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Evaluation and Management of Cardiac Amyloidosis

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Relevant RWI: None

Case Report

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- 78 yr old male, presented to your office with SOB
- History: DM, high cholesterol, CKD st 2, no history HTN
- Physical exam consistent with signs of volume overload
- Echo: No valvular disease, LVH, enlarged LA, EF 45%
- Stress perfusion imaging normal
- Dx: Heart Failure with Preserved EF
- Diuresis => improved symptoms, became asymptomatic
- GDMT –
  - spironolactone (TOPCAT)
  - sacubitril/valsartan (PARAGON) – only tolerated low dose
  - dapagliflozin (DELIVER)
- Is this patient well-managed ??

Evaluation and Management of Cardiac Amyloidosis

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- Classification, pathophysiology and clinical manifestations
- Prevalence
- Making a diagnosis
- Therapeutics

Systemic Amyloidoses: Cardiac Involvement

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- AL (light-chain)
  - Plasma cell dyscrasia
  - Expression of monoclonal light chains (λ, κ)→ form amyloid fibrils
- Transthyretin Amyloid (ATTR)
- Hereditary (ATTRh)
  - TTR gene mutation→ unstable protein structure due to amino acid substitution
- Wild-type (ATTRwt) - sporadic
  - Wild-type transthyretin (previously called “senile” amyloidosis)

Transthyretin (TTR) Amyloid

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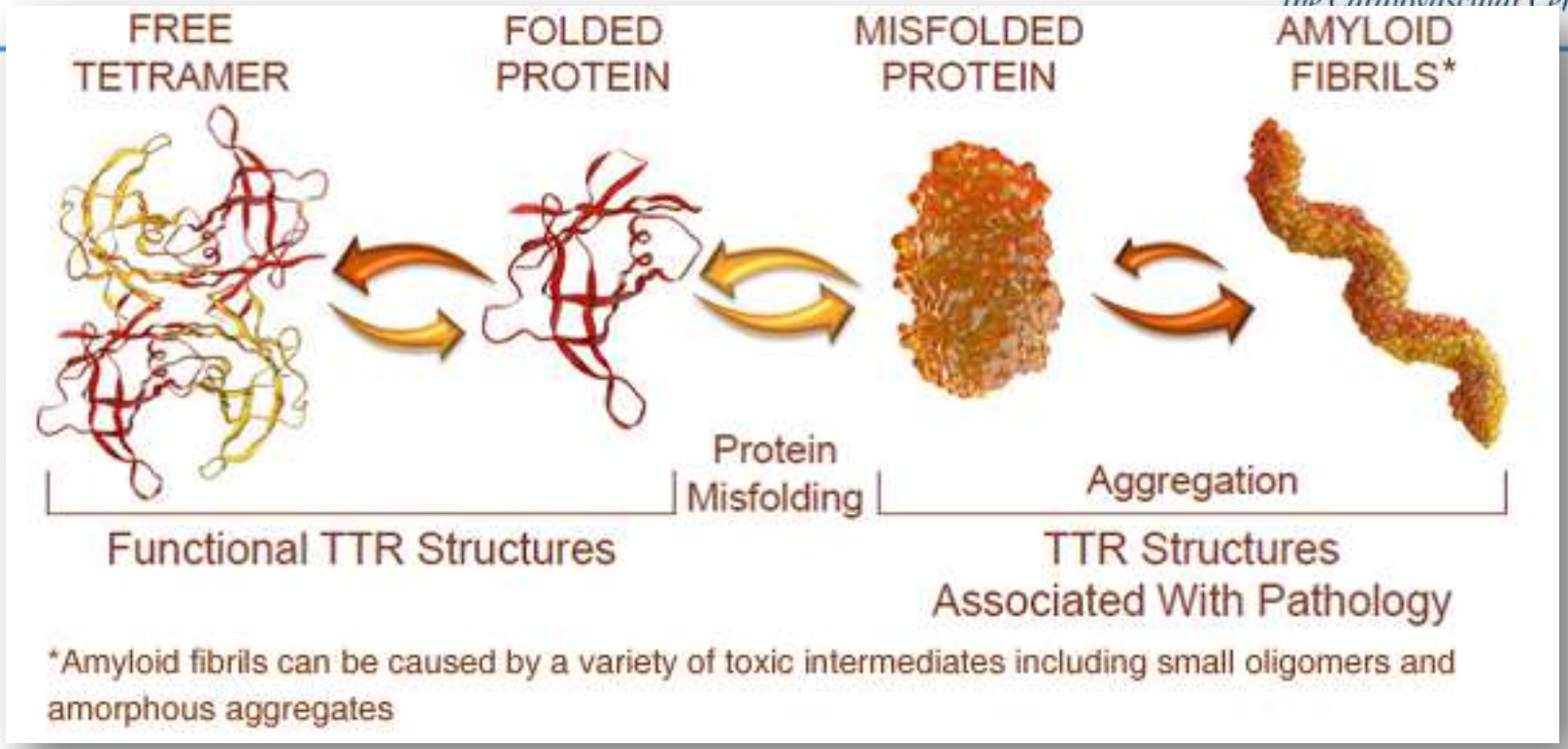

- **Protein produced in liver**
- **Transports thyroxin and retinol**
- **Tetramer shape critical for its function**
- **ATTRh: Incorrect formation due to TTR gene mutation**
- **ATTRwt: Post-translational changes in genetically normal TTR**

Characteristics of ATTRwt

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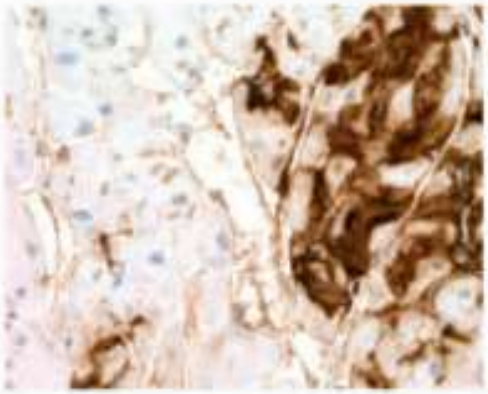
ATTRwt`s clinical spectrum

Mode of presentation:
- **HF** (67.6%)
- **AV block** (7.4%)
- **Stroke**
- **HCM or RCM** (13.9%)
- **Degenerative AS**
- **Incidental** (11.1%)



Age, gender and comorbidities
- Males (81.5%)
- **Females (18.5%)**
- Late 70s symptoms onset
- HTN (54.6%)

ECG
- **AF (55.6%)**
- **Pseudoinfarct** pattern (63.2%)
- Low voltage (22%)
- LVH (10.5%)
- L/RBBB (17-15%)

Echocardio
- Symmetric LVH (75.7%)
- **Asymmetric LVH (23.4%)**
- **LVEF<50% (36.8%)**
- Restrictive diastolic pattern (35%)
- Pericardial effusion (42.1%)

Survival

Overall survival at 12, 24 and 36 months: **93, 89** and **74%**, respectively

Gonzalez-Lopez et al, Eur Heart J 2017

Orthopedic Manifestations of wt-ATTR

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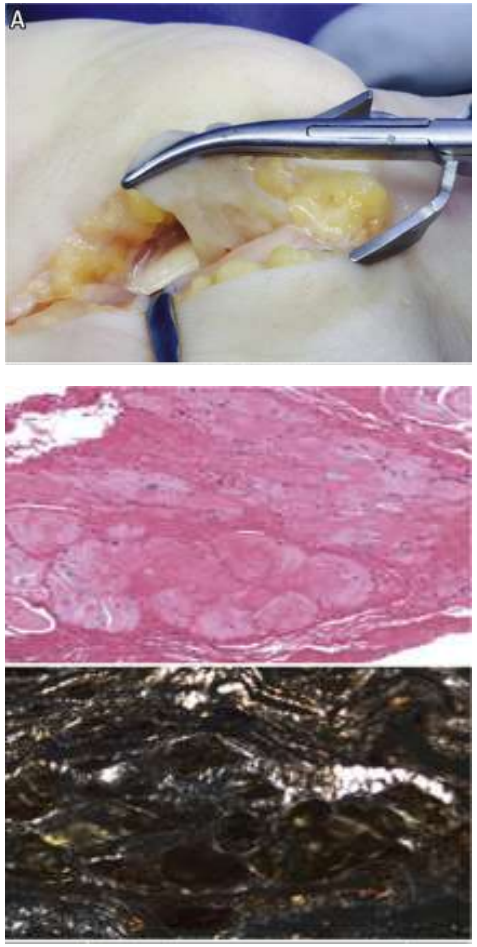
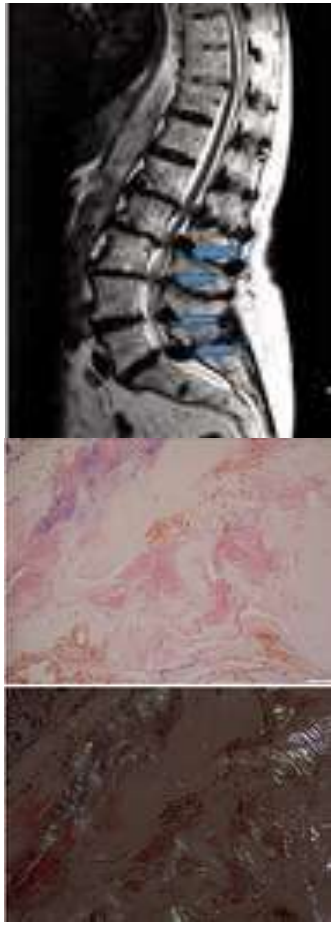
CARPAL TUNNEL SYNDROME



Sperry et al, JACC 2018

SPINAL STENOSIS



Godara et al, Amyloid 2021

BICEPS TENDON RUPTURE

Geller et al, Circulation 2015

Genotype-Phenotype Spectrum in ATTR-h

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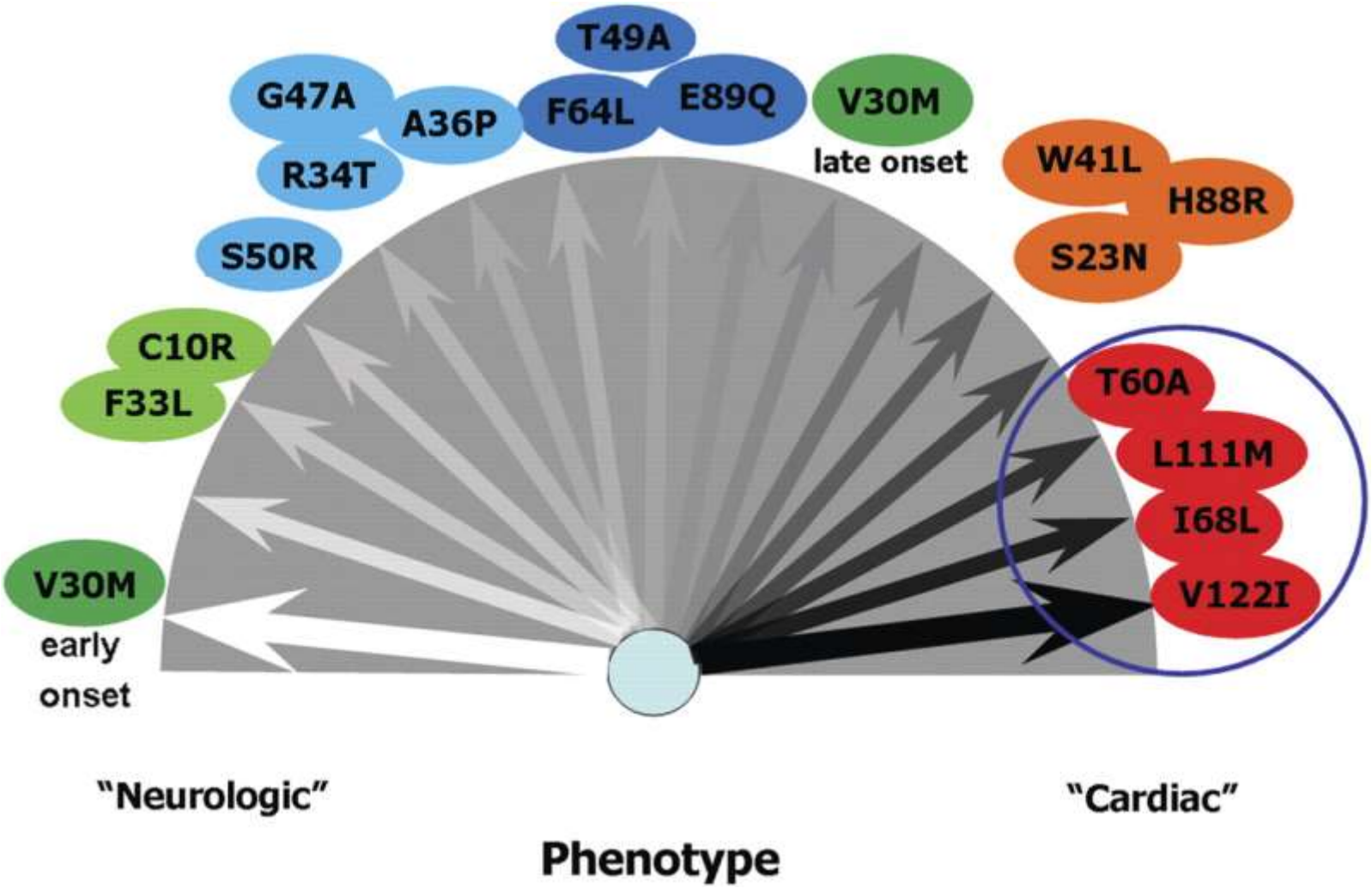

Rapezzi et al, Eur Heart J 2012

Evaluation and Management of Cardiac Amyloidosis

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- **Classification, pathophysiology and clinical manifestations**
- ***Prevalence***
- **Making a diagnosis**
- **Therapeutics**

When Do I Consider Evaluation for ATTR Cardiac Amyloidosis?

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Prevalence in pts w HF:

- HFpEF w LVH
- HFrEF nonischemic + poorly tolerant to meds, LVH, RVH
- Aortic Stenosis
- HCM

Adapted from Ruberg et al. J Am Coll Cardiol. 2019

Prevalence of ATTR-CM in HFpEF with Increased WT

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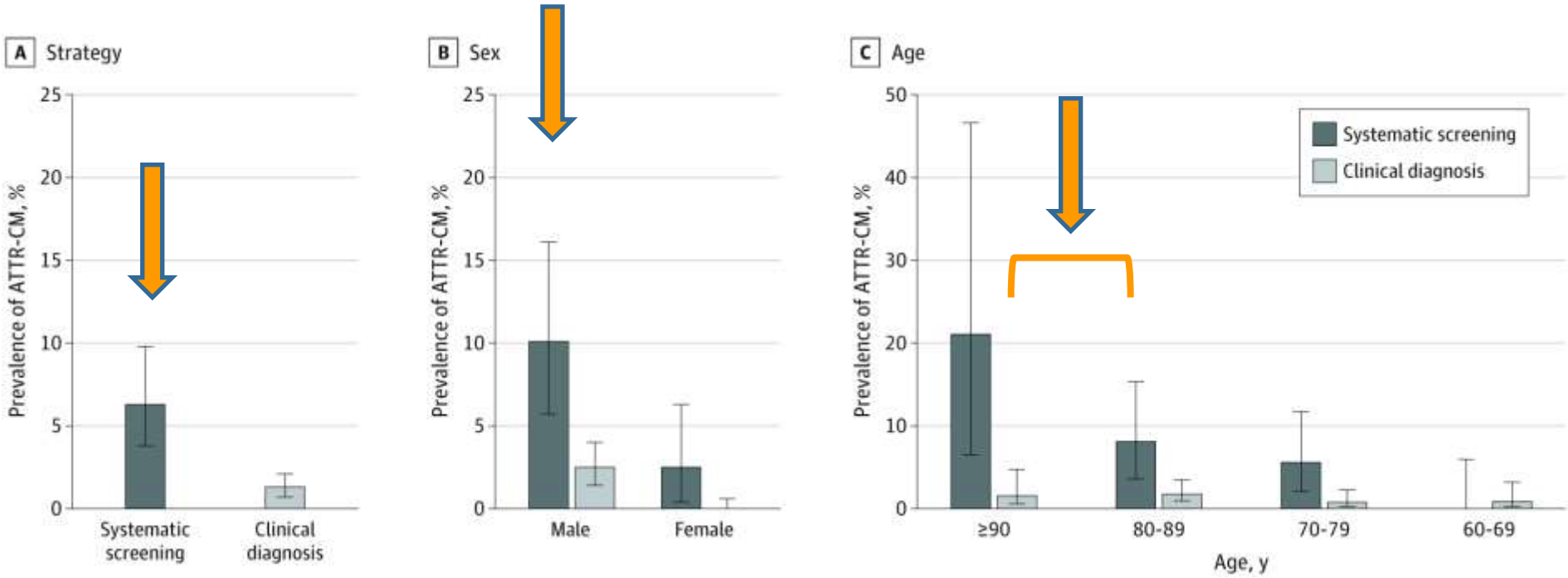

AbouEzzeddine et al. JAMA Cardiol 2021

Prevalence of ATTRwt CA in TAVR

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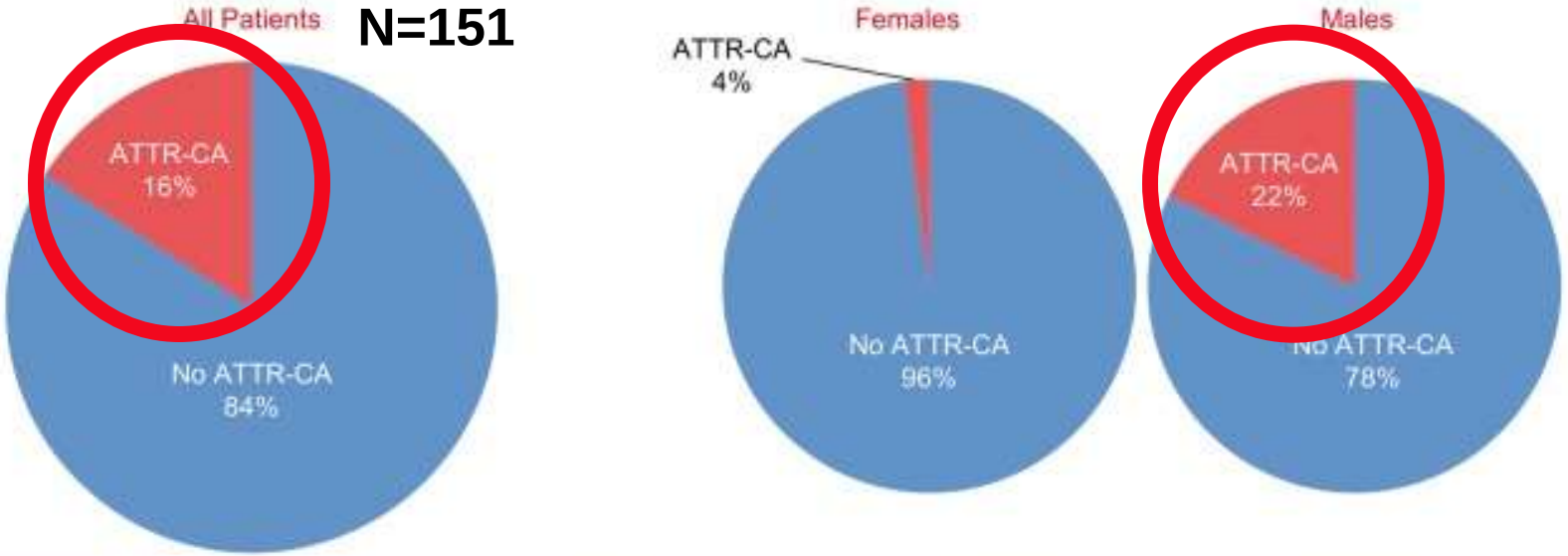
A **Prevalence of ATTR-CA**



B **Features that Should Elevate Suspicion for Cardiac Amyloidosis in Patients with Severe Symptomatic AS**

Clinical & Demographic
- ✓ Older adult male
- ✓ Low-flow/low-gradient AS
- ✓ Low systolic blood pressure
- ✓ Elevated BNP

Electrocardiographic
- ✓ Low ECG voltage-to-mass ratio
- ✓ Increased QRS duration
- ✓ Presence of RBBB

Echocardiographic, Speckle-strain, & Tissue Doppler
- ✓ Heart failure mid-range ejection fraction (HFmrEF)
- ✓ Increased wall thickness
- ✓ Left atrial enlargement
- ✓ Low SV index
- ✓ Low-flow low-gradient (stage D2)
- ✓ Low myocardial contraction fraction
- ✓ Advanced diastolic dysfunction
- ✓ Impaired global longitudinal strain
- ✓ Low mitral annular tissue Doppler S' (average septal and lateral annulus)

Castano et al, Eur Heart J; 2017; 38

Evaluation and Management of Cardiac Amyloidosis

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- **Classification, pathophysiology and clinical manifestations**
- **Prevalence**
- ***Making a diagnosis***
- **Therapeutics**

The Most Important Slide !

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The most important aspect of making a diagnosis of cardiac amyloid is SUSPECTING the diagnosis

“Red Flags” for ATTR CMP

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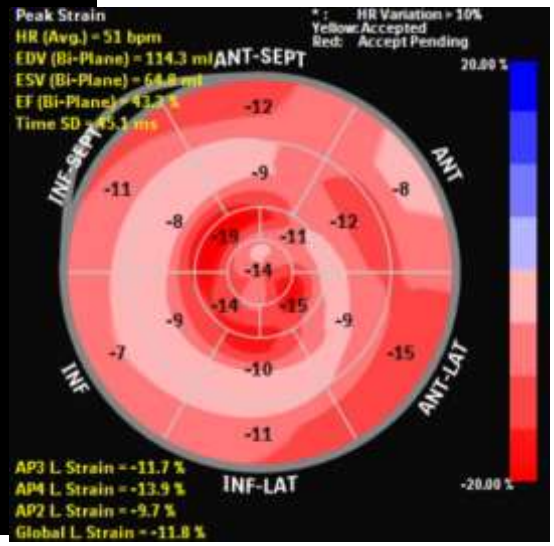
In Male age >65 or Female age >70:

- **Discrepancy between increased LV wall thickness and ECG voltage**
- **AV block in context of increased wall thickness**
- **History of bilateral carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture**
- **Mild elevation of troponin level on serial evaluation**
- **Aortic stenosis with low flow low gradient +/or LV wall thickness >=14 mm**

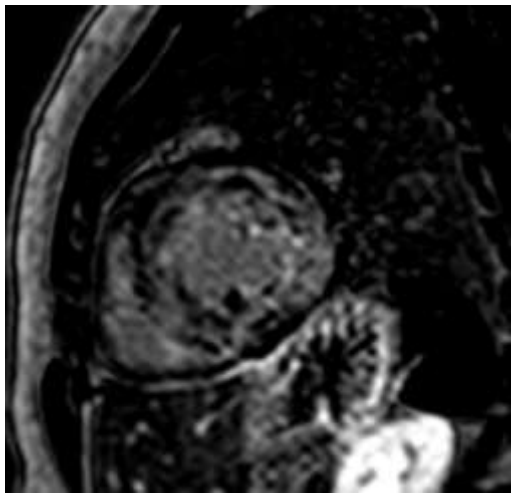
Kittleson et al,
Circ 2020,
AHA Scientific Statement

Imaging “Red Flags”



Abnormal LSt

Diffuse DE



- **Increased LV wall thickness (esp ≥ 14 mm)**
- **Apical sparing pattern**
- **Increased RV wall thickness`**
- **Low flow low gradient AS**
- **Valve thickening, biatrial enlargement**

Tc99m-PYP Imaging for TTR Cardiac Amyloid: Interpretation

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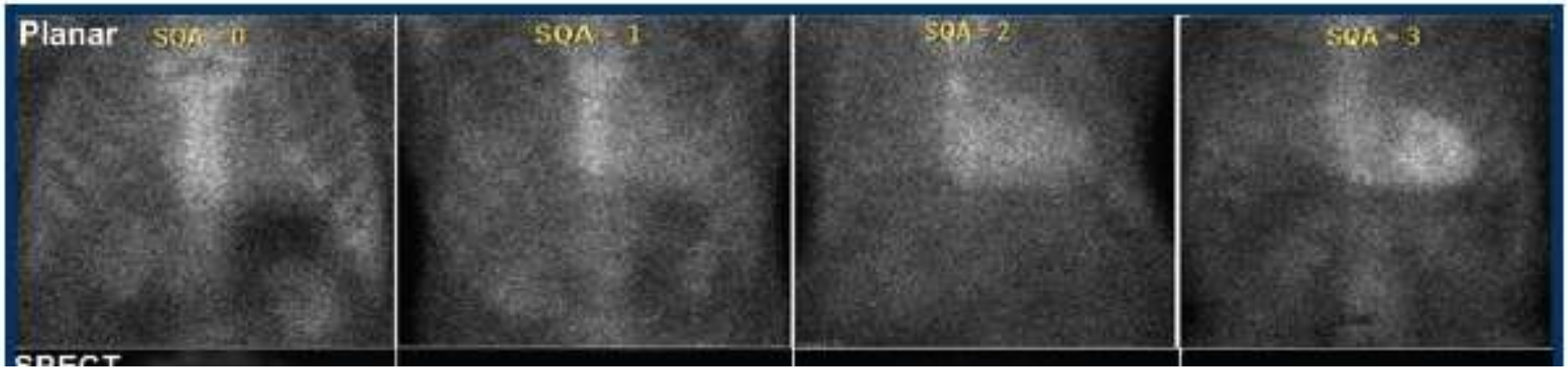
- **Step 1 – Planar Images – Visual grading of uptake in region of the heart**



Grade: 0 1 2 3

Tc99m-PYP Imaging for TTR Cardiac Amyloid: Interpretation

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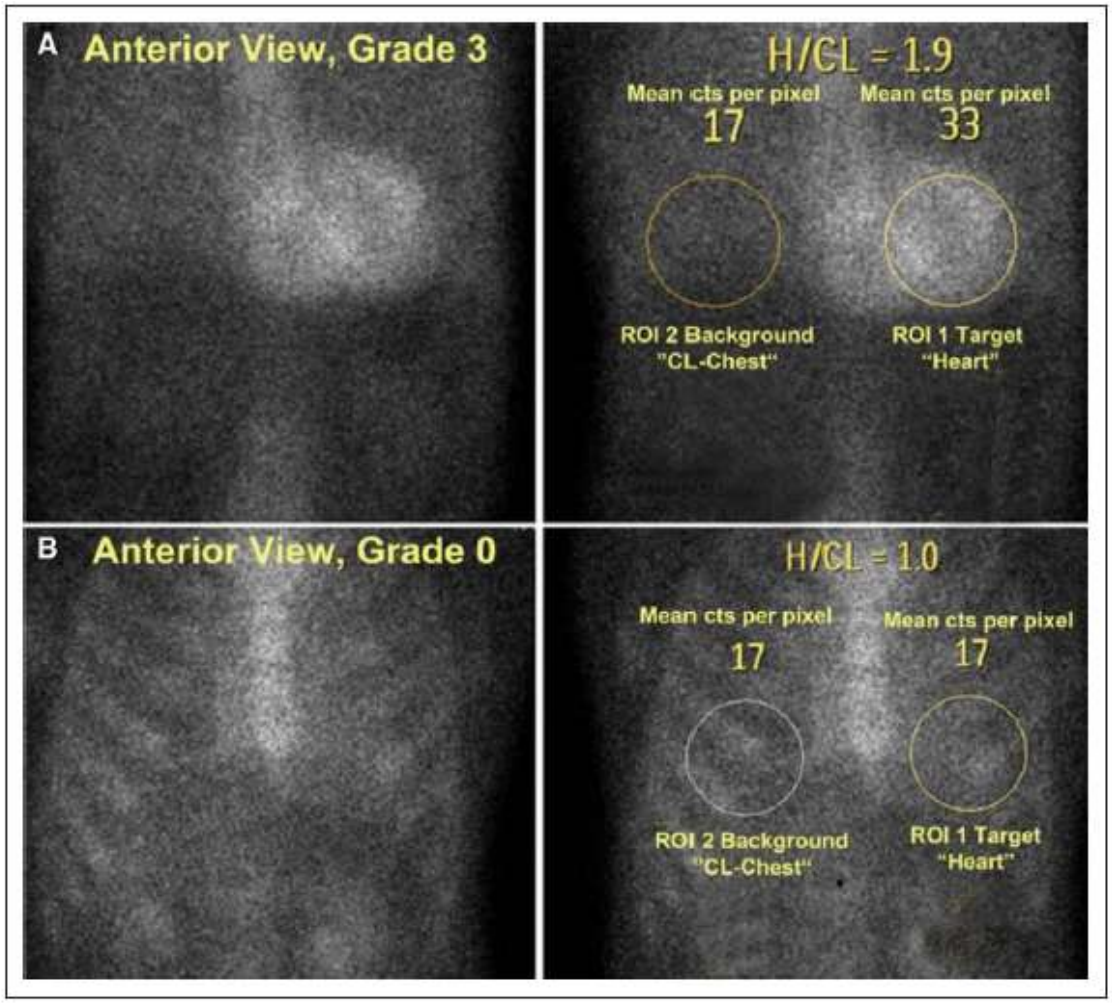
- **Step 2 – Planar Images – Heart-to-Contralateral Lung Ratio**



Tc99m-PYP Imaging for TTR Cardiac Amyloid: Interpretation

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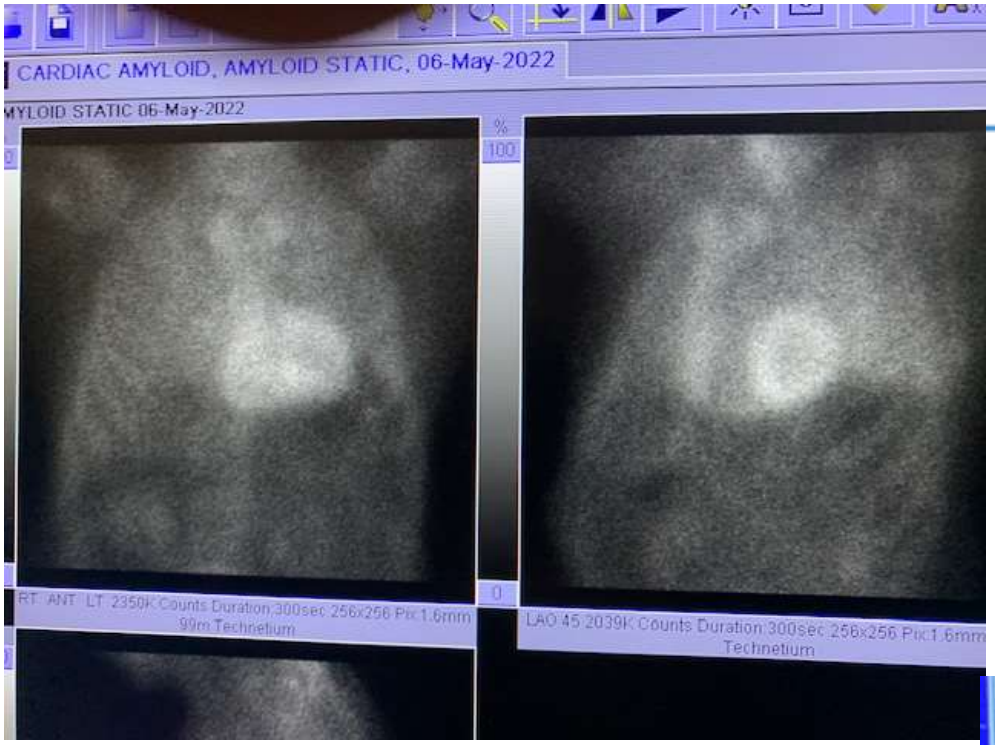
Step 3 – SPECT Imaging –

- **MOST IMPORTANT !! - is the PYP uptake in the myocardium?**

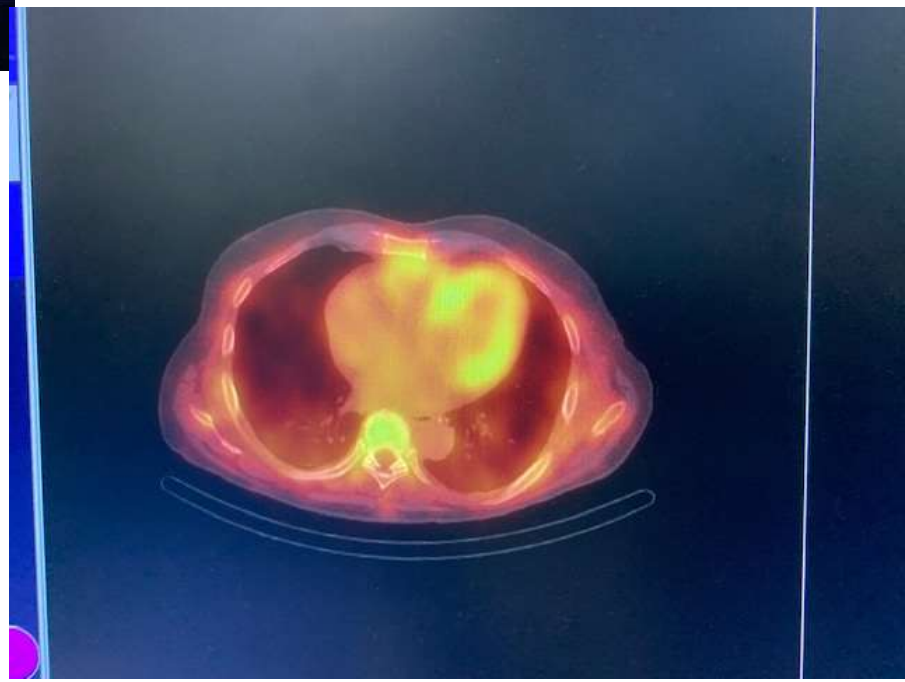
- **High false positive rate for grade 1 or 2 planar imaging without SPECT (due to blood pool uptake)**



Planar imaging: Grade 3 uptake

SPECT: Uptake is in the LV and RV myocardium

“Positive”



Tc99 PYP Scan: Blood Pool Uptake

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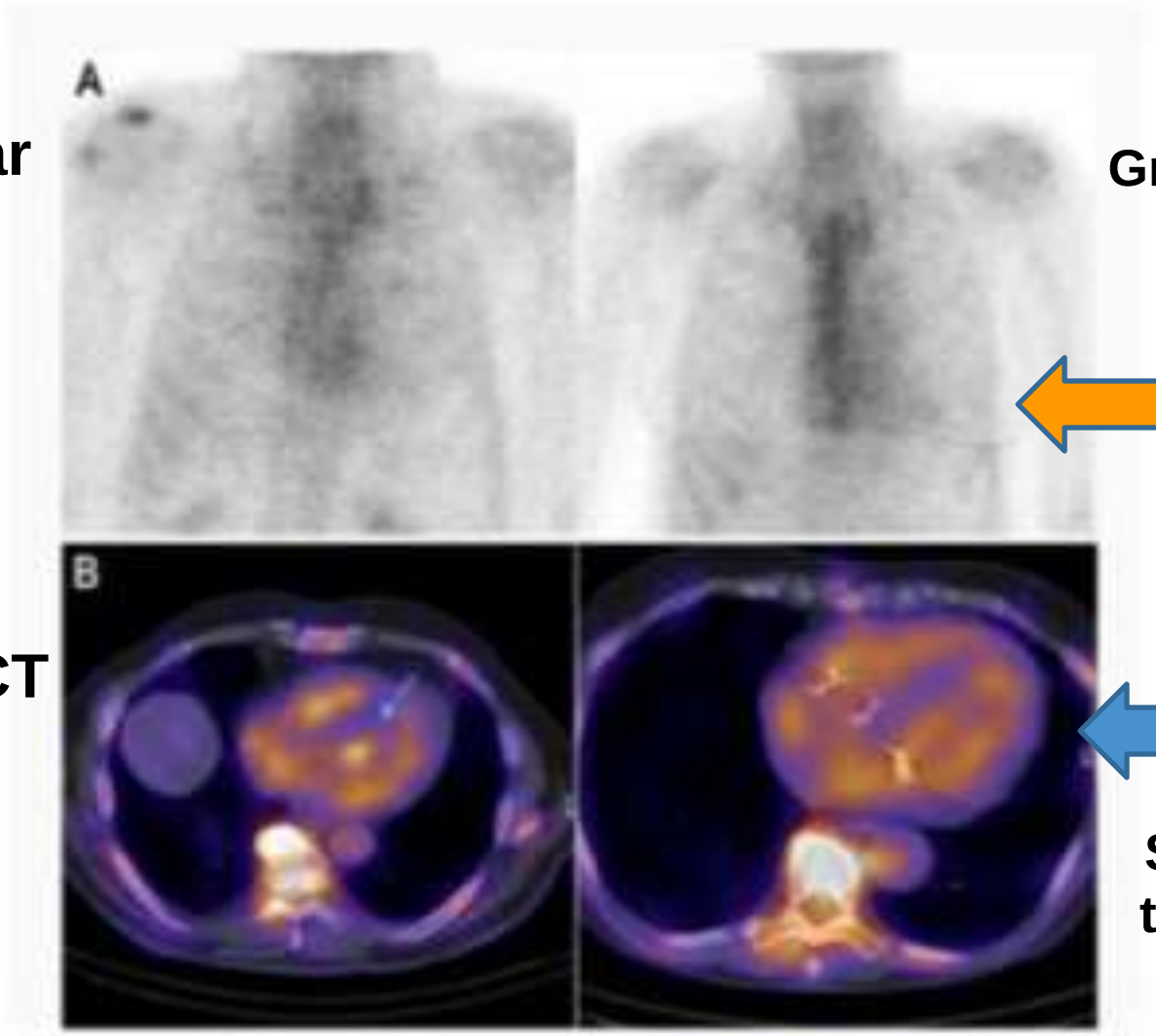
Planar

SPECT



Planar imaging: Grade 1 uptake in the region of the heart

SPECT: Uptake is in the blood pool, NOT the myocardium

Orange: tracer in blood pool
Purple: No tracer in myocardiumn

=> “Negative”

Noninvasive Diagnosis of TTR Cardiac Amyloid

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- **Positive PYP scan alone:**
  "…consistent with TTR cardiac amyloid"

- **Positive PYP scan AND negative serum FLC/serum, urine IFE for light chains:**

  "…diagnostic for TTR cardiac amyloid"

  - **No need for endomyocardial bx, sufficient to begin therapy**

Diagnostic Sensitivity of Abdominal Fat Pad Aspirate for AL, ATTRm, and ATTRwt

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Amyloid Type	N	Sensitivity (CI)
AL amyloidosis	216	84% (78-88%)
ATTRm	113	45% (36-54%)
• *Val122Ile*	69	33%
• *Thr60Ala*	21	67%
ATTRwt	42	15% (11-20%)

Quarta CC et al, Eur Heart J 2017

Evaluation and Management of Cardiac Amyloidosis

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- **Classification, pathophysiology and clinical manifestations**
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Management of ATTR CMP

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- General Supportive Care
  - Diuretics (torsemide, bumetanide)
  - Spironolactone
  - ACE-inhibitors/BB may not be well tolerated due to low BP
  - Beta blockers may not be tolerated due to fixed stroke volume
  - Non-dihydropyridine calcium channel blockers contraindicated
  - Digoxin may be used, with caution

TTR Production and Targets of Therapy

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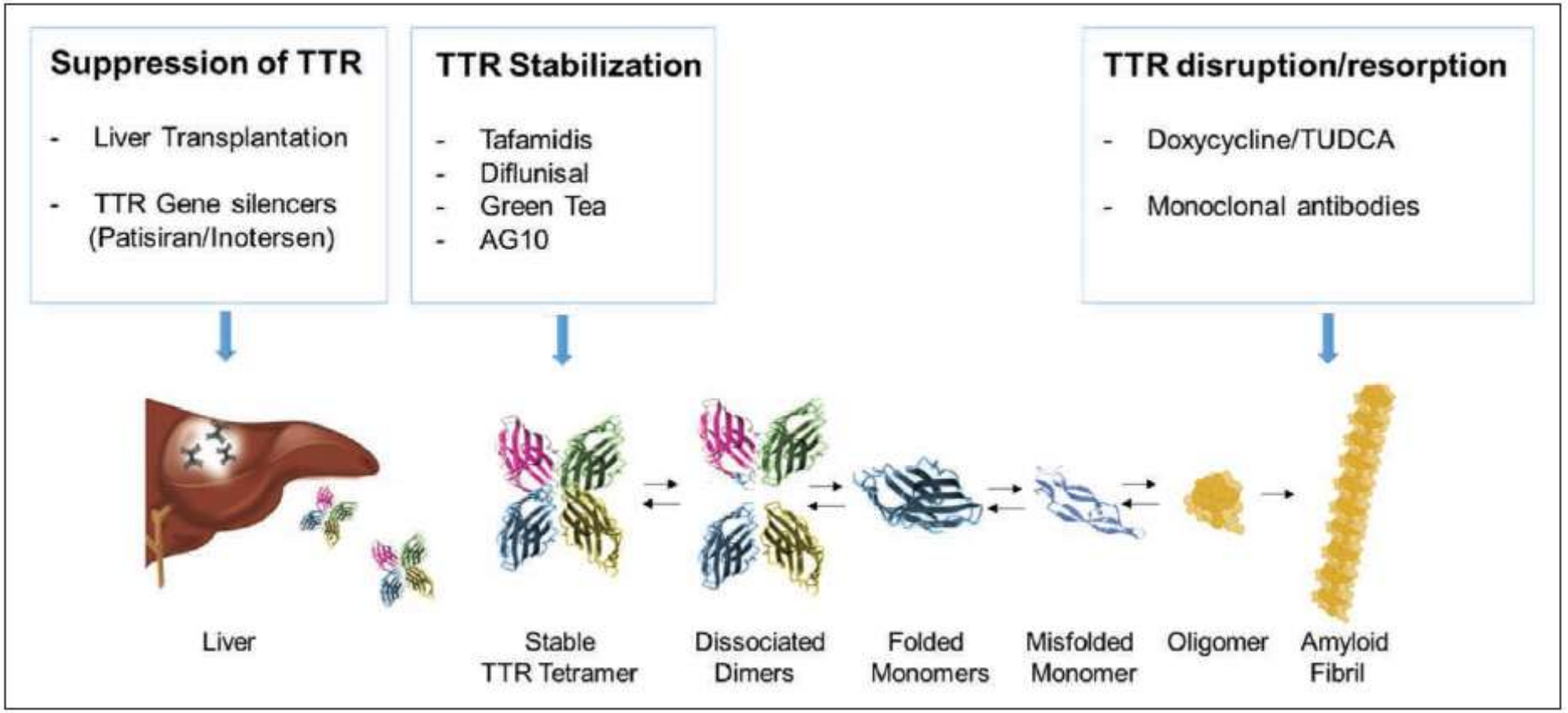

Kittleson et al, Circ 2020, AHA Scientific Statement

ATTR-ACT (Tafamidis in ATTR-CM)

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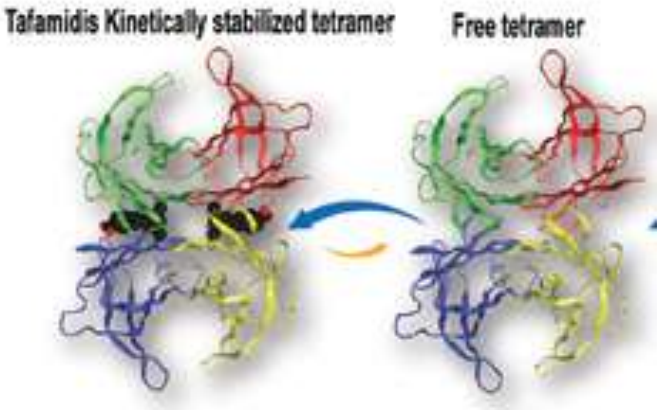
- **RCT Tafamidis (80 mg, 20 mg) vs placebo, 30 months**
  - **ATTRh and ATTRwt CMP, 441 subjects**
- **Primary Endpoint:**
  - **Hierarchically assessed all-cause mortality, frequency of CV hosp**
- **Key Secondary Endpoints:**
  - **6-Minute Walk Test (6MWT)**
  - **Kansas City Cardiomyopathy Questionnaire (KCCQ)**



Maurer M et al, N Engl J Med; 2018

Tafamidis for ATTR Cardiac Amyloid

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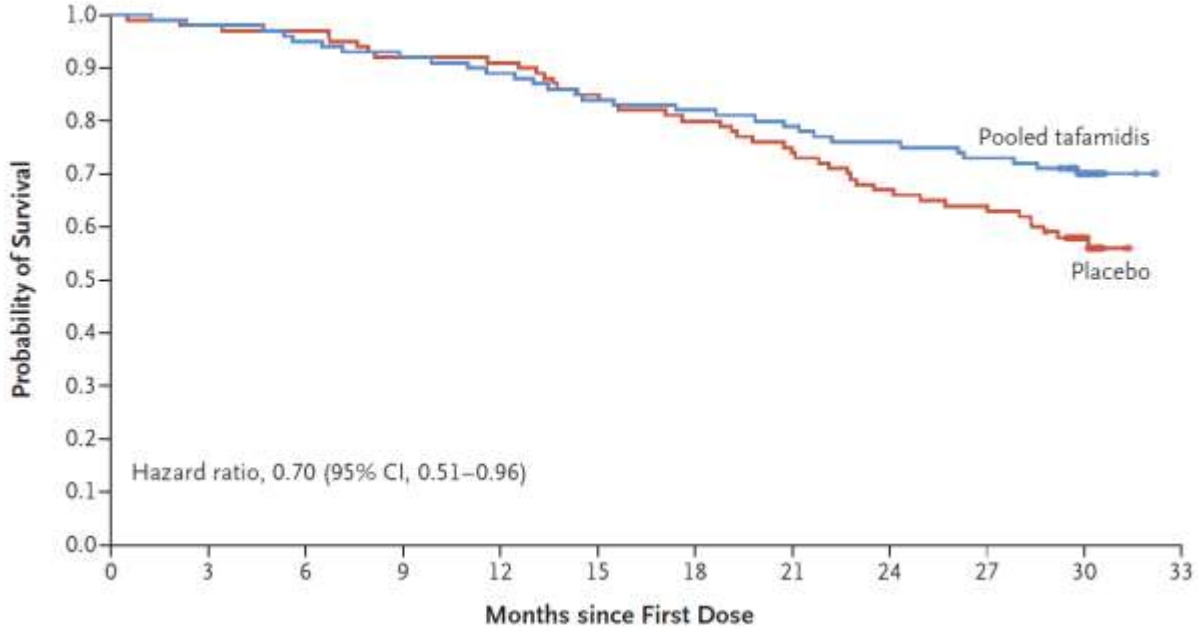
A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



HF Hosp
HR 0.68 (0.56-0.81)

Mauer et al. NEJM 2018

ATTR-ACT

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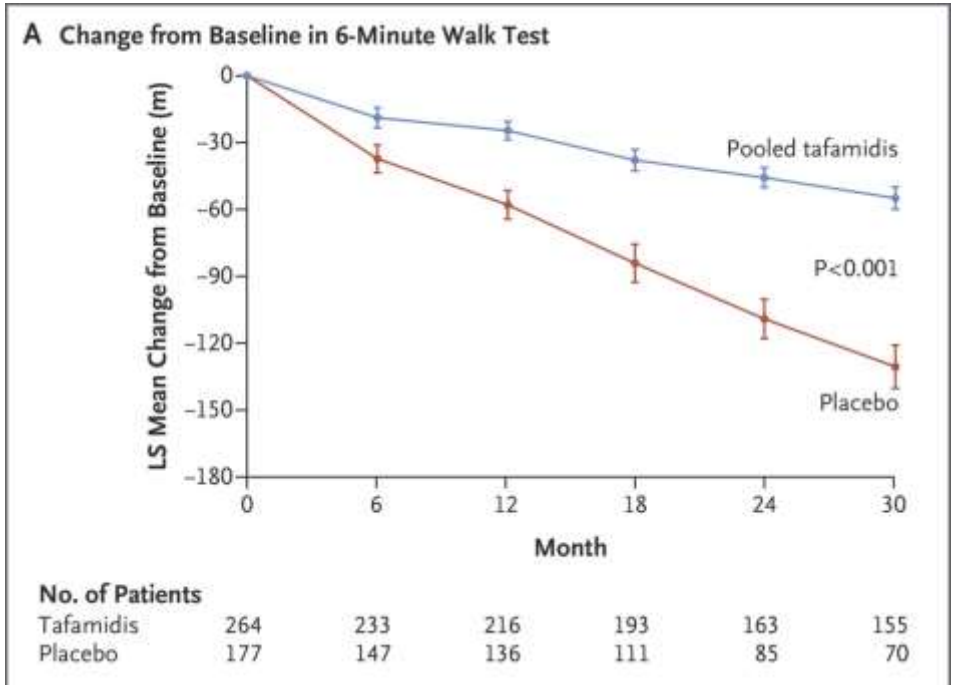
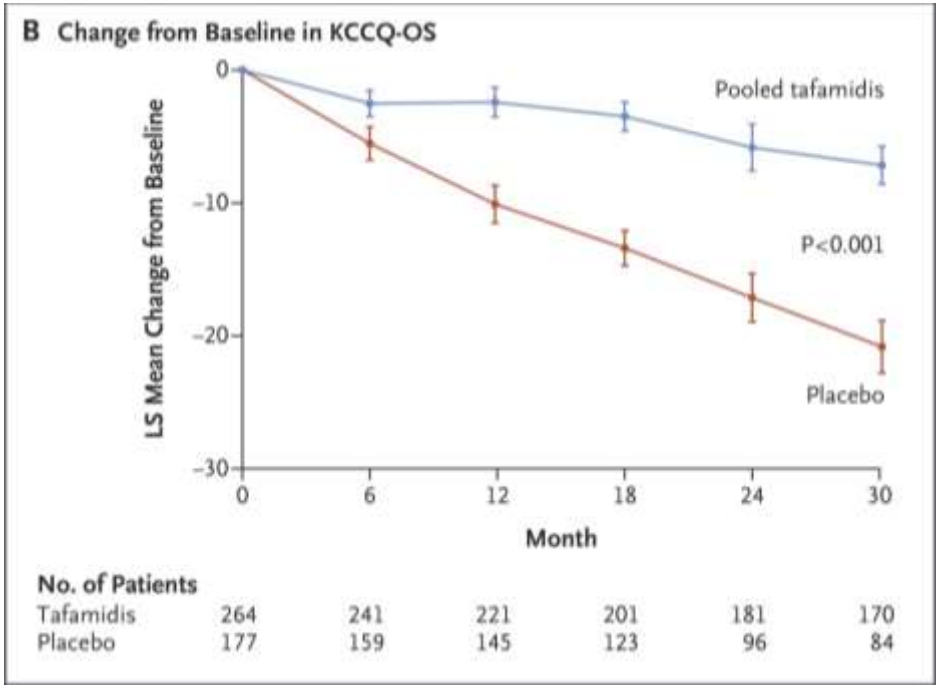
6 MW Test



KCCQ



Maurer M et al, N Engl J Med; 2018

ATTR-ACT

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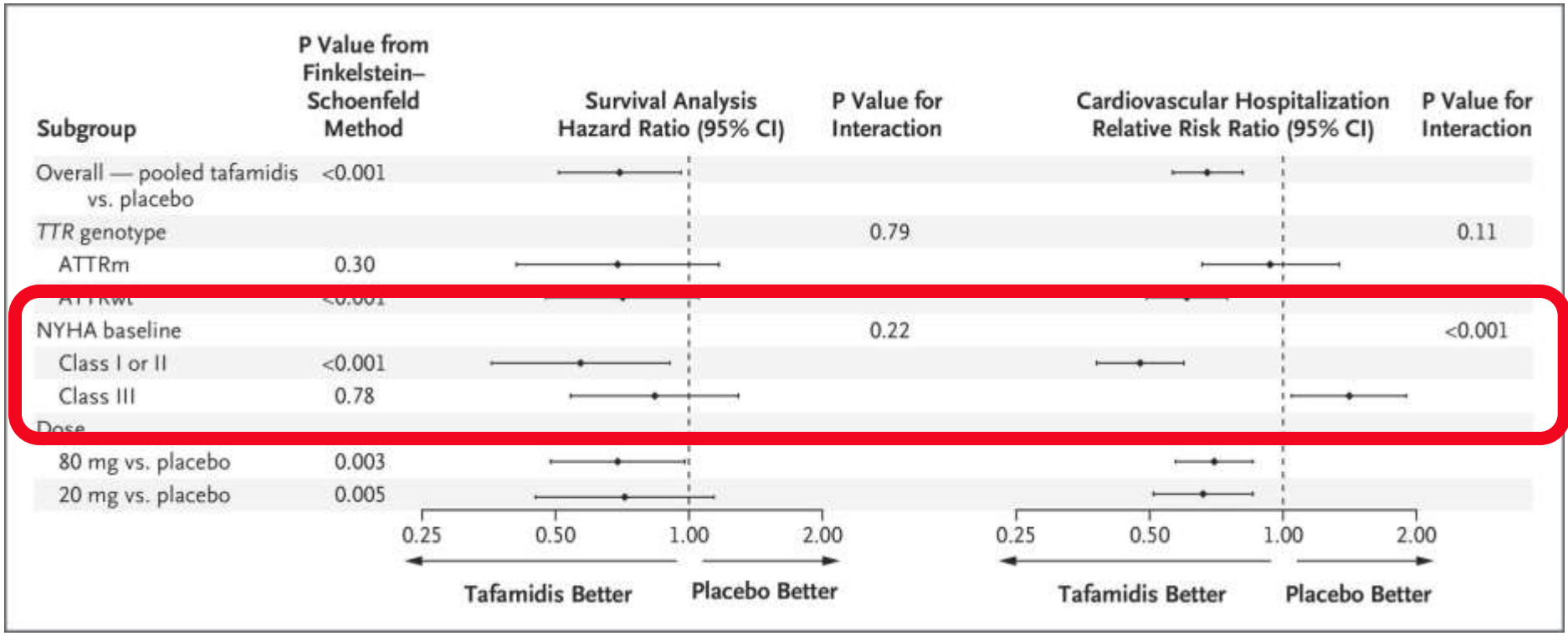

Tafamidis - $$$, ₹₹₹

Maurer M et al, N Engl J Med 2018

Tafamidis and Guidelines

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Recommendations for treatment of patients with HF and amyloidosis	
Tafamidis is recommended in patients with genetic testing proven hTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.	I
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.	I

ESC HF Guidelines 2021

Recommendations for Treatment of Cardiac Amyloidosis
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
Value Statement: Low Value (B-NR)		2. At 2020 list prices, tafamidis provides low economic value (>$180 000 per QALY gained) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis.[2]

ACC AHA HF Guidelines 2022

CRISPR-Cas9 TTR Gene Editing: NTLA-2001

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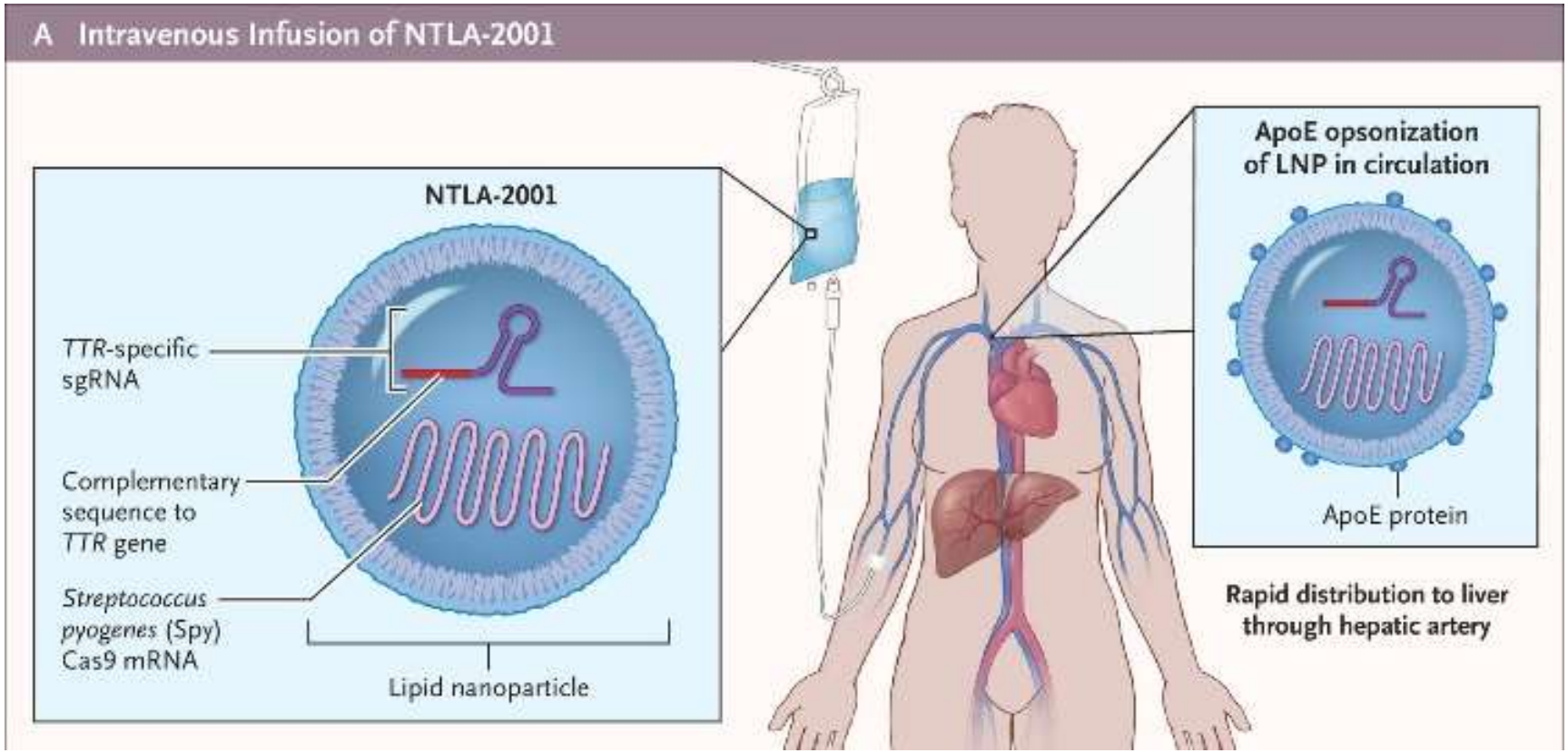
6 patients with h-ATTR PN



- **Administered by IV infusion**
- **Edits the gene encoding TTR in hepatocytes**

Gillmore et al, NEJM 2021

Reduction in Serum TTR With NTLA-2001

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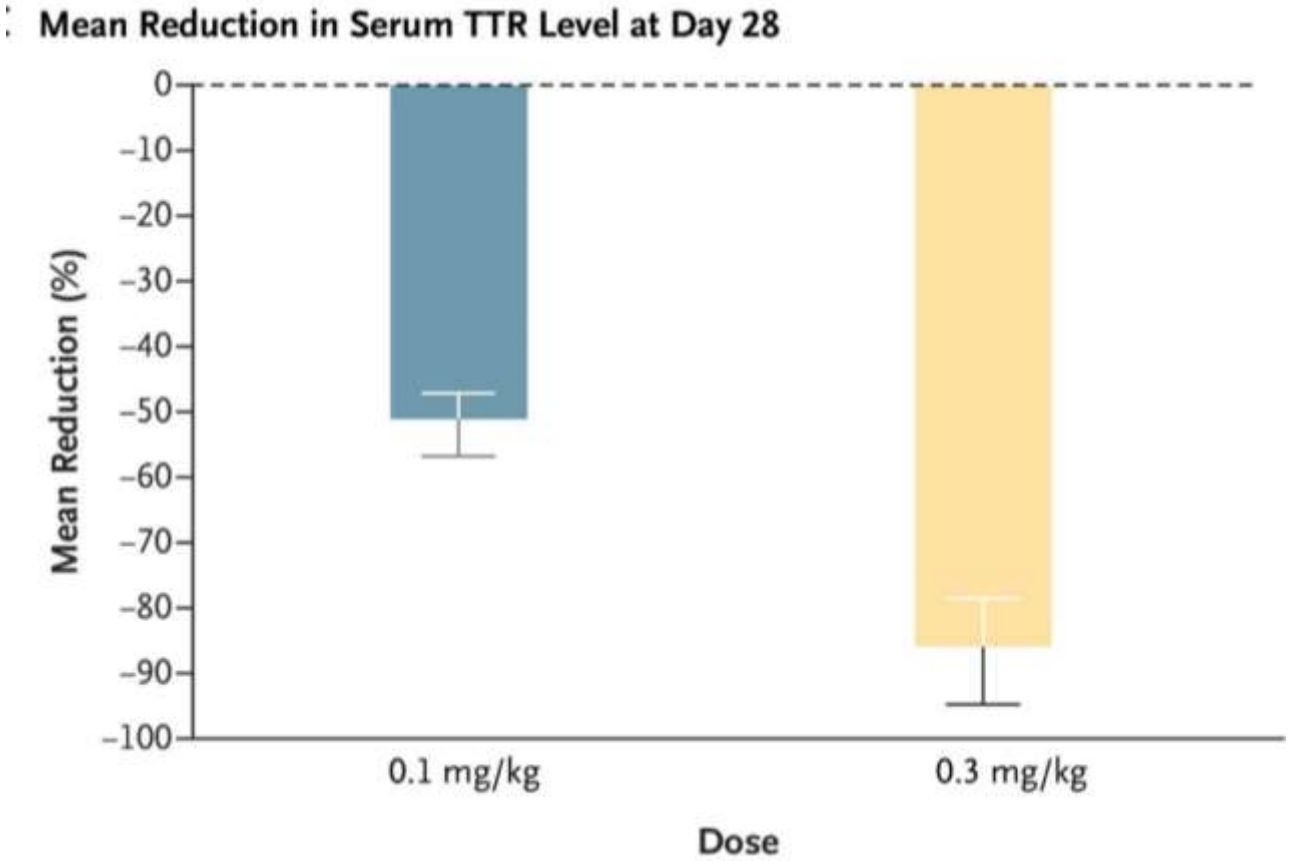

- **52% reduction in patients who received 0.1 mg/kg**
- **87% reduction in patients who received 0.3 mg/kg**
- **50% with mild adverse effects; None with SAEs**
- **Vitamin A supplementation required**

Gillmore et al, NEJM 2021

Management of ATTR CMP

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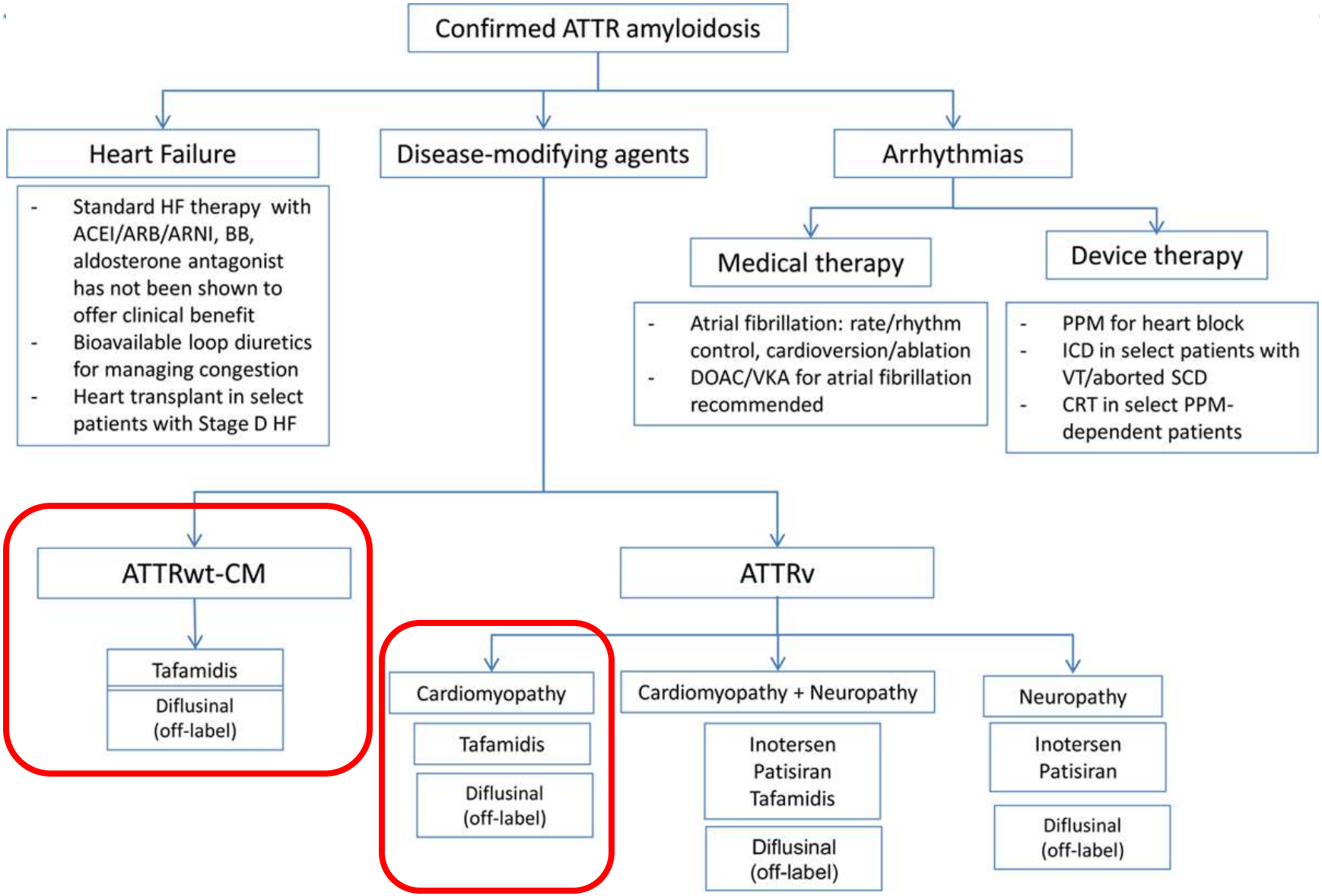

Kittleson MM et al, Circulation 2020

Earlier Diagnosis and Improving Prognosis in ATTR CMP

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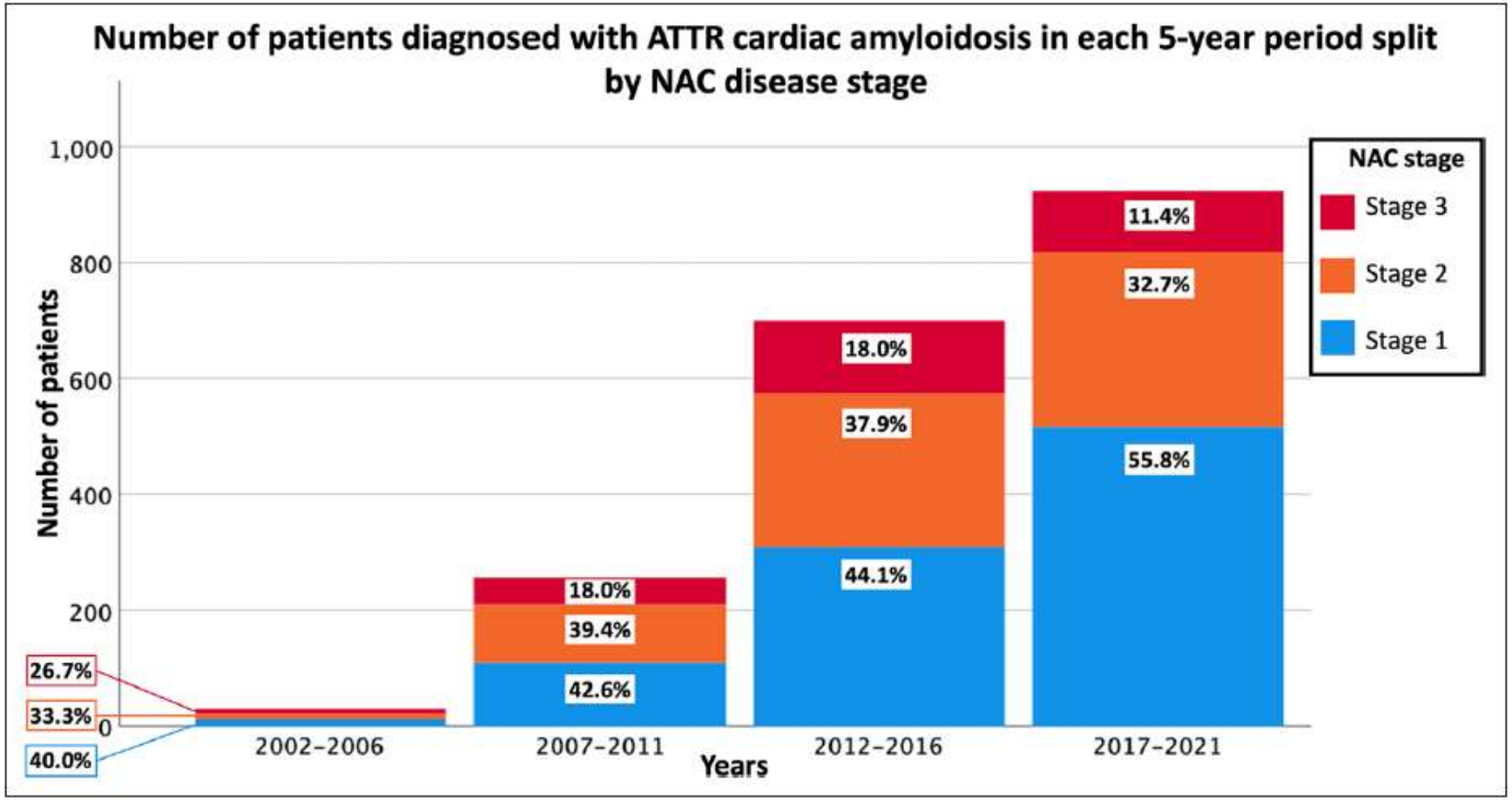

Ioannou et al, Circulation 2022

Earlier Diagnosis and Improving Prognosis in ATTR CMP

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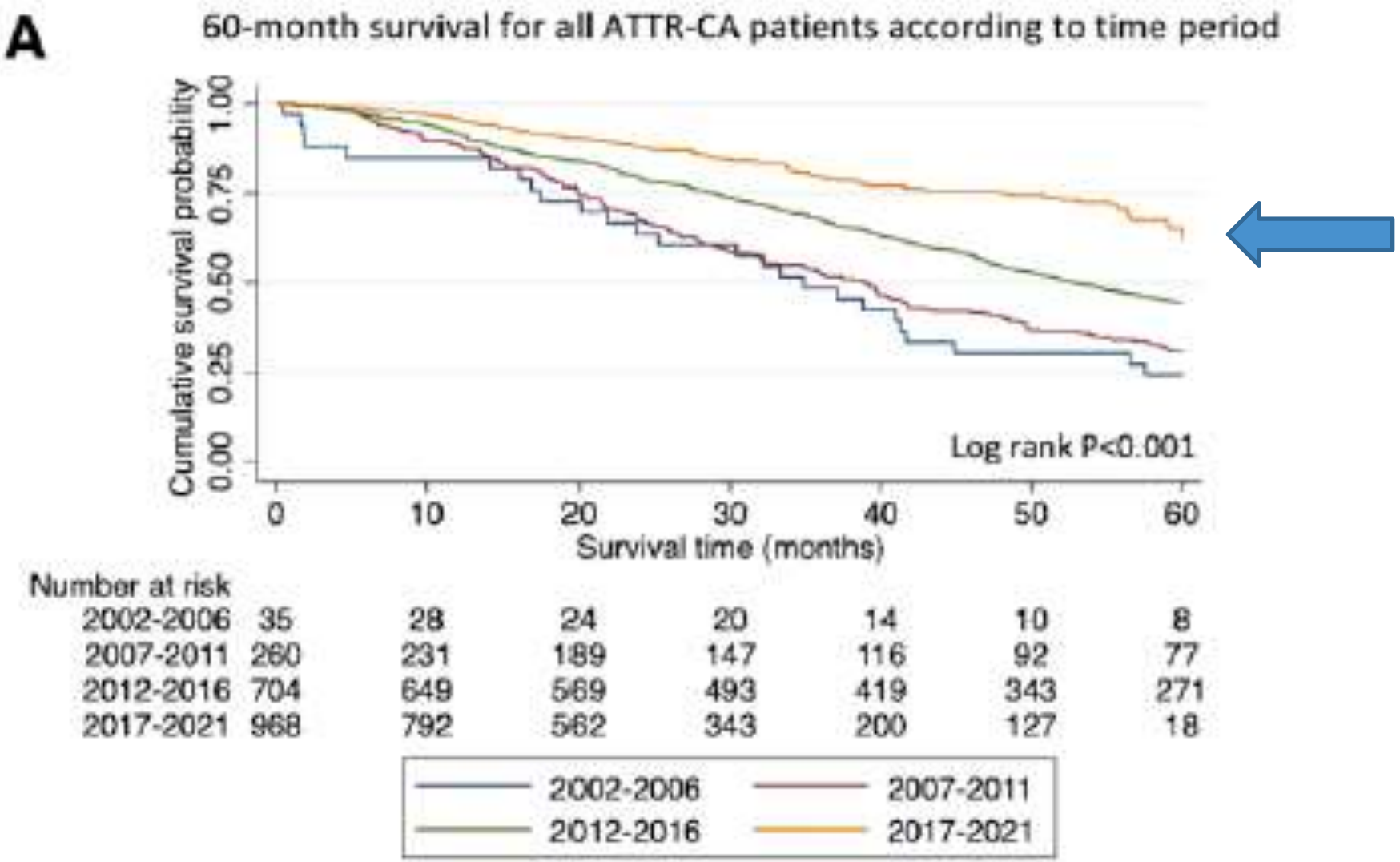

Ioannou et al, Circulation 2022

Case Report

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- 78 yr old male, presented to your office with SOB
- History: DM, high cholesterol, CKD st 2, no history HTN
- Physical exam consistent with signs of volume overload
- Echo: No valvular disease, LVH, enlarged LA, EF 45%
- Stress perfusion imaging normal
- Dx: Heart Failure with Preserved EF
- Diuresis => improved symptoms, became asymptomatic
- GDMT –
  - spironolactone (TOPCAT)
  - sacubitril/valsartan (PARAGON) – only tolerated low dose
  - dapagliflozin (DELIVER)
- Is this patient well-managed ??

Case Report

Tufts Medical Center
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- **Is this patient well-managed ?? ….no**
- ***78 yr old male*, presented to your office with SOB**
- **History: DM, high cholesterol, CKD st 2, *no history HTN***
- **Physical exam consistent with signs of volume overload**
- **Echo: No valvular disease, *LVH*, enlarged LA, EF 45%**
- **Stress perfusion imaging normal**
- **Dx: Heart Failure with Preserved EF**
- **Diuresis => improved symptoms, became asymptomatic**
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  - **dapagliflozin (DELIVER)**

Tc99m-PYP Imaging

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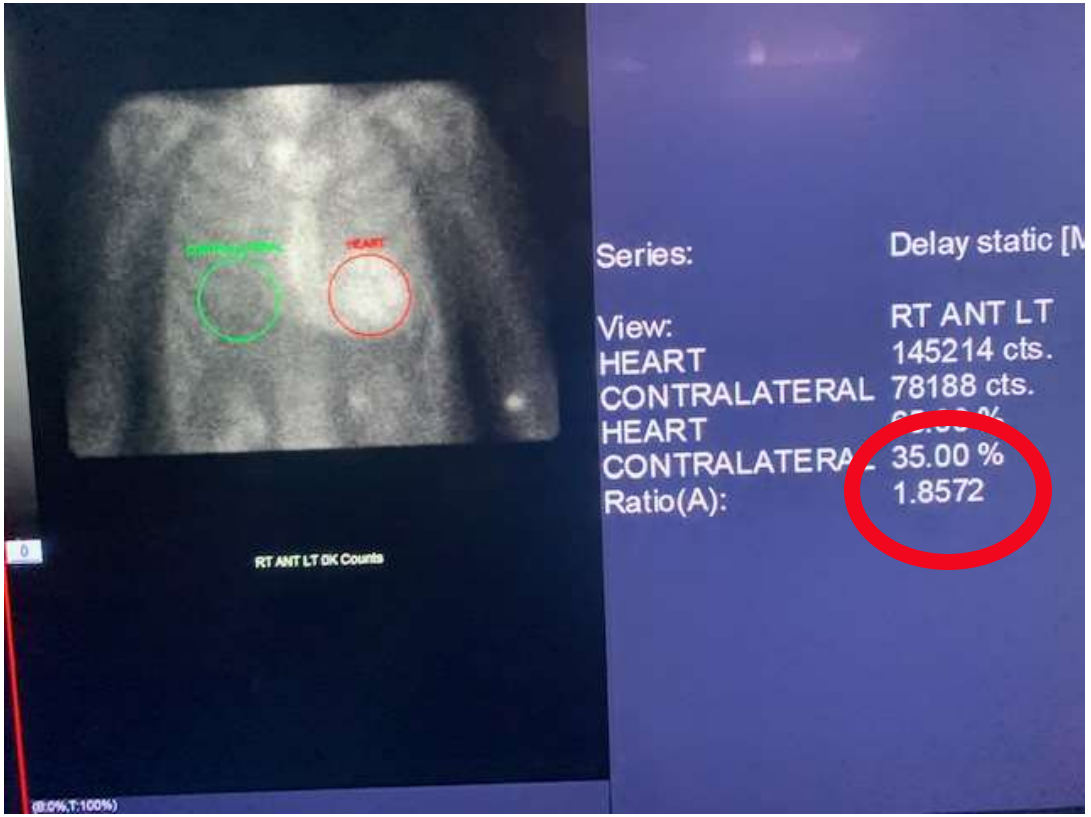

Tc99m-PYP Imaging

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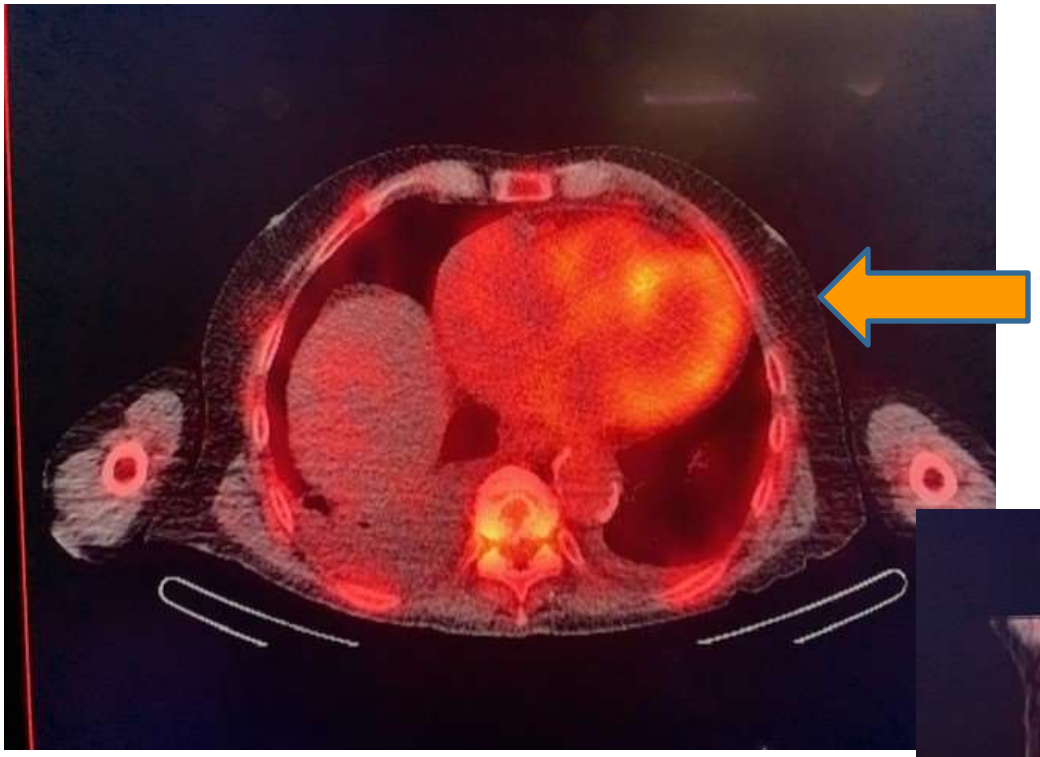

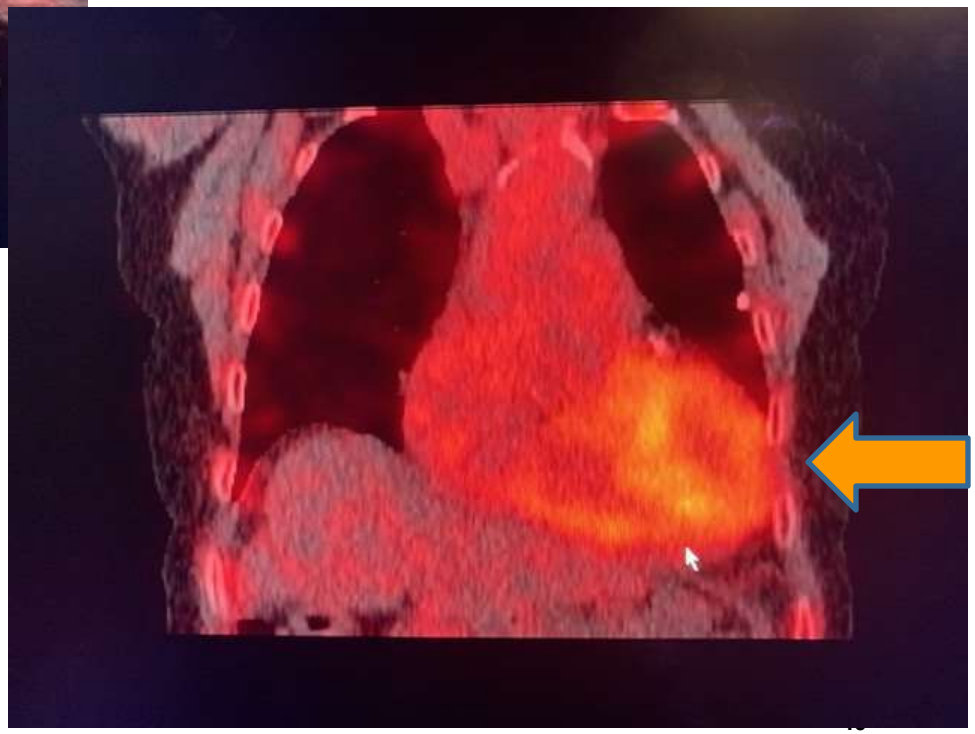

Case Report

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- **Tc99m-PYP strongly positive, consistent with TTR cardiac amyloid**
- **Serum and urine studies negative for light chains**

=> Diagnostic for TTR cardiac amyloid

=> Started tafamidis, discontinued sacubitril/valsartan

Summary Points

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- ***Suspicion of TTR amyloid CMP***
  - **Unexplained increased LV wall thickness**
  - **Low-flow low-gradient AS**
  - **Presence of increased RV wall thickness**
  - **Associated findings (carpal tunnel, spinal stenosis, conduction disease, low BP)**
- ***ATTRwt is more common than once thought***
  - **Tc^{99} PYP imaging (with SPECT) in pts with echo/MRI findings that are suspicious for amyloid**
  - **Must always screen for monoclonal gammopathy**
- ***Rapid developments in therapeutic agents***
- ***Early diagnosis is critical in context of available and emerging therapies***

Tc99 PYP Scan: Blood Pool Uptake

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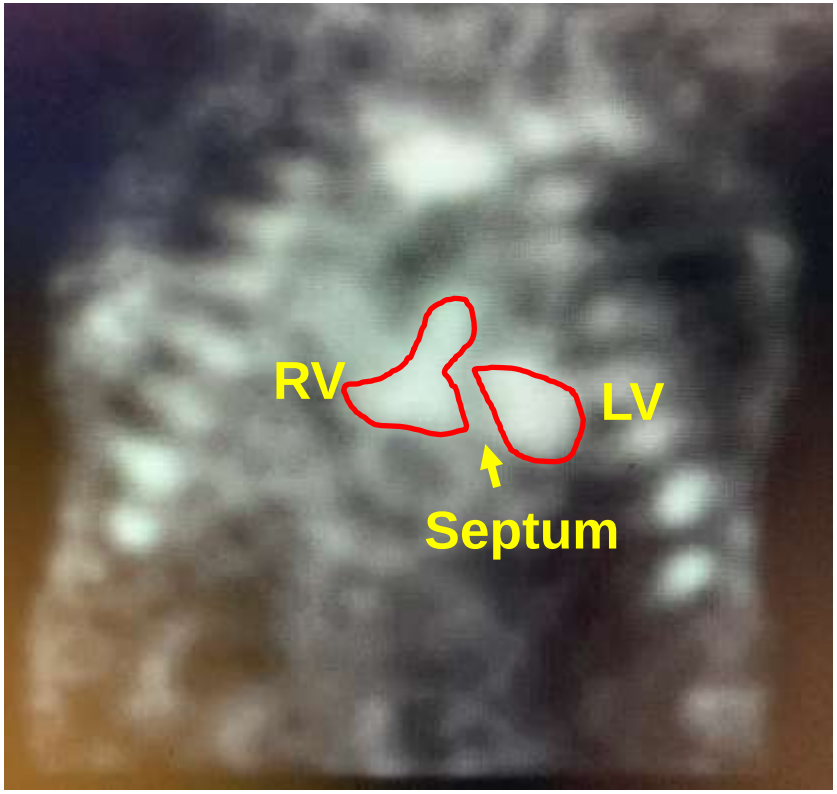

SPECT CORONAL PLANE

69yo w +TTR in ligament; LAE on echo

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ANTERIOR PLANAR
H:CL ratio 1.3

SPECT CORONAL PLANE

Tc99m-PYP Imaging for TTR Cardiac Amyloid: Technique

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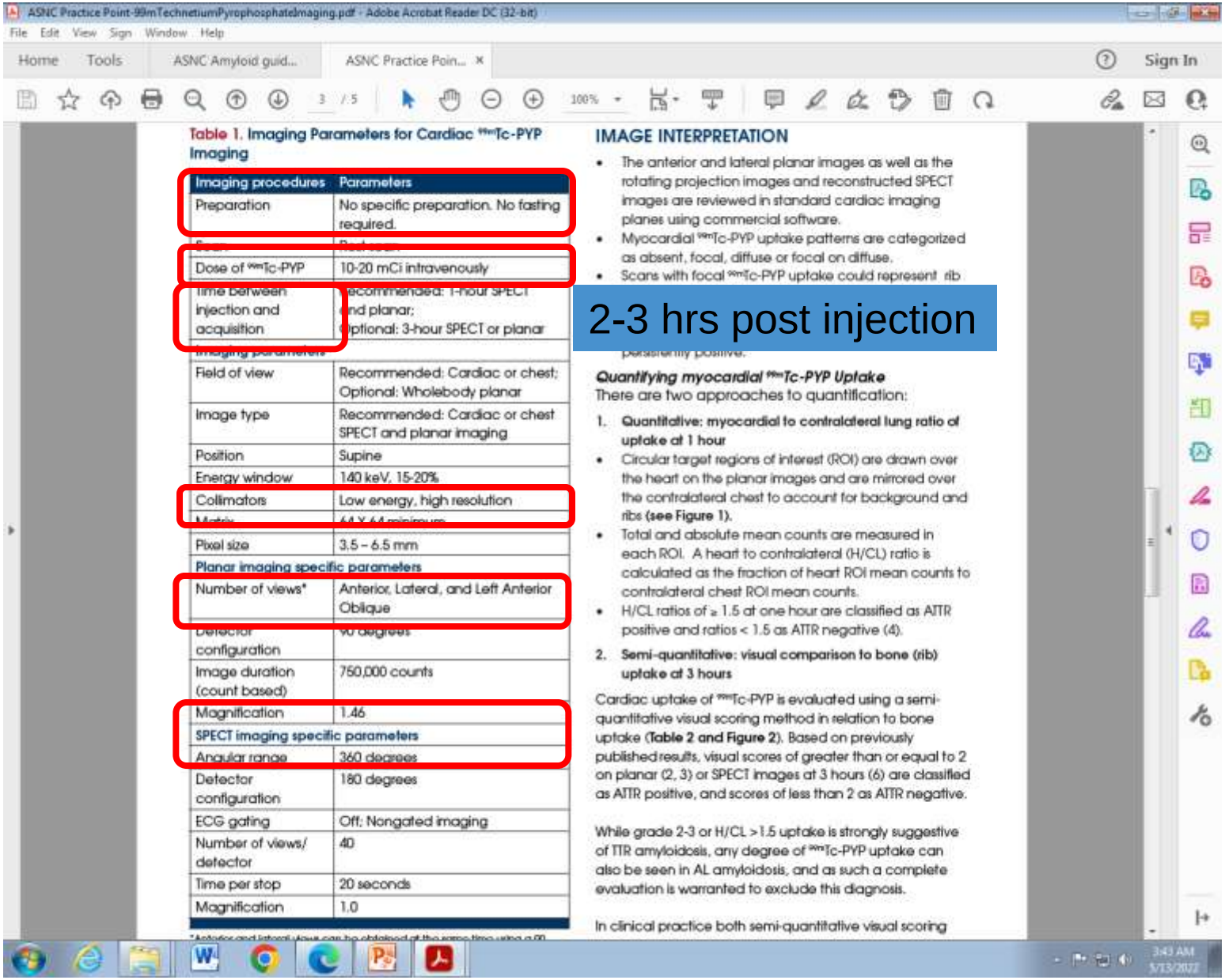

ASNC Practice Point-99mTechnetiumPyrophosphateImaging.pdf - Adobe Acrobat Reader DC (32-bit)

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Table 1. Imaging Parameters for Cardiac ^{99m}Tc-PYP Imaging

Imaging procedures	Parameters
Preparation	No specific preparation. No fasting required.
Dose of ^{99m}Tc-PYP	10-20 mCi intravenously
Time between injection and acquisition	Recommended: 1-hour SPECT and planar; Optional: 3-hour SPECT or planar
Imaging parameters	
Field of view	Recommended: Cardiac or chest; Optional: Wholebody planar
Image type	Recommended: Cardiac or chest SPECT and planar imaging
Position	Supine
Energy window	140 keV, 15-20%
Collimators	Low energy, high resolution
Matrix	64 X 64 minimum
Pixel size	3.5 – 6.5 mm
Planar imaging specific parameters	
Number of views*	Anterior, Lateral, and Left Anterior Oblique
Detector configuration	90 degrees
Image duration (count based)	750,000 counts
Magnification	1.46
SPECT imaging specific parameters	
Angular range	360 degrees
Detector configuration	180 degrees
ECG gating	Off; Nongated imaging
Number of views/ detector	40
Time per stop	20 seconds
Magnification	1.0

*Anterior and lateral views can be obtained at the same time using a 90

IMAGE INTERPRETATION

- The anterior and lateral planar images as well as the rotating projection images and reconstructed SPECT images are reviewed in standard cardiac imaging planes using commercial software.
- Myocardial ^{99m}Tc-PYP uptake patterns are categorized as absent, focal, diffuse or focal on diffuse.
- Scars with focal ^{99m}Tc-PYP uptake could represent rib

2-3 hrs post injection

persistently positive.

Quantifying myocardial ^{99m}Tc-PYP Uptake

There are two approaches to quantification:

1. **Quantitative: myocardial to contralateral lung ratio of uptake at 1 hour**
   - Circular target regions of interest (ROI) are drawn over the heart on the planar images and are mirrored over the contralateral chest to account for background and ribs **(see Figure 1)**.
   - Total and absolute mean counts are measured in each ROI. A heart to contralateral (H/CL) ratio is calculated as the fraction of heart ROI mean counts to contralateral chest ROI mean counts.
   - H/CL ratios of ≥ 1.5 at one hour are classified as ATTR positive and ratios < 1.5 as ATTR negative (4).
2. **Semi-quantitative: visual comparison to bone (rib) uptake at 3 hours**

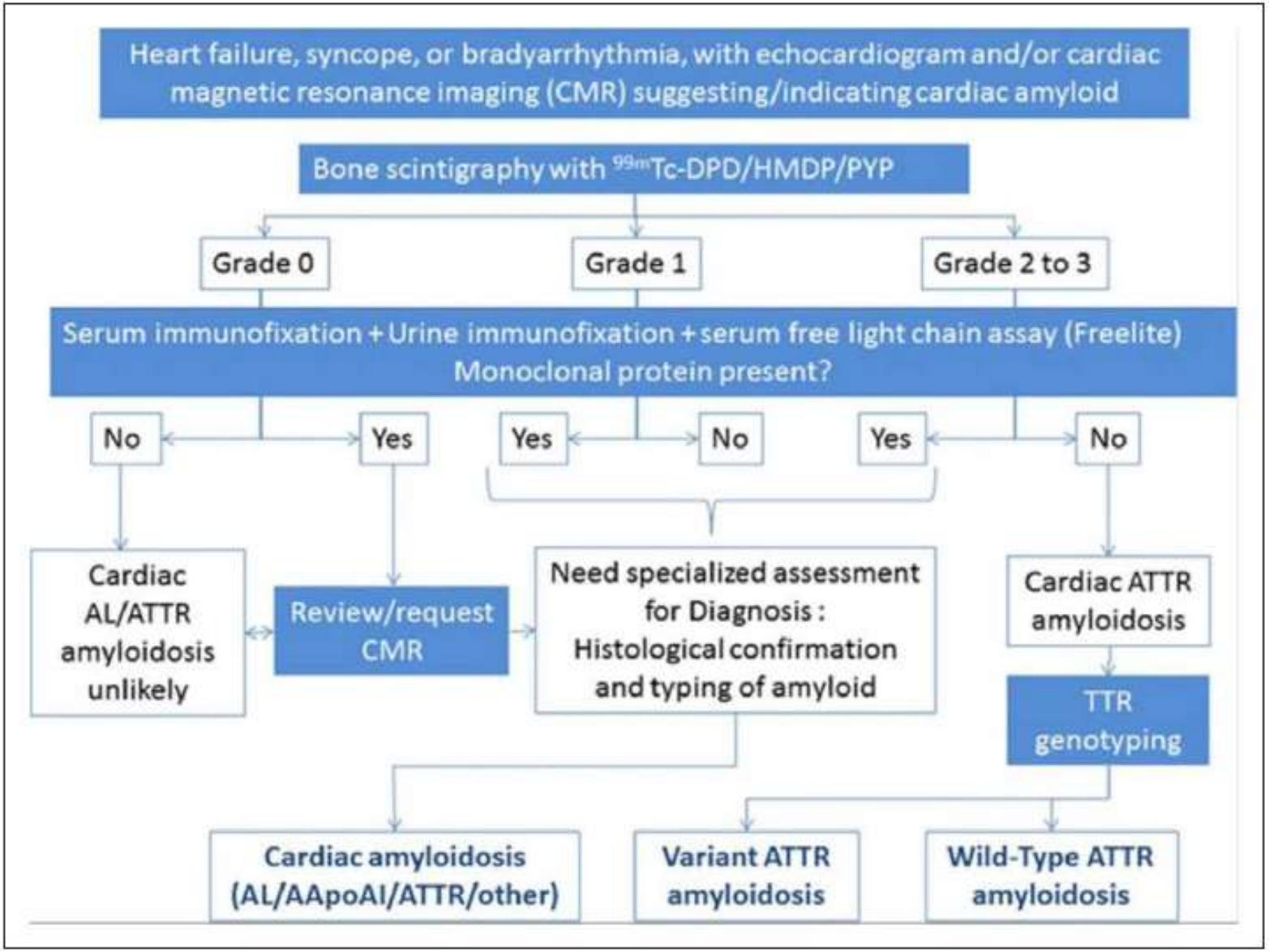
Cardiac uptake of ^{99m}Tc-PYP is evaluated using a semi-quantitative visual scoring method in relation to bone uptake (**Table 2 and Figure 2**). Based on previously published results, visual scores of greater than or equal to 2 on planar (2, 3) or SPECT images at 3 hours (6) are classified as ATTR positive, and scores of less than 2 as ATTR negative.

While grade 2-3 or H/CL >1.5 uptake is strongly suggestive of TTR amyloidosis, any degree of ^{99m}Tc-PYP uptake can also be seen in AL amyloidosis, and as such a complete evaluation is warranted to exclude this diagnosis.

In clinical practice both semi-quantitative visual scoring

Consensus Algorithm for Diagnosis of Cardiac Amyloidosis

Tufts Medical Center
The CardioVascular Center



Dorbala et al, JACC Img 2021

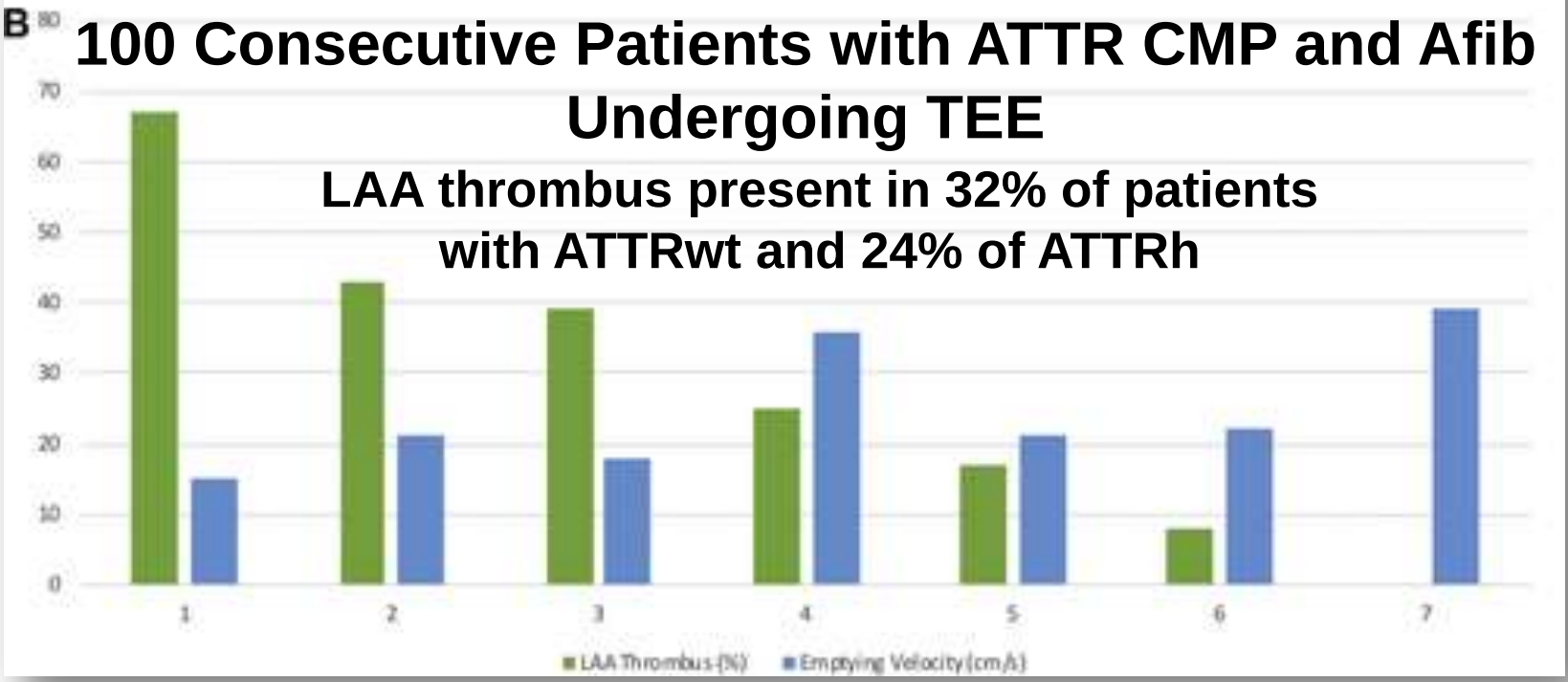
Retrospective Cohort: No Assoc Betw CHADS-VASc Score and LAA Thrombus

Tufts Medical Center
The CardioVascular Center

A

	CHADS-VASc							
	1	2	3	4	5	6	7	p-value
LAA Thrombus	2 (67%)	6 (43%)	14 (39%)	5 (25%)	2 (17%)	1 (8%)	0	0.14
LAA Emptying Velocity (cm/s)	15±7	21±10	18±8	36±26	21±7	22±12	39±18	0.8
Anticoagulation	3 (100%)	10 (71%)	26 (72%)	17 (85%)	10 (83%)	7 (58%)	2 (67%)	0.86

B



Donnellan et al, J Am Coll Cardiol Clin EP 2019

Therapeutic Approaches: Tetramer Stabilization

Tufts Medical Center
The CardioVascular Center

- Complex w/ thyroxin binding site-> stabilize transthyretin tetramer
  - Tafamidis
  - Diflunisal (NSAID)

- AG10 (Acoramidis)
  - Protective T119M mutation
  - Stabilization of TTR, mimicking T119M

Stabilizers: Diflunisal

Tufts Medical Center
The CardioVascular Center

- **Nonsteroidal anti-inflammatory analgesic**
- **Stabilizes transthyretin tetramer (off-label use)**
- **Potential Side Effects: anti-cyclooxygenase activity**
  - **GI bleeding**
  - **Renal dysfunction**
  - **Volume retention**

Diflunisal for TTR CMP

Tufts Medical Center
The CardioVascular Center

- Retrospective cohort study in wt-ATTR CMP (n=104)
- 35 received diflunisal (eGFR>45 mL/min/1.73 m^2)
- 52 deaths over median of 3.2 years
- 14 patients (40%) discontinued diflunisal (3 in the first year)
- Mean eGFR w diflunisal from 67 ±17 to 59 ±17 ml/min/1.73m^2 at 1 year ($p = 0.03$)
- Diflunisal associated with improved survival in unadjusted (HR 0.13, 95% CI 0.05 – 0.36, $p < 0.001$), and adjusted (HR 0.18, 95% CI 0.06 – 0.51, $p = 0.0006$) analyses

Siddiqui/Ruberg et al; Amyloid 2022

ATTRibute-CM

Tufts Medical Center
The CardioVascular Center

- **Phase III trial**
- **Acoramidis (AG10) 800 mg twice daily PO versus placebo in symptomatic ATTR CMP**
- **Primary outcomes**
  - **6 minute walk test at 12 months→ *did not meet***
  - **Frequencies of deaths, CV-related hospitalizations, and change in distance walked on the 6MWT at 30 months → ongoing**

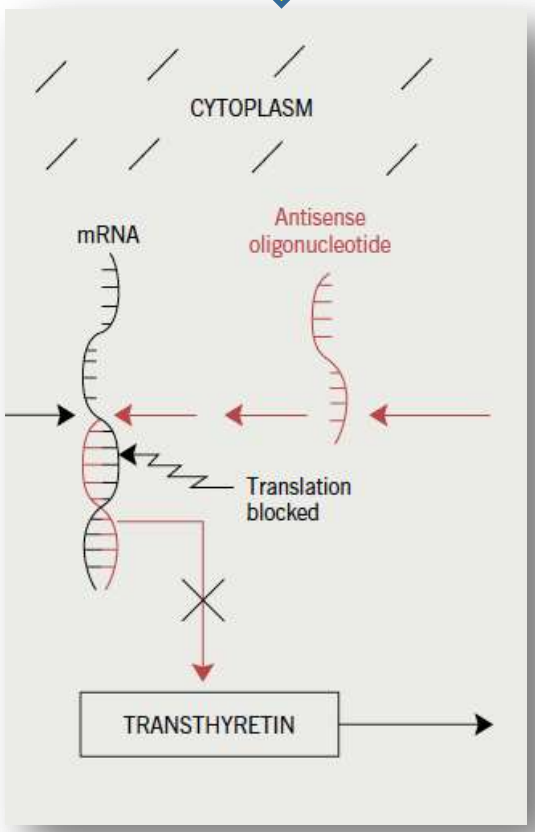
Elimination of TTR Expression: Gene Silencing

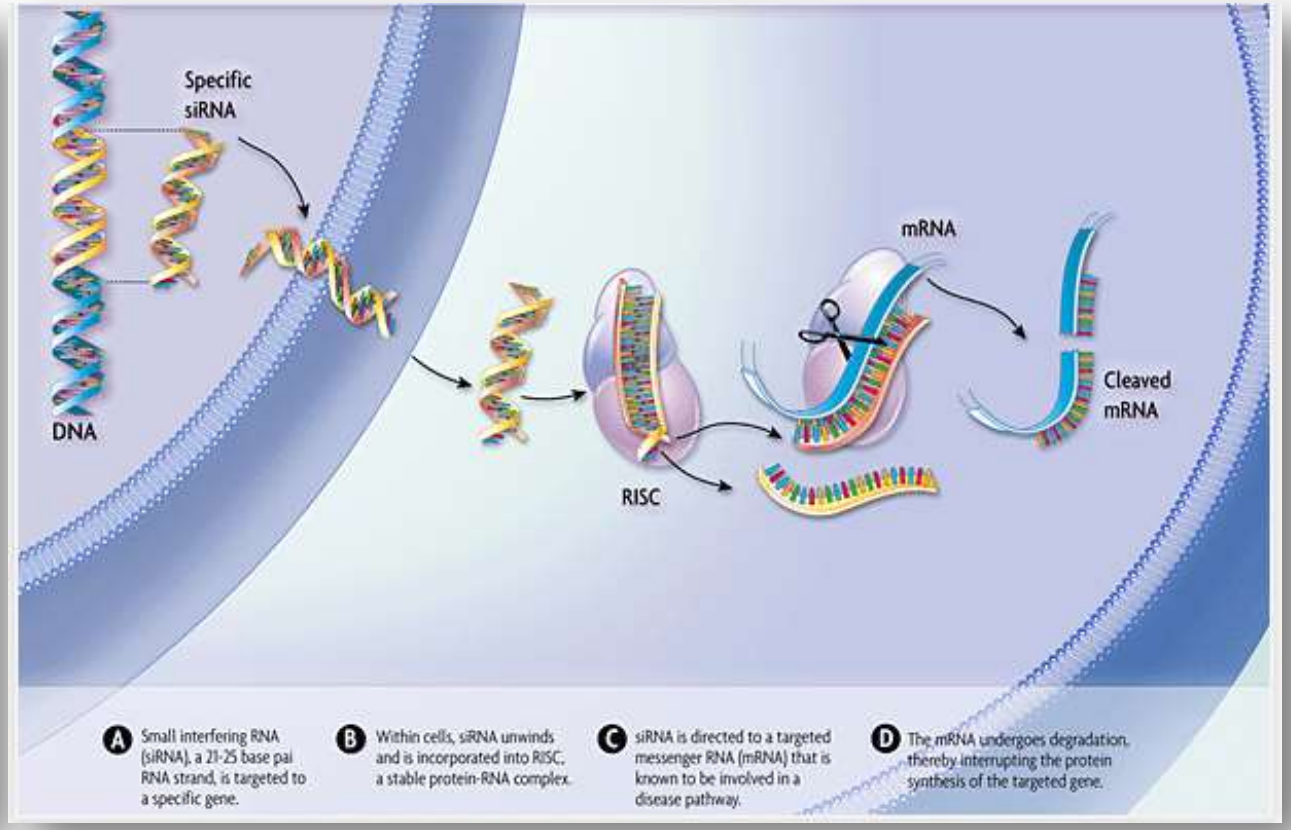
Tufts Medical Center
The CardioVascular Center

Antisense oligonucleotides (short ss-DNA) directed against ATTR mRNA suppresses TTR translation

Small interfering RNA (double stranded oligonucleotide) silence mRNA via RISC (RNA induced silencing complex)

in cytoplasm siRNA bonds and forms RNA silencing complex →mRNA degradation





Dubrey, BJC 2013

Tc99m-PYP Imaging for TTR Cardiac Amyloid: Interpretation

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- For a study to be positive, must see PYP in the myocardium
- Grade 0 = negative
- Grades 1 or 2, SPECT blood pool = negative
- Grades 2 or 3, SPECT myocardial = positive

- Grades 1,2,3 on planar, and cannot tell by SPECT if in the myocardium = equivocal

Bone Scintigraphy for Detection of Cardiac ATTR

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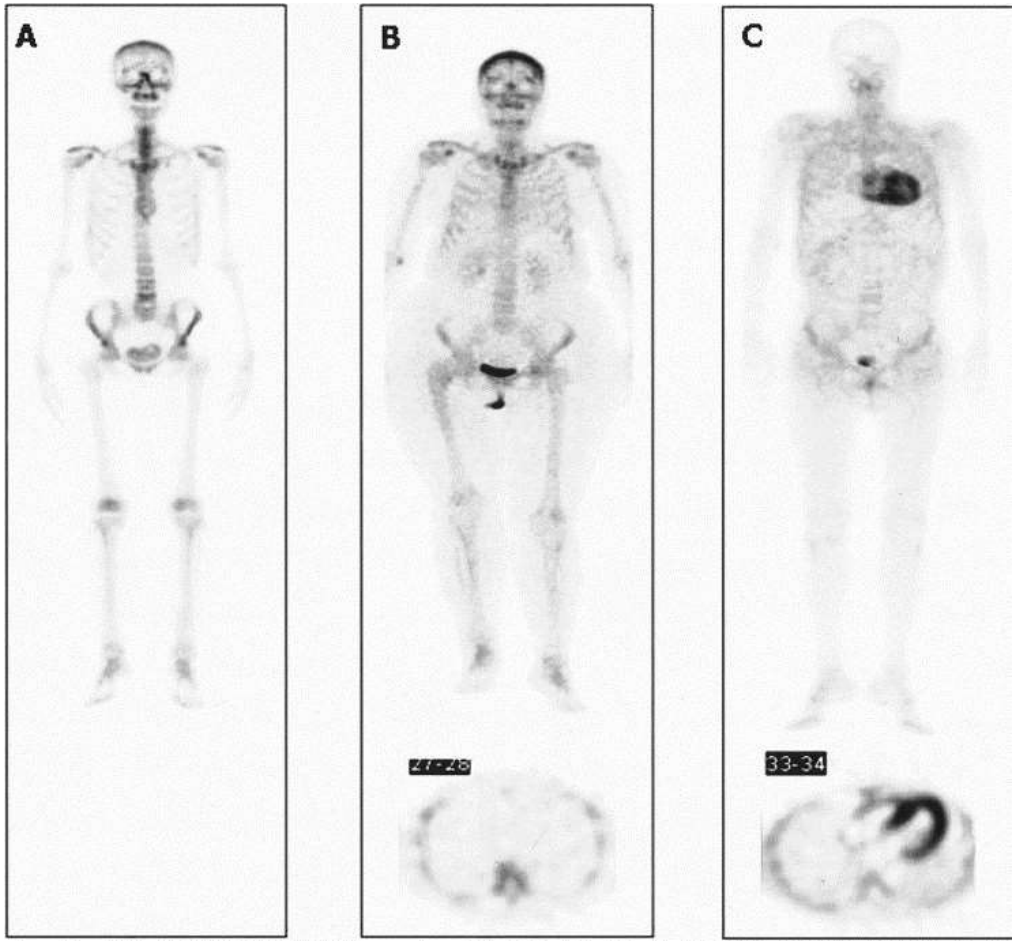

Control (n=10)

AL Amyloid (n=10)

TTR Amyloid (n=15; TTRm=10)

Qualitative Scoring

0= absent heart uptake, normal bone uptake

1=mild heart uptake, inferior to bone uptake

2=moderate heart uptake, attenuated bone uptake

3=strong heart uptake, mild/absent bone uptake

Perugini, Rapezzi et al, JACC 2005

AG10 Stabilizes TTR in ATTR CMP (NYHA Class II-III)

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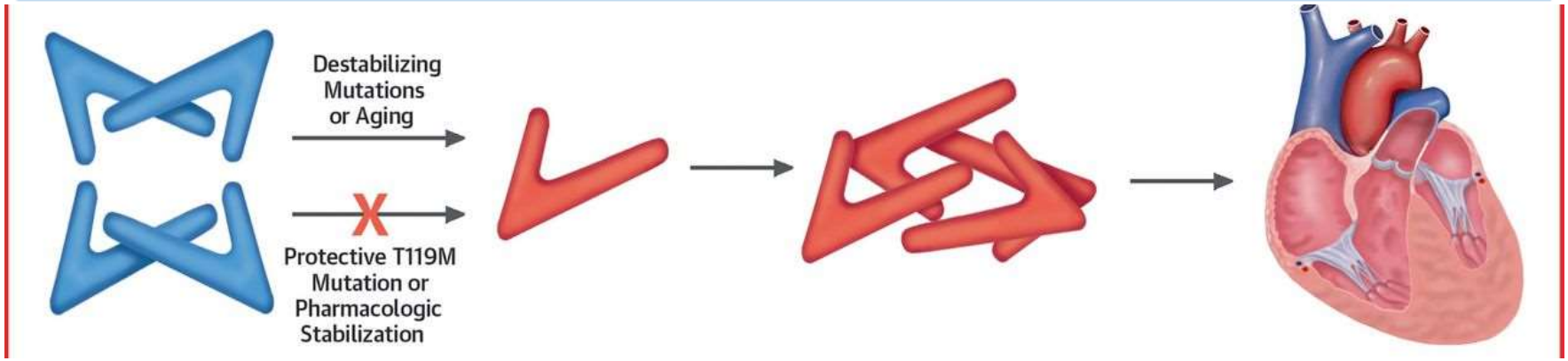

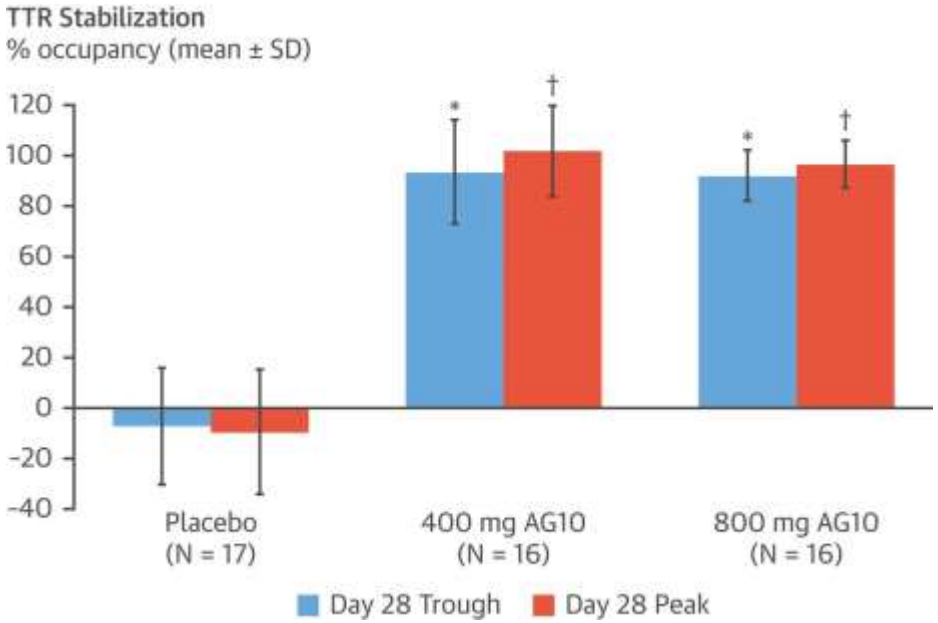

- **Phase III trial**
- **Primary outcomes**
  - **6 MW test at 12 mos→ *did not meet***
  - **Deaths, CV-hosp, and change in 6MWT at 30 months → ongoing**

Judge D et al; J Am Coll Cardiol 2019