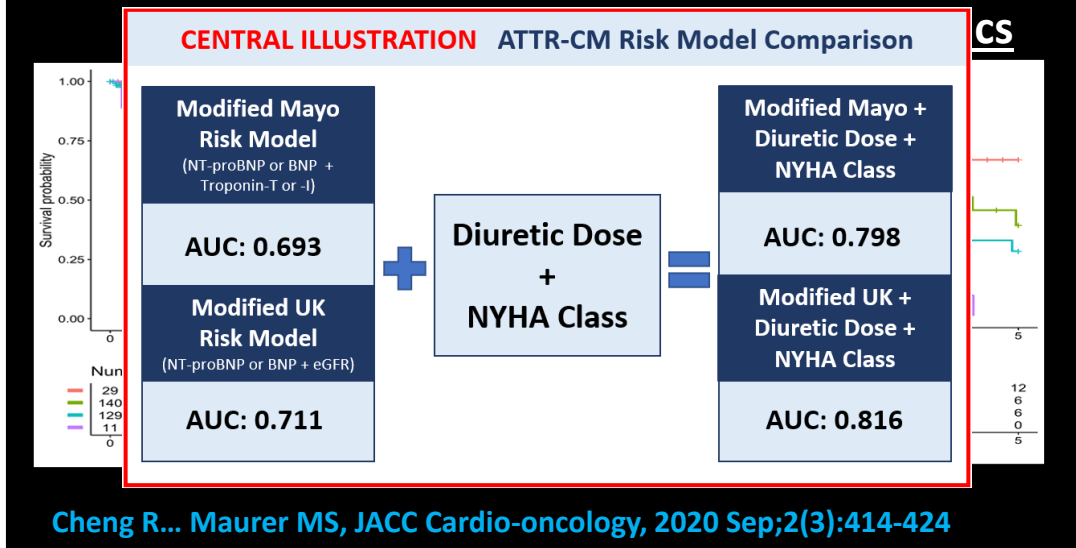


J Clin Oncol 30:989-995;

JACC.2016;68(10):1014-20; EHJ. 2018;39(30):2799-2806.

56

NYHA Class and Diuretic Dose Add to Existing Staging Systems for ATTR-CA



57

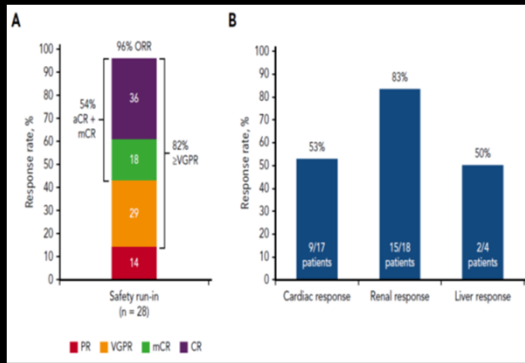
Treatment for AL Amyloid

Don't Do this Alone – Get a Hematologist

- **Plasma cell therapy**
 - Oral melphalan and dexamethasone
 - Thalidomide and dexamethasone
 - Bortezomib, Carfilzomib and Ixazomib
 - Lenalidomide and Pomalidomide
 - Daratumumab, Isatuximab and Elotuzumab
 - Venetoclax (for t11,14 translocations)
 - Intermediate- or high-dose melphalan and stem cell transplant

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Daratumumab (subcutaneously) – A new standard of care in AL Amyloidosis

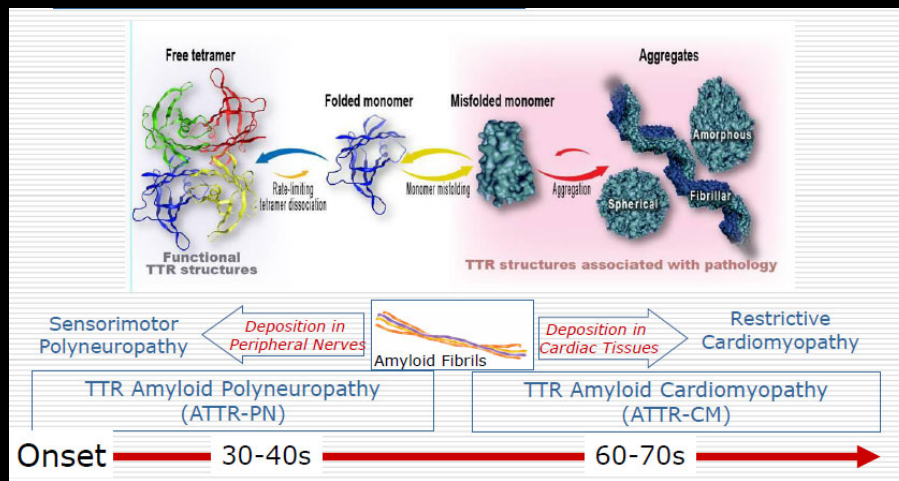


- Daratumumab is a human immunoglobulin monoclonal antibody targeting CD38 that is uniformly expressed on clonal plasma cells.
- ANDROMEDA met is primary endpoint with met the primary endpoint of percentage of patients with hematologic complete response (53.3% with CyBorgD + Dara versus 18.1% of patients who were treated with CyBorD alone (odds ratio of 5.1 (95% CI 3.2 – 8.2, p<0.0001)).

Blood. 2020;136(1):71-80

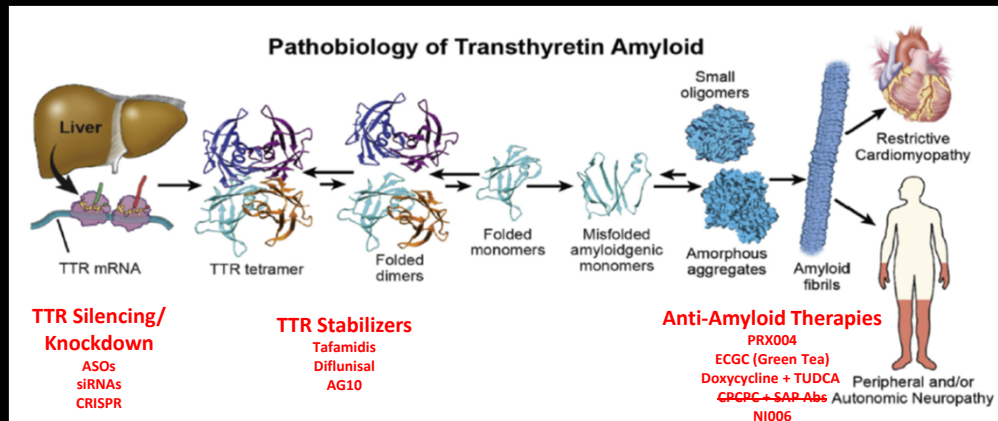
59

Pathogenesis of ATTR Amyloidosis



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Therapies for transthyretin amyloidosis have emerged from elucidation of underlying biology.

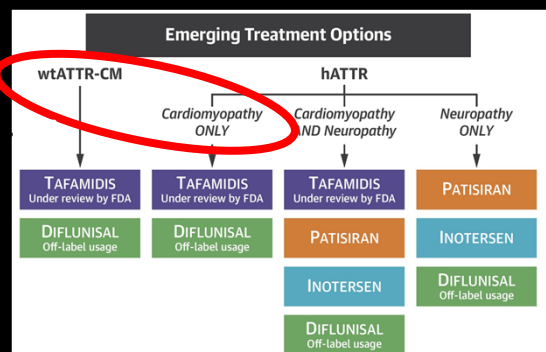


JACC. 2019;73(22):2872-2891

61

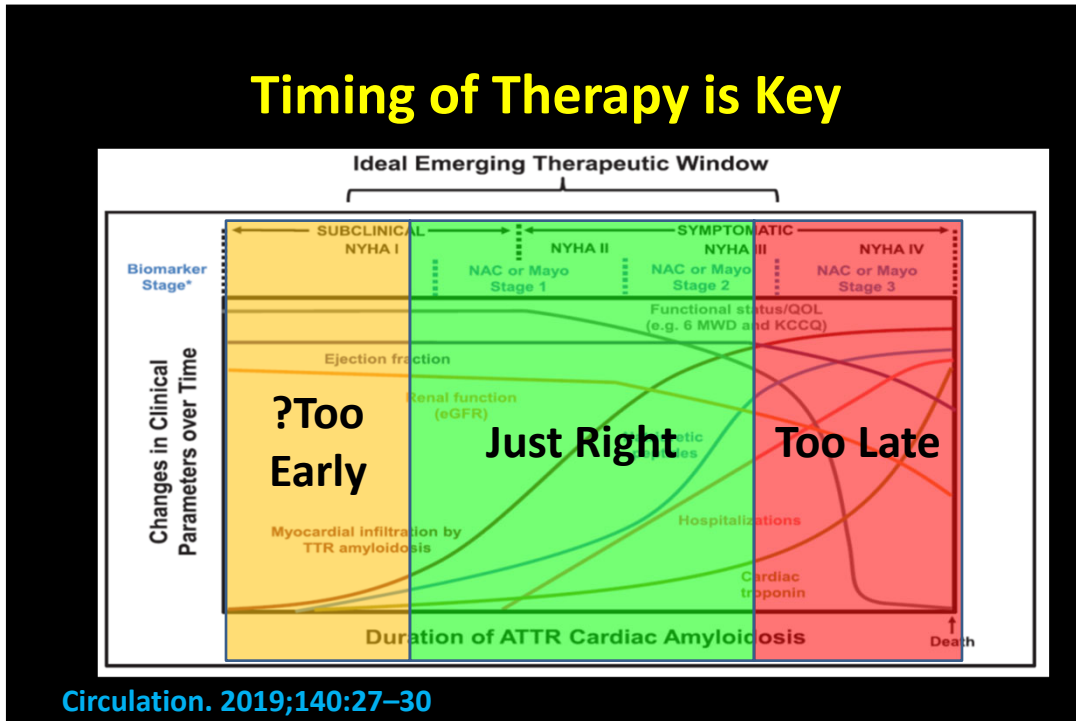
ATTR Cardiomyopathy without Neuropathy Clinically Available Options

- Tafamidis -
 - Approved
 - Convincing Phase 3 data
 - Cost could limit access
- Diflunisal
 - Off label use
 - NSAID – use cautiously
 - No recent decompensation
 - eGFR > 40
 - Daily diuretic dose < 80 mg Lasix, no metolozone
 - ? Use with anticoagulation



Ruberg, F, JACC. 2019;73(22):2872-2891

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Three Little Bears as Applied to Therapy for TTR Cardiac Amyloidosis

Too Early??	Just Right!!	Too Late!!
<p>Asymptomatic allele carriers of a mutation without evidence of a cardiac phenotype</p>	<ul style="list-style-type: none"> • NYHA class II • + Phenotype +scintigraphy +biopsy • EF preserved 	<ul style="list-style-type: none"> • NYHA class IV • eGFR < 25 • Unable to ambulate • mBMI < 600

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ATTRwt: Too Late

- 87 year old male with ATTRwt cardiac amyloidosis
- 4 previous hospitalizations for heart failure in last 6 months
- Non ambulatory, frail appearing in a wheelchair
- Exam
 - BP is 92/70 (after taking midodrine 5 mg), HR of 104, BMI of 19
 - JVP > 15 cm, decreased breath sounds at right lung 1/3 way up, no gallop, II/IV holosystolic murmur at LLSB, liver 3 cm below costal margin, 2-3+ edema, cool
- Labs: eGFR -21 ml/kg/min, NTproBNP 9,836 pg/ml, Troponin T = 0.15, albumin of 2.7
- Echo shows IVS of 24 mm, EF of 25%, moderate-severe RV dysfunction

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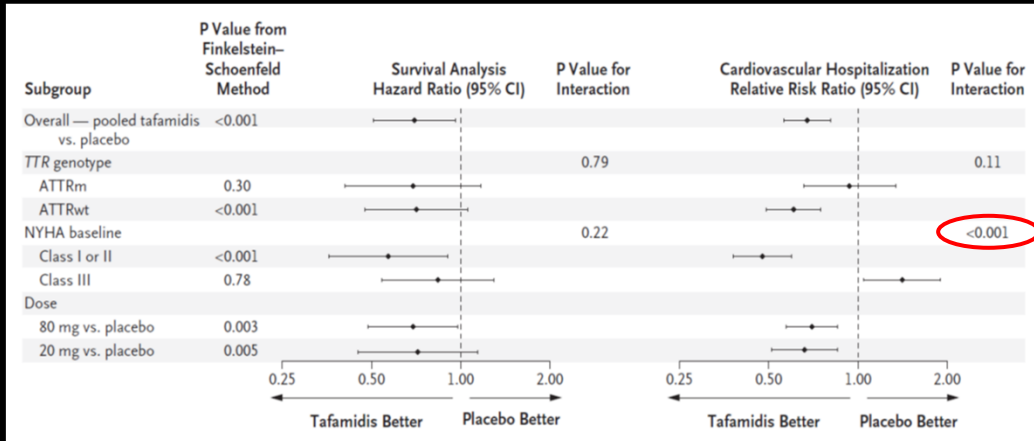
ATTR-ACT Inclusion/Exclusion Criteria¹

- **Key Inclusion Criteria**
 - Presence of amyloid deposits in biopsy tissue (cardiac or non-cardiac) and TTR precursor protein identification by mass spectrometry, immunohistochemistry or scintigraphy
 - Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm
 - A medical history of heart failure (HF) with at least 1 prior hospitalization for HF signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretic for improvement
 - NT-proBNP concentration ≥ 600 pg/mL
 - 6-Minute Walk Test distance >100 meters
- **Key Exclusion Criteria**
 - New York Heart Association (NYHA) class IV
 - Glomerular filtration rate (eGFR) of <25 mL/min/1.73 m²
 - Concurrent treatment with non-steroidal anti-inflammatory drugs
 - Modified body mass Index (mBMI) <600 kg/m²·g/L

¹Maurer MS, et al. *Circ Heart Fail* 2017;10.

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Pre-specified Subgroup Results: All-cause Mortality, and CV-related Hospitalization



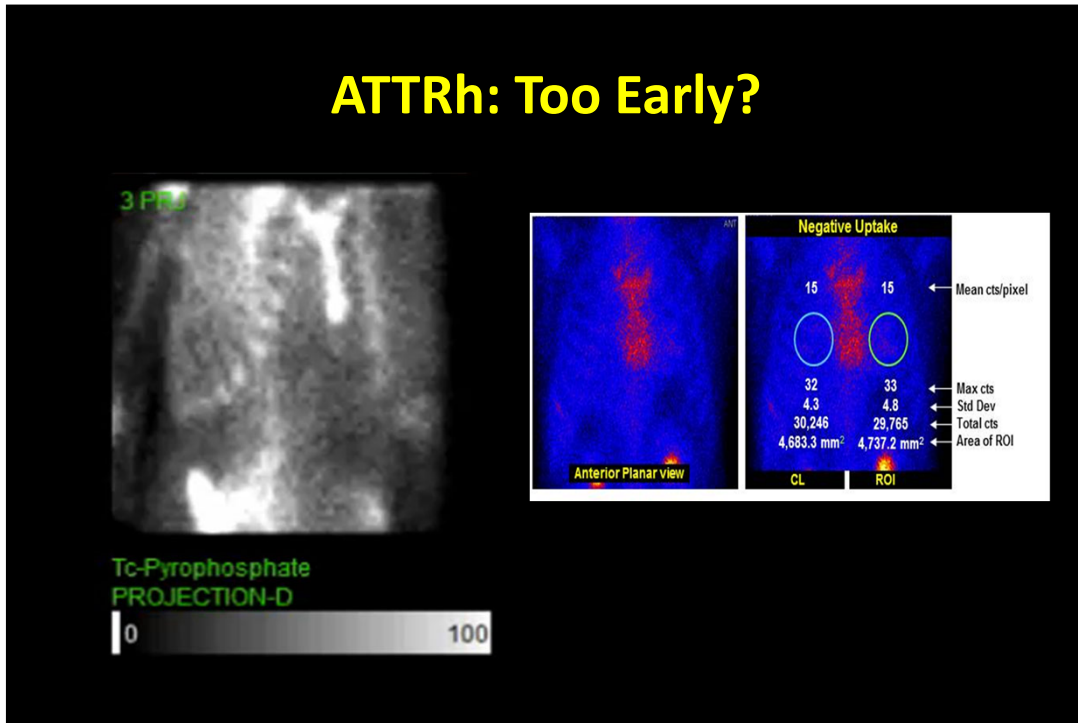
Maurer MS, et al. *N Engl J Med.* 2018 Aug 27.

67

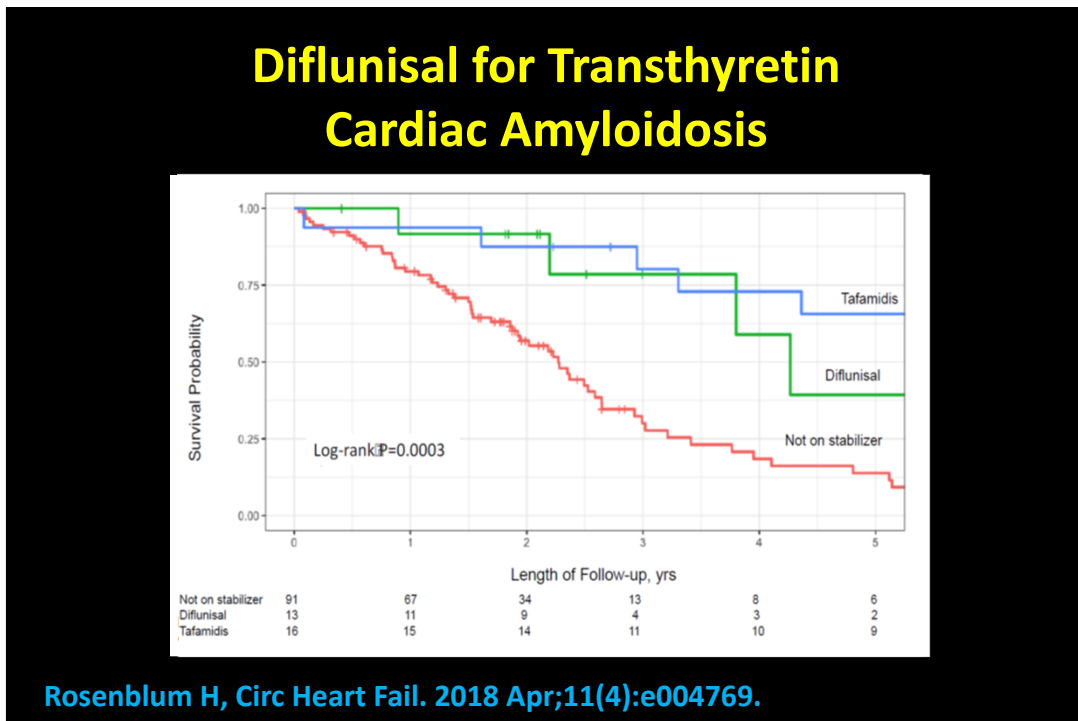
ATTRh: Too Early?

- 48 year old women with family history of ATTR-CA
 - Father died from progressive heart failure 2° Val122Ile
 - Mother is also carrier of Val122Ile but asymptomatic
- Patient is homozygous for Val122Ile
- Exam normal: BP=128/74, HR=72, no JVP, no gallop
- EKG: no conduction disease; no low voltage nor Q waves
- Echo: E/E' = 8, MWT = 10 mm, strain -22%, no apical sparing
- Labs: prealbumin =18 mg/dl (normal 22-38 mg/dl), NTproBNP = 84 pg/ml, Troponin T <0.01

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ATTRwt: Just Right

- 64 year old male with NYHA class II symptoms
- Has had previous biceps tendon rupture
- EKG shows pseudoinfarcts but not low voltage
- Echo: IVS of 15 mm, PWT of 14 mm, EF of 52%, GLS of -11%, E/E' of 18
- Labs
 - NTproBNP = 400 pg/ml, Troponin T <0.01, eGFR of 58 ml/min/m2, SPIE negative and normal K/L free light chains
- PYP scan grade 3, H/CL of 2.1 and SPECT show myocardial retention of PYP.

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Baseline Clinical Characteristics

Characteristic	Pooled Tafamidis (N=264)	Placebo (N=177)
Age, mean (SD)	74.5 (7.2)	74.1 (6.7)
Male, n (%)	241 (91.3)	157 (88.7)
ATTRwt, n (%)	201 (76.1)	134 (75.7)
LV ejection fraction, mean (SD)	48.4 (10.3)	48.6 (9.5)
Interventricular wall thickness, mean (SD)	16.7 (3.8)	16.2 (3.5)
LV stroke volume mean (SD)	45.8 (16.1)	45.1 (16.9)
Global longitudinal strain, mean (SD)	-9.3 (3.5)	-9.4 (3.6)
NYHA Class, n (%)		
NYHA Class I	24 (9.1)	13 (7.3)
NYHA Class II	162 (61.4)	101 (57.1)
NYHA Class III	78 (29.5)	63 (35.6)
NT-proBNP, median (Q1, Q3)	2996 (1752, 4862)	3161 (1864, 4825)
Troponin I, median (Q1, Q3)	0.14 (0.09, 0.20)	0.14 (0.08, 0.19)

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Primary Analysis using Finkelstein-Schoenfeld (F-S) Method

	Pooled Tafamidis n=264	Placebo n=177
P-value from F-S method	0.0006	
Patients alive ^a at Month 30, n (%)	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalizations during 30 mo (per pt per yr) among those alive at Month 30	0.297	0.455
Win-Ratio ^b (95% CI)	1.695 (1.255, 2.289)	

^aHeart transplant and implantation of a cardiac mechanical assist device were treated as death for this analysis

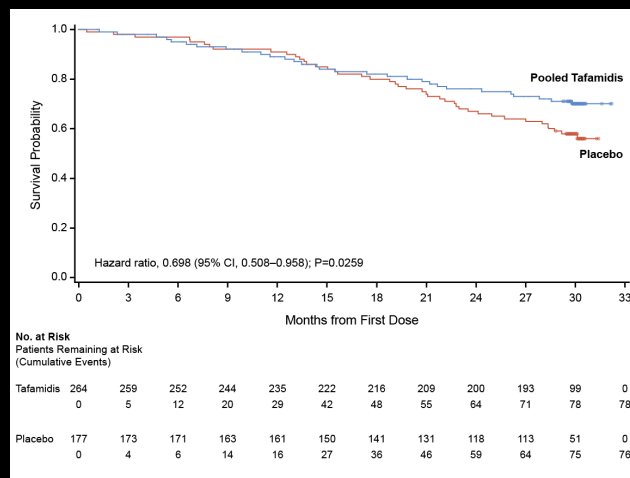
^bNumber of pairs of tafamidis-treated patient wins divided by number of pairs of placebo patient wins

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Tafamidis Reduces All-cause Mortality and Hospitalizations.

33% reduction (P=0.018) in overall mortality – need to treat 7-8 patients to prevent one death over 2 ½ years

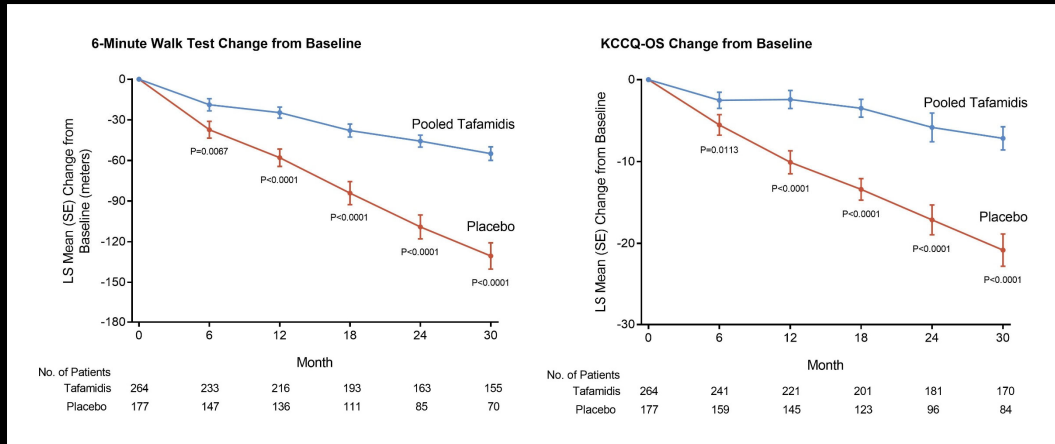
There was a 32% reduction in the rate of hospitalization with tafamidis compared with placebo – need to treat 4 patients to prevent 1 hospitalization per year.



Maurer MS, et al. N Engl J Med. 2018 Aug 27.

74

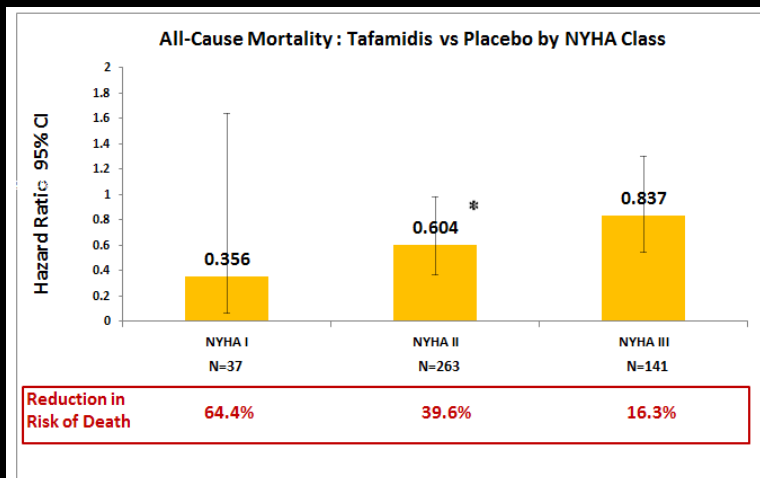
Key Secondary Endpoints: 6-minute Walk Test and KCCQ-OS



Maurer MS, et al. N Engl J Med. 2018 Aug 27.

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The Earlier the Better!!!



Maurer MS, et al. N Engl J Med. 2018 Aug 27.

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Progression of ATTR-CA Transthyretin Cardiac Amyloidosis Study (TRACS)

Parameter	6-Month Rate of Change
Six minute walk distance (meters)	-25.8
NT-pro-BNP (pg/ml)	1816.0
LV EF (%)	-3.22

Am Heart J. 2012 Aug;164(2):222-228

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Screening for Cardiac Amyloidosis using Nuclear imaging in Minority Populations (SCAN-MP) Study.

- Overall Goal:

To change the approach transthyretin cardiac amyloidosis, which is a devastating disease, by screening and early diagnosis

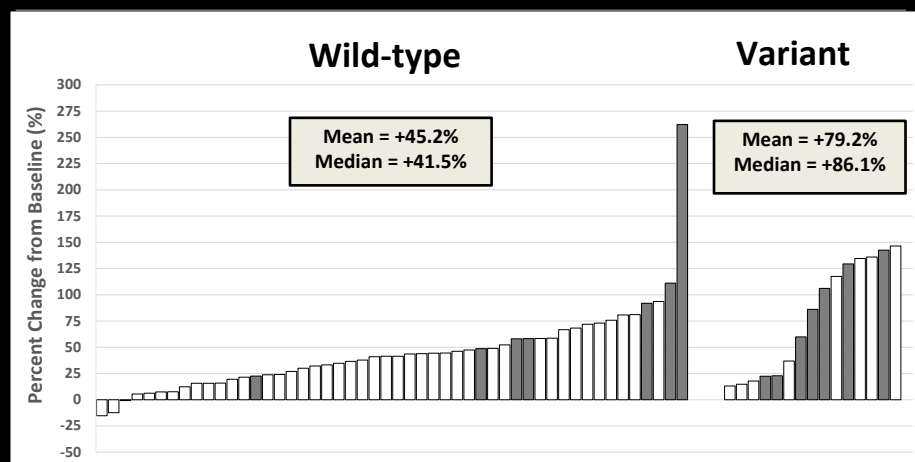
78

Screening for Cardiac Amyloidosis using Nuclear imaging in Minority Populations (SCAN-MP) Study

- Prospective, cohort study in 800 participants
- Black and Hispanic subjects with heart failure
- Undergo Tc⁹⁹-PYP imaging, clinical, biochemical, electrocardiographic, echocardiographic measures along with genetic evaluation.
- Evaluate the prevalence, phenotype and outcomes of ATTR-CA in minorities with genetic and non-genetic causes.

79

AG10: Another TTR Stabilizer



Judge D, JACC 2019; 2019 Jul 23;74(3):285-295

Saith S... Maurer MS, Amyloid, accepted

80

Therapeutic Hypothesis for siRNA and ASO in TTR Cardiac Amyloid

Production of mutant and wild type TTR



siRNA and ASO acts to knock down hepatic mutant and wild-type TTR production

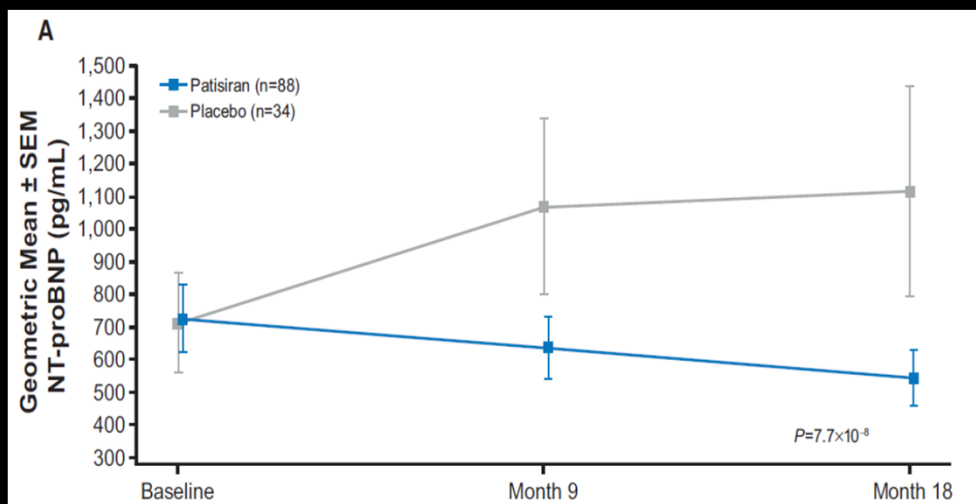
Reduction of unstable circulating TTR tetramers

Prevention of organ deposition of TTR monomers and amyloid fibrils (and potential clearance)

Stabilization of cardiomyopathy/neuropathy (and potential recovery)

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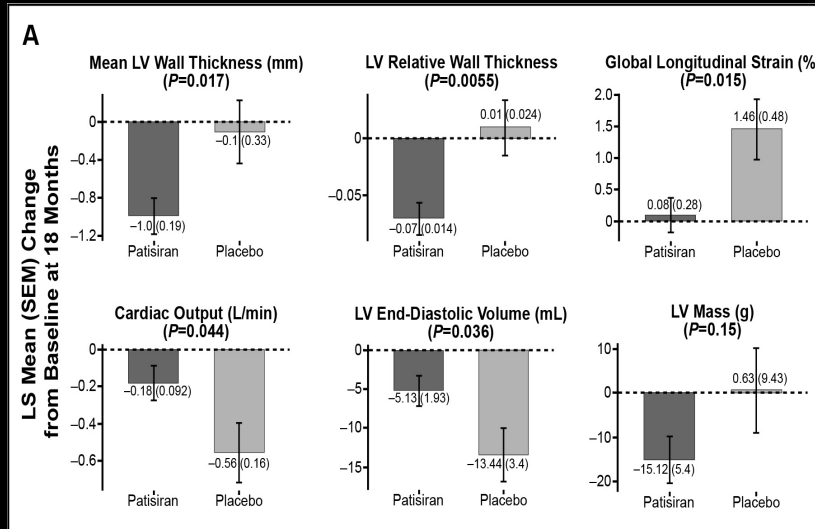
Patisiran Effects on NTproBNP



Solomon S, Circulation. 2019;139(4):431-44

82

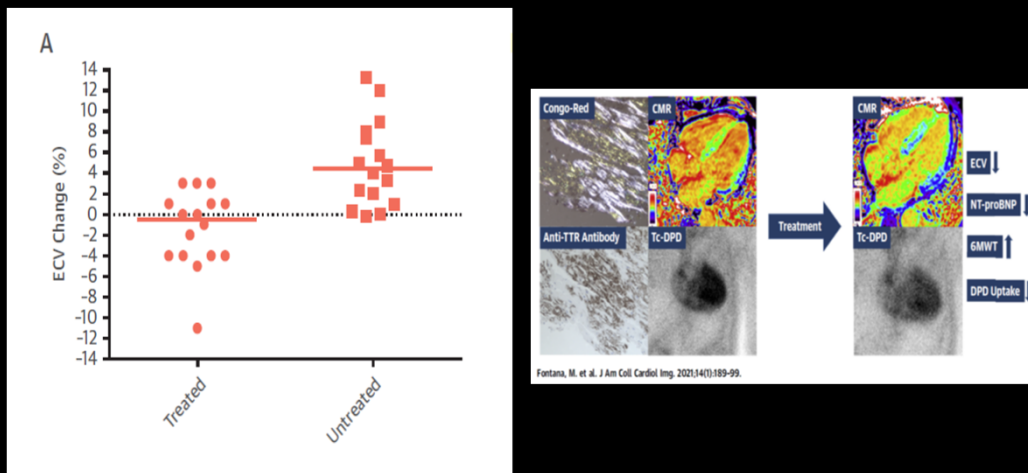
Cardiac Effects of siRNA



Solomon, S, *Circulation*. 2019;139(4):431-44

83

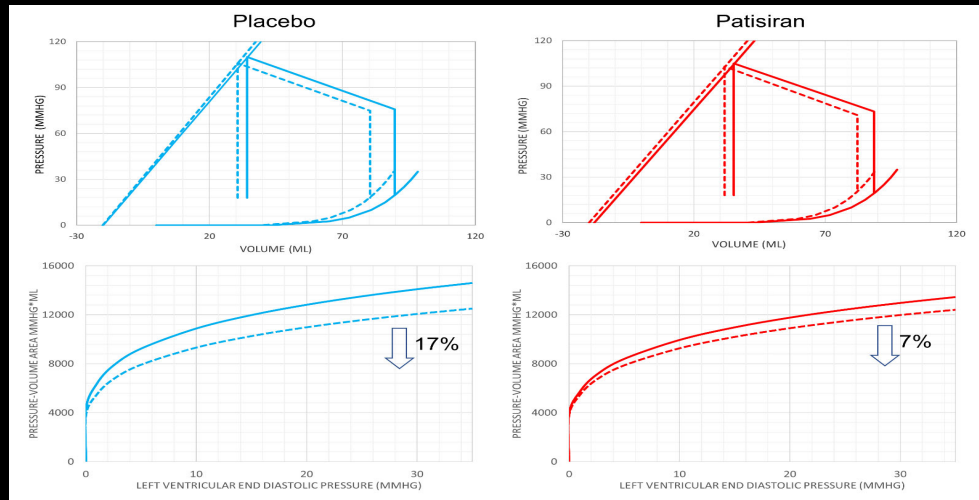
Reduction in CMR Derived Extracellular Volume With Patisiran Suggests Cardiac Amyloid Regression



JACC Cardiovasc Imaging. 2021 Jan;14(1):189-199.

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Cardiac Mechanics in APOLLO with Patisiran



Rosenblum H..... Maurer MS, Under preparation

85

ATTR Cardiomyopathy without Neuropathy Phase 3 Trials

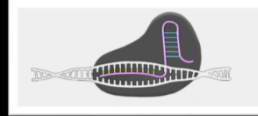
- AG10- ATTRIBUTE-CM
 - Oral compound
 - Phase 3 trial — fully enrolled
 - 510 Participants Planned
 - 2:1 Randomization
 - Co-Primary Endpoints
 - » 6MWT at 12 months
 - » Mortality and CV hospitalizations at 30 months
- Patisiran — APOLLO-B
 - IV administration every 3 weeks
 - 300 participants - Anticipated enrollment closed in Q2 of 2021
 - 1:1 randomization
 - Change in 6MWT at 12 months
- AKCEA-TTR-L_{RX} : CardioTTRansform
 - SQ compound dose 1 a month
 - 750 participants
 - 1:1 Randomization
 - Primary - hierarchical composite endpoint of cardiovascular mortality and recurrent cardiovascular clinical events analyzed by the Andersen-Gill method
- Vutrisiran — Helios B
 - SQ Compound dose every 3 months
 - 600 participants
 - 1:1 Randomization
 - All-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) by Andersen-Gill model

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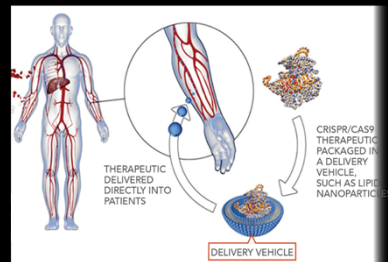
Gene Editing for TTR Amyloidosis with CRISPR/Cas9 system

- CRISPR/Cas9 enables editing of unhealthy genes, acting as programmable molecular scissors
- For ATTR, Cas9 may be used to silence expression of TTR in hepatocytes, reducing the release of misfolded protein
- CRISPR can be delivered efficiently to the liver using lipid nanoparticles (LNPs), with transient expression but lasting changes
- A single administration may be sufficient to halt the pathogenic process

Cas9 can specifically disrupt the TTR gene



LNPs enable efficient delivery to liver



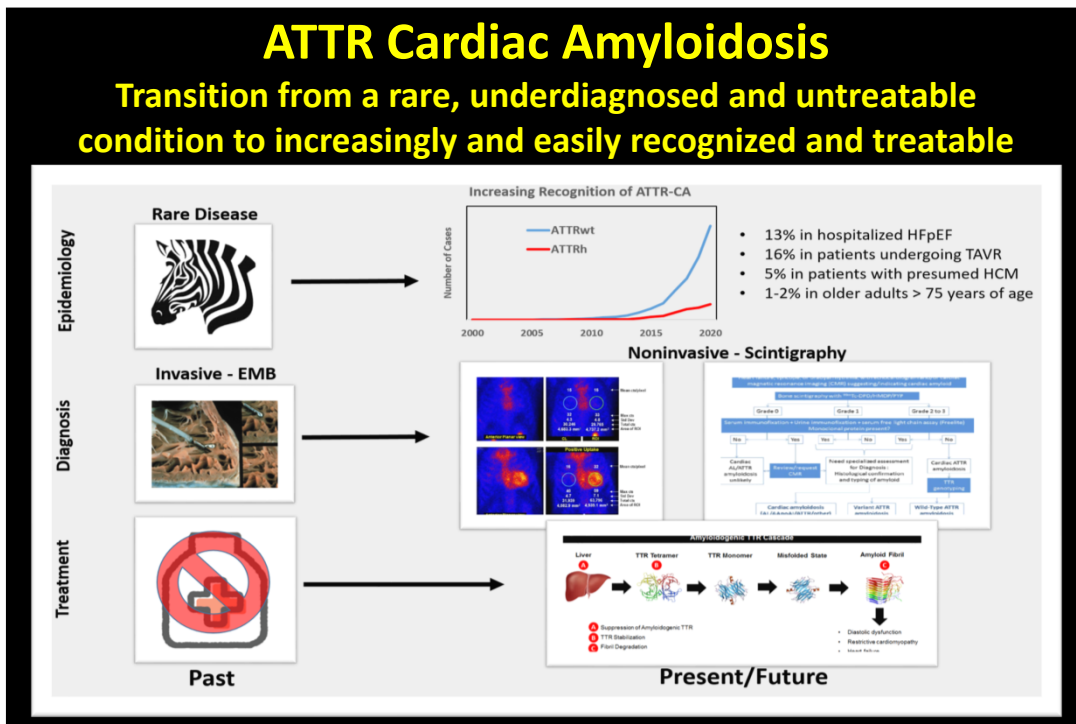
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TTR Amyloid Cardiomyopathy *The Great Pretender*

- Challenging
- Fascinating
- Mysterious
- Not as rare as supposed
- Relatively easy to detect (when suspected!)
- **Treatable**

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Objectives

1. Identify the phenotype of cardiac amyloidosis in order to facilitate early diagnosis
 - The diagnosis of cardiac amyloidosis continues to be made in patients with late-stage disease
 - More needs to be done to improve awareness of its clinical manifestations and the potential of therapeutic intervention to improve prognosis
2. Distinguish underlying causes of cardiac amyloidosis given differences in prevalence, prognosis and treatment
 - Light chain cardiac amyloidosis, in particular, if recognized early and treated with targeted plasma cell therapy, can be managed very effectively.
 - With the aging of population, ATTRwt will become the most commonly form of cardiac amyloidosis.

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Objectives

3. Enumerate three emerging strategies to address TTR cardiac amyloidosis
 - Therapies based on a biologic understanding have been shown to be effective in late phase clinical trials.
 - Non biopsy diagnosis of TTR cardiac amyloidosis can be made with bone scintigraphy assuming there is no evidence of a monoclonal protein.