An Overview and New Treatment Options for Amyloid Cardiomyopathy

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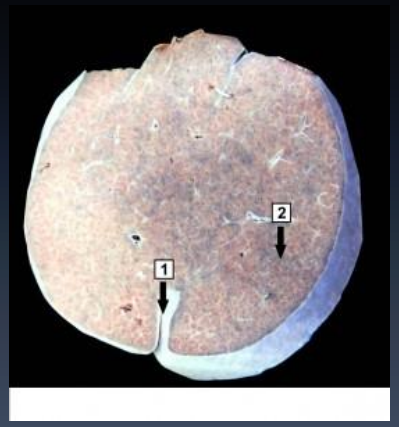
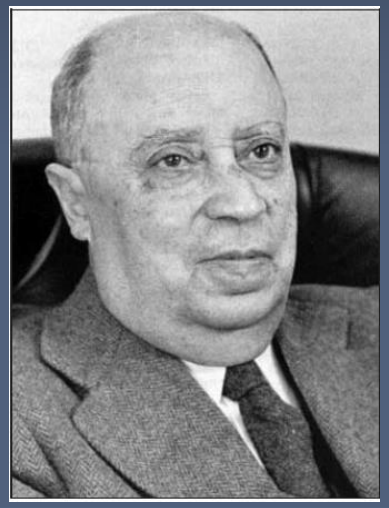
Amyloidosis

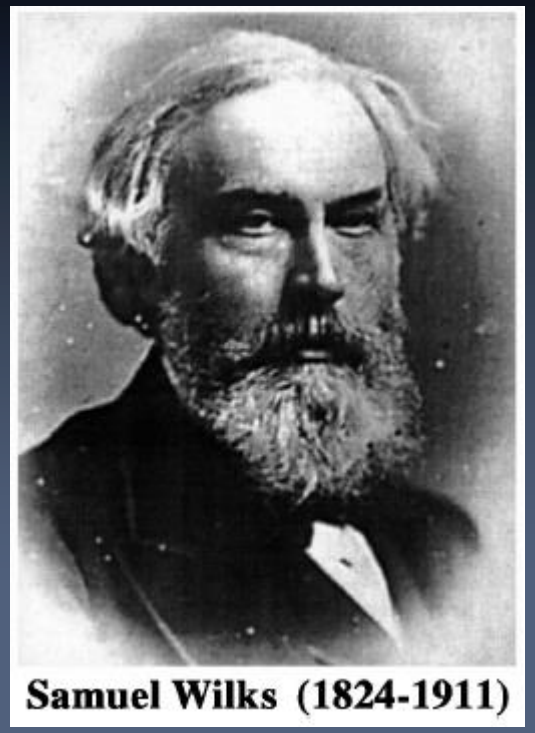
Historical Review

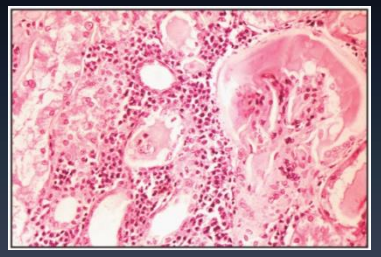
AMYLOIDOSIS: A CONVOLUTED STORY

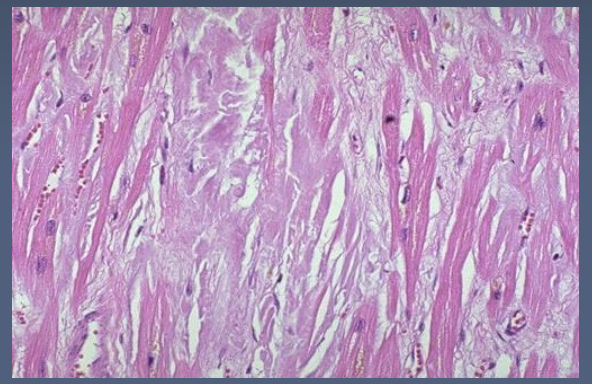

RESPONSIONVM
&
CURATIONVM
MEDICINALIVM
LIBER VNVS.
Autore
NICOLAO FONTANO, IOH.
Filio, Medico Amstelodamensi.
AMSTELODAMI,
Typis IOANNIS IANSSONII.
Anno M. DC. XXXIX.






Samuel Wilks (1824-1911)

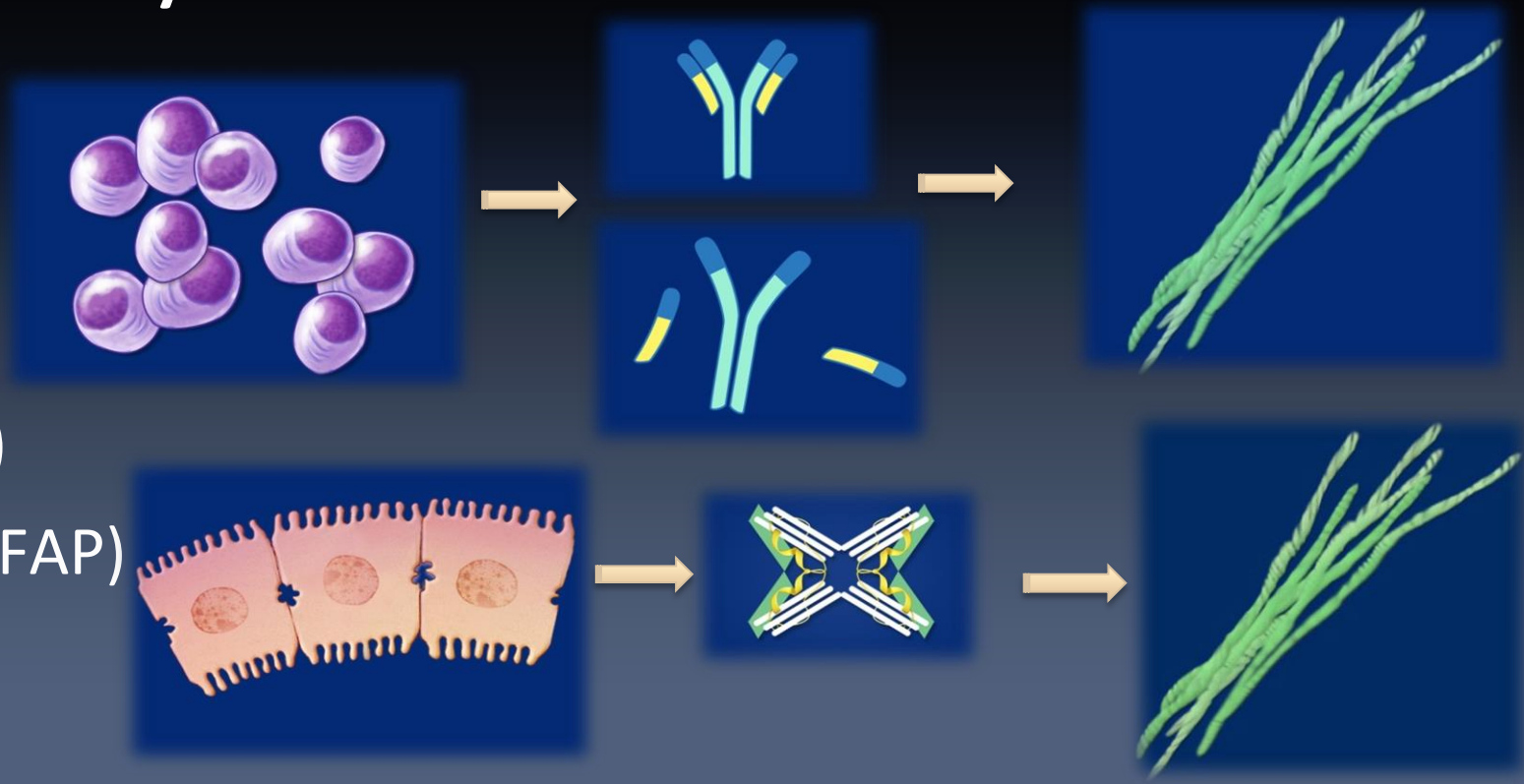




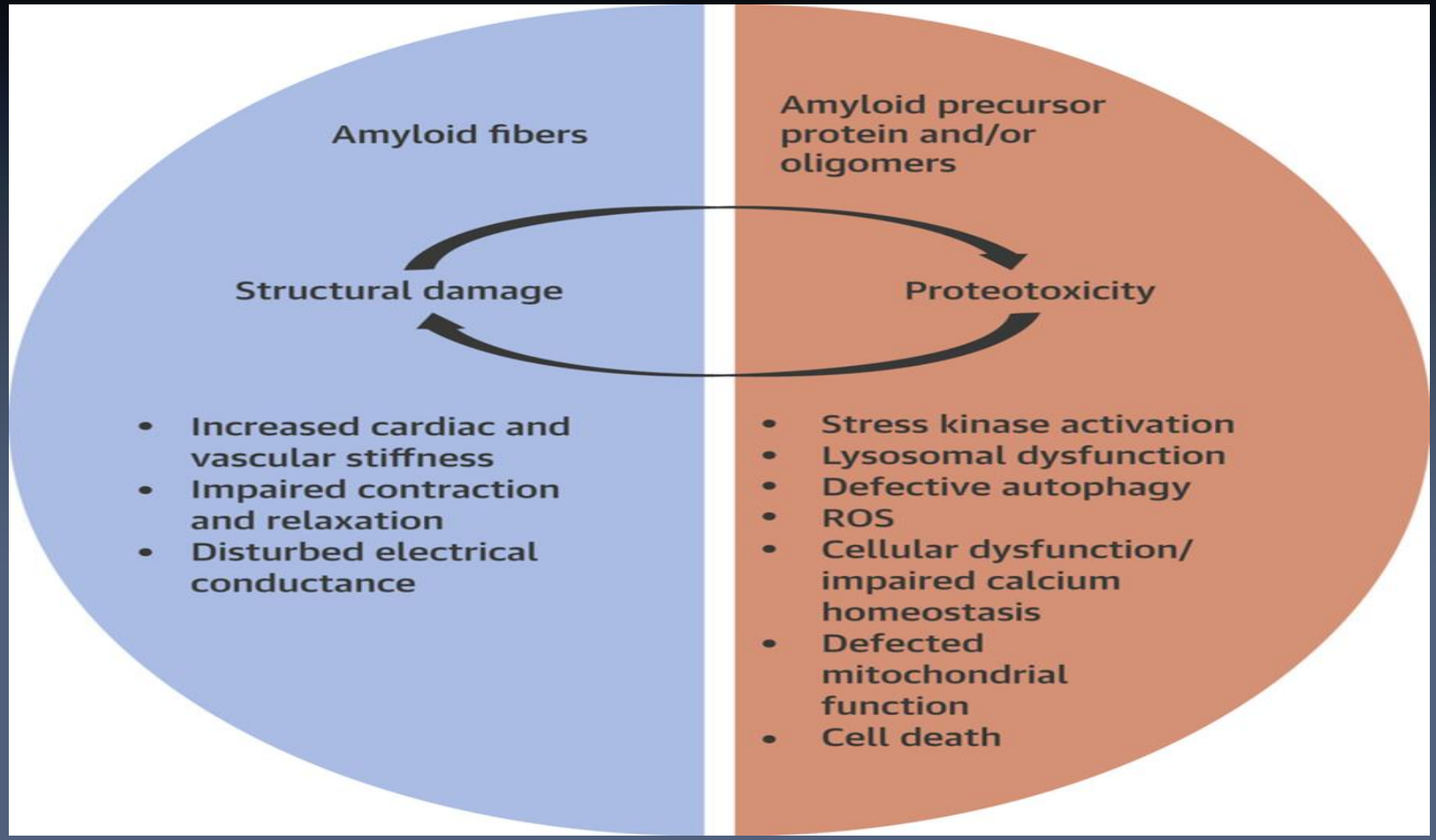
British Journal of Haematology, 2001, 114, 529±538

Types of Amyloid – Systemic

- Light chain (AL)
  - "Primary"
  - AL-CA
- Transthyretin (ATTR)
  - Hereditary (Familial/FAP)
  - Wild type (Senile)
  - ATTR-CA
- Serum amyloid A (AA) – "Secondary"

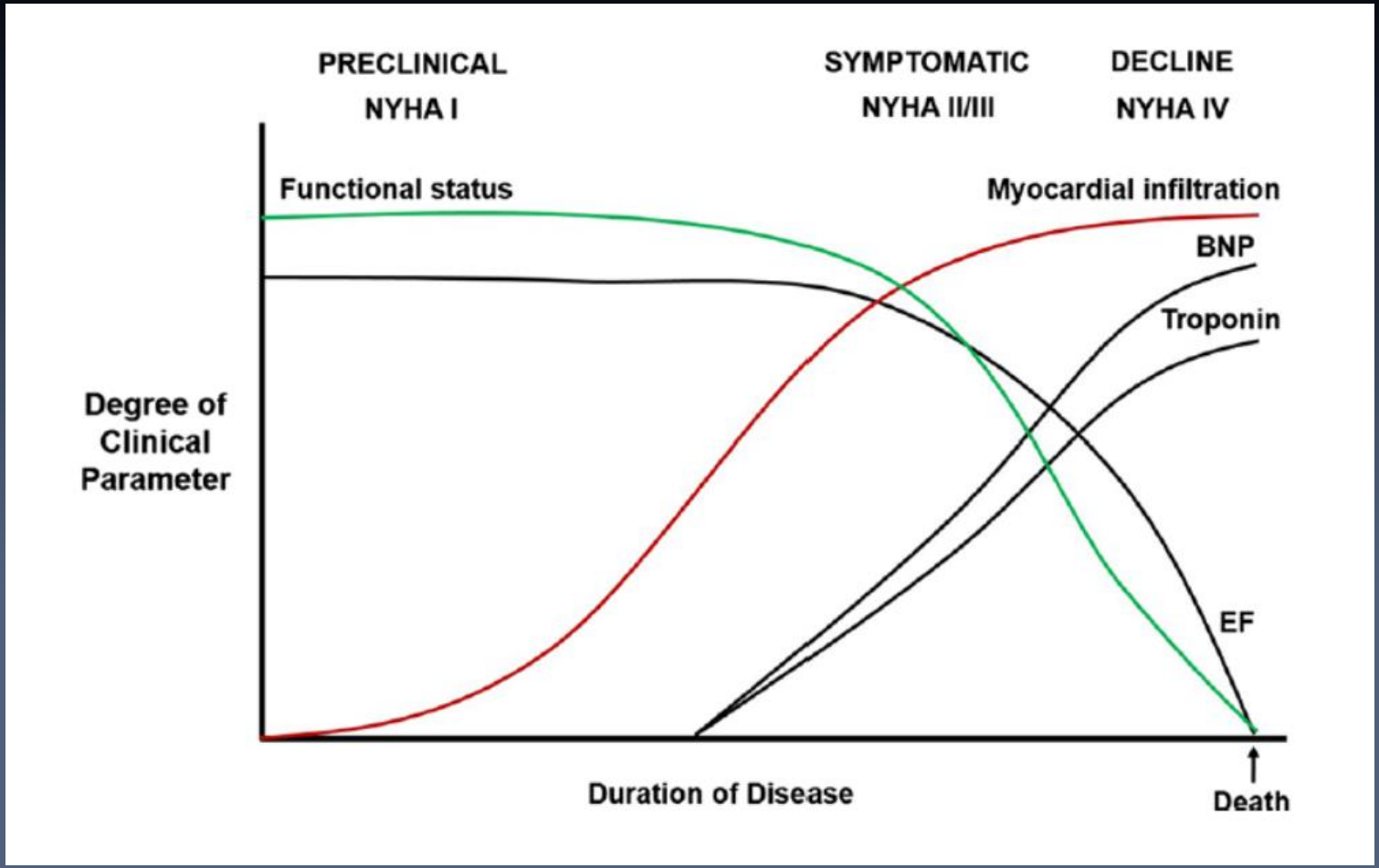


Mechanisms of Amyloid Protein Cardiotoxicity



Falk, R et al. J Am Coll Cardiol. 2016;68:1323-1341

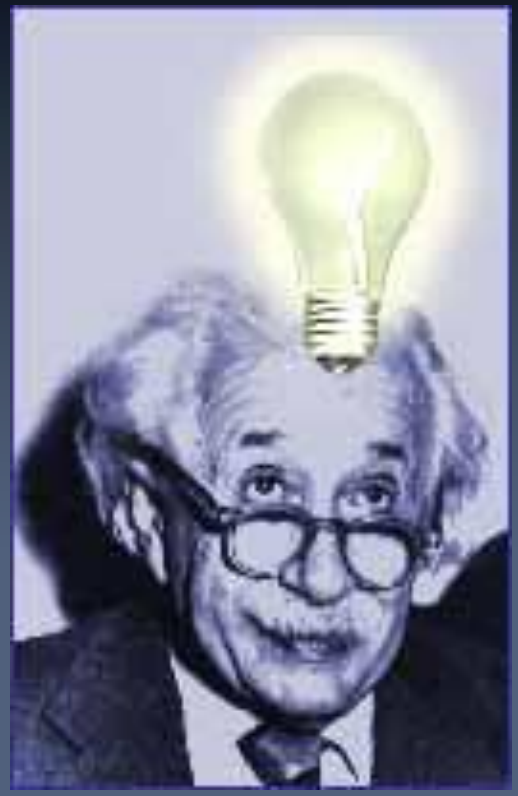
Natural History of Cardiac Amyloidosis



Heart Fail Rev (2015) 20:163–178

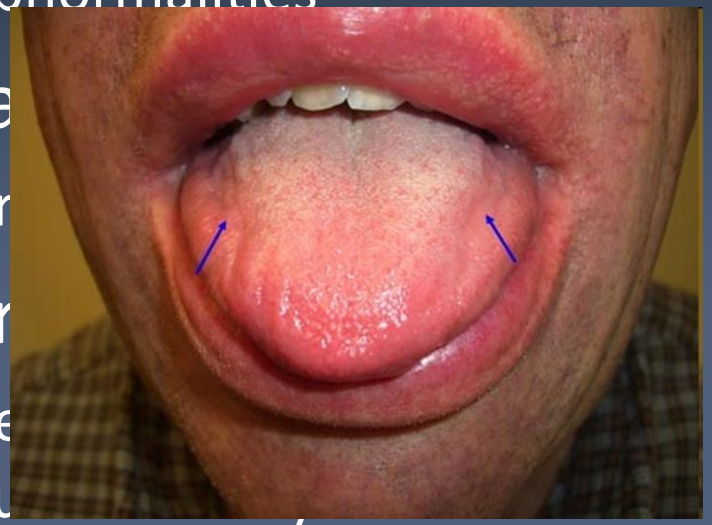
Amyloidosis: Diagnosis

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

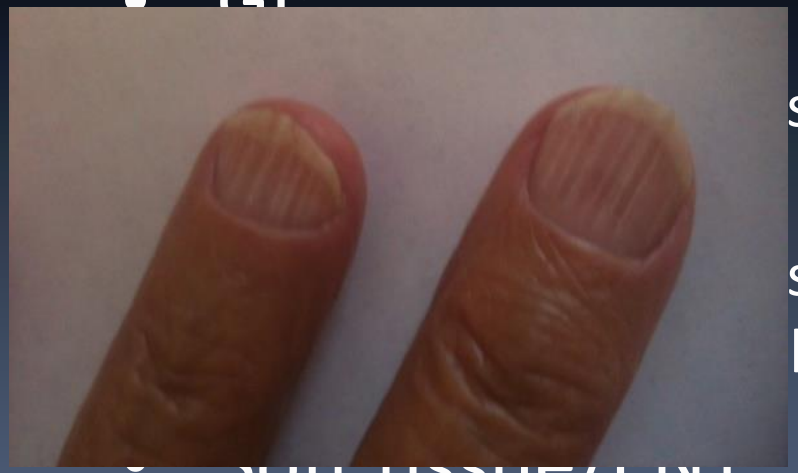


Amyloidosis: Clinical Features

- Cardiac
  - Heart failure, arrhythmias
  - Hypotension, imaging abnormalities
- Rena
  - Pr
- Neur
  - Pe
    au



- GI:



sorption, GI

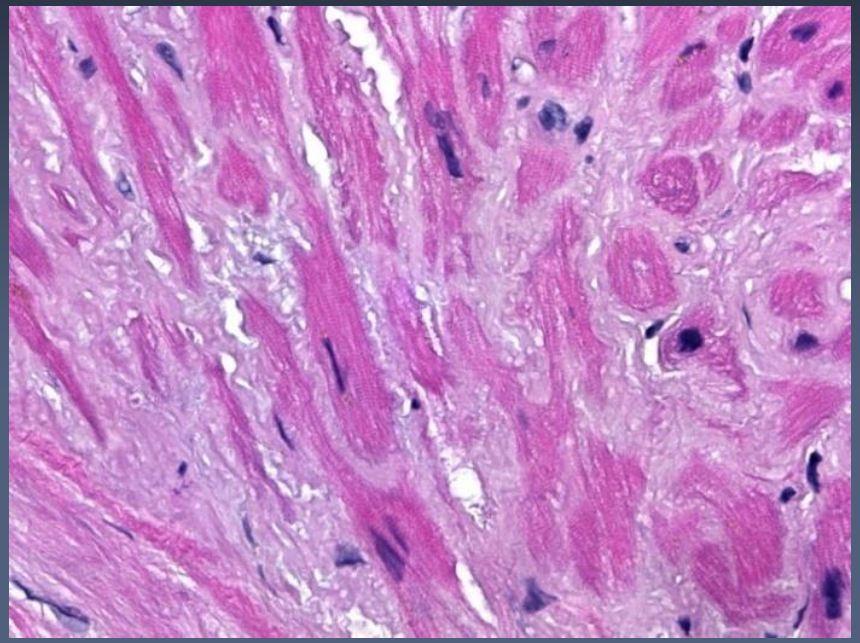
sea, liver

hos elevation)

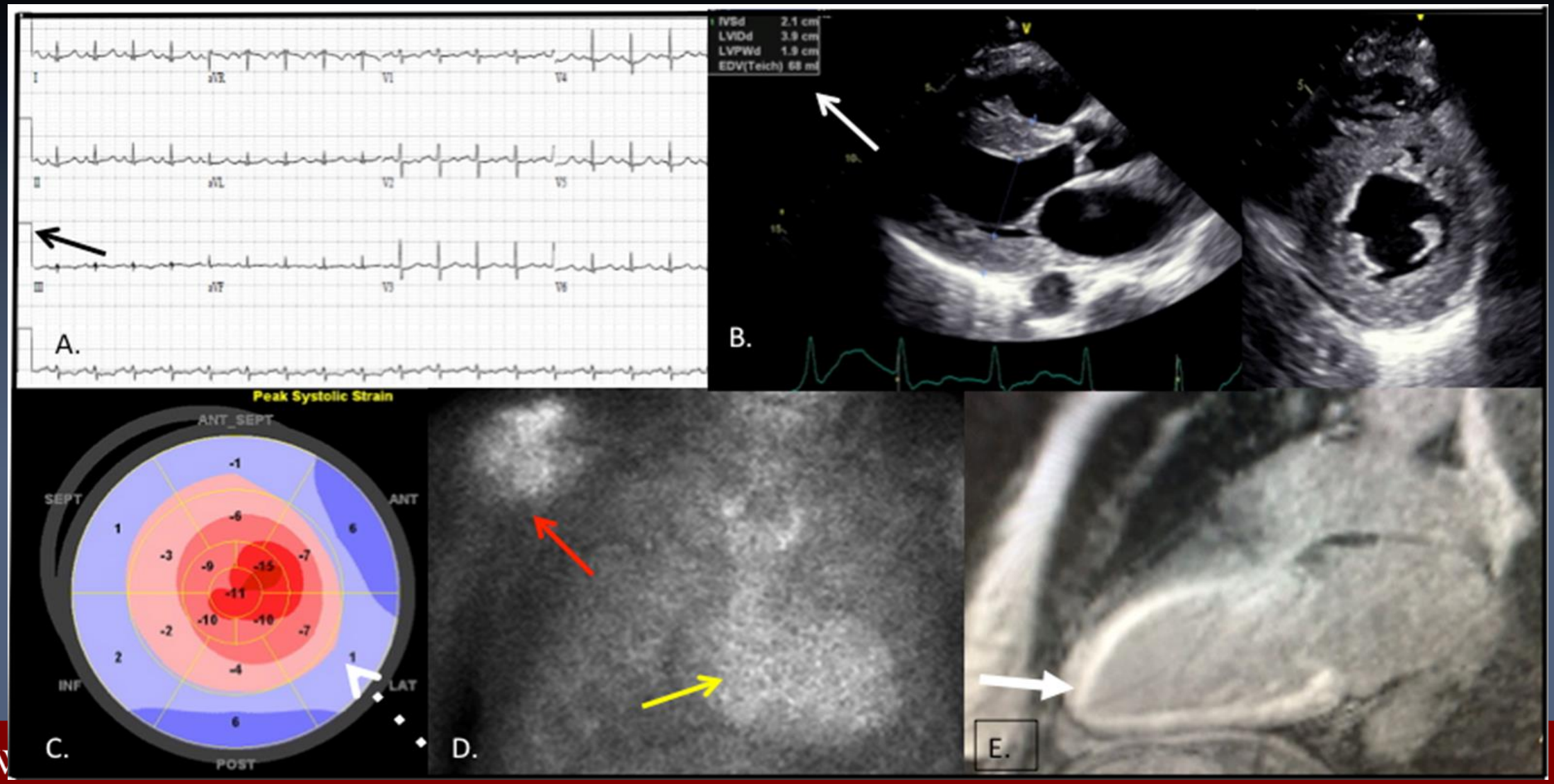
- Soft tissue/ ENT
  - Macroglossia, carpal tunnel syndrome
  - Voice changes, nail changes

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/NT proBNP



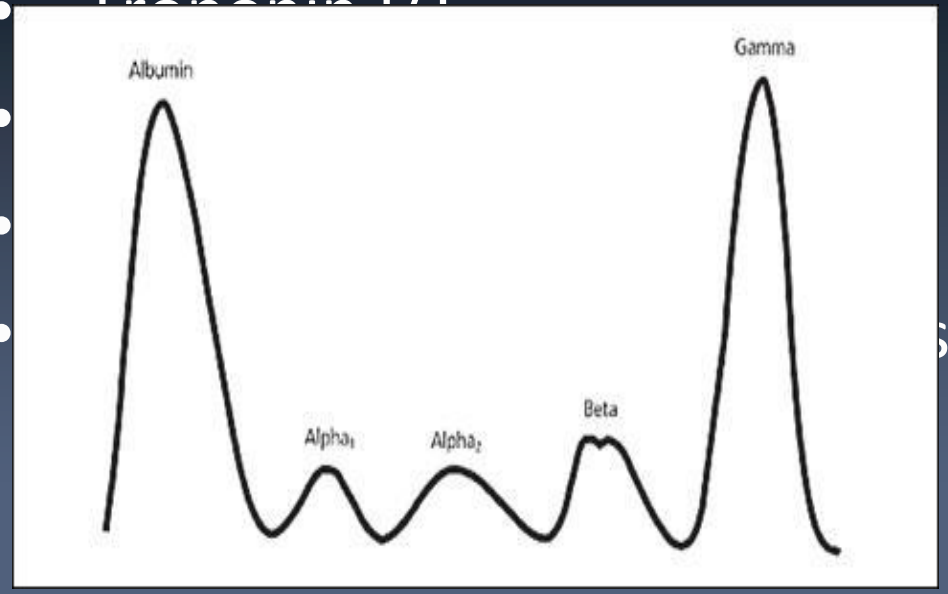
Typical Imaging Characteristics in Amyloidosis



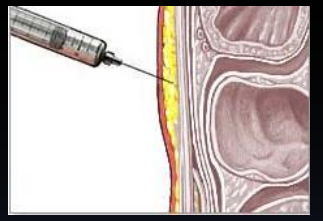
Adjunctive Laboratory Tests

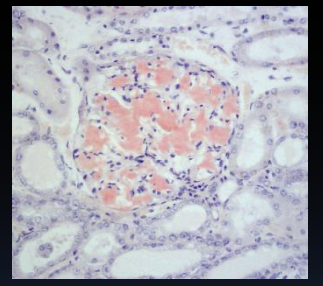
- SPEP
  - Monoclonal immunoglobulins in serum
- UPEP
  - Monoclonal light chains in urine
- Free light chain assay (SFLC)
  - Measures ratio of κ to λ in serum
  - Normal ratio: Approximately 1:1
  - Significant excess: Implies monoclonal light chain production
  - Main assay to assess hematologic response to Rx

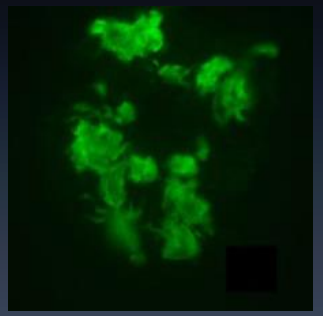
- BNP/NT proBNP
- Tropon
-
-
- sting



How to Diagnose – Biopsy!







- Cannot be excluded with lab assessment alone
- Technetium-pyrophosphate scans may be helpful
- Our general practice:
  - Biopsy of clinically involved organ
- Testing for amyloid subtype – plan ahead!
  - Know pathologist
  - Congo Red
  - Immunofluorescence if light chains are present
  - Mass spectrometry (sent to Mayo)
- Organ (Sensitivity)
  - Abdominal fat pad “70%” (?)
  - Bone marrow 50-56%
  - Rectal 70-85%
  - Clinically involved organ Nearly 100%

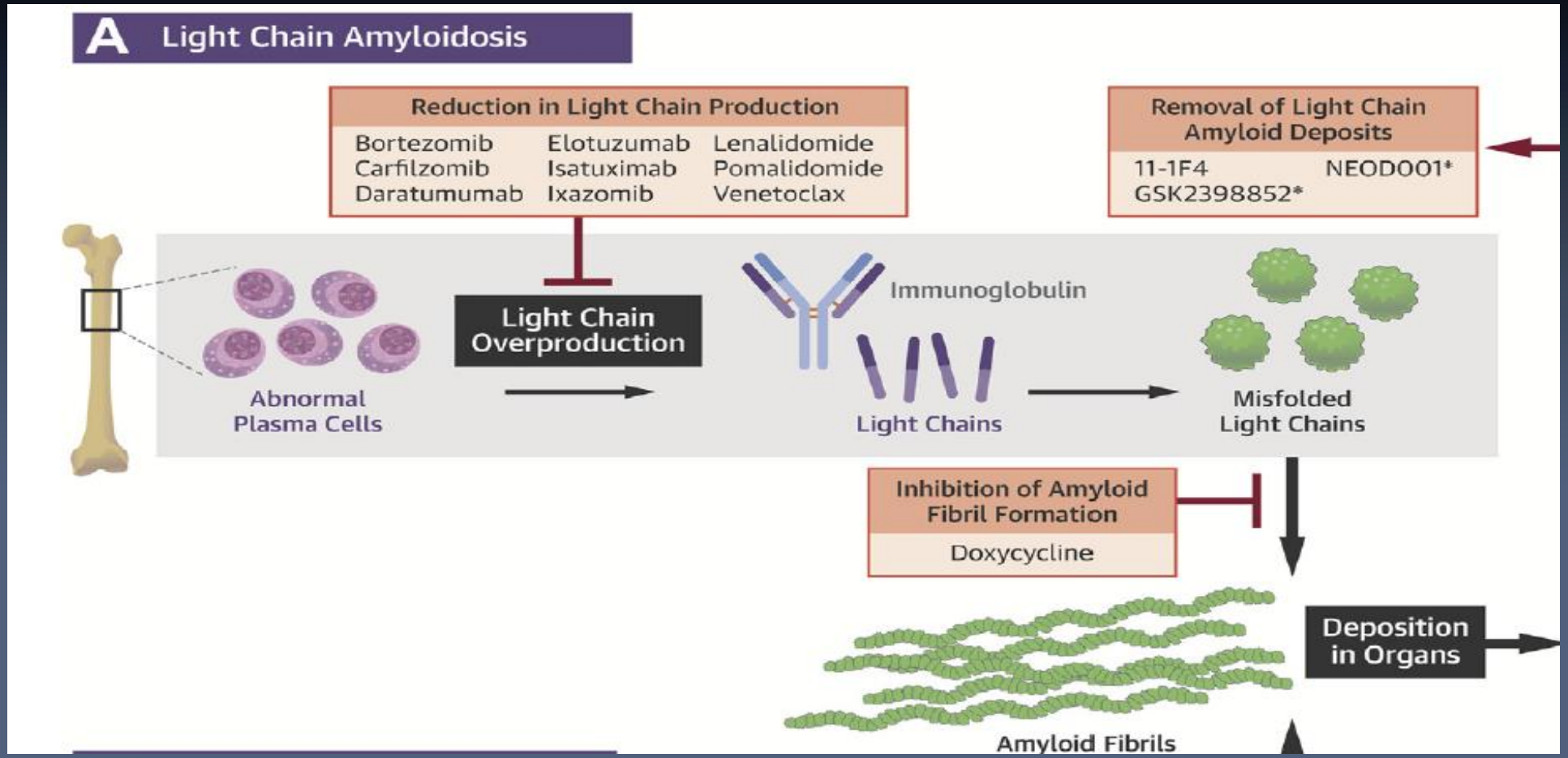
Endomyocardial Biopsy?

- No tissue biopsy confirmation/and a definitive diagnosis is needed
- Positive biopsy for amyloid from noncardiac site
  - Uncertain ATTR genotype
  - Familial ATTR genotype but confounding information
- Patients considered for cardiac transplantation
- Hemodynamic assessment for medical management
- Can usually be avoided
  - Suspected familial/wild-type ATTR amyloid w positive radionuclide scan/SFLC ratio
    - ATTR genotype from peripheral blood /saliva can aid in identifying known mutation
  - AL amyloid -Dx can often be made with a combination of SFLC and extracardiac biopsy

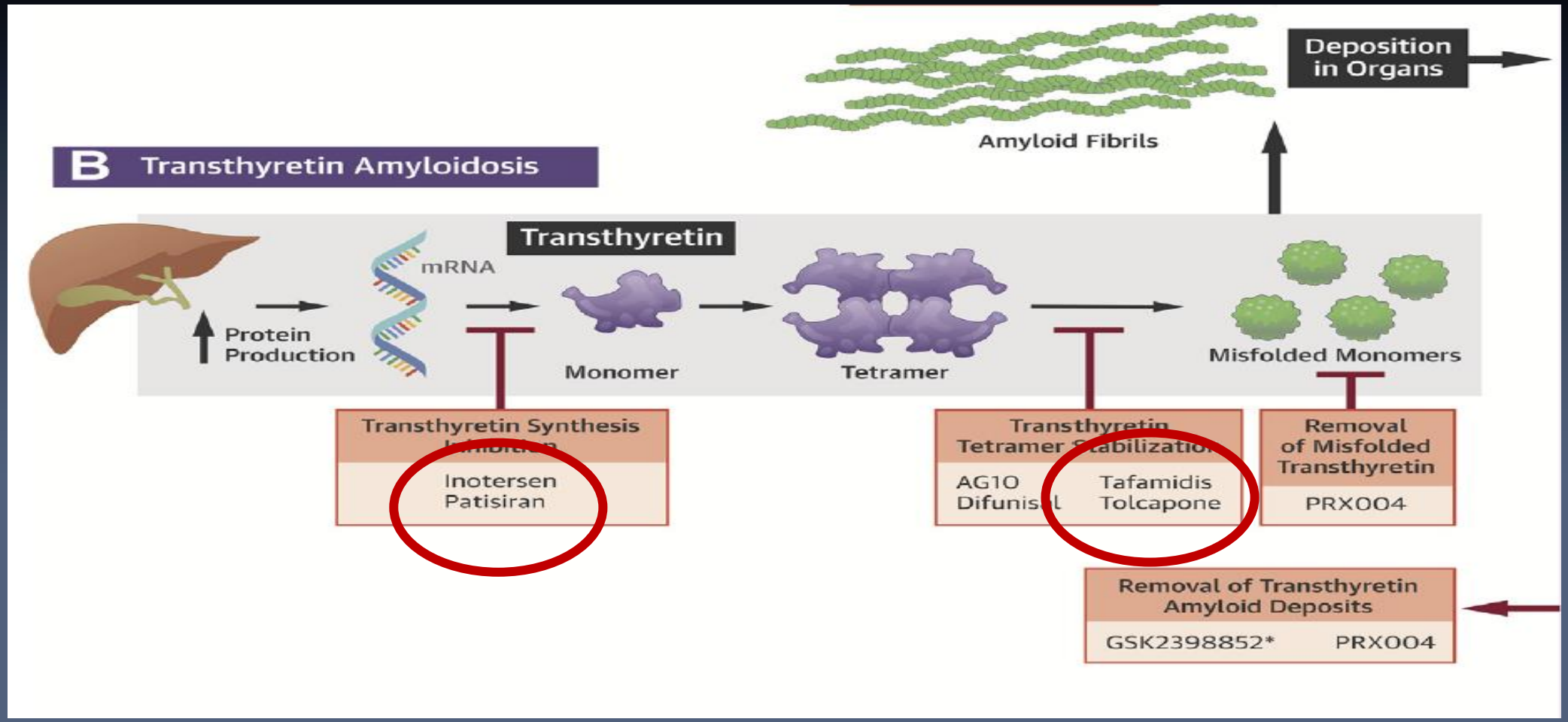
Treatment: Cardiac-Specific

- 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
- Treatment of atrial & ventricular arrhythmias

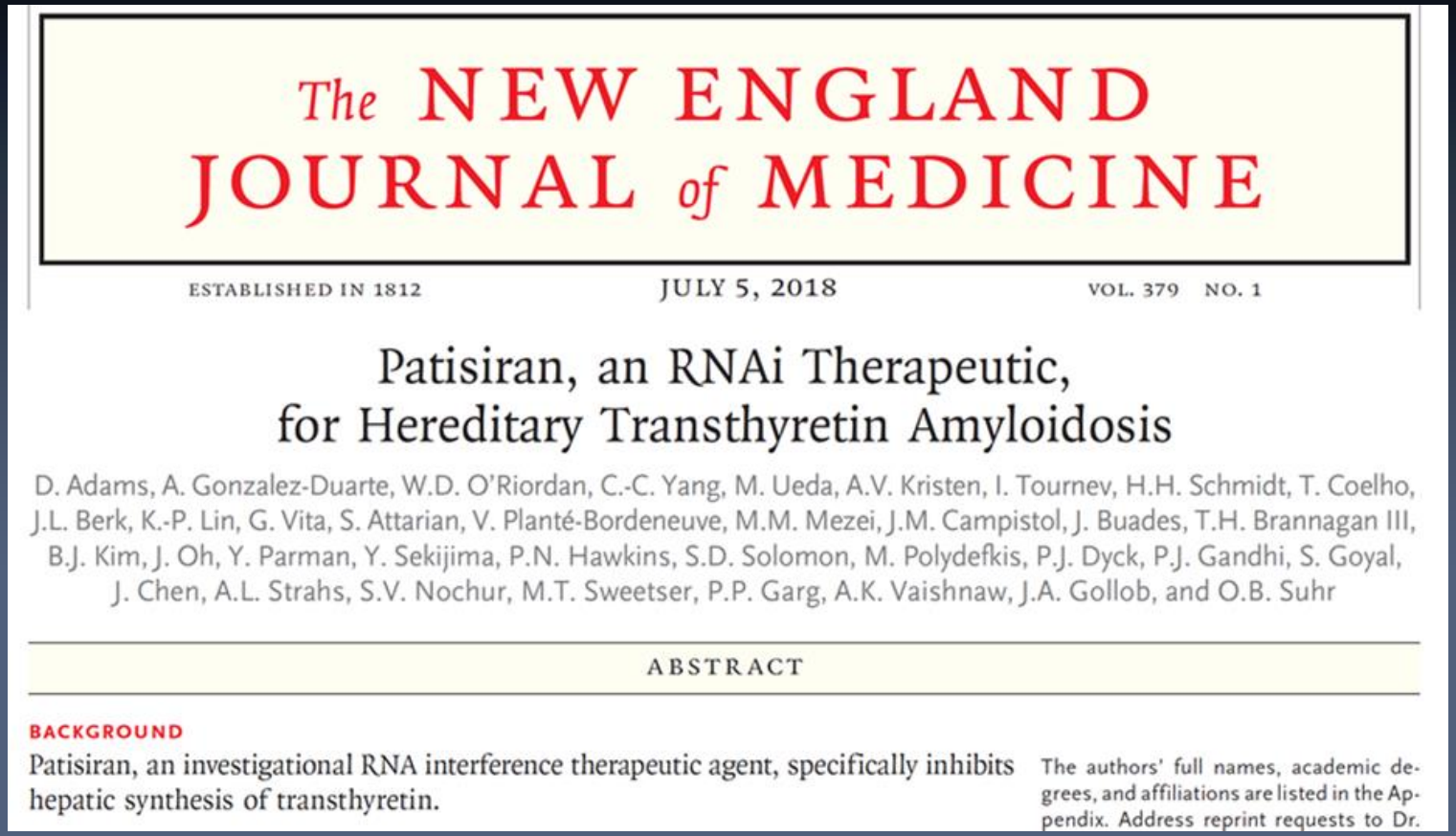
Therapeutic approaches to AL -CA



Therapeutic approaches to ATTR - CA



APOLLO – Hereditary with polyneuropathy



The NEW ENGLAND JOURNAL of MEDICINE

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

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

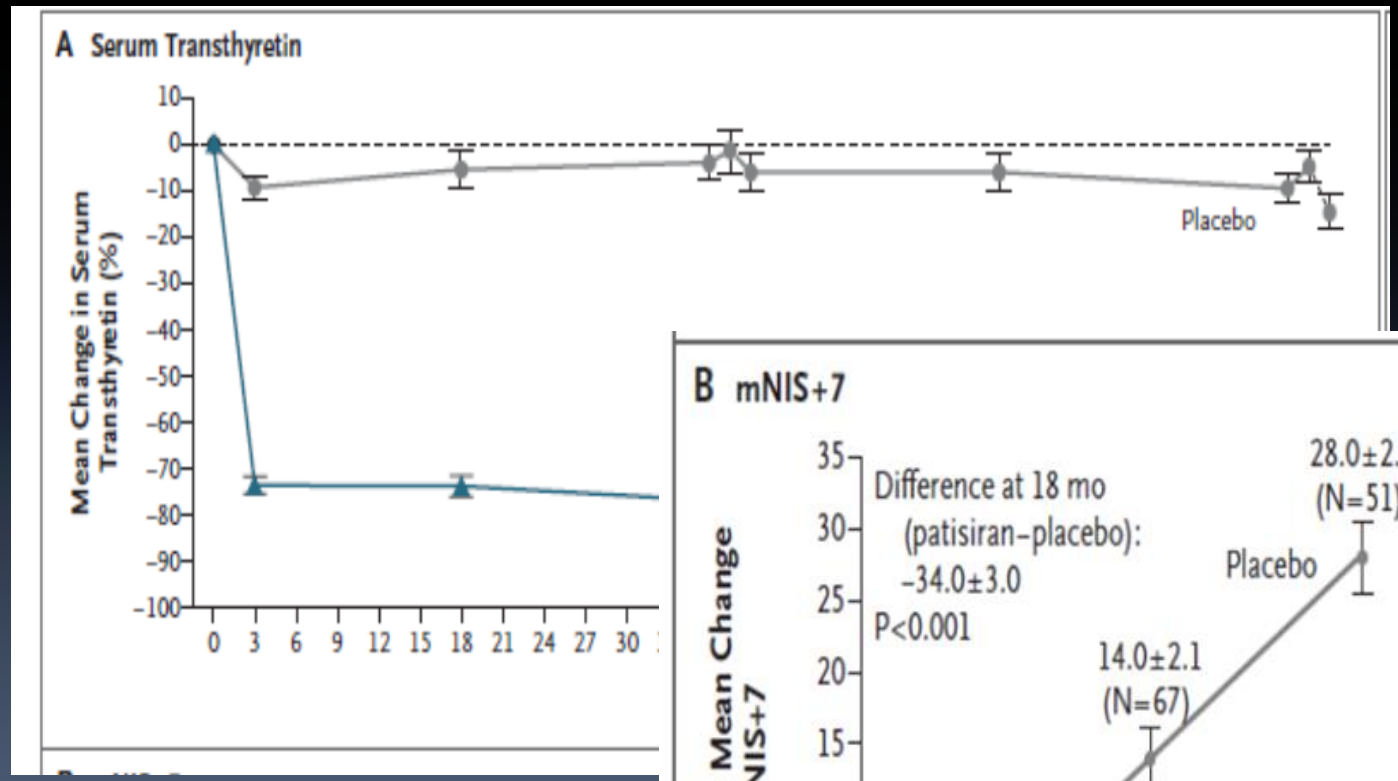
D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. 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

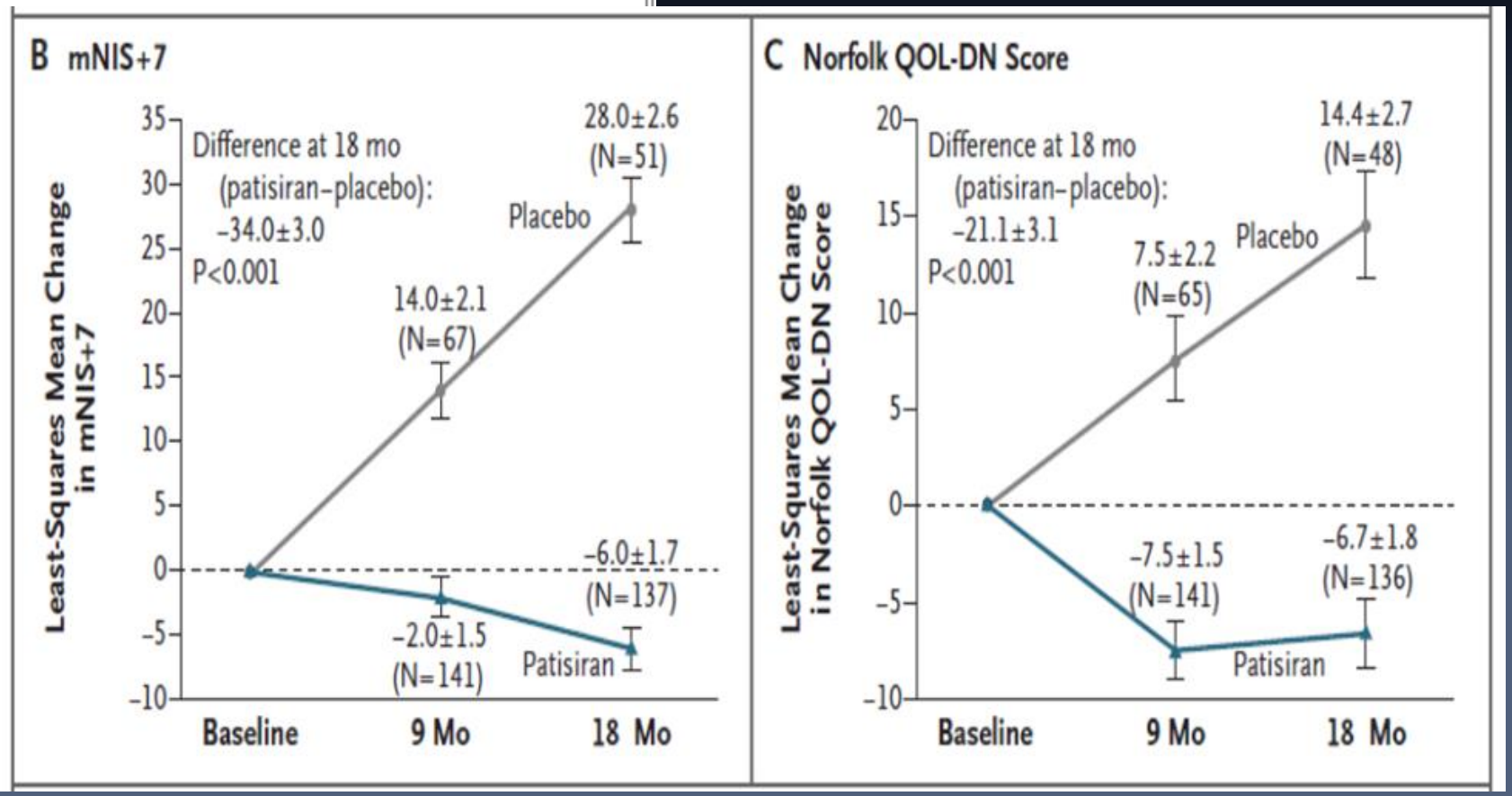
ABSTRACT

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.


A Serum Transthyretin
Mean Change in Serum Transthyretin (%)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 3 6 9 12 15 18 21 24 27 30
Placebo


B mNIS+7
Least-Squares Mean Change in mNIS+7
35
30
25
20
15
10
5
0
-5
-10
Difference at 18 mo
(patisiran–placebo):
-34.0±3.0
P<0.001
28.0±2.6
(N=51)
Placebo
14.0±2.1
(N=67)
-6.0±1.7
(N=137)
-2.0±1.5
(N=141)
Patisiran
Baseline
9 Mo
18 Mo
C Norfolk QOL-DN Score
Least-Squares Mean Change in Norfolk QOL-DN Score
20
15
10
5
0
-5
-10
Difference at 18 mo
(patisiran–placebo):
-21.1±3.1
P<0.001
14.4±2.7
(N=48)
Placebo
7.5±2.2
(N=65)
-7.5±1.5
(N=141)
-6.7±1.8
(N=136)
Patisiran
Baseline
9 Mo
18 Mo

ATTRACT – Wild type and mutation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

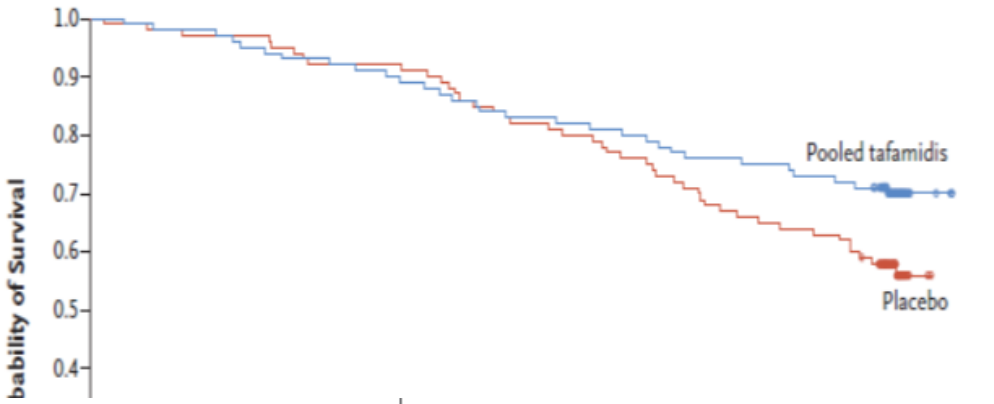
Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, 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*

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients / at Mo
				no. (%
Pooled Tafamidis	264			186 (70
		<0.001	1.70 (1.26–2.29)	
Placebo	177			101 (57

Average Cardiovascular-Related

B Analysis of All-Cause Mortality



15 18 21 24 27 30 33

nths since First Dose

9) 222 (42) 216 (48) 209 (55) 200 (64) 193 (71) 99 (78) 0 (78)
6) 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	
Placebo	177	107 (60.5)	0.70	0.68 (0.56–0.81)

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.

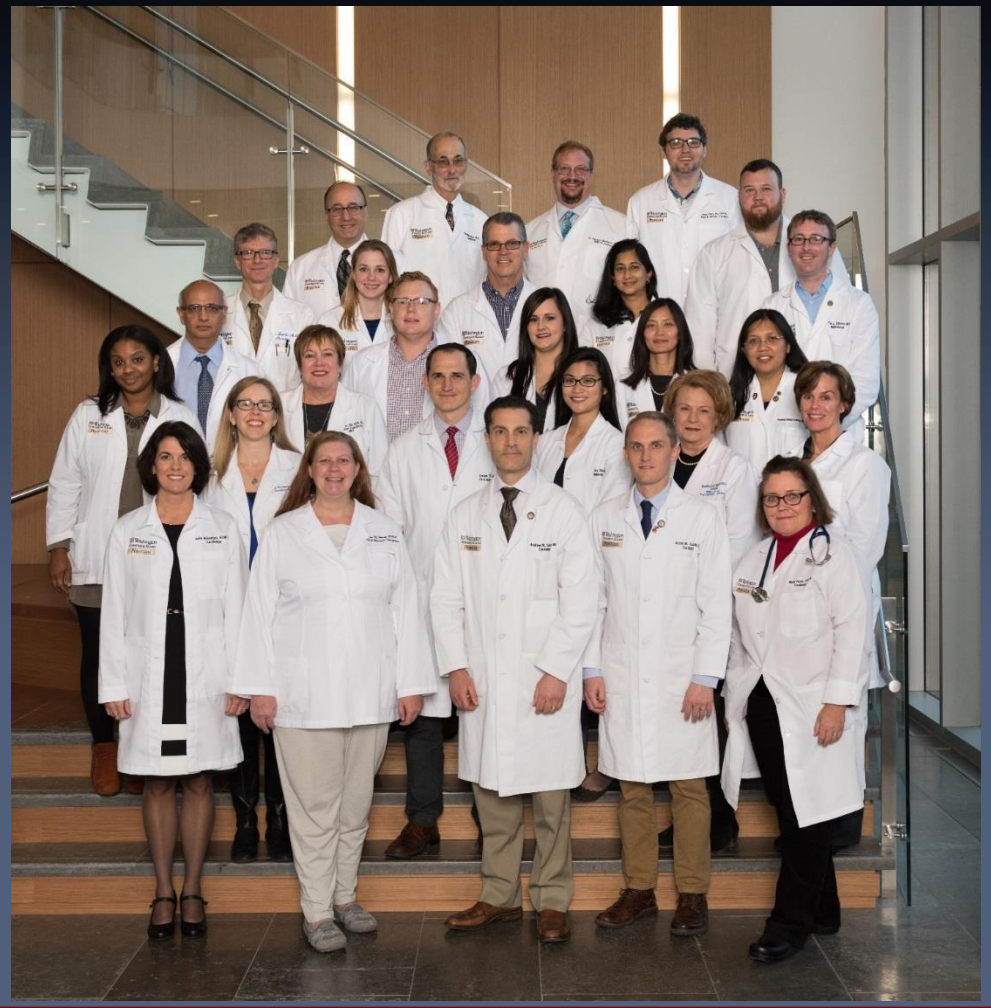
Current strategies

- Clinical awareness and early diagnosis are critical
- Cardiac amyloidosis results from distinctive disease processes
  - Differing treatment strategies and prognoses
- Initial presentation is insidious
  - LVH on imaging is commonly the first phenotypic abnormality
- Optimal treatment varies greatly from the usual treatment of HF
- Many potential targets for therapies
- New therapies are in development and now available

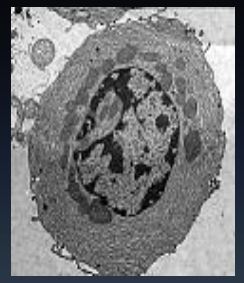
Amyloidosis Center of Excellence (ACE) @ Wash U

Multidisciplinary Team

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



Immunoglobulin light chain amyloidosis (AL)



Plasma cell clone

Misfolded light chain

Interactions with cells & microenvironment (GAGs, metals, proteases, shear forces) of target organs

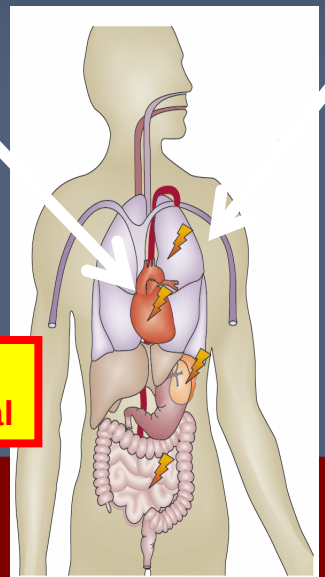
SAP

- **Heart 76%**
  - (NYHA≥II, 47%)
- **Kidney 68%**
  - Nephrotic s. 42%
  - Renal failure 45%
- Liver 15%
- GI 8%
- Soft tissues 17%
- PNS/ANS 12%/10%

Proteotoxicity

Oligomers

Amyloid fibrils



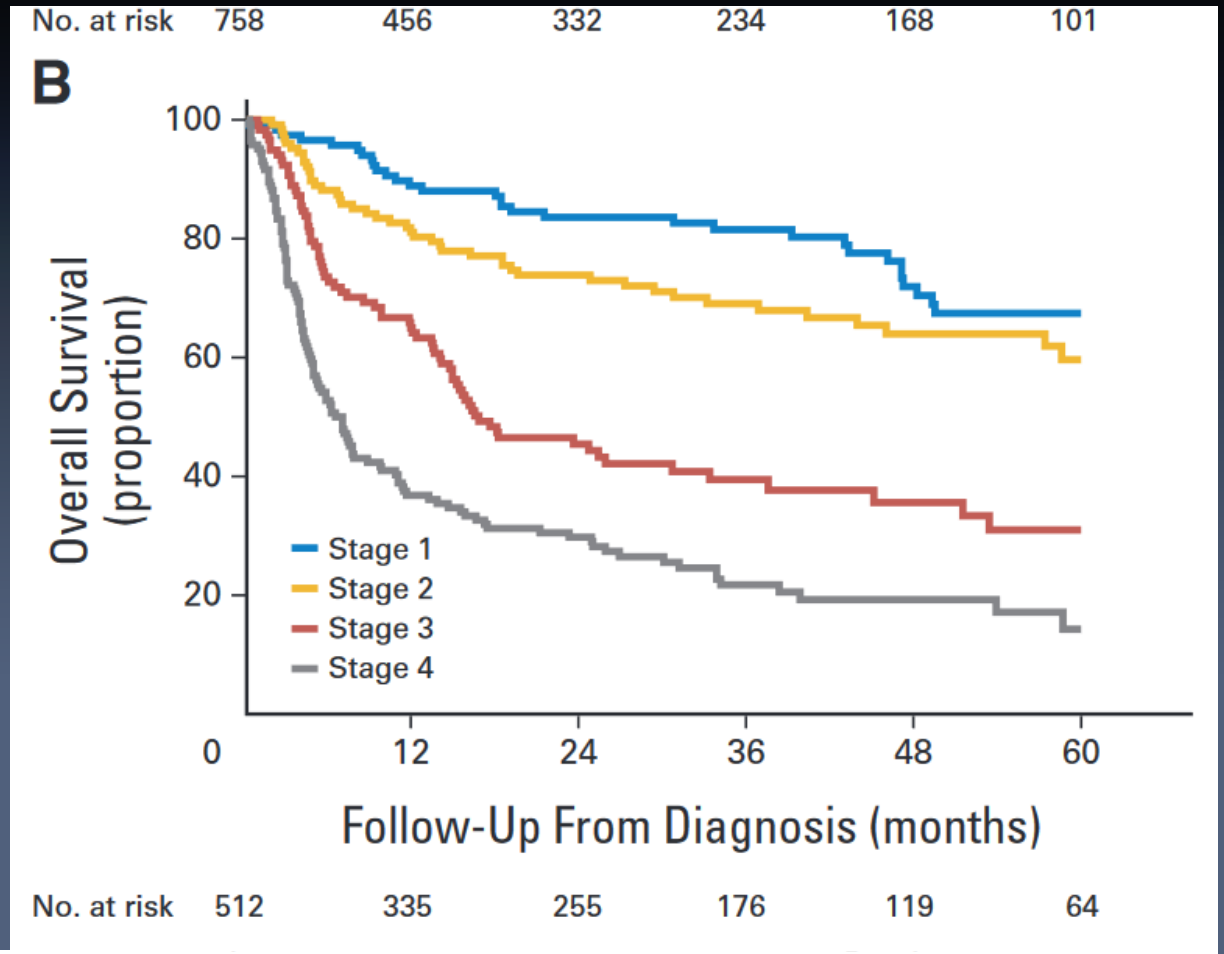
Organ dysfunction and reduced survival

Adapted from Merlini

Staging for AL Amyloidosis

Using 1 point for each cutoff:

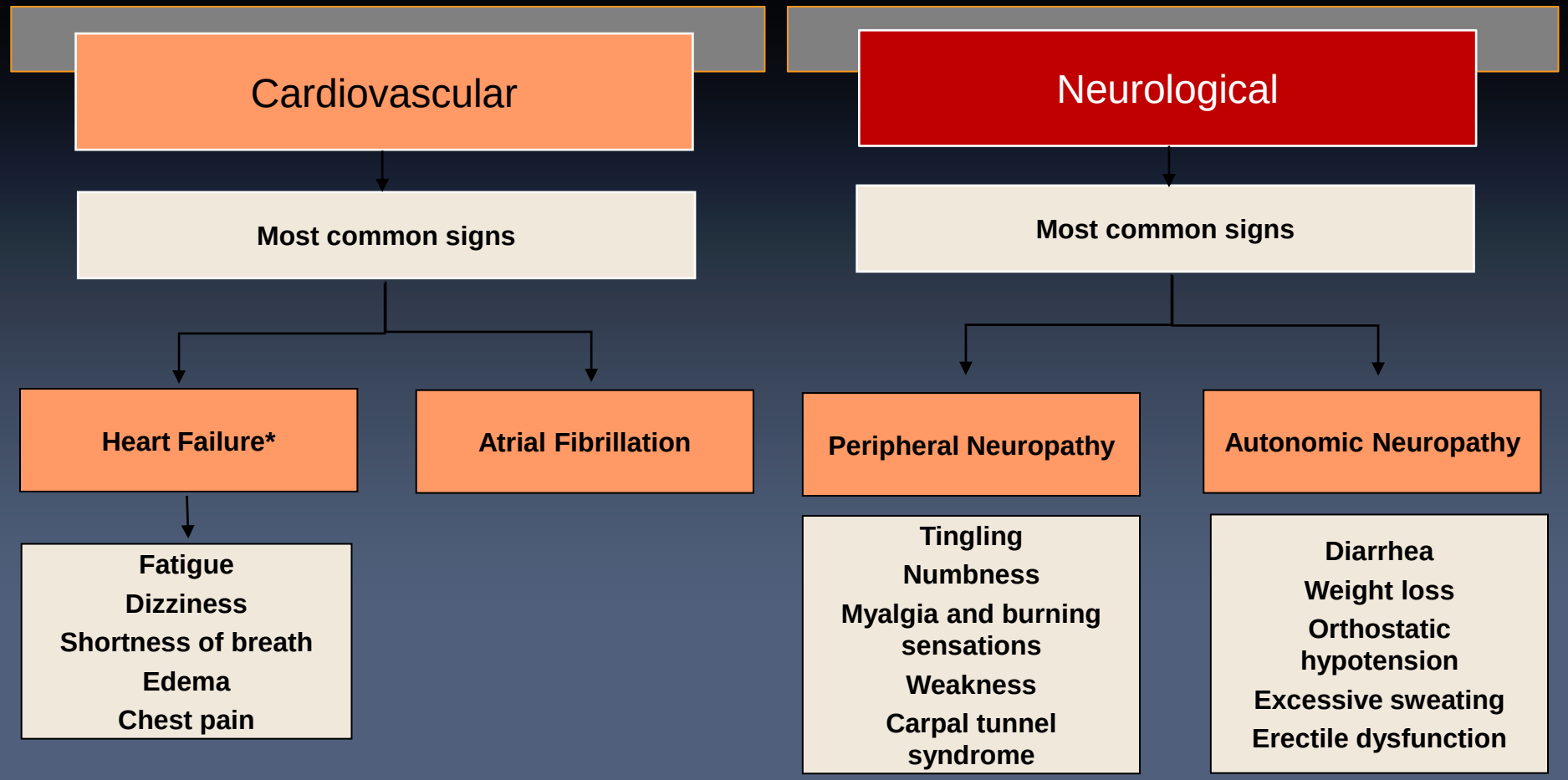
TnT > 0.025
NTproBNP >1800
Free Light chain> 18mg/dL



(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

Kumar, S et al JCO 2012

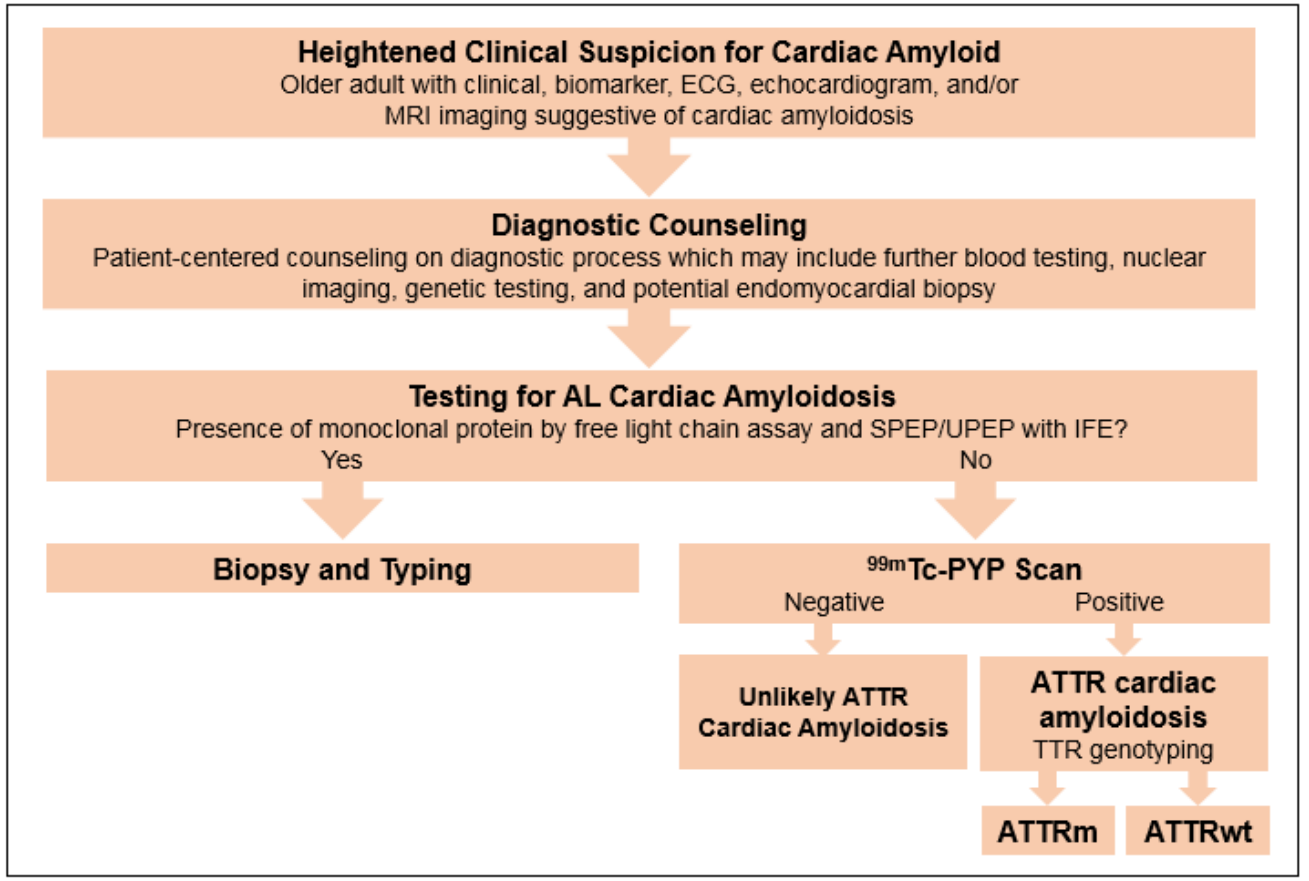
Clinical presentation of ATTR-CM can have cardiovascular or neurological origins



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

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.

Proposed staging for ATTR

Cutoffs:

- NTproBNP >3000 ng/L
- EGFR <45ml/min/1.73m2
- If both negative= Stage I
- If both present= Stage III

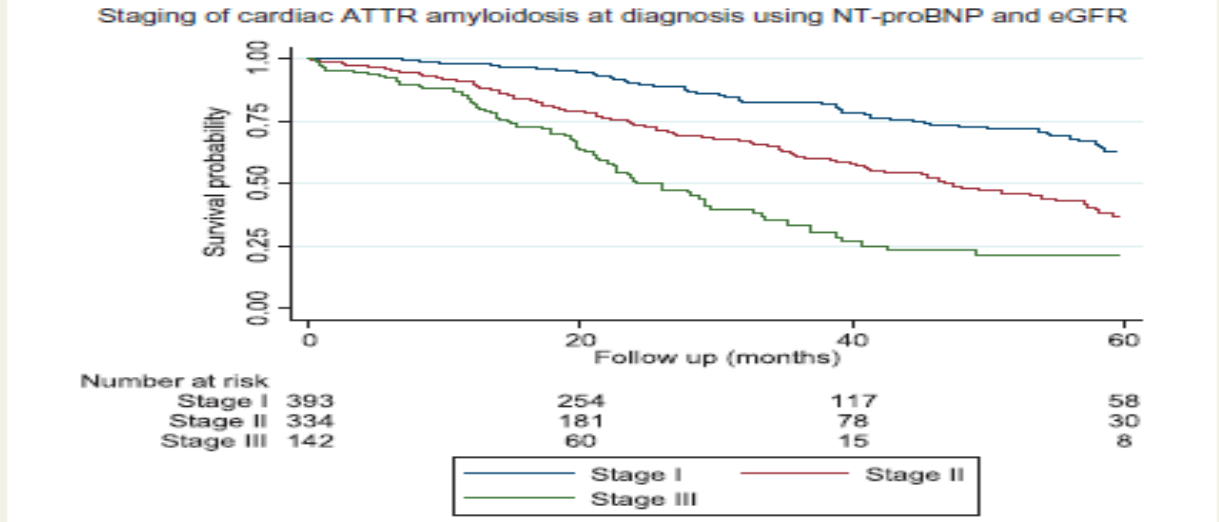


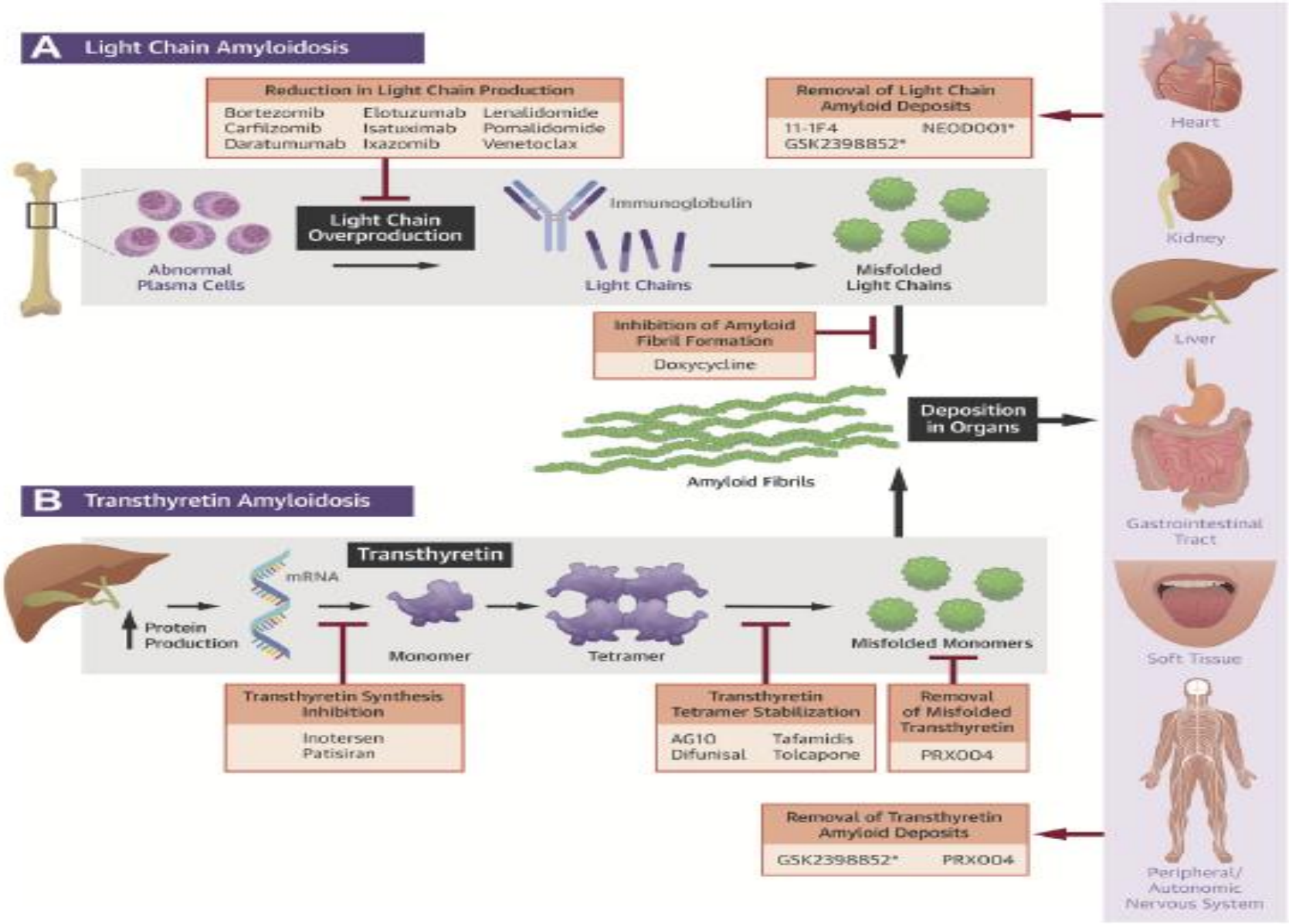
Figure 2 Kaplan–Meier curves showing survival probabilities in 869 patients with cardiac transthyretin amyloidosis stratified by disease stage (log-rank test; Stage I vs. Stage II, $P < 0.0001$; Stage II vs. Stage III, $P < 0.0001$). Stage I patients had a median survival of 69.2 months (95% CI lower 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

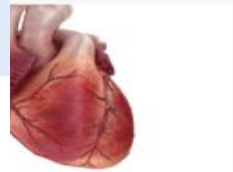
A. Li

B. T

CENTRAL ILLUSTRATION Pathophysiology of Light Chain and Transthyretin Amyloidosis and Mechanism of Action of Novel Therapeutics



Zhang, K.W. et al. J Am Coll Cardiol Basic Trans Science. 2019;■(■):■-■.


Heart


Kidney


Liver


ntestinal Tract


oft Tissue


al/Autonomic
us System

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]

amyloidosis.org

Our key priorities:

- Raising awareness in the medical field for an earlier diagnosis.
- Educating medical professionals through our Grand Rounds program and attendance at medical conferences.
- Empowering patients through our comprehensive range of services, including accurate up to date information.