ONPATTRO® (patisiran)

For the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated (ATTR) amyloidosis in adults to slow the decline in functional capacity and reduce symptoms

September 13, 2023

Cardiovascular and Renal Drugs Advisory Committee

Alnylam Pharmaceuticals

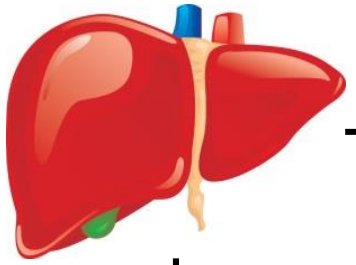
Introduction

Pushkal P. Garg, MD

Chief Medical Officer

Alnylam Pharmaceuticals

ATTR Amyloidosis: Multisystem Disease Caused by Misfolding of Hepatic Transthyretin (TTR)



TTR – transport protein for Vitamin A

vTTR

wtTTR

Misfolded TTR

Amyloid Fibrils

Peripheral Nerves

Heart

Polyneuropathy

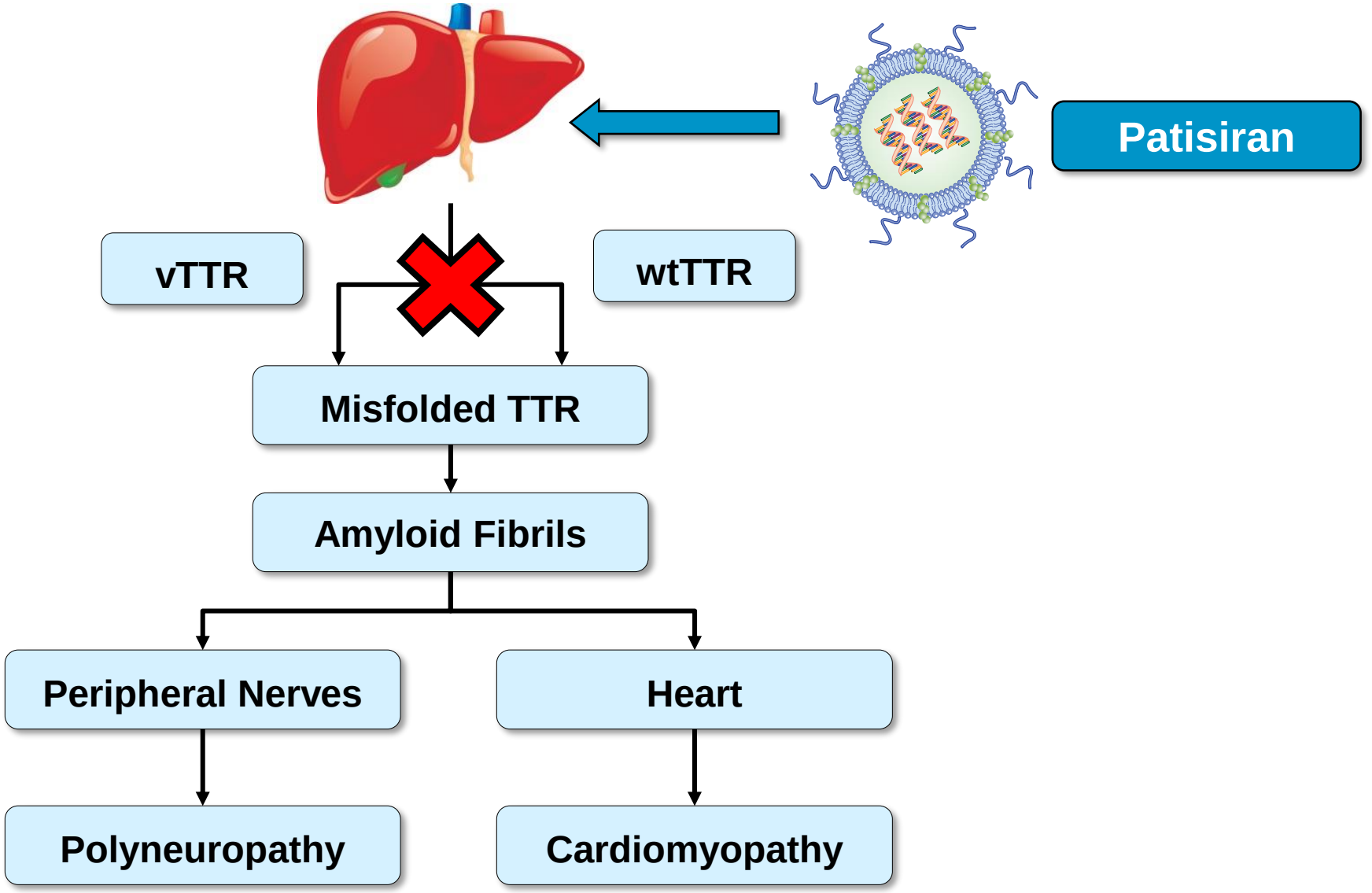
Cardiomyopathy

vTTR = variant transthyretin
wtTTR = wild-type transthyretin

Patisiran Silences Hepatic TTR Production

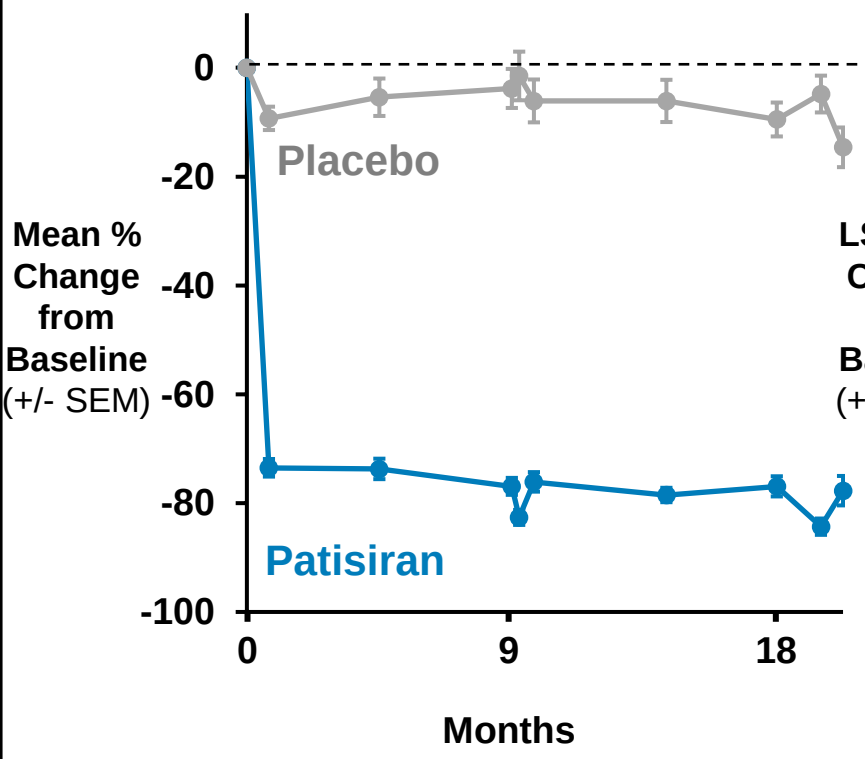
- Small interfering RNA
- Targets highly conserved region of TTR gene
- Formulated as lipid nanoparticle for liver-specific delivery
- Administered intravenously 0.3 mg/kg every 3 weeks

Patisiran: Reduces Hepatic TTR Production Via RNA Interference

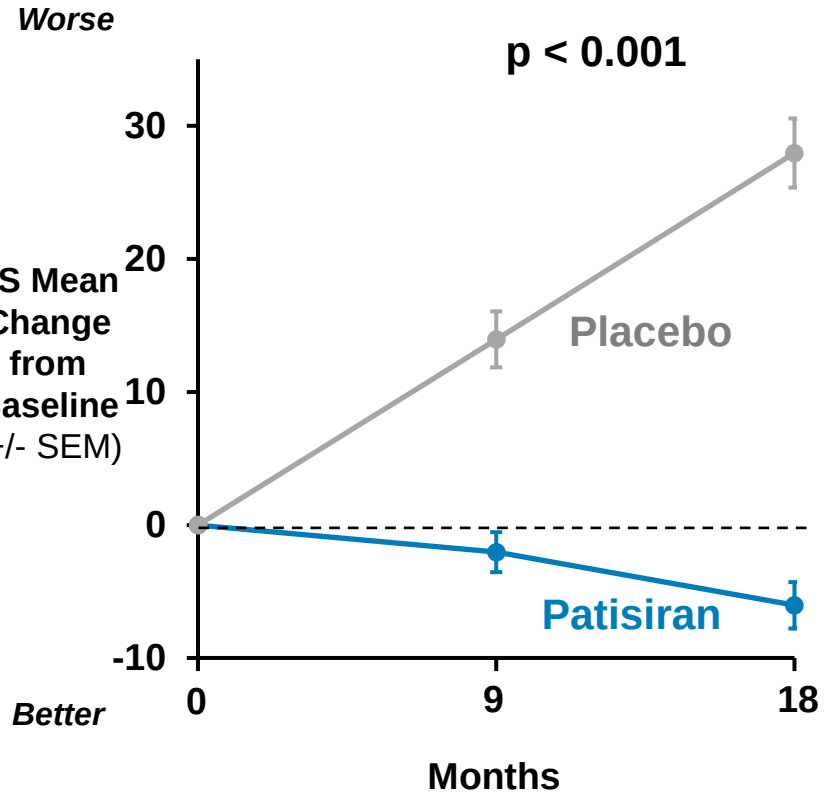


APOLLO: Patisiran Improved Polyneuropathy of hATTR Amyloidosis

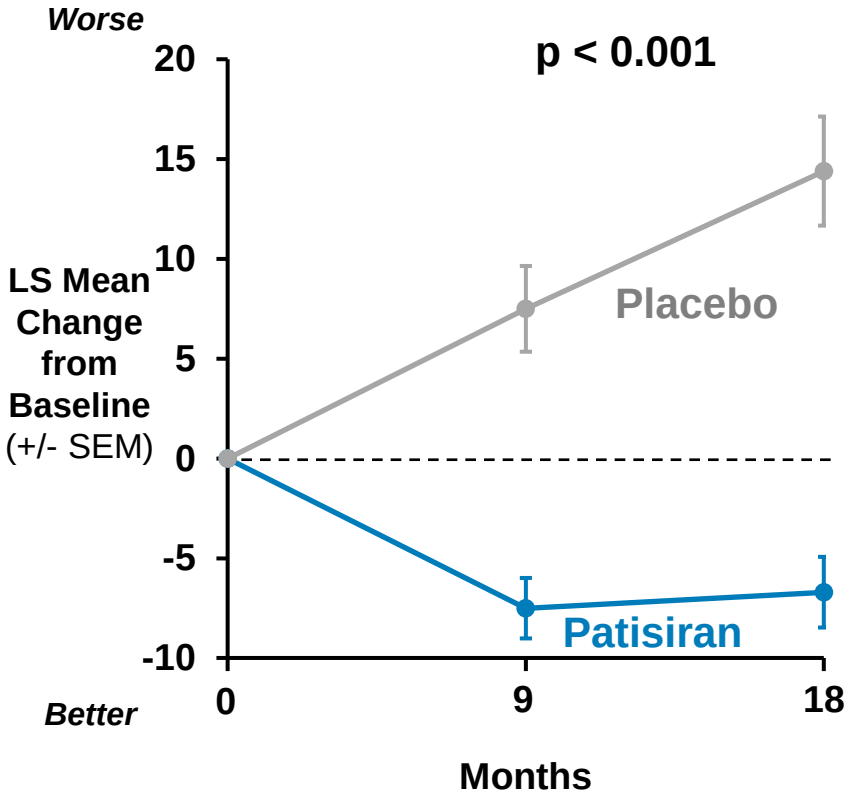
Serum TTR Reduction



Neuropathy Impairment (mNIS+7)



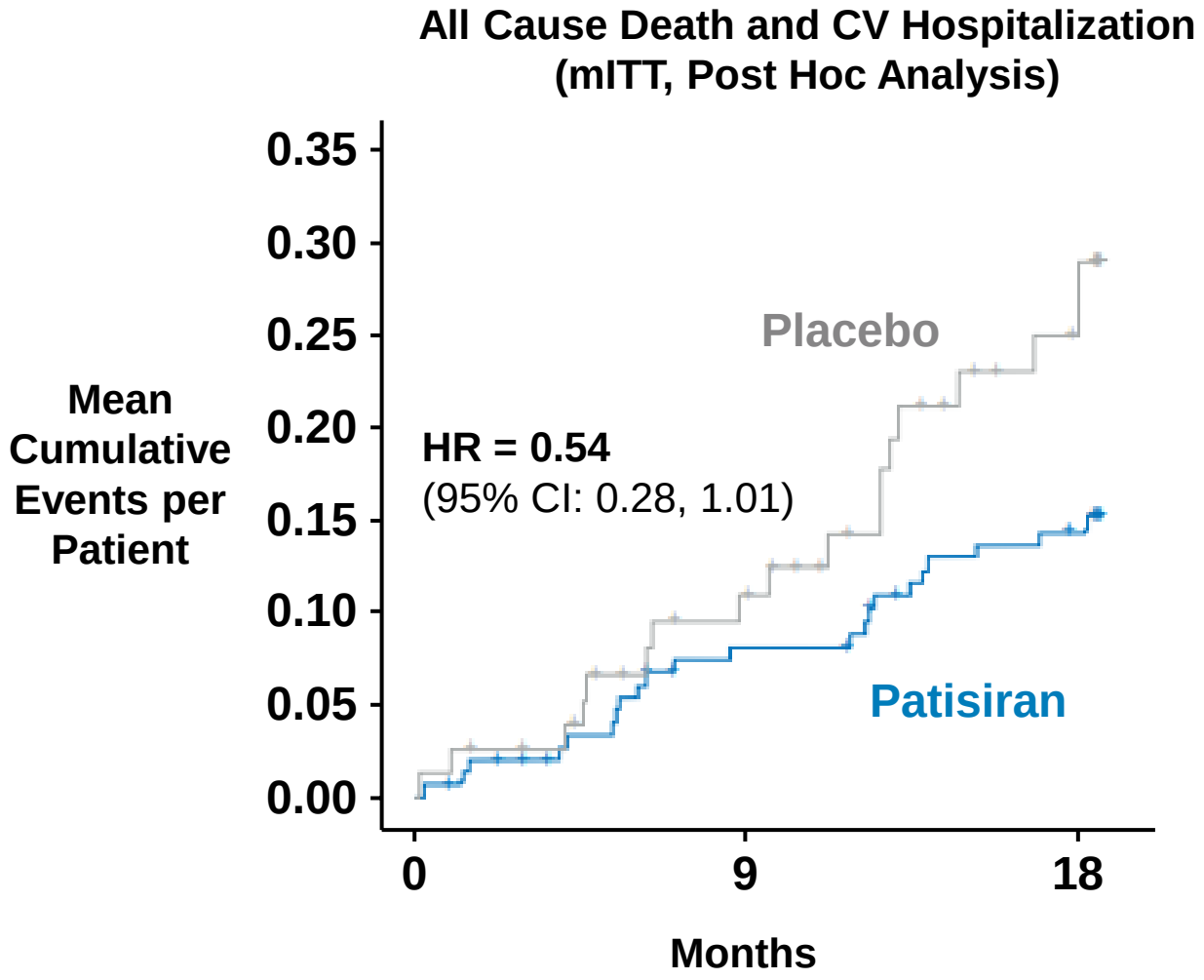
Patient Reported QoL (Norfolk QOL-DN)



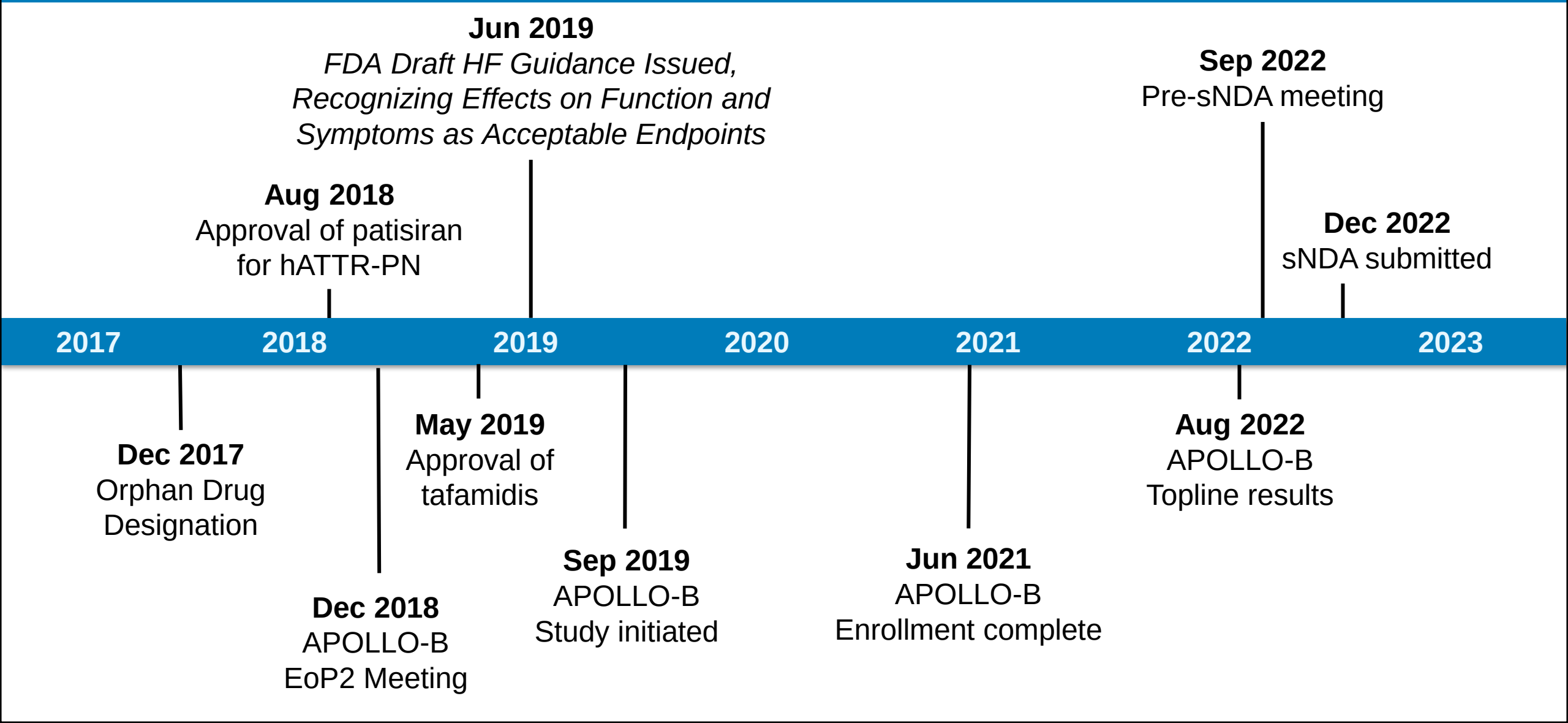
N = 225 (148 patisiran; 77 placebo)

APOLLO: Patisiran Improved Cardiac Manifestations

- 56% of APOLLO patients had evidence of cardiac amyloidosis
- Patisiran resulted in favorable changes relative to placebo
  - LV wall thickness
  - Global longitudinal strain
  - NT-proBNP
  - Cardiac outcomes



APOLLO-B: Key Development & Regulatory Milestones



APOLLO-B: Patisiran Demonstrated Benefits on Patient Function and Symptoms in ATTR Cardiomyopathy

Results Consistent with APOLLO Data in Polyneuropathy

	APOLLO-B Cardiomyopathy	APOLLO Polyneuropathy
Rapid, Robust, Sustained TTR Reduction	> 85%	> 85%
Impact on Functional Ability	Slowed Decline; Comparable to Normal Aging	Improved Neuropathy Impairment & Ambulation
Effect on Patient Reported Health Status and QoL	Stable Health Status, Symptoms and QoL	Improved QoL; Reduced Disability & Autonomic Signs
Improvement in Clinically Relevant Biomarkers	NT-proBNP Troponin I	NT-proBNP

Favorable safety profile, consistent with 5-year postmarketing experience

Patisiran Offers Meaningful Benefits That Address Important Patient Needs

High Unmet Need

- Patients greatly value maintenance of functional ability and health status
- Disease progression common despite current approved therapy

Clinically Meaningful Benefits

- Reduces disease progression according to multiple measures
  - Objective evaluation of physical function
  - Patient-reported health status and symptoms
  - Clinician assessments
- Well tolerated with an acceptable safety profile

Residual Uncertainty

- Effects in combination with tafamidis unknown

Proposed Indication

For the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated (ATTR) amyloidosis in adults to slow the decline in functional capacity and reduce symptoms

Unmet Need	**John Berk, MD** Professor of Medicine Clinical Director of Amyloidosis Center Boston University
Efficacy	**John Vest, MD** Senior Vice President, Clinical Research Alnylam Pharmaceuticals
Impact of Patisiran on Patient Health Status	**John Spertus, MD, MPH** Professor, Daniel J. Lauer / Missouri Endowed Chair in Metabolic and Vascular Disease Research University of Missouri-Kansas City
Safety	**Elena Yureneva, MD, MHA** Executive Director, Head of Medical Safety & Risk Management Alnylam Pharmaceuticals
Clinical Perspective	**Ronald Witteles, MD** Professor of Cardiovascular Medicine Co-Director, Stanford Amyloid Center Stanford University School of Medicine

Additional Experts

Brian Drachman, MD

Associate Professor of Clinical Medicine
Associate Chief of Cardiovascular Medicine
Perelman School of Medicine
University of Pennsylvania Health System

Marianna Fontana, MD, PhD

Professor of Cardiology and Honorary Consultant
Cardiologist, Division of Medicine
National Amyloidosis Centre
University College London

Craig Mallinckrodt, PhD

Statistician
Pentara Corporation

James Signorovitch, PhD

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Analysis Group

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Nancy Silliman, PhD

Senior Vice President
Data Sciences and Statistics
Alnylam

Andrew Slugg, MS, MBA

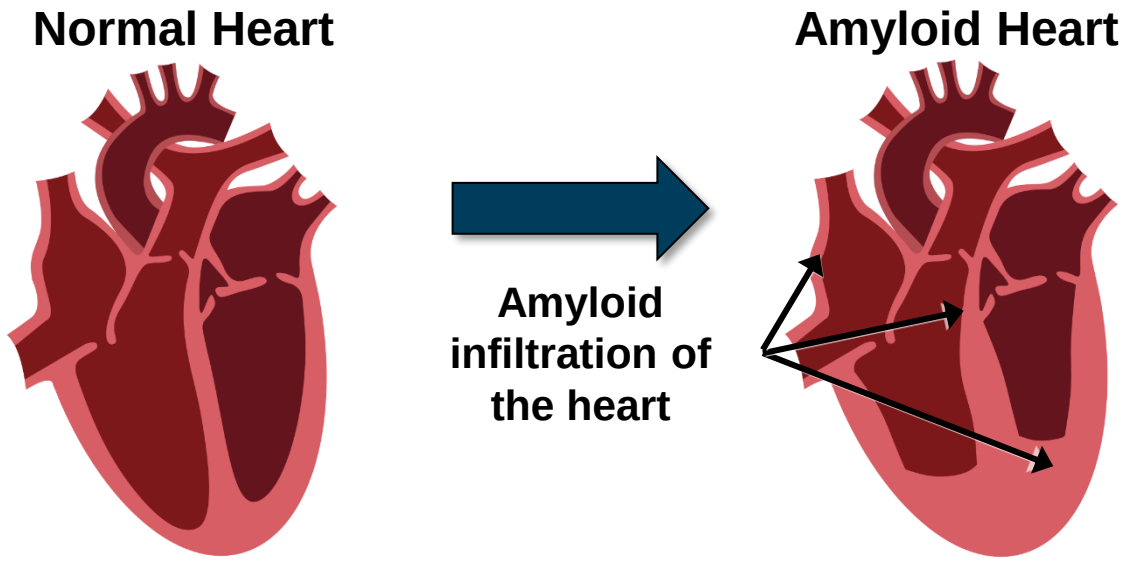
Senior Vice President
Global Regulatory Affairs
Alnylam

Unmet Need

John Berk, MD

Professor of Medicine
Assistant Director, Amyloidosis Center
Boston University School of Medicine

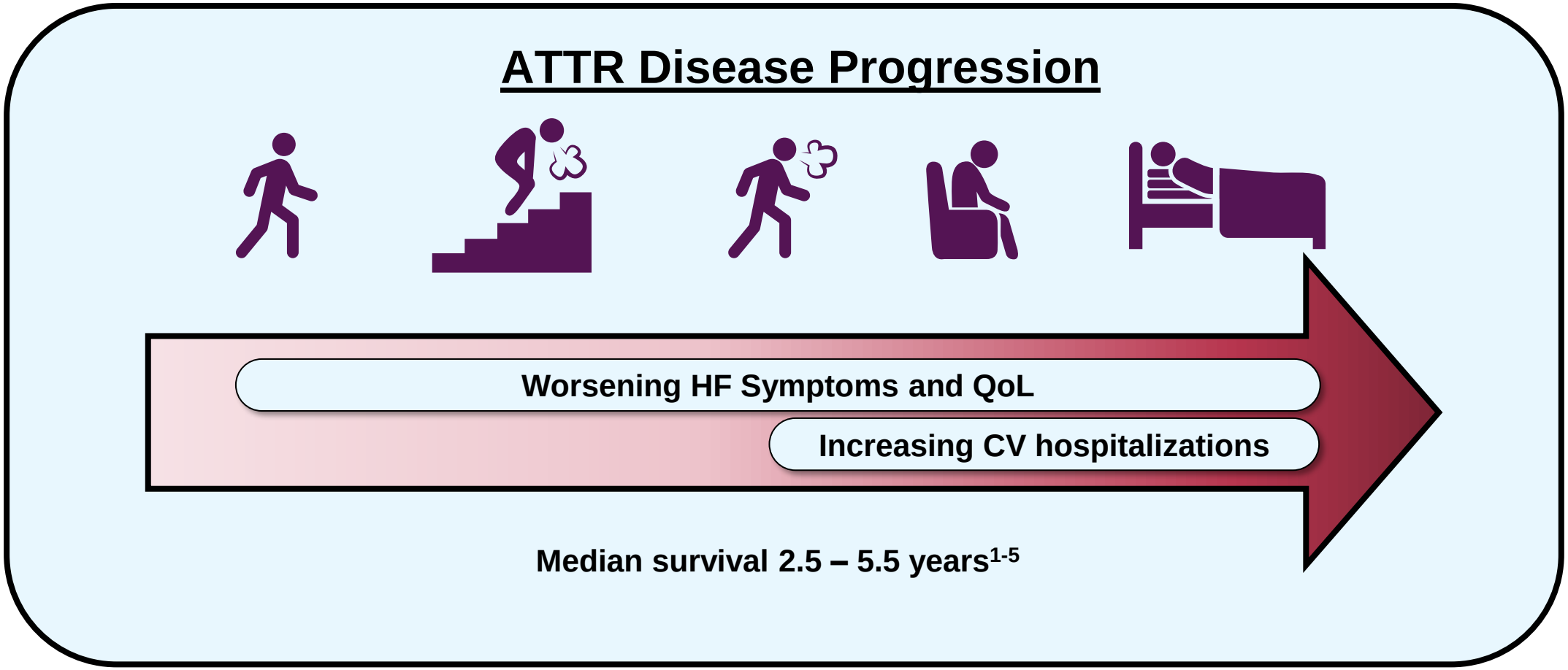
ATTR Cardiomyopathy
Due to TTR Amyloid Infiltration of the Heart



Signs of Disease

- Thick and stiff myocardium + reduced chamber volumes
- Decreased cardiac output due to systolic and diastolic dysfunction
- Congestive heart failure → Shortness of breath, fatigue, peripheral edema
- Atrial fibrillation, atrioventricular block, and sinus node dysfunction

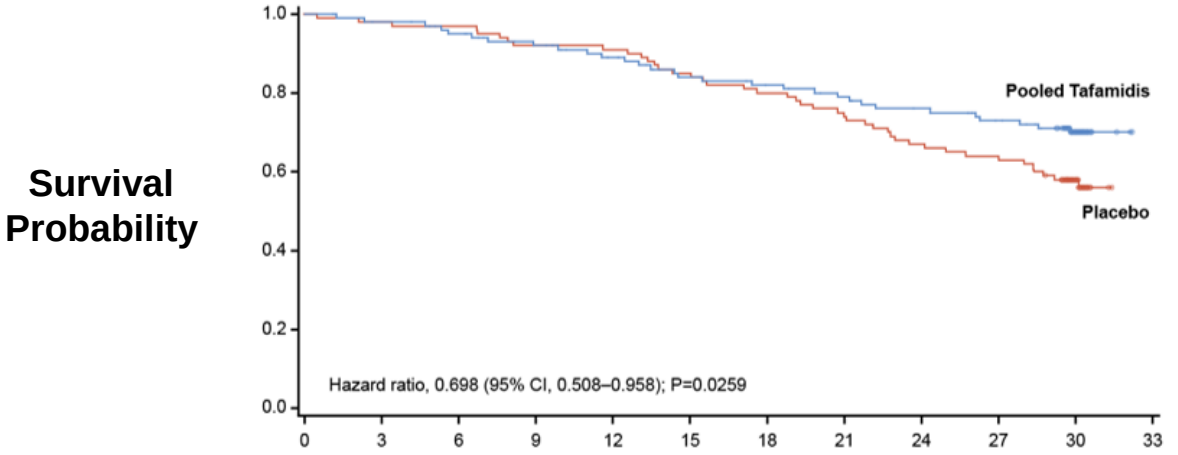
ATTR Cardiomyopathy: An Unrelenting Disease



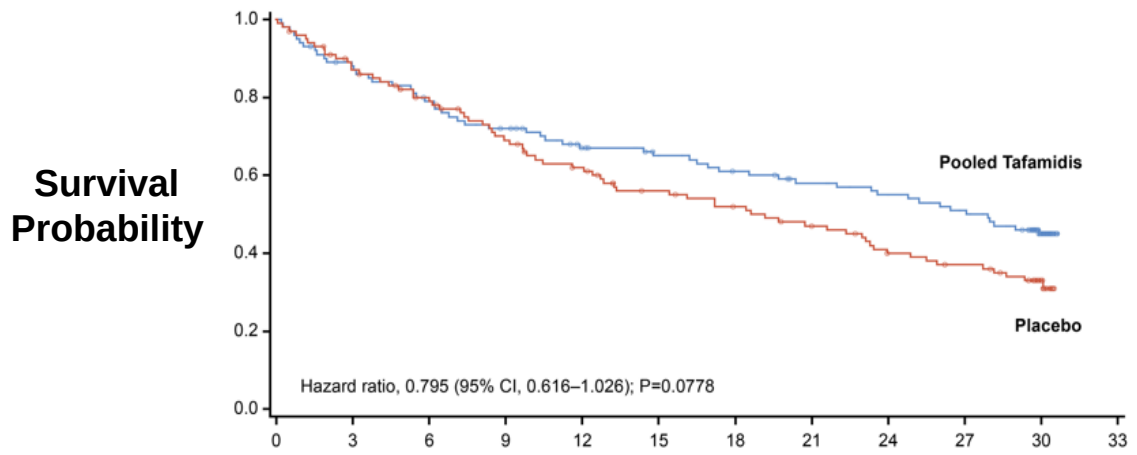
1. Antonopoulos, 2022; 2. Castano, 2015; 3. Damy, 2015; 4. Dungu, 2012; 5. Hawkins, 2015

Tafamidis: Only Drug Approved to Treat ATTR Cardiomyopathy

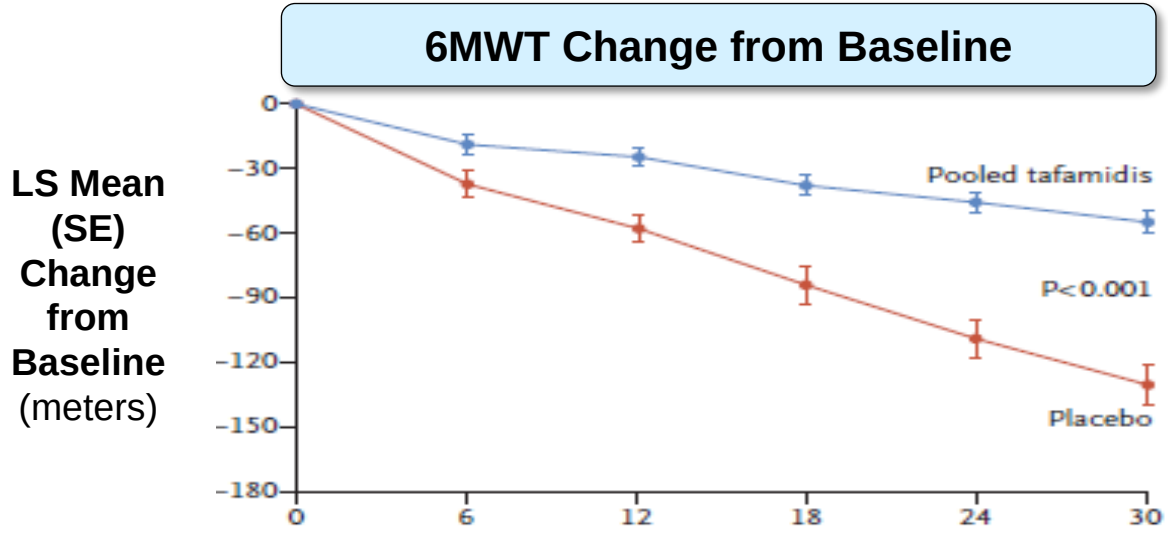
All Cause Mortality



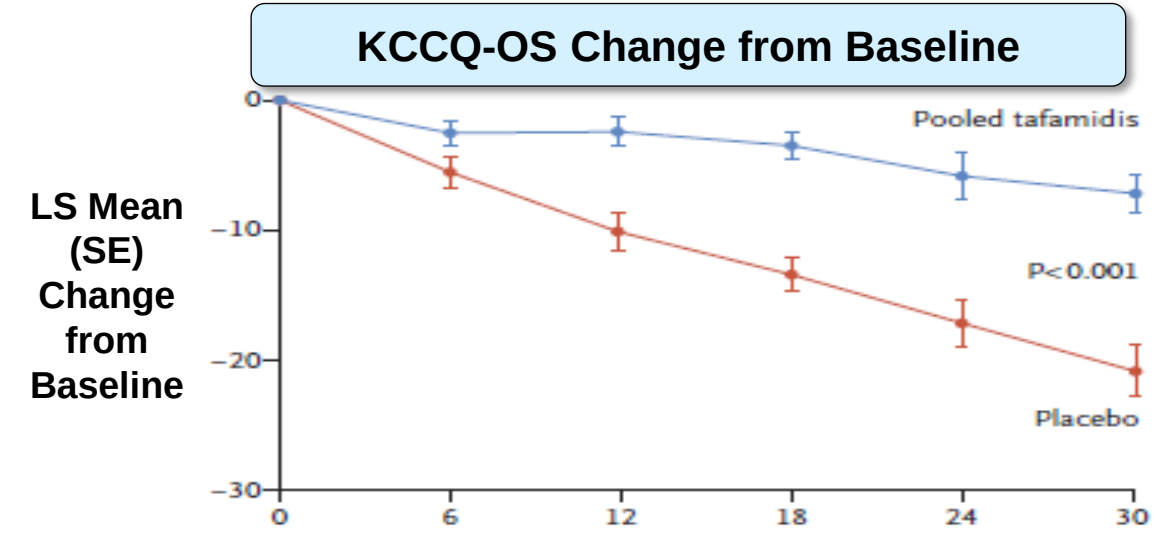
Time to First CV Hospitalization



6MWT Change from Baseline

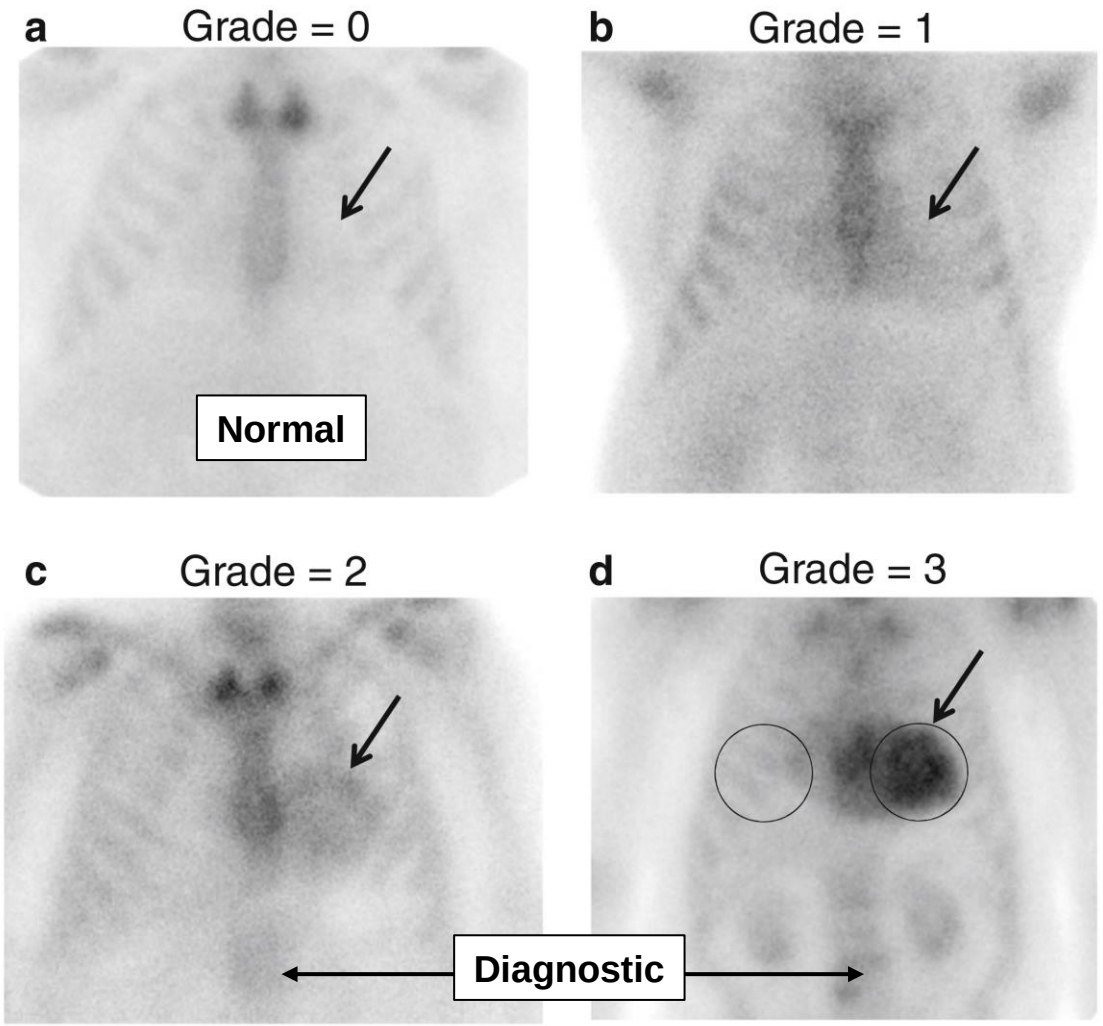


KCCQ-OS Change from Baseline



Maurer, 2018

Technetium Scintigraphy Has Led to Earlier and Increased Diagnoses



- Rapid adoption of a simple, non-invasive diagnostic test, replacing cardiac biopsy
- More patients than ever being diagnosed
- Slower disease progression observed in recent years because of earlier diagnosis

Gillmore, 2016; Chen, 2018.

High Unmet Need for New Therapies

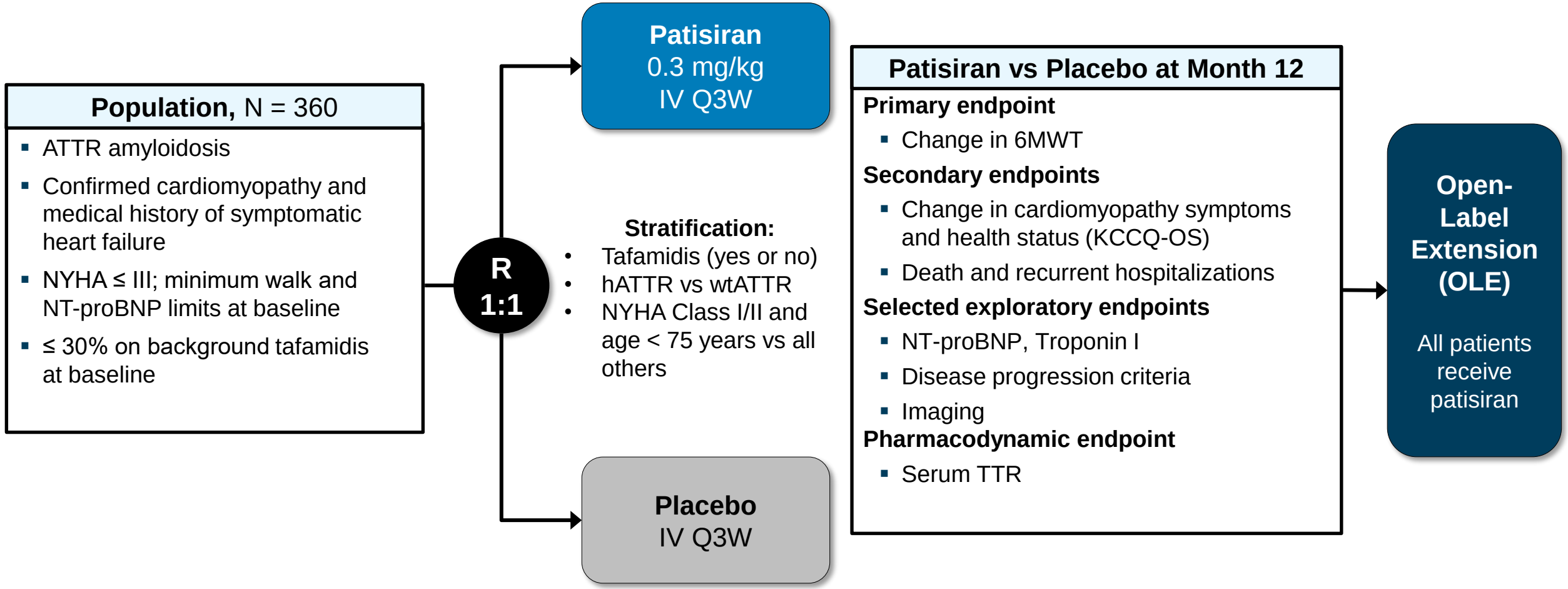
- ATTR cardiomyopathy is a rare, debilitating, progressive disease
- Disease progression continues despite single approved therapy
- Patients value their functional capacity and quality of life
- Need for new therapeutic approaches and early intervention before irreversible disability
- Patisiran, a TTR gene silencer, works upstream of stabilizers and has potential to address this unmet need

Efficacy

John Vest, MD

Senior Vice President, Clinical Research
Alnylam Pharmaceuticals

APOLLO-B Study Design



Baseline Demographics Similar Between Groups

	Patisiran N = 181	Placebo N = 178
Median Age at Screening, years (min, max)	**76** (47, 85)	**76** (41, 85)
≥ 75 years old	**59%**	**57%**
Male	**89%**	**90%**
Race		
White	**76%**	**79%**
Asian	**13%**	**8%**
Black or African American	**9%**	**8%**
Other or Not reported	**2%**	**4%**
Hispanic or Latino	**12%**	**11%**
Region		
North America	**25%**	**29%**
Western Europe	**39%**	**38%**
ROW	**37%**	**33%**

Baseline Characteristics Indicated Wide Range of Disease Severity

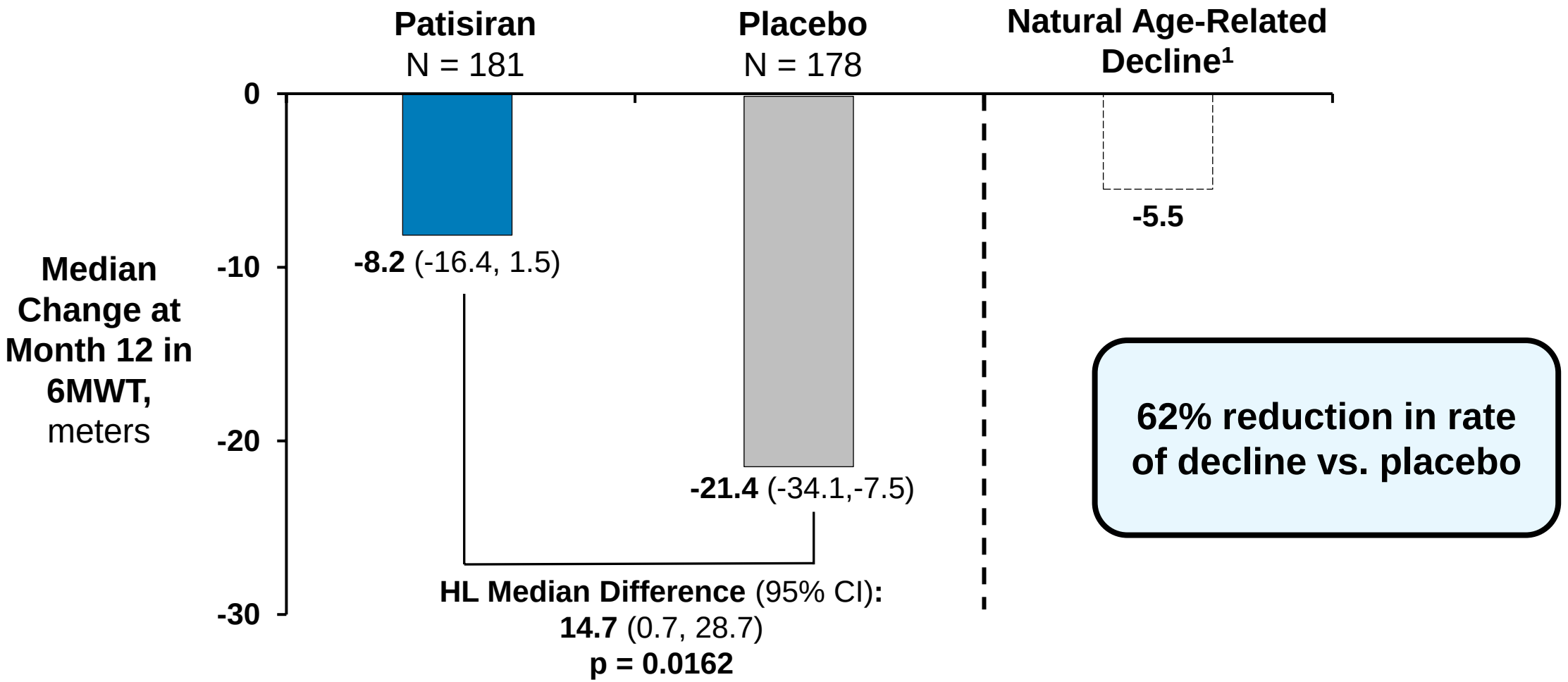
		Patisiran N = 181	Placebo N = 178
ATTR amyloidosis type	**wtATTR**	**80%**	**81%**
	hATTR	**20%**	**19%**
Median time since diagnosis, years (min, max)		**0.8** (0, 6)	**0.4** (0, 10)
Baseline tafamidis use		**25%**	**25%**
NYHA class	**I**	**6%**	**8%**
	II	**86%**	**84%**
	III	**8%**	**7%**
Median NT-proBNP, ng/L (Q1, Q3)		**2008** (1135, 2921)	**1813** (952, 3079)
Median baseline 6MWT, meters (Q1, Q3)		**358** (295, 420)	**368** (300, 444)
Mean baseline KCCQ-OS Score (SEM)		**69.8** (1.6)	**70.3** (1.6)

Primary Efficacy Results

- 6MWT
- KCCQ-OS

APOLLO-B Met Primary Endpoint (6MWT)

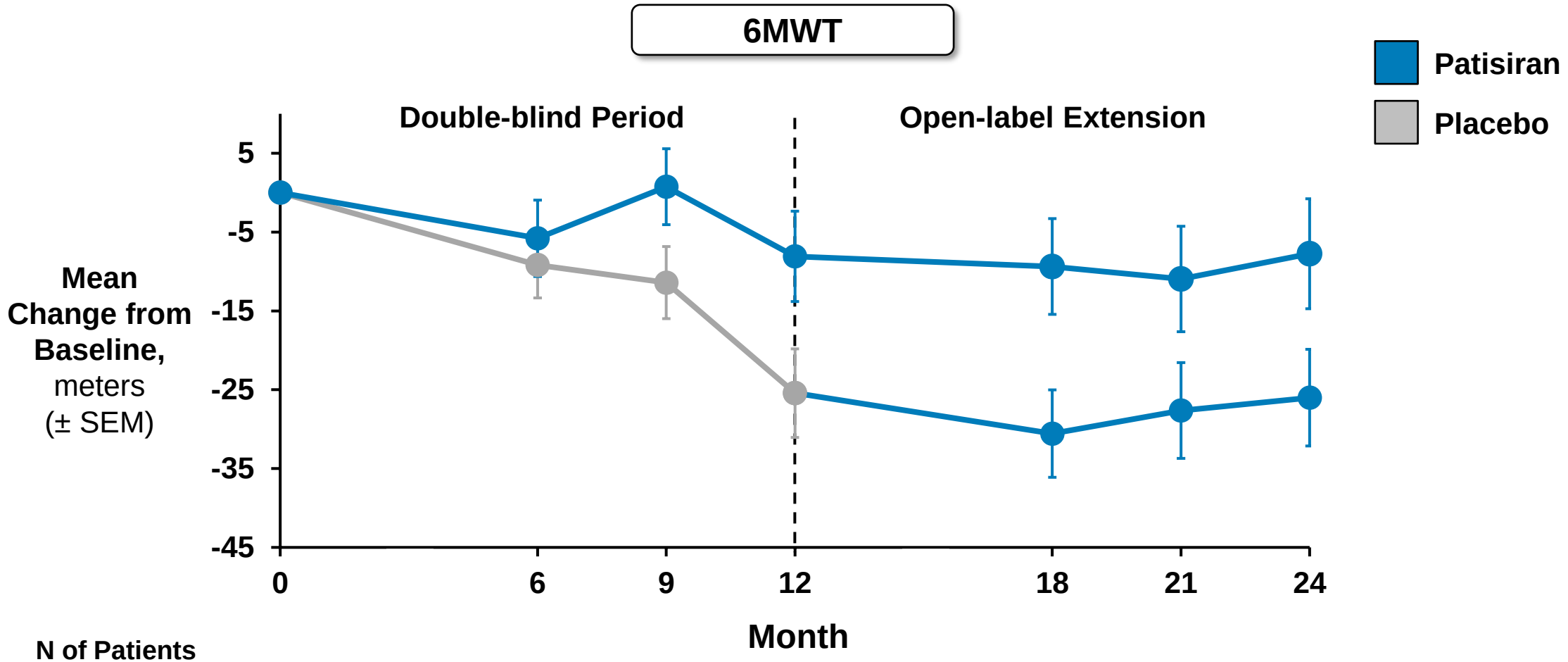
Reduced Decline in Functional Capacity Comparable to Normal Aging



HL = Hodges-Lehmann; p-value based on Wilcoxon Rank Sum test stratified by background tafamidis use

1. Enright, 1998

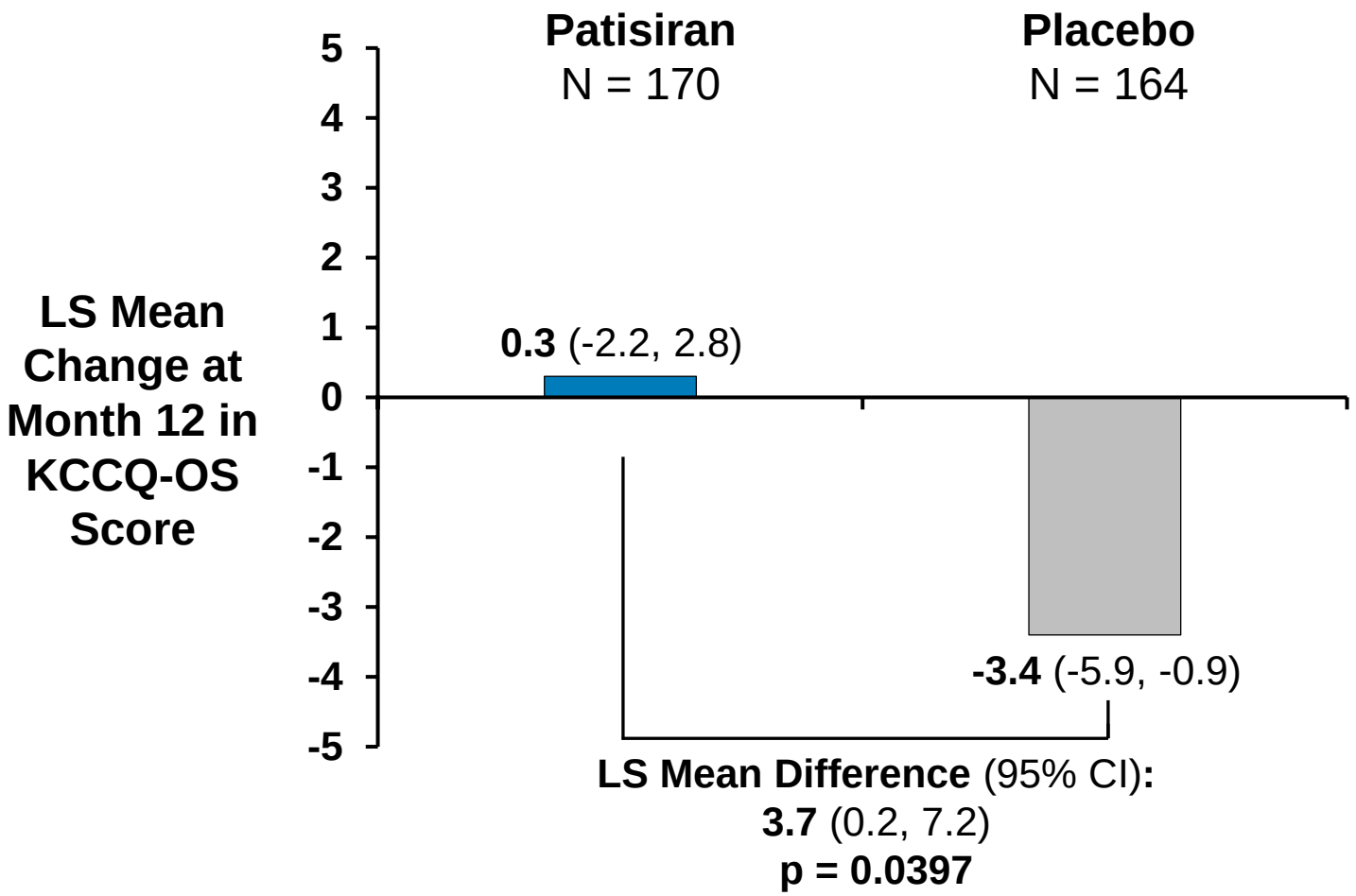
Patisiran Preserved Functional Capacity Through 24 Months



N of Patients							
Patisiran	181	162	167	167	148	148	137
Placebo/ Patisiran	178	165	165	164	143	137	128

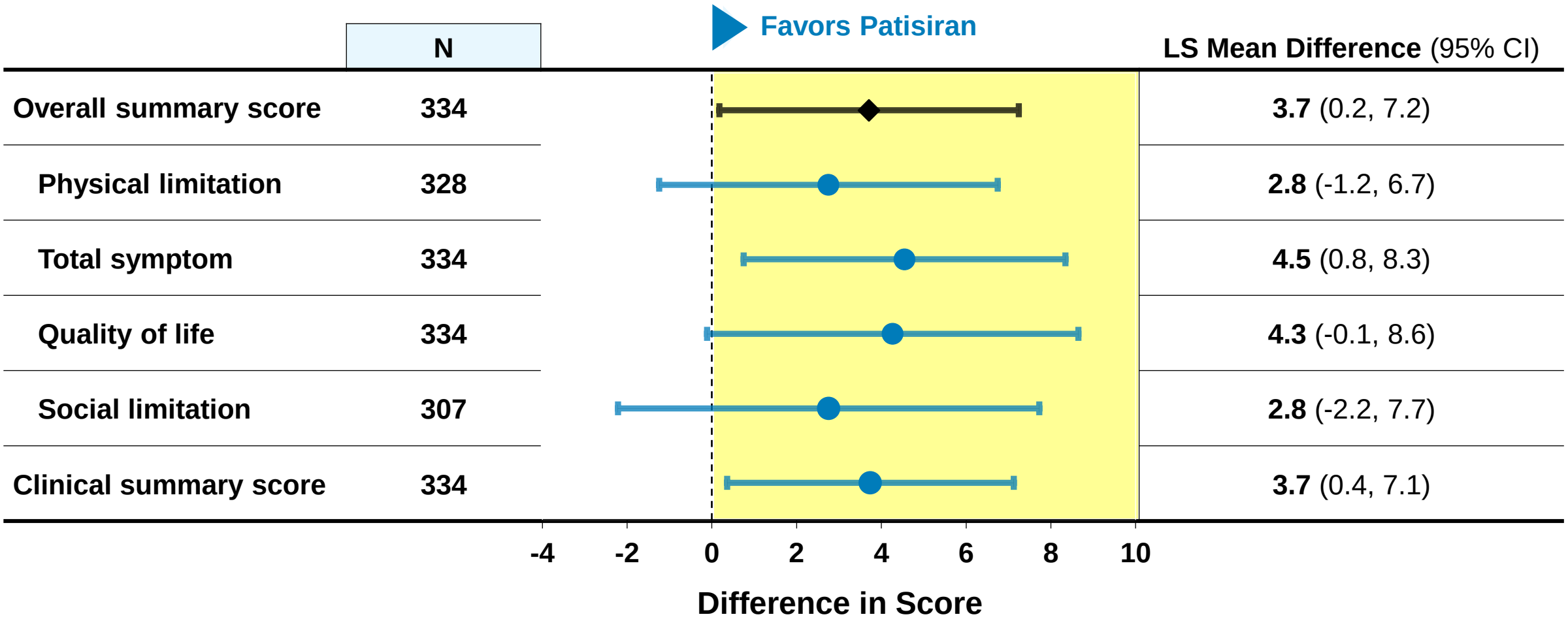
APOLLO-B Met Key Secondary Endpoint (KCCQ-OS)

Patisiran Demonstrated Stability in Health Status and Quality of Life

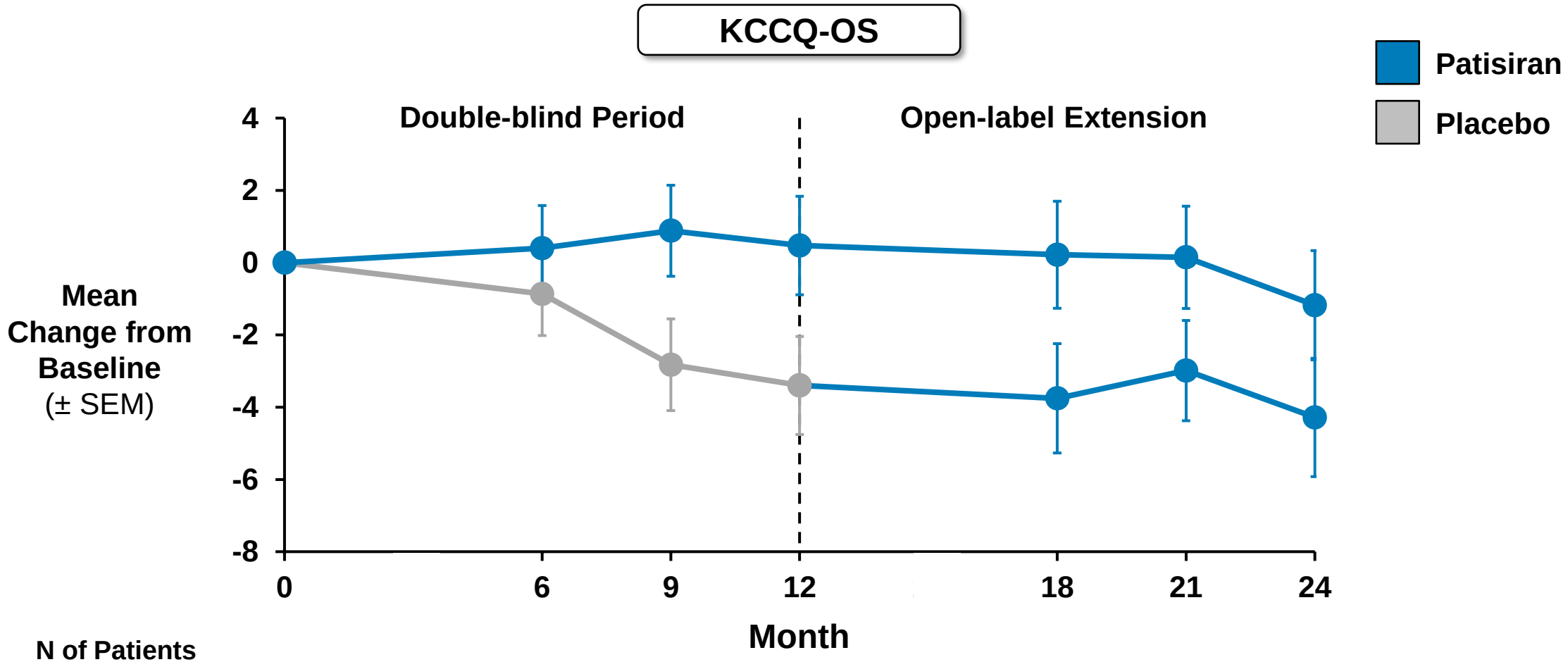


p-value based on a Mixed Model for Repeated Measures (MMRM) model

Consistent Favorable Effects Across All KCCQ Domains



Patisiran Preserved Health Status Through 24 Months



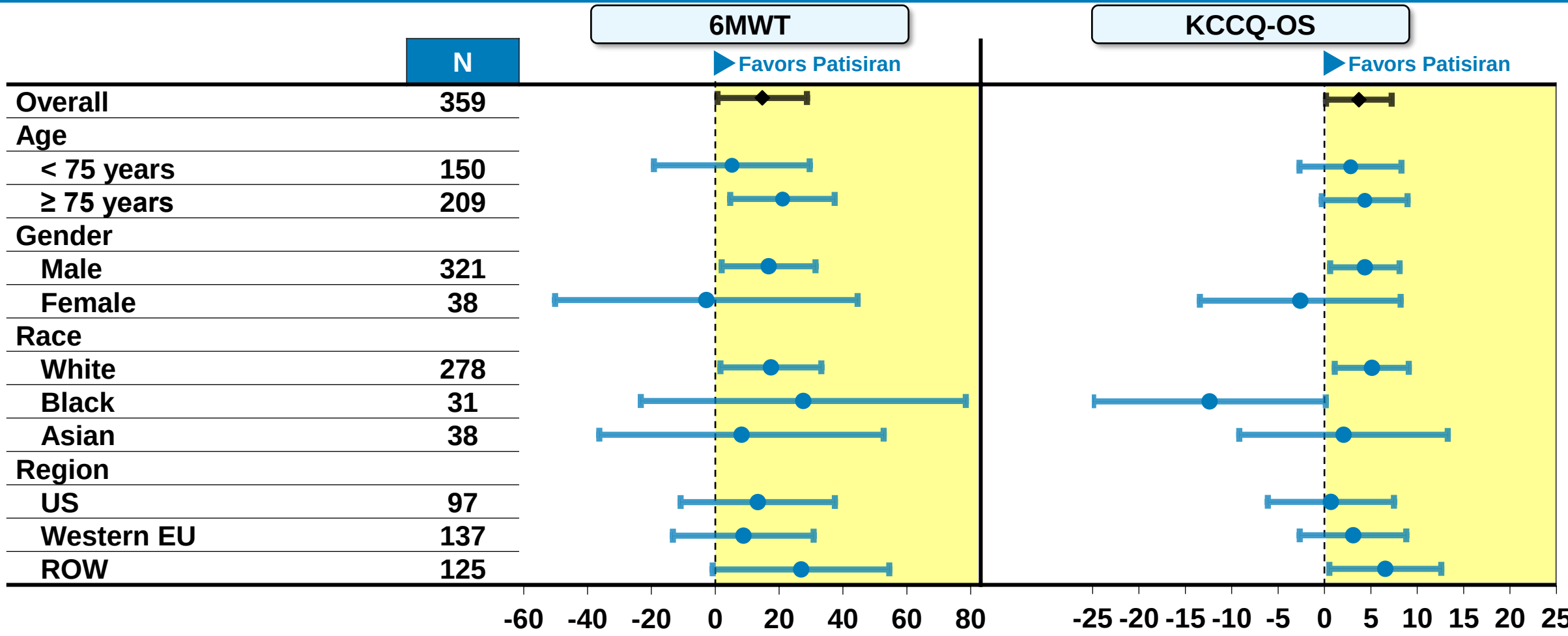
N of Patients							
Patisiran	181	169	170	170	155	155	148
Placebo/ Patisiran	178	170	167	164	151	146	140

Key Efficacy Topics

- Efficacy in Subgroups
- Mechanistic Data Supporting Efficacy
- Impact on Outcomes
- Clinical Meaningfulness

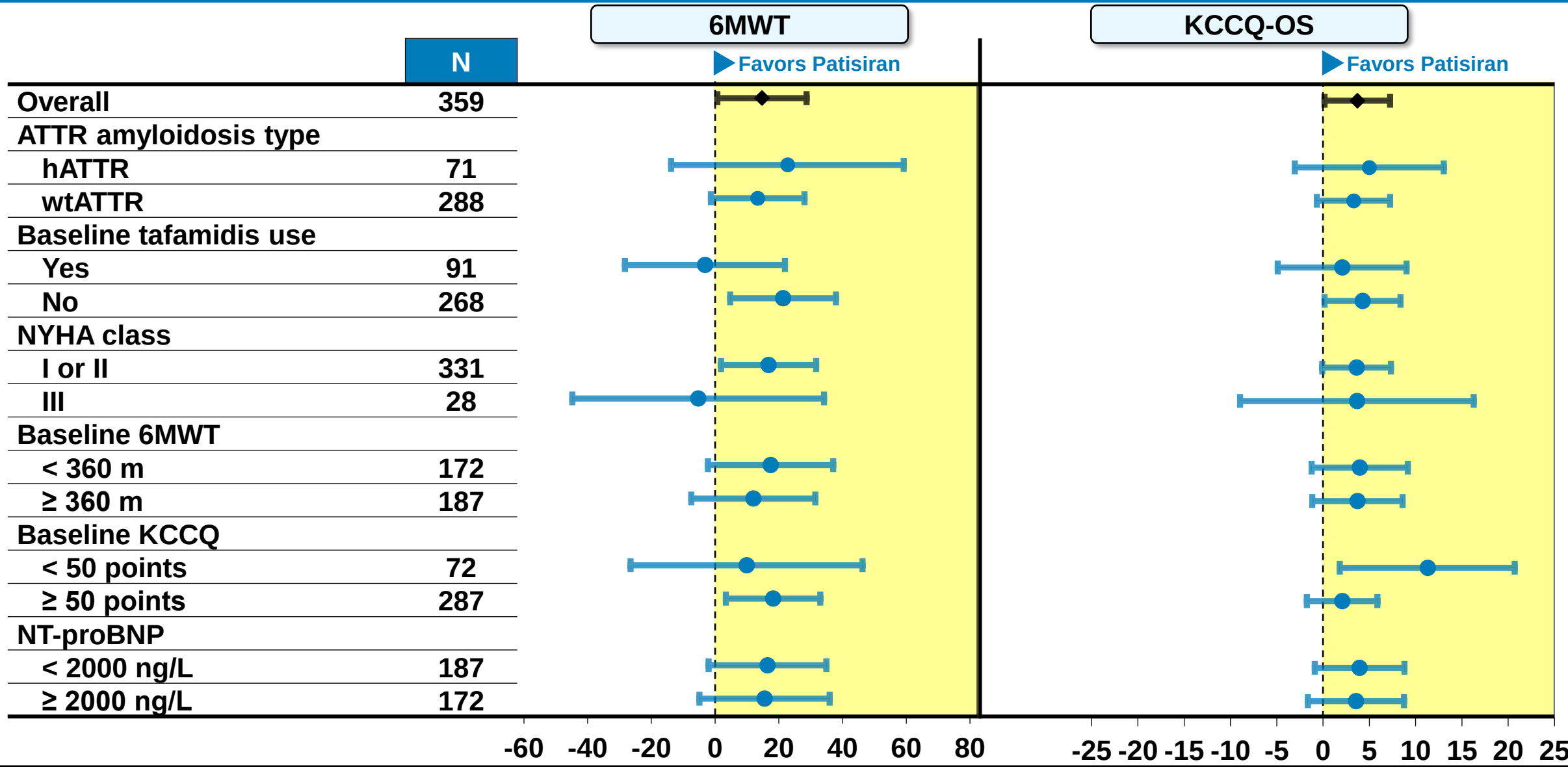
Patisiran Treatment Effect Generally Consistent Across Subgroups

Baseline Demographics

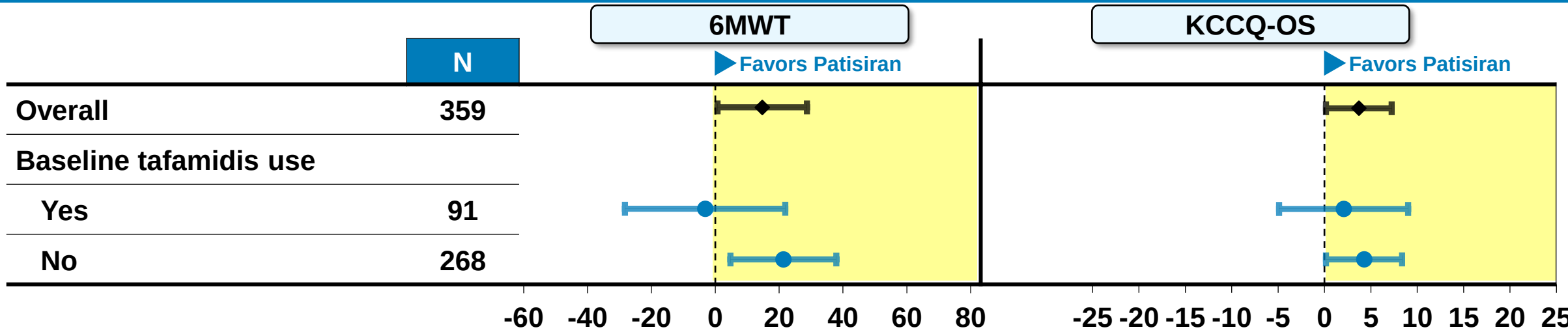


Patisiran Treatment Effect Generally Consistent Across Subgroups

Baseline Disease Characteristics



Patisiran Treatment Effect on Background Tafamidis Not Established in APOLLO-B



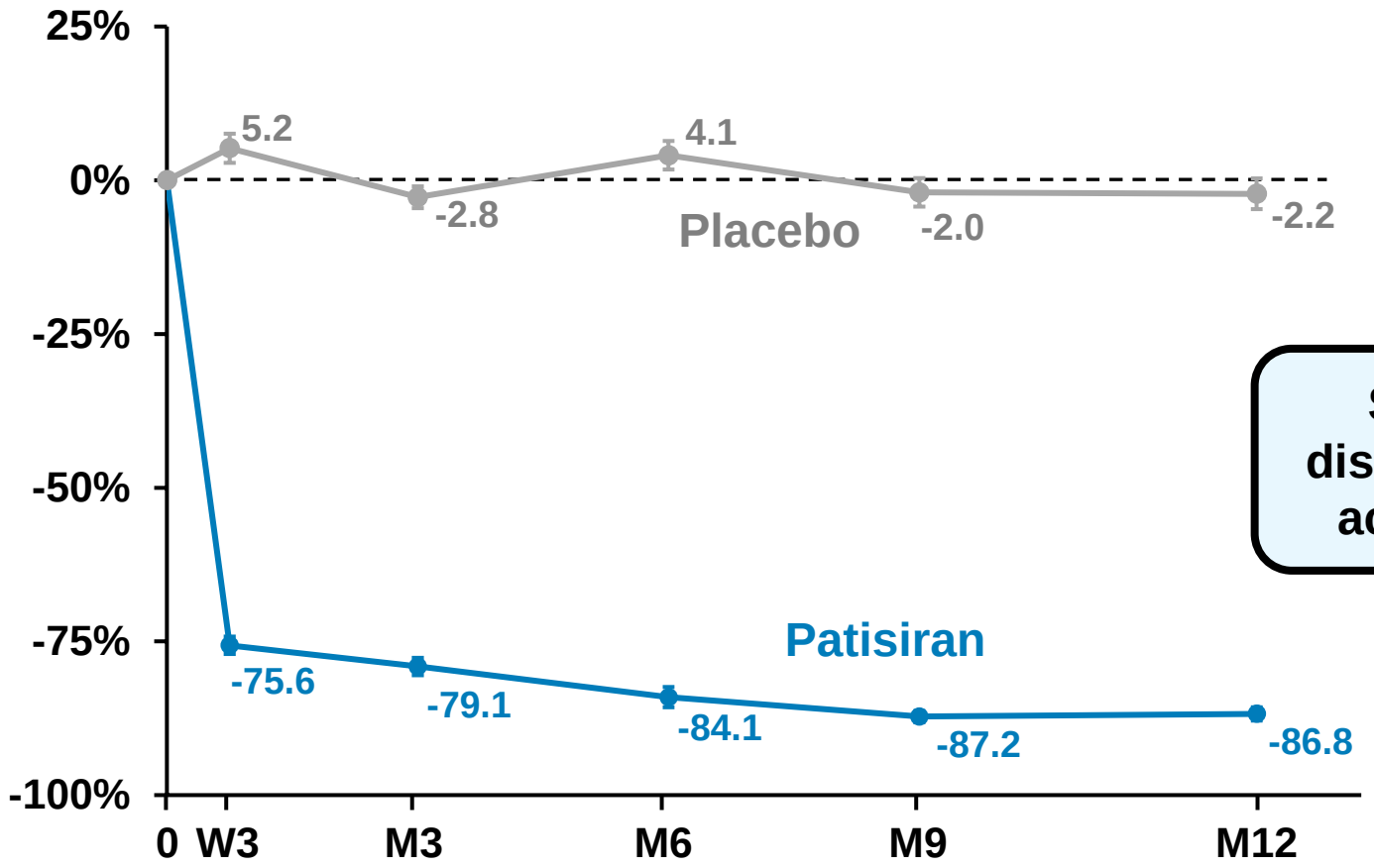
Background tafamidis

- Small subgroup (n ~ 45 per arm)
- Effect for 6MWT and KCCQ less than monotherapy
  - Confidence intervals wide and overlapping
  - TTR reduction similar

Key Efficacy Topics

- Efficacy in Subgroups
- Mechanistic Data Supporting Efficacy
- Impact on Outcomes
- Clinical Meaningfulness

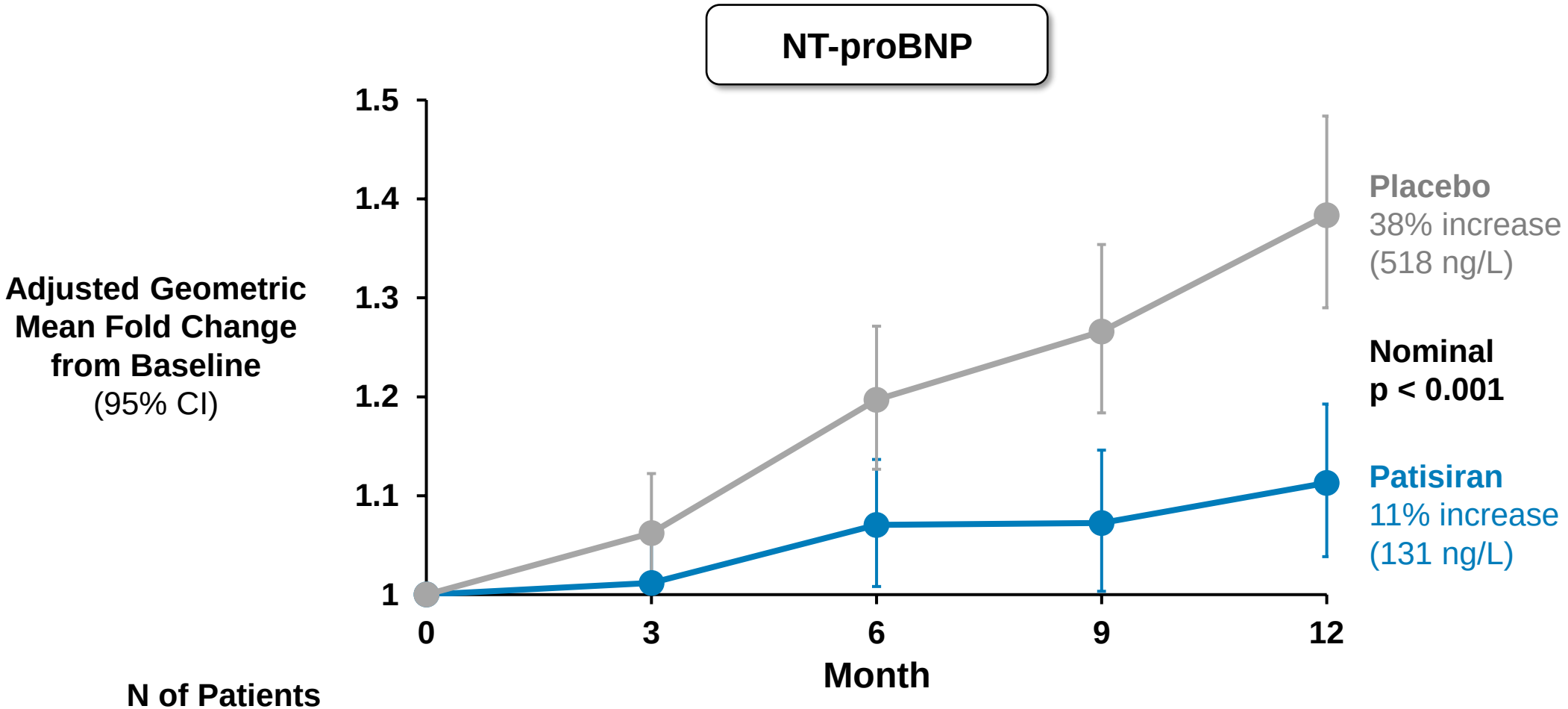
Patisiran Reduced Pathogenic Protein (TTR) > 85%



Same PD effect on disease causing protein across all subgroups

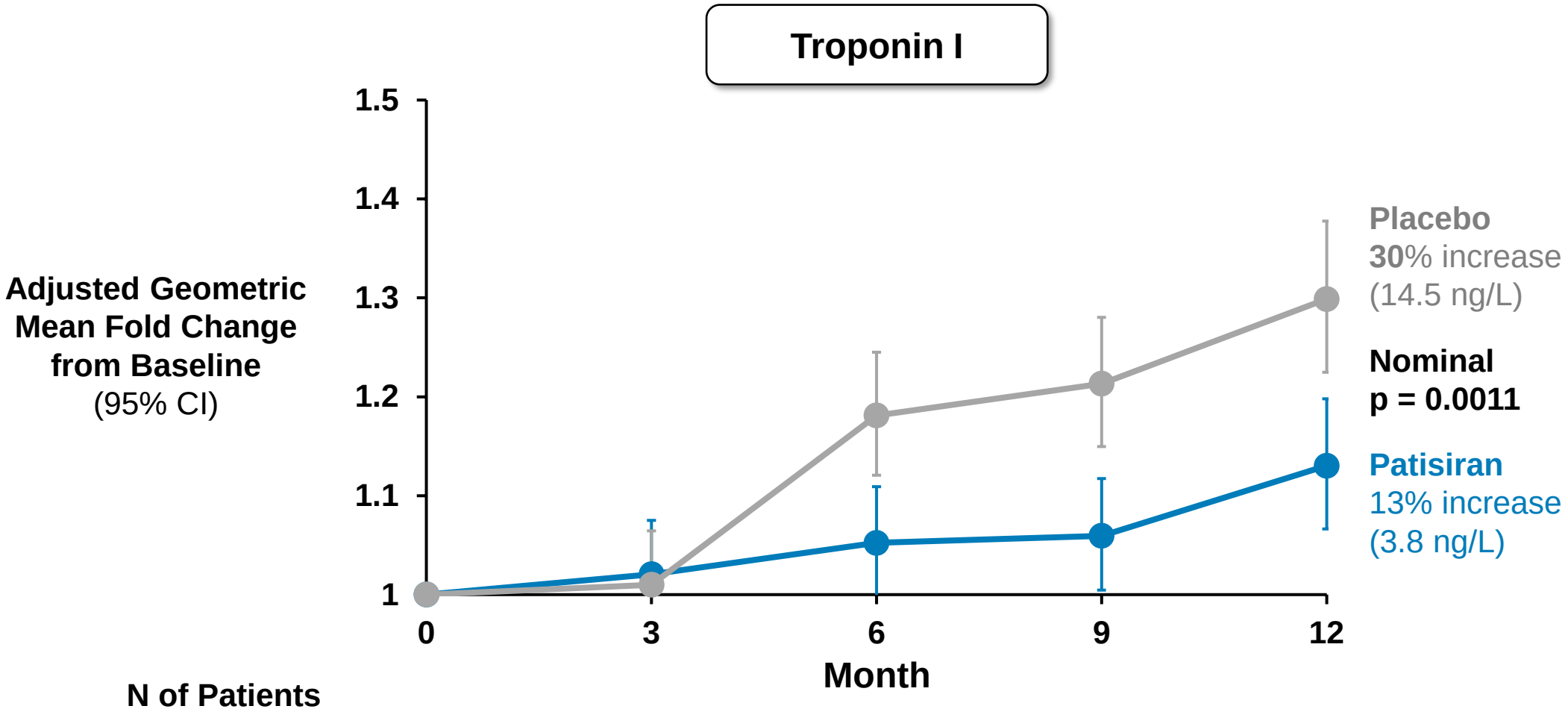
N of Patients					
Patisiran	181 169	152	164	167	158
Placebo	178 170	153	162	162	164

Favorable Patisiran Treatment Effect Demonstrated on NT-proBNP



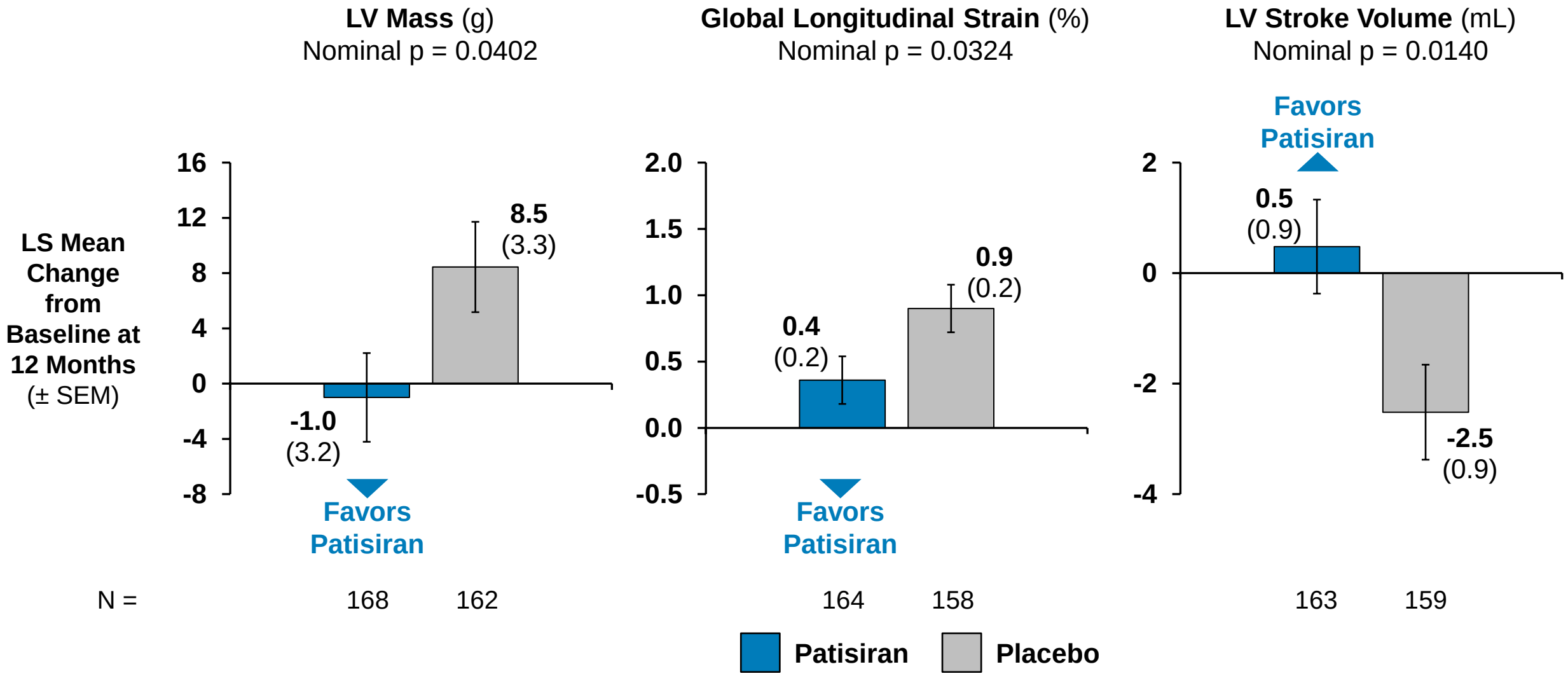
N of Patients					
Patisiran	181	171	169	169	167
Placebo	178	168	165	164	163

Favorable Patisiran Treatment Effect Demonstrated on Troponin I



N of Patients					
Patisiran	174	161	162	160	158
Placebo	172	158	162	156	155

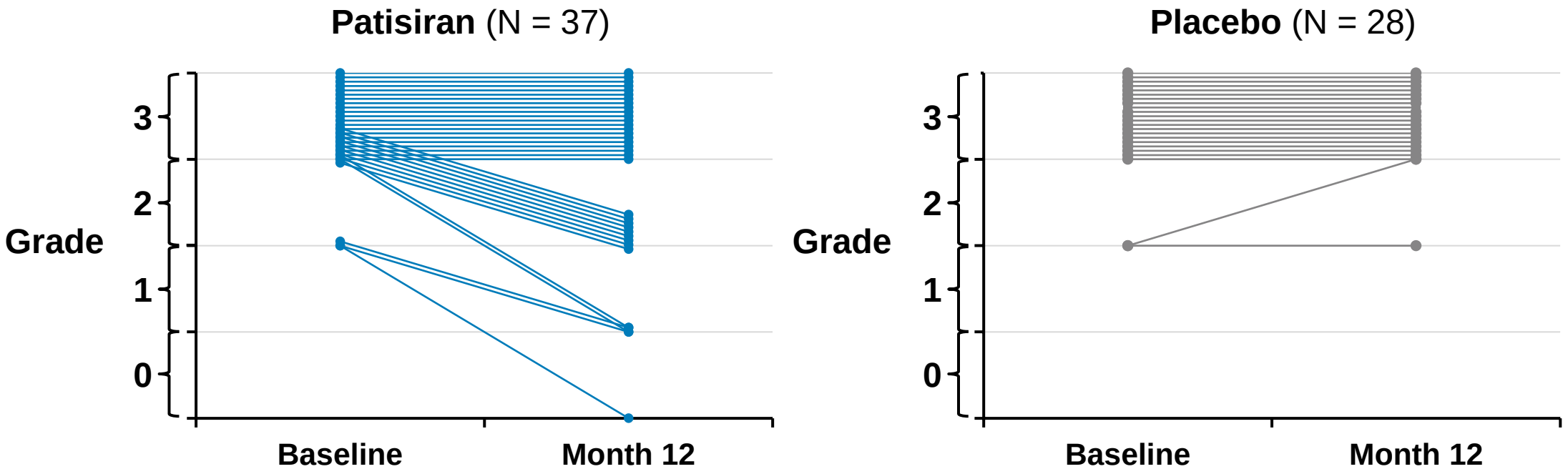
Favorable Patisiran Treatment Effects Demonstrated in Cardiac Structure and Function



Evidence of Improvement in ^{99m}Tc Uptake

Perugini grade (0 – 3) widely used in diagnosis (≥ grade 2) of ATTR amyloidosis

- Visually assesses ^{99m}Tc uptake in myocardium compared to bones
- Centrally read by assessor blinded to treatment and timepoint

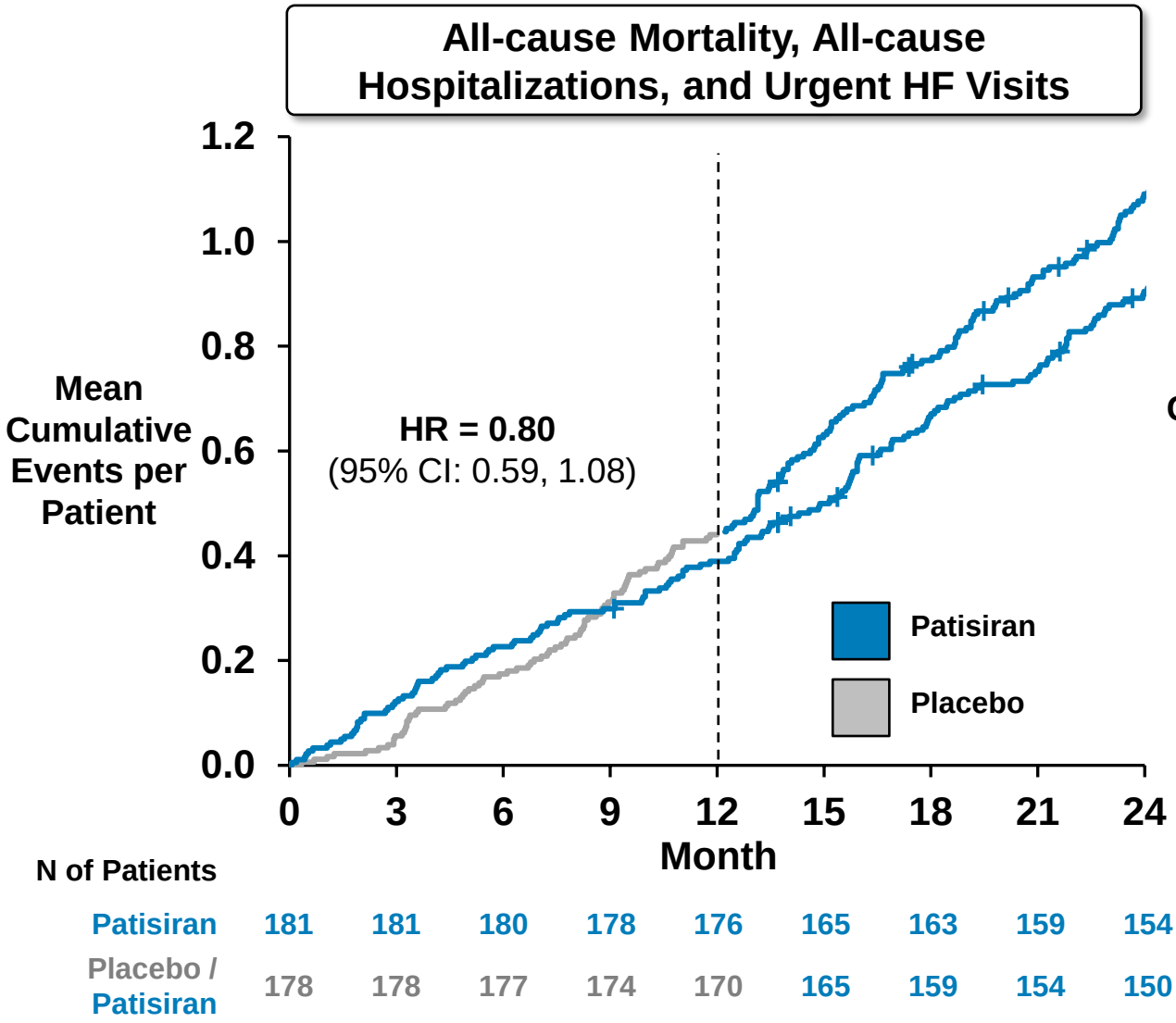


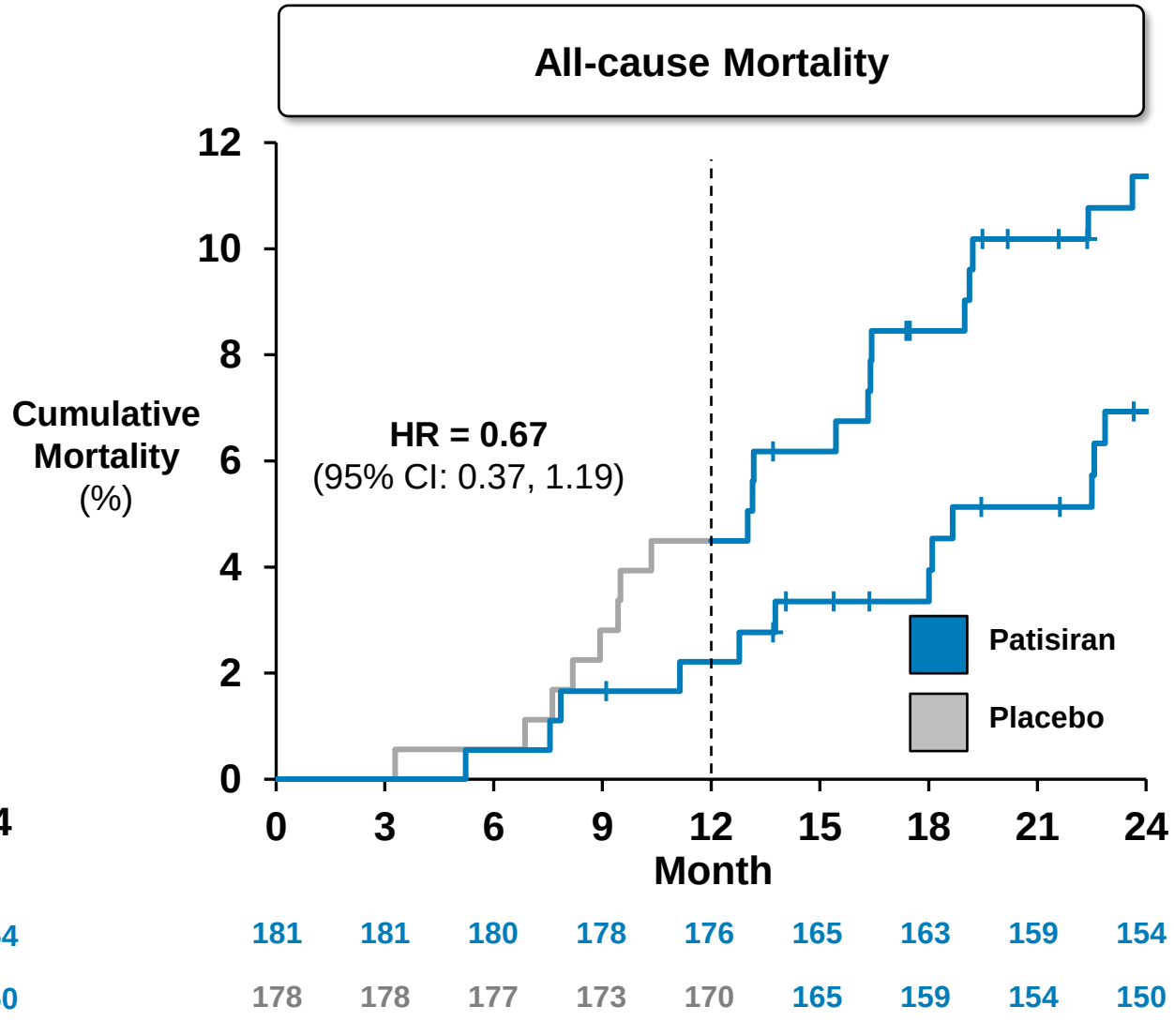
- 38% (14) improved ≥ 1 grade
  - 5 patients < threshold for diagnosis
- 0% improved

Key Efficacy Topics

- Efficacy in Subgroups
- Mechanistic Data Supporting Efficacy
- Impact on Outcomes
- Clinical Meaningfulness

Fewer Events in Patisiran Arm Through Month 24 in APOLLO-B

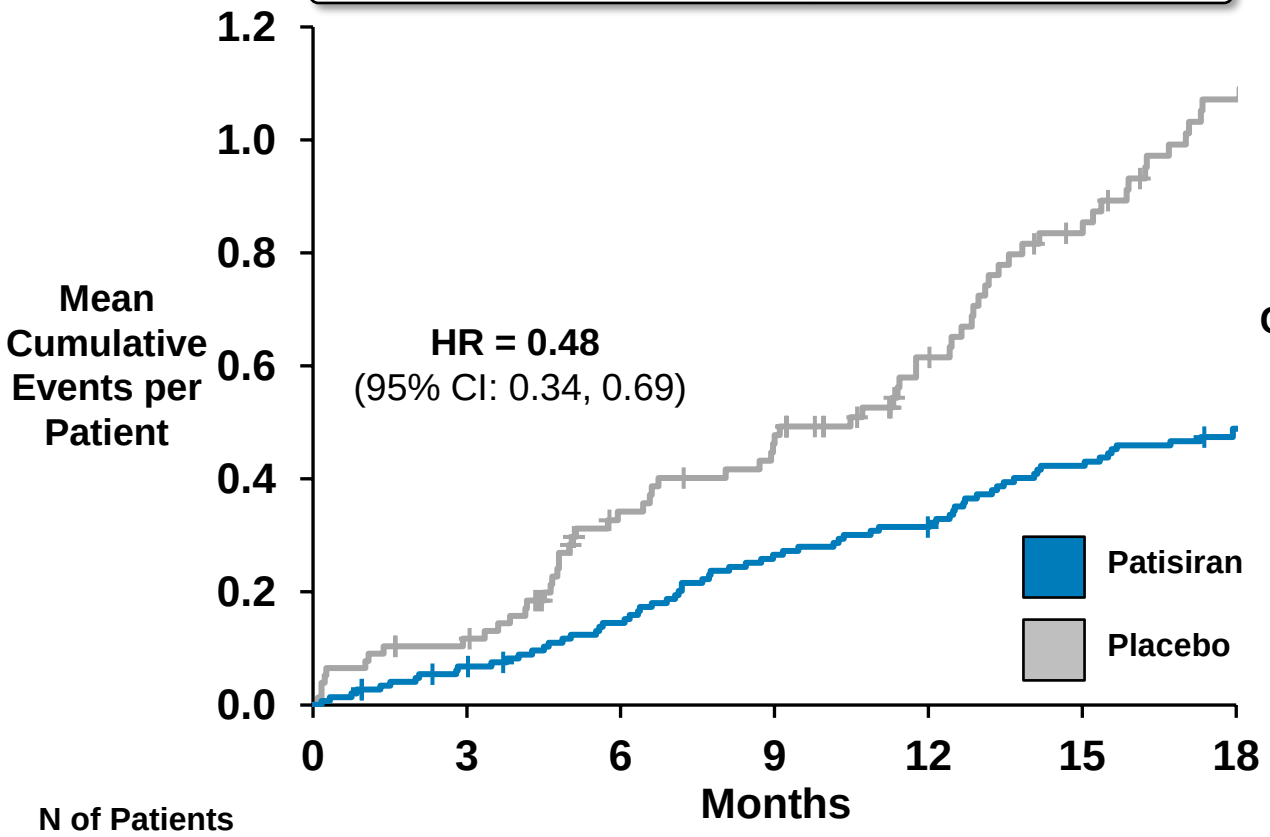




Fewer Events on Patisiran Also Demonstrated in APOLLO

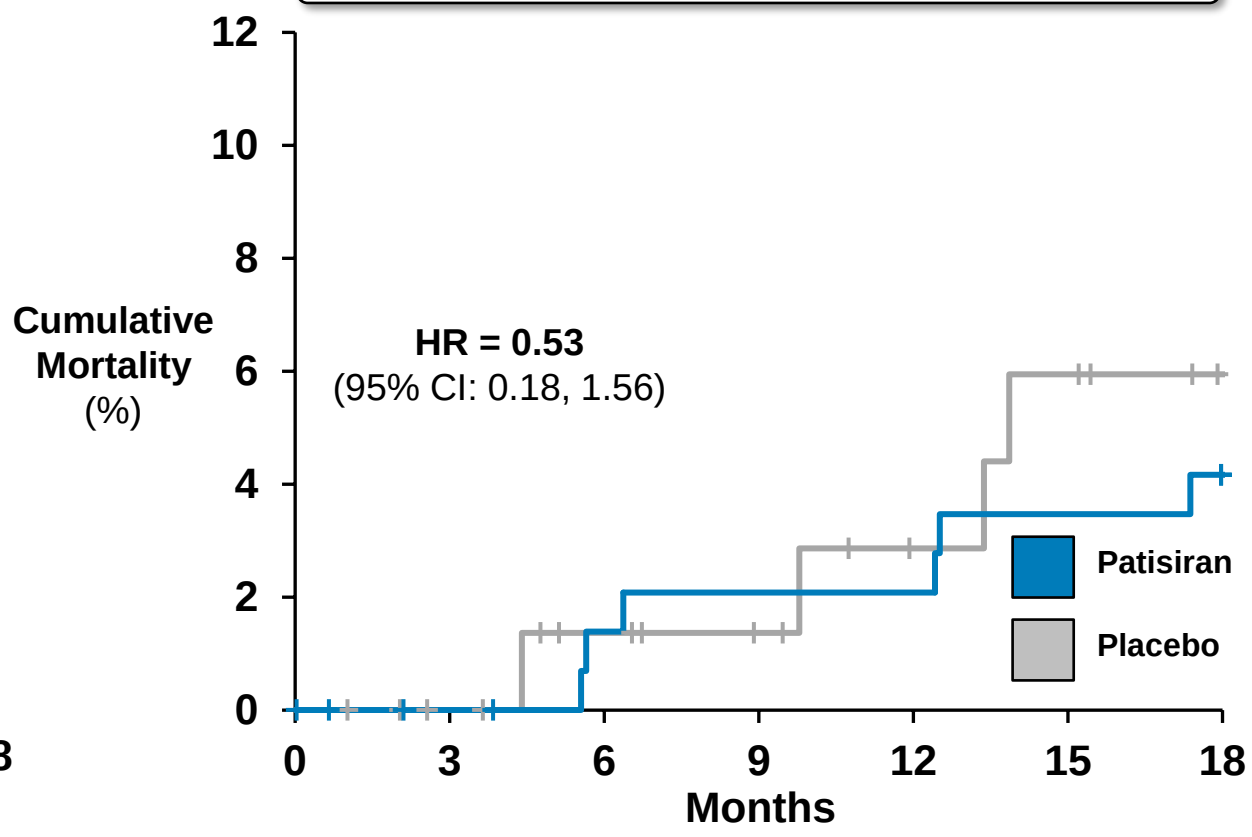
Post Hoc Analysis of Safety Data

All-cause Mortality and All-cause Hospitalization



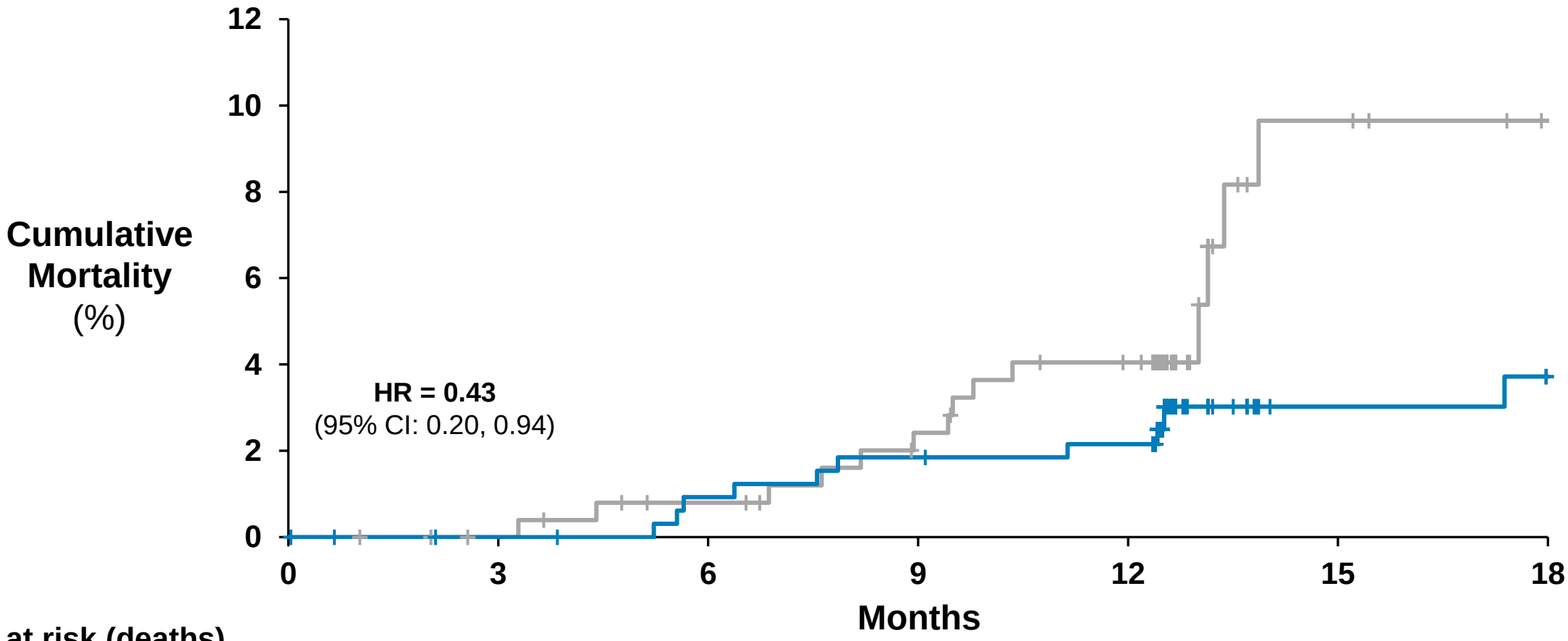
N of Patients							
Patisiran	148	145	143	141	141	138	137
Placebo	77	75	67	66	56	53	50

All-cause Mortality



Patisiran	148	145	142	141	141	139	136
Placebo	77	74	70	67	63	61	57

Pooled Mortality from APOLLO and APOLLO-B Through Double-Blind Periods



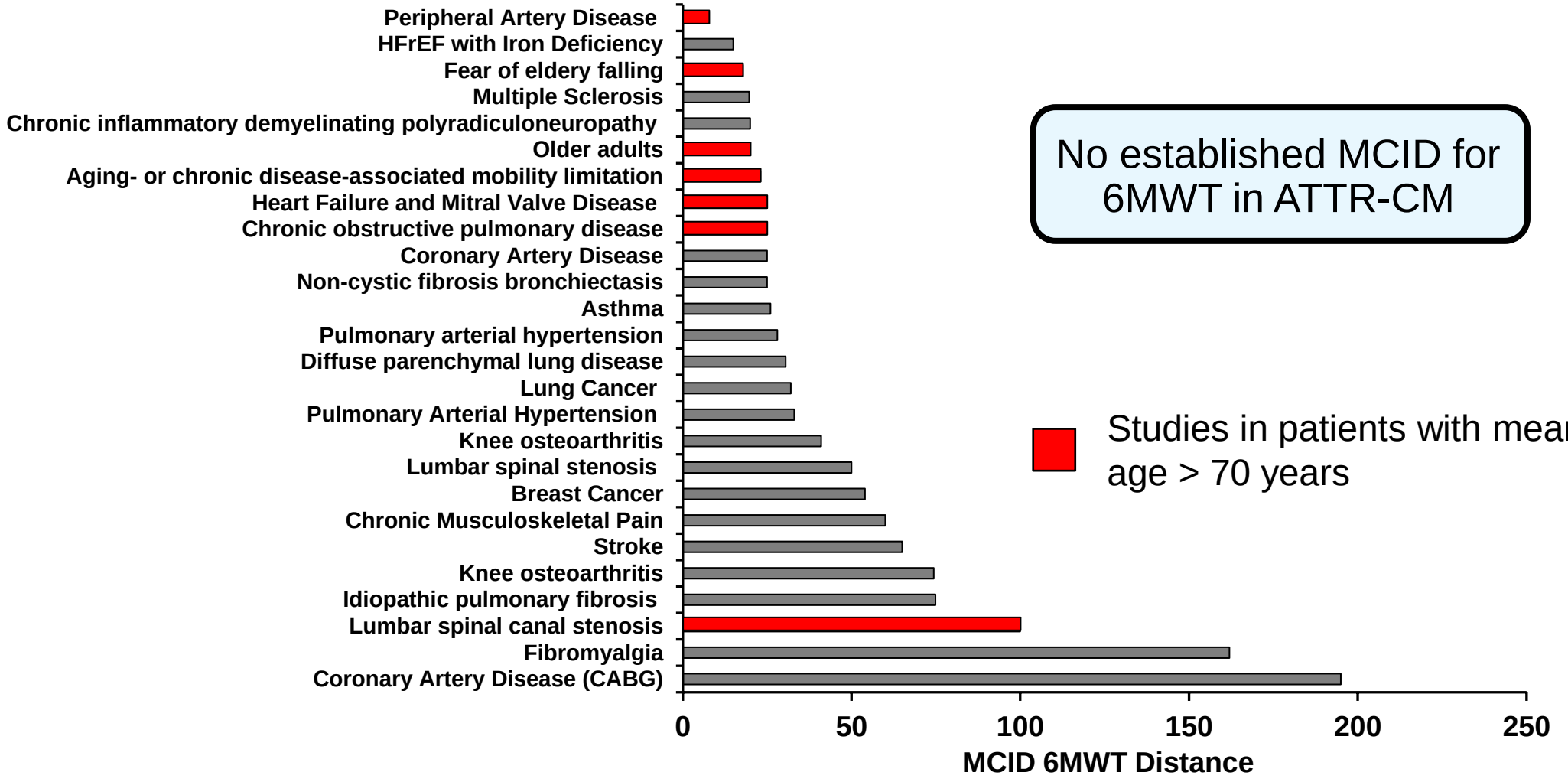
N at risk (deaths)

Patisiran	329 (0)	326 (0)	322 (3)	319 (6)	317 (7)	139 (9)	136 (10)
Placebo	255 (0)	252 (0)	247 (2)	240 (6)	233 (10)	61 (14)	57 (14)

Key Efficacy Topics

- Efficacy in Subgroups
- Mechanistic Data Supporting Efficacy
- Impact on Outcomes
- Clinical Meaningfulness

6MWT MCID Varies Widely: Age is a Major Determinant



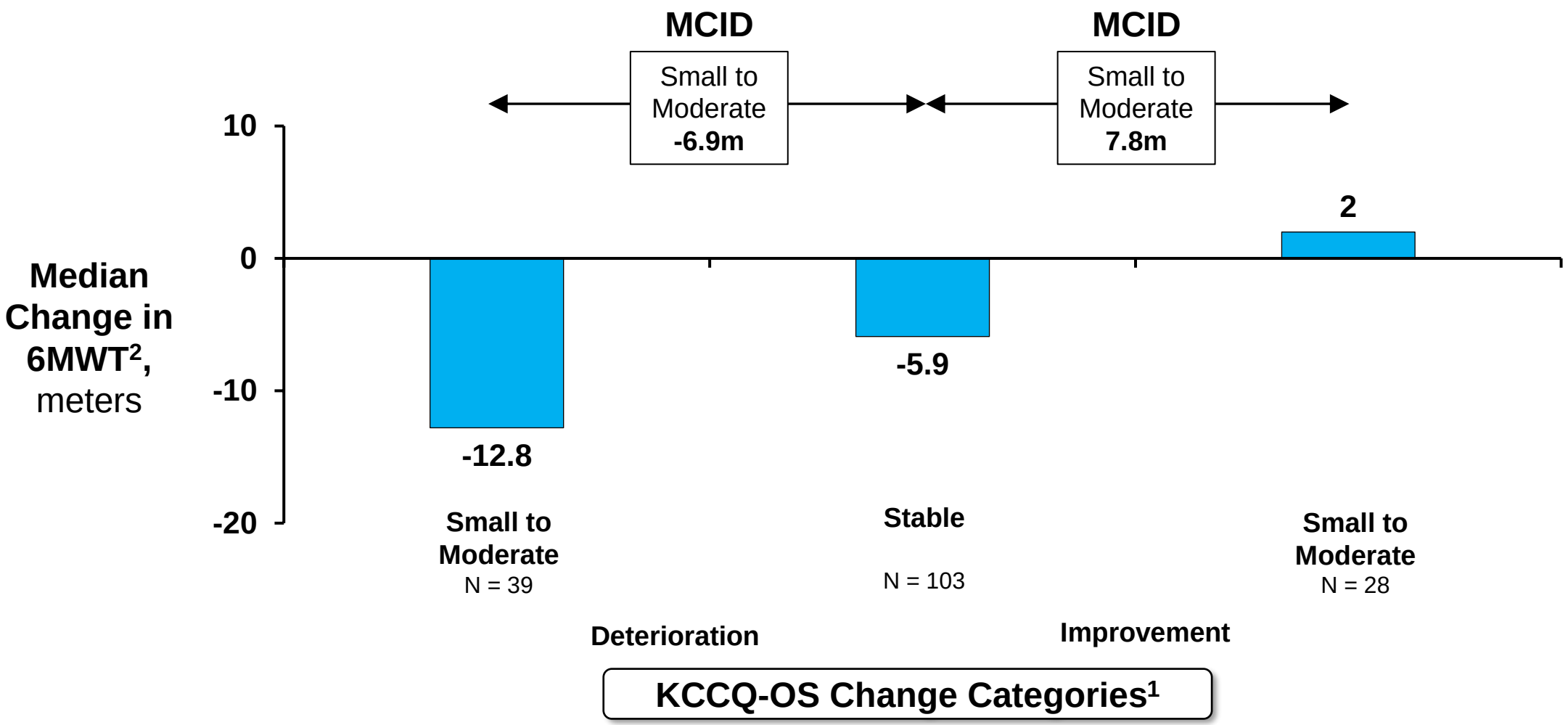
McDermott, 2021; Khan, 2022; Kwok, 2013; Oosterveer, 2022; Spina, 2019; Perera, 2006; Stephens-Shields 2021; Jain, 2021; Holland, 2010; Gremeaux, 2011; Lee, 2014; Zampogna, 2021; Moutchia, 2023; Holland, 2009; Granger, 2015; Mathai, 2012; Naylor, 2016; Takenaka, 2022; Cantarero-Villanueva, 2023; Benaim, 2019; Fulk 2018; King 2022; Kang 2021; Takenaka 2023; Kaleth, 2016; Sheraz, 2022.

Minimal Clinically Important Difference for 6MWT in ATTR-CM

- Derived thresholds for meaningful change in 6MWT using all APOLLO-B data (patisiran and placebo)
- KCCQ used as anchor
- Change in 6MWT calculated for established categorical changes in KCCQ
- KCCQ as anchor conforms with recent FDA Guidance[1]
  - Includes assessment of physical functioning (what 6MWT measures)
  - Well-established thresholds for meaningful within-patient changes
  - Plainly understood by respondents
  - Changes correlate with change in 6MWT
  - Assessed at same time points

1. Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making, April 2023

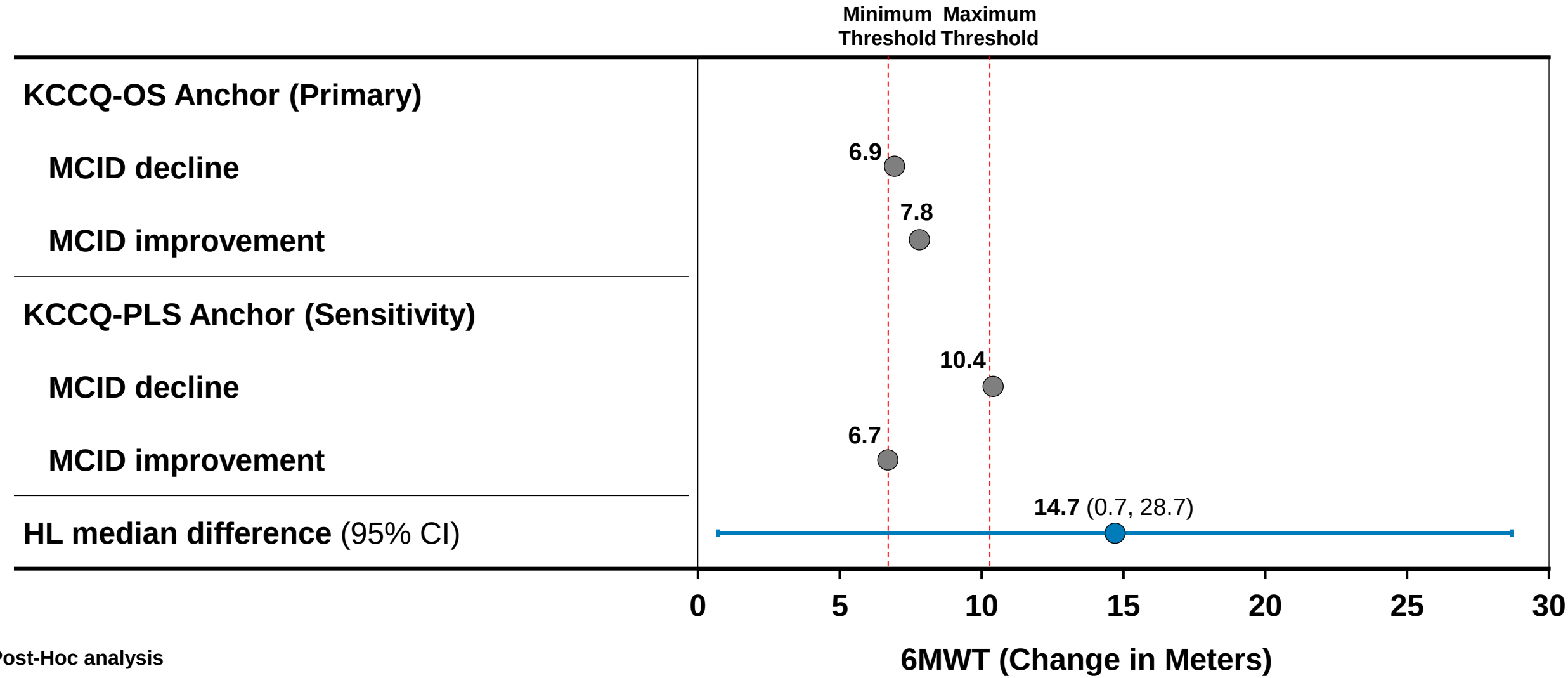
Derivation of Clinically Meaningful Differences in 6MWT in APOLLO-B



Post-Hoc analysis

1. KCCQ-OS categories: Deterioration - Small to Moderate >-10 to -5, Stable >-5 to <5, Improvement - Small to Moderate 5 to <10. Spertus, 2005.
2. APOLLO-B overall population (patisiran and placebo)

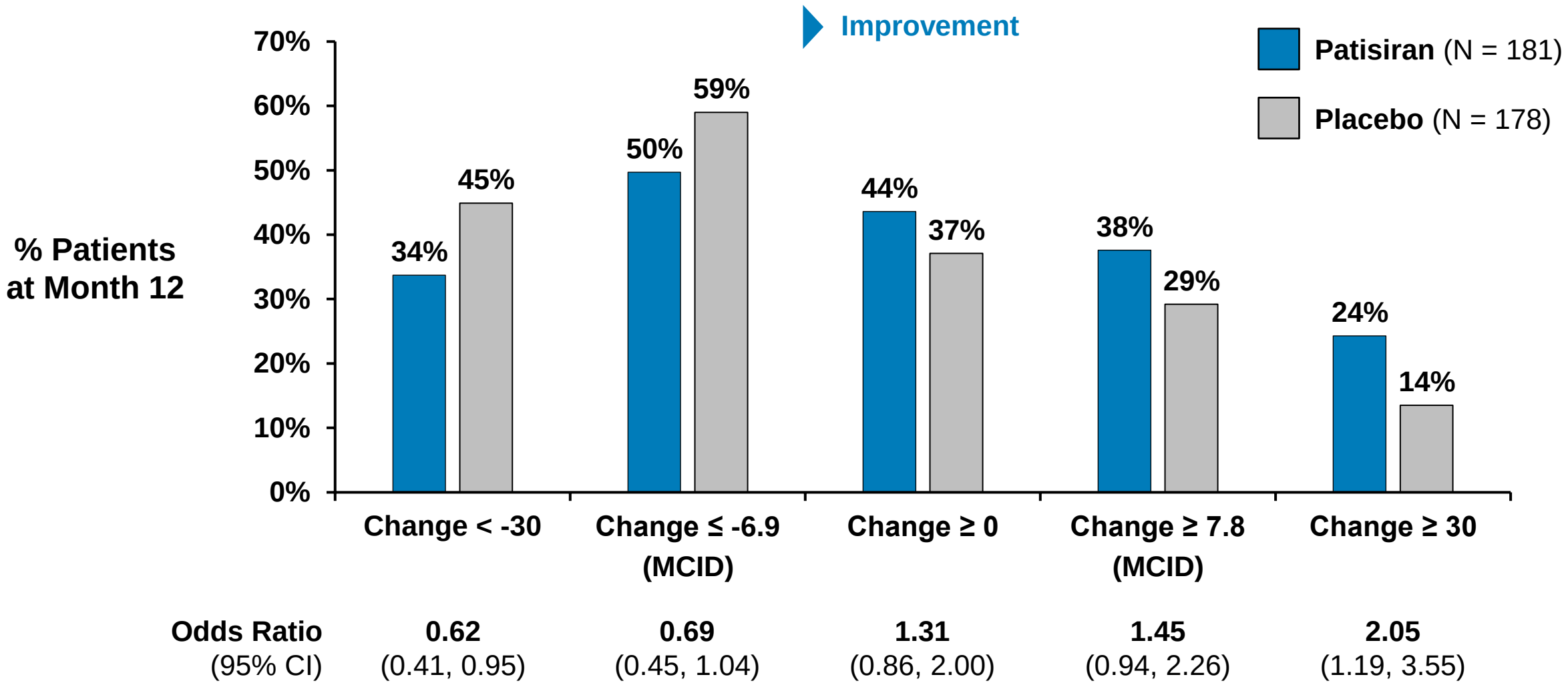
6MWT Treatment Effect Meaningful to Majority of Patients



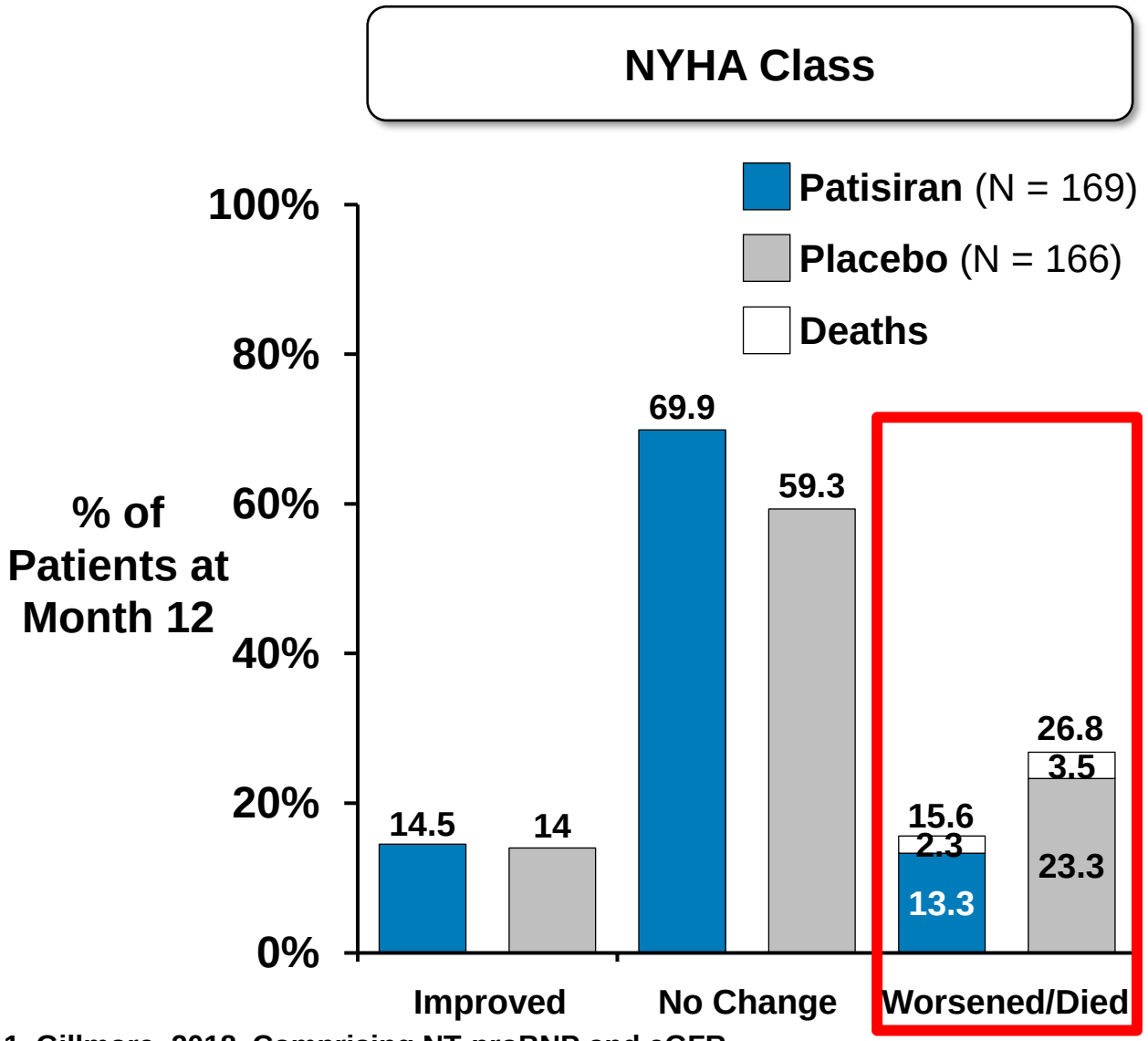
Post-Hoc analysis

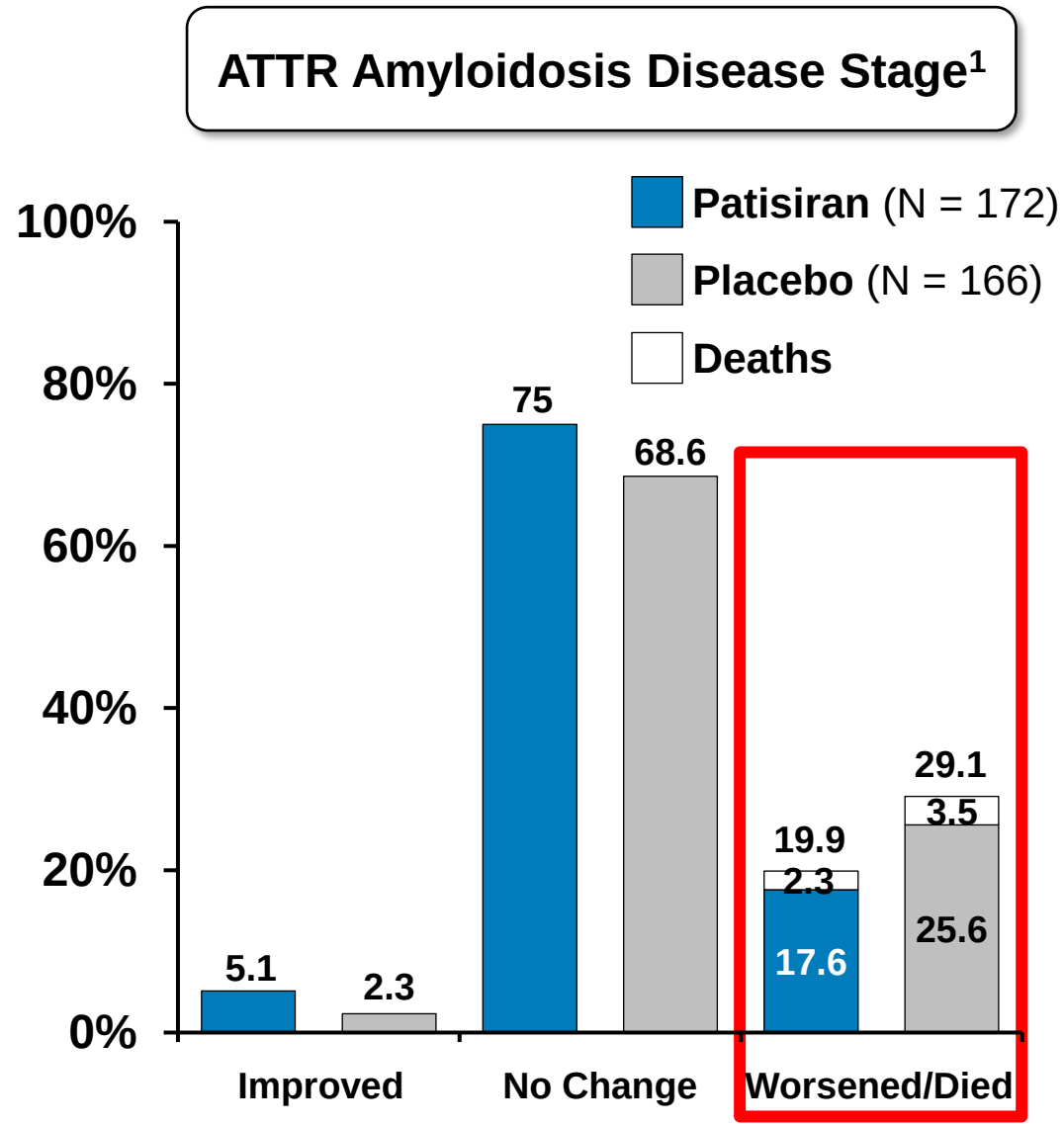
MCID calculated using observed data (patisiran and placebo)

Best 6MWT Outcomes More Likely on Patisiran
Worst Outcomes More Likely on Placebo



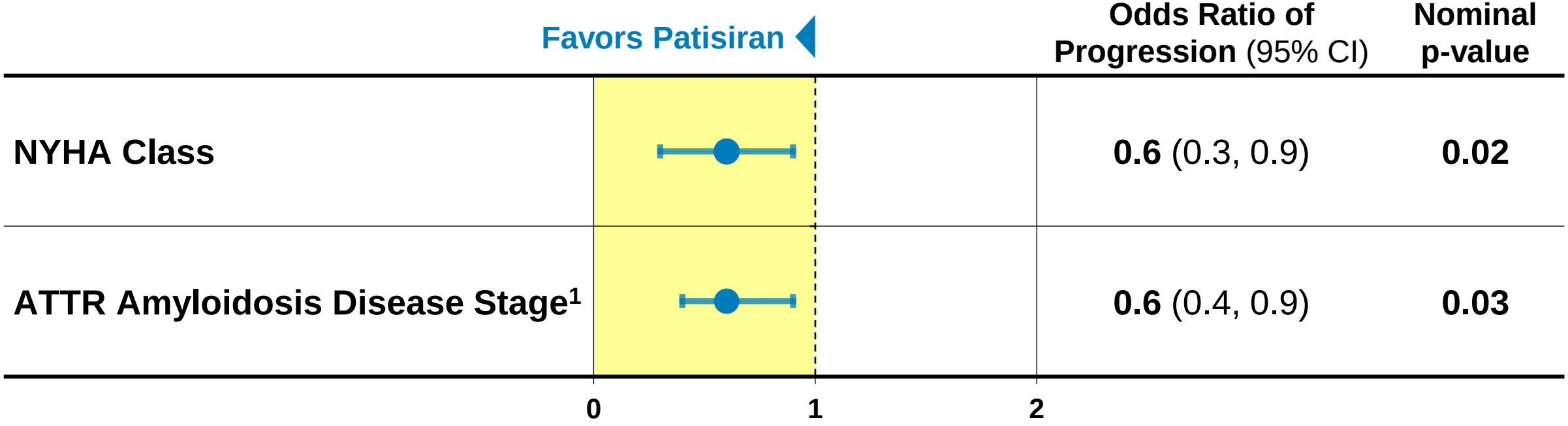
Clinical Assessments Highlight Lower Likelihood of Disease Progression on Patisiran





1. Gillmore, 2018. Comprising NT-proBNP and eGFR

Lower Likelihood of Disease Progression on Patisiran



Post-Hoc analysis

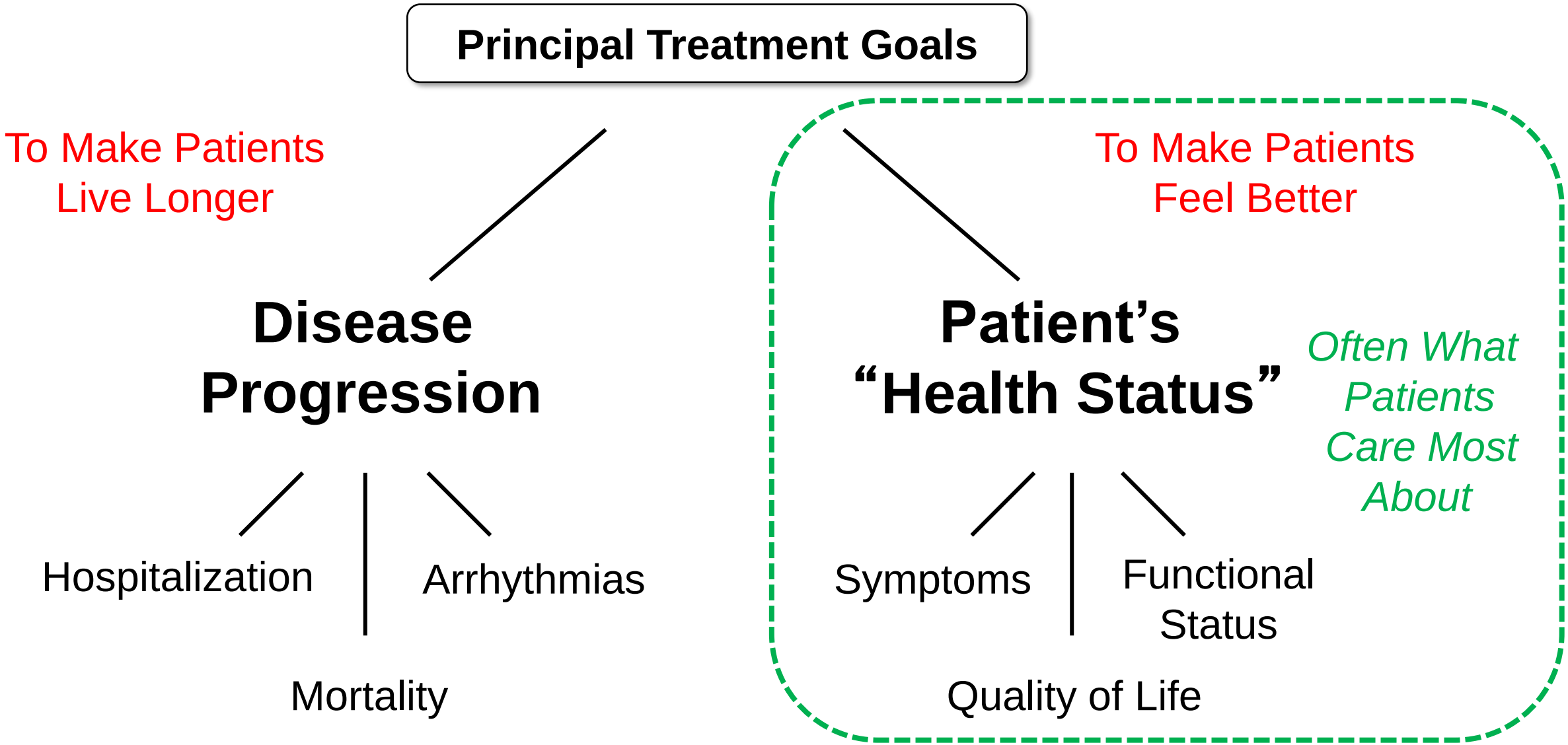
1. Gillmore, 2018. Comprising NT-proBNP and eGFR

Impact of Patisiran on Patient Health Status

John A. Spertus, MD, MPH

Professor, Lauer / Missouri Endowed Chair
Director, University of Missouri – Kansas City Healthcare Institute for Innovations in Quality
Clinical Director, Outcomes Research
Saint Luke's Mid America Heart Institute

Treatment Goals for Heart Failure



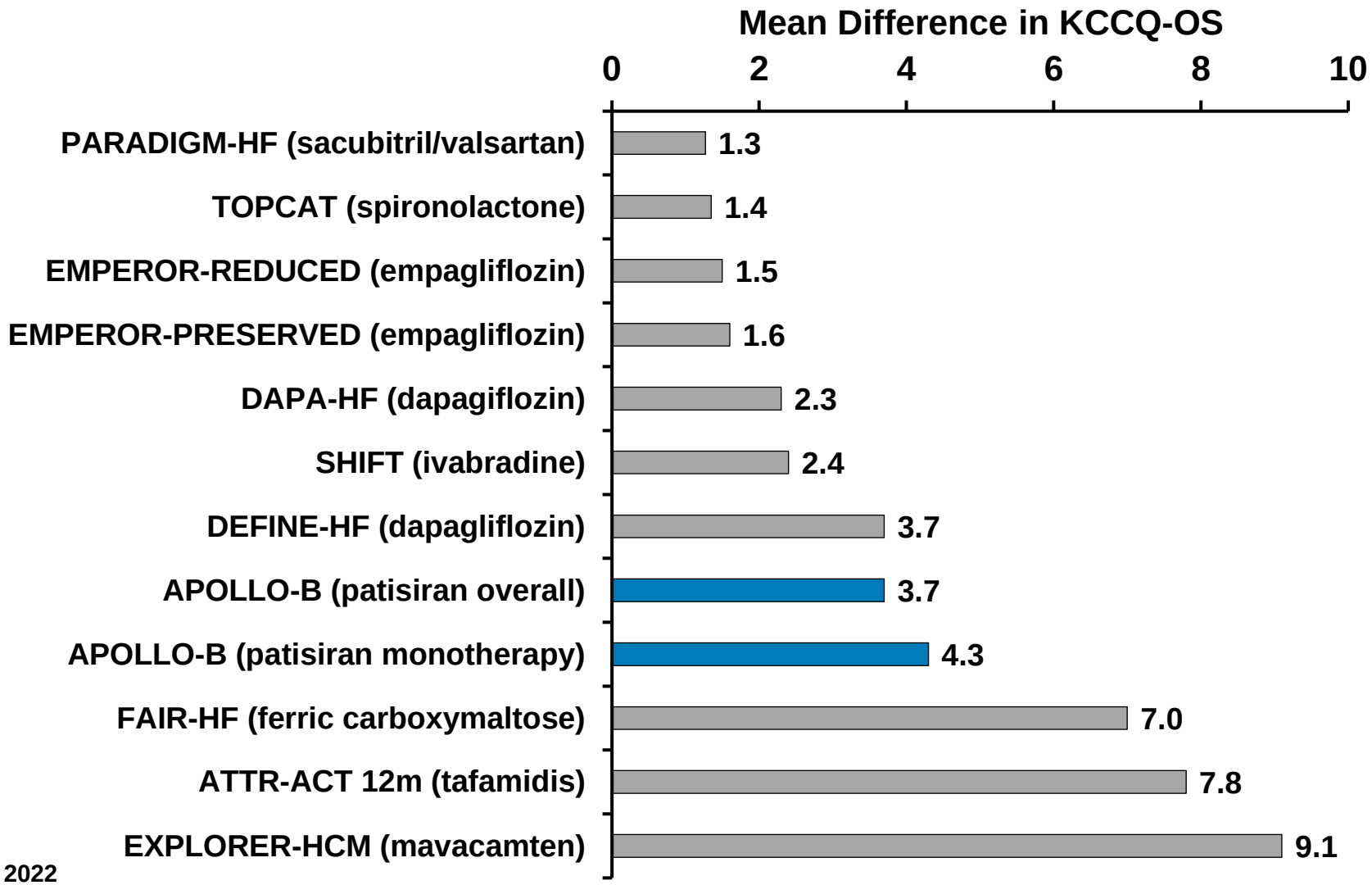
The Kansas City Cardiomyopathy Questionnaire (KCCQ)

- 23 items that measure 5 clinically relevant domains
  - Physical Limitation
  - Symptoms:
    - Frequency
    - Severity
    - Change
  - Social Limitation
  - Quality of Life
  - Self-Efficacy

Total Symptom Score → Clinical Summary Score → Overall Summary Score

- Represents the patient's perspective of their HF, regardless of etiology
- Established validity, reliability and responsiveness
  - *Well-established thresholds for clinically meaningful change*
- Qualified by FDA's CDRH and CDER as a Clinical Outcomes Assessment

Mean Patisiran Effect Compares Well to Other Heart Failure Therapies



Study Date Range: 2009 – 2022

Study timepoint of KCCQ-OS measurement (Paradigm-HF: 8 months, EMPEROR-REDUCED: 12 months, EMPEROR-PRESERVED: 12 months, TOPCAT: 12 months, DAPA-HF: 8 months, SHIFT: 12 months, DEFINE-HF: 3 months, APOLLO-B: 12 months, ATTR-ACT: Month 12 data shown, FAIR-HF: 6 months, EXPLORER-HCM: 7.5 months).

Categorical Changes are Most Relevant to Understand the Clinical Impact of a Therapy

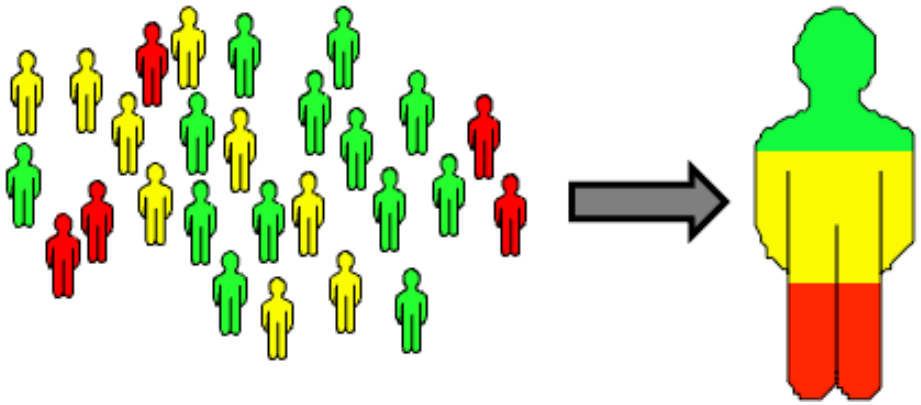
= Marked Improvement

= Minimal Change

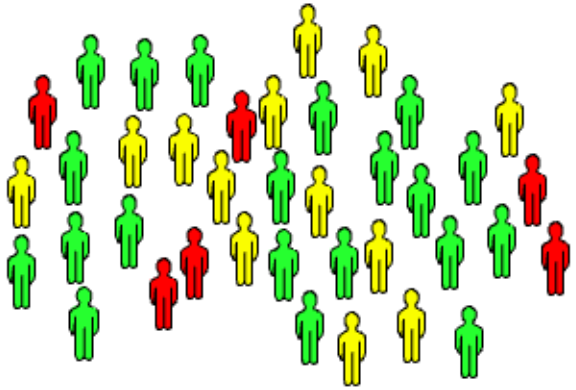
= Marked Deterioration

Outcomes from a Study

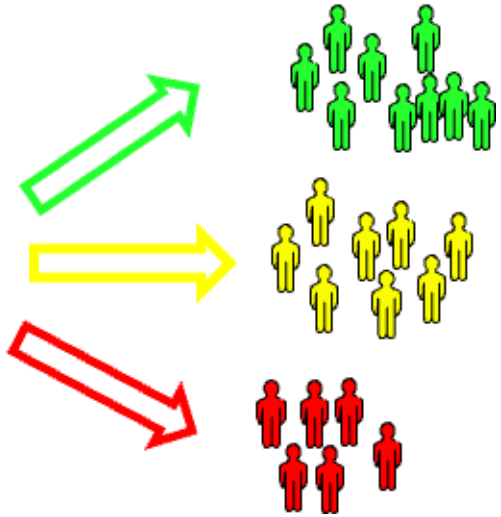
Mean Treatment Difference



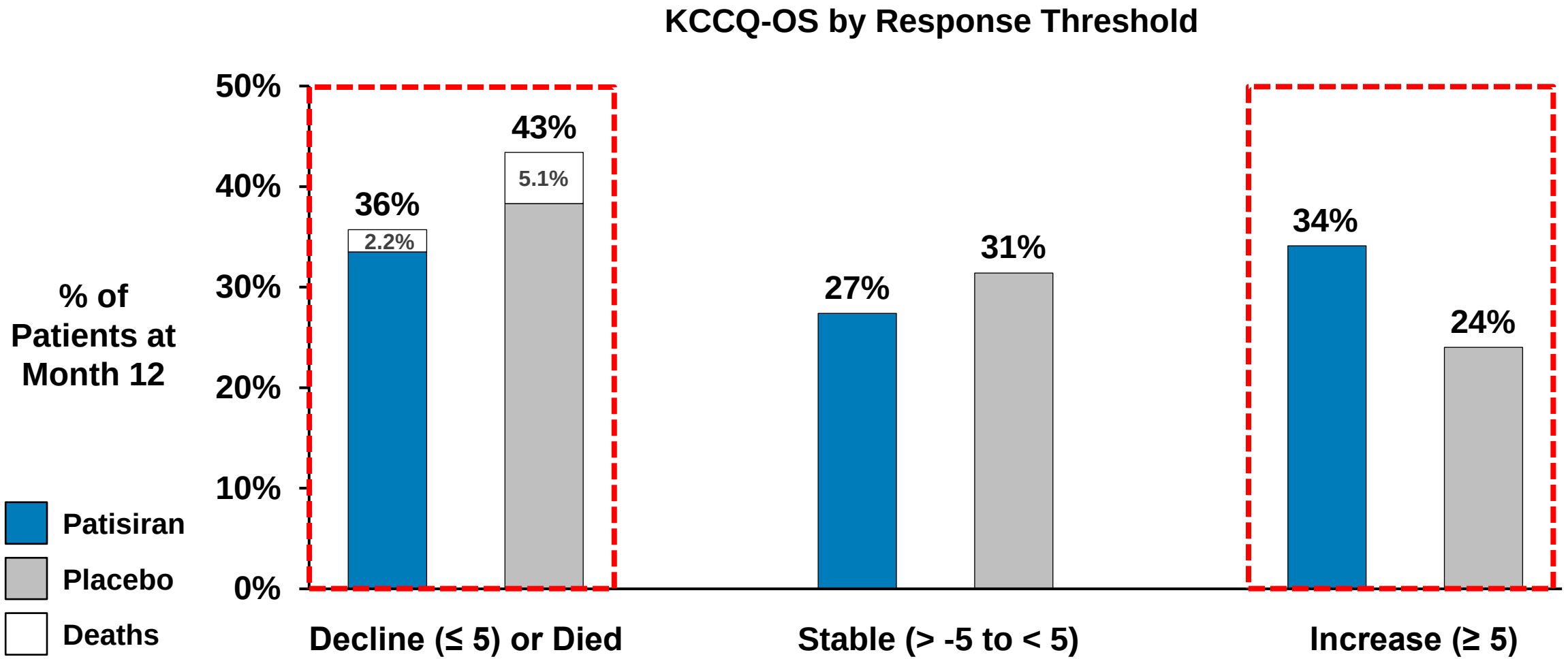
Outcomes from a Study



Distribution of Change



Patient-Level Changes Demonstrate Clinically Meaningful Benefits with Patisiran



KCCQ is Sensitive to Clinically Meaningful Changes

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	X	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	X	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	X	❑	❑	❑	❑

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

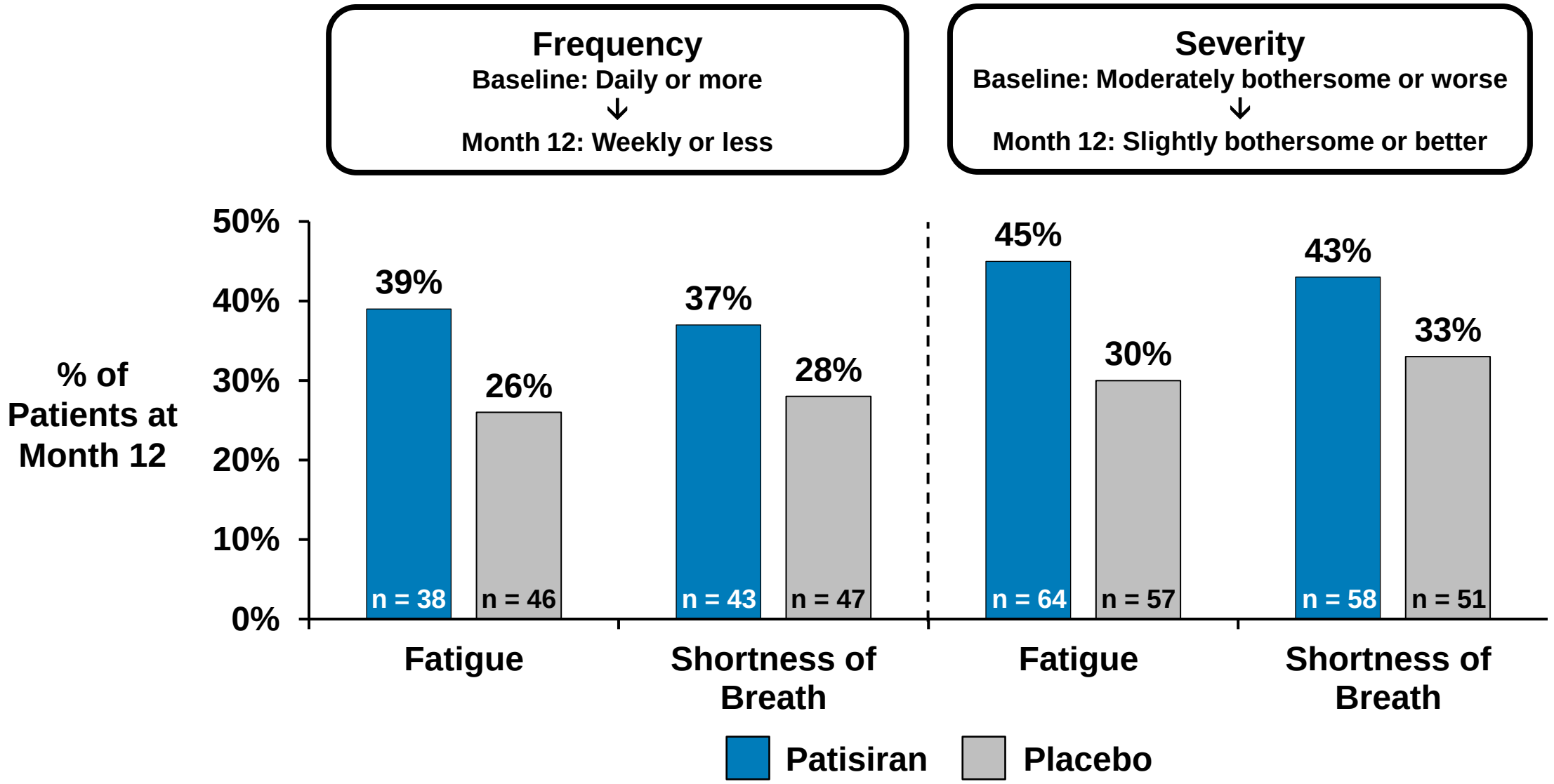
Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	X	❑	❑	❑

- Fatigue Decreases from Several Times a day to Weekly
  - ➢ +2 points
- Shortness of breath goes from Daily to Weekly
  - ➢ +1 point
- Severities of both symptoms go from Moderately to Slightly Bothersome
  - ➢ +1 point each

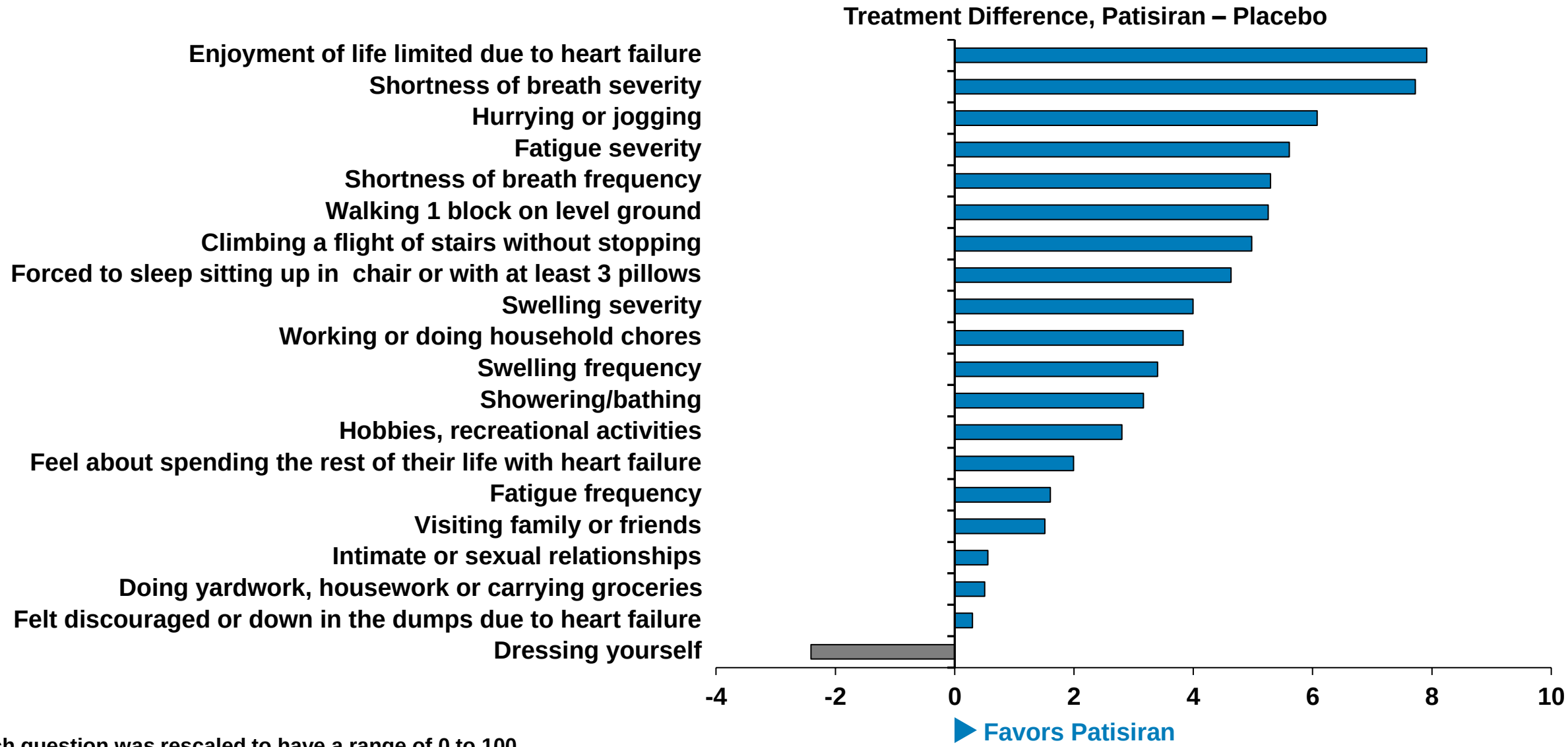
➢ *For an individual patient, a 5-point change is clinically meaningful*

Illustrative Example from APOLLO-B

Improvements in Fatigue and Shortness of Breath



Broad Impact of Patisiran on Patient Health Status and Quality of Life in APOLLO-B



Each question was rescaled to have a range of 0 to 100.

KCCQ Conclusions

- The KCCQ is an extensively validated patient-reported outcome tool with well-established thresholds that relate change in score to clinical change in heart failure status
- The average treatment effect of patisiran is comparable to other heart failure drugs that help patients feel better
- Most importantly, patisiran has a clinically meaningful impact on improving ***individual patients'*** health status and quality of life

Safety

Elena Yureneva MD, MHA

Executive Director
Head of Medical Safety and Risk Management
Alnylam Pharmaceuticals

Patisiran Exposure in APOLLO-B

- APOLLO-B: 347 patients with ATTR amyloidosis with cardiomyopathy treated with patisiran for up to 43 months
- Safety profile of patisiran in patients with ATTR amyloidosis with cardiomyopathy in APOLLO-B consistent with that previously established

	APOLLO-B Double-blind and OLE All Patisiran N = 347
Median treatment duration, months (range)	**23.0** (0 – 43 months)
Cumulative Treatment Exposure, patient-years	**629.7**
Treatment Duration (cumulative months), n **(%)**	
≥ 12 months	311 **(89.6%)**
≥ 18 months	215 **(62.0%)**
≥ 24 months	171 **(49.3%)**
≥ 30 months	68 **(19.6%)**

Data Cut-off: 26 Jun 2023

Patisiran was Well-Tolerated in APOLLO-B

At least one event, n (%)	Patisiran N = 181	Placebo N = 178
AEs	165 **(91%)**	168 **(94%)**
Severe AEs	47 **(26%)**	52 **(29%)**
SAEs	61 **(34%)**	63 **(35%)**
AEs leading to treatment discontinuation	5 **(3%)**	5 **(3%)**
Deaths (safety analysis)[1]	5 **(3%)**	9 **(5%)**

- AEs observed more commonly on patisiran than placebo (> 3%) are known ADRs: infusion-related reaction, arthralgia, and muscle spasms
- Safety profile comparable between subgroups including demographic, disease characteristics and patients on patisiran monotherapy or background tafamidis

1. Safety analysis includes deaths on-study and after withdrawal from the study. One placebo patient stopped study participation during the DB period and died after the pre-specified window for the statistical analysis of deaths during the DB period

Similar Proportion of Patients Experienced SAEs Between Groups

Preferred Term (≥ 2% in Any Group), n (%)	Patisiran N = 181	Placebo N = 178
Any SAE	61 **(34%)**	63 **(35%)**
Cardiac failure	15 **(8%)**	13 **(7%)**
Atrial fibrillation	5 **(3%)**	4 **(2%)**
AV block complete	2 **(1%)**	4 **(2%)**
Syncope	2 **(1%)**	4 **(2%)**
Amyloidosis	1 **(0.6%)**	4 **(2%)**

Deaths on Patisiran Numerically Lower than on Placebo

Adjudicated Cause of Death, n (%)	Patisiran N = 181	Placebo N = 178
Total	5 **(3%)**	9 **(5%)**[1]
Heart Failure	1	4
Infection	0	1
Sudden cardiac death	1	0
Pancreatitis	1	0
Cholangitis	0	1
Pancreatic cancer	0	1
COVID-19	1	0
Death (Cause not reported)	1	2

- No deaths were considered related to study drug by investigators

1. Includes all deaths on-study and after withdrawal from the study. One placebo patient stopped study participation during the DB period and died after the pre-specified window for the statistical analysis of deaths during the DB period

Safety Topics of Interest

- Cardiac Events
- Infusion Related Reaction
- Ocular Events

Incidence of Cardiac Events in Patisiran Group Similar or Lower than Placebo Group

Type of AE, n (%)	Patisiran N = 181	Placebo N = 178
AEs in the cardiac disorder SOC	82 **(45%)**	100 **(56%)**
SAEs in the cardiac disorder SOC	32 **(18%)**	28 **(16%)**
Cardiac failure SMQ (narrow) AEs	65 **(36%)**	78 **(44%)**
Cardiac failure SMQ (broad and narrow) AEs	69 **(38%)**	84 **(47%)**
Cardiac arrhythmia HLGT AEs	35 **(19%)**	48 **(27%)**
Cardiac conduction disorders HLT	8 **(4%)**	10 **(6%)**
Rate and rhythm disorders NEC HLT	5 **(3%)**	4 **(2%)**
Supraventricular arrhythmias HLT	24 **(13%)**	36 **(20%)**
Ventricular arrhythmias and cardiac arrest HLT	5 **(3%)**	8 **(5%)**

All Infusion-Related Reactions Mild to Moderate, None Reported as SAEs

Most Frequent Symptoms of IRR in Patisiran Group Preferred Term (≥ 2% in Patisiran Group), n (%)	Patisiran N = 181	Placebo N = 178
At least 1 IRR	22 **(12%)**	16 **(9%)**
Back pain	8 **(4%)**	1 **(0.6%)**
Flushing	4 **(2%)**	2 **(1%)**
Fatigue	3 **(2%)**	**0**

- Patients receive premedication with corticosteroid, acetaminophen, and antihistamines
- IRRs not treatment limiting. One patient discontinued from the study due to a mild IRR
- Proportion of IRRs and number of symptoms decreased over first 6 months

No Manifestations of Vitamin A Deficiency Identified

Preferred Term (≥ 2% in Any Group), n (%)	Patisiran N = 181	Placebo N = 178
At least 1 AE in Eye Disorders SOC	31 **(17%)**	21 **(12%)**
Cataract	4 **(2%)**	2 **(1%)**
Conjunctival hemorrhage	7 **(4%)**	0
Eye pain	1 **(1%)**	3 **(2%)**
Ocular hyperemia	3 **(2%)**	1 **(1%)**
Vision blurred	6 **(3%)**	4 **(2%)**
Vision impairment	3 **(2%)**	1 **(1%)**

- Patients referred for ophthalmology consult in case of vision AEs
- No evidence of vitamin A deficiency observed in clinical trials or post-marketing

No Change in Safety Profile with Longer Term Exposure

Preferred Term (≥ 10% in All Patisiran DB+OLE Group)	Patisiran DB N = 181, PY = 408		Placebo DB N = 166, PY = 222		All Patisiran DB+OLE N = 347, PY = 630	
	%	ER	%	ER	%	ER
Any AE	**97%**	598.8	**96%**	759.7	**97%**	655.5
Cardiac failure	**43%**	39.5	**33%**	39.2	**38%**	39.4
Covid-19	**28%**	13.5	**34%**	27.0	**31%**	18.3
Atrial fibrillation	**19%**	13.0	**14%**	12.6	**17%**	12.9
Constipation	**20%**	9.6	**12%**	9.5	**16%**	9.5
IRR	**15%**	29.9	**16%**	74.3	**15%**	45.6
Fall	**12%**	8.1	**16%**	20.7	**14%**	12.5
Arthralgia	**15%**	10.8	**8%**	7.7	**12%**	9.7
Gout	**12%**	9.1	**11%**	12.2	**11%**	10.2
Diarrhea	**12%**	11.8	**10%**	12.6	**11%**	12.1
Back pain	**14%**	6.9	**7%**	7.7	**11%**	7.1

ER = exposure-adjusted event rate per 100 patient-years; PY = patient-years

All-Patisiran 24M Datacut 26 Jun 2023

Patisiran was Well Tolerated with Acceptable Safety Profile

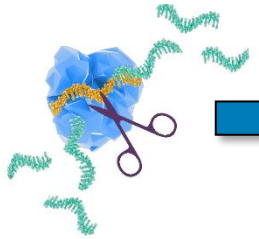
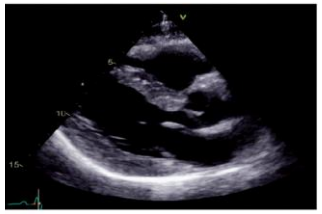
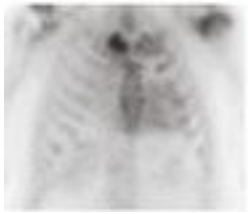
- Consistent safety profile in cardiomyopathy and polyneuropathy
  - 5 years of postmarketing experience
  - > 8,500 patient-years of exposure with patisiran worldwide
- No safety concerns among subgroups
- Primary safety considerations
  - Low incidence of mild-to-moderate IRRs
    - Managed by pre-medications
  - No evidence of ocular manifestations of Vitamin A deficiency
    - Supplementation recommended

Clinical Perspective

Ronald Witteles, MD

Professor of Cardiovascular Medicine
Co-Director, Stanford Amyloid Center
Stanford University School of Medicine

Compelling Patisiran MoA Drives Consistent Effects Across Multiple Important Disease Manifestations

Reduction in TTR	Slowed Increase in Cardiac Biomarkers	Reduced Decline in Cardiac Structure and Function	Stability/ Improvement in ^{99m}Tc Uptake	Reduced Decline in Functional Capacity	Stability in Patient Reported Health Status and QoL
					
Reduced TTR > 85 %	NT-proBNP Troponin I	• LV Mass • Global Longitudinal Strain • LV Stroke Volume	Improved Perugini Grade	6MWT	KCCQ-OS

Importantly, patisiran has a favorable safety profile

Patients Care Most About Preserving Function, Feeling Well and Enjoying Life

- Quality of life is what patients care about most
- Preventing erosion of ability to engage and enjoy life is a key priority
- Patients are typically in their 70s or 80s with corresponding goals and expectations; simple things matter tremendously

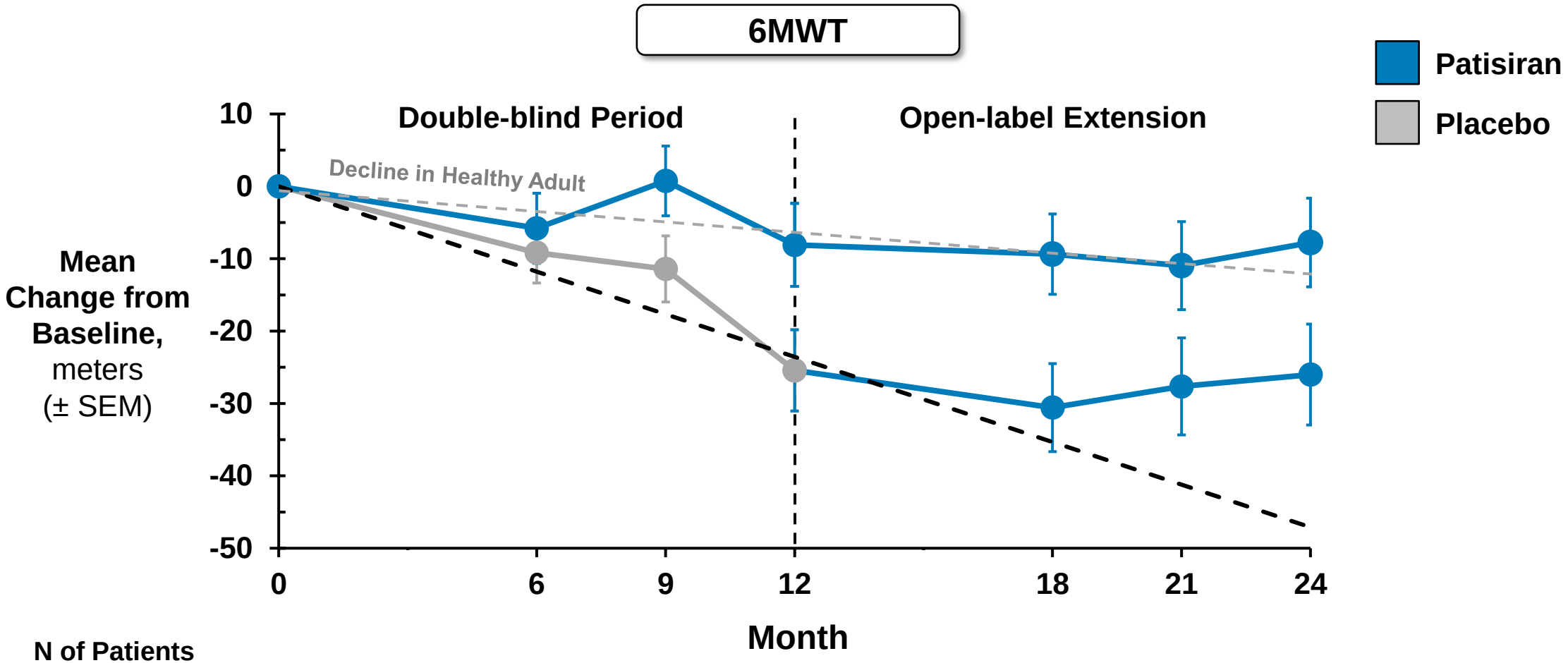
What I See in Patisiran Data Are Disease Stability and Less Progression

	Key Observation
6MWT	**Relative Stability** Comparable to expected decline in healthy adults over 24 months
KCCQ	**Relative Stability** No change from baseline to Month 24
NYHA Class	**Less Progression** OR of progression (≥ 1 class) 0.6 OR of stable or improved 1.8
ATTR Disease Stage	**Less Progression** OR of progression (≥ 1 stage) 0.6 OR of stable or improved 1.7

6MWT treatment effect at Month 12 comparable to saving 2-3 years of age-related decline; meaningful to patients in 70s and 80s

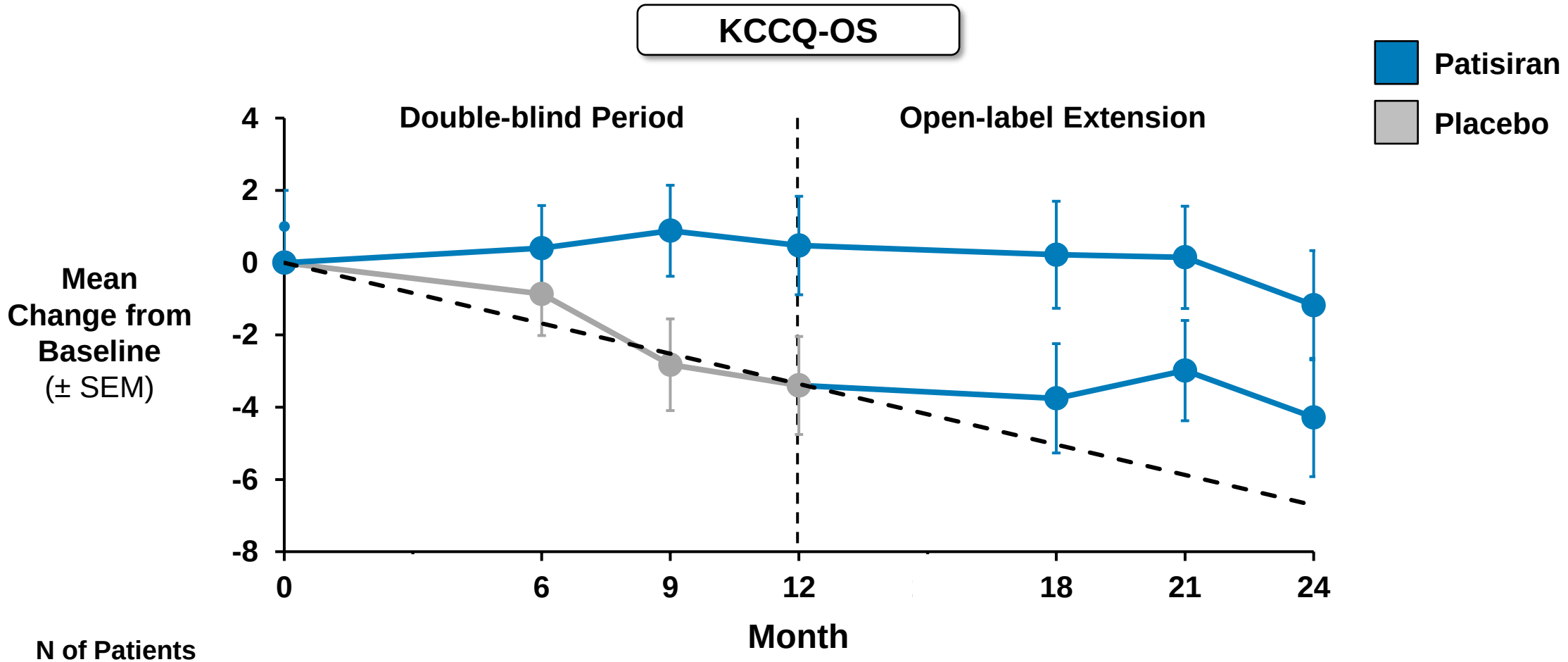
OR = odds ratio

Continued Stability in Functional Capacity Through 24 Months; Meaningful Given Expected Natural History of Steady Decline



N of Patients							
Patisiran	181	162	167	167	148	148	137
Placebo/ Patisiran	178	165	165	164	143	137	128

Stability in Health Status Through 24 Months Corroborates Meaningful Slowing of Progression



N of Patients							
Patisiran	181	169	170	170	155	155	148
Placebo/ Patisiran	178	170	167	164	151	146	140

ATTR Patients I Would Consider for Use of Patisiran

- **First-line monotherapy**
  Particular value for patients with mixed PN and CM phenotype

- **Switch for patients progressing on tafamidis**
  Currently nothing to offer as patients accumulate irrecoverable disability

- **Add on to tafamidis**
  Following informed discussion acknowledging lack of clear data to support but reasonable given safety and orthogonal MoA (biologically rational)

Positive Benefit-Risk of Patisiran

- ATTR-CM is a serious, progressive, and devastating disease with only a single approved treatment option
- Patients and physicians need alternative therapies that positively impact decline in functional ability and symptoms
- Patisiran demonstrated clear efficacy and clean safety profile with unique MoA
- My hope is patisiran becomes an option I can discuss with my patients

ONPATTRO® (patisiran)

For the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated (ATTR) amyloidosis in adults to slow the decline in functional capacity and reduce symptoms

September 13, 2023

Cardiovascular and Renal Drugs Advisory Committee

Alnylam Pharmaceuticals

Back-Up Slides Shown

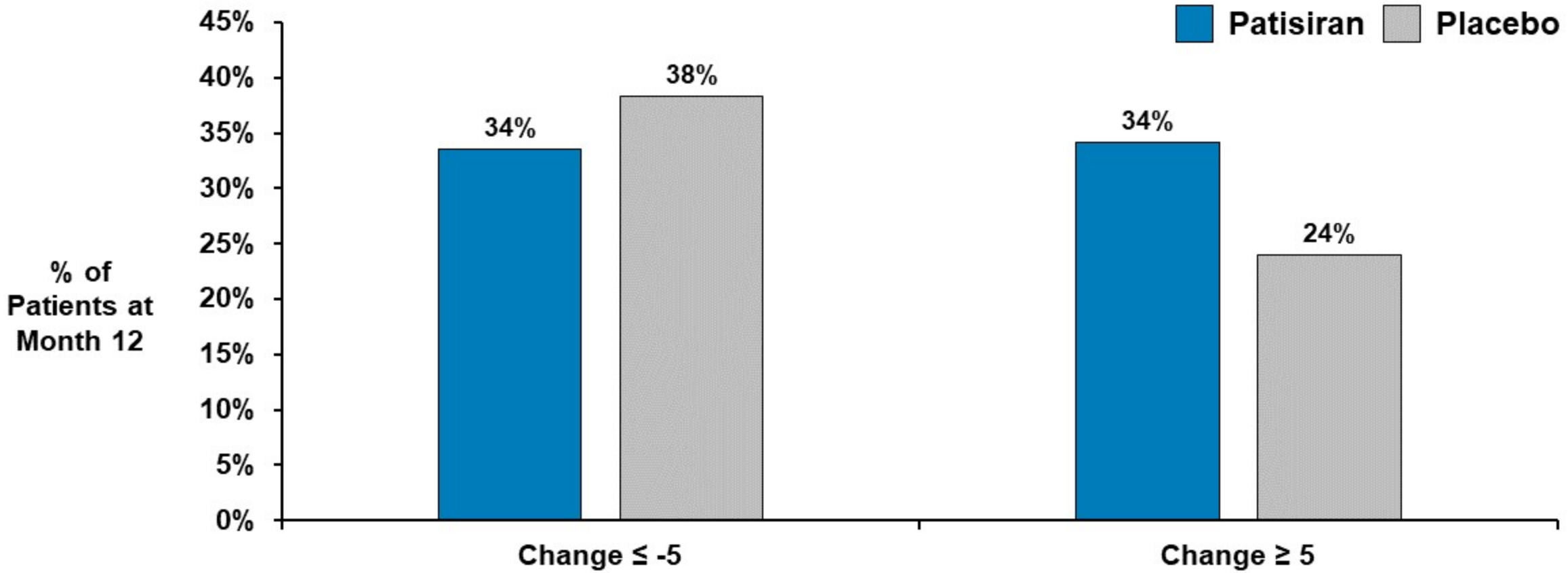
Using KCCQ-OS[1] (Overall Score) as Anchor Conforms to FDA Guidance[2] (Meets all 5 Criteria)

FDA Guidance Criteria for Anchor	How KCCQ-OS Meets Criteria
"*Ideally, the concept assessed by an anchor variable* **[KCCQ-OS]** *should match or be inclusive of the concept of interest* **[physical functioning]** *being assessed by the COA-based endpoint* **[6MWT]**"	**KCCQ-OS incorporates assessment of physical functioning**
"*An anchor should have a well-justified definition for meaningful change or for meaningful increments*"	**Established thresholds: Stable [-5 to +5]; Small to Moderate Improvement / Decline [5 to 10, -5 to -10][3]**
"*An anchor should be plainly understood by respondents in the context of use*"	**Confirmed as part of development of KCCQ-OS**
"*Differences in COA scores should be related to differences documented by one or more anchors*"	**Validation of KCCQ-OS showed correlation r=0.37 with 6MWT, p < 0.001[4]**
"*Selected anchors should be assessed at comparable time points to the target COA*"	**6MWT and KCCQ-OS assessed at same study visits**

- Guidance acknowledges identifying external dataset in rare diseases challenging and supports use of internal data.

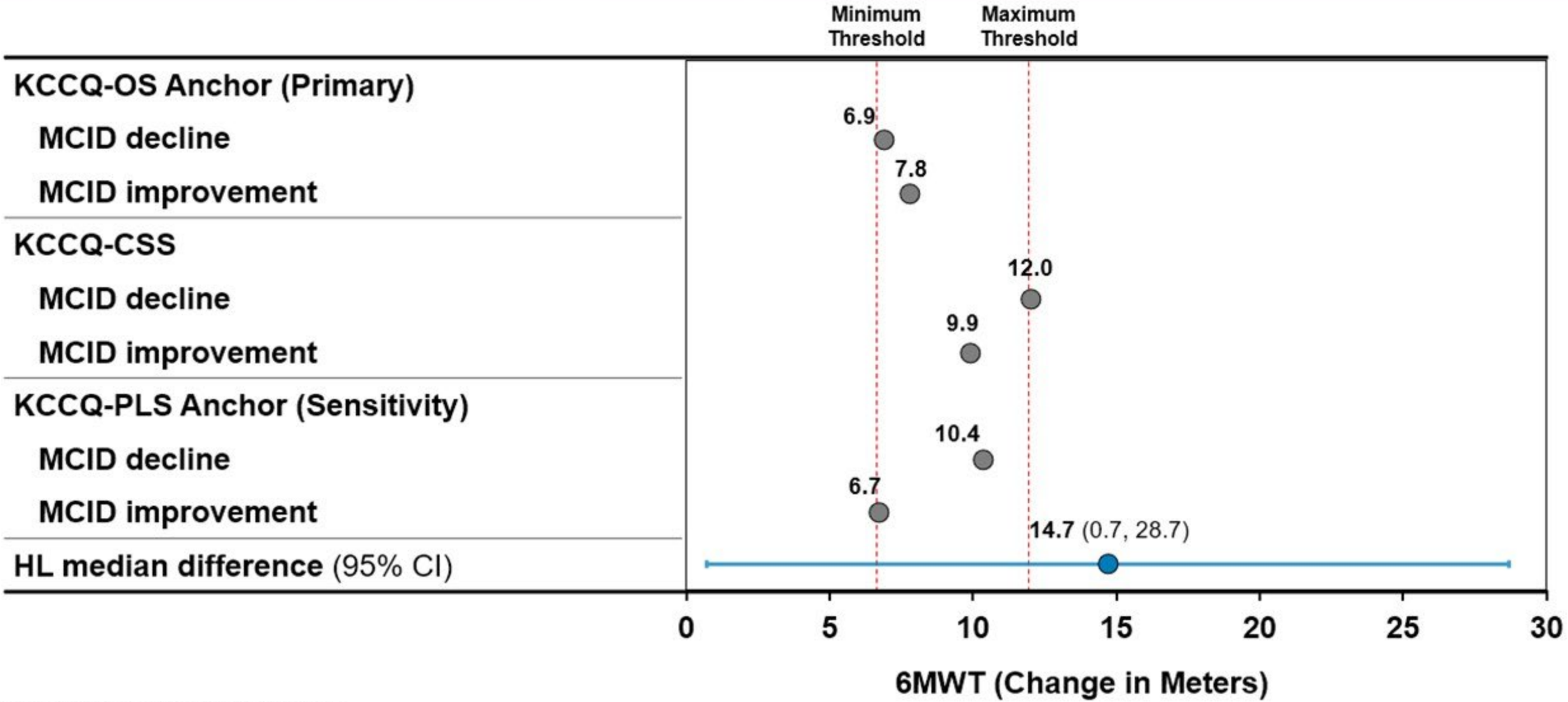
[1]MCID Primary Analysis [2]Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments (COA) Into Endpoints For Regulatory Decision-Making
[3]Spertus 2005 [4]Kao 2007

KCCQ Responder Analysis (All Patients)



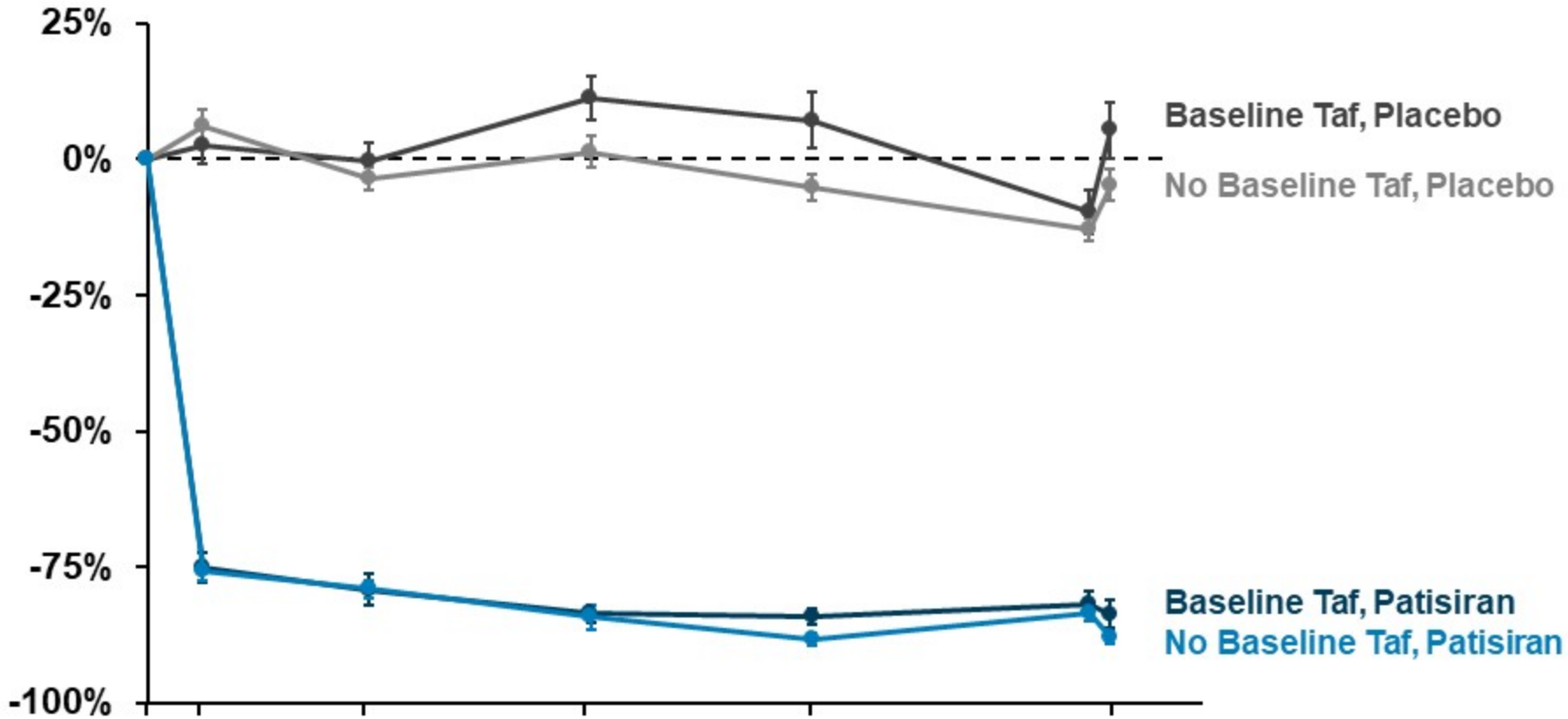
	Change ≤ -5	Change ≥ 5
Odds Ratio (95% CI)	**0.78** (0.51, 1.15)	**1.64** (1.03, 2.60)

MCID Estimates Suggest that Average Treatment Effect on 6MWT Corresponds to a Difference in Experience that Majority of Patients Would Consider Meaningful



MCID calculated using observed data

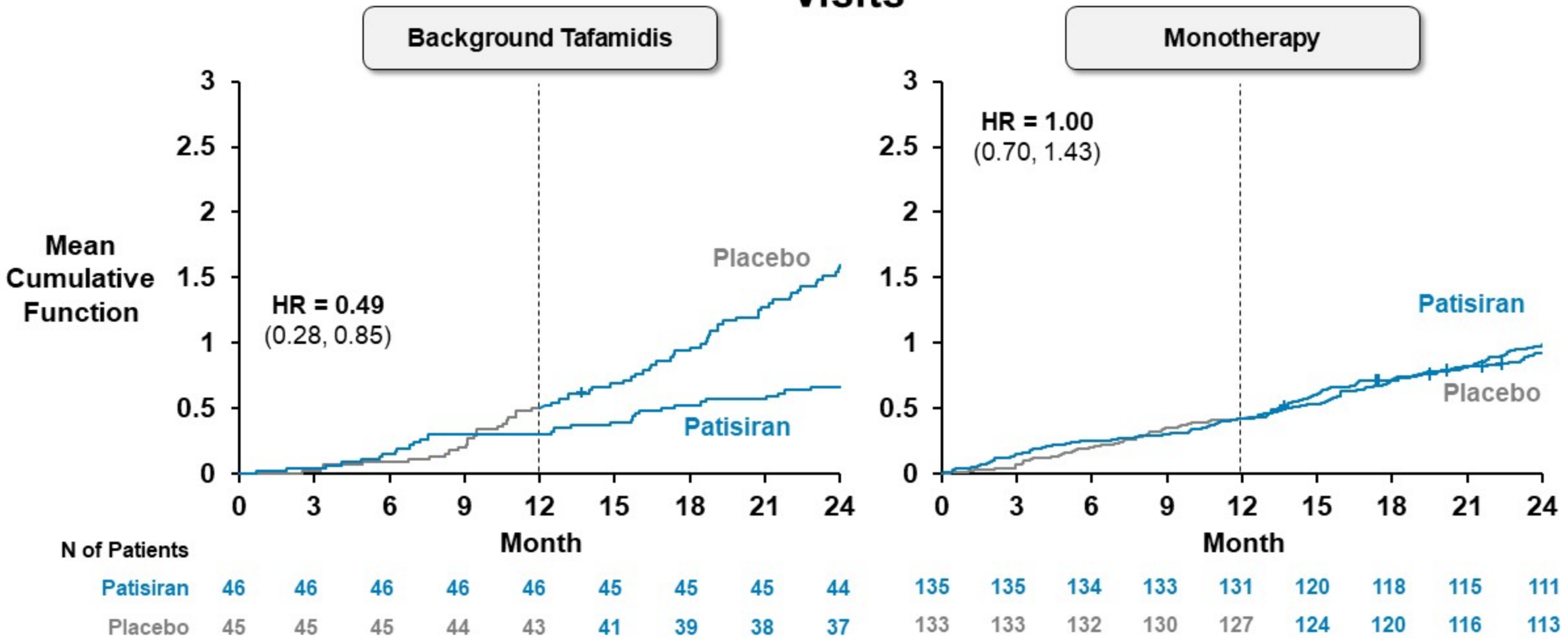
Comparable TTR Reduction With Tafamidis Use



N of Patients						
Baseline Taf, Placebo	45	43	38	43	42	41
Baseline Taf, Patisiran	46	44	35	43	44	43
No Baseline Taf, Placebo	133	127	115	119	120	123
No Baseline Taf, Patisiran	135	125	117	121	123	115

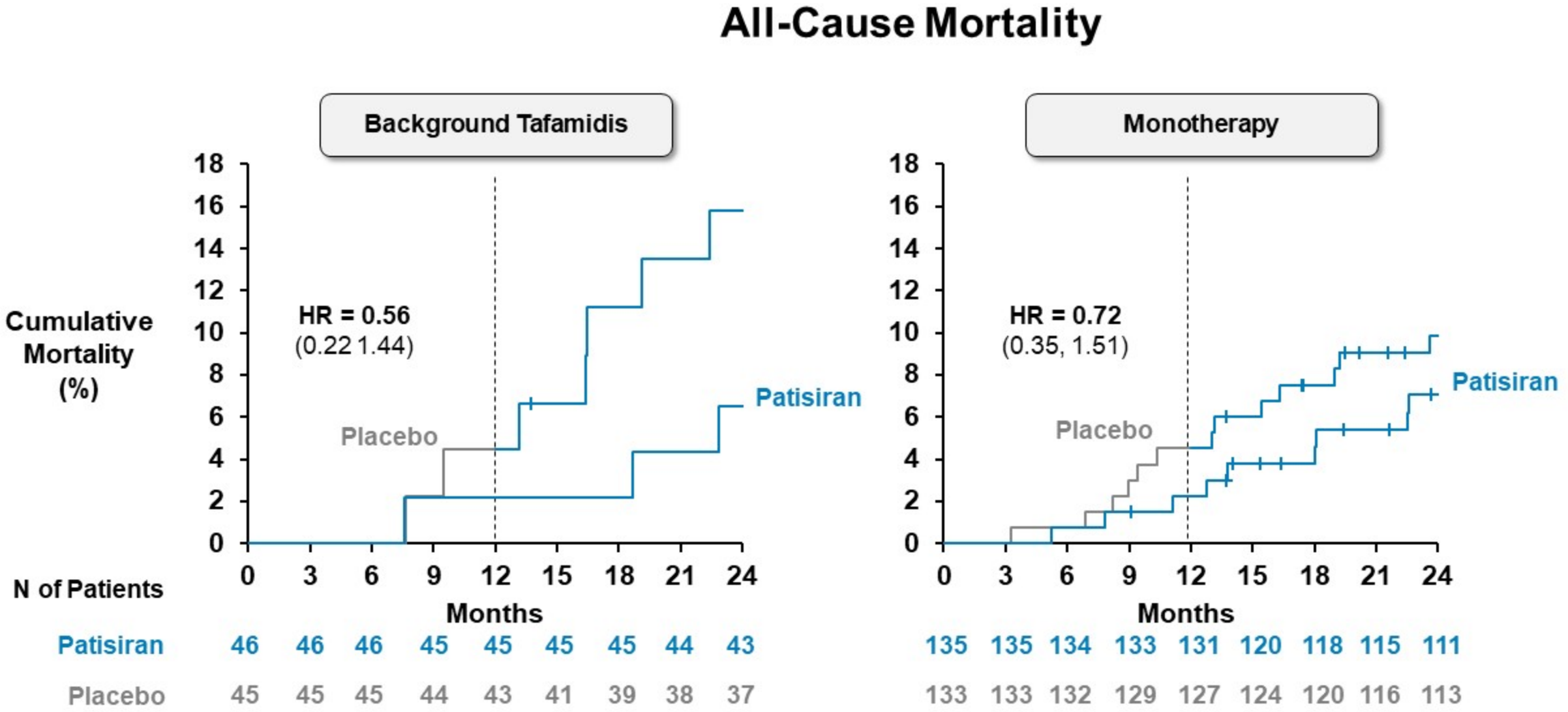
All-cause Mortality, Hospitalizations, UHF Visits (Month 24 Data Cut)

All-Cause Mortality, Hospitalizations, Urgent Heart Failure Visits

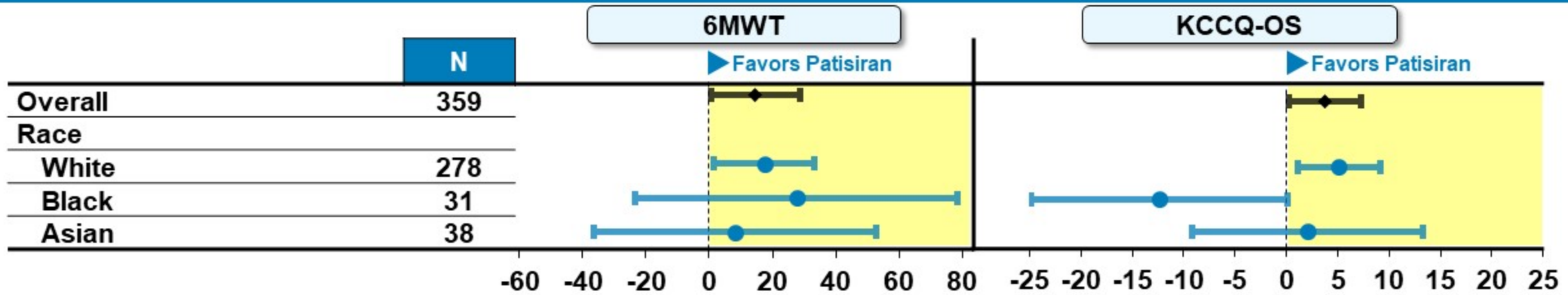


N of Patients																		
Patisiran	46	46	46	46	46	45	45	45	44	135	135	134	133	131	120	118	115	111
Placebo	45	45	45	44	43	41	39	38	37	133	133	132	130	127	124	120	116	113

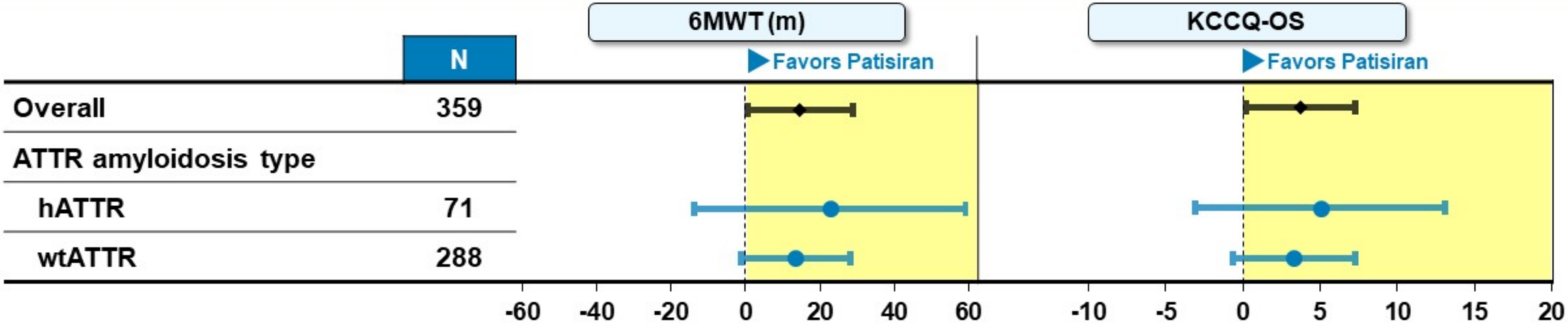
All Cause Mortality (Month 24 Data Cut)



Patisiran Treatment Effect (6MWT and KCCQ) Subgroups: Race/Ethnicity



Patisiran Treatment Effect (6MWT and KCCQ) Subgroups: ATTR Amyloidosis Type



Tafamidis Drop-in During APOLLO-B Study (DB or OLE) is Low

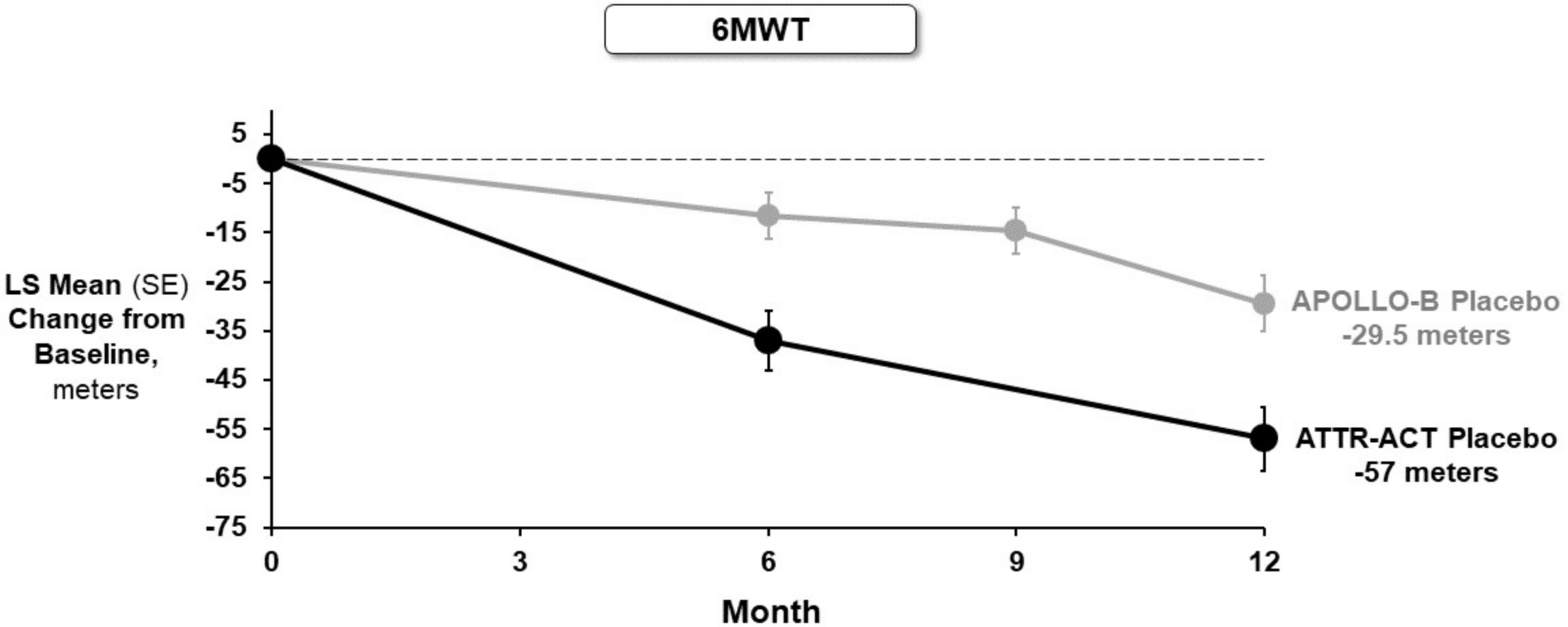
n (%)	Patisiran Monotherapy Group	
	Patisiran (N = 135)	**Placebo** (N = 133)
Patients who initiated tafamidis during the DB period	5 **(3.7%)**	3 **(2.3%)**
Patients who initiated tafamidis during the DB or OLE periods	6 **(4.4%)**	10 **(7.5%)**

Patient Characteristics: APOLLO-B versus ATTR-ACT

	APOLLO-B	ATTR-ACT
Baseline Characteristics		
Age	76	74
NYHA III	7%	35%
Mean 6MWT (meters)	375	353
KCCQ points	70	66
NT pro-BNP	1,813	3,161
Placebo Decline at Month 12 (LS Mean Change from Baseline)		
6MWT (meters)	-29.5	-57
KCCQ points	-3.4	-10

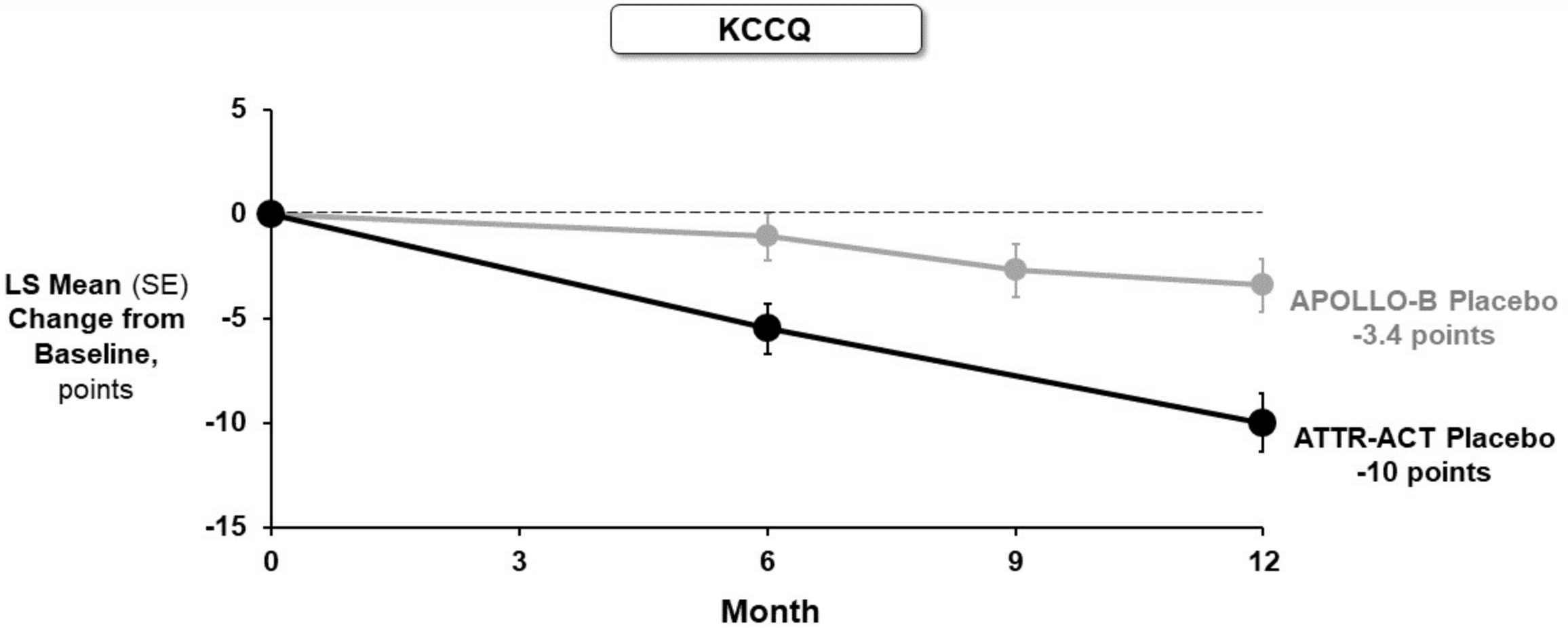
ATTR-ACT values derived from Maurer 2018

6MWT Placebo Decline in APOLLO-B vs ATTR-ACT



ATTR-ACT values derived from Maurer 2018
For visualization purposes, not intended as cross-study comparison

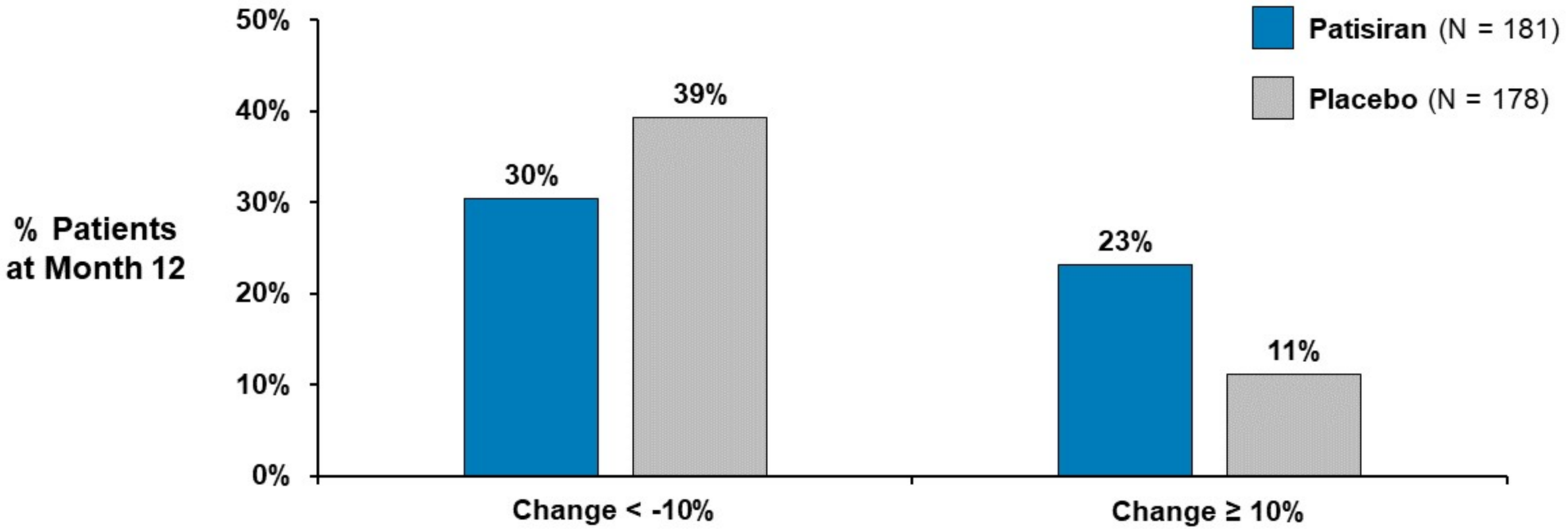
KCCQ Placebo Decline in APOLLO-B vs ATTR-ACT



ATTR-ACT values derived from Maurer 2018
For visualization purposes, not intended as cross-study comparison

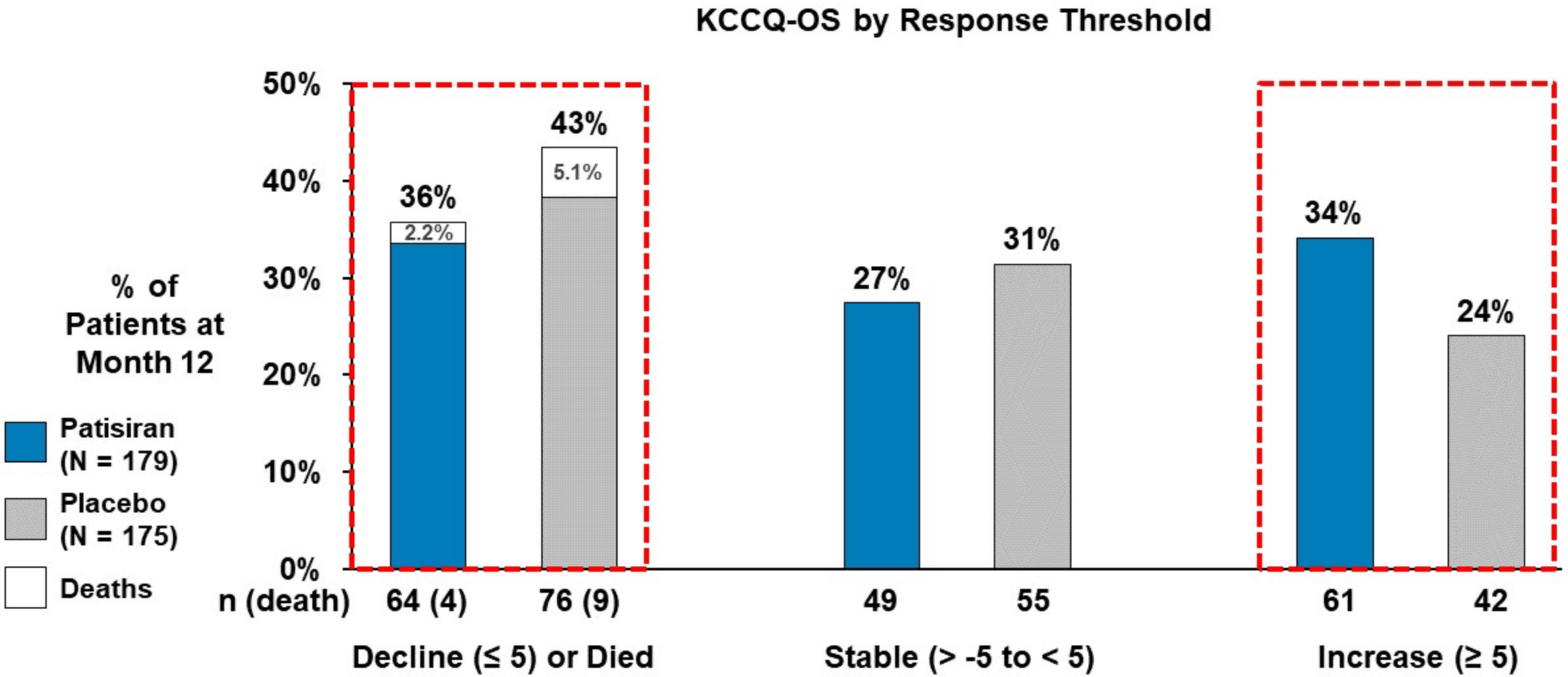
6MWT Performance at Month 12

Patisiran: ≥10% Improvement More Likely
Placebo: >10% Deterioration More Likely



Odds Ratio (95% CI)	**0.67** (0.43, 1.04)	**2.35** (1.32, 4.18)

Patient-Level Changes Demonstrate Clinically Meaningful Benefits with Patisiran



KCCQ-OS: Patient-Level Changes Demonstrate Clinically Meaningful Benefits with Patisiran

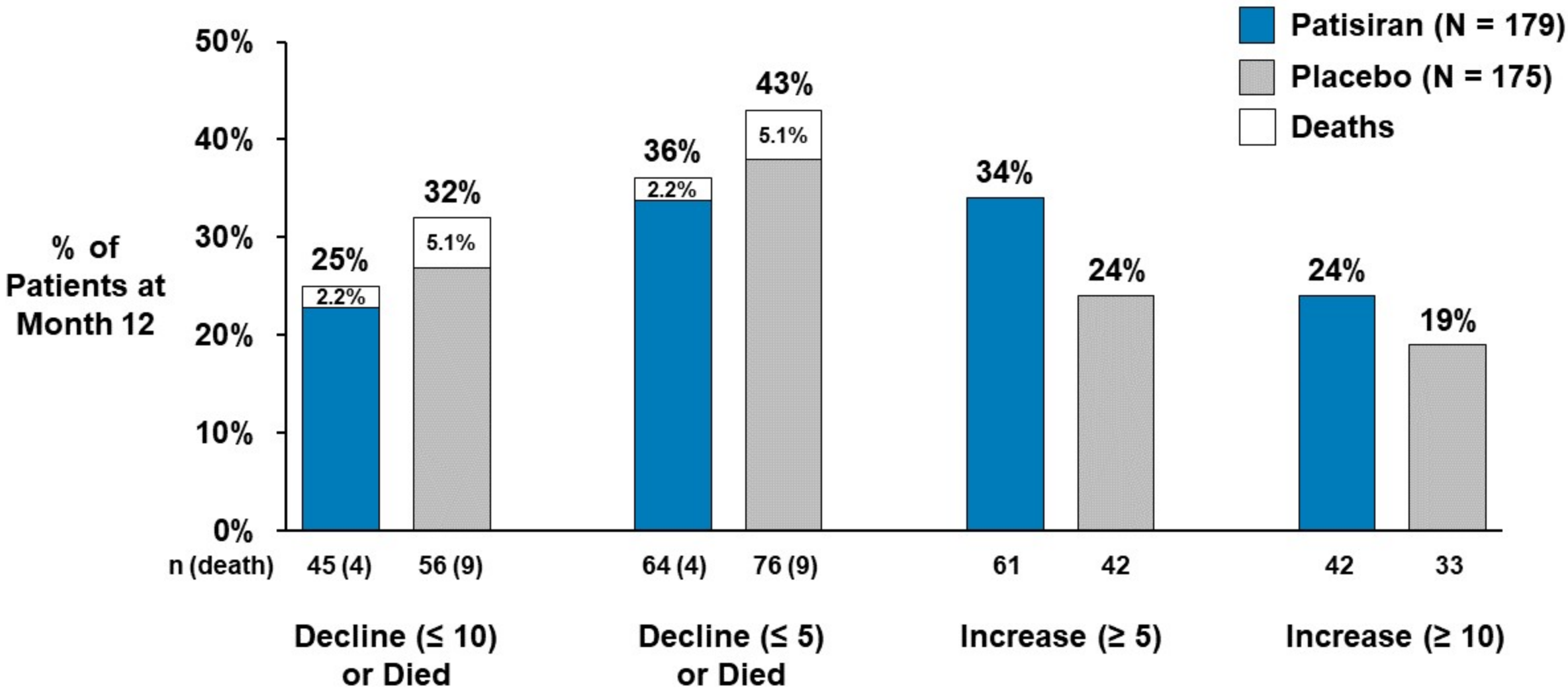
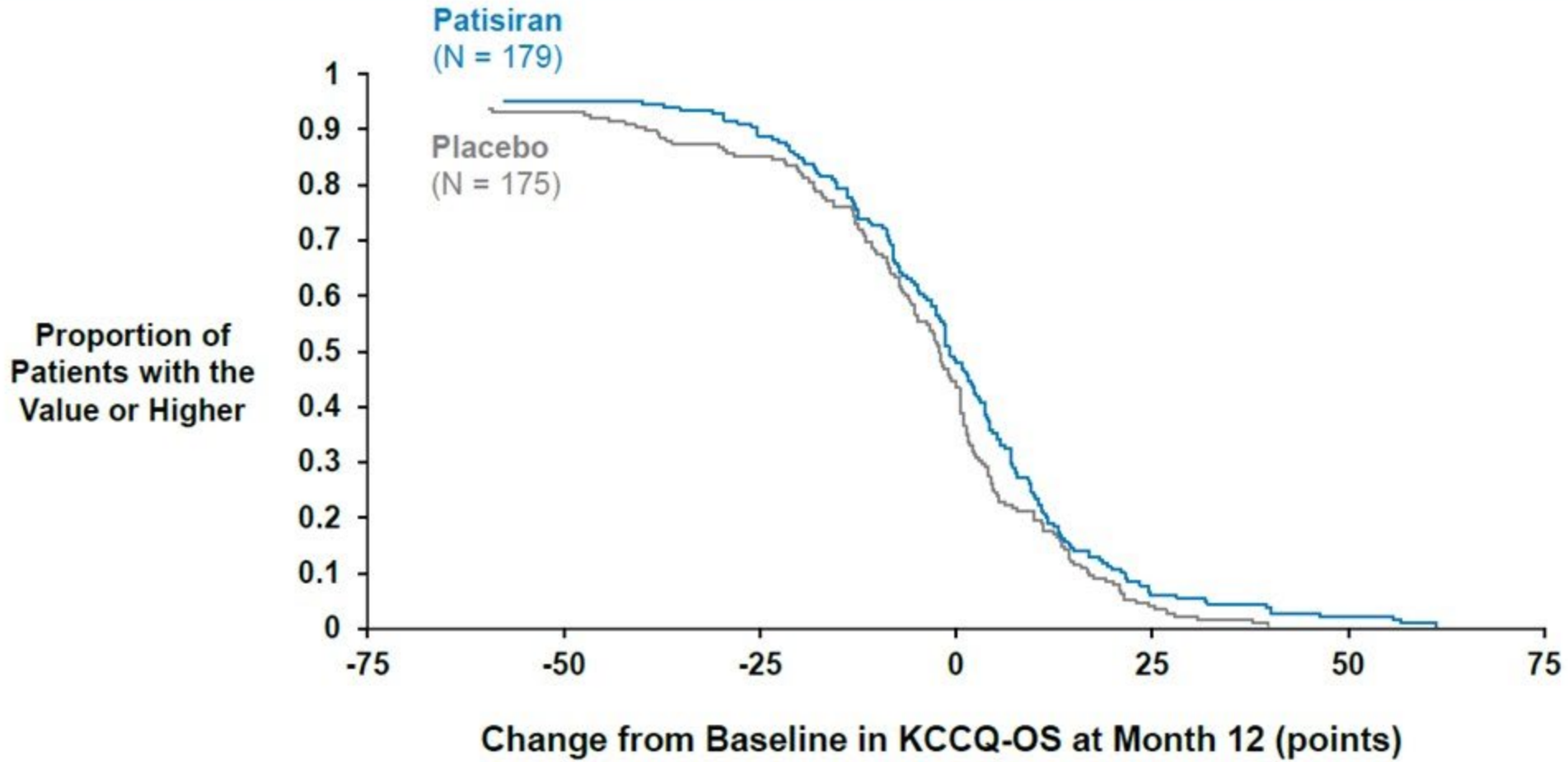


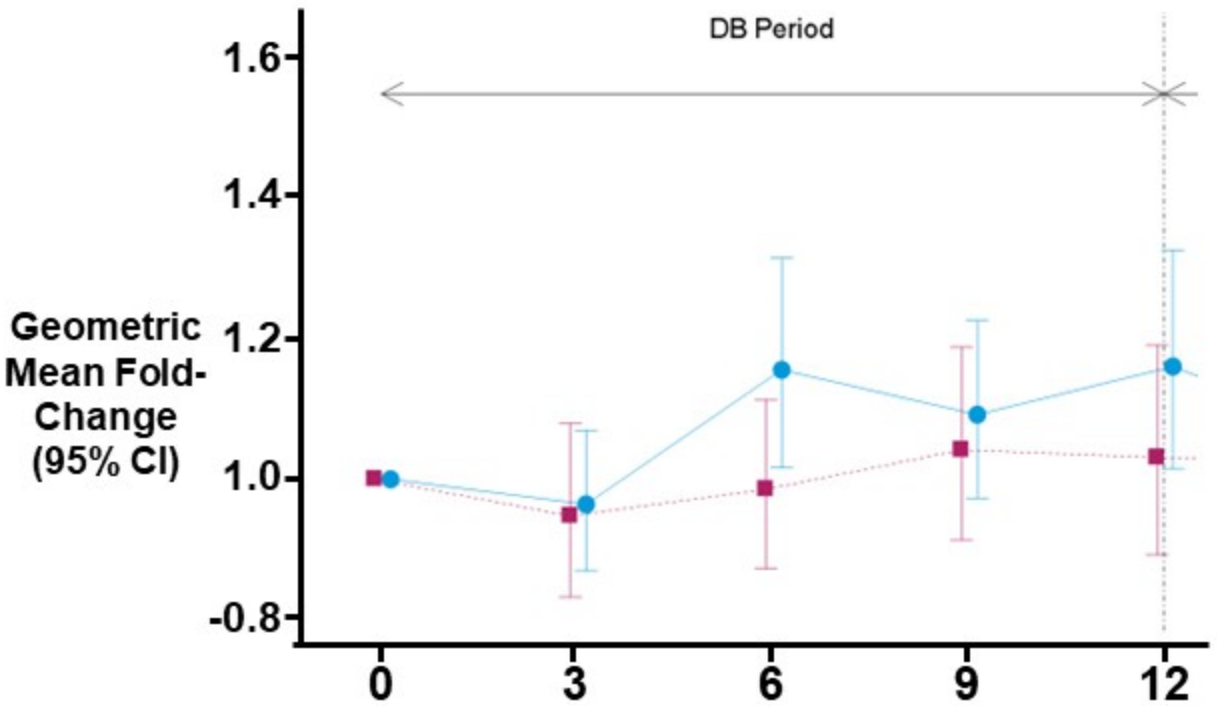
Figure 44: Cumulative Distribution Function of Change From Baseline in KCCQ-OS at Month 12 (Full Analysis Set)



Note: Figure presents observed KCCQ-OS data.
Note: Patients who had their Month 12 assessment on or after a serious COVID-19 adverse event are excluded from the analysis.
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

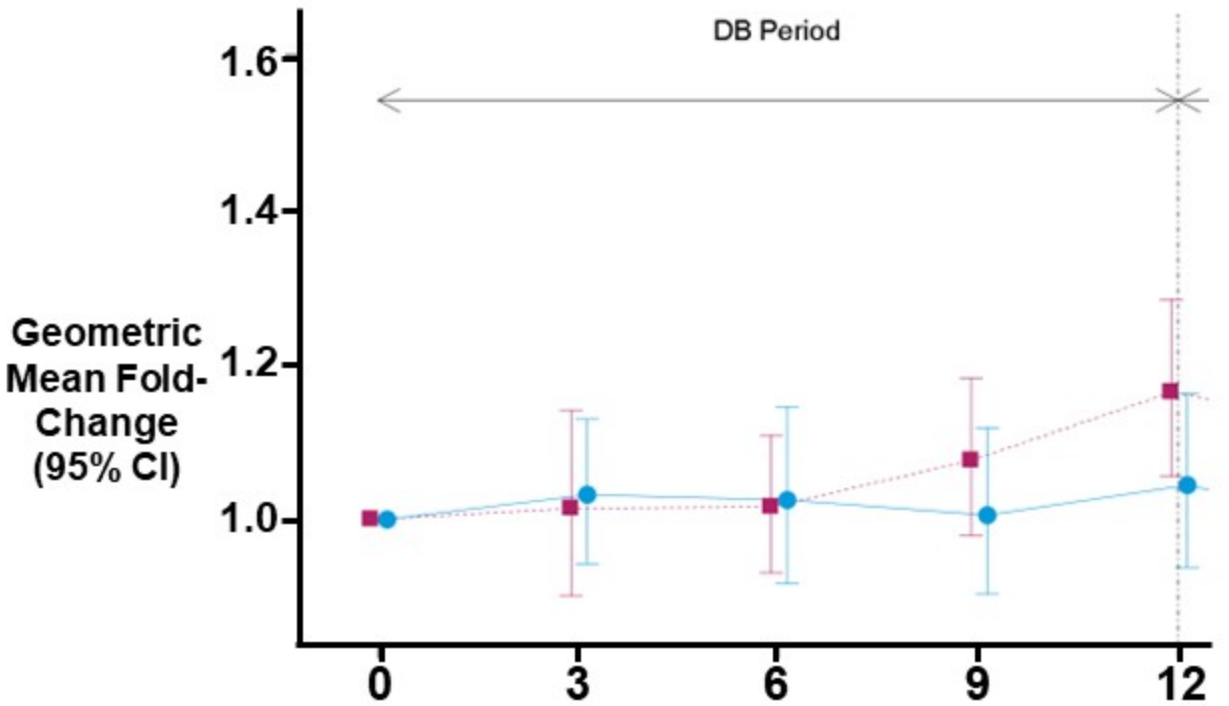
Biomarker DB Results Background Tafamidis

NT-proBNP



Patisiran	46	43	43	45	43
Placebo	45	41	42	43	41

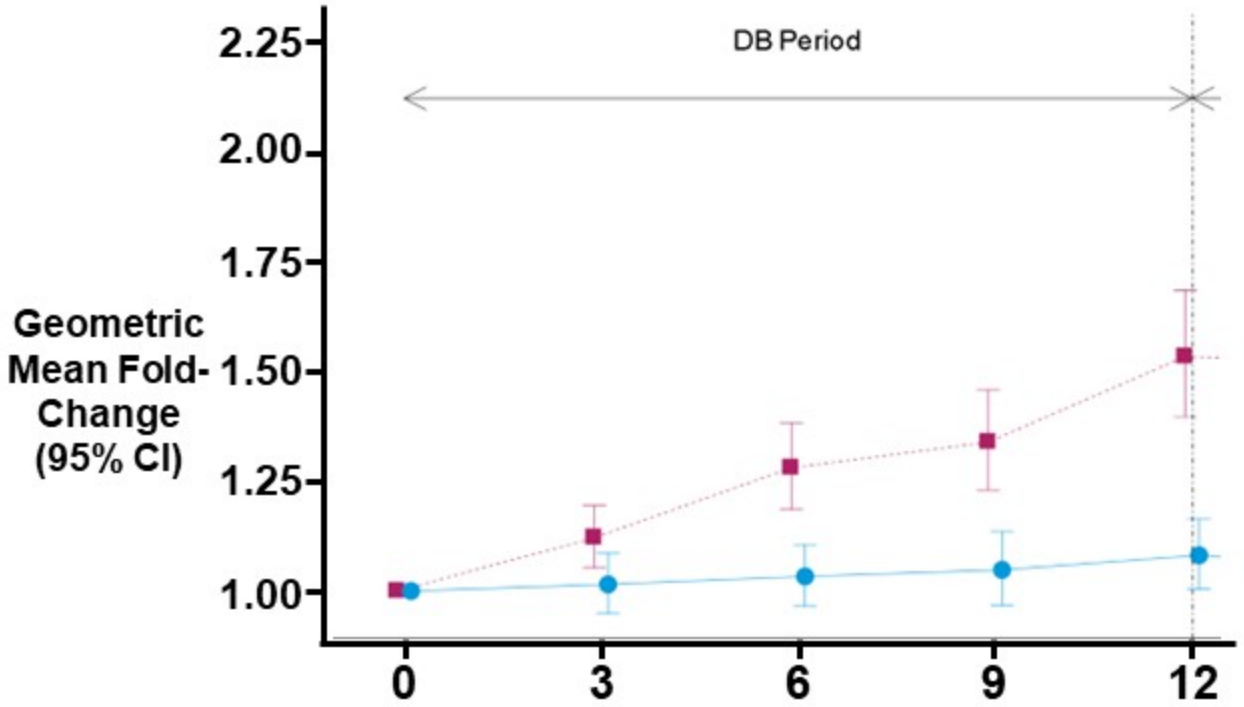
Troponin I



Patisiran	44	41	41	42	42
Placebo	45	41	43	41	41

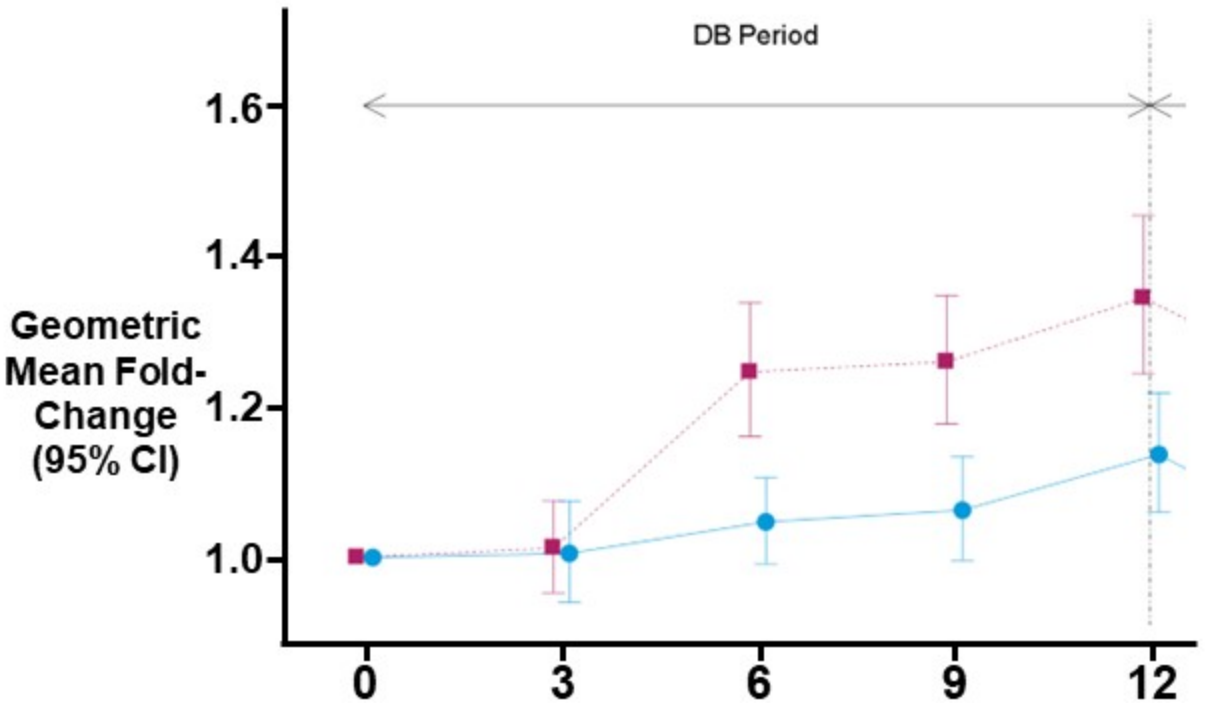
Biomarker DB Results Patisiran Monotherapy

NT-proBNP



Patisiran	135	128	126	124	124
Placebo	133	127	123	121	122

Troponin I



Patisiran	130	120	121	118	116
Placebo	127	117	119	115	114

Model Predicted TTR Reduction by Dose at Steady State: TTR Reduction Plateaus at Doses ≥ 0.3 mg/kg