Treating ATTR-CM with a Novel Therapeutic Approach: Understanding the ATTRibutes to Success

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

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Disclosures

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Agenda

- Updates on ATTR-CM Disease State
- Change in ATTR-CM Management Strategy
- ATTR-CM Mechanism of Action
- ATTR-CM Statistical Review
- ATTR-CM Current and Future Therapeutic Options
- Faculty Discussion/Q&A

Learning Objectives

- Describe the pathophysiology and genetic variation of ATTR-CM amyloidosis
- 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

Marianna Fontana, MD
Director of the UCL CMR Unit, Royal Free Hospital
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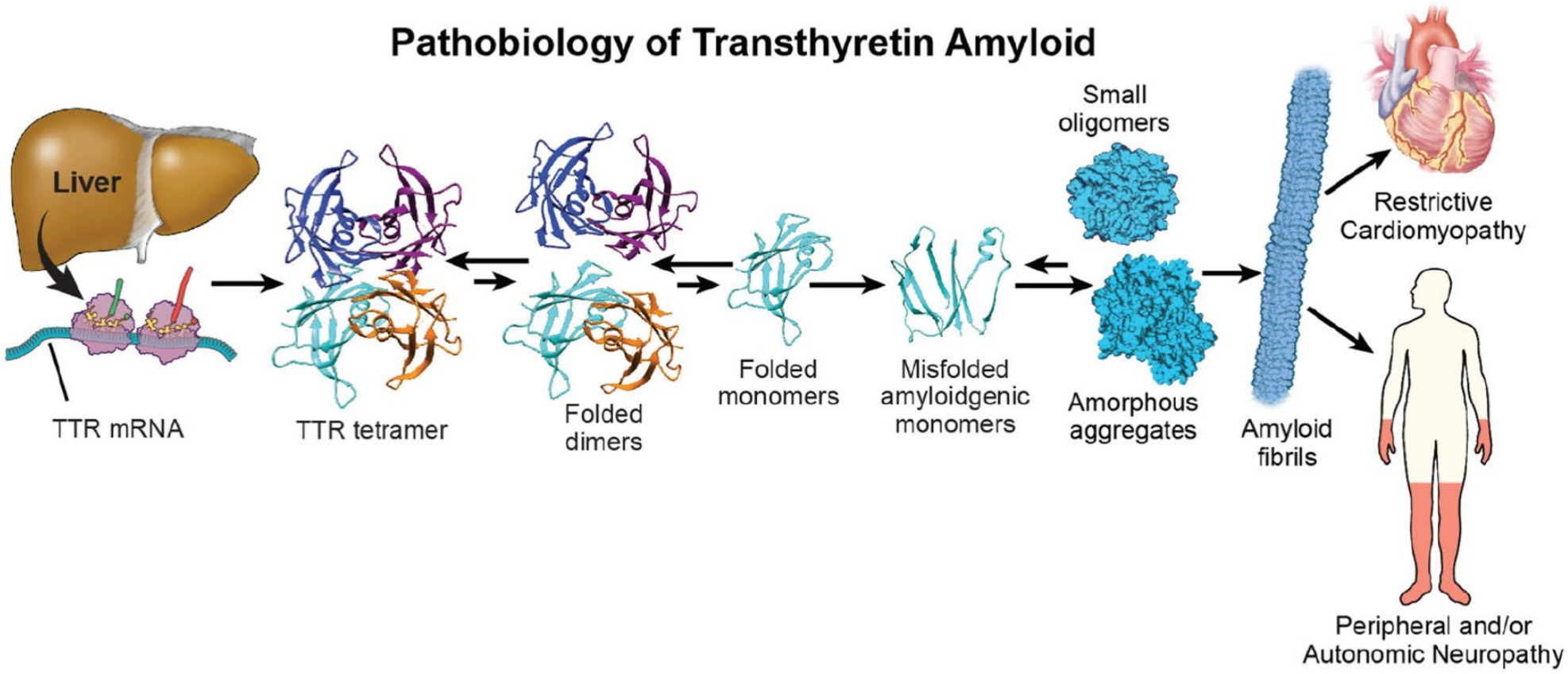
Transthyretin Amyloidosis (ATTR)

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.

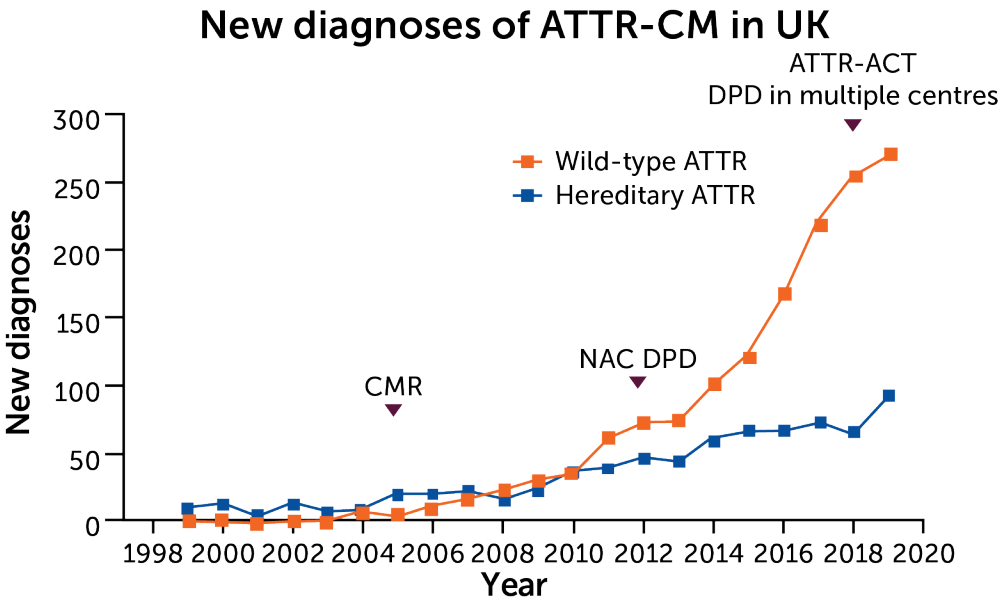
Transthyretin Amyloidosis (ATTR)

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)
- Autopsy studies indicate that cardiac ATTR amyloid deposits are present in ~25% of men over 80 years of age
- Majority not diagnosed with amyloidosis in life
- Prevalence not known (misdiagnoses vs clinically insignificant?)

Hereditary ATTR:

- Causes cardiomyopathy and neuropathy
- Estimated 50,000 affected individuals 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)



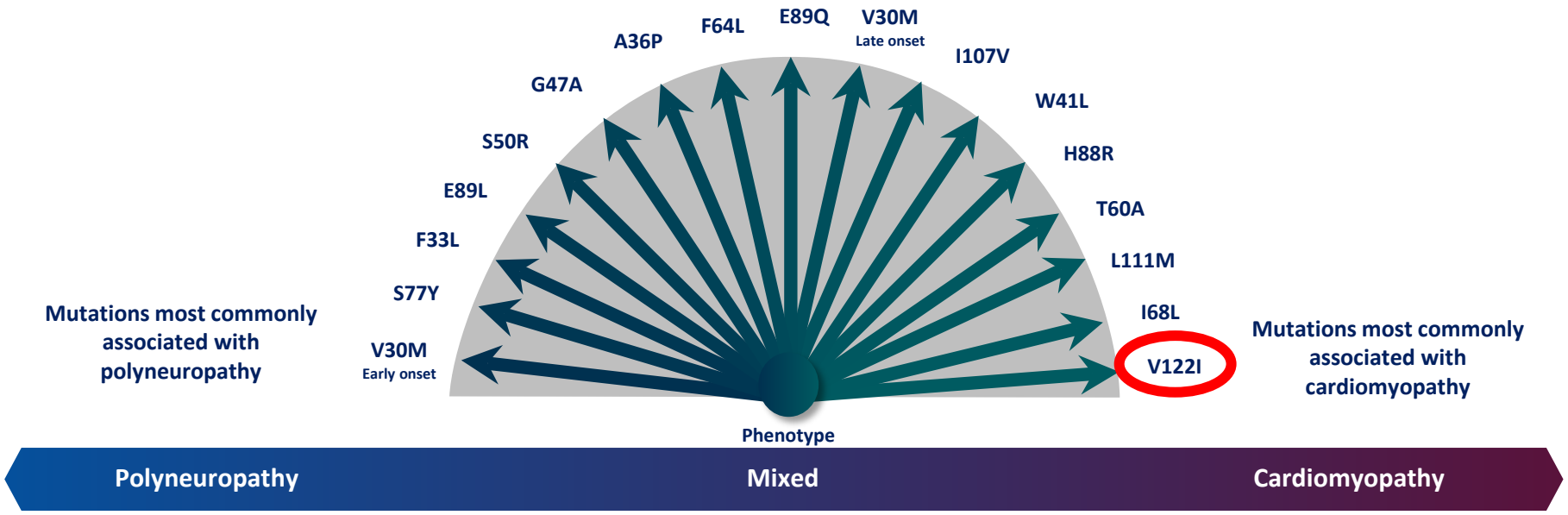
ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiovascular magnetic resonance; CTS, carpal tunnel syndrome; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; HF, heart failure; NAC, National Amyloidosis Centre; TTR, transthyretin.

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.

Hereditary ATTR Amyloidosis

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

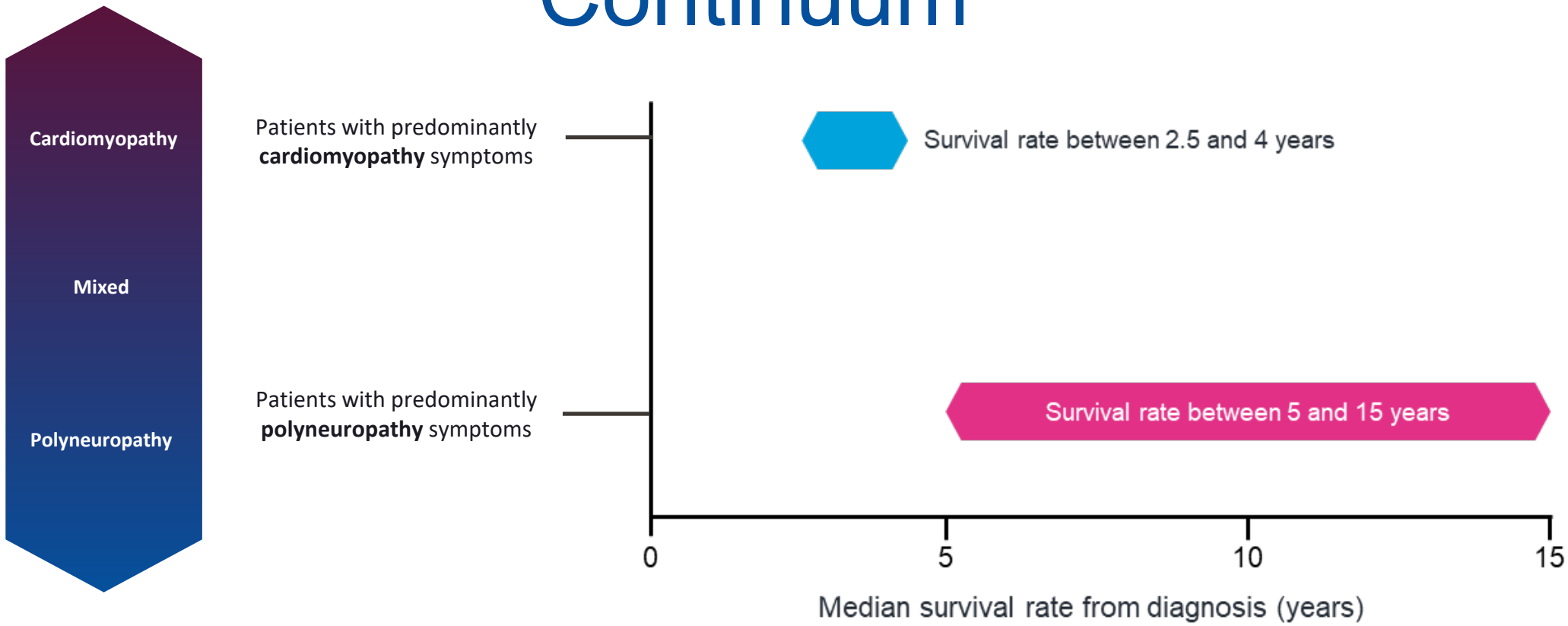
Possible genotypic–phenotypic association in hereditary ATTR amyloidosis[1,2]



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

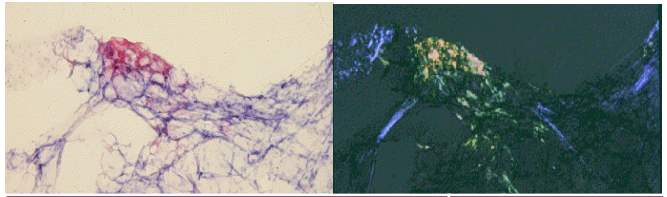


Early diagnosis will become increasingly important in improving patient outcomes

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

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]
    - > **Rarely performed by UK cardiologists**
- Screening biopsy
  - Rectal: more invasive, less sensitive[1]
  - 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 Fontana. AL, amyloid light chain; ATTR, transthyretin amyloidosis; ATTRwt, wild-type ATTR; FNAFP, fine-needle aspiration of abdominal fat pad; SAP, serum amyloid P. 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.

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]

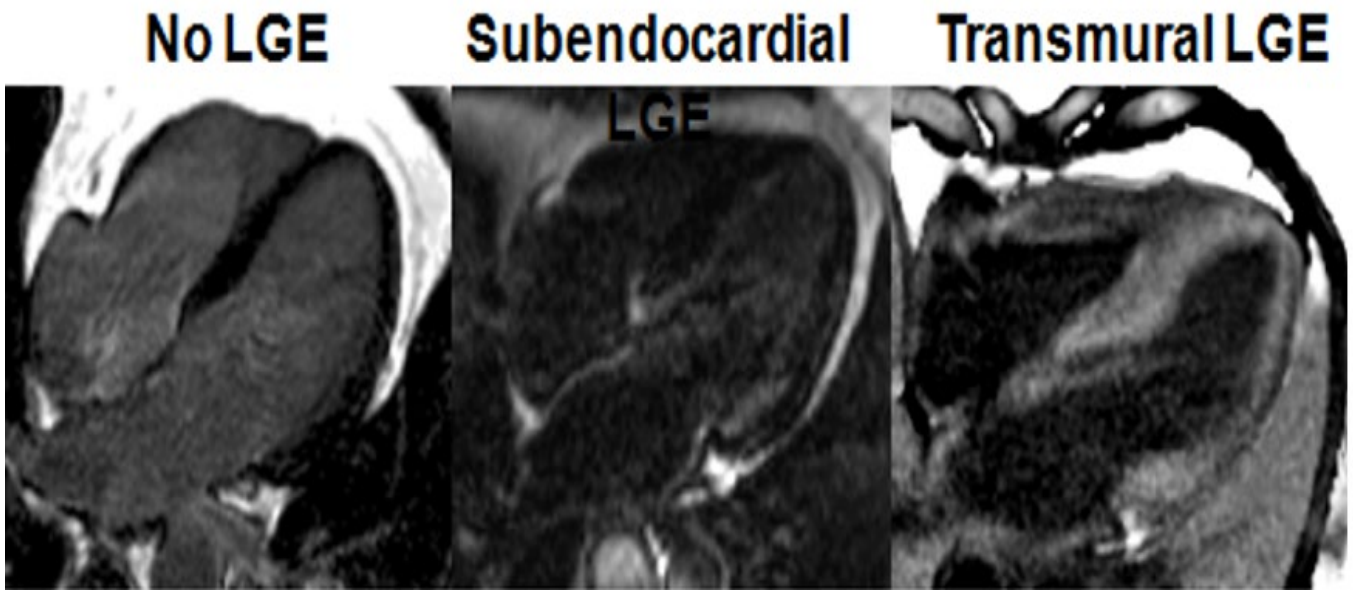
Table 2 Echocardiographic and cardiac magnetic resonance criteria for non-invasive and invasive (with extracardiac biopsy-proven amyloidosis) diagnosis of cardiac amyloidosis

CMR

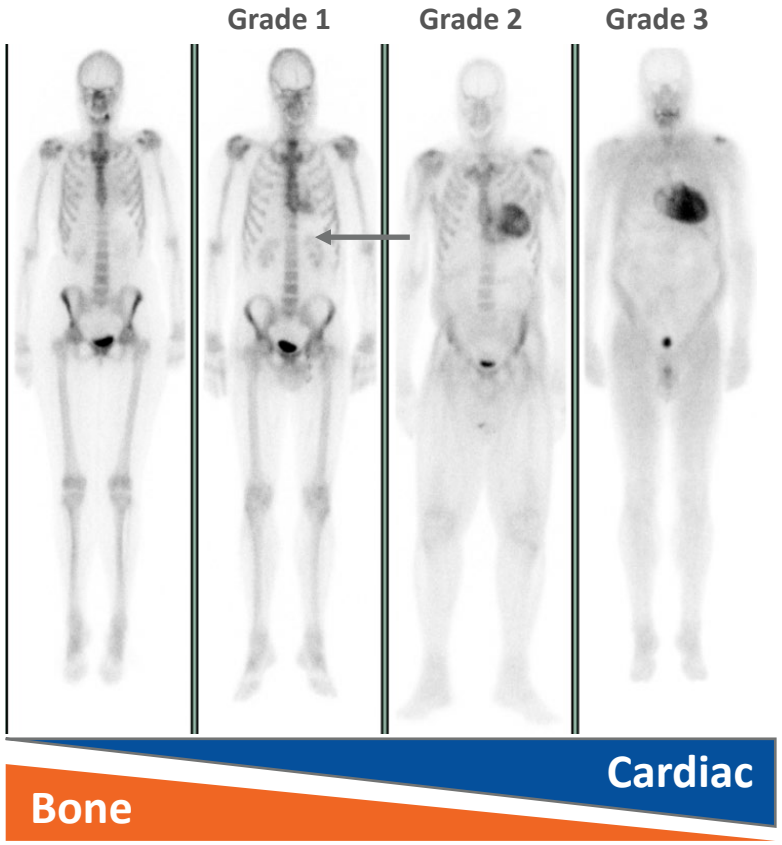
Characteristic CMR findings (a and b have to be present):

a. Diffuse subendocardial or transmural LGE
b. Abnormal gadolinium kinetics[a]
c. ECV ≥0.40% (strongly supportive, but not essential/diagnostic)

Eur Heart J. 2021 Apr 21;42(16):1554-1568



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

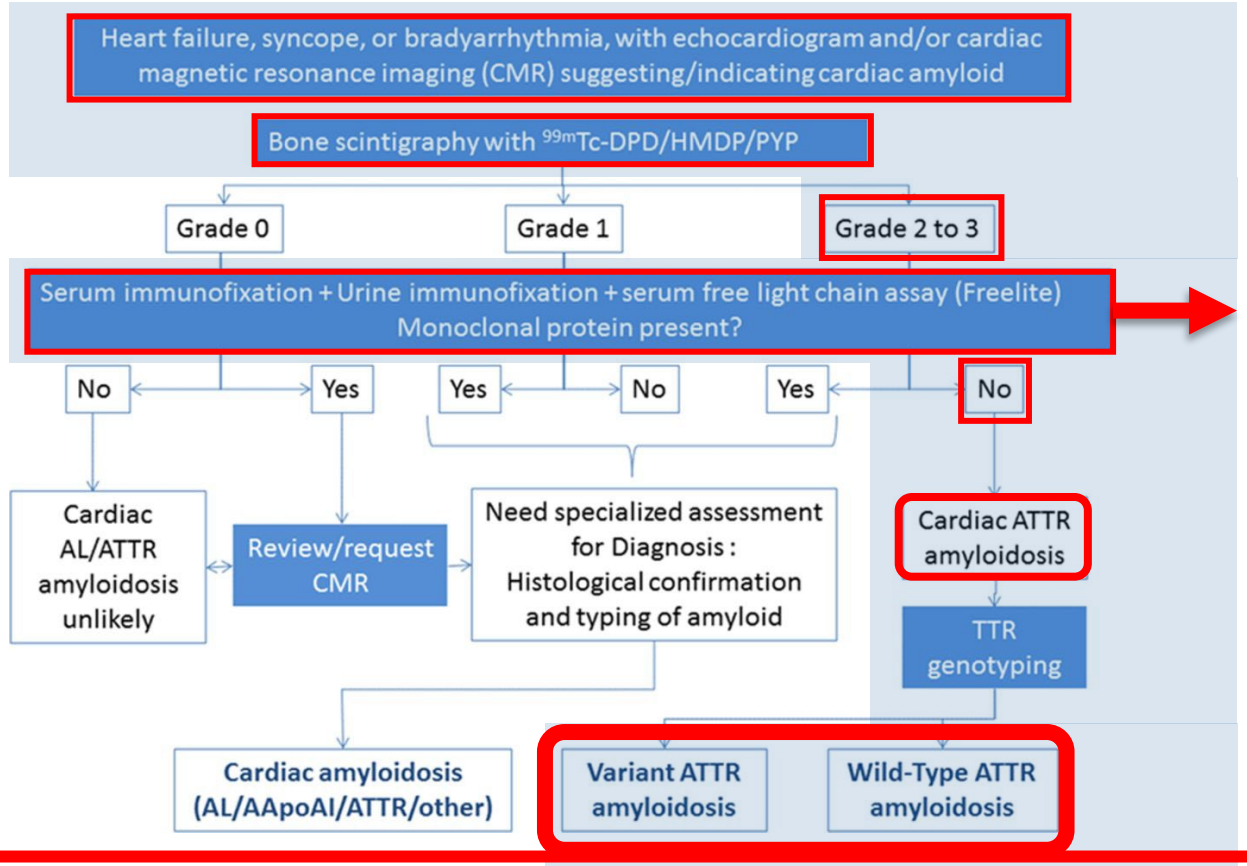


- **Grade 1**: mild cardiac uptake with no attenuation of bone uptake[1,2]
- **Grade 2**: moderate cardiac uptake, greater than bone[1,2]
- **Grade 3:** strong cardiac uptake with little or no bone signal[1,2]

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

Image adapted from Hutt DF, et al. 2014.[1]
^{99m}Tc-DPD, ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ATTR, transthyretin amyloidosis.
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.

Bone Scintigraphy: How to Diagnose Cardiac Amyloidosis

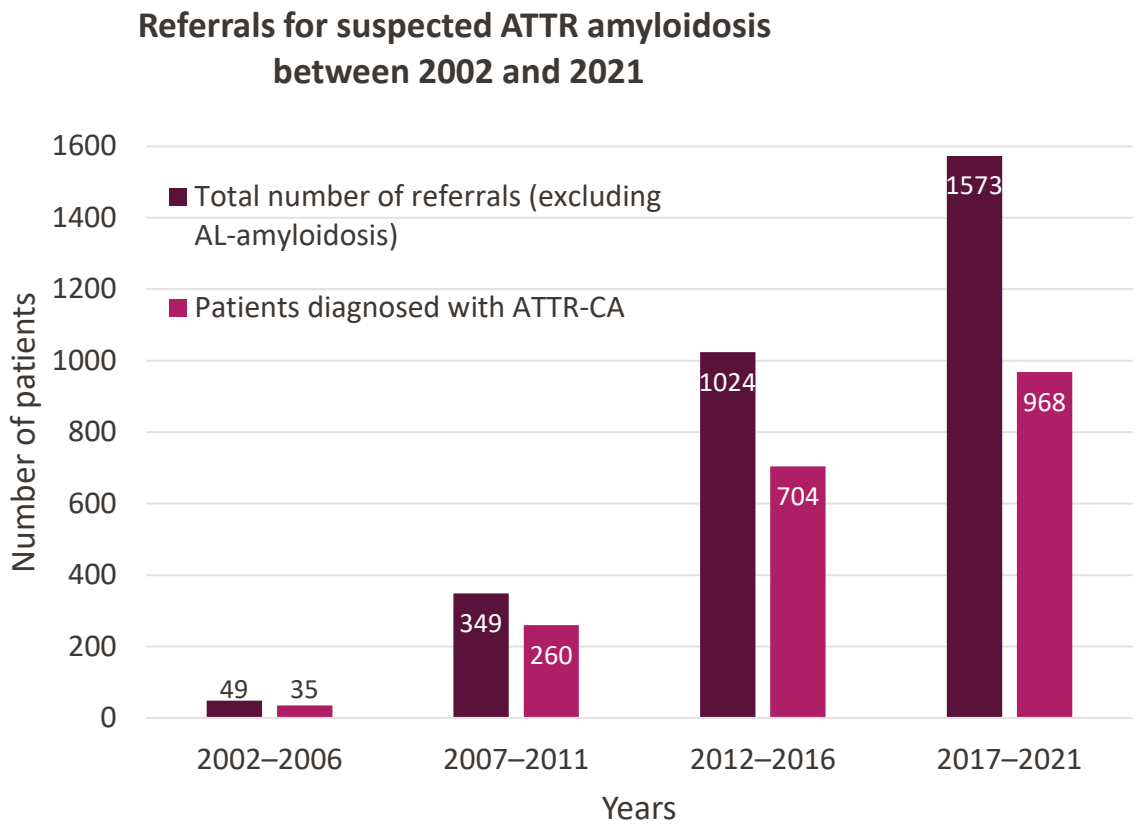


70-80% of patients are diagnosed using the noninvasive algorithm

Gillmore JD, et al. *Circulation*. 2016;133(24):2404-2412.

Changes in the Diagnosis Over the Past 20 Years: Heightened Awareness

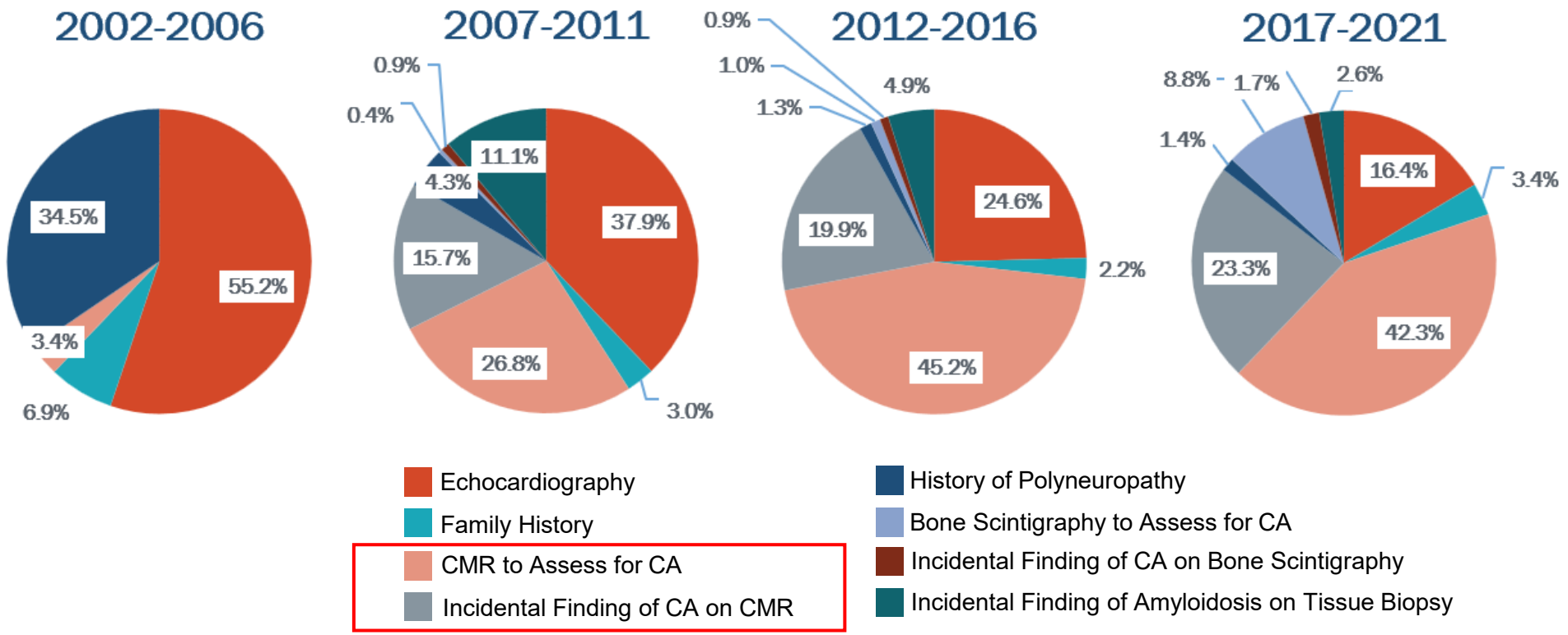
Observational cohort study of all patients with predominantly cardiac signs and symptoms of ATTR amyloidosis referred to the UK National Amyloidosis Centre (2002–2021)



AL, amyloid light chain/primary amyloidosis; ATTR, transthyretin-mediated amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis; LV, left ventricular.
Ioannou A, et al. *Circulation* 2022;146(22):1657-1670.

Changes in the Diagnosis Over the Past 20 Years: Shift in Referral Pathways

Referral Pathway for Patients Diagnosed With ATTR-CA at the NAC According to Time Period

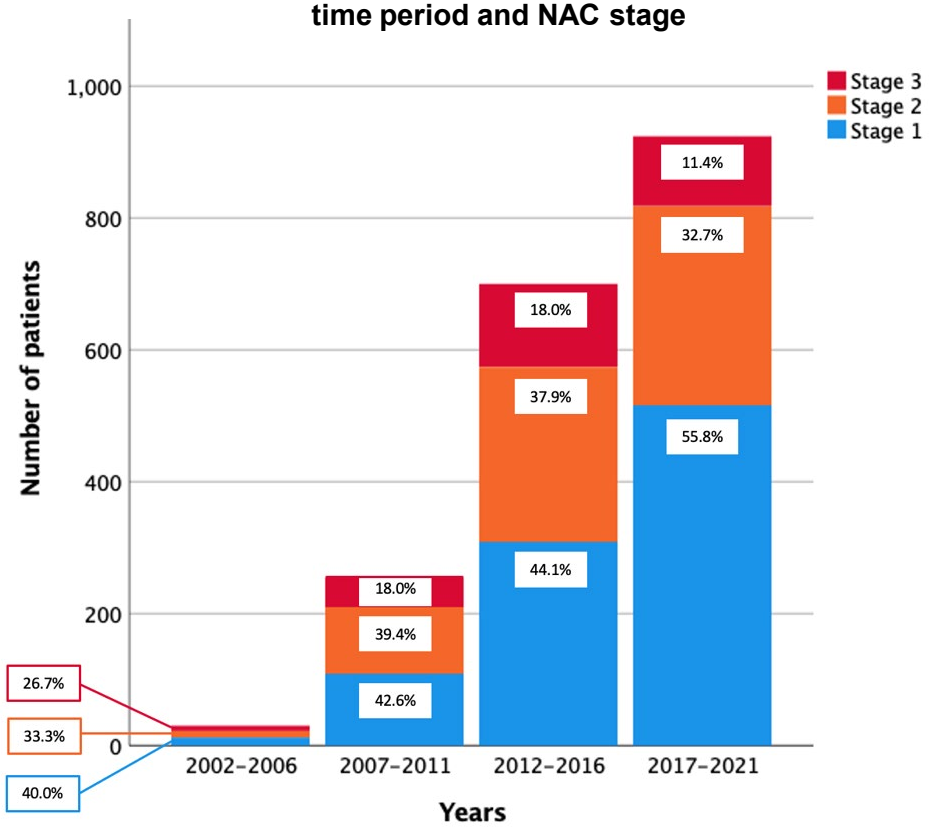


ATTR-CA, transthyretin cardiac amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiovascular magnetic resonance; NAC, National Amyloidosis Centre. Ioannou A, et al. *Circulation*. 2022;146(22):1657-1670.

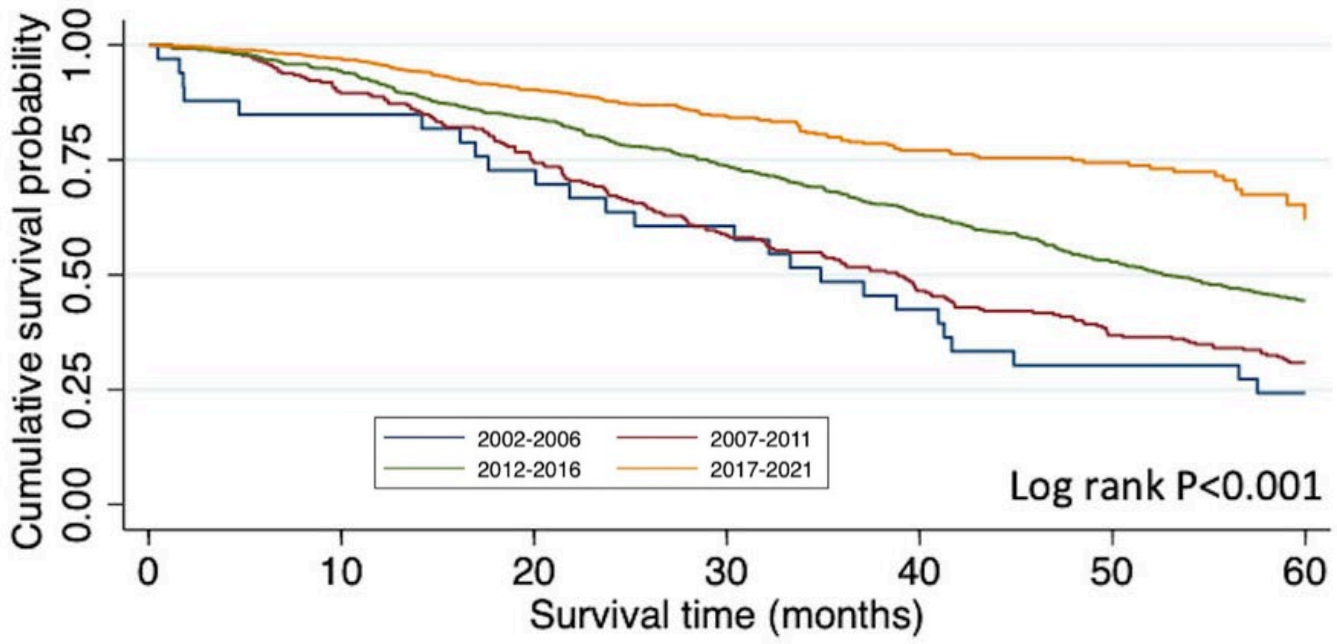
Changes in the Diagnosis Over the Past 20 Years: Lower Disease Burden and Better Prognosis at Diagnosis

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



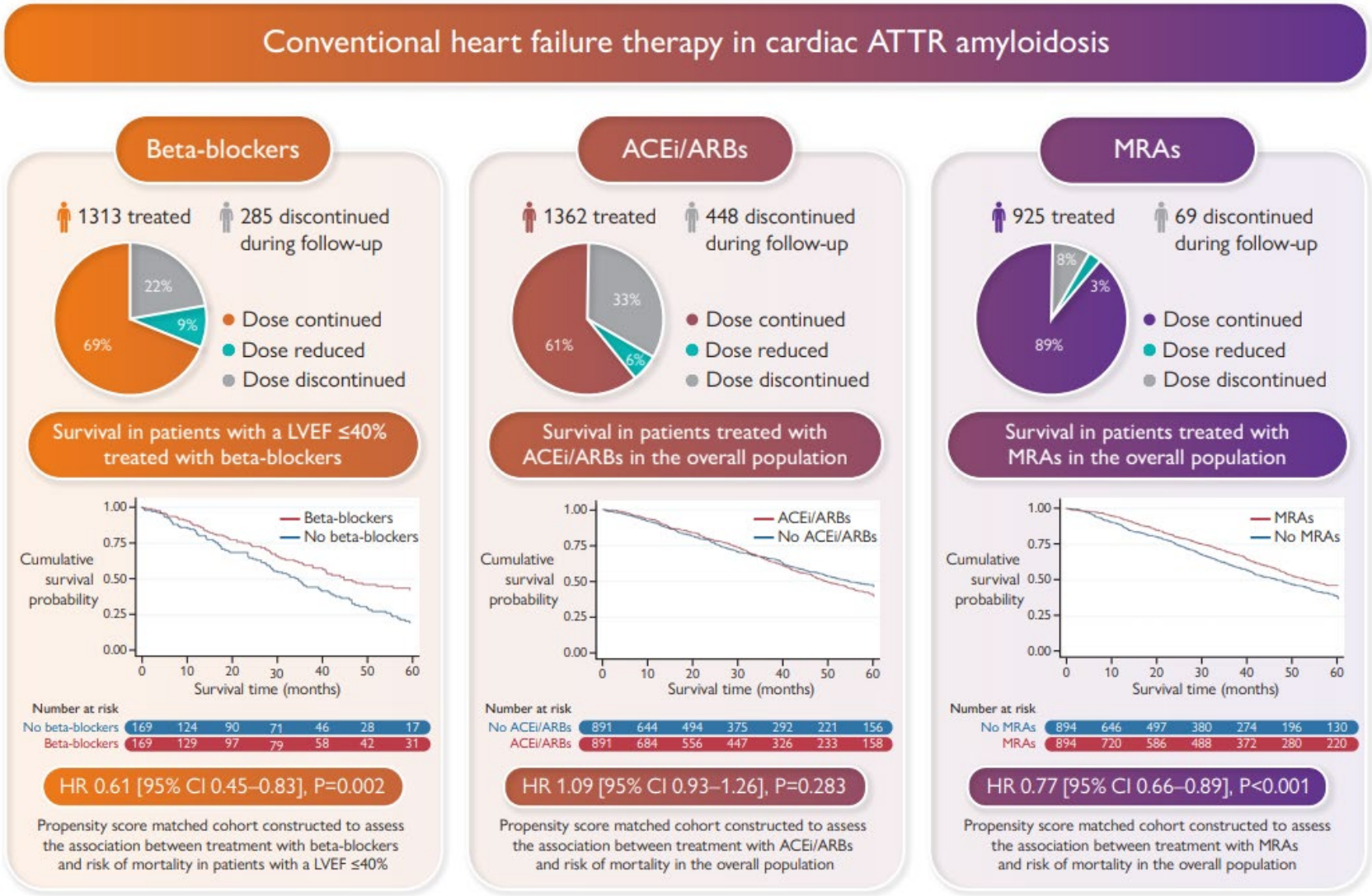
60-month survival in all ATTR-CA patients by time period at diagnosis



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

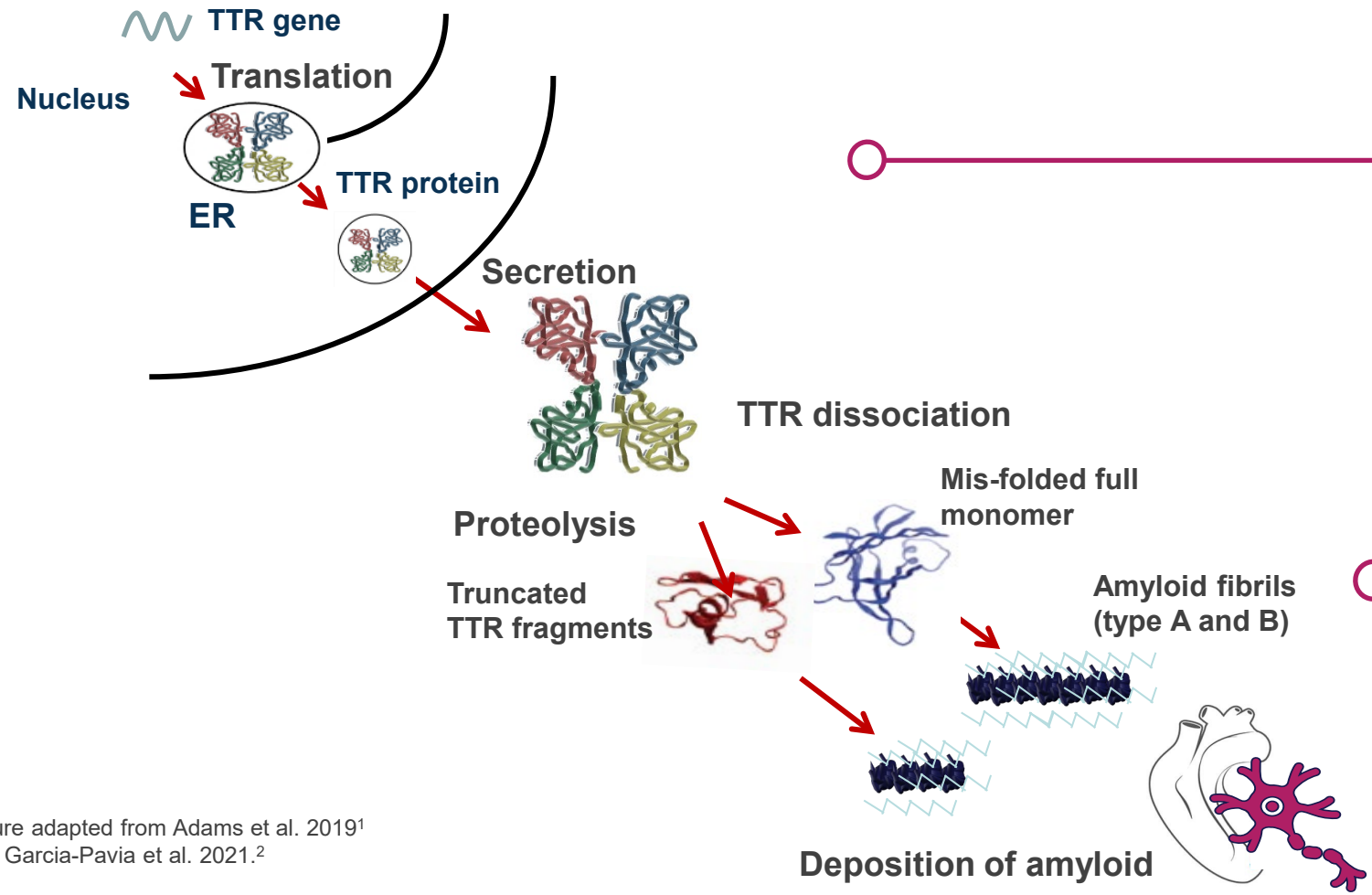
Ioannou A, et al. *Circulation* 2022;146(22):1657-1670.

Changes in Supportive Heart Failure Treatment



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

Disease-Modifying Treatment: Completed Phase 3 ATTR-CM Clinical Trials



Suppression of TTR synthesis

Gene silencing – RNAi therapy

- Patisiran – APOLLO-B

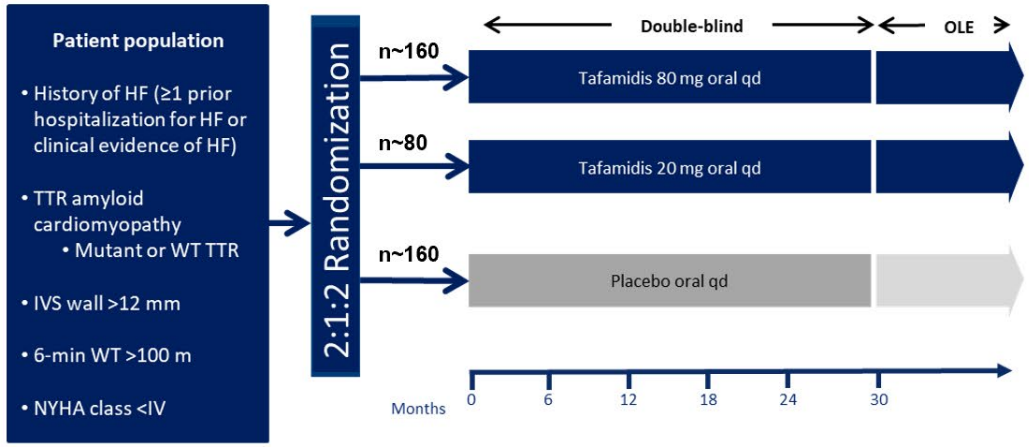
TTR stabilization

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

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

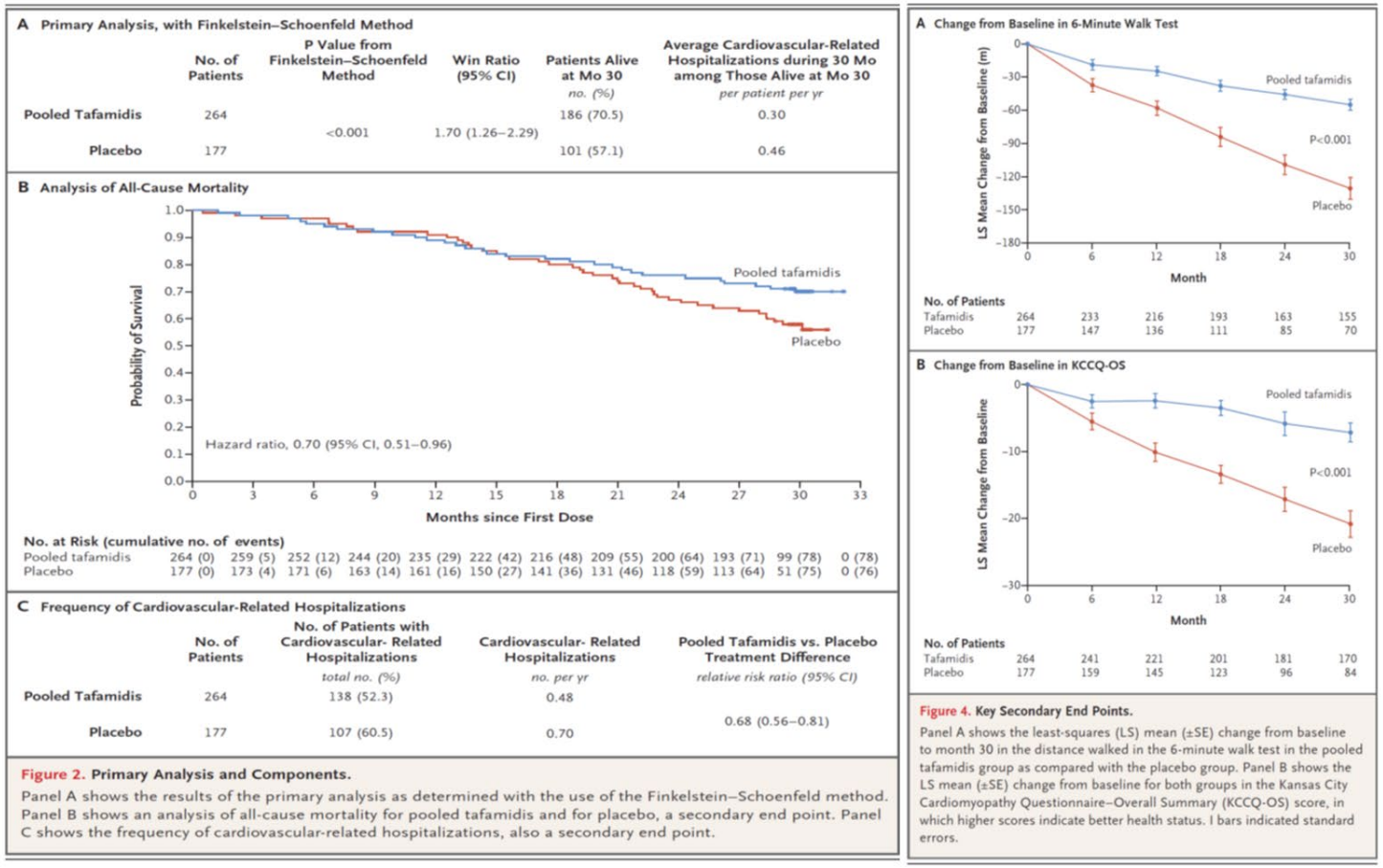
ASO, antisense oligonucleotide; ATTR, transthyretin-mediated amyloidosis; ER, endoplasmic reticulum; PN, polyneuropathy; RNAi, RNA interference; TTR, transthyretin. 1. Adams D, et al. *Nat Rev Neurol.* 2019;15(7):387-404. 2. Garcia-Pavia P, et al. *Eur Heart J.* 2021;42(16):1554-1568. 3. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 4. Onpattro (patisiran). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf 5. Amvuttra (vutrisiran). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf 6. Tegsedi (inotersen). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/tegsedi-epar-product-information_en.pdf 7. Vyndaqel (tafamidis). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf

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

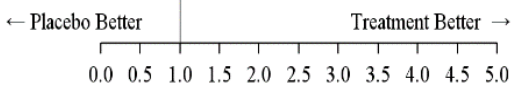
Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

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.

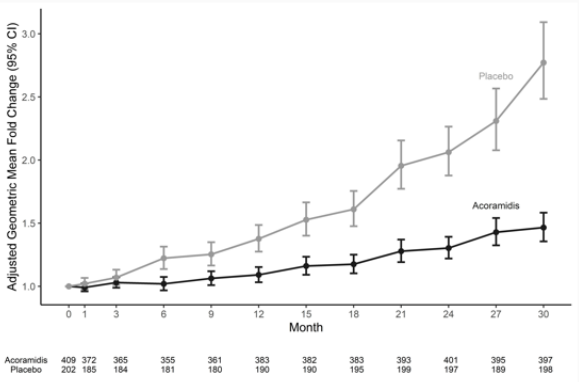
Maurer SM, et al. *N Engl J Med*. 2018;379(11):1007-1016.

ATTRibute-CM – Acoramidis

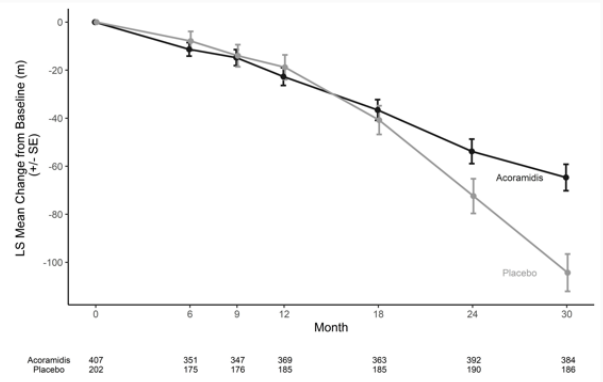
Subgroup	No.(%) of Patients	Win Ratio	Win Ratio [95% CI]	FS test p-value
Overall	611(100.0)		1.772 [1.417, 2.217]	<0.0001
ATTR-CM Genotype				
ATTRm-CM	59(9.7)		2.529 [1.303, 4.911]	0.0061
ATTRwt-CM	552(90.3)		1.756 [1.396, 2.208]	<0.0001
NT-proBNP (pg/mL)				
<= 3000	401(65.6)		1.787 [1.373, 2.325]	<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



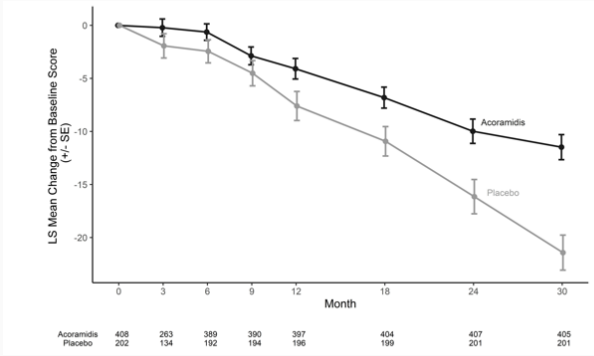
Change from Baseline in NT-proBNP[1]



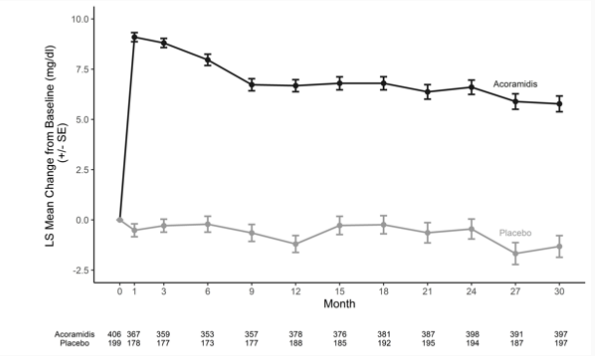
Change from Baseline in 6MWD[1]



Change from Baseline in KCCQ-OS[1]

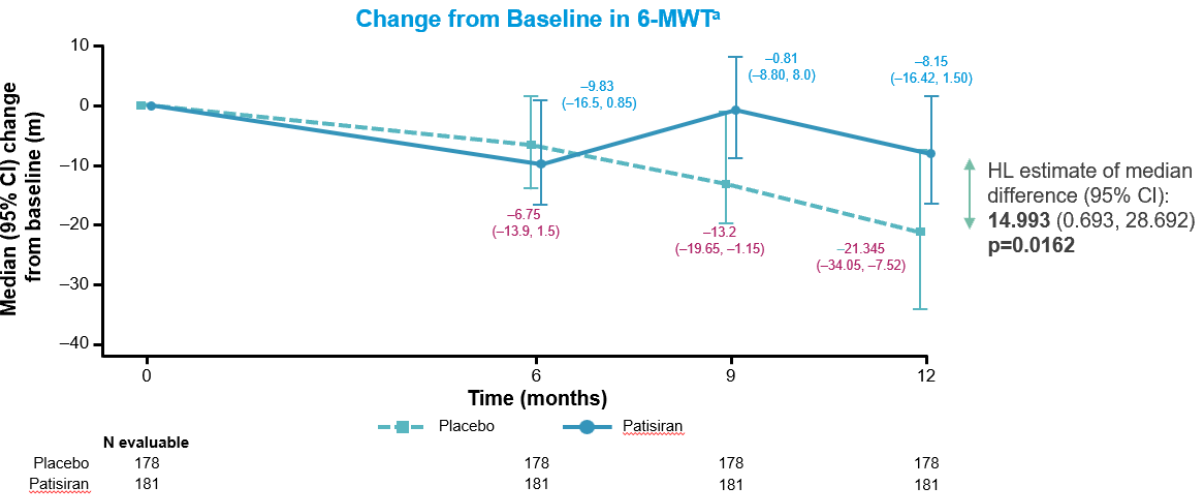


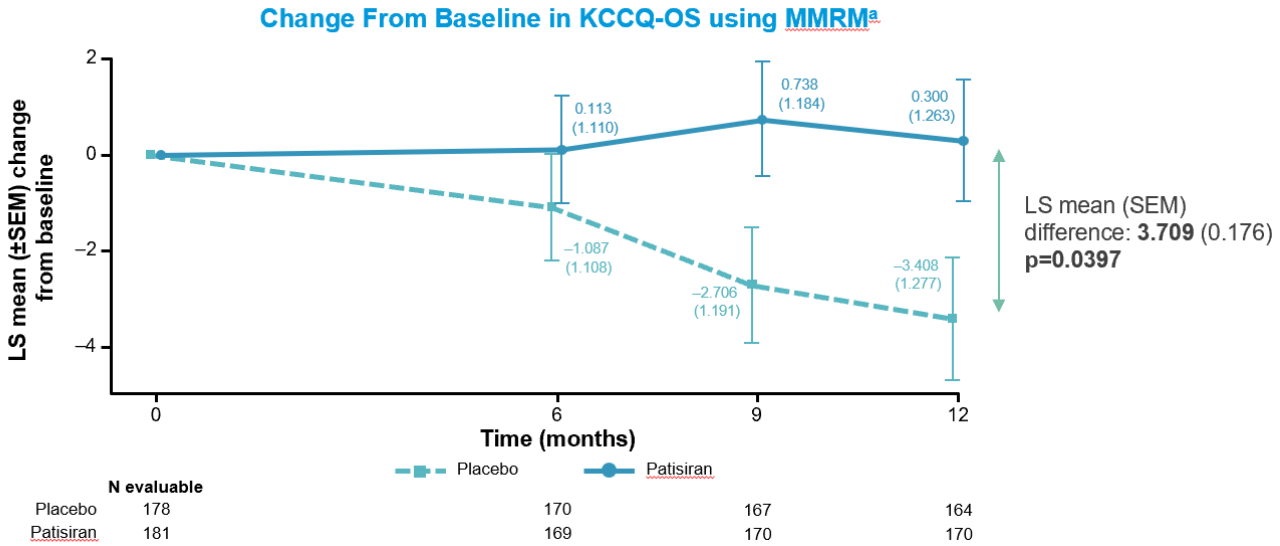
Change from Baseline in Serum TTR

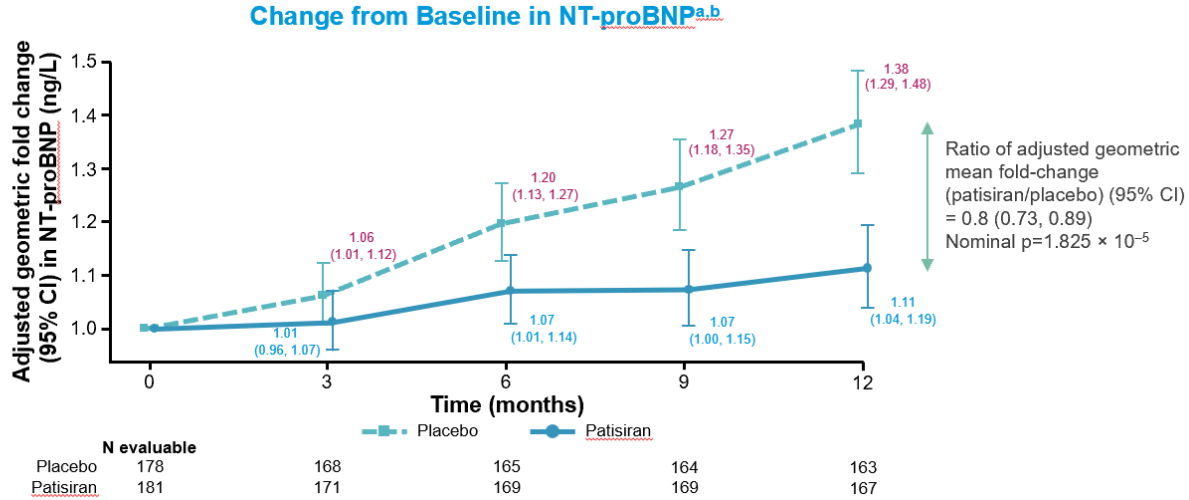


6MWD, 6-minute walking distance; FS, Finkelstein-Schoenfeld; KCCQ, Kansas City Cardiomyopathy Questionnaire; TTR, transthyretin.
Gillmore, J et al. Presented at Annual Meeting of the European Society of Cardiology: 2023; Amsterdam, NL; 25-28 August 2023.

APOLLO-B – Patisiran







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.

Fontana, M et al. Presented at Annual Meeting of the European Society of Cardiology: Heart Failure 2023; Prague, CZ; 20-23 May,2023.

Can we compare the results of the phase 3 clinical trials, and are the results applicable to the current population?

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 – dramatic change in clinical phenotype over the last 20 years, with patients now presenting at an earlier stage, better functional phenotype, better prognosis
- There are several differences in the ATTR-CM phase 3 clinical trials, including diagnostic pathway, baseline characteristics, study design, concomitant medications, better supportive treatment
- Evolution from a largely unrecognized and unmanaged disease to early diagnosis, early treatment initiation, effective management and monitoring, lower disability, and improved survival

ATTR-CM Mechanism of Action

Nitasha Sarswat, MD

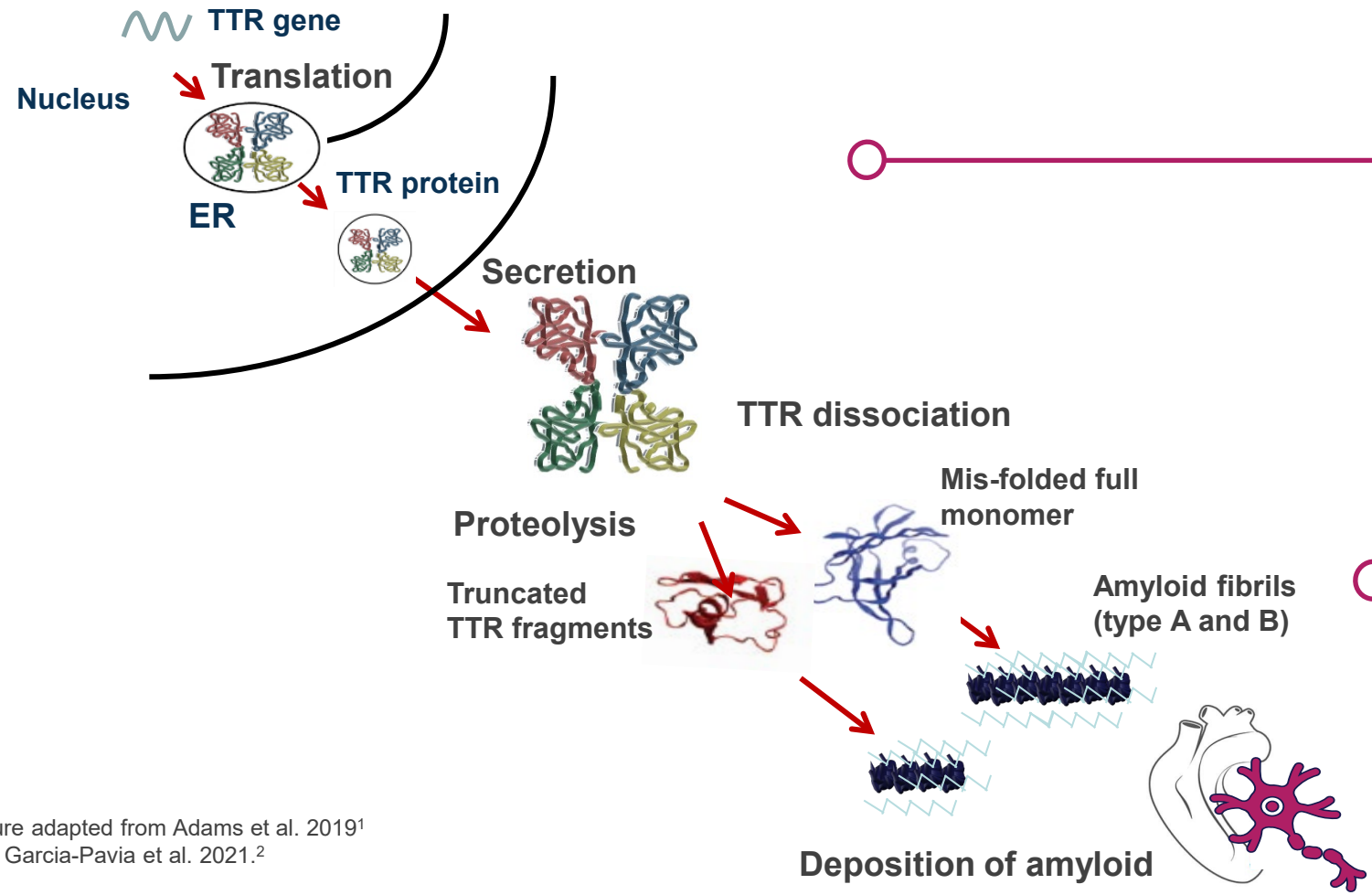
Director, Infiltrative Cardiomyopathy Program

Advanced Heart Failure, Mechanical Circulatory Support and Transplantation

University of Chicago Hospital

Chicago, IL

Disease-Modifying Treatment: Completed Phase 3 ATTR-CM Clinical Trials



Suppression of TTR synthesis

Gene silencing – RNAi therapy

- Patisiran – APOLLO-B

TTR stabilization

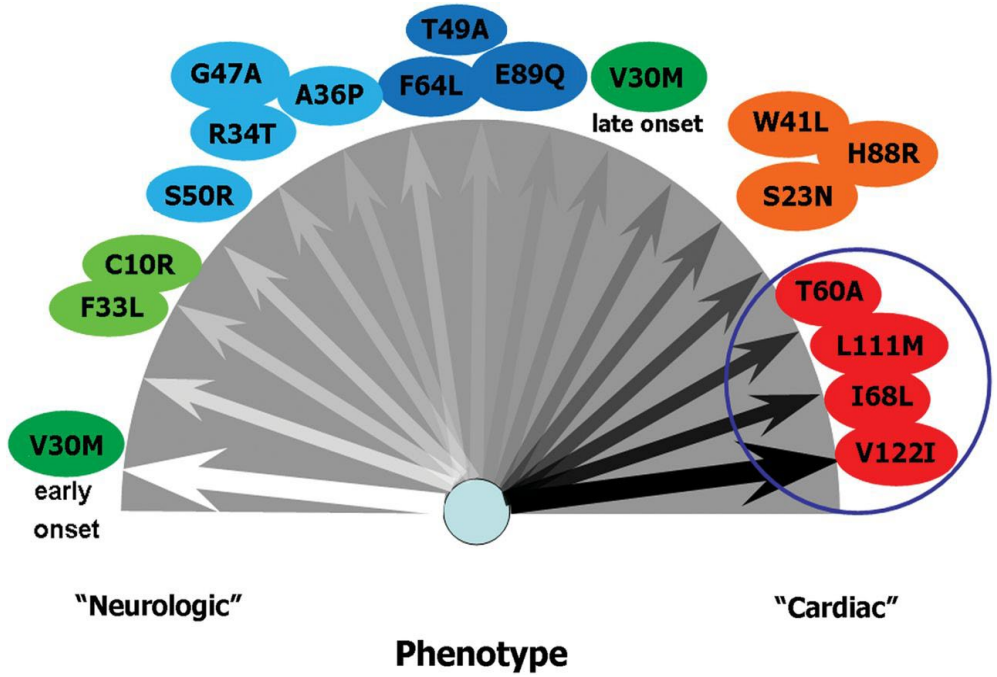
- Tafamidis – ATTR-ACT
- Acoramidis – ATTRibute-CM

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

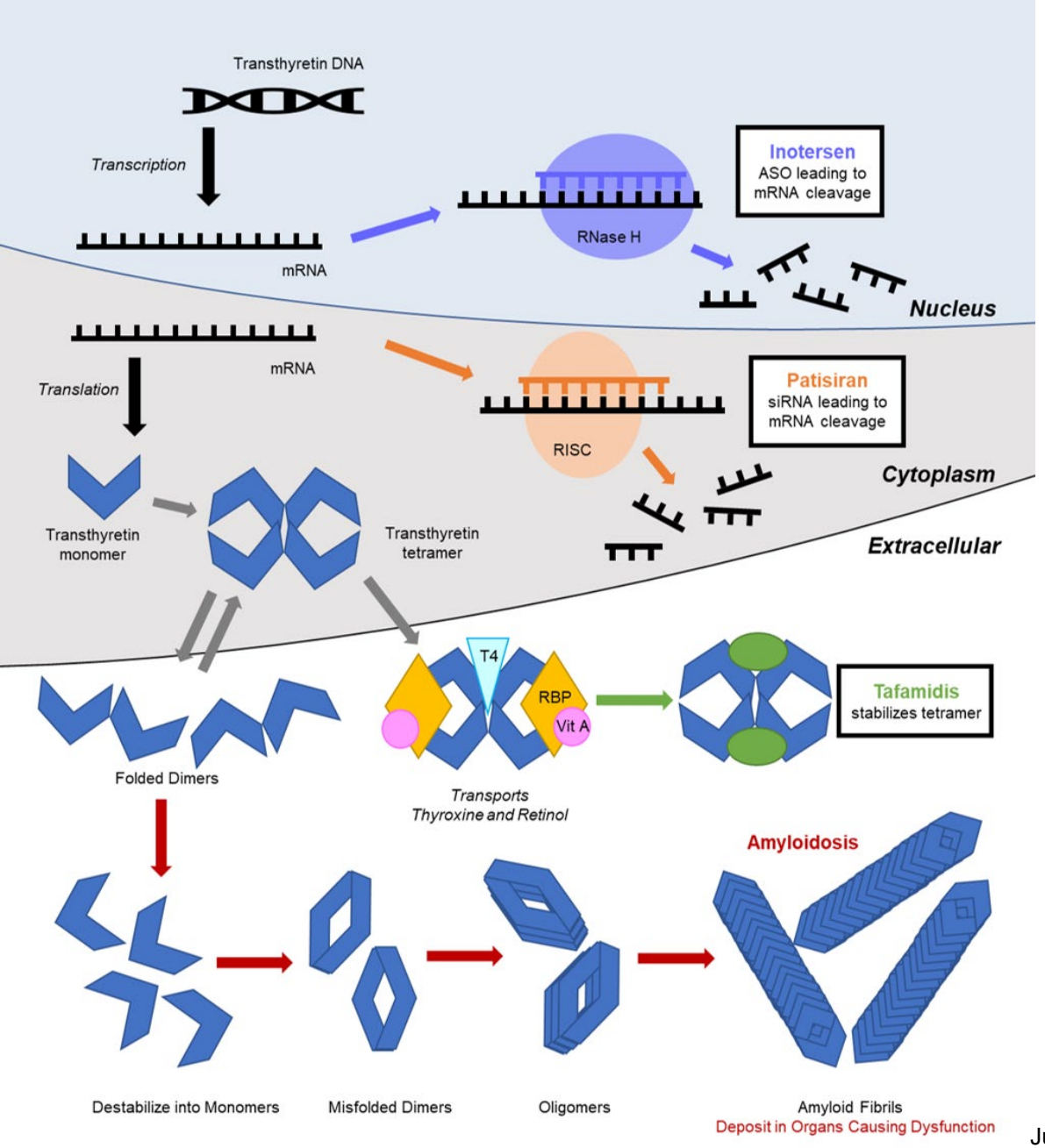
ASO, antisense oligonucleotide; ATTR, transthyretin-mediated amyloidosis; ER, endoplasmic reticulum; PN, polyneuropathy; RNAi, RNA interference; TTR, transthyretin. 1. Adams D, et al. *Nat Rev Neurol.* 2019;15(7):387-404. 2. Garcia-Pavia P, et al. *Eur Heart J.* 2021;42(16):1554-1568. 3. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 4. Onpattro (patisiran). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf 5. Amvuttra (vutrisiran). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf 6. Tegsedi (inotersen). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/tegsedi-epar-product-information_en.pdf 7. Vyndaqel (tafamidis). Accessed May 2023. https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf

Hereditary TTR

- Over 100 known mutations
  - 3 most common *TTR* mutations: Thr60Ala, Val30Met, Val122Ile
- Patients with the Val122Ile variant are generally older and have a higher degree of cardiac infiltration than patients with the other 2 mutations
  - 3.9% of African Americans and 23% of African Americans who have cardiac amyloidosis
- Val30Met
  - Most common mutation worldwide
  - Neuropathy at presentation
  - Development of cardiomyopathy later in the disease course



Rapezzi C, et al. *Eur Heart J*. 2013;34(7):520-528.



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-CM Statistical Review

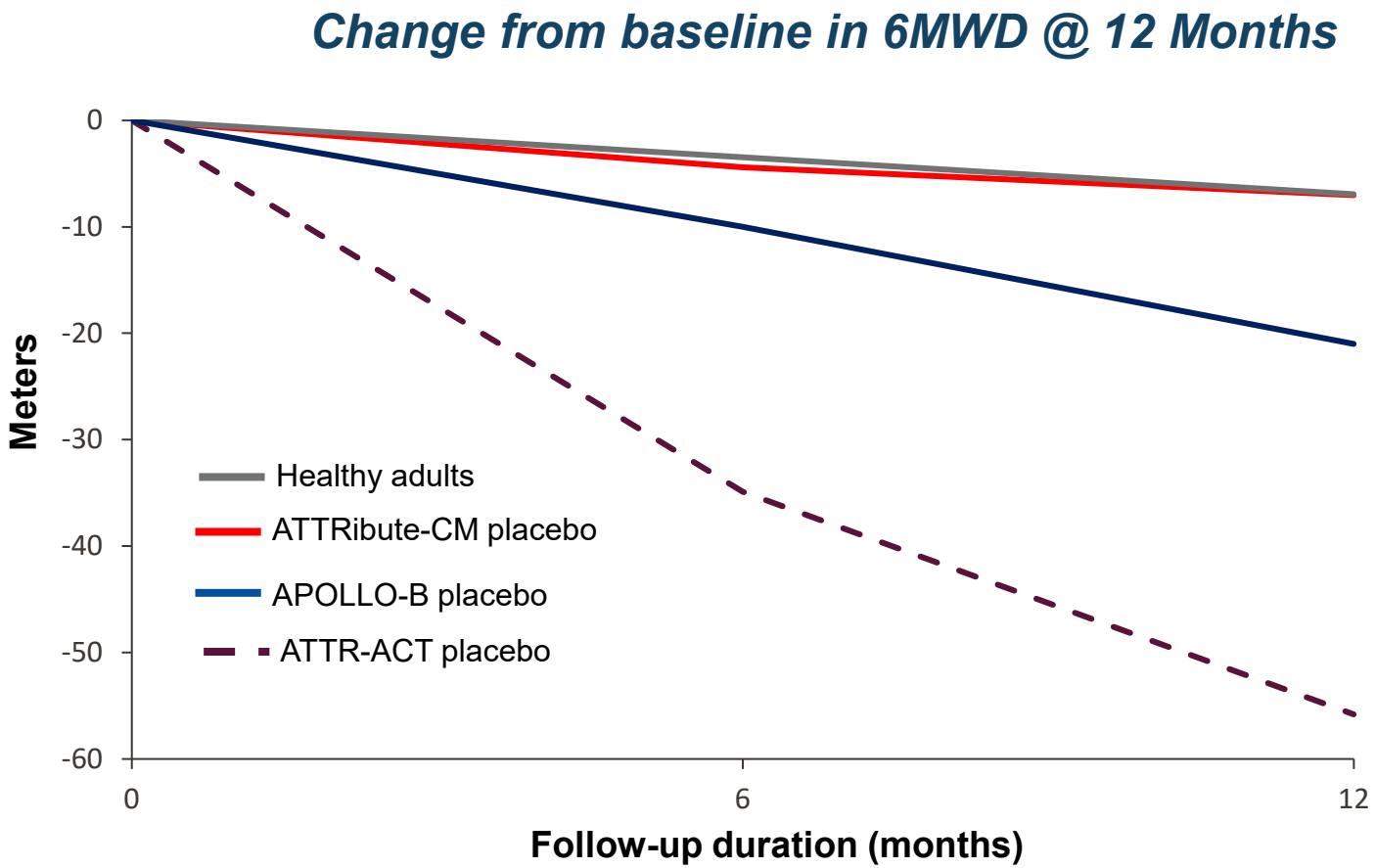
1. Phase 3 ATTR-CM Trials: Different Endpoints

		ATTR-ACT[1] Tafamidis	ATTRibute-CM[2] Acoramidis	APOLLO-B[3] Patisiran
Primary Endpoints	Clinical	30-month hierarchical composite of ACM and CVH	30-month hierarchical composite of ACM, CVH, Δ NT-proBNP, and Δ 6MWD	
	Functional		12-month Δ 6MWD	12-month Δ 6MWD
Key Secondary Endpoints	Clinical		30-month ACM	12-month ACM and CVH
	Functional	30-month Δ 6MWD	30-month Δ 6MWD	
	QoL	30-month Δ KCCQ-OS	30-month Δ KCCQ-OS	12-month Δ KCCQ-OS
	Biomarkers		30-month Δ sTTR	

6MWD, 6-minute walk distance; ACM, all-cause mortality, ATTR-CM, transthyretin amyloid cardiomyopathy; CVH, cardiovascular hospitalization; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life; sTTR, serum transthyretin.

1. Maurer MS, et al. *N Engl J Med*. 2018;379(11):1007-1016.
2. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Acoramidis (AG10) in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial. Statistical Analysis Plan. Version: 3.0. Effective: 03 August 2022.
3. Maurer MS, et al. Poster Presented at: Heart Failure Society of America Annual Meeting; Washington, DC; September 30, 2022.

2. Phase 3 ATTR-CM Trials: Different Population at Baseline



Approximate decline at 12 months from baseline

Healthy adult (N = 117): –5 m*
ATTRibute-CM placebo (n = 211): –7 m
APOLLO-B placebo (n = 179): –21 m
ATTR-ACT placebo (n = 177): –<60 m‡

‡Represents annual decline for a healthy elderly male, calculated using the source's provided reference equations.

1. BridgeBio. Corporate Presentation. February 2022. 2. Maurer MS, et al. *N Engl J Med*. 2018;379(11):1007-1016. 3. Maurer MS, et al. Poster Presented at: Heart Failure Society of America Annual Meeting; Washington, DC; September 30, 2022. 4. Nativi-Nicolau J, et al. *ESC Heart Fail*. 2021;8(5):3875-3884.

2. Phase 3 ATTR-CM Trials: Different Population at Baseline

	ATTR-ACT		ATTRibute-CM		APOLLO-B	
	Tafamidis	Placebo	Acoramidis	Placebo	Patisiran	Placebo
Age, years						
Median	75.0	74.0	78.0	78.0	76.0	76.0
NYHA class						
Class I	9.1	7.3	12.1	8.1	5.5	8.4
Class II	61.4	57.1	69.6	76.8	86.2	84.3
Class III	29.5	35.6	18.3	15.2	8.3	7.3
6MWT, meters						
Mean	351	353	361	348	361	375
NT-proBNP, ng/L						
Median	2996	3161	2326	2306	2008	1813
TTR Genotype, %						
Variant	23.9	24.3	9.7%	9.5%	20.4	19.1

Higher NYHA class and variant *TTR* gene status are established drivers of poor outcomes in ATTR-CM[4]

6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; mITT, modified intention-to-treat population; NT-proBNP, N-terminal pro-brain natriuretic peptide; NR, not reported; NYHA, New York Heart Association; TTR, transthyretin.

1. BridgeBio. Corporate Presentation. February 2022. 2. Maurer MS, et al. *N Engl J Med*. 2018;379(11):1007-1016. 3. Maurer MS, et al. Poster Presented at: Heart Failure Society of America Annual Meeting; Washington, DC; September 30, 2022. 4. Nativi-Nicolau J, et al. *ESC Heart Fail*. 2021;8(5):3875-3884.

3. Phase 3 ATTR-CM Trials: Different Inclusion and Exclusion Criteria

	ATTR-ACT[1] Tafamidis	ATTRibute-CM[2] Acoramidis	APOLLO-B[3] Patisiran
Age, years	18–90	18–90	18–85
Tafamidis inclusion	N/A	**None at baseline; drop-in after 12 months**	**"Progressors" allowed at baseline; up to 30% baseline tafamidis use**
NYHA	I–III symptoms	I–III symptoms	I–III symptoms **Excludes III at high risk**
6MWT	≥100 m	**≥150 m on 6MWT**	**≥150 m on 6MWT**
NT-proBNP	≥600 pg/mL	**≥300 pg/mL & ≤8500 pg/mL**	**>300 ng/L & <8500 ng/L (>600 ng/L & <8500 ng/L in AF)**
eGFR	≥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; ATTR-CM, transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

1. ClinicalTrials.gov Identifier: NCT01994889. Maurer MS, et al. *N Engl J Med*. 2018;379(11):1007-1016; 2. ClinicalTrials.gov Identifier: NCT03860935; 3. ClinicalTrials.gov Identifier: NCT03997383.

ATTR-CM Statistical Review: ATTRibute

- Randomized, double blind, placebo-controlled trial
- The primary endpoint, analyzed at 30 months, was a hierarchical analysis by the Finklestein-Schoenfeld method of all-cause mortality, cardiovascular-related hospitalization, NT-proBNP, and 6-minute walking distance (6MWD).
- Secondary endpoints included the components of the primary endpoint, KCCQ-OS, and serum transthyretin levels.
- Results showed a highly statistically significant primary hierarchical endpoint analysis, resulting in a win ratio of 1.8 (95% CI 1.4 to 2.2; $P < 0.0001$).
- Researchers observed a consistent, positive treatment effect across all components of the primary endpoint analysis, including a numerical reduction in all-cause mortality, with an absolute risk reduction of 6.4%, relative risk reduction of 25%, and hazard ratio of 0.772.
- Additionally, the cumulative frequency of cardiovascular-related hospitalizations was reduced by about 50% in the acoramidis group, and improvements in NT-proBNP from baseline as well as 6MWD were greater in the acoramidis group as well.

Gillmore, J, et al. Presented at: European Society of Cardiology Congress 2023; Amsterdam, NL; 25-28 August 2023.

Finkelstein-Schoenfeld Method

- Used to analyze data with a composite endpoint where different components for the composite endpoint have different levels of importance
- Aimed at weighting results in analysis of composite endpoints
- Based on the pairwise comparisons – the value/outcome from each subject in treatment group A is compared to each of all subjects in treatment group B

Finkelstein DM, Schoenfeld DA. *Stat Med*. 1999;18(11):1341-1354.

Win Ratio

- Based on the Finkelstein-Schoenfeld method
- An estimate which helps to summarize the ratio of the number of patients who fared better versus worse on the experimental arm
- The ratio of the wins over losses in the treatment group is called the win ratio. The treatment is beneficial compared to the control if the win ratio is greater than 1
- Created explicitly for analyzing the composite endpoint
- Pairwise comparisons -> scores are calculated based on the comparison of the importance of the outcome.

Win Ratio= # of treatment wins/# of placebo wins

- Also used in ATTR-ACT and the PARTNER trial (pivotal TAVR trial)

Pocock SJ, Ariti CA, Collier TJ, Wang D. *Eur Heart J*. 2012;33(2):176-182.

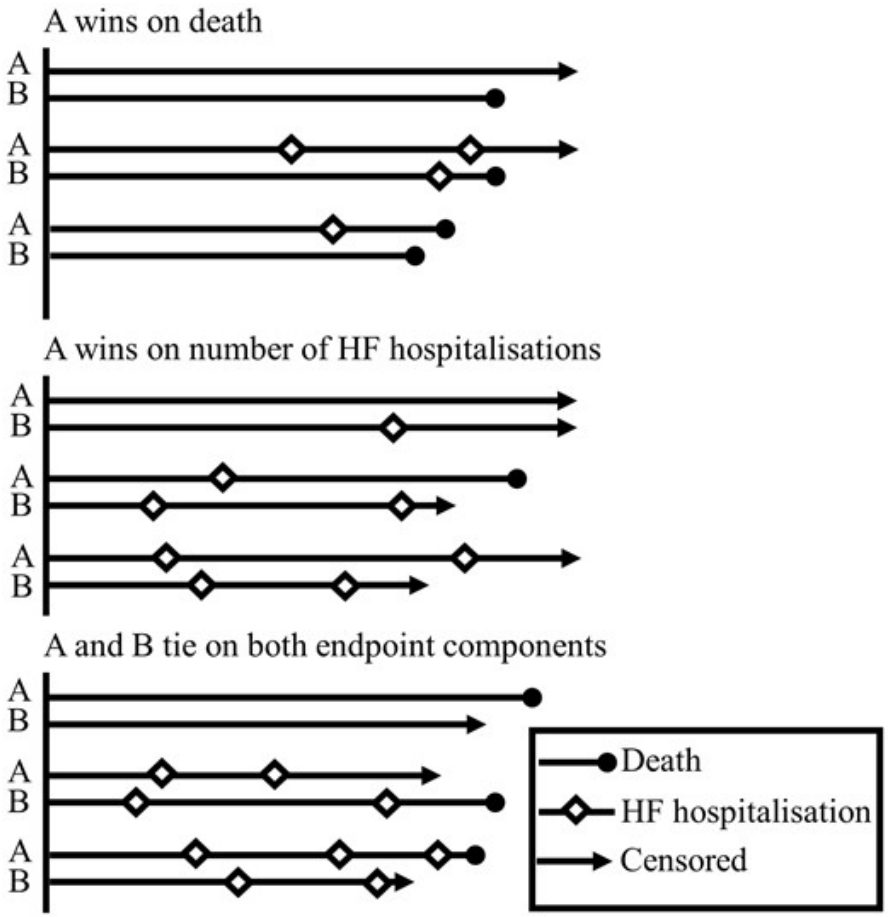
Win Ratio

The probability win ratio of greater than 1 indicates evidence of treatment effect in favor of the treatment group.

Pocock SJ, Ariti CA, Collier TJ, Wang D. *Eur Heart J*. 2012;33(2):176-182.

General Principle Behind the Win Ratio Approach.

Pairwise comparison of the composite time to death (first level in the hierarchy) and number of HF hospitalizations (second level in the hierarchy).



Patient A wins on death if he/she remains alive longer than patient B, irrespective of who was hospitalized the most times.

If neither patient dies, then patient A wins on number of HF hospitalizations if he/she had been hospitalized fewer times than patient B over the course of their shared follow-up time.

If both patients remained alive and neither patient was hospitalized or both patients were hospitalized the same number of times over the course of their shared follow-up time, then the patients are considered to tie.

Alternatively, this tie may be broken by specifying the time to first hospitalization as an additional level of discrimination. HF, heart failure.

Redfors B, G et al. *Eur Heart J*. 2020;41(46):4391-4399.

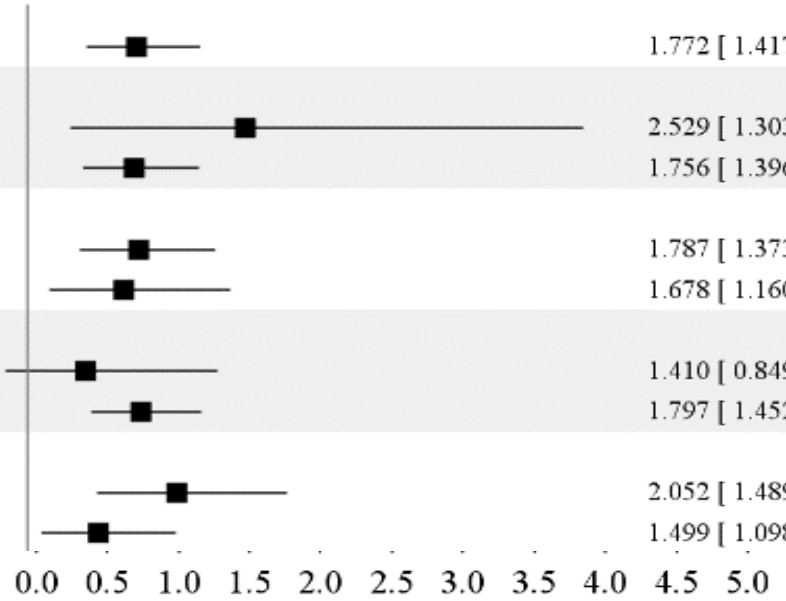
Wins Ratio Take Home Messages

Advantages	Challenges
1. All Key Elements Included The win ratio recognizes all events, not just the first one, e.g. a death after a non-fatal event gets included in the analysis	1. Lack of Familiarity The win ratio is a relatively new statistical method: *This article should facilitate a better understanding of the concept and its potential value.*
2. Clinical Priorities Recognized The win ratio forms the component outcomes into a hierarchy based on their relative clinical importance, e.g. death gets top priority.	2. Statistical Software Calculation of the win ratio (and its CI and p-value) requires statistical programs being readily available: *We provide links to such software.*
3. Repeat Events Easily Incorporated The win ratio can be readily extended to account for recurrent events (e.g. hospitalizations) without statistical complexity.	
4. Non-Event Outcomes can be Included The win ratio can be extended to include visit-related items, e.g. quality of life scores and physiological measures.	3. Determining Sample Size Power calculations for the win ratio entail simulations: *We have created new software to facilitate this task*
5. Conceptually Straightforward Counting up the “winners” and “losers” across all pairwise comparisons is a simple concept, compared to explaining what a hazard ratio means.	

Redfors B, G et al. *Eur Heart J*. 2020;41(46):4391-4399.

ATTRibute-CM – Acoramidis Wins Ratio

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	<0.0001
Age (years)				0.6292
< 78	299(48.9)	2.052 [1.489, 2.829]	<0.0001	
>= 78	312(51.1)	1.499 [1.098, 2.045]	0.0107	



6MWD, 6-minute walking distance; FS, Finkelstein-Schoenfeld; KCCQ, Kansas City Cardiomyopathy Questionnaire; TTR, transthyretin.
Gillmore, J et al. Presented at Annual Meeting of the European Society of Cardiology: 2023; Amsterdam, NL; 25-28 August 2023.

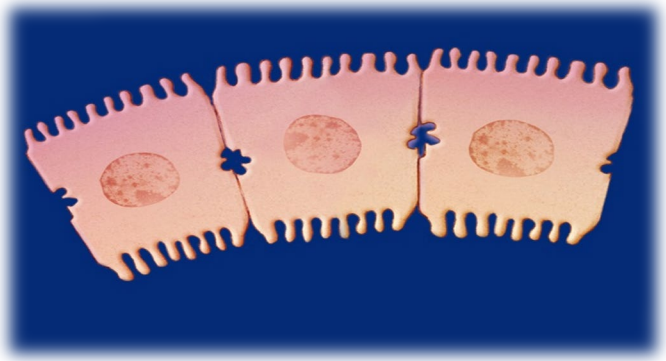
ATTR-CM Current and Future Therapeutic Options

Martha Grogan, MD, FACP, FACC
Director, Cardiac Amyloid Clinic
Associate Professor of Medicine
Department of Cardiovascular Diseases
Mayo Clinic
Rochester, MN

medtelligence℠

TTR Amyloid

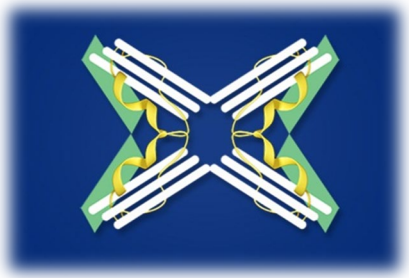
Treatment Options



Liver – Stop production

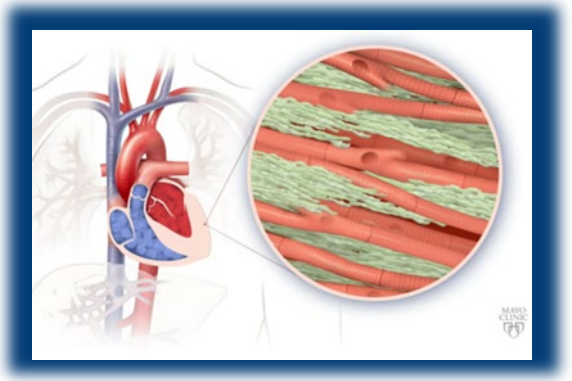
RNA silencer therapy
Patisiran[1], Inotersen[1],Vutrisiran[1,4]
Eplontersen [4,5]

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



Stabilize protein

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

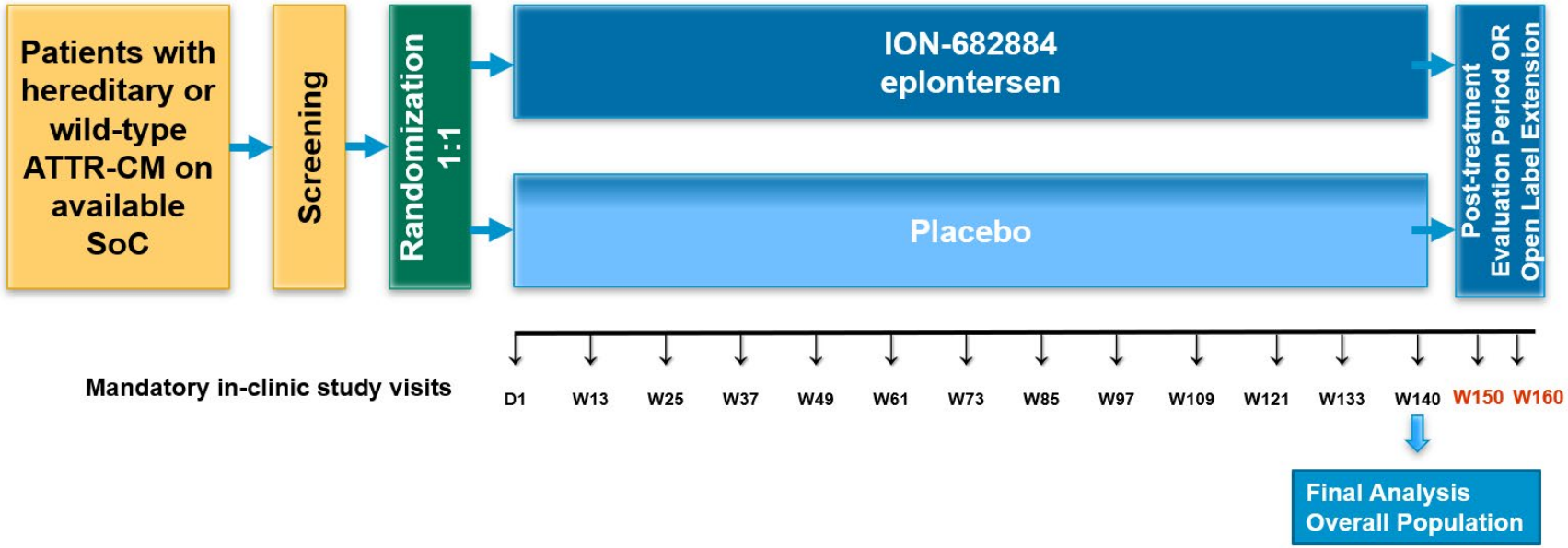


Amyloid Fibril Depleter

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

CARDIO-TTRansform Study Design

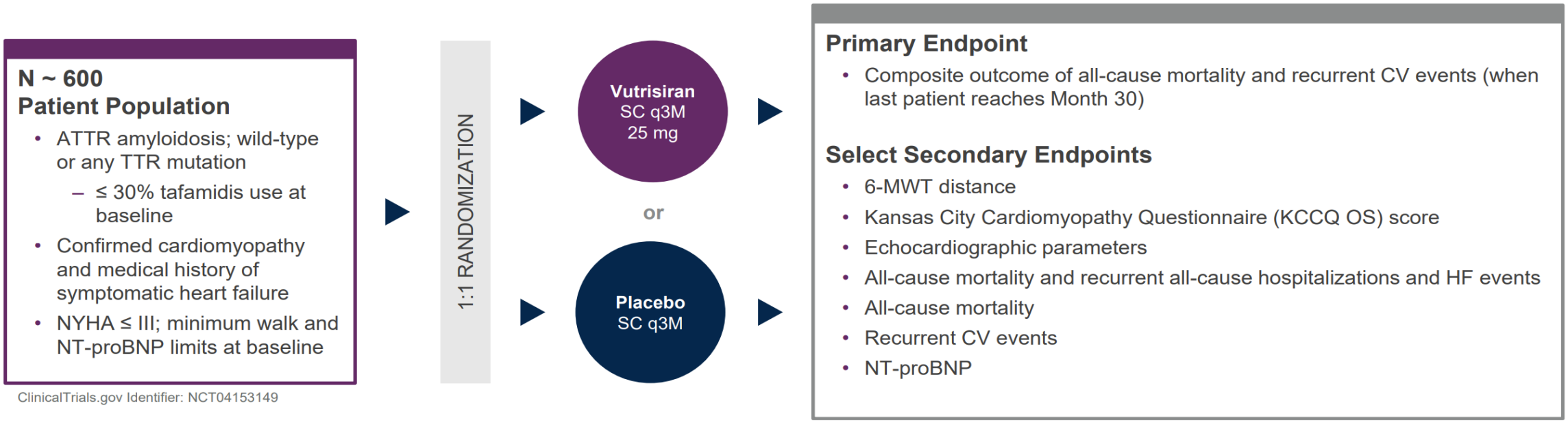


- **Concomitant use of tafamidis is allowed at any time during the study**
- Total number of patients ~1400
- 1:1 Randomization: ION-682884 – **eplontersen** -(45 mg) or placebo
- 140 Week Treatment Period with subcutaneous (SC) injections **once every 4 weeks** (last dose Week 137)

Viney NJ, Guo S, Tai LJ, et al. *ESC Heart Fail.* 2021;8(1):652-661.

Vutrisiran HELIOS-B Phase 3 Study

Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy



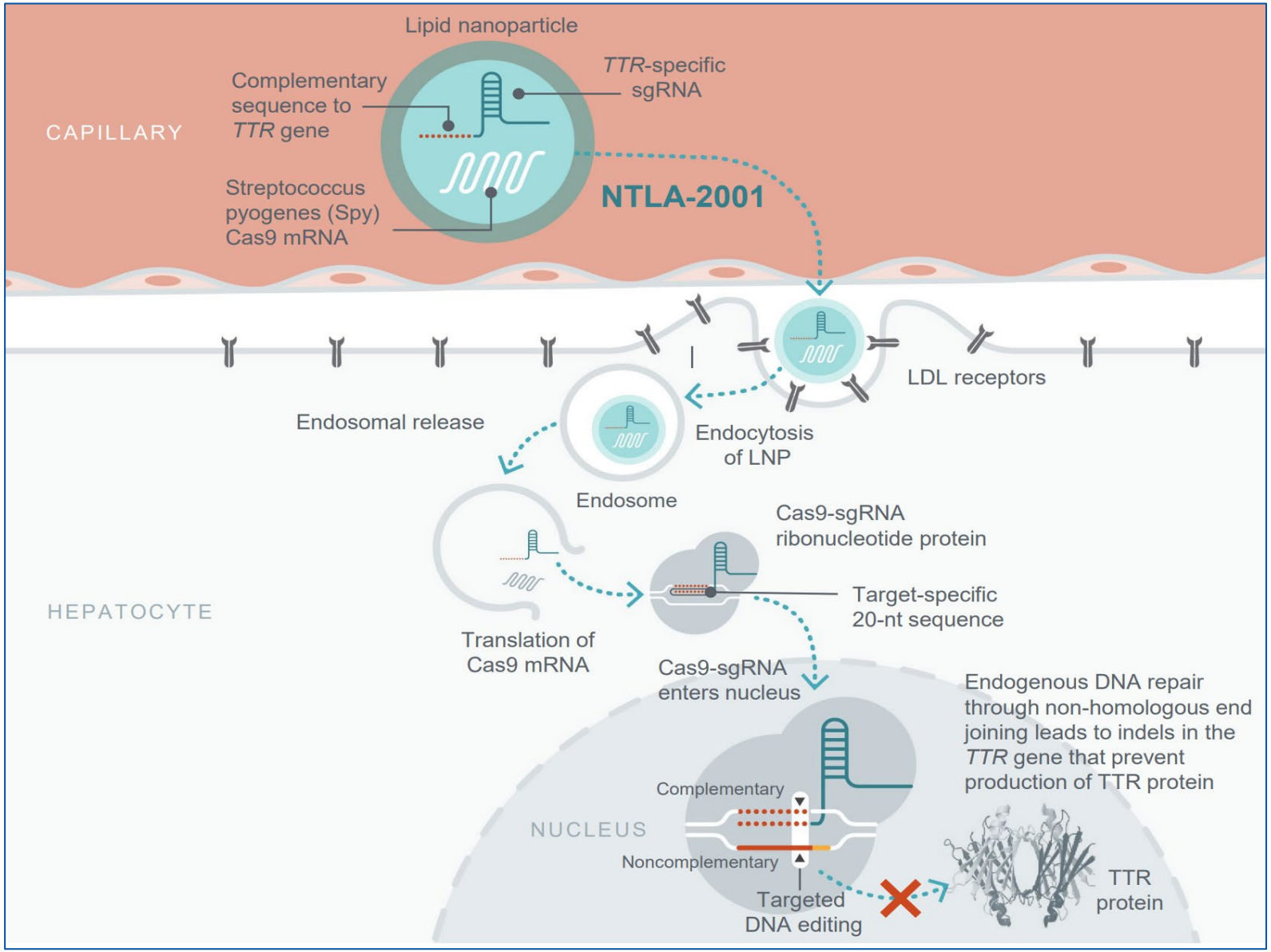
ClinicalTrials.gov Identifier: NCT04153149

Excluded: ATTR-CM NAC Stage 3 (NTproBNP > 3000 and GFR < 45) combined with NYHA Class III

HELIOS-B: Results 2nd Qtr 2024

Clinicaltriall.gov Identifier: NCT04153149. Alnylam Pharmaceuticals (2023). HELIOS Fact Sheet [Fact sheet]. Retrieved from https://www.alnylam.com/sites/default/files/pdfs/HELIOS-Fact-Sheet.pdf. Accessed on October 31, 2023

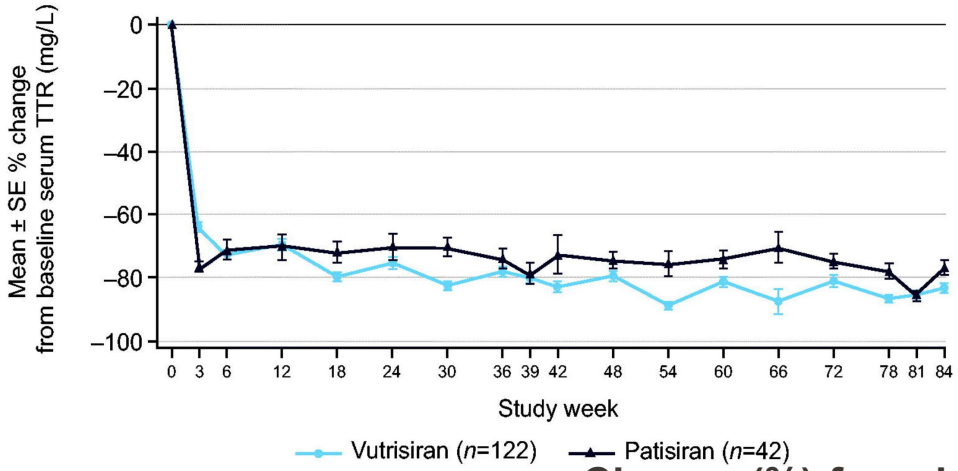
NTLA-2001: Silencing the TTR Gene By Gene Editing



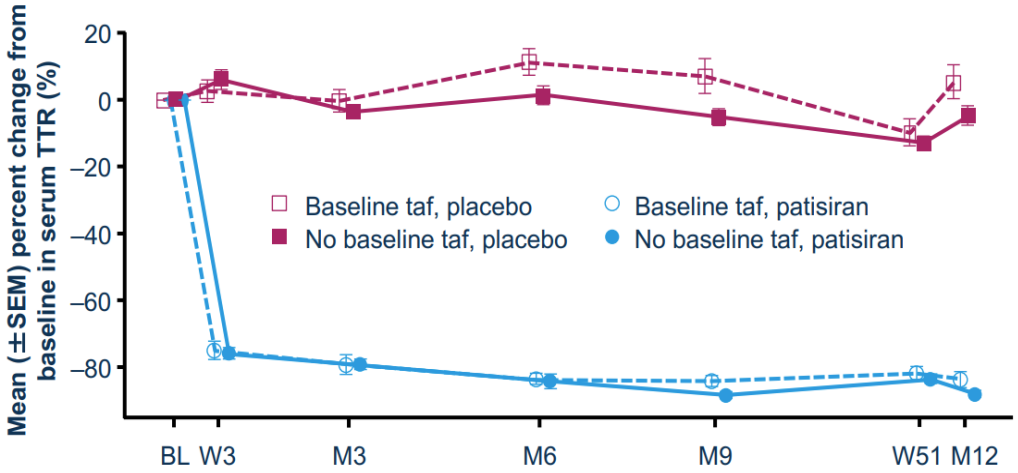
Gillmore et al. presented at American Heart Association: Scientific Session 2022; Chicago, IL; 11-13 November, 2023.

Current Silencers Achieve ~80% TTR Reduction

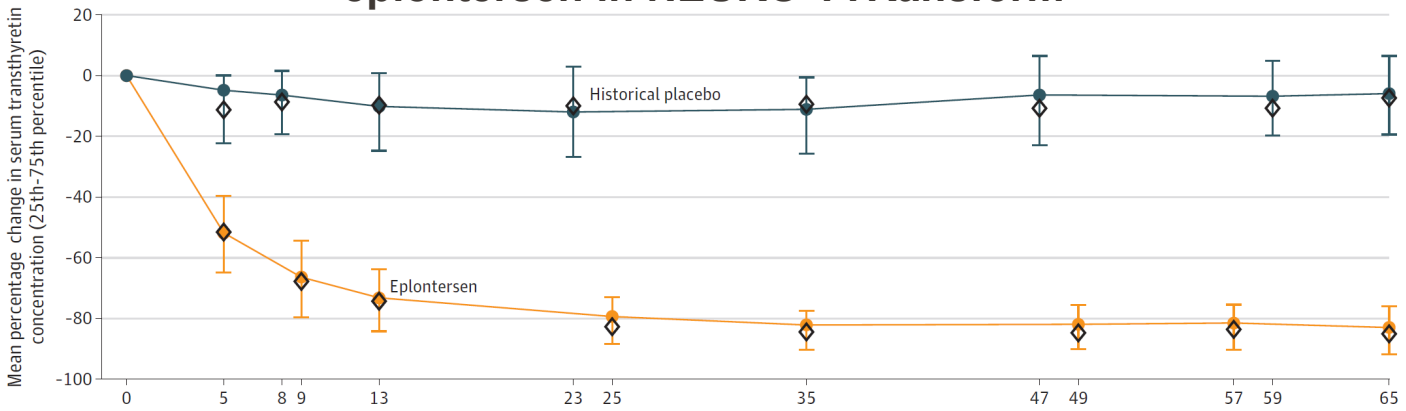
Change (%) from baseline in serum TTR levels with vutrisiran and patisiran through 18 months of the HELIOS-A study



Change (%) from baseline in serum TTR levels with patisiran in APOLLO-B

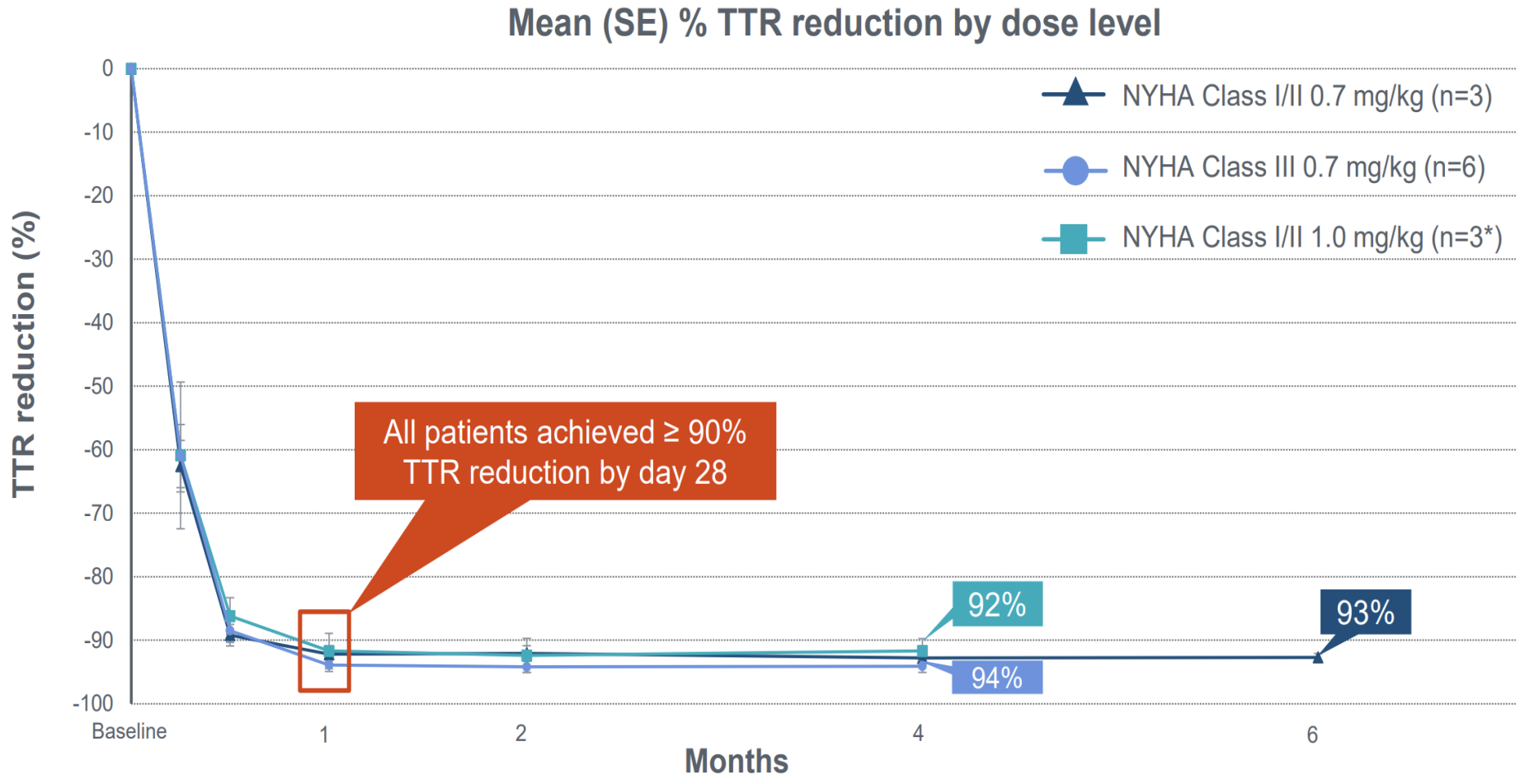


Change (%) from baseline in serum TTR levels with eplontersen in NEURO-TTRansform



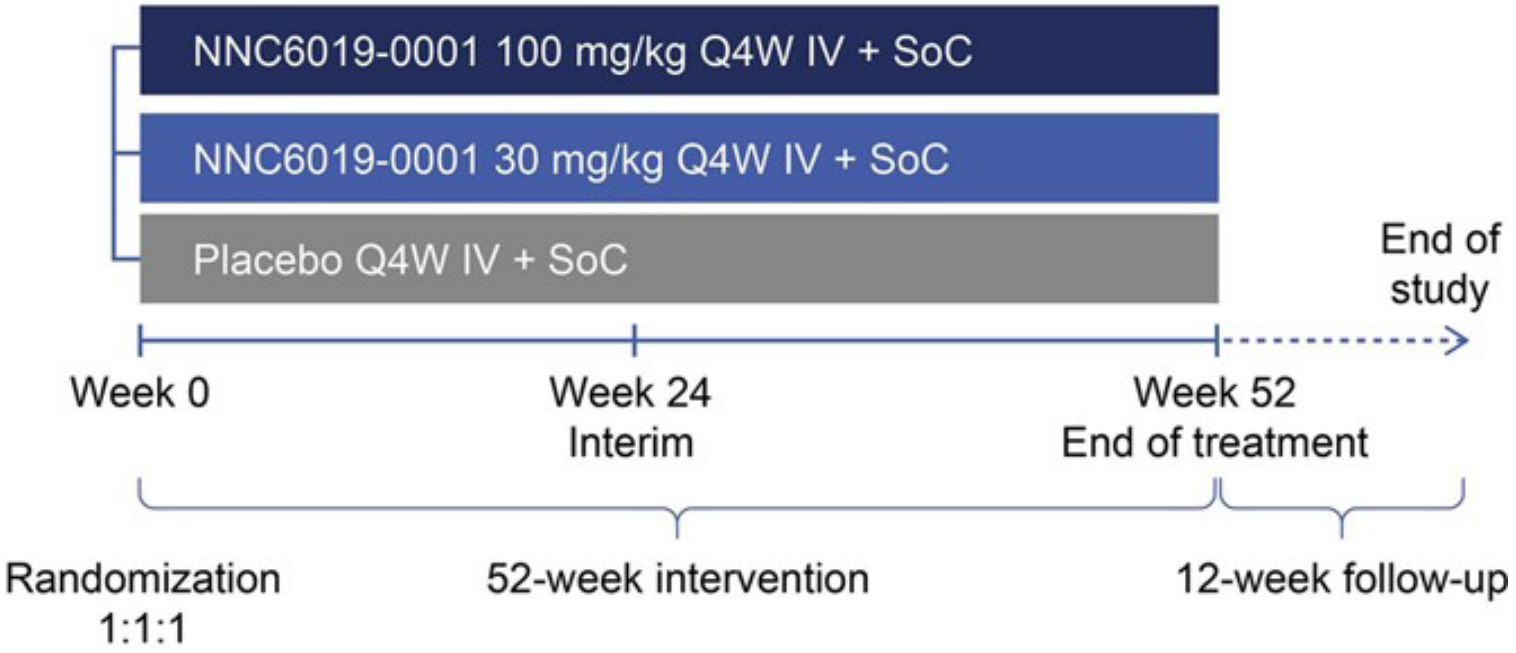
1. Adams D, Tournev IL, Taylor MS, et al. *Amyloid*. 2023;30(1):1-9; 2. Maurer et al. Presented Heart Failure Society of America (HFSA) Annual Scientific Meeting, Washington, DC, September 30–October 3, 2022; 3. Coelho T, Marques W Jr, Dasgupta NR, et al. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. *JAMA*. 2023;330(15):1448-1458.

Is >90% TTR Silencing Beneficial? Adverse effects?



Gillmore et al. presented at American Heart Association: Scientific Session 2022; Chicago, IL; 11-13 November 2023.

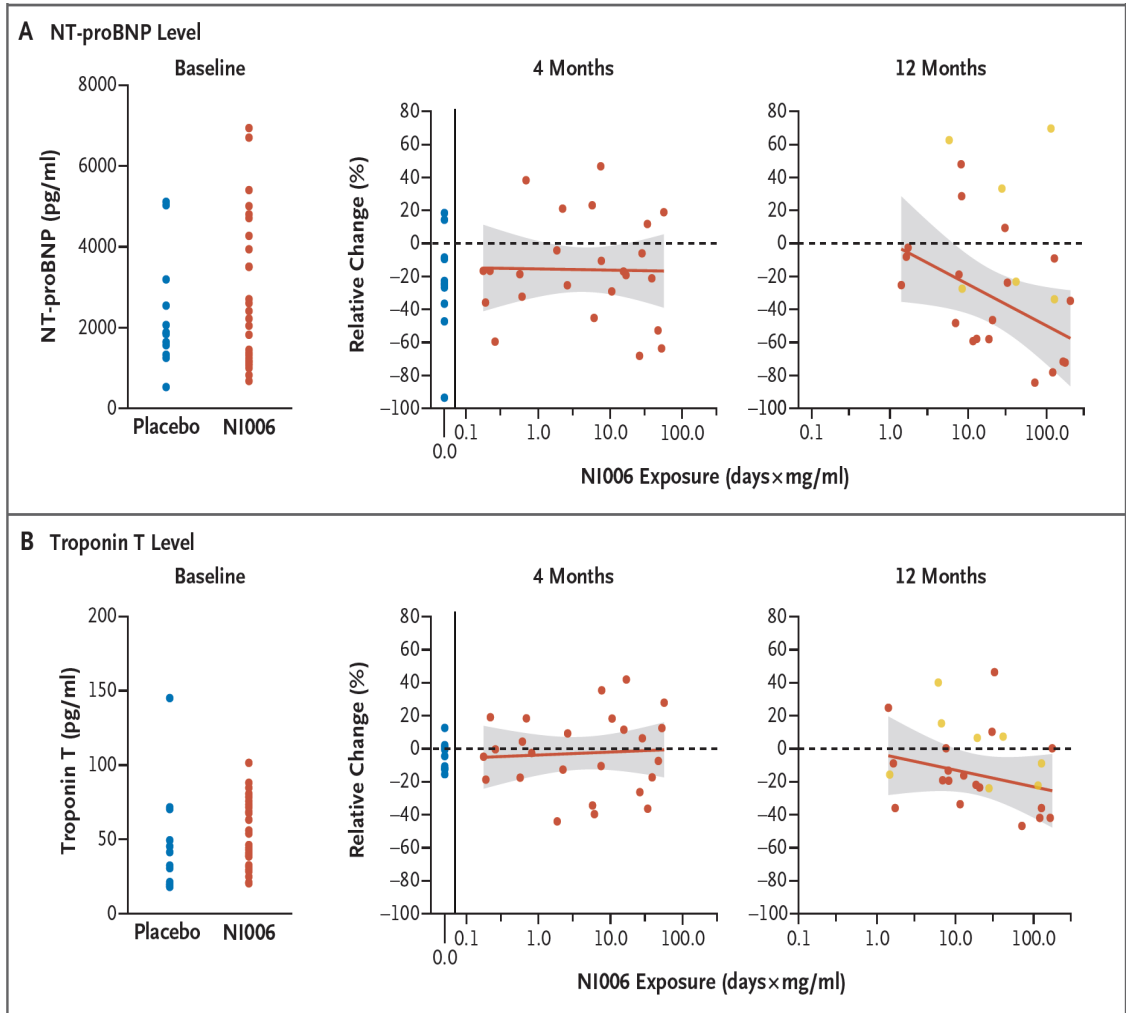
Phase 2 Trial Design of NNC6019-001 in Patients with ATTR-CM

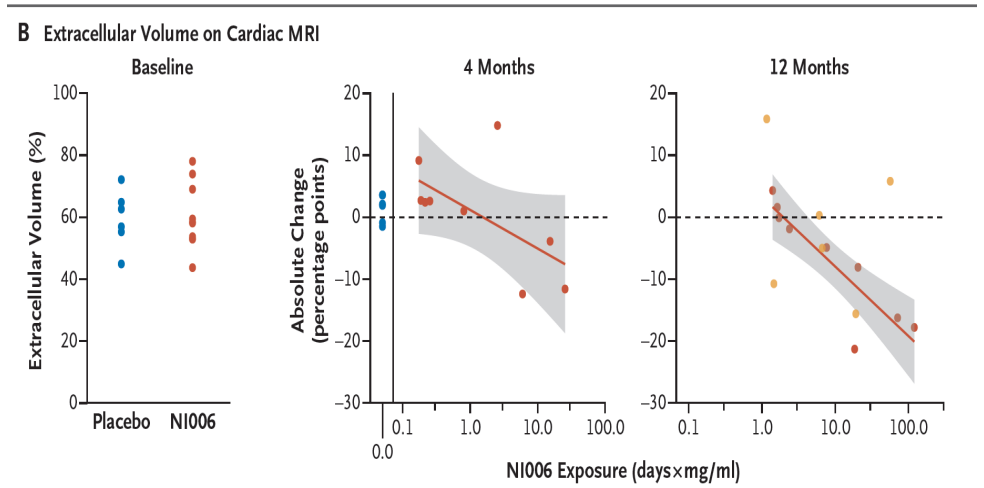


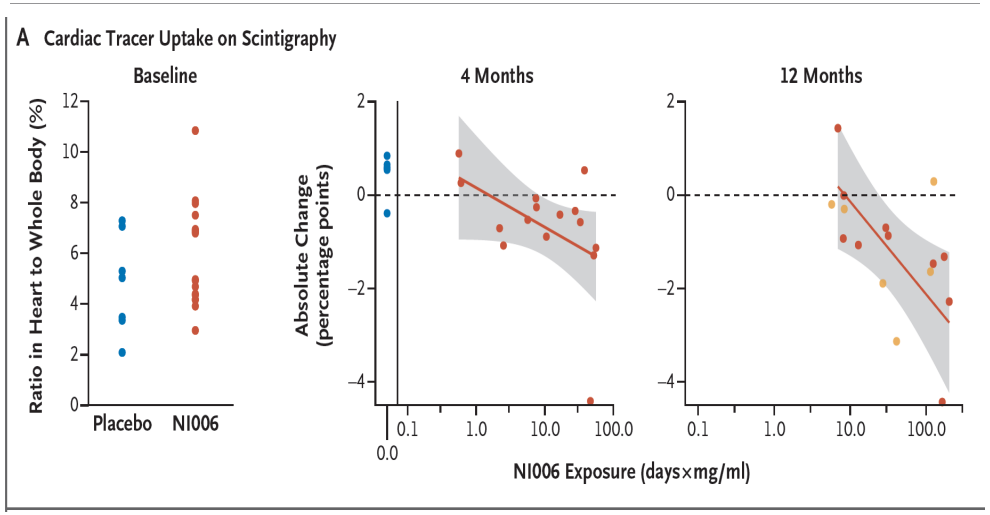
Phase II in progress

ATTR-CM, transthyretin amyloid cardiomyopathy; IV, intravenous; Q4W, every 4 weeks; SoC, standard of care.
Fontana, M. et al. *Eur Heart J*, Volume 43, Issue Supplement_2, October 2022, ehac544.1767

NI006 (ALXN2220) Fibril Depleter Phase I



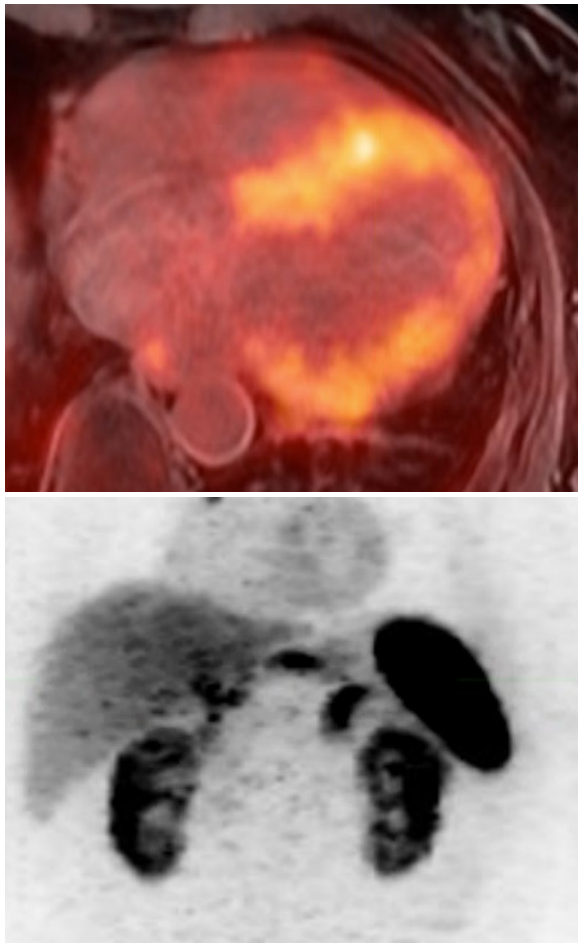


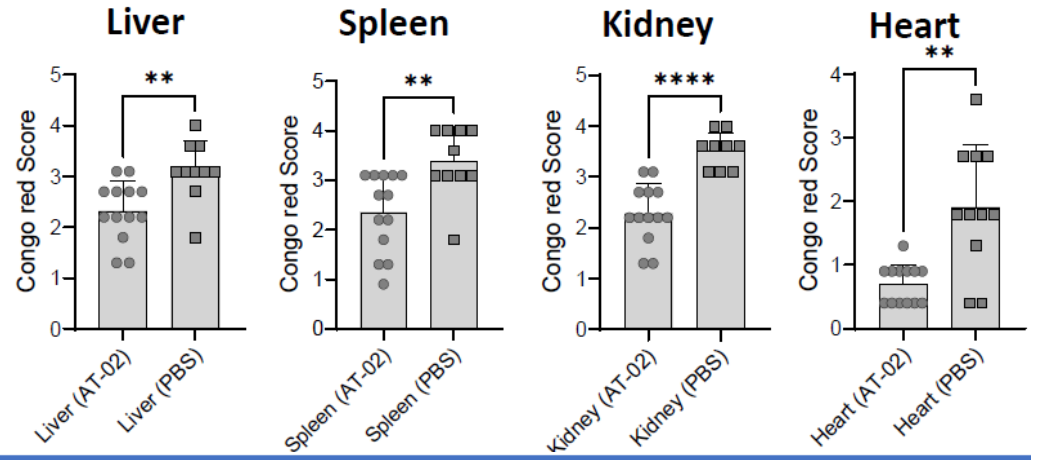


Garcia-Pavia P, Aus dem Siepen F, Donal E, et al.. *N Engl J Med.* 2023;389(3):239-250.

AT-02 Pan Amyloid Depleter

Phase I





Organ	AT-02 median (n)	PBS median (n)	Mann- Whitney Sig.
Liver	2.2 (*n*=13)	3.1 (*n*=10)	p=0.0029
Spleen	2.7 (*n*=13)	3.35 (*n*=10)	p=0.0023
Kidney	2.2 (*n*=13)	3.6 (*n*=9)	p<0.0001
Heart	0.9 (*n*=13)	1.8 (*n*=11)	p=0.0017

Wall, J, et al. Presented at International Symposium on Amyloidosis (ISA) 2022; Heidelberg, Germany; 4-8 September 2022.

Summary: Future Treatment of ATTR-CM

- Silencer vs Stabilizers, unclear role of combination
- Permanent silencing vs ongoing treatment
  - Cost-effectiveness and safety
- Anti-fibril (depleter) therapy
  - Secondary option
- Earlier Diagnosis and Treatment will transform ATTR-CM from an almost universally fatal disease to a chronic cardiovascular condition

Key Takeaway

Faculty Discussion/Q&A