Update in Internal Medicine 2020

Cardiac Amyloidosis

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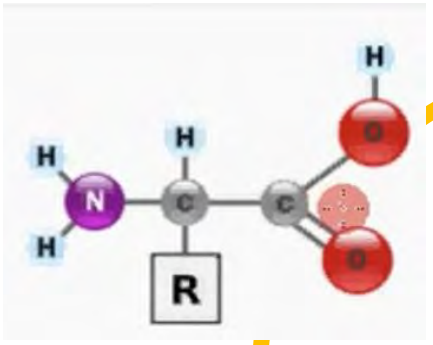
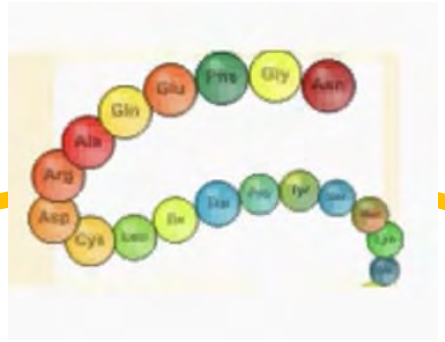
University of Pittsburgh

Protein Folding

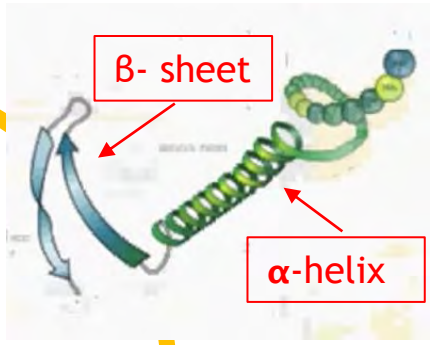
Amino acid

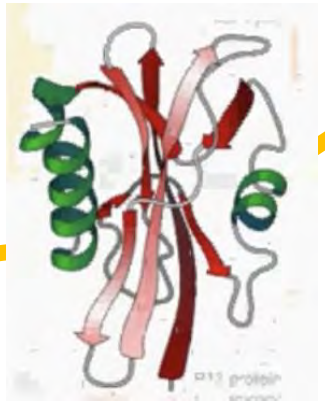


Primary structure



Secondary structure

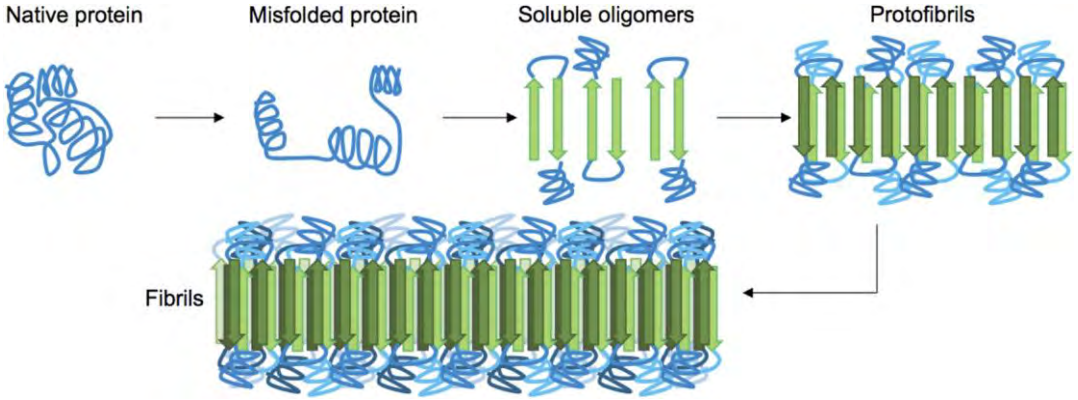


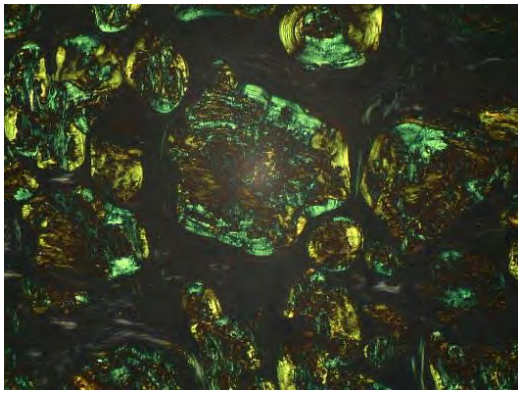


Tertiary structure

Quaternary structure

Amyloidosis: Protein Misfolding





Cardiac Amyloidosis

- **AL**
- **ATTR**
  Mutant and WT
- **Rare varieties**
  Apolipoprotein A
  Immunoglobulin heavy chain
  Fibrinogen alpha chain
  Gelsolin

> 95%

Kaminski CF. Neurophotonics 2016
doi:10.1117/1.NPh.3.4.041807

TTR Cardiac Amyloidosis Is Not A Rare Disease

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

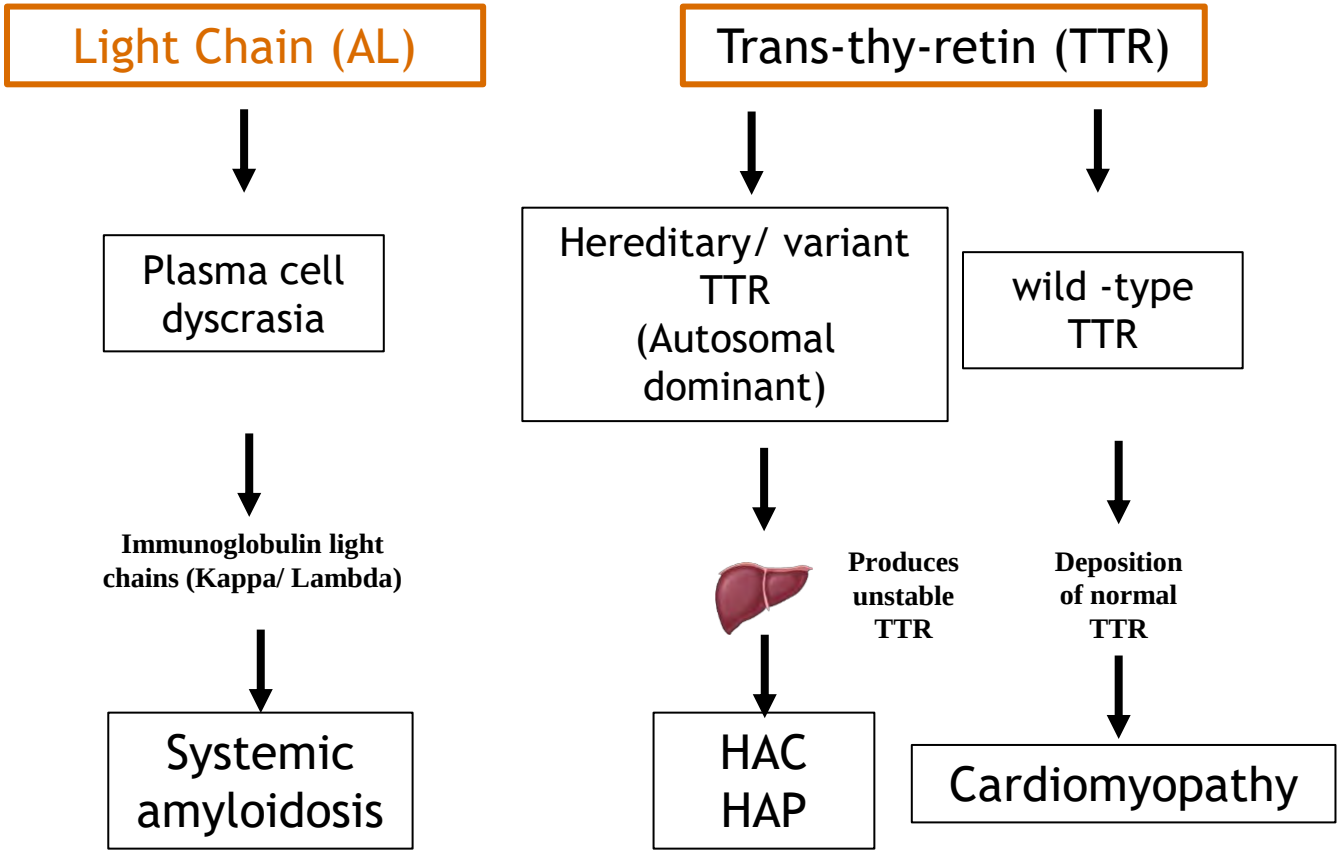
CLINICAL RESEARCH
Heart failure/cardiomyopathy

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

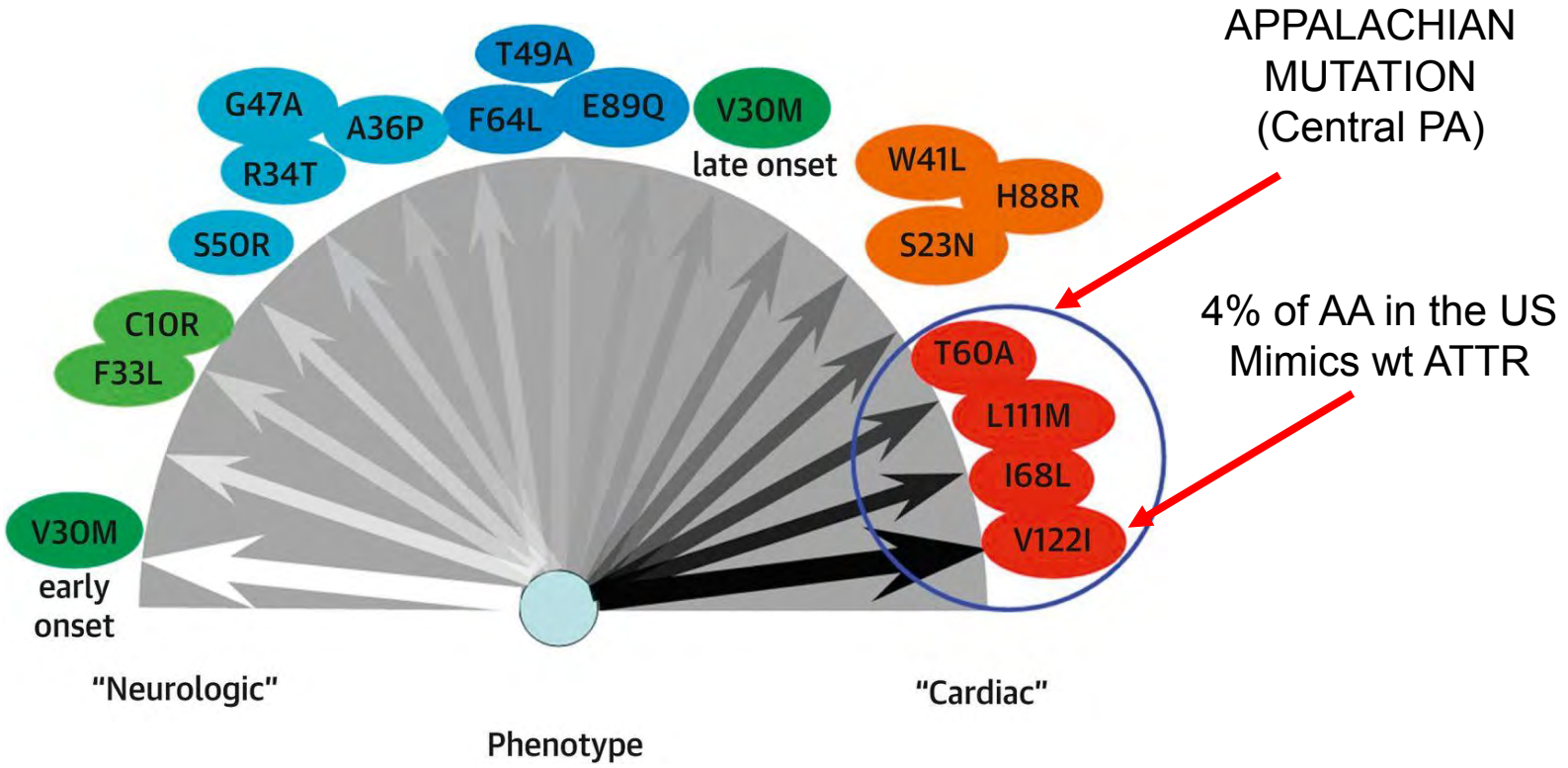
Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*

- 13% of HFpEF patients with thick LV
- 12% of patients with low gradient severe aortic stenosis

Cardiac Amyloidosis



Genotypes and phenotypes of common TTR mutations



TTR gene: Long arm of chromosome 18

V122I or pV144I

JACC 2016; 68:173-5.

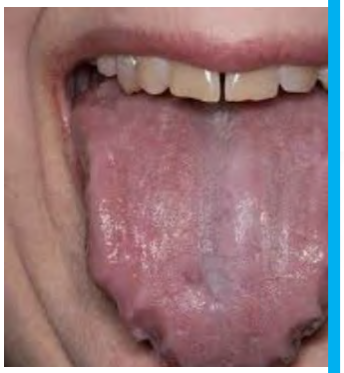
When to suspect cardiac amyloid?

Diagnosis of Cardiac Amyloidosis

- Requires a high degree of suspicion
- Diagnosis is generally delayed by 2-3 years after the initial presentation

Clinical Features

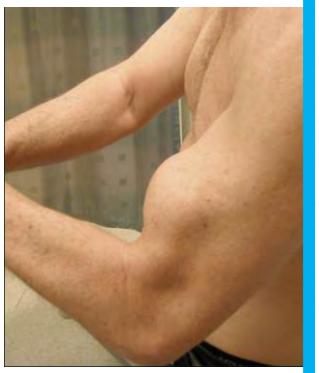
SYSTEMIC (AL) AM



MACROGLOSSIA

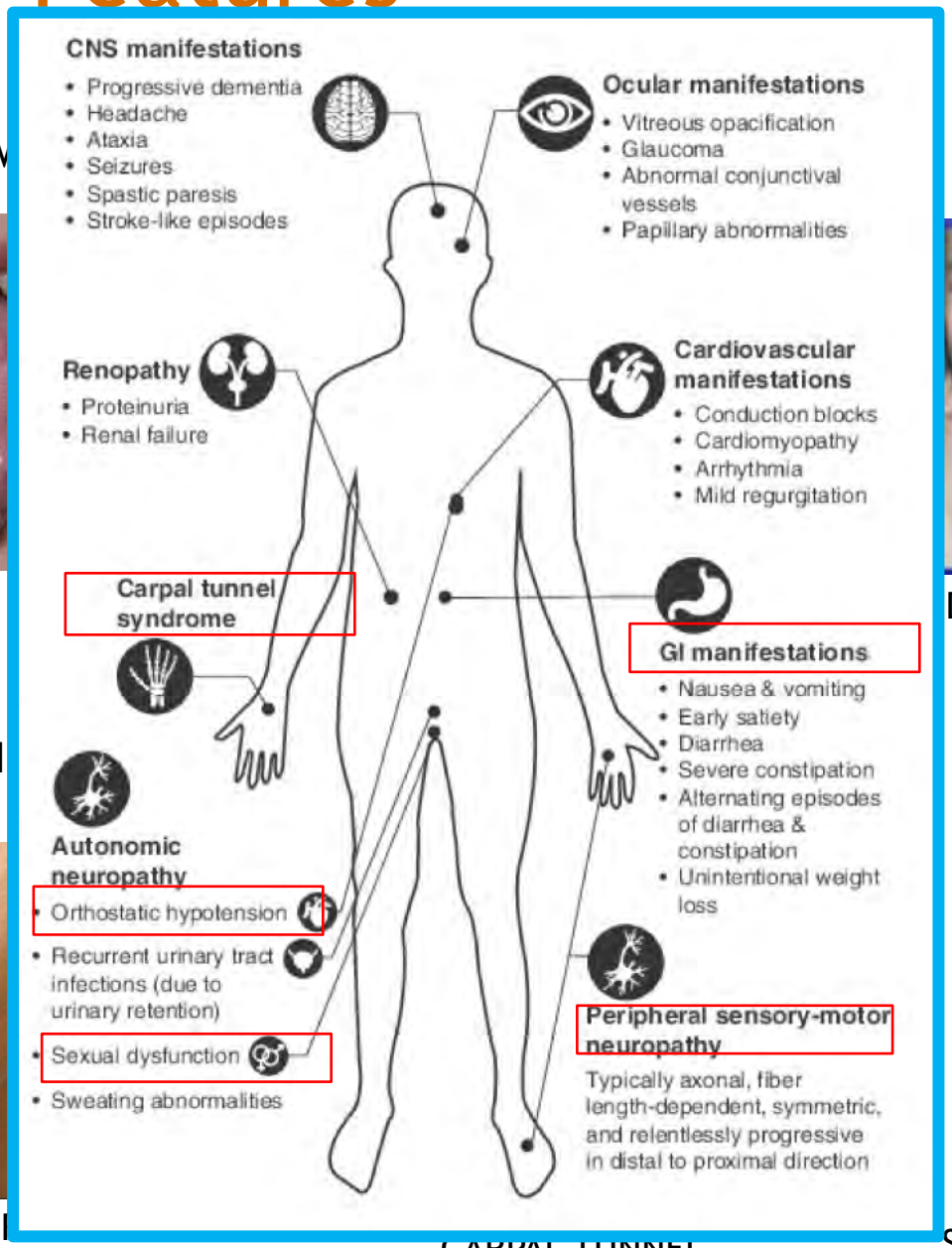
D DEPOSITS

ATTRwt AMYLOI



TENDON RUPTUI

SPINAL STENOSIS



CARPAL TUNNEL

Clinical Alerts for amyloidosis

- B/L carpal tunnel in male with HFpEF (50% in w-ATTR, ~5-7 year before diagnosis)
- Unexplained LVH, Discrepant ECG voltage
- New Dx of HCM ≥ 60 y: asymmetrical LV thickening is not uncommon in amyloidosis
- Orthostatic hypotension, Unexplained neuropathic pain
- wt ATTR is not exclusively a disease of men

ECG in Cardiac Amyloidosis

"Classic" ECG

Low Voltage ECG is Uncommon in Amyloidosis

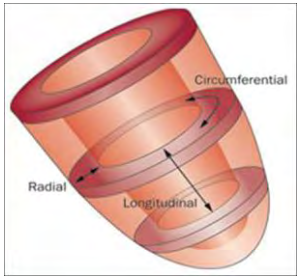
Low Voltage ECG:AL-50%; ATTR-25%

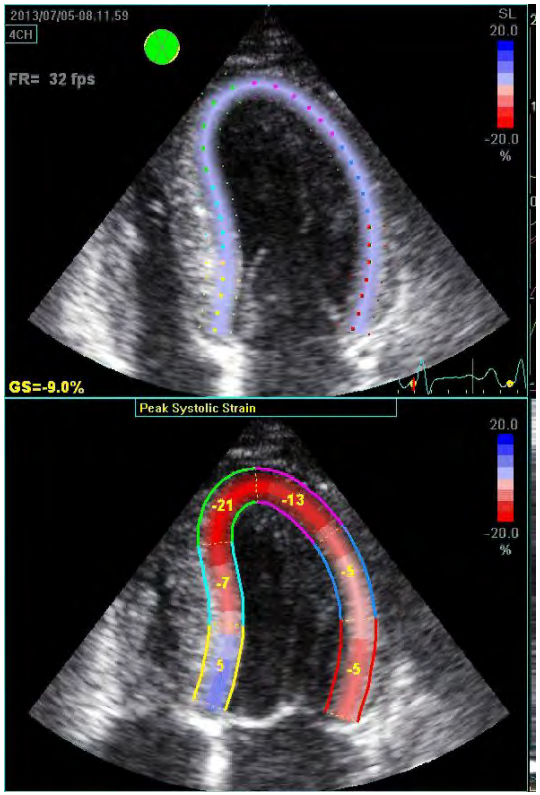
Commonest ECG: pseudo infarct pattern/ AV block

10-20% have overt LVH

Voltage –LV thickness discordance: Total QRS score to LWT ratio

Echocardiography





Thick LV

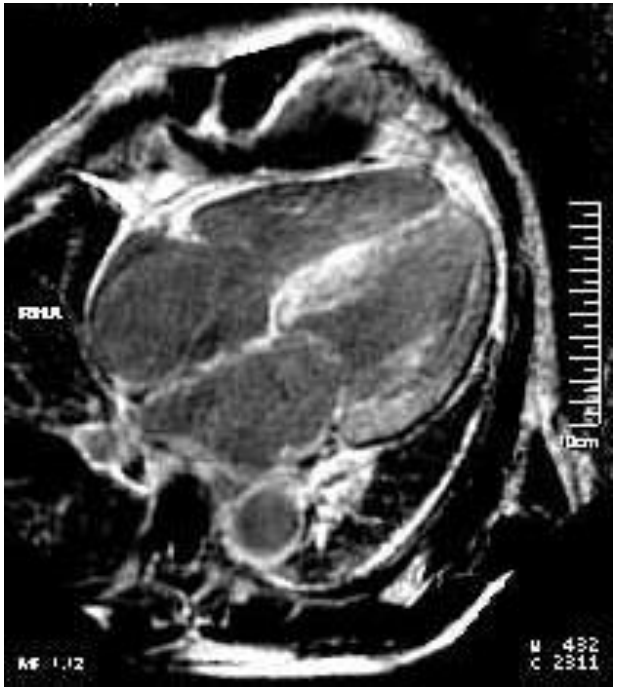
+ Pericardial effusion, thick IAS

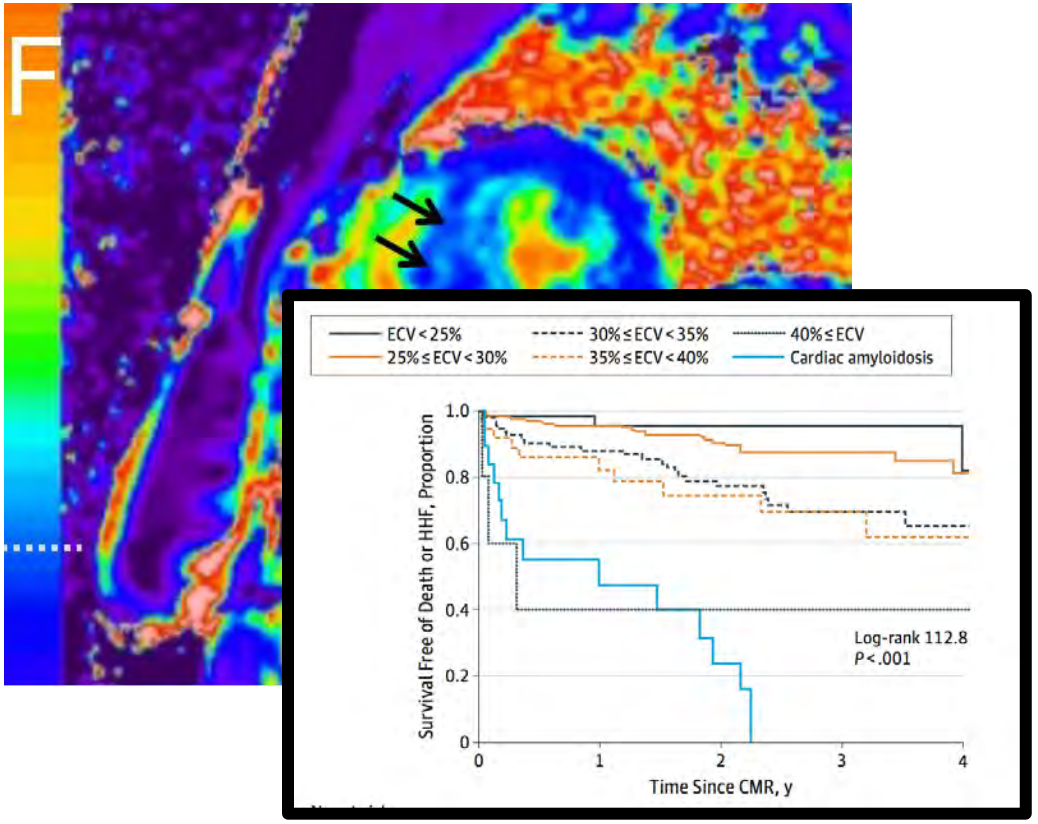
thick RV, thick valves, large atria

Asymmetrical septal hypertrophy can occur

Apex- sparing longitudinal strain abnormality

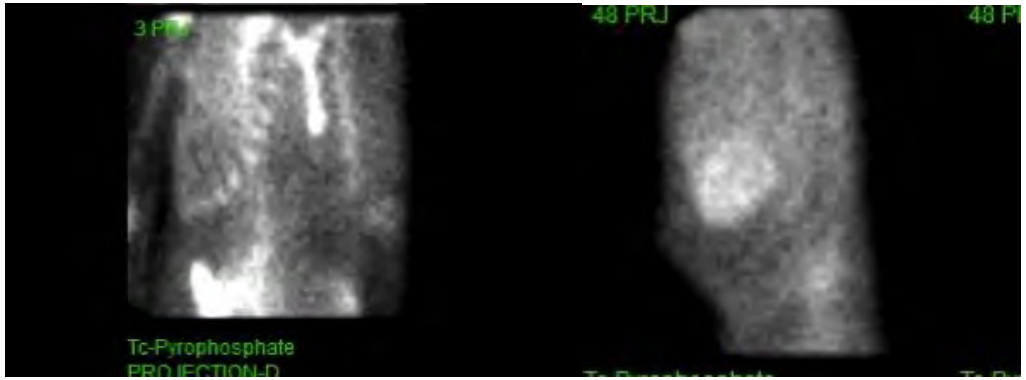
Cardiac MRI



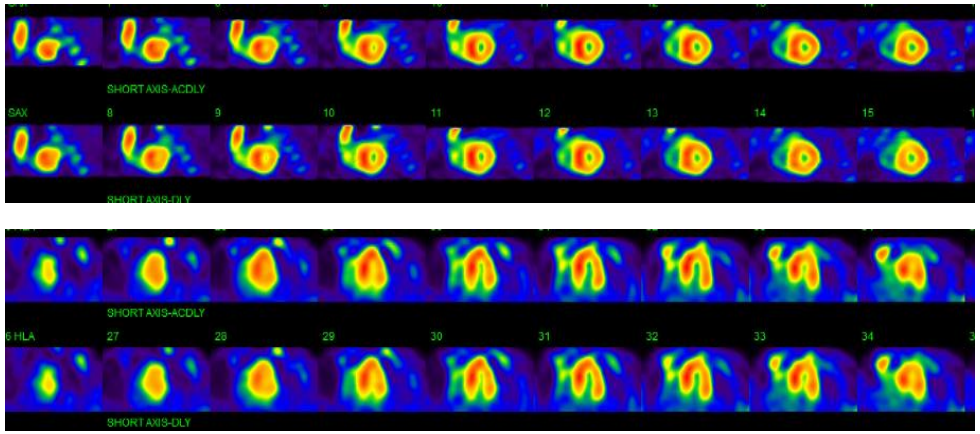


Timothy Wong/ Erik Schelbert. JAHA 2013

Tc- Pyrophosphate Scan (Bone-seeking tracer)



Planar



SPECT

Circulation

ORIGINAL ARTICLE

Non-Biopsy Diagnosis of Cardiac Transthyretin Amyloidosis

Julian D. Gillmore, Mathew S. Maurer, Rodney H. Falk, Giampaolo Merlini, Thibaud Damy, Angela Dispenzieri, Ashutosh D. Wechalekar, John L. Berk, Candida C. Quarta, Martha Grogan, Helen J. Lachmann, Sabahat Bokhari, Adam Castano, Sharmila Dorbala, Geoff B. Johnson, Andor W.J.M. Glaudemans, Tamer Rezk, Marianna Fontana, Giovanni Palladini, Paolo Milani, Pierluigi L. Guidalotti, Katarina Flatman, Thirusha Lane, Frederick W. Vonberg, Carol J. Whelan, James C. Moon, Frederick L. Ruberg, Edward J. Miller, David F. Hutt, Bouke P. Hazenberg, Claudio Rapezzi and Philip N. Hawkins

DOI http://dx.doi.org/10.1161/CIRCULATIONAHA.116.021612

Published Ahead of Print: April 22, 2016

Tc-PYP must be interpreted with serum/urine studies to exclude AL

Serum Free Light Chains, Ratio

+

Serum and Urine Immunofixation electrophoresis (IFE)

(not SPEP/UPEP)

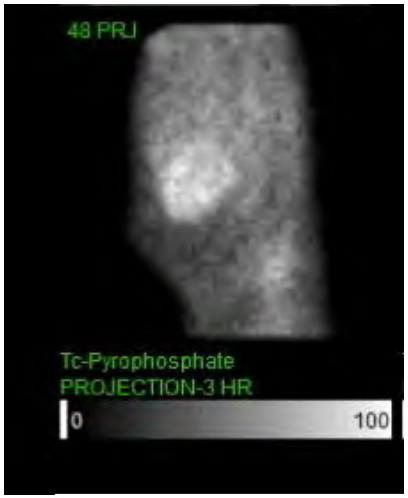
	Sensitivity	Specificity
All grades	>99%	86%
Grades II and III	90%	97%*

*Grade II or III + normal serum = 100% specific

AL MAY SHOW MILD UPTAKE

Gilmore J. Circulation 2016

Definitive Diagnosis of ATTR CM



+ve PYP

+

Free Light Chains + Ratio

Serum and Urine Immunofixation Electrophoresis

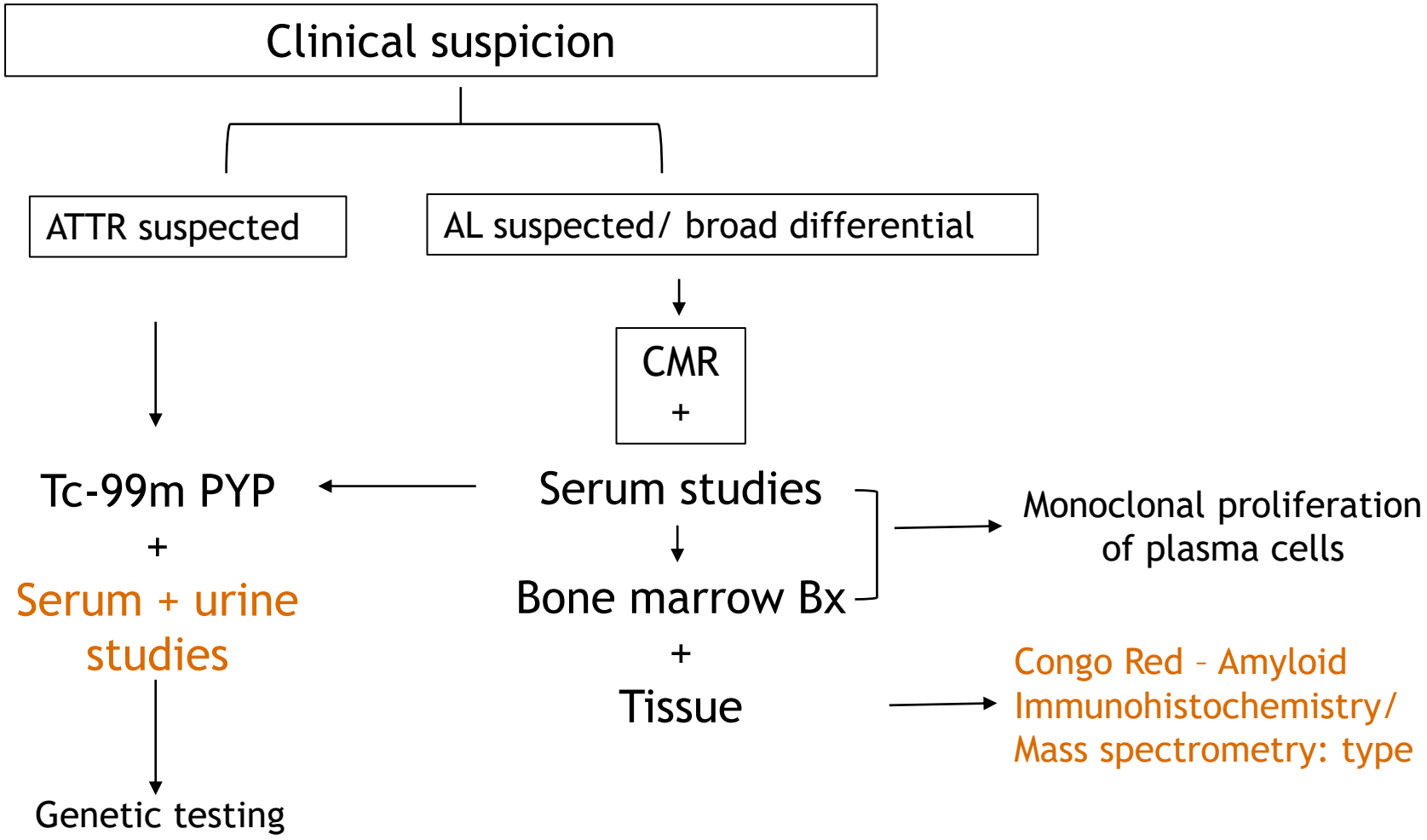
-ve paraprotein

OR

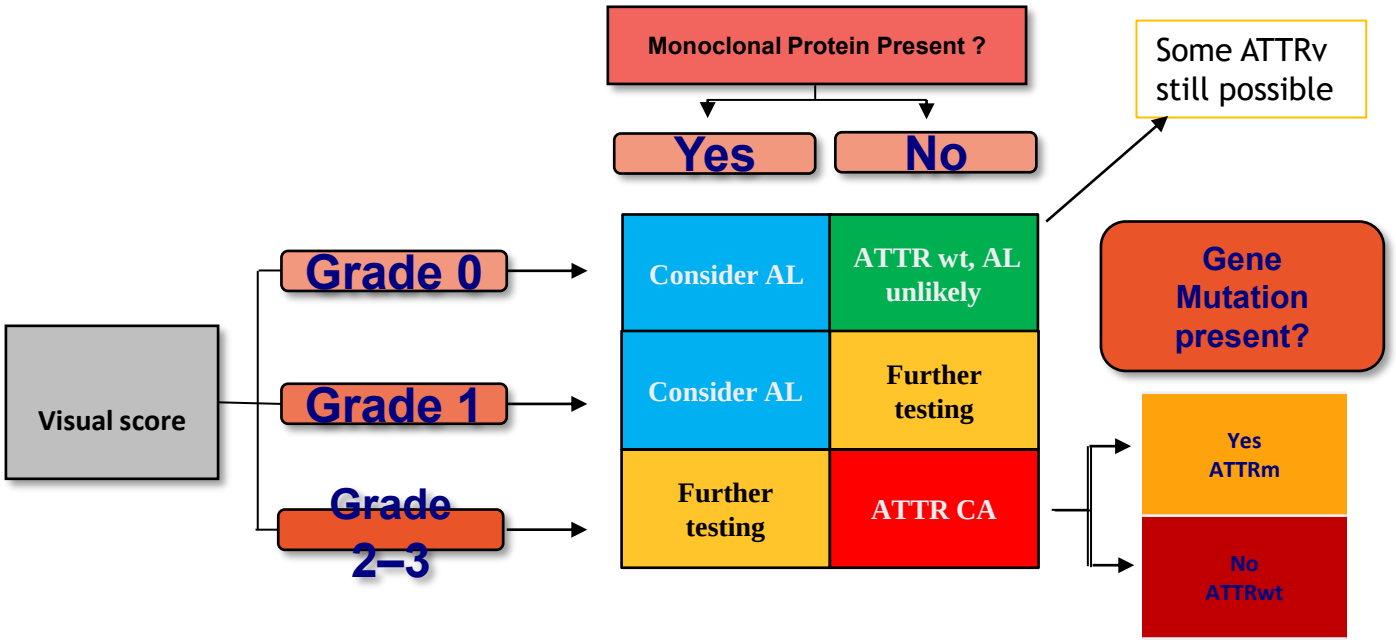
Biopsy + amyloid typing by Immunohistochemistry, Immunoelectron microscopy, laser microdissection/mass spectrometry

Critical to differentiate from AL

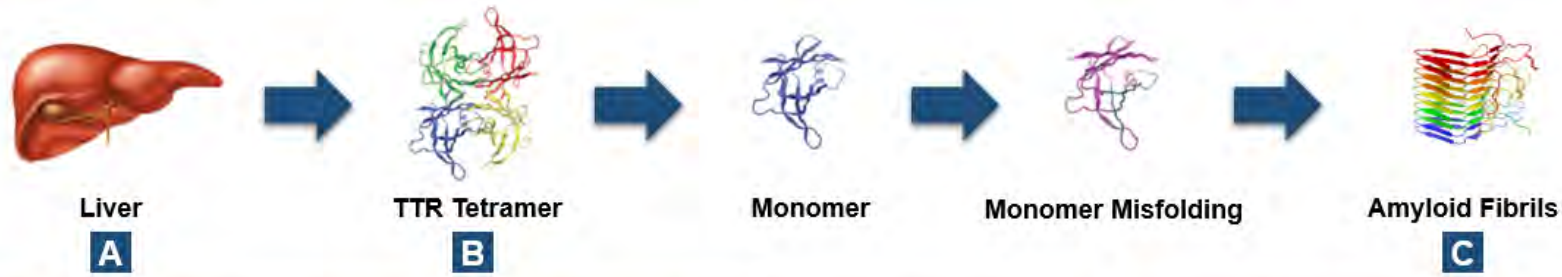
Diagnostic Principles



Making a Diagnosis of ATTR CA Using PYP and Monoclonal Protein

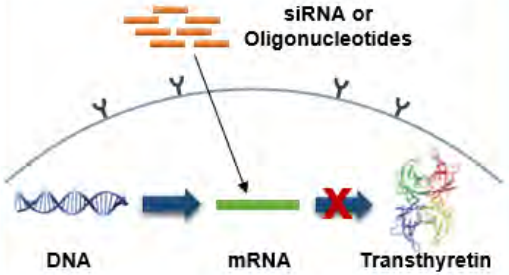


TTR Therapies



A Suppression of TTR Synthesis

- ❑ Liver transplantation
- ❑ Gene silencing
  - Patisiran: (SiRNA)
  - Inotersan: (ASO)



B TTR Stabilization

- ❑ Diflunisal (non-selective)
- ❑ Tafamidis (selective)
- ❑ AG-10 (selective)
- ❑ Tolcapone
- ❑ EGCG (Green Tea)

C Fibril Degradation & Reabsorption

- ❑ Doxycycline
- ❑ Doxycycline + TUDCA
- ❑ CPHPC + SAP Antibodies
- ❑ NEOD001
- ❑ Anti-amyloid mAb 11-1F4

Liver Transplantation

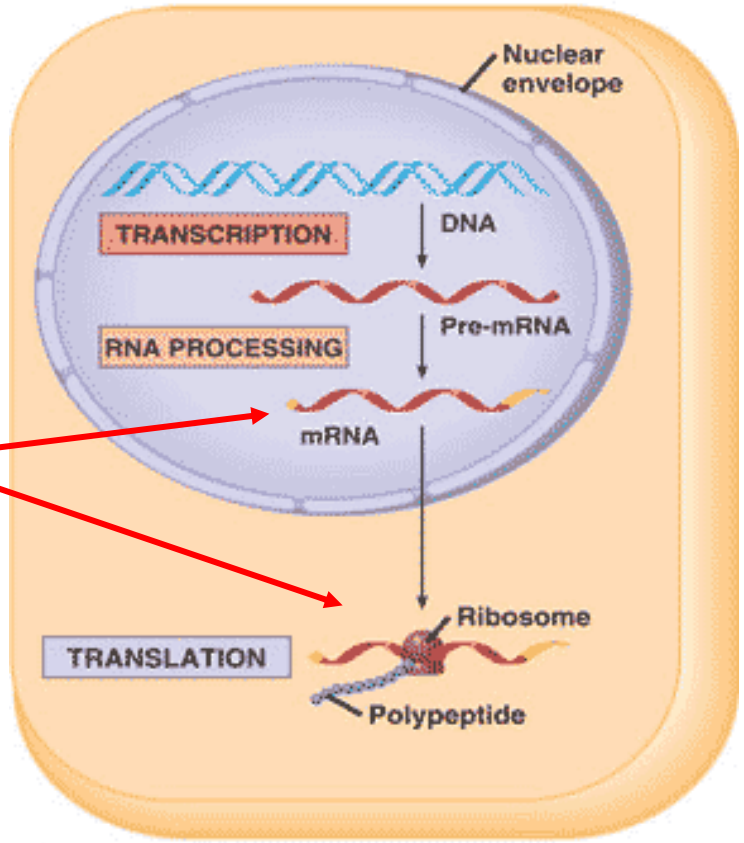
- ~2000 so far (more non-US/ neuropathy)
- 10-year survival is 80%
- Retards progress/ does not reverse (cardiomyopathy can progress)
- Domino transplants discontinued

RNA Silencing Mechanism
Protein Synthesis

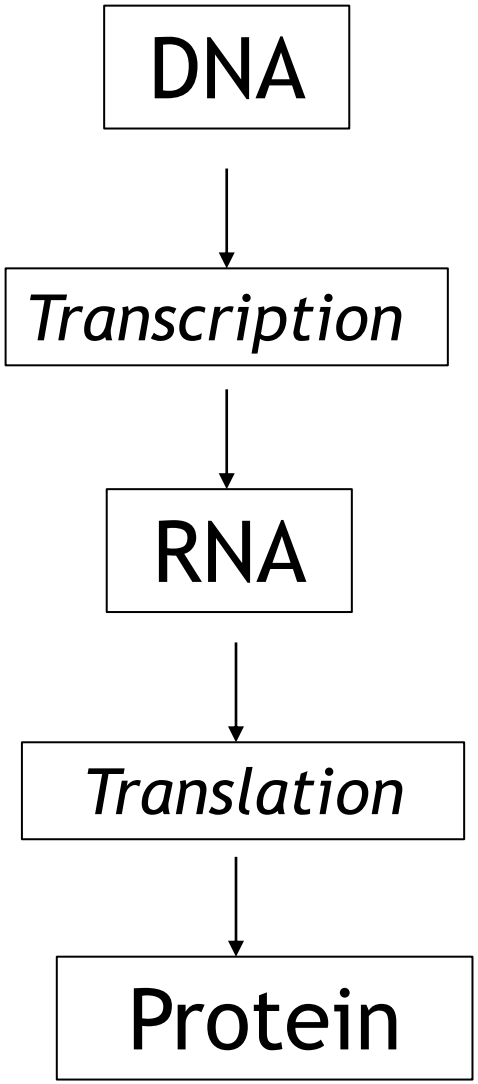
RNA Silencing

Antisense Oligonucleotide (ASO)

Small Interfering RNA (SiRNA)



They knock down WT and variant TTR by 70-80%



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

Merrill D. Benson, M.D., Márcia Waddington-Cruz, M.D., Ph.D., John L. Berk, M.D., Michael Polydefkis, M.D., M.H.S., Peter J. Dyck, M.D., Annabel K. Wang, M.D., Violaine Planté-Bordeneuve, M.D., Fabio A. Barroso, M.D., Giampaolo Merlini, M.D., Laura Obici, M.D., Morton Scheinberg, M.D., Thomas H. Brannagan, III, M.D., et al.

ORIGINAL ARTICLE

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

David Adams, M.D., Ph.D., Alejandra Gonzalez-Duarte, M.D., William D. O'Riordan, M.D., Chih-Chao Yang, M.D., Mitsuharu Ueda, M.D., Ph.D., Arnt V. Kristen, M.D., Ivailo Tournev, M.D., Hartmut H. Schmidt, M.D., Teresa Coelho, M.D., John L. Berk, M.D., Kon-Ping Lin, M.D., Giuseppe Vita, M.D., et al.

Articl

26 Refe

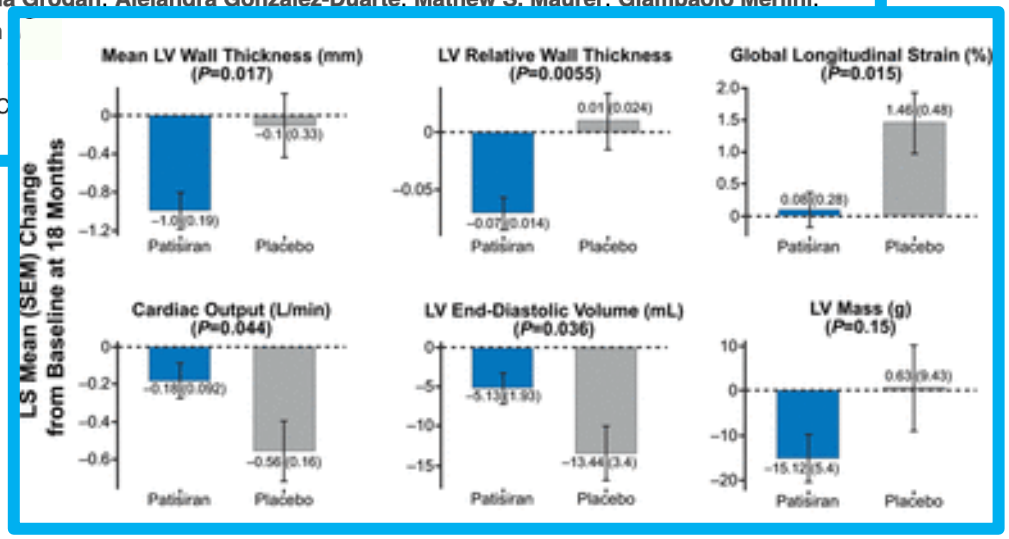
Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Analysis of the APOLLO Study

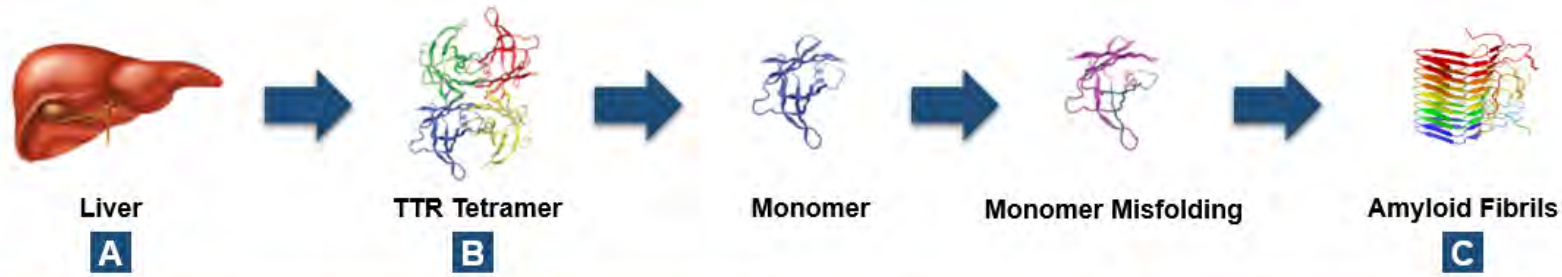
Circulation 2018

Scott D. Solomon, David Adams, Arnt Kristen, Martha Grogan, Alejandra González-Duarte, Mathew S. Maurer, Giampaolo Merlini, Thibaud Damy, Michel S. Slama, Thomas H. Brannagan
Akshay Vaishnaw, Verena Karsten, Jihong Chen, Jared

Originally published 14 Sep 2018 | https://doi.org/10.1161/CIRC



TTR Amyloidosis: Stabilizers



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- ❑ Gene silencing
  - Patisiran: (SiRNA)
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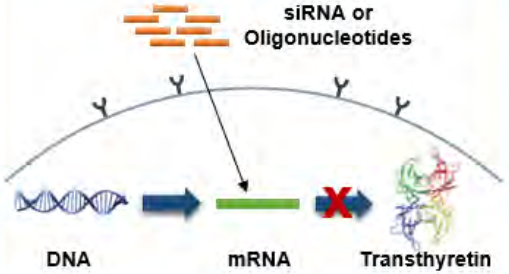

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- ❑ AG-10 (selective)
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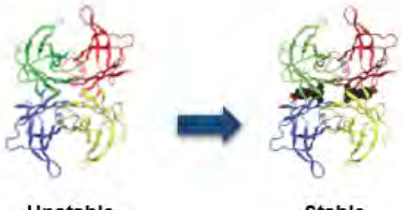
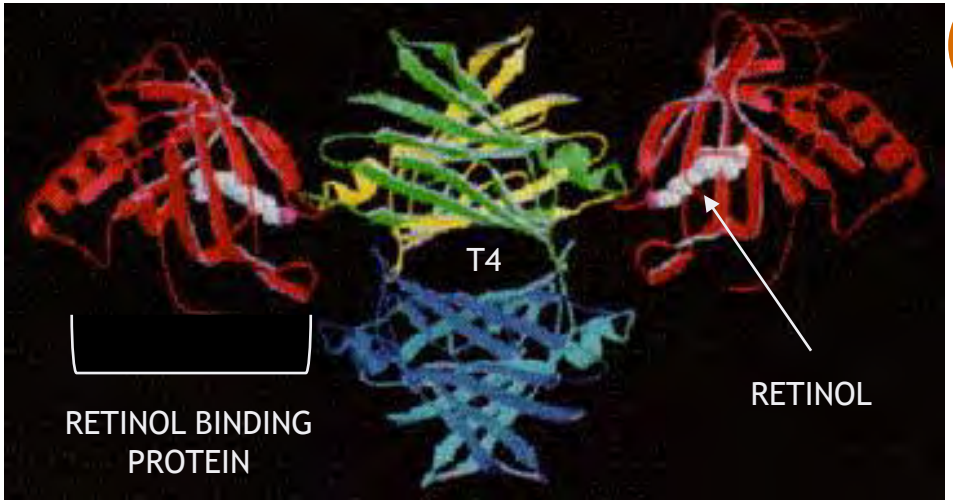


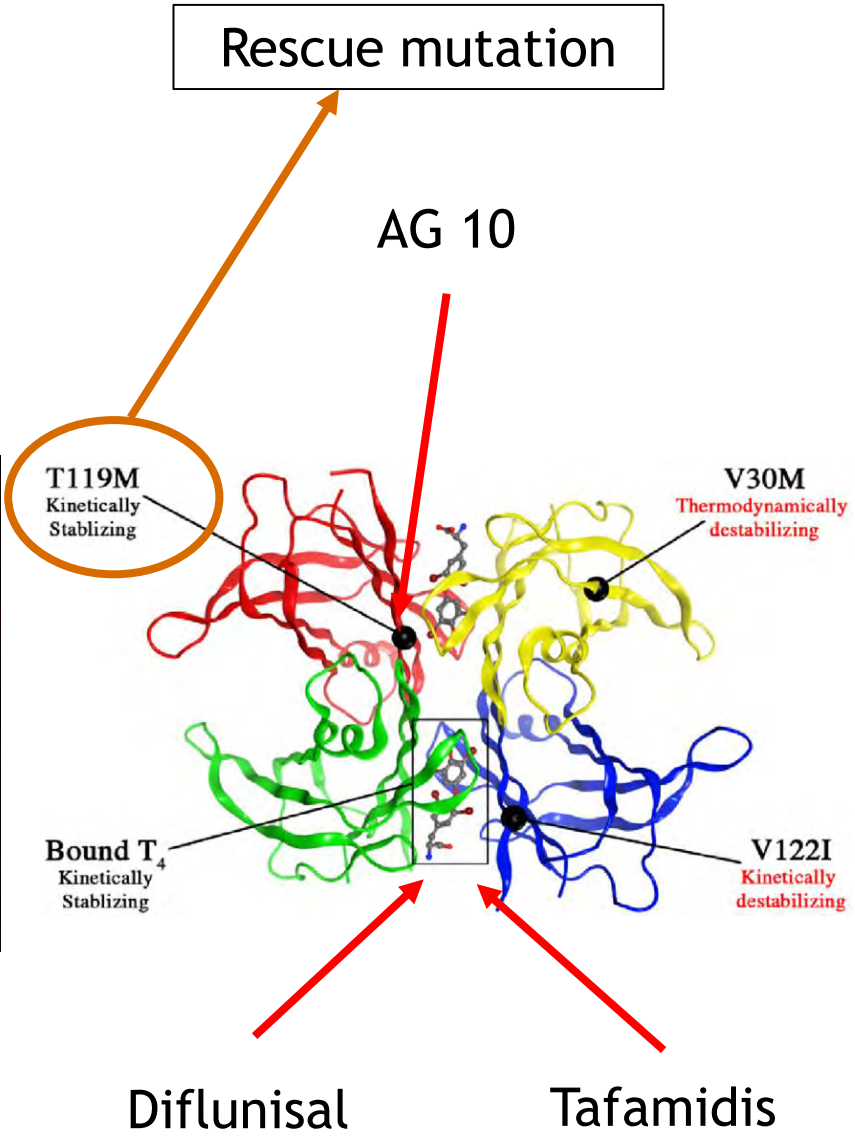
C Fibril Degradation & Reabsorption

- ❑ Doxycycline
- ❑ Doxycycline + TUDCA
- ❑ CPHPC + SAP Antibodies
- ❑ NEOD001
- ❑ Anti-amyloid mAb 11-1F4

TTR STRUCTURE



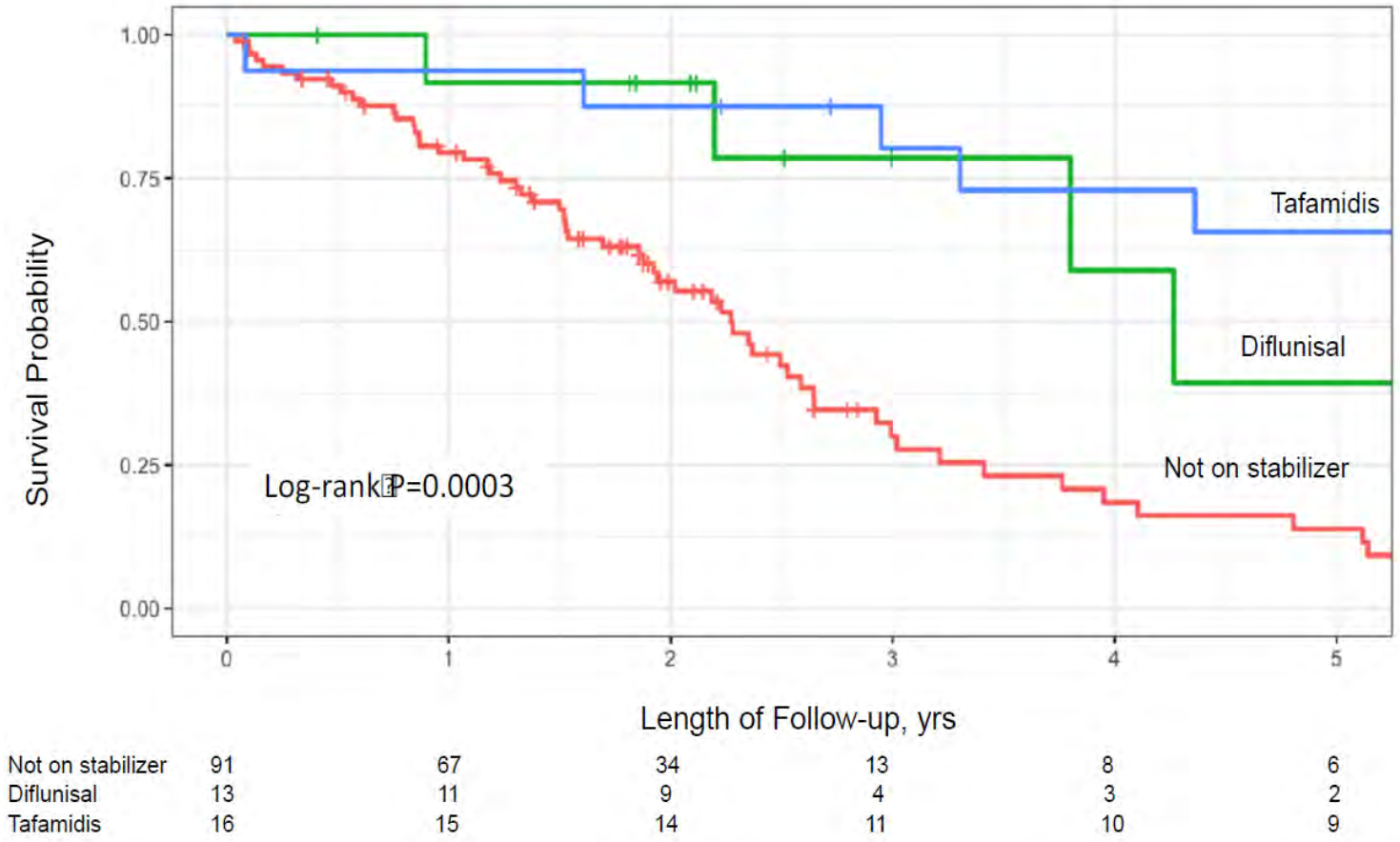
TTR TETRAMER



Raghu P. https://doi.org/10.1016/j.bbapap.2004.09.023

Penchala S. PNAS. 2013;110(24):9992-7.

Diflunisal in ATTR CM:
Sparse data, difficult to use in HF



Not on stabilizer	91	67	34	13	8	6
Diflunisal	13	11	9	4	3	2
Tafamidis	16	15	14	11	10	9

Castano A. Circ HF 2018; 11: e004769

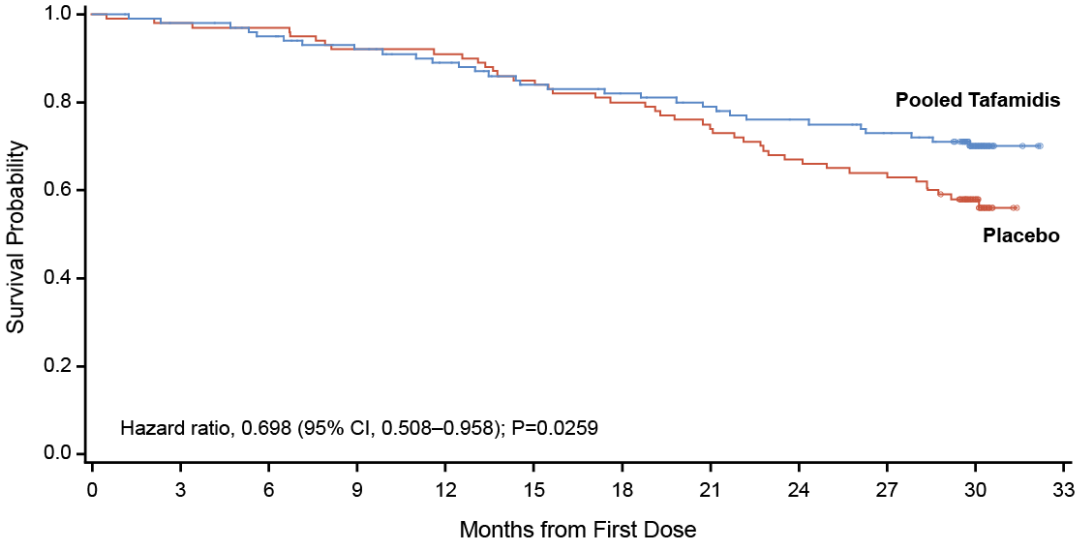
Slide: Maurer MS

Tafamidis Reduces All-cause Mortality and CV Hospitalizations

ATTR- ACT

33% mortality reduction (P=0.018)
NNT: 7-8 per one death over 2 ½ years

32% reduction in CV Hosp
NNT: 4 per 1 hosp per year.

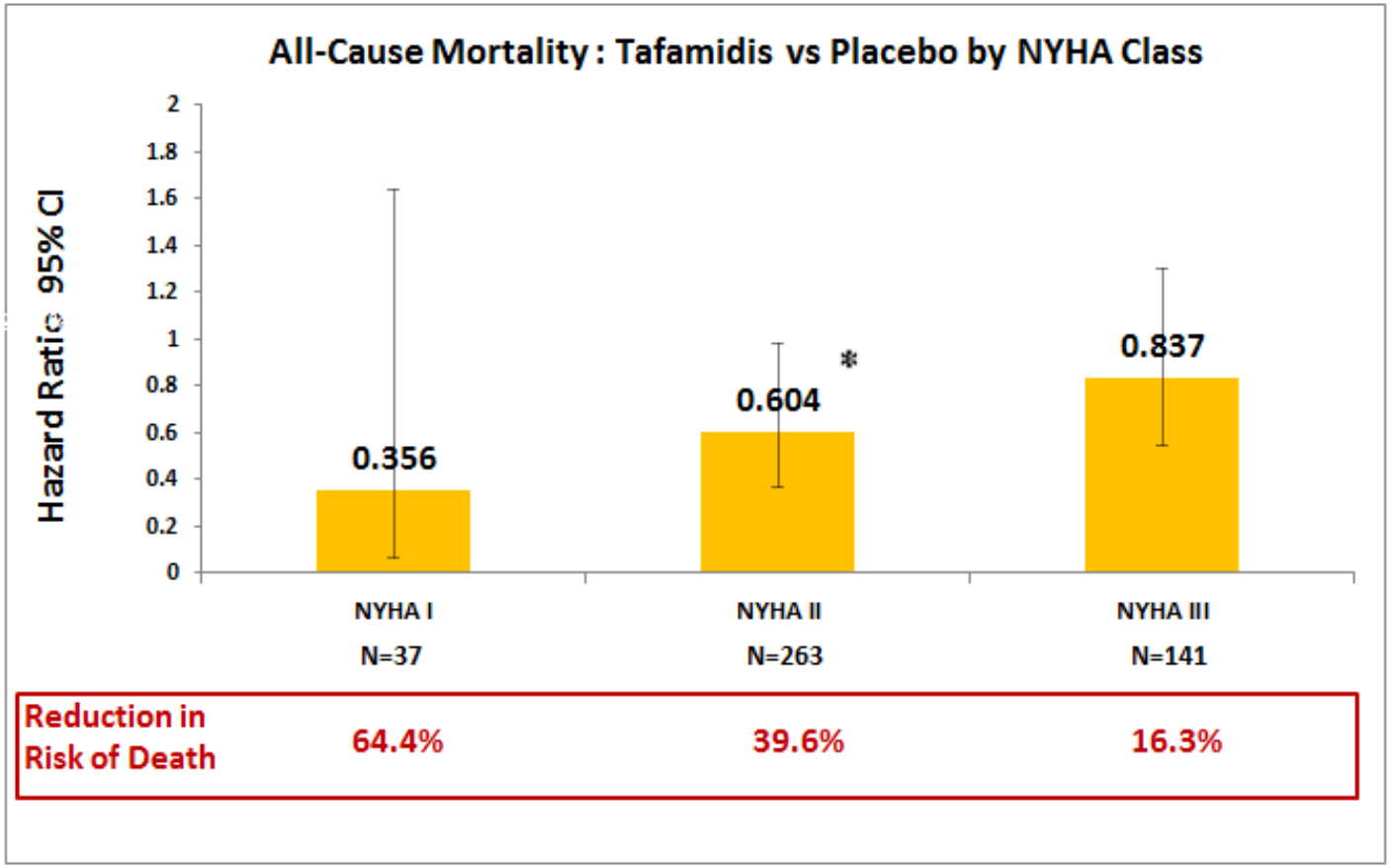


No. at Risk
Patients Remaining at Risk
(Cumulative Events)

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

Maurer MS, et al. NEJM Sept 2018

All-Cause Mortality Benefit

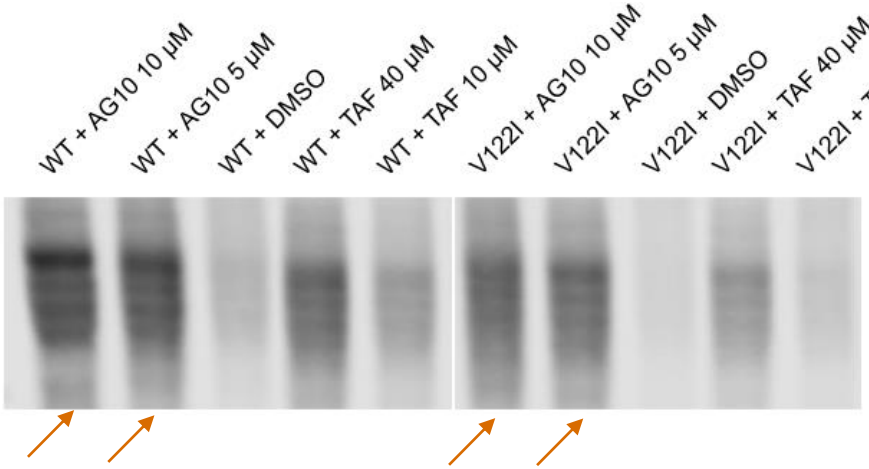


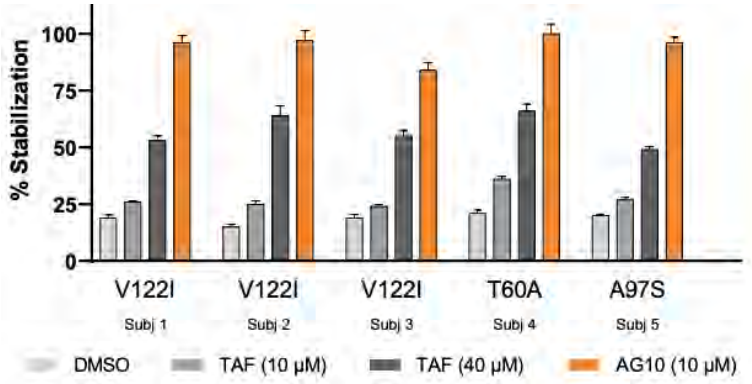
Maurer MS, et al. NEJM Sept 2018

Slide: Maurer MS

Differential Ex Vivo Stabilization Of Transthyretin By AG10 And Tafamidis In Samples From Patients With Moderately Or Severely Destabilizing Mutations

Paul W Wong, BS[1], Alan X Ji, PhD[1], Jonathan Fox, MD, PhD[1], John L Berk, MD[2], Uma Sinha, PhD[1]
[1] Eidos Therapeutics Inc, San Francisco, CA. [2] Boston Univ School of Medicine and Boston Medical Center, Boston, MA





Phase 2 OLE results

- Safety & Tolerability: AE profile consistent with ATTR disease severity
- Improvement in serum TTR and stability of cardiac biomarkers
- Lower mortality and hospitalization compared to the placebo arm of the tafamidis trial

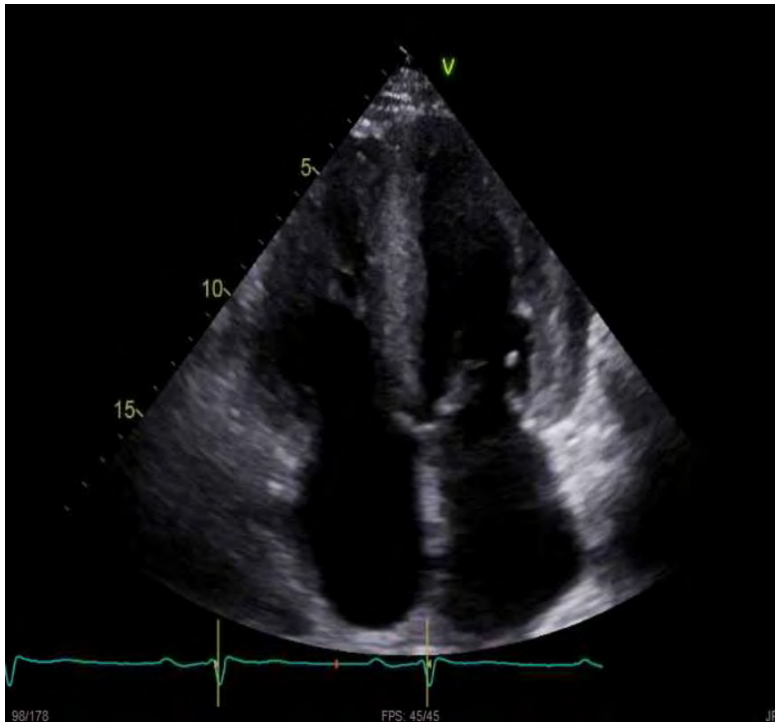
ATTRIBUTE-CM

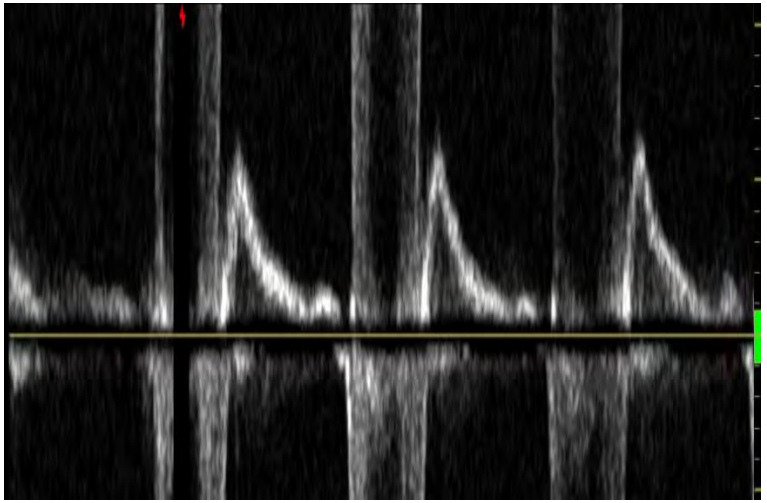
Heart Failure Management

- Digoxin and Calcium blockers should be stopped
- Beta blocker are best stopped
- ACEI if tolerated
- Diuretics including spironolactone are mainstay

- Very low threshold for anticoagulation
  - Any Afib (irrespective of CHADS)
  - ? Sinus rhythm

Atrial Mechanical Dysfunction





Final Thoughts

Think of cardiac amyloidosis!

This is the first step in making a diagnosis.