Navigating the Evolving Landscape: Advanced Decision-Making in ATTR-CM

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Welcome, Introductions, Pre-Assessment Questions, and Program Overview

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Disclosures

Jennifer L. Day, PharmD

Consulting Fees: Janssen Pharmaceuticals

Courtney M. Campbell, MD, PhD

Consulting Fees: Alnylam Pharmaceuticals, Inc., Pfizer

Research: Akari Therapeutics, Alnylam Pharmaceuticals, Pfizer

Dejan Landup, PharmD, HF-Cert

No relevant relationships reported.

Agenda

- Updates on ATTR-CM Disease State
- Clinical Trials in ATTR
- Specialty Pharmacy Relevance in ATTR-CM
- Panel Discussion and Audience Q&A

Learning Objectives

- Describe the pathophysiology and genetic variation of transthyretin amyloid cardiomyopathy (ATTR-CM)
- Discuss the clinical manifestations and diagnosis of ATTR-CM
- Compare the treatment options available for patients with ATTR-CM

Updates on ATTR-CM Disease State

Courtney M. Campbell, MD, PhD, FACC
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Dallas, TX

Amyloidosis
Pathophysiology and Epidemiology

Amyloidosis

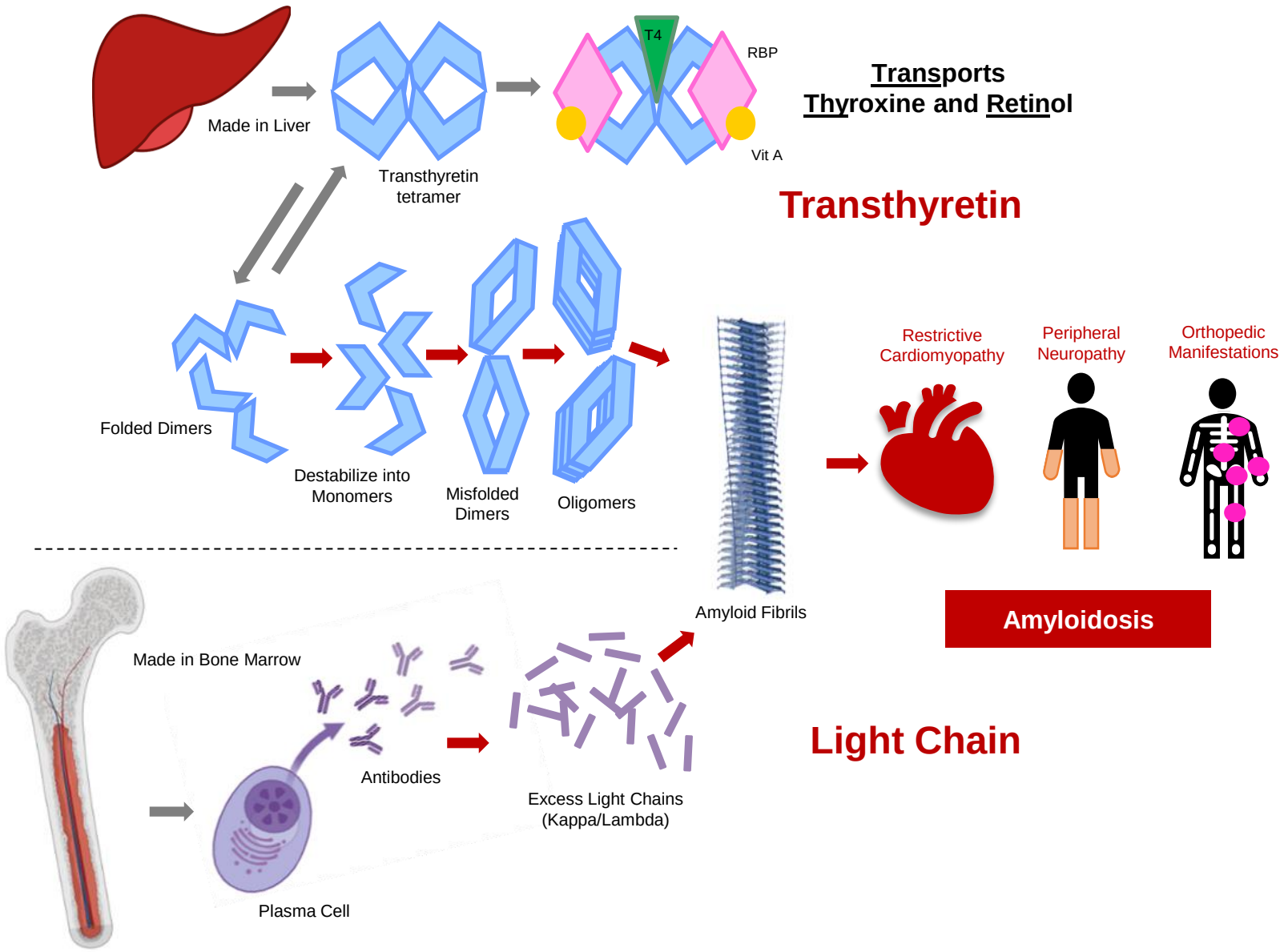
Rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by misfolded protein that accumulates as amyloid fibrils in multiple organs[1-5]

1. Hanna M. *Curr Heart Fail Rep.* 2014;11(1):50-57. 2. Mohty D, et al. *Arch Cardiovasc Dis.* 2013;106(10):528-540. 3. Adams D, et al. *Neurology.* 2015;85(8):675-682. 4. Maurer MS, et al. *Circ Heart Fail.* 2019;12(9):e006075. 5. Hawkins PN, et al. *Ann Med.* 2015;47(8):625-638.

Amyloidosis

- Amyloidoses are a heterogeneous group of disorders characterized by the deposition of insoluble protein aggregates (amyloid deposits) in tissues
- Amyloidosis can be
  - Acquired or inherited
  - Systemic or localized
  - Caused by >120 proteins
- Most common amyloidosis types that affect the heart
  - Light Chain and Transthyretin

Amyloidosis Pathophysiology



Addison D, et al. *J Am Heart Assoc.* 2021;10(9):e019840.

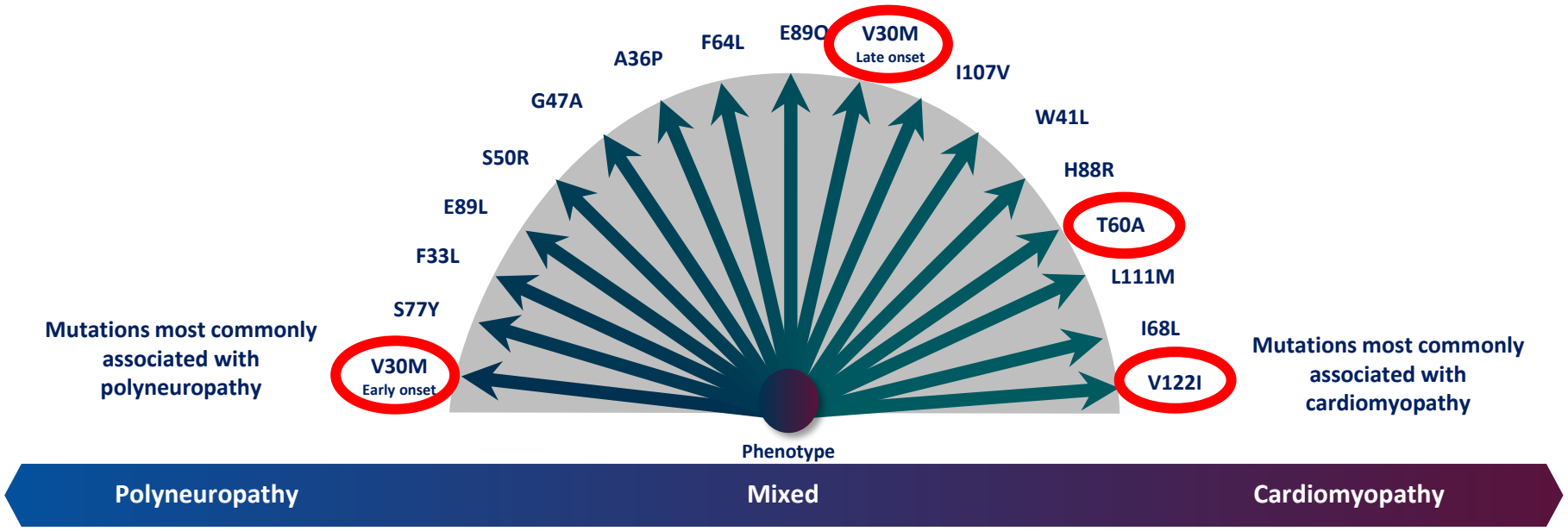
Amyloidosis Epidemiology

	AL	ATTR-wild type	ATTR-variant
Sex	M>F	M>>F	M>F
Age	• >65 years old	• 60-70 years old	• V122I: >65 years old • T60A: >45 years old • V30M: >50 years old
Prevalence and Incidence	• 40.5 cases per million; • 14.0 cases per million person-years	• Uncertain	• V122I – 3-4% African-Caribbean descent • T60A – 1% Northwest Irish descent • V30M – 0.1%, with Japan, Sweden, and Portugal predominance

Variant ATTR Amyloidosis

There are >120 *TTR* mutations that can result in hereditary ATTR amyloidosis[3]

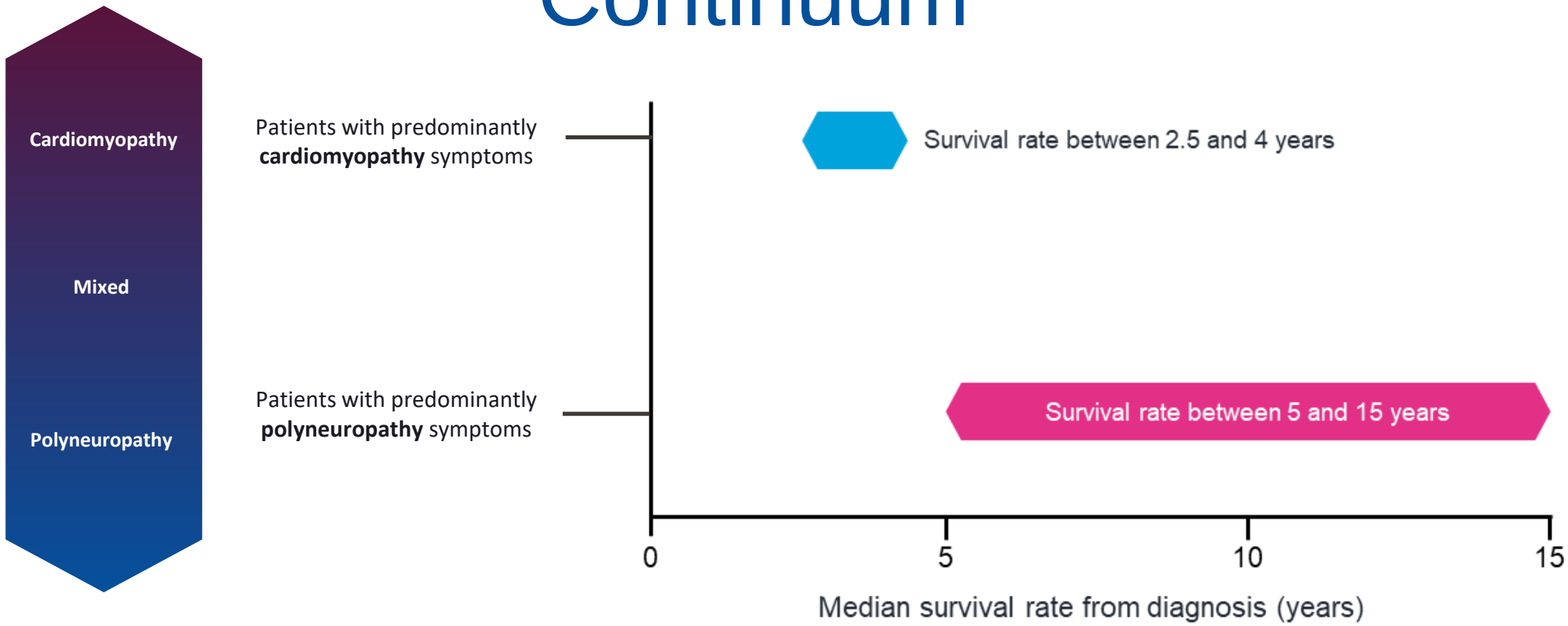
Possible genotypic–phenotypic association in hereditary ATTR amyloidosis[1,2]



Clinical manifestations can also vary among patients carrying the same genetic mutation[1]

1. Rapezzi C, et al. *Eur Heart J.* 2013;34(7):520-528. 2. Semigran MJ. *J Am Coll Cardiol*. 2016;68(2):173-175. 3. Sekijima Y. *J Neurol Neurosurg Psychiatry*. 2015;86(9):1036-1043.

Survival Rates Vary Across the Disease Continuum

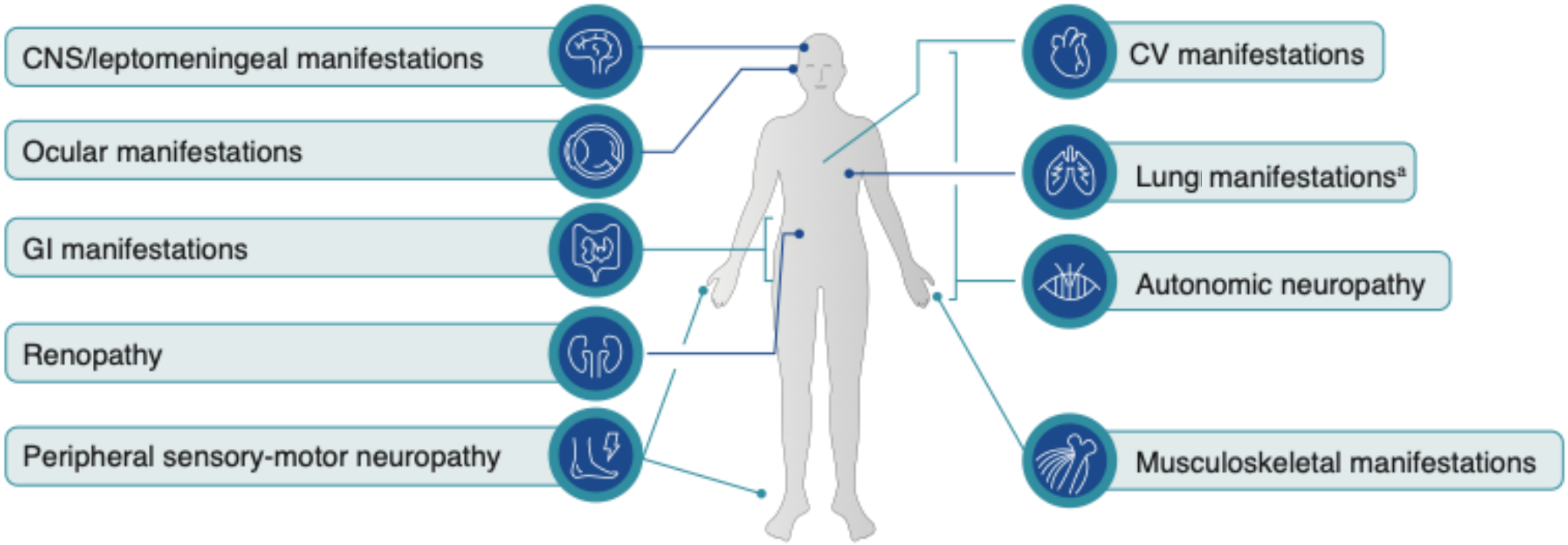


Early diagnosis will become increasingly important in improving patient outcomes

Hawkins PN, et al. *Ann Med*. 2015;47(8):625-638.

Recognizing Amyloidosis

Possible Constellation of Symptoms in Patients With Amyloidosis



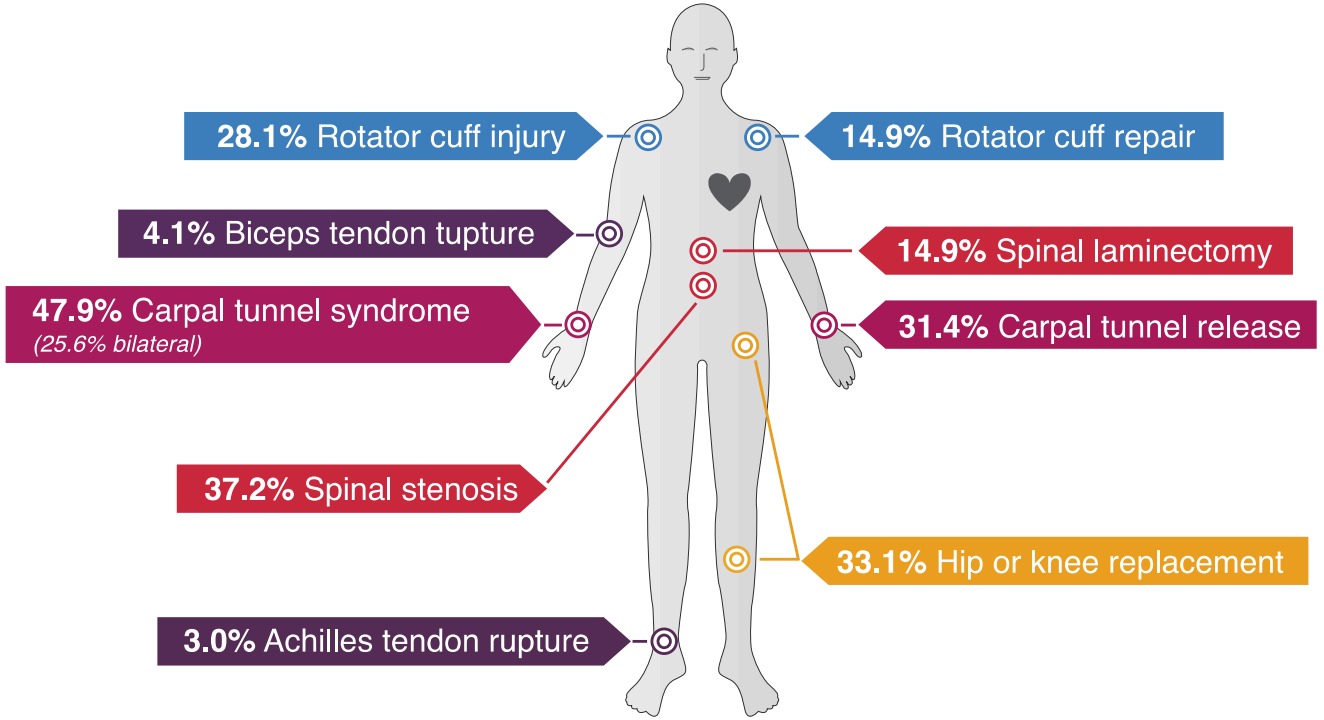
[a]Individual case reports.
CNS, central nervous system; CV, cardiovascular; GI, gastrointestinal.
Nativi-Nicolau JN, et al. *Heart Fail Rev*. 2022;27(3):785-793.

Amyloidosis Symptoms Overlap With Common Diagnoses

Manifestations of ATTR amyloidosis[1-3]	Potential misdiagnoses/misattributions
Cardiac hypertrophy	Hypertension[3]
Neuropathy	Diabetes[3]
Carpal tunnel syndrome	Repetitive motion or wrist injury[4]
Back pain and joint issues	Aging or injury[5-7]
Indigestion	Acid reflux[8]
Constipation	Poor diet or medication side effect[9-11]

1. Conceição I, et al. *J Peripher Nerv Syst.* 2016;21:5-9. 2. Nativi-Nicolau, et al. *Heart Fail Rev.* 2022;27(3):785-793. 3. Gertz, et al. *BMC Fam Pract.* 2020;21(1):198. 4. Genova, et al. *Cureus.* 2020;12(3):e7333. 5. Wong, et al. *Scoliois Spinal Disord.* 2017;12:14. 6. El Sayed M, Callahan AL. Mechanical back strain. *StatPearls [Internet].* https://www.ncbi.nlm.hih.gov/books/NBK542314. 7. Havelin, King. *Curr Osteoporos Rep.* 2018;16(6):763-771. 8. Clarett. *Mo Med.* 2018;115(3):214-218. 9. Rollet, et al. *Nutrients.* 2022;14(1):122. 10. Nelson, Camilleri. *Ther Adv Gastroenterol.* 2015;8(4):206-220. 11. Fragakis, et al. *Int J Environ Res Public Health.* 2018;15(2):226.
ATTR, transthyretin amyloidosis.

Frequency of Orthopedic Diagnoses and Procedures Amongst Patients With Cardiac Amyloidosis (n = 116)



74% Orthopedic diagnosis

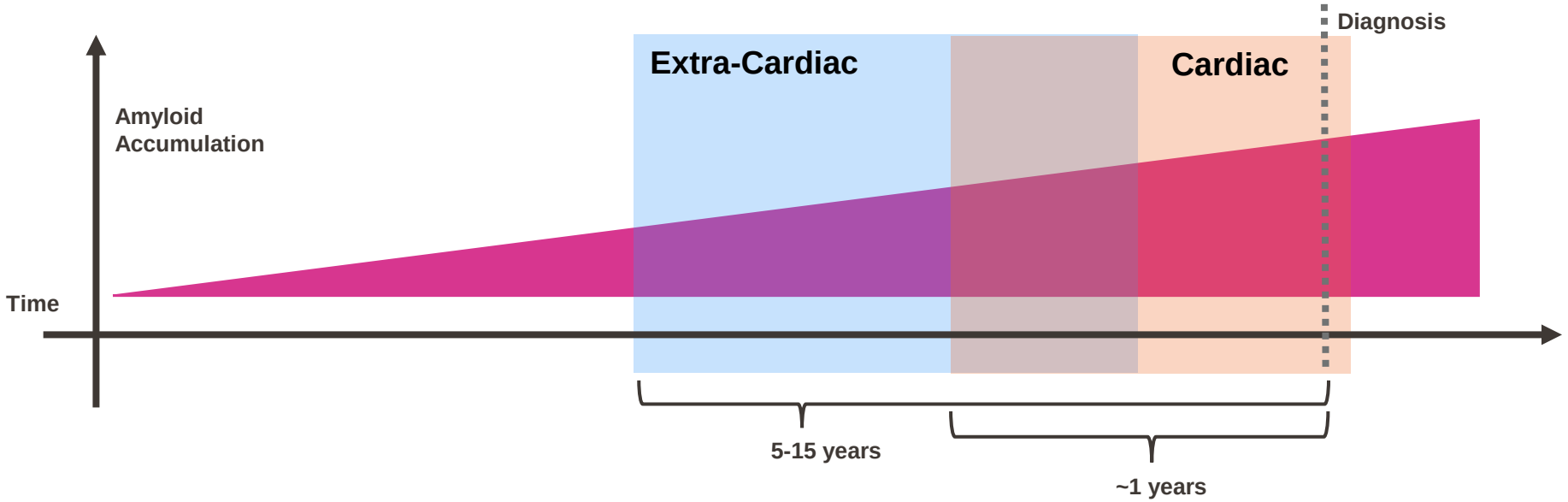
57% Orthopedic procedure
(37% with 2+ orthopedic procedures)

General Population Prevalence by age 70:

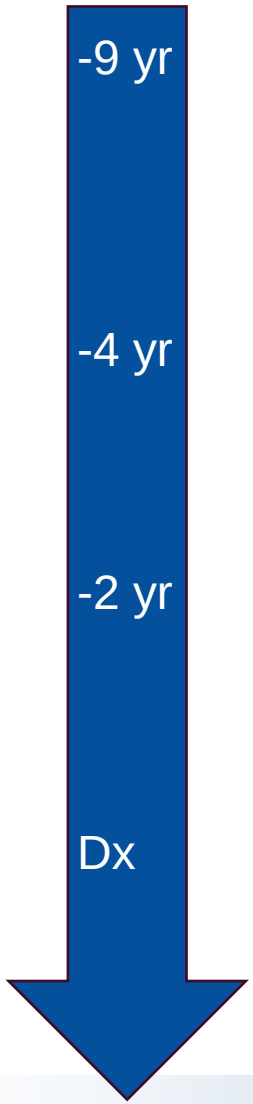
- Knee Replacement	7%
- Hip Replacement	3%
- Spinal Stenosis	0.1%
- Carpal Tunnel Syndrome	5%

Campbell, et al. 2020 ISA Congress.

Amyloidosis Progresses Over Years



71M Diagnosed With ATTR-wt Amyloidosis



MSK
Bilateral biceps tendon tear

Bilateral carpal tunnel release
Rotator cuff injury

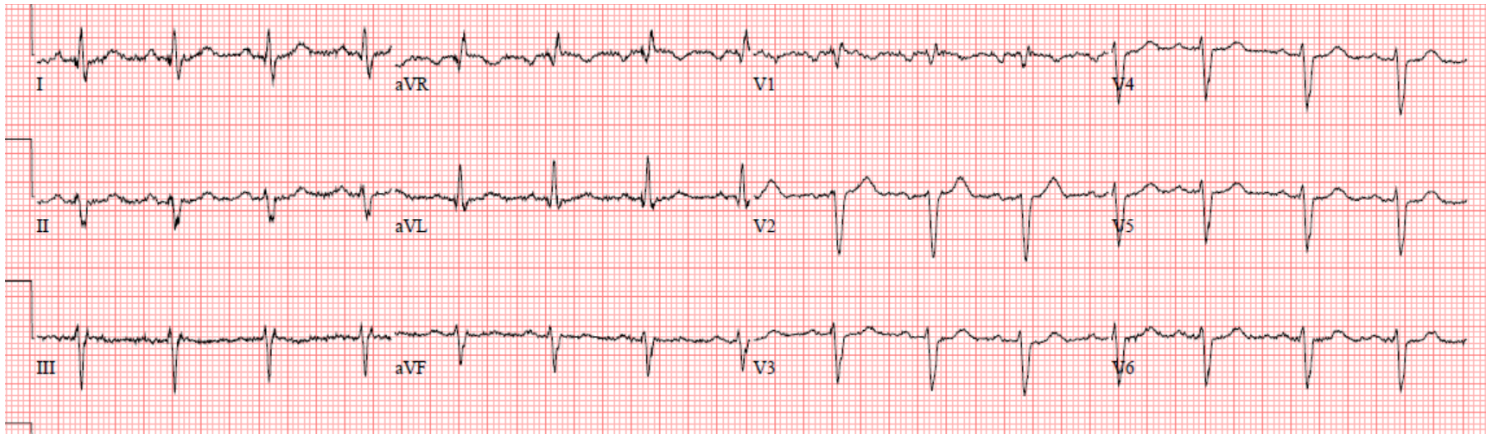
Left hip replacement

Cardiac

Shortness of breath
Decreased exercise capacity

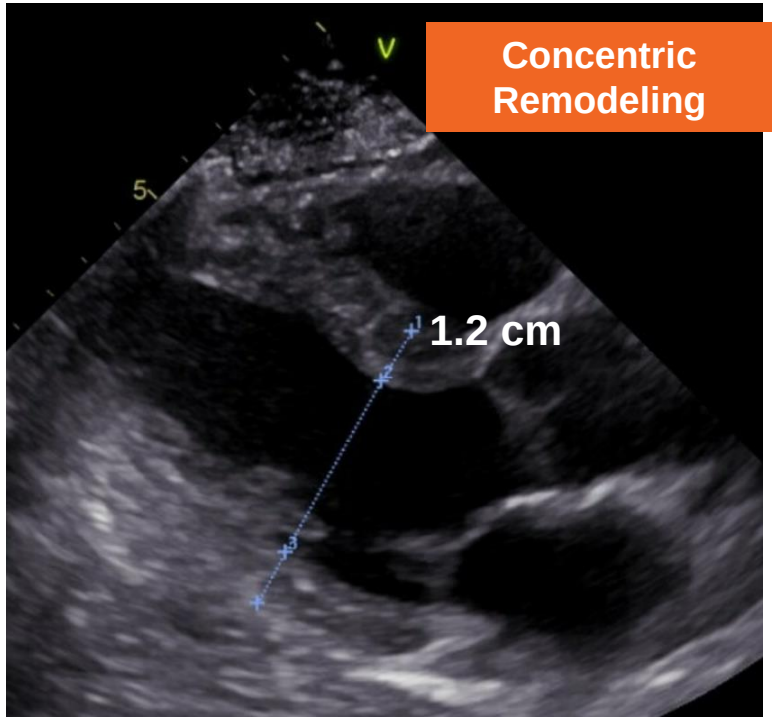
Recognizing Early Amyloid Cardiomyopathy

Electrocardiogram



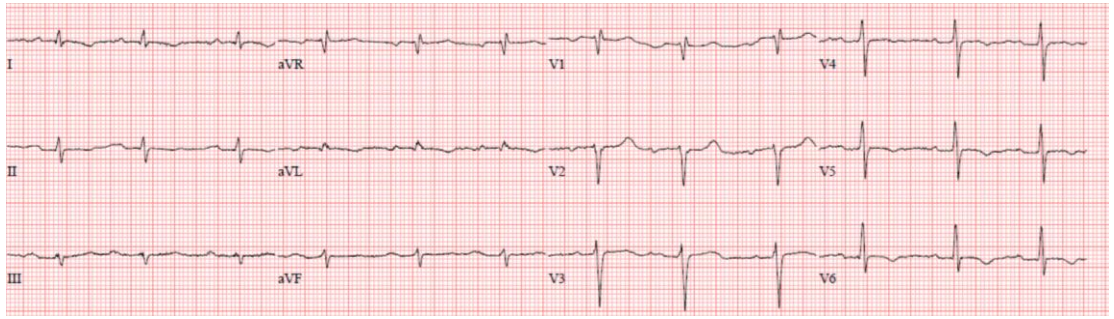
Normal Voltage

Transthoracic Echocardiogram



Red Flags for Late Amyloid Cardiomyopathy

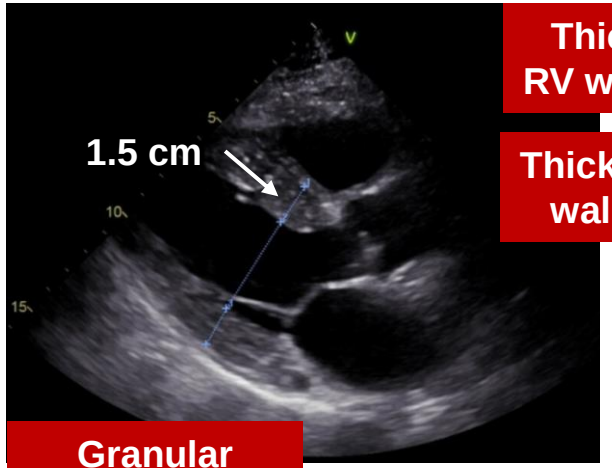
Electrocardiogram



Low Voltage Limb Leads

Lateral Lead Voltage Normal, despite LVH

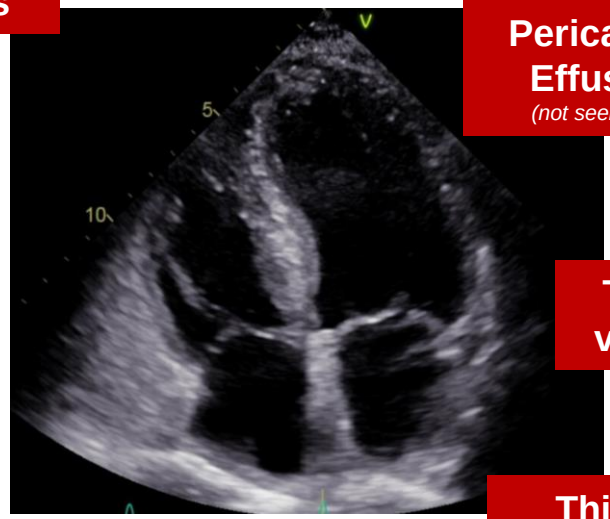
Transthoracic Echocardiogram



Thick RV walls

Thick LV walls

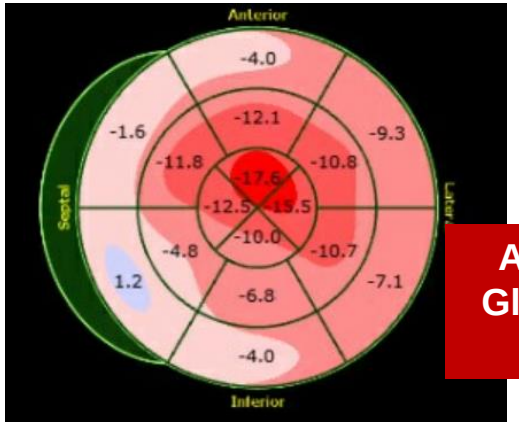
Granular 'sparkling' appearance



Pericardial Effusion *(not seen here)*

Thick valves

Thick Intra-atrial septum



Apical Sparing on Global Longitudinal Strain

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Diagnosing Amyloidosis

Amyloidosis Diagnosis Algorithm

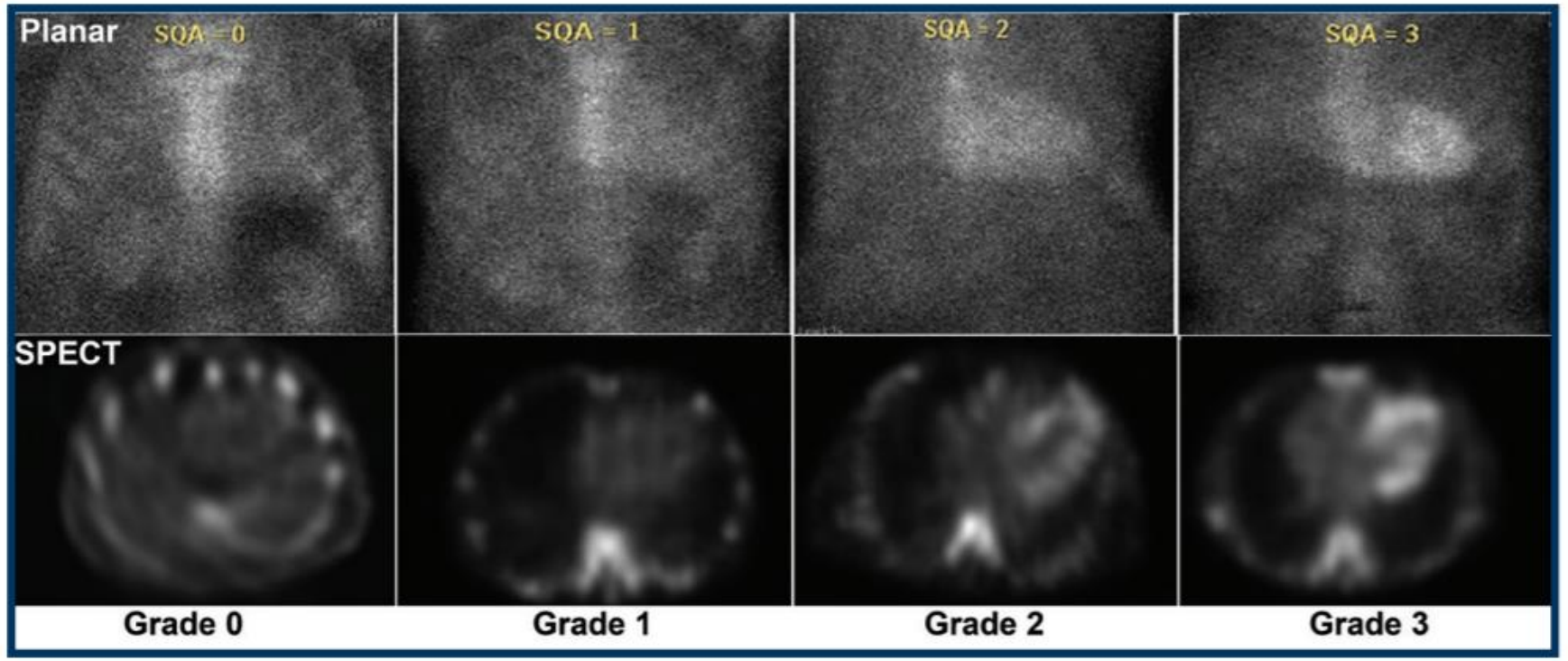
1. Check labs to rule out light chain amyloidosis
   - Free light chains, serum and urine protein electrophoresis and immunofixation (SPEP/UPEP)
2. If labs are negative, technetium-99 nuclear pyrophosphate scan (PYP)
   - If PYP is positive, genetic testing for variant ATTR
   - If PYP is equivocal, consider cardiac biopsy and mass spectrometry for a definitive diagnosis

   - *70-80% of patients can be diagnosed with non-invasive approach*

Gillmore JD, et al. *Circulation.* 2016;133:2404-2412.

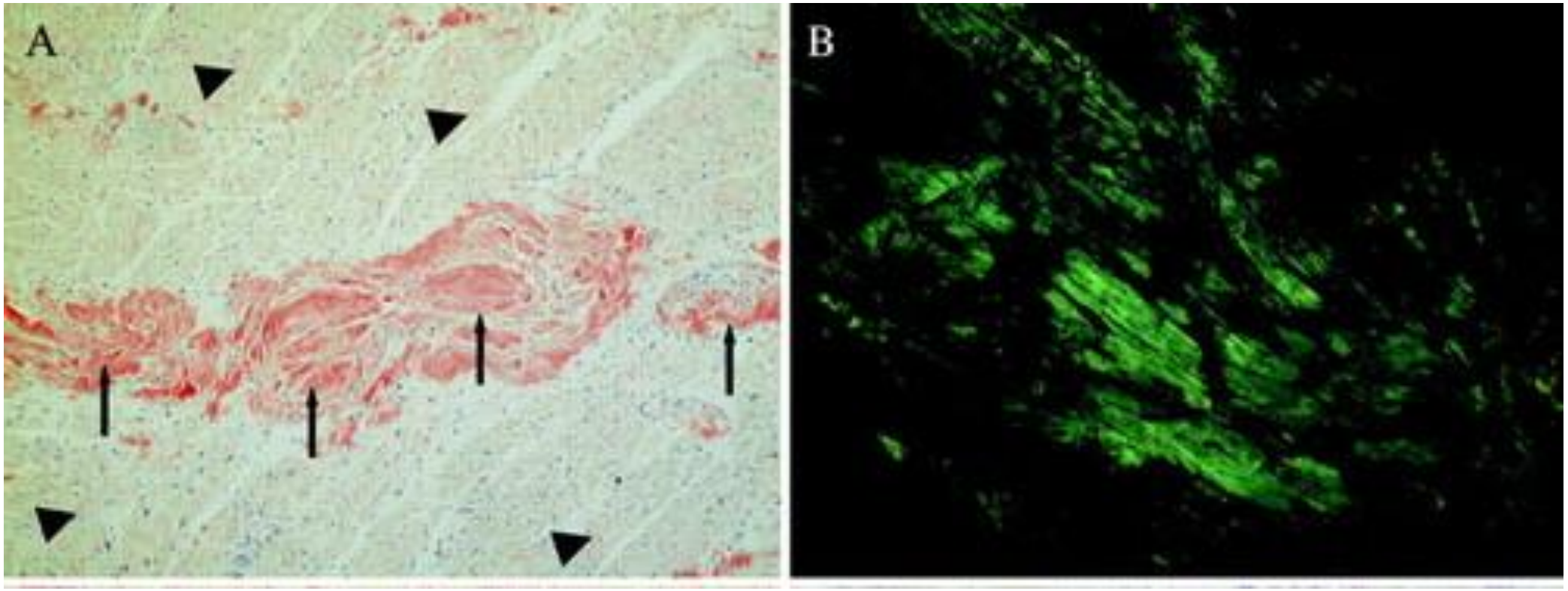
Pyrophosphate (PYP) Scan

Figure 2. Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images



American Society of Nuclear Medicine. ASNC Cardiac Amyloidosis Practice Points. Accessed April 19, 2024. https://www.asnc.org/files/19110%20ASNC%20Amyloid%20Practice%20Points%20WEB(2).pdf

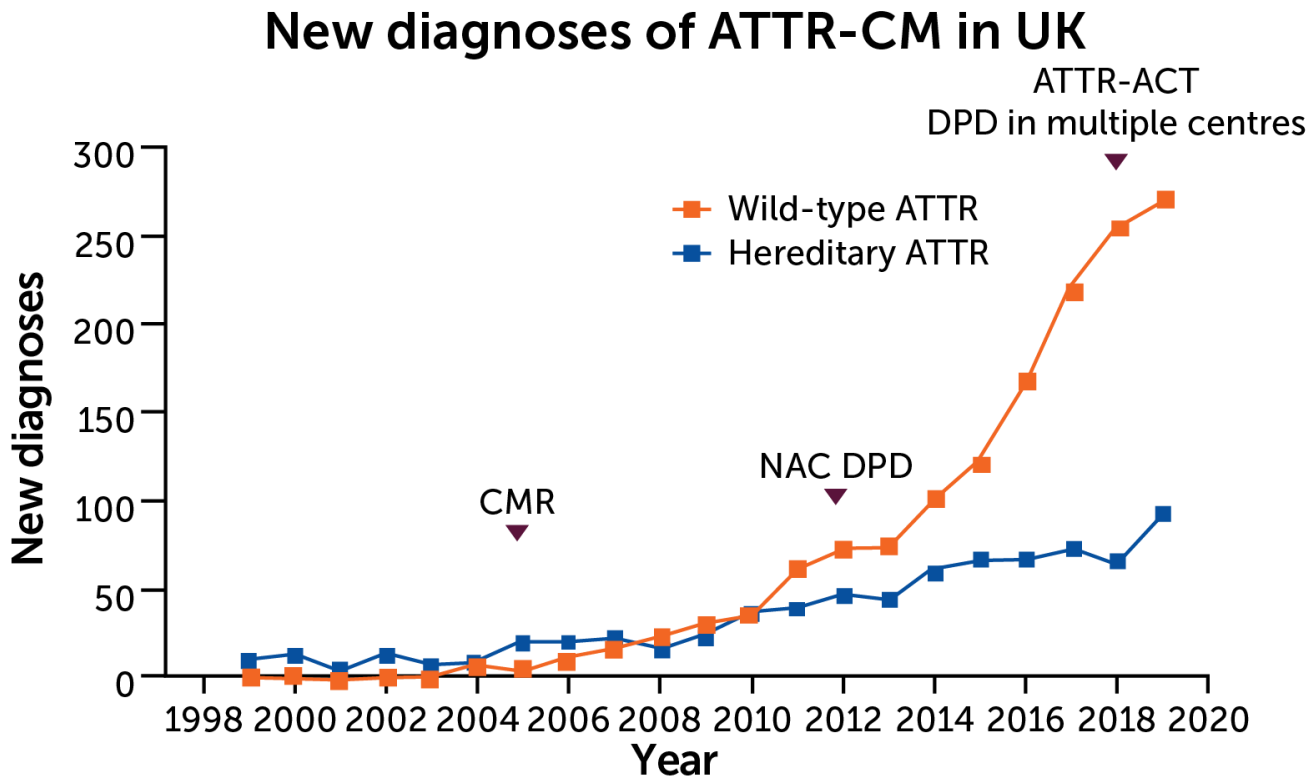
Congo Red Staining of Affected Organ is the GOLD standard for Amyloidosis Diagnosis



Maceira AM, et al. *Circulation*. 2005;111(2):186-193.

Amyloidosis Is Under Recognized!

Increasing Recognition of ATTR Amyloidosis

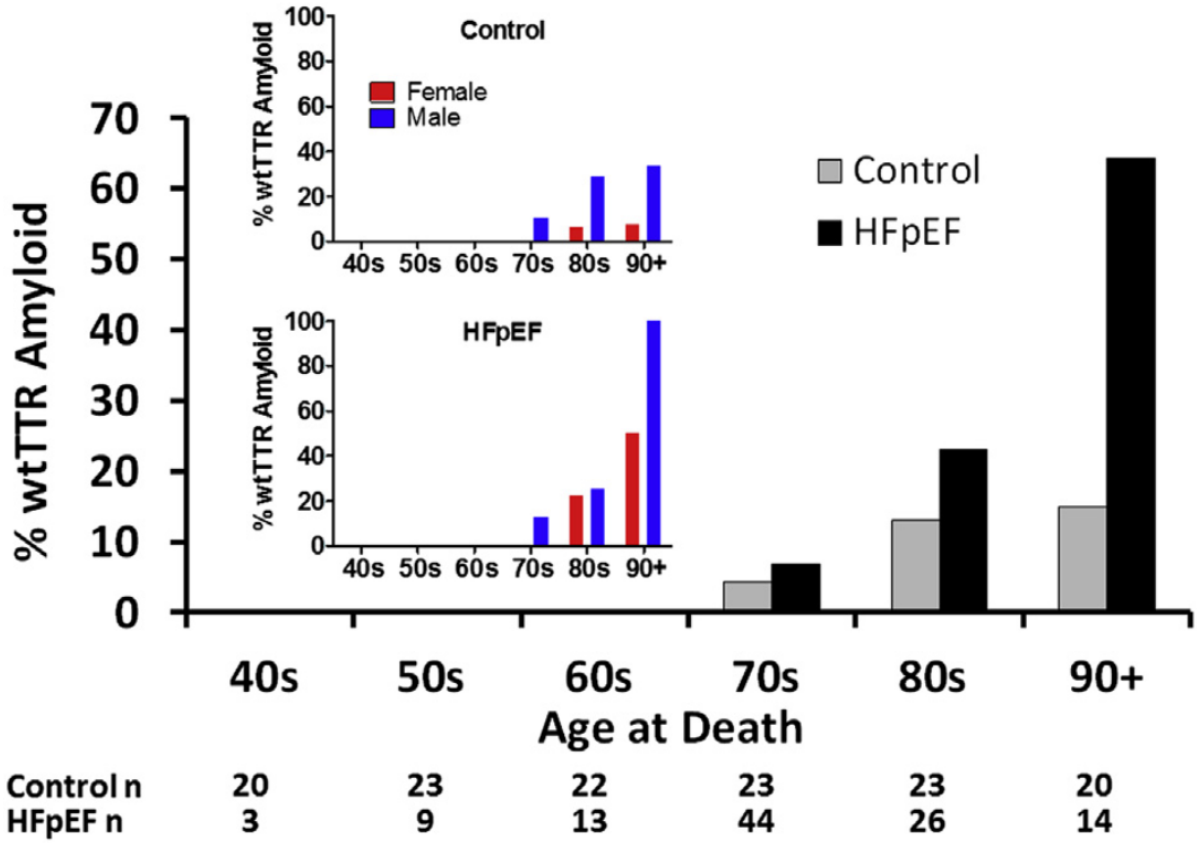


1. Donnelly JP, Hanna M. *Cleve Clin J Med*. 2017;84(12 Suppl 3):12-26. 2. Lane T, et al. *Circulation*. 2019;140(1):16-26. 3. Pinney JH, et al. *J Am Heart Assoc*. 2013;2(2):e000098. 4. Tanskanen M, et al. *Ann Med*. 2008;40(3):232-239. 5. Rowczenio D, et al. Presented at: First European Meeting for ATTR Amyloidosis for Doctors and Patients; Paris, France; November 2-3, 2017. Poster P1.

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiovascular magnetic resonance; CTS, carpal tunnel syndrome; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; HF, heart failure; NAC, National Amyloidosis Centre; TTR, transthyretin.

ATTR-wt Prevalence

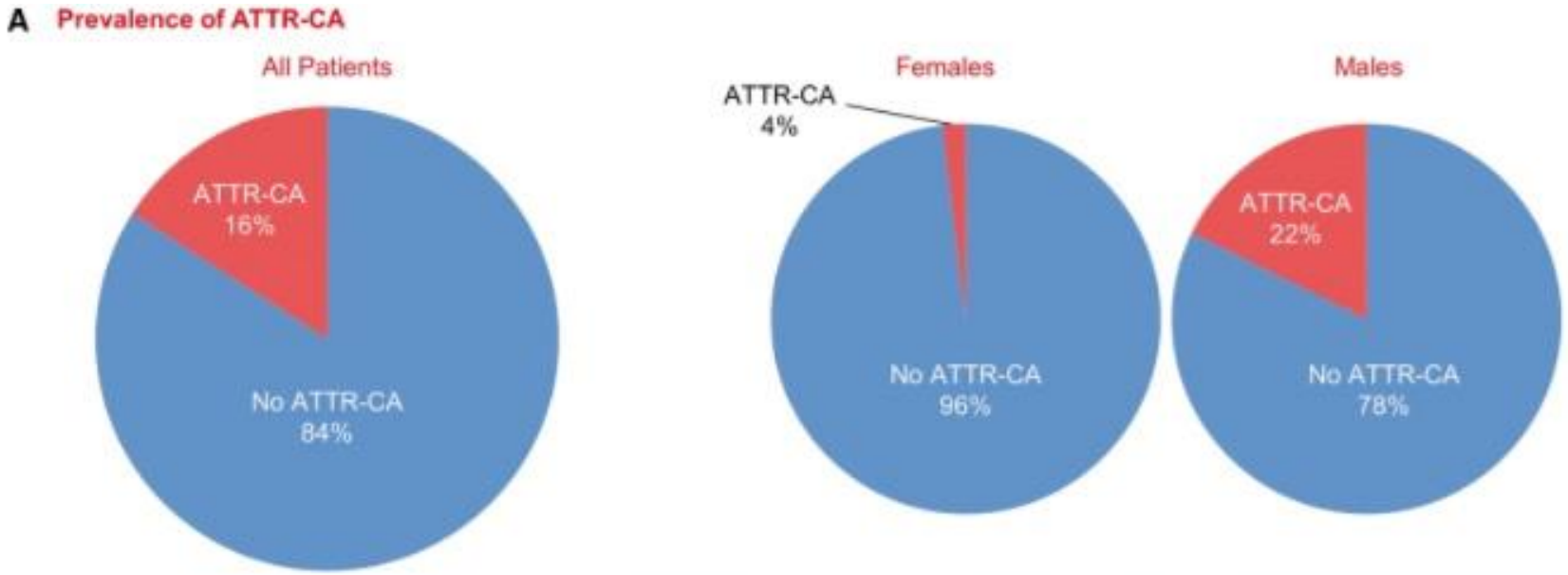
- Reviewed autopsies from:
  - 109 patients with antemortem diagnosis of HFpEF without any clinical suspicion of amyloidosis
  - Age-matched control patients without antemortem HF diagnosis
- Blinded pathology review



Adapted from Mohammed SF, et al. *J Am Coll Cardiol HF*. 2014;2:113-122.

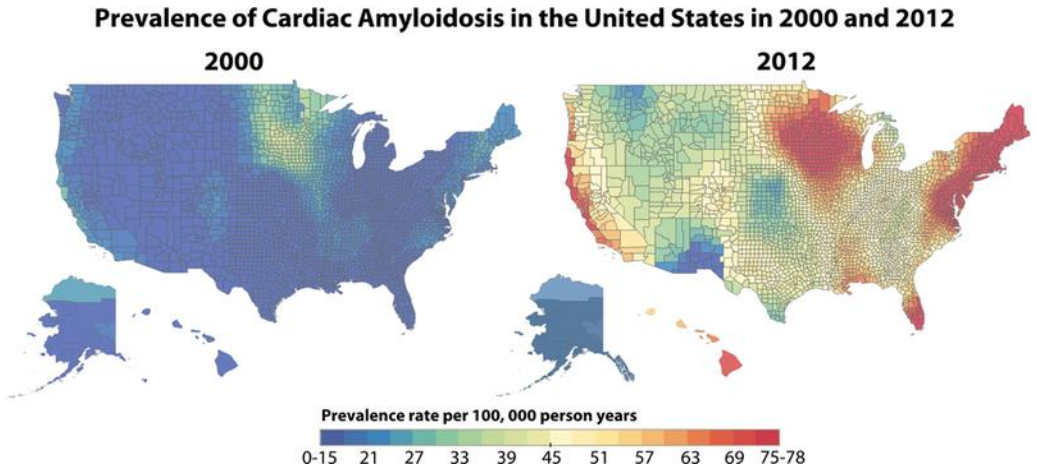
ATTR in TAVR Patients

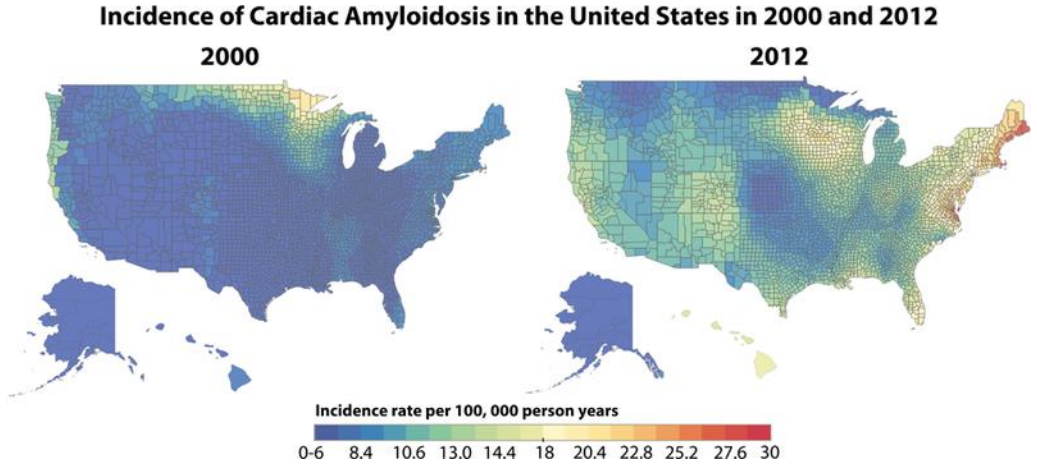
- 151 patients referred for TAVR, 68% men, mean age 84 years
  - PYP scans performed on all
- Results: High incidence of undiagnosed ATTR amyloidosis!



Castaño A, et al. *Eur Heart J.* 2017;38:2879-2887.

Geographic Disparities of Cardiac Amyloidosis



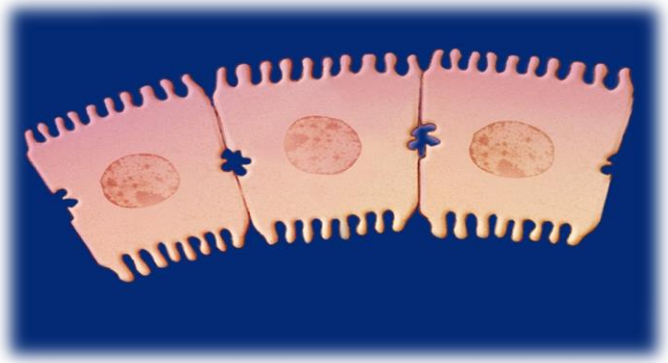


- Age-adjusted amyloidosis-related death rate per 1M people:
  - Mower County, MN: 31.73
  - Olmsted County, MN: 25.45
  - National average: 4.95

1. Gilstrap LG, et al. *Circ Heart Fail.* 2019;12(6):e005407. 2. Data adapted from Ron Witteles.

Amyloidosis Treatment Strategies

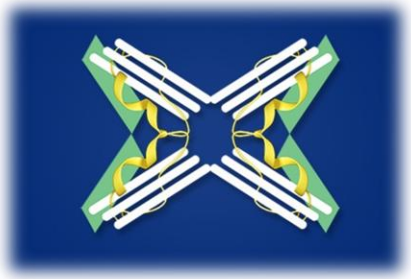
TTR Amyloid Treatment Options



Liver – Stop production

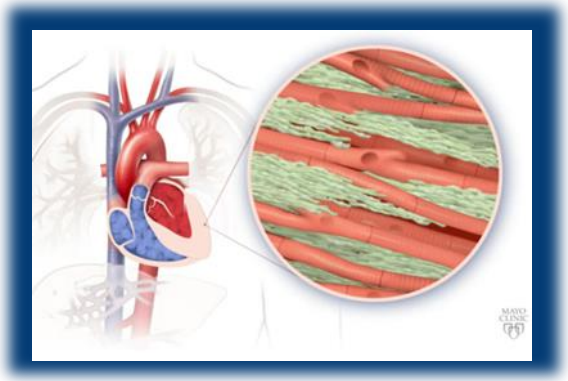
RNA silencer therapy
Patisiran[1], Inotersen[1],Vutrisiran[1,4]
Eplontersen[4,5]

CRISPR -DNA – gene editing
NTLA-2001[4]



Stabilize protein

Tafamidis[2]
Diflunisal[3]
Acoramidis[5]

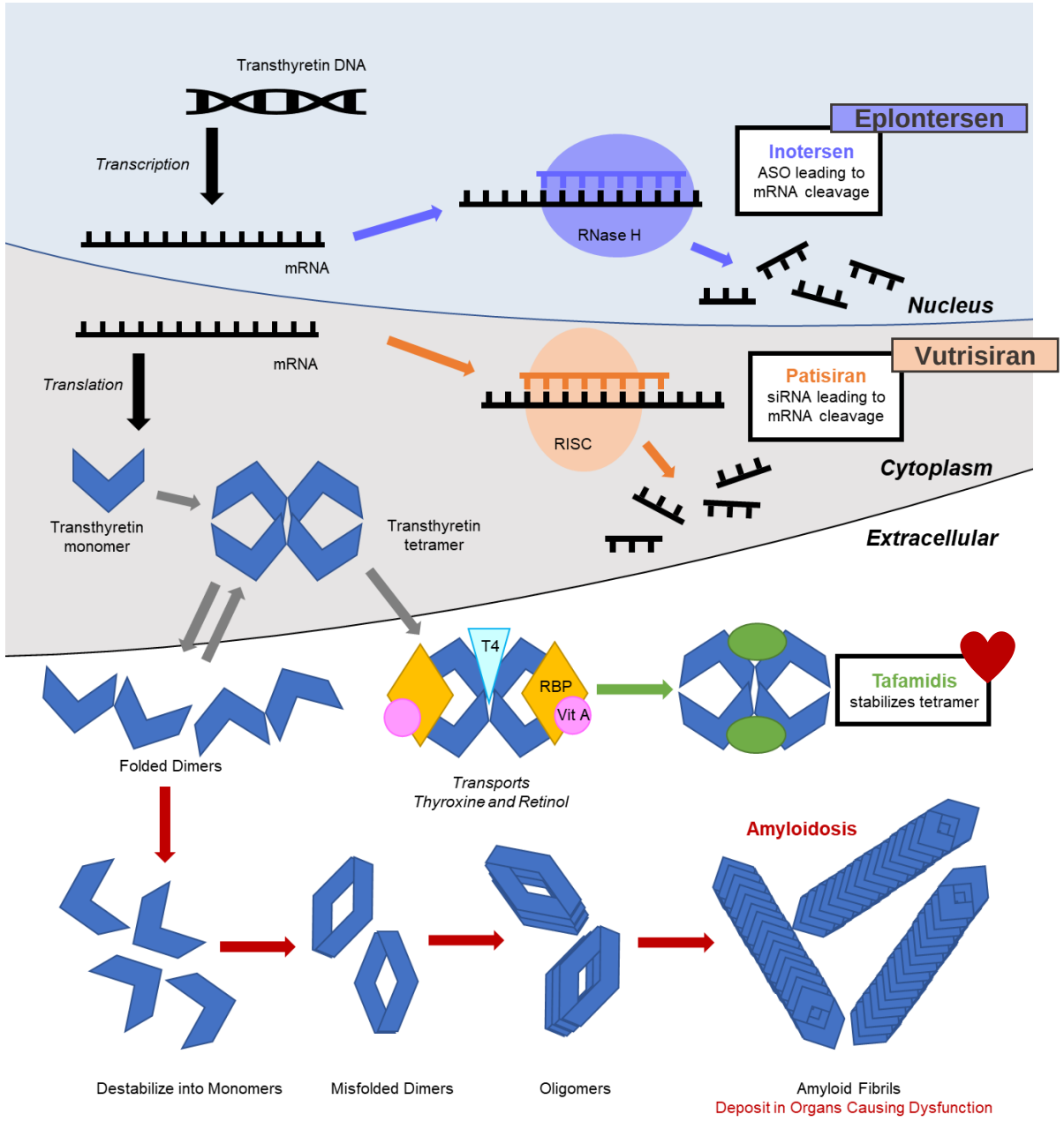


Amyloid Fibril Depleter

Monoclonal antibody
NNC6019-0001[4], N1006[4,]
AT-02[4]

[1]FDA approved, ATTRm neuropathy. [2]FDA approved for ATTR-cardiac. [3]Clinical trial – neuropathy. [4]Clinical trials for ATTR-cardiac in progress or development.
[5]FDA submission/decision pending.

FDA-Approved ATTR Therapy in 2023



Judge DP, et al. *J Am Coll Cardiol*. 2019;74(3):285-295.

Summary

- Cardiac ATTR amyloidosis is emerging as an underdiagnosed cause of heart failure
- Increased awareness, transformation in the diagnostic imaging pathways, and availability of disease-modifying treatment has led to an exponential increase in the diagnosis
- The exponential increase in diagnosis has also been associated with earlier clinical phenotype – a dramatic change in clinical phenotype over the last 20 years, with patients now presenting at an earlier stage, better functional phenotype, better prognosis
- Evolution from a largely unrecognized and unmanaged disease to early diagnosis, early treatment initiation, effective management and monitoring, lower disability, and improved survival

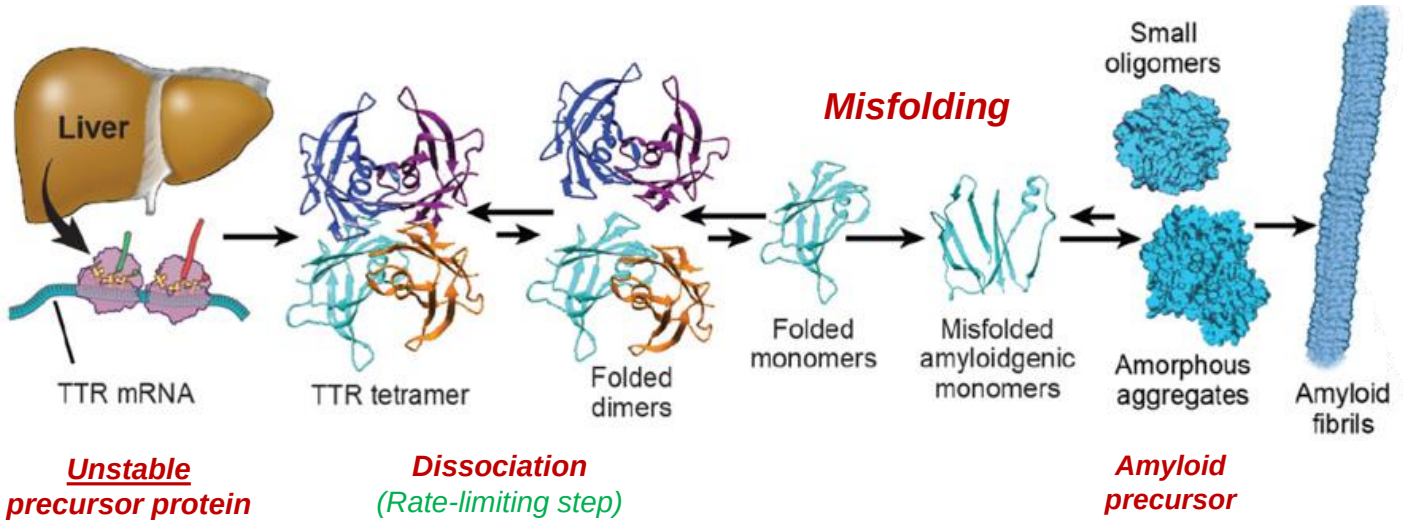
Clinical Trials in ATTR-CM

Dejan Landup, PharmD, HF-Cert
Cardiovascular Clinical Pharmacist
Heart Failure and Chronic Disease Management Clinic
Advocate Medical Group - Evergreen Center
Chicago, IL

Transthyretin at the Molecular Level

Transthyretin

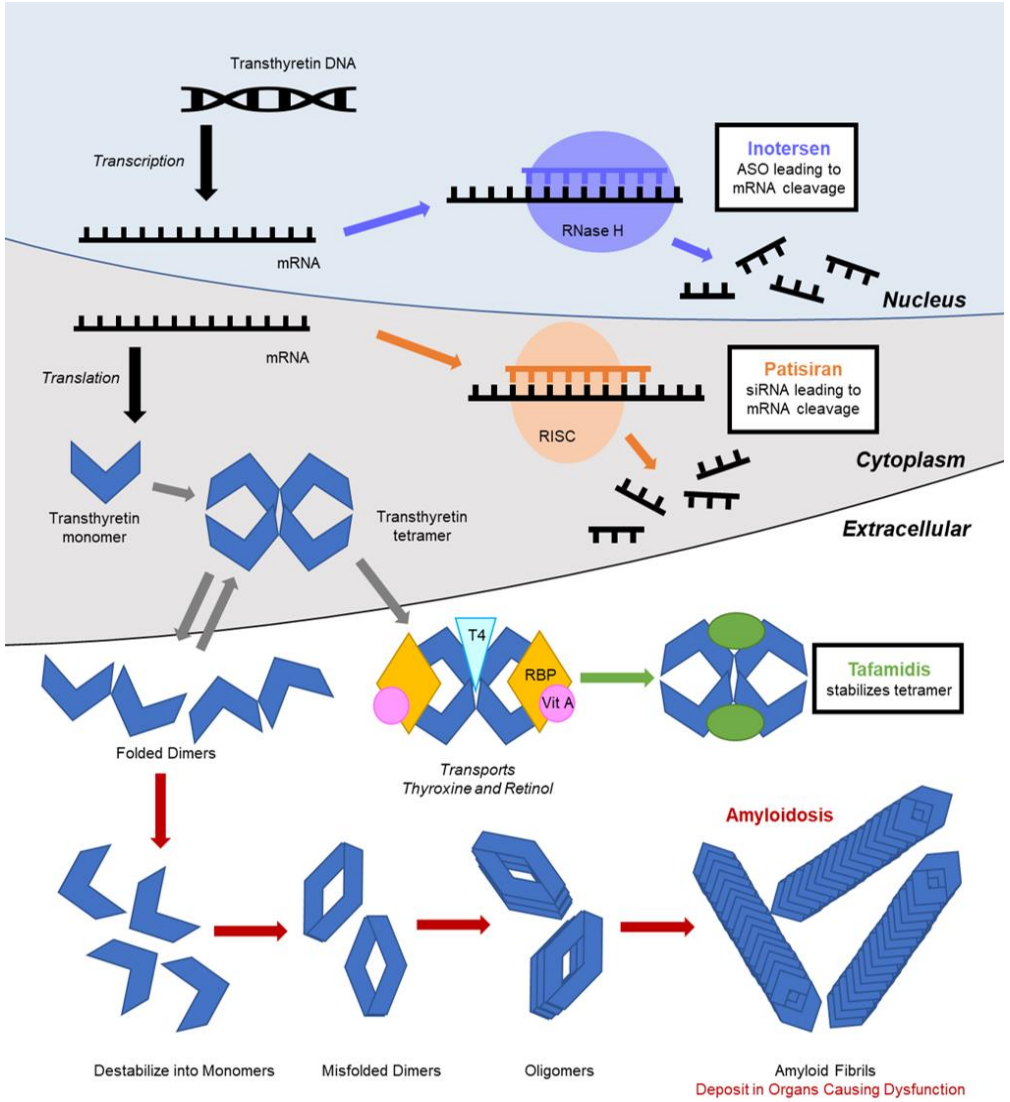
- Homotetrameric protein predominantly produced in the liver responsible for transport of thyroxine and retinol-binding protein
- Intrinsically amyloidogenic
  - ATTRwt → TTR dissociation in the absence of a known gene mutation
  - ATTRv → genetic mutations lead to a dysfunctional TTR protein facilitating dissociation and amyloidogenesis
    - > More than 120 mutations identified
    - > Certain mutations (T119M) are protective and reduce dissociation rate of tetrameric TTR
      - Basis for drug development → acoramidis mechanism of binding mimics protective effects of T119M
- Current and emerging therapies all target various steps in the amyloidogenic process



ATTR-CM occurs when normally soluble transthyretin dissociates, misfolds, aggregates, and deposits as insoluble amyloid fibrils in the myocardium

ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; TTR, transthyretin.

Kittleson MM, et al. *Circulation*. 2020;142:e7-e22.Yee AW, et al. *Nat Commun*. 2019;10(1):925.



Pathogenic TTR mutations destabilize the native tetramer:

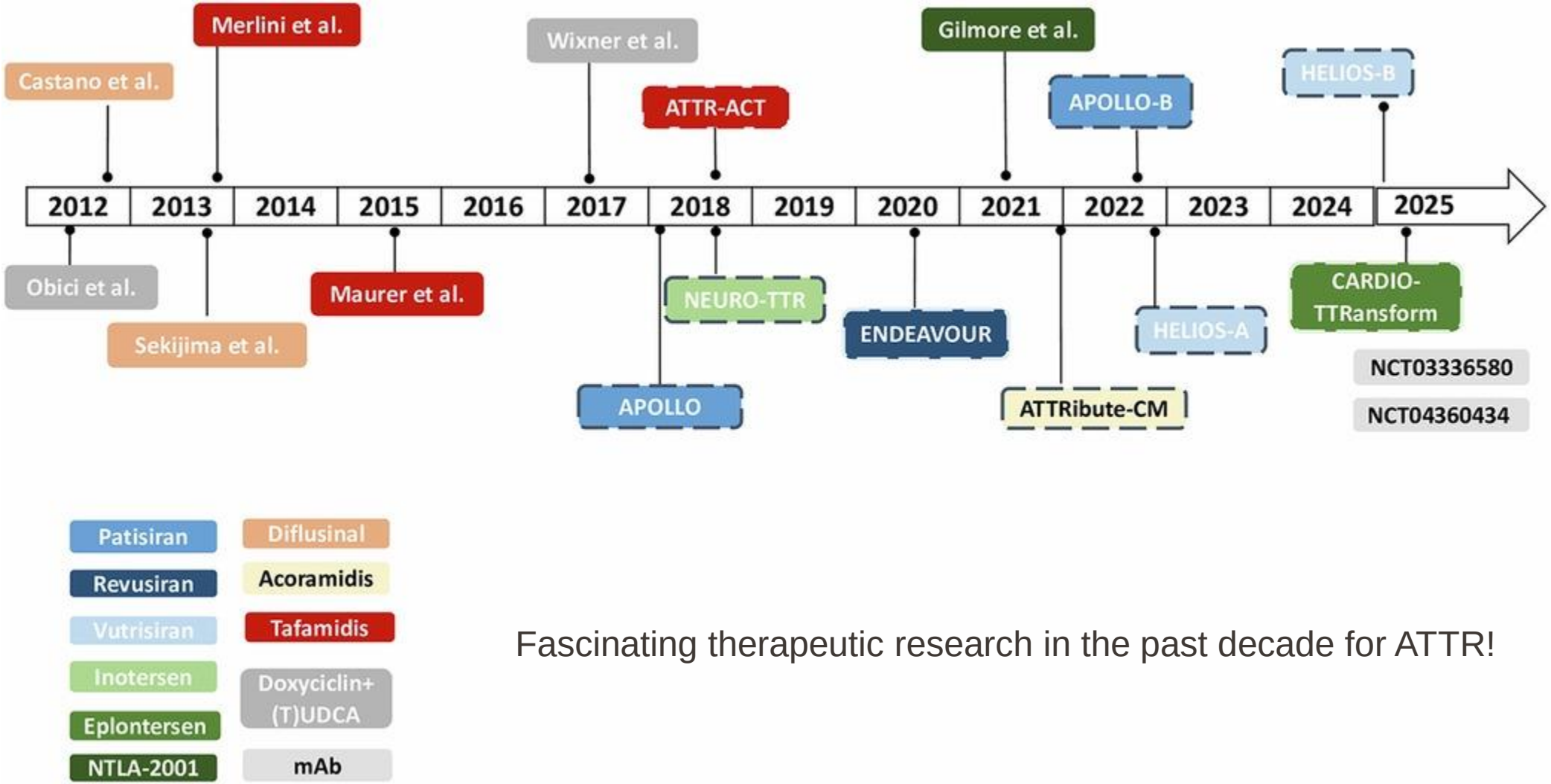
1. The more destabilizing the mutation, the more penetrant and severe the phenotype
2. V122I variant dissociates approximately twice as rapidly as wild-type TTR, is associated with more aggressive ATTR-CM compared with wild type, and is associated with lower circulating TTR levels

T119M:

1. Protects carriers from the disease
2. Reduces the dissociation rate of tetrameric TTR
3. Likely due to the formation of hydrogen bonds between neighboring serine residues at position 117 of each monomer
4. T119M carriers have on average 20% higher serum TTR levels, are at lower risk of cerebrovascular events, and live 5 to 10 years longer compared with the general population

By preventing dissociation of the tetramer, stabilizers are predicted to reduce the rate of generation of unstable monomers, thereby slowing or halting ATTR disease progression

Judge DP, et al. *J Am Coll Cardiol*. 2019;74(3):285-295.



Fascinating therapeutic research in the past decade for ATTR!

Tomasoni D, et al. *Front Cardiovasc Med*. 2023;10:1154594.

Disease Modifying Treatment in ATTR-CM

Prevent formation of TTR[#]

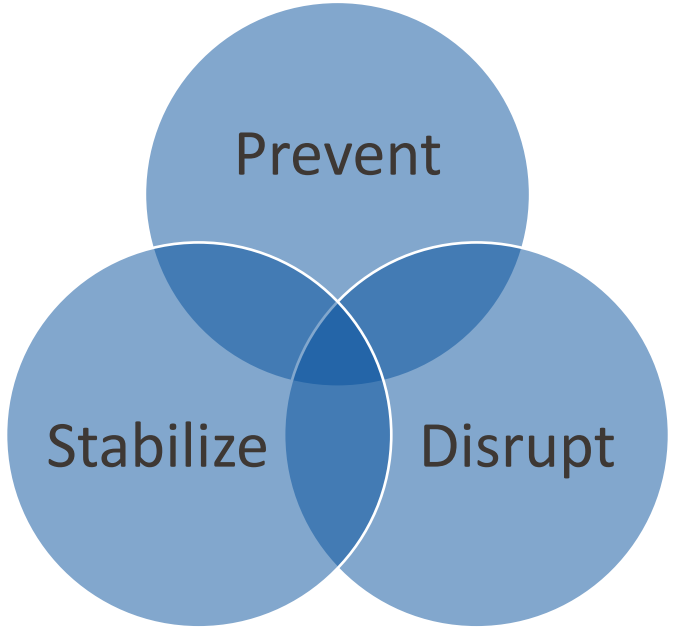
Small interfering RNA (siRNA)
Antisense oligonucleotides (ASOs)
CRISPR-Cas9 in vivo gene editing

Stabilize TTR protein

Tafamidis[1]
Diflunisal[2]
Acoramidis

Disrupt deposited amyloid fibrils

Doxycycline + TUDCA/UDCA
Monoclonal antibodies



[#]*Serum TTR (prealbumin) levels can be measured and will change in response to disease-modifying treatment; TTR levels will ↓ with TTR silencing therapies and ↑ with TTR stabilizer treatment.*

APOLLO-B[*] *(patisiran)*
Cardio-TTRansform[+] *(eplontersen)*
HELIOS-B[+] *(vutrisiran)*
NTLA-2001[^]

ATTR-ACT[*] *(tafamidis)*
ATTRibute-CM[*] *(acoramidis)*

NNC6019-0001 (PRX004)[^]
NI006 (NI301A)[^]
AT-02[^]

[*]*Phase 3 trials completed*
[+]*Ongoing phase 3 clinical trials*
[^]*Early phase trials at various stages of development*

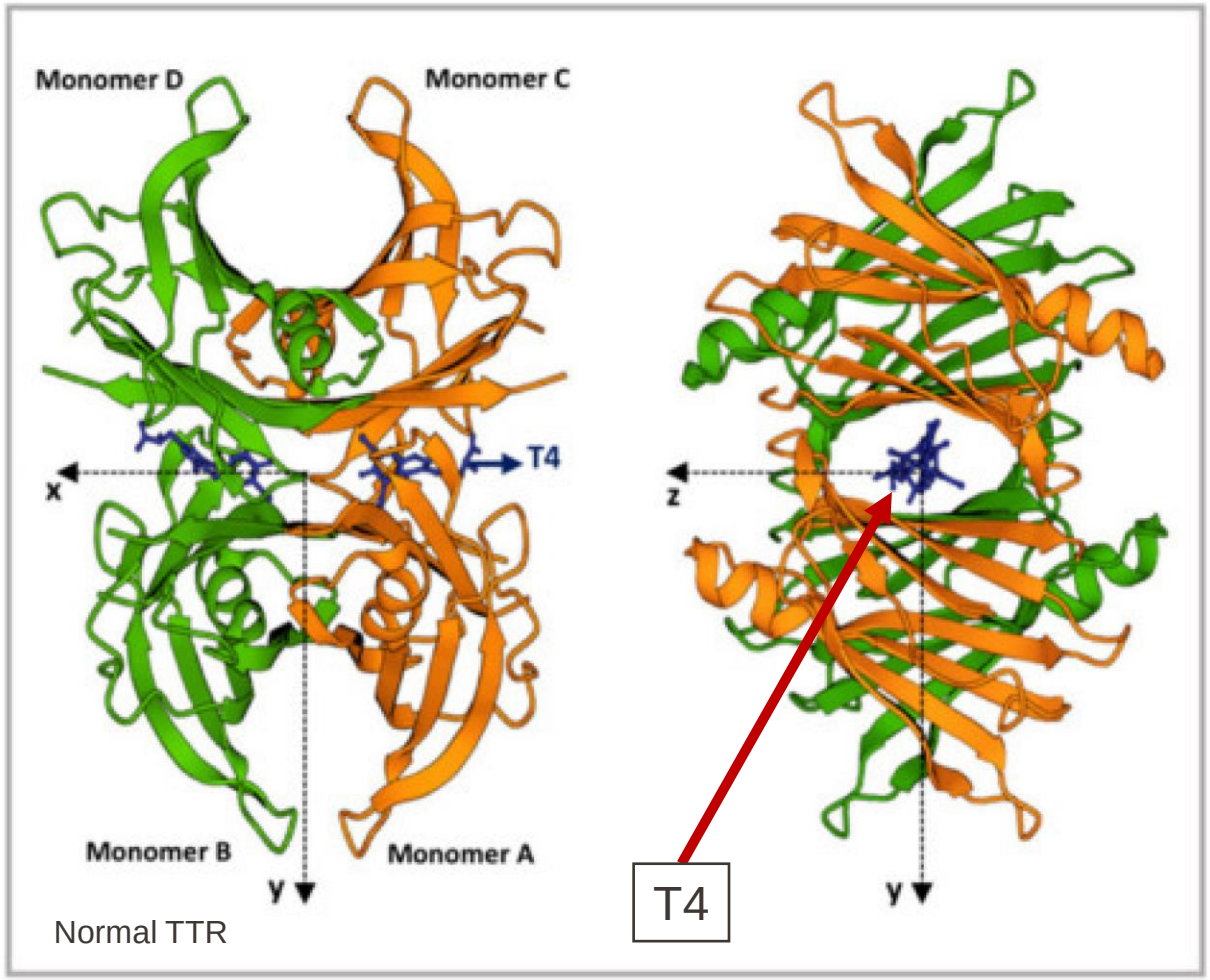
[1]FDA-Approved for ATTR-CM
[2]Generic NSAID. Occasionally used off-label for ATTR-CM in select cases

Maurer MS. *Am J Cardiol*. 2022;185(Suppl 1):S23-S34.
Maurer MS, et al. *JAMA*. 2024;331(9):778-791.

ATTR-CM, transthyretin amyloid cardiomyopathy; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease system; NSAID, nonsteroidal anti-inflammatory drug; RNA, ribonucleic acid; TTR, transthyretin; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

TTR Stabilizers: Mechanism of Action

- Prevent TTR tetramers from dissociating by binding to the T4-binding site on TTR (eg, tafamidis, diflunisal)
- Mimic the stabilizing effect of TTR variant T119M likely by forming hydrogen bonds with Ser117 TTR monomers (eg, acoramidis)



Judge DP, et al. *J Am Coll Cardiol*. 2019;74(3):285-295

Tafamidis in ATTR-CM: ATTR-ACT

***Objective**: Evaluate the safety and efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy*

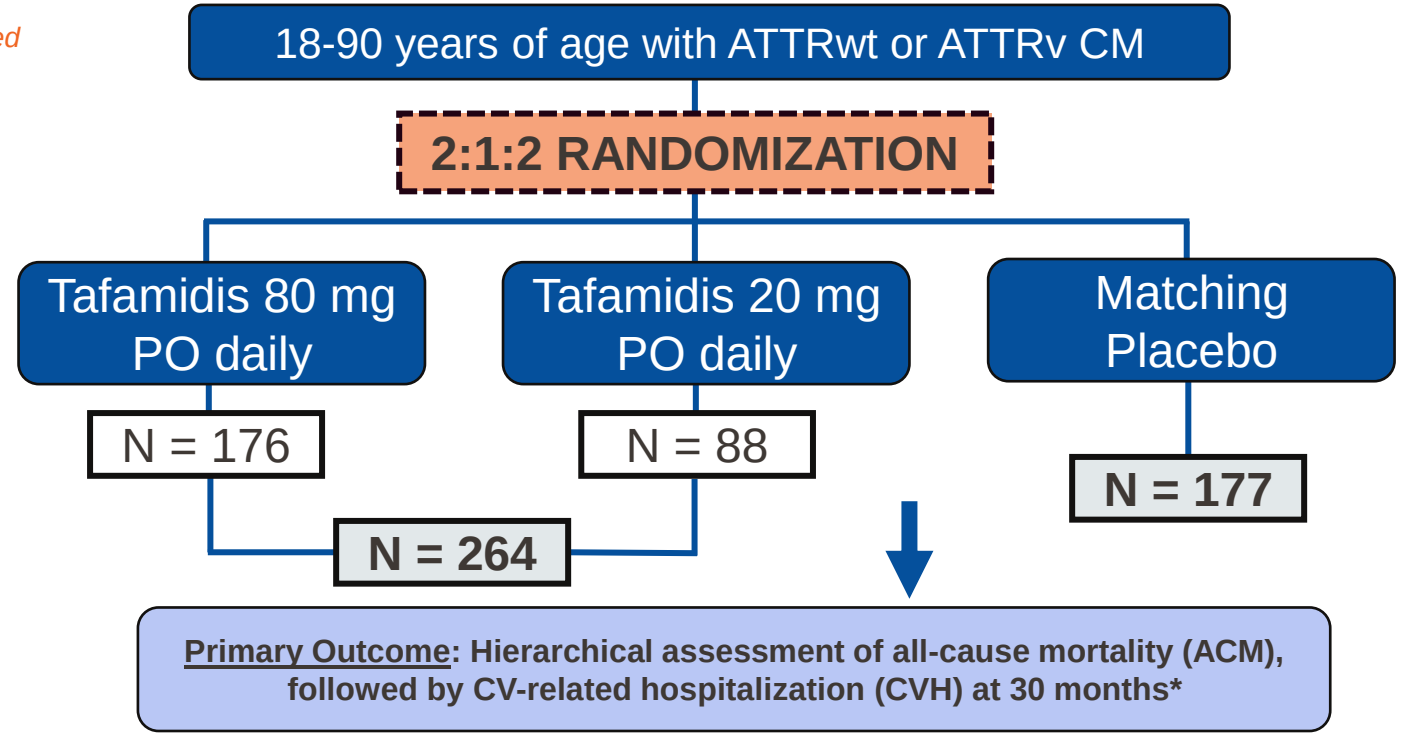
Multicenter, randomized, double-blind, parallel-design, placebo-controlled

Pertinent inclusion criteria:

1. End-diastolic intraventricular septal wall thickness > 12 mm
2. History of heart failure with at least one HFH or clinical evidence of HF without hospitalization
3. NT-proBNP > 600 pg/mL
4. 6MWT distance > 100 m (328 feet)

Pertinent exclusion criteria:

1. NYHA FC IV heart failure
2. Presence of AL amyloidosis
3. Implanted LVAD
4. eGFR < 25 mL/min/1.73m2
5. Liver transaminase levels > 2x ULN
6. Concurrent use of NSAIDs, tauroursodeoxycholate, docyclycline, CCBs or digitalis



*Using the Finkelstein-Schoenfeld method

Key secondary outcomes: Change in 6MWT and change in KCCQ-OS score

Maurer MS, et al. *N Engl J Med*. 2018;379:1007-1016.
Finkelstein DM, et al. *Stat Med*. 1999;18:1341-1354.

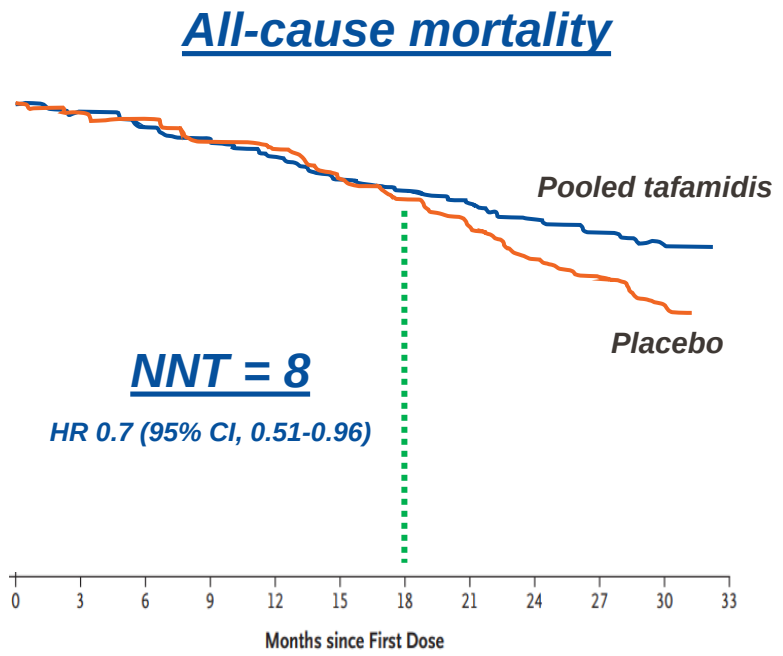
6MWT, six-minute walk test; AL, light chain amyloidosis; ATTR-ACT, The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CCB, calcium channel blocker; CM, cardiomyopathy; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall summary; HFH, hospitalization for heart failure; LVAD, left-ventricular assist device; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ULN, upper limit of normal.

ATTR-ACT

Average patient was a 75-year-old White male with NYHA FC II HF. 76% with ATTRwt and 24% with ATTRv.

- Tafamidis superior to placebo in primary efficacy analysis (P < 0.001) with a win ratio of 1.695; (95% CI, 1.255-2.289)
- Frequency of CV hospitalizations also lower in tafamidis group* (0.48 vs. 0.7 per year); RRR 0.68; (95% CI, 0.56-0.81); NNT = 4
- Decreased rate of decline in 6MWT and KCCQ-OS with tafamidis compared with placebo with benefit observed at 6 months
- Safety profiles similar with tafamidis and placebo

*Subgroup analyses favoring tafamidis except for patients with NYHA FC III HF at baseline

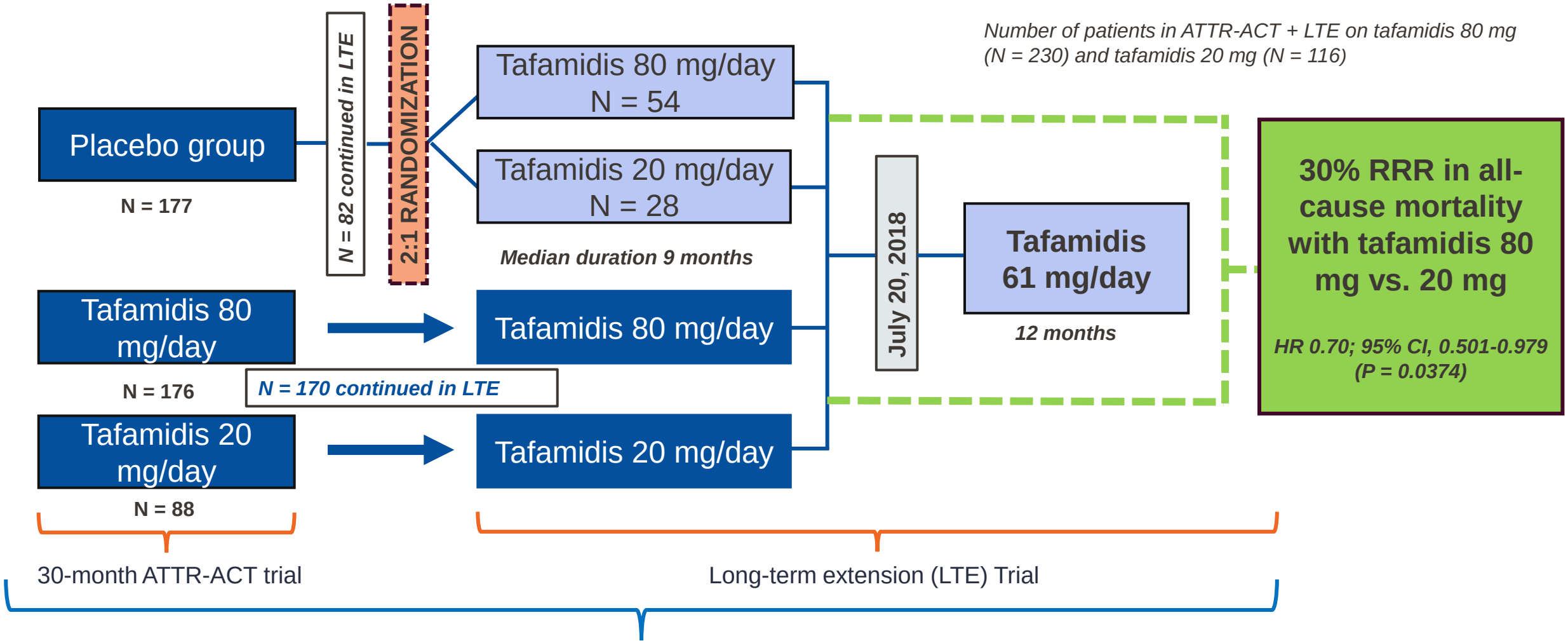


Trial duration: 30 months

Maurer MS, et al. *N Engl J Med*. 2018;379:1007-1016.

6MWT, six-minute walk test; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; FC, functional class; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall summary; NNT, number needed to treat; RRR, relative risk reduction; NYHA, New York Heart Association.

ATTR-ACT Extension Trial



Damy T, et al. *Eur J Heart Fail*. 2021;23:277-285.
RRR, relative risk reduction.

Acoramidis in ATTR-CM: ATTRibute-CM

***Objective**: Evaluate the safety and efficacy of a novel TTR stabilizer, acoramidis, in patients with ATTR-CM*

Multicenter, randomized, double-blind, parallel-design, placebo-controlled

18-90 years of age with ATTR-CM + clinical HF*

2:1 RANDOMIZATION

- Acoramidis 800 mg PO twice daily N = 421
- Matching placebo twice daily N = 211

***Clinical HF = At least 1 previous HFH, signs/symptoms of volume overload, or HF requiring decongestive therapy**

Pertinent inclusion criteria: End-diastolic intraventricular septal wall thickness > 12 mm, NT-proBNP ≥ 300 pg/mL, 6MWT distance > 150 m (492 feet)

Primary Outcome: Four-step hierarchical assessment of all-cause mortality, cumulative frequency of CV-related hospitalization, change in NT-proBNP from baseline, and change in 6MWT distance from baseline*

*Using the stratified Finkelstein-Schoenfeld method

Key secondary outcomes: Change from baseline to month 30 in 6MWT distance, KCCQ-OS score and serum TTR level
All-cause mortality

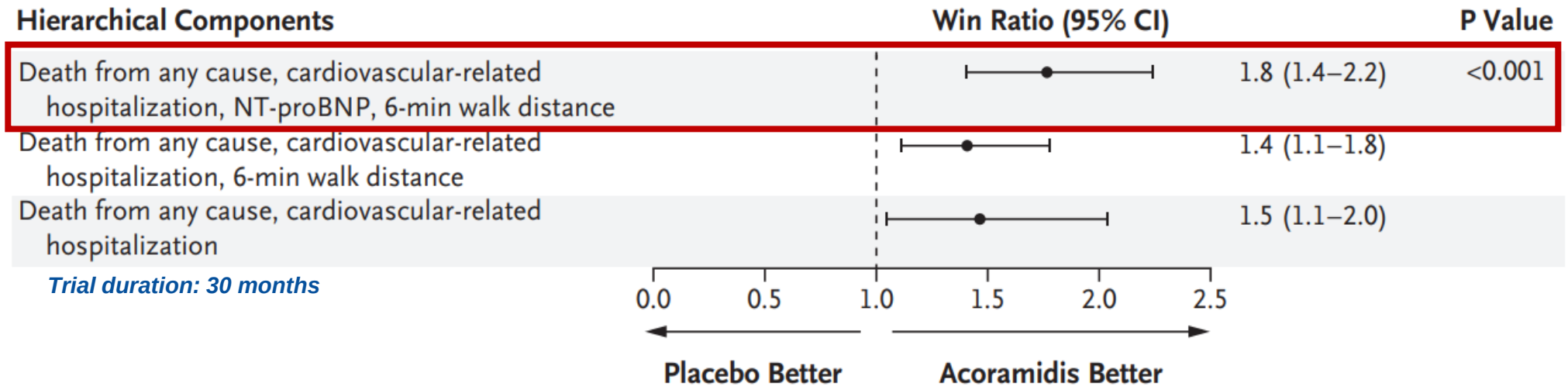
Pertinent exclusion criteria: NYHA FC IV heart failure, presence of AL amyloidosis, liver transaminase levels > 2x ULN, total bilirubin > 3x ULN, NT-proBNP ≥ 8500 pg/mL, eGFR < 15 mL/min/1.73m^2, treatment with tafamidis during the initial 12 months of the trial

Gillmore JD. *N Engl J Med.* 2024;390(2):132-142.

6MWT, six-minute walk test; AL, light chain amyloidosis; ATTRibute-CM, Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy; CM, cardiomyopathy; CV, cardiovascular; FC, functional capacity; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall summary; HFH, hospitalization for heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin; ULN, upper limit of normal.

ATTRibute-CM

Average patient was a 77-year-old White male with NAC stage 1 ATTRwt CM and NYHA FC II symptoms. Mean NT-proBNP was 2946 pg/mL and mean eGFR 61 mL/min/1.73m^2

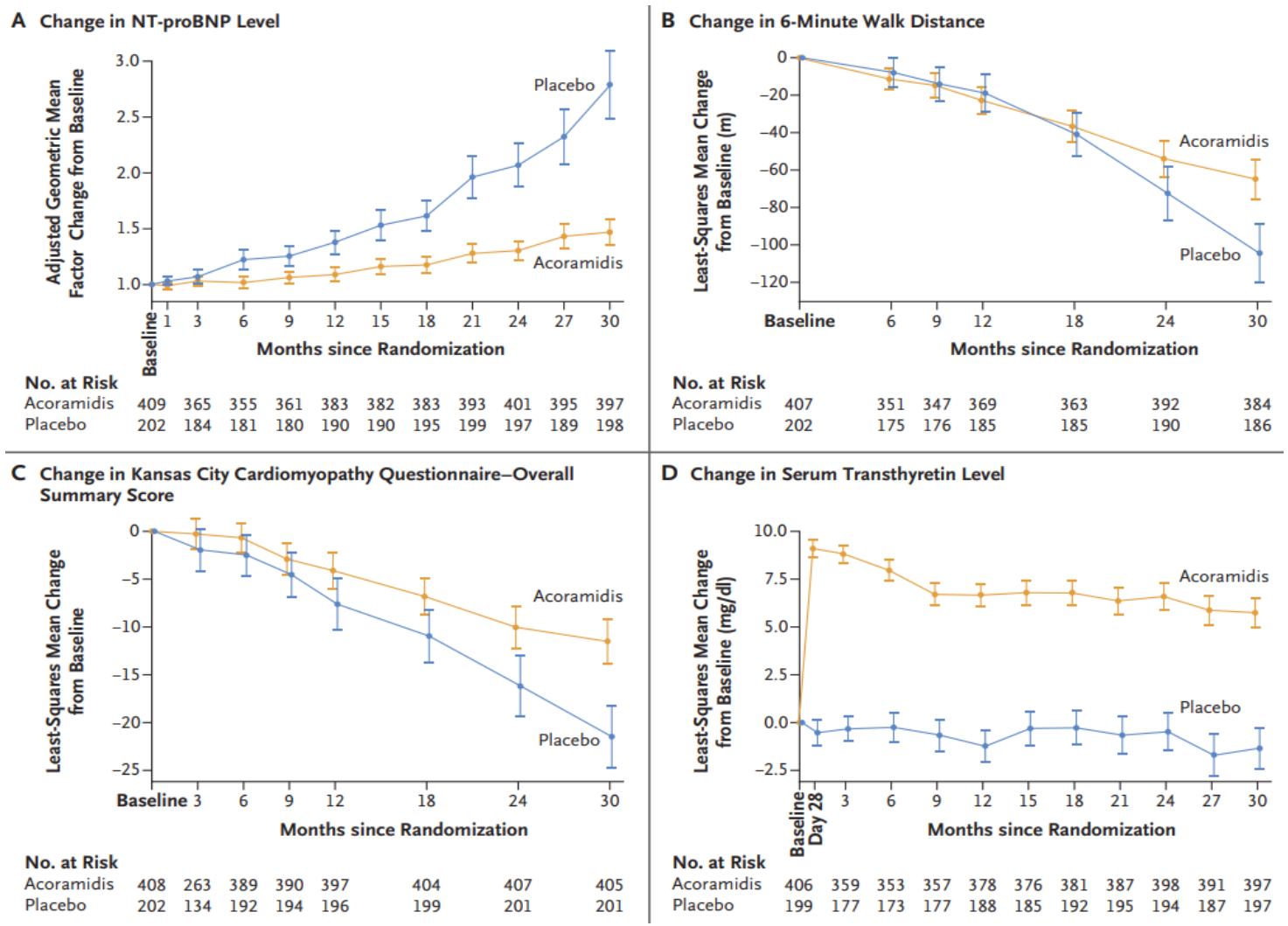


- ***Acoramidis superior to placebo in primary efficacy analysis (P < 0.001) with win ratio of 1.8***
- ***Frequency of CV hospitalizations lower in the acoramidis group; RRR 0.496; (95% CI, 0.355-0.695)***
- ***Safety profiles similar with acoramidis and placebo***

Gillmore JD. *N Engl J Med*. 2024;390(2):132-142.
ATTRwt, wild-type transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; FC, functional class; NAC, national amyloidosis centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RRR, relative risk reduction.

ATTRibute-CM

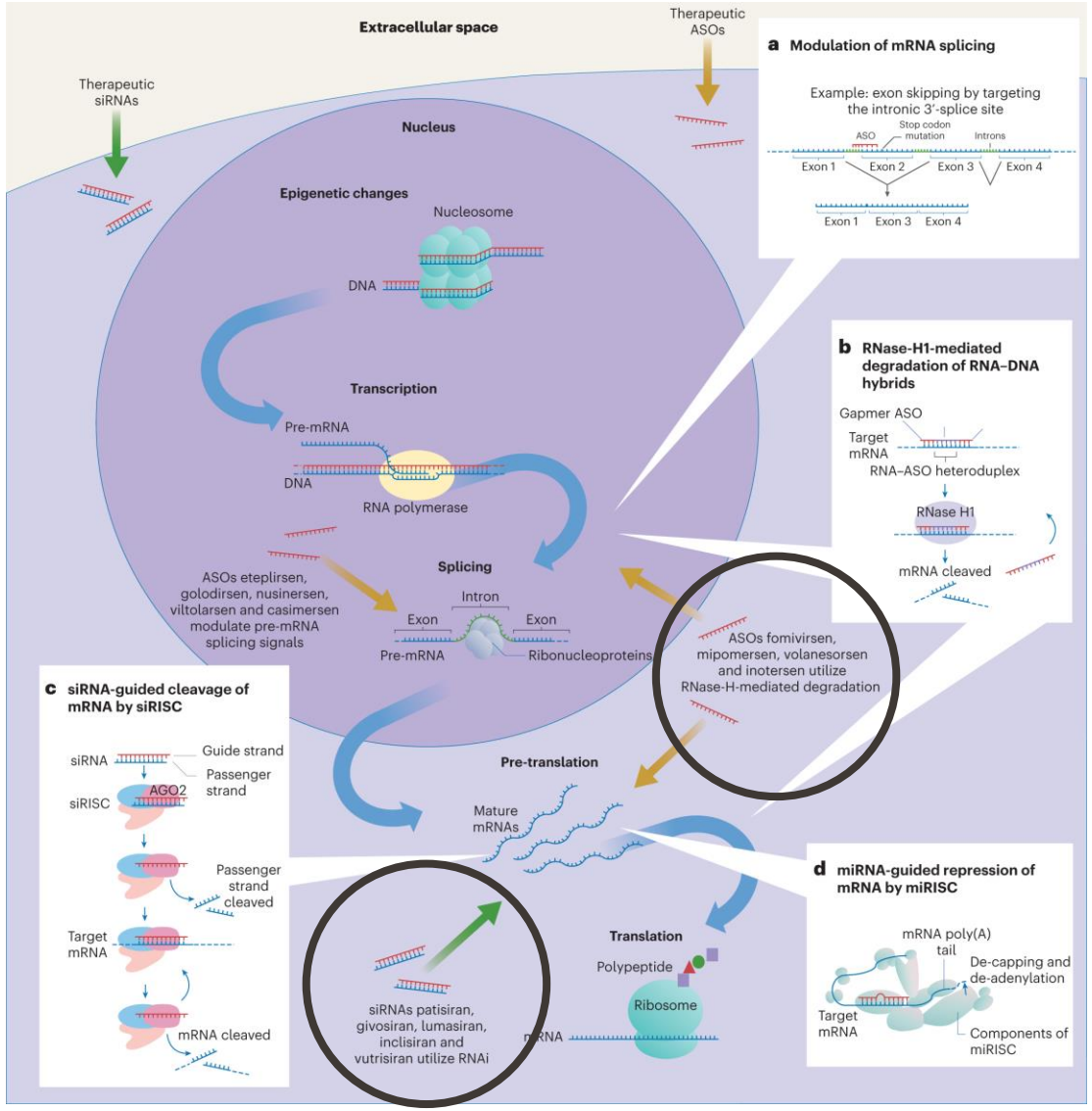
- Significant difference seen with respect to change in NT-proBNP, 6MWT distance and KCCQ-OS score in the acoramidis group.
- Significantly higher serum TTR levels seen with acoramidis compared with placebo at month 30.



Gillmore JD. *N Engl J Med*. 2024;390(2):132-142.
6MWT, six-minute walk test; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall summary; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

TTR Silencers: Mechanism of Action

- Antisense oligonucleotide (ASOs)
  - Modulate pre-mRNA splicing or engage endogenous ribonuclease H after recognition of target RNA
  - Inotersen, eplontersen
- Small interfering RNA (siRNA)
  - Harness the endogenous RNA-induced silencing complex (RISC)
  - Patisiran, vutrisiran

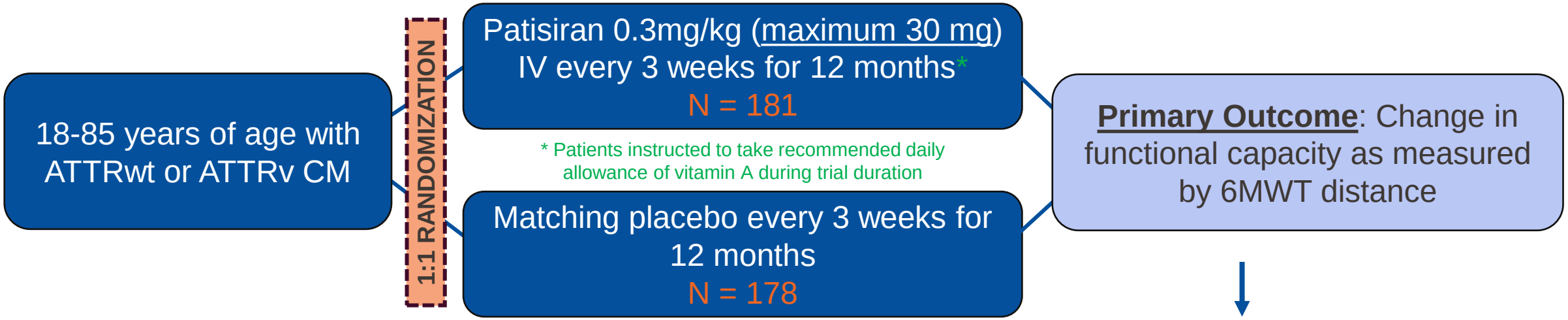


Jadhav V, et al. *Nat Biotechnol.* 2024;42(3):394-405.

Patisiran in ATTR-CM: APOLLO-B

***Objective**: Evaluate the safety and efficacy of a siRNA, patisiran, in patients with wild-type or variant ATTR-CM*

International, randomized, phase 3, multicenter, double-blind



Pertinent inclusion criteria:
1. End-diastolic intraventricular septal wall thickness > 12 mm
2. History of heart failure

Pertinent exclusion criteria:
1. NYHA FC III heart failure and ATTR amyloidosis stage of 3 (NT-proBNP > 3000 pg/mL **and** eGFR < 45 mL/min/1.73m^2)
2. NYHA FC IV symptoms
3. 6MWT distance < 150 m (492 feet)

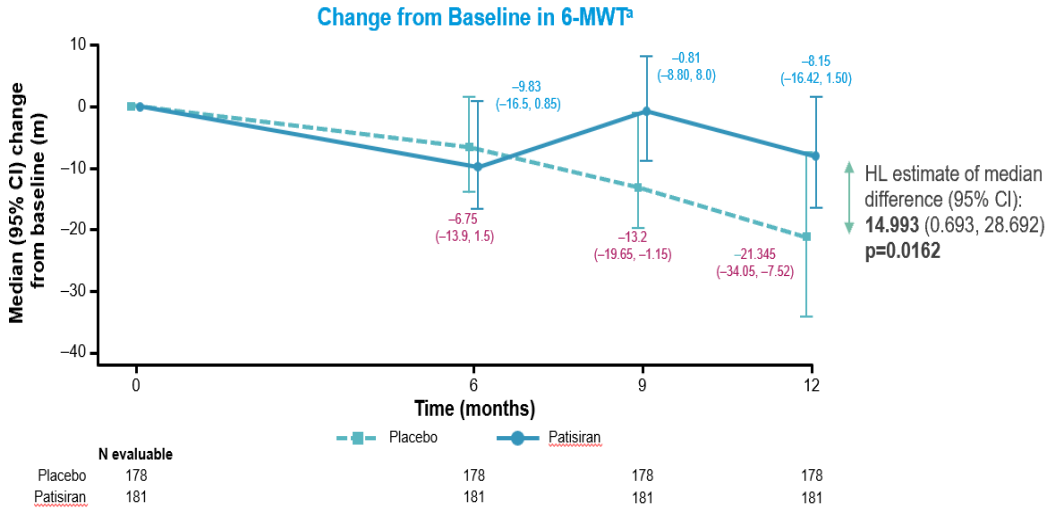
Key secondary outcomes: Change in KCCQ-OS; change in NT-proBNP; composite of all-cause mortality, CV events and change in 6MWT from baseline to 12 months; composite of all-cause mortality, all-cause hospitalizations, and urgent visits for HF over 12 months; echocardiographic measures of cardiovascular structure and function

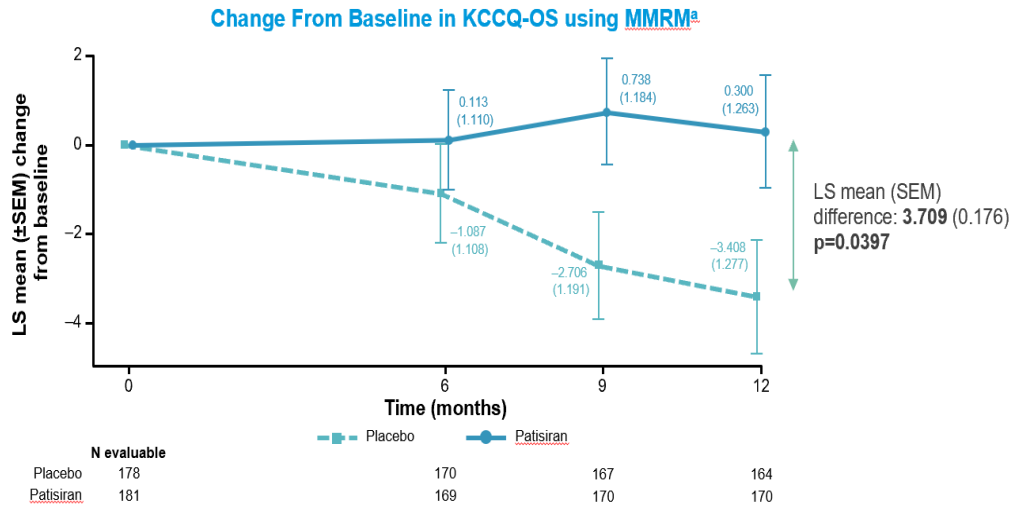
Maurer MS, et al. *N Engl J Med.* 2023;389(17):1553-1565.

6MWT, six-minute walk test; APOLLO-B, A Study to Evaluate Patisiran in Participants with Transthyretin Amyloidosis with Cardiomyopathy; ATTRwt, wild-type transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; CM, cardiomyopathy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FC, functional class; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall summary; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; siRNA, small interfering RNA; TTR, transthyretin.

APOLLO-B*

Average patient was a 76-year-old White male with stage 1 ATTRwt CM and FC II symptoms; median 6MWT distance of 358 m; KCCQ-OS score of 70 points; 25% of patients treated with tafamidis at baseline





- No significant difference seen in the secondary endpoints
- Smaller change from baseline in NT-proBNP and troponin I seen in patisiran group
- Rapid and sustained decrease in transthyretin levels with patisiran
  - Around 87% reduction at 12 months
- Safety profile similar compared with placebo

*Denied FDA-approval for ATTR-CM in September 2023. Anlylam Pharmaceuticals will no longer pursue expanded indication for ATTRM-CM. Patisiran (Onpattro®) is FDA-approved for ATTRv polyneuropathy

Maurer MS, et al. *N Engl J Med.* 2023;389(17):1553-1565.
Alnylam Pharmaceuticals. News Release. Published October 9, 2023. https://investors.alnylam.com/press-release?id=27741

6-MWT, 6-minute walk test; CI, confidence interval; HL, Hodges-Lehmann; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall summary; LS, least squared; MMRM, mixed model for repeated measures; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SEM, standard error of mean.

Comparison of Phase 3 ATTR-CM Trials

All three phase 3 clinical trials included patients with wild-type or variant ATTR-CM, however notable differences are seen with respect to assessed primary endpoints, patient population, and inclusion/exclusion criteria

Trial Criteria	ATTR-ACT[1] Tafamidis	ATTRibute-CM[2] Acoramidis	APOLLO-B[3] Patisiran
Tafamidis use	N/A	None at baseline; allowed after 12 months	25% at baseline; 2-3% started during 12-month trial duration
NYHA Class	I–III symptoms	I–III symptoms	I–III symptoms Excluded III at high risk
6MWT	≥ 100 m	≥ 150 m	≥ 150 m
NT-proBNP	≥ 600 pg/mL	≥ 300 pg/mL & ≤ 8500 pg/mL	>300 pg/mL & < 8500 pg/mL (> 600 pg/mL & < 8500 pg/mL in AF)
eGFR cutoff	≥ 25 mL/min/1.73 m^2	>15 mL/min/1.73 m^{2*}	≥ 30 mL/min/1.73 m^2

*Minimum intention to treat (mITT) specified eGFR ≥ 30

6MWT, 6-minute walk test; 6WMD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CVH, cardiovascular hospitalization; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

	ATTR-ACT[1]		ATTRibute-CM[2]		APOLLO-B[3]	
	Tafamidis	Placebo	Acoramidis	Placebo	Patisiran	Placebo
Primary Endpoint	30-month hierarchical composite of ACM and CVH		30-month hierarchical composite of ACM, CVH, Δ NT-proBNP, Δ 6MWD		12-month Δ 6MWD	
Age, years						
Median	75	74	78	78	76	76
NYHA class. %						
Class I	9.1	7.3	12.1	8.1	6	8
Class II	61.4	57.1	69.6	76.8	86	84
Class III	29.5	35.6	18.3	15.2	8	7
6MWT, meters						
Mean	351	353	361	348	360	375
NT-proBNP, pg/mL						
Median	2996	3161	2326	2306	2008	1813
TTR Genotype, %						
Variant	23.9	24.3	9.7	9.5	20	19

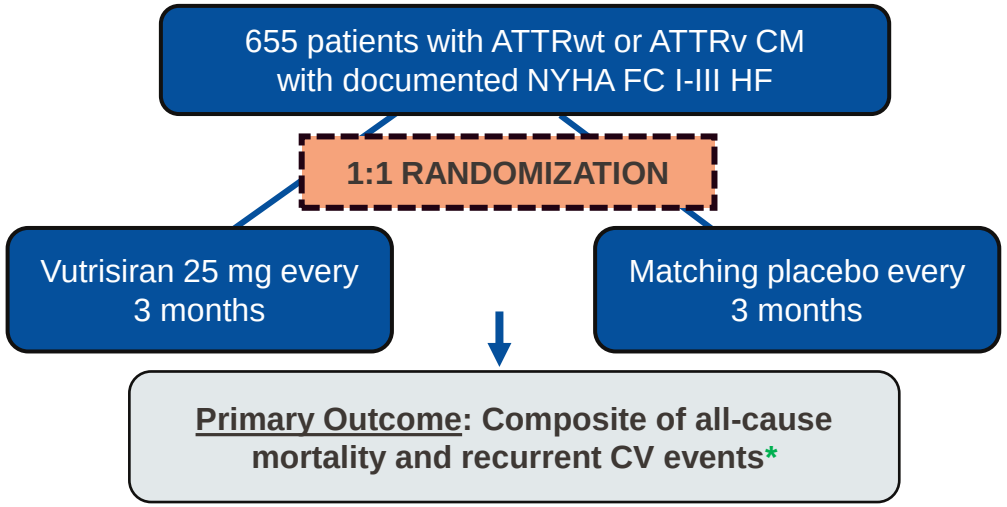
1. Maurer MS, et al. *N Engl J Med*. 2018;379:1007-1016. 2. Gillmore JD. *N Engl J Med*. 2024;390(2):132-142. 3. Maurer MS, et al. *N Engl J Med.* 2023;389(17):1553-1565.

ATTR-CM: Ongoing Trials and Future Directions

Ongoing Trials

HELIOS-B (Vutrisiran)

Subcutaneous siRNA



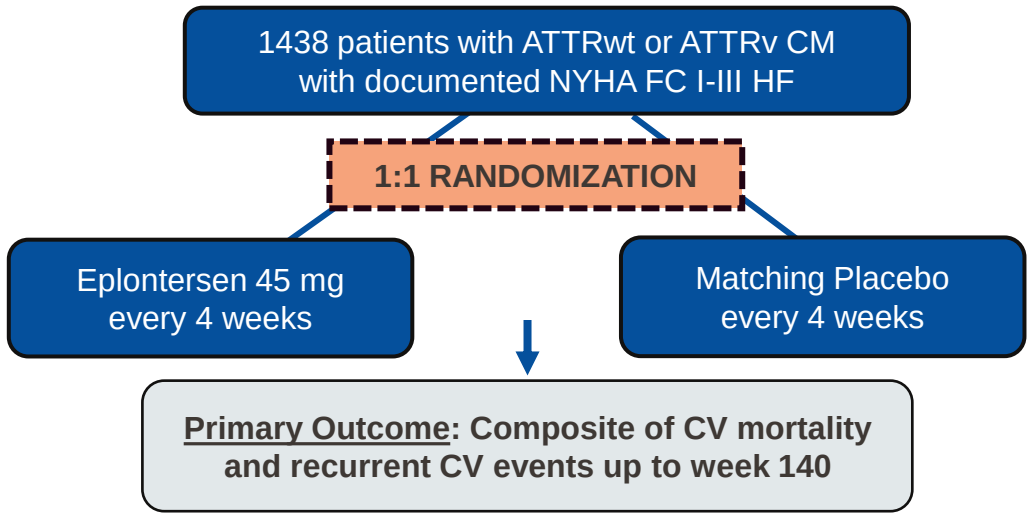
**CV hospitalizations and urgent HF visits*

Key secondary endpoints: Change in 6MWT from baseline to month 30; Change in KCCQ-OS score from baseline to month 30; Change in LV wall thickness and GLS from baseline to month 30; Composite of all-cause mortality and recurrent all-cause hospitalization and urgent HF visits; change in NT-proBNP from baseline to month 30.

Key exclusion: ATTR-CM NAC Stage 3 (NT-proBNP > 3000 pg/mL and eGFR < 45 mL/min/1.73m^2) with NYHA FC III symptoms; NYHA FC IV HF; eGFR < 30 mL/min/1.73m^2; receipt of prior TTR lowering treatment

Cardio-TTRansform (Eplontersen)

Subcutaneous ASO



Key secondary endpoints: Change in 6MWT from baseline to week 121; Change in KCCQ score from baseline to week 121; CV clinical events up to week 140; CV mortality up to week 140; all-cause mortality up to week 140

Key exclusion: NYHA FC IV HF; platelet count < 125 K/mcL; urine protein/creatinine ratio ≥ 750 mg/g; current or previous treatment with inotersen or patisiran; current treatment with diflunisal, doxycycline with or without ursodeoxycholic acid (patients on these agents require mandatory 14-day washout prior to randomization)

Study Details | HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy | ClinicalTrials.gov
Study Details | CARDIO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM) | ClinicalTrials.gov

6MWT, six-minute walk test; CM, cardiomyopathy; CV, cardiovascular; FC, functional class; GLS, global longitudinal strain; KCCQ, Kansas City Cardiomyopathy Questionnaire; NAC, national amyloidosis centre; NYHA, New York Heart Association.

Future Directions – Monoclonal Antibodies

***Goal**: Remove deposited amyloid fibrils from organs and tissues*

- NNC6019-0001 (PRX004)
  - Humanized monoclonal antibody
    - > Targets and binds unique epitope present only on misfolded and aggregated TTR → facilitating removal via antibody-mediated phagocytosis
  - Early phase trial showed improvement in neuropathy and left ventricular systolic function
  - Phase 2 trial underway assessing two different doses *(10 mg and 60 mg/kg every 4 weeks)* compared with placebo in 99 patients with ATTR-CM
    - > Phase 2 extension study planned for 2024
- NI006 (NI301A)
  - Recombinant human immunoglobulin-G1 monoclonal antibody
    - > Targets misfolded and aggregated TTR → stimulating macrophage-mediated clearance
  - Phase 1 trial completed
- AT-02
  - Humanized immunoglobulin-G1 monoclonal antibody fused with a pan-amyloid removal (PAR) peptide
    - > Stimulates macrophage-mediated clearance of multiple types of amyloid fibrils *(both AL and ATTR)*
  - Phase 1 dose-finding study and phase 2 trial for systemic amyloidosis are ongoing
- AT-06
  - Preclinical therapeutic candidate
    - > PAR peptide with a chimeric antigen receptor expressed in monocytes (CAR-M)
    - > Enables immune system-mediated removal of amyloid fibrils

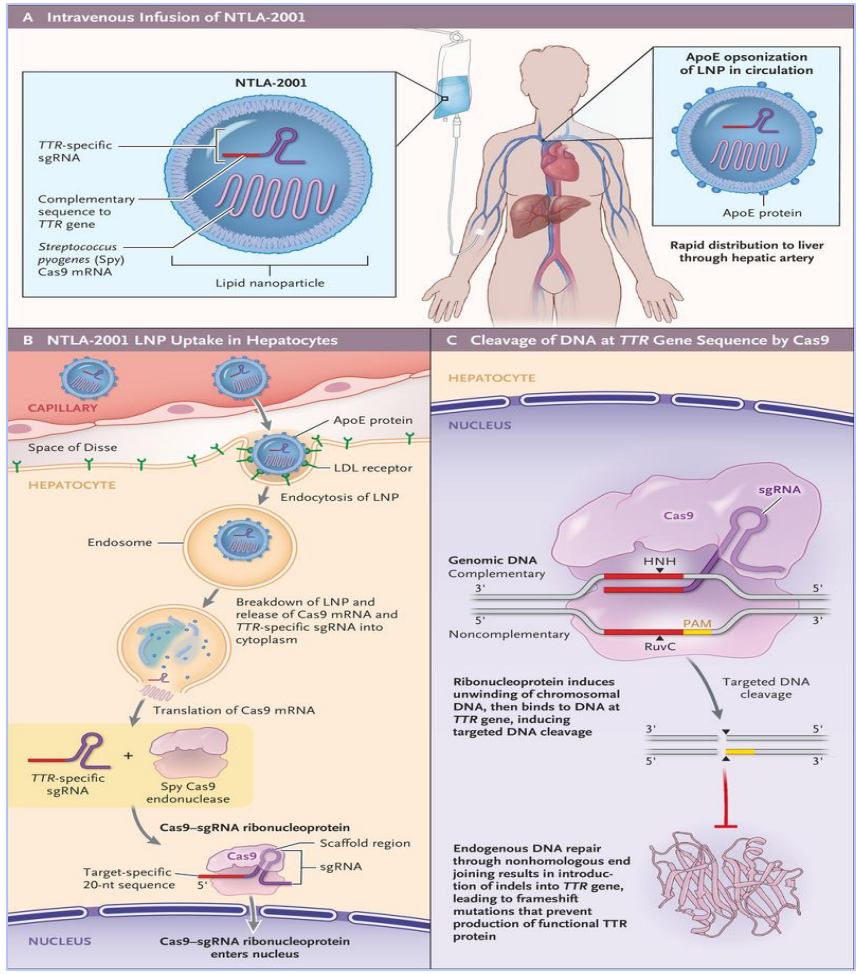
Maurer MS. *Am J Cardiol.* 2022;185(Suppl 1):S23-S34.
Maurer MS, et al. *JAMA.* 2024;331(9):778-791.
ATTR-CM, transthyretin amyloid cardiomyopathy; TTR, transthyretin.

Future Directions – Gene Editing

- CRISPR-Cas9 in vivo gene editing
  - Prevention of TTR gene transcription
    - > Molecular “scissor” that slices DNA
      - Biological “copy and paste”
  - Administered as a single intravenous transfusion
  - Targeted knockout of gene encoding for TTR
    - > Decrease in production of both wild-type and variant TTR
  - Phase 1 dose-ranging study with NTLA-2001
    - > Dose-dependent reductions in serum TTR levels

Dose (mg/kg)	Mean ↓ in TTR (%) by day 28
0.1 mg/kg	52%
0.3 mg/kg	87%
0.7 mg/kg	86%
1 mg/kg	93%

  - Phase 3 trial underway (MAGNITUDE)
    - > Estimated completion in 2027



Gillmore JD. *N Engl J Med.* 2021;385(6):493-502.
Maurer MS. *Am J Cardiol.* 2022;185(Suppl 1)S23-S34.
CRISPR-Cas9, Clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease system; TTR, transthyretin.

Summary

- Therapeutic options for ATTR-CM continue to expand with multiple agents in phase 3 clinical trials and novel agents in early phase trials

- Several agents available that target different steps in the amyloidogenic process
  - Silencing TTR formation *(siRNA, OSA, CRISPR-Cas9)*
  - Stabilizing circulating TTR *(tafamidis, acoramidis, diflunisal)*
  - Removing deposited amyloid fibrils *(monoclonal antibodies, doxycycline +TUDCA/UDCA)*

- At present, only tafamidis is FDA-approved for ATTR-CM
  - New drug application (NDA) for acoramidis accepted by FDA; tentative action date of November 29th, 2024

- There are no head-to-head comparisons of different agents
  - Not a *"one size fits all"* approach
  - Role of combination therapy is unclear at present

- ***Continued emphasis for timely and accurate diagnosis early in the disease process is crucial, where benefits of current therapies are most pronounced***

Specialty Pharmacy Relevance in ATTR-CM

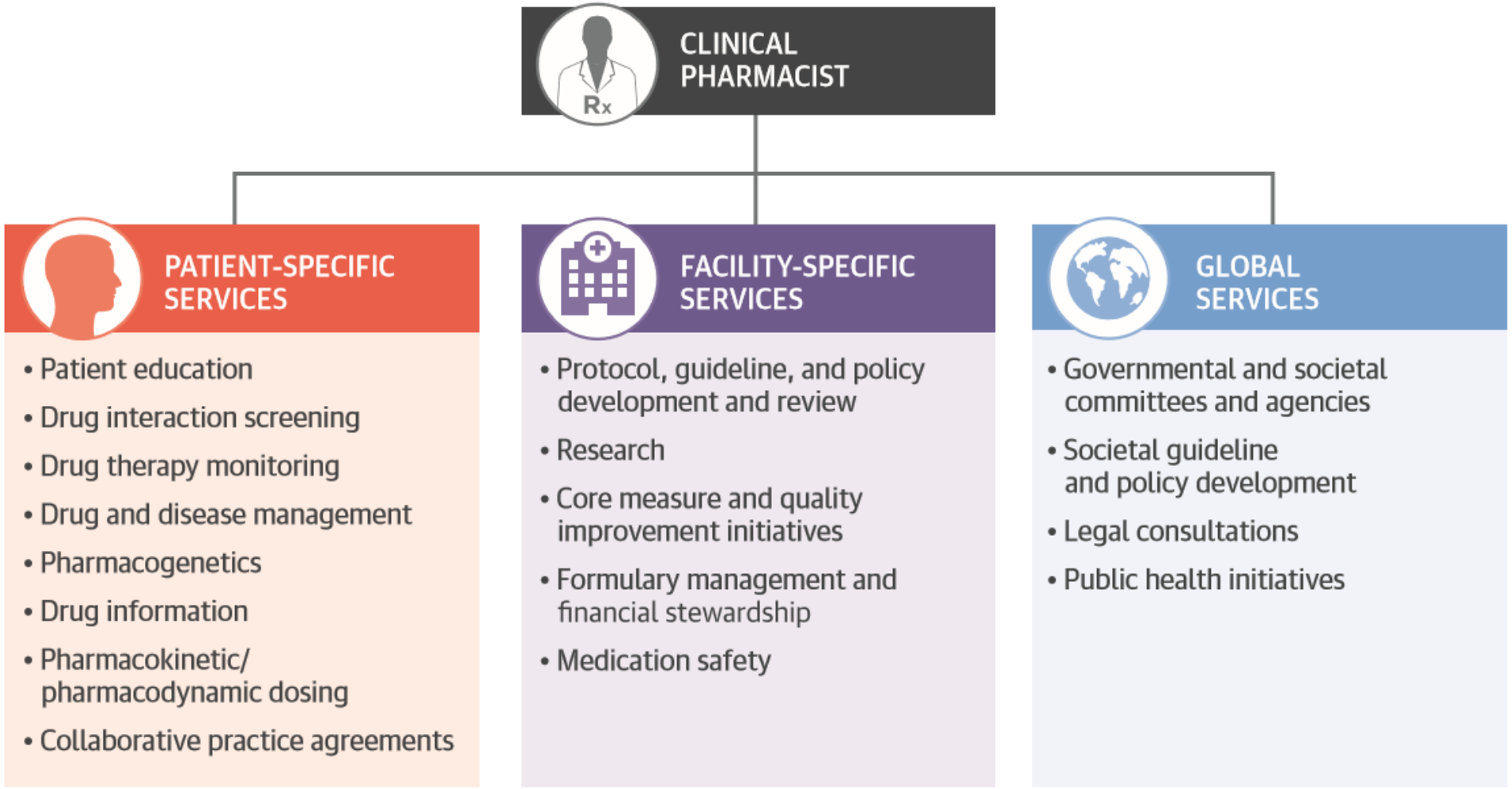
Jennifer L. Day, PharmD

Clinical Transplant Pharmacist

Baptist Health Heart Failure and Transplant Institute

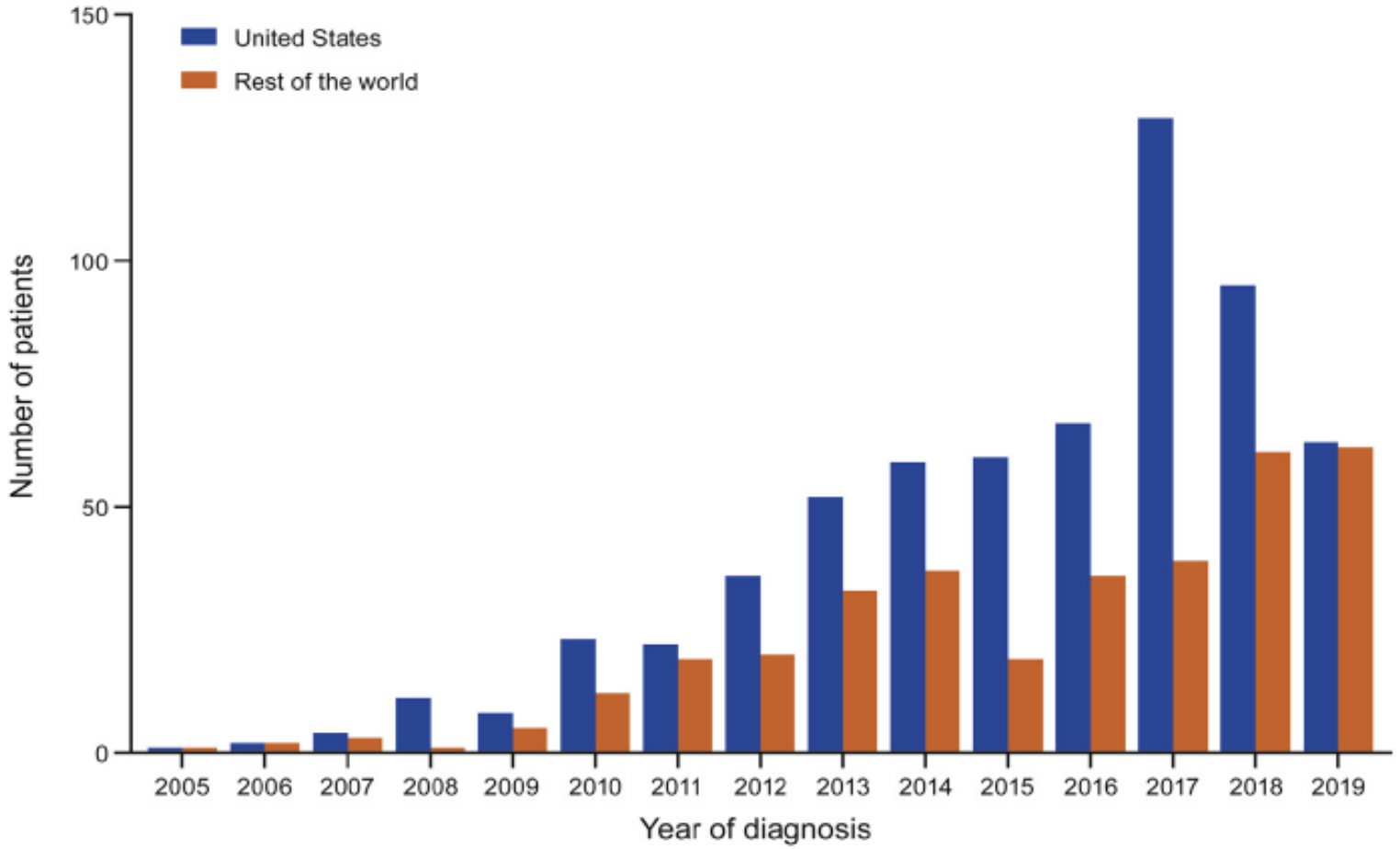
Little Rock, AR

Role of Pharmacist in CV Care



Dunn SP, et al. *J Am Coll Cardiol.* 2015;66(19):2129-2139.

Increasing Prevalence of ATTR-CM US and Worldwide



Diagnoses in the United States versus the rest of the world in THAOS (the Transthyretin Amyloidosis Outcomes Survey) are shown by year.*

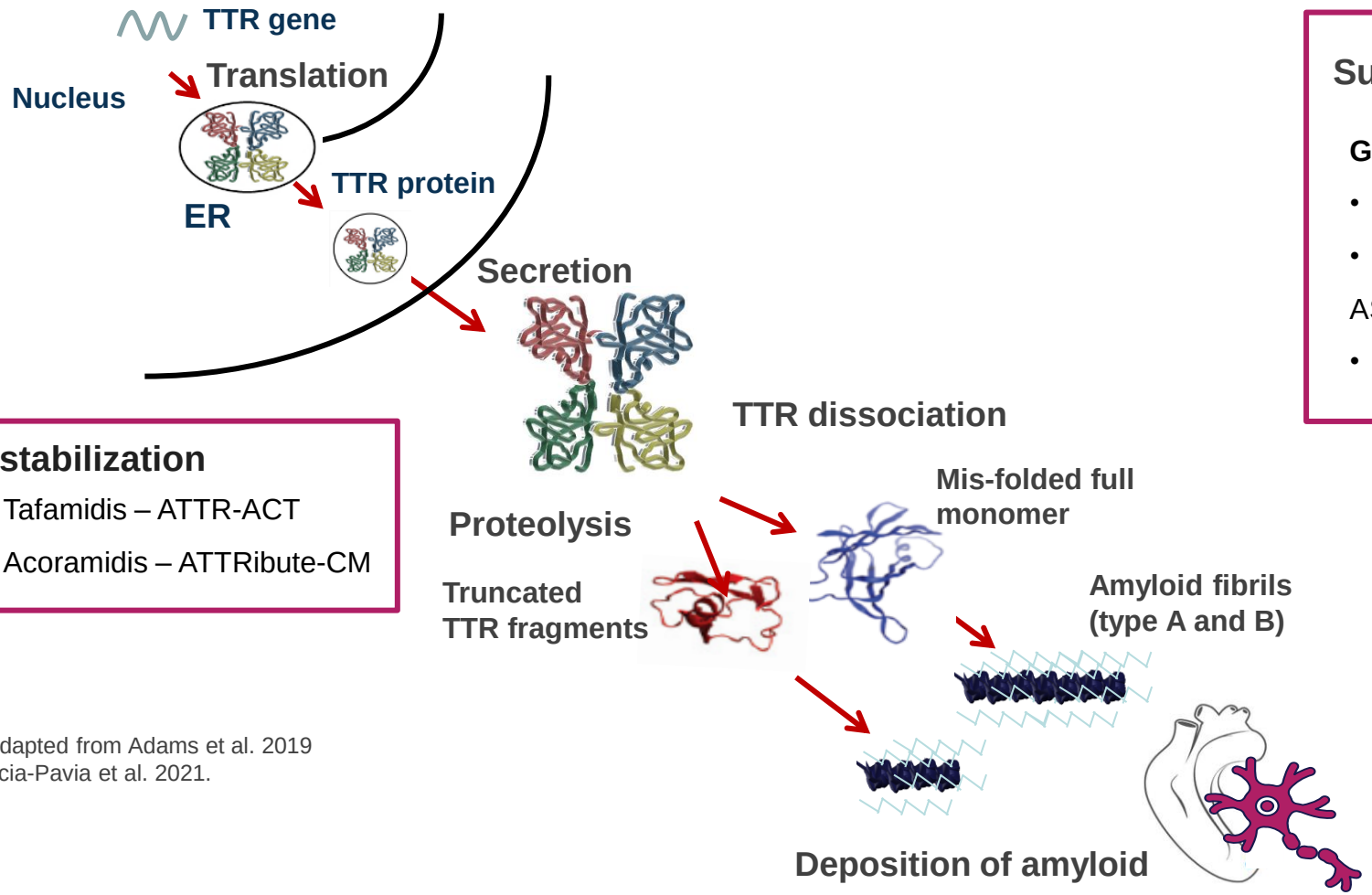
*Year of diagnosis missing for 45 patients in the United States and 42 in the rest of the world

Nativi-Nicolau J, et al. JACC CardioOncol. 2021;3(4):537-546.

ATTR-CM Pharmacological Review

Drug	Manufacturer	Indication	Route	Potential Barriers
Tafamadis (Vyndaqel, Vyndamax)	Pfizer	TTR Cardiomyopathy	Oral	Prior Authorization
Eplontersen (Wainua)	AstraZeneca	TTR Polyneuropathy	Subcutaneous	Prior Authorization Injection Technique
Patisiran (OnPattro)	Alnylam	TTR Polyneuropathy	Intravenous infusion	Prior Authorization Infusion site/staff
Vutrisiran (AmVuttra)	Alnylam	TTR Polyneuropathy	Subcutaneous	Prior Authorization Injection Technique

The Evolving Landscape of ATTR-CM Targeted Therapeutic Options



TTR stabilization

- Tafamidis – ATTR-ACT
- Acoramidis – ATTRibute-CM

Suppression of TTR synthesis

Gene silencing – RNAi therapy

- Patisiran – APOLLO-B
- Vutrisiran – HELIOS-B

ASO therapy

- Eplontersen – CARDIO-TTRansform

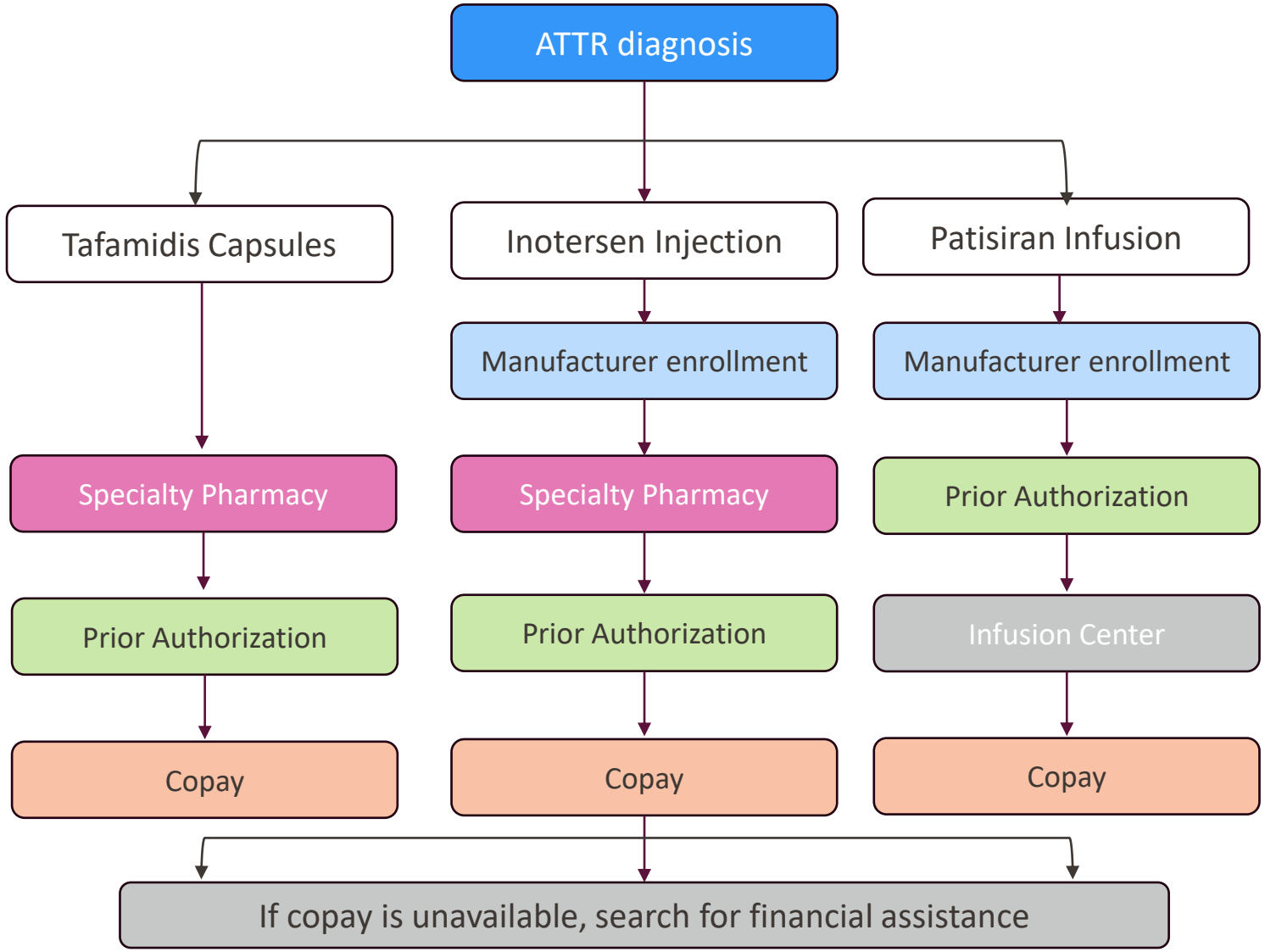
Figure adapted from Adams et al. 2019 and Garcia-Pavia et al. 2021.

Adams D, et al. *Nat Rev Neurol.* 2019;15(7):387-404. Garcia-Pavia P, et al. *Eur Heart J.* 2021;42(16):1554-1568. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. Onpattro (patisiran). https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf. Amvuttra (vutrisiran). https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf. Vyndaqel (tafamidis). https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf.

ASO, antisense oligonucleotide; ATTR, transthyretin-mediated amyloidosis; ER, endoplasmic reticulum; PN, polyneuropathy; RNAi, RNA interference; TTR, transthyretin.

Where Does Specialty Pharmacy Fit In?

Note: This is based on currently available therapeutics



Chen H, et al. *J Am Heart Assoc.* 2022;11(7):e023895.

Where Does Specialty Pharmacy Fit In?

- Patient Access
  - Educational resources
  - Benefits investigation
- Prior Authorization
  - Pre-populated forms by payor
- Complexities of management
  - Ongoing interaction screening
  - Administration technique training

Tips on Genetic Testing

- Once a diagnosis of cardiac amyloidosis is confirmed, genetic testing can be done via buccal swab or blood while drawing standard labs
- If PYP scan is positive before receiving genetic results, ATTR-CM treatment can be initiated

Medication Screening

- Screen the patient's medication profile for potential interactions
- Make recommendations for changes as necessary

Use of Standard Heart Failure Therapies in ATTR-CM

	Yes	*Sometimes*	*No*
Diuretics ± aldosterone antagonists	✓		
Renin-angiotensin system inhibitors		−	
Beta-adrenoreceptor blockers		−	
Alpha-1-adrenoreceptor agonists		−	
Calcium channel blockers			✗
Digoxin *			✗

- Supportive treatment limited to management of HF symptoms and arrhythmias
- Goal is to maintain euvolemia and reduce ventricular filling pressures without causing hypotension
- Most HF therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers are generally not well tolerated, especially in advanced disease

Ioannou A, et al. *Eur Heart J.* 2023;44(31):2893-2907.
ATTR-CM, transthyretin amyloidosis cardiomyopathy; HF, heart failure.

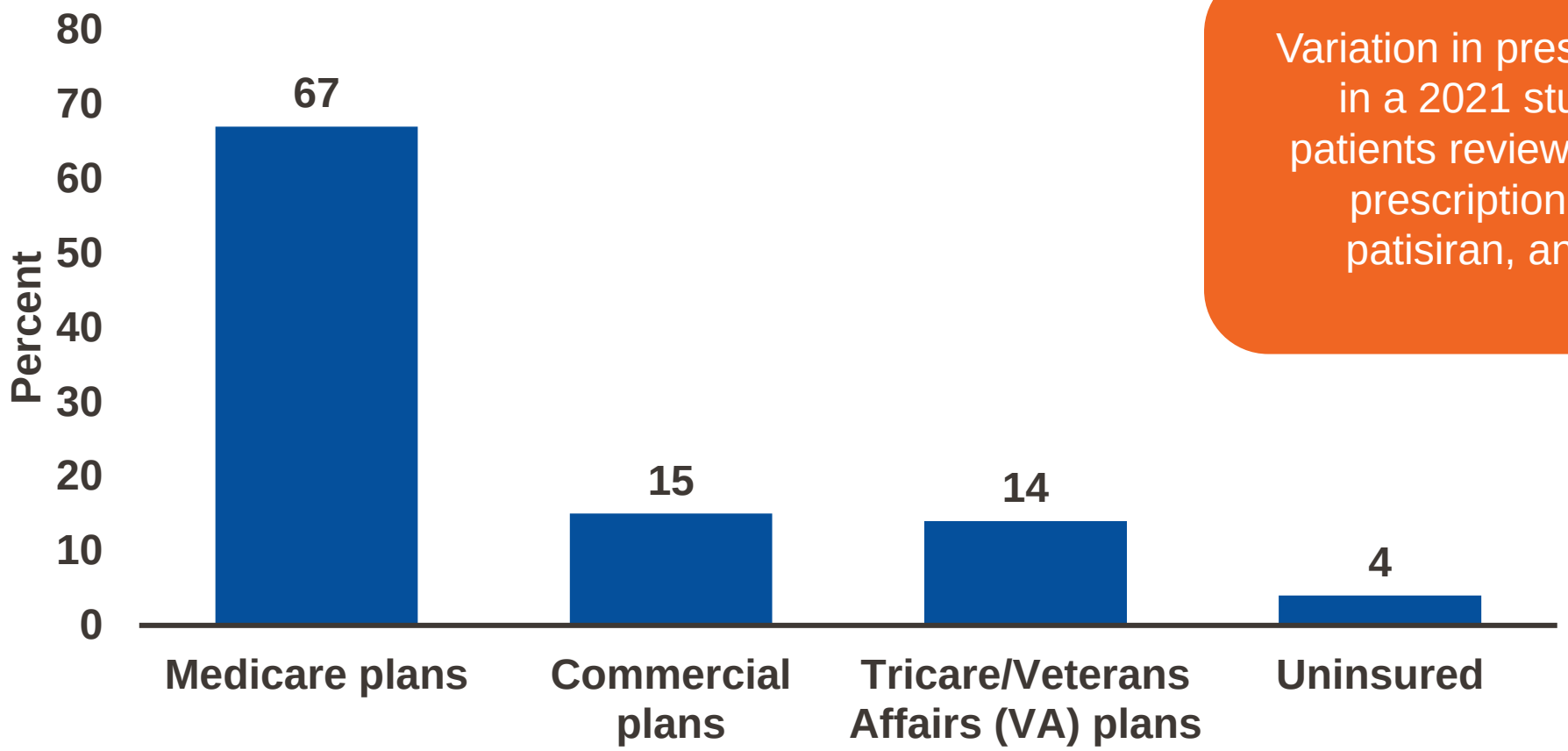
Tips on Medication Selection

- Weigh the benefits
  - Hereditary vs wild-type ATTR
- Type of insurance and extent of prescription coverage
  - Medicare, commercial, uninsured?
  - Financial assistance programs
- Access to care
  - Clinic vs home administration
- Patient preference
  - Talk to the patient

Open communication and shared decision-making are key to improving patient outcomes

ATTR, transthyretin amyloidosis.

Financial Assistance Will Vary



Variation in prescription coverage in a 2021 study of 72 clinic patients reviewed with an active prescription for inotersen, patisiran, and/or tafamidis

Chen H, et al. *J Am Heart Assoc.* 2022;11(7):e023895.

Patient Follow-Up

- Review medications
  - Ensure all patients on silencer therapy continue taking a daily multivitamin
- Reinforce counseling points based on available literature or handouts
- Ask if they have any questions

Practice Tip:

- Include progress notes with each amyloid patient visit in the EMR. This helps with prior authorization efforts and helps completing documentation for prescription renewals.
- This also includes a hard stop for the physician to document Polyneuropathy Disability Score, Familial Amyloid Polyneuropathy Stage and NYHA heart failure symptom classification

NYHA, New York Heart Association.

Case-Study- Ms. TL

- 62 y/o Caucasian female
- Presented to clinic with worsening symptoms of heart failure.
- History of non-ischemic cardiomyopathy which was thought to be due to chemotherapy she previously received for treatment of breast cancer.
- Atrial fibrillation which was treated with beta blockers for rate control.
- Symptoms failed to improve and at follow up she was NYHA function class III - IV.
- She also has peripheral neuropathy and has undergone carpal tunnel surgery twice on her right arm.
- Sent for a nuclear medicine scan (PYP)

NYHA, New York Heart Association.

Case-Study- Ms. TL (cont'd)

- Ms. TL has tested positive for cardiac amyloidosis by PYP scan (ratio 1.67 and SPECT Grade 2)
- Ms. TL was prescribed tafamidis 61 mg daily and placed on Doxycycline and (T)UDCA.
- No suspicion of AL
- Genetic testing was negative for TTR, so diagnosis was confirmed wt-ATTR.

- Today she continues follow-up visits every 6 months but is NYHA functional class II and continues on therapy with tafamidis.

NYHA, New York Heart Association.

Case-Study - Mr. JS

- Mr. JS is seen in clinic following findings of positive hereditary-type transthyretin amyloidosis (hATTR). He has been on tafamidis, since 2019 following an EMB finding
- A recent genetic panel confirmed presence of Val142Ile hereditary-type.
- Prescribed patisiran for polyneuropathy of hATTR

Medications:

Aspirin 81 mg daily
Atorvastatin 40 mg HS daily
Cetirizine 10 mg daily PRN
Doxycycline 100 mg BID
Gabapentin 300 mg HS daily
Lansoprazole 30 mg daily PRN
Metformin 1000 mg BIDcc
KCL 20 mEq - takes 40 mEq BID
Sacubitril-valsartan 24-26 mg BID
Tafamidis 61 mg daily
TUDCA 500 mg BID
Torsemide 20 mg - takes 40 mg BID

Case-Study - Mr. JS (cont'd)

Working with the patient for best outcomes:

- Mr. JS was initially unhappy with the thought of injections.
- We discussed the indication for the new medication and importance of therapy given his diagnosis
- An alternative, inotersen, was offered, but he chose patisiran based on the drug safety profile
- His prescription was eventually changed to vutrisiran for polyneuropathy associated with his diagnosis.
- He continues to take tafamidis as well which is covered by his pharmacy benefits and indicated for his cardiomyopathy.

Panel Discussion and Audience Q&A

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Don’t forget to complete the evaluation!

You will receive an email with a link to the evaluation this week.

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