TTR Amyloidosis

Daniel J Lenihan, MD
Professor, Division of Cardiovascular Medicine
Director, Cardio-Oncology Center of Excellence
Washington University in St Louis

Cardio Oncology

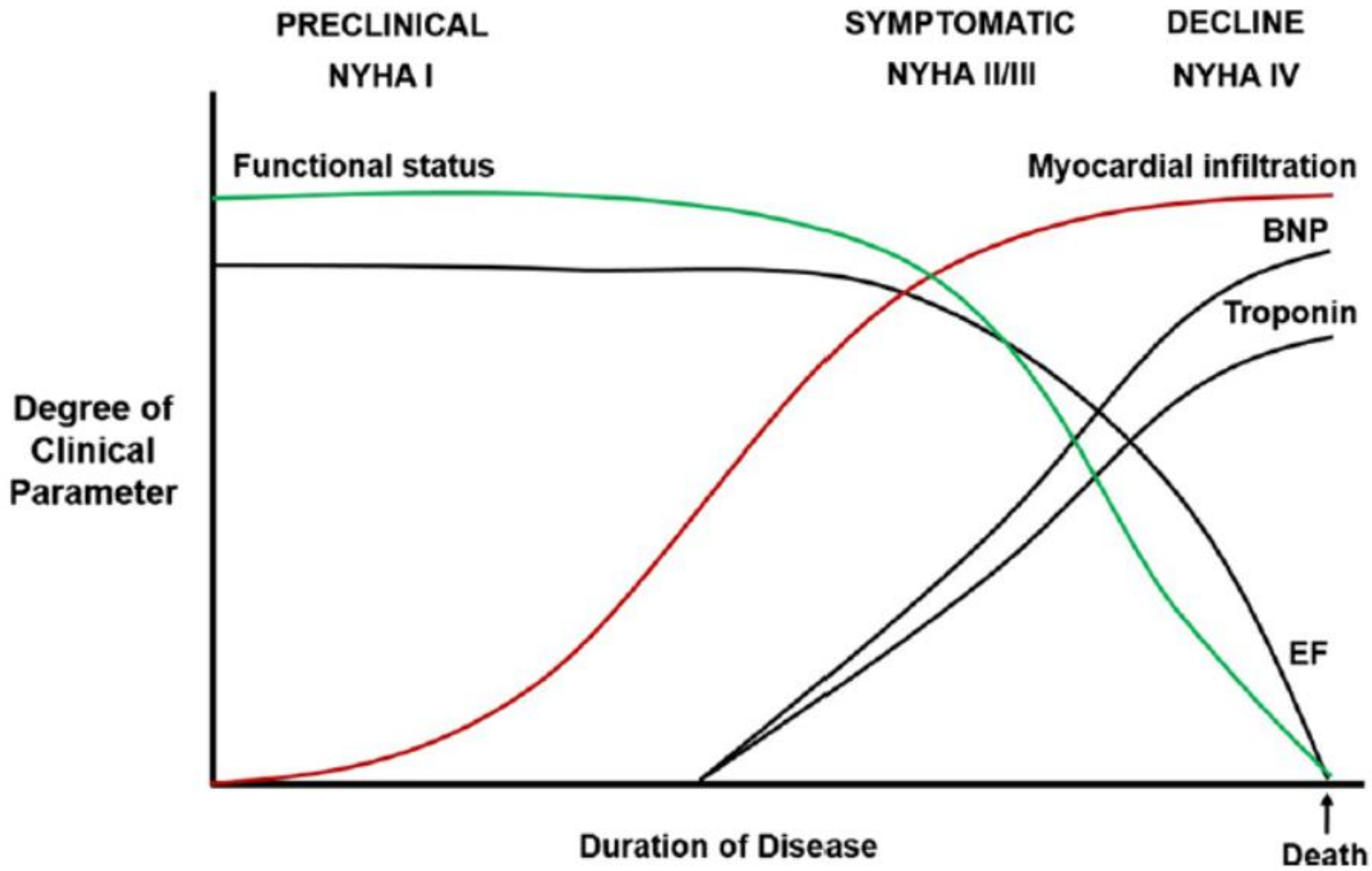
Heart & Vascular Center

BARNES-JEWISH Hospital BJC HealthCare | Washington University in St. Louis Physicians

NATIONAL LEADERS IN MEDICINE

AMERICAN COLLEGE of CARDIOLOGY

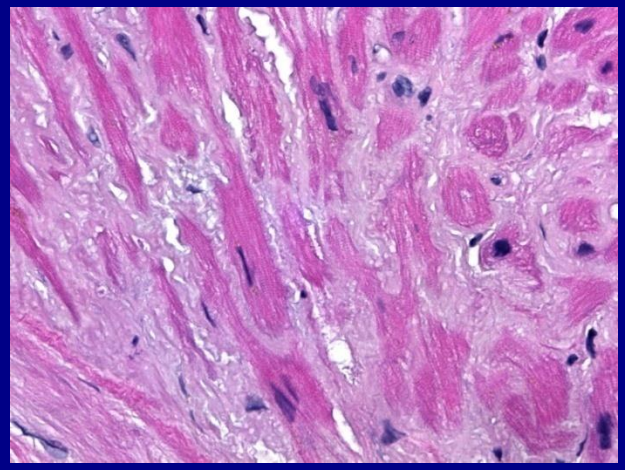
Apparent Natural History of Cardiac Amyloidosis



Heart Fail Rev (2015) 20:163–178

Cardiac Manifestations

- Heart failure
  - Diastolic dysfunction (impaired relaxation) > Systolic dysfunction (impaired contraction)
- Electrophysiologic
  - Heart block
  - Tachyarrhythmias
  - Low voltages on EKG (*)
- Imaging/Laboratory
  - Left ventricular “hypertrophy”
  - Elevated troponin/BNP/NTproBNP



Key to Screening for Cardiac Amyloid Understand *Amyloid Types*

- >30 proteins can form amyloid
- Only a few deposit in the heart

Only two types to know:

1. AL – "primary systemic" – bone marrow
2. Transthyretin* - liver
   a) Familial – mutation – less stable protein
   b) Wild type – (formerly "senile") - unknown

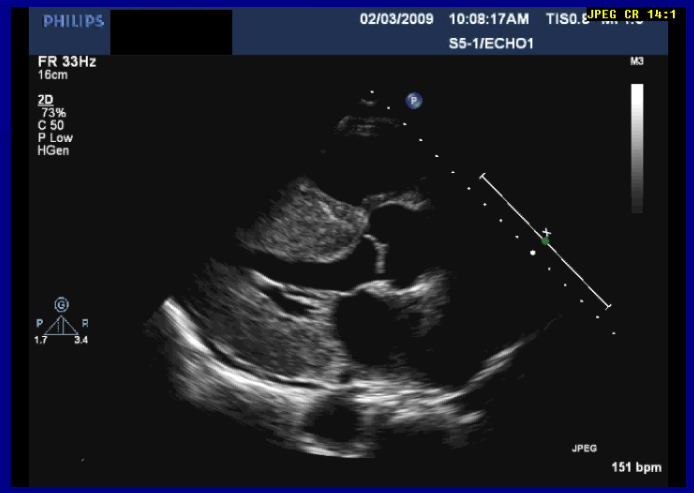
Transports Thyroxine and Retinol – "TTR"

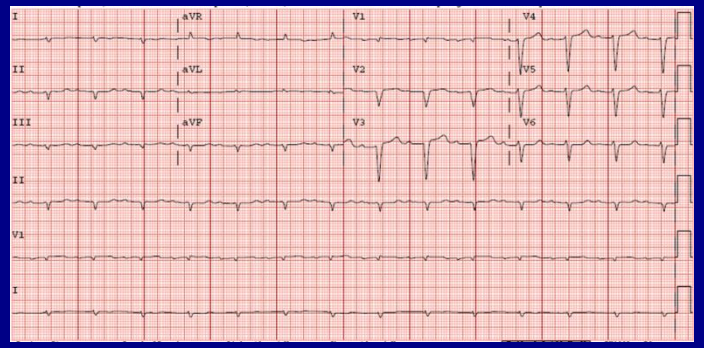
MAYO CLINIC

Cardiac Amyloid: Diagnosis by Imaging

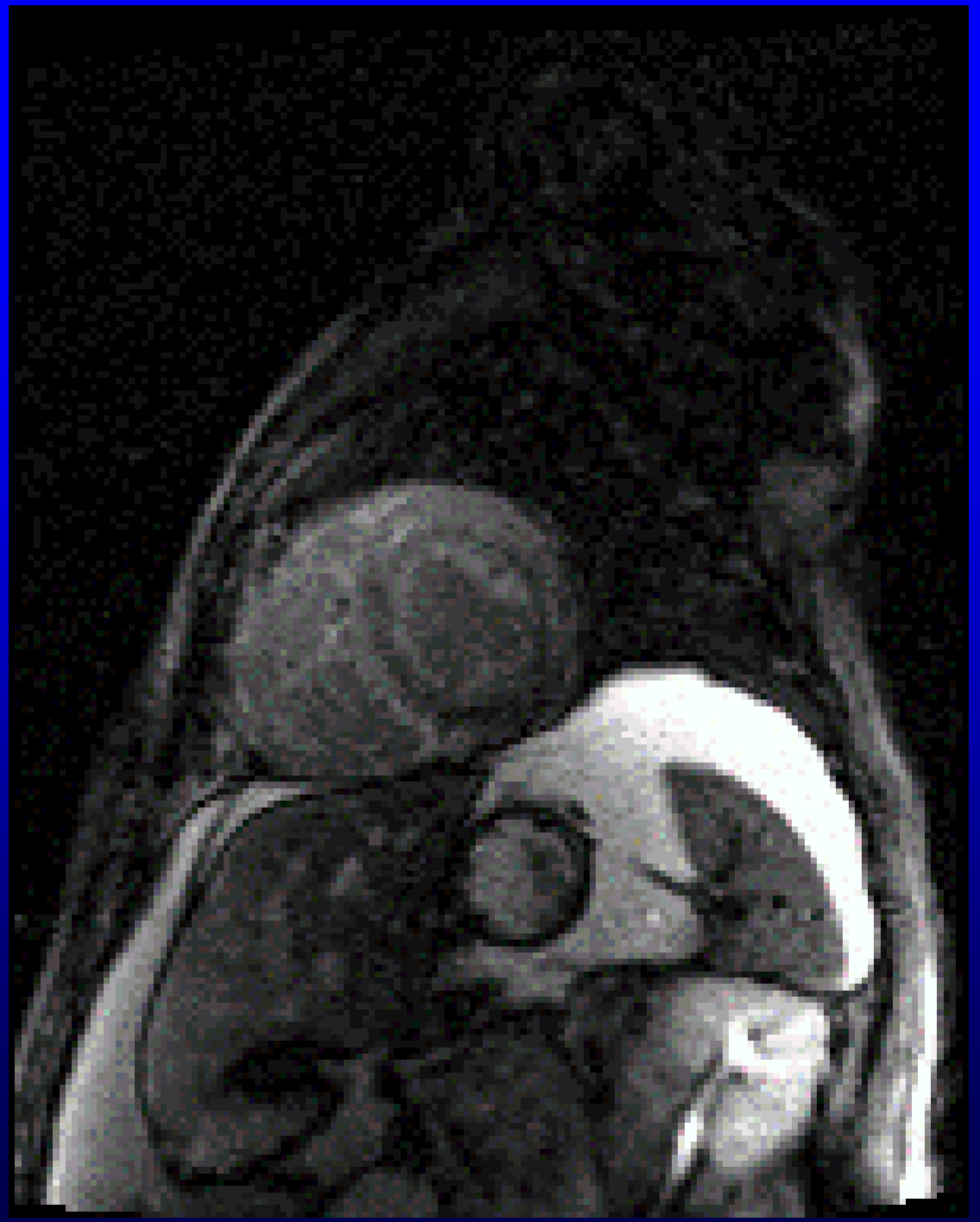
- Increased ventricular thickness
  - RV thickened as well

- Combination of increased ventricular mass & low voltages → quite specific for amyloid.

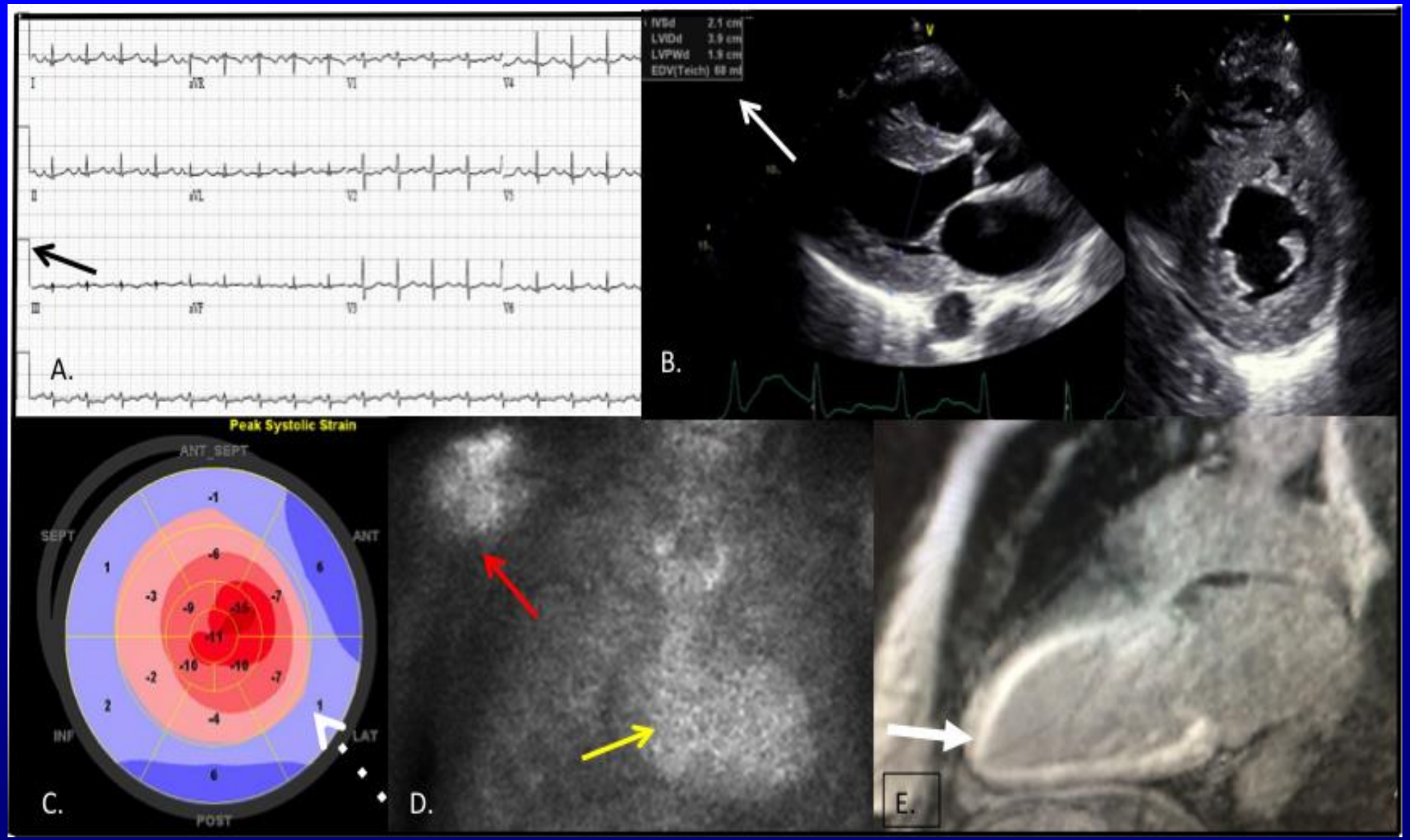




MRI

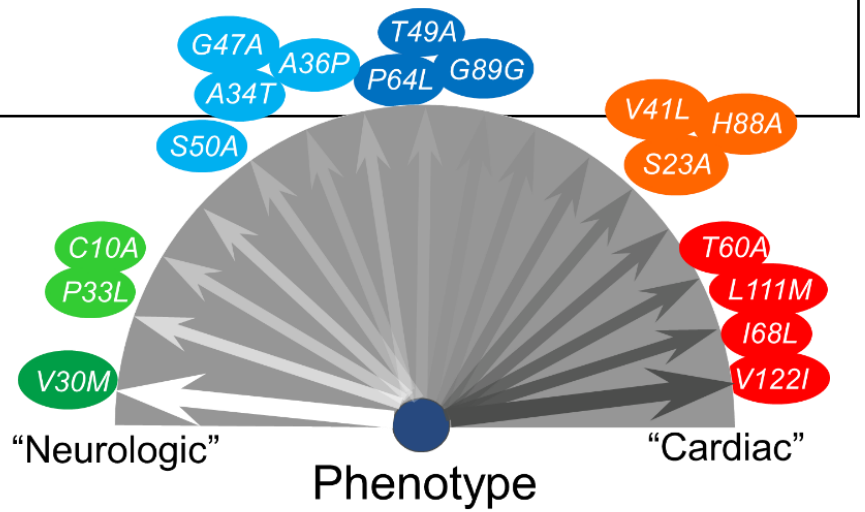


Typical Imaging Characteristics in Amyloidosis



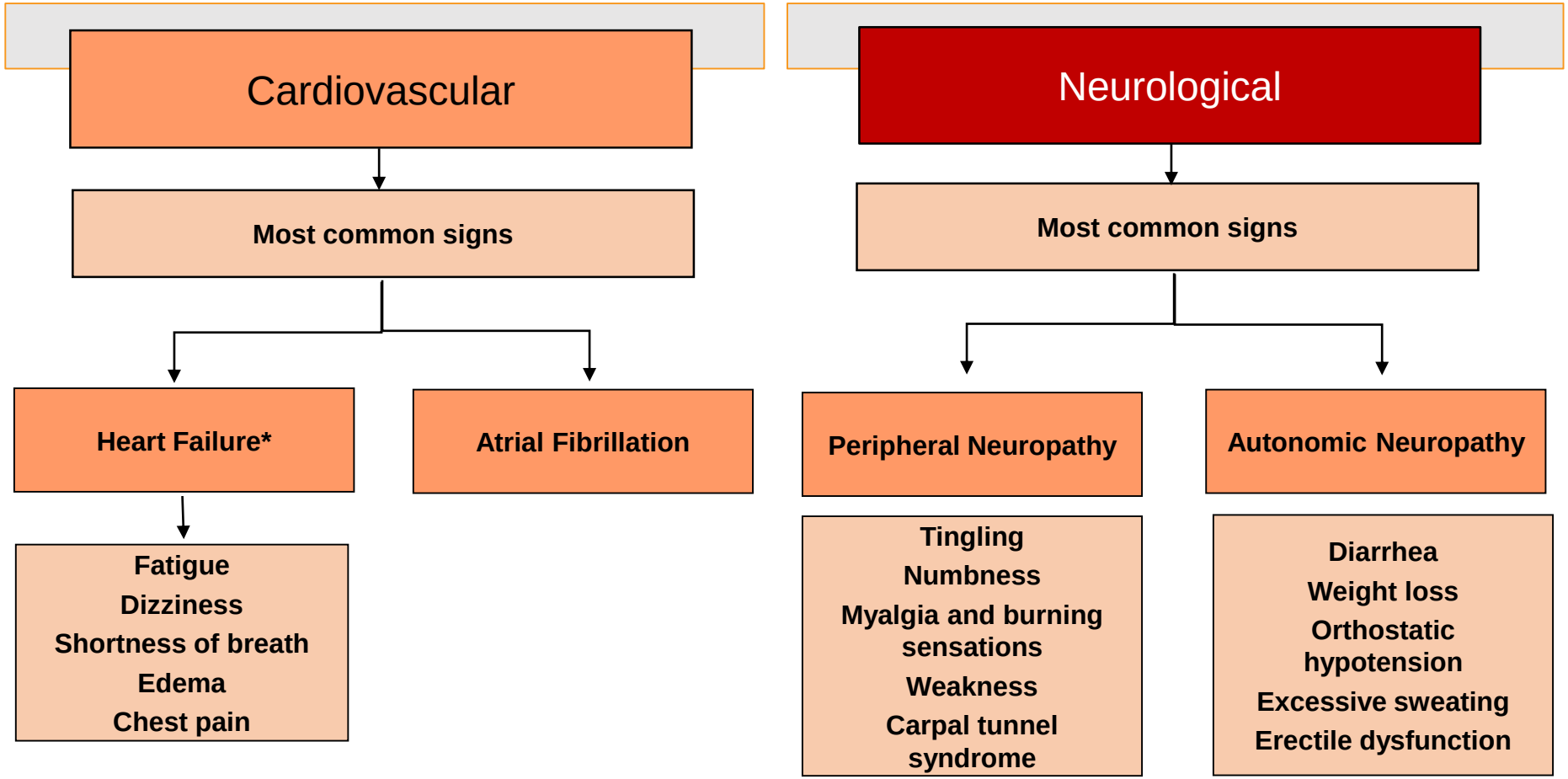
Characteristics of ATTR-CM[1-4]

Wild-Type (WT)	Familial / Variant
• Estimated higher prevalence versus familial/variant • Predominantly seen in **men** age **≥65** • **Uncommon in females**; however, the onset is usually later than in males (age 80–90) • Typically **Caucasian**	• Seen in **men and women** age **>55** • **3–4% of African Americans** in the US are carriers of the V122I mutation, however disease penetrance is unknown • **Heart failure is more common** in people with a *TTR* gene mutation



1. Dubrey SW, et al. *Heart.* 2011;97:75–84. 2. Connors LH, et al. *Am Heart J.* 2009;158:607–14; 3. Jacobson DR, et al. *Hum Genet.* 1996;98(2):236–8 . 4. Quarta CC. *New Engl J Med.* 2015:372:21-29. 5. Maurer MS et al. *Circulation.* 2017;135:1357-1377.

Clinical presentation of ATTR-CM can have cardiovascular or neurological origins



1. Nakagawa M et al. *Amyloid.* 2016;23(1):58–63. 3. Gertz MA et al. *JACC.* 2015;66(21):2451-2466.

Prevalence of ATTR-CM

- Exact prevalence of ATTR-CM is unknown[1]
  - In Americans of European descent, transthyretin amyloidosis is estimated to affect one in 100,000 people
  - ATTR-CM is more common among people with African ancestry
    - It is estimated to affect ~3-4% of African Americans
      - ~5% of people in some areas of West Africa

- The prevalence of ATTR-CM **is presently unknown**; however, it is estimated that **less than 1%** of people with the disease **are diagnosed**[2]

JACC VOL. 72, NO. 17, 2018
OCTOBER 23, 2018:2040–50

TABLE 2 Demographics and Diagnostic Criteria of Patients Diagnosed With Amyloidosis

Patient	Age, yrs	Sex	African American	Bilateral Symptoms	Prior CTS Release	Amyloid Type	Genetic Mutation	Kappa, mg/l	Lambda, mg/l	FLC Ratio	Monoclonal Protein
#1	73	F	No	Yes	Yes	ATTR	Ala81Thr	46.0	25.7	1.79	Yes
#2	82	F	No	Yes	Yes	ATTR	None	21.1	13.9	1.52	No
#3	85	M	No	Yes	Yes	AL	N/A	33.1	15.6	2.12	No
#4	78	F	No	Yes	Yes	AL	N/A	20.4	299.6	0.07	Yes
#5	67	M	No	Yes	Yes	ATTR	None	12.3	10.0	1.23	No
#6	56	M	No	Yes	Yes	ATTR	Leu58His	15.5	9.9	1.57	No
#7	62	M	No	Yes	No	ATTR	None	13.9	11.3	1.23	Yes
#8	72	F	No	Yes	Yes	Presumed ATTR*	None	20.9	11.2	1.87	No
#9	65	M	Yes	Yes	No	ATTR	None	29.7	26.3	1.13	Yes
#10	80	M	No	Yes	No	ATTR	None	14.7	18.6	0.79	Yes

*Mass spectrometry and immunohistochemistry without sufficient tissue to accurately subtype sample.
CTS = carpal tunnel syndrome; FLC = free light chain ratio (kappa/lambda) with reference range 0.26 to 1.65.

1. Transthyretin amyloidosis. https://ghr.nlm.nih.gov/condition/transthyretin-amyloidosis#definition. Accessed August 9, 2018.
2. Press Release. Pfizer announces positive topline results from phase 3 ATTR-ACT study of tafamidis in patients with transthyretin cardiomyopathy www.pfizer.com/news/press-release/press releasedetail/Pfizer _announces_positive _topline_results_from_phase_3_attr_act_study_of_tafamidis_in_patients_with_transthyretin_cardiomyopathy. March 29, 2018. Accessed September 5, 2018

ATTR “Wild Type” Identification and Diagnosis

European Heart Journal (2015) **36**, 2585–2594
doi:10.1093/eurheartj/ehv338

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*

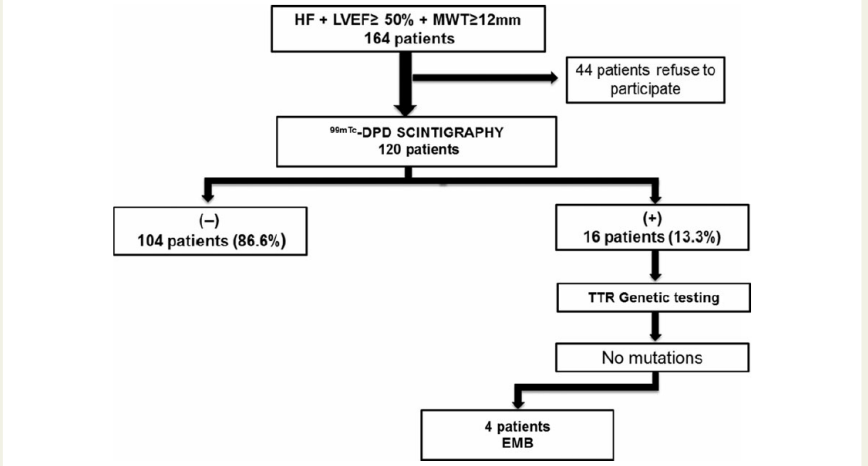
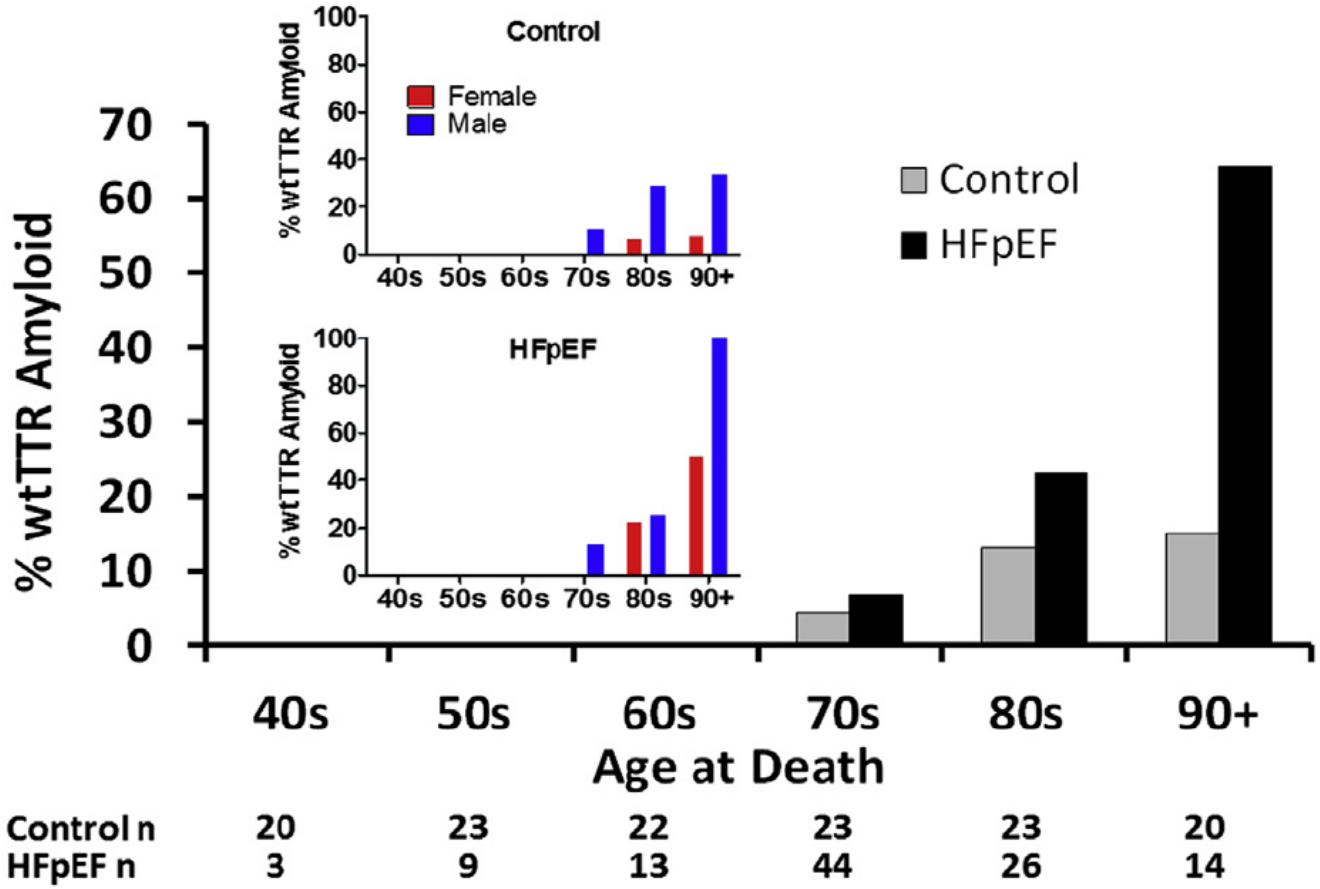


Figure 3 Assembly of the cohort and participant flow. LVEF, left ventricular ejection fraction; MWT, maximal wall thickness; EMB, endomyocardial biopsy; HF, heart failure; TTR, transthyretin.

ATTRwt found in 13% of patients with HFpEF, ≥ 60 years, ≥ 12 mm wall thickness

- LVEF=left ventricular ejection fraction.
- González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J.* 2015;36(38):2585-2594.

ATTR Wild Type and cause of Heart Failure with preserved LVEF

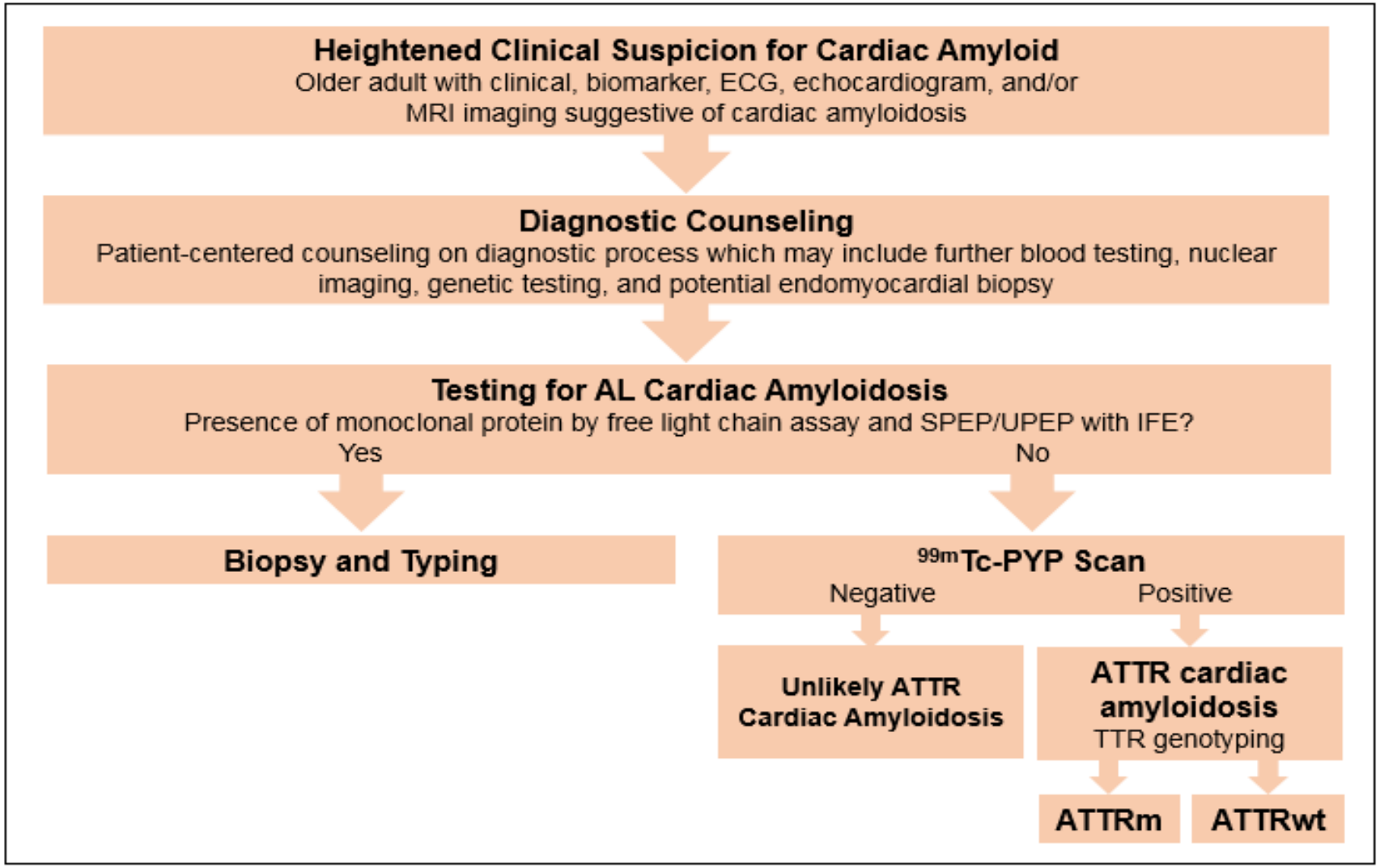


Prevalence of left ventricular ATTRwt in control (n = 131) and HFpEF (n = 109) patients by age

Mohammed SF, Mirzoyev SA, Edwards WD, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail*. 2014;2(2):113-122.

Diagnosis of TTR Cardiac Amyloidosis

Figure 1: Proposed Diagnostic Algorithm for Older Patients with Suspected TTR Cardiac Amyloidosis



Circulation. 2016;133:2404-2412.
DOI: 10.1161/CIRCULATIONAHA.116.021612.

Table 1. Red Flags and Caveats in Cardiac Amyloidosis

A high index of suspicion is mandatory for the recognition of CA (ie, if you don't think of it, you won't diagnose it).
Cardiac amyloid should be suspected in any patient with heart failure, unexplained increased LV wall thickness, and a nondilated LV.
In a patient with a suspicion for HCM, look for the infiltrative features that suggest amyloid such as pericardial effusion, AV block, interatrial septal and valvular thickening, and apical sparring.
A distinctive sign of CA is the abnormal ratio between LV thickness and QRS voltages rather than low QRS voltages alone. The absence of low QRS voltages does not rule out a CA and up to 20% of subjects with CA can have electrocardiographic evidence of LV hypertrophy.
In an elderly man with unexplained symmetrical LV hypertrophy, especially in the absence of hypertension, always consider the possibility of ATTRwt-CA.
CA in an elderly patient with a monoclonal gammopathy is not necessarily attributable to AL: consider the possibility of ATTRwt and MGUS.
Longitudinal LV function can be severely depressed despite a normal LVEF, and the myocardial contraction fraction is often low, suggesting reduced global myocardial shortening.
Myocardial deformation is reduced in cardiac amyloidosis, but the apex is generally spared.
On cardiac MRI, both T1 signal abnormalities and marked extracellular volume expansion in patients with LV hypertrophy are strongly suggestive of CA. LGE distribution is heterogeneous, and subendocardial enhancement is not the only pattern.
A history of bilateral carpal tunnel syndrome in a man with HCM-like phenotype on echocardiography is highly suggestive of ATTRwt-CA.

AL indicates immunoglobulin light chain; ATTR, amyloid transthyretin; ATTRwt, wild-type amyloid transthyretin; AV, atrioventricular; CA, cardiac amyloidosis; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; and MGUS, monoclonal gammopathy of undetermined significance.

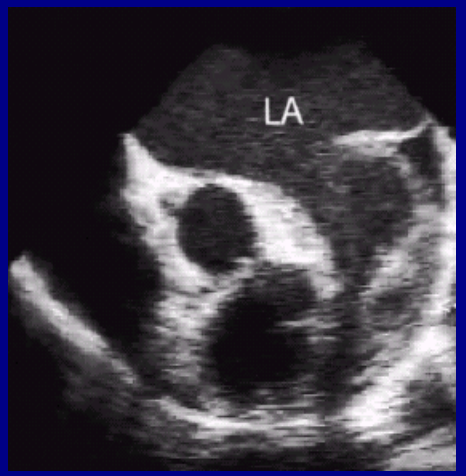
Circulation. 2017;135:1357–1377. DOI: 10.1161/CIRCULATIONAHA.116.024438

The value of specific cardiac testing for the diagnosis of Amyloidosis

Diagnostic Test	Utility in Cardiac Amyloid TTR vs AL
ECG	AL: Reduced voltage in 46-60%, atrial fibrillation in 20%, Pseudoinfarct pattern TTR: Reduced voltage in 25-40%, atrial fibrillation in 10-30% [10]
Echocardiography	With "speckled" appearance of LV: sensitivity 87% and specificity 81% which improved to specificity when finding atrial septal thickening to 100%[10] Decrease of longitudinal strain in mid and basal wall regions relative to the apical region has 90-95% sensitivity and 80-85% specificity in diagnosis of CA[11]
Biomarkers (BNP, NT-proBNP, Troponin T)	BNP as a sensitive marker to myocardial dysfunction. BNP has 93% sensitivity and 40% specificity as a predictor of echocardiography involvement.[10] NT-proBNP and Troponin T are used for staging in AL amyloidosis. [5]
Cardiac Magnetic Resonance	Late gadolinium enhancement is one of the most accurate predictors of endomyocarial biopsy-positive amyloidosis Subendocardial enhancement more common with AL RV enhancement was 100% TTR vs 72% AL CMR 100% sensitivity and 80% specificity in AL[10]
Radionuclide Scans (Tc99m PYP Tc99m DPD)	Useful in TTR (both mutated and wild-type). Reported high sensitivity and specificity in differentiating TTR from AL[10]
Biopsy (abdominal fat pad vs endomyocardial)	Abdominal fat aspirate with congo red staining 70-90% sensitive for AL but 15-45% for TTR. If high suspicion, and negative fat pad biopsy will need endomyocardial biopsy with nearly 100% sensitivity (Gold Standard)[10]

Treatment: Cardiac-Specific

- **Diuretics/salt restriction**
  - Often have large amounts of peripheral edema/ascites, made worse by hypoalbuminemia
- ***To generally be avoided:***
  - Digoxin
  - Beta-blockers
  - Calcium-blockers
  - Vasodilators (ACE-I/ARBs) unless proteinuria is a prominent feature
- Midodrine/Droxidopa
  - Can be useful in orthostatic hypotension/autonomic dysfunction that is common
- Treatment of atrial & ventricular arrhythmias

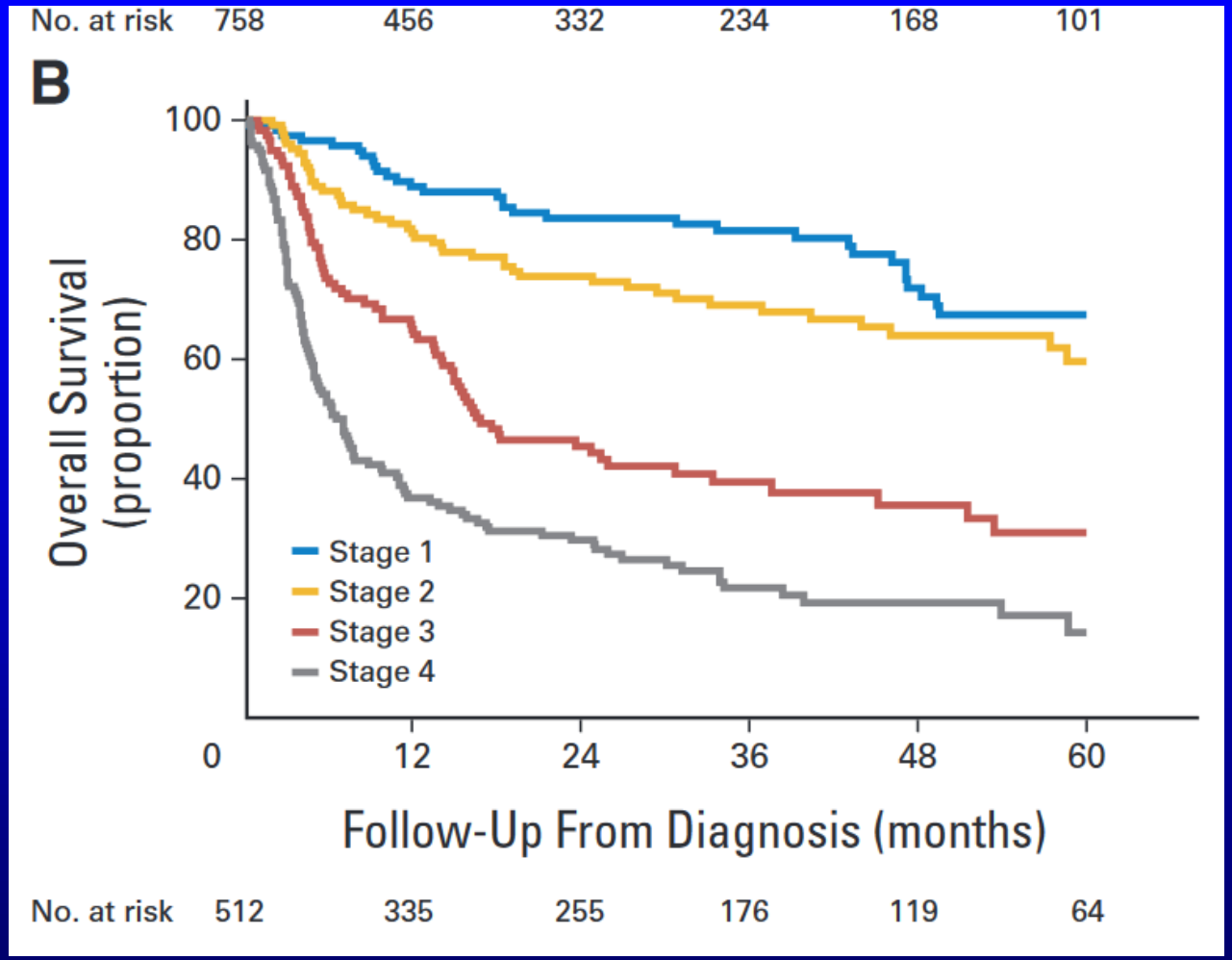


Staging for AL Amyloidosis

Kumar, S et al
JCO 2012

Using 1 point for each cutoff:

TnT > 0.025
NTproBNP >1800
Free Light chain> 18mg/dL



(cTnT ≥ 0.025 ng/mL, NT-ProBNP ≥ 1,800 pg/mL, and FLC-diff ≥ 18 mg/dL); this was used to divide patients into four stages (I, II, III, and IV) with scores of 0, 1, 2, and 3, respectively. Fifty-two patients did

Proposed staging for ATTR

Cutoffs:

NTproBNP >3000 ng/L

EGFR <45ml/min/1.73m2

If both negative= Stage I
If both present= Stage III

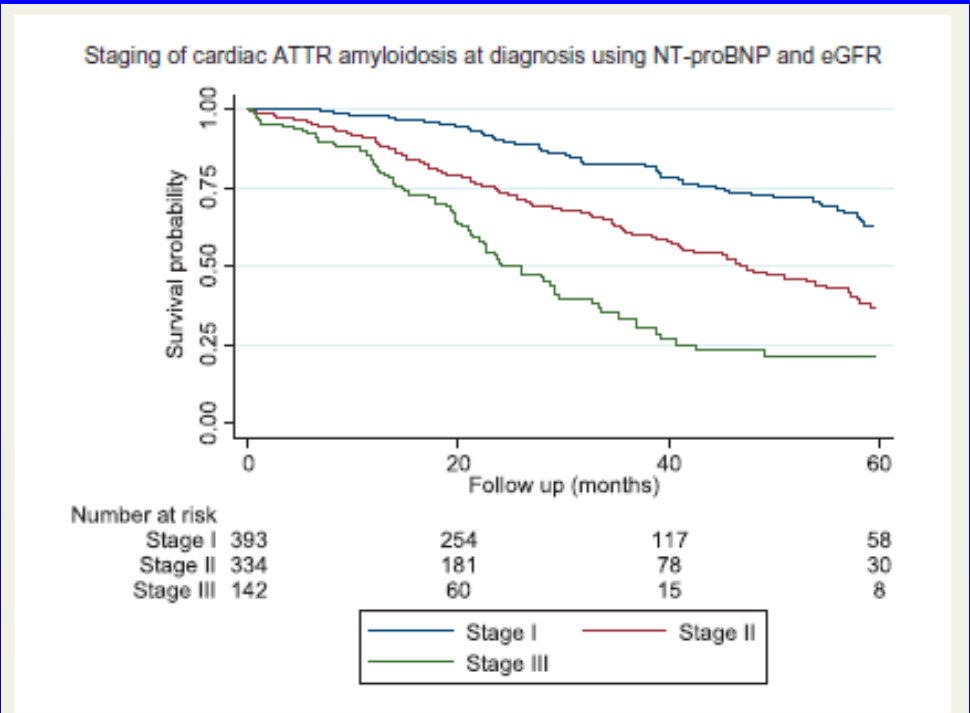
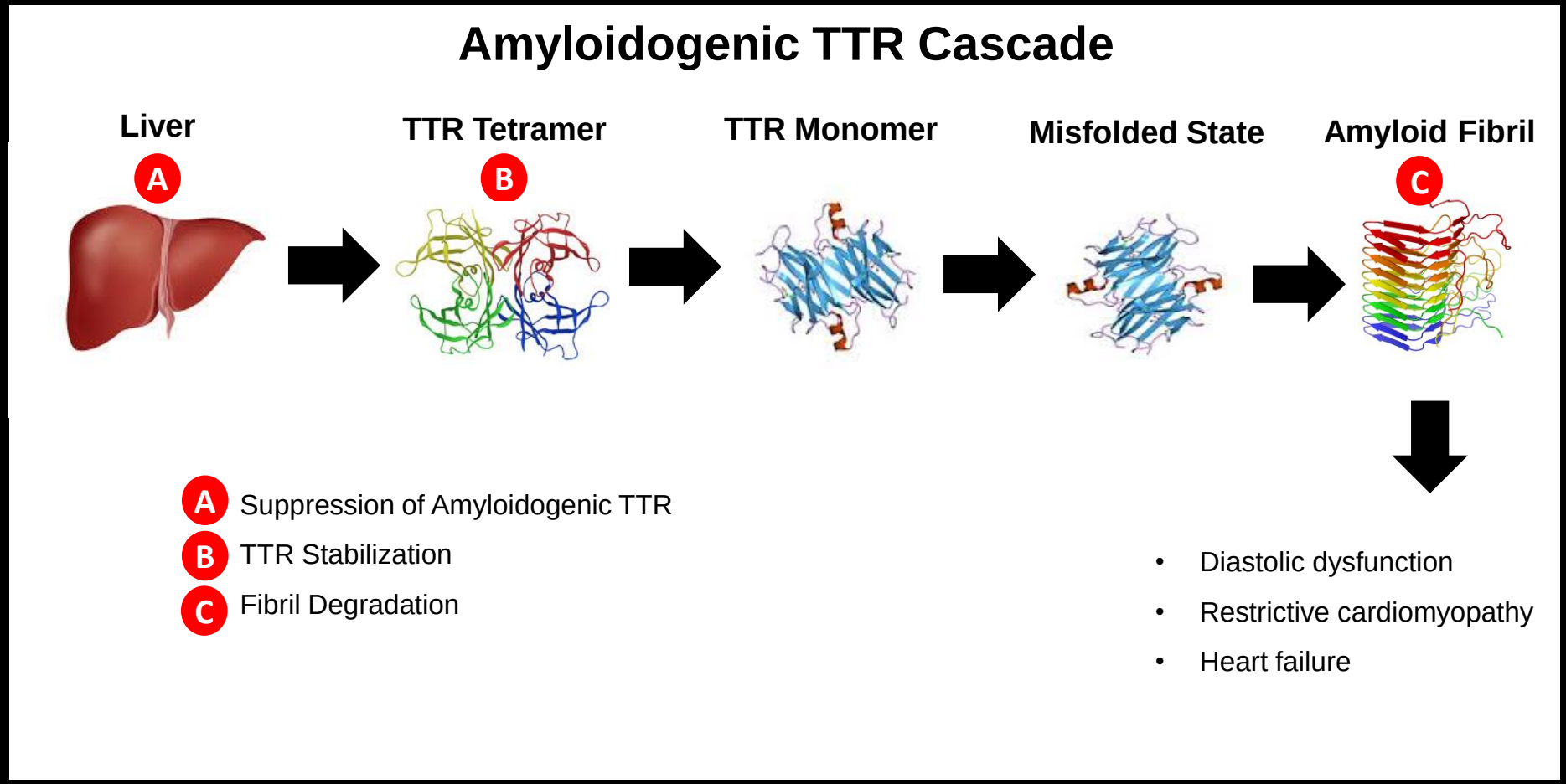


Figure 2 Kaplan–Meier curves showing survival probabilities in 869 patients with cardiac transthyretin amyloidosis stratified by disease stage (log-rank test; Stage I vs. Stage II, $P < 0.0001$; Stage II vs. Stage III, $P < 0.0001$). Stage I patients had a median survival of 69.2 months (95% CI lower limit 62.9 months, upper limit indeterminable), Stage II patients had a median survival of 46.7 months (95% CI 40.2–57.0 months), and Stage III patients had a median survival of 24.1 months (95% CI 21.2–29.6 months ($P < 0.0001$ for Stage I vs. II and $P < 0.0001$ for Stage II vs. III). By Cox proportional hazards regression analysis, compared with Stage I, the HR for death was 2.05 (95% CI 1.54–2.72, $P < 0.001$) for Stage II and 3.80 (95% CI 2.73–5.28, $P < 0.001$) for Stage III patients. The HR for death in patients with Stage III cardiac ATTR amyloidosis compared with Stage II was 1.86 (95% CI 1.38–2.48, $P < 0.001$). Harrell's *c*-statistic was 0.69.

European Heart Journal (2018) 39, 2799–2806
doi:10.1093/eurheartj/ehx589

Disease modifying therapeutic opportunities for TTR amyloidosis



Both WT and Hereditary Cardiac Amyloidosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

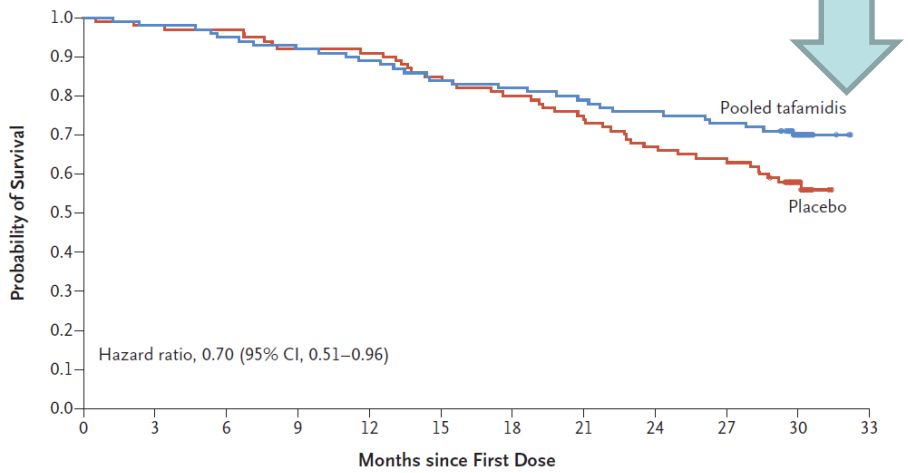
CONCLUSIONS

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo. (Funded by Pfizer; ATTR-ACT ClinicalTrials.gov number, NCT01994889.)

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	

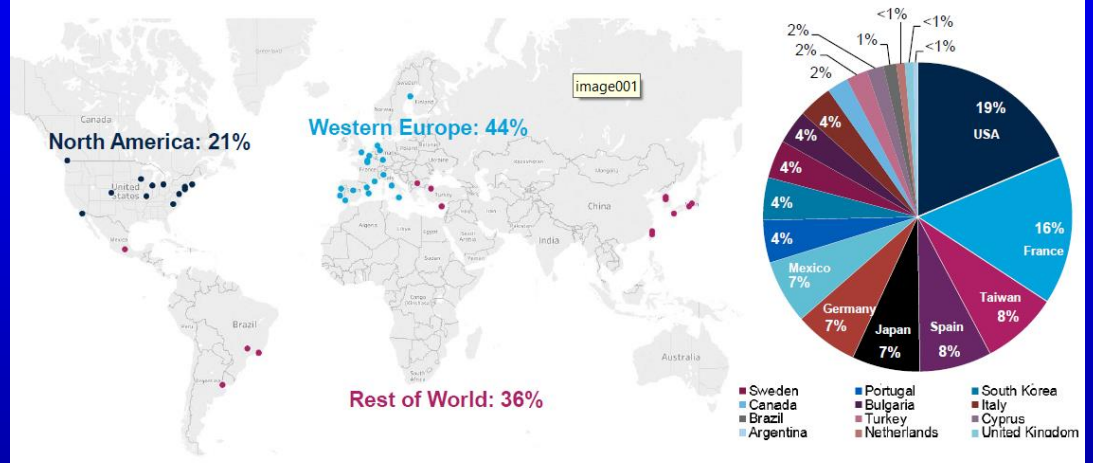
Figure 2. Primary Analysis and Components.

Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.

Patisiran Phase 3 APOLLO Study Results

Study Enrollment

225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between Dec 2013 and Jan 2016



*North America: USA, CAN; Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; Rest of world: Asia: JPN, KOR, TWN, Eastern Europe: BGR, CYP, TUR; Asia: JPN, KOR, TWN; Central & South America: MEX, ARG, BRA

APOLLO

Emerging Options for ATTR Patients and Physicians

Inotersen

- Disease progression and quality of life benefit compared to placebo arm
- Benefit compared to placebo by 8 months
- One subcutaneous administration once a week
- At-home, self administration
- No chronic treatment with other medications
- No pre-treatment regimen
- Simple, routine monitoring every other week
- Thrombocytopenia and renal events observed in NEURO-TTR study
- Saline formulation

Patisiran

- Disease progression and quality of life benefit compared to placebo+steroid arm
- Infusion center administration
- Multi-hour infusions every 3 weeks
- HCP and infusion center visits for administration
- Chronic pre-treatment with steroids with potential associated complications
- Infusion reactions in Phase 2 open-label study and Phase 3 APOLLO study
- Lipid nanoparticle formulation

Hereditary Polyneuropathy only

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

ABSTRACT

BACKGROUND

Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr.

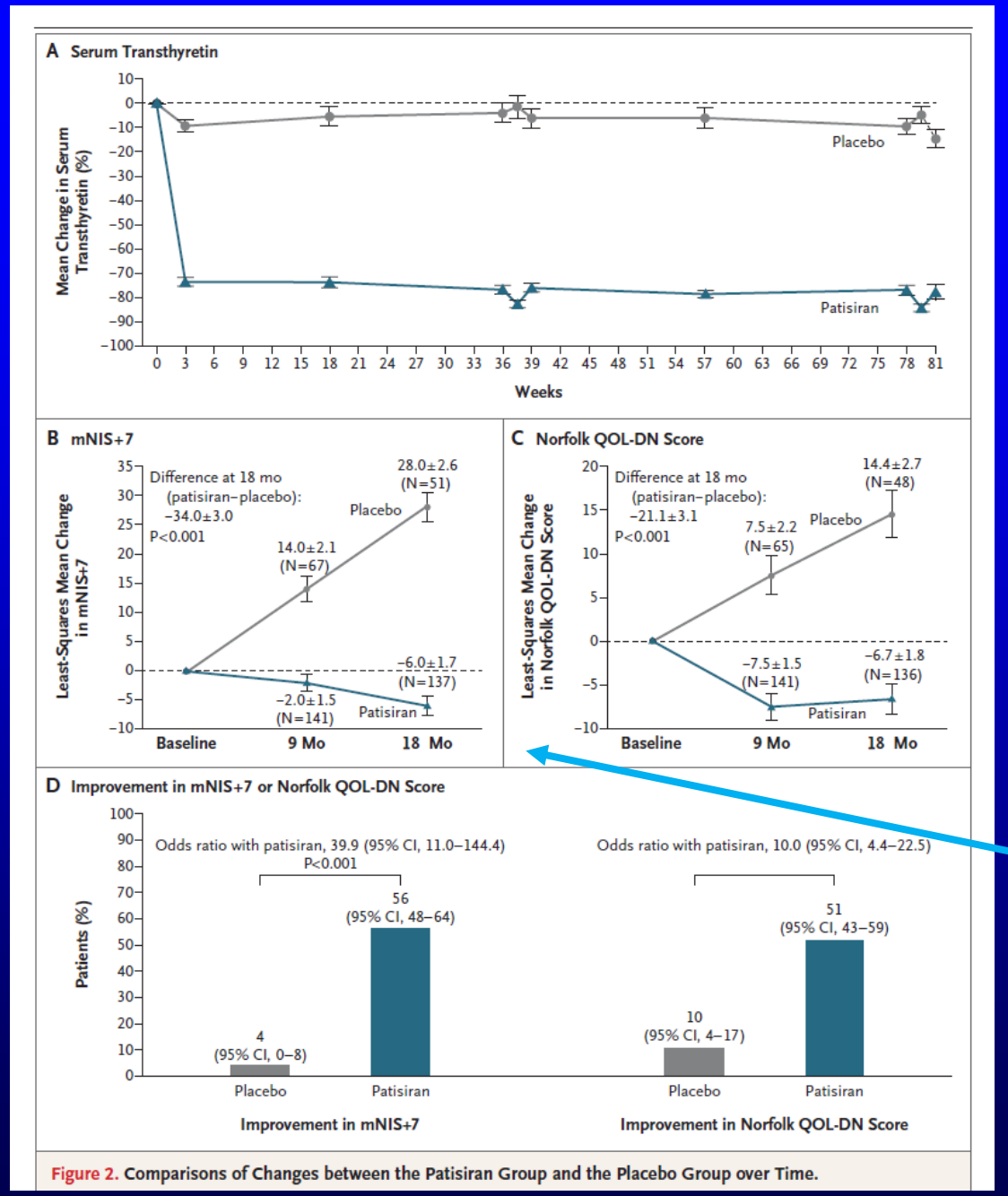
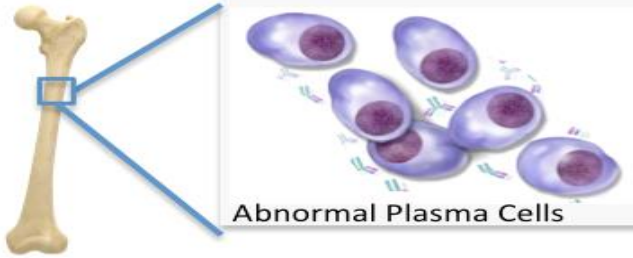


Figure 2. Comparisons of Changes between the Patisiran Group and the Placebo Group over Time.

The current treatment landscape for Amyloidosis

A. Light Chain Amyloidosis



Abnormal Plasma Cells

Reduction in Light Chain Production

Carfilzomib
Daratumumab
Elotuzumab
Isatuximab
Ixazomib
Pomalidomide
Venetoclax

Light Chain Overproduction

Misfolded Light Chain

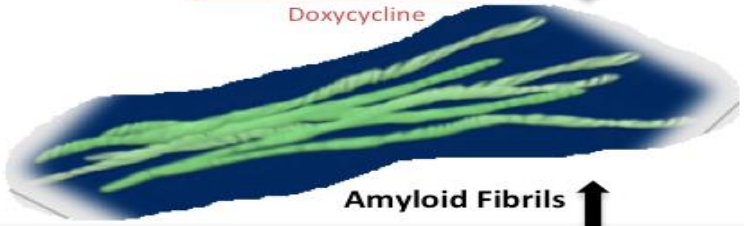
Removal of Light Chain Amyloid Deposits

11-1F4
NEOD001
GSK2398852

Light chain
Heavy chain

Inhibition of Amyloid Fibril Formation

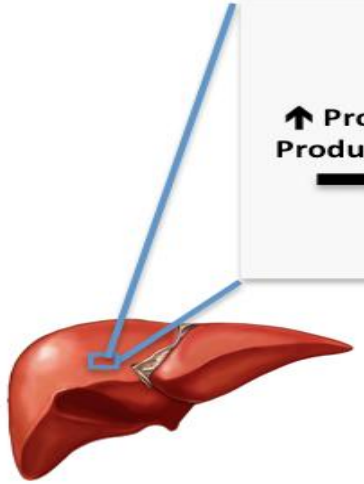
Doxycycline



Amyloid Fibrils

Deposition in Organs

B. Transthyretin Amyloidosis



Transthyretin

Protein Production

mRNA

Monomer

Tetramer

Misfolded Monomers

Transthyretin Synthesis Inhibition

Inotersen
Patisiran

Transthyretin Tetramer Stabilization

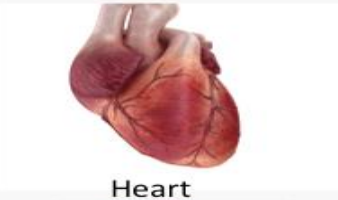
AG10
Diflunisal
Tafamidis
Tolcapone

Removal of Misfolded Transthyretin

PRX004

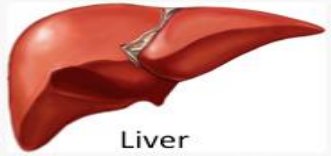
Removal of Transthyretin Amyloid Deposits

GSK2398852
PRX004



Heart

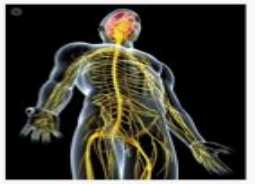
Kidney



Liver

Gastrointestinal Tract

Soft Tissue



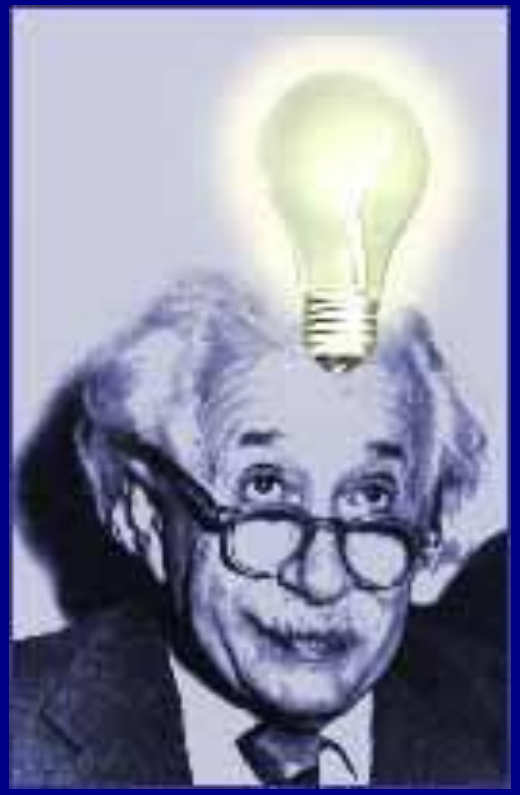
Peripheral/Autonomic Nervous System

Drugs used for the treatment of Amyloidosis

Mechanism of Action	Drug names	Current use
Stabilizers that inhibit dissociation of **TTR** into monomers	1. Tafamidis 2. Diflusinal 3. AG10 (selective to TTR-V112I)	1. Currently in a phase 3 clinical trial [30] 2. Randomized controlled trial data available [8] 3. Currently in a Phase 1 clinical trial [32]
Binding leads to degradation and reduced transcription of **TTR**	1. Patisiran (with siRNA) 2. Ionis (of ASO)	1. Phase 3 clinical trial in patients with FAP [33] 2. Phase 2/3 randomized controlled trial in patients with FAP [35]
Disruption of **TTR** amyloid deposition	1. Doxycycline 2. TUDCA 3. Combination of Doxy/TUDCA	1. Currently in a Phase 2 clinical trial alone [69] 2. Not studied alone 3. Currently in a Phase 2 clinical trial [37]
Clearance of **TTR** with antibody	1. PRX004	1. Not yet recruiting for phase 1 clinical trial in patients with hTTR amyloidosis [63]
Normalization of **AL** amyloid light chain concentration	1. High dose Melphalan (alkalating agent) 2. Bortezomib (proteasome inhibitor) 3. CyBorD (alkylator with PI)	1-3. First line therapy [38-41]
Normalizing **AL** amyloid light chain concentrations with immunmodulatory drugs	1. Thalidomide following low-dose Melphalan 2. Lenalidomide 3. Pomalidomide	1. Phase 2 clinical trial in patients with cardiac amyloidosis [67] 2. Phase 2 clinical trial in patients with AL amyloidosis [68] 3. Currently in a Phase 2 clinical trial [49]
Normalizing **AL** amyloid light chain concentrations with proteasome inhibitors	1. Bortezomib (reversible) 2. Carfilzomib (irreversible) 3. Ixazomib (reversible)	1. Phase 3 clinical trial in patients with AL amyloidsosis [40] 2. Phase 1 clinical trial data for patients with AL amyloidosis [48] 3. Currently in a Phase 3 clinical trial [47]
Normalization of **AL** amyloid light chain concentrations with monoclonal antibody	1. Daratumumab	1. Currently in a Phase 3 clinical trial [47]
Clearance of **AL** amyloid light chain concentrations with directed monoclonal antibodies	1. mAb anti-SAP 2. mAb NEOD001 3. mAb 11-1F4	1. Currently in a phase 2 clinical trial[54] 2. Phase 1/2 clinical trial in patients with AL amyloidosis [52] 3. Currently in a Phase 1 clinical trial [55]

Amyloidosis: Diagnosis

"The only way to diagnose amyloidosis is to consider the diagnosis."

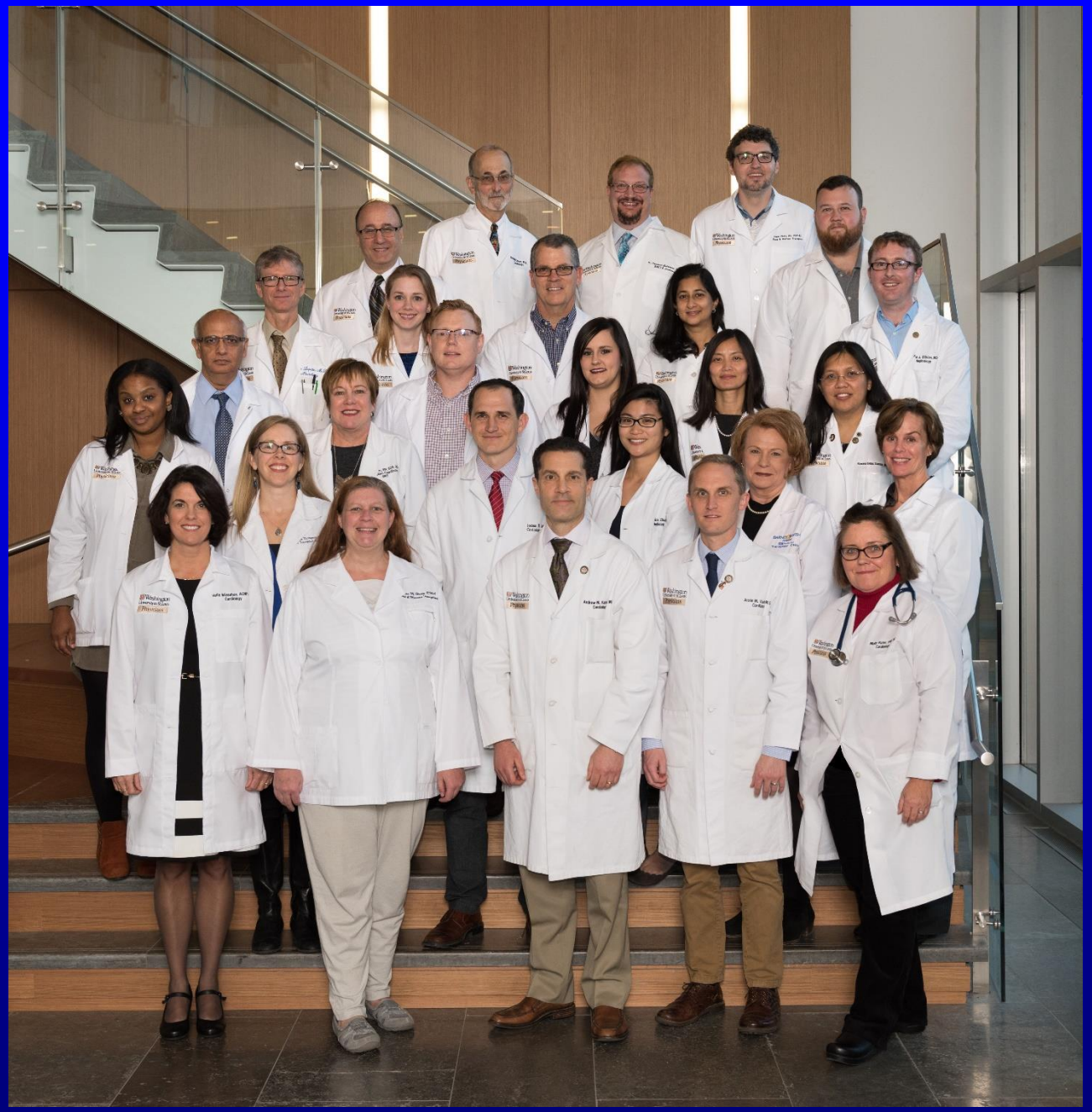


Cardiac Amyloidosis

Current strategies

- Clinical awareness and early diagnosis are critical.
- Cardiac amyloidosis results from distinctive disease processes with differing treatment strategies and prognoses.
- Initial presentation is insidious, LVH on imaging is commonly the first phenotypic abnormality
- The optimal treatment varies greatly from the usual treatment of HF
- Transplantation may provide a mostly definitive therapy in selected patients with AL and ATTR cardiac amyloidosis
- New therapies are needed and are in development

Amyloidosis Center of Excellence (ACE) @ Wash U



Washington University Amyloid Center of Excellence ACE@WU

Multidisciplinary Team

- Cardiology
- Neurology
- Nephrology
- Gastroenterology
- Hepatology
- BMT
- Hematology
- Pulmonology
- Radiology
- Pathology