Cardiac Amyloid: Contemporary Approach to Diagnosis and Advances in Treatment

Cardiac Nursing Symposium

October 17, 2019

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Heart Failure Nurse Practitioner

Learning objectives

- Describe the different types of cardiac amyloidosis (Disease)
- Recognize clinical manifestations of cardiac amyloidosis
- Implement strategies for diagnosis of cardiac amyloidosis (Diagnosis)
- Utilize recent clinical evidence for decisions about treatment of cardiac amyloidosis (Drugs and devices)

What is the **disease** amyloidosis?

- First described by Rudolf Virchow in 1858 describing the reaction of tissue deposits with iodine and sulfuric acid.
- A disorder of misfolded proteins
- Proteins circulate in the bloodstream and perform many functions in the body
- Should be dissolved, in other words, liquid
- In amyloid they become solid and deposit in organs and tissues in the body and cause problems

Red flags for Cardiac Amyloidosis

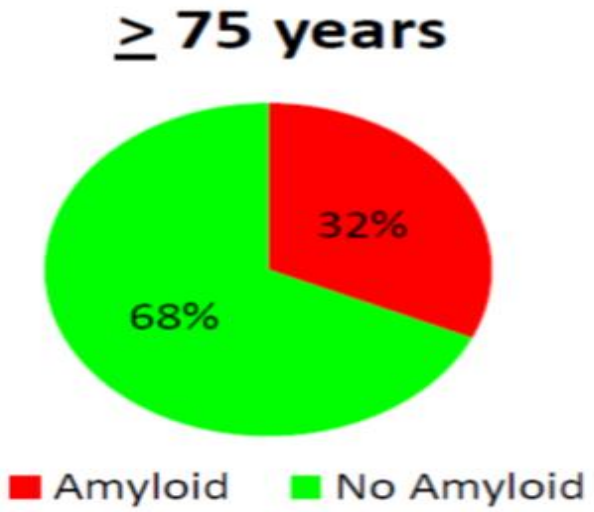
- Echocardiography
  - Low voltage on ECG and thickening of the septum/posterior wall>1.2 cm (unexplained increase in thickness)
  - Thickening of the RV free wall, valves

Intolerance to bet blockers or ACEI

Low normal BP inpatients with a previous historv of HTN

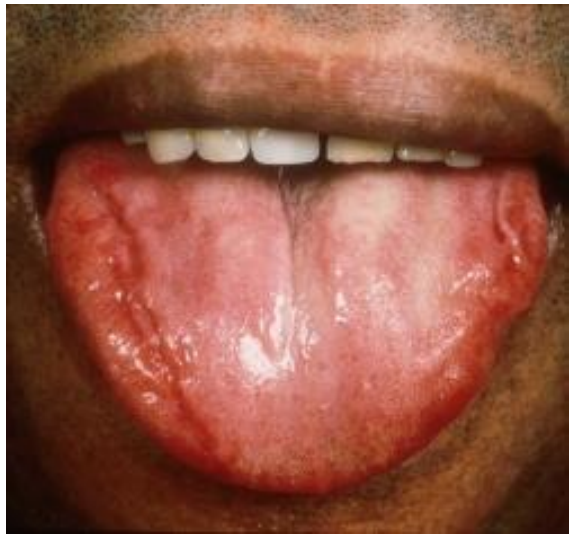
Donnelly and Hanna, 2017

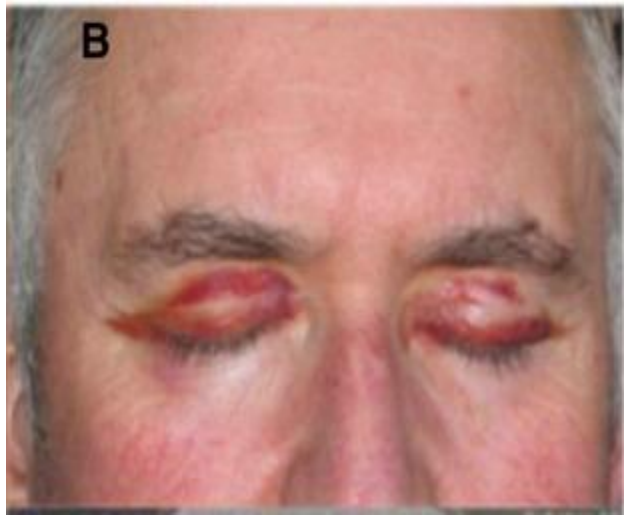
JACC 2014



Red flags for AL

- HFpEF + Nephrotic syndrome
- Macroglossia and/or periorbital purpura
- Orthostatic hypotension
- Peripheral neuropathy
- MGUS





- Donnelly and Hanna, 2017

Red flags for ATTR

- White male age>60 with HFpEF + history of carpal tunnel syndrome and or/spinal stenosis
- African American age>60 with HFpEF without history of HTN
- New diagnosis of hypertrophic cardiomyopathy in an elderly patient
- New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
- Family history of ATTR amyloidosis

- Donnelly and Hanna, 2017

Summary of flags for Cardiac Amyloidosis

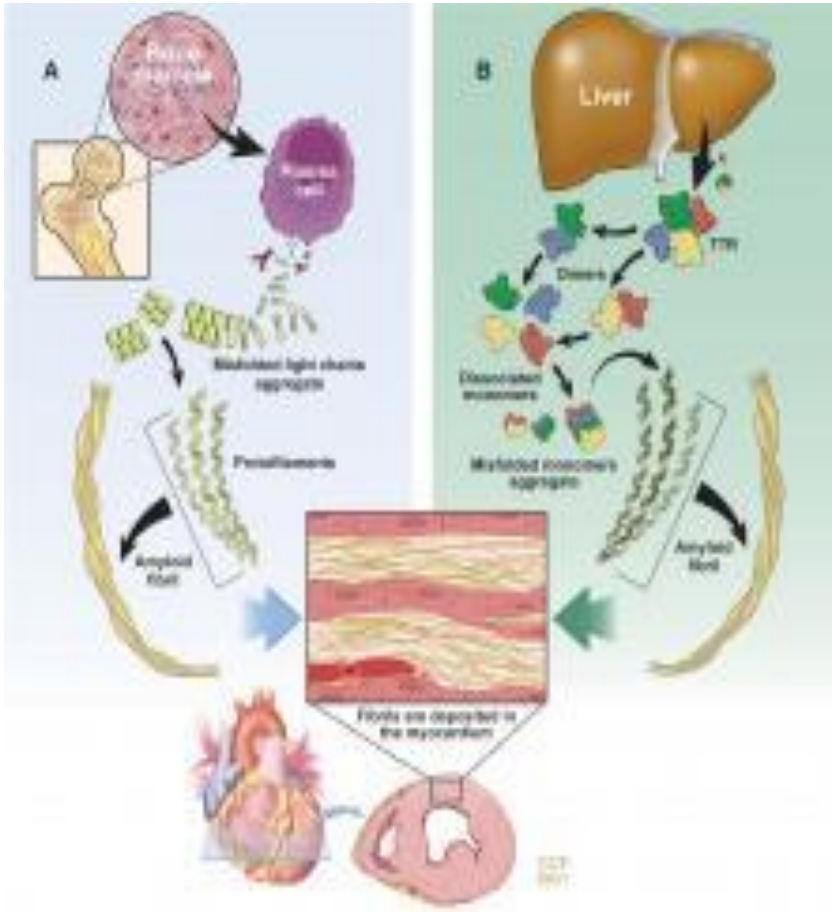
TABLE 1
Symptoms that raise suspicion of cardiac amyloidosis

Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

ACE = angiotensin-converting enzyme; AL = immunoglobulin light chain amyloidosis; ATTR = transthyretin amyloidosis; ECG = electrocardiogram; ATTRm = hereditary mutant variant ATTR; HFpEF = heart failure with preserved ejection fraction ("diastolic heart failure"); MGUS = monclonal gammopathy of undetermined significance

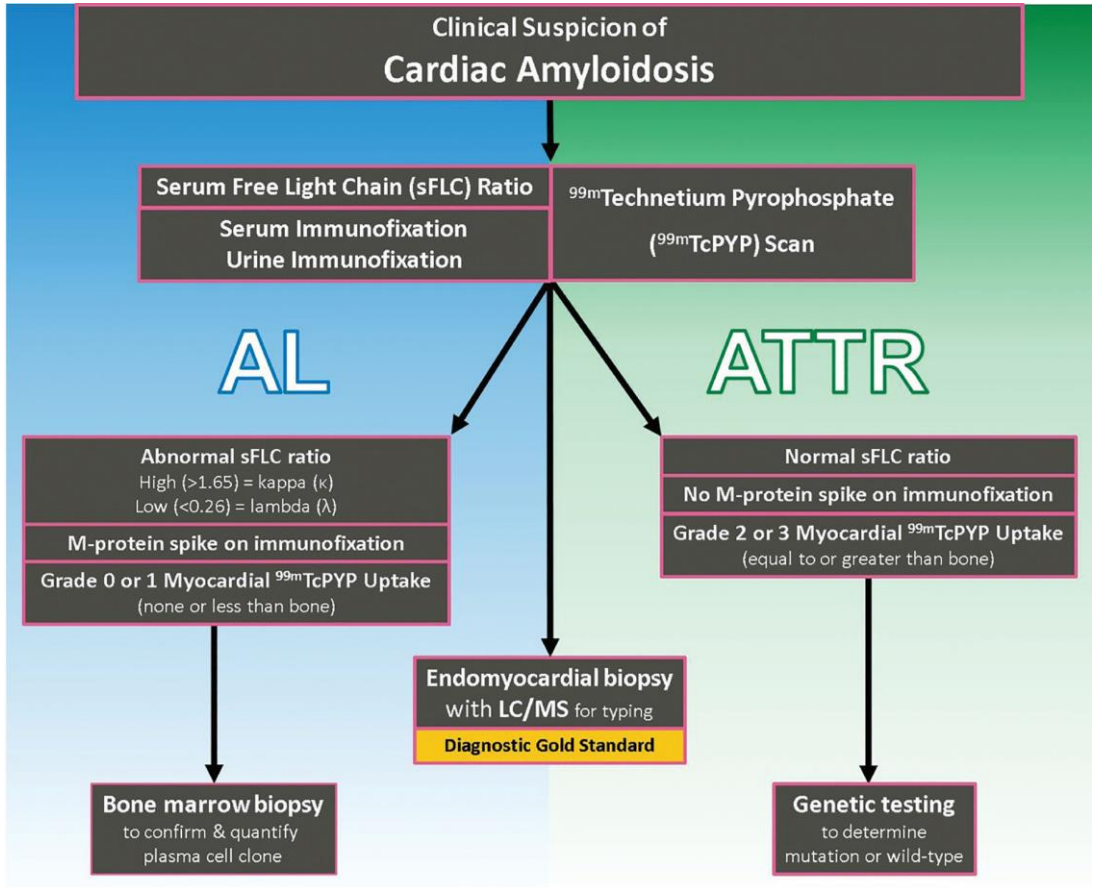
Comparison of AL Amyloidosis and ATTR Amyloidosis

Donnelly and Hanna, 2017

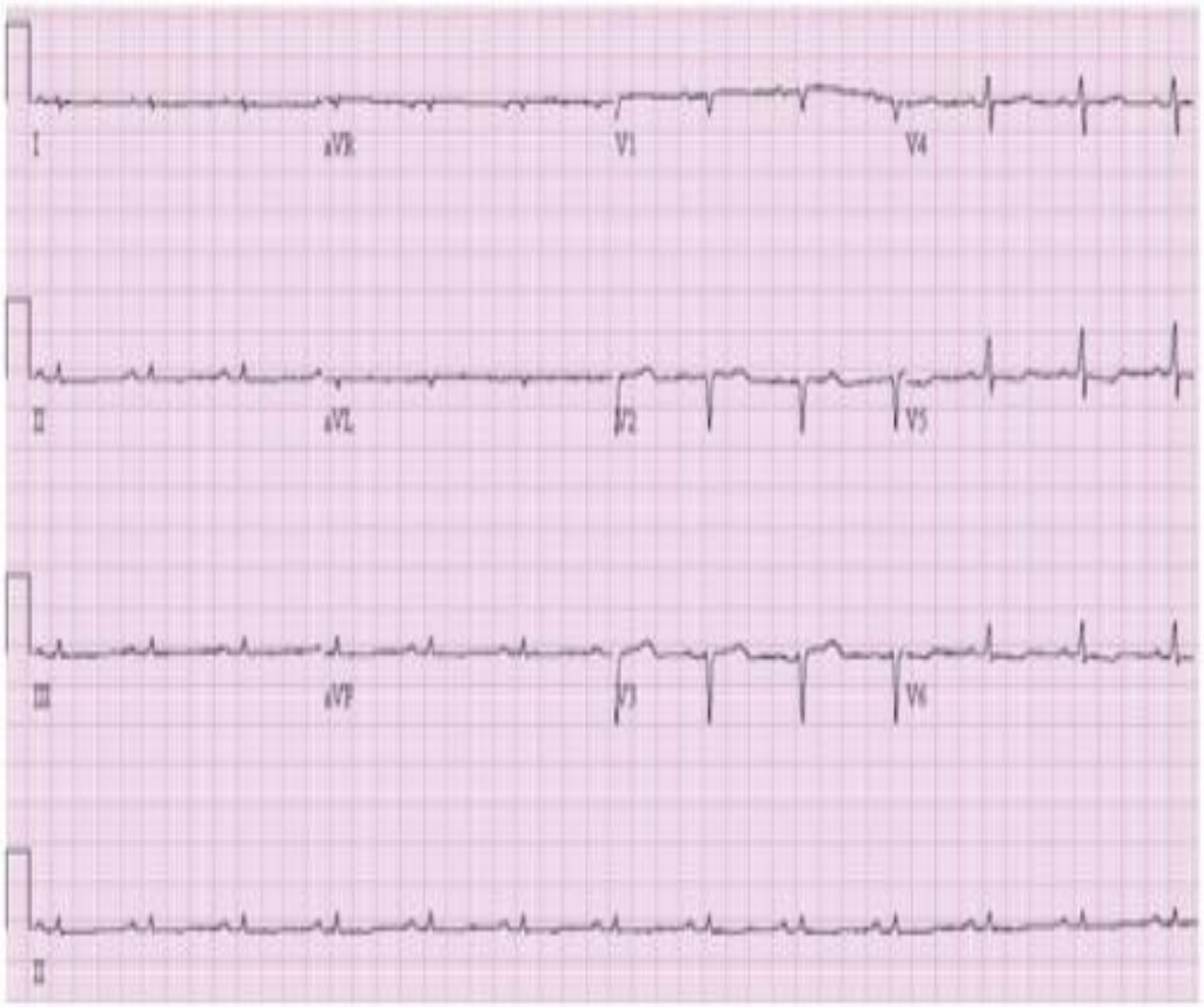


Diagnostic evaluation

Donnelly and Hanna, 2017



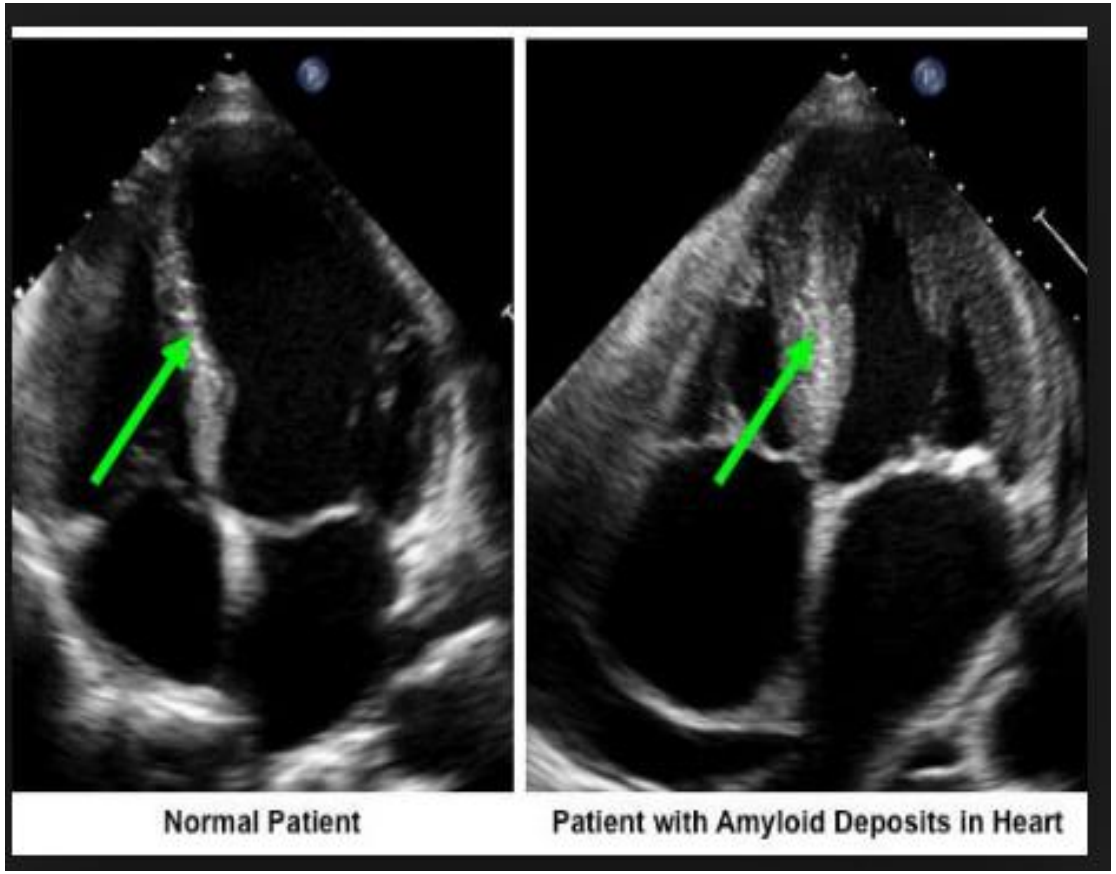
EKG Findings



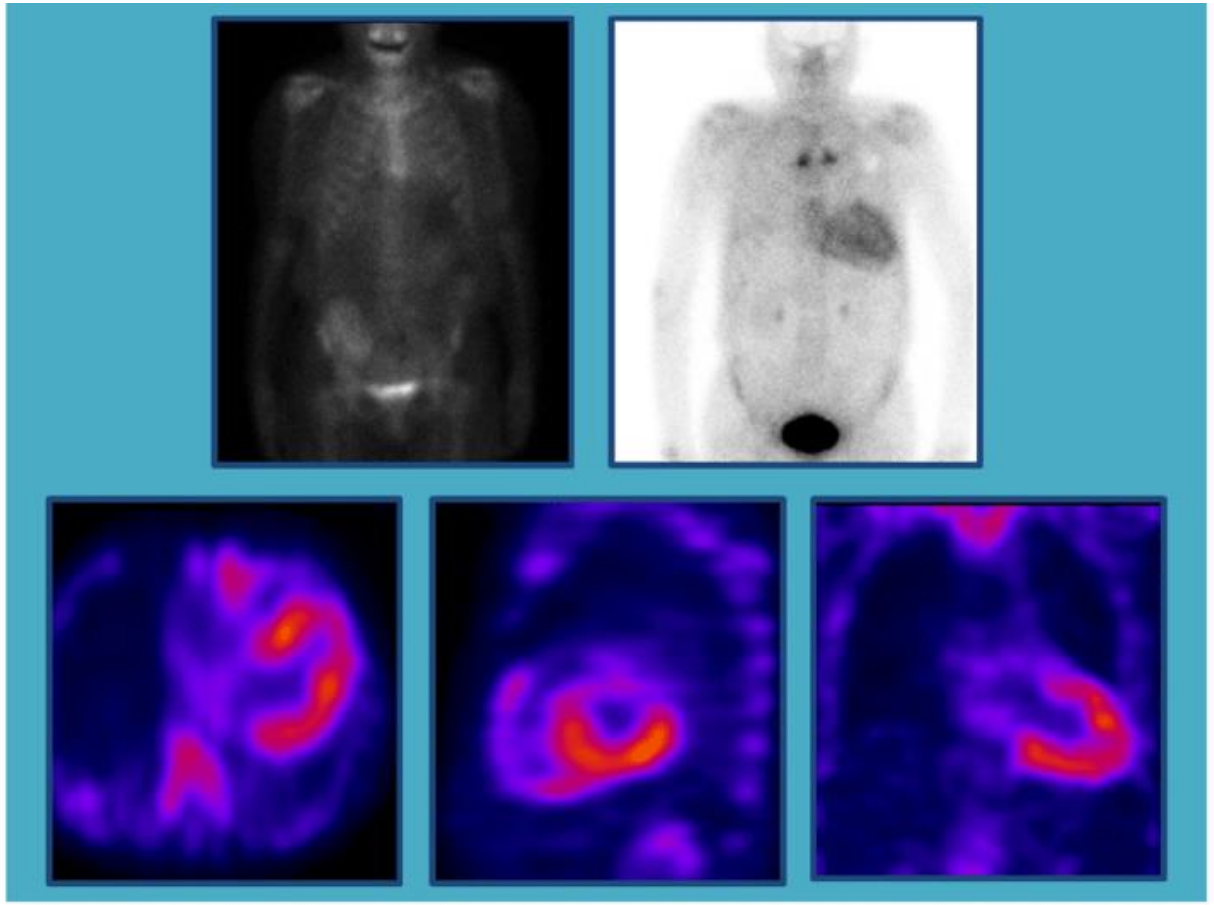
Amyloid on Echo

Mean LV wall thickness>12 mm in absence of HTN
Pts with RV thickening, DD and normal SBP should be considered for EMB

Example from Stanford Health



TC-PYP



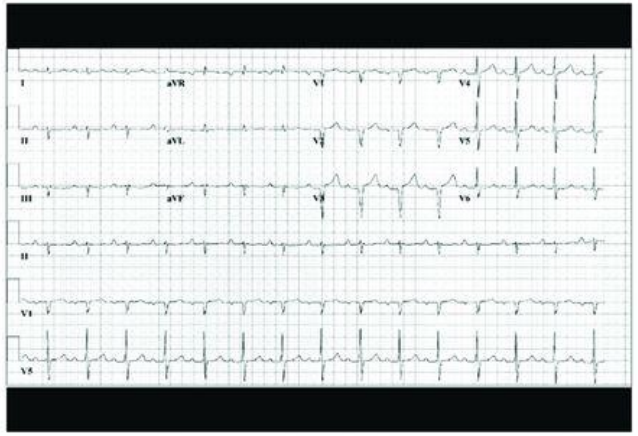
Cardiac amyloidosis pathology.

Donnelly and Hanna, 2017

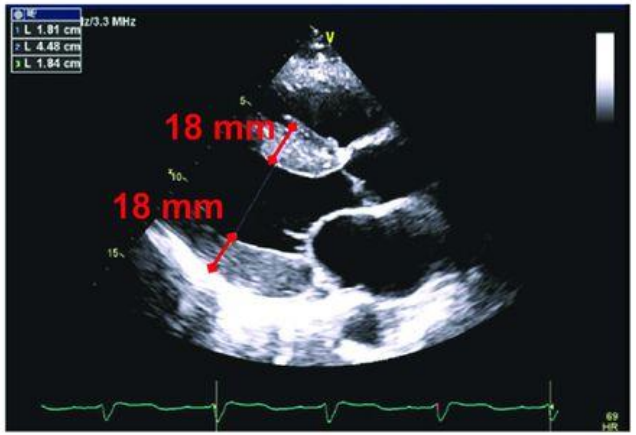
Diagnosis: Imaging

Donnelly and Hanna, 2017

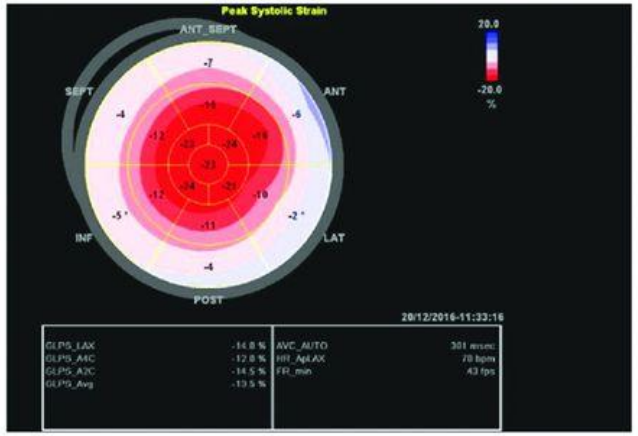
A ECG



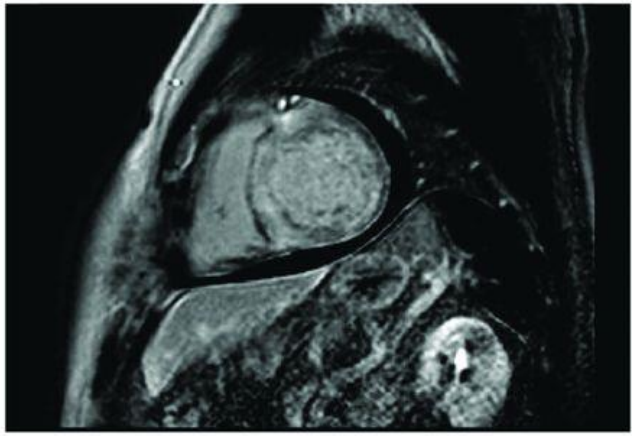
B ECHO



C Strain Rate Imaging



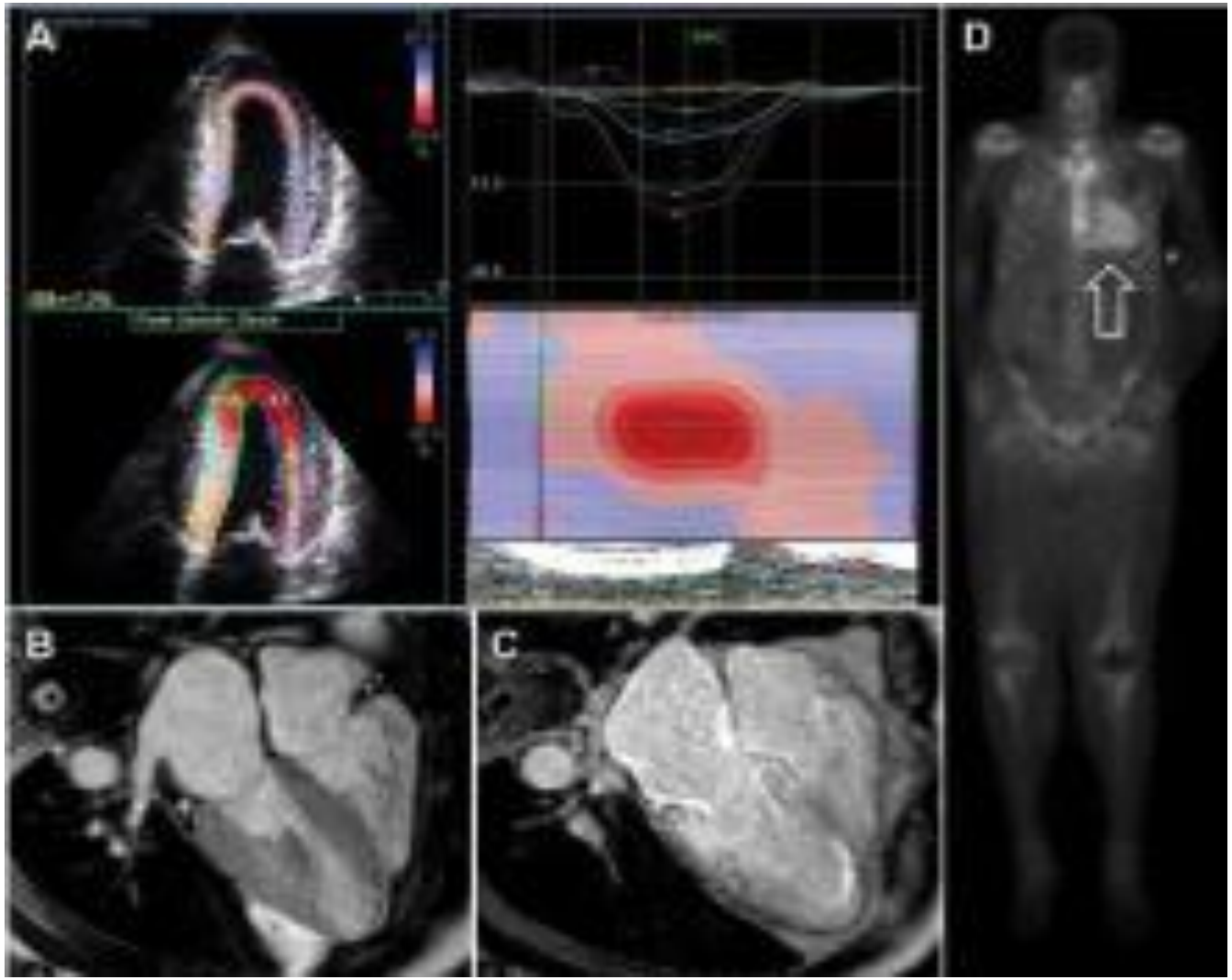
D CMR



CMR, cardiovascular magnetic resonance imaging; ECG, electrocardiography; ECHO, echocardiography.

Noninvasive imaging:

- Longitudinal strain imaging echo
- CMRI Donnelly and Hanna, 2017
- TCPYP

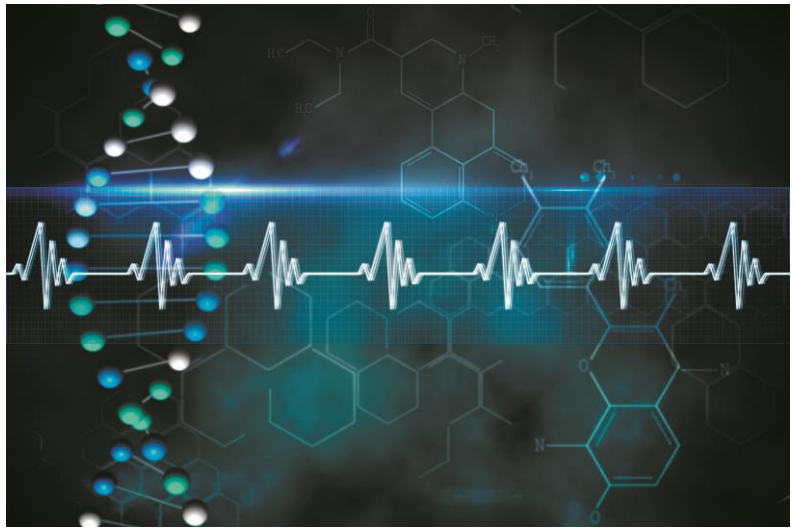


Genetic testing

- HTTR amyloidosis is transmitted in autosomal dominant manner, with variable penetrance
- HTTR typically associated with a single amino acid substitution caused by a mutation in the TTR gene.

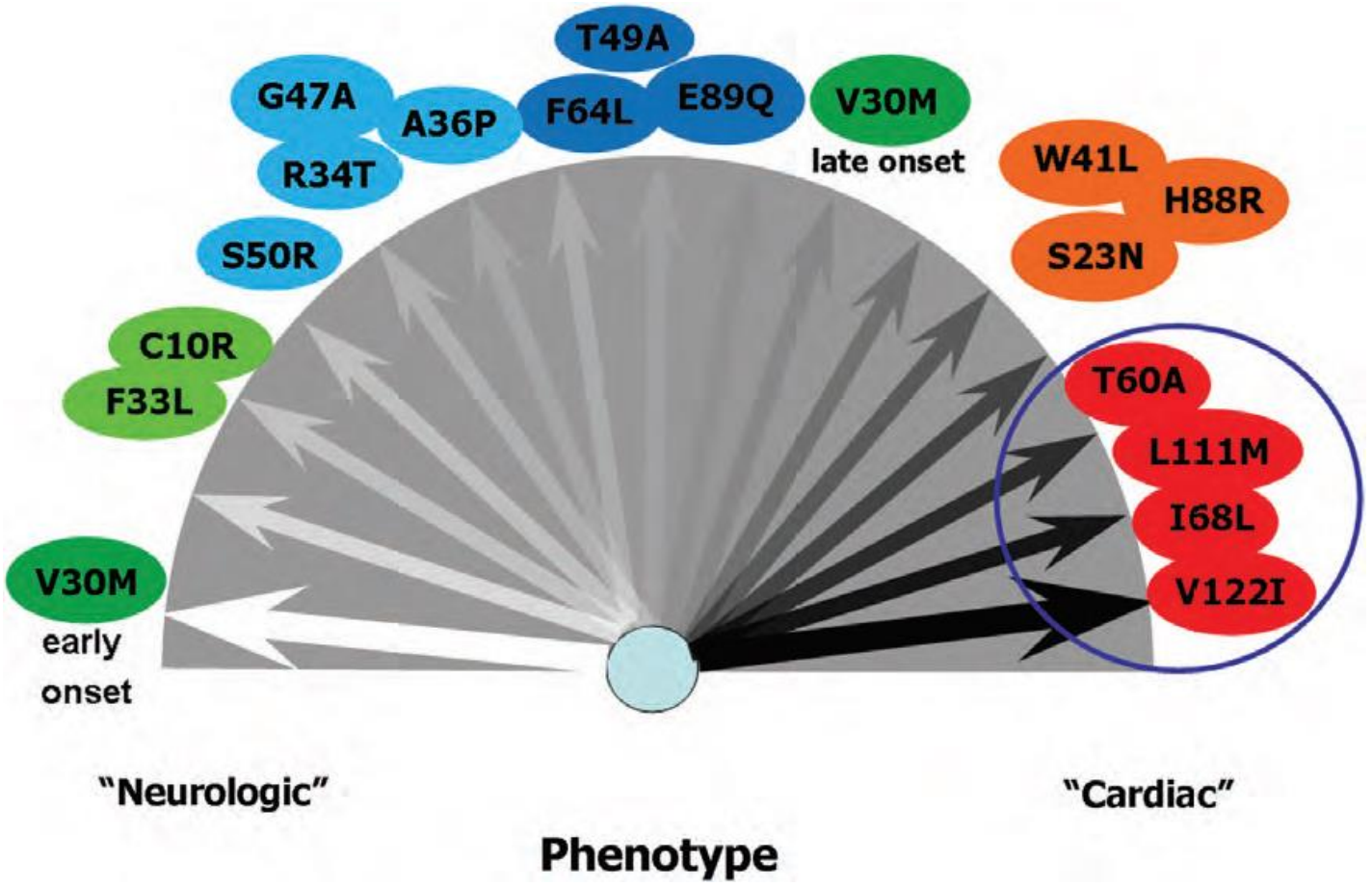
INVITAE

Ambry Genetics®
A Konica Minolta Company

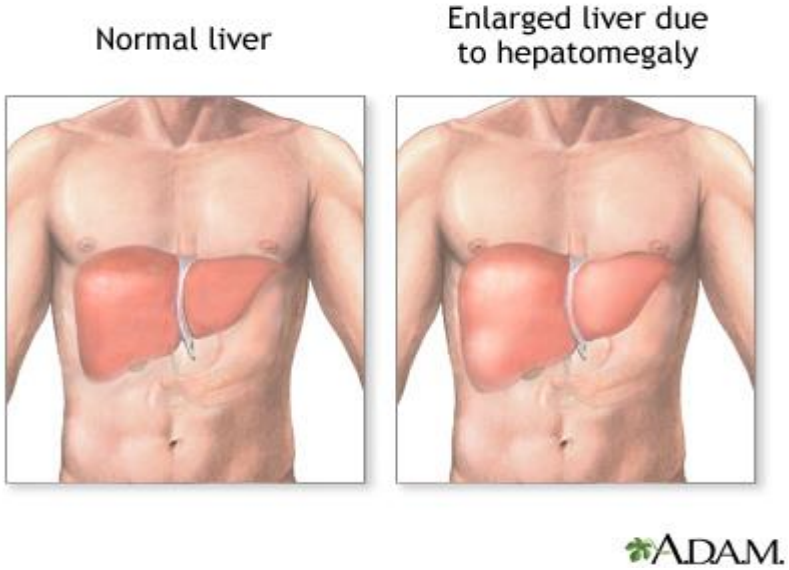


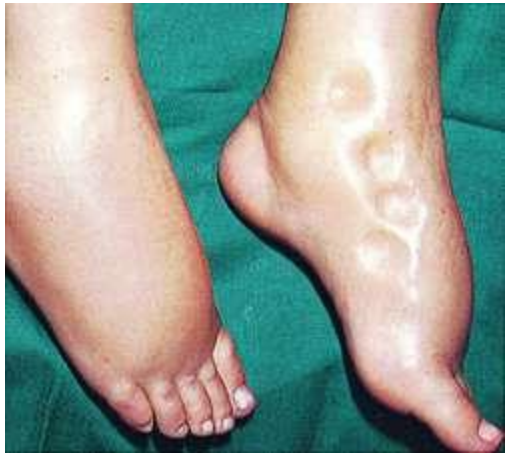
Spectrum of genotype-phenotype correlations in transthyretin amyloidosis.

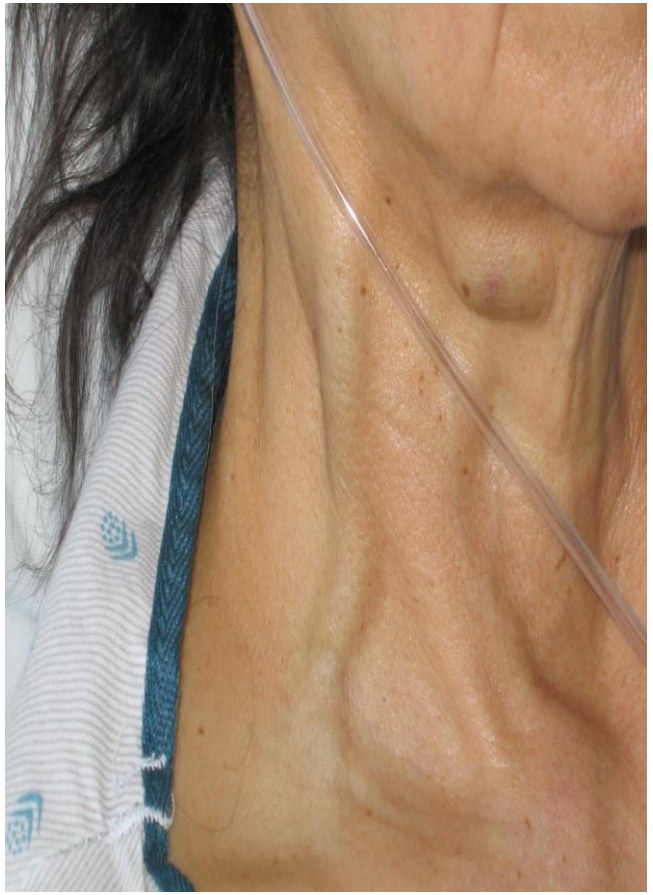
Rapezzi, C et al, 2012 European Heart Journal



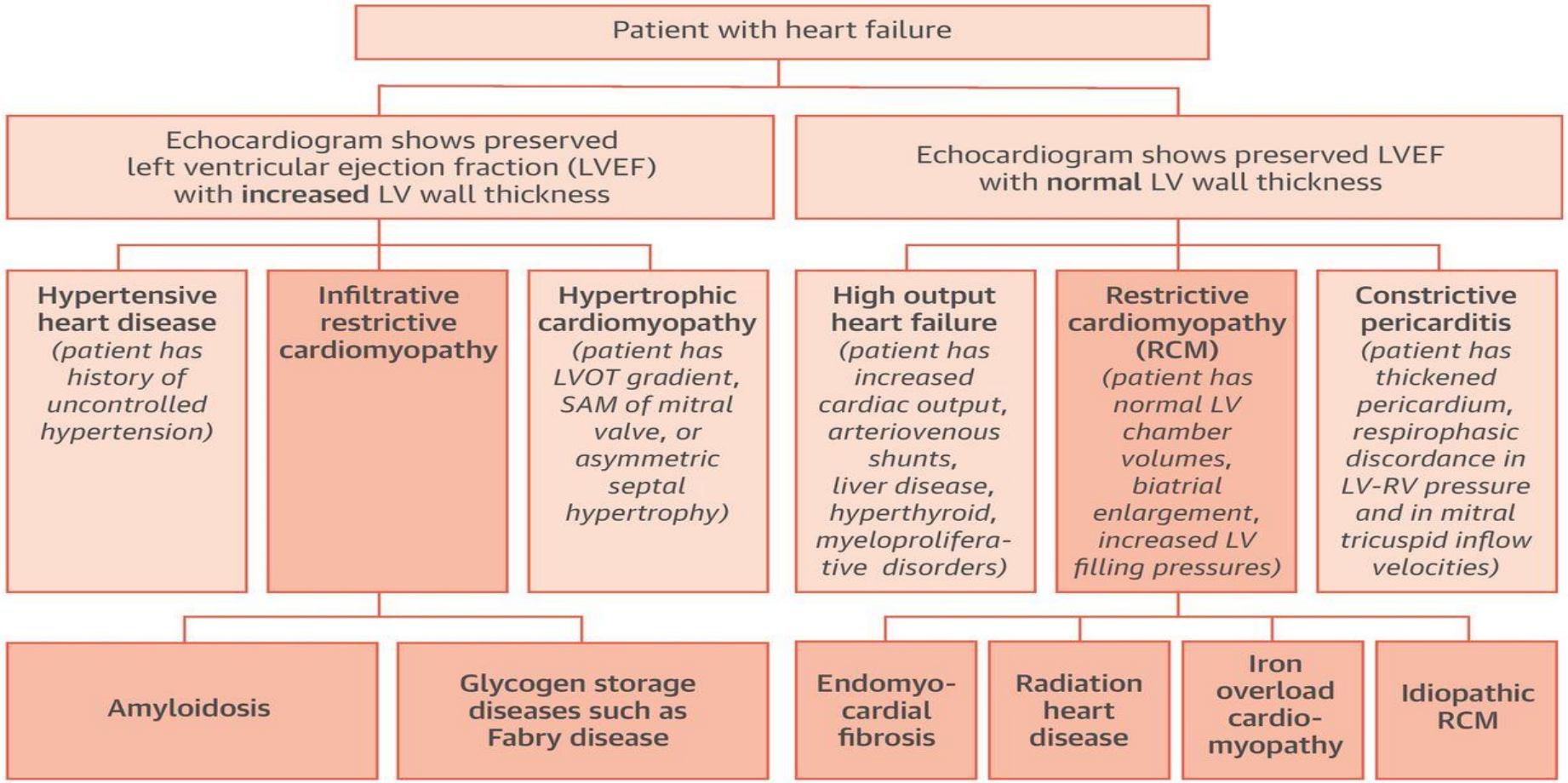
Right sided failure







CENTRAL ILLUSTRATION: Diagnostic Approach to Various Causes of Restrictive Cardiomyopathy When Patients Present With Heart Failure With Preserved Ejection Fraction



Pereira, N.L. et al. J Am Coll Cardiol. 2018;71(10):1130–48.

Types of Cardiac Amyloidosis

Features	AL	HATTR	Wild Type ATTR
Precursor protein	Light chain	Mutant ATTR	ATTR
Average age	55 (30-75)	50 (30-70)	75 (60-100)
Gender, % male	60	80	95
Cardiac involvement	~30	Variable	All
Fat pad biopsy%	>70	<20	<20
Primary referral	Hematology Cardiology Nephrology	Neurology Cardiology	Cardiology
Extra-cardiac manifestations	Nephrotic syndrome Autonomic dysfunction Purpura Carpal tunnel	Autonomic dysfunction Carpal tunnel	Carpal tunnel ?Neuropathy
Median survival, months	13 (4-6 with HF)	70	75

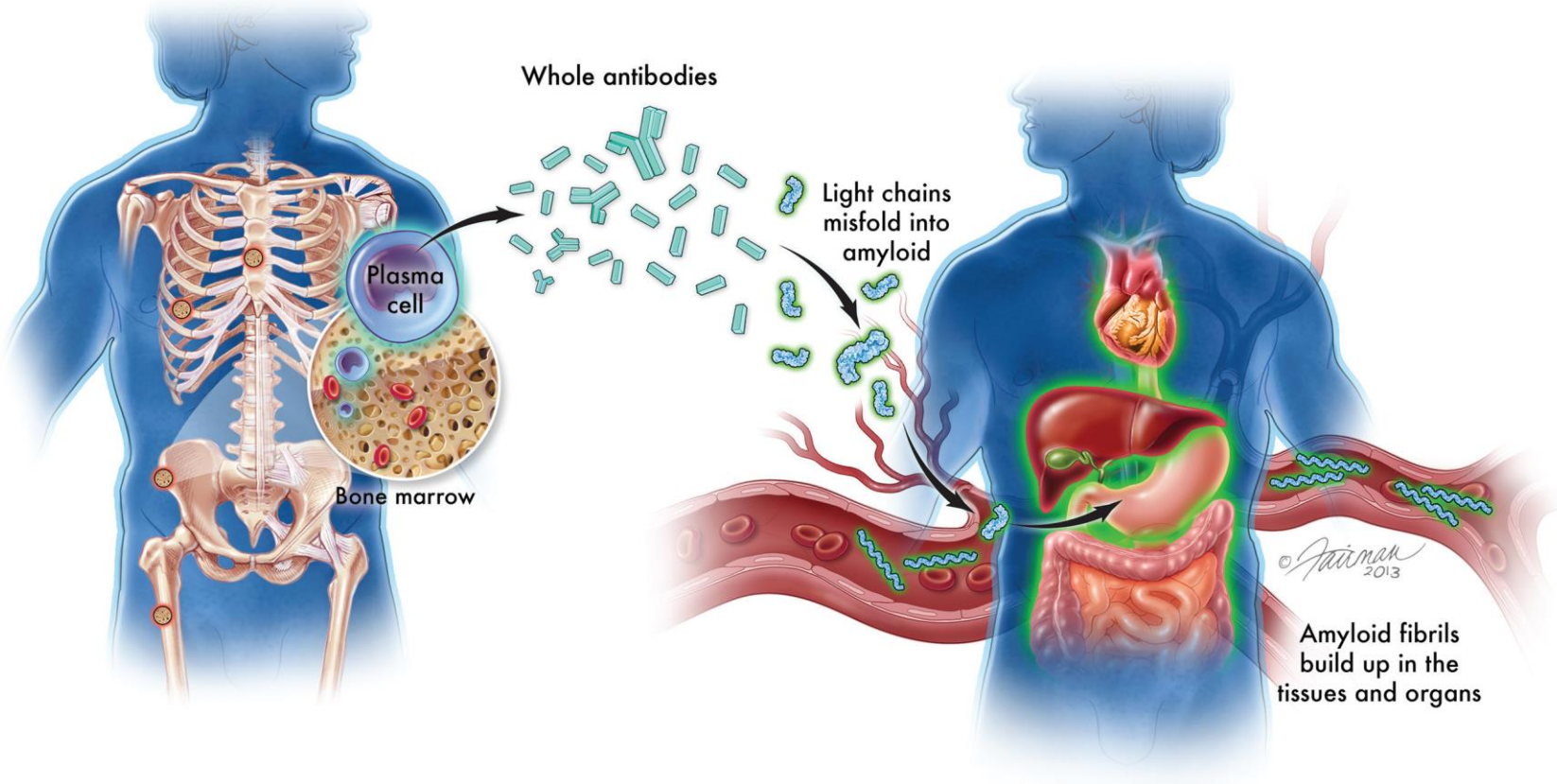
Case Study #1

- 53 y.o female admitted with fluid retention and lethargy
- Admitting labs
  - Na 116
  - K 1.9
  - Creat 0.70
  - Albumin 1.9
  - BNP 1140
  - Had been on Lasix and metolazone for peripheral edema
  - PCP had been working her up for MS

Case Study #1

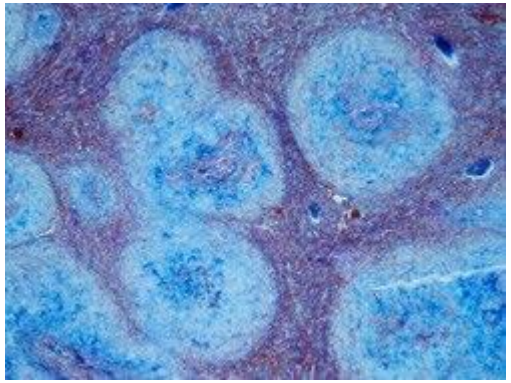
- Kappa 0.86 (normal 0.33-1.94)
- Lambda 29.17 (normal 0.57-2.6)
- FLC ratio 0.03 (normal 0.26-1.65)
- 3+ proteinuria
- Urine electrophoresis showed M spike
- CMRI: Failure to null the myocardium c/w with AL cardiac amyloidosis.
- Renal biopsy positive for AL Amyloidosis
- Sent referral for oncology
- Treated with CyBorD followed by Velcade/Dex, sCR
- Stem cell transplant

In AL Amyloidosis plasma cells in the bone marrow produce too many “free light chain antibodies”



AL Amyloidosis

- Systemic disease affecting the heart ,kidneys, GI and nervous systems. “AL is a more aggressive disease than ATTR with a median untreated survival of less than 6 months in patients who present with heart failure (Donnely, J and Hanna, M),
- A clonal plasma cell disorder, treated with chemotherapy to eradicate the underlying clone
- Incidence/Prevalence
  - ~2500 cases/year
  - 50% cardiac involvement



AL Amyloidosis

- Plasma cells make antibodies, reside in the bone marrow
- Antibodies: made of up light chains and heavy chains
  - Heavy chain: 5 types determine class of antibody and the antibody's specificity
  - Light chains: 2 types- kappa and lambda determine part of antibody's specificity
  - Development of plasma cell population
    - Plasma cell clones dominate % of bone marrow
    - Plasma cells produce a clonal antibody
    - Plasma cells produce excess mis-folded light chains (amyloid)

MGUS: Monoclonal gammopathy of undetermined significance

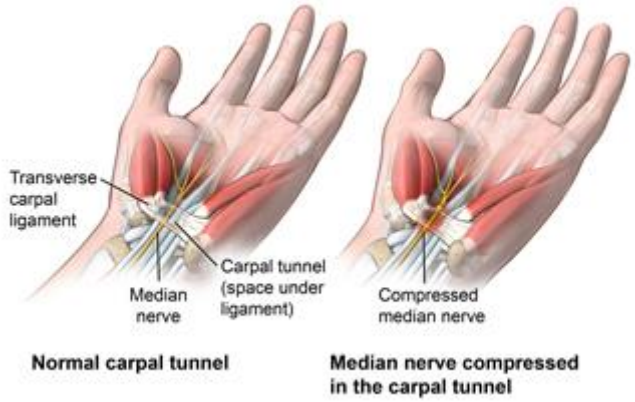
- Pre-malignant clonal plasma cell
- Lymphoproliferative disorder
- 3% of population
- incidental finding with protein electrophoresis as part of an evaluation for peripheral neuropathy, vasculitis, hemolytic anemia, skin rashes, hypercalcemia, or elevated erythrocyte sedimentation rate

Diagnostic challenges

- Low index of suspicion with disease unawareness
- Non-specific symptoms overlap with more common conditions
- Delays between initial symptoms and diagnosis, as well as mis-diagnosis.
- Clinical presentations of hATTR often indistinguishable from acquired monoclonal immunoglobulin light chain (AL amyloidosis) and patients may receive ineffective and potentially harmful treatments
- hATTR with polyneuropathy commonly misdiagnosed as CIDP (chronic inflammatory demyelinating polyneuropathy)

Physical findings

- Fatigue
- Early satiety
- Weight loss
- Malnutrition
- Carpal tunnel syndrome
- Voice changes/hoarseness
- Paresthesia



Therapies

- Daratumumab: monoclonal antibody . Once the antibodies are given, they recruit other parts of the immune system to destroy the targeted antigen, (i.e. amyloid), may bind, neutralize and clear amyloid in AL Amyloidosis.
- Velcade: Protease inhibitors (e.g. Bortezomib)
- Dexamethasone: steroid

Case Study #2

- 77 y.o. AA male, presented in August 2018
- Previous care provided at OSH
- Diagnostic Testing:
  - Cardiac MRI → bi-atrial enlargement as well as left ventricular septal thickening and a reduction in EF, diffuse circumferential subendocardial delayed enhancement of the LV as well
  - ***Genetic testing***: positive for c.424G>A (p.Val142Ile), identified in transthyretin amyloidosis.

Case Study #2

- Echo: EF 25%, grade III DD, IVS 2.43
- RA 13
- RV 77/7
- PAP 75/26
- PAM 44
- PCWP 24
- CO 3.2, CI 1.6
- EMB + Congo red stain with bifringence of deposits

Case Study #2: Treatment and Diagnosis

Cardiogenic Shock:

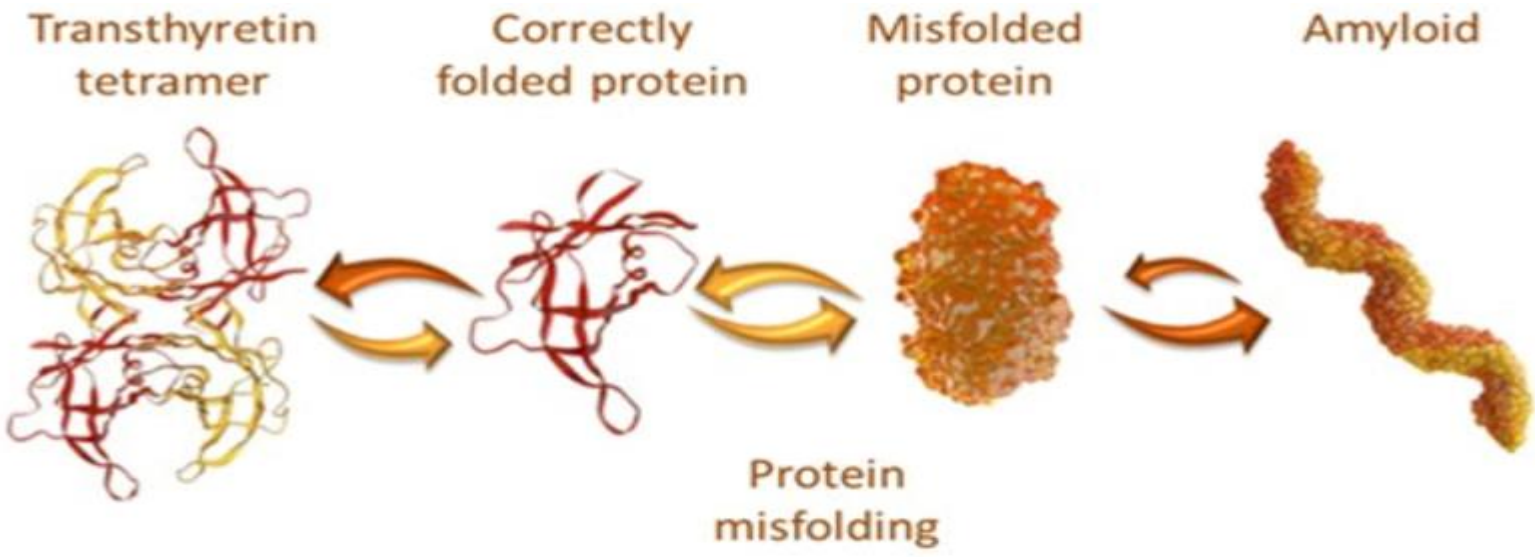
- Low cardiac output
- Milrinone gtt Initiated
- Palliative Care Consult
- Neurology Consult-EMG for documentation of neuropathic symptoms.

Amyloid Treatment:

- Onpattro (Patisiran) infusions every 3 weeks.

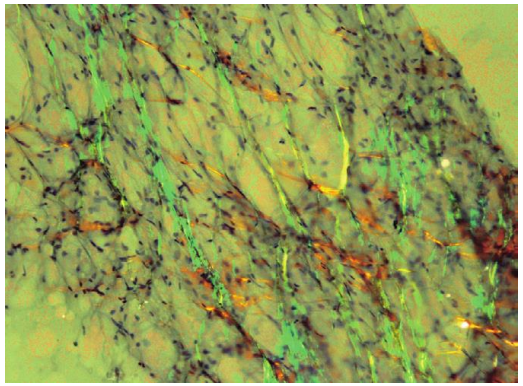
Transthyretin

- A plasma protein mainly produced by the liver that functions as a backup transporter for thyroxine and as a primary transporter of the retinol-binding protein/vitamin A complex.
- *Transthyretin trans*ports *thy*roxine and *retin*ol
- Important in behavior, cognition , nerve regeneration and axonal growth.



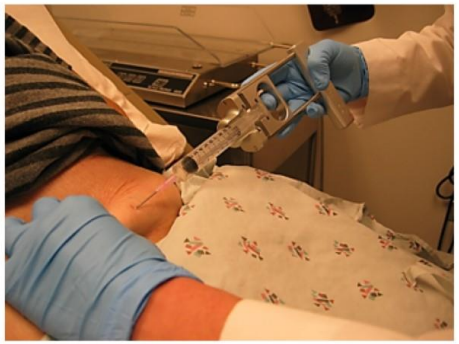
Hereditary Amyloidosis

- Due to destabilization of transthyretin (TTR) protein into monomers or oligomers, which aggregate into amyloid fibrils. These insoluble fibrils accumulate in the myocardium and result in diastolic dysfunction, restrictive cardiomyopathy and eventual congestive heart failure (Castano, A. et al).
- Affinity for Congo red staining with binds to the B-pleated sheets produces apple-green birefringence under light microscopy

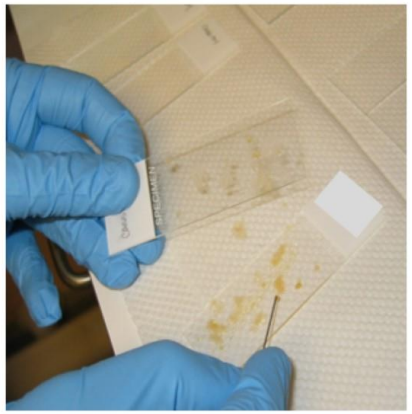


Biopsy techniques

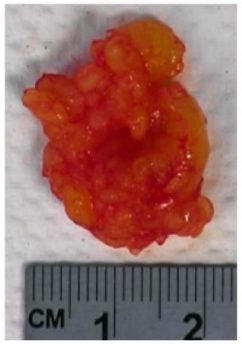
Clinical Suspicion of Amyloidosis



Fine needle aspiration biopsy from site previously locally anesthetized



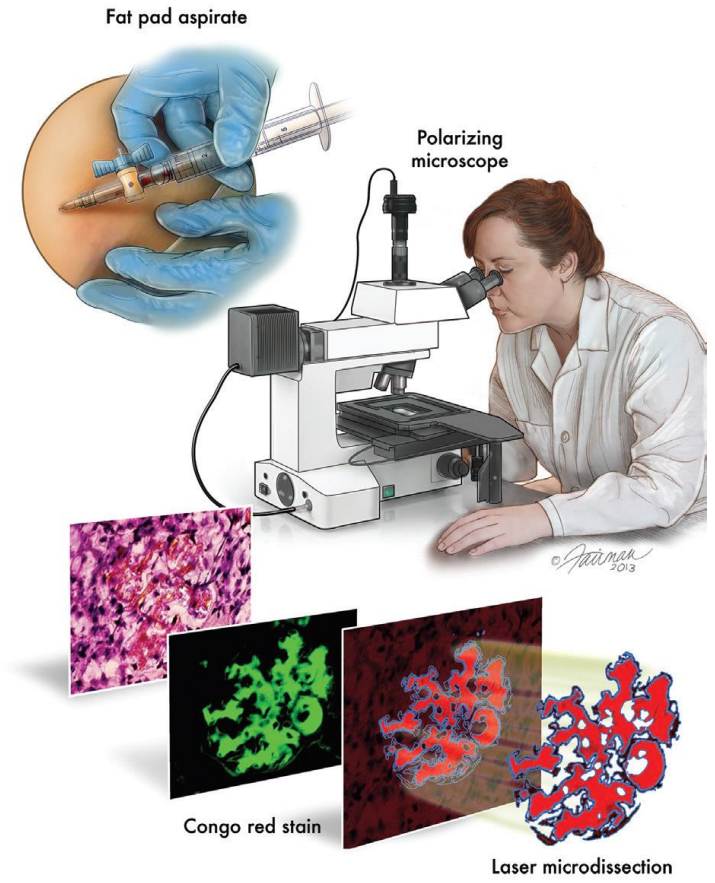
Need small fragments of tissue (not just blood)



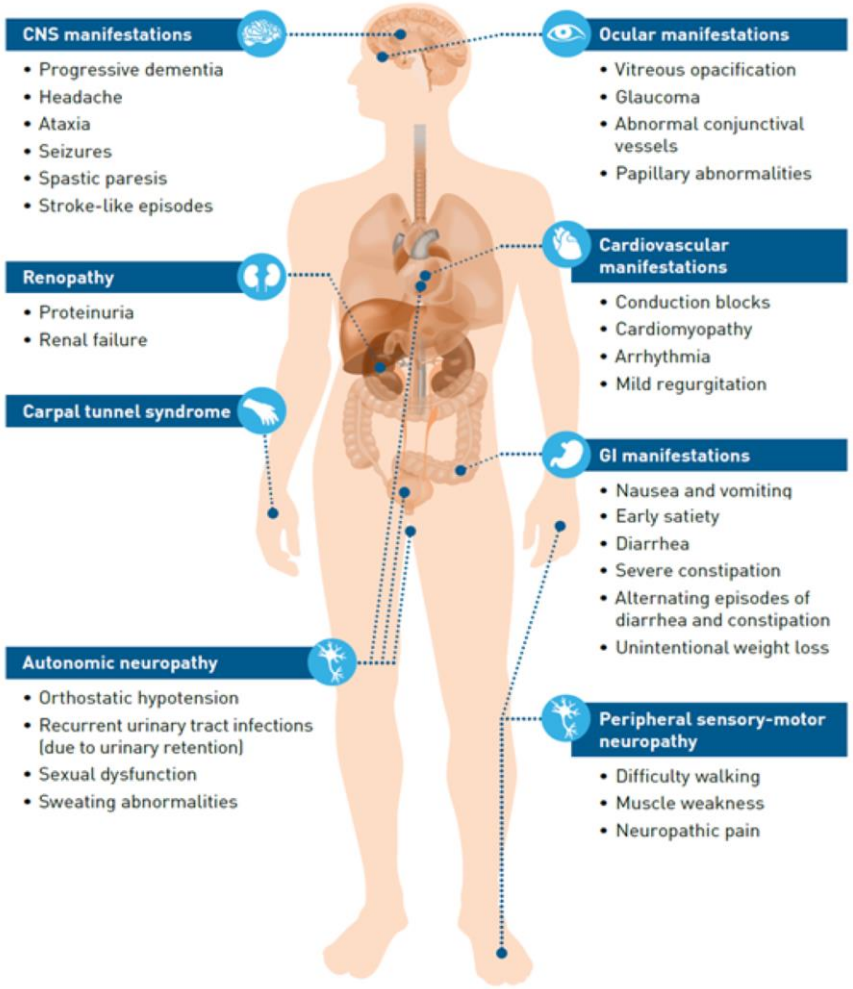
Alternatively a small surgical fat biopsy to secure enough tissue for diagnosis and typing

Images courtesy of Maria M. Picken, MD, PhD.
Picken MM. *Adv Anat Pathol*. 2013;20:424-439.

Gold standard



Systemic manifestations of hATTR amyloidosis

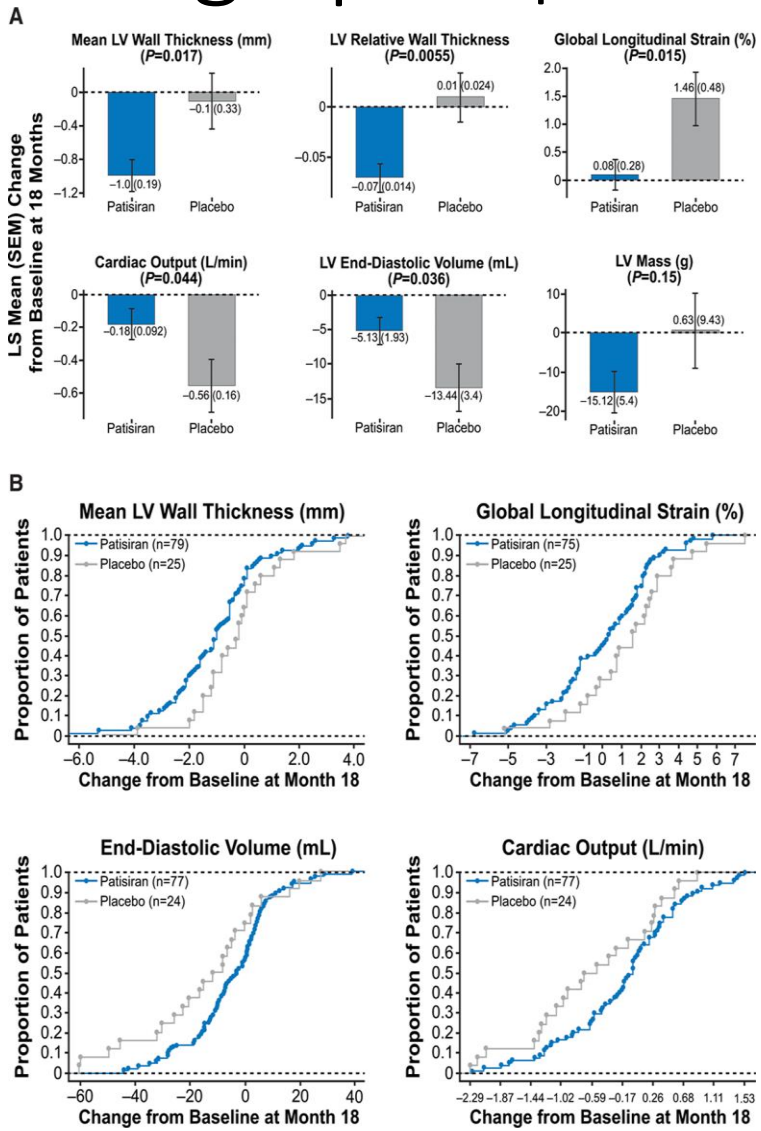


CNS indicates central nervous system; GI, gastrointestinal; hATTR, hereditary transthyretin-mediated amyloidosis. Reprinted with permission from Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Periph Nerv Syst*. 2016;21(1):5-9. doi: 10.1111/jns.12153. © 2015 The Authors. *Journal of the Peripheral Nervous System* published by Wiley Periodicals, Inc. on behalf of Peripheral Nerve Society.

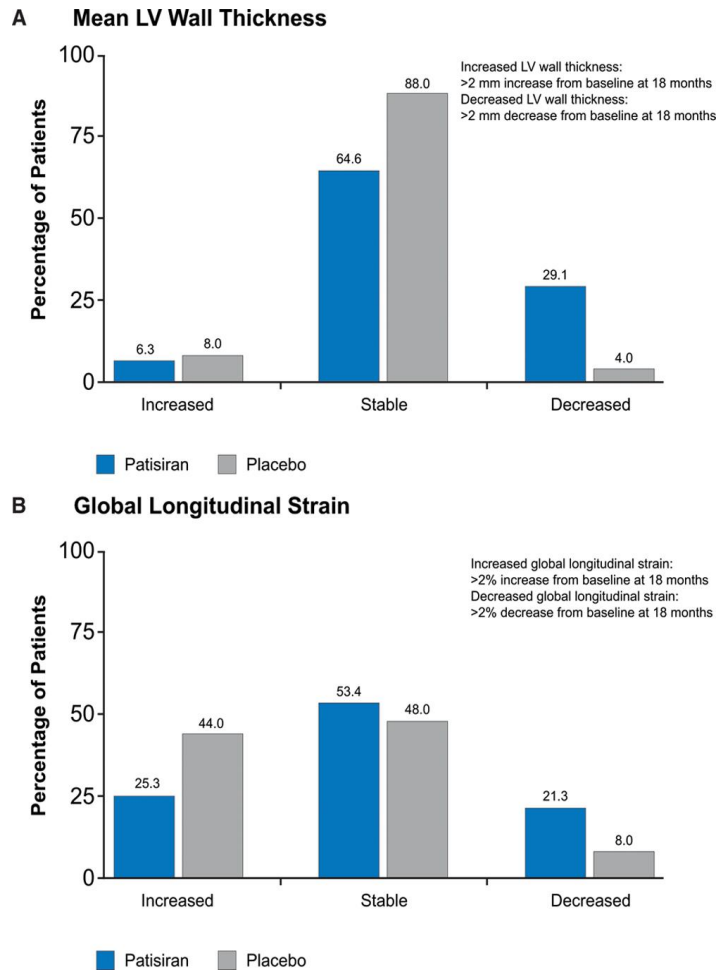
Patisiran (Onpattro)

- Apollo trial: international, randomized, double-blind, placebo controlled phase 3 trial
- 225 patients ranging from 24-83 years old (median age 62 years); 74% male and 26% female
- 39 different TTR mutations; 53% of patients had the V30 M mutation
- 99% of eligible patients who completed the 18 month study elected to enter into open-label extension
- Median serum TTR reduction after 18 months was 81%
- FDA approval August 10, 2018

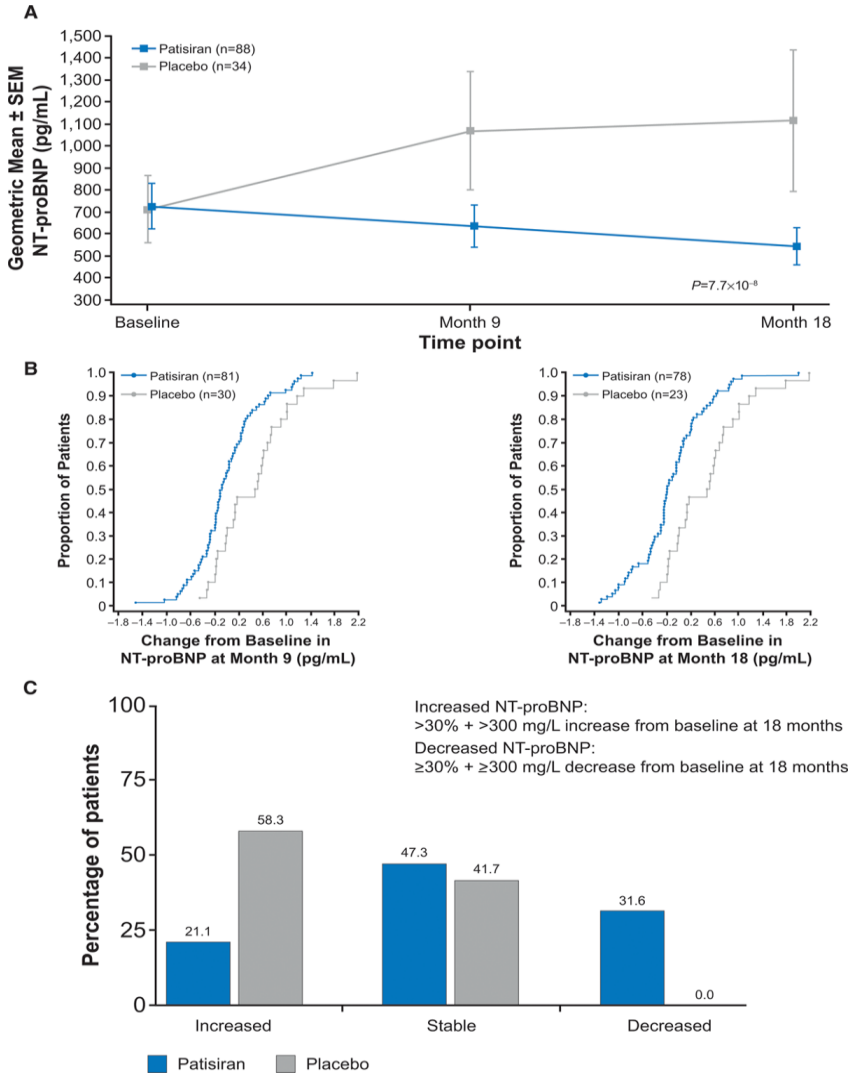
Change in echocardiographic parameters at 18 mo.



LV wall thickness and global longitudinal strain



Change in NT-pro BNP

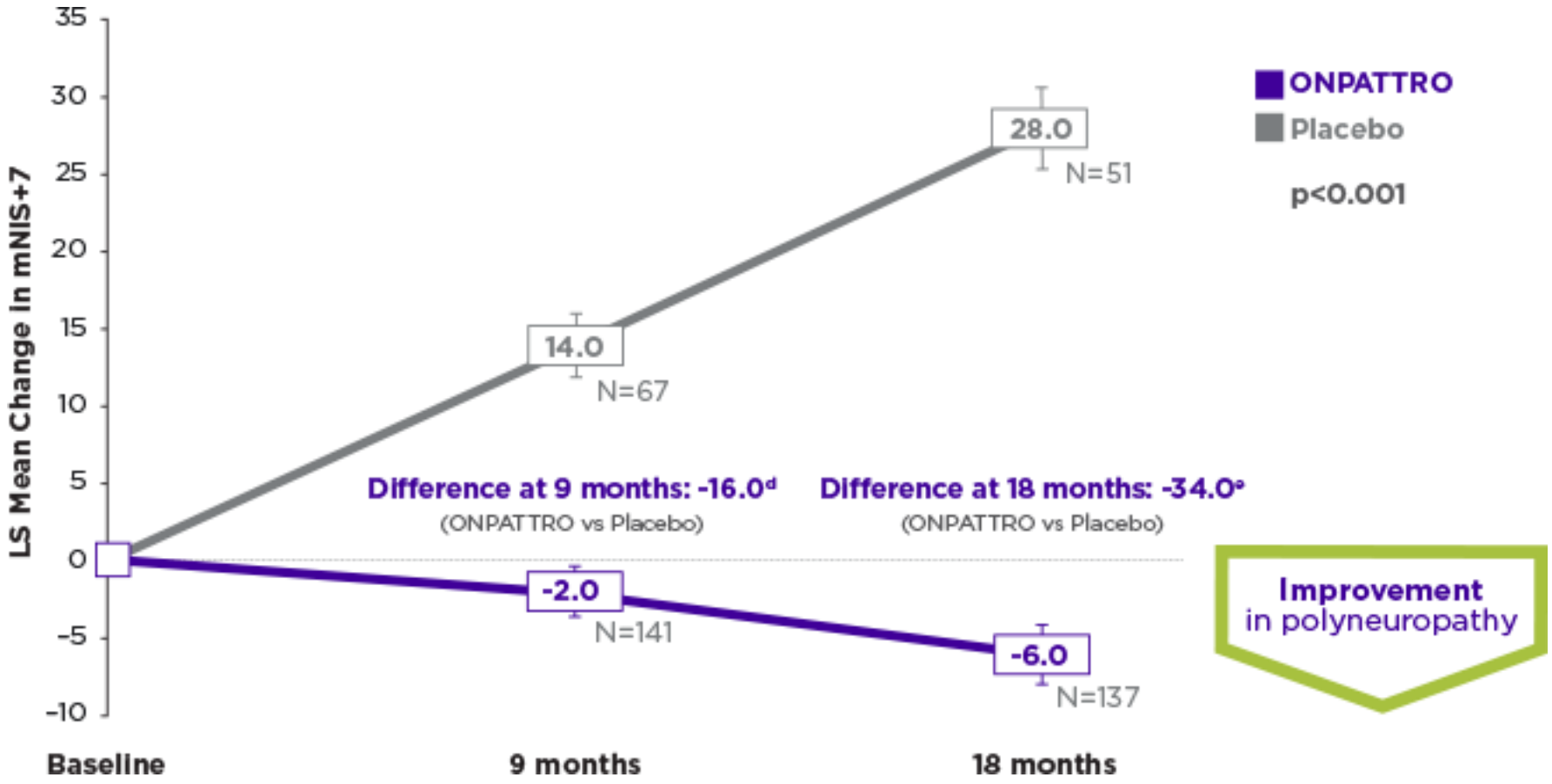


Patisiran Infusion Protocol

- Pre-medication one hour prior to infusion with
  - 500 mg acetaminophen
  - 10 mg dexamethasone IV
  - 50 mg diphenhydramine IV
  - IV Pepcid 20 mg

  - Infusion
  - 0.3 mg/kg in 200 ml NS infused for 80 minutes at a rate of 1 ml/min for 15 minutes, then 3 ml/min until done
  - Either Dr. Shah or myself are on premise the 1st 2 infusions

Reduction in polyneuropathy symptoms



Adverse reactions from the placebo controlled trial

Adverse reaction	Onpattro N=148	Placebo N=77
Upper respiratory infections	29	21
Infusion related reaction	19	9
Dyspepsia	8	4
Muscle spasms	8	1
Arthralgia	7	0
Erythema	7	3
Bronchitis	7	3
Vertigo	5	1

Inotersen: treatment of hereditary transthyretin amyloidosis

- Decreases hepatic production
- Neuro-TTR trial
- 112 in inotersen arm
- 60 in placebo trial
- Weekly 300 mg SQ administration
- Primary outcome was less progression in neuropathy in the inotersen group
- SE: 3% had severe thrombocytopenia, inc 1 death d/r ICH. Needs weekly platelet counts
- 3%Glomerulonephritis

Case study # 3 74 y.o female

- Echo EF 70 %
- LVIDD 2.73 cm (Range: 3.8 - 5.2)LVIDS 1.75 cm (Range: 2.2 - 3.5)
- IVS 1.41 cm (Range: 0.6 - 0.9)
- LV PW 1.89 cm (Range: 0.6 - 0.9)
- TCPYP Two hour heart/contralateral lung (H/CL) ratio: 2.07 . The quantitative heart to contralateral lung ratio is markedly elevated and highly suggestive of ATTR cardiac amyloidosis.
- Genetic testing: no pathologic variant found

Any other testing?

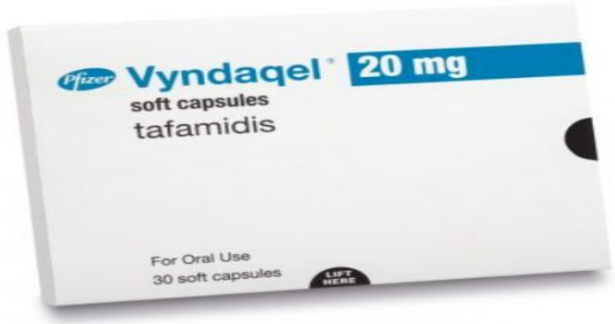
- Kappa 1.3
- Lambda 1.39
- FLC ratio .94

Wild type Amyloidosis

- Precursor protein ATTR
- Average age at presentation 75
- 95% male
- Primary cardiac involvement
- Non-hereditary

Tafadamis

- **U.S. FDA Approves VYNDAQEL® and VYNDAMAX™ for Use in Patients with Transthyretin Amyloid Cardiomyopathy, a Rare and Fatal Disease-May 6, 2019**
  - **Small molecule drug that promotes the maintenance of TTR protein in its normal soluble nonamyloid conformation**
  -



Tafamidis

- ATTR-ACT study- phase 2 open label trial in 31 patients
- Binds to transthyretin, preventing tetramer dissociation of tetramers into monomers and amyloidogenesis
- More than 120 pathogenic mutations that result in variable phenotypic presentation.
- 548 patients were screened, 441 patients underwent randomization, 264 patients were pooled to tafamidis, 117 had placebo. 173 patients completed study in tafamidis, 85 completed placebo arm
- 13% prevalence in patients with HFpEF
- 5% of hypertrophic cardiomyopathy patients (Mauer et al 2019)

Tafamidis

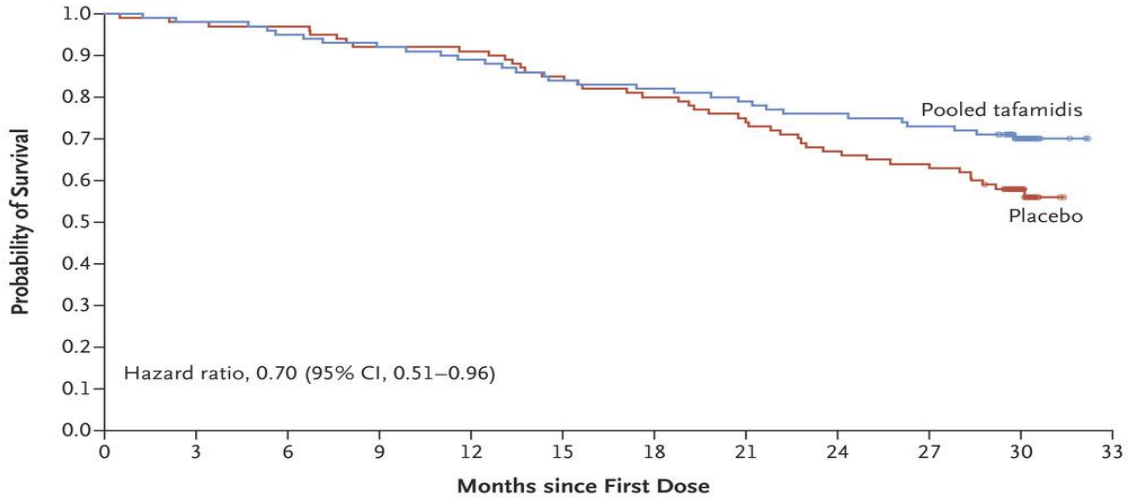
- Previously studied in neuropathy patients
- Patients treated with tafamidis for 30 months had 55.9% greater preservation of neurologic function as measured by the NISLL than patients in whom tafamidis was initiated later (Coelho et al, 2013)
- 30% reduction in mortality vs. placebo (Mauer et al)

Tafamidis results

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



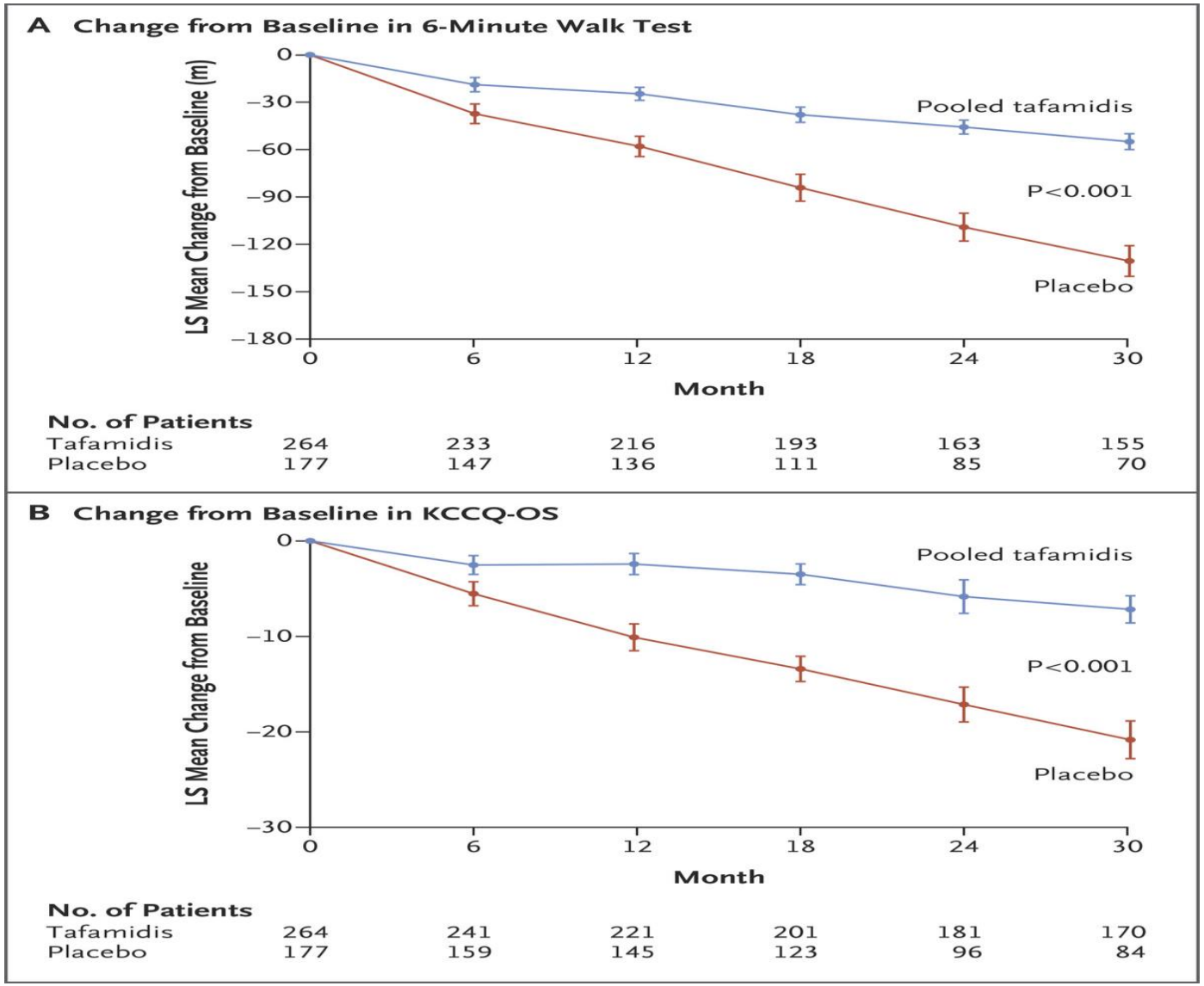
No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Tafamidis results



General Amyloid Treatment

- Diuretics (both loop and aldosterone antagonists)
- Avoiding ACE, ARB, BB, CCB and digoxin
- AICD: most cases of SCD are due to EMD, little role in AICD
- Pacing: ?Biventricular to prevent further decrease in SV
- Non-cardiac medications: managing diarrhea/constipation

General tips

- Diuretics: may need torsemide or bumex
- Avoidance of BB, ACEI
- Digoxin: at risk of life-threatening arrhythmias, even at therapeutic serum levels because digoxin binds avidly to amyloid fibrils
- Anticoagulation: Patients with severe amyloid infiltration of atria have impaired contractility, leading to blood stasis and thrombosis even if in sinus rhythm .

Orthostatic hypotension

- Alpha-adrenergics: may need midodrine or northera to help avoid orthostasis
- Dosing: am dose before rising, noon dose and early afternoon dose to avoid supine hypertension.
- May need compression stockings/abdominal binder
- Instructing to avoid constipation (risk of Valsalva), alcohol, hot showers/hot weather.
- Low sodium, high protein diet

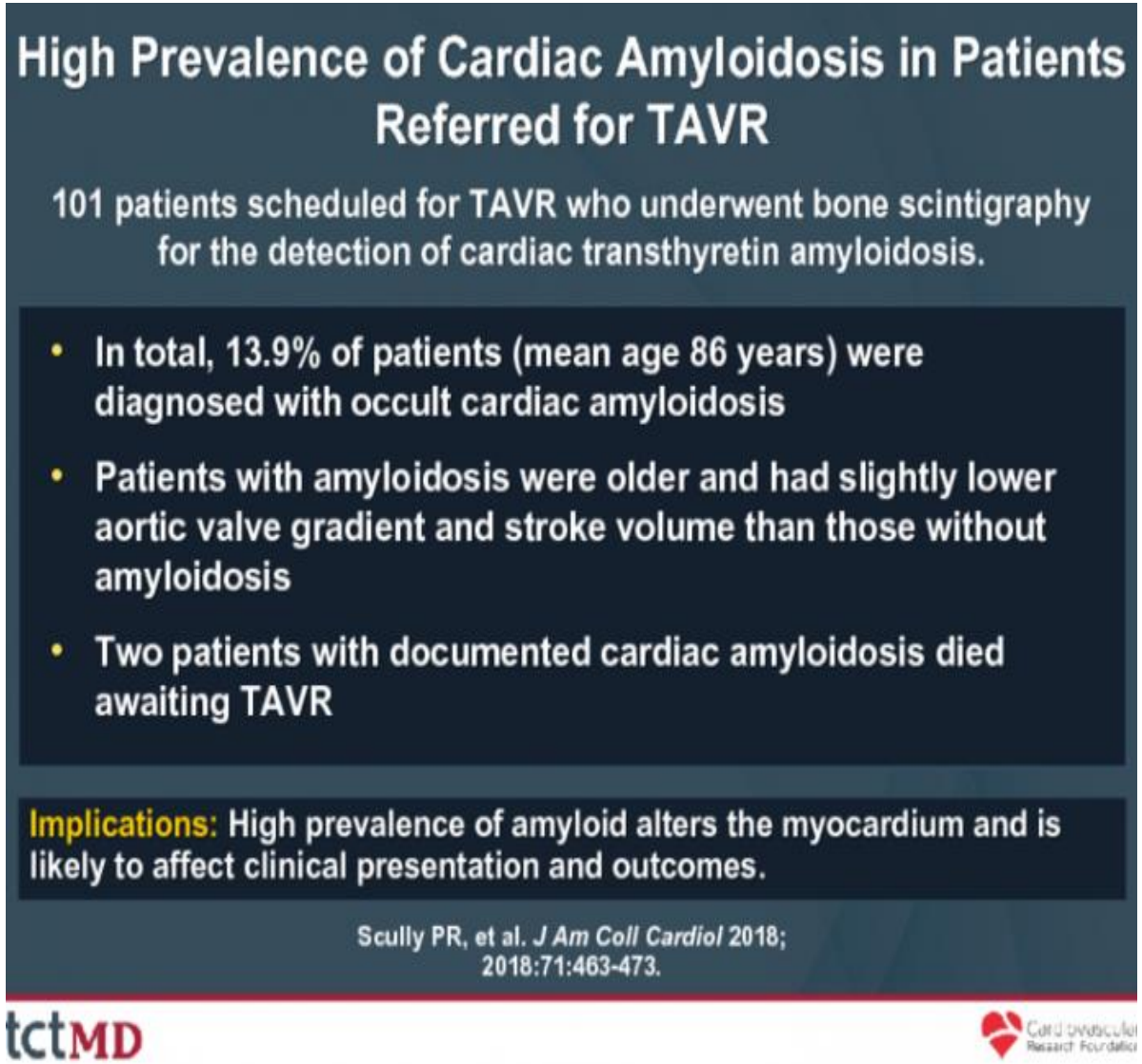
KCCQ

- 23 item patient reported measure that quantifies physical function symptoms (frequency, severity and stability), social function, self efficacy and QOL
- Scale of 0-100, with higher scores reflecting better health status
- Mean difference of 5 points on the overall summary score is considered a clinically significant
- A decline of 10 points is considered prognostically significant.

Ongoing challenges

- Access to and coordination of care
- Early implementation of appropriate treatment is imperative!
- Treatment has gone from nothing to liver transplant and disease modifying therapy including
  - TTR stabilizers
  - SiRNA
  - ASO

TAVR


High Prevalence of Cardiac Amyloidosis in Patients Referred for TAVR
101 patients scheduled for TAVR who underwent bone scintigraphy for the detection of cardiac transthyretin amyloidosis.
In total, 13.9% of patients (mean age 86 years) were diagnosed with occult cardiac amyloidosis
Patients with amyloidosis were older and had slightly lower aortic valve gradient and stroke volume than those without amyloidosis
Two patients with documented cardiac amyloidosis died awaiting TAVR
Implications: High prevalence of amyloid alters the myocardium and is likely to affect clinical presentation and outcomes.
Scully PR, et al. J Am Coll Cardiol 2018; 2018:71:463-473.
tctMD

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