Heart Failure II – Who should be tested for TTY-Amyloid heart disease now that there are tests and target therapy available?

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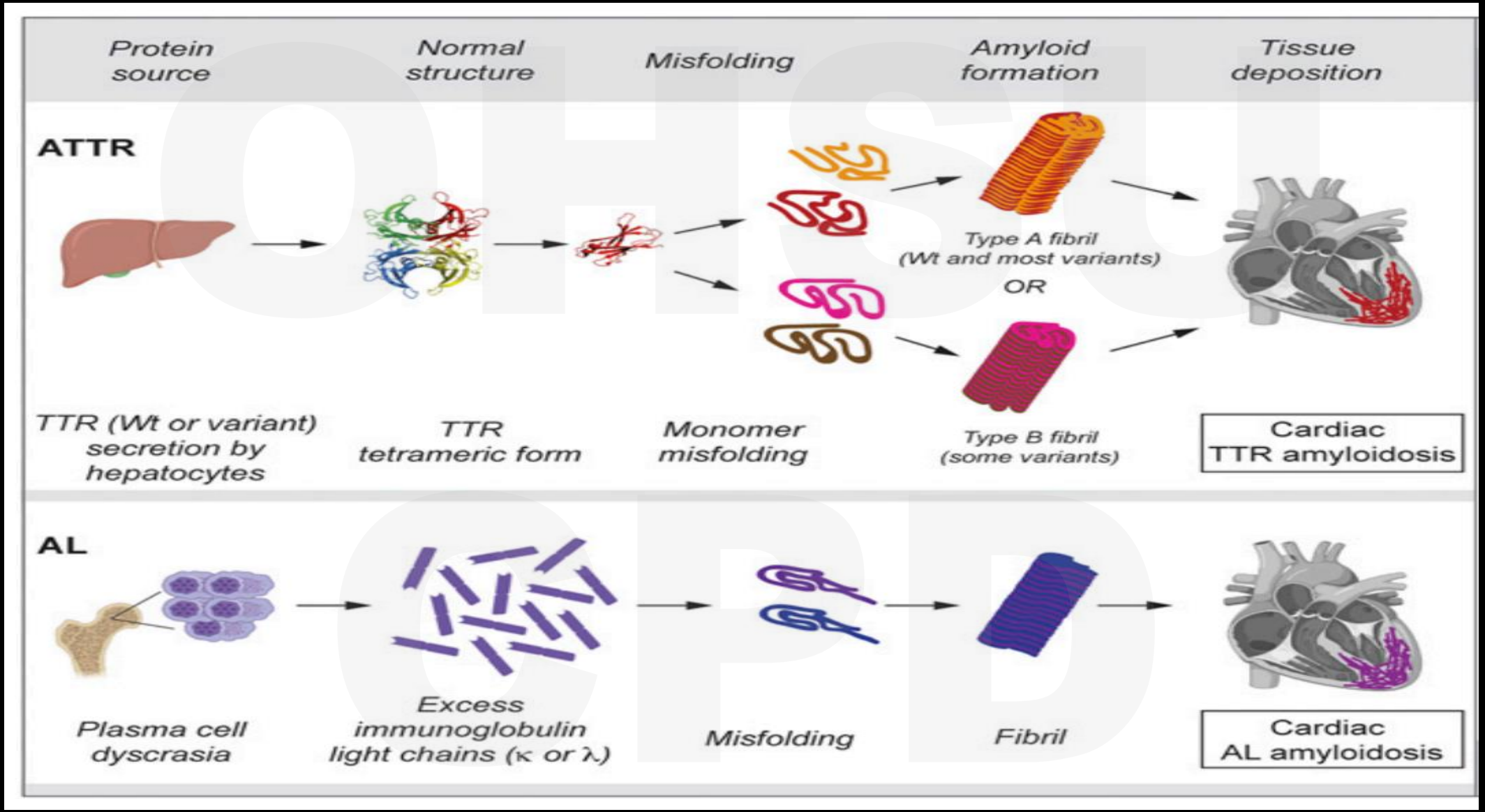
Disclosures

- Research Grants from Pfizer, Ionis, Attralus, Cytokinetics and Janssen.

- Fees from Cytokinetics, BMS, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Edgewise, Rocket, Lexeo, Prothena, BioMarin, AstraZeneca, and Tenaya.

Cardiac Amyloidosis



Masri A et al. J Nucl Med. 2020;61:965-970.

ATTR-CM: A Historical Challenge

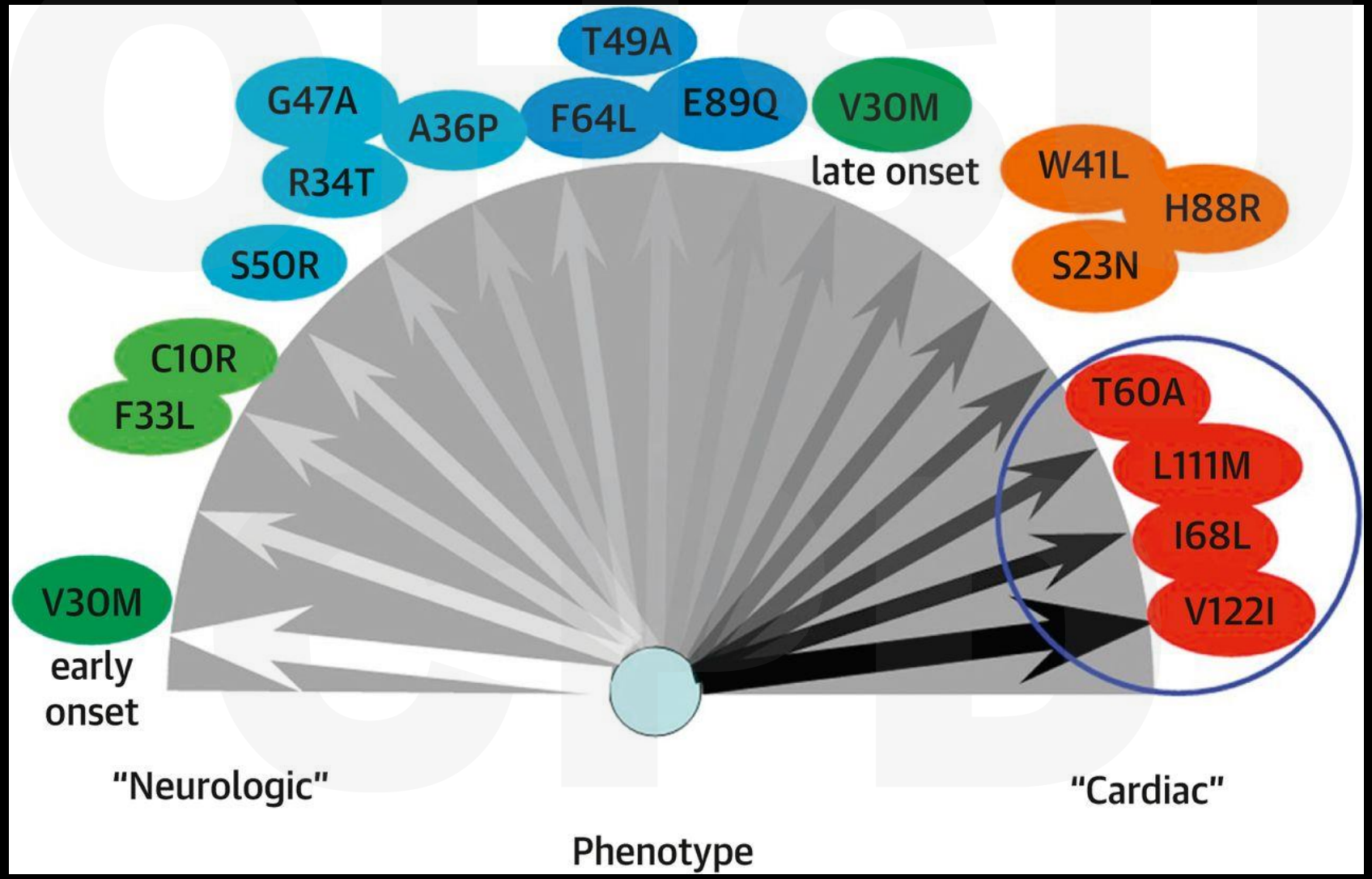
- Late diagnosis until advanced phenotype is seen
- Need for cardiac biopsy
- No available therapies that were shown to improve survival

ATTR-CM is a Rare Disease

Wild type: wtATTR	Hereditary: hATTR
Median age at dx 74 years	Median age dx varies by mutation
Heart failure	conduction dz
Minimal peripheral neuropathy	Peripheral +/- Autonomic neuropathy
Bilateral carpal tunnel syndrome Spinal Stenosis Biceps tendon rupture	-Bilateral carpal tunnel syndrome -Vitreous opacities -GI symptoms / Weight loss
-Median survival 3-4 years	-Median survival varies by mutation

Transthyretin gene testing

Genotype and Tissue Tropism



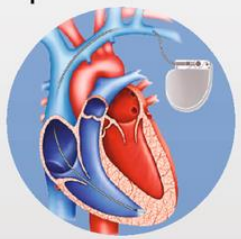
Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. *European heart journal* 2013; **34**(7): 520-8.

Cardiac

Heart failure

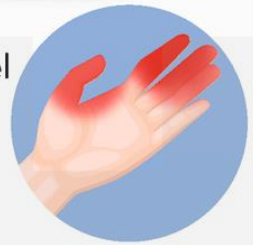
Atrial fibrillation

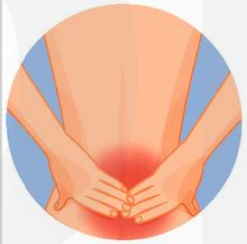
Bradyarrhythmias/ conduction abnormalities/ pacemakers



Musculoskeletal

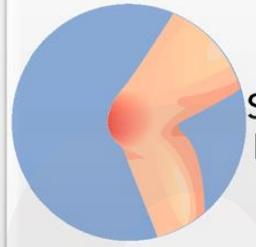
Carpal tunnel syndrome





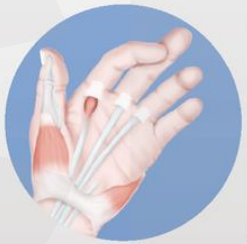
Back pain/lumbar spinal stenosis

Ruptured distal biceps tendon/ Popeye sign



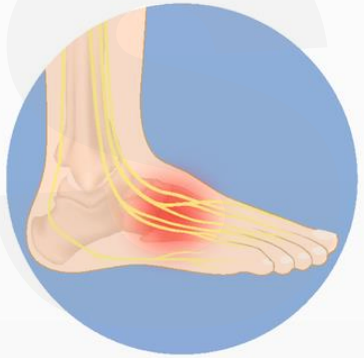
Shoulder, knee and hip pain or surgery

Trigger finger



Polyneuropathy

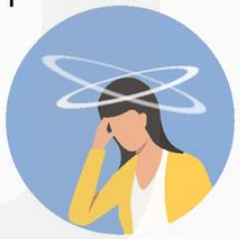
Painful neuropathy in hands and feet



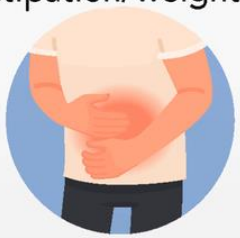
Muscle weakness, difficulty walking, and falls

Autonomic Dysfunction

Orthostatic hypotension/ intolerance to blood pressure meds



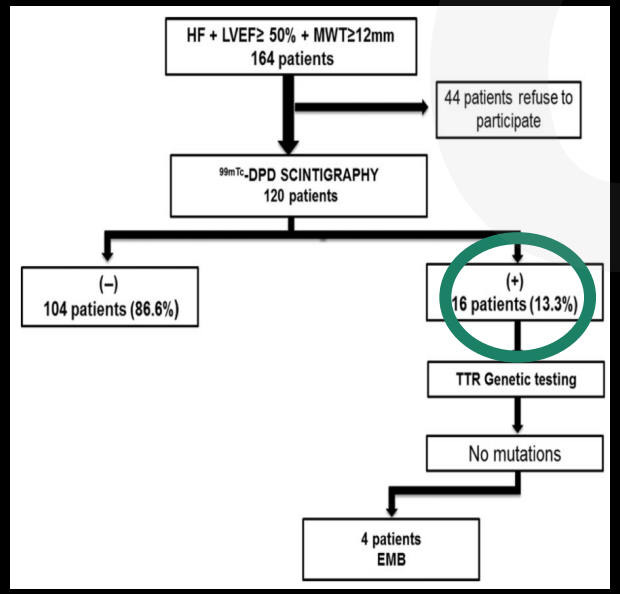
Chronic diarrhea/ constipation/weight loss



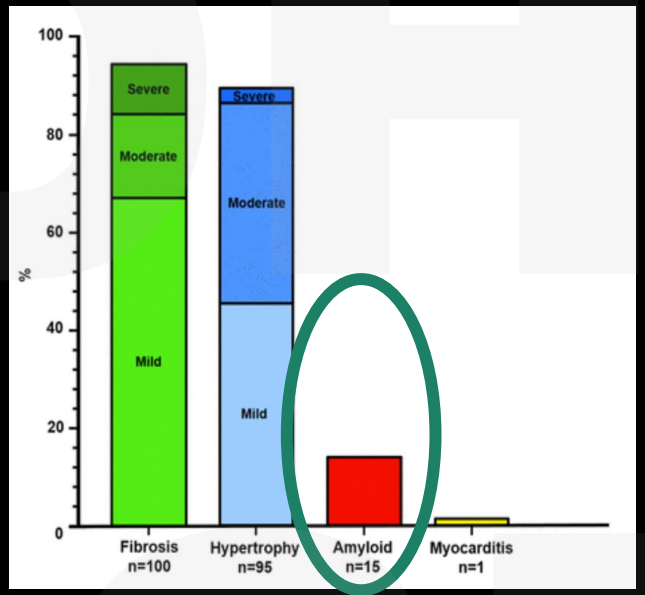
Erectile dysfunction

Nativi-Nicolau et al.
Heart Failure Reviews 2021

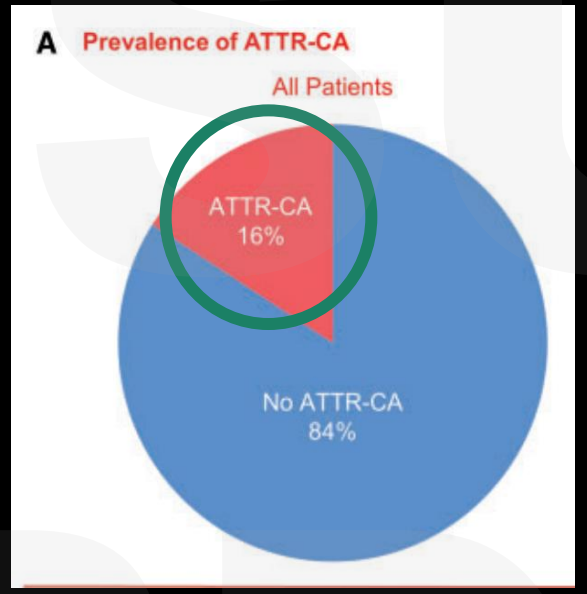
ATTR-CM is Highly Prevalent



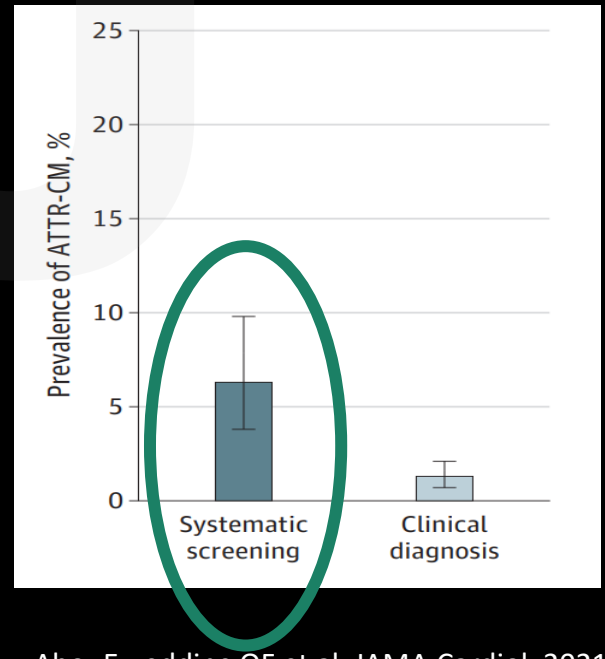
Gonzalez-Lopez E et al. Eur Heart J. 2015



Hahn VS et al. JACC HF. 2020

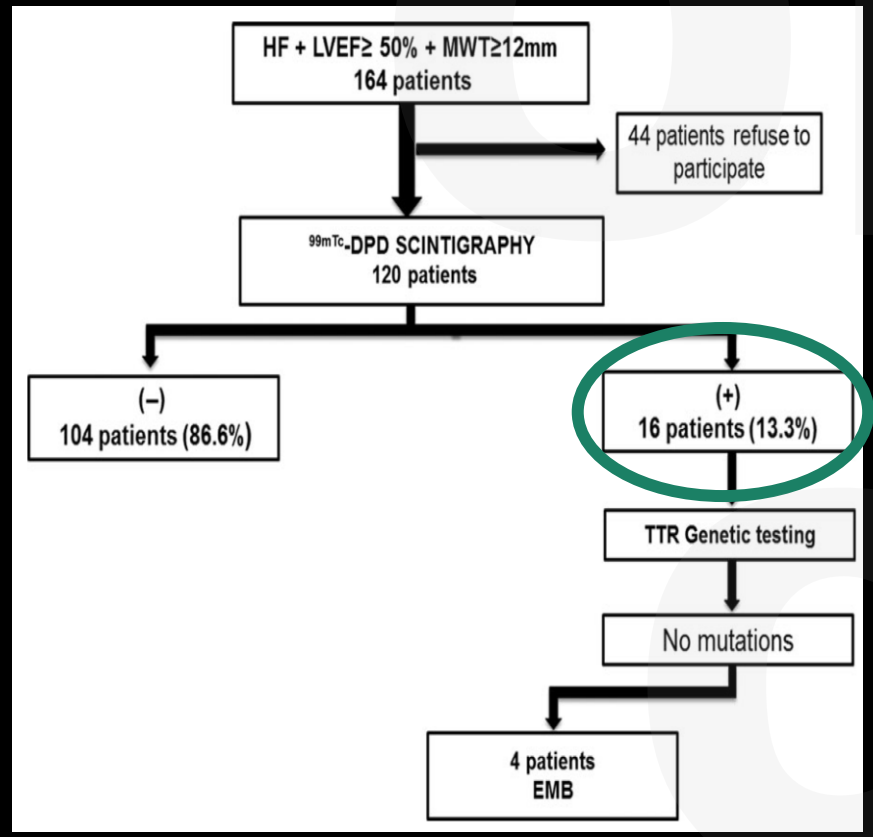


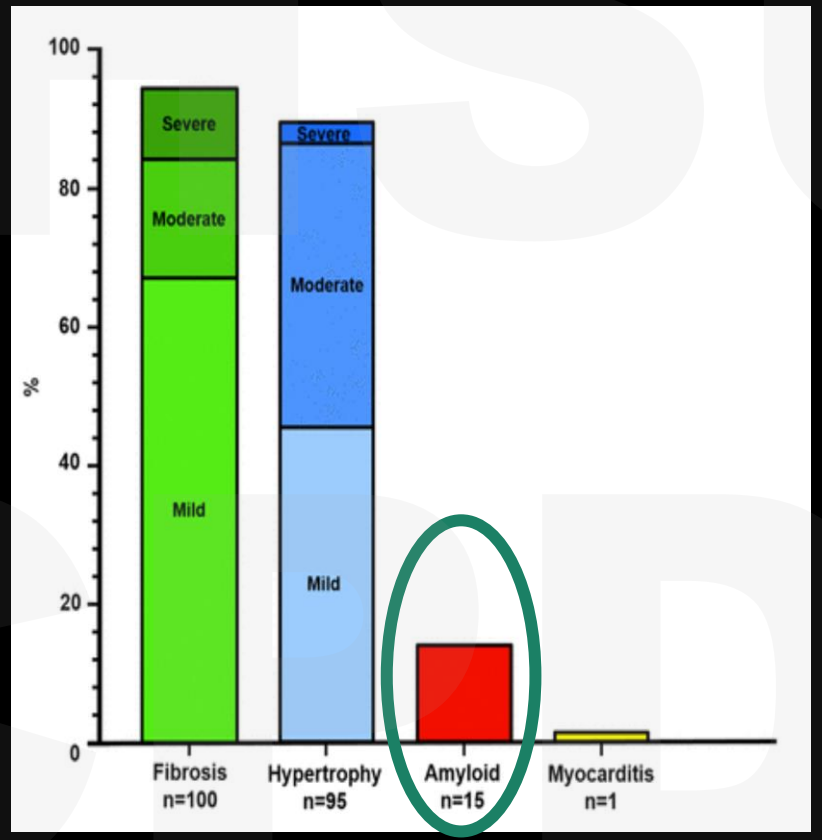
Castano A et al. Eur Heart J. 2017

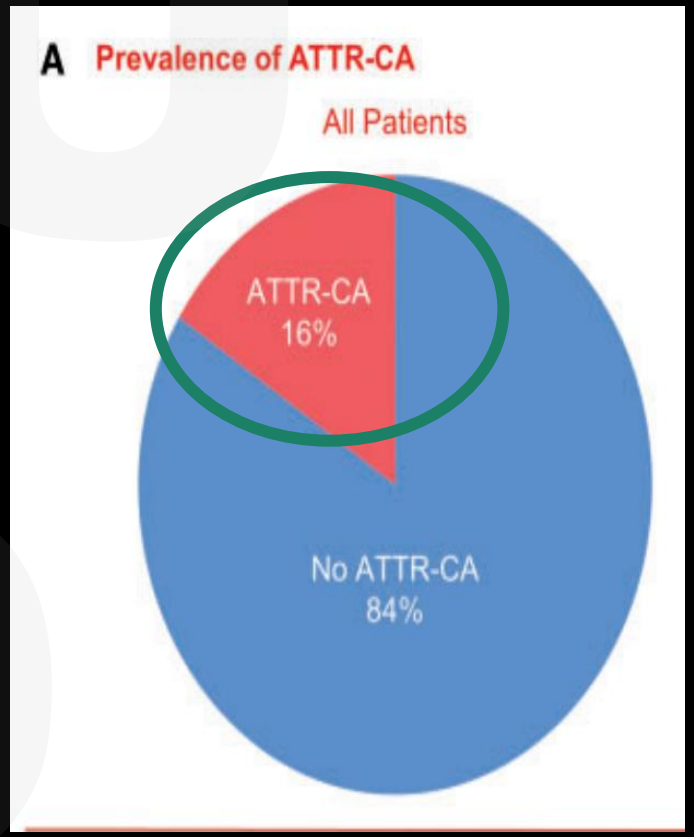


AbouEzzeddine OF et al. JAMA Cardiol. 2021

ATTR-CM is Highly Prevalent







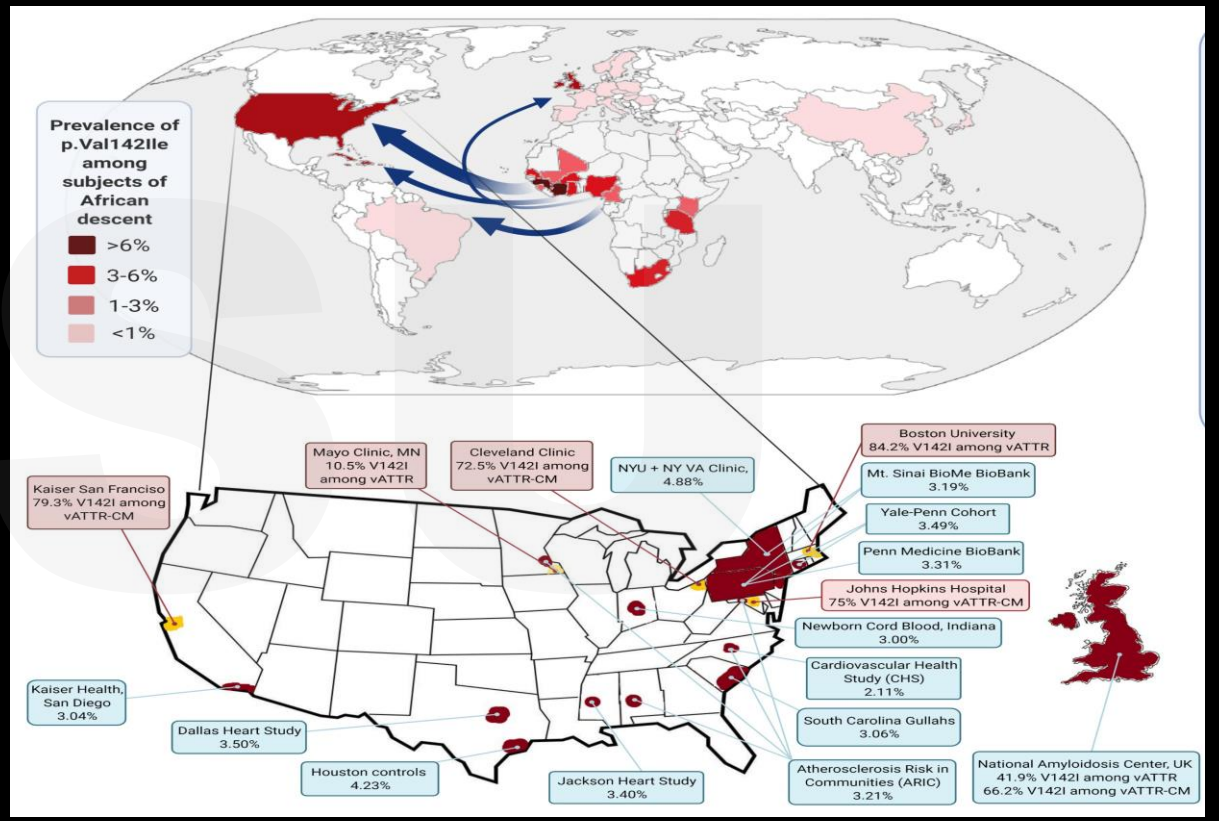
Gonzalez-Lopez E et al. Eur Heart J. 2015;36:2585-94.

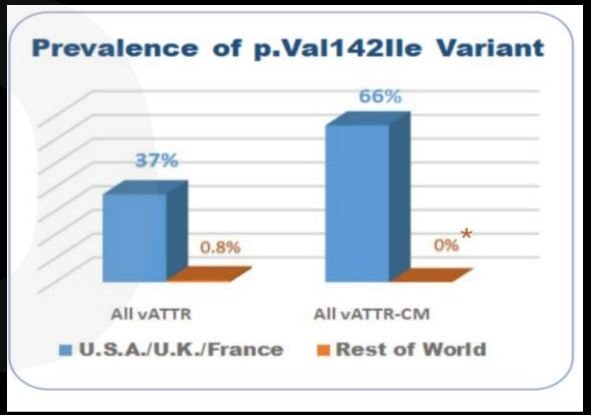
Hahn VS et al. JACC HF. 2020;8:712−724.

Castano A et al. Eur Heart J. 2017;38:2879-2887.

V122I (p.V142I)

- First described in 1988 in an African-American man
- Unique – predominantly in patients with African descent
- Age-dependent autosomal dominant
- Prevalence of ~3.4% of African Americans
  - 1.6 Million carriers*
  - ~150,000, aged ≥65 years*
- If you have experience/ideas about community engagement please reach out





*Estimation based on US Census.

Chandrashekar P et al. Circ Genom Precis Med. 2021 Oct;14(5):e003356.

Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release

Brett W. Sperry, MD,[a,b] Bryan A. Reyes, MD,[c] Asad Ikram, MBBS,[a] Joseph P. Donnelly, MD,[a] Dermot Phelan, MD, PhD,[a] Wael A. Jaber, MD,[a] David Shapiro, MD,[c] Peter J. Evans, MD, PhD,[c] Steven Maschke, MD,[c] Scott E. Kilpatrick, MD,[d] Carmela D. Tan, MD,[d] E. Rene Rodriguez, MD,[d] Cecilia Monteiro, MD,[e] W.H. Wilson Tang, MD,[a] Jeffery W. Kelly, PhD,[e] William H. Seitz, Jr, MD,[c] Mazen Hanna, MD[a]

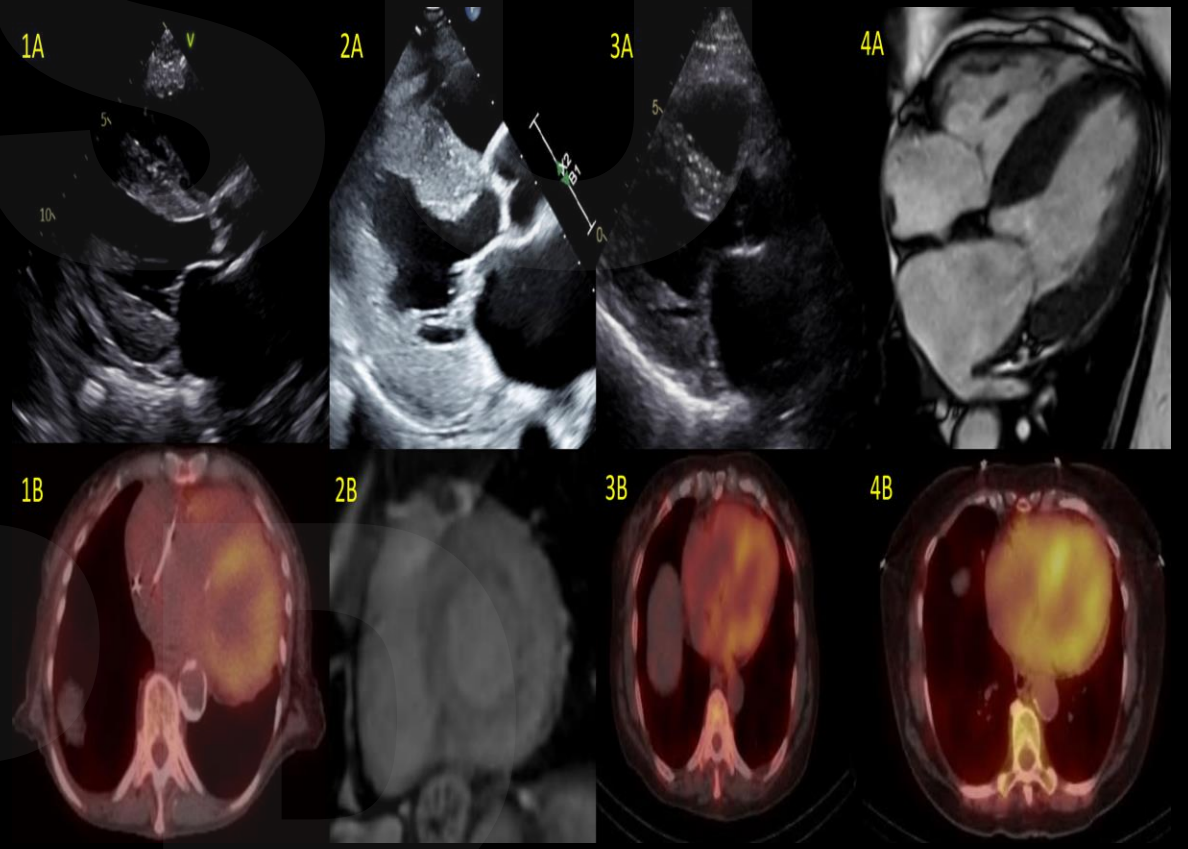
RESULTS Of 98 patients enrolled (median age 68 years, 51% male), 10 (10.2%) had a positive biopsy for amyloid (7 ATTR, 2 light chain [AL], 1 untyped). Two patients were diagnosed with hereditary ATTR (Leu58His and Ala81Thr), 2 were found to have cardiac involvement (1 AL, 1 ATTR wild-type), and 3 were initiated on therapy. In those patients who had biopsy-diagnosed ATTR, there was no difference in plasma TTR concentration or tetramer kinetic stability.

- **10%** of biopsies from carpal tunnel release surgery had amyloid deposits
- **2%** had hereditary ATTR
- **2%** had cardiac disease
- **3%** were initiated on therapy

Sperry BW et al. J Am Coll Cardiol. 2018;72:2040-2050.

Evolving Epidemiology of ATTR-CM in Oregon

- From 2005 to 2015, we had 21 patients with ATTR-CM
- From 2016-2019, 100 new patients
- Since then, hundreds more
- Zero women were diagnosed with wild type ATTR-CM (0%) pre-2019, compared to 11.3% 2019-2022



Chandrashekar, Masri ESC 2021
Prasad, Masri et al. IJC 2023

Variant ATTR is a Rare Disease

- Partly driven by focusing on the most severe forms.
- False dichotomy of the phenotype – it is a continuum
- Frequent underdiagnosis and misdiagnosis
- Up to 40,000 individuals worldwide
  - However, likely an under-estimation given what we know about common variants such as V122I.

- In the UK Biobank, 1 out of 1,000 are carriers of a TTR variant.

Schmidt et al. Muscl Nerve 2018
Aung et al. JAMA Cardiol 2024

Devastating Progressive Disease

PND Stages

I	Sensory disturbances, preserved walking capability
II	Impaired walking capability but ability to walk without a stick or crutches
IIa	Walking only with the help of 1 stick or crutch
IIIb	Walking with the help of 2 sticks or crutches

https://fapnewstoday.com/stages-of-familial-amyloid-polyneuropathy/

AMYLOID NEUROPATHY VS CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

- EMG - Axonal
- Progressive over months/years
- Proximal muscle weakness
- Weight loss, autonomic symptoms

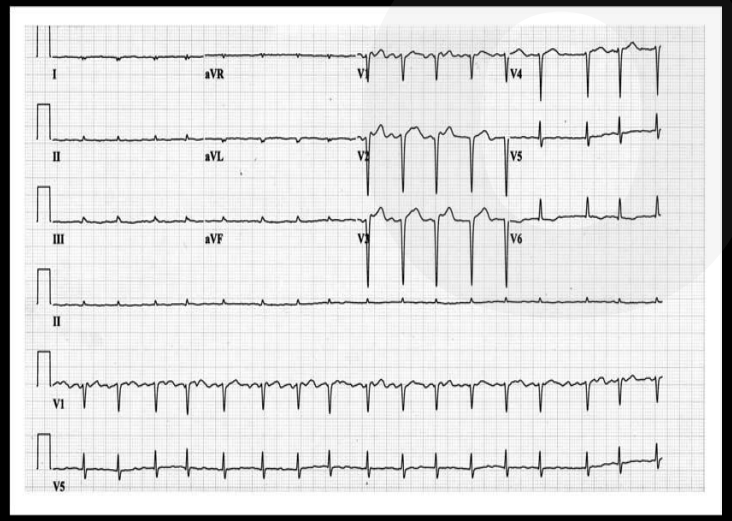
- EMG – Demyelinating
- Progressive over months/years
- Proximal muscle weakness
- NO Weight loss, autonomic symptoms

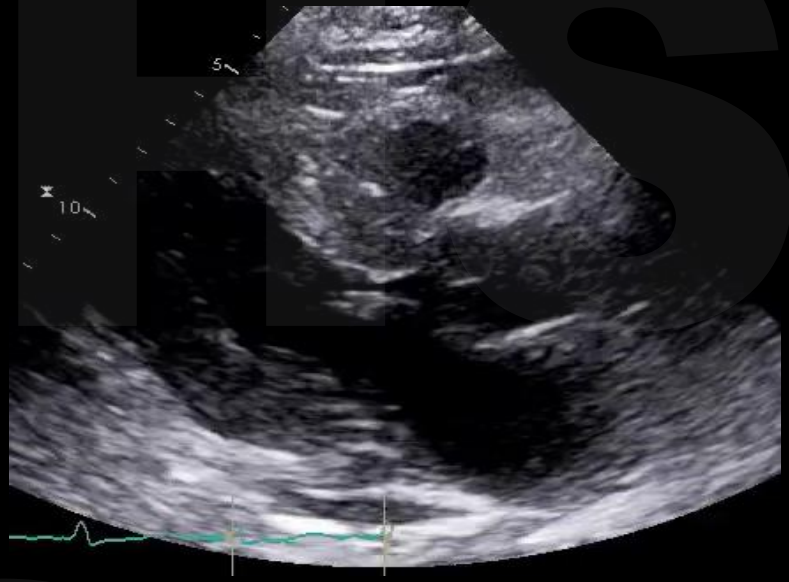
Courtesy of Sami Khella

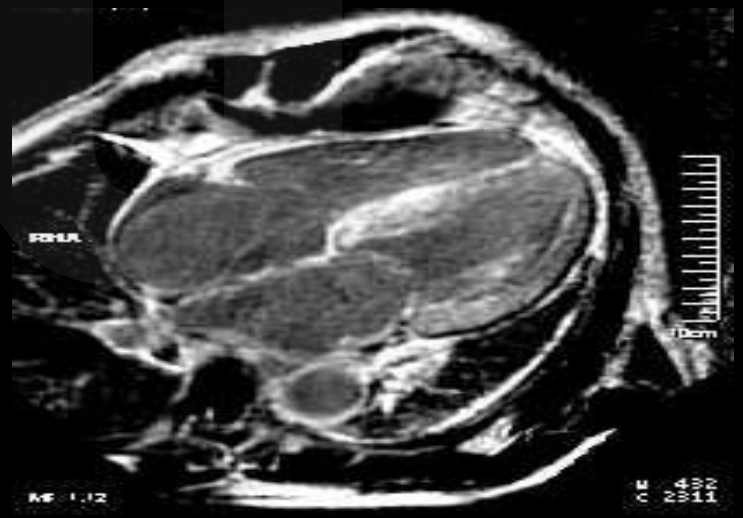
Typical Work Up in Variant ATTR Amyloidosis

- EMG / NCS
- Autonomic function testing
- Tissue biopsy
- Amyloid typing in certain cases
- Transthyretin level
- Electrocardiogram
- Echocardiogram
- Bone-avid myocardial scintigraphy (PYP/HMDP/DPD)
- NT-proBNP and troponin

Traditional Approach

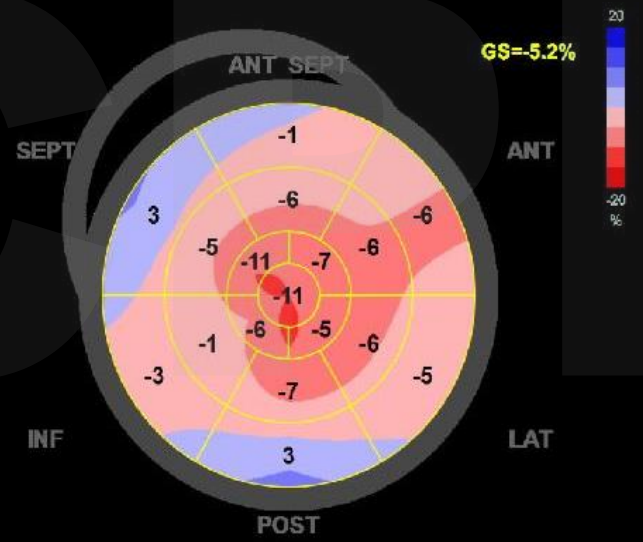






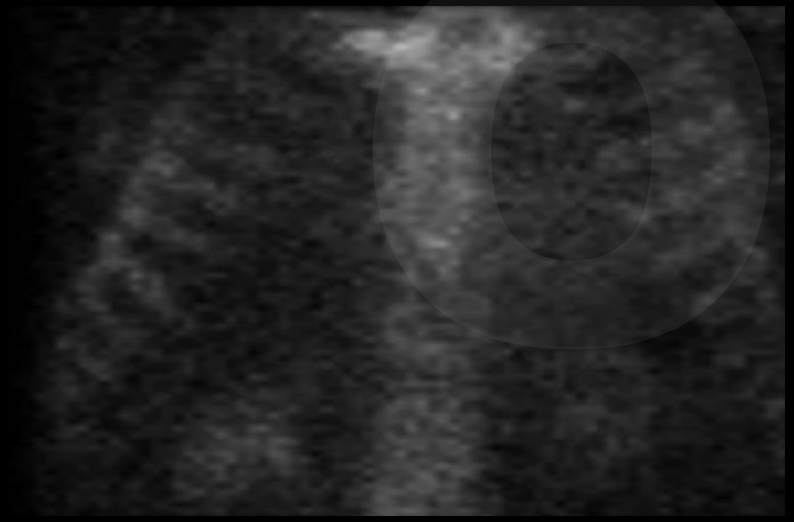
Low voltage 50% in AL

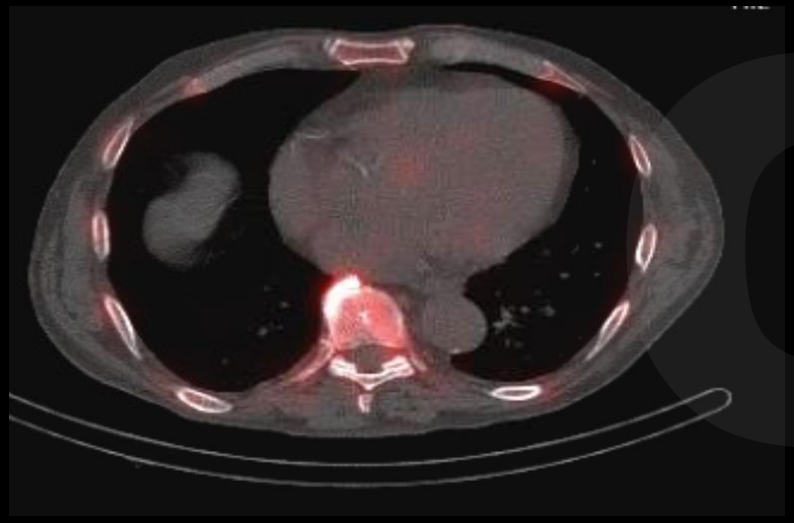
Low voltage 25% in ATTR



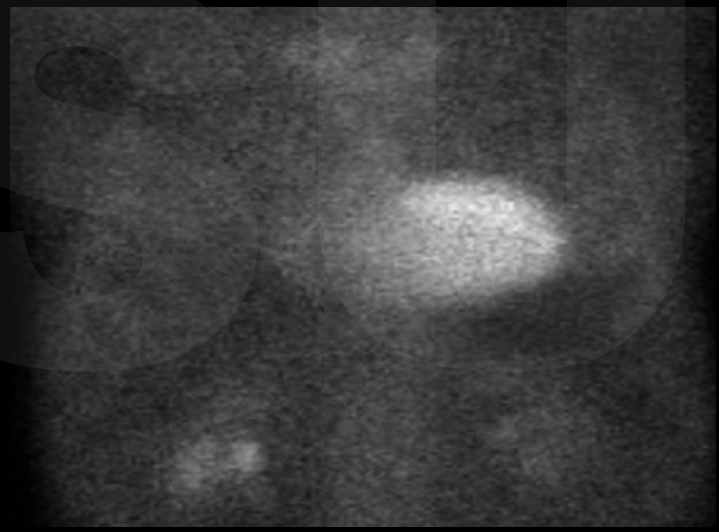
Technetium pyrophosphate scintigraphy (Tc-PYP)
DPD/H(M)DP

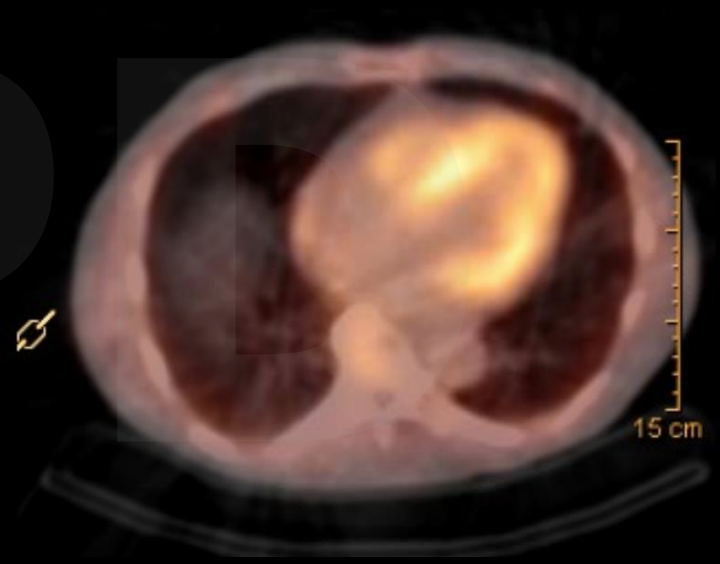
Negative scan



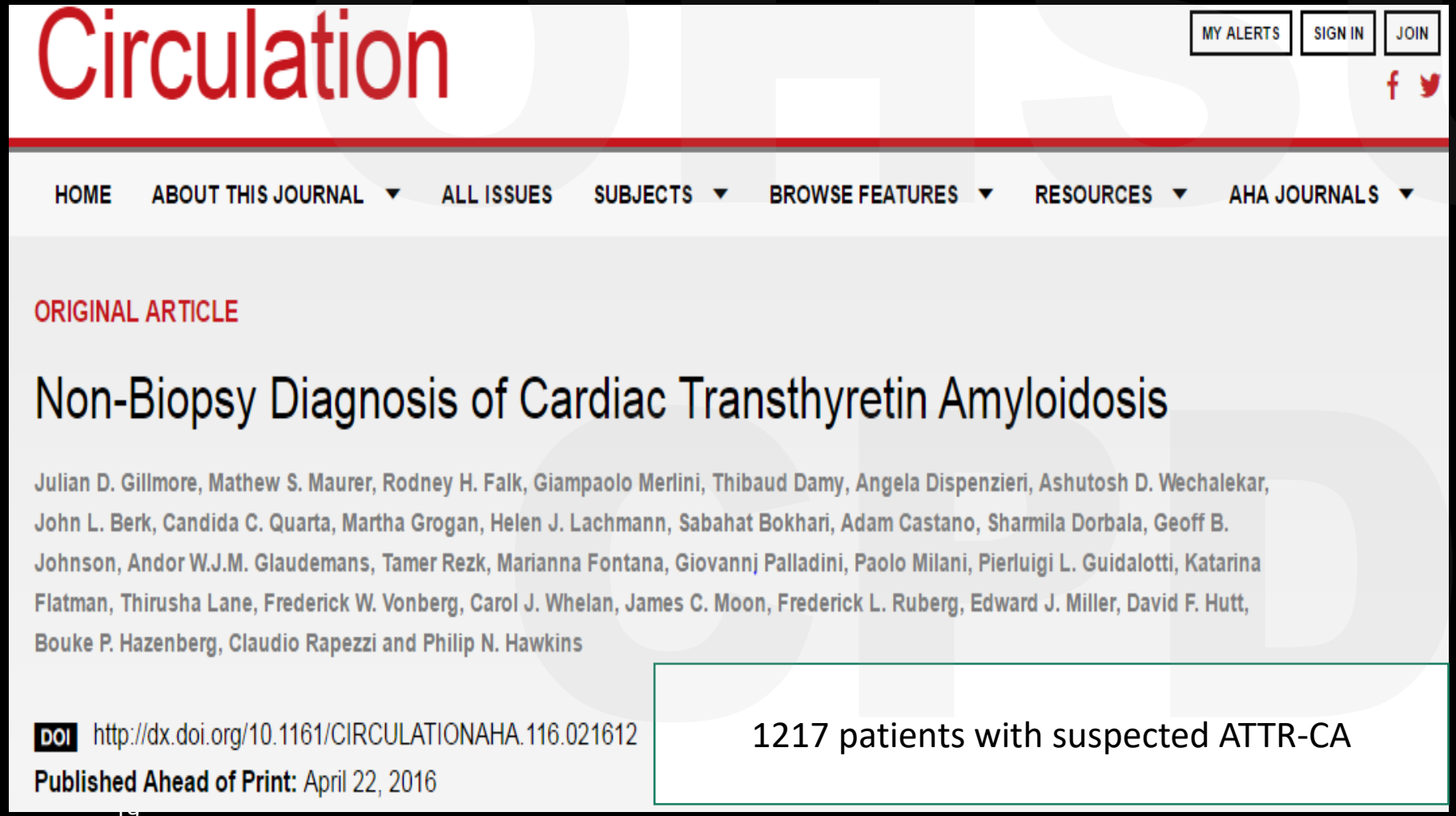


Positive scan





Bottom-line → A positive Tc-PYP in the setting of a clinical phenotype + absence of serum monoclonal antibody → 99% sensitive, 100% specific



Circulation

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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

1217 patients with suspected ATTR-CA

22% false positive rate (if serum studies were not included for AL rule out) was due to planar only utilization and not SPECT imaging (i.e. blood pool in AL)

Work up for AL Amyloidosis

- Serum free light chains
- Serum and urine DIRECT immunofixation (NOT SPEP/UPEP with reflex)
- Check urine protein creatinine ratio
- NTproBNP and troponin

Once done, please think about ATTR

Diagnostic Pathways

Think Amyloidosis (unexplained LVH, proteinuria, worsening hypotension (or new normal BP), orthopedic red flags (carpal tunnel, biceps rupture, spinal stenosis), unexplained neuropathy)

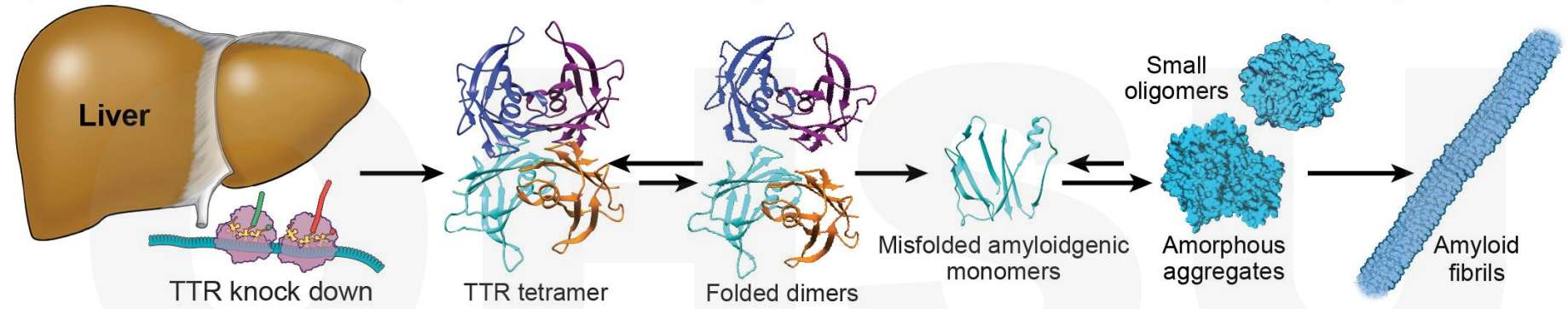
1) Rule out Light Chain Amyloidosis (serum and urine immunofixation/immunotyping, serum free light chains)

2) Bone scintigraphy (PYP or HDP)

Think Amyloidosis

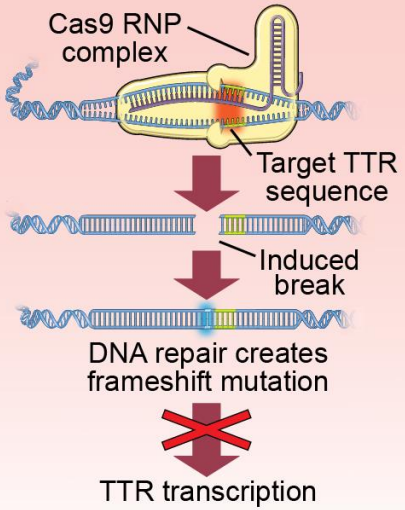
- Carpal tunnel syndrome in patients > 60 years of age
  - Atraumatic, not related to rheumatological condition or ongoing occupational exposure
  - Especially when bilateral
- Coexistent unexplained neuropathy
- Heart failure with any of the following:
  - Autonomic dysfunction features
  - Any unexplained increase in LV wall thickness (LV wall >/= 12 mm)
  - Abnormal LV voltage/mass ratio (or simply slightly thick LV, and low voltage limb leads)
- Calcific aortic stenosis with ≥ 1.2 cm LV (not bicuspid or rheumatic)
- Atrial flutter or fibrillation with ≥ 1.2 cm LV , LEVF ≥ 40%, and no other cardiomyopathies present
- Use strain in all LVH (IVS ≥ 1.2 cm)

Pathogenesis of Transthyretin Cardiac Amyloidosis and Disease Modifying Therapies



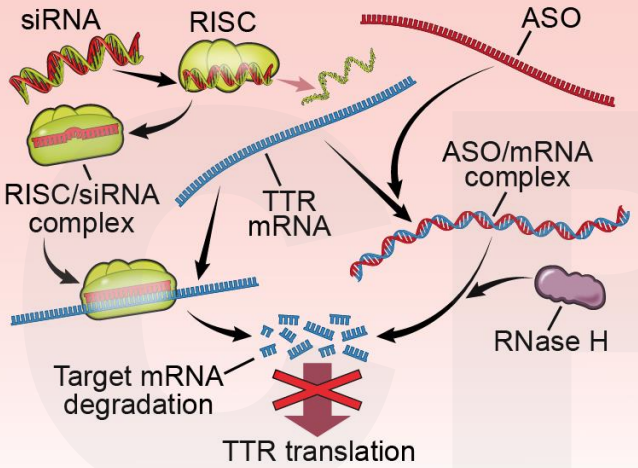
Gene Editing

- Nex-z (NTLA-2001)



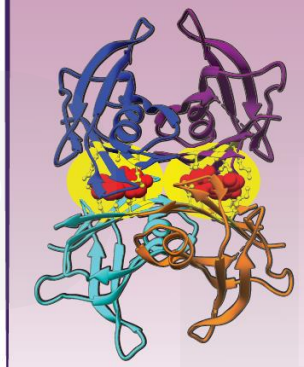
Block Protein Synthesis

- Vutrisiran
- Patisiran
- Eplontersen



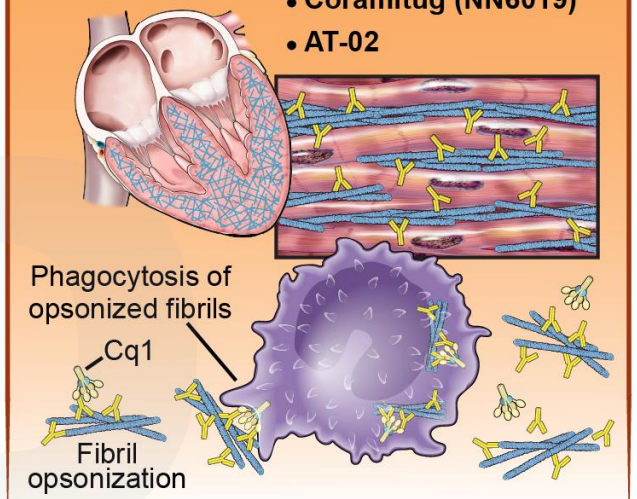
Stabilize Tetramer

- Tafamidis
- Acoramidis
- Diflunisal*



Remove Amyloid Fibrils

- ALXN 2220
- Coramitug (NN6019)
- AT-02



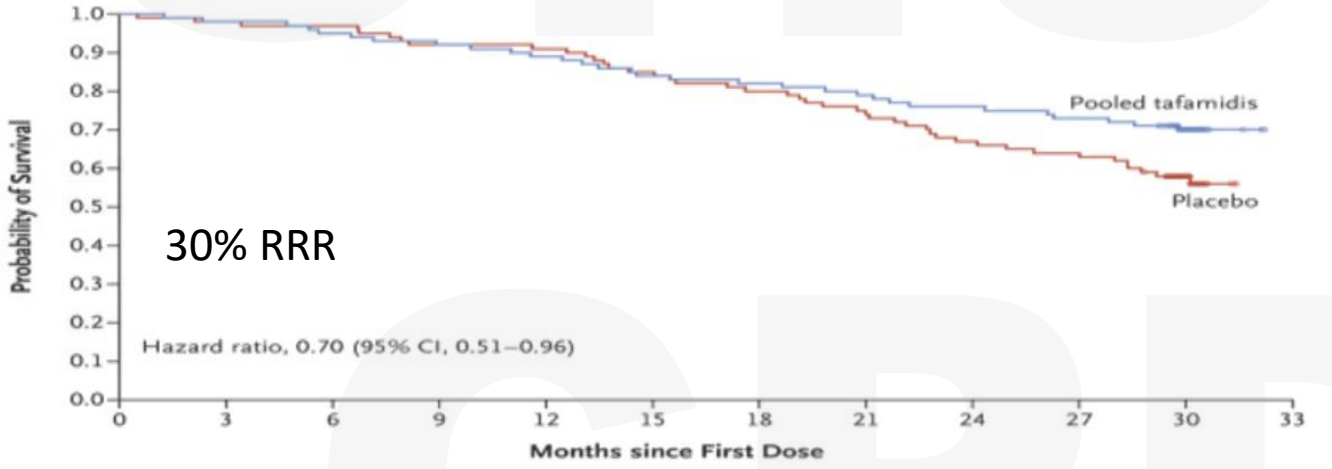
Griffin et al. JACC HF In Press

Tafamidis in ATTR Cardiac Amyloidosis

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 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *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)

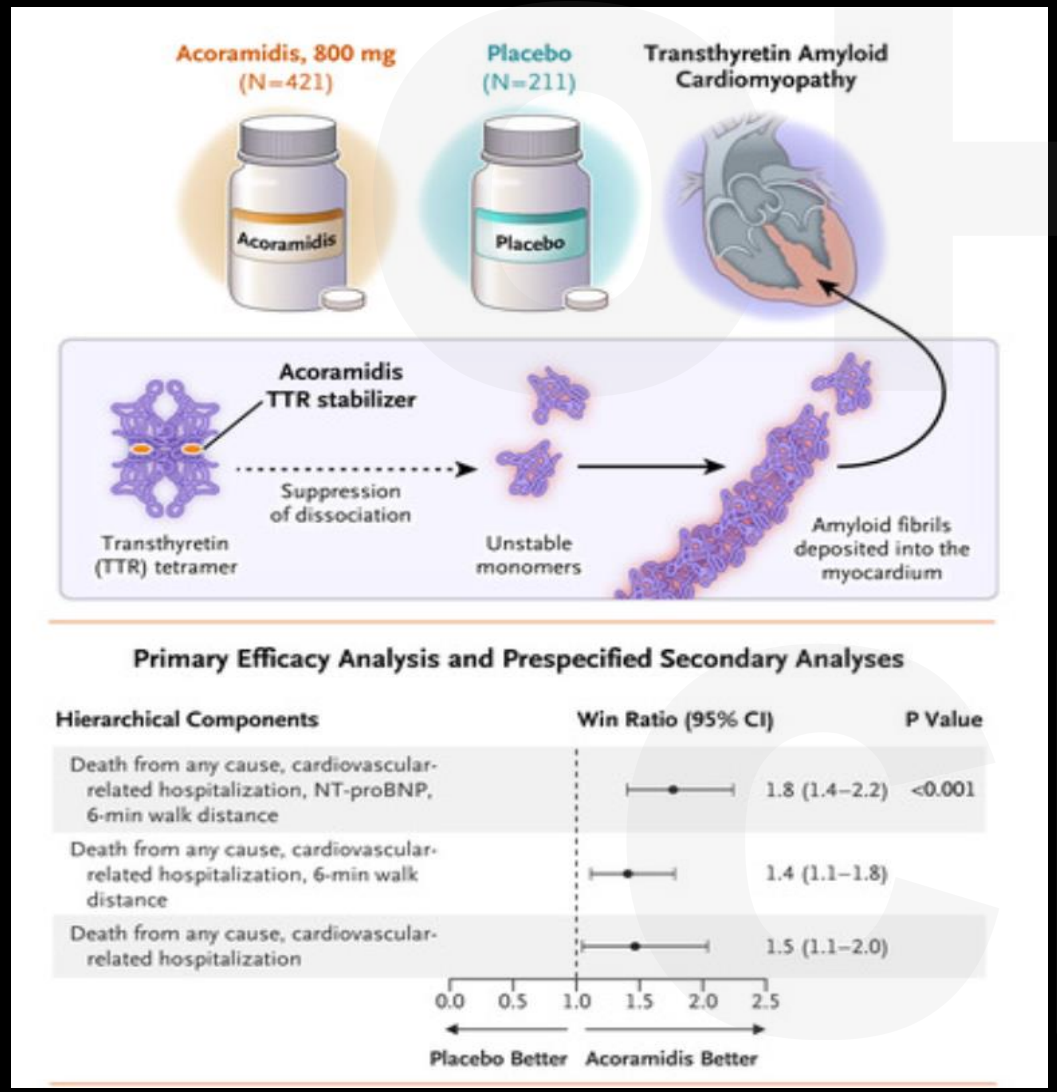
C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations *total no. (%)*	Cardiovascular- Related Hospitalizations *no. per yr*	Pooled Tafamidis vs. Placebo Treatment Difference *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	

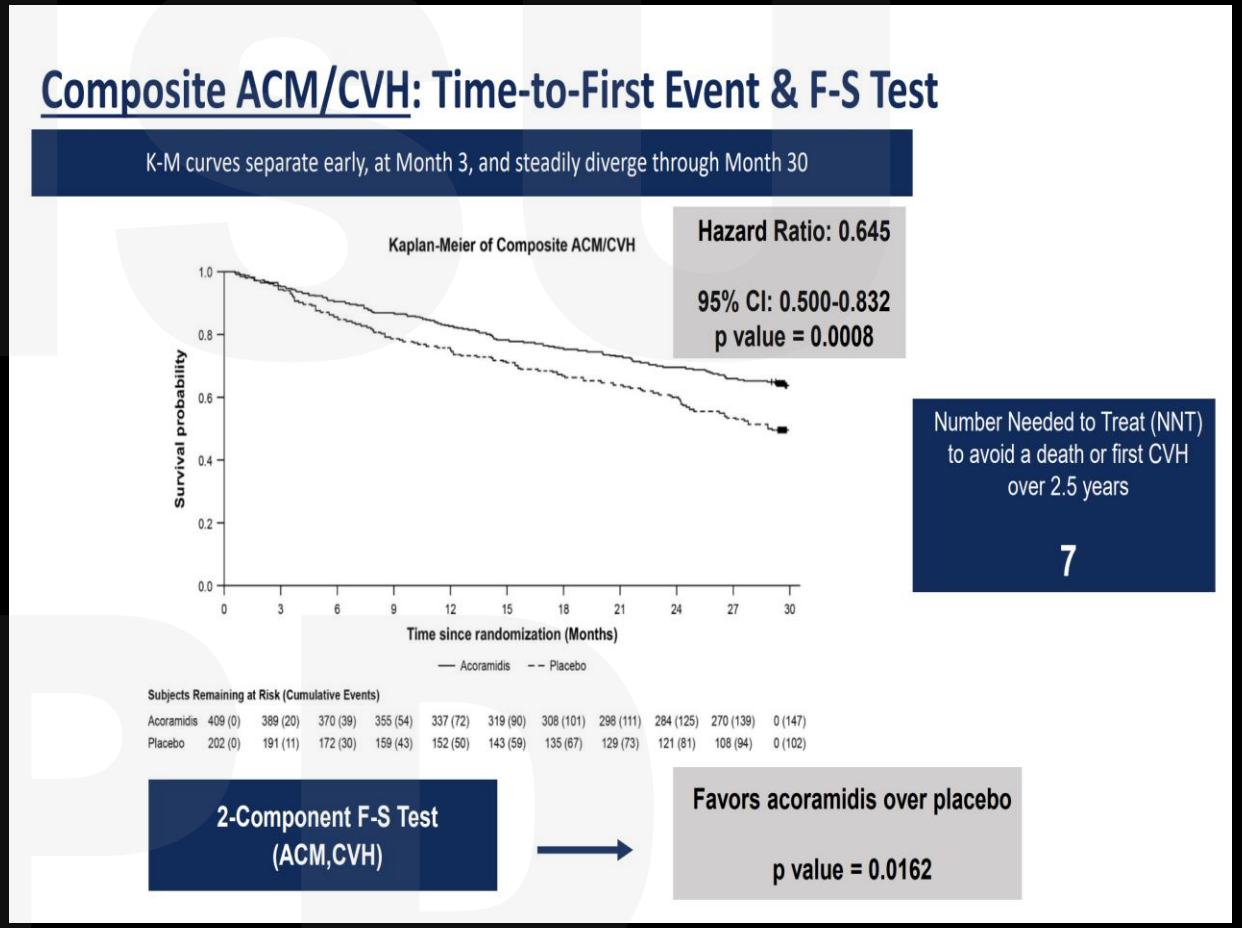
- NNT to prevent 1 death at 30 months – 7.5
- NNT to prevent 1 CV admission at 30 months – 4.5

Maurer NEJM 2018

Acoramidis in ATTR-CM

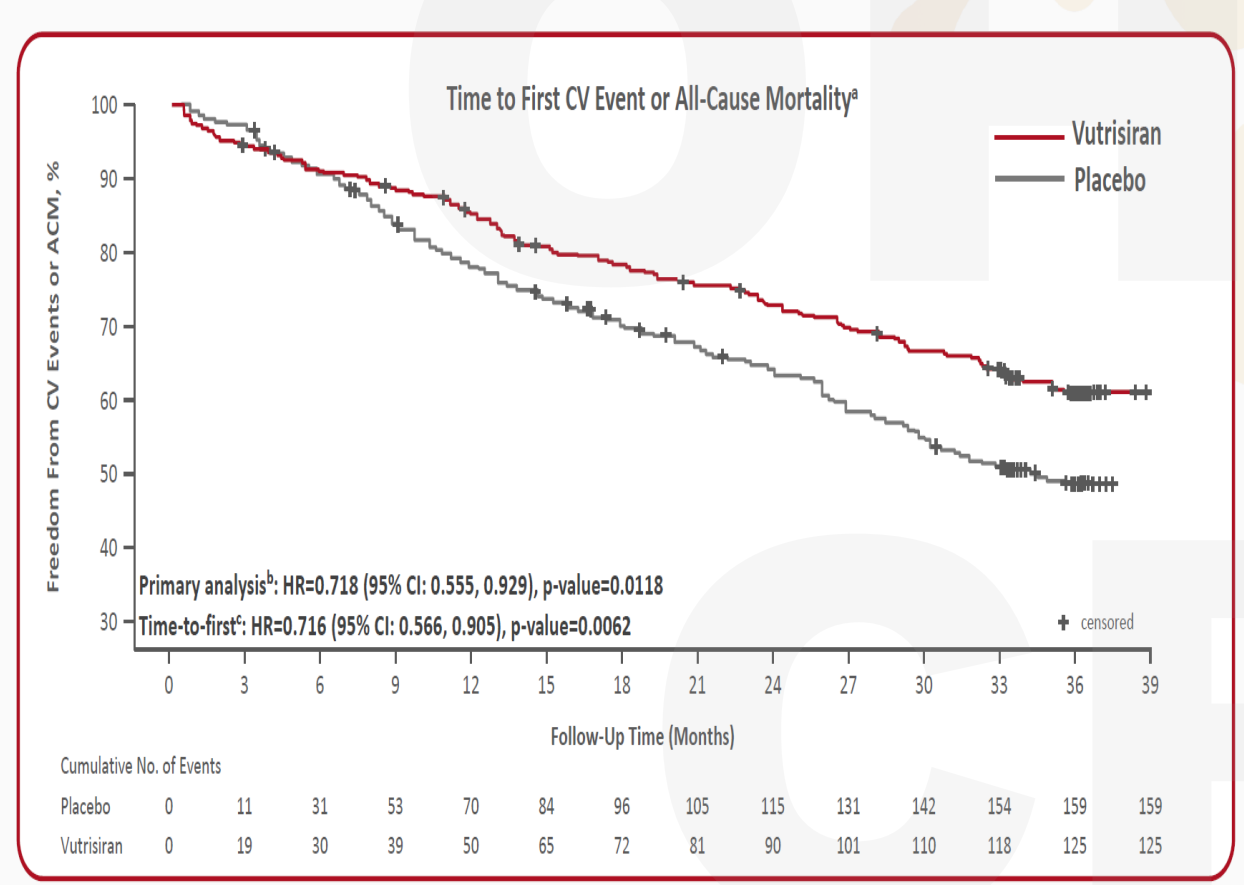


Gillmore,.., Masri et al. NEJM 2023



Judge, Masri et al. AHA 2023

Vutrisiran in ATTR-CM

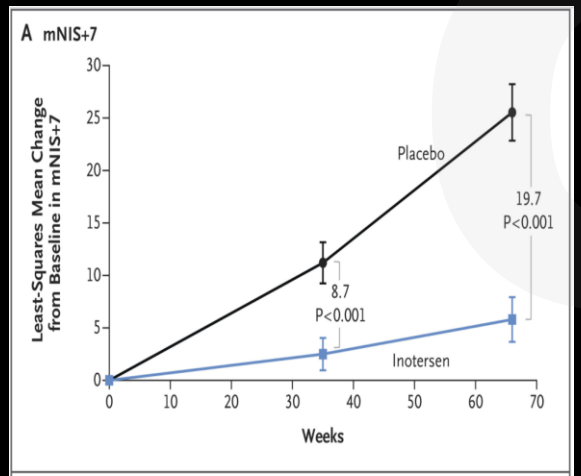


Endpoint		Overall population (N=654)		Monotherapy population (N=395)	
	Treatment effect estimation	Treatment effect	p-value	Treatment effect	p-value
Primary endpoints: Composite outcome of all-cause mortality and recurrent CV events	Hazard ratio	0.718	0.0118	0.672	0.0162
Secondary endpoints					
6-MWT change at Month 30	LS Mean difference	26.46	0.00008	32.09	0.0005
KCCQ-OS change at Month 30	LS Mean difference	5.80	0.0008	8.69	0.0003
All-cause mortality through Month 42	Hazard ratio	0.645	0.0098	0.655	0.0454
NYHA class: % stable or improved at Month 30	Adjusted % difference	8.7%	0.0217	12.5%	0.0121

Fontana et al. ESC 2024 and NEJM 2024

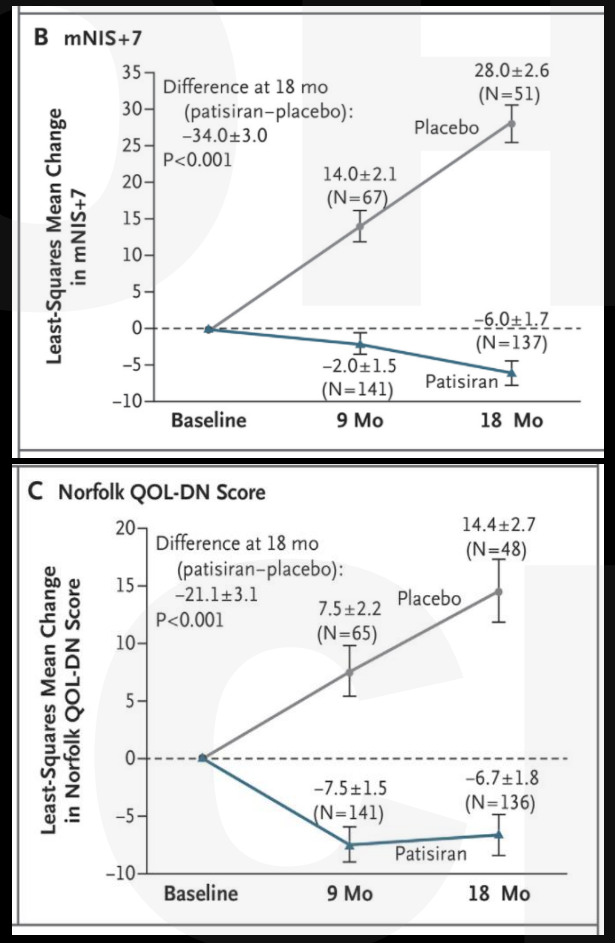
Variant ATTR Polyneuropathy Trials

Inotersen



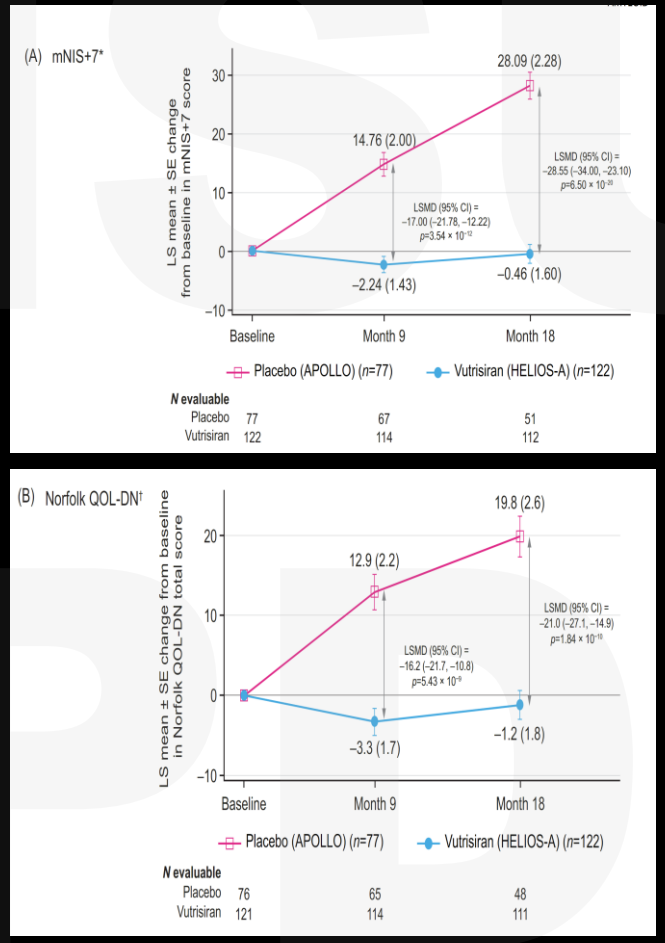
Benson et al. NEJM 2018

Patisiran



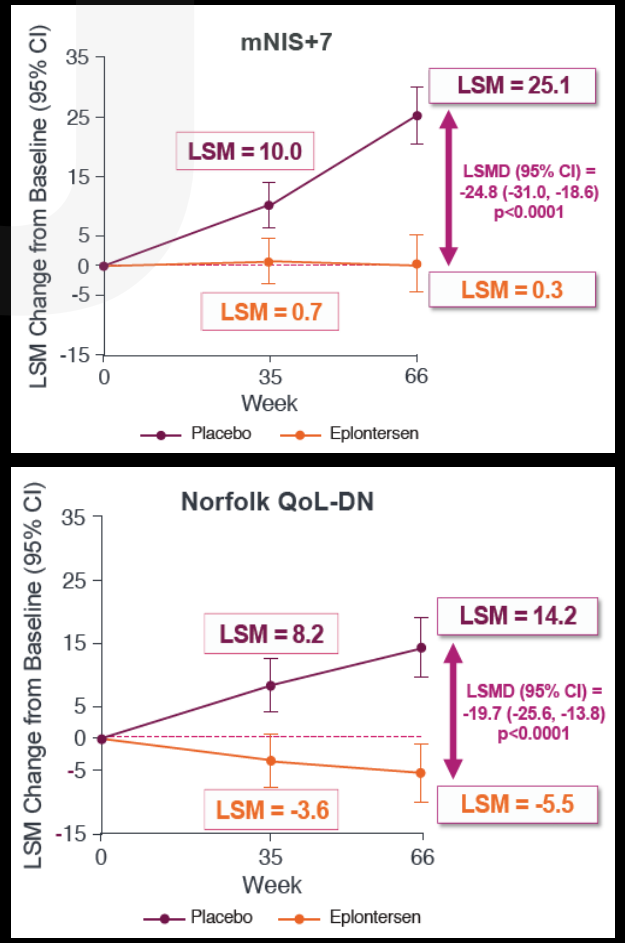
Adams et al. NEJM 2018

Vutrisiran



Adams et al. Amyloid 2022

Eplontersen



Khella et al. AAN 2023

Current Treatment Approaches

- ATTR-CM
  - Deprescribe heart failure therapy as appropriate
  - Loop diuretics, MRA, SGLTi
  - Tafamidis, Acoramidis, Vutrisiran

- AL-CM
  - Deprescribe heart failure therapy as appropriate
  - Loop diuretics, MRA
  - Dara-CyBorD and reassessment for bone marrow transplant

Multidisciplinary Amyloidosis Program

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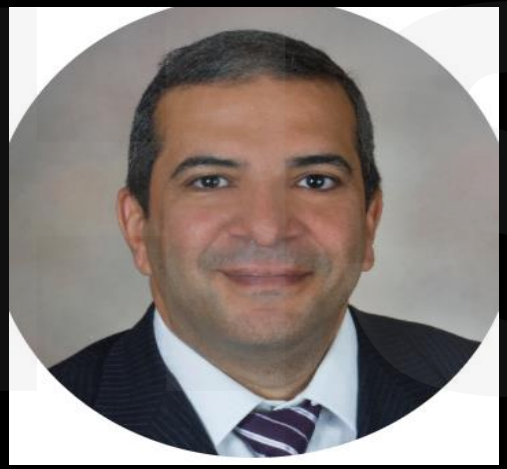
Cardiology



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Cardiac Amyloidosis in 2025

- Just under 6 years – a disease is transformed from being fatal to being addressable/chronically managed and now we are entering an era of regressing disease and potential cure

- Enabled by integrating research into the routine care of patients and cultivating relationships with the community

- “Rare” becomes not so rare when you can diagnose and treat

Conclusions

- Cardiac Amyloidosis is common and is evolving rapidly
  - A treatable cause of heart failure

- Early diagnosis is paramount
  - Avoid misdiagnosis

- Work up has evolved to the non-invasive approach
  - Still need endomyocardial biopsy in 5-10%

- Recognition is key to improving outcomes