Alnylam®

RNAi DATA NAVIGATOR:

Focus on Vutrisiran

EXPLORE

Welcome to the Alnylam RNAi Data Navigator

This is the home page, designed to give you an overview of the content in this document.
Return here from anywhere by pressing the **home** button at the bottom left of the page.

AMVUTTRA®
(vutrisiran)
INDICATIONS, SAFETY
INFORMATION,
AND PRESCRIBING
INFORMATION

Overview of ATTR-CM

- ATTR amyloidosis overview
- ATTR-CM pathophysiology
- ATTR-CM prognosis
- ATTR-CM identification and diagnosis

RNAi Therapeutics

- Rationale behind RNAi therapeutics
- How RNAi therapeutics work
- Features of RNAi therapeutics
- Overview of RNAi therapeutics, ASO therapeutics, and stabilizers

Vutrisiran, an RNAi Therapeutic in ATTR-CM

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- Cardiac biomarkers
- Functional capacity (6-MWT) and QOL (KCCQ-OS)
- Primary composite endpoint
- CV events
- All-cause mortality
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- Safety

Alnylam's Commitment

- Future of RNAi therapeutics
- Discover our RNAi pipeline
- TRITON-CM study design

Some sections have further data to explore. When this button appears active, tap to **find out more**.

6-MWT, 6-minute walk test; **ASO**, antisense oligonucleotide; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CV**, cardiovascular; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **QOL**, quality of life; **RNAi**, ribonucleic acid interference.

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INDICATIONS

AMVUTTRA® (vutrisiran) is indicated for the treatment of the:

- Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- Cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits

WARNINGS AND PRECAUTIONS

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

ADVERSE REACTIONS

In a study of patients with hATTR-PN, the most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

In a study of patients with ATTR-CM, no new safety issues were identified.

SCAN FOR AMVUTTRA FULL PRESCRIBING INFORMATION

6-MWT, 6-minute walk test; **ASO**, antisense oligonucleotide; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CV**, cardiovascular; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **QOL**, quality of life; **RNAi**, ribonucleic acid interference.

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ATTR-CM: Progressive Infiltrative Cardiomyopathy—With Pathogenic Misfolded TTR as the Root Cause

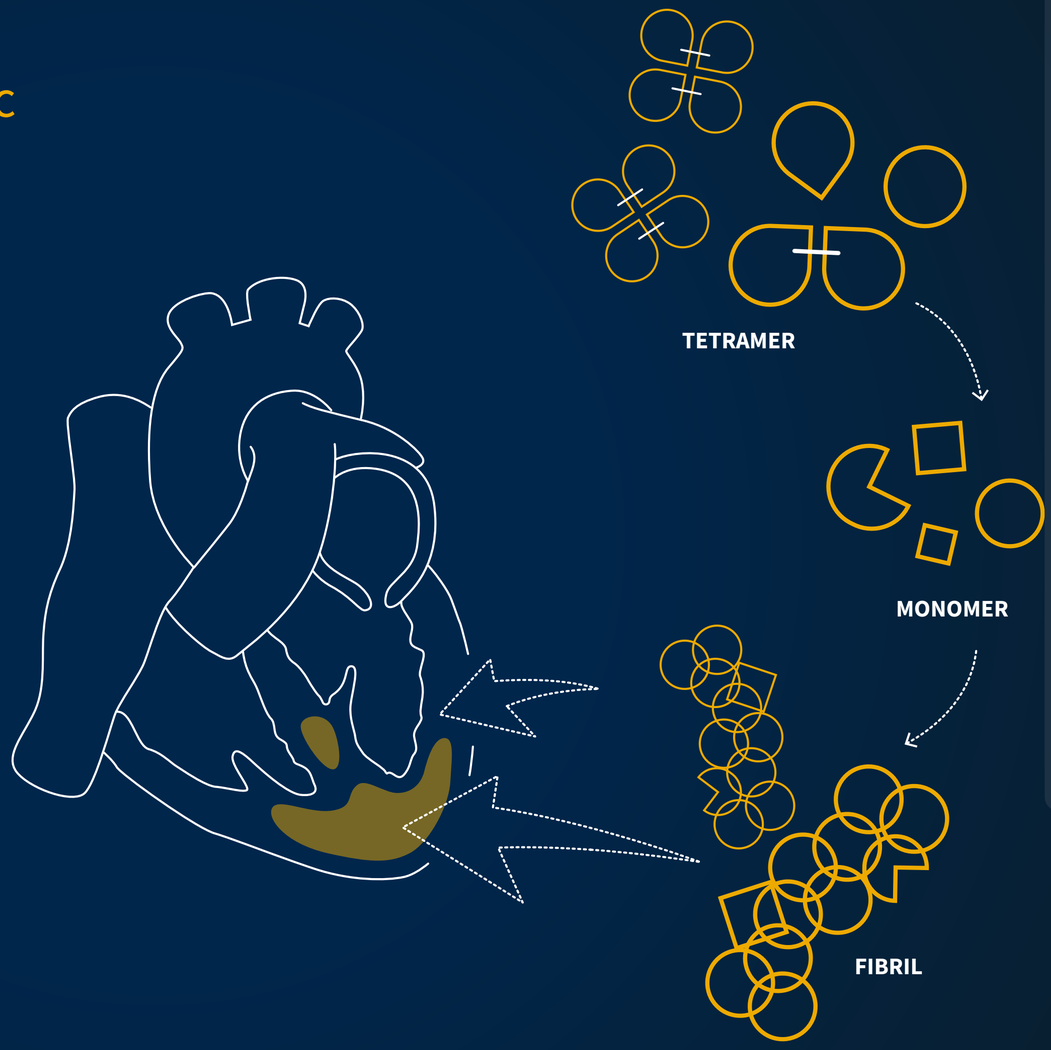
ATTR amyloidosis (hereditary or wild-type)[1,2] is an aggressive, disabling disease affecting multiple organ systems[3-7]

Damage is caused by extracellular deposition of TTR aggregates and amyloid fibrils in tissues in the body[7,8]

ATTR-CM is specific to amyloid deposition in the heart, leading to reduced overall survival, quality of life, and functional capacity[9-11]

ATTR-CM presentation is nonspecific and heterogeneous,[12,13] but awareness of high-risk populations and suspicious symptoms may help in early diagnosis[14-20]

ATTR Amyloidosis:
Mechanism of Disease Video



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

ABBREVIATIONS

ATTR, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **TTR**, transthyretin.

ATTR Amyloidosis: Mechanism of Disease

ATTR, transthyretin amyloidosis.

ATTR amyloidosis can be hereditary or wild-type

There are **2 different types** of ATTR amyloidosis[1,2]:

1. Hereditary ATTR amyloidosis (hATTR amyloidosis) occurs due to inherited *TTR* gene variants and runs in families
2. Wild-type ATTR amyloidosis (wtATTR amyloidosis) is nonhereditary, occurs spontaneously, and may be associated with aging

	hATTR amyloidosis	wtATTR amyloidosis
Genetics[3]	Autosomal dominant, at least 1 *TTR* gene variant is present	Nonhereditary, no *TTR* gene variant
US prevalence	~46 000[a]	~125 000[a]
Age at symptom onset[4]	>20 years (dependent on *TTR* gene variant)	>50 years
Male, %[4]	76-86	91-97
Median survival following diagnosis, years	4.7[5]	2.5-5.5[6-8]
Clinical manifestations[4]		
• Cardiac	Yes	Yes
• Peripheral nerves	Yes	Occasionally
• Autonomic nerves (including GI)	Yes	Rare
• Kidney	Yes	Rare
• Ophthalmologic	Vitreous deposition	Not prominent
• Musculoskeletal	Yes	Yes

[a]Information based on Alnylam modeling data.

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ABBREVIATIONS

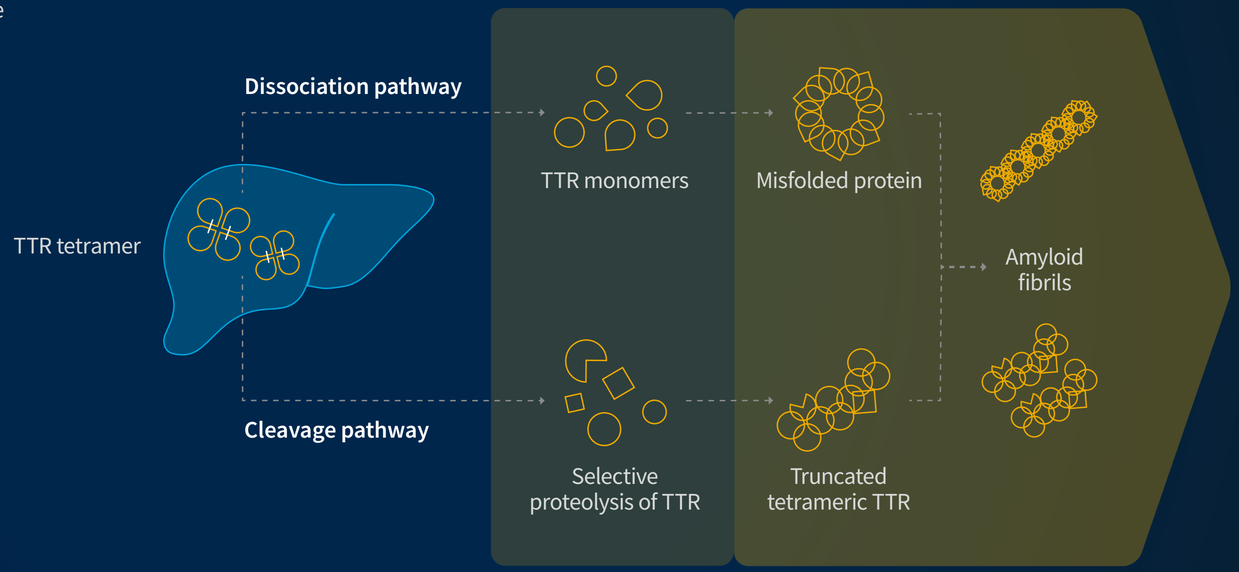
ATTR, transthyretin amyloidosis; **GI**, gastrointestinal; **hATTR**, hereditary transthyretin amyloidosis; **TTR**, transthyretin; **US**, United States of America; **wtATTR**, wild-type transthyretin amyloidosis.

ATTR amyloidosis pathophysiology is driven by TTR amyloid formation

TTR is a protein produced in the liver that normally circulates as a tetramer; its normal role is to bind and transport vitamin A and thyroxine (T4) around the body[1,2]

In ATTR amyloidosis, TTR tetramers can dissociate or are cleaved into monomers and other small fragments that misfold and aggregate to form amyloid fibrils[1-4]

TTR Amyloid Formation[3-5]



Damage occurs with extracellular deposition of aggregated TTR or TTR fibrils in tissues[3,4]

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ABBREVIATIONS

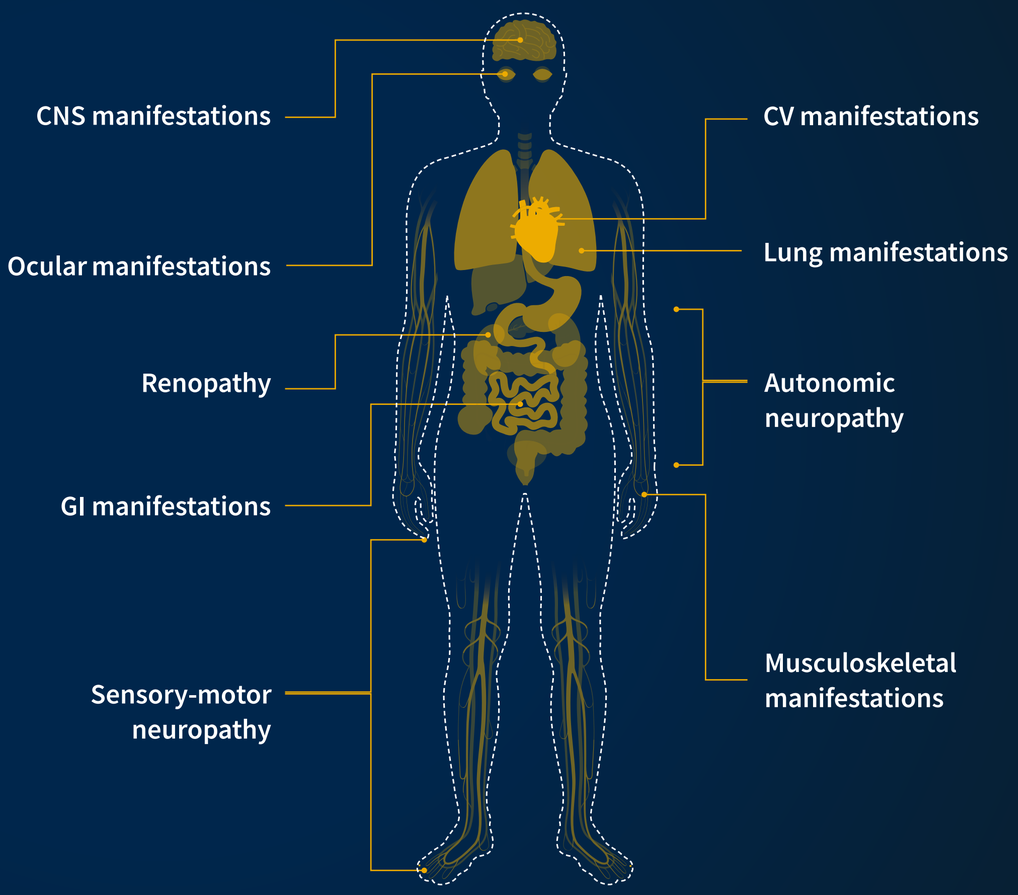
ATTR, transthyretin amyloidosis;
TTR, transthyretin.

Alnylam

ATTR amyloidosis is an aggressive, disabling disease affecting multiple organ systems,[1-5] caused when extracellular deposition of TTR aggregates and amyloid fibrils occurs in tissues in the body[5-8]

ATTR amyloidosis is a progressive, debilitating, and ultimately fatal multisystem disease caused by pathogenic misfolded transthyretin (TTR) protein accumulating as amyloid deposits in multiple organs and tissues in the body, including the nerves and heart[1-5,9]

Due to the diverse sites of amyloid deposition, ATTR amyloidosis often presents with multisystem involvement, including cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) or a mixed combination of both[5,10-12]



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ABBREVIATIONS

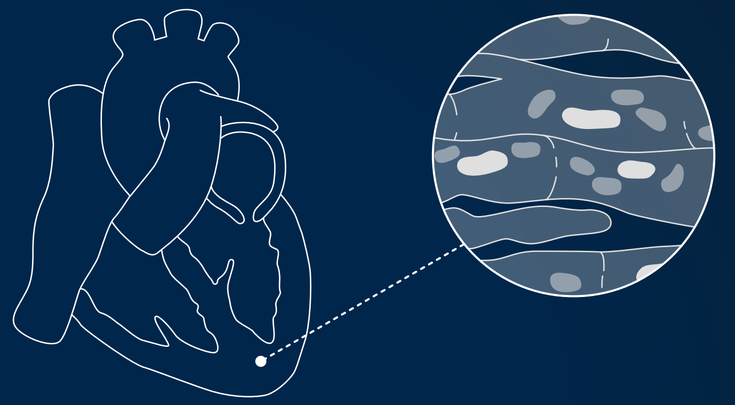
ATTR, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **ATTR-PN**, transthyretin amyloidosis with polyneuropathy; **CNS**, central nervous system; **CV**, cardiovascular; **GI**, gastrointestinal; **TTR**, transthyretin.

ATTR-CM is specific to amyloid deposition in the heart

In ATTR-CM, amyloid deposits accumulate in the cardiac tissue,[1] making the myocardium stiff and rigid and eventually affecting the heart's mechanical function[2]

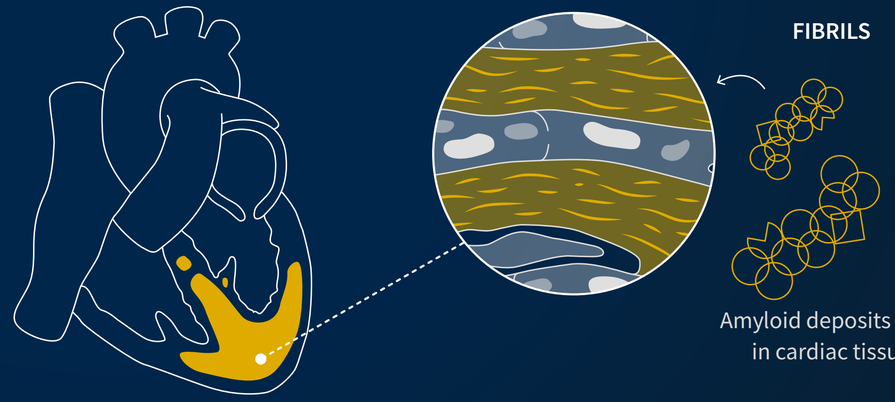
Patients commonly present with signs of heart failure, diastolic dysfunction, and arrhythmias[1]

Normal Heart



Healthy cardiac tissue

Amyloid Heart



Amyloid deposits form in cardiac tissue

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ABBREVIATION

ATTR-CM, transthyretin amyloidosis with cardiomyopathy.

Patients with ATTR-CM have reduced overall survival[1,2]

ATTR amyloidosis is rapidly progressive with significant morbidity and mortality[3-5]

In ATTR amyloidosis, cardiac involvement is a critical determinant of survival, with cardiac involvement at diagnosis associated with a poor prognosis[6-8]

Rising levels of NT-proBNP and troponin I are well-established prognostic biomarkers of increased mortality in ATTR-CM[9-11]

Life expectancy for patients who develop ATTR-CM is about 2 to 6 years from the point of diagnosis, if untreated[2,9,12]

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ABBREVIATIONS

ATTR, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **hATTR-CM**, hereditary transthyretin amyloidosis with cardiomyopathy; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **wtATTR-CM**, wild-type transthyretin amyloidosis with cardiomyopathy.

ATTR-CM has a profound impact on quality of life and functional capacity[1,2]

Untreated patients with ATTR-CM have been shown to experience a marked decline in functional capacity (decrease in 6-MWT), health status and quality of life (decline in KCCQ-OS score)[1]

REFERENCES

1. Nativi-Nicolau JN, et al. *Heart Fail Rev*. 2022;27:785-793.

2. Lane T, et al. *Circulation.* 2019;140:16-26.

ABBREVIATIONS

6-MWT, 6-minute walk test; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **hATTR-CM**, hereditary transthyretin amyloidosis with cardiomyopathy; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **SD**, standard deviation; **wtATTR-CM**, wild-type transthyretin amyloidosis with cardiomyopathy.

ATTR amyloidosis disease presentation is often nonspecific, heterogeneous, and multisystemic[1,2]

A range of manifestations can develop over many years[1]; symptoms may start more than 10 years before diagnosis[1,3,4]

In ATTR-CM, awareness of common early signs and symptoms in patients should raise suspicion of the disease[1,5]

Awareness of **high-risk populations** may also help in diagnosis[6-11]:

- Atrial fibrillation
- Heart failure with preserved ejection fraction
- LV hypertrophy
- Aortic stenosis
- Extracardiac musculoskeletal manifestations, including carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture

Common Signs and Symptoms of ATTR-CM[5]

- Discrepancy between LV thickness and QRS voltage
- Reduction in longitudinal strain with apical sparing
- Atrioventricular block, in the presence of increased LV wall thickness
- Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum, and RV free wall
- Marked extracellular volume expansion, abnormal nulling time for the myocardium, or diffuse late gadolinium enhancement on CMR
- Mild increase in troponin levels on repeated occasions
- Symptoms of polyneuropathy and/or dysautonomia
- History of bilateral carpal tunnel syndrome

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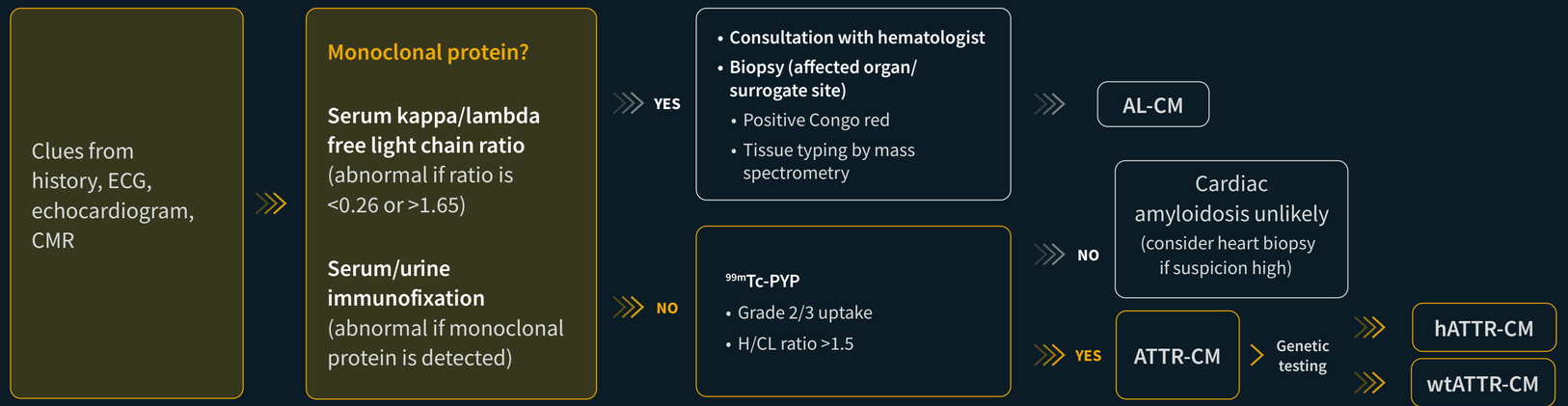
ATTR, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CMR**, cardiac magnetic resonance; **LV**, left ventricular; **RV**, right ventricular.

The ACC diagnostic algorithm assesses for suspected cardiac amyloidosis

Once early signs and symptoms have been identified, cardiac assessment tools can be used to diagnose ATTR amyloidosis[1-6]

A diagnosis of ATTR amyloidosis can be confirmed by tissue biopsy or scintigraphy if cardiac involvement is suspected[3-6]

ACC Diagnostic Algorithm for Suspected Cardiac Amyloidosis[5,6]



- Cardiac scintigraphy could be ordered simultaneously for efficiency but must be interpreted in the context of a negative monoclonal protein screen[5]
- If cardiac scintigraphy is not available, proceed with endomyocardial biopsy[6]
- Avoid false positives: SPECT imaging to exclude blood pool uptake[5]
- Avoid false negatives: consider biopsy if scan is negative/equivocal but clinical suspicion is high[5]

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ABBREVIATIONS

99mTc-PYP, 99m-technetium-pyrophosphate; **ACC**, American College of Cardiology; **AL-CM**, primary/amyloid light chain cardiac amyloidosis; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CMR**, cardiac magnetic resonance; **ECG**, electrocardiogram; **hATTR-CM**, hereditary transthyretin amyloidosis with cardiomyopathy; **H/CL**, heart/contralateral lung ratio; **SPECT**, single-photon emission computed tomography; **wtATTR-CM**, wild-type transthyretin amyloidosis with cardiomyopathy.

HCPs and patients may have different expectations from ATTR-CM therapy[1]

Disease-modifying approaches for ATTR-CM aim to intervene at various stages of the amyloidogenic cascade[2]

Approaches with approved therapies and investigational agents include suppressing hepatic production of TTR through gene silencing, stabilizing the TTR tetramer to prevent dissociation, using anti-TTR antibodies, inhibiting oligomer aggregation, and promoting the breakdown of existing amyloid deposits[2]

ATTR-CM therapies aim to slow disease progression, preserve functional capacity and quality of life, and improve patient outcomes[2]

Primary Treatment Objectives in ATTR-CM[1]

HCPs[1]

- Reduce CV-related mortality and minimize HF worsening
- Preserve both quality of life and functional capacity for patients

Patients[1]

- ATTR-CM results in significant limitations in daily function and quality of life, so maintaining or improving outcomes on functional assessments and patient-reported measures, such as 6-MWT and KCCQ, is typically important for patients

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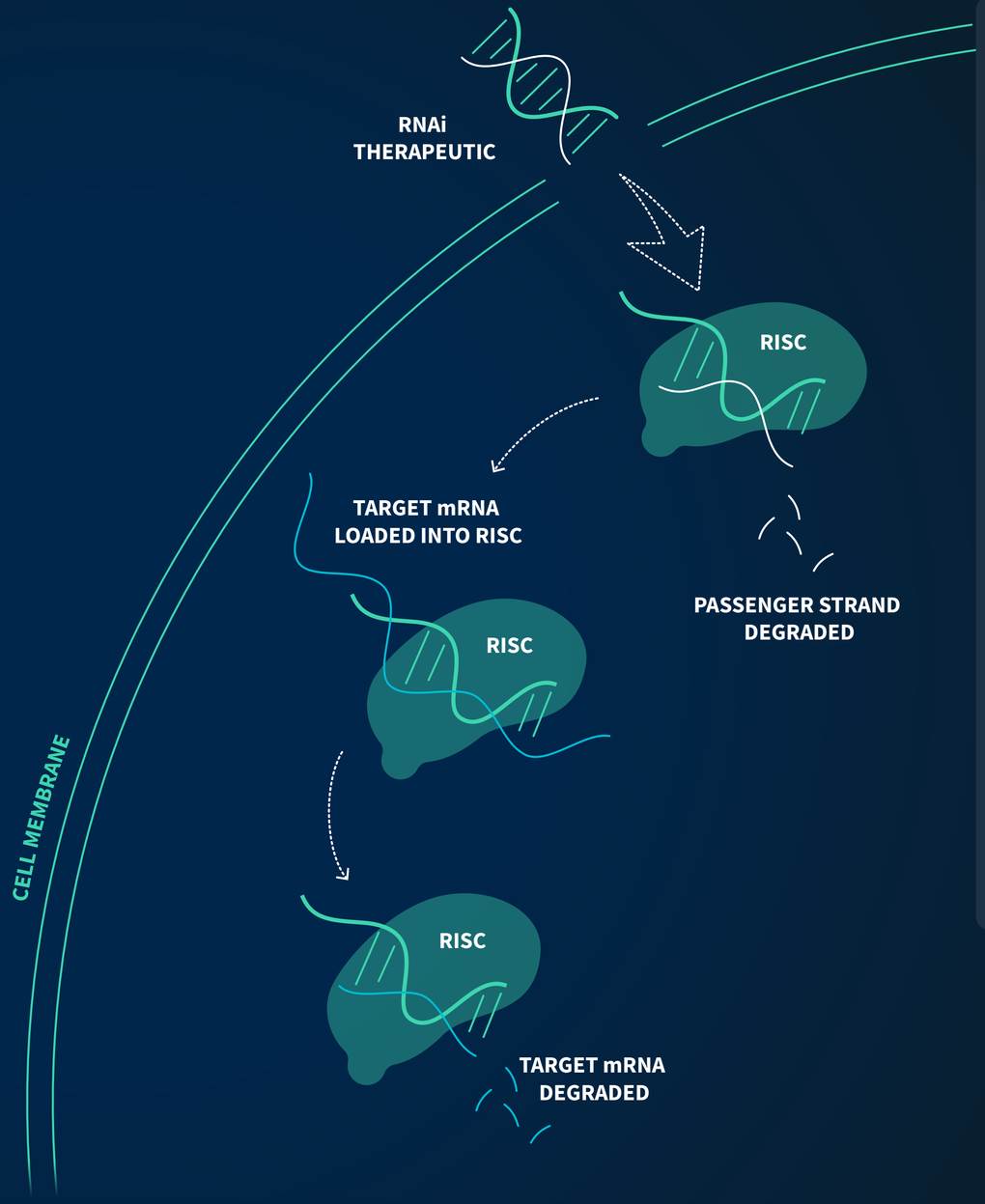
ABBREVIATIONS

6-MWT, 6-minute walk test; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CV**, cardiovascular; **HCP**, healthcare professional; **HF**, heart failure; **KCCQ**, Kansas City Cardiomyopathy Questionnaire; **TTR**, transthyretin.

Silencing the Disease Process:
Targeting the Underlying Pathology

RNAi therapeutics harness a natural process of regulating gene expression[1-7] causing rapid, targeted, and sustained decreases in the levels of disease-causing proteins[1,8-11]

As short, double-stranded molecules, RNAi therapeutics are highly selective for a specific target mRNA,[1,8,9,12-19] and have a prolonged duration of action allowing for less frequent administration[12,20,21]



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ABBREVIATIONS

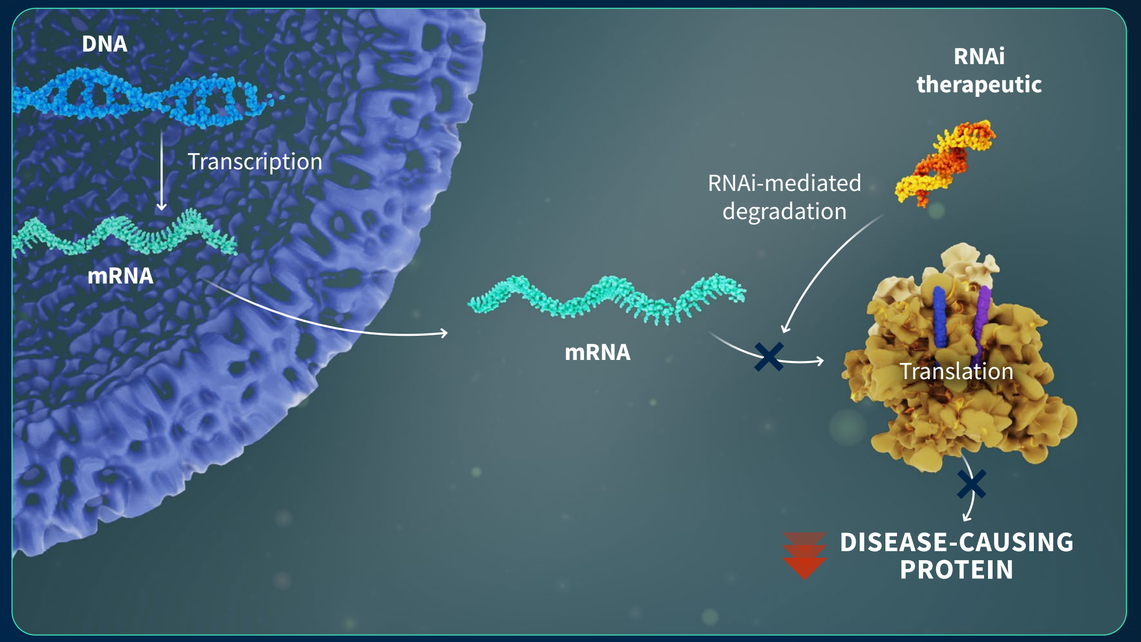
mRNA, messenger ribonucleic acid; **RISC**, ribonucleic acid-induced silencing complex; **RNAi**, ribonucleic acid interference.

RNAi came from the application of Nobel Prize-winning science

Fire and Mello received the Nobel Prize in 2006 for the discovery of RNA interference (RNAi), an endogenous mechanism of gene silencing[1-4]

RNAi therapeutics leverage this natural biological mechanism that silences gene expression by reducing the production of specific disease-causing proteins[1,5-8]

Diseases that result from the accumulation of disease-associated proteins warrant a targeted therapeutic approach that suppresses production of the protein at its source[1,2]



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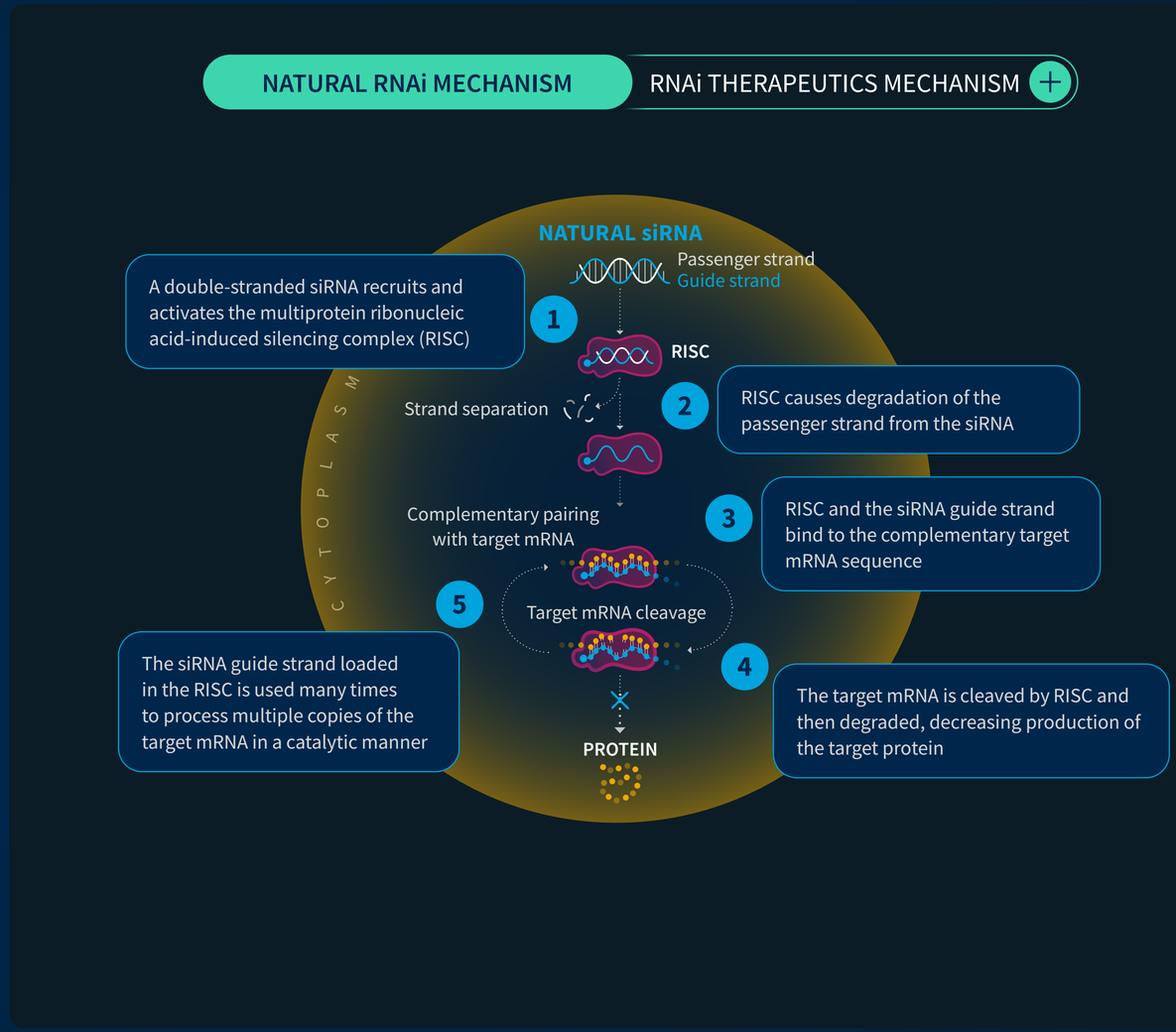
ABBREVIATIONS

DNA, deoxyribonucleic acid; **mRNA**, messenger ribonucleic acid; **RNA**, ribonucleic acid; **RNAi**, ribonucleic acid interference.

RNAi therapeutics harness a natural biological mechanism that regulates gene expression[1-7]

Since the discovery of RNAi, research has led to the development of several approved RNAi therapeutics to treat a variety of diseases[8]



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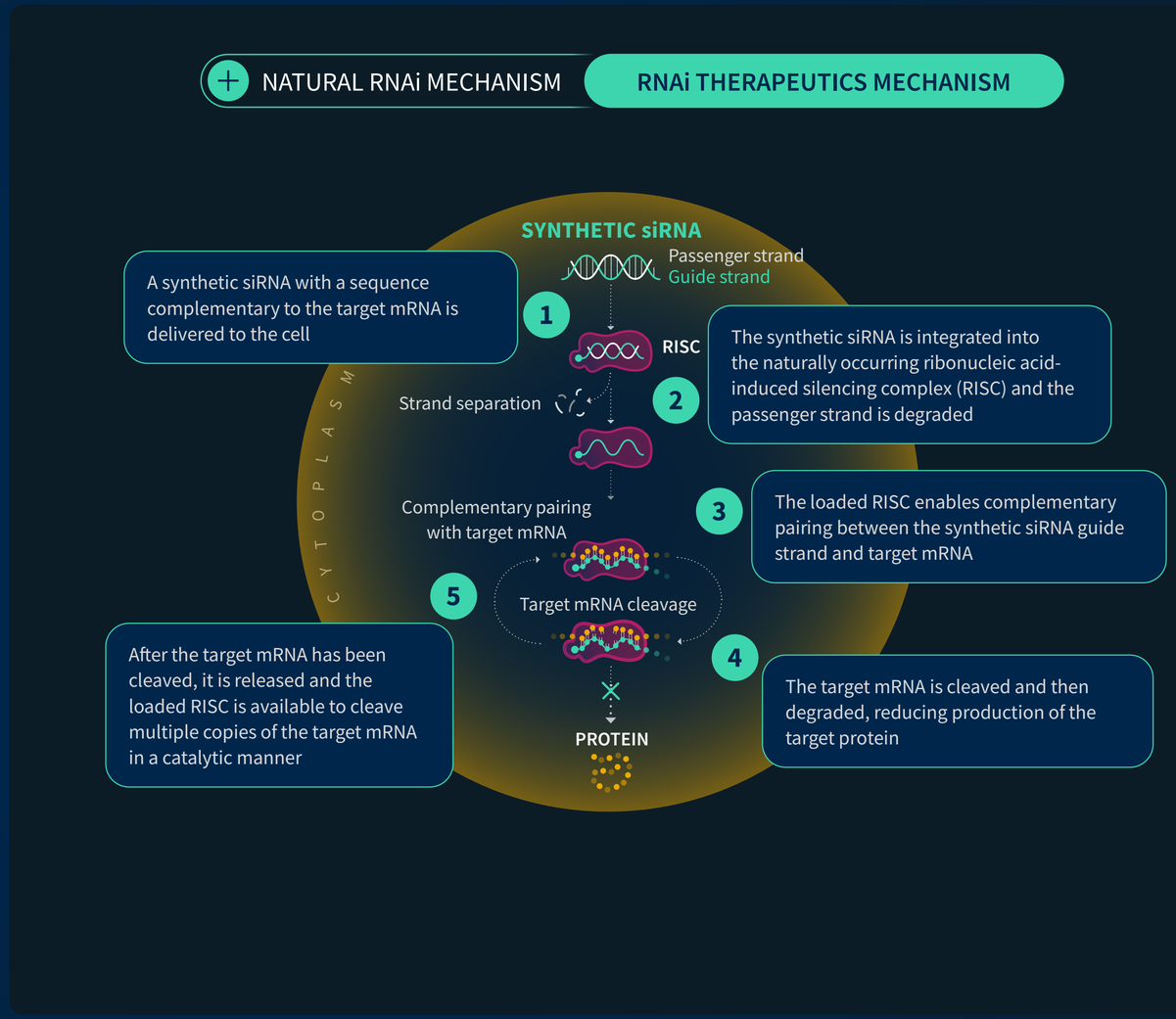

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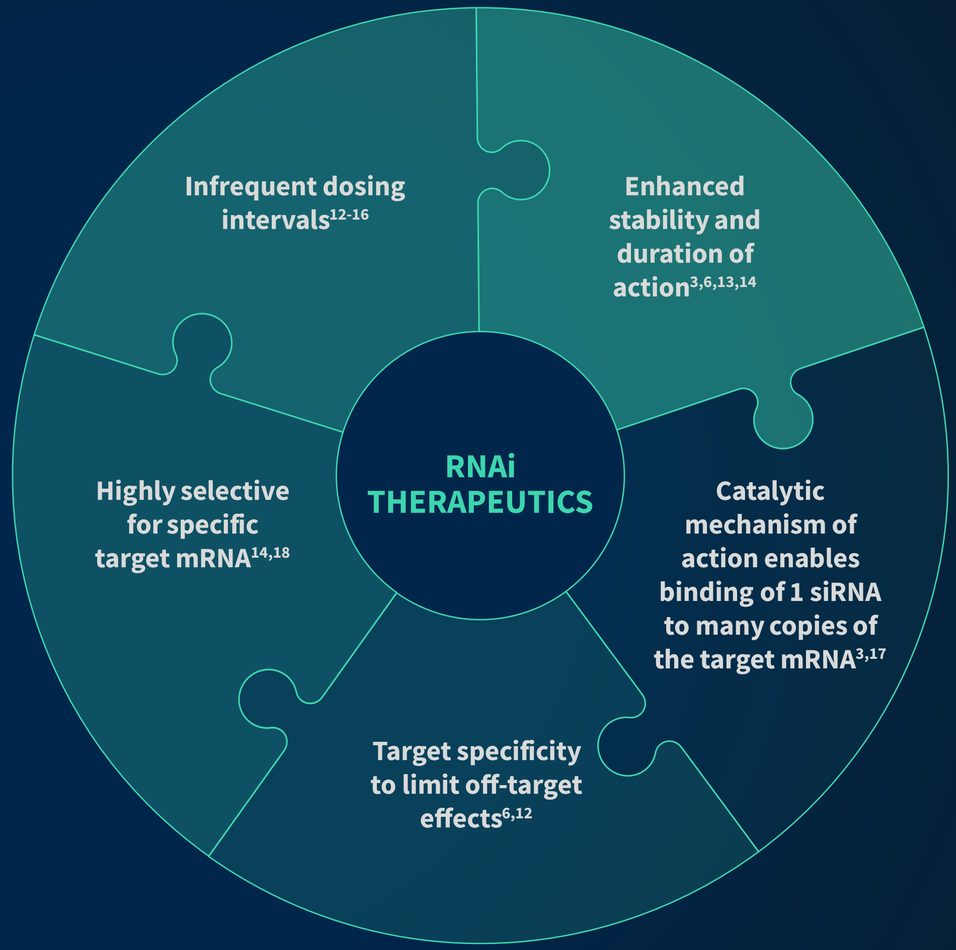
Alnylam

RNAi therapeutics are short, double-stranded molecules, highly selective for a specific target mRNA[1-11]

RNAi therapeutics are designed for targeted delivery to the organ where the protein is produced[1-11]



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ABBREVIATIONS

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Alnylam

RNAi therapeutics are made up of synthetic siRNAs and specific delivery systems that enable uptake and delivery to the source of the target protein[1-3]

Modifications to siRNAs provide enhanced stability and prolonged duration of action, while compound properties impact dosing frequency and support infrequent dosing intervals[1-3]

Delivery Systems Developed for Specific Organ Targeting[1,3-6]

	Lipid nanoparticles (LNPs)	GalNAc–siRNA conjugates	C16–siRNA conjugates (investigational)[a]
Delivery mechanism	Synthetic siRNAs encapsulated in LNPs[3,4]	Metabolically stabilized synthetic siRNA conjugated to a GalNAc ligand[3,5]	C16 lipid chains attached to siRNA provide lipophilicity to interact with cell membrane proteins[6]
Target organ delivery	Natural pathway involving affinity for ApoE, a ligand for LDL receptors expressed on hepatocytes[3]	Natural pathway involving the GalNAc ligand binding to the ASGPR on hepatocytes[3,4]	Potential uptake into multiple cell types, including in the CNS, eye, and lung[6]
Current mode of administration	IV[7]	SC[7]	IT[8]
Dosing frequency	Every 3 weeks[9]	Monthly to biannually[9]	Potential for infrequent dosing[6]

[a]C16 conjugates are used in investigational RNAi therapeutics currently in phase 1 or 2 development, such as mivelsiran and ALN-HTT02.[8,10]

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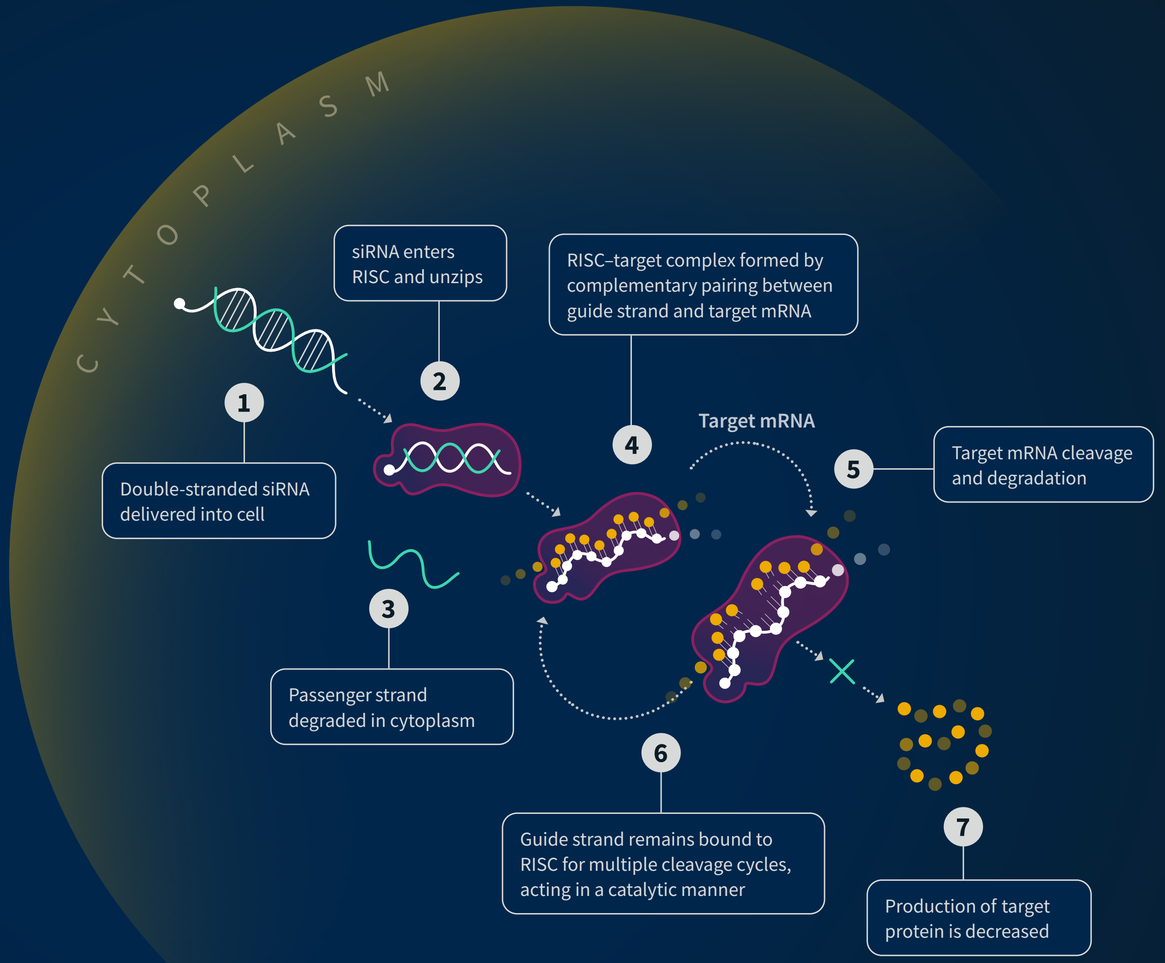
ABBREVIATIONS

ApoE, apolipoprotein E; **ASGPR**, asialoglycoprotein receptor; **CNS**, central nervous system; **GalNAc**, *N*-acetylgalactosamine; **IT**, intrathecal; **IV**, intravenous; **LDL**, low-density lipoprotein; **LNP**, lipid nanoparticle; **RNAi**, ribonucleic acid interference; **SC**, subcutaneous; **siRNA**, small interfering ribonucleic acid.

RNAi therapeutics leverage the natural RNAi mechanism to decrease production of the target protein and silence gene expression[1-4]

A single siRNA bound to RISC can cleave multiple mRNAs during its lifetime,[1-3,5] and it can cause a rapid, targeted, and sustained decrease in the levels of disease-causing protein[1-3,6,7]



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ABBREVIATIONS

mRNA, messenger ribonucleic acid; **RISC**, ribonucleic acid-induced silencing complex; **RNAi**, ribonucleic acid interference; **siRNA**, small interfering ribonucleic acid.

RNAi, ASO, and TTR stabilizer therapies are distinct, varying by mechanism and site of action, administration, and pharmacology[1-4]

TTR silencers (RNAi and ASO therapeutics) reduce *TTR* gene expression and suppress TTR protein synthesis in the liver[1,4-7]

TTR stabilizers bind to TTR tetramers in the serum, preventing their dissociation[1,4]

No head-to-head studies have been conducted to compare the clinical profiles of these therapeutics

***TTR* gene expressed in liver**

TTR tetramer

TTR monomers and fragments

Amyloid fibrils

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ABBREVIATIONS

ASO, antisense oligonucleotide; **RNAi**, ribonucleic acid interference; **TTR**, transthyretin.

HELIOS-B Phase 3 Trial: Vutrisiran Demonstrated Positive Impact vs Placebo in a Contemporary ATTR-CM Patient Population Representative of Clinical Practice Today

SILENCING THE DISEASE PROCESS[1,2]

Vutrisiran achieved sustained and rapid knockdown of serum TTR

CARDIAC STRUCTURE AND FUNCTION[3]

Cardiac structural and functional decline was slowed, halted, or reversed as measured on echocardiography

CARDIAC BIOMARKERS[4]

Relative stability of NT-proBNP and troponin I were maintained

FUNCTIONAL CAPACITY AND QOL[1,5]

Positive effects on functional capacity (6-MWT), patient-reported health status and health-related QOL (KCCQ-OS), and heart failure symptom severity (NYHA)

CLINICAL EVENTS[1,6,7]

- Reduced composite of all-cause mortality and recurrent CV events vs placebo (primary endpoint)
- Fewer CV hospitalizations and urgent heart failure visits
- Reduced risk of death from any cause
- Overall mortality in the vutrisiran arm approached the age-expected mortality for an average, similarly aged, person without ATTR-CM[8]

SAFETY PROFILE[1]

Vutrisiran showed a safety and tolerability profile consistent with previous studies. Due to possible effects on vitamin A transport, patients were advised to take the recommended daily allowance of vitamin A

HELIOS-B evaluated vutrisiran in two populations: the overall population (all patients) and a monotherapy population[a] (~60%) who initiated vutrisiran as first-line therapy without baseline tafamidis. The monotherapy population demonstrated comparable or greater treatment effects across most outcomes relative to the overall population[1,5,6]

[a]Approximately 98% of patients in the monotherapy population were treatment-naïve to stabilizer therapy; the 2% of patients who previously received a stabilizer all underwent a washout period of ≥30 days before trial dosing.[2]

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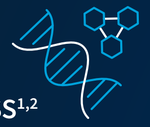
ABBREVIATIONS

6-MWT, 6-minute walk test; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CV**, cardiovascular; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **NYHA**, New York Heart Association; **QOL**, quality of life; **TTR**, transthyretin.

HELIOS-B Phase 3 Trial: Vutrisiran Demonstrated Positive Impact vs Placebo in a Contemporary ATTR-CM Patient Population Representative of Clinical Practice Today



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INDICATIONS

AMVUTTRA® (vutrisiran) is indicated for the treatment of the:

- Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- Cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits

WARNINGS AND PRECAUTIONS

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

ADVERSE REACTIONS

In a study of patients with hATTR-PN, the most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

In a study of patients with ATTR-CM, no new safety issues were identified.

SCAN FOR AMVUTTRA FULL PRESCRIBING INFORMATION

HELIOS-A investigated vutrisiran in hATTR-PN

HELIOS-A[1] | HELIOS-B[2]

The completed study supported the approval of vutrisiran for hATTR-PN

Study Design

Global, randomized, open-label, phase 3 study

Study Regimen

Vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg IV every 3 weeks for 18 months or external placebo group from APOLLO

Patient Population

Patients with a diagnosis of hATTR amyloidosis with a documented *TTR* variant and neuropathy

3:1 RANDOMIZATION

- **Vutrisiran** 25 mg SC q3m (n=122)
- **Patisiran (reference arm)** 0.3 mg/kg IV q3w (n=42)
- **External placebo group** from APOLLO (n=77)

Primary endpoint

Change in mNIS+7 from baseline at 9 months

Select secondary endpoints[b]

Change from baseline in:

- Norfolk QOL-DN
- mNIS+7
- 10-MWT
- mBMI
- R-ODS
- Non-inferiority in serum TTR level percentage reduction compared with the within-study patisiran group

Safety

Assessment of AEs

[a]Study patients were 18-85 years of age and had a diagnosis of hATTR-PN caused by any *TTR* variant, a PND score ≤IIIB, a NIS of 5-130 and a KPS score ≥60%, and they were permitted to have previously used TTR stabilizers.
[b]Endpoints were assessed at 9 and 18 months.

REFERENCES

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2. Fontana M, et al. *N Engl J Med.* 2025;392:33-44.

ABBREVIATIONS

6-MWT, 6-minute walk test; **10-MWT**, 10-meter walk test; **AE**, adverse event; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CV**, cardiovascular; **EQ-5D-5L**, EuroQol 5-Dimension 5-Level; **hATTR**, hereditary transthyretin amyloidosis; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **HF**, heart failure; **IV**, intravenous; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **KPS**, Karnofsky Performance Status; **mBMI**, modified body mass index; **mNIS+7**, modified Neuropathy Impairment Score +7; **NIS**, Neuropathy Impairment Score; **Norfolk QOL-DN**, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **NYHA**, New York Heart Association; **PND**, polyneuropathy disability; **q3m**, every 3 months; **q3w**, every 3 weeks; **R-ODS**, Rasch-built Overall Disability Scale; **SC**, subcutaneous; **TTR**, transthyretin.

HELIOS-B was a phase 3 study of vutrisiran in ATTR-CM

HELIOS-A[1] | **HELIOS-B[2]**

Study Design

International, multicenter, double-blind, placebo-controlled, randomized, phase 3 study

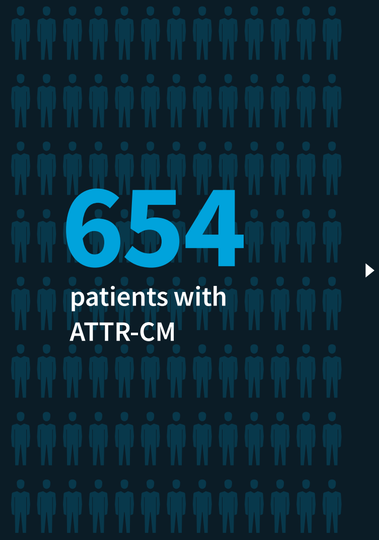
Study Regimen

Vutrisiran 25 mg or placebo SC every 3 months for up to 36 months

Patient Population

Patients with ATTR amyloidosis with confirmed cardiomyopathy (wild-type or any *TTR* variant) and medical history of HF[a]

Screening period → Double-blind period (33-36 months)



1:1 RANDOMIZATION[b]

Vutrisiran
25 mg SC q3m (n=326)

Placebo
SC q3m (n=328)

Primary endpoint

Composite outcome of death from any cause and recurrent CV events[c] during the double-blind period (Months 33-36)

Secondary endpoints

- Change from baseline to Month 30 in 6-MWT distance
- Change from baseline to Month 30 in KCCQ-OS score
- All-cause mortality up to Month 42[d]
- Change from baseline to Month 30 in NYHA class

Select exploratory and pharmacodynamic endpoints (assessed at Month 30)

Change from baseline in:

- Levels of NT-proBNP
- Levels of troponin I
- Peak longitudinal strain
- EQ-5D-5L index
- Levels of serum TTR

Safety

Assessment of AEs

Select exclusion criteria

- NYHA class IV HF
- NYHA class III HF and considered high risk based on prespecified criteria
- PND score IIIA, IIIB, or IV at the screening visit
- Received prior TTR-lowering treatment

[a]A clinical history of HF was required, with at least 1 previous hospitalization for HF or clinical evidence of HF, with signs and symptoms of volume overload or elevated intracardiac pressures warranting diuretic treatment.
[b]Randomization was stratified according to tafamidis use at baseline (yes vs no), ATTR amyloidosis disease type (variant vs wild-type), and NYHA class and age at baseline (NYHA class I or II and age <75 years vs all others). [c]CV hospitalizations or urgent HF visits.
[d]This included up to 6 months of data from the open-label extension, in which all remaining patients in the placebo arm were eligible to receive vutrisiran.

REFERENCES

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HELIOS-B was designed to enroll a contemporary patient population representative of those commonly seen in clinical practice today[1]

Patients were randomly assigned in a 1:1 ratio to receive vutrisiran 25 mg or placebo subcutaneously every 12 weeks for up to 36 months

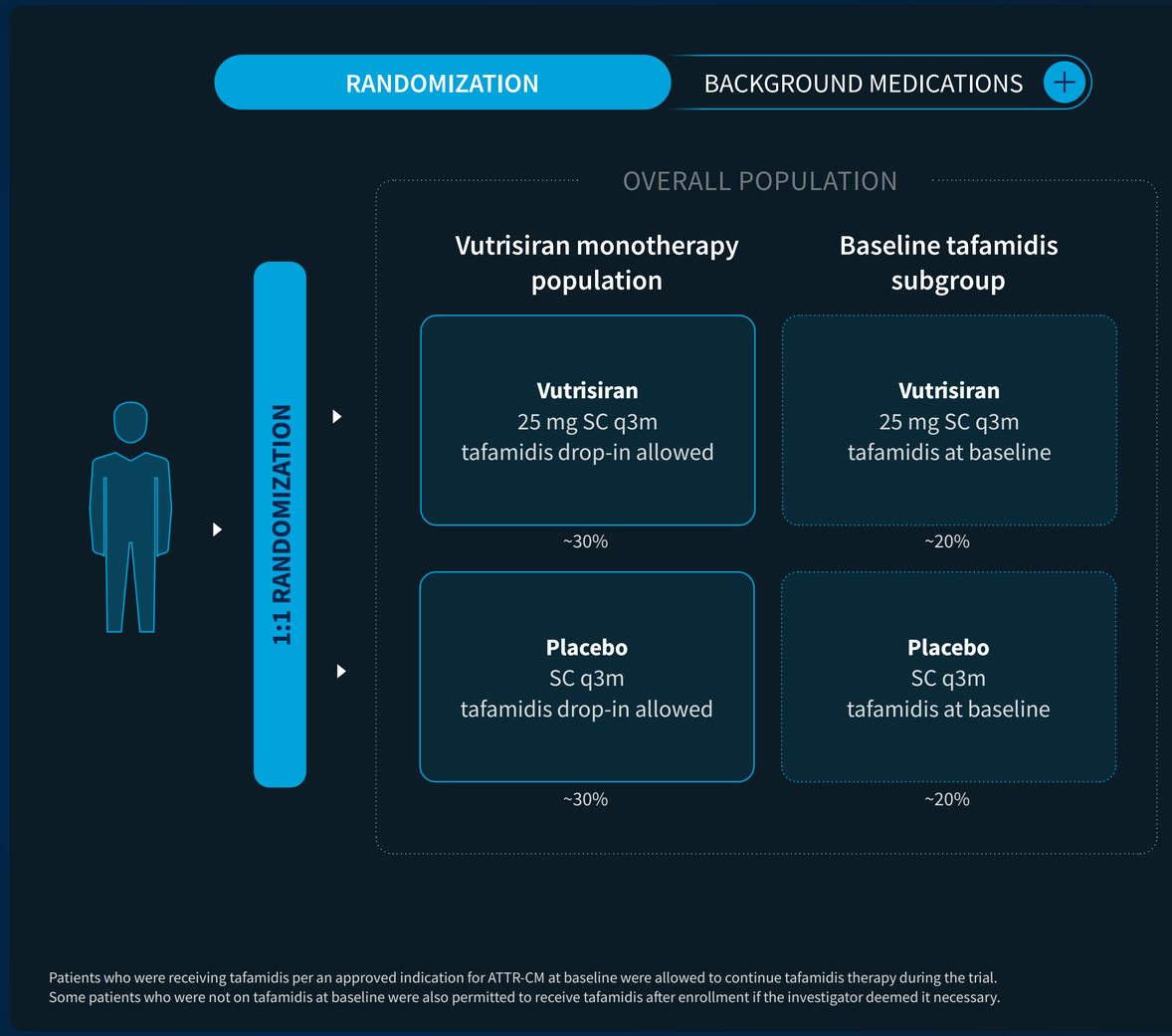
Randomization was stratified according to tafamidis use at baseline (yes vs no)

The HELIOS-B monotherapy population reflects first-line treatment[a]

Patients were at an earlier and less severe stage of disease than reported in previous trials, and had substantial use of background medication at baseline

This approach allowed for assessment of today's patients, evaluating the effects of vutrisiran when taken as a first-line monotherapy or with concurrent tafamidis

[a]Approximately 98% of patients in the monotherapy population were treatment-naïve to stabilizer therapy; the 2% of patients who had previously received a stabilizer all underwent a washout period of ≥30 days before trial dosing.[2]



Patients who were receiving tafamidis per an approved indication for ATTR-CM at baseline were allowed to continue tafamidis therapy during the trial. Some patients who were not on tafamidis at baseline were also permitted to receive tafamidis after enrollment if the investigator deemed it necessary.

REFERENCES

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

2. Alnylam Pharmaceuticals. Data on file.

ABBREVIATIONS

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; **q3m**, once every 3 months; **SC**, subcutaneous; **SGLT2**, sodium-glucose cotransporter 2.

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RANDOMIZATION | **BACKGROUND MEDICATIONS**

Substantial Use of Effective Background Medications

Tafamidis

- Baseline ~40% in both treatment arms
- Drop-in among monotherapy population during double-blind period was ~21% and ~22% for placebo and vutrisiran, respectively

SGLT2 inhibitors

- Baseline ~3% in both treatment arms
- Drop-in during double-blind period was ~35% and ~31% for placebo and vutrisiran, respectively

Diuretics

- Baseline ~80% in both treatment arms
- Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

[a]Approximately 98% of patients in the monotherapy population were treatment-naïve to stabilizer therapy; the 2% of patients who previously received a stabilizer all underwent a washout period of ≥30 days before trial dosing.[2]

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1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

2. Alnylam Pharmaceuticals. Data on file.

ABBREVIATIONS

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; **q3m**, once every 3 months; **SC**, subcutaneous; **SGLT2**, sodium-glucose cotransporter 2.

HELIOS-B baseline characteristics were similar between groups[1]

PATIENT DEMOGRAPHICS | PATIENT CLINICAL CHARACTERISTICS

Patient Demographics at Baseline

CHARACTERISTIC	MONOTHERAPY POPULATION		OVERALL POPULATION	
	Vutrisiran (n=196)	**Placebo** (n=199)	**Vutrisiran** (n=326)	**Placebo** (n=328)
Age at randomization, median (range), years	**77.5** (46-85)	**76.0** (53-85)	**77.0** (45-85)	**76.0** (46-85)
Male sex, n (%)	**178** (91)	**183** (92)	**299** (92)	**306** (93)
Race, n (%)				
White	**169** (86)	**169** (85)	**277** (85)	**275** (84)
Asian	**12** (6)	**15** (8)	**18** (6)	**19** (6)
Black	**10** (5)	**11** (6)	**23** (7)	**24** (7)
Other/not reported	**5** (3)	**4** (2)	**8** (2)	**10** (3)
wtATTR amyloidosis genotype, n (%)	**173** (88)	**174** (87)	**289** (89)	**289** (88)
Time since diagnosis of ATTR amyloidosis, median (range), years	**0.50** (0-8.3)	**0.63** (0-6.2)	**0.86** (0-11.1)	**1.03** (0-10.8)
Tafamidis use at baseline, n (%)	–	–	**130** (40)	**129** (39)
Duration of tafamidis use before start of trial, median (range), months	–	–	**9.2** (1.1-65.3)	**11.3** (1.1-65.5)

REFERENCE

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

ABBREVIATIONS

6-MWT, 6-minute walk test; **ATTR**, transthyretin amyloidosis; **BMI**, body mass index; **eGFR**, estimated glomerular filtration rate; **IQR**, interquartile range; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire–Overall Summary; **mBMI**, modified body mass index; **NAC**, National Amyloidosis Centre; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **NYHA**, New York Heart Association; **SD**, standard deviation; **wtATTR**, wild-type transthyretin amyloidosis.

Alnylam

HELIOS-B baseline characteristics were similar between groups[1]

PATIENT DEMOGRAPHICS | PATIENT CLINICAL CHARACTERISTICS

Patient Clinical Characteristics at Baseline

CHARACTERISTIC	MONOTHERAPY POPULATION		OVERALL POPULATION	
	Vutrisiran (n=196)	**Placebo** (n=199)	**Vutrisiran** (n=326)	**Placebo** (n=328)
NYHA class, n (%)				
I	**15** (8)	**12** (6)	**49** (15)	**35** (11)
II	**172** (88)	**169** (85)	**250** (77)	**258** (79)
III	**9** (5)	**18** (9)	**27** (8)	**35** (11)
NAC ATTR amyloidosis stage, n (%)[a]				
I	**113** (58)	**138** (69)	**208** (64)	**229** (70)
II	**68** (35)	**55** (28)	**100** (31)	**87** (27)
III	**15** (8)	**6** (3)	**18** (6)	**12** (4)
6-MWT, mean (SD), m[b]	**362.7** (102.7)	**372.8** (98.1)	**372.0** (103.7)	**377.1** (96.3)
KCCQ-OS, mean (SD), points[c]	**70.3** (20.2)	**69.9** (20.8)	**73.0** (19.4)	**72.3** (19.9)
Laboratory parameters, median (IQR)				
NT-proBNP level, pg/mL	**2402** (1322-3868)	**1865** (1067-3099)	**2021** (1138-3312)	**1801** (1042-3082)
High-sensitivity troponin I level, pg/mL	**76.3** (48.4-138.8)	**62.2** (39.2-105.6)	**71.9** (44.9-115.9)	**65.2** (41.1-105.5)
mBMI[d]	**1188.7** (1087.3-1335.2)	**1206.1** (1094.9-1324.1)	**1183.8** (1082.7-1306.1)	**1210.9** (1098.5-1333.5)
eGFR, mL/min/1.73 m^2	**64** (50-81)	**65** (54-81)	**64** (50-81)	**65** (53-81)
Creatinine, µmol/L	**97** (80-124)	**97** (80-106)	**97** (80-124)	**97** (80-115)
Coexisting conditions, n (%)				
Hypertension	**107** (55)	**111** (56)	**185** (57)	**187** (57)
Diabetes mellitus	**35** (18)	**39** (20)	**56** (17)	**55** (17)
Atrial fibrillation	**115** (59)	**111** (56)	**197** (60)	**196** (60)

[a]NAC stages are determined on the basis of the levels of the serum biomarkers NT-proBNP and eGFR. [b]6-MWT values were assessed at baseline in 325 patients in the vutrisiran arm of the overall population. [c]KCCQ-OS values were assessed at baseline in 325 patients in the vutrisiran arm and 327 patients in the placebo arm of the overall population, and in 195 patients in the vutrisiran arm and 198 patients in the placebo arm of the monotherapy population. [d]The mBMI was calculated as the conventional BMI (weight in kilograms divided by the square of the height in meters) multiplied by the serum albumin level in grams per liter.

REFERENCE

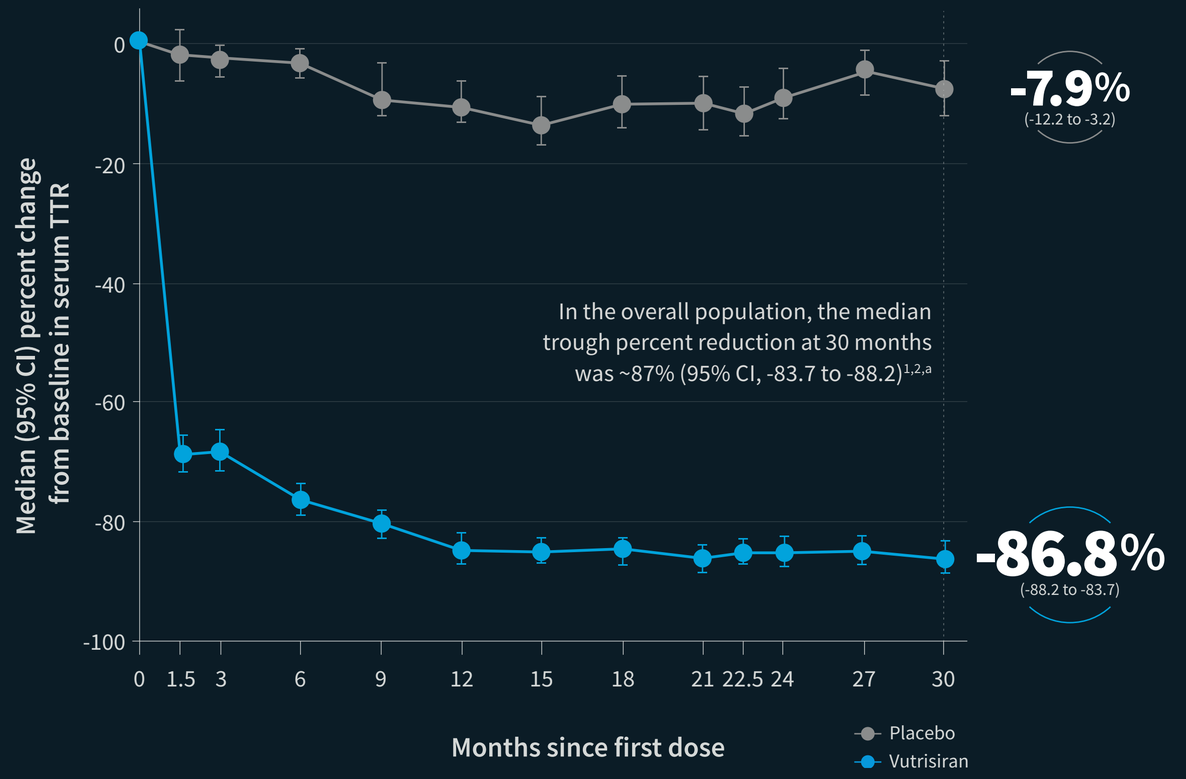
1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

ABBREVIATIONS

6-MWT, 6-minute walk test; **ATTR**, transthyretin amyloidosis; **BMI**, body mass index; **eGFR**, estimated glomerular filtration rate; **IQR**, interquartile range; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire–Overall Summary; **mBMI**, modified body mass index; **NAC**, National Amyloidosis Centre; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **NYHA**, New York Heart Association; **SD**, standard deviation; **wtATTR**, wild-type transthyretin amyloidosis.

Rapid and sustained reduction in serum TTR levels from baseline observed with vutrisiran vs placebo in the monotherapy and overall populations[1,2]

Percent Change From Baseline in Serum TTR Levels (Overall Population)[1]



[a]The earliest time point at which serum TTR levels were evaluated was 1.5 months.[1]

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1. Alnylam Pharmaceuticals. Data on file.

2. Fontana M, et al. *N Engl J Med.* 2025;392:33-44.

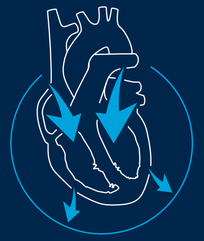
ABBREVIATIONS

CI, confidence interval; **TTR**, transthyretin.

In the overall population of HELIOS-B, patients treated with vutrisiran experienced slowed, halted, or reversed cardiac structural and functional decline at 30 months, with some effects emerging as early as 12 months[1-4,a]

Cardiac Structure[4]

LV hypertrophy and remodeling worsening attenuated by Month 30



Diastolic Function[4]

- LV filling pressure improved from baseline as early as 12 months
- LV relaxing and filling worsening attenuated (at Month 30)

Systolic Function[4]

Halted/attenuated worsening of:

- RV systolic function
- LVEF
- Absolute peak longitudinal strain
- LV stroke volume (at Month 30)

Worsening of systolic and diastolic function is associated with an increased risk of all-cause mortality in patients with ATTR-CM[2]

The effects on cardiac structure and function provide a potential mechanistic explanation for the observed changes in cardiac biomarkers and clinical outcomes[2]

[a]Analyses were exploratory and were not controlled for multiplicity.

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1. Maurer MS, et al. Presented at: Annual Scientific Meeting of the Heart Failure Society of America; September 29-30, 2024; Virtual.

2. Jering K, et al. Poster presented at: American College of Cardiology Scientific Session; March 29-31, 2025; Chicago, IL, USA.

3. Maurer MS, et al. Presented at: American College of Cardiology Annual Scientific Session; March 29-31, 2025; Chicago, IL, USA.

4. Jering K, et al. Presented at: Annual Scientific Meeting of the Heart Failure Society of America; September 29-30, 2024; Virtual.

ABBREVIATIONS

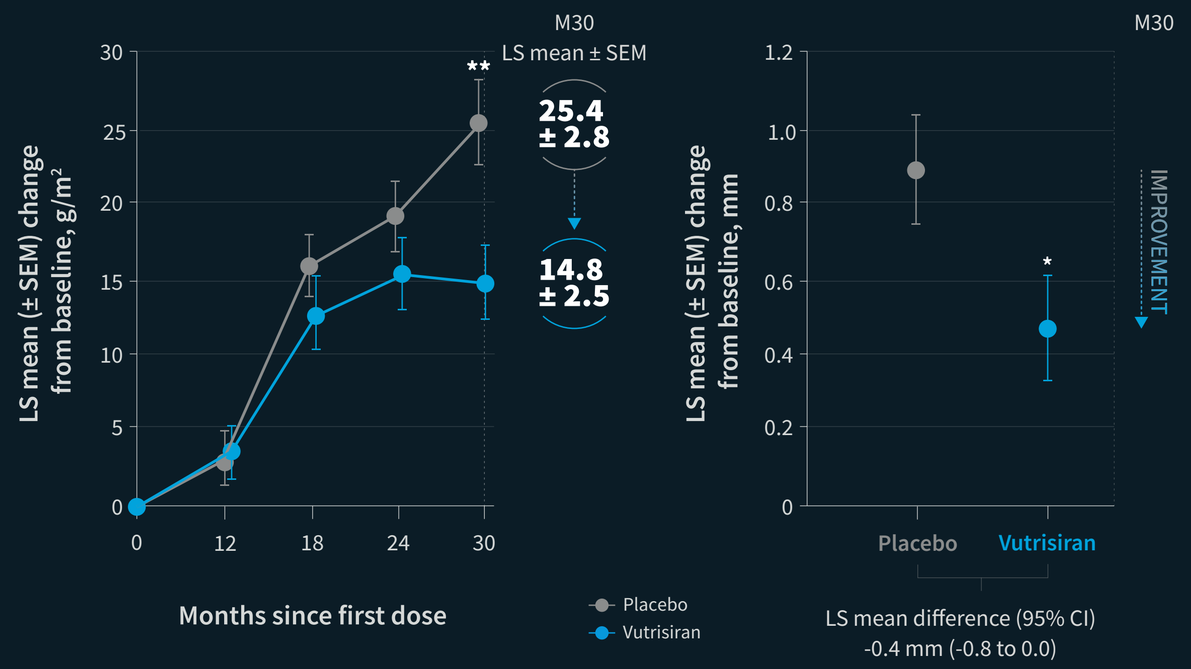
ATTR-CM, transthyretin amyloidosis with cardiomyopathy; **LV**, left ventricular; **LVEF**, left ventricular ejection fraction; **RV**, right ventricular.

In the overall population in HELIOS-B, patients receiving vutrisiran had attenuated LV hypertrophy and cardiac remodeling vs those receiving placebo by Month 30[1,a]

As **LV mass index** has been correlated with amyloid burden, attenuated increases in LV mass index likely reflect diminished amyloid deposition[2]

LV MASS INDEX AND WALL THICKNESS

CARDIAC STRUCTURE



Figures adapted from Jering et al., Nature Medicine, ©2025, The Author(s), Licensed under CC-BY-4.0, https://doi.org/10.1038/s41591-025-03851-z

Results are from an MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group.

*Nominal $P<0.05$; **Nominal $P<0.01$.

[a]Analyses were exploratory and were not controlled for multiplicity.

[b]LV mass index is the LV mass adjusted for body size, used to assess for LV hypertrophy and overall cardiac remodeling.

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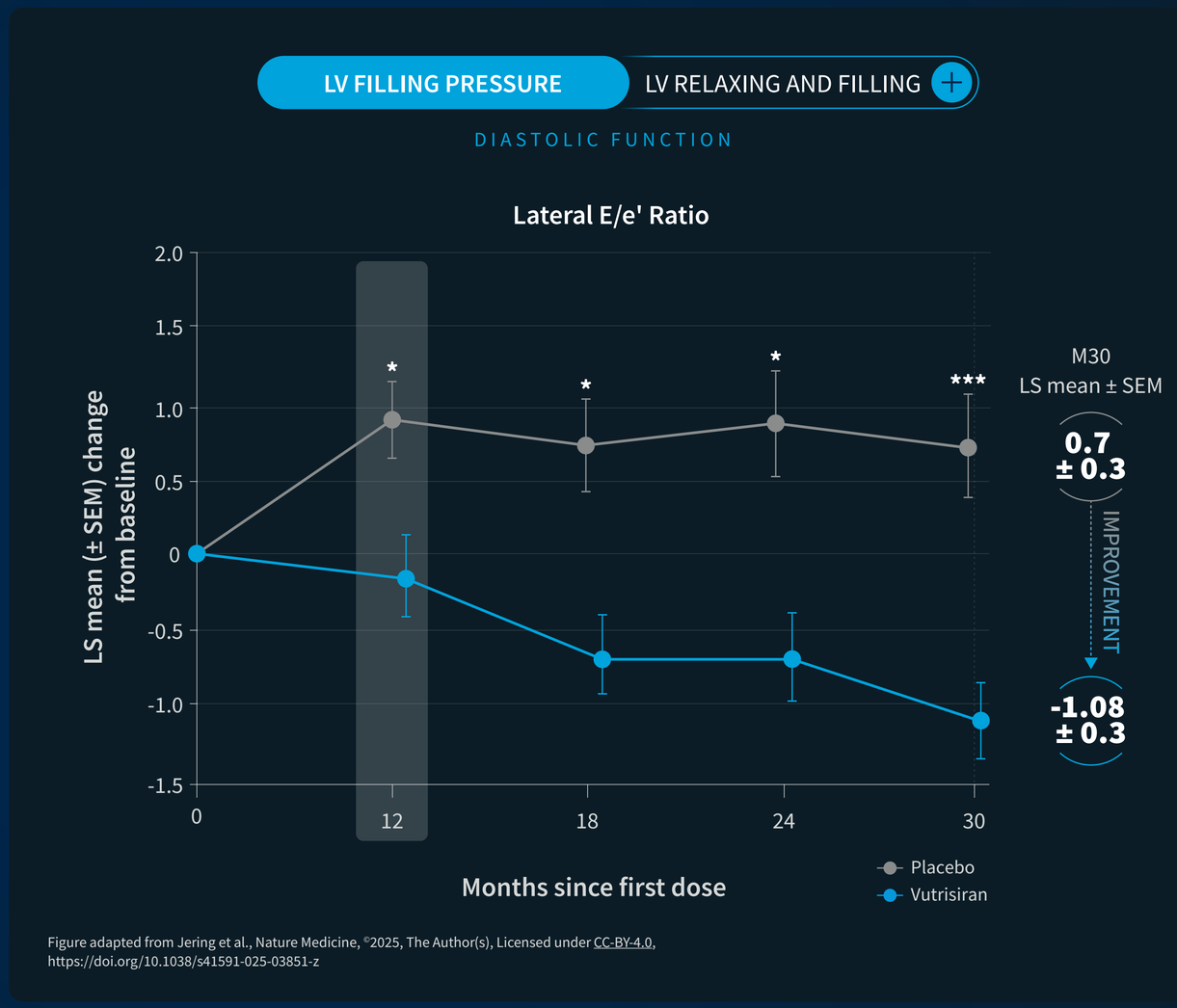
2. Cuddy SAM, et al. *JACC Cardiovasc Imaging.* 2020;13:1325-1336.

ABBREVIATIONS

ATTR, transthyretin amyloidosis; **CI**, confidence interval; **LS**, least squares; **LV**, left ventricular; **M**, Month; **MMRM**, mixed model for repeated measures; **SEM**, standard error of the mean.

In the overall population in HELIOS-B, patients receiving vutrisiran had improved LV filling pressure vs those receiving placebo at Month 30, with improvements emerging as early as Month 12[1,a]

The E/e' ratio estimates LV filling pressure, where “E” represents early mitral inflow velocity and “e'” represents early diastolic mitral annular velocity[2]



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*Nominal *P*<0.05; ***Nominal *P*<0.001.

[a]Analyses were exploratory and were not controlled for multiplicity.

REFERENCES

1. Jering KS, et al. *Nat Med.* 2025. doi: 10.1038/s41591-025-03851-z. Online ahead of print.

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3. Okada K, et al. *Eur J Echocardiogr.* 2011;12:917-923.

ABBREVIATIONS

ATTR, transthyretin amyloidosis; **CI**, confidence interval; **E/A**, ratio of early to late diastolic transmitral inflow velocities; **E/e'**, ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; **LS**, least squares; **LV**, left ventricular; **M**, Month; **MMRM**, mixed model for repeated measures; **SEM**, standard error of the mean; **TDI lateral e'**, lateral peak early diastolic mitral annular tissue velocity.

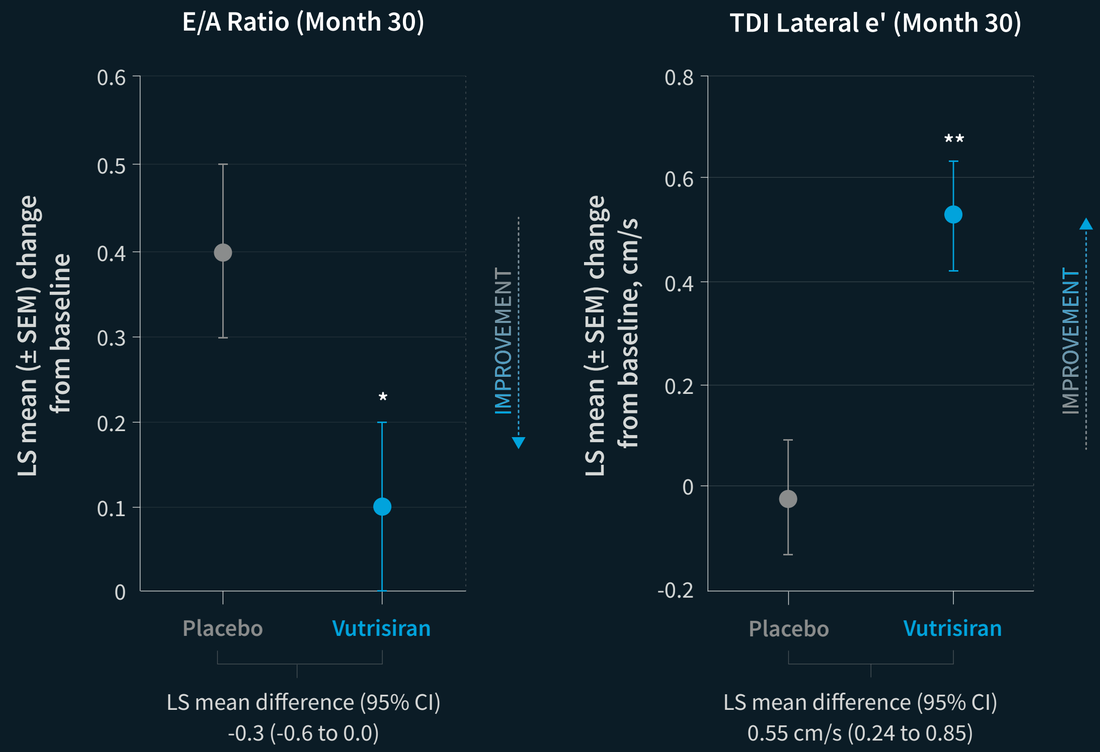
In the overall population in HELIOS-B, patients receiving vutrisiran had attenuated worsening in LV relaxing and filling vs those receiving placebo at Month 30[1,a]

The E/A ratio compares early (E) to late (A) ventricular filling velocities across the mitral valve, helping to assess how well the left ventricle relaxes and fills[2]

TDI lateral e' measures early diastolic velocity at the lateral mitral annulus, used to evaluate LV relaxation and diastolic function[3]

LV FILLING PRESSURE | LV RELAXING AND FILLING

DIASTOLIC FUNCTION



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REFERENCES

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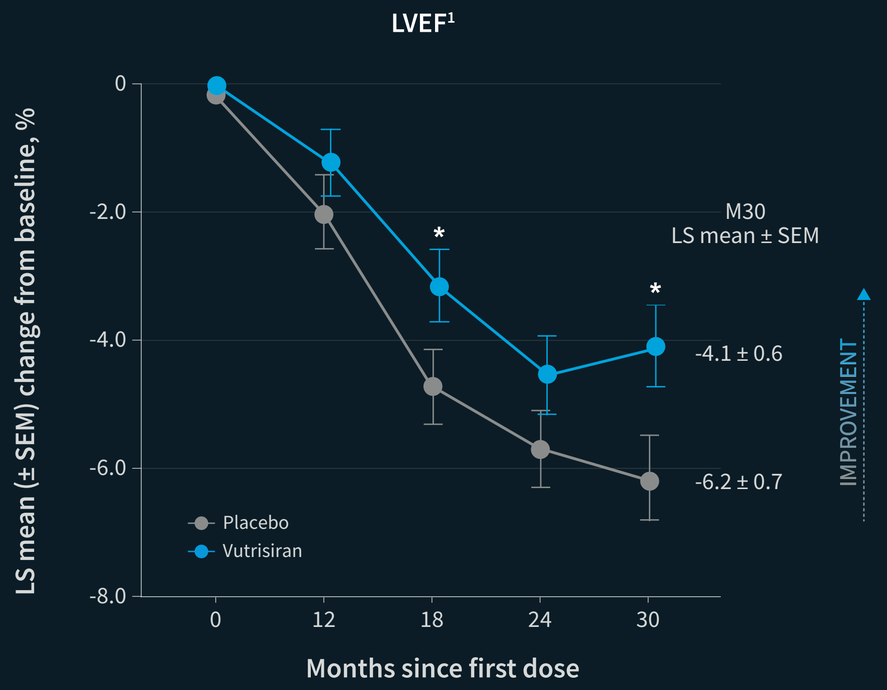
In the overall population in HELIOS-B, patients receiving vutrisiran had attenuated worsening in LVEF vs those receiving placebo at Month 30[1,a]

Left ventricular ejection fraction (LVEF) is the percentage of blood the left ventricle pumps out with each contraction, used to assess overall systolic function[2]

LVEF | RV S'/LV STROKE VOL. + | ABSOLUTE GLS +

SYSTOLIC FUNCTION



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*Nominal *P*<0.05.

[a]Analyses were exploratory and were not controlled for multiplicity.[1]

REFERENCES

1. Jering KS, et al. *Nat Med.* 2025. doi: 10.1038/s41591-025-03851-z. Online ahead of print.

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3. Jering K, et al. Presented at: Annual Scientific Meeting of the Heart Failure Society of America; September 29-30, 2024; Virtual.

4. Hameed A, et al. *Curr Heart Fail Rep.* 2023;20:194-207.

5. Bruss ZS, Raja A. *Physiology, Stroke Volume.* Treasure Island (FL): StatPearls Publishing; 2022.

6. Gowsini J, et al. *Echo Res Pract.* 2019;6:81-89.

ABBREVIATIONS

ATTR, transthyretin amyloidosis; **CI**, confidence interval; **GLS,** global longitudinal strain; **LS**, least squares; **LV**, left ventricular; **LVEF**, left ventricular ejection fraction; **M**, Month; **MMRM**, mixed model for repeated measures; **RV**, right ventricular; **RV S'**, right ventricular systolic excursion velocity; **SEM**, standard error of the mean.

In the overall population in HELIOS-B, patients receiving vutrisiran maintained RV systolic function and attenuated worsening in LV stroke volume vs patients receiving placebo, at Month 30[1,a]

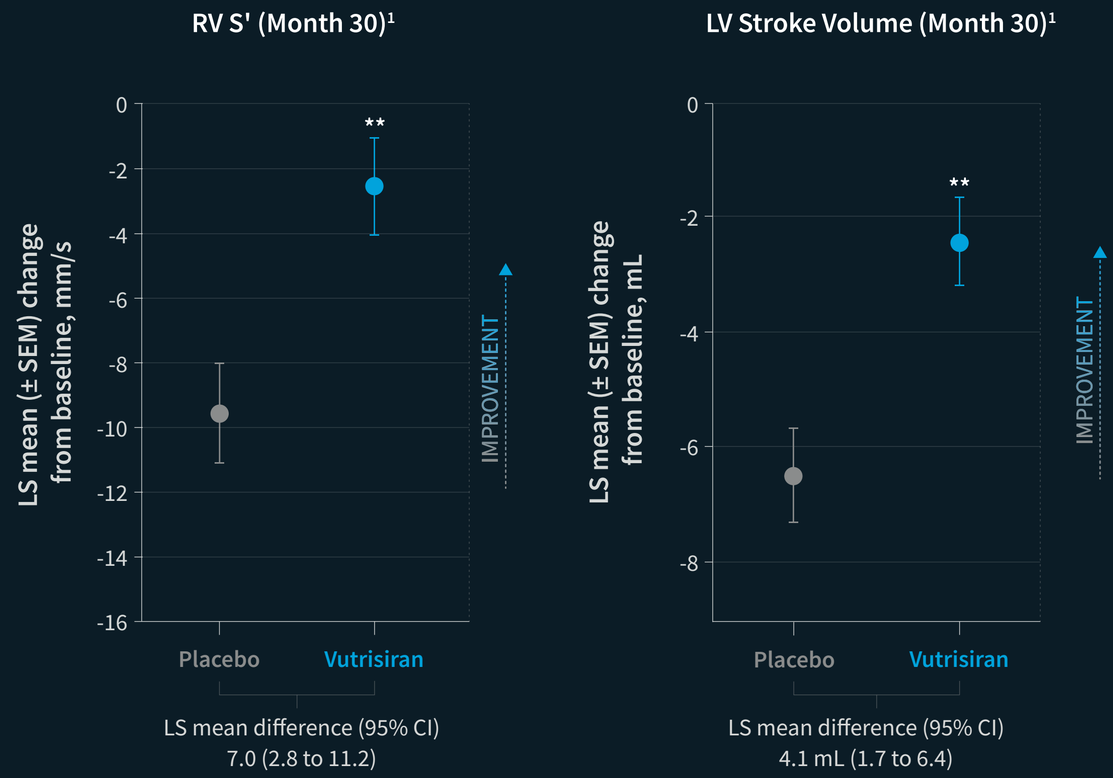
Attenuation of worsening in RV systolic function observed as early as 18 months[3]

RV S' (RV systolic excursion velocity) measures the peak systolic velocity of the tricuspid annulus, used to assess RV systolic function[4]

LV stroke volume is the amount of blood ejected by the left ventricle with each heartbeat, calculated as the difference between end-diastolic and end-systolic volumes[5]

LVEF | **RV S'/LV STROKE VOL.** | ABSOLUTE GLS

SYSTOLIC FUNCTION



Figures adapted from Jering et al., Nature Medicine, ©2025, The Author(s), Licensed under CC-BY-4.0, https://doi.org/10.1038/s41591-025-03851-z

Results are from an MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group.[1]

**Nominal $P<0.01$.

[a]Analyses were exploratory and were not controlled for multiplicity.[1]

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In the overall population in HELIOS-B, patients receiving vutrisiran had attenuated worsening in absolute global longitudinal strain vs those receiving placebo at Month 30, with separation emerging as early as Month 18[1,a]

Absolute GLS (global longitudinal strain) is a myocardial deformation analysis that assesses the function of subendocardial longitudinally oriented fibers, which are most prone to ischemic damage and can exhibit abnormal contraction patterns in the setting of apparently normal LVEF readings[6]

LVEF | RV S'/LV STROKE VOL. | **ABSOLUTE GLS**

SYSTOLIC FUNCTION

Absolute GLS[1,3]

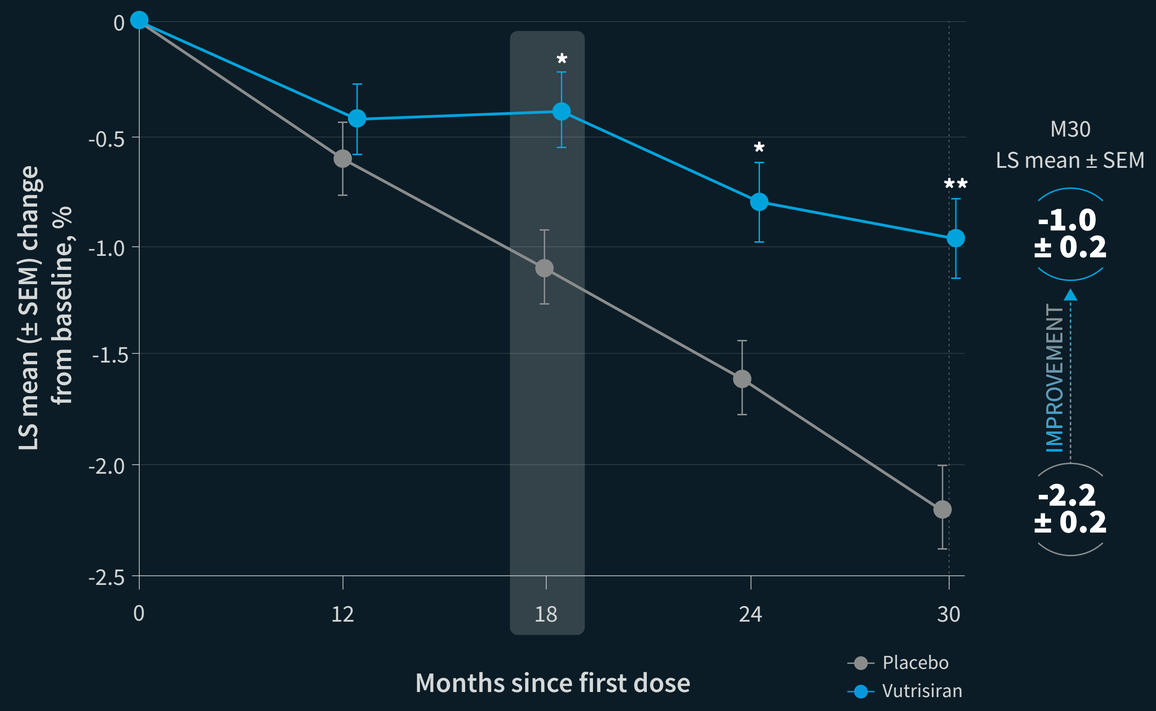

Figure adapted from Jering et al., Nature Medicine, ©2025, The Author(s), Licensed under CC-BY-4.0, https://doi.org/10.1038/s41591-025-03851-z

Results are from an MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group.[1]

*Nominal *P*<0.05; **Nominal *P*<0.01.

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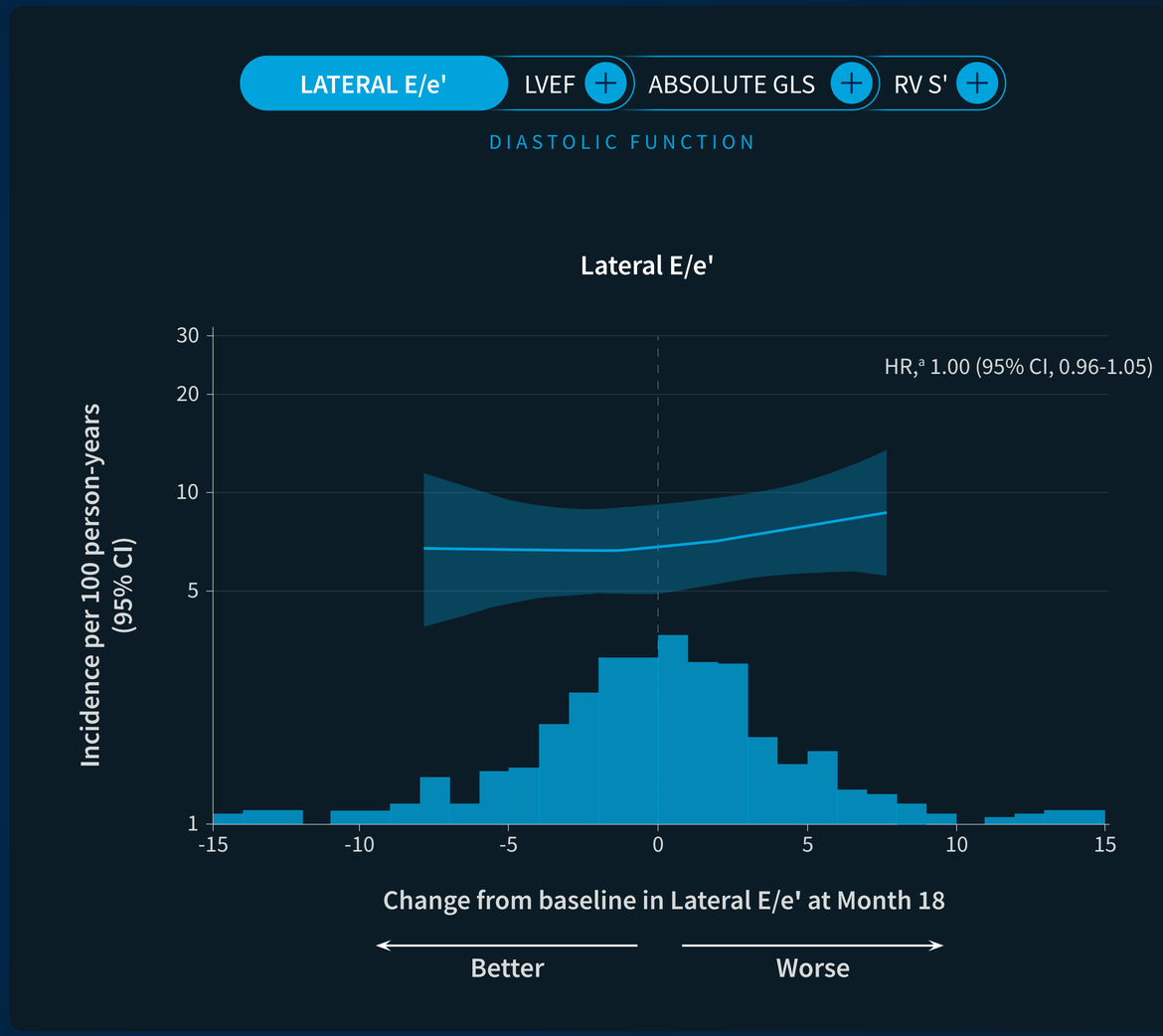
Echocardiographic indicators of systolic and diastolic function correlated with clinical outcomes in ATTR-CM[1]

Worsening diastolic and systolic function indices over 18 months were associated with a heightened risk of subsequent all-cause mortality in the overall population of HELIOS-B



[a]HR per 1-unit increase adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR amyloidosis disease type (wild-type vs variant), and National Amyloidosis Centre ATTR amyloidosis stage, and stratified by baseline tafamidis use and treatment assignment. *P* for nonlinearity >0.15 for all. The histograms illustrate the distribution of change from baseline at 18 months.

REFERENCE

1. Jering KS, et al. *J Am Coll Cardiol.* 2025;86:444-455.

ABBREVIATIONS

ATTR, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CI**, confidence interval; **E/e'**, ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; **GLS**, global longitudinal strain; **HR**, hazard ratio; **LVEF**, left ventricular ejection fraction; **RV S'**, right ventricular systolic excursion velocity.

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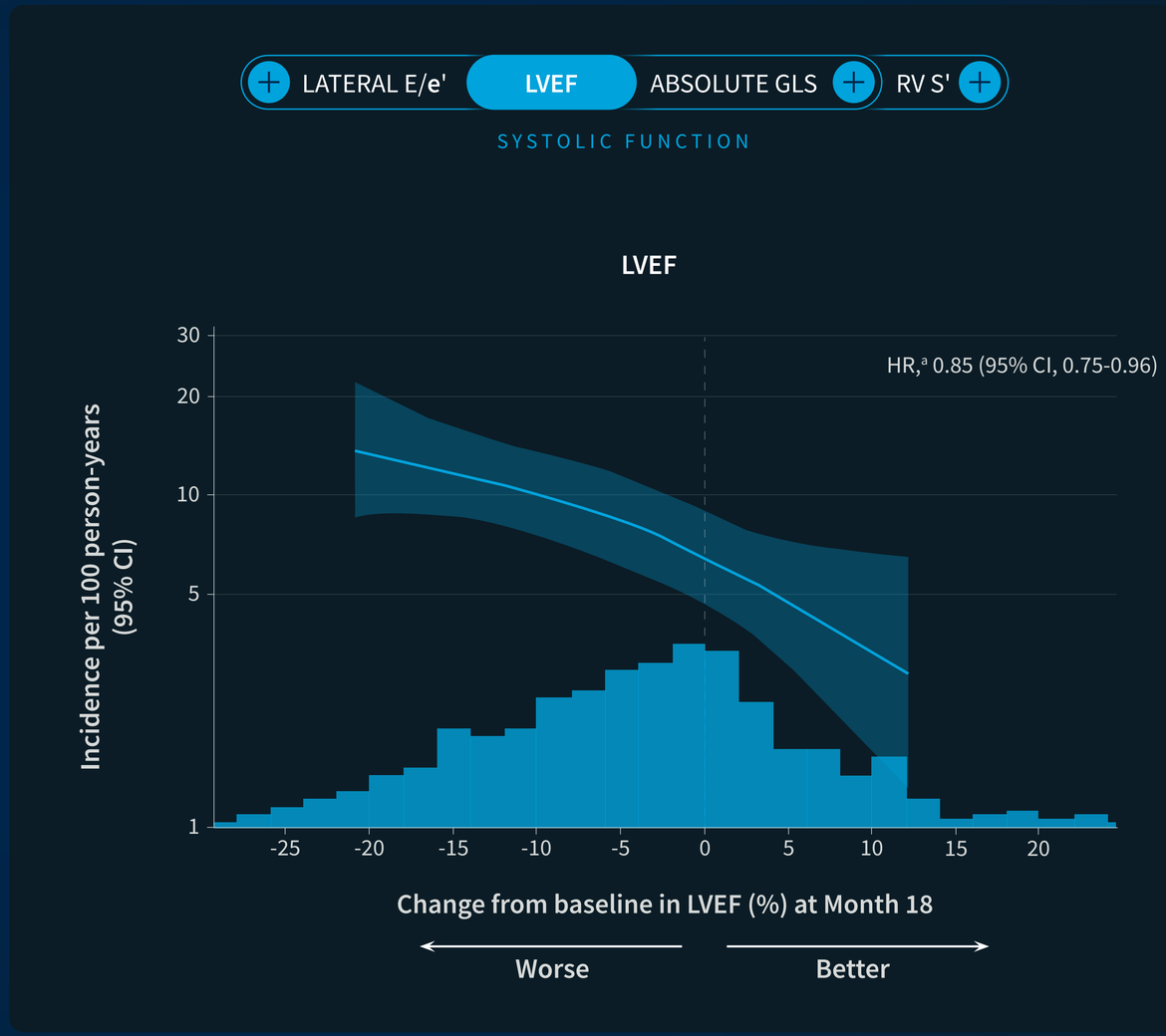
Worsening diastolic and systolic function indices over 18 months were associated with a heightened risk of subsequent all-cause mortality in the overall population of HELIOS-B



[a]HR per 5% increase adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR amyloidosis disease type (wild-type vs variant), and National Amyloidosis Centre ATTR amyloidosis stage, and stratified by baseline tafamidis use and treatment assignment. *P* for nonlinearity >0.15 for all. The histograms illustrate the distribution of change from baseline at 18 months.

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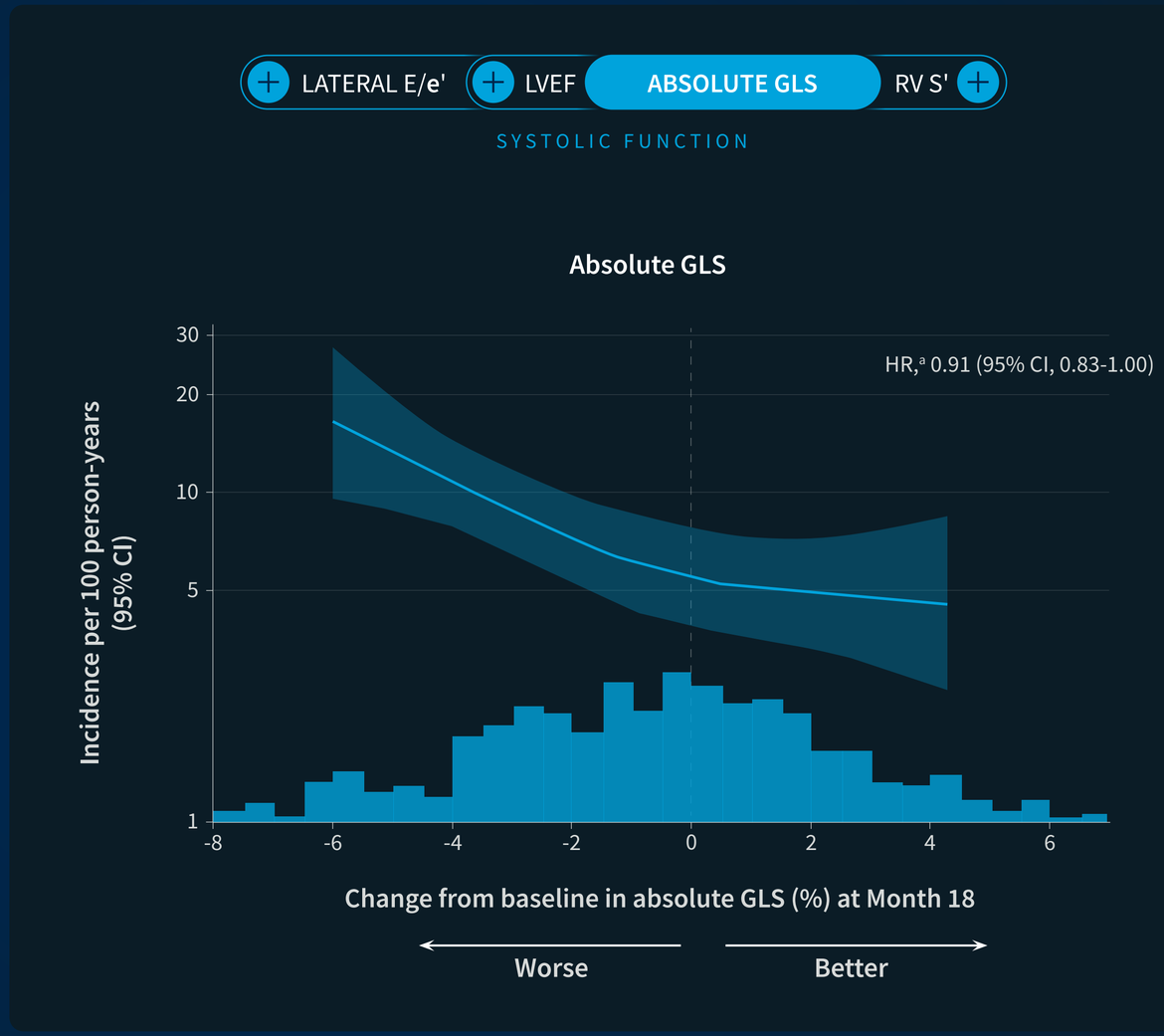

[a]HR per 1% increase adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR amyloidosis disease type (wild-type vs variant), and National Amyloidosis Centre ATTR amyloidosis stage, and stratified by baseline tafamidis use and treatment assignment. *P* for nonlinearity >0.15 for all. The histograms illustrate the distribution of change from baseline at 18 months.

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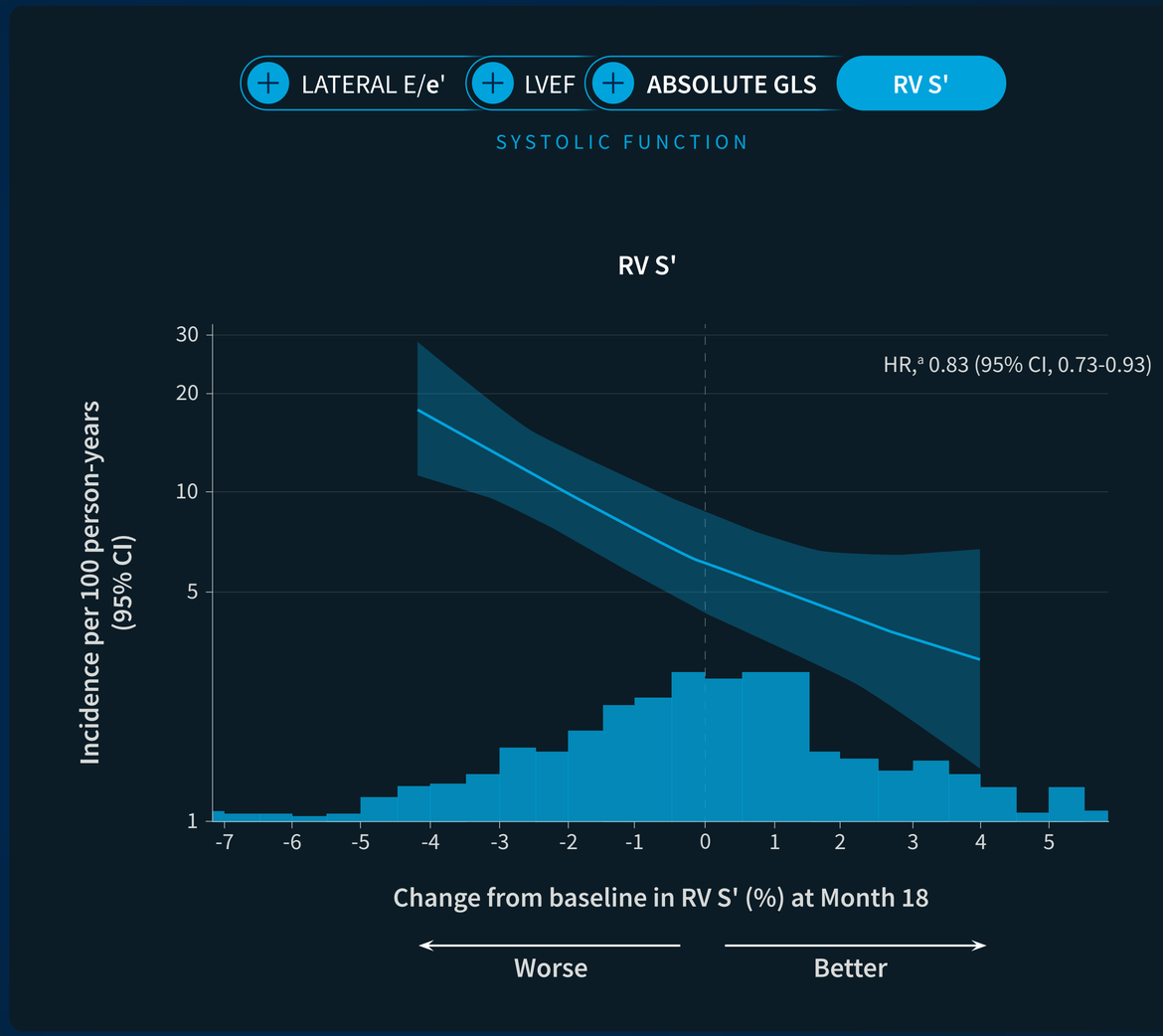
1. Jering KS, et al. *J Am Coll Cardiol.* 2025;86:444-455.

ABBREVIATIONS

ATTR, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CI**, confidence interval; **E/e'**, ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; **GLS**, global longitudinal strain; **HR**, hazard ratio; **LVEF**, left ventricular ejection fraction; **RV S'**, right ventricular systolic excursion velocity.

Echocardiographic indicators of systolic and diastolic function correlated with clinical outcomes in ATTR-CM[1]

Worsening diastolic and systolic function indices over 18 months were associated with a heightened risk of subsequent all-cause mortality in the overall population of HELIOS-B



[a]Adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR amyloidosis disease type (wild-type vs variant), and National Amyloidosis Centre ATTR amyloidosis stage, and stratified by baseline tafamidis use and treatment assignment. *P* for nonlinearity >0.15 for all. The histograms illustrate the distribution of change from baseline at 18 months.

REFERENCE

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Patients receiving vutrisiran maintained stable levels of NT-proBNP and troponin I compared with patients receiving placebo, with a larger effect in the monotherapy population[1]

NT-proBNP[2-4] and troponin I[4] are well-established prognostic biomarkers of increased mortality in ATTR-CM

- Favorable treatment effects of vutrisiran vs placebo were observed as early as 6 months, and these grew over time[1,a]

Relative reduction of NT-proBNP and troponin I (Month 30)[1]

- Vutrisiran monotherapy: 43% and 45%, respectively
- Overall population: 32% (both biomarkers)

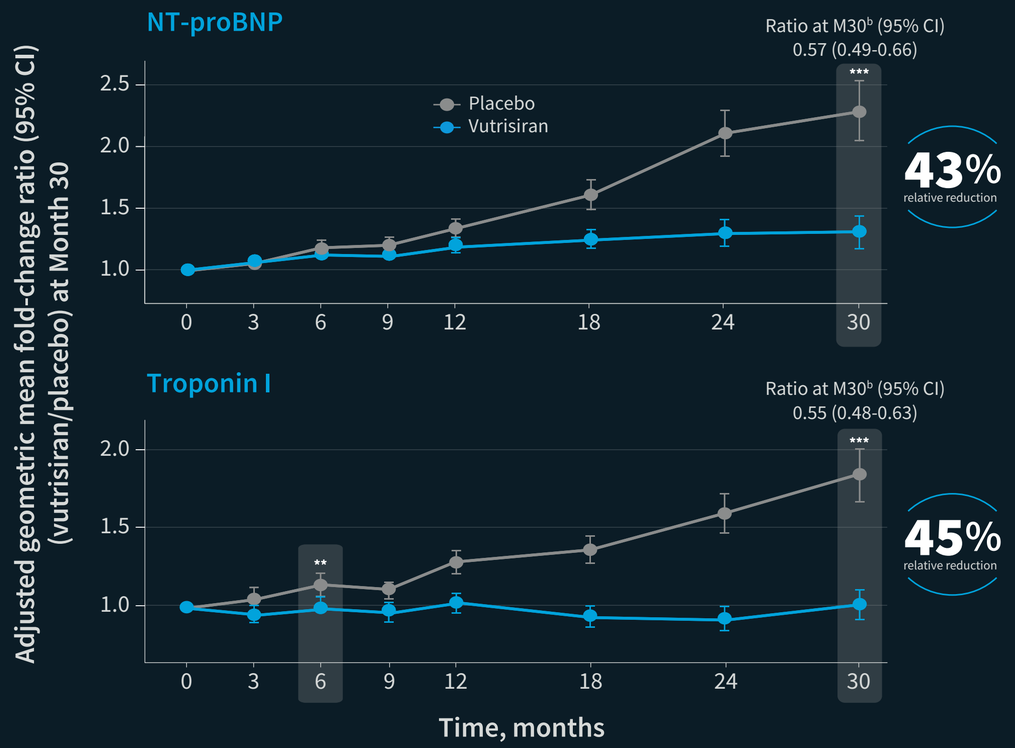
Beneficial impact of vutrisiran on cardiac biomarkers by baseline heart failure severity[5]

- The beneficial effects of vutrisiran on NT-proBNP and troponin I were consistent in all prespecified subgroups (age, baseline tafamidis use, ATTR amyloidosis type, NYHA class, and baseline NT-proBNP)[1,5]

**Nominal *P*<0.01.
***Nominal *P*<0.001.
[a]Nominal statistical significance.

MONOTHERAPY POPULATION | OVERALL POPULATION

Vutrisiran Treatment Effect on NT-proBNP and Troponin I Compared With Placebo[1]



Figures adapted from Maurer et al., Journal of the American College of Cardiology, ©2025, The Author(s), Licensed under CC-BY-NC-ND, https://doi: 10.1016/j.jacc.2025.04.055

[b]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP/troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP/troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR amyloidosis, and age group.

REFERENCES

1. Maurer SM, et al. *J Am Coll Cardiol*. 2025;86:459-475.
2. Grogan M, et al. *J Am Coll Cardiol*. 2016;68:1014-1020.
3. Damy T, et al. *Amyloid*. 2016;23:194-202.
4. Kristen AV, et al. *PLoS One*. 2017;12:e0173086.
5. Maurer MS, et al. Presented at: American College of Cardiology Annual Scientific Session; March 29–31, 2025; Chicago, IL, USA.

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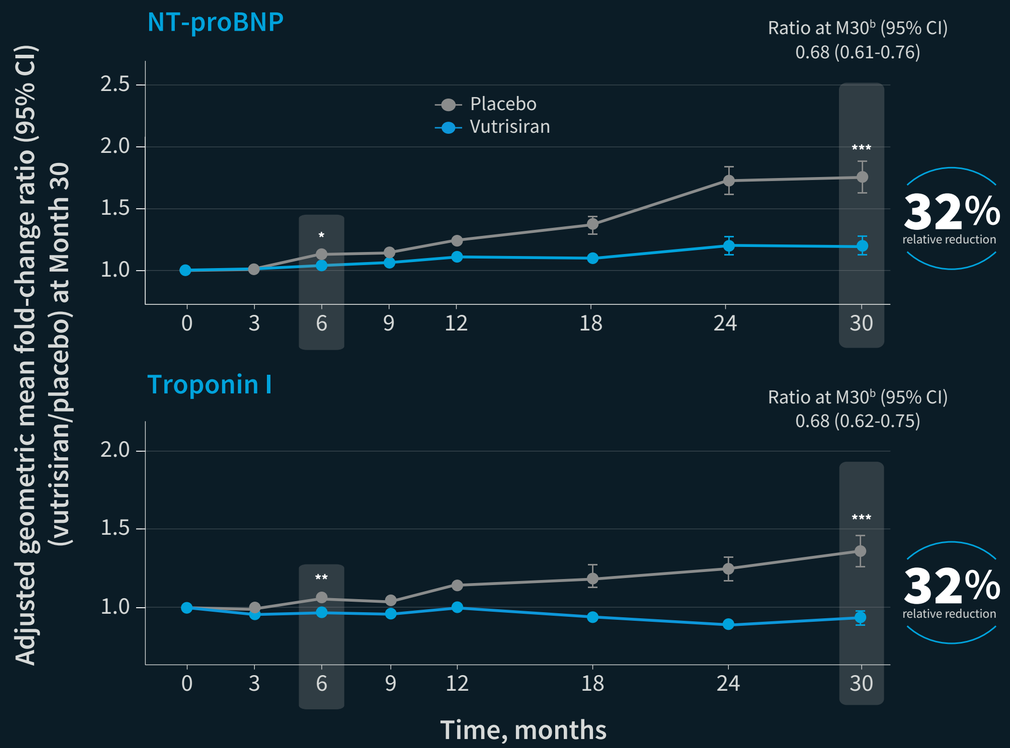
*Nominal $P<0.05$.
**Nominal $P<0.01$.
***Nominal $P<0.001$.
[a]Nominal statistical significance.

MONOTHERAPY POPULATION | **OVERALL POPULATION**

Vutrisiran Treatment Effect on NT-proBNP and Troponin I Compared With Placebo[1]



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REFERENCES

1. Maurer SM, et al. *J Am Coll Cardiol*. 2025;86:459-475.
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EXPLORATORY ANALYSES

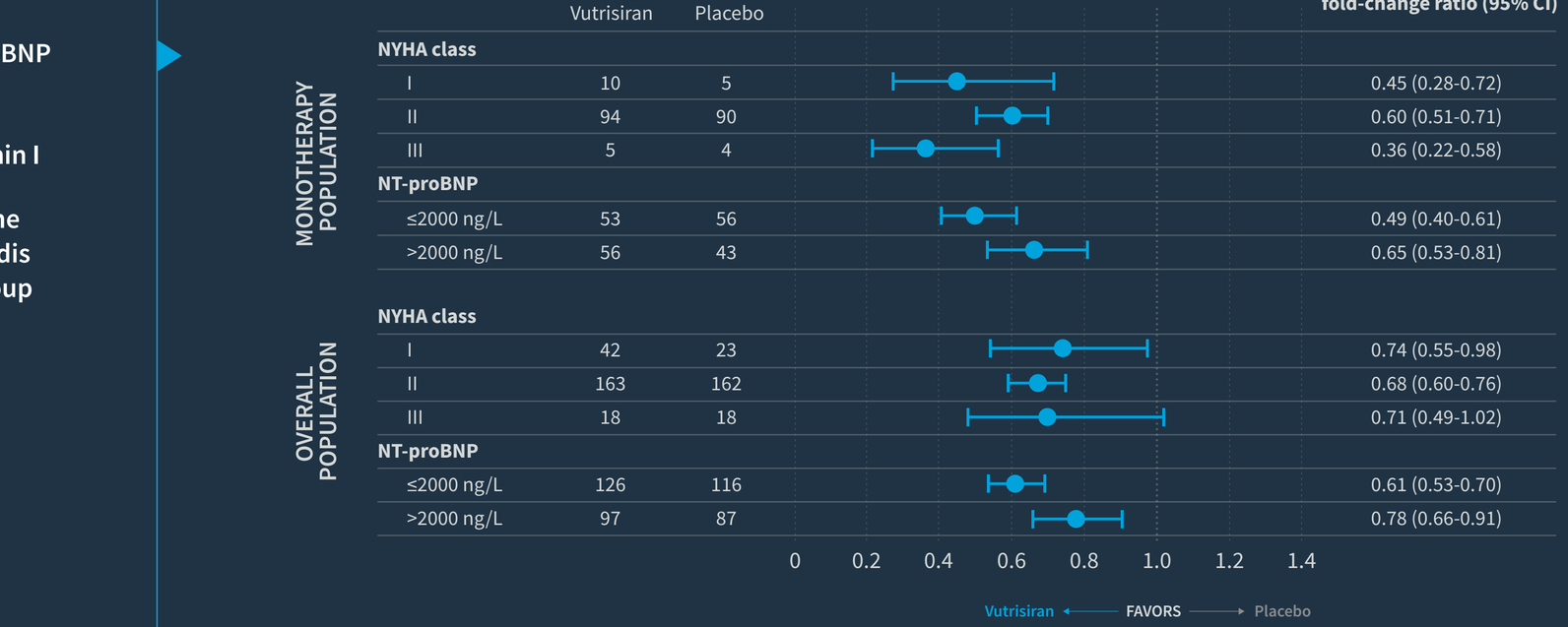
- NT-proBNP
- Troponin I
- Baseline tafamidis subgroup

Impact of vutrisiran on cardiac biomarkers by baseline heart failure severity[1]

Benefits in NT-proBNP levels were observed with vutrisiran vs placebo across baseline heart failure severity subgroups in the overall and monotherapy populations enrolled in HELIOS-B. Similar or greater magnitude of benefit was observed in the monotherapy population

Adjusted Geometric Mean Fold-Change Ratio in NT-proBNP Levels From Baseline to Month 30, by Baseline Heart Failure Severity, in the Monotherapy and Overall Populations

	Subgroup	Number of patients: Vutrisiran	Number of patients: Placebo	Adjusted geometric mean fold-change ratio (95% CI)
MONOTHERAPY POPULATION	**NYHA class**			
	I	10	5	0.45 (0.28-0.72)
	II	94	90	0.60 (0.51-0.71)
	III	5	4	0.36 (0.22-0.58)
	NT-proBNP			
	≤2000 ng/L	53	56	0.49 (0.40-0.61)
	>2000 ng/L	56	43	0.65 (0.53-0.81)
OVERALL POPULATION	**NYHA class**			
	I	42	23	0.74 (0.55-0.98)
	II	163	162	0.68 (0.60-0.76)
	III	18	18	0.71 (0.49-1.02)
	NT-proBNP			
	≤2000 ng/L	126	116	0.61 (0.53-0.70)
	>2000 ng/L	97	87	0.78 (0.66-0.91)



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1. Maurer MS, et al. *J Am Coll Cardiol*. 2025;85:1927-1939. https://www.jacc.org/doi/10.1016/j.jacc.2025.03.477

EXPLORATORY ANALYSES

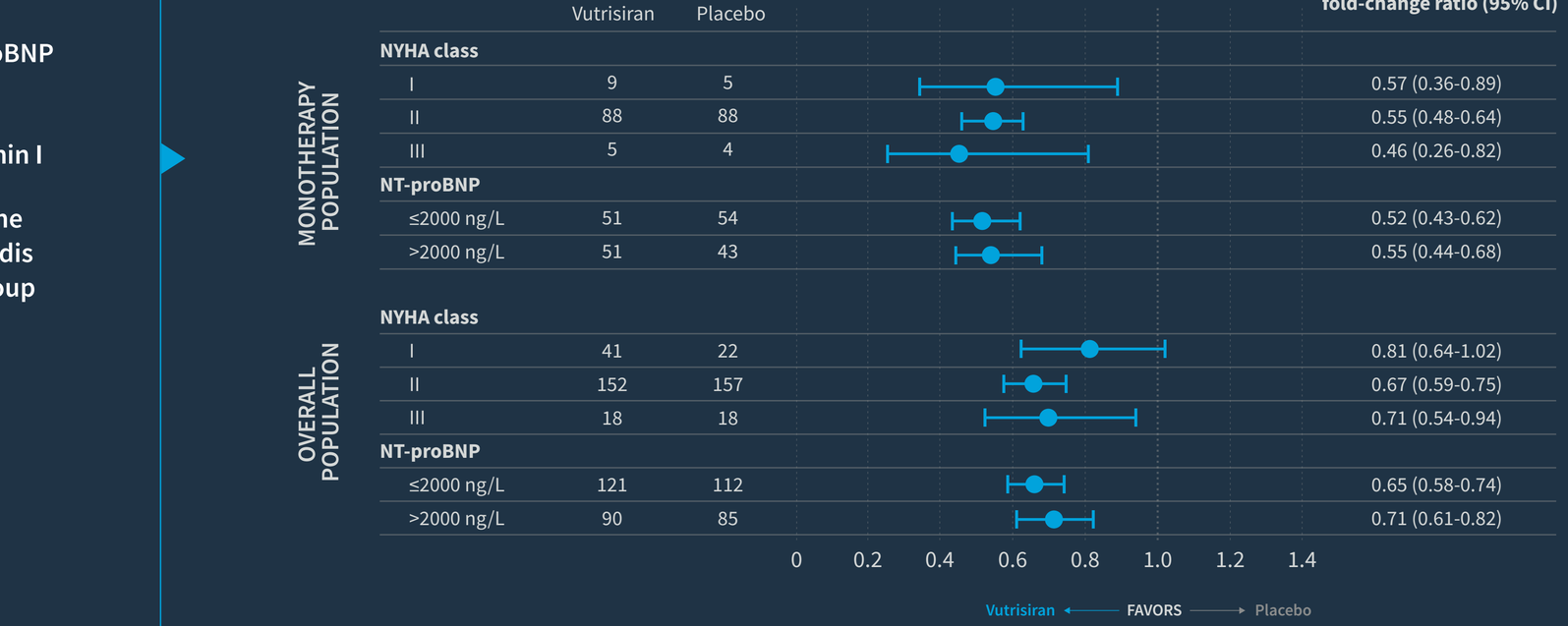
- NT-proBNP
- Troponin I
- Baseline tafamidis subgroup

Impact of vutrisiran on cardiac biomarkers by baseline heart failure severity[1]

Benefits in troponin I levels were observed with vutrisiran vs placebo across baseline heart failure severity subgroups in the overall and monotherapy populations enrolled in HELIOS-B. Similar or greater magnitude of benefit was observed in the monotherapy population

Adjusted Geometric Mean Fold-Change Ratio in Troponin I Levels From Baseline to Month 30, by Baseline Heart Failure Severity, in the Monotherapy and Overall Populations

	Subgroup	Number of patients: Vutrisiran	Number of patients: Placebo	Adjusted geometric mean fold-change ratio (95% CI)
MONOTHERAPY POPULATION	**NYHA class**			
	I	9	5	0.57 (0.36-0.89)
	II	88	88	0.55 (0.48-0.64)
	III	5	4	0.46 (0.26-0.82)
	NT-proBNP			
	≤2000 ng/L	51	54	0.52 (0.43-0.62)
	>2000 ng/L	51	43	0.55 (0.44-0.68)
OVERALL POPULATION	**NYHA class**			
	I	41	22	0.81 (0.64-1.02)
	II	152	157	0.67 (0.59-0.75)
	III	18	18	0.71 (0.54-0.94)
	NT-proBNP			
	≤2000 ng/L	121	112	0.65 (0.58-0.74)
	>2000 ng/L	90	85	0.71 (0.61-0.82)



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EXPLORATORY ANALYSES

- NT-proBNP
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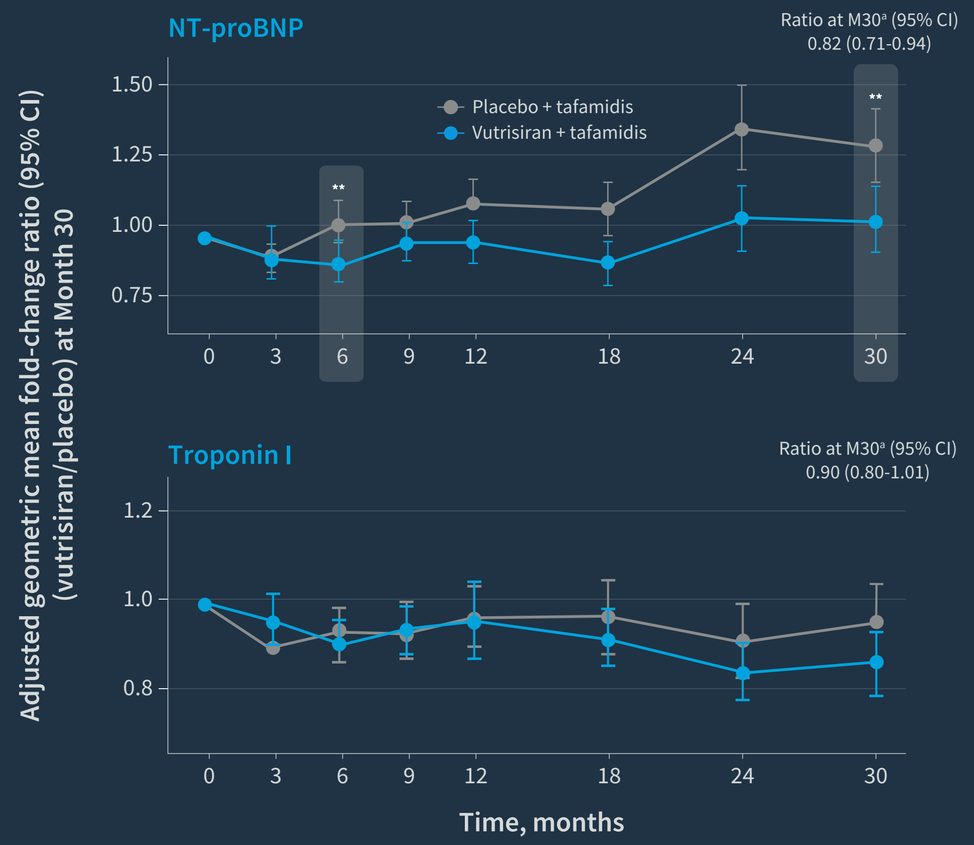
- Baseline tafamidis subgroup

Relative reduction of NT-proBNP and troponin I (Month 30)[1]



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**Nominal *P*<0.01.

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Patients receiving vutrisiran had improved functional capacity, patient-reported health status and health-related QOL vs patients receiving placebo, and had stabilized or improved heart failure symptom severity vs patients receiving placebo, with a larger treatment effect observed in the first-line monotherapy population[1,a]

Change From Baseline at 30 Months in Functional Capacity (6-MWT), Patient-Reported Health Status and Health-Related QOL (KCCQ-OS), and Heart Failure Symptom Severity (NYHA Class) vs Placebo

Baseline characteristics	Monotherapy population		Overall population	
	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=326)	Placebo (n=328)
6-MWT change from baseline at 30 months in distance, meters[b]				
LS mean (95% CI)	**-59.7** (-72.7 to -46.7)	**-91.8** (-104.4 to -79.2)	**-45.4** (-54.5 to -36.3)	**-71.9** (-81.3 to -62.4)
Measure of effect: LS mean difference (95% CI), *P*-value	**32.1** (14.0 to 50.2), <0.001		**26.5** (13.4 to 39.6), <0.001	
KCCQ-OS score change from baseline at 30 months, points[b]				
LS mean (95% CI)	**-10.8** (-14.1 to -7.5)	**-19.5** (-22.9 to -16.1)	**-9.7** (-12.0 to -7.4)	**-15.5** (-18.0 to -13.0)
Measure of effect: LS mean difference (95% CI), *P*-value	**8.7** (4.0 to 13.4), <0.001		**5.8** (2.4 to 9.2), <0.001	
NYHA class change from baseline at 30 months				
Stable or improved, %	**66**	**56**	**68**	**61**
Measure of effect: Adjusted difference in % of patients with stable or improved NYHA class (95% CI), *P*-value	**12.5** (2.7 to 22.2), 0.01		**8.7** (1.3 to 16.1), 0.02	

Less decline from baseline in 6-MWT distance and KCCQ-OS with vutrisiran vs placebo at 30 months (both populations)

Vutrisiran-treated patients were more likely to maintain or improve functional status (NYHA class) than those on placebo at 30 months, with the effect largely attributed to stable patients

[a]Approximately 98% of patients in the monotherapy population were treatment-naïve to stabilizer therapy; the 2% of patients who previously received a stabilizer all underwent a washout period of ≥30 days before trial dosing.[2]
[b]For 6-MWT and KCCQ-OS, assessments missing due to death (including heart transplantation and left ventricular assist device placement) and inability to walk as a result of ATTR amyloidosis disease progression (for 6-MWT only), data were imputed from resampling of the worst 10% of observed changes. For 6-MWT, a further distance walked indicates better function; for KCCQ-OS, scores range from 0 to 100, with higher scores indicating better QOL.

REFERENCES

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

2. Alnylam Pharmaceuticals. Data on file.

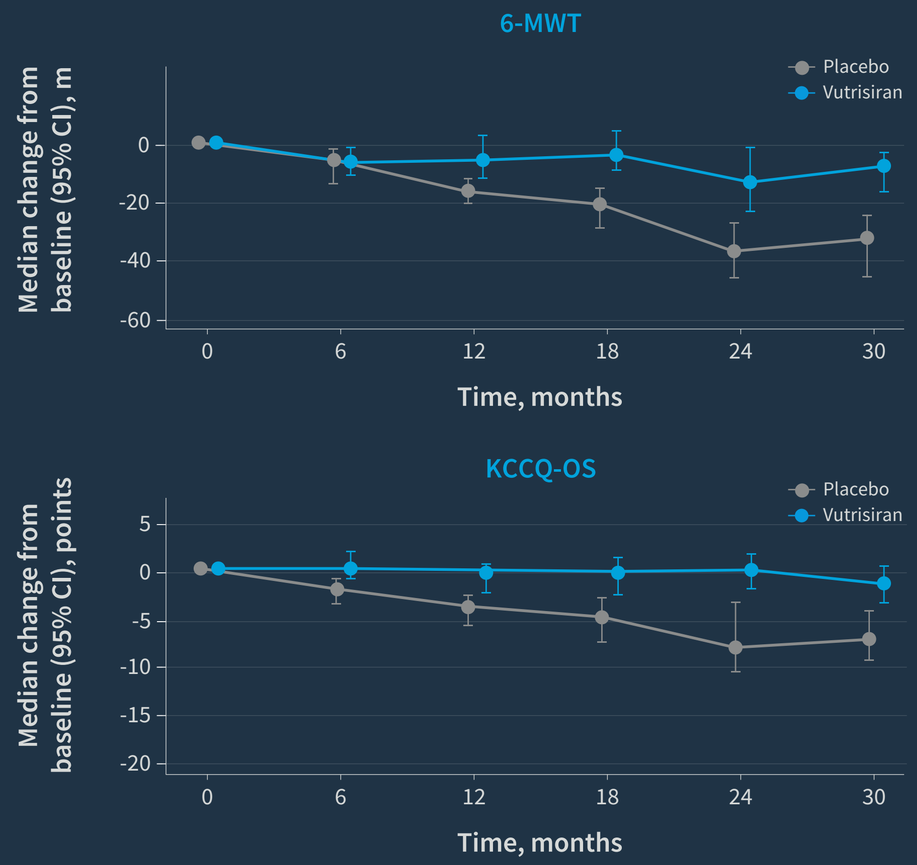
ABBREVIATIONS

6-MWT, 6-minute walk test; **ATTR,** transthyretin amyloidosis; **CI**, confidence interval; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **LS**, least squares; **NYHA**, New York Heart Association; **QOL**, quality of life.

SECONDARY ENDPOINT ANALYSES

6-MWT and KCCQ-OS

Patients treated with vutrisiran had improved functional capacity (6-MWT), patient-reported health status and health-related QOL (KCCQ-OS) vs patients treated with placebo in the overall population (observed data)[1]

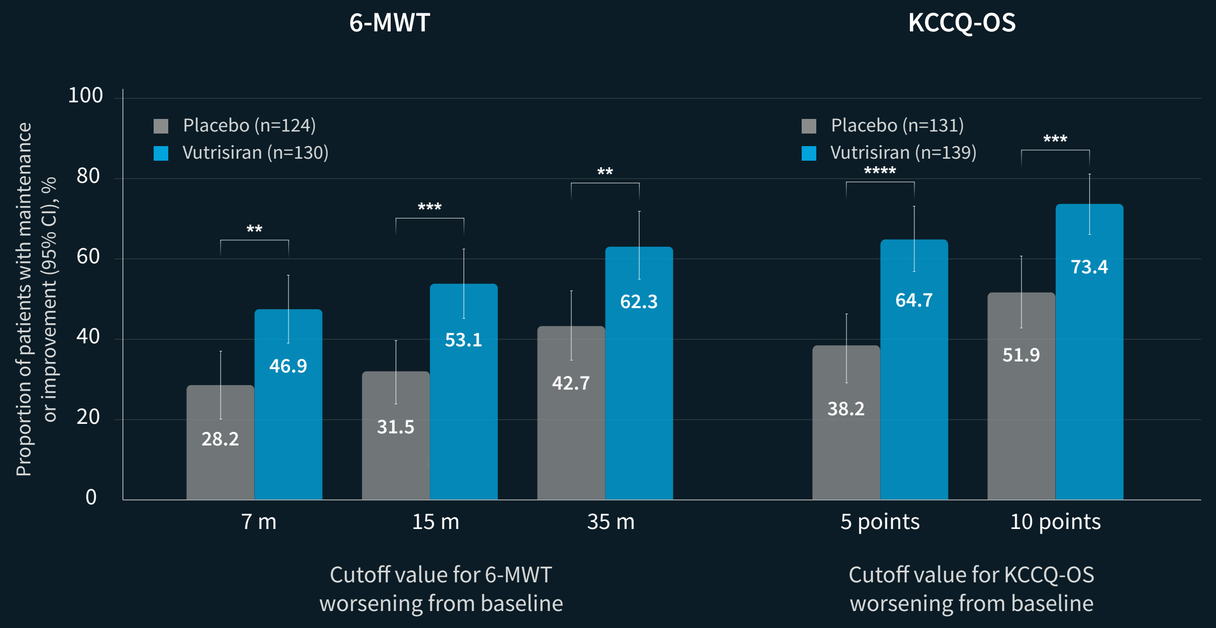


From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.
Median representation is based on observed data only, no imputations due to death/unable to walk due to disease progression.
6-MWT, 6-minute walk test; **CI**, confidence interval; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **m**, meter; **QOL**, quality of life.

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

Patients treated with vutrisiran had maintained or improved functional capacity, health status and quality of life over 30 months compared with patients treated with placebo and across all cutoff values applied[1]

MONOTHERAPY POPULATION | OVERALL POPULATION



6-MWT and KCCQ-OS were assessed at baseline and every 6 months until Month 30.[1] Maintenance or improvement was defined as not having a decrease from baseline of >7 m, >15 m, or >35 m (6-MWT), and >5 points or >10 points (KCCQ-OS). Analyses based on observed data with no imputation.

***P*<0.01. ****P*<0.001. *****P*<0.0001.

REFERENCE

1. Sheikh FH, et al. *J Am Coll Cardiol.* 2025;85:1943-1955. https://www.jacc.org/doi/10.1016/j.jacc.2025.03.454

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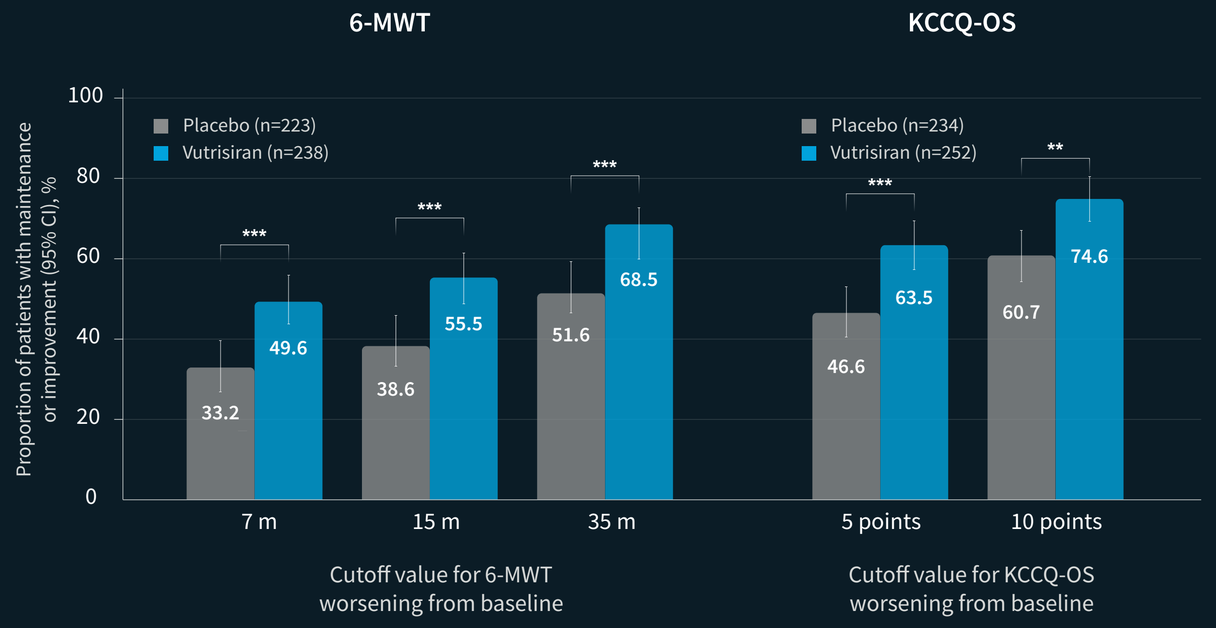
MONOTHERAPY POPULATION | **OVERALL POPULATION**



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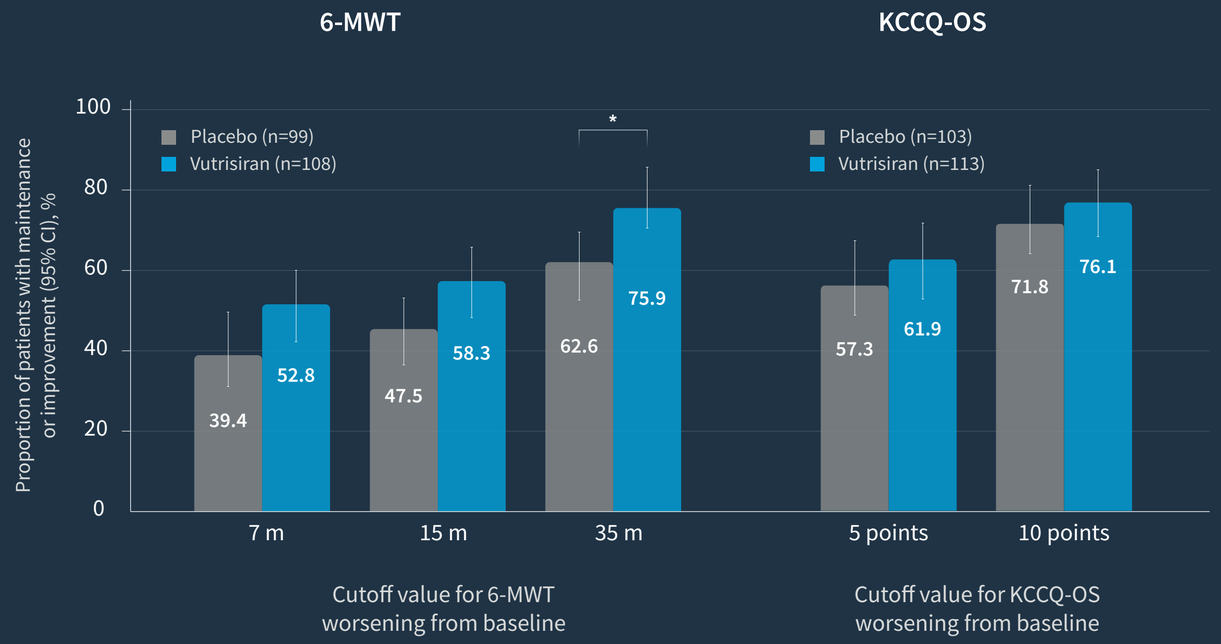
ANALYSES OF SECONDARY ENDPOINTS

Baseline tafamidis subgroup

Patients treated with vutrisiran had maintained or improved functional capacity, health status and quality of life over 30 months[1]

More patients treated with vutrisiran maintained or improved functional capacity, health status, and quality of life over 30 months compared with placebo, across all cutoff values applied



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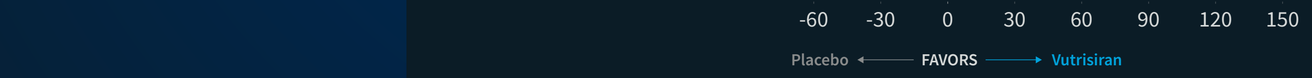
Benefits in functional capacity, health status, and QOL observed in patients treated with vutrisiran were consistent across the prespecified subgroups and KCCQ-OS subdomains[1]

Clinical benefits with vutrisiran on **functional capacity** vs placebo were consistent across prespecified subgroups

6-MWT | KCCQ-OS + | KCCQ-OS SUBDOMAINS +

Change From Baseline to Month 30 in 6-MWT

	LS mean difference, m (vutrisiran vs placebo)	95% CI
Monotherapy population (N=395)	32.09	(14.03 to 50.15)
Age		
<75 years (n=153)	37.35	(8.79 to 65.90)
≥75 years (n=242)	29.83	(6.67 to 52.99)
ATTR amyloidosis disease type		
hATTR (n=48)	53.07	(-7.44 to 113.58)
wtATTR (n=347)	29.66	(10.74 to 48.58)
NYHA class		
I/II (n=368)	29.47	(10.67 to 48.26)
III (n=27)	72.19	(2.70 to 141.68)
Baseline NT-proBNP		
≤2000 ng/L (n=188)	44.02	(17.46 to 70.58)
>2000 ng/L (n=207)	32.06	(8.64 to 55.48)
Overall population (N=654)	26.46	(13.38 to 39.55)
Age		
<75 years (n=257)	31.02	(10.60 to 51.44)
≥75 years (n=397)	24.60	(7.66 to 41.55)
Baseline tafamidis use		
No (n=395)	32.09	(14.03 to 50.15)
Yes (n=259)	18.44	(0.42 to 36.47)
ATTR amyloidosis disease type		
hATTR (n=76)	14.04	(-30.04 to 58.12)
wtATTR (n=578)	27.70	(13.96 to 41.43)
NYHA class		
I/II (n=592)	26.53	(12.67 to 40.39)
III (n=62)	28.39	(-12.10 to 68.89)
Baseline NT-proBNP		
≤2000 ng/L (n=342)	35.19	(17.58 to 52.81)
>2000 ng/L (n=312)	21.71	(2.80 to 40.62)



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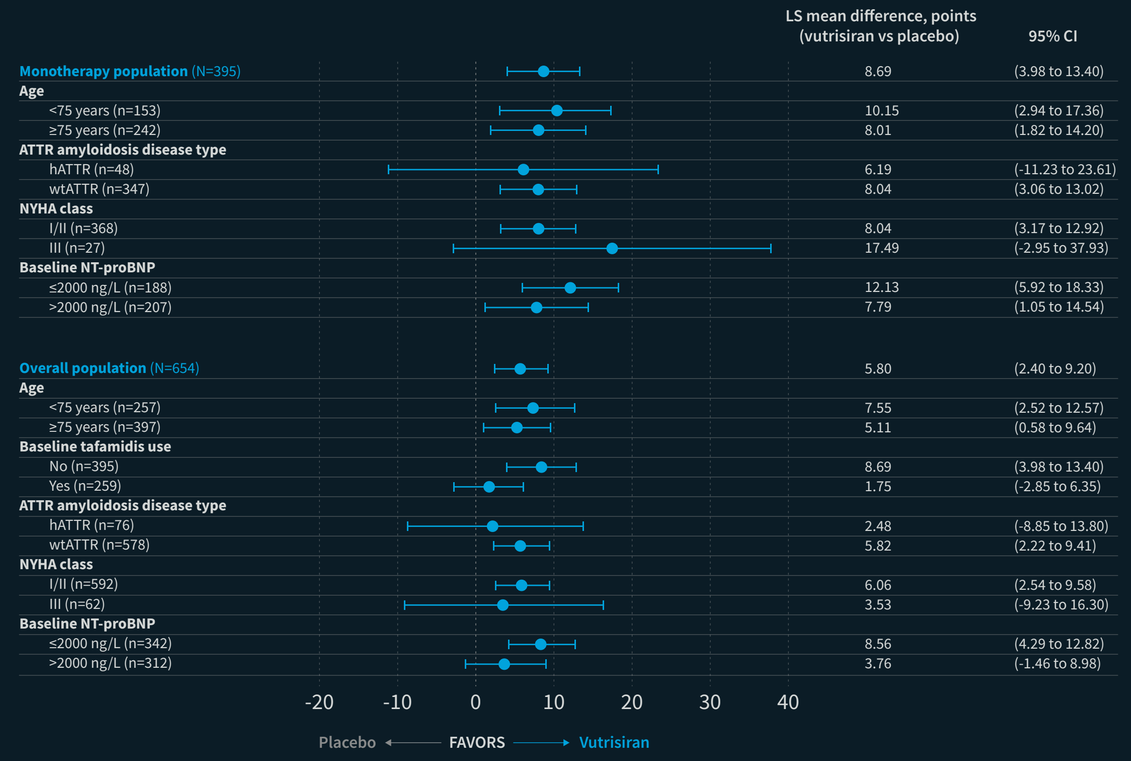
Benefits in functional capacity, health status, and QOL observed in patients treated with vutrisiran were consistent across the prespecified subgroups and KCCQ-OS subdomains[1]

Clinical benefits with vutrisiran on **health status and QOL** vs placebo were consistent across prespecified subgroups

6-MWT | **KCCQ-OS** | KCCQ-OS SUBDOMAINS

Change From Baseline to Month 30 in KCCQ-OS



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1. Sheikh FH, et al. *J Am Coll Cardiol.* 2025;85:1943-1955. https://www.jacc.org/doi/10.1016/j.jacc.2025.03.454

ABBREVIATIONS

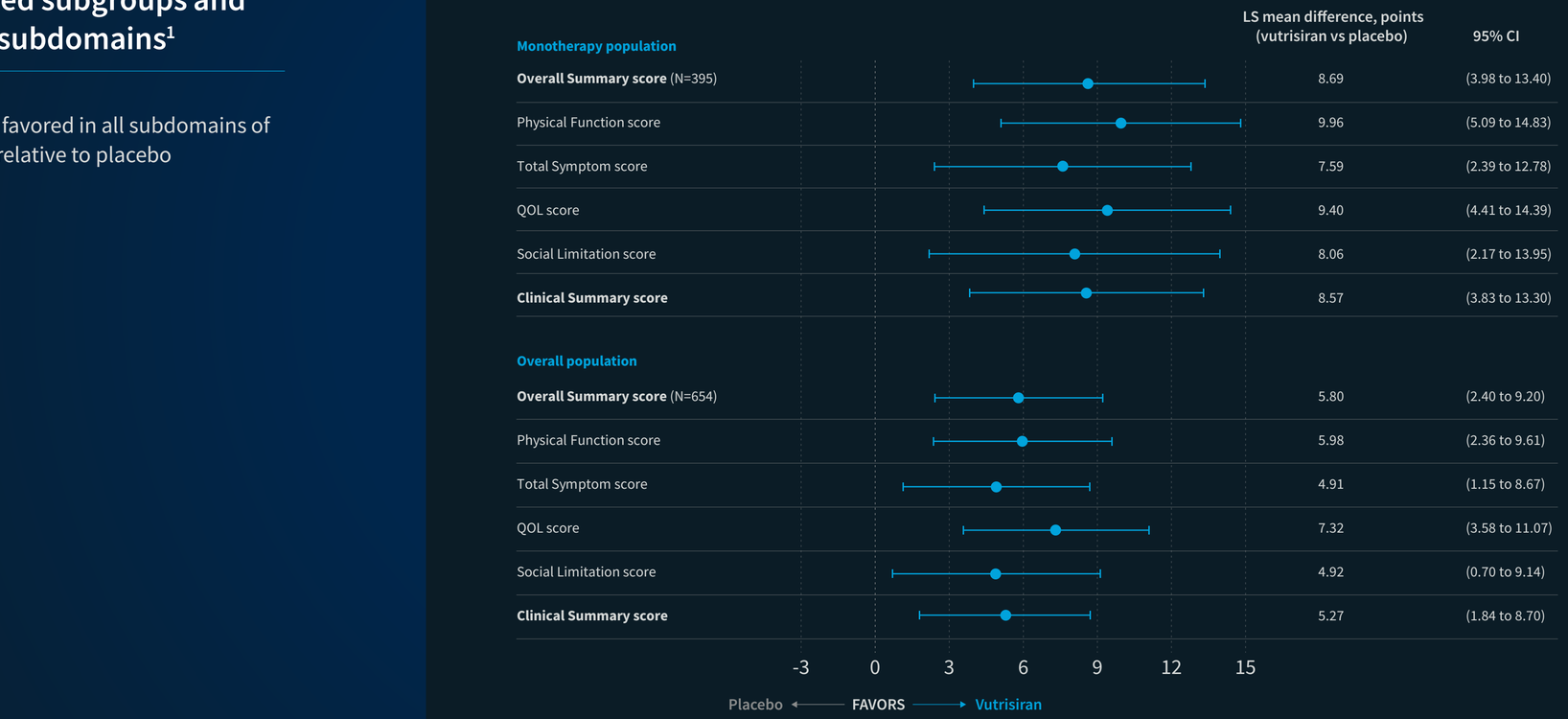
6-MWT, 6-minute walk test; **ATTR**, transthyretin amyloidosis; **CI**, confidence interval; **hATTR**, hereditary transthyretin amyloidosis; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **LS**, least squares; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **NYHA**, New York Heart Association; **QOL**, quality of life; **wtATTR**, wild-type transthyretin amyloidosis.

Benefits in functional capacity, health status, and QOL observed in patients treated with vutrisiran were consistent across the prespecified subgroups and KCCQ-OS subdomains[1]

Vutrisiran was favored in all subdomains of the **KCCQ-OS** relative to placebo

6-MWT | KCCQ-OS | **KCCQ-OS SUBDOMAINS**

Change From Baseline to Month 30 in KCCQ-OS Subdomains



REFERENCE

1. Sheikh FH, et al. *J Am Coll Cardiol.* 2025;85:1943-1955. https://www.jacc.org/doi/10.1016/j.jacc.2025.03.454

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Compared with placebo, vutrisiran reduced the risk of the composite primary endpoint by 33% in the monotherapy population, and 28% in the overall population[1]

Components of the composite endpoint (monotherapy population)

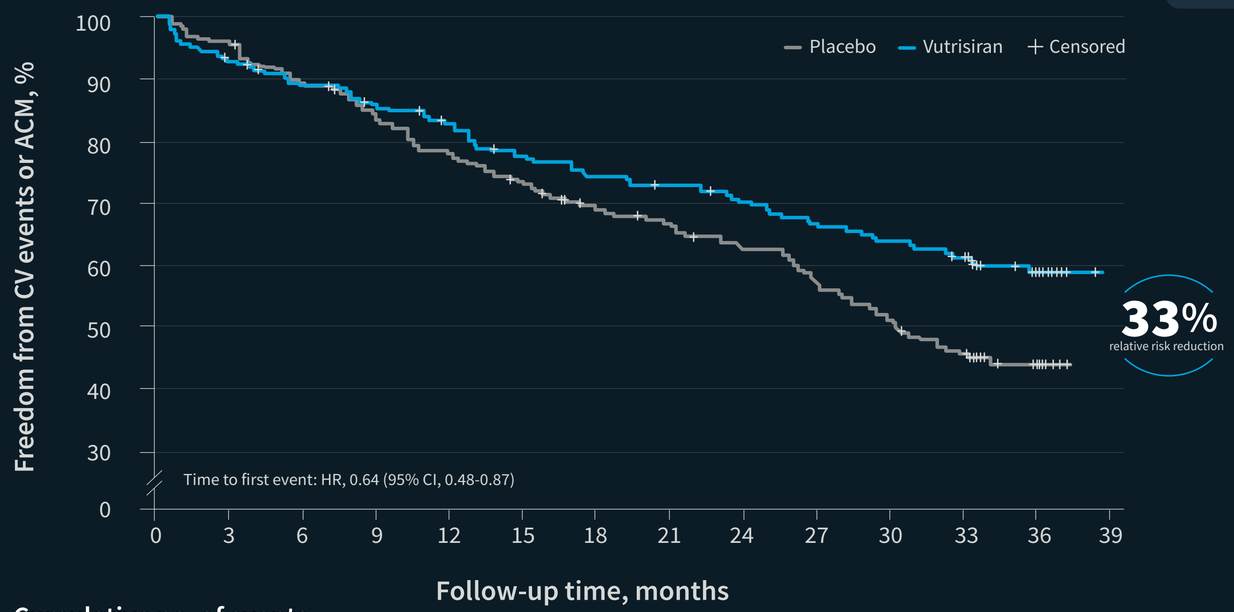
Death from any cause:
HR, 0.71 (95% CI, 0.47-1.06), *P*=0.12

Recurrent CV events:
RRR, 0.68 (95% CI, 0.53-0.86), *P*=0.001

Number needed to treat to prevent one all-cause mortality/CV event over 36 months: **3**[2,3]

MONOTHERAPY POPULATION | OVERALL POPULATION

Time to First CV Event or All-Cause Mortality[a]



Cumulative no. of events

Placebo	0	22	43	60	72	93	105	105
Vutrisiran	0	22	34	49	57	69	76	76

From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.

Composite of all-cause mortality and recurrent CV events during the double-blind period (33-36 months) in the monotherapy population. Analysis for components of the composite not adjusted for multiplicity.

Primary analysis: HR, 0.67 (95% CI, 0.49-0.93), *P*=0.02.

[a]The primary endpoint was a composite of death from any cause and recurrent CV events (defined as CV hospitalizations or urgent visits for heart failure).[1]

REFERENCES

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

2. Fontana M, et al. Presented at: European Society of Cardiology Congress; August 30-September 2, 2024; London, UK.

3. Alnylam Pharmaceuticals. Data on file.

ABBREVIATIONS

ACM, all-cause mortality; **CI**, confidence interval; **CV**, cardiovascular; **HR**, hazard ratio; **RRR**, relative rate ratio.

Compared with placebo, vutrisiran reduced the risk of the composite primary endpoint by 33% in the monotherapy population, and 28% in the overall population[1]

Components of the composite endpoint (overall population)

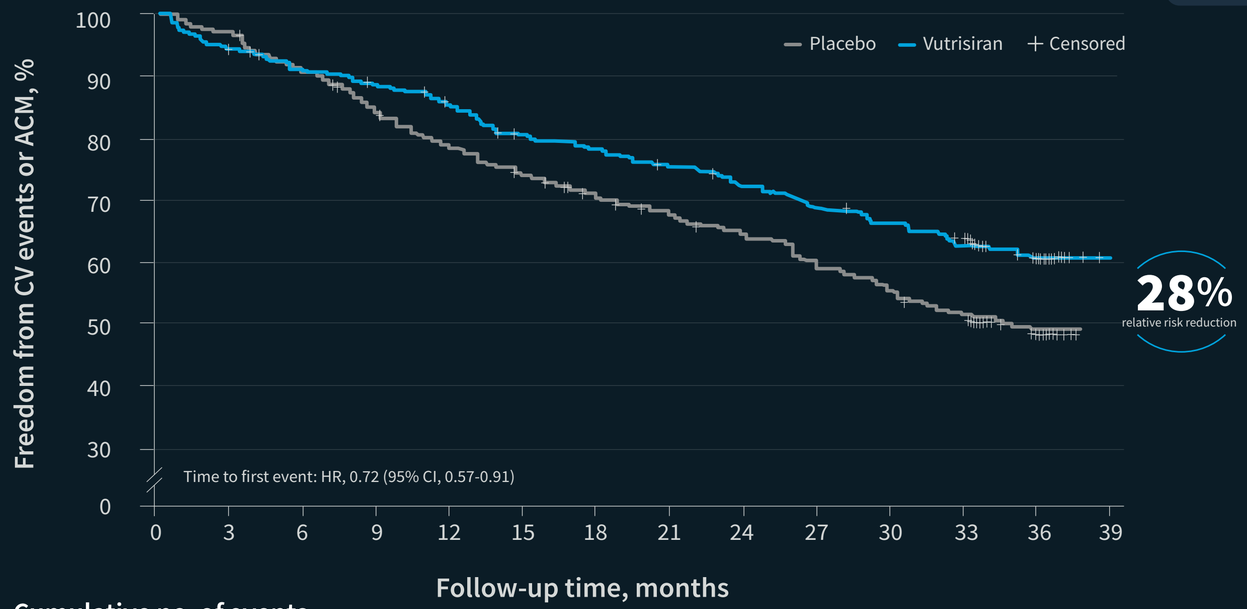
Death from any cause:
HR, 0.69 (95% CI, 0.49-0.98), *P*=0.04

Recurrent CV events:
RRR, 0.73 (95% CI, 0.61-0.88), *P*=0.001

Number needed to treat to prevent one all-cause mortality/CV event over 36 months: **4**[2,3]

MONOTHERAPY POPULATION | **OVERALL POPULATION**

Time to First CV Event or All-Cause Mortality[a]



Cumulative no. of events

Placebo	0	31	70	96	115	142	159	159
Vutrisiran	0	30	50	72	90	110	125	125

From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.

Composite of all-cause mortality and recurrent CV events during the double-blind period (33-36 months) in the overall population. Analysis for components of the composite not adjusted for multiplicity.

Primary analysis: HR, 0.72 (95% CI, 0.56-0.93), *P*=0.01.

[a]The primary endpoint was a composite of death from any cause and recurrent CV events (defined as CV hospitalizations or urgent visits for heart failure).[1]

REFERENCES

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

2. Fontana M, et al. Presented at: European Society of Cardiology Congress; August 30-September 2, 2024; London, UK.

3. Alnylam Pharmaceuticals. Data on file.

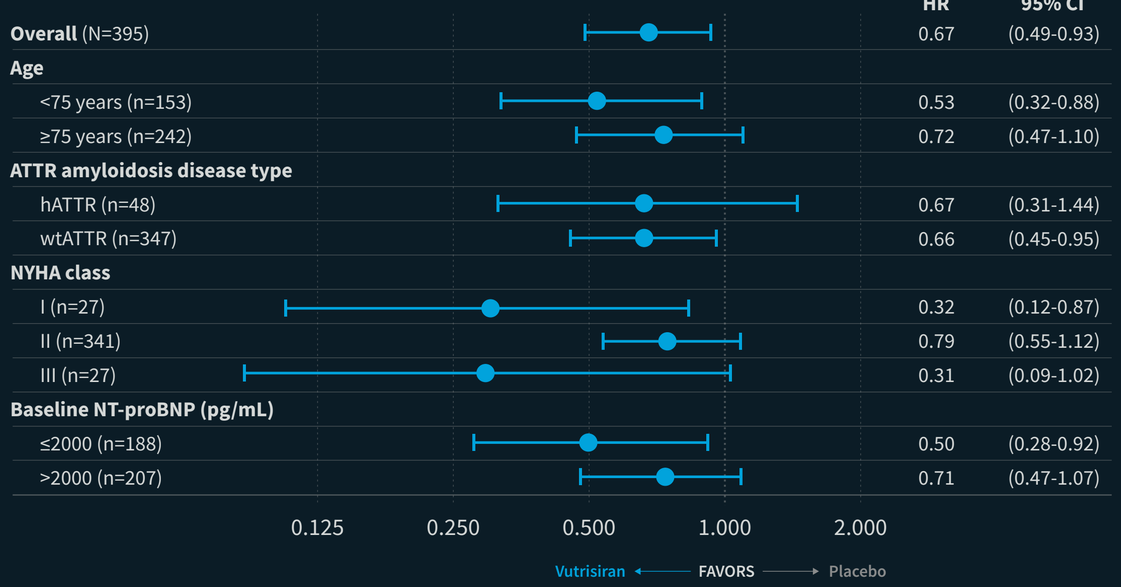
ABBREVIATIONS

ACM, all-cause mortality; **CI**, confidence interval; **CV**, cardiovascular; **HR**, hazard ratio; **RRR**, relative rate ratio.

Patients treated with vutrisiran had similar benefit across all prespecified subgroups (monotherapy and overall populations) with respect to death from any cause and recurrent CV events[1,2]

MONOTHERAPY POPULATION | OVERALL POPULATION

Subgroup Analyses of the Primary Composite Endpoint[1,2]



From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.

Composite of all-cause mortality and recurrent CV events during the double-blind period (33-36 months) in the overall population.[1,2]

REFERENCES

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44.

2. Maurer MS, et al. *J Am Coll Cardiol*. 2025;85:1927-1939. https://www.jacc.org/doi/10.1016/j.jacc.2025.03.477

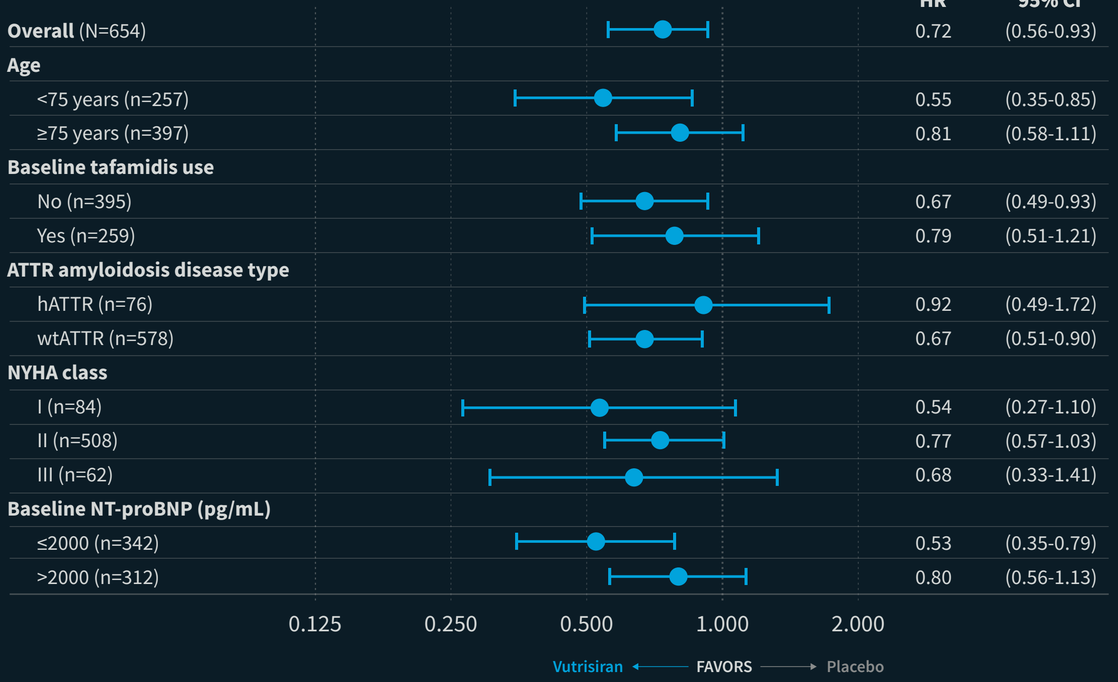
ABBREVIATIONS

ATTR, transthyretin amyloidosis; **CI**, confidence interval; **CV**, cardiovascular; **hATTR**, hereditary transthyretin amyloidosis; **HR**, hazard ratio; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **NYHA**, New York Heart Association; **wtATTR**, wild-type transthyretin amyloidosis.

Patients treated with vutrisiran had similar benefit across all prespecified subgroups (monotherapy and overall populations) with respect to death from any cause and recurrent CV events[1,2]

MONOTHERAPY POPULATION | **OVERALL POPULATION**

Subgroup Analyses of the Primary Composite Endpoint[1,2]



From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.

Composite of all-cause mortality and recurrent CV events during the double-blind period (33-36 months) in the overall population.[1,2]

REFERENCES

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44.

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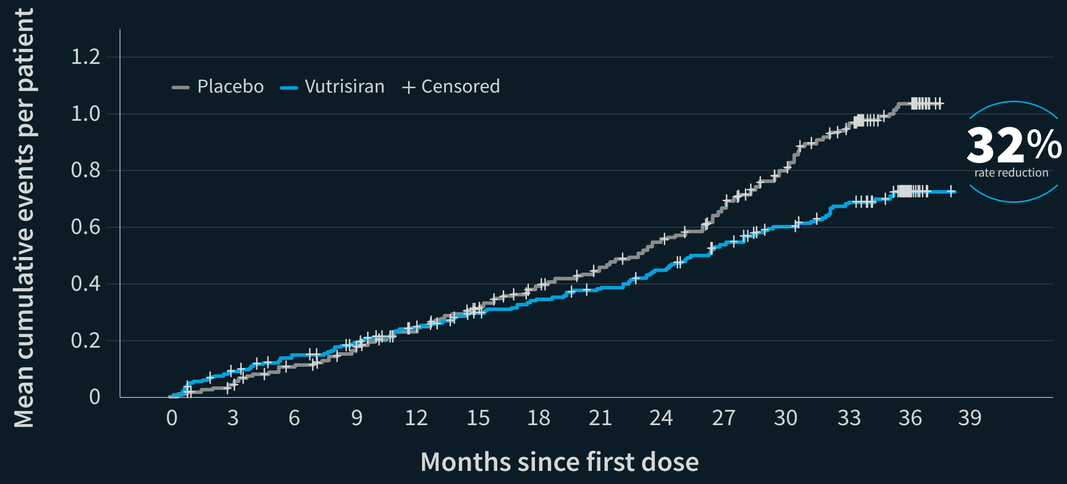
Patients treated with vutrisiran had a reduced risk of CV events[a] through 36 months vs patients treated with placebo[1]

MONOTHERAPY POPULATION | OVERALL POPULATION

Rate Reduction of 32% Through 36 Months in the Monotherapy Population



	Vutrisiran (n=196)	Placebo (n=199)
Events per 100 person-years (SE)	20.67 (9.75)	30.58 (8.28)
Rate ratio (95% CI)	0.68 (0.53-0.86)	
P-value	<0.01	

[a]CV events include CV hospitalizations and urgent HF visits.

REFERENCE

1. Witteles RM, et al. *J Am Coll Cardiol.* 2025;85:1959-1970.

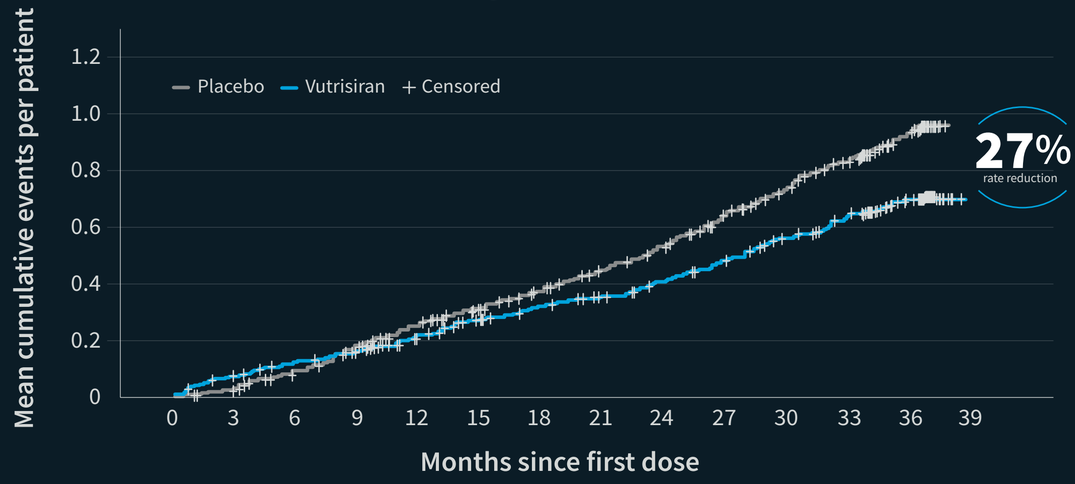
ABBREVIATIONS

CI, confidence interval; **CV**, cardiovascular; **HF**, heart failure; **SE**, standard error.

Patients treated with vutrisiran had a reduced risk of CV events[a] through 36 months vs patients treated with placebo[1]

MONOTHERAPY POPULATION | **OVERALL POPULATION**

Rate Reduction of 27% Through 36 Months in the Overall Population



	Vutrisiran (n=326)	Placebo (n=328)
Events per 100 person-years (SE)	21.09 (7.35)	28.76 (6.49)
Rate ratio (95% CI)	0.73 (0.61-0.88)	
P-value	<0.01	

[a]CV events include CV hospitalizations and urgent HF visits.

REFERENCE

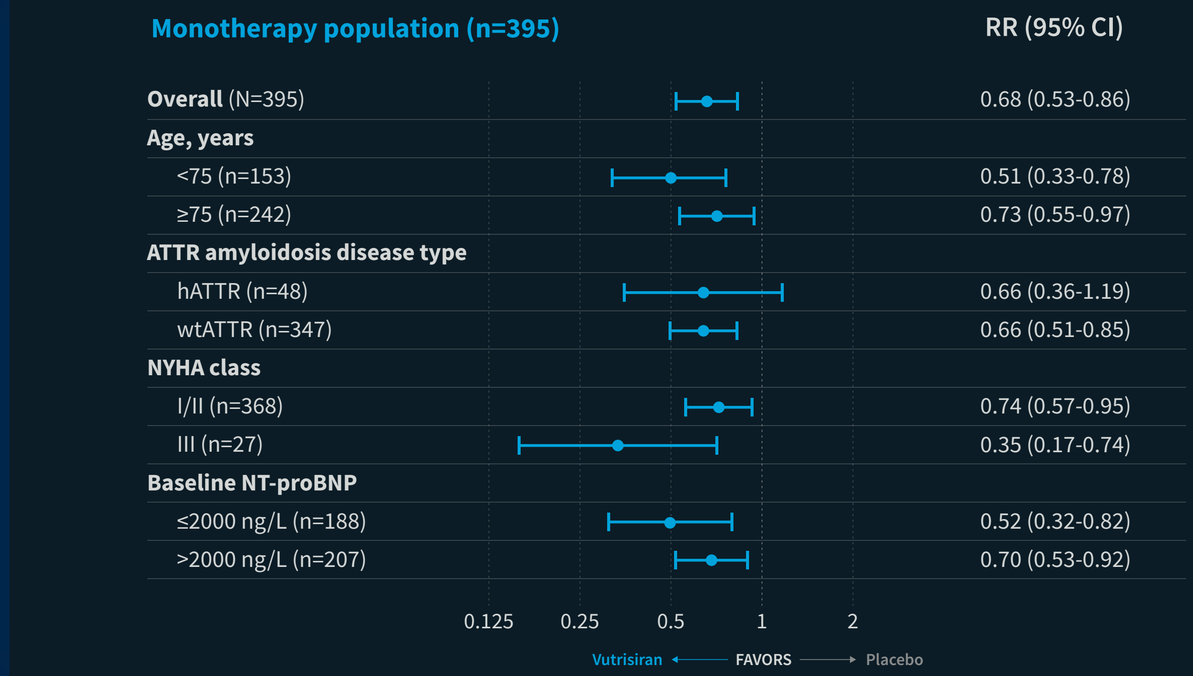
1. Witteles RM, et al. *J Am Coll Cardiol.* 2025;85:1959-1970.

ABBREVIATIONS

CI, confidence interval; **CV**, cardiovascular; **HF**, heart failure; **SE**, standard error.

CV events in prespecified subgroups consistently favored patients treated with vutrisiran[1]

MONOTHERAPY POPULATION | OVERALL POPULATION



Analyzed using Poisson regression model including treatment group, baseline tafamidis use, and log-transformed NT-proBNP as covariates, and the logarithm of the follow-up time as an offset variable. Analysis is based on subgroup data only. For subgroup analysis of baseline tafamidis use, the model includes treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group as covariates.

REFERENCE

1. Witteles RM, et al. *J Am Coll Cardiol*. 2025;85:1959-1970 (and supplementary appendix). https://www.jacc.org/doi/10.1016/j.jacc.2025.04.008

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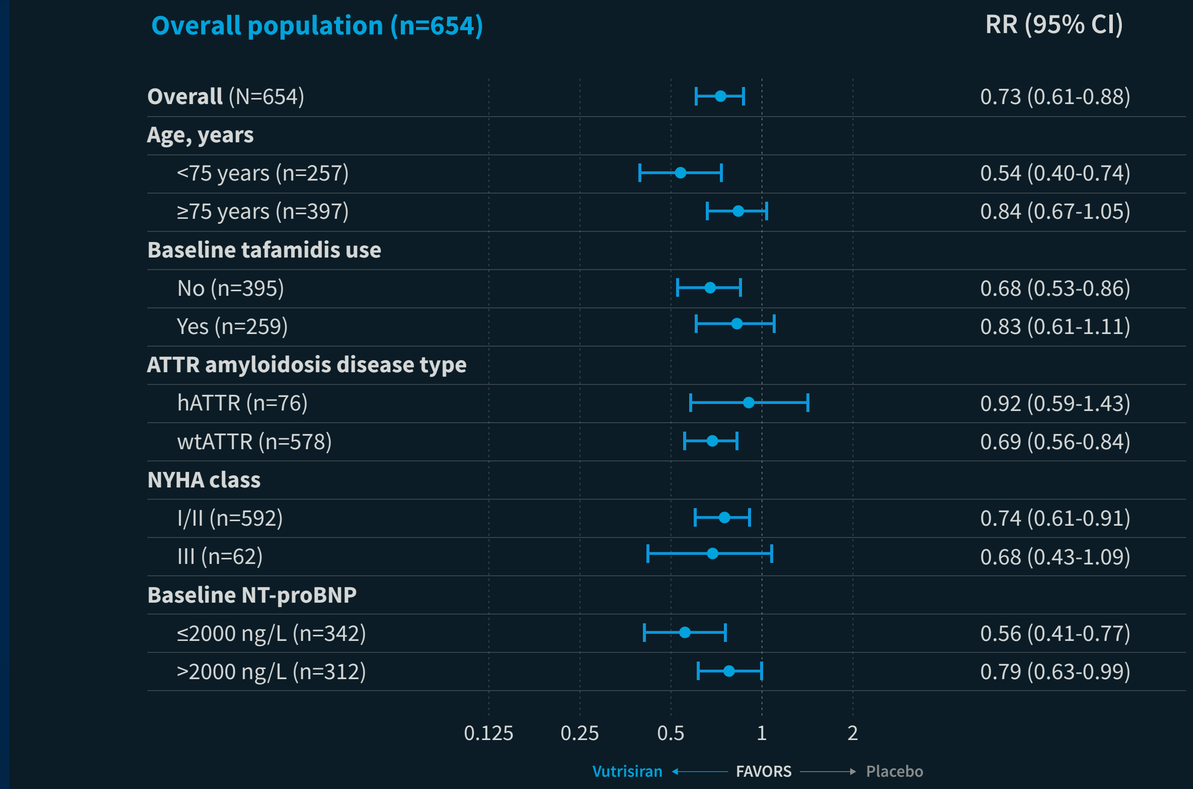
CV events in prespecified subgroups consistently favored patients treated with vutrisiran[1]

MONOTHERAPY POPULATION | **OVERALL POPULATION**



Analyzed using Poisson regression model including treatment group, baseline tafamidis use, and log-transformed NT-proBNP as covariates, and the logarithm of the follow-up time as an offset variable. Analysis is based on subgroup data only. For subgroup analysis of baseline tafamidis use, the model includes treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group as covariates.

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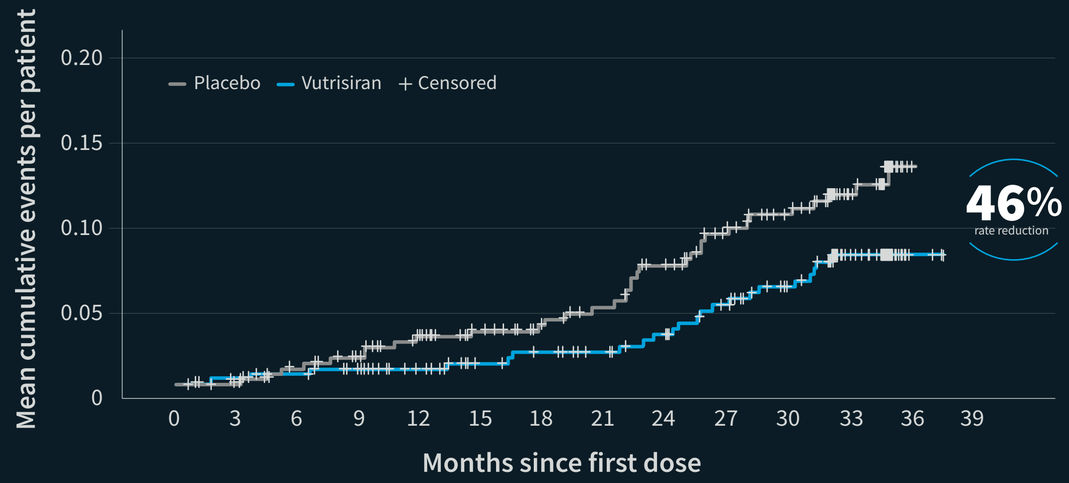
Patients treated with vutrisiran had a reduced rate of urgent HF visits, HF hospitalizations, and CV event components through 36 months vs patients treated with placebo (overall population)[1]

These results demonstrate the robust and consistent effect of vutrisiran across a spectrum of CV and HF outcomes, with a notably large impact on urgent HF visits

URGENT HF VISITS | HF HOSPITALIZATIONS + | CV EVENT COMPONENTS +

Rate Reduction Through 36 Months for Urgent HF Visits[1]



No. at risk (cumulative no. of events)

Placebo	328 (0)	318 (3)	305 (8)	284 (10)	273 (21)	252 (29)	73 (34)	0 (34)
Vutrisiran	326 (0)	320 (2)	305 (3)	291 (6)	281 (8)	268 (17)	87 (22)	0 (22)

	Vutrisiran (n=326)	Placebo (n=328)
Events per 100 person-years (SE)	2.01 (25.17)	3.70 (18.16)
Rate ratio (95% CI)	0.54 (0.30-0.98)	
P-value	0.041	

HF hospitalizations included all hospitalizations adjudicated as HF admissions. Urgent HF visits included healthcare visits adjudicated as urgent HF visits, and per investigator if conducted at home but not adjudicated.[1]

REFERENCES

1. Witteles RM, et al. Presented at: Annual Congress of the Heart Failure Association of the European Society of Cardiology; May 17-20, 2025; Belgrade, Serbia.

2. Witteles RM, et al. *J Am Coll Cardiol.* 2025;85:1959-1970 (and supplementary appendix). https://www.jacc.org/doi/10.1016/j.jacc.2025.04.008

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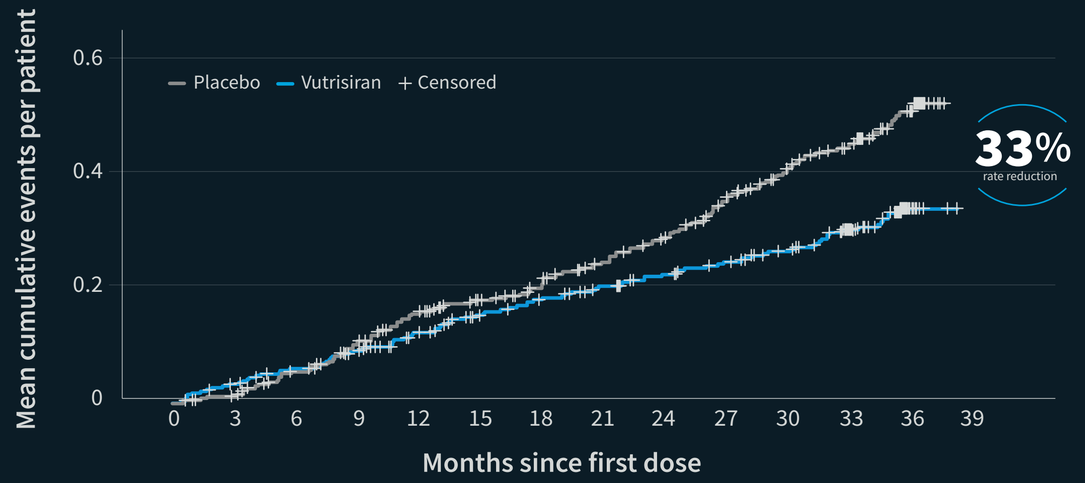
These results demonstrate the robust and consistent effect of vutrisiran across a spectrum of CV and HF outcomes, with a notably large impact on urgent HF visits

URGENT HF VISITS | **HF HOSPITALIZATIONS** | CV EVENT COMPONENTS

Rate Reduction Through 36 Months for HF Hospitalizations[1]



No. at risk (cumulative no. of events)

Placebo	328 (0)	318 (18)	305 (51)	284 (68)	273 (89)	252 (122)	73 (143)	0 (143)
Vutrisiran	326 (0)	320 (20)	305 (40)	291 (57)	281 (69)	268 (81)	87 (98)	0 (98)

	Vutrisiran (n=326)	Placebo (n=328)
Events per 100 person-years (SE)	9.41 (10.84)	14.11 (9.33)
Rate ratio (95% CI)	0.67 (0.52-0.86)	
P-value	0.002	

HF hospitalizations included all hospitalizations adjudicated as HF admissions. Urgent HF visits included healthcare visits adjudicated as urgent HF visits, and per investigator if conducted at home but not adjudicated.[1]

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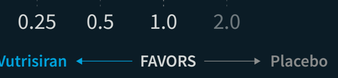
Patients treated with vutrisiran had a reduced rate of urgent HF visits, HF hospitalizations, and CV event components through 36 months vs patients treated with placebo (overall population)[1]

These results demonstrate the robust and consistent effect of vutrisiran across a spectrum of CV and HF outcomes, with a notably large impact on urgent HF visits

URGENT HF VISITS | HF HOSPITALIZATIONS | CV EVENT COMPONENTS

CV and HF Events[1,2]

	Adjusted events per 100 person-years (SE)		RR (95% CI)	*P*-value
	Vutrisiran	Placebo		
CV hospitalizations				
Overall population	18.76 (7.81)	25.05 (6.95)	0.75 (0.62-0.91)	0.004
Monotherapy population	33.95 (13.59)	51.16 (11.75)	0.66 (0.51-0.86)	0.002
HF hospitalizations				
Overall population	9.41 (10.84)	14.11 (9.33)	0.67 (0.52-0.86)	0.002
Monotherapy population	20.77 (17.31)	33.45 (14.58)	0.62 (0.45-0.86)	0.004
Urgent HF visits				
Overall population	2.01 (25.17)	3.70 (18.16)	0.54 (0.30-0.98)	0.041
Monotherapy population	2.46 (47.90)	3.25 (45.31)	0.76 (0.40-1.42)	0.387
Arrhythmia hospitalizations				
Overall population	3.42 (18.46)	3.98 (17.35)	0.86 (0.53-1.41)	0.546
Monotherapy population	3.80 (43.37)	4.91 (40.87)	0.77 (0.41-1.47)	0.434



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ABBREVIATIONS

CI, confidence interval; **CV**, cardiovascular; **HF**, heart failure; **RR**, rate ratio; **SE**, standard error.

Patients treated with vutrisiran had a lower risk of death from any cause through 42 months, compared with placebo[1,2]

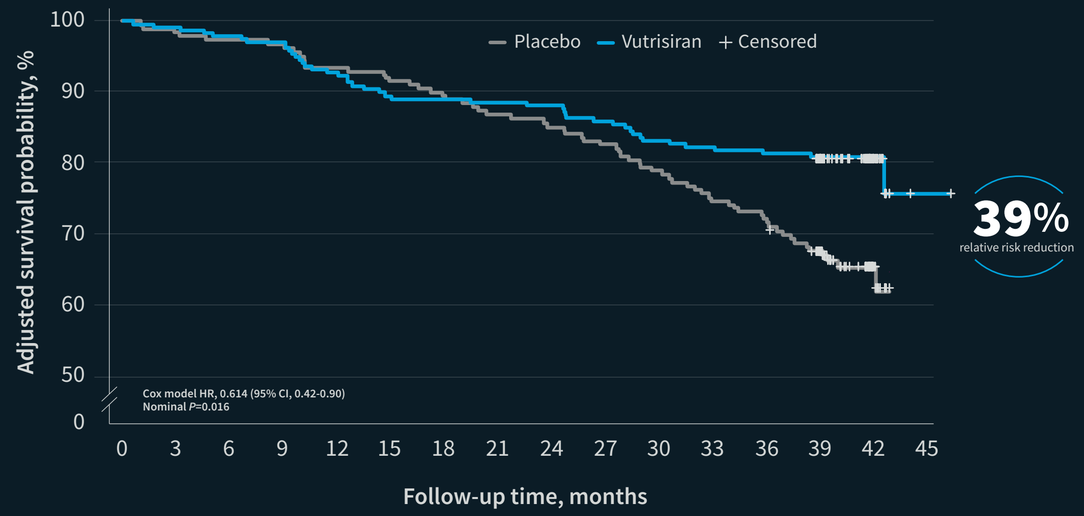
There was a relative risk reduction of **39%** through 42 months in the **monotherapy population**[2]

Forty-two months included up to 6 months of data from the open-label extension, in which all remaining patients randomized to placebo during the double-blind period received vutrisiran[3]

At the time of this analysis[a] (Nov 22, 2024), vital status was ascertained for >99% of randomized patients, and 96.3% of ongoing patients had data through 42 months[2]

MONOTHERAPY POPULATION | OVERALL POPULATION

Time to All-Cause Mortality (Monotherapy Population)[1]



Cumulative no. of events

Placebo	0	5	11	19	27	39	52	63	64
Vutrisiran	0	5	17	25	27	38	42	44	45

[a]Analysis was not controlled for multiplicity.

REFERENCES

1. Alnylam Pharmaceuticals. Data on file.
2. Witteles RM, et al. *J Am Coll Cardiol*. 2025:S0735-1097(25)06170-4.
3. Fontana M, et al. *N Engl J Med*. 2025;392:33-44.

ABBREVIATIONS

CI, confidence interval; **HR**, hazard ratio.

Patients treated with vutrisiran had a lower risk of death from any cause through 42 months, compared with placebo[1,2]

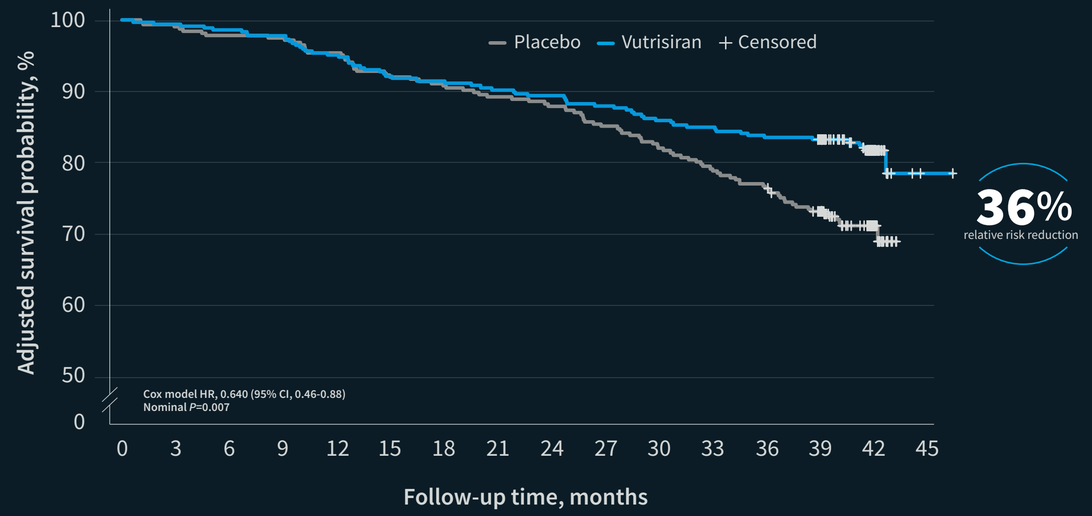
There was a relative risk reduction of **36%** through 42 months in the **overall population**[2]

Forty-two months included up to 6 months of data from the open-label extension, in which all remaining patients randomized to placebo during the double-blind period received vutrisiran[3]

At the time of this analysis[a] (Nov 22, 2024), vital status was ascertained for >99% of randomized patients, and 96.3% of ongoing patients had data through 42 months[2]

MONOTHERAPY POPULATION | **OVERALL POPULATION**

Time to All-Cause Mortality (Overall Population)[1]



Cumulative no. of events

Placebo	0	7	14	29	38	57	75	90	91
Vutrisiran	0	5	18	30	37	49	57	63	64

[a]Analysis was not controlled for multiplicity.

REFERENCES

1. Alnylam Pharmaceuticals. Data on file.
2. Witteles RM, et al. *J Am Coll Cardiol*. 2025:S0735-1097(25)06170-4.
3. Fontana M, et al. *N Engl J Med*. 2025;392:33-44.

ABBREVIATIONS

CI, confidence interval; **HR**, hazard ratio.

PRESPECIFIED SECONDARY ENDPOINT

MONOTHERAPY POPULATION

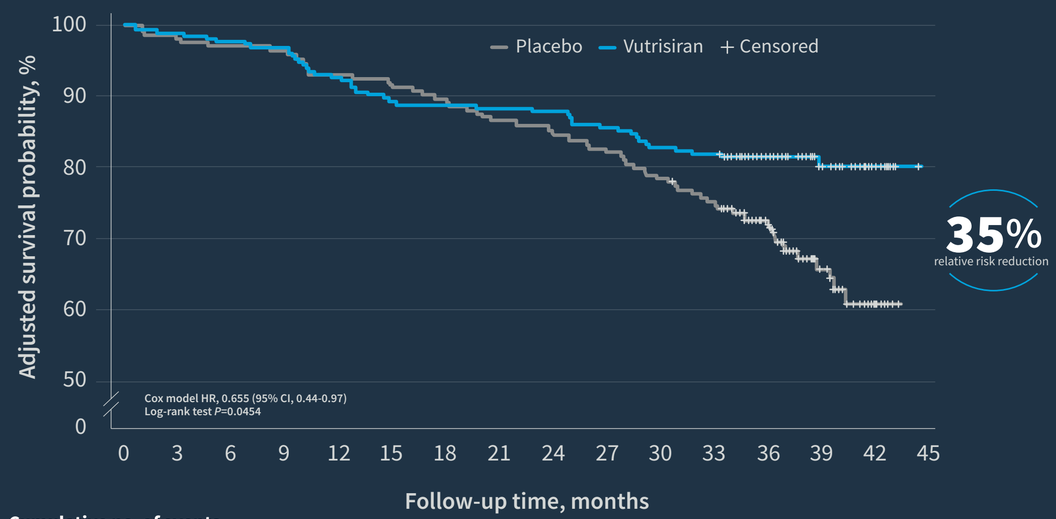
OVERALL POPULATION

Treatment with vutrisiran resulted in a lower risk of death from any cause through 42 months than placebo[1]

In the primary analysis, there was a **35%** reduction in relative risk of all-cause mortality through 42 months[a,b] with vutrisiran vs placebo in the **monotherapy population**[2]

Number needed to treat to prevent 1 death over 42 months: **6**[2,3]

Time to All-Cause Mortality (Monotherapy Population)[2]



Cumulative no. of events

Placebo	0	5	11	19	27	39	51	58	58
Vutrisiran	0	5	17	25	27	38	41	43	43

From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.

[a]This included up to 6 months of data from the open-label extension, in which all remaining patients in the placebo arm were eligible to receive vutrisiran.[1,2]

[b]At the time of this initial analysis (May 8, 2024), 42.4% of patients had complete data through 42 months.[4]

CI, confidence interval; **HR**, hazard ratio.

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix). **2.** Fontana M, et al. Presented at: European Society of Cardiology Congress; August 30-September 2, 2024; London, UK. **3.** Alnylam Pharmaceuticals. Data on file. **4.** Witteles RM, et al. *J Am Coll Cardiol*. 2025:S0735-1097(25)06170-4.

PRESPECIFIED SECONDARY ENDPOINT

MONOTHERAPY POPULATION

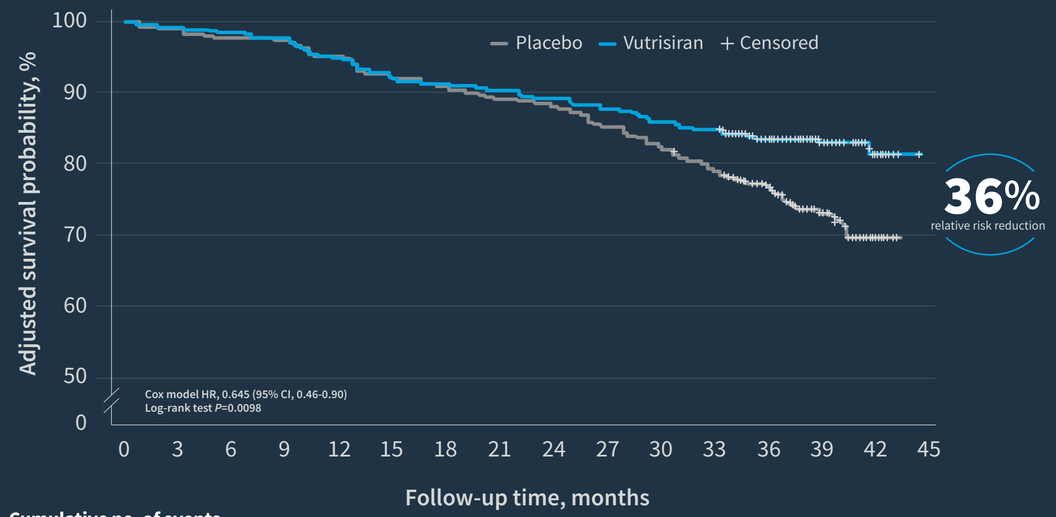
OVERALL POPULATION

Treatment with vutrisiran resulted in a lower risk of death from any cause through 42 months than placebo[1]

In the primary analysis, there was a **36%** reduction in relative risk of all-cause mortality through 42 months[a,b] with vutrisiran vs placebo in the **overall population**[2]

Number needed to treat to prevent 1 death over 42 months: **9**[2,3]

Time to All-Cause Mortality (Overall Population)[2]



Cumulative no. of events

Placebo	0	7	14	29	38	57	74	85	85
Vutrisiran	0	5	18	30	37	49	56	60	60

From N Engl J Med, Fontana et al., Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy, 392:33-44. ©2024 Massachusetts Medical Society. Figure adapted with permission from Massachusetts Medical Society.

[a]This included up to 6 months of data from the open-label extension, in which all remaining patients in the placebo arm were eligible to receive vutrisiran.[1,2]

[b]At the time of this initial analysis (May 8, 2024), 42.4% of patients had complete data through 42 months.[4]

CI, confidence interval; **HR**, hazard ratio.

1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix). **2.** Fontana M, et al. Presented at: European Society of Cardiology Congress; August 30-September 2, 2024; London, UK. **3.** Alnylam Pharmaceuticals. Data on file. **4.** Witteles RM, et al. *J Am Coll Cardiol*. 2025:S0735-1097(25)06170-4.

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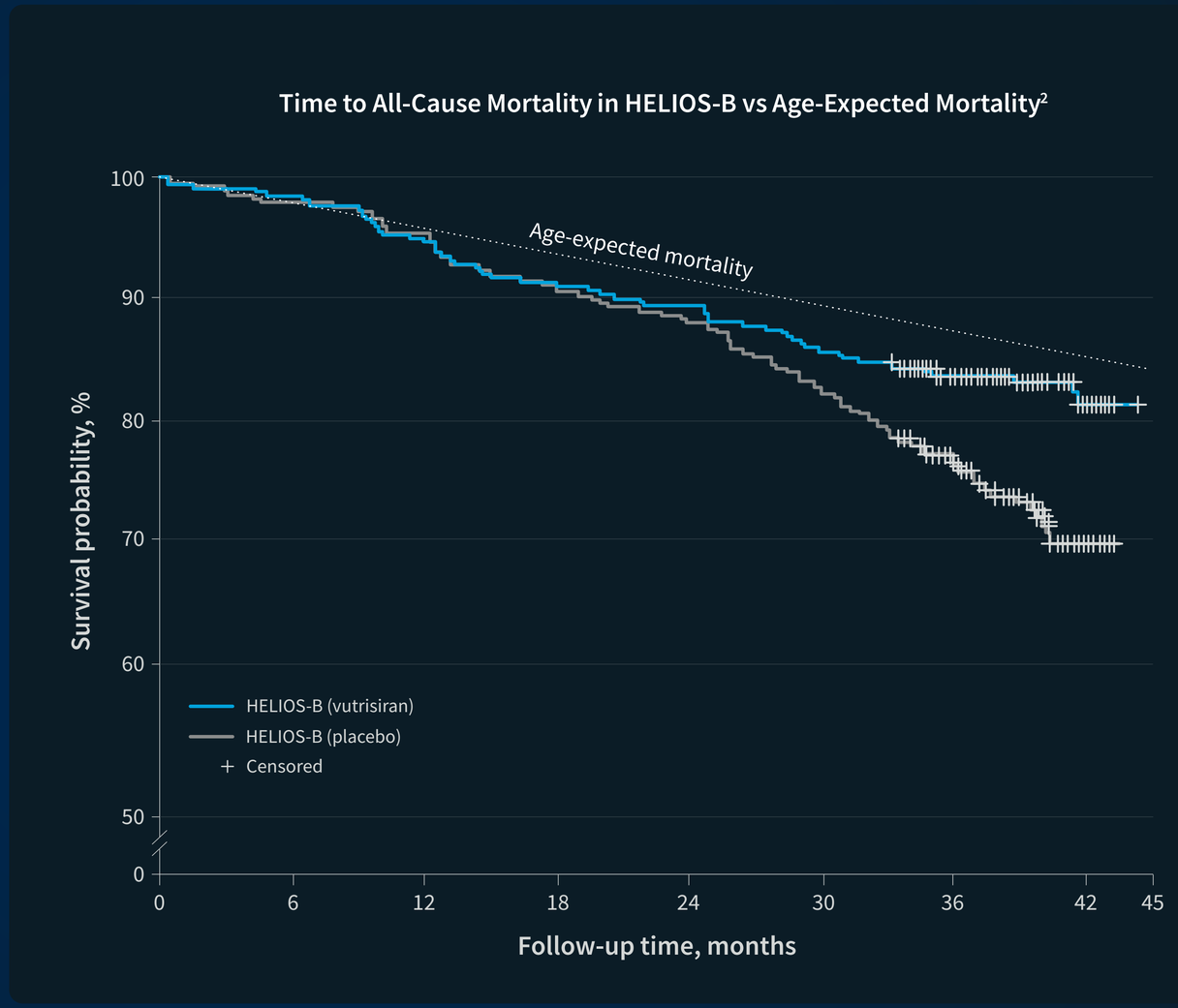
In the overall population of HELIOS-B,[1] the overall mortality in the vutrisiran arm approached the age-expected mortality for an average, similarly aged person without ATTR-CM[2]

Alongside HELIOS-B data, population age-expected mortality is also depicted, based upon the Social Security Actuarial Life Table (4.1% mortality per year based upon 2019 Life Table for median age of 77 years with 91% males)[2]



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ABBREVIATION

ATTR-CM, transthyretin amyloidosis with cardiomyopathy.

Safety in the overall population during the double-blind period (33-36 months)[1]

- In the overall population, the proportion of patients with at least 1 AE was similar between treatment arms (vutrisiran, 99% [n=322]; placebo, 98% [n=323])[1]
- In the vutrisiran and placebo arms, SAEs occurred in 62% (n=201) and 67% (n=220) of patients, respectively, and AEs leading to study drug discontinuation occurred in 3% (n=10) and 4% (n=13) of patients, respectively[1]
- No clinically relevant changes in laboratory measures were observed in either treatment arm[1]
- All patients were instructed to take the recommended daily allowance of vitamin A[1]
- Safety and tolerability profiles were consistent with those observed in previous clinical studies[1,2]

Safety Summary (Overall Population)[1]

Event, n (%)	**Vutrisiran** (n=326)	**Placebo** (n=328)
At least 1 AE	322 (99)	323 (98)
AEs occurring in ≥15% of patients in either arm		
Cardiac failure	101 (31)	128 (39)
COVID-19	87 (27)	99 (30)
Atrial fibrillation	69 (21)	68 (21)
Gout	48 (15)	51 (16)
Dyspnea	43 (13)	51 (16)
Fall	42 (13)	69 (21)
Any SAE[a]	201 (62)	220 (67)
Any severe AE[a]	158 (48)	194 (59)
SAEs occurring in ≥5% of patients in either arm		
Cardiac failure	38 (12)	57 (17)
Atrial fibrillation	26 (8)	20 (6)
Cardiac failure acute	13 (4)	18 (5)
Cardiac AEs	227 (70)	242 (74)
Cardiac SAEs	116 (36)	124 (38)
Any AE leading to discontinuation	10 (3)	13 (4)
Any AE leading to death[b]	49 (15)	63 (19)

[a]SAEs were defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators. All AEs were graded for severity. Severe AEs were defined as AEs for which more than minimal, local, or noninvasive intervention was received; which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.[1]

[b]All fatal SAEs were summarized, regardless of the treatment-emergent classification. Deaths that occurred after the end-of-study visit or after the data cutoff date were not included.[1]

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1. Fontana M, et al. *N Engl J Med*. 2025;392:33-44 (and supplementary appendix).

2. Adams D, et al. *Amyloid*. 2023;30:18-26.

ABBREVIATIONS

AE, adverse event; **COVID-19**, coronavirus disease 2019; **SAE**, serious adverse event.

TTR silencing reduces vitamin A levels[1-3]

Decreased vitamin A levels are a known adverse drug reaction of vutrisiran[4]

- Treatment with vutrisiran reduces serum TTR levels,[1,2] resulting in reduced levels of RBP and vitamin A in the serum[2]
- Although TTR is involved in the transport of vitamin A, there is evidence to suggest that vitamin A transport and uptake can occur through alternative mechanisms[5]
- In the HELIOS-A study, vutrisiran reduced the mean steady state serum vitamin A levels by 62% over 9 months.[4] In HELIOS-B, vutrisiran reduced the mean steady state serum vitamin A by 65% over 36 months[4]
- Supplementation at the RDA of vitamin A is advised for patients taking vutrisiran. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with vutrisiran, as serum vitamin A levels do not reflect the total vitamin A in the body[4]
- Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness)[4]

No new safety concerns have been identified to date related to long-term reduction in TTR levels from Alnylam's clinical studies, open-label extension studies, or post-marketing surveillance[1-3,6]

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1. Adams D, et al. *Amyloid*. 2023;30:18-26.
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3. Adams D, et al. *JAMA Neurol*. 2025;82:228-236.
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5. Kawaguchi R, et al. *Membranes (Basel)*. 2015;5:425-453.
6. Alnylam Pharmaceuticals. Data on file.

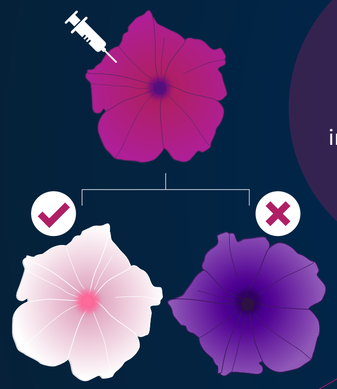
ABBREVIATIONS

RBP, retinol-binding protein; **RDA**, recommended daily allowance; **TTR**, transthyretin.

Alnylam

Alnylam's Continued Innovation in Pioneering RNAi Therapeutics

RNAi therapeutics are being researched for possible applications across diverse therapy areas due to their potential ability to target any gene in the genome[1,2]



1990
Napoli and Jorgensen reported that gene overexpression in violet petunias turned them white instead of deeper violet[3]

2002
Alnylam founded

1998
Fire and Mello reported (Nobel Prize-winning) gene-silencing in worms, coined RNA interference[4]

DISCOVERY OF RNAi

RNAi PLATFORM TECHNOLOGY

CLINICAL PIPELINE

PATISIRAN[5]
First RNAi therapeutic approved (hATTR-PN)

VUTRISIRAN[6]
Approved for hATTR-PN, then ATTR-CM

NUCRESIRAN[7]
and other investigational RNAi therapeutics in development

REFERENCES

1. Traber GM, Yu AM. *Mol Pharmacol.* 2024;106:13-20.
2. Friedrich M, Aigner A. *BioDrugs.* 2022;36:549-571.
3. Napoli C, et al. *Plant Cell.* 1990;2:279-289.
4. Fire A, et al. *Nature.* 1998;391:806-811.
5. ONPATTRO US Prescribing Information. January 2023.
6. AMVUTTRA US Prescribing Information. February 2023.
7. Fontana M, et al. Presented at: Annual Congress of the Heart Failure Association of the European Society of Cardiology; May 17-20, 2025; Belgrade, Serbia.

ABBREVIATIONS

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **RNA**, ribonucleic acid; **RNAi**, ribonucleic acid interference.

FUTURE OF RNAi THERAPEUTICS | DISCOVER OUR RNAi PIPELINE | TRITON-CM STUDY DESIGN

JUMP TO OUR SCIENCE

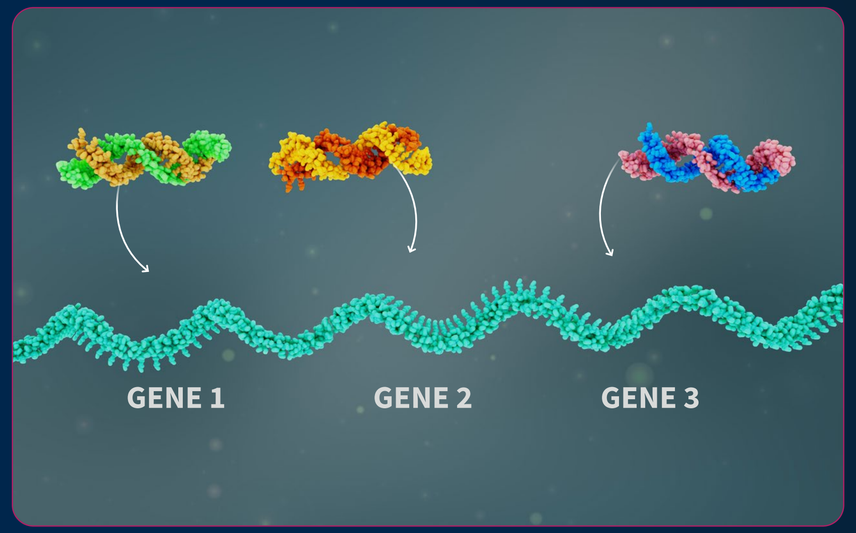
OVERVIEW OF ATTR-CM | RNAi THERAPEUTICS | VUTRISIRAN, AN RNAi THERAPEUTIC IN ATTR-CM | ALNYLAM'S COMMITMENT

Alnylam

RNAi therapeutics are being researched for possible applications across diverse therapy areas due to their potential ability to target any gene in the genome[1,2]

There are numerous potential applications for RNAi therapeutics, including[3,4]:

- **Rare diseases**
- **Cardiovascular diseases**
- **Metabolic diseases**
- **Neurologic diseases**



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4. Alnylam.com. Our pipeline. Updated July 2025. Accessed August 2025. https://www.alnylam.com/alnylam-rnai-pipeline.

ABBREVIATIONS

RNAi, ribonucleic acid interference.

Alnylam

ABBREVIATIONS

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **MAPT**, microtubule associated protein tau; **PLG**, plasminogen; **RNAi**, ribonucleic acid interference; **SOD1**, superoxide dismutase 1; **TTR**, transthyretin.

Programs are researching investigational therapeutics for which efficacy and safety have not been established or approved by a health authority

DISCOVER OUR RNAi PIPELINE

KEY

- TTR
- Rare
- CV
- Metabolic
- Neurologic
- Other

PHASE 1

- **ALN-CFB** — Paroxysmal nocturnal hemoglobinuria[a]
- **AG-236** (ALN-TMP) — Polycythemia vera[a]
- **Zilebesiran + REVERSIR** — Hypertension[b]
- **ALN-4324** (GRB14)[e] — Type 2 diabetes mellitus
- **ALN-PNP** — Non-alcoholic fatty liver disease (NAFLD)[c]
- **ALN-APOC3** — Dyslipidemia[a]
- **ALN-CIDEB** — Metabolic dysfunction-associated steatohepatitis (MASH)[a]
- **Mivelsiran** (ALN-APP) — Alzheimer's disease[d]
- **ALN-HTT02** — Huntington's disease[b]
- **ALN-SOD** — SOD1 amyotrophic lateral sclerosis (ALS)[c]
- **ALN-5288** (MAPT)[e] — Alzheimer's disease[b]
- **ALN-BCAT** — Hepatocellular carcinoma
- **ALN-ANG3** — Healthy volunteers[a]
- **ALN-F1202** — Healthy volunteers[a]

PHASE 2

- **ALN-6400** (PLG)[e] — Bleeding disorders
- **Rapirosiran** (ALN-HSD) — Metabolic dysfunction-associated steatohepatitis (MASH)[a]
- **Mivelsiran** (ALN-APP) — Cerebral amyloid angiopathy (CAA)[d]

PHASE 3

- **Nucresiran** — ATTR-CM
- **Nucresiran** — hATTR-PN
- **Zilebesiran** — Hypertension[b]
- **Cemdisiran** (± pozelimab) — Myasthenia gravis[a]
- **Cemdisiran** (+ pozelimab) — Paroxysmal nocturnal hemoglobinuria[a]
- **Cemdisiran** (± pozelimab) — Geographic atrophy[a]
- **Elebsiran** (+ tobevibart) — Hepatitis D virus infection[a]

RNAi pipeline as of October 2025.

[a] Out-licensed.
[b] Partnered, Alnylam-led development.
[c] Partner-led.
[d] Developed as part of a collaboration with Regeneron.
[e] Gene target.

TRITON-CM[a] is a phase 3 study of nucresiran 300 mg in ATTR-CM[1]

Study Design

Global, double-blind, event-driven, randomized, phase 3 CV outcomes study

Study Regimen

Nucresiran 300 mg or placebo SC every 6 months for a minimum of 24 months (event driven)

Patient Population

Patients with wild-type or any variant ATTR-CM with confirmed cardiomyopathy and NYHA class I-III

Study Status and Timeline

The TRITON-CM study (NCT07052903)[2] is actively recruiting, with an estimated primary completion date of May 28, 2030

Screening period → Double-blind period (minimum 24 months [event driven]) → OLE period (up to 24 months)

1250 patients with ATTR-CM

2:1 RANDOMIZATION

- **Nucresiran** 300 mg SC q6m (n=840)
- **Placebo** SC q6m (n=410)

Primary endpoint

Composite of all-cause mortality and recurrent CV events (event driven)

Secondary endpoints

- Time to first CV event (CV hospitalizations and urgent HF visits) or all-cause mortality
- All-cause mortality
- Recurrent CV events
- Change from baseline in KCCQ-OS

Nucresiran 300 mg SC q6m

[a]TRITON-PN, a separate study conducted in patients with hATTR-PN, is also planned.[3]

REFERENCES

1. Fontana M, et al. Presented at: Annual Congress of the Heart Failure Association of the European Society of Cardiology; May 17-20, 2025; Belgrade, Serbia.

2. ClinicalTrials.gov. Updated July 8, 2025. Accessed July 2025. https://clinicaltrials.gov/study/NCT07052903

3. Alnylam Press Release. Accessed August 2025. https://investors.alnylam.com/press-release?id=28716

ABBREVIATIONS

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; **CV**, cardiovascular; **hATTR-PN**, hereditary transthyretin amyloidosis with polyneuropathy; **HF**, heart failure; **KCCQ-OS**, Kansas City Cardiomyopathy Questionnaire-Overall Summary; **NYHA**, New York Heart Association; **OLE**, open-label extension; **q6m**, every 6 months; **SC**, subcutaneous.

TRITON-CM inclusion and exclusion criteria[1]

Key Inclusion Criteria

- Adults (18-85 years) with wild-type or variant ATTR-CM
- NYHA class I-III
- End-diastolic interventricular septal wall thickness >12 mm for males and >11 mm for females by echocardiography
- NT-proBNP >300 and <8500 ng/L at screening[a]
- Background TTR stabilizer permitted
- Medical history of HF with ≥1 prior hospitalization for HF or clinical evidence[b] of HF that requires treatment with a diuretic
- Demonstration of cardiomyopathy of ATTR amyloidosis by 1 of the following:
  - Documented TTR amyloid deposits in cardiac tissue regardless of MGUS status
  - In the absence of MGUS, ^{99m}Tc scintigraphy with grade 2 or 3 cardiac uptake
  - In the presence of MGUS, documentation of TTR protein in noncardiac tissue and grade 2 or 3 cardiac uptake on ^{99m}Tc scintigraphy

Key Exclusion Criteria

- NYHA class IV HF; or NYHA class III HF and ATTR amyloidosis disease stage III[c]
- PND score ≥IIIA at screening visit[d]
- eGFR <30 mL/min/1.73 m^2
- Non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease
- Received prior TTR-lowering therapy or plan for or anticipate beginning treatment during screening or the first 24 months following randomization

[a]NT-proBNP >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation. [b]Manifested by signs and symptoms of volume overload or elevated intracardiac pressures.
[c]Defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min. [d]Requires cane or stick to walk or uses a wheelchair due to polyneuropathy.

REFERENCE

1. Fontana M, et al. Presented at: Annual Congress of the Heart Failure Association of the European Society of Cardiology; May 17-20, 2025; Belgrade, Serbia.

ABBREVIATIONS

^{99m}Tc, technetium-99m; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **eGFR**, estimated glomerular filtration rate; **HF**, heart failure; **MGUS**, monoclonal gammopathy of undetermined significance; **NYHA**, New York Heart Association; **NT-proBNP**, *N*-terminal prohormone of brain-type natriuretic peptide; **PND**, polyneuropathy disability; **TTR**, transthyretin.