Strategic Excellence: Mastering the Expanding ATTR-CM Therapeutic Landscape in Pharmacy Practice

New Orleans, LA

April 16, 2024

medtelligence℠

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

Hongya Chen, PharmD, BCCP

Cardiology Clinical Pharmacist

Oregon Health & Science University

Portland, OR

Faculty

Chair

Hongya Chen, PharmD, BCCP
Cardiology Clinical Pharmacist
Oregon Health & Science University
Portland, OR

Faculty

Jennifer L. Day, PharmD
Clinical Transplant Pharmacist
Baptist Health Heart Failure and
Transplant Institute
Little Rock, AR

Keith C. Ferdinand, MD, FACC, FAHA, FASPC, FNLA
Gerald S. Berenson Endowed Chair
in Preventive Cardiology,
Professor of Medicine
Tulane University School of Medicine
New Orleans, LA

Disclosures

Hongya Chen, PharmD

Consulting Fees: BMS, MyoKardia

Jennifer Day, PharmD

Consulting Fees: Janssen Pharmaceuticals

Keith C. Ferdinand, MD

Consulting Fees: Amgen, Boehringer-Ingelheim, Eli Lilly, Medtronic, Janssen Pharmaceuticals

Agenda

- Past and Present Outlook in ATTR
- ATTR-CM Mechanism of Action
- Past and Ongoing Clinical Trials
- The Pharmacist’s Role in Managing ATTR
- Faculty Discussion/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

Ready. Set. Poll.

Have your mobile devices ready to respond to the learning assessment questions coming up.

Join at

slido.com

#AMCP

Past and Present Outlook in ATTR

Keith C. Ferdinand, MD, FACC, FAHA, FASPC, FNLA

Gerald S. Berenson Endowed Chair

in Preventive Cardiology,

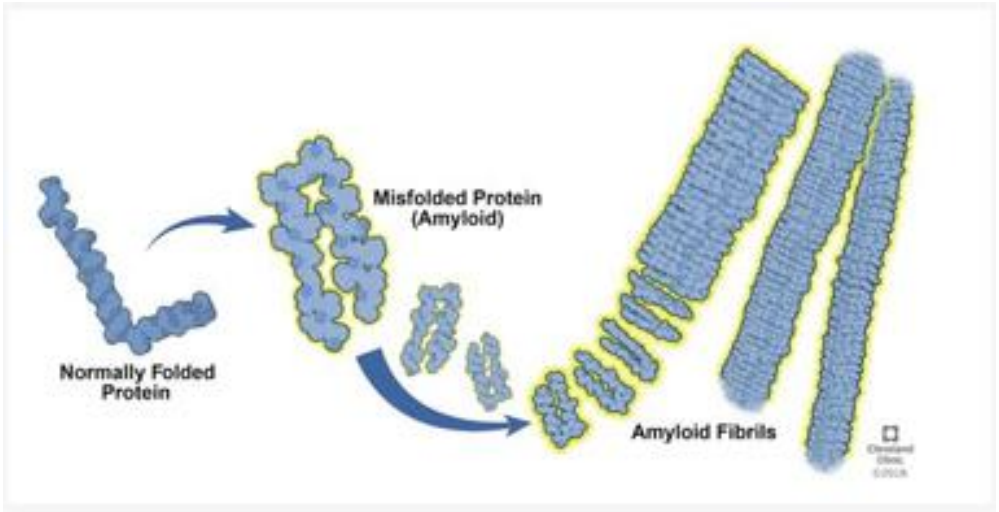
Professor of Medicine

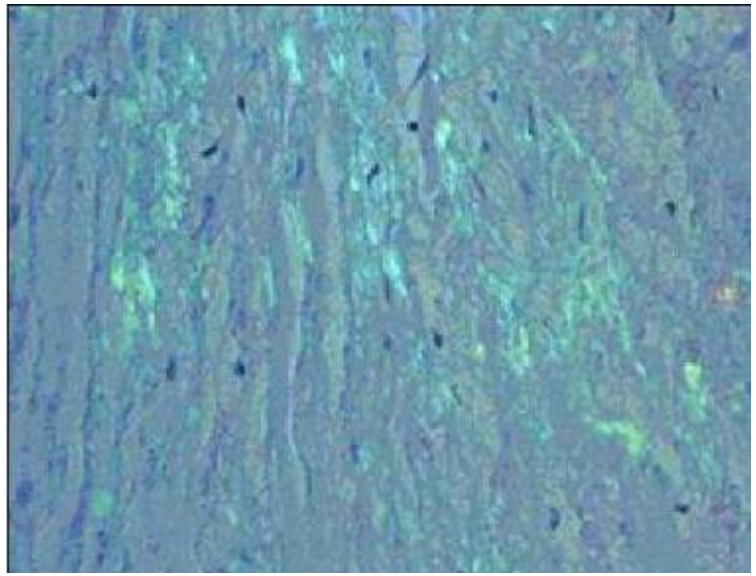
Tulane University School of Medicine

New Orleans, LA

What is Amyloidosis?
A protein disorder

- Proteins change shape (misfold), then clump together and form amyloid fibrils which deposit in organs.
- As amyloid fibrils build up, they lead to tissue and organ dysfunction.
- Several proteins that can cause amyloidosis.
- Most common: Light chain (AL) and transthyretin (ATTR) amyloidosis.





Apple green birefringence on Congo Red staining

Seldin DC, et al. *Heart Fail Clin.* 2011;7(3):385-393. Sanchorawala V. *Clin J Am Soc Nephrol.* 2006;1:1331-1341.

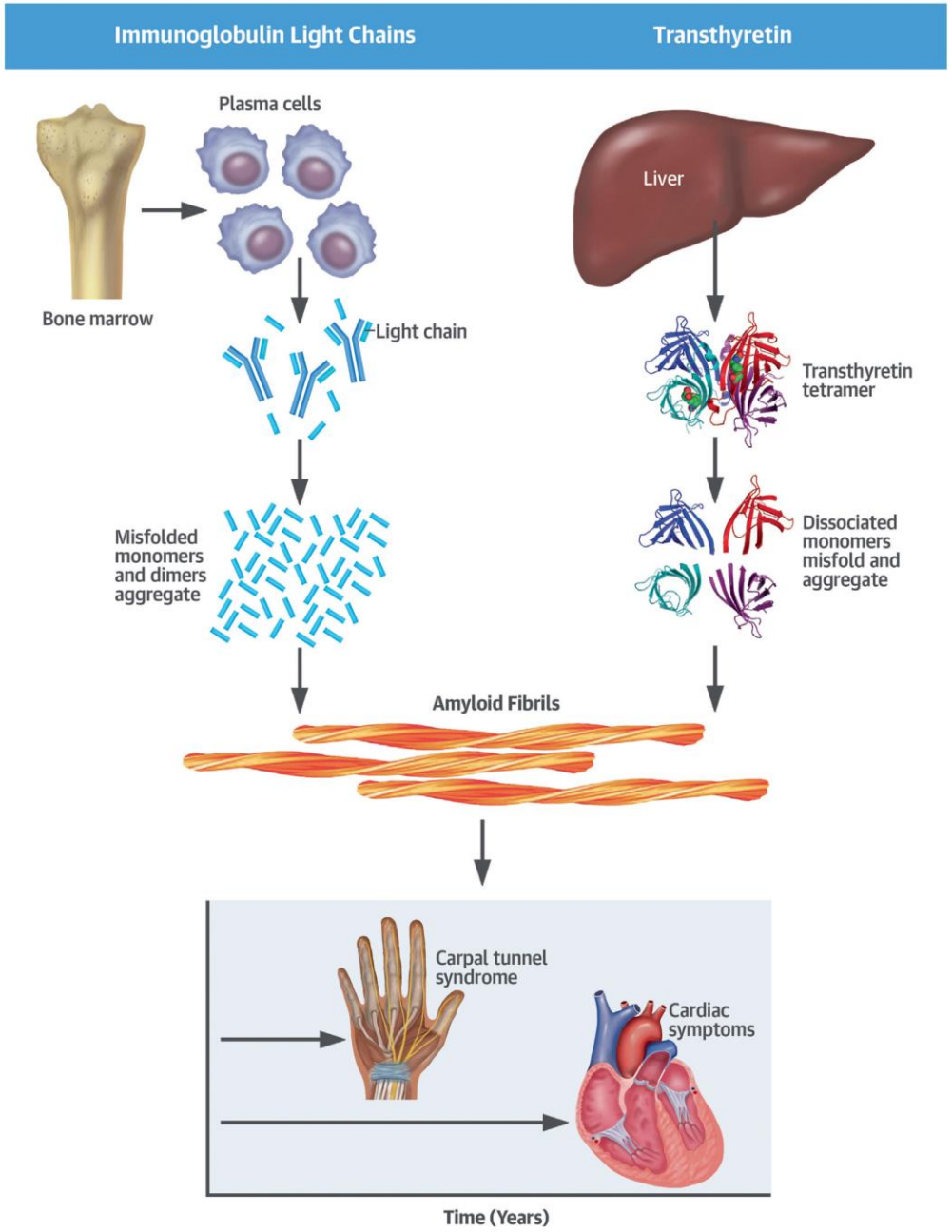
What is Transthyretin?

Transthyretin (TTR) is a transport protein in the plasma and cerebrospinal fluid that transports the thyroid hormone thyroxine (T_4) and retinol to the liver.

Buxbaum JN, Reixach N. *Cell Mol Life Sci*. 2009;66(19):3095-3101.

Mechanism of Amyloid Deposition

- AL & ATTR precursor proteins >95% CM cases.
- AL amyloidosis: aberrant monoclonal plasma cells in bone marrow secrete light chains that misfold and aggregate→ form insoluble amyloid fibrils.
- ATTR amyloidosis: liver-derived protein transthyretin (normally tetramer) dissociates into monomers→ misfold and aggregate as insoluble amyloid fibrils.
- AL more rapidly deposits than ATTR over time
- Bilateral carpal tunnel syndrome often presents years before onset cardiac symptoms.



Sperry BE, et al. *J Am Coll Cardiol.* 2018;72(17):2040-2050.

Epidemiology of ATTR-CM: **Underrecognized, Undertreated**

AL Amyloid **RARE**	~2500 Cases per year 50% have cardiac involvement **RARE**
hATTR **NOT SO RARE**	4% of African Americans are carriers 25,000-120,000 US patients **NOT SO RARE**
wt ATTR **NOT RARE**	~10-25% of adults >80 years ~1 million **NOT RARE**

Gustavsson A, et al. *Lab Invest*. 1995;73:703.

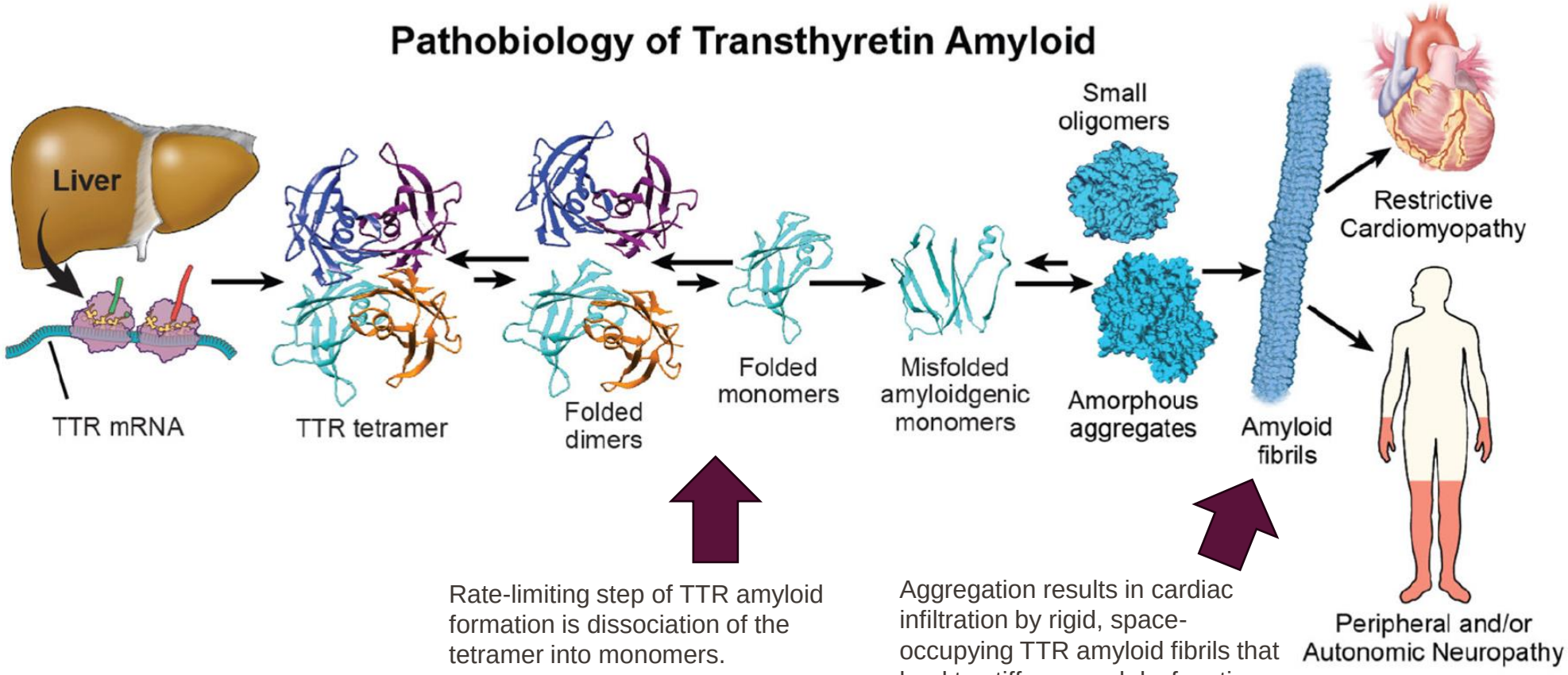
Symptoms That Raise Suspicion of Cardiac Amyloidosis

Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

Donnelly J, Hanna M. *Cleve Clin JMed.* 2017;84(12 suppl 3):12-26.

Transthyretin Amyloidosis (ATTR)

The Mechanism of TTR Protein Dissociation, Misfolding, and Aggregation as Amyloid Fibrils, Which Results in Organ Dysfunction



ATTR, transthyretin amyloidosis; TTR, transthyretin.

Ruberg FL. *J Am Coll Cardiol.* 2019;73(22):2872-2891.

Transthyretin Amyloidosis (ATTR)

Wild-type ATTR:

- Cardiomyopathy
- Increasingly recognized cause of HF in over 50s (94% men)
- Progressive and fatal within 3-10 years
- Extra-cardiac features include CTS and lumbar canal stenosis (red flags)
- Prevalence not known (misdiagnoses vs clinically insignificant?)

Hereditary ATTR:

- Cardiomyopathy and neuropathy
- Estimated prevalence 50,000 worldwide
- More than 130 amyloidogenic mutations of TTR gene
- **V122I TTR variant present in ~4% of African Americans and African Caribbeans**
- T60A TTR variant most prevalent in White British population (Irish)

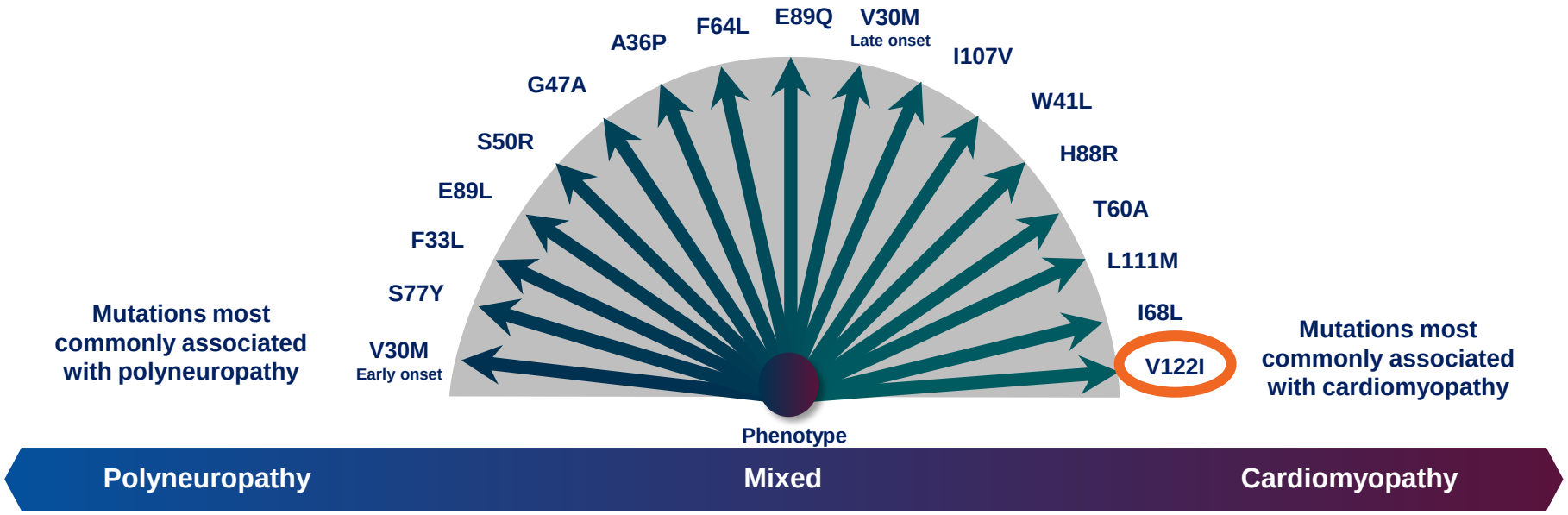
ATTR, transthyretin amyloidosis; CTS, carpal tunnel syndrome; HF, heart failure; TTR, transthyretin.

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. First European Meeting for ATTR Amyloidosis for Doctors and Patients. Poster P1.

Genotype–Phenotype Correlations in hATTR-CM

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.

Original Article

Afro-Caribbean Heart Failure in the United Kingdom
Cause, Outcomes, and ATTR V122I Cardiac Amyloidosis

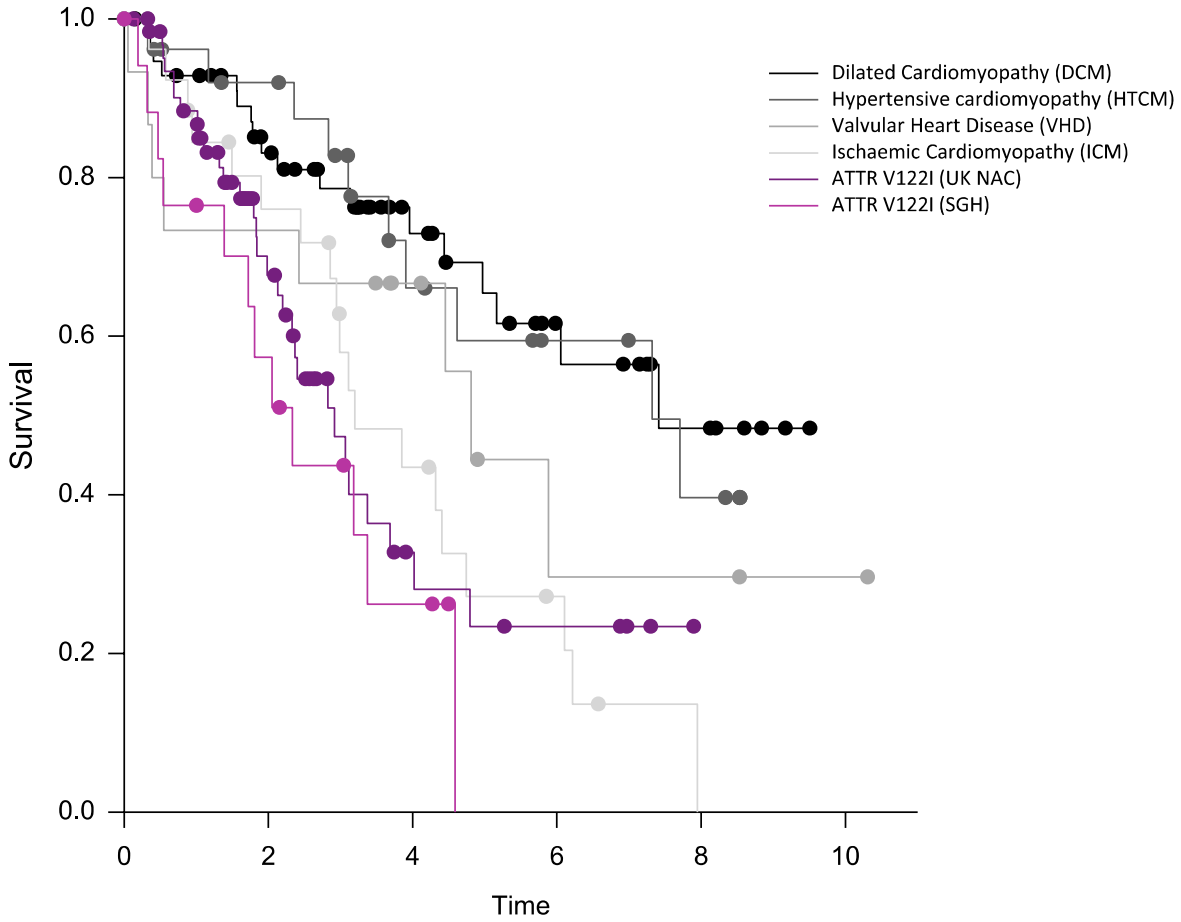
Jason N. Dungu, PhD, MRCP; Sofia A. Papadopoulou, MD; Katharine Wykes, MBBS; Ihtisham Mahmood, MBBS; Joseph Marshall, MBBS; Oswaldo Valencia, MSc, MD;

	Afro Caribbean Patients (n=211)	White Patients (n=974)	P value
Age (years)	71 (54-77)	74 (64-82)	<0.0001
Ischemic CM Non-ischemic	13% 87%	41% 59%	<0.001
HTN cardiomyopathy	12.3%	2.2%	<0.001
Cardiac Amyloid	**11.4%**	**1.6%**	**<0.001**
ATTR V122I	**8%**	**0.3%**	**<0.001**

Comparison of Patients With Heart Failure at St George's Hospital According to Ethnicity

Dungu JN, et al. *Circ Heart Fail*. 2016;9:e003352.

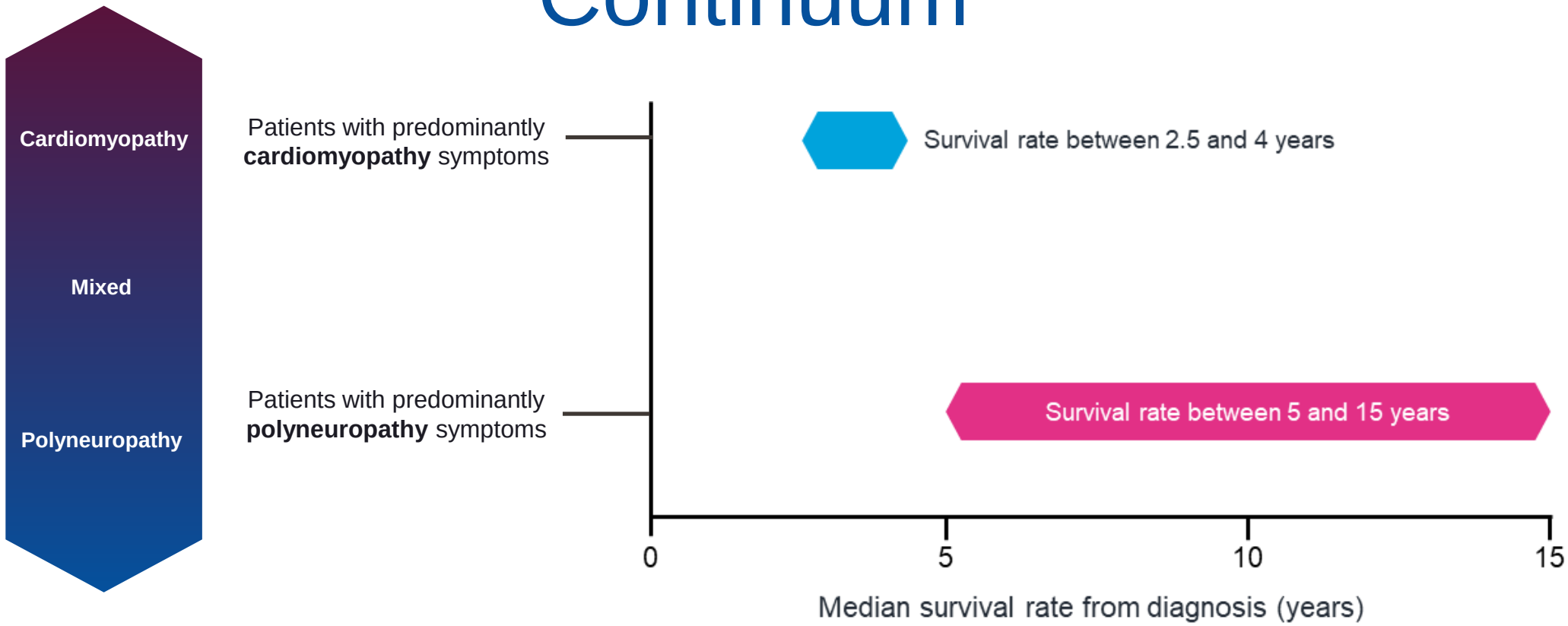
Top 5 Diagnoses in Afro-Caribbean Heart Failure Patients



Difference in survival according to the top 5 causes of heart failure in Afro-Caribbean patients attending the general heart failure clinic and 64 Afro-Caribbean patients with ATTR V122I

ATTR, transthyretin amyloidosis; NAC, National Amyloidosis Center; SGH, St George's Hospital.
Dungu JN, et al. *Circ Heart Fail*. 2016;9:e003352.

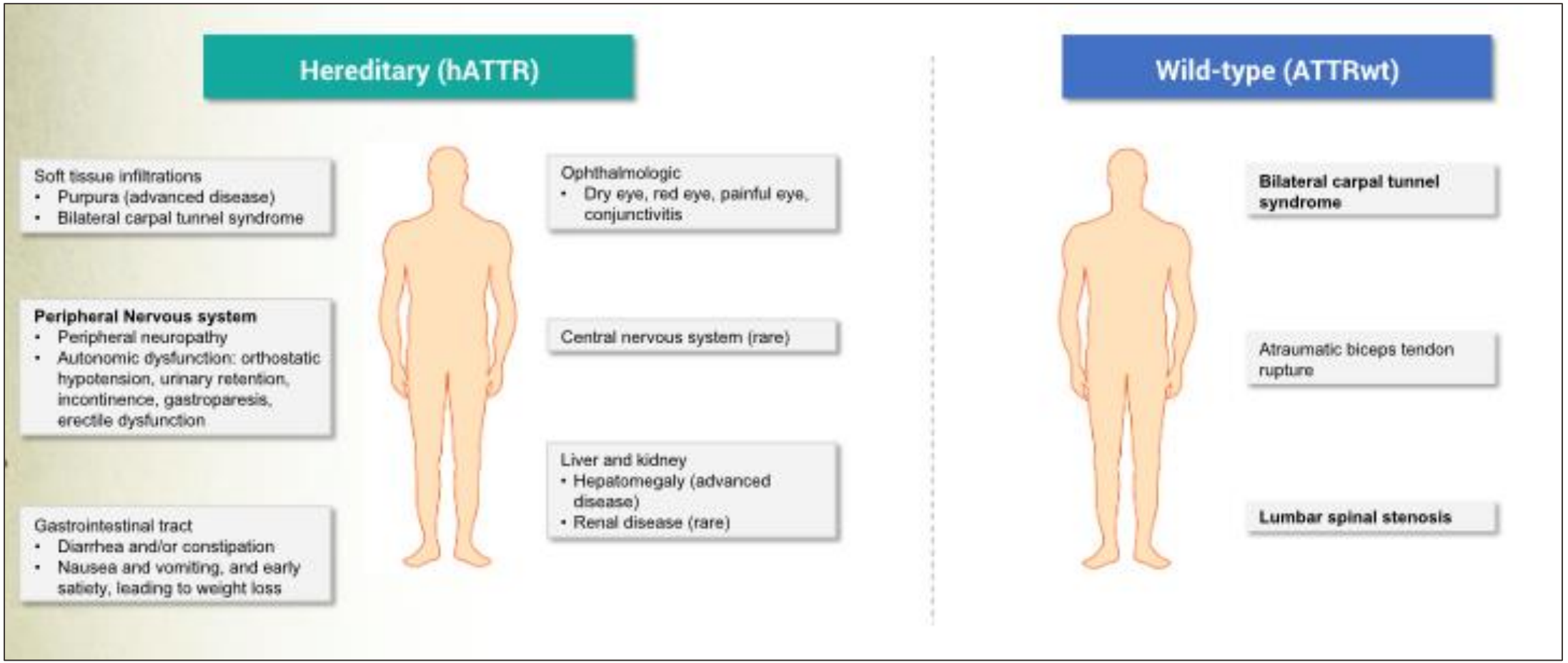
Survival Rates Vary Across the Disease Continuum



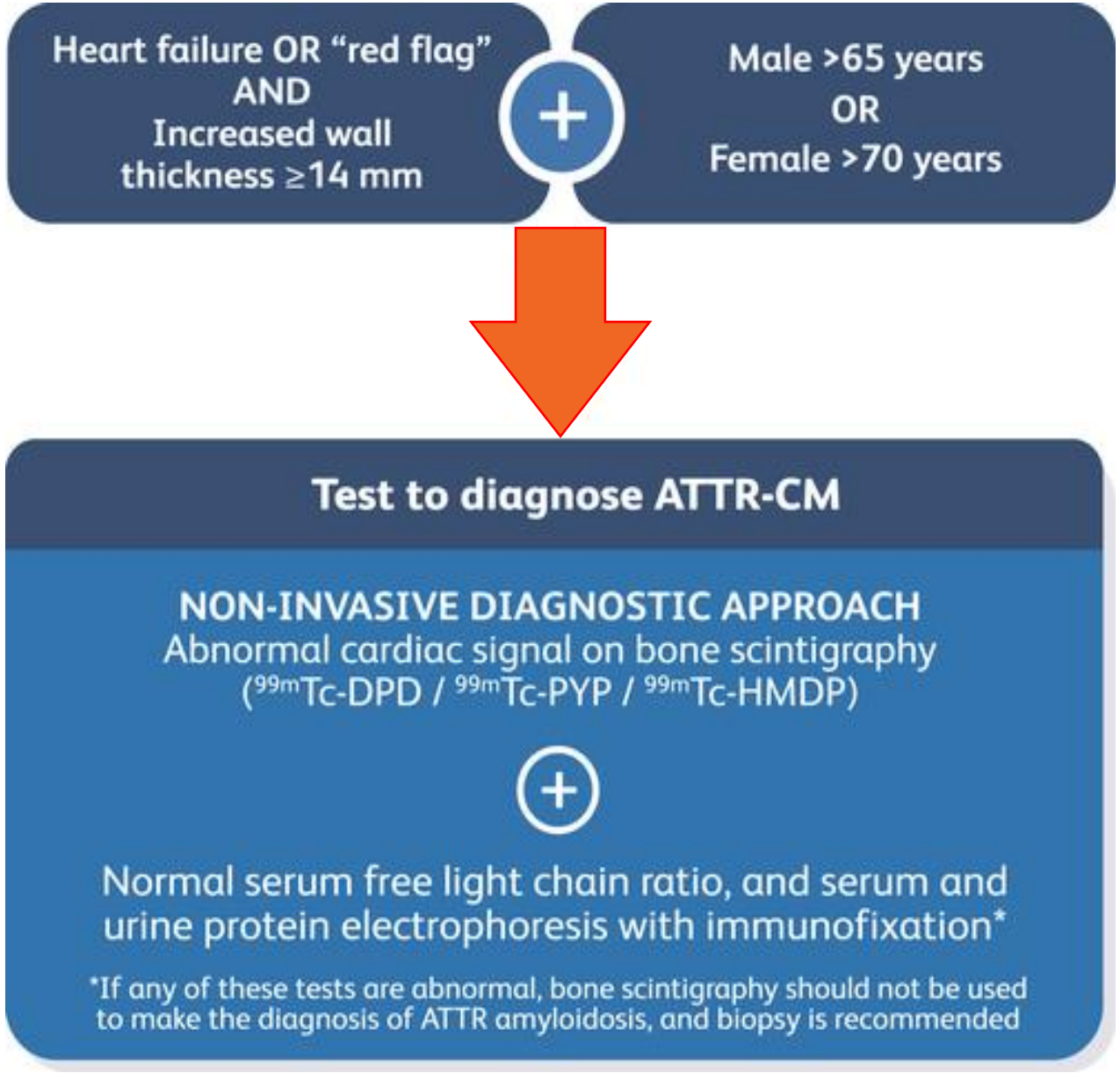
Early diagnosis will become increasingly important in improving patient outcomes

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

Clinical Spectrum of ATTR-CM is Heterogenous: Non-Cardiac Clues



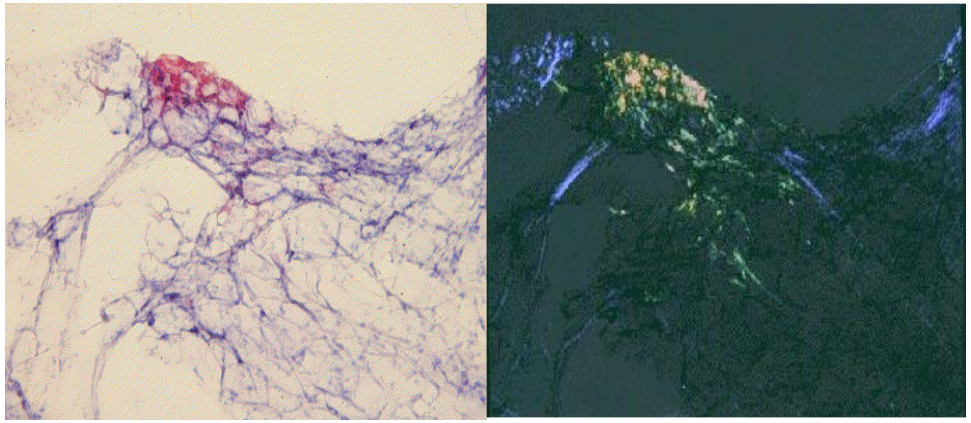
1. Ruberg FL, Grogan M, Hanna M, et al. *J Am Coll Cardiol*. 2019;73(22):2872-2891. Maurer M. *Circ Heart Fail*. 2019;12:e006075.



Ronald M. Witteles et al. *J Am Coll Cardiol HF* 2019; 7:709-716.

Cardiac Biopsy as Diagnostic Reference Standard

- Biopsy and staining of affected organ with Congo red and antibody panel
  - Renal biopsy: standard nephrology practice[1]
  - Heart biopsy: involves risk, introduces delay, expensive[1-3]
- Screening biopsy
  - Rectal: more invasive, less sensitive1
  - Abdominal fat aspirate: highly variable sensitivity[1,2]
- Reporting
  - Challenges to read the CR staining
  - Challenges related to typing



Amyloid type and load by SAP scintigraphy scan[3]	FNAFP sensitivity
AL amyloidosis	
Large burden	100%
Moderate burden	97%
Small burden	78%
ATTR amyloidosis	
hATTR	45%
ATTRwt	15%

Images courtesy of Dr Marianna Fontana.

1. van Gameren II, et al. *Arthritis Rheum*. 2006;54:2015-2021. 2. Ansari-Lari MA, et al. *Diagn Cytopathol*. 2004;30:178-181. 3. Quarta CC, et al. *Eur Heart J*. 2017;38:1905-1908.

AL, amyloid light chain; ATTR, transthyretin amyloidosis; ATTRwt, wild-type ATTR; FNAFP, fine-needle aspiration of abdominal fat pad; SAP, serum amyloid P.

Noninvasive Testing is Key!

- Don’t stop at ECG/Echo
- Echo with strain (cherry on top)
- CMR
- PYP

	Suggestive features
Electrocardiography	Low voltages in context of increased echocardiographic wall thickness Caution: low voltage seen in < 50% of cases with ATTR-CM (ref18)
Echocardiography	1. Increased left +/− right ventricular wall thickness 2. Apical sparing regional longitudinal strain pattern (>2:1 ratio) or increased LVEF to global longitudinal strain ratio (>4)
Cardiac magnetic resonance imaging (CMR)	1. Diffuse sub-endocardial or transmural late gadolinium enhancement 2. Increased myocardial native T1 3. Increased extracellular volume fraction (typically > 0.4) 4. Inability to suppress myocardial signal with PSIR LGE imaging
Nuclear imaging with bone avid tracers	1. Grade 2 or 3 tracer uptake in conjunction with no evidence of monoclonal gammopathy by serum/urine testing

Ruberg FL, et al. *J Am Coll Cardiol*. 2019;73(22):2872-2891.

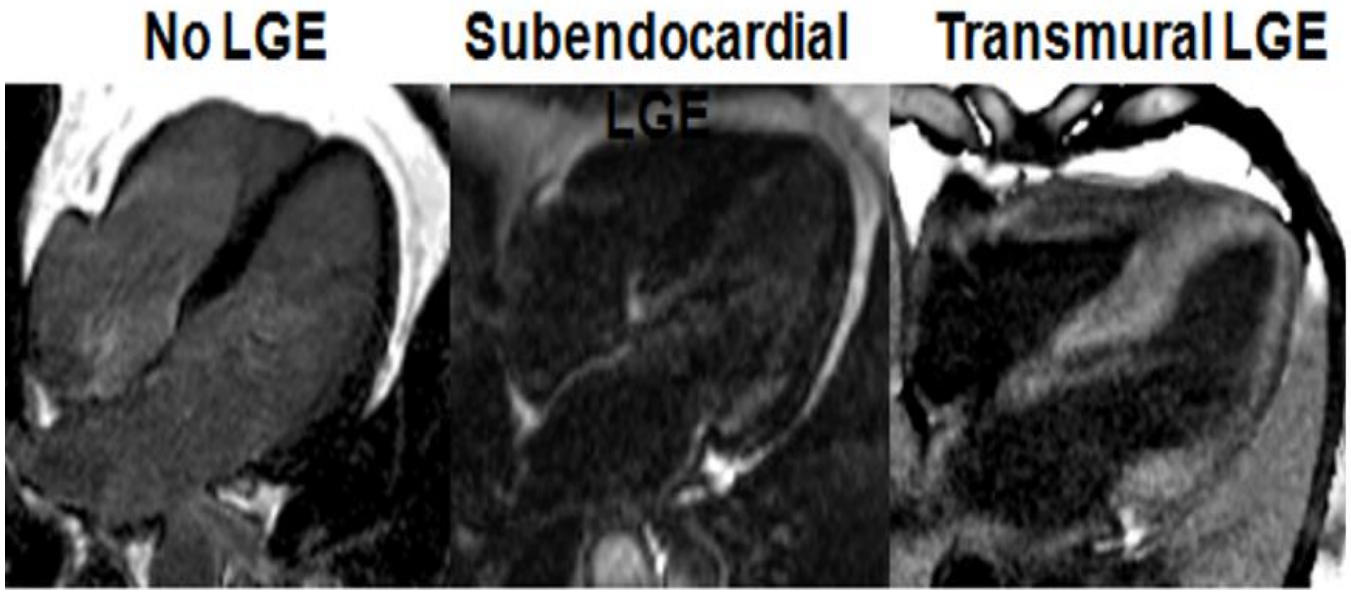
Cardiovascular Magnetic Resonance

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Pablo Garcia-Pavia [1,2,3]*, Claudio Rapezzi[4,5], Yehuda Adler[6], Michael Arad[7], Cristina Basso [3,8,9], Antonio Brucato [10], Ivana Burazor [11], Alida L.P. Caforio [3,12], Thibaud Damy [3,13], Urs Eriksson [14], Marianna Fontana [15], Julian D. Gillmore [15], Esther Gonzalez-Lopez[1,3], Martha Grogan[16], Stephane Heymans[17,18,19], Massimo Imazio [20], Ingrid Kindermann[21], Arnt V. Kristen [22,23], Mathew S. Maurer[24], Giampaolo Merlini [25,26], Antonis Pantazis[27], Sabine Pankuweit[28], Angelos G. Rigopoulos[29], and Ales Linhart [30]

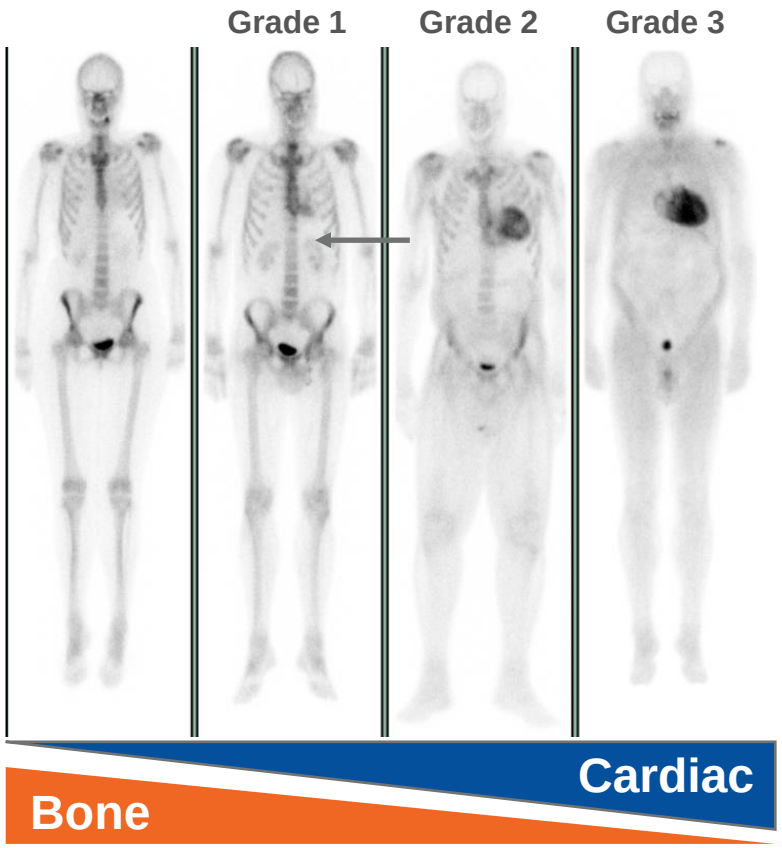
Table 2 Echocardiographic and cardiac magnetic resonance criteria for non-invasive and invasive (with extracardiac biopsy-proven amyloidosis) diagnosis of cardiac amyloidosis

CMR
Characteristic CMR findings (a and b have to be present):
a. Diffuse subendocardial or transmural LGE
b. Abnormal gadolinium kinetics[a]
c. ECV ≥0.40% (strongly supportive, but not essential/diagnostic)



Garcia-Pavia P, et al. *Eur Heart J.* 2021;42(16):1554-1568.

^{99m}Tc-DPD (Bone) Scintigraphy Has High Sensitivity and Specificity for Cardiac ATTR



- **Grade 1**: mild cardiac uptake with no attenuation of bone uptake[1,2]
- **Grade 2**: moderate cardiac uptake, greater than bone[1,2]
- **Grade 3:** strong cardiac uptake with little or no bone signal[1,2]

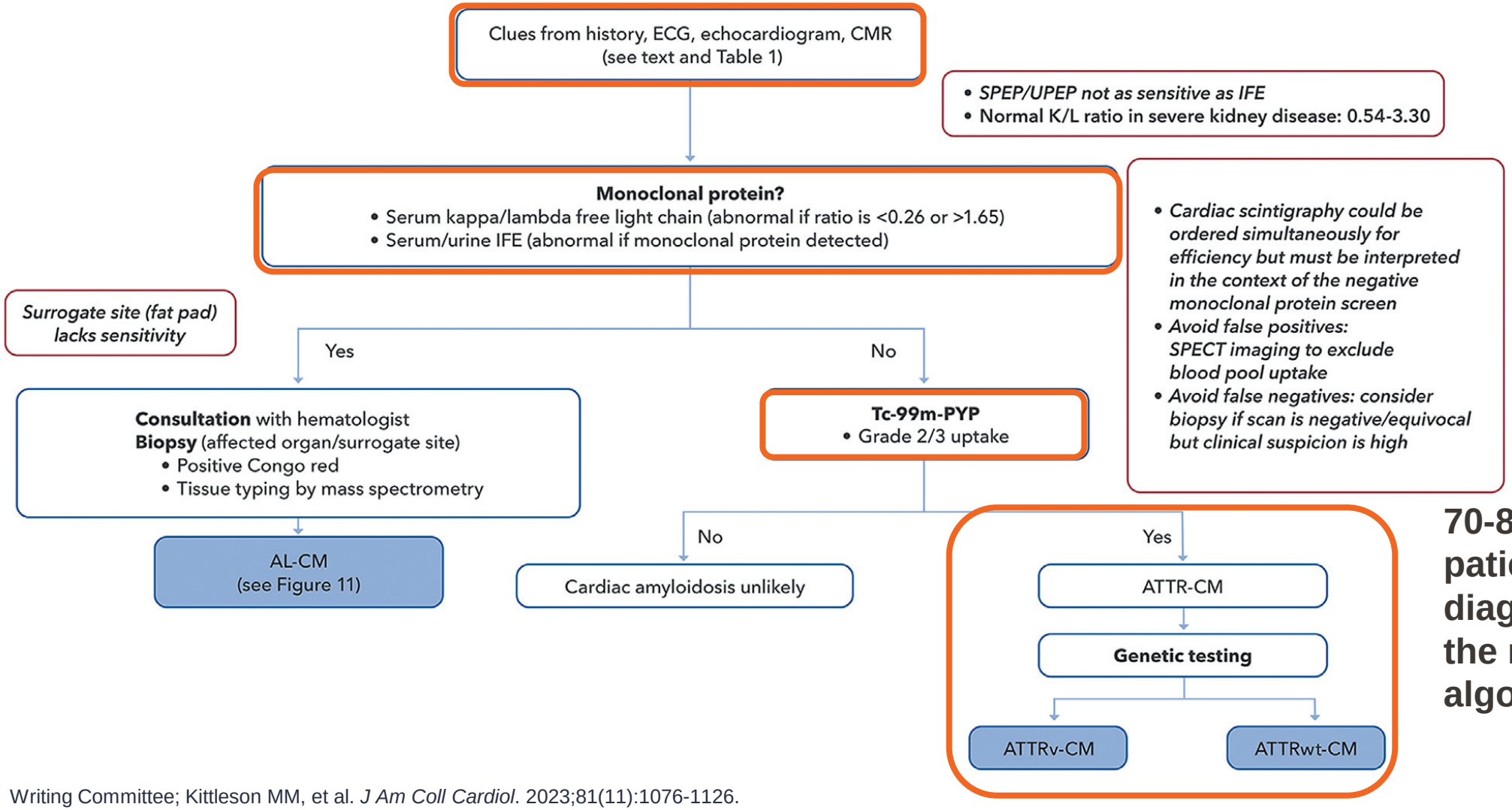
Cardiac ATTR[1]
Positive: >99% sensitive
Grade 2/3: >90% specific

Image adapted from Hutt DF, et al, 2014.[1]

1. Hutt DF, et al. *Eur Heart J Cardiovasc Imaging*. 2014;15(11):1289-1298. 2. Rapezzi C, et al. *JACC Cardiovasc Imaging*. 2011;4(6):659-670.

^{99m}Tc-DPD, ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ATTR, transthyretin amyloidosis.

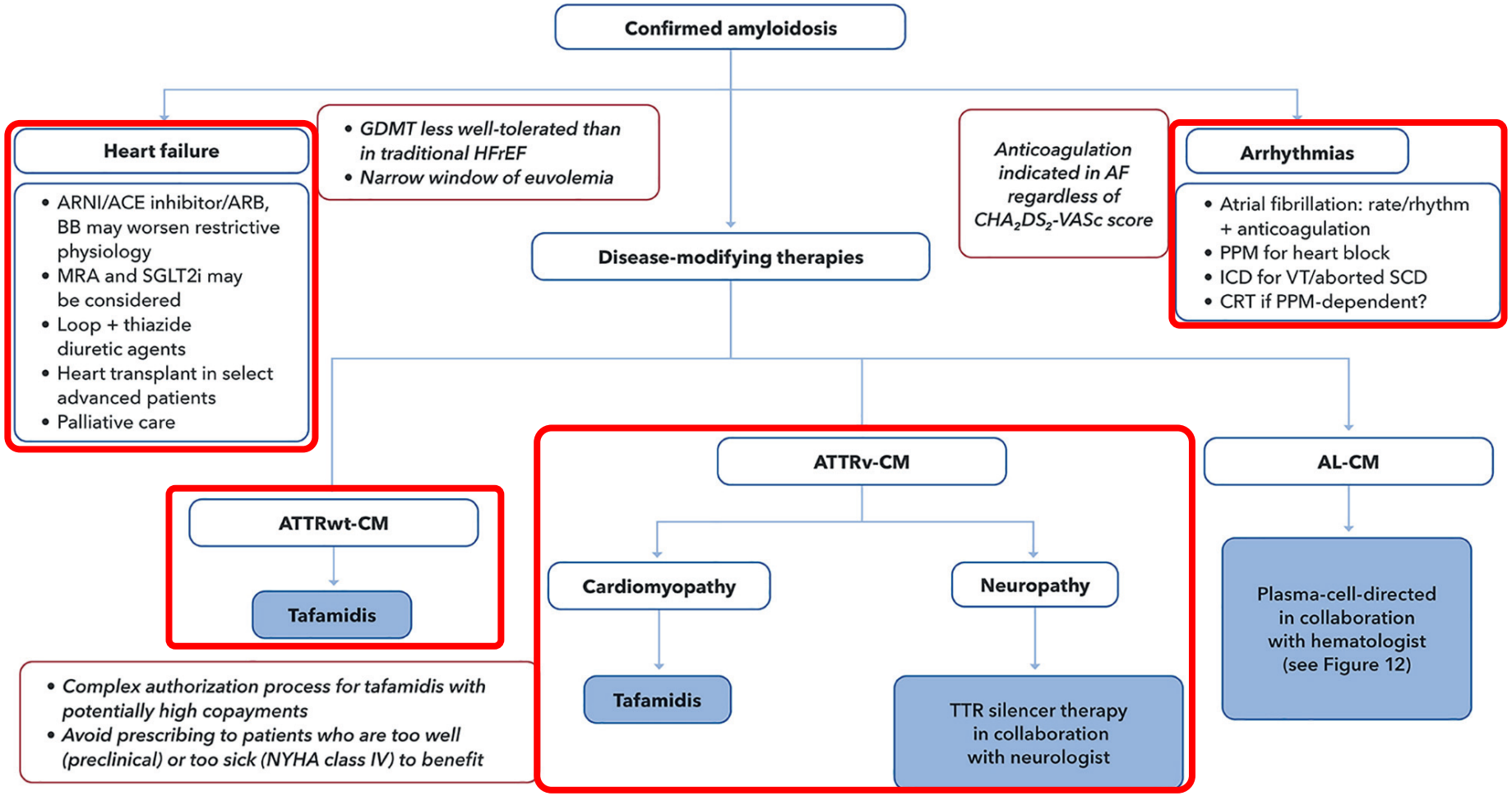
Diagnostic Algorithm for Cardiac Amyloidosis



70-80% of patients are diagnosed using the noninvasive algorithm

Writing Committee; Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126.
AL-CM , amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM, amyloid transthyretin cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance; ECG, electrocardiogram; IFE, immunofixation electrophoresis; K/L, kappa/lambda; PYP, pyrophosphate; SPECT, single-photon emission computed tomography; SPEP/UPEP, serum/urine protein electrophoresis.

Cardiac Amyloidosis Management

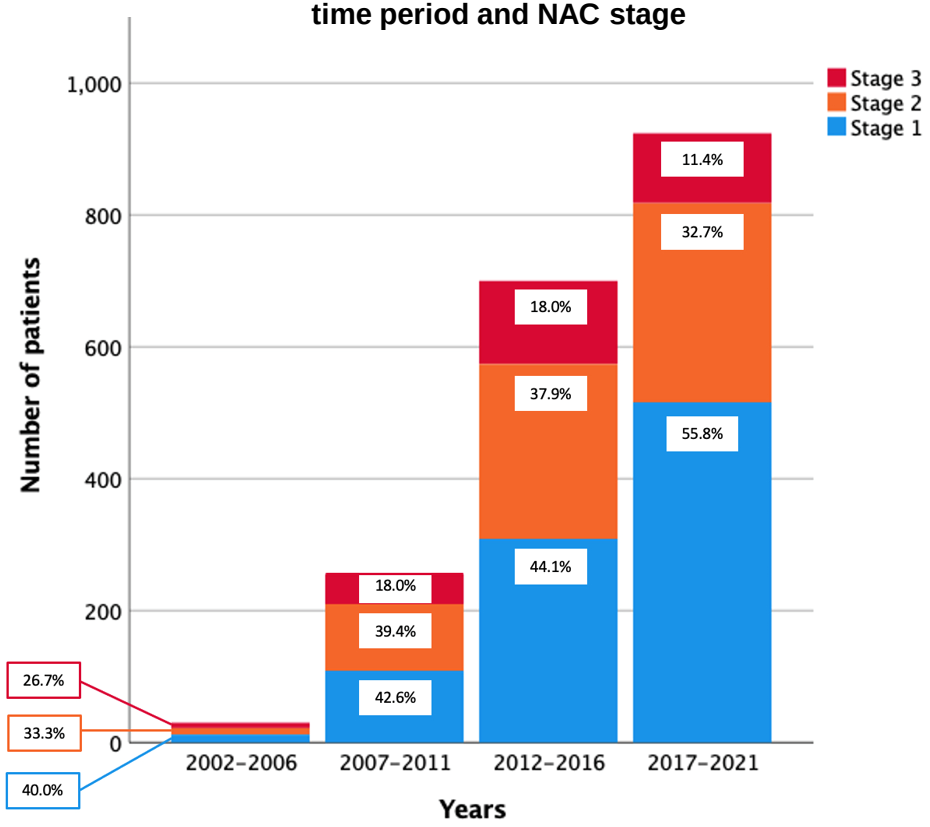


Writing Committee; Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126.
AF, atrial fibrillation; ARNI/ACE inhibitor/ARB, renin-angiotensin system inhibitors; AL-CM, amyloid monoclonal immunoglobulin light chain; ATTR, amyloid transthyretin; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; BB, beta-blocker; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PPM, permanent pacemaker; SCD, sudden cardiac death; SGLT2i, sodium glucose cotransporter 2 inhibitor; TTR, transthyretin; VT, ventricular tachycardia.

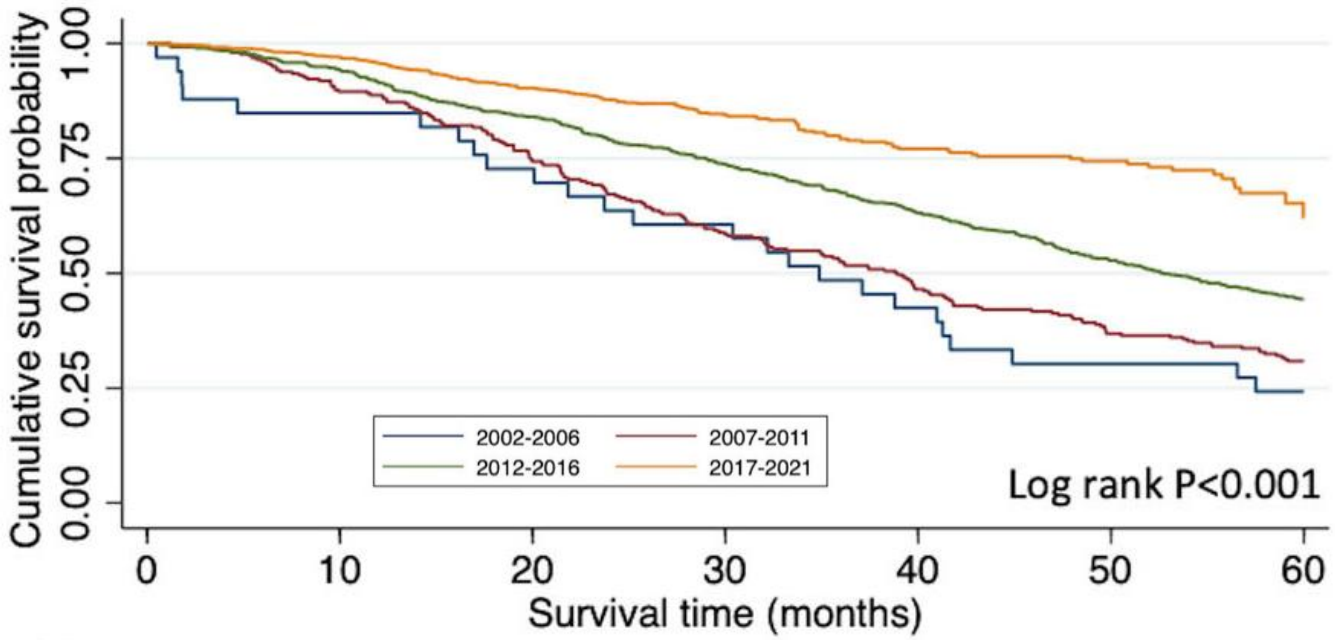
Changes in the Diagnosis Over the Past 20 Years: Lower Disease Burden and Better Prognosis at Diagnosis

Observational cohort study of all patients with predominantly cardiac signs and symptoms of ATTR amyloidosis referred to the UK National Amyloidosis Centre (2002–2021)

Diagnoses of ATTR cardiac amyloidosis according to time period and NAC stage



60-month survival in all ATTR-CA patients by time period at diagnosis



ATTR, transthyretin-mediated amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis.

Ioannou A, et al. *Circulation* 2022;146(22):1657-1670.

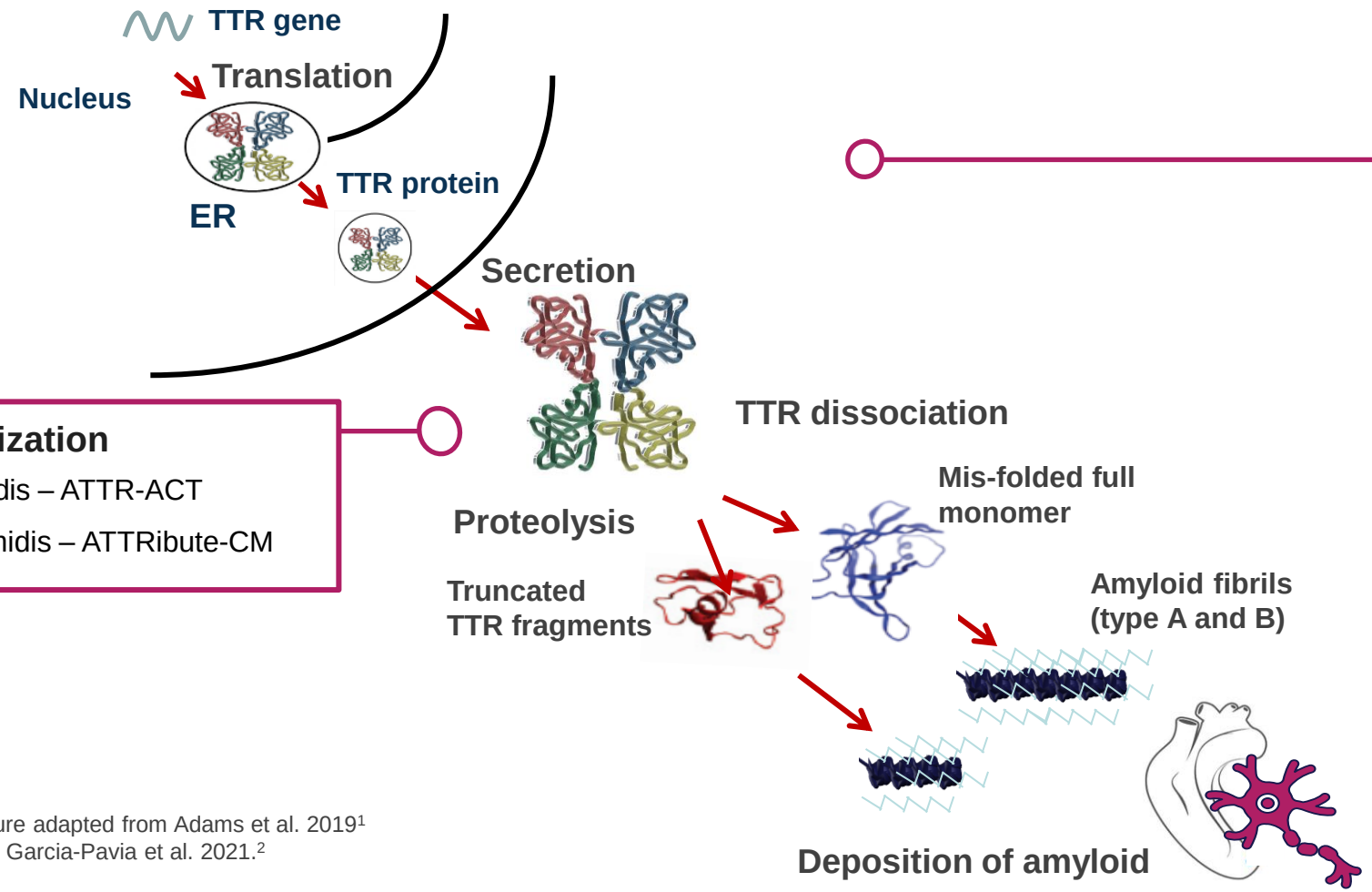
Changes in Supportive Heart Failure Treatment in Cardiac ATTR Amyloidosis

- Conventional heart failure medications were not widely prescribed in ATTR-CA
- Patients that receive heart failure medication have more severe cardiac disease
- Beta-blockers and ACEi/ARBs were often discontinued, but low-dose beta-blockers were associated with reduced risk of mortality in patients with a LVEF ≤40
- MRAs were rarely discontinued and were associated with reduced risk of mortality in the overall population; but these findings require confirmation in prospective randomized controlled trials.

Analysis of 2371 consecutive patients diagnosed with ATTR-CA at the National Amyloidosis Centre between 2000 and 2022

Ioannou A, et al. *Eur Heart J*. 2023;44(31):2893-2907.

Disease-Modifying Treatment: ATTR-CM Therapeutic Options



Suppression of TTR synthesis

Gene silencing – RNAi therapy

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

ASO therapy

- Eplontersen - CARDIO-TTRansform
- Inotersen -

TTR stabilization

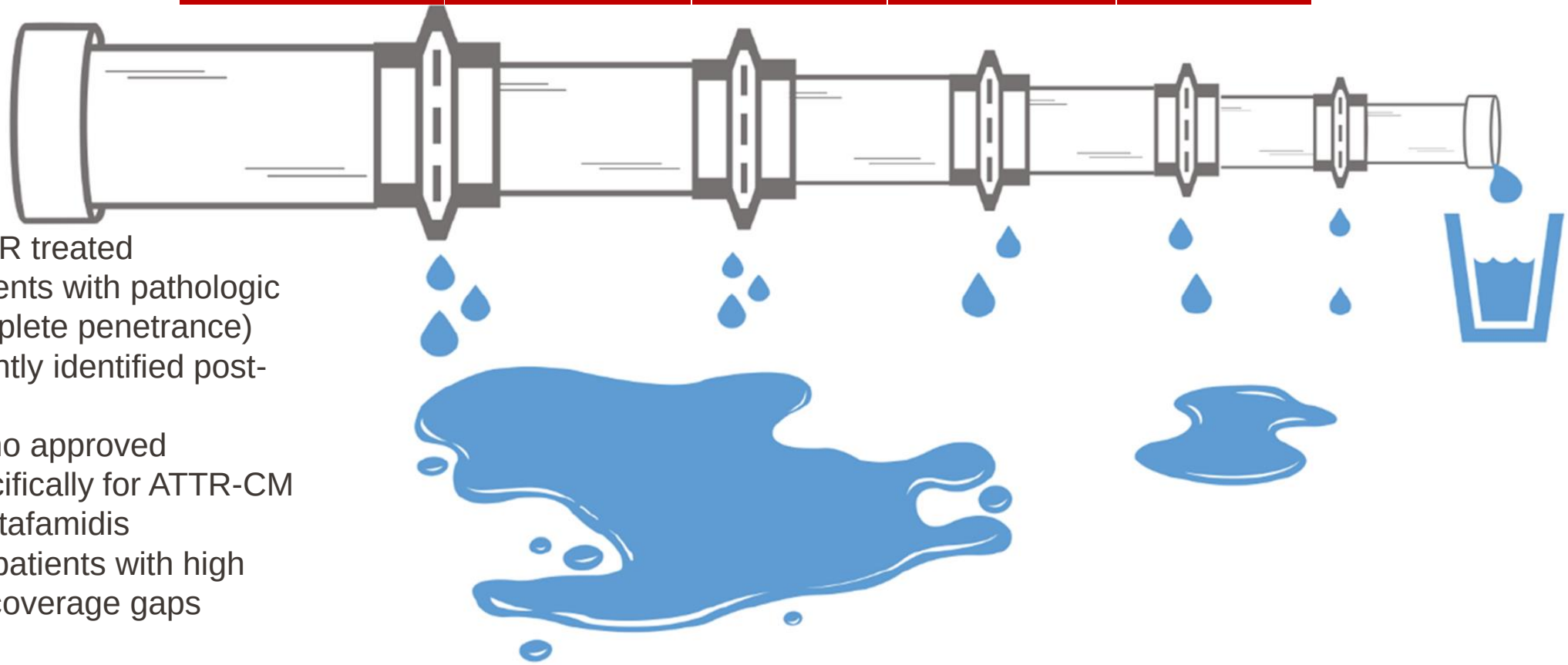
- Tafamidis – ATTR-ACT
- Acoramidis – ATTRibute-CM

Figure adapted from Adams et al. 2019[1] and Garcia-Pavia et al. 2021.[2]

1. Adams D, et al. *Nat Rev Neurol.* 2019;15(7):387-404. 2. Garcia-Pavia P, et al. *Eur Heart J.* 2021;42(16):1554-1568. 3. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 4. Onpattro (patisiran). https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf. 5. Amvuttra (vutrisiran). https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf. 6. Tegsedi (inotersen). https://www.ema.europa.eu/en/documents/product-information/tegsedi-epar-product-information_en.pdf. 7. 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.

Leaky Pipeline for TTR amyloidosis

Pathologic TR Deposition	Symptomatic Disease	Timely Diagnosis	Therapeutic Approved	Insurance Coverage



- Only fraction ATTR treated
- CM not in all patients with pathologic mutations (incomplete penetrance)
- ATTR CM frequently identified post-mortem
- Until May 2019, no approved therapeutics specifically for ATTR-CM
- Cost >$200,000, tafamidis
- Unaffordable for patients with high deductibles and coverage gaps

Spencer-Bonilla G, et al. *Curr Cardiovasc Risk Rep*. 2021;15(6):8.

Summary

- ATTR-CM: life-threatening, progressive disease, often underdiagnosed and misdiagnosed
- Certain clinical scenarios (red flags) have been identified for ATTR-CM
- ATTR-CM definitive diagnosis usually achieved noninvasively
- Accurate, early diagnosis ATTR-CM key to enabling appropriate patient care

Summary

- There are therapies available that address the underlying cause of hATTR amyloidosis and can help decrease amount TTR protein made in body or stabilize protein already present
- Due to progressive nature hATTR amyloidosis, managing symptoms ongoing process, clinicians may prescribe medications to treat symptoms and reduce impact
- Additional treatment options for hATTR amyloidosis currently being researched

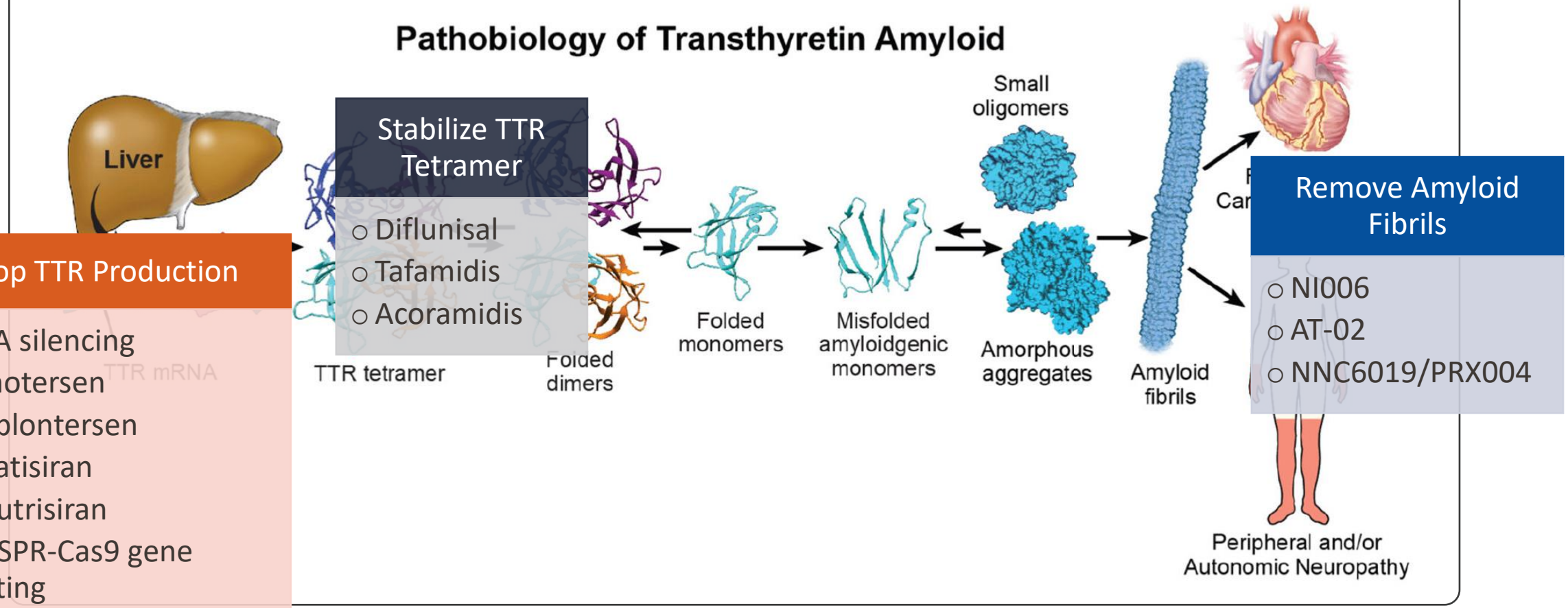
ATTR in Clinical Trials

Hongya Chen, PharmD, BCCP
Cardiology Clinical Pharmacist
Oregon Health & Science University
Portland, OR

medtelligence℠

TTR to Amyloid

The Mechanism of TTR Protein Dissociation, Misfolding, and Aggregation as Amyloid Fibrils, Which Results in Organ Dysfunction



Stop TTR Production

- RNA silencing
  - Inotersen
  - Eplontersen
  - Patisiran
  - Vutrisiran
- CRISPR-Cas9 gene editing
  - NTLA-2001 (phase 3)

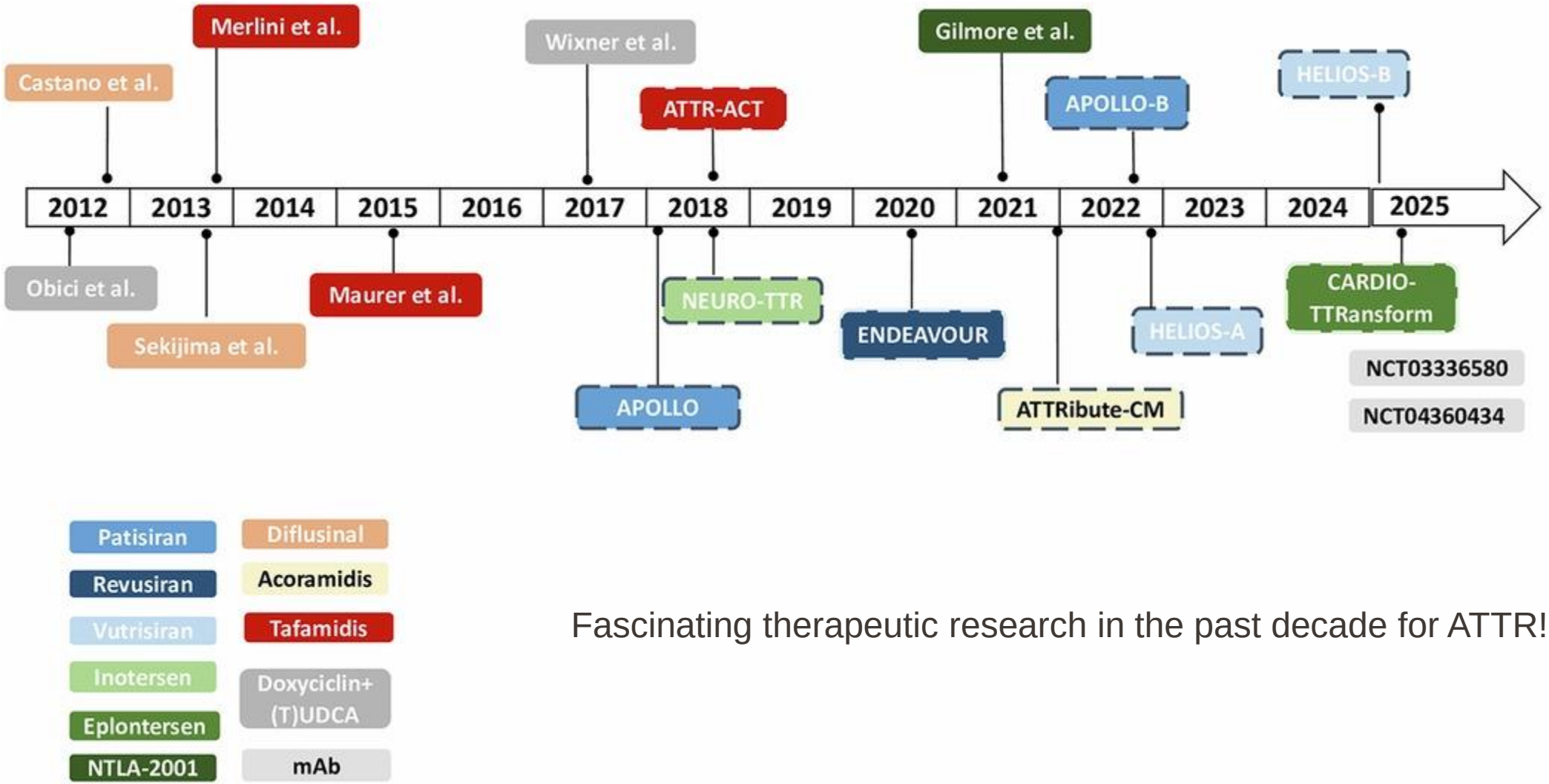
Stabilize TTR Tetramer

- Diflunisal
- Tafamidis
- Acoramidis

Remove Amyloid Fibrils

- NI006
- AT-02
- NNC6019/PRX004

ATTR, transthyretin amyloidosis; TTR, transthyretin.
Ruberg FL. *J Am Coll Cardiol.* 2019;73(22):2872-2891.

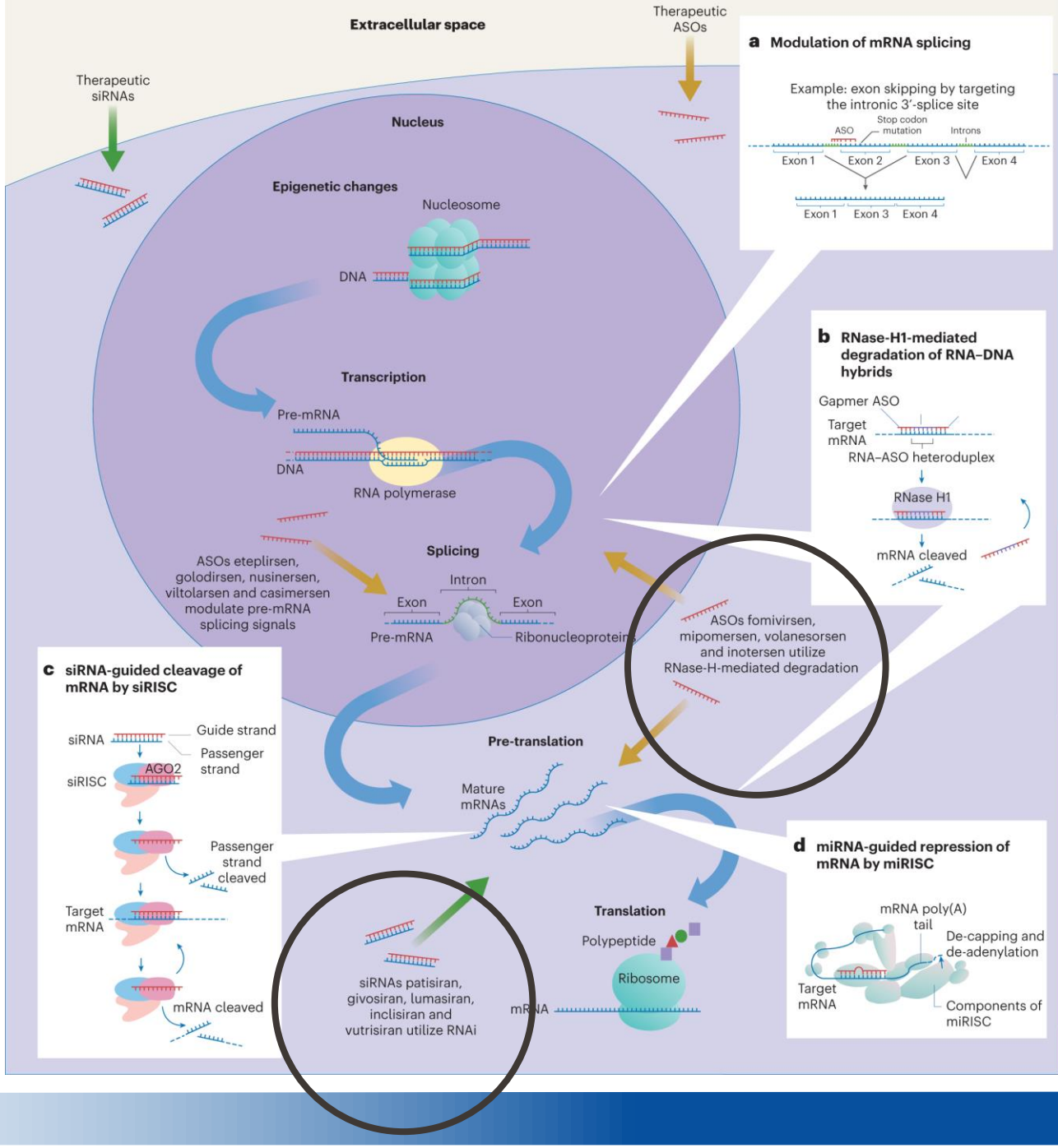


Fascinating therapeutic research in the past decade for ATTR!

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

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



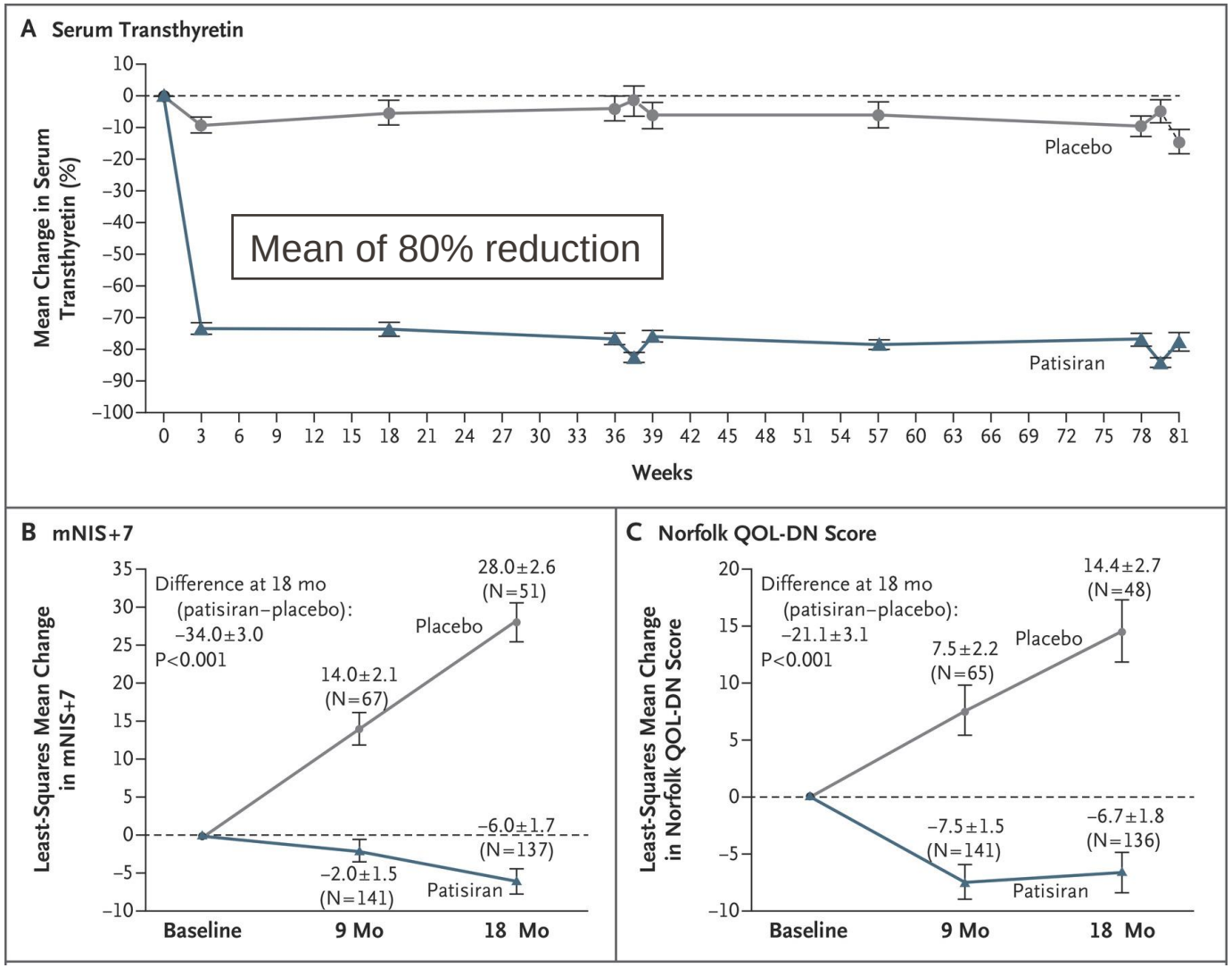
Jadhav V, et al. *Nat Biotechnol.* 2024;42(3):394-405.

APOLLO-A: Patisiran for hATTR with PN

- Randomized, placebo-controlled phase 3 study
- Enrolled 225 subjects with a diagnosis of hATTR with peripheral neuropathy
- Randomized in a 2:1 ratio to receive IV patisiran once every 3 weeks
- Excluded history of liver transplant or NYHA Class III-IV
- Primary endpoint was modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months
- Select secondary endpoint included Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) score

Adams D, et al. *New Engl J Med.* 2018;379(1):11-21.

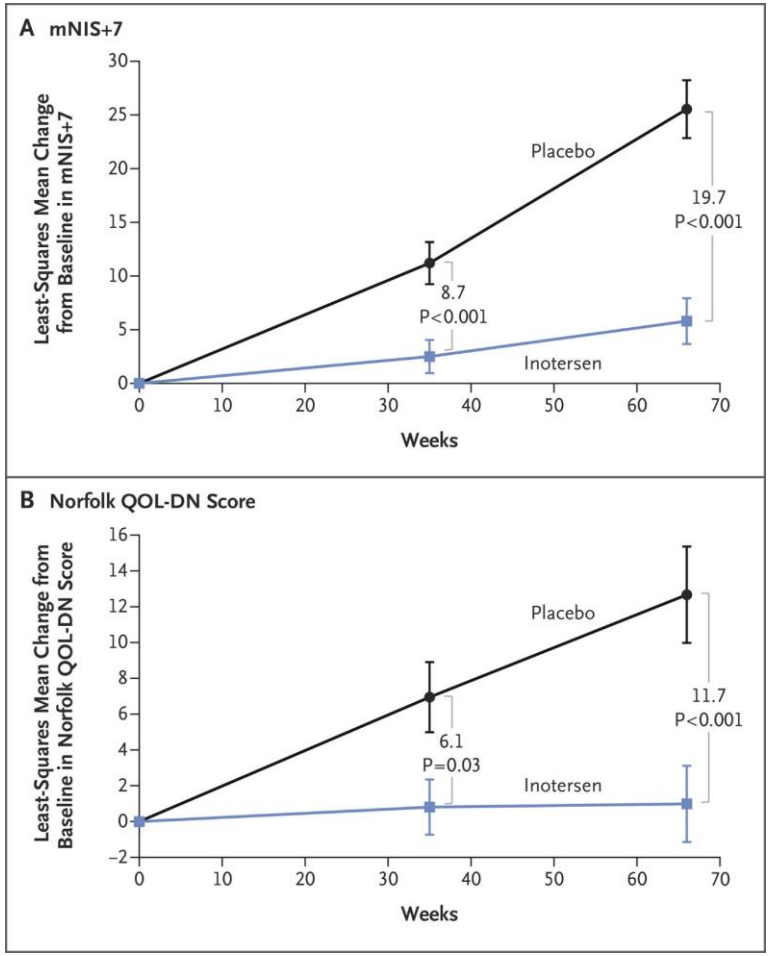
APOLLO-A: Patisiran for hATTR with PN



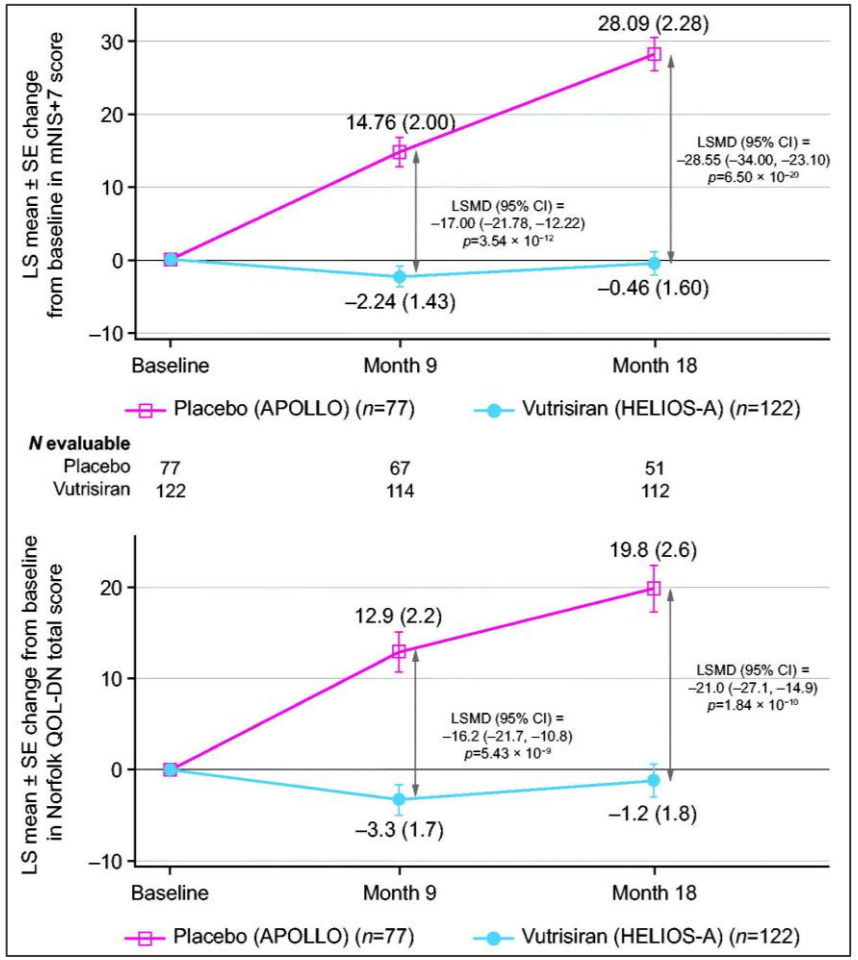
Adams D, et al. *New Engl J Med.* 2018;379(1):11-21.

Similar Results in Other Silencer Trials

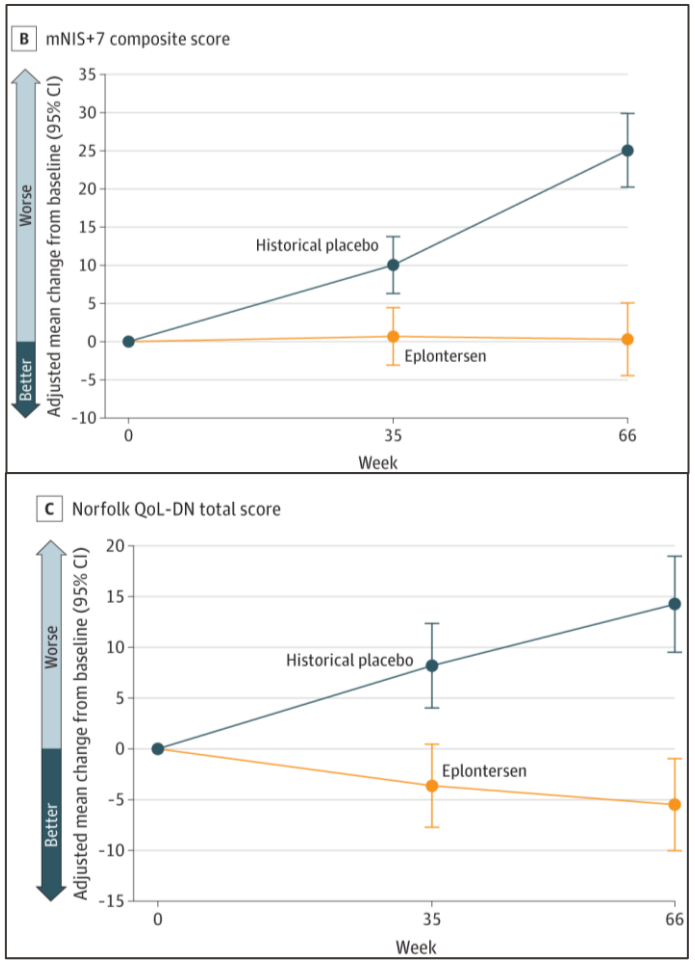
Inotersen (NEURO-TTR, 2018)



Vutrisiran (Helios-A, 2022)



Eplontersen (NEURO-TTRansform, 2023)



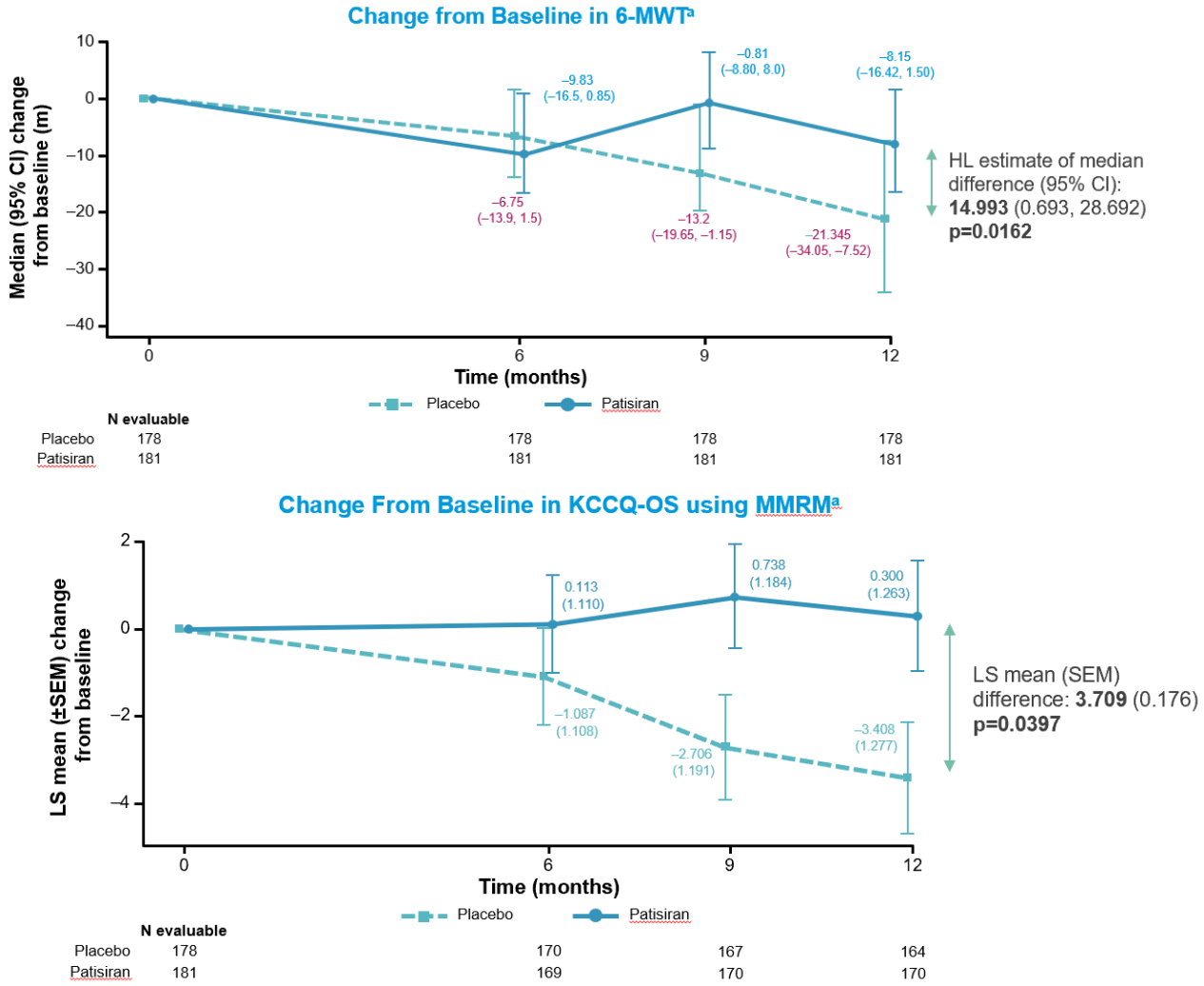
medtelligence℠

APOLLO-B: Patisiran for ATTR-CM

- Randomized, placebo-controlled phase 3 study
- Enrolled 360 subjects with a diagnosis of hATTR or wild-type ATTR cardiac amyloidosis
- Randomized in a 1:1 ratio to receive IV patisiran once every 3 weeks
  - 25% on tafamidis
- Excluded NYHA Class III (and NT-proBNP >3000 pg/mL) or Class IV
- Primary endpoint was 6-minute walk test (6MWT) at 12 months
- Select secondary endpoint included Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score

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

APOLLO-B – Patisiran



The FDA denied the request to expand patisiran's indication of ATTR cardiomyopathy:

- Despite statistically significant primary endpoint and secondary KCCQ-QS, the effects were both small, of questionable clinical meaningfulness
- Effects of 6MWT appeared confined to patients not on background therapy with tafamidis

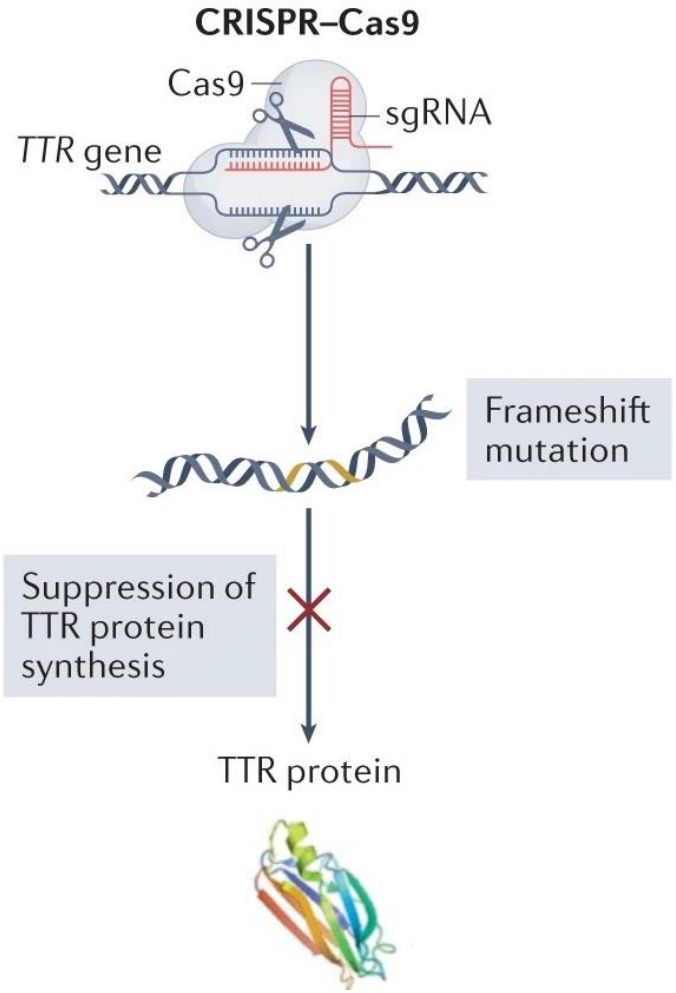
Fontana M, et al. Presented at Heart Failure 2023.
6-MWT, 6-minute walk test; CI, confidence interval; HL, Hodges-Lehmann; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, least squared; MMRM, mixed model for repeated measures; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; SEM, standard error of mean.

Ongoing Silencer Trials for ATTR-CM

- CARDIO-TTRansform (NCT04136171)
  - Enrolled 1438 subjects
  - Eplontersen SC every 4 weeks vs placebo
  - All allowed to be on tafamidis
  - Primary endpoint: composite cardiovascular (CV) mortality and recurrent CV clinical events up to 35 months

- HELIOS-B (NCT04153149)
  - Enrolled 655 subjects
  - Vutrisiran 25 mg SC every 3 months vs placebo
  - 30% on tafamidis
  - Primary endpoint: composite all-cause mortality and recurrent CV events over 30-36 months

MAGNITUDE: NTLA-2001 for ATTR-CM

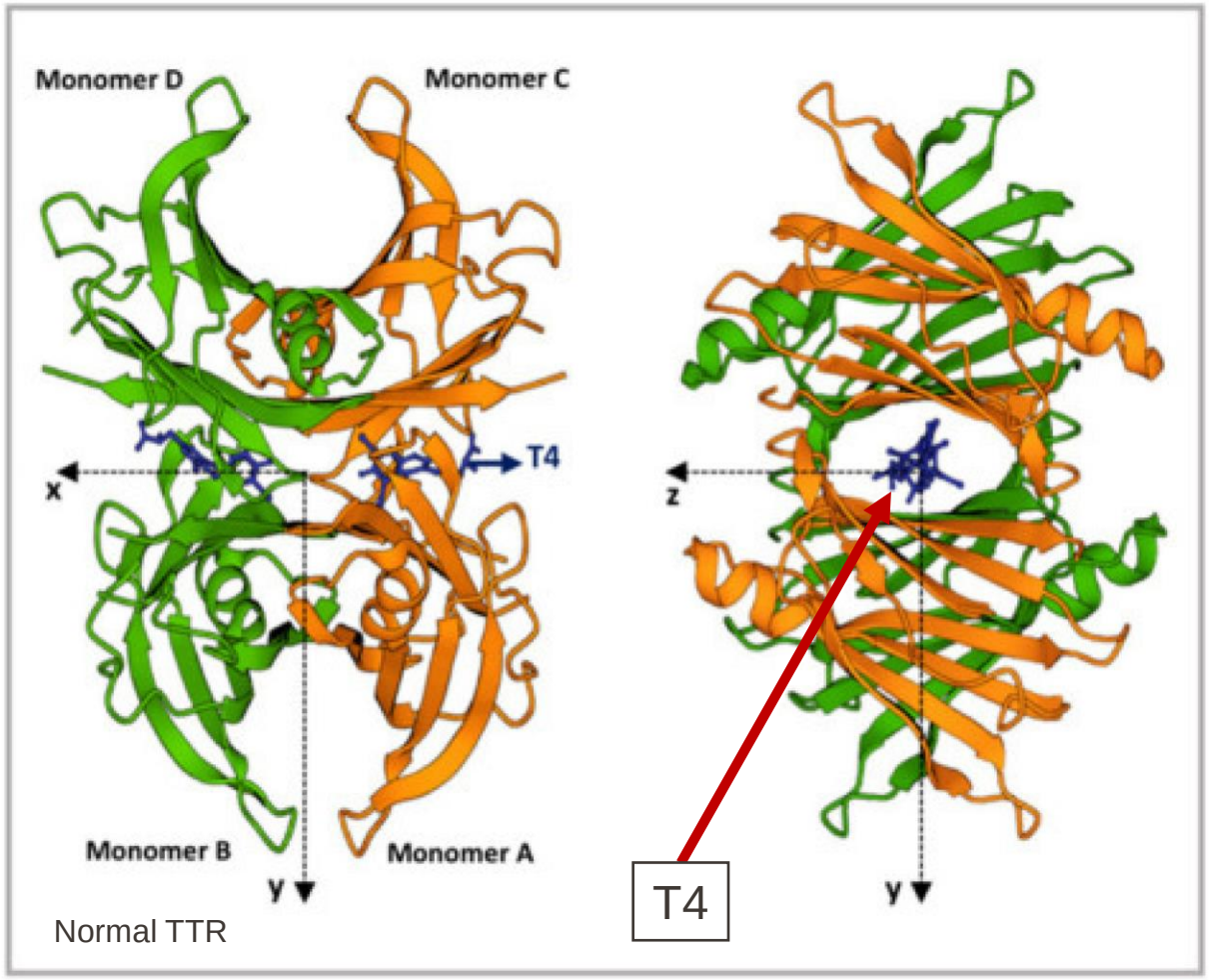


- Phase 3 study
- Single infusion of NTLA-2001
- Estimated 765 subjects, randomized 2:1 ratio
- Primary endpoint: composite CV mortality and CV events between 18 to 48 months

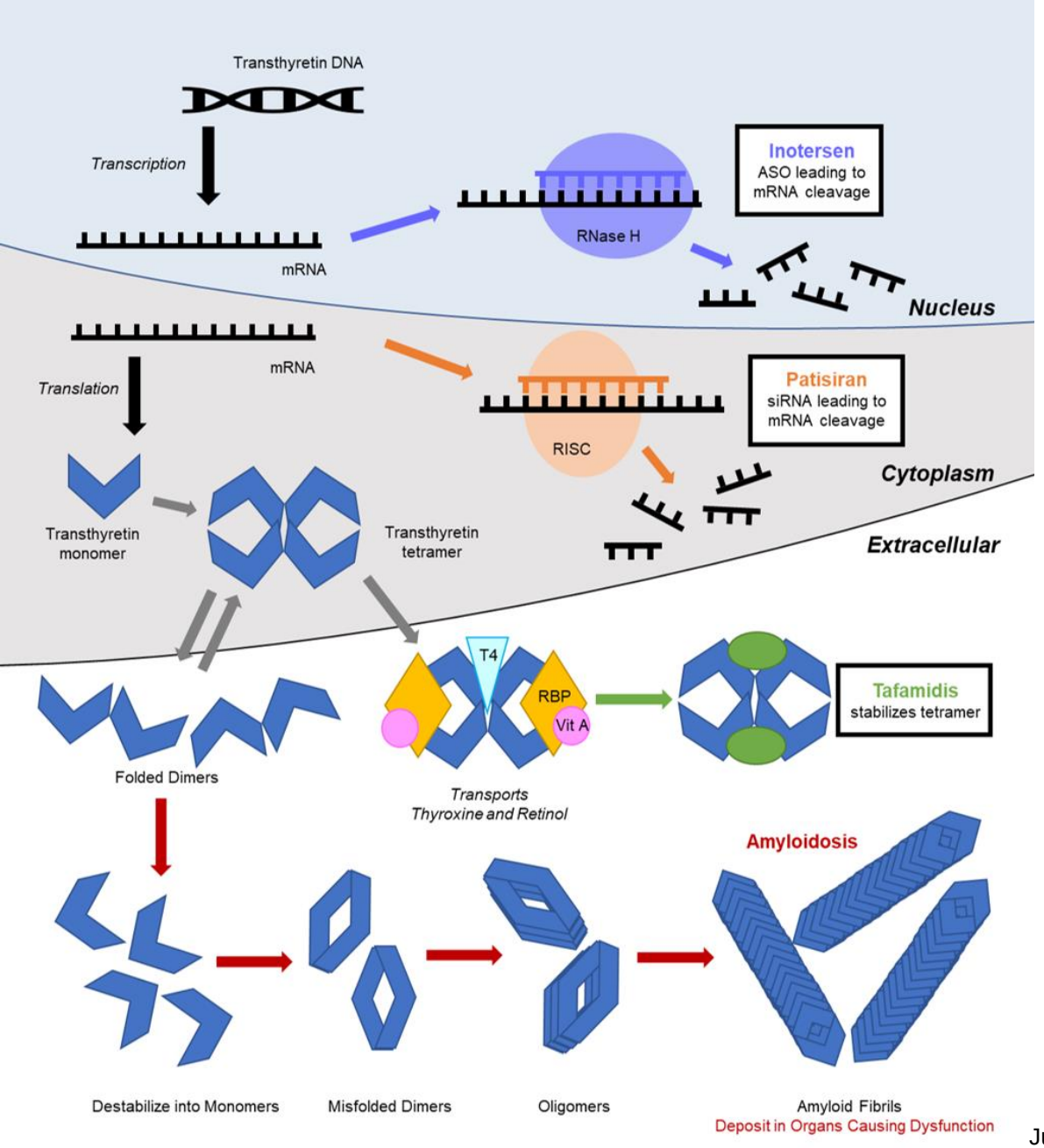
ClinicalTrials.gov. NCT06128629.

TTR Stabilizers: Mechanism of Action

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



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



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

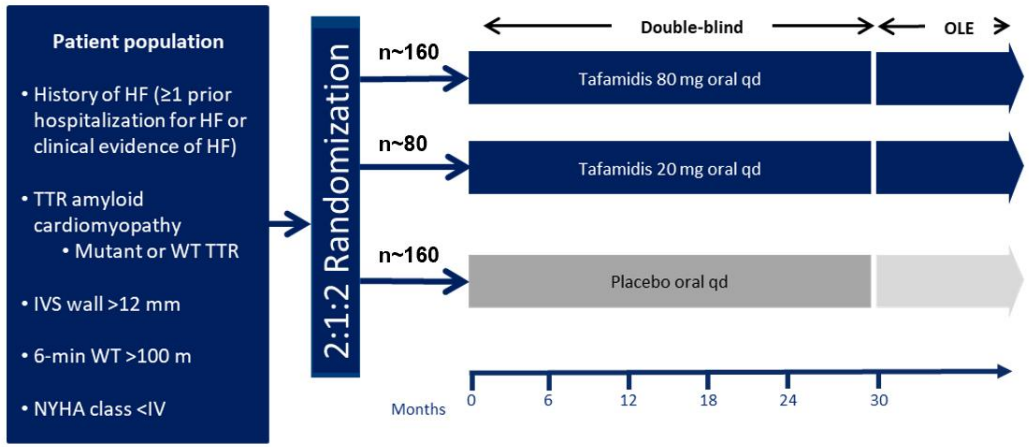
T119M:

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

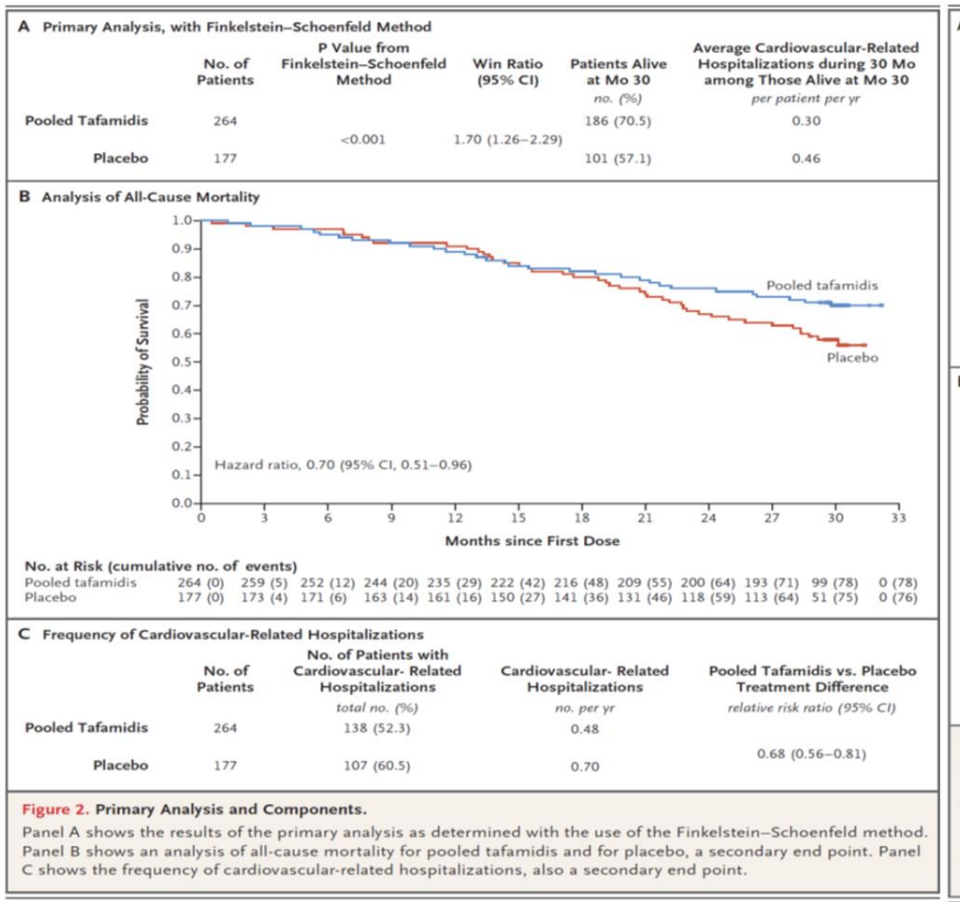
Judge DP, et al. *J Am Coll Cardiol*. 2019;74(3):285-295.

ATTR-ACT – Tafamidis



Primary endpoints: Hierarchical composite of all-cause mortality (ACM) and frequency of CV-related hospitalizations (CVH) at 30 months

Secondary endpoints: 6MWT and KCCQ



A Primary Analysis, with Finkelstein–Schoenfeld Method

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

B Analysis of All-Cause Mortality

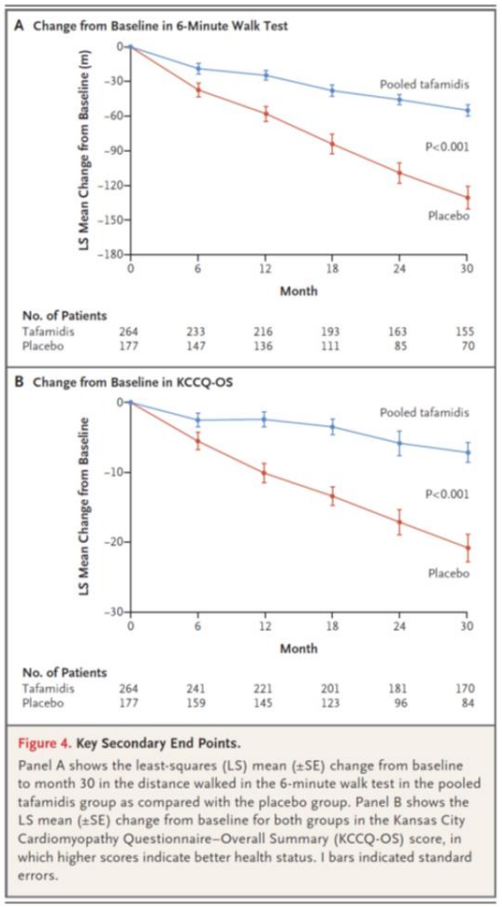
No. at Risk (cumulative no. of events)

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

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations *total no. (%)*	Cardiovascular- Related Hospitalizations *no. per yr*	Pooled Tafamidis vs. Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Figure 2. Primary Analysis and Components.
Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.



A Change from Baseline in 6-Minute Walk Test

No. of Patients

Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

B Change from Baseline in KCCQ-OS

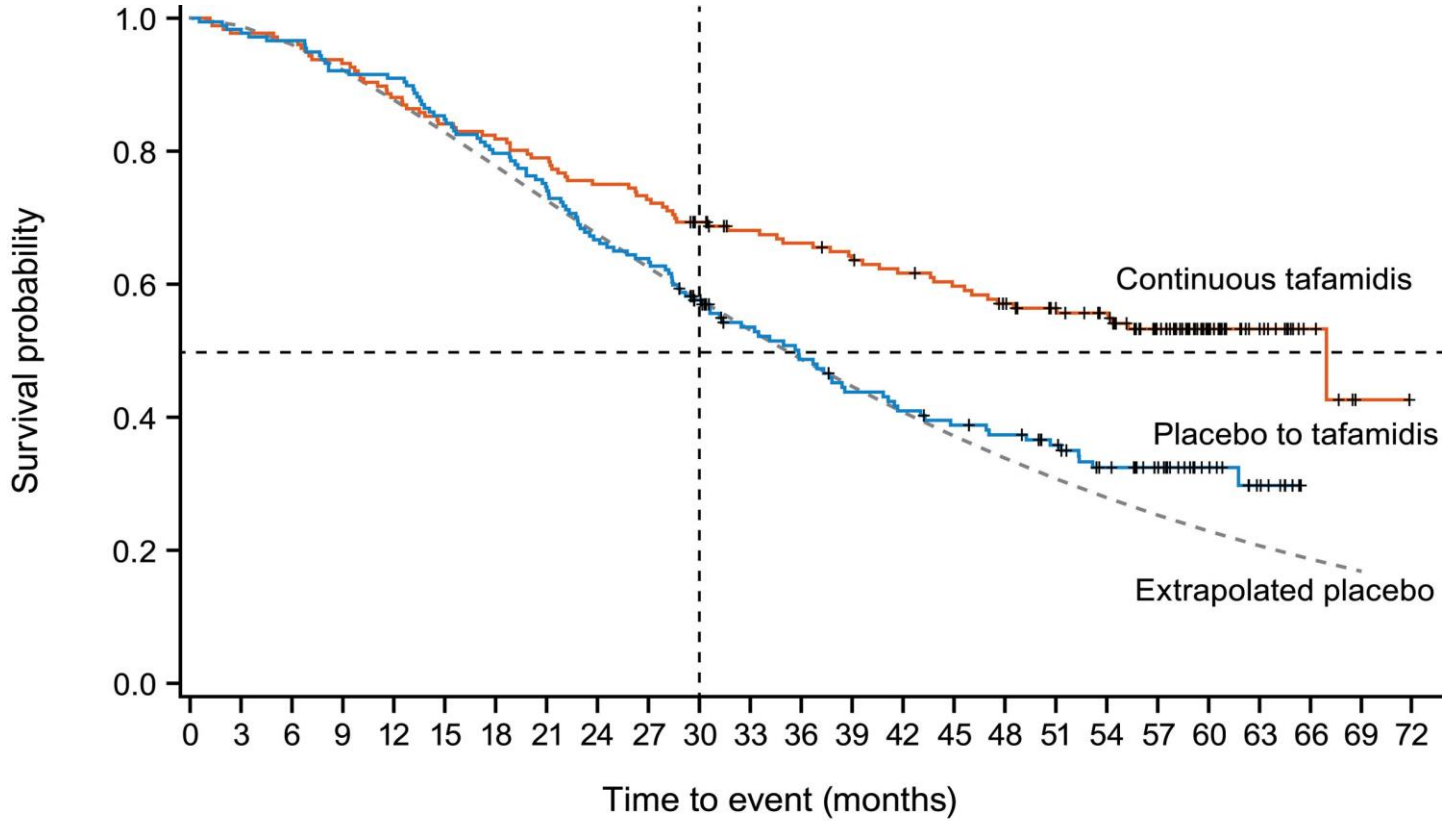
No. of Patients

Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

Figure 4. Key Secondary End Points.
Panel A shows the least-squares (LS) mean (±SE) change from baseline to month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. Panel B shows the LS mean (±SE) change from baseline for both groups in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score, in which higher scores indicate better health status. I bars indicated standard errors.

Maurer SM, et al. *N Engl J Med*. 2018;379(11):1007-1016.

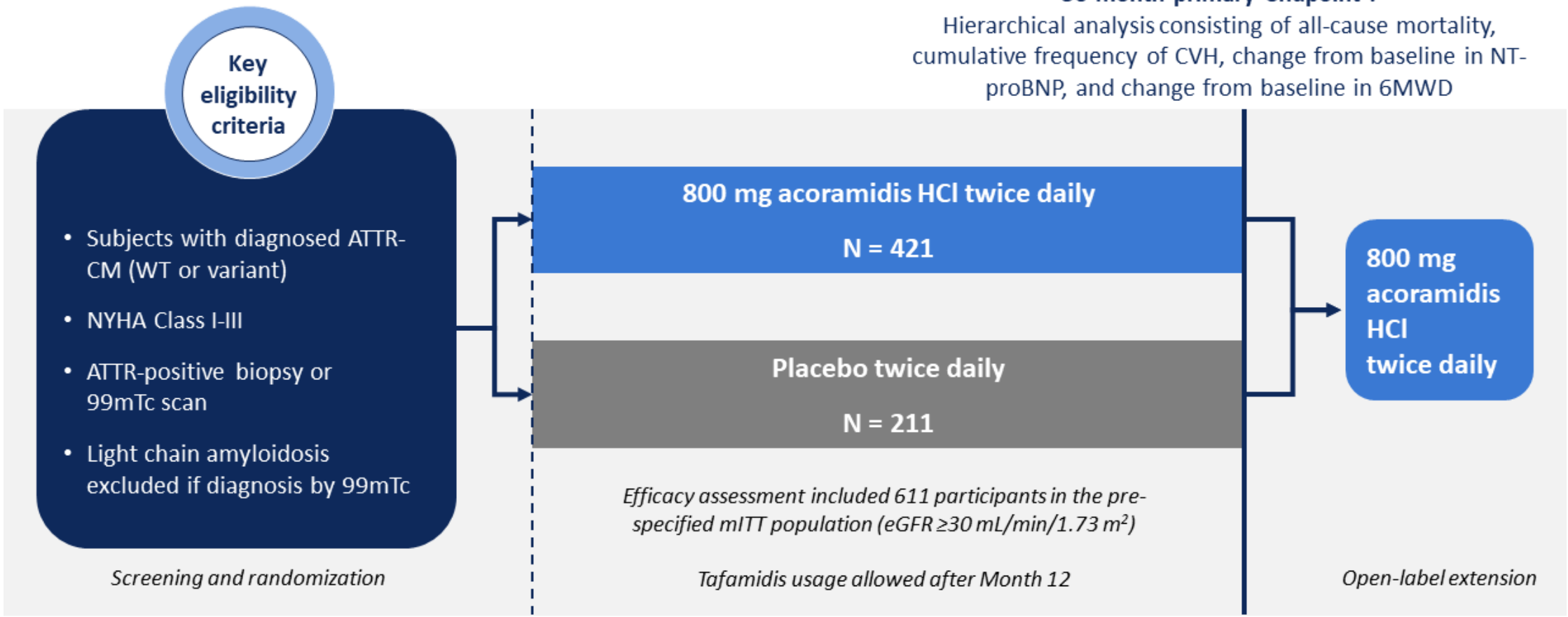
ATTR-ACT: Long-Term Extension Data



- Significantly better survival in patients who first treated with tafamidis than placebo
- Importance in early diagnosis and treatment in ATTR-CM

Elliott P, et al. *Circ Heart Fail.* 2022;15(1):e008193.

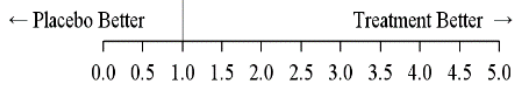
ATTRibute-CM Study Design



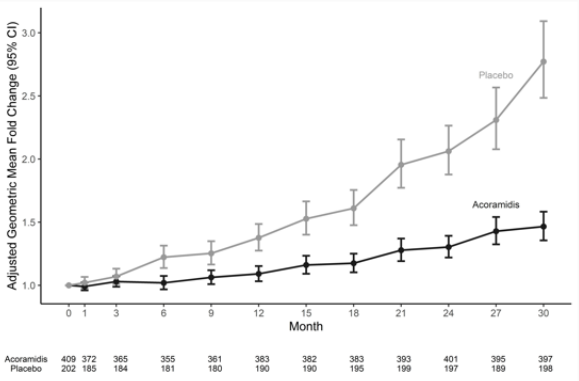
1. ClinicalTrials.gov. NCT03860935. 2. Gillmore JD, et al. *Circulation.* 2019;140(1):14214. 3. Primary analysis assessed using the Finkelstein-Schoenfeld method. 6MWD, six-minute walk distance; 99mTC, Technetium labeled pyrophosphate (PYP) or bisphosphonate (eg, DPD); eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; NYHA, New York Heart Association.

ATTRibute-CM – Acoramidis

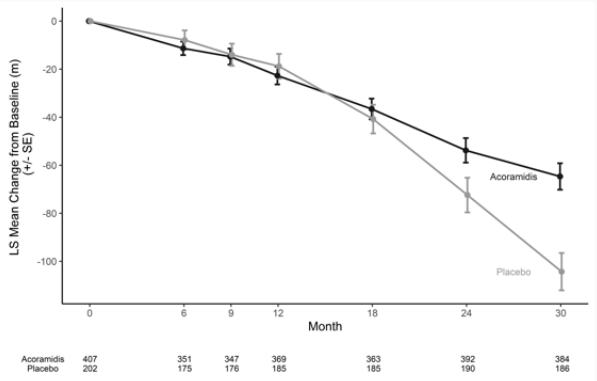
Subgroup	No.(%) of Patients	Win Ratio [95% CI]	FS test p-value
Overall	611(100.0)	1.772 [1.417, 2.217]	<0.0001
ATTR-CM Genotype			
ATTRm-CM	59(9.7)	2.529 [1.303, 4.911]	0.0061
ATTRwt-CM	552(90.3)	1.756 [1.396, 2.208]	<0.0001
NT-proBNP (pg/mL)			
<= 3000	401(65.6)	1.787 [1.373, 2.325]	<0.0001
> 3000	210(34.4)	1.678 [1.160, 2.426]	0.0060
eGFR (mL/min/1.73m2)			
< 45	94(15.4)	1.410 [0.849, 2.341]	0.1841
>= 45	517(84.6)	1.797 [1.452, 2.226]	<0.0001
Age (years)			
< 78	299(48.9)	2.052 [1.489, 2.829]	<0.0001
>= 78	312(51.1)	1.499 [1.098, 2.045]	0.0107
NYHA Class			
I, II	512(83.8)	1.892 [1.479, 2.419]	<0.0001
III	99(16.2)	1.150 [0.652, 2.030]	0.6292



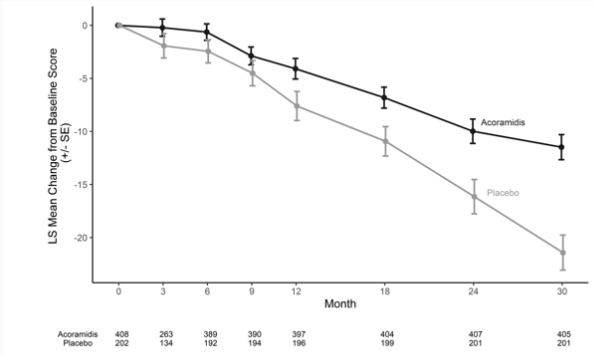
Change from Baseline in NT-proBNP[1]



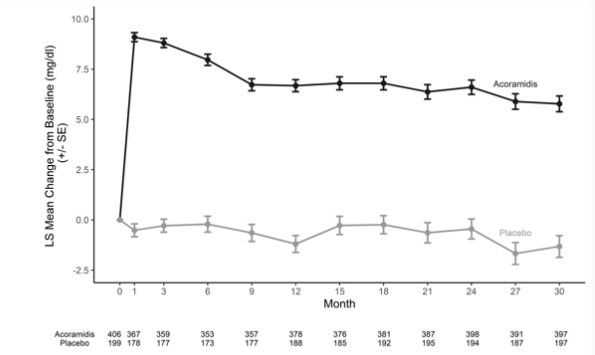
Change from Baseline in 6MWD[1]



Change from Baseline in KCCQ-OS[1]



Change from Baseline in Serum TTR

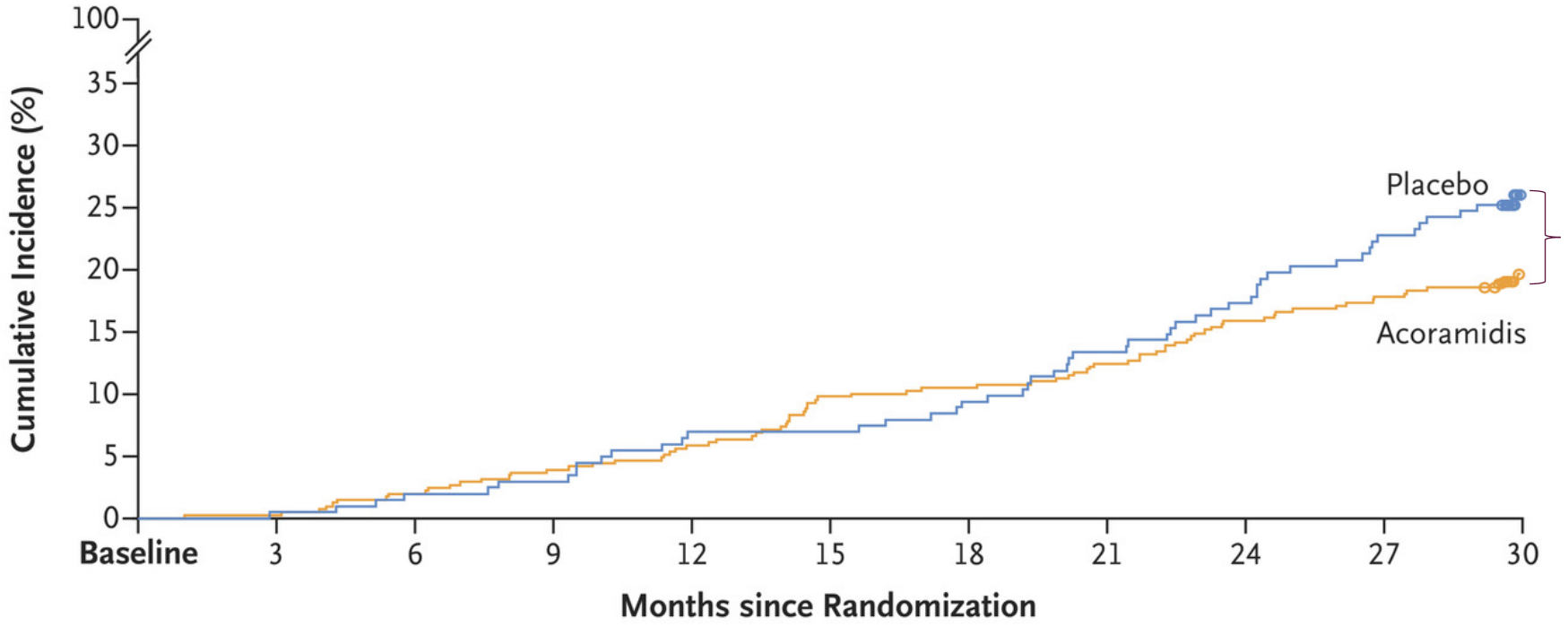


Gillmore J, et al. ESC 2023.
6MWD, 6-minute walking distance; FS, Finkelstein-Schoenfeld; KCCQ, Kansas City Cardiomyopathy Questionnaire; TTR, transthyretin.

Death from Any Cause - ATTRibute-CM

Death from Any Cause

The Cumulative Incidence Curve for Death from Any Cause



ARR = 6.4%
RRR = 25%

Tafamidis in ATTR-ACT
ARR = 13%
RRR = 33%

No. at Risk (no. of events)

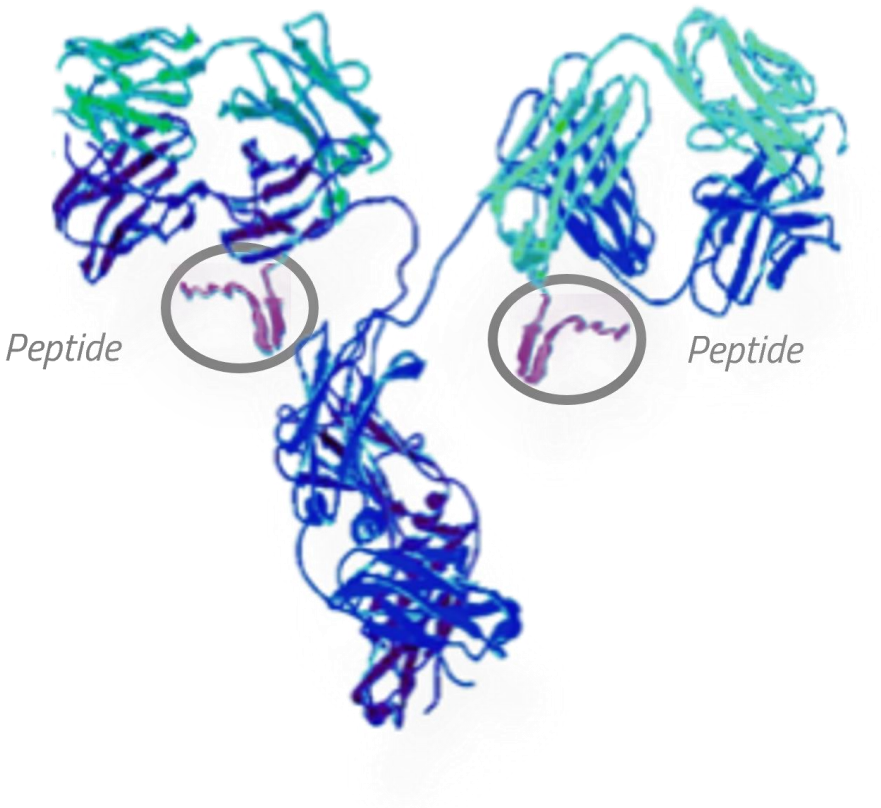
Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

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

Amyloid Depleters

- TTR stabilizers can prevent misfolding of TTR and slow the disease progression; TTR gene silencers are still being studied for cardiomyopathy
- No treatment is currently available to remove the existing amyloid deposits
- Current development of a new class of treatment that intends to remove amyloid fibrils in hopes of reversing cardiac dysfunction

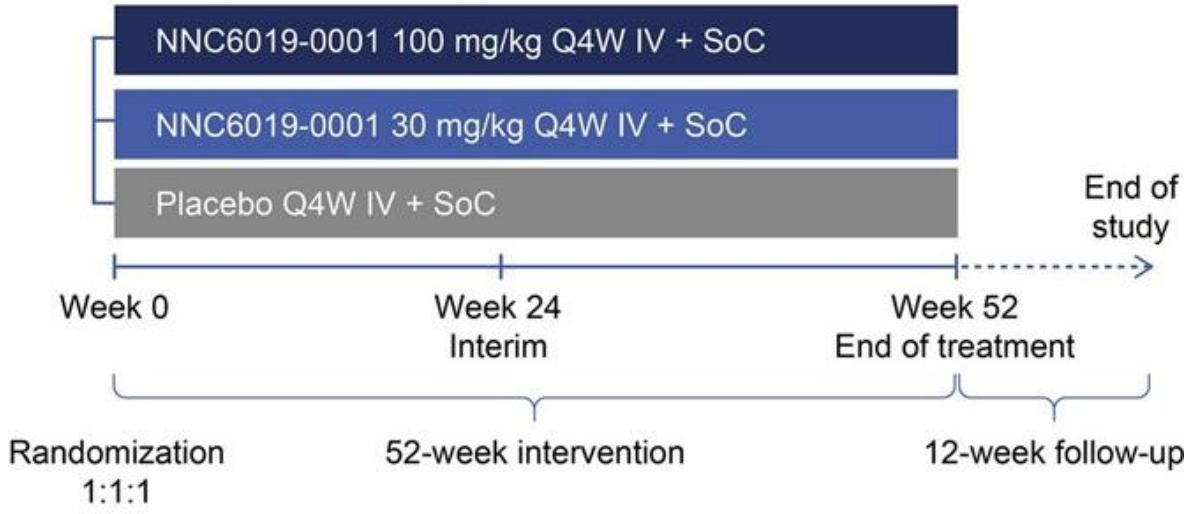
AT-02: Phase 2

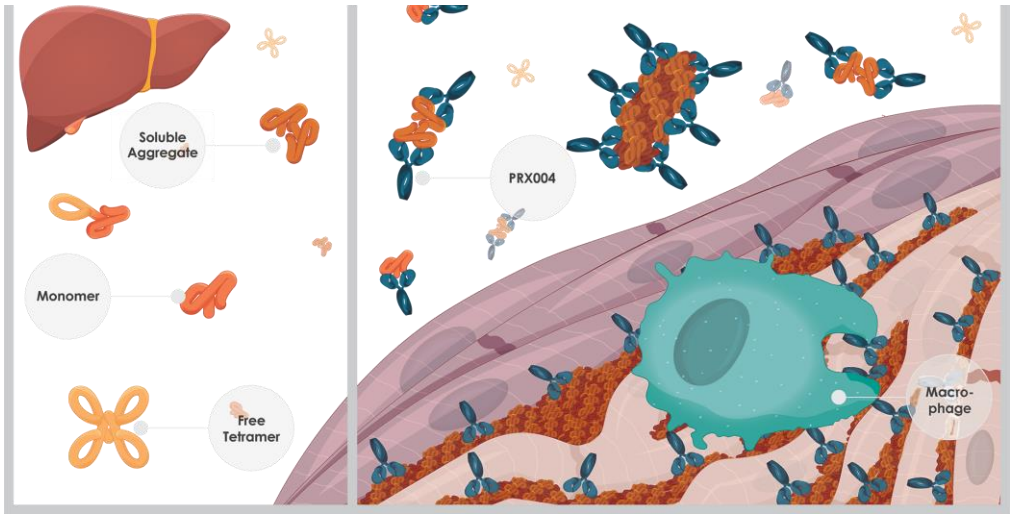


- A fusion of pan-amyloid removal (PAR)-peptide with
- An IgG1 antibody
- PAR-peptide binds to all types of amyloids and delivers the antibody to the site and activate macrophages

Wall J, et al. International Symposium on Amyloidosis (ISA) 2022.

NNC6019-0001 (PRX004): Phase 2





- NNC6019-0001 is a humanized monoclonal antibody that:
  - Inhibits amyloid fibril formation
  - Neutralizes soluble aggregate forms of misfolded TTR
  - Promotes clearance of insoluble amyloid fibrils through antibody-mediated phagocytosis

Fontana M, et al. Eur Heart J. 2022;43(supplement 2):ehac544.1767.
ATTR-CM, transthyretin amyloid cardiomyopathy; IV, intravenous; Q4W, every 4 weeks; SoC, standard of care.

NI0006 (ALXN2220): Phase 3

- Recombinant human anti-ATTR monoclonal IgG1 antibody
- The antibody selectively binds amyloid conformations of both wild-type and variant TTR, but it does not bind to physiologically folded TTR
- NI006 depletes ATTR by inducing antibody-mediated phagocytosis of ATTR fibrils and removal of ATTR deposits from tissues
- Estimated 1000 participants
- Primary endpoint: composite of all-cause mortality and total CV events up to 48 months

Garcia-Pavia P, et al. *N Engl J Med.* 2023;389(3):239-250.

Drug	FDA-approved indication	Studies	Considerations
Tafamidis	ATTR-CM (2019)	ATTR-ACT (completed)	• BCRP/ABCG2 inhibitions
Acoramidis		ATTRibute-CM (completed)	• FDA accepted NDA in 2/2024
NTLA-2001		Magnitude (ongoing)	• Single infusion
Inotersen	hATTR with PN (2018)	NEURO-TTR (completed)	• REMS for thrombocytopenia and glomerulonephritis • Retiring effected 9/2024
Eplontersen	hATTR with PN (2023)	NEURO-TTRansform (completed)	• Self-administered SC auto-injector every month
		CARDIO-TTRansform (ongoing)	
Patisiran	hATTR with PN (2018)	APOLLO-A (completed)	• IV infusion every 3 weeks requiring pre-medications to prevent infusion-related reactions
		APOLLO-B (ongoing)	
Vutrisiran	hATTR with PN (2022)	HELIOS-A (completed)	• SC injection every 3 months by health-care provider only
		NEURO-TTRansformHELIOS-B (ongoing)	
AT-02		Phase 2 (NCT05951049)	• IV infusion
NNC6019-0001		Phase 2 (NCT05442047)	• IV infusion
NI0006		Phase 3 (NCT04360434)	• IV infusion

Evolving Landscape

- Silencer vs stabilizer
- Role of combination therapy
- Amyloid depleters and potential reversal of cardiomyopathy
- Early diagnosis and treatment of ATTR remains crucial

Pharmacy Relevance in Managed Care

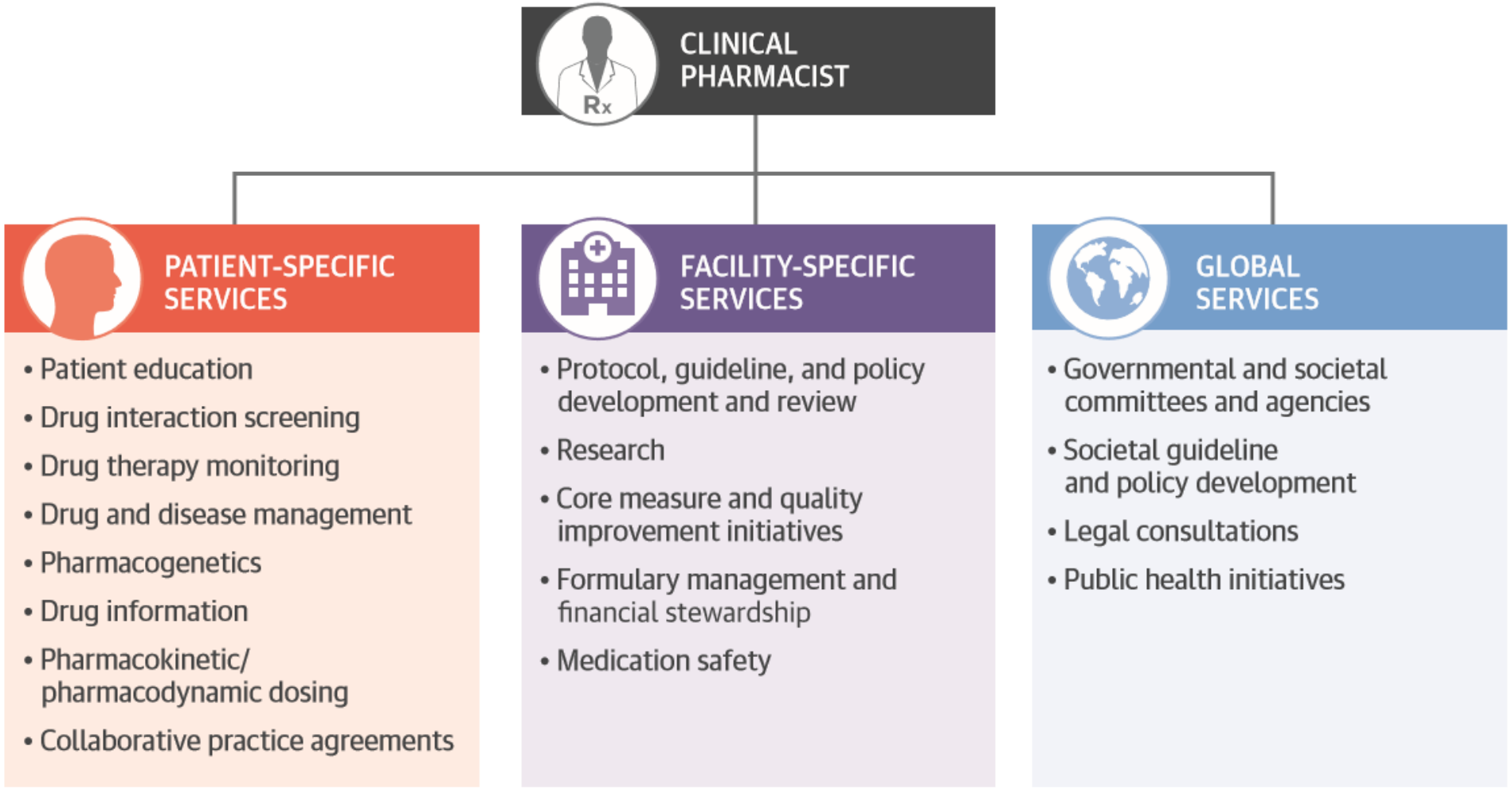
Jennifer L. Day, PharmD

Clinical Transplant Pharmacist

Baptist Health Heart Failure and Transplant Institute

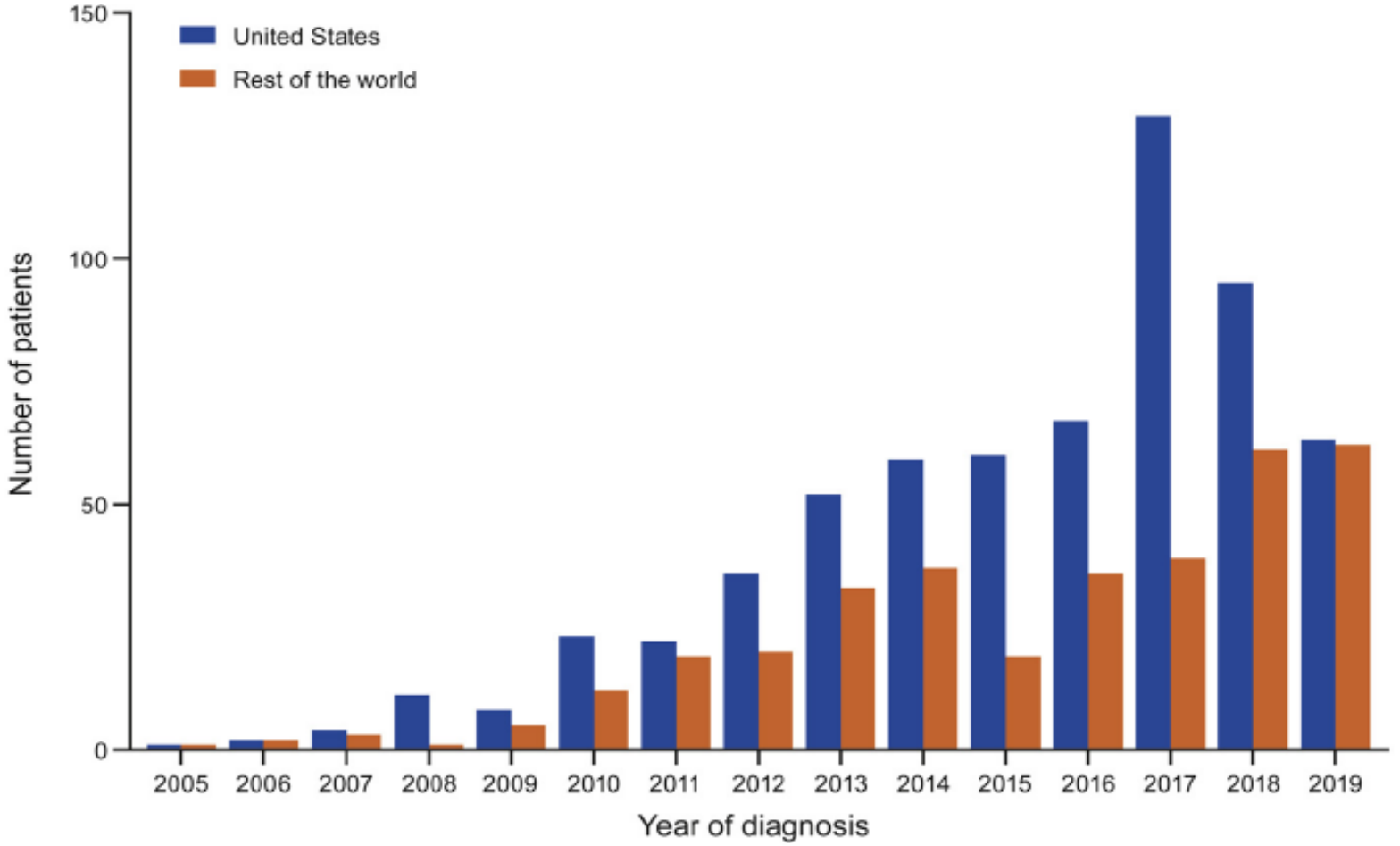
Little Rock, AR

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

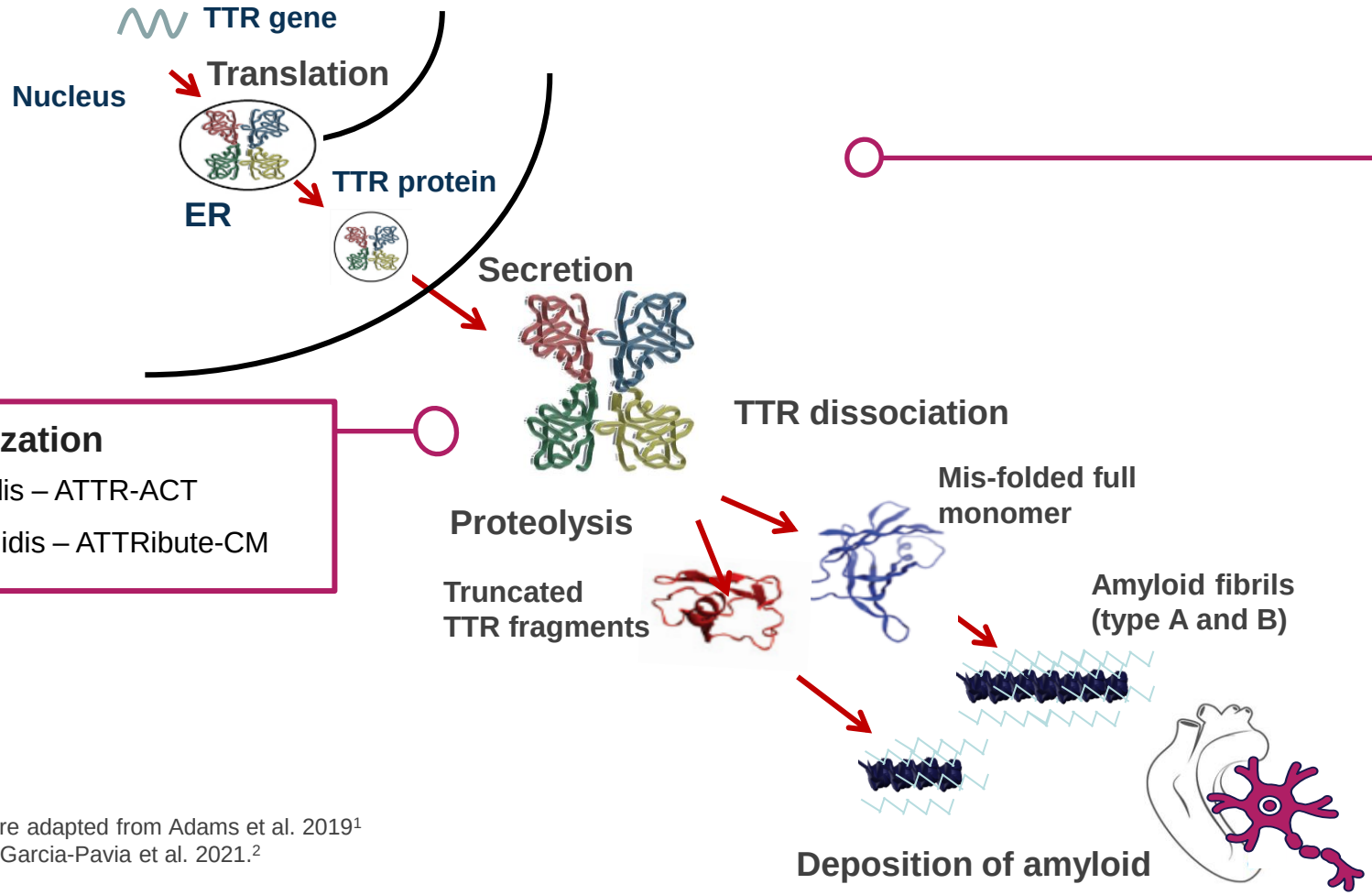


Diagnoses in the United States versus the rest of the world in THAOS (the Transthyretin Amyloidosis Outcomes Survey) are shown by year.*

*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.

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

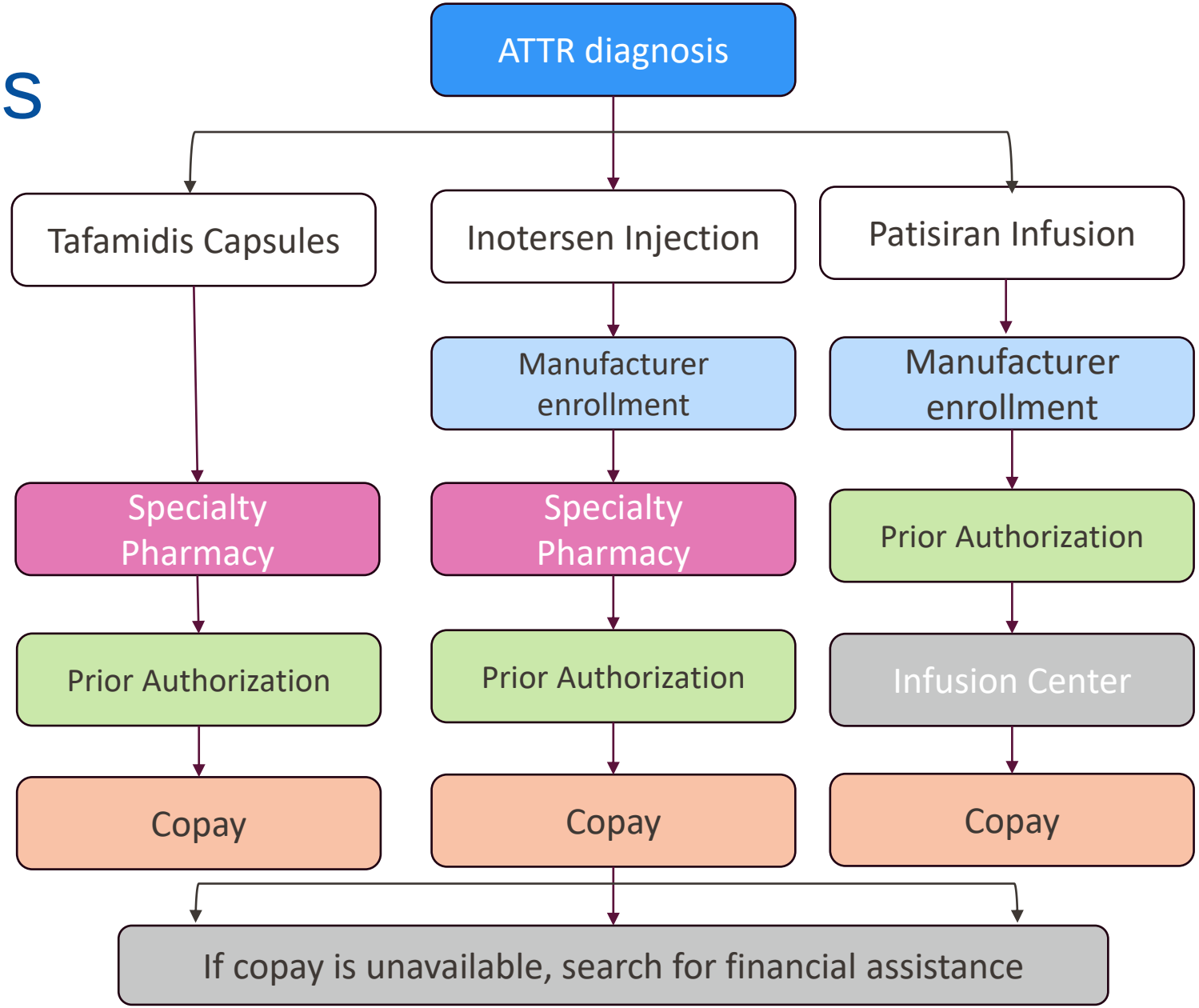
- Eplontersen - CARDIO-TTRansform
- Inotersen -

Figure adapted from Adams et al. 2019[1] and Garcia-Pavia et al. 2021.[2]

1. Adams D, et al. *Nat Rev Neurol.* 2019;15(7):387-404. 2. Garcia-Pavia P, et al. *Eur Heart J.* 2021;42(16):1554-1568. 3. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 4. Onpattro (patisiran). https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf. 5. Amvuttra (vutrisiran). https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf. 6. Tegsedi (inotersen). https://www.ema.europa.eu/en/documents/product-information/tegsedi-epar-product-information_en.pdf. 7. 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.

Stepwise Processes from Diagnosis to Treatment

Note: This is based on currently available therapeutics



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

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 with cardiomyopathy; HF, heart failure.

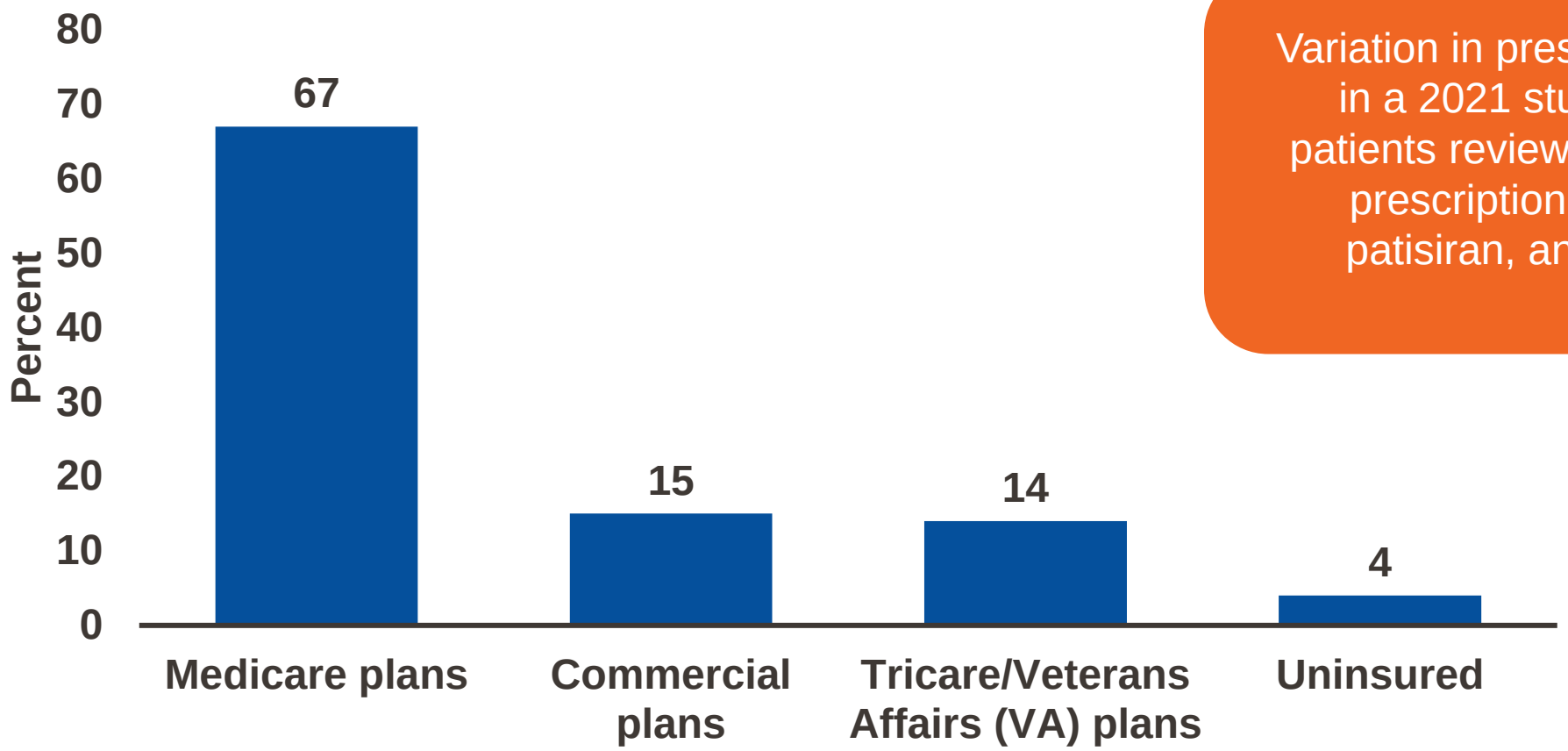
Tips on Medication Selection

- 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)

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.

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.

Ready. Set. Poll.

Have your mobile devices ready to respond to the learning assessment questions coming up.

Join at

slido.com

#AMCP

Panel Discussion and Audience Q&A

Hongya Chen, PharmD, BCCP
Cardiology Clinical Pharmacist
Oregon Health & Science University
Portland, OR

Jennifer L. Day, PharmD
Clinical Transplant Pharmacist
Baptist Health Heart Failure and Transplant Institute
Little Rock, AR

Keith C. Ferdinand, MD, FACC, FAHA, FASPC, FNLA
Gerald S. Berenson Endowed Chair in Preventive Cardiology,
Professor of Medicine
Tulane University School of Medicine
New Orleans, LA

Don’t forget to complete the evaluation!

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

medtelligence℠

Visit
Medtelligence.net
to explore other CE programs!

THANK YOU!

medtelligence℠