Wake Up and Look Around: Early Recognition, Diagnosis, and Treatment of Cardiac Amyloidosis

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@NotNoninvasive

DISCLOSURES

Research Support

- Intersocietal Accreditation Commission (IAC)
- Pfizer Inc.

Application Reviewer

- Intersocietal Accreditation Commission (IAC)

Speakers Bureau: Pfizer Inc., Alnylam

Advisory Board: Pfizer Inc., Alnylam, BridgeBio

LEARNING OBJECTIVES

1) Describe amyloidosis, including specific types, cardiac features, and disease burden.

2) Identify barriers to patient identification and understand the “red flags” to optimize early detection.

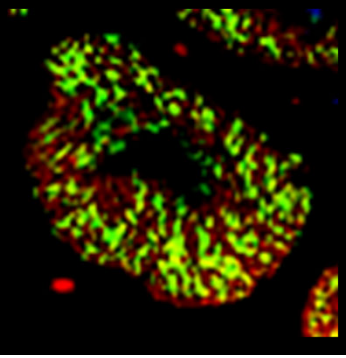
3) Discuss varying disease presentation and the role of multimodality imaging, genetics, and screening.

4) Summarize the diagnostic evaluation for cardiac amyloidosis including the differential diagnosis.

5) Recognize the benefits of disease modifying therapies on amyloid specific heart failure outcomes.

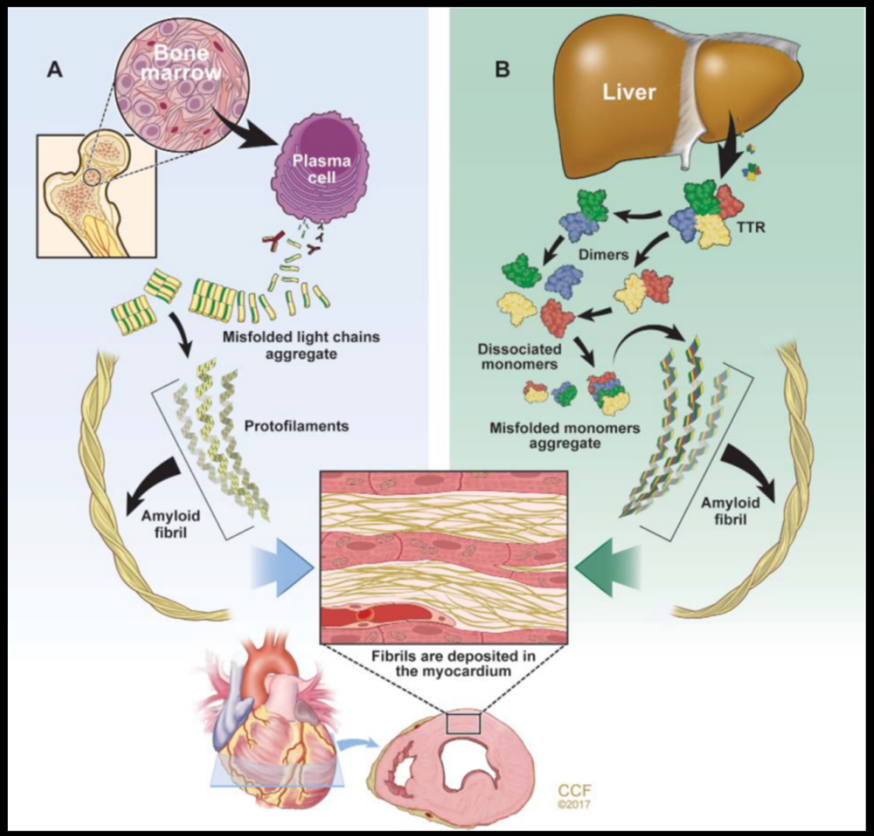
Cardiac Amyloidosis and Its Clinical Features

- Deposition of abnormal protein fibrils in the myocardium
- Deposits are resistant to proteolysis
- Restrictive cardiomyopathy/diastolic dysfunction
- Under recognized cause of HFpEF



Pathogenesis of Cardiac Amyloidosis

Light Chain Amyloidosis (AL)



Transthyretin Amyloidosis (ATTR)

- Fibrils are resistant to proteolysis
- Restrictive cardiomyopathy/diastolic dysfunction

Donnelley and Hanna, Cleve Clin J Med., 2017

Cardiac Amyloidosis

Types of Amyloidosis

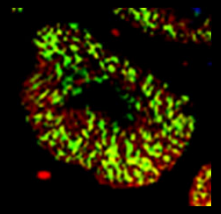
Table. Classification of the Subtypes of Cardiac Amyloidosis

Amyloidosis Type	Protein	Cardiac Involvement	Median Survival, mo	Extracardiac Manifestations
Primary (AL)	Light chain	22%-34%	13 (4 mo if heart failure present at diagnosis)	Renal failure, proteinuria, hepatomegaly, autonomic dysfunction, macroglossia, purpura, neuropathy, carpal tunnel syndrome
Hereditary (ATTR)	Mutant TTR	Variable	70	Severe neuropathy, autonomic dysfunction, renal failure, blindness
Senile systemic (ATTR)	TTR	Common	75	Diffuse organ involvement
Isolated atrial (AANF)	Atrial natriuretic factor	Limited to heart	. . .	None
Reactive (AA)	Amyloid A	<10%	24½	Renal failure, proteinuria, hepatomegaly associated with chronic inflammatory conditions
Dialysis-related (β_2-microglobulin)	β_2-Microglobulin	Unknown, asymptomatic	. . .	Arthralgias, carpal tunnel syndrome, arthropathies, bone cysts, pathologic fractures

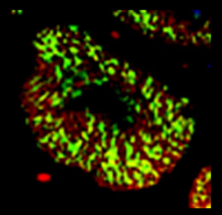
>95% of all Amyloidosis

Wild-type

Shah et al, *Arch Int Med*, 2006



ATTR Cardiac Amyloidosis



Characteristics of Wild-type and hATTR Cardiac Amyloidosis

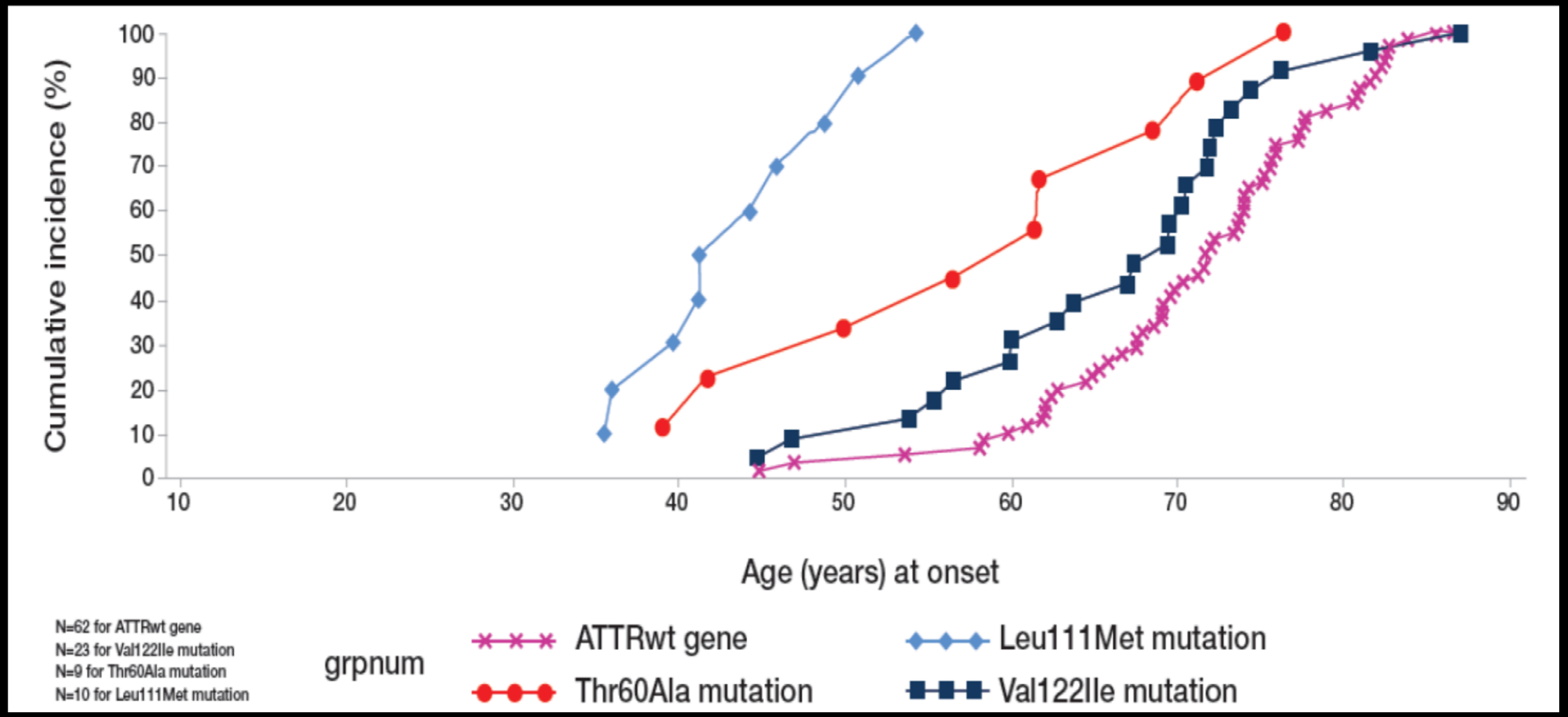
Mutation	Origin	Prevalence	Male:Female Ratio	Onset	Organs
Wild-type	Worldwide	25% >85 y	25:1 to 50:1	>60 y	Heart, ST
V122I/**V142I**	United States, Caribbean, Africa	4% Black	1:1 Gene (+) 3:1 Disease	>65 y	Heart, PNS, ST
V30M	Portugal, Sweden, Japan	1:1000	2:1	>50 y	PN/ANS, heart
T60A	United Kingdom, Ireland	1% Northwest Ireland	2:1	>45 y	Heart, PNS/ANS

SSA indicates senile systemic amyloidosis, wild-type (no mutation); ST, soft tissue; PNS, peripheral nervous system; and ANS, autonomic nervous system.

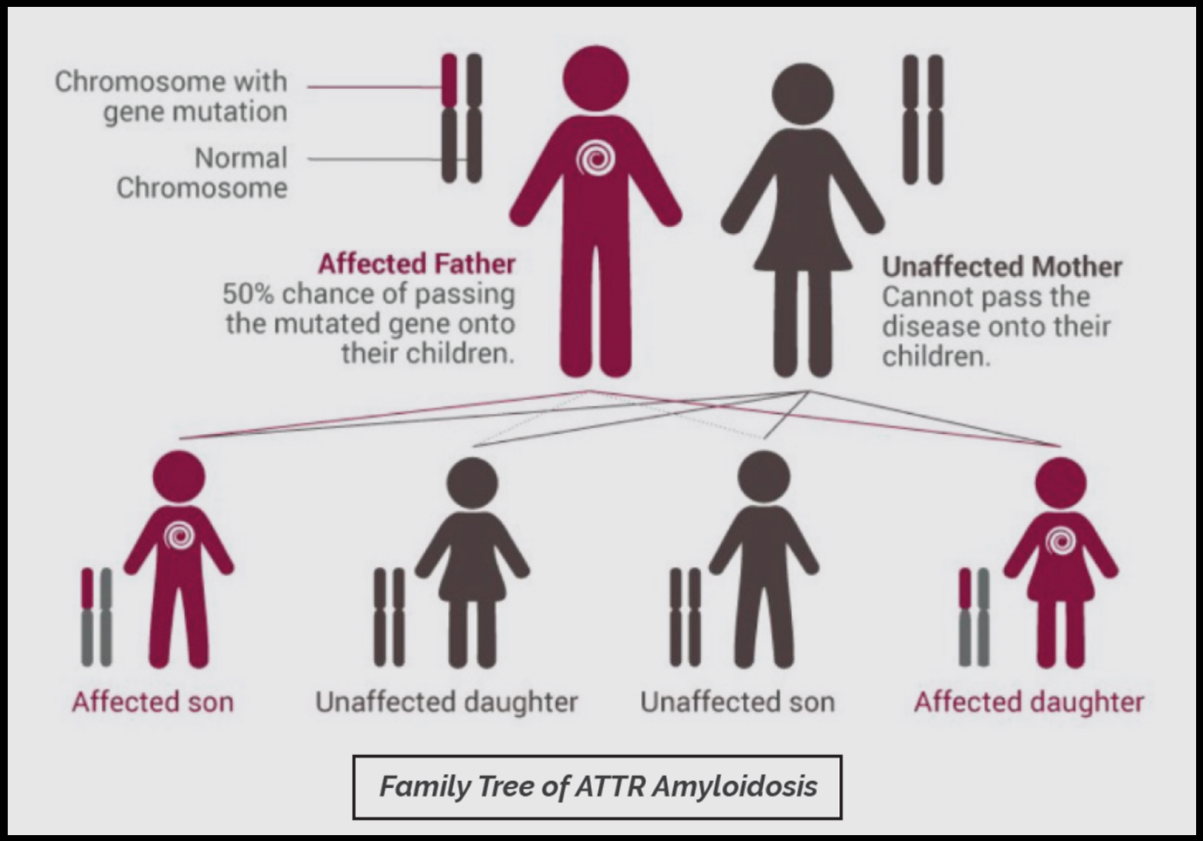
- Wild type ATTR more often seen in elderly men
- wtATTR and hATTR have significant clinical overlap
- Knowledge of population mix is important

Ruberg et al., Circulation, 2012

Mutations Influence Age Dependent Disease Penetrance



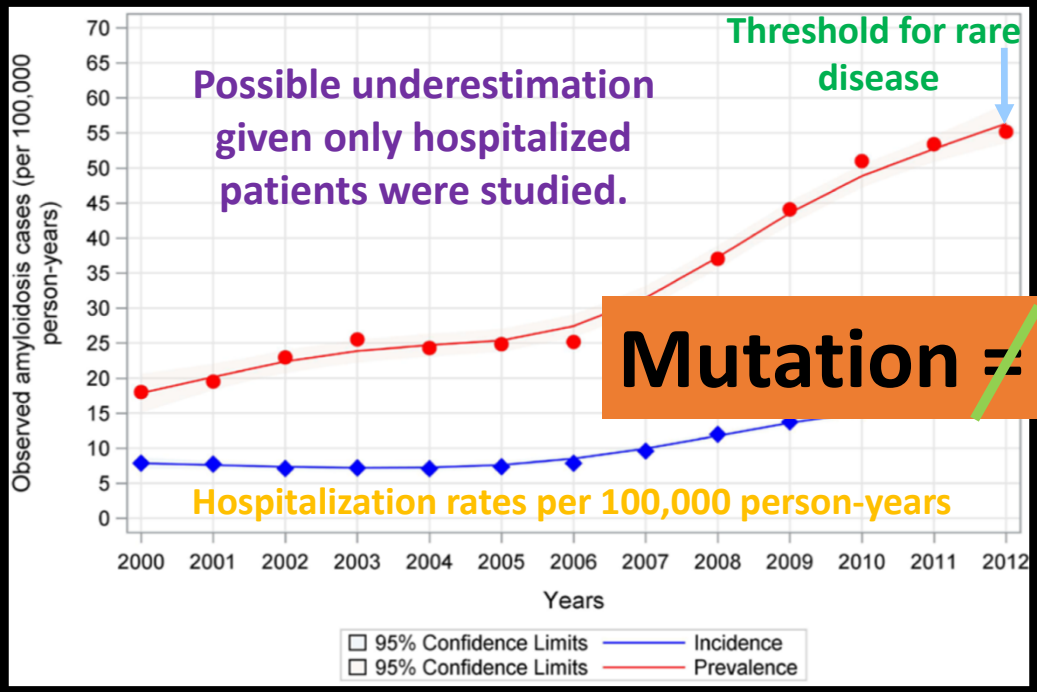
hATTR Cardiac Amyloidosis is Inherited in an Autosomal Dominant Fashion



Think Amyloid Patient Guide, ASNC Amyloidosis Toolkit

Cardiac Amyloidosis: Rare Disease?

Increasing Prevalence of Amyloidosis



Mutation ≠ Disease

Cook County: 1.25 million African American

4% V142I prevalence

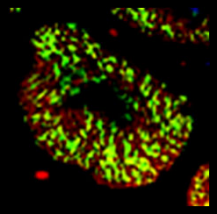
Cook County: 50,000 carriers of V122I mutation

Davidson County: 184,000 African American

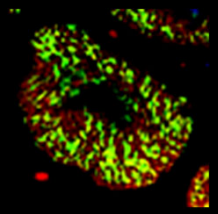
4% V142I prevalence

Davidson County: 7,400 carriers of V1221 mutation

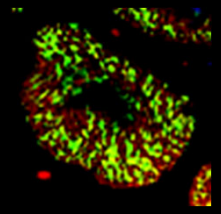
Gilstrap et al., Circulation HF, 2019



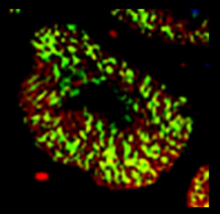
Prevalence of Cardiac Amyloidosis in Contemporary Clinical Practice



- 85 years (Autopsy study) — 25% (n=256)
- Carpal Tunnel release — 10% (n=98)
- HFpEF and LVH — 13% (n=120)
- Severe AS — 5% (n=112)
- TAVR population — 16% (n=151)



Cardiac Amyloidosis:
A Rare Disease?



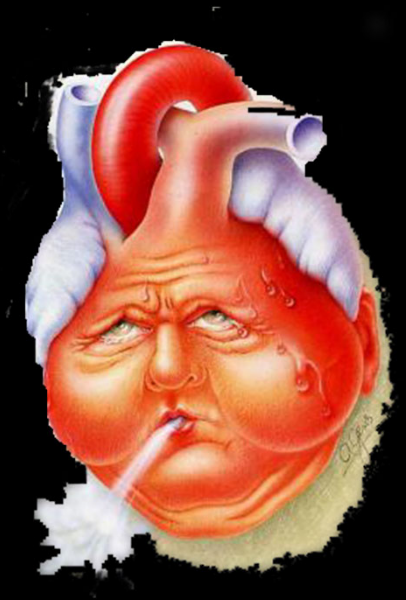
Cardiac Amyloidosis Type	Incidence/Prevalence
AL Amyloid	~2500 cas[illegible]ually 50% with [illegible]ac involvement
ATTRv/hATTR	4% Af[illegible]ans are carriers Severa[illegible]ses
ATTRwt (SSA)	10-25[illegible]ears (M>F) ~ 1 million

Rare

Not so rare

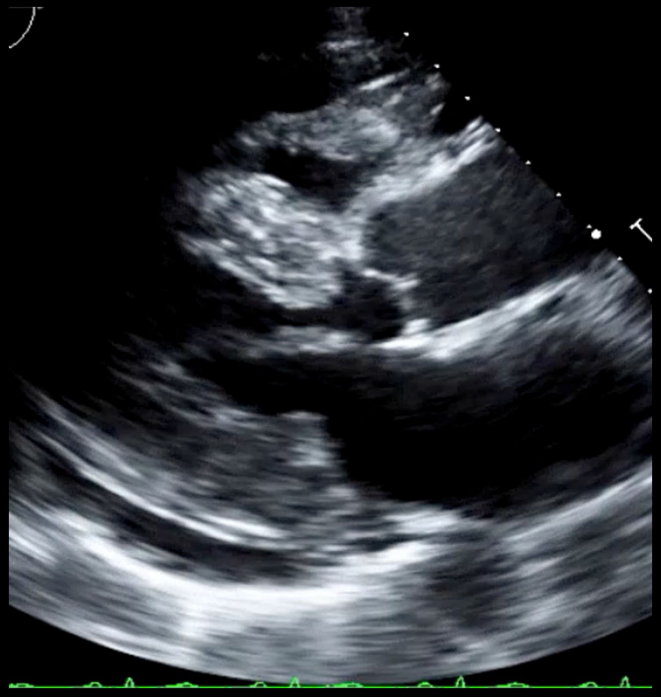
Not rare at all!

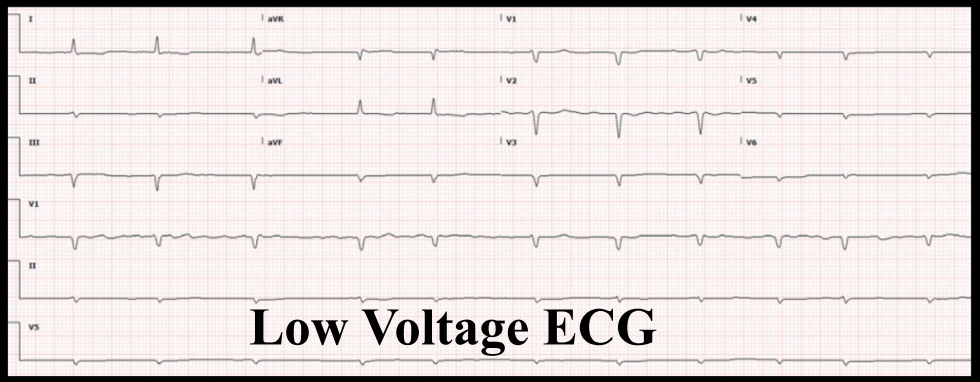
Cardiac Amyloidosis:
Classic Presentation



HFpEF

Left ventricular hypertrophy (LVH)
Speckling pattern on echo

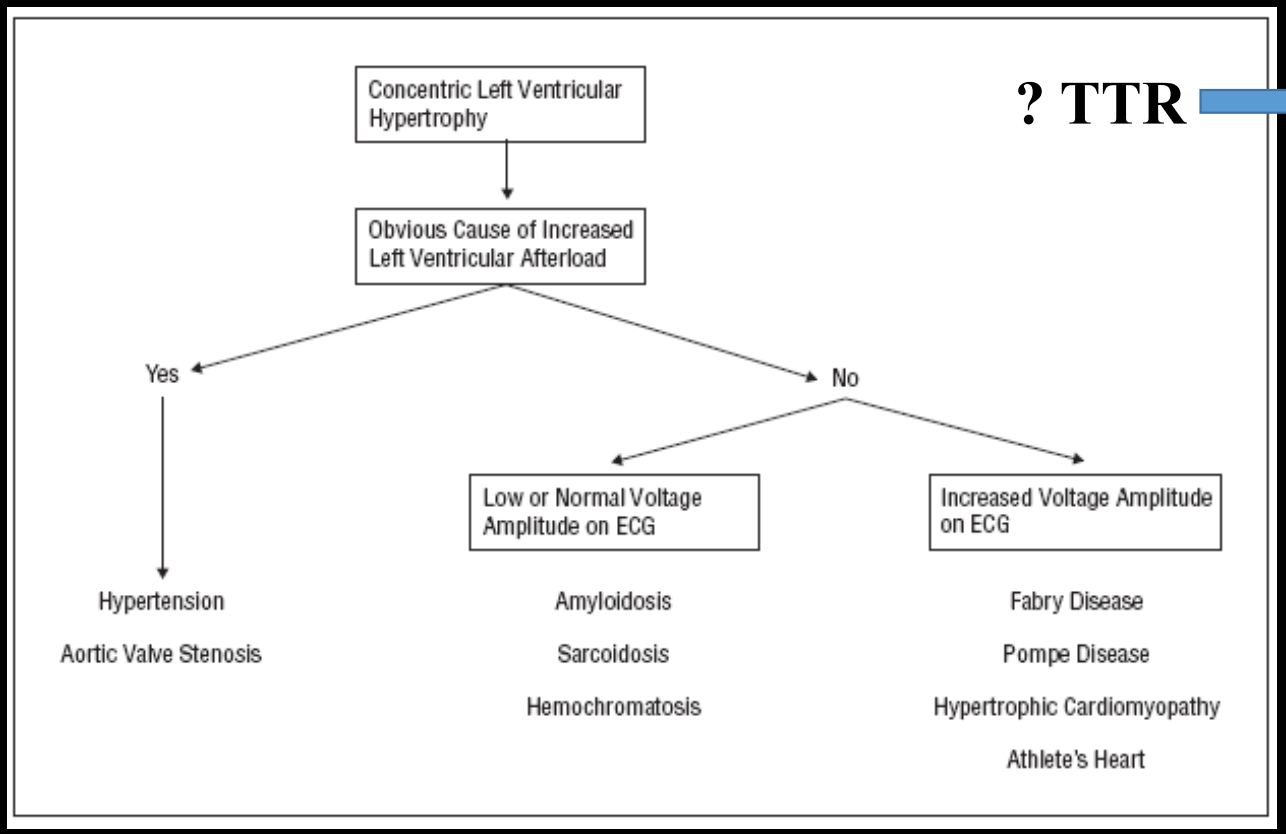




Low Voltage ECG

Cardiac Amyloidosis

Diagnostic Challenges



? TTR

- Disease of the elderly
- Long standing HTN
- LVH is common
- AS is common

Amyloid deposits on biopsy

- ~25% over 80 years
- ~50% over 90 years

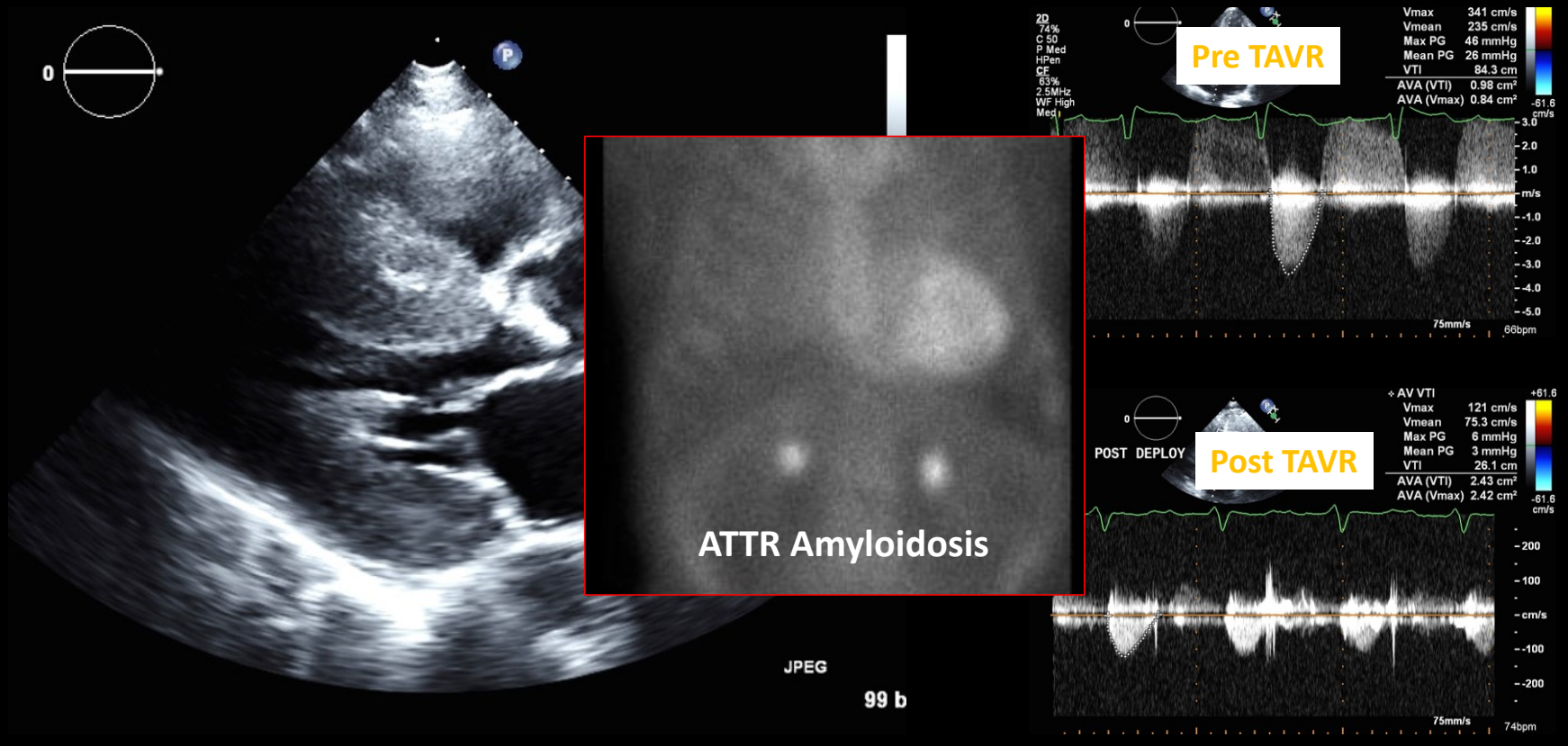
Aortic stenosis

- 10-30% patients have CA
- No difference in prevalence by presence/absence of AS

Shah et al, *Arch Int Med*, 2006

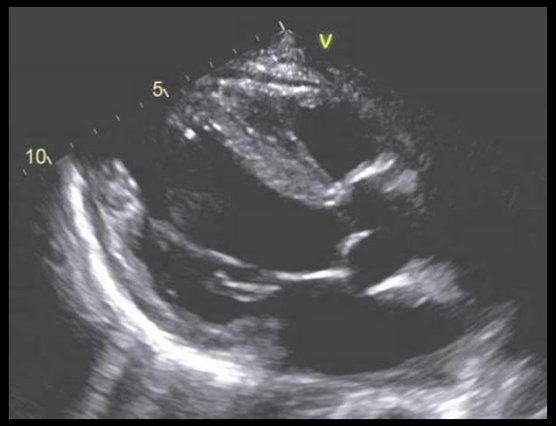
No Cardiac Amyloidosis if Significantt Aortic Stenosis?

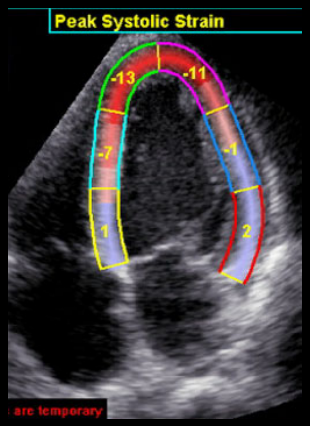
84 yo Caucasian male with severe symptomatic aortic stenosis, with no improvement after TAVR.



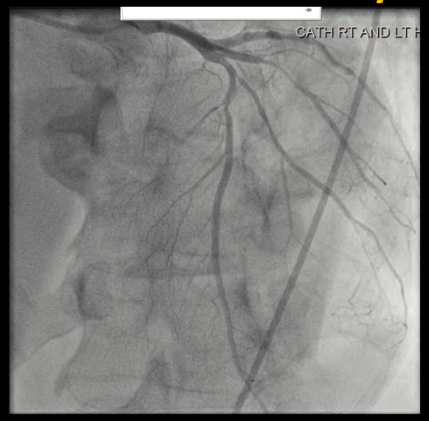
HFpEF as the Characteristic Phenotype of Cardiac Amyloidosis?

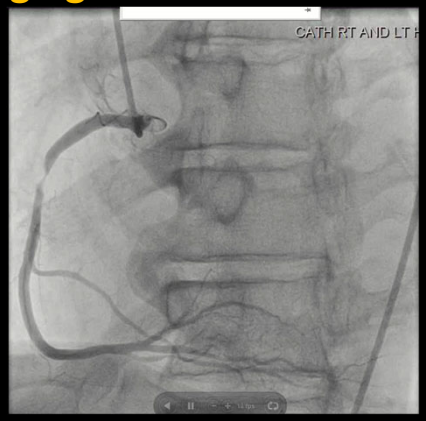
Echocardiogram



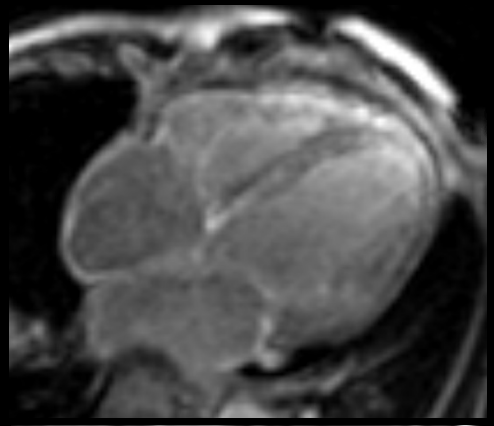


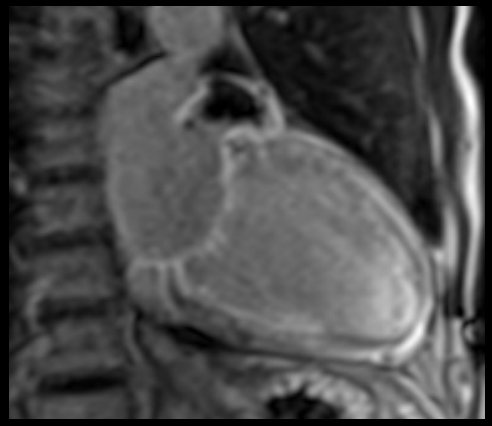
Coronary Angiogram



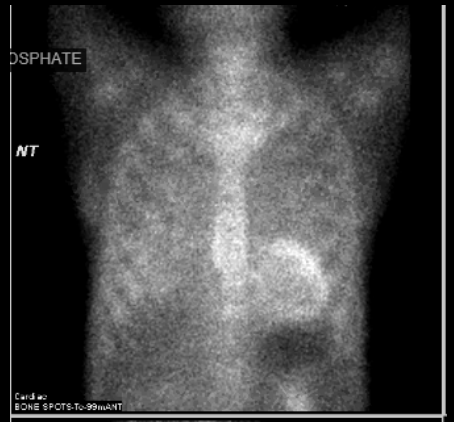


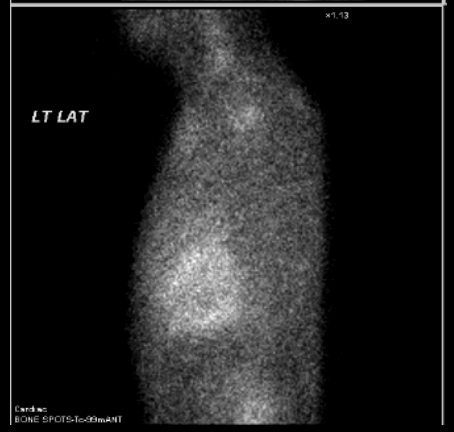
Cardiac MRI





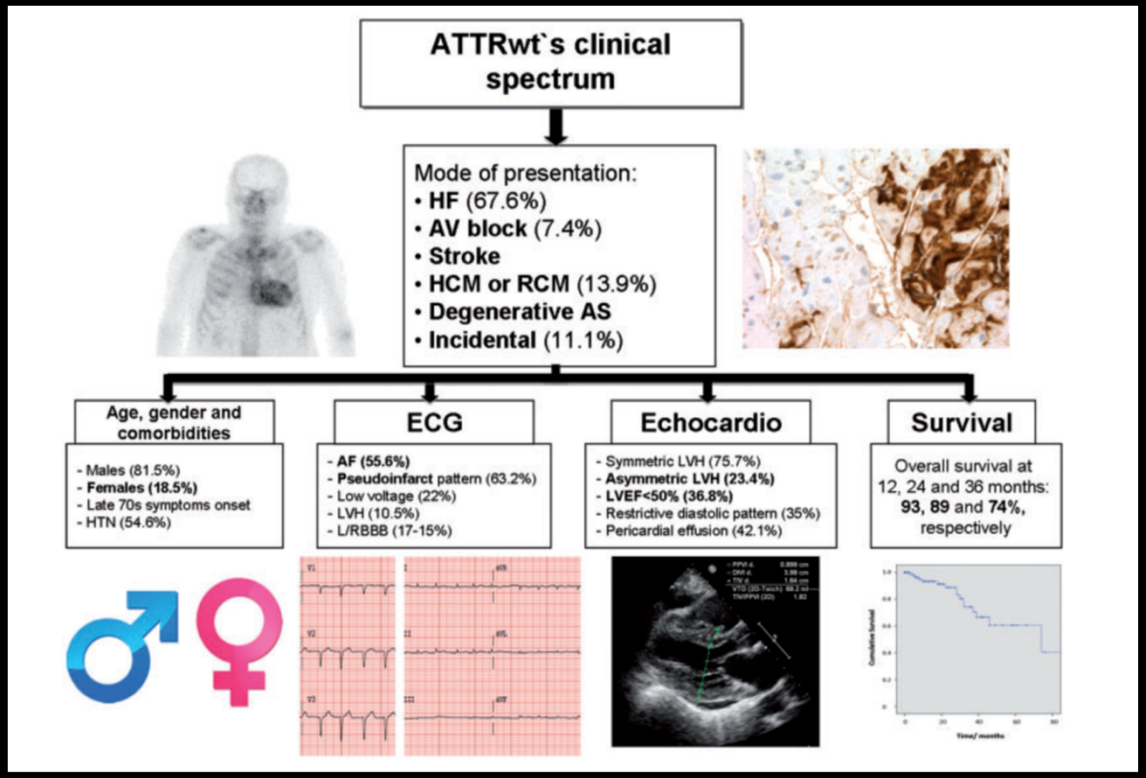
Cardiac PYP Scan





Cardiac Amyloidosis

High Prevalence of HFrEF in Patients with TTR Amyloidosis



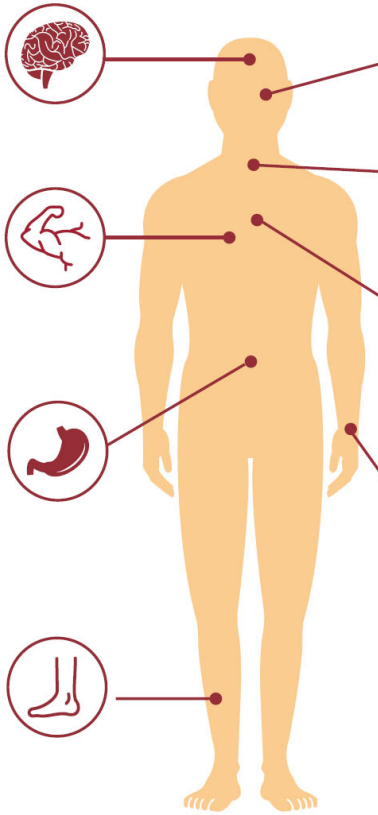
- n=108
- Mean age 78 years
- Mean EF at diagnosis 52%
- 37% with low EF
- 1/3rd of patients had prior misdiagnosis (HTN/HCM/AS)
- >30% with HFrEF

Lopez et al. *European Heart Journal*, 2017

Talal/Malhotra, Journal of Nuclear Cardiology, 2020

Amyloidosis is a Systemic Disease!

Amyloidosis Red Flags



Neurology
Cardiology
Head & Neck
Lightheadedness on standing
Bulging neck veins
Enlargement of tongue

Eyes
Ophthalmology
Opacities
Floaters
Optic neuropathy
Glaucoma

Ortho/Neurology
Arms
Biceps tendon rupture
Numbness, burning or tingling
(peripheral neuropathy)

Back
Neurology
Back pain and difficulty walking
(spinal stenosis)

Cardiology/EP
Heart & Lungs
Shortness of breath and fatigue
Chest pain
Dizziness or passing out
Slow heart beat or heart block,
Irregular heart beat (atrial fibrillation)

GI
Stomach & Intestines
Poor appetite
Feeling of fullness in the stomach
after eating a small meal
Diarrhea/constipation
Weight loss

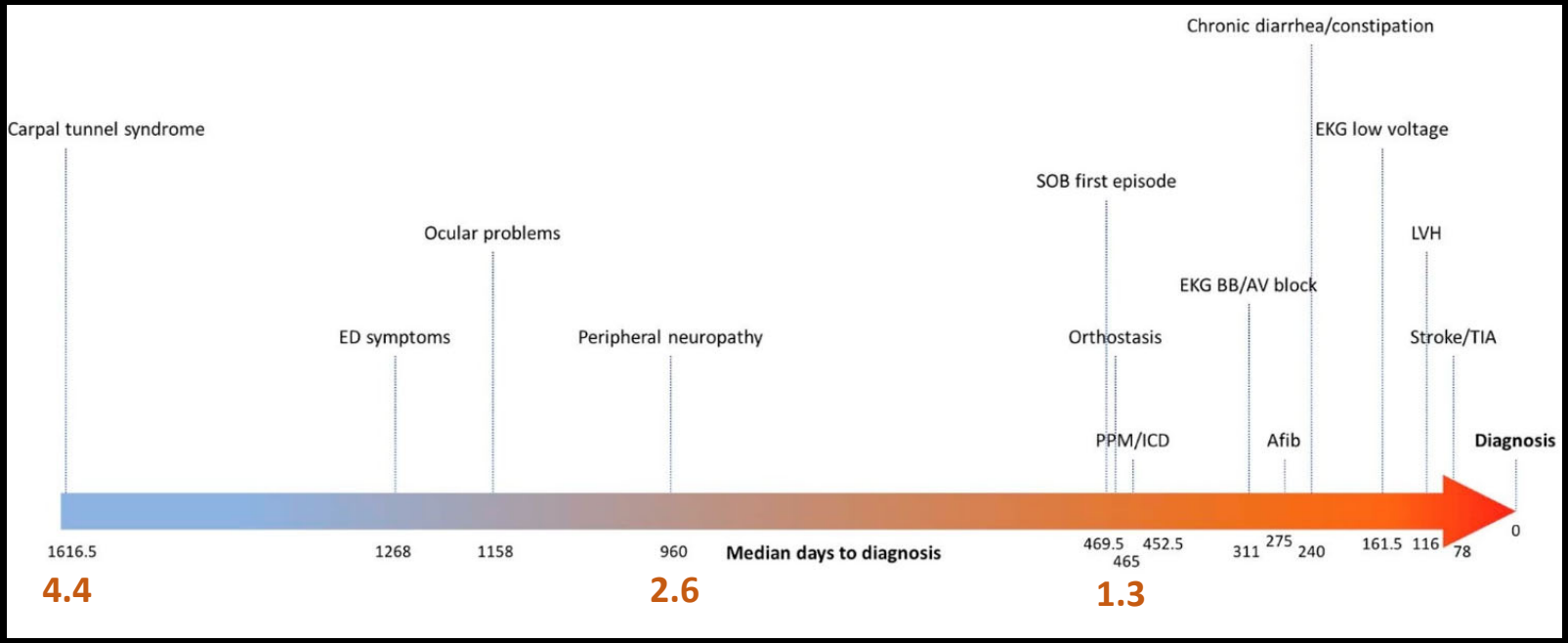
Hands
Neurology/Ortho
Carpal tunnel syndrome

Neurology
Cardiology
Legs
Swelling of feet or legs
Numbness, burning and/or tingling
(peripheral neuropathy)
Muscle weakness
Difficulty walking

Think Amyloid Patient Guide, ASNC Amyloidosis Toolkit

Cardiac Amyloidosis

Cardiac involvement if often late in the disease

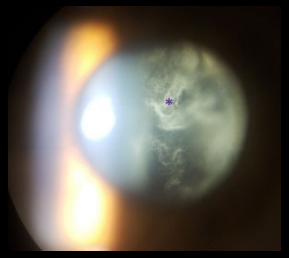


74/M admitted to the hospital with atrial fibrillation and LE edema with DOE. Patient used to be a painter by occupation, and used both hands for painting. History of b/l CTS and release in 2013 with continued peripheral neuropathy.

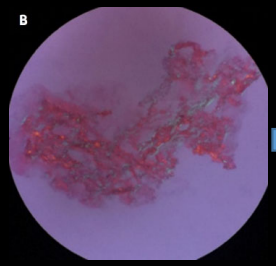
Papoutsidakis et al., J Card Failure 2018

Amyloidosis Patients are Hiding in Plain "Sight"

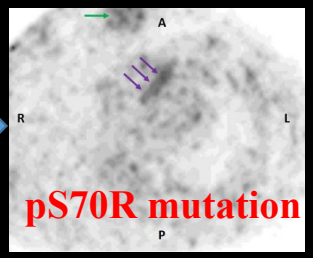
A) 52/M with worsening vision. Reports fam. h/o amyloidosis.



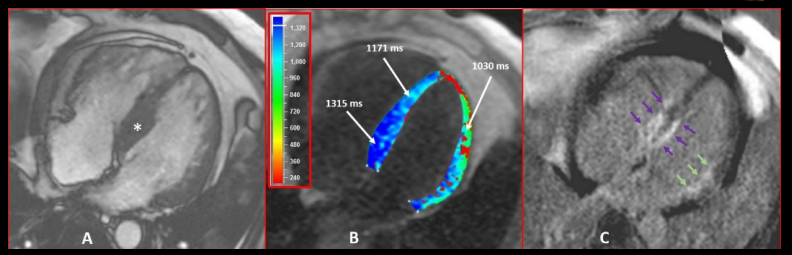
Vitreous Opacity



+ Congo RED



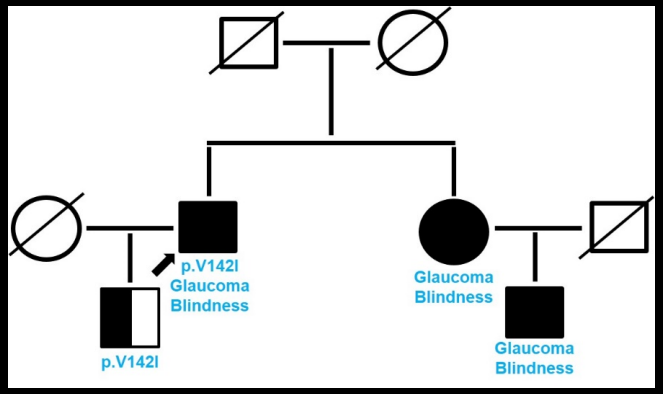
Focal PYP Uptake



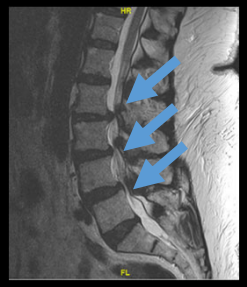
MRI Confirms Focal Amyloid Infiltration

Asif/Malhotra et al., JNC 2021

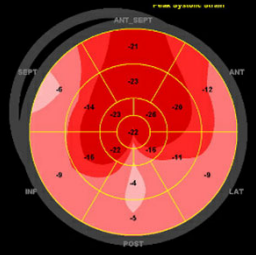
B) 76/M with blindness from glaucoma for several years. New HF in 2021. Family h/o glaucoma and blindness. pV142I mutation



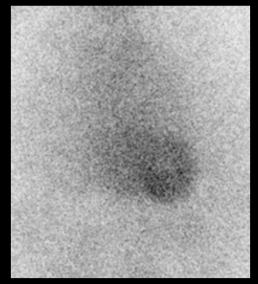
C) 80/F with LS, low back pain. No HF symptoms.



Lumbar Stenosis 2016



Pre-op echo 2020

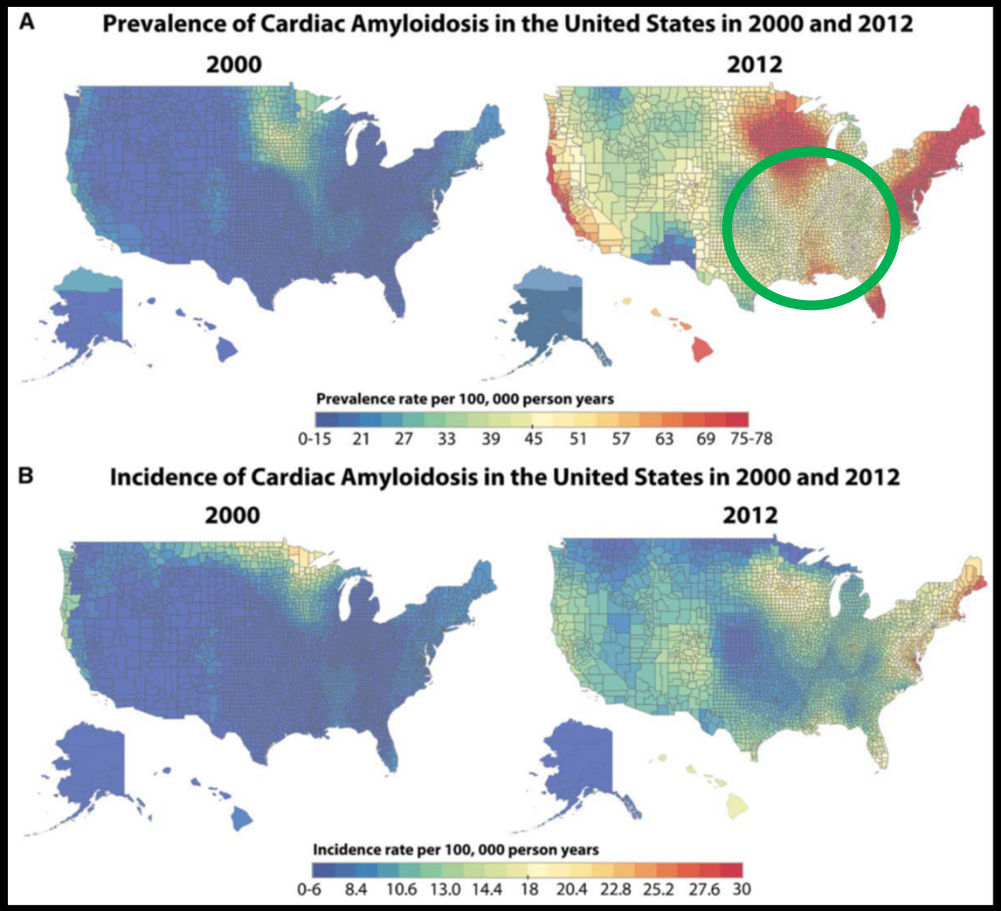


Positive PYP 2020

pV142I mutation

Varied Distribution of Amyloidosis in the US

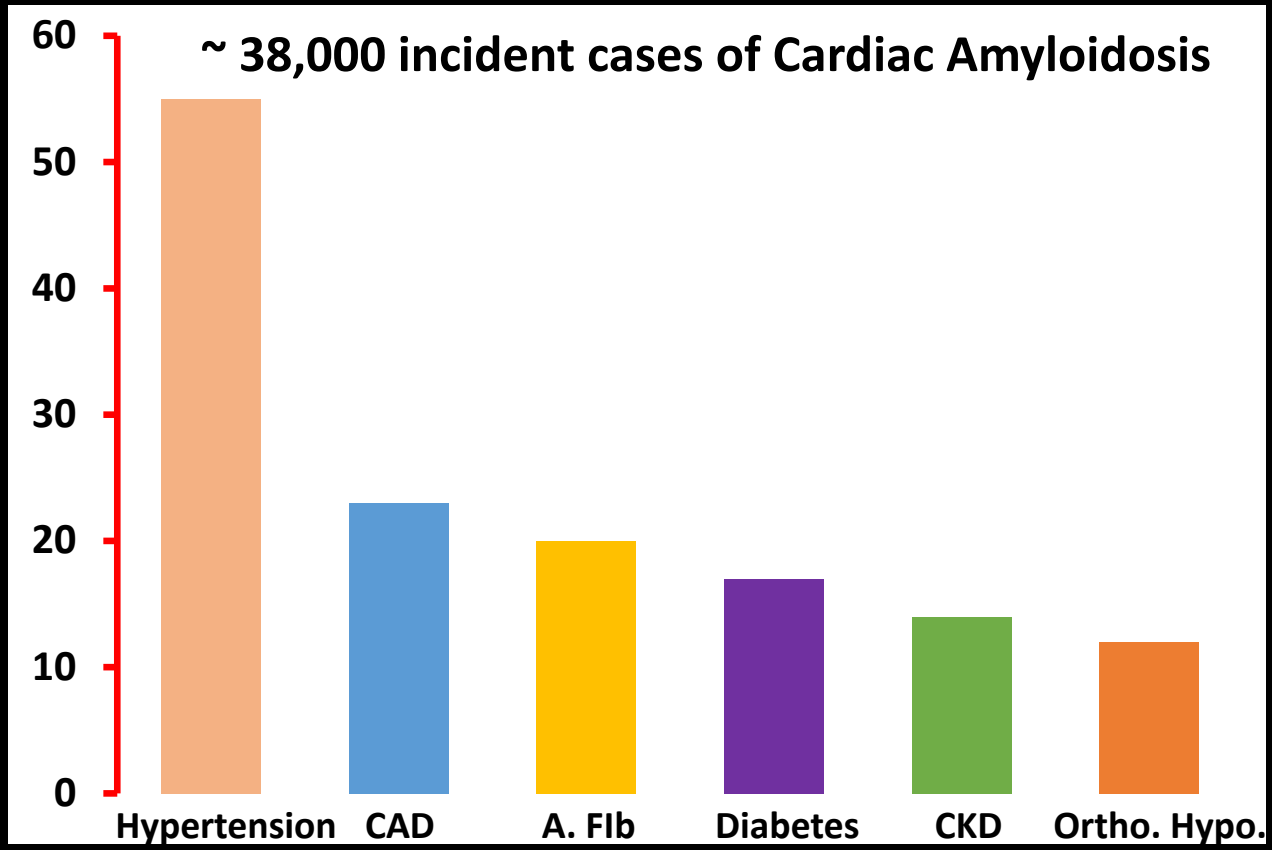
Racial and Ethnic Disparities are Barriers to Diagnosis



BUT…lowest prevalence in the South: 50% of US Black population

Gilstrap, Circulation HF, 2019

Prevalence of Co-morbid Conditions Among Patients with Cardiac Amyloidosis



Gilstrap, Circulation HF, 2019

Genetic Mutations Cause Disease Heterogeneity

Peripheral neuropathy

Gait disturbances

Lumbar stenosis

CTS

Autonomic neuropathy

GI disturbances

Orthostatic hypotension

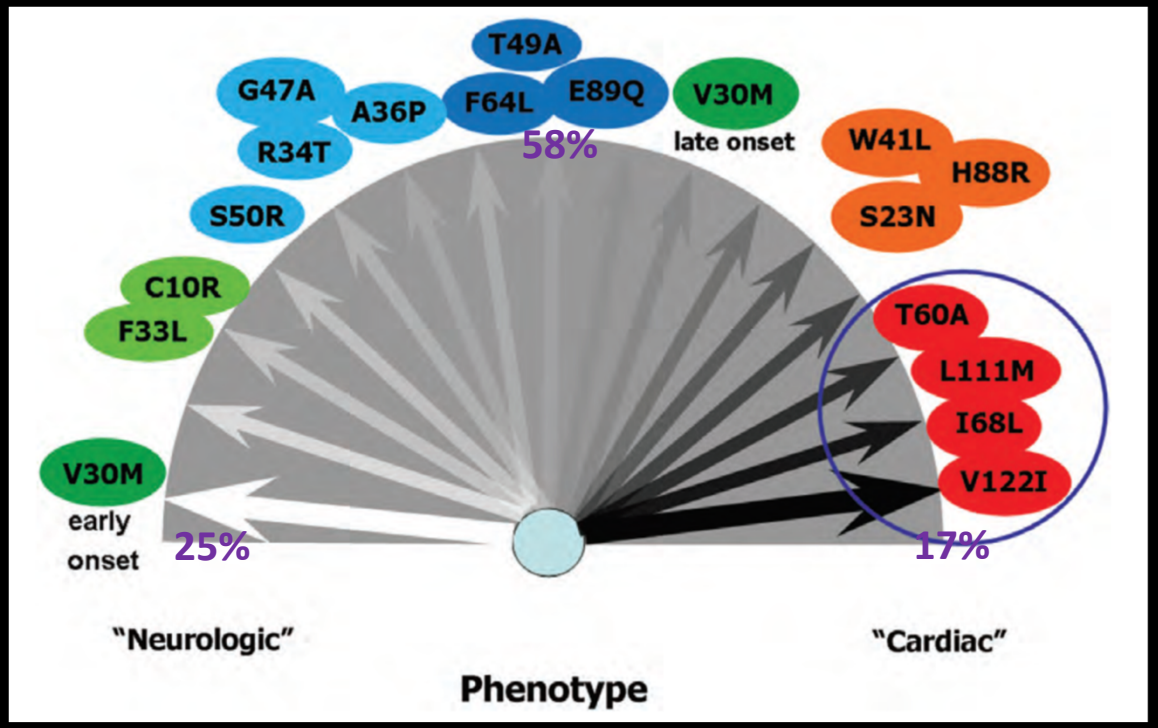
Syncope

VHD

Arrhythmias

Heart blocks

Pump failure



Early onset → **Late onset**

Rapezzi, et al. *European Heart Journal*, 2013

Suspecting Cardiac Amyloidosis

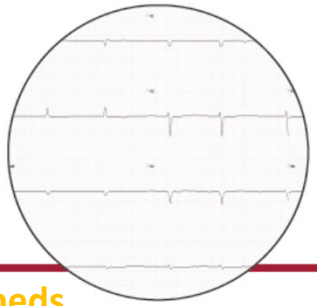
Think Amyloid!

Patients >60 years with clinical HF, and:

African American descent
4% prevalence of hereditary transthyretin amyloidosis; V142I mutation

Elderly
Prevalence of wild-type ATTR-CA increases with age

Increased LV wall thickness



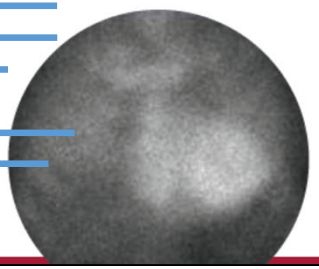
Low voltage ECG

Apical Sparing Strain Pattern

"Red Flags": Intolerance to HF meds

- Low voltage ECG
- Apical sparing strain pattern (cherry on top) echocardiography
- Repeat heart failure (HF) admissions
- Chronic low-level troponin elevation
- Bilateral carpal tunnel syndrome
- Atrial fibrillation/bradycardia/heart block
- Gastroparesis/vomiting/constipation
- Autonomic dysfunction (orthostatic hypotension or syncope)
- Polyneuropathy

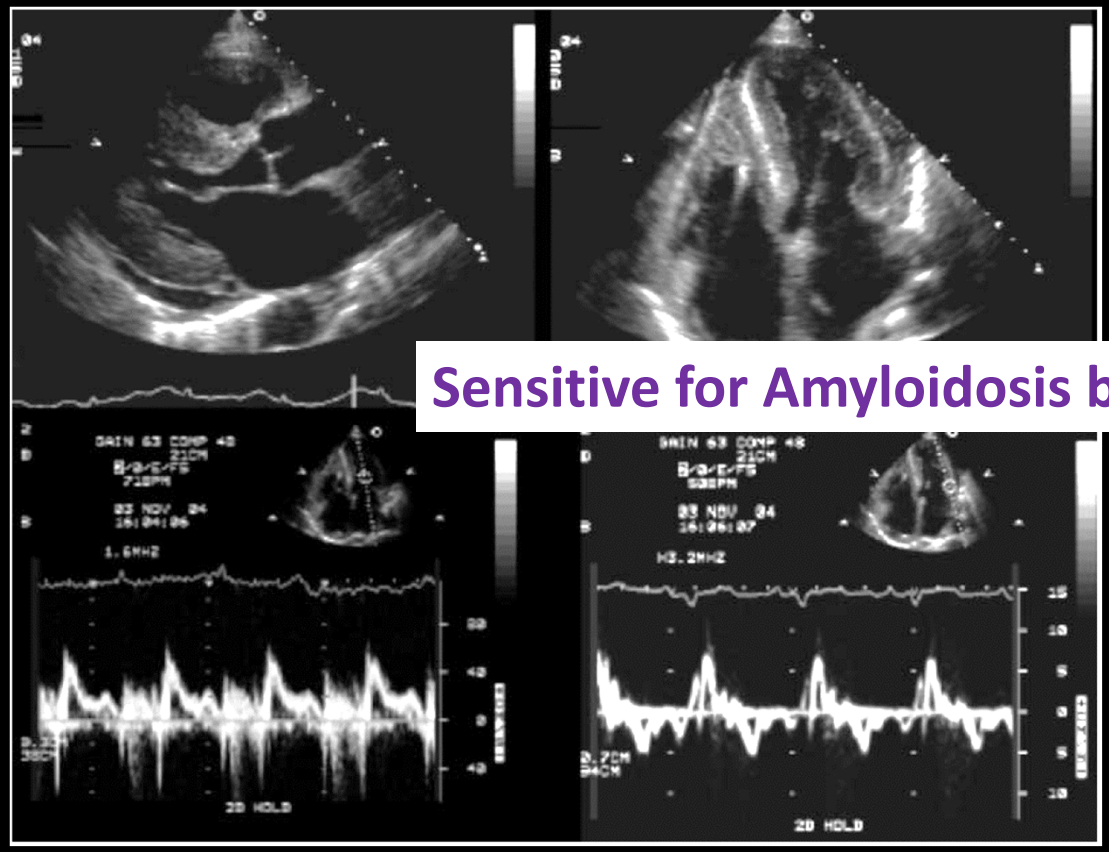
Unexplained LVH



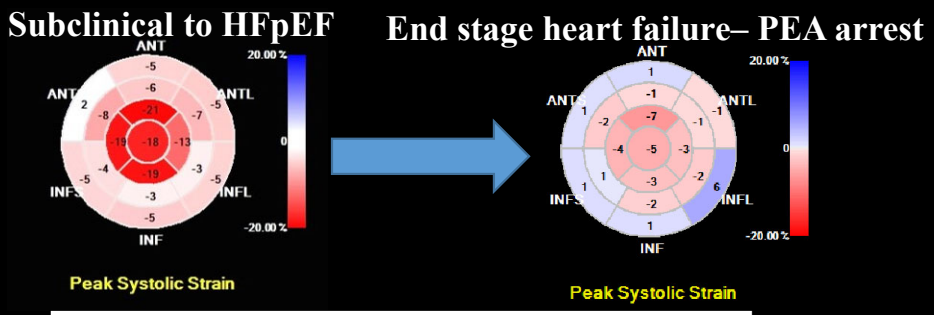
ASNC Amyloidosis Toolkit

Pathway to Confirmation of Cardiac Amyloidosis

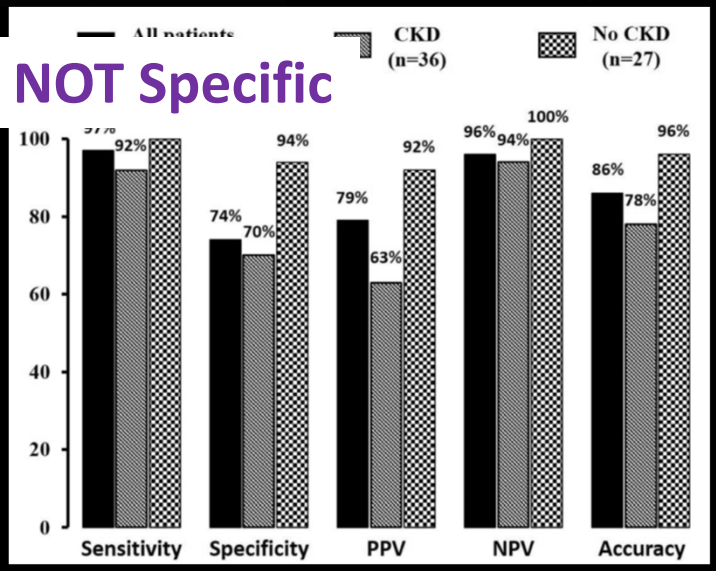
Echocardiography: often the 1st test



Strain Imaging



Sensitive for Amyloidosis but NOT Specific



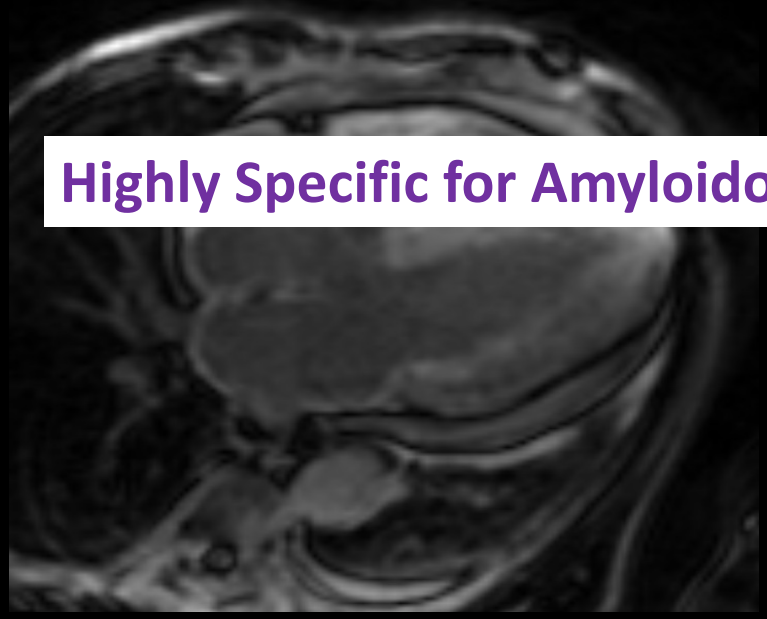
Wall thickness, Myocardial speckling and Diastolic dysfunction

Singh, Soman and Malhotra, JASE, 2020

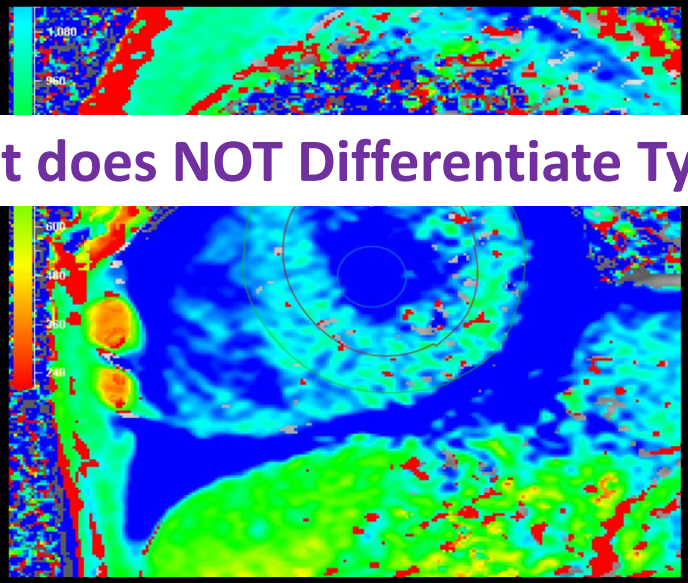
Pathway to Confirmation of Cardiac Amyloidosis

Cardiac Magnetic Resonance

Diffuse late gadolinium enhancement (LGE)



Increased native T1 and Extracellular volume (ECV)



Highly Specific for Amyloidosis but does NOT Differentiate Type

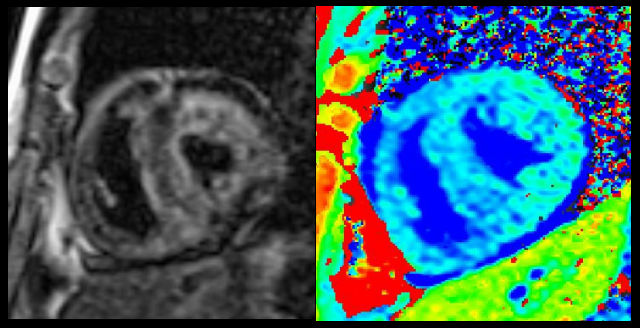
Lee Chuy and Malhotra, Cardio-oncology, Atlas

Nuclear Imaging Clarifies the Etiology of Cardiac Amyloidosis Noted on CMR

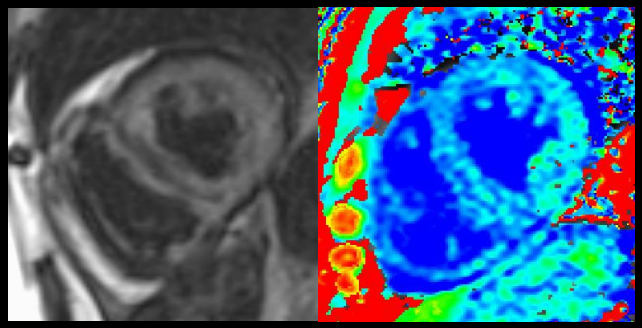
CMR: Sensitivity=85% and Specificity=92%

Subendocardial or Transmural LGE; Elevated native T1 and ECV

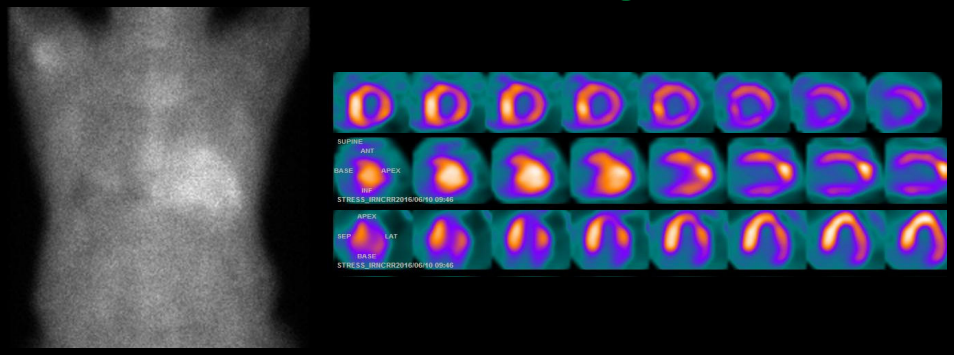
Patient A: T1=1128 ms; ECV=54%



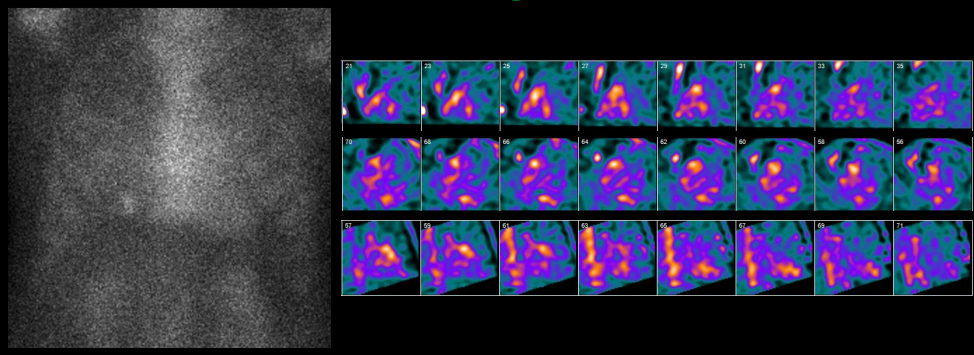
Patient B: T1=1194 ms; ECV=54%



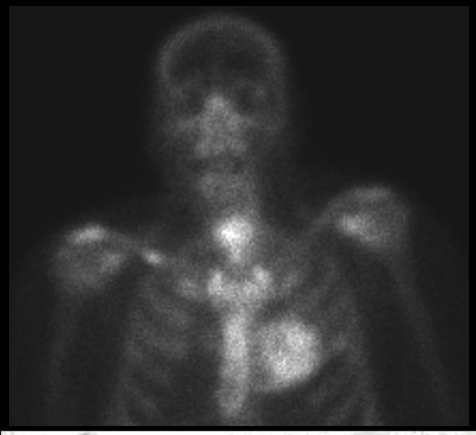
ATTR-CA

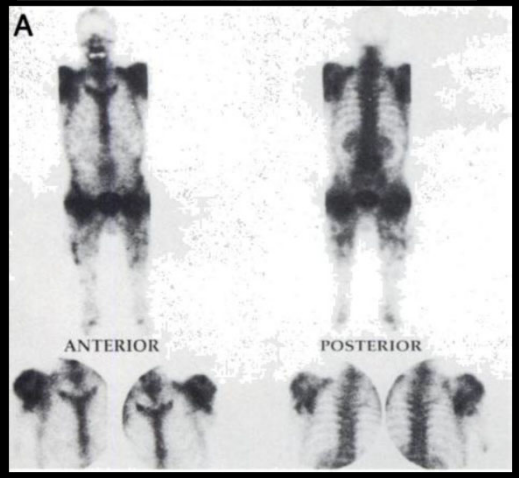


AL-CA



Nuclear Imaging for Cardiac Amyloidosis:
Pyrophosphate (PYP) Imaging





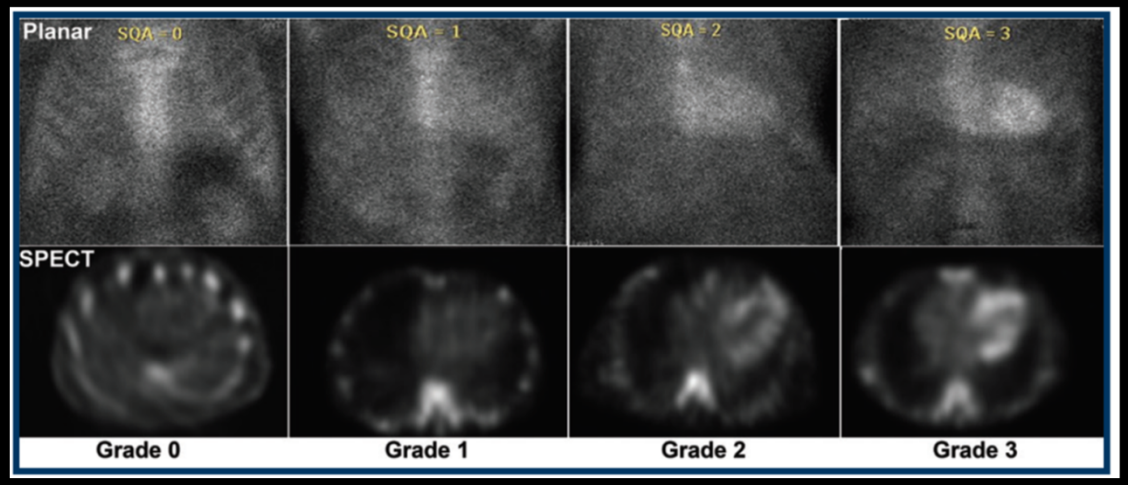
Worsley et al, *JNM*, 1993

- Sporadic case reports on cardiac uptake on bone scans
- Extra cardiac soft tissue uptake of bone tracers among patients with amyloidosis

- Renewed interest
- Increasing prevalence (?bias or increasing life expectancy/treatment of valvular heart disease)
    - Ease and accuracy of imaging
    - Novel drug therapies

Pathway to Confirmation of Cardiac Amyloidosis

PYP Imaging



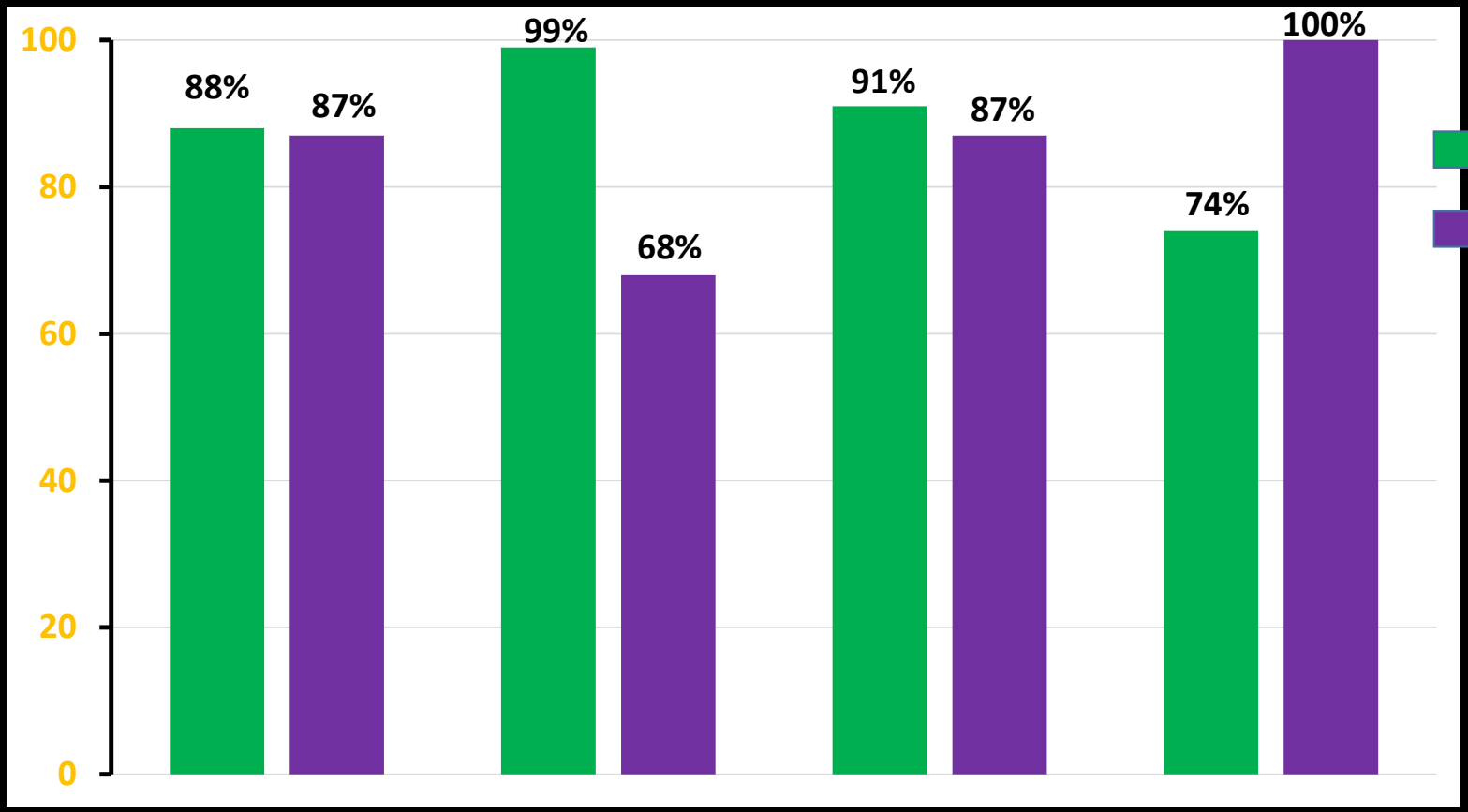
- Single dose of isotope
- Image at 1 hour (3 hours)
- NPO not needed
- No stress involved
- Most labs can perform
- No special cameras needed

Grade	Myocardial ^{99m}Tc-PYP Uptake
Grade 0	no uptake and normal bone uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/ absent rib uptake

Widely Available
Labs doing nuclear stress test
Easy to perform
"Easy" to interpret

American Society of Nuclear Cardiology, PYP-SPECT, Practice Points, 2016.

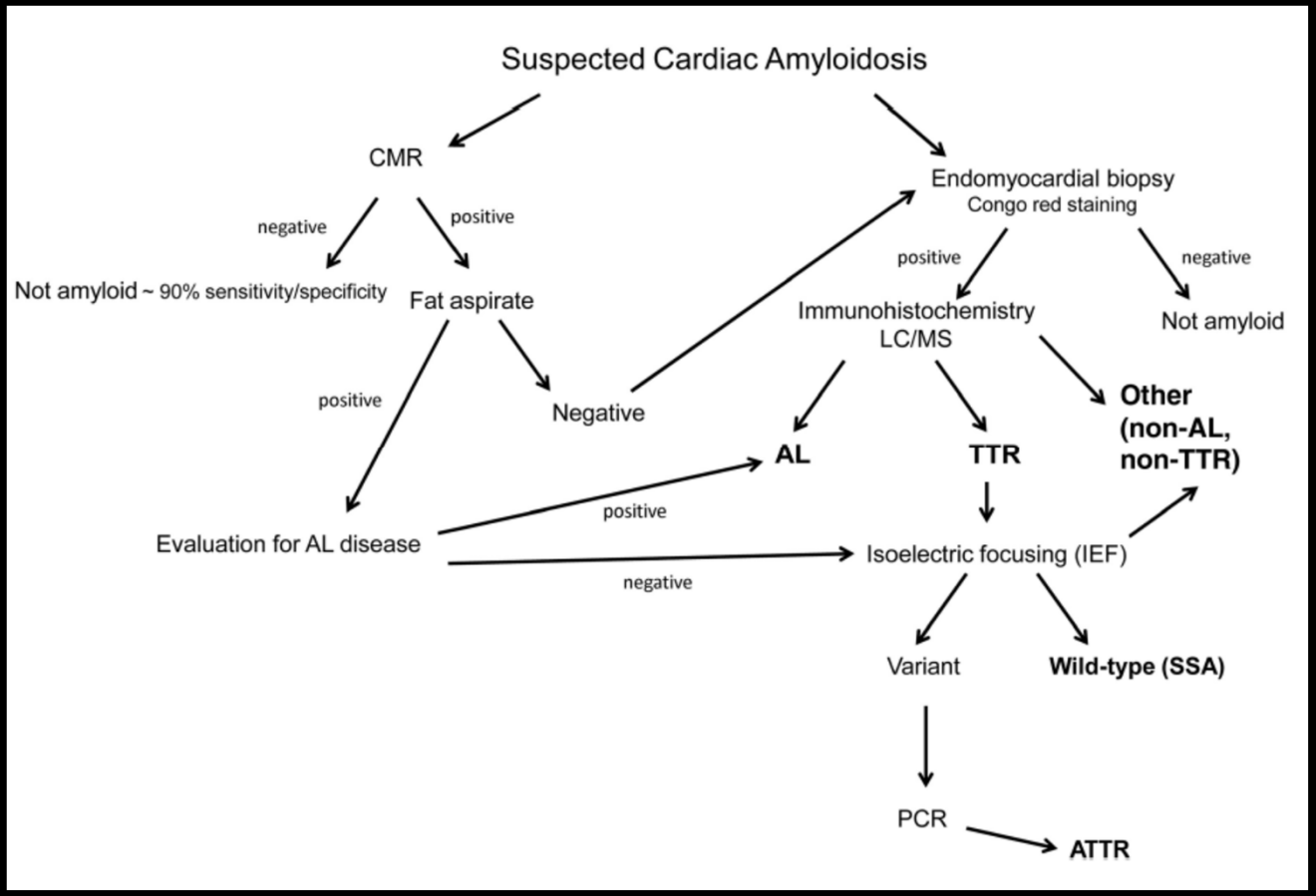
High Accuracy of PYP Imaging for Cardiac Amyloidosis



Gillmore et al., Circulation, 2016

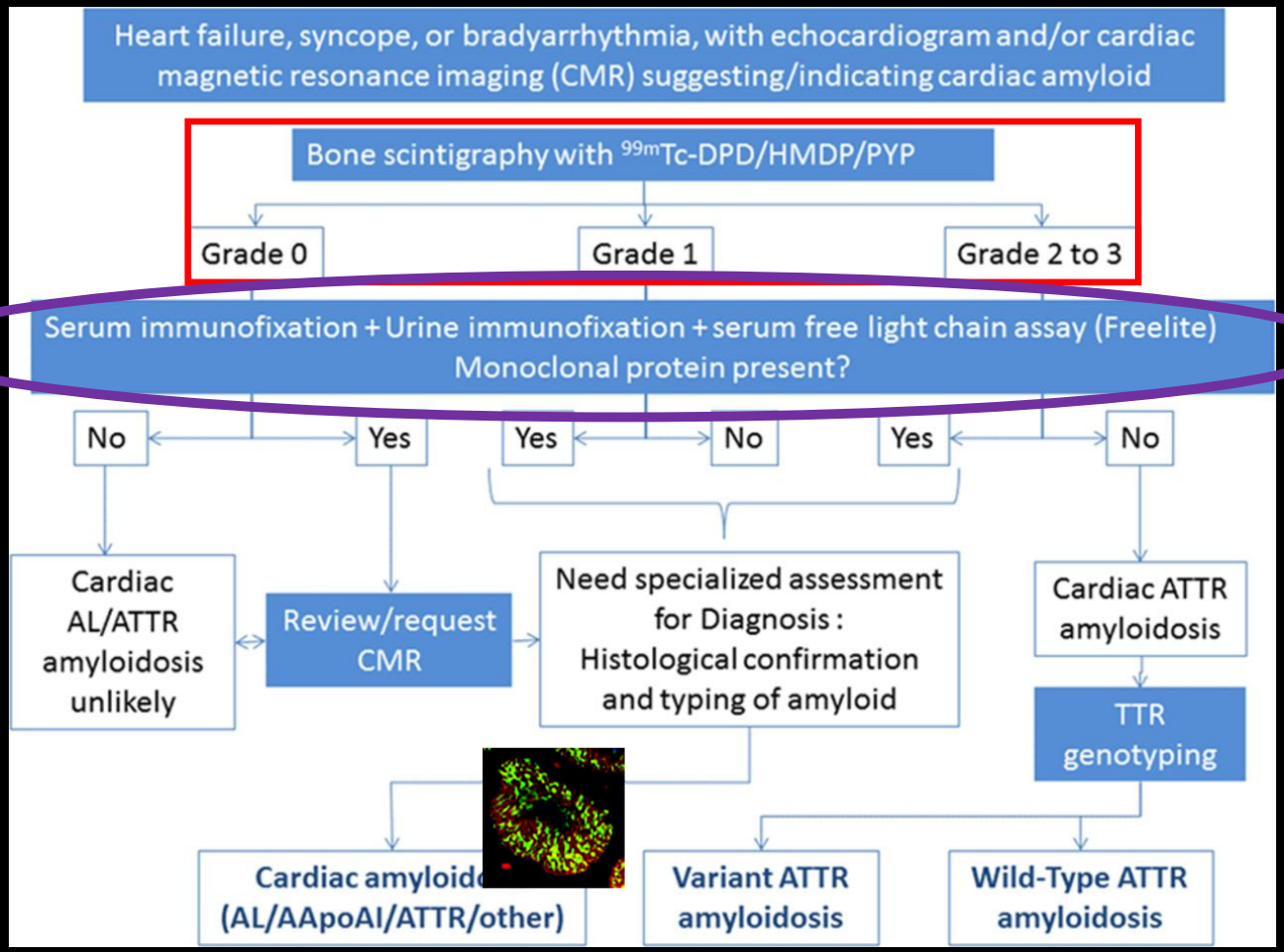
Cardiac Amyloidosis

Diagnostic Evaluation was Complicated



Ruberg et al., Circulation, 2012

Pathway for Diagnostic Evaluation of Cardiac Amyloidosis



Simultaneous rule out of Light chain dz.

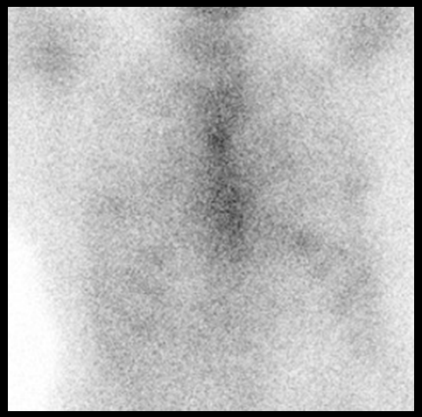
Gillmore…..Ruberg et al., Circulation, 2016

Cardiac Amyloidosis is a Spectrum

Preclinical CA (at risk)

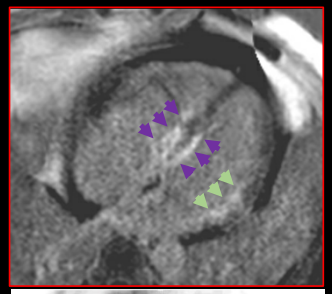
No HF; +/- PN

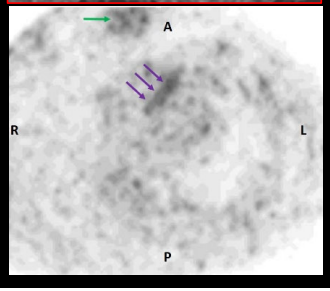
+ mutation (p.V142I)



Subclinical CA

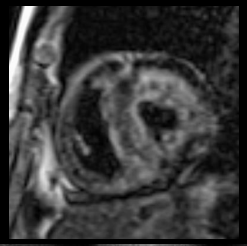
No HF; +/- PN

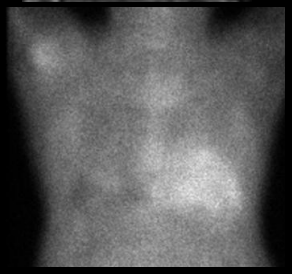




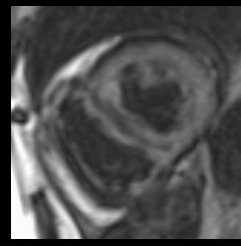
Clinical CA

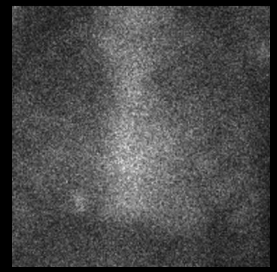
HF; +/- PN



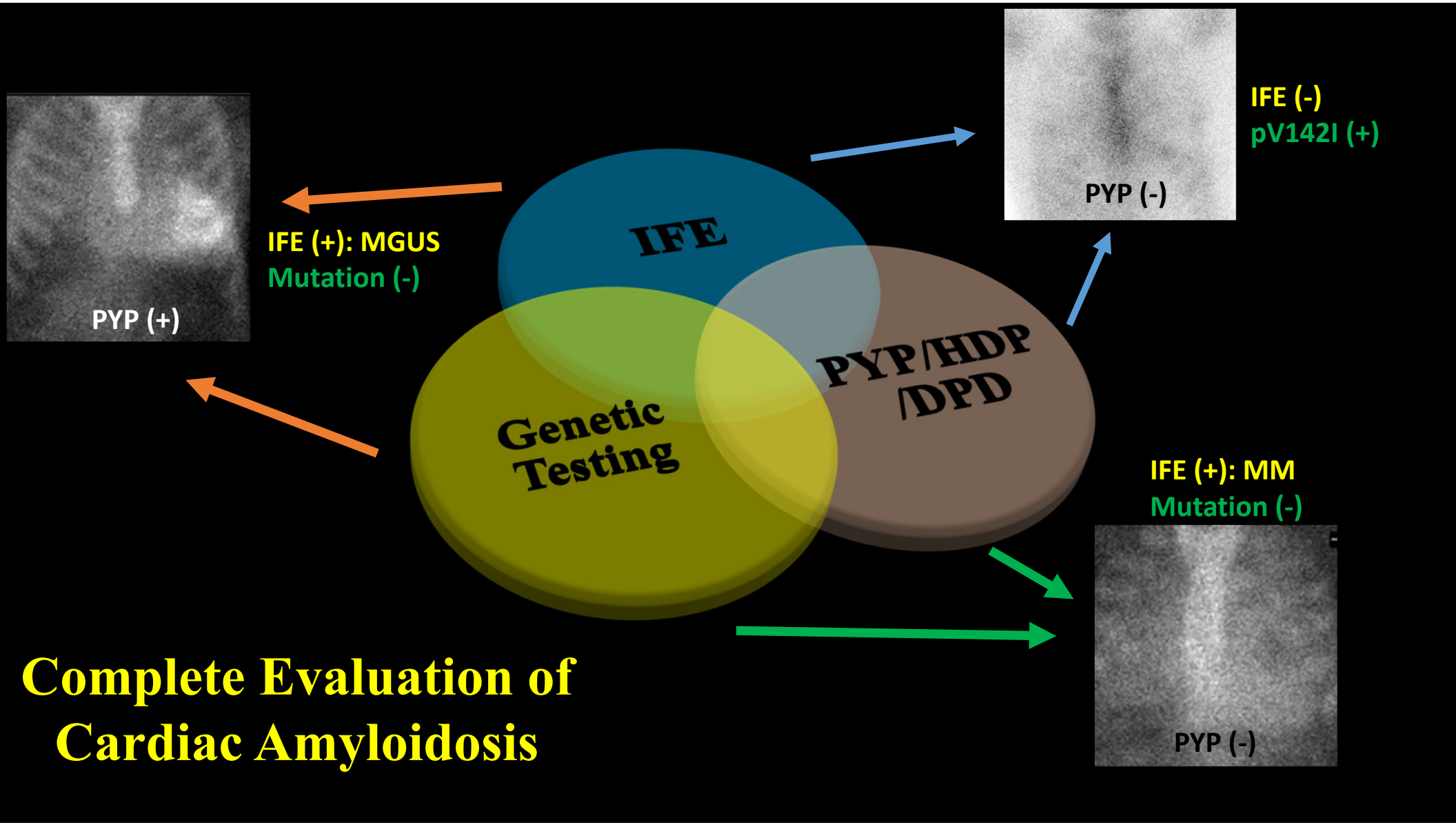


ATTR-CA

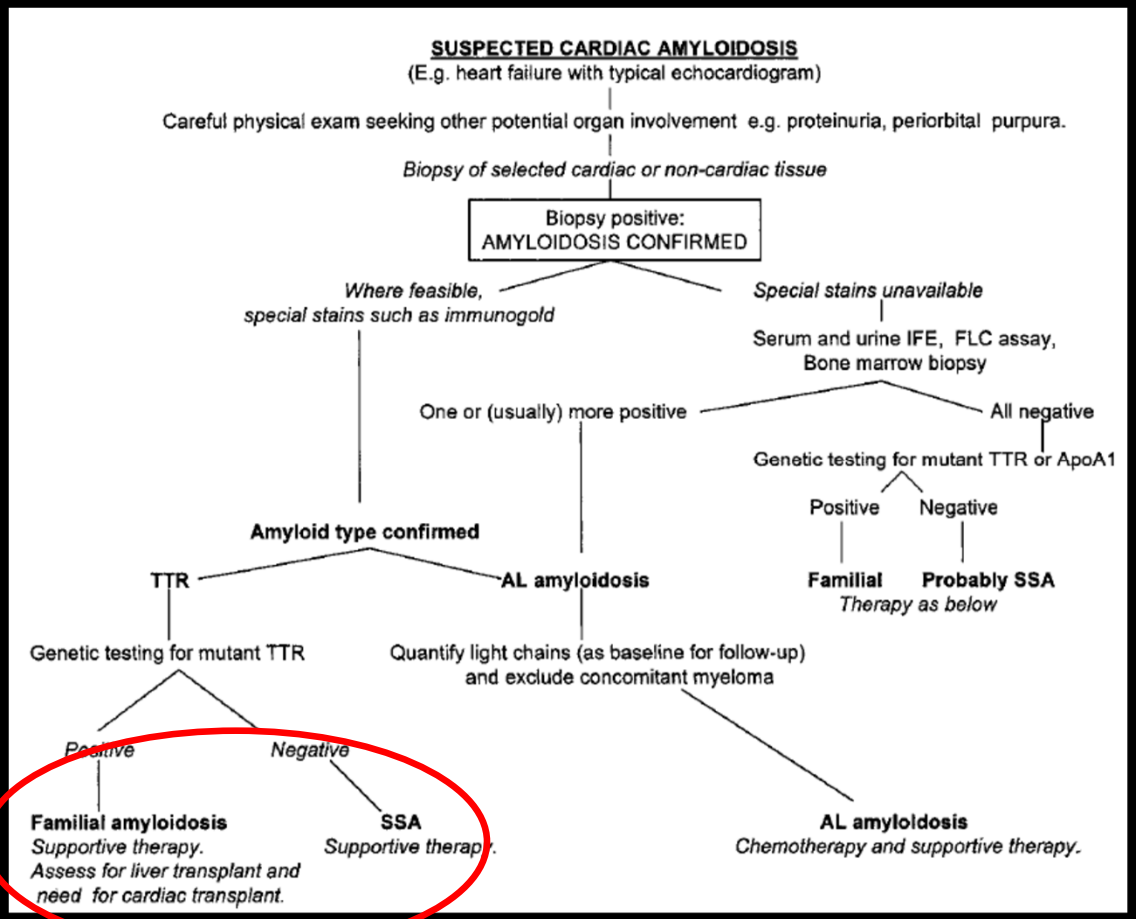




AL-CA

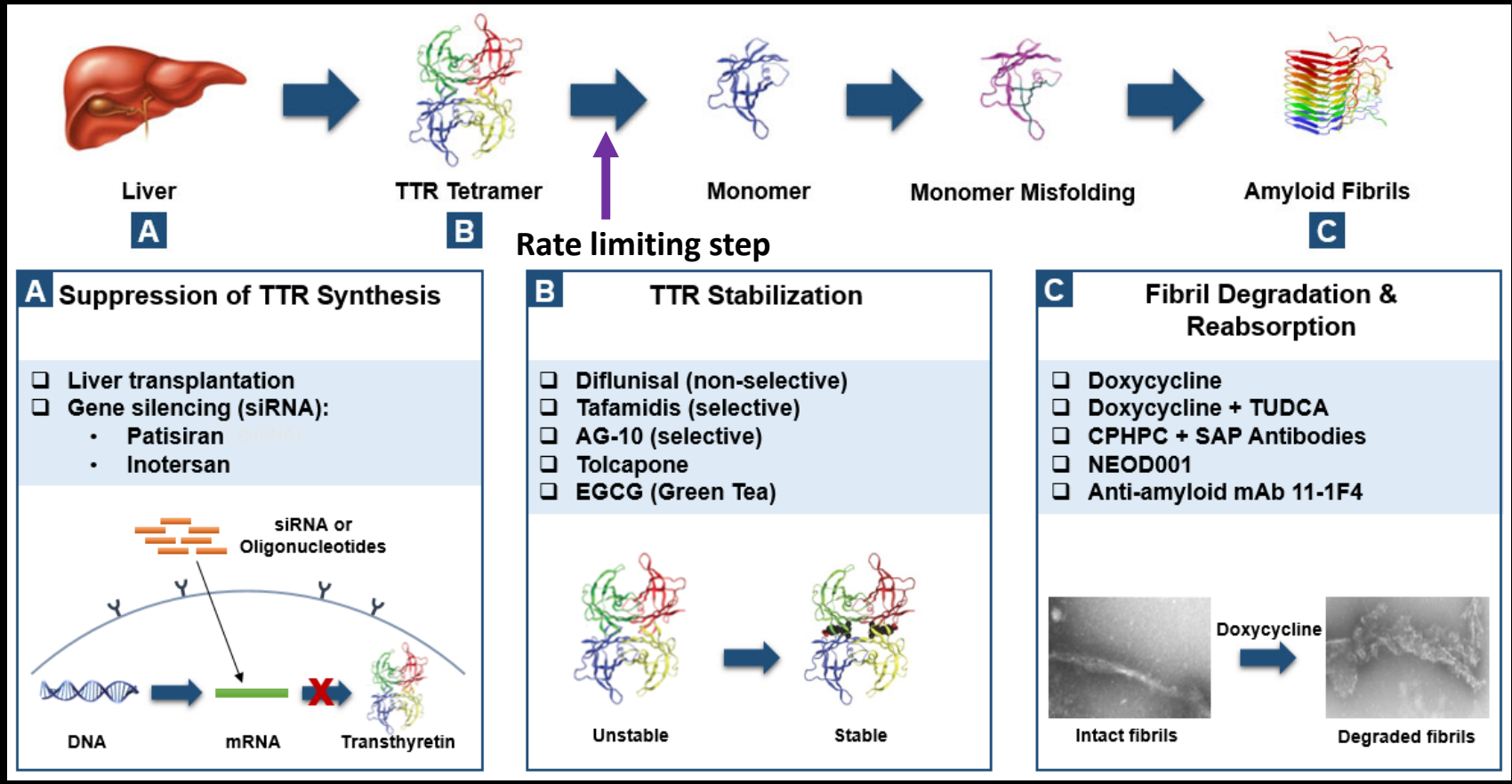

IFE
PYP/HDP
/DPD
Genetic
Testing
PYP (+)
IFE (+): MGUS
Mutation (-)
PYP (-)
IFE (-)
pV142I (+)
IFE (+): MM
Mutation (-)
PYP (-)
Complete Evaluation of
Cardiac Amyloidosis

Treatment of Cardiac Amyloidosis: The Past

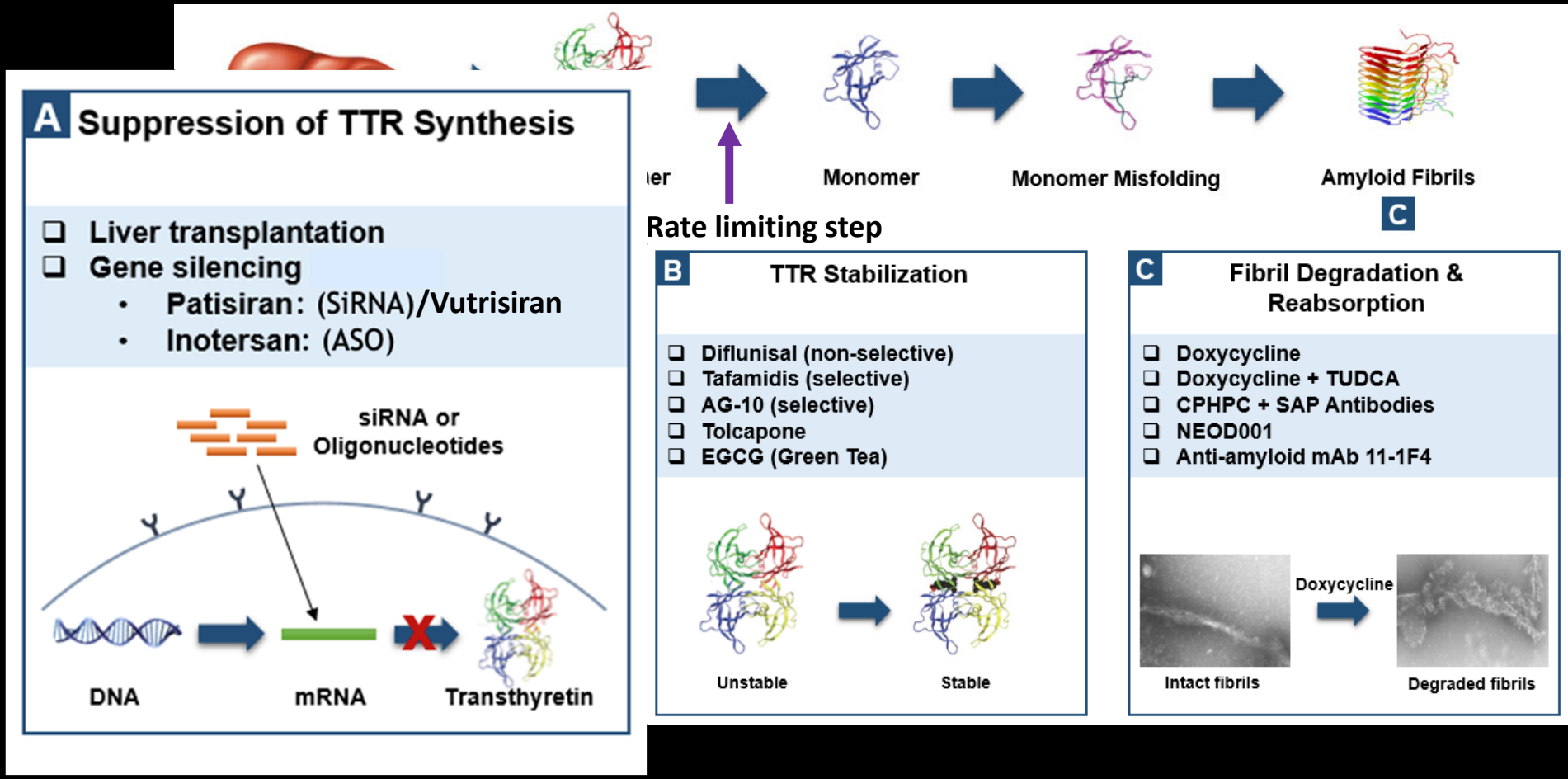


Falk, *Circulation,* 2005

Novel ATTR Therapies Target Crucial Steps in Amyloidogenesis



TTR Silencers



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.

FDA Approved for Treatment of hATTR Polyneuropathy

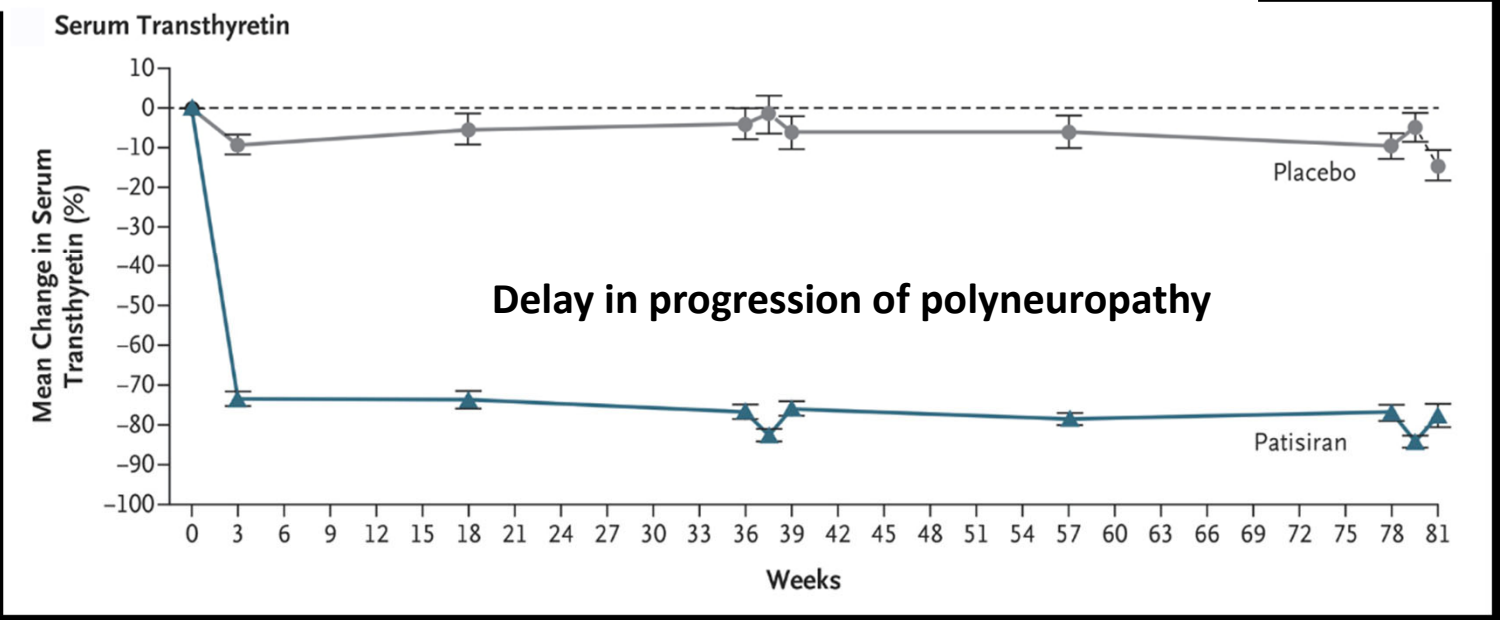
ORIGINAL ARTICLE

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

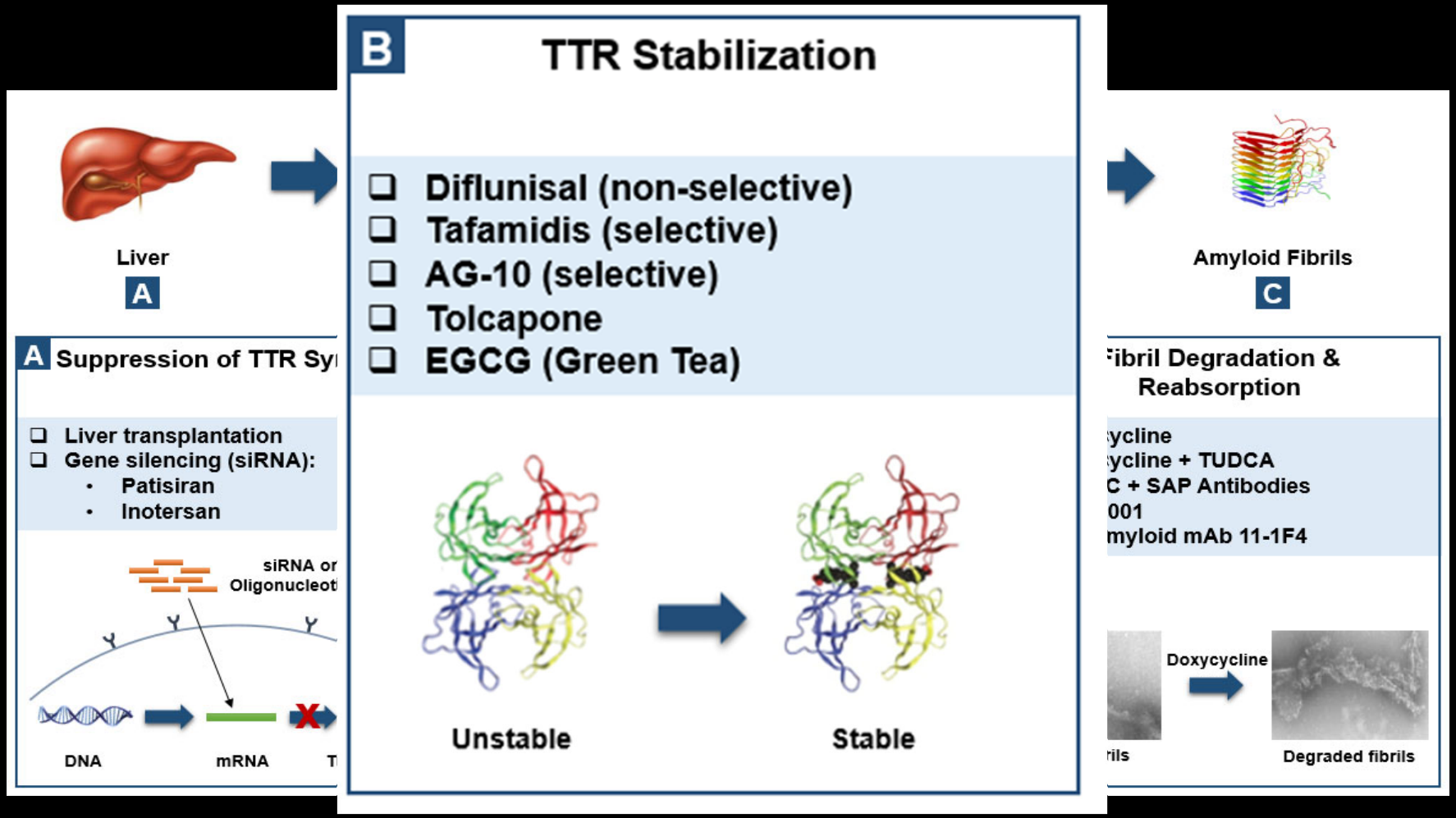
David Adams, M.D., Ph.D., Alejandra Gonzalez-Duarte, M.D., William D. O'Riordan, M.D., Chih-Chao Yang, M.D., Mitsuharu Ueda, M.D., Ph.D., Arnt V. Kristen, M.D., Ivailo Tournev, M.D., Hartmut H. Schmidt, M.D., Teresa Coelho, M.D., John L. Berk, M.D., Kon-Ping Lin, M.D., Giuseppe Vita, M.D., et al.

70-80% TTR knockdown

Pre-albumin levels fall



TTR Stabilizers



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

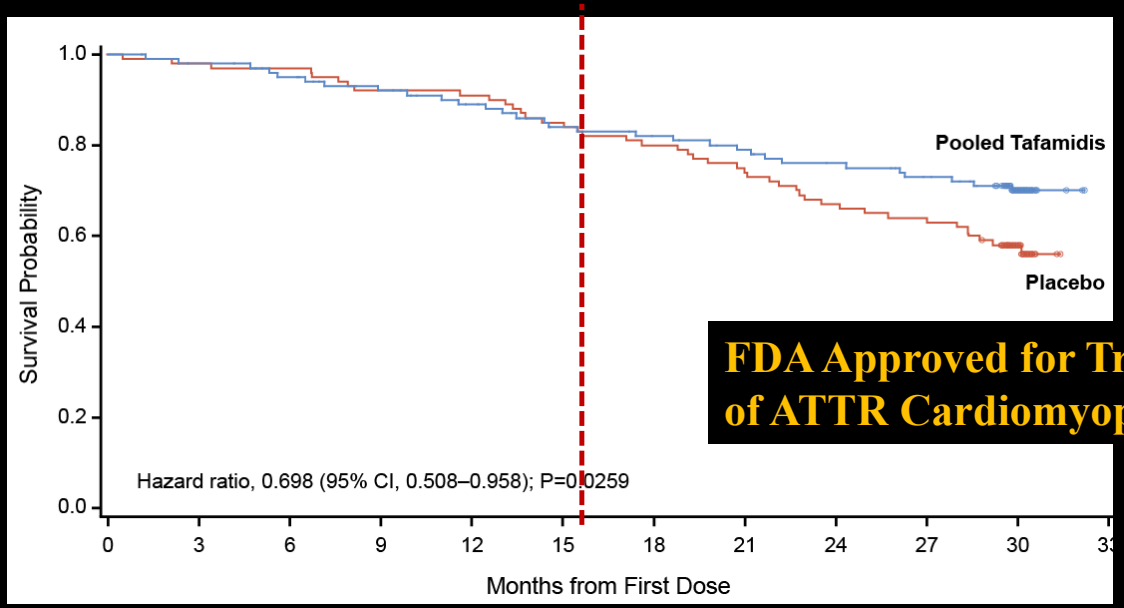
32% reduction in CV Hosp
NNT: 4 per 1 hosp. per patient-year.

Effects seen at 18 M

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

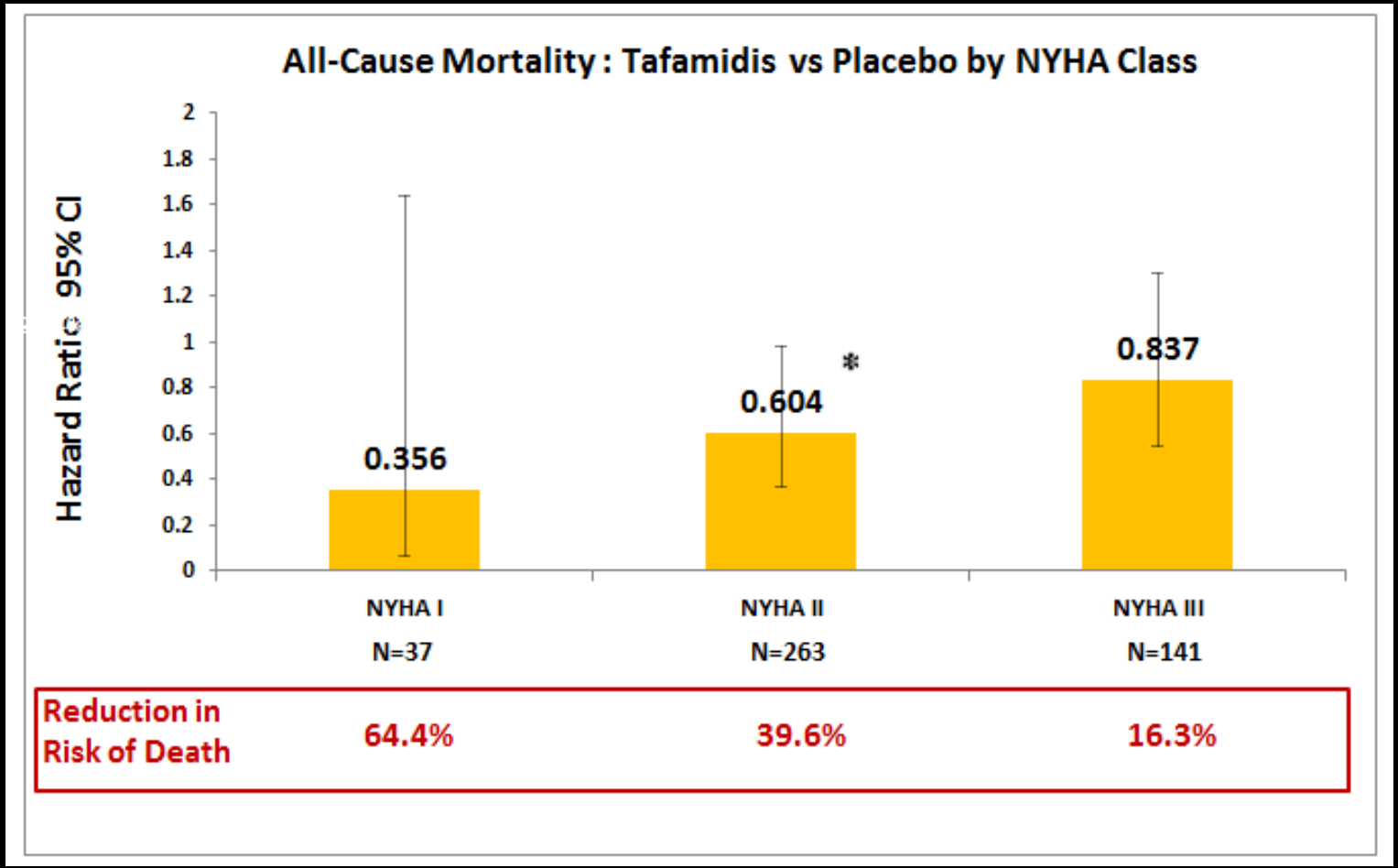


FDA Approved for Treatment of ATTR Cardiomyopathy

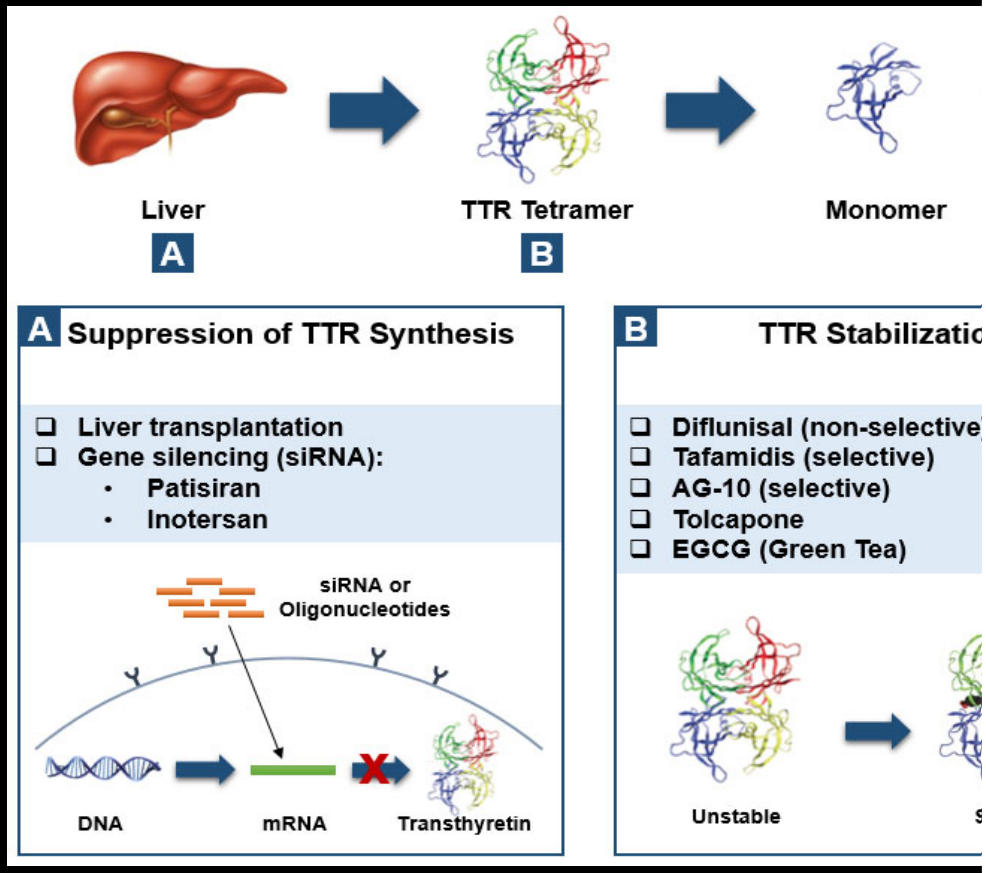
Tafamidis Reduces All-cause Mortality and CV Hospitalizations: ATTR-ACT

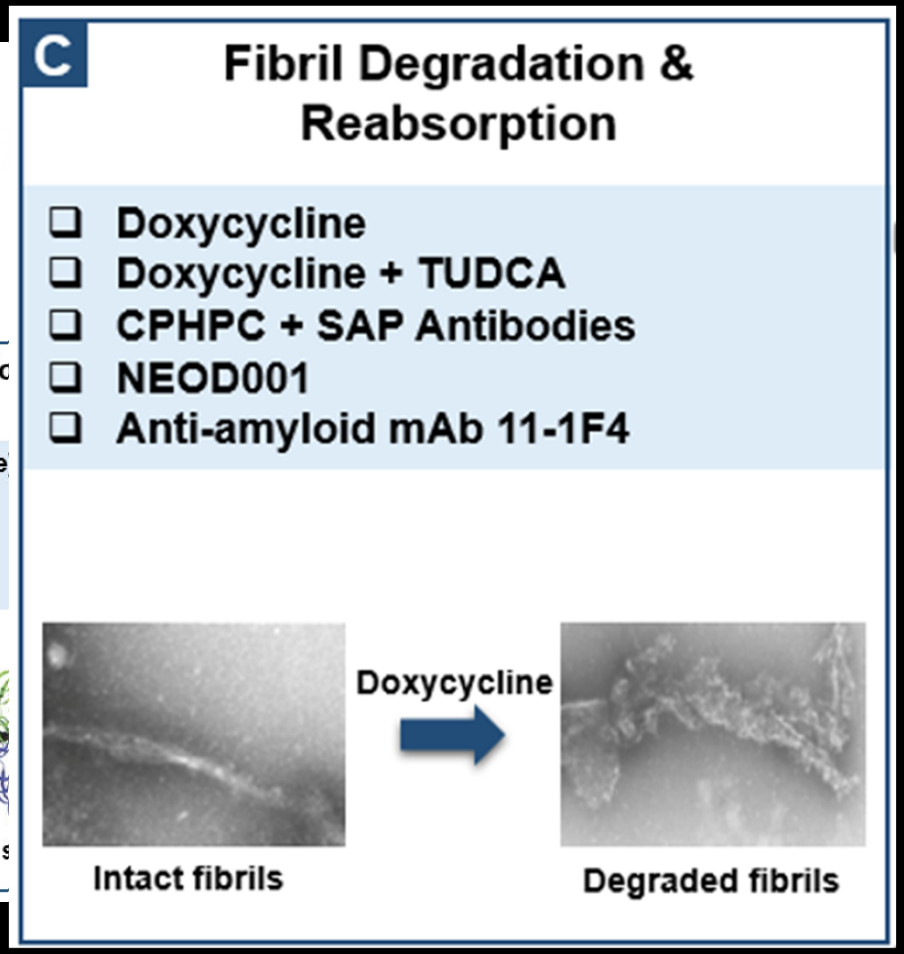
Maurer MS, et al. NEJM Sept 2018

Early Therapy is Associated with Better Outcomes



Amyloid Fibril Disrupters





No RCT data; Not FDA approved

Treatment of Cardiac Amyloidosis: The Future

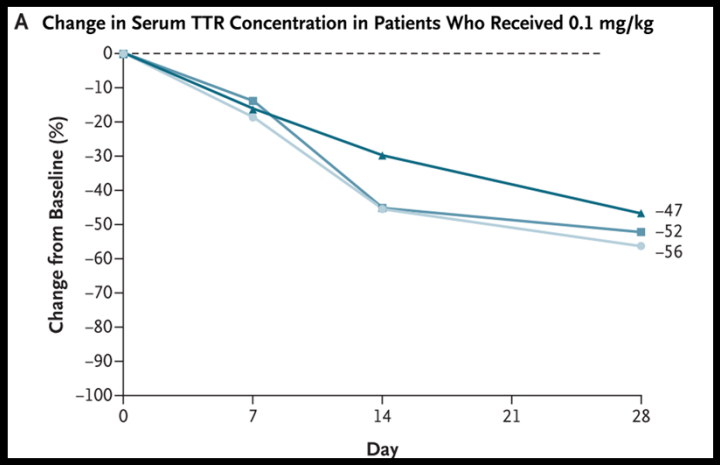
The NEW ENGLAND JOURNAL of MEDICINE

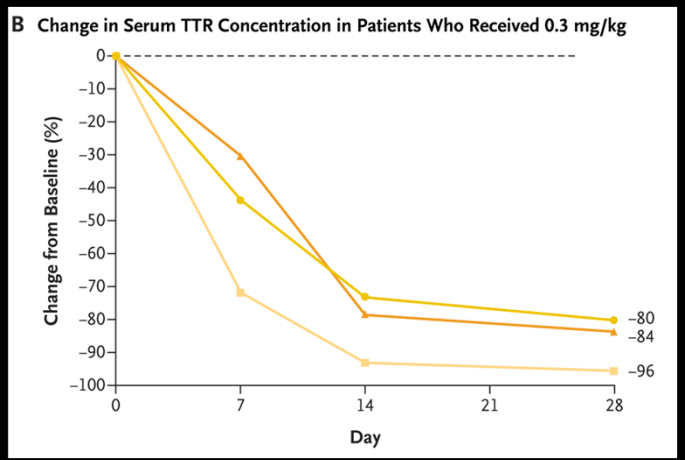
ORIGINAL ARTICLE June 2021

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., et al.,

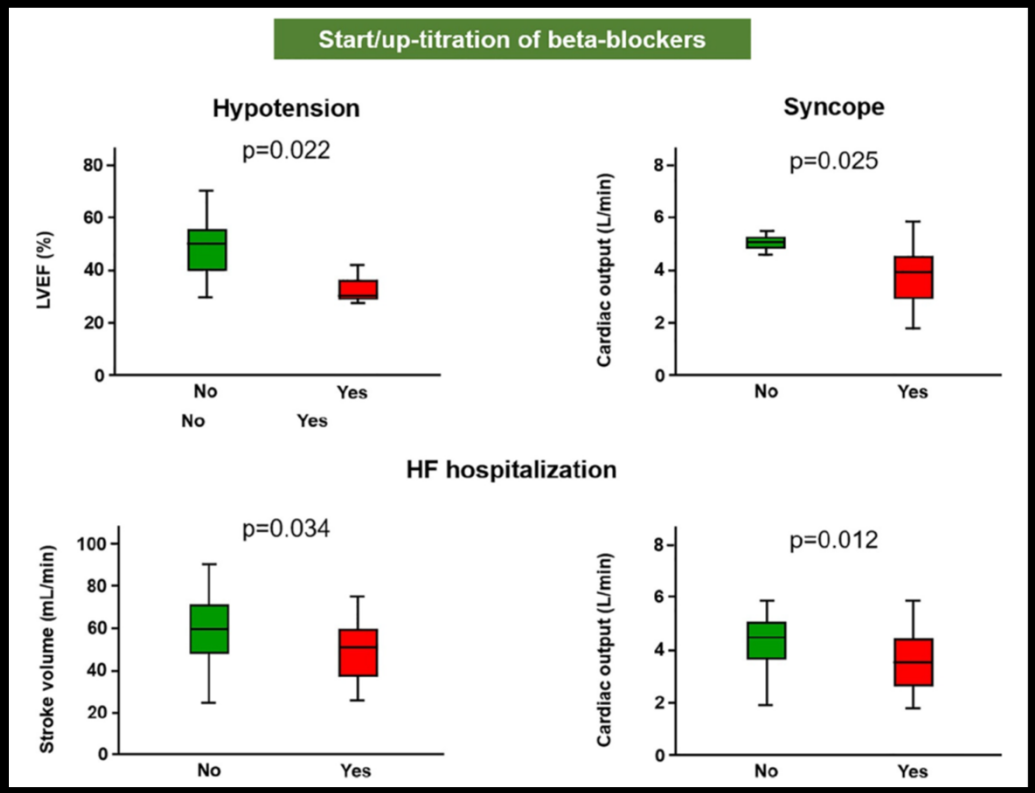
NTLA 2001 given to 6 patients with hereditary amyloid polyneuropathy





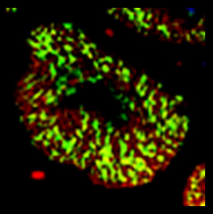
1997

Conventional HF Therapy is Poorly Tolerated

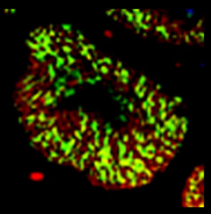


- HR dependent to maintain cardiac output
- Bradycardia: fatigue, syncope
- Autonomic dysfunction: ACEi & ARB use can worsen orthostatic hypotension
- Digoxin: binds to amyloid fibrils; increased toxicity

Aimo, et al. Eur J Internal Med, 2020



There is a Sprint in this Marathon!



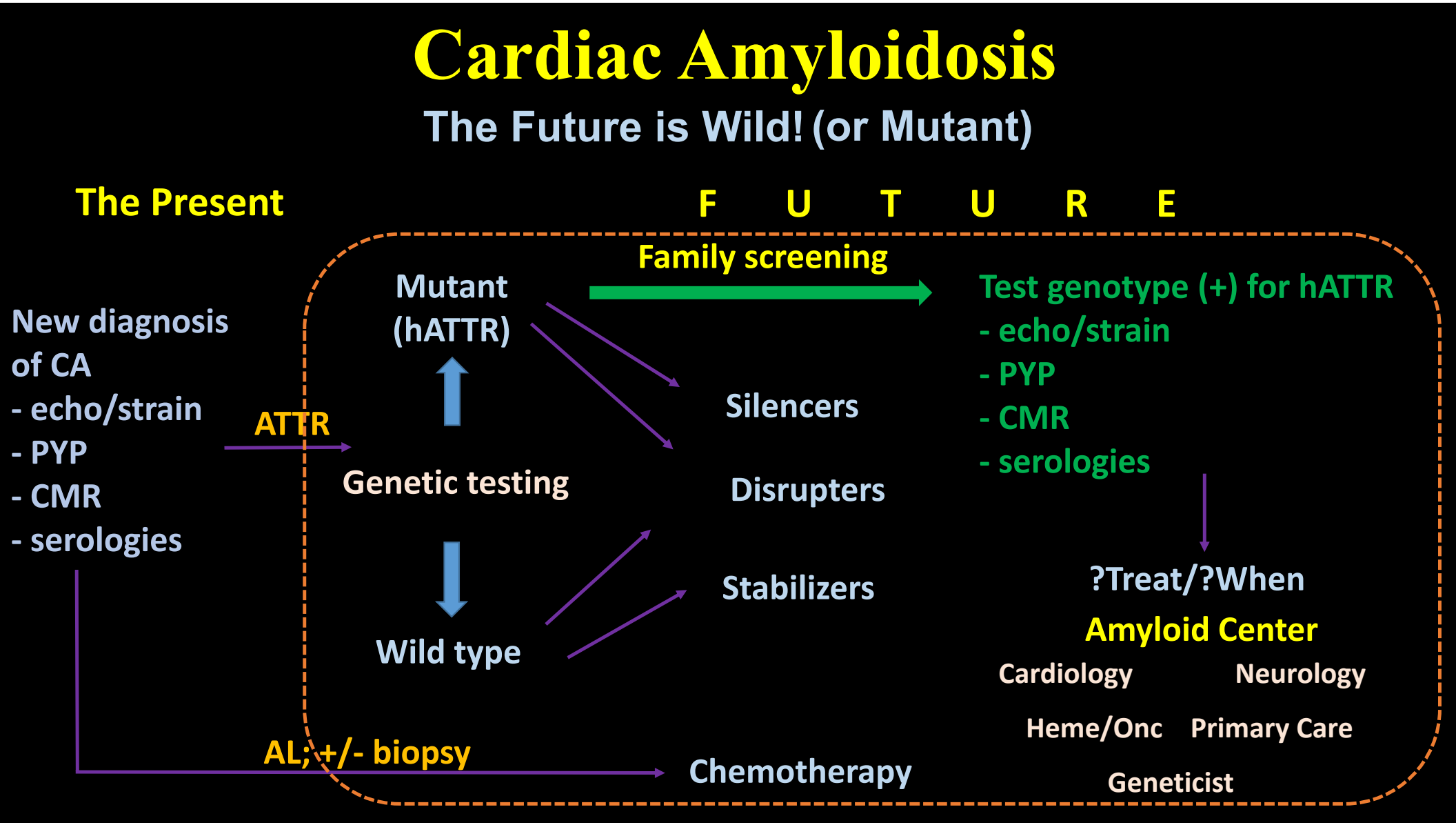
- ? Comfort Care
- ? Palliative Care

Non-targeted Symptomatic Management

- reduction or discontinuation of beta blockers
- reduction or discontinuation of ACEi/ARBs
- avoid Digoxin
- Diuretic therapy is mainstay
- Treatment of orthostatic hypotension
- Prokinetic agents for gastroparesis
- Management of arrhythmias: A fib
- Pacemakers for heart blocks; ?CRT

Cardiac Amyloidosis

The Future is Wild! (or Mutant)



CARDIAC AMYLOIDOSIS

- Cardiac amyloidosis is a disease of the masses.
  - Knowledge of at risk population (hATTR)

- It is no longer a rare disease.
  - Prevalence increases with age
  - wtATTR: no known RF

- Early disease recognition is critical
  - Do not ignore non-cardiac signs/symptoms

- Many patients may not have HFpEF
  - HF GDMT is poorly tolerated

CARDIAC AMYLOIDOSIS

- Diagnostic pathway is easier
  - Must rule out light chain disease/myeloma

- Accurate diagnostic tests are available
  - PYP imaging has high specificity/widely available
  - Must perform genetic testing in all with ATTR

- Novel targeted therapies are now available
  - Stabilizer vs. Silencer: CMP vs. PN
  - Loop diuretics for HF

- Need for multidisciplinary collaboration

ASNC

American Society of Nuclear Cardiology

Masterclass in Cardiac Amyloidosis:

Disease Spectrum, Diagnosis and Management

June 2-4, 2023

Live Virtual
Complimentary Registration

www.asnc.org/masterclass

@NotNoninasive
saurabh.malhotra@cookcountyhhs.org