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RESEARCH ARTICLE

# Efficacy and safety of vutrisiran in transthyretin amyloid cardiomyopathy across the age spectrum: The HELIOS-B trial

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**Aims** Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive condition primarily affecting older adults, who are at increased risk of morbidity and mortality. In HELIOS-B, vutrisiran reduced all-cause mortality and recurrent cardiovascular events versus placebo in patients with ATTR-CM. This prespecified analysis evaluated efficacy and safety outcomes by age category (<75, 75 to <80, and ≥80 years) and across age as a continuous measure.

**Methods and results** HELIOS-B randomized patients with ATTR-CM in a 1:1 ratio to vutrisiran 25 mg or placebo every 12 weeks for up to 36 months. Eligible patients were aged 18–85 years. We assessed the primary composite of all-cause mortality and recurrent cardiovascular events, changes in 6-min walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS), and safety outcomes across age groups. Among 654 patients (aged 45–85 years; mean 75.3 ± 6.7), 257 (39.3%) were <75, 201 (30.7%) 75 to <80, and 196 (30.0%) ≥80 years. Vutrisiran reduced the risk of the primary composite outcome in all age categories ($p_{interaction} = 0.56$) and across the age spectrum as a continuous function ($p_{interaction} = 0.50$). Consistent benefits were seen for individual outcome components, with no significant interaction between treatment and age. Functional capacity and quality of life were preserved across age groups ($p_{interaction} = 0.35$ and = 1.00 for KCCQ-OSS and 6MWT, respectively). Safety was comparable across groups, with no increase in adverse events in older patients.

**Conclusions** Vutrisiran reduced all-cause mortality and cardiovascular events and maintained function and quality of life in patients with ATTR-CM across the age spectrum, including those ≥80 years.

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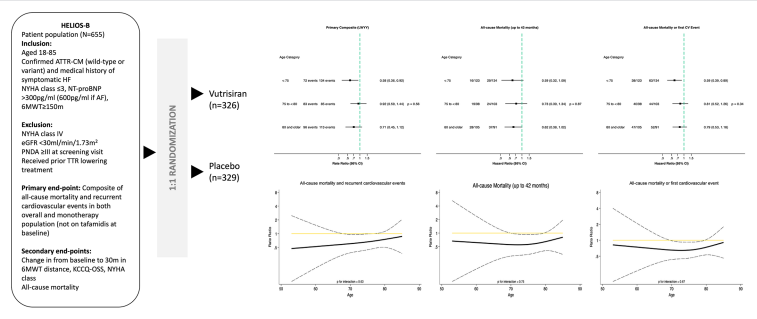
## Graphical Abstract




Summary of the HELIOS-B trial design. Right: Forest (top) and spline (bottom) plots demonstrating the effect of vutrisiran versus placebo on clinical outcomes across age groups in HELIOS-B. Age-stratified outcomes with vutrisiran in transthyretin amyloid cardiomyopathy. 6MWT, 6-min walk test; AF, atrial fibrillation; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire overall summary score; LWYY, Lin-Wei-Yang-Ying; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; TTR, transthyretin.

**Keywords** Transthyretin cardiomyopathy • Vutrisiran • HELIOS-B • Functional capacity • Mortality • Cardiovascular outcomes

# Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, infiltrative cardiomyopathy caused by the deposition of misfolded transthyretin (TTR) fibrils in the myocardial extracellular space.[1] The non-inherited, wild-type disease (ATTRwt) affects mostly elderly patients, with a median age of onset of approximately 75 years and a median survival ranging from 2 to 6 years following diagnosis if untreated.[2] ATTR-CM is associated with substantial morbidity, including progressive heart failure, reduced functional capacity, frequent hospitalizations, and increased mortality.[3]

Older adults with ATTR-CM face a disproportionate burden of disease, including higher risk of death and hospitalization, that significantly contribute to health system costs. Additionally, the high burden of comorbidities in older patients associated with frailty, polypharmacy and the limited remaining lifespan, leads to physician concerns about the possibility of attenuated treatment effects and potential safety issues. These concerns and the limited evidence from clinical trials likely contribute to the observed lower utilization of guideline-directed medical therapies in older adults with heart failure.[4–6] Given the ageing global population, the prevalence of ATTR-CM and its contribution on heart failure-related negative outcomes and healthcare utilization are expected to increase, reinforcing the need for therapies that are both effective and well tolerated in this population.[7]

Over the past decade, stepwise advancements have been made in pharmacotherapy for patients with ATTR-CM. Two drug classes have been shown to reduce mortality in patients with ATTR-CM: stabilizers, which prevent TTR misfolding by stabilizing the TTR protein in its native conformation, and more recently gene silencers, which knock down circulating TTR levels by reducing hepatic TTR production.[8,9] The efficacy and safety of vutrisiran, a gene silencer that rapidly knocks down both wild-type and variant TTR, were evaluated in patients with ATTR-CM in the phase 3 HELIOS-B Study (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149).[10,11] Treatment with vutrisiran led to a lower risk of death from any cause and cardiovascular events compared with placebo and preserved functional capacity and quality of life in patients with ATTR-CM.

This prespecified analysis provides an in-depth evaluation of the efficacy and safety of vutrisiran across the age spectrum, including patients aged ≥80 years.

# Methods

The HELIOS-B trial was an international, multicentre, double-blind, phase 3, randomized, placebo-controlled trial evaluating the efficacy and safety of vutrisiran in patients with ATTR-CM.[11] Adults aged 18–85 years with a confirmed diagnosis of ATTR-CM (either wild-type or variant) based on biopsy-proven TTR amyloid deposition or validated scintigraphy criteria in the absence of monoclonal gammopathy were included.[1,12] Cardiac involvement was required for patients to be included in the study, and was defined by interventricular septal wall thickness >12 mm with a history of heart failure. Patients were required to have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level >300 pg/ml and <8500 pg/ml (or >600 pg/ml and <8500 pg/ml for patients with atrial fibrillation) and to walk at

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**Table 1** **Baseline characteristics by age categories – overall and monotherapy populations**

| | Baseline characteristics by age categories | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall ($n = 654$) (trend-$p$) | | | | Monotherapy ($n = 395$) (trend-$p$) | | | |
| | <75 ($n = 257$) | 75 to <80 ($n = 201$) | ≥80 ($n = 196$) | $p$-values | <75 ($n = 153$) | 75 to <80 ($n = 105$) | ≥80 ($n = 137$) | $p$-value |
| Baseline characteristics | | | | | | | | |
| Age, years | 68.7 ± 5.4 | 77.2 ± 1.4 | 82.2 ± 1.8 | < 0.001 | 69.2 ± 5.2 | 77.2 ± 1.3 | 82.2 ± 1.8 | < 0.001 |
| Male | 233 (90.7) | 191 (95.0) | 181 (92.3) | 0.43 | 137 (89.5) | 100 (95.2) | 124 (90.5) | 0.73 |
| Ethnicity | | | | | | | | |
| White | 207 (80.5) | 165 (82.1) | 180 (91.8) | | 124 (81.0) | 88 (83.8) | 126 (92.0) | 0.008 |
| Asian | 20 (7.8) | 11 (5.5) | 6 (3.1) | | 14 (9.2) | 8 (7.6) | 5 (3.6) | |
| Black or African American | 25 (9.7) | 14 (7.0) | 8 (4.1) | 0.001 | 12 (7.8) | 4 (3.8) | 5 (3.6) | |
| Other | 1 (0.4) | 3 (1.5) | 0 (0.0) | | 1 (0.7) | 3 (2.9) | 0 (0.0) | |
| Not reported | 4 (1.6) | 8 (4.0) | 2 (1.0) | | 2 (1.3) | 2 (1.9) | 1 (0.7) | |
| Comorbidities | | | | | | | | |
| Diabetes | 42 (16.3) | 28 (13.9) | 41 (20.9) | 0.24 | 27 (17.6) | 18 (17.1) | 29 (21.2) | 0.45 |
| Hypertension | 151 (58.8) | 120 (59.7) | 117 (59.7) | 0.83 | 88 (57.5) | 57 (54.3) | 80 (58.4) | 0.90 |
| Ischaemic heart disease | 52 (50.2) | 64 (31.8) | 64 (32.7) | 0.002 | 29 (19.0) | 36 (34.3) | 41 (29.9) | 0.031 |
| ATTR diagnosis history | | | | | | | | |
| Wild-type ATTR | 208 (80.9) | 183 (91.0) | 187 (95.4) | < 0.001 | 121 (79.1) | 97 (92.4) | 129 (94.2) | < 0.001 |
| Time from ATTR diagnosis, years | 1.01 [0.32–2.07] | 0.96 [0.37–1.94] | 0.80 [0.26–1.79] | 0.34 | 0.54 [0.16–1.54] | 0.60 [0.24–1.66] | 0.61 [0.21–1.50] | 0.92 |
| Time from ATTR diagnosis, years | min 0.02, max 11.10 | min 0.04, max 8.39 | min 0.01, max 10.76 | | min 0.02, max 5.80 | min 0.04, max 8.34 | min 0.01, max 5.19 | |
| Tafamidis use | | | | | | | | |
| Baseline tafamidis use | 104 (40.5) | 96 (47.8%) | 59 (30.1) | 0.044 | | | | |
| Tafamidis use duration, months | 11.35 [5.06–17.69] | 10.50 [5.11–18.14] | 9.30 [5.78–16.43] | 0.42 | | | | |
| Tafamidis use duration, months | min 1.12, max 65.31 | min 1.41, max 30.85 | min 1.15, max 65.54 | | | | | |
| Baseline NYHA class | | | | | | | | |
| I | 34 (13.2) | 26 (12.9) | 24 (12.2) | 0.84 | 7 (4.6) | 9 (8.6) | 11 (8.0) | 0.75 |
| II | 199 (77.4) | 155 (77.1) | 154 (78.6) | | 137 (89.5) | 89 (84.8) | 115 (83.9) | |
| III | 24 (9.3) | 20 (10.0) | 18 (9.2) | | 9 (5.9) | 7 (6.7) | 11 (8.0) | |
| Amyloidosis disease NAC stage | | | | | | | | |
| 1 | 183 (71.2) | 134 (66.7) | 120 (61.2) | | 105 (68.6) | 65 (61.9) | 81 (59.1) | 0.08 |
| 2 | 66 (25.7) | 58 (28.9) | 63 (32.1) | 0.018 | 42 (27.5) | 34 (32.4) | 47 (34.3) | |
| 3 | 8 (3.1) | 9 (4.5) | 13 (6.6) | | 6 (3.9) | 6 (5.7) | 9 (6.6) | |
| Biomarkers | | | | | | | | |
| NT-proBNP at baseline, ng/L | 1649 [903–2990] | 2062 [1138–3083] | 2330 [1340–3742] | < 0.001 | 1763 [1029–3194] | 2199 [1258–3455] | 2481 [1325–4056] | 0.018 |
| NT-proBNP at baseline, ng/L | min 317, max 8306 | min 334, max 8892 | min 427, max 8777 | | min 381, max 8306 | min 335, max 8892 | min 427, max 8777 | |
| Troponin I, serum, ng/L | 63.1 [39.3–93.2] | 68.6 [41.1–120.7] | 73.8 [47.3–121.6] | 0.013 | 63.9 [43.3– 104.8] | 74.6 [39.0–133.7] | 71.8 [43.3–126.3] | 0.17 |
| Troponin I, serum, ng/L | min 10.0, max 2315.0 | min 10.0, max 8712.0 | min 10.0, max 30 827.7 | | min 10.0, max 2315.0 | min 10.0, max 992.8 | min 10.0, max 30 827.7 | |
| 6MWT, m | 409.9 ± 99.9 | 369.2 ± 94.0 | 333.9 ± 89.5 | < 0.001 | 404.3 ± 100.7 | 369.7 ± 96.5 | 325.6 ± 86.4 | <0.001 |
| 6MWT | min 60.0, max 664.8 | min 125.2, max 655.1 | min 145.5, max 540.0 | | min 60.0, max 632.0 | min 125.2, max 655.1 | min 145.5, max 540.0 | |

Data are expressed as mean ± standard deviation, *n* (%), or median [interquartile range].
6MWT, 6-min walk test; ATTR, transthyretin amyloidosis; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

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least 150 m during a 6-min walk test. Exclusion criteria included New York Heart Association (NYHA) class IV symptoms, NYHA class III with National Amyloidosis Centre (NAC) stage 3 disease (NT-proBNP >3000 pg/ml and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 $m^2$), non-ATTR-CM, polyneuropathy disability IIIa or greater, and eGFR <30 ml/min/1.73 $m^2$. Participants were randomly assigned 1:1 to receive vutrisiran 25 mg or placebo via subcutaneous injection every 12 weeks. Randomization was stratified by baseline tafamidis use, ATTR subtype (wild-type vs. variant), and NYHA class and age at baseline (NYHA class I or II and age <75 years vs. all others). The study was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice guidelines and all applicable regulatory requirements. All patients provided written informed consent before enrolment.

This prespecified subgroup analysis of the HELIOS-B trial evaluated the efficacy and safety of vutrisiran across the following age categories: <75 years, 75 to <80 years, and ≥80 years. Analyses were conducted in both the overall and monotherapy populations (patients not receiving tafamidis at baseline), that were pre-defined. Baseline characteristics were summarized by age group and compared using linear regression for continuous variables and the $\chi^2$ test for trend for categorical variables. Non-parametric trend testing across age strata was performed using Cuzick's test.

The primary endpoint for this analysis was the composite of all-cause mortality and recurrent cardiovascular events, defined as cardiovascular hospitalizations or urgent visits for heart failure, during the 36-month double-blind treatment period. Rate ratios and 95% confidence intervals for the primary endpoint were estimated within each group using modified Andersen–Gill models (Lin–Wei–Yang–Ying), stratified by baseline tafamidis use and adjusted for TTR genotype (wild-type vs. variant). Recurrent cardiovascular events, a component of the primary endpoint, were also analysed separately. Secondary endpoints for this analysis included all-cause mortality up to 42 months, and changes from baseline to month 30 for 6-min walk test (6MWT) distance and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS). A prespecified analysis also evaluated a composite of all-cause mortality or first cardiovascular event, to assess time-to-first clinically significant outcomes. These outcomes were analysed using Cox or linear regression models, as appropriate.

Restricted cubic spline models were used to assess treatment effect as a continuous function of age, with interaction *p*-values calculated to test for effect modification by age categories and continuously. Safety endpoints, including the incidence of serious adverse events (SAEs) and adverse events leading to treatment discontinuation were summarized descriptively by age group and analysed using logistic regression.

All statistical analyses were performed using STATA version 19.5 (StataCorp, College Station, TX, USA). A *p*-value of <0.05 was considered statistically significant.

# Results

## Patient characteristics

A total of 654 patients were included in this analysis: 257 (39.3%) were aged <75, 201 (30.7%) were 75 to <80, and 196 (30.0%) were ≥80 years. Baseline characteristics (*Table 1*) varied by age in the overall population, with older patients significantly more likely to be white (91.8% in ≥80 years vs. 80.5% in <75 years, $p = 0.001$), while Asian and Black patients were more commonly represented

**Table 2** Clinical outcomes according to age categories (overall population)

| Outcome | <75 years | | | 75 to <80 years | | | ≥80 years | | | Interaction *p*-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vutrisiran (*n* = 123) | Placebo (*n* = 134) | HR or RR (95% CI) | Vutrisiran (*n* = 98) | Placebo (*n* = 103) | HR or RR (95% CI) | Vutrisiran (*n* = 105) | Placebo (*n* = 91) | HR or RR (95% CI) | |
| Composite primary outcome | | | | | | | | | | |
| All-cause mortality and recurrent cardiovascular events | 72 events [21.5/100py] | 134 events [38.7/100py] | RR 0.58 (0.36–0.92) | 83 events [31.1/100py] | 85 events [31.5/100py] | RR 0.92 (0.59–1.44) | 96 events [36.7/100py] | 113 events [50.1/100py] | RR 0.71 (0.45–1.12) | 0.56 |
| Components of the composite primary outcome | | | | | | | | | | |
| Recurrent cardiovascular events | 59 events [17.6/100py] | 111 events [32.1/100py] | RR 0.57 (0.34–0.93) | 67 events [25.1/100py] | 69 events [25.5/100py] | RR 0.93 (0.59–1.47) | 74 events [28.3/100py] | 83 events [36.8/100py] | RR 0.74 (0.43–1.27) | 0.50 |
| Secondary outcomes | | | | | | | | | | |
| All-cause mortality (up to 42 months) | 16 (13%) [4.1/100py] | 29 (22%) [7.1/100py] | HR 0.59 (0.32–1.09) | 19 (19%) [6.1/100py] | 24 (23%) [7.5/100py] | HR 0.73 (0.39–1.34) | 28 (27%) [9.2/100py] | 37 (41%) [14.0/100py] | HR 0.62 (0.38–1.02) | 0.87 |
| Difference in score (95% CI) | | | | | | | | | | |
| KCCQ-OSS change from baseline to month 30 | +5 (−0, +10) | | | +2 (−4, +8) | | | +9 (+3, +16) | | | 0.35 |
| 6MWT distance change from baseline to month 30 | +22 (+4, +41) | | | +23 (+1, +46) | | | +23 (0, +46) | | | 1.00 |

6MWT, 6-min walk test; CI, confidence interval; HR, hazard ratio; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire overall summary score; py, patient-years; RR, rate ratio.

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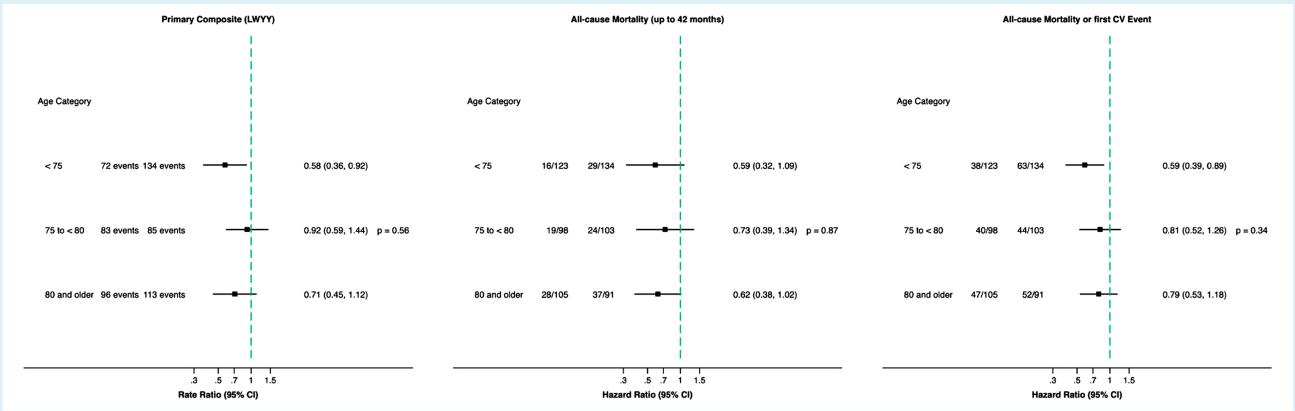


**Figure 1** Forest plot of primary composite outcome, all-cause mortality and the composite of all-cause death or first cardiovascular (CV) event – overall population. Each panel displays hazard ratios with 95% confidence intervals (CIs) for three age groups (<75 years, 75 to <80 years, and ≥80 years) comparing vutrisiran with placebo. The left panel shows the primary composite endpoint of all-cause mortality and recurrent cardiovascular events up to 36 months based on the Lin–Wei–Yang–Ying (LWYY) method; the middle panel shows all-cause mortality up to 42 months; and the right panel presents a composite based on time-to-first-event (all-cause mortality or first CV event). The vertical dashed line represents the line of no effect (hazard ratio 1.0). Event counts are shown as number of events/total patients per group. Squares indicate hazard ratio point estimates; horizontal lines represent 95% CIs.

in the younger cohorts. Older patients had significantly lower percentage of treatment with tafamidis at baseline, higher percentage of ATTRwt (95.4% in ≥80 vs. 80.9% in <75 years, $p < 0.001$), more advanced disease stage and elevated cardiac biomarkers. NAC stage 3 disease was more prevalent among patients ≥80 years (6.6%) compared with those <75 years (3.1%, $p = 0.018$). NT-proBNP levels were higher in those ≥80 years compared with those <75 years (median 2330 ng/L vs. 1649 ng/L, $p < 0.001$). Troponin I levels demonstrated a similar trend ($p = 0.013$). Findings in the monotherapy population were generally similar (*Table 1*).

## Clinical outcomes and efficacy of vutrisiran compared to placebo according to age

Exposure-adjusted event rates for the primary composite outcome of all-cause mortality and recurrent cardiovascular events and its components did not significantly differ between the age categories, while all-cause mortality rates increased by age (*Table 2*).

In the overall population, vutrisiran resulted in a reduction in the primary composite outcome of all-cause mortality and recurrent cardiovascular events compared to placebo regardless of age category (*Table 2*, $p_{interaction} = 0.56$). The reduction in the secondary outcome of all-cause mortality through up to 42 months of follow-up was also similar across age categories ($p_{interaction} = 0.87$) (*Figure 1*). Functional capacity and quality of life also favoured vutrisiran compared to placebo in all age groups ($p_{interaction} = 0.35$ for KCCQ-OSS, $p_{interaction} = 1.00$ for 6MWT distance). In the monotherapy population, findings were consistent with those observed in the overall population (*Table 3*).

To further assess the consistency of treatment effect across the age spectrum, restricted cubic spline models were used to evaluate vutrisiran efficacy as a continuous function of age (*Figure 2*). In the overall population, the estimated treatment effect of vutrisiran remained consistent across age for the primary composite of all-cause mortality and recurrent cardiovascular events ($p_{interaction} = 0.63$), all-cause mortality up to 42 months ($p_{interaction} = 0.75$) and the composite of all-cause mortality or first cardiovascular event ($p_{interaction} = 0.67$). Findings were similar in the monotherapy population, with no evidence of effect modification by age for the same outcomes ($p_{interaction} = 0.23$, 0.65 and 0.62, respectively).

## Safety outcomes

In the overall population, the safety profile of vutrisiran remained favourable across age categories, with no significant increase in SAEs, discontinuation due to adverse events, and discontinuation due to SAEs in any category ($p_{interaction} = 0.53$, 0.19, and 0.21, respectively) (*Table 4*). In the monotherapy group, safety outcomes were similar to the overall population.

# Discussion

In patients with ATTR-CM enrolled in the HELIOS-B trial, treatment with vutrisiran was associated with a significantly reduced risk of all-cause mortality and recurrent cardiovascular events compared to placebo, while maintaining functional capacity and quality of life across all age-groups – including patients aged ≥80 years, without evidence of diminished efficacy or increased safety concerns (*Graphical Abstract*).

The HELIOS-B study enrolled a contemporary cohort of patients with ATTR-CM, with 61% of participants aged over 75 years. Older patients had more advanced disease at baseline, including higher rates of NAC stage 3, elevated NT-proBNP and troponin levels, and reduced functional capacity compared with

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younger patients. Compared with ATTR-ACT and ATTRibute-CM, HELIOS-B included an older population and permitted broader background therapy use, including sodium–glucose co-transporter 2 inhibitors, reflecting a more contemporary trial population than prior studies.[8,9,11]

Despite these differences in baseline characteristics, vutrisiran treatment was associated with consistent clinical benefit across age categories. The benefits of vutrisiran on the primary outcome and its components were consistent across the whole age spectrum studied, including among those ≥80 years, where vutrisiran reduced the primary composite outcome by 29%, demonstrating benefit for the oldest patient group. Importantly, spline-based analyses, modelling age as a continuous variable, confirmed that the effect of vutrisiran did not significantly change by age for key outcomes, including the primary composite outcome of all-cause mortality and recurrent cardiovascular events, all-cause mortality, and the composite of all-cause mortality or first cardiovascular event. Although hazard ratios and confidence intervals appeared less favourable in the 75–<80 year subgroup relative to the <75 and ≥80 year subgroups, the smaller sample size and event counts are subject to random variation, resulting in estimates that may be less precise, rather than reflecting a true attenuation of treatment effect. Importantly, both categorical and continuous analyses showed no significant interaction with age, supporting consistency of efficacy across the spectrum.

Symptoms related to functional capacity and quality of life may be as important as higher life expectancy, particularly in older patients. Decline in functional capacity and quality of life, assessed by 6MWT distance and KCCQ-OSS, was attenuated with vutrisiran compared to placebo across all age groups, including among those aged ≥80 years, supporting the effect on these critical parameters in elderly patients with ATTR-CM. Overall, these results confirm that clinical benefit of vutrisiran extends across the entire age spectrum of HELIOS-B participants, a contemporary patient population with ATTR-CM.

Consistent with prior reports from both heart failure and amyloidosis populations, the incidence of adverse events increased with age, reflecting the overall higher burden of comorbidities in older patients.[3] Nevertheless, discontinuation of vutrisiran due to adverse events remained low across all age categories, and there was no evidence of an excess in SAEs attributable to treatment in elderly participants. These results reinforce the favourable safety and tolerability profile of vutrisiran, even in the context of advanced age and systemic disease and demonstrates that vutrisiran can be used in all age groups in patients with ATTR-CM without compromising safety.

There is a historical undertreatment of elderly patients with heart failure, likely due to several factors including concerns regarding frailty, polypharmacy, limited remaining life expectancy, and perceived marginal benefit.[6,7] Our findings challenge these assumptions and suggest that age alone should not preclude the initiation of an effective treatment like vutrisiran in elderly patients with ATTR-CM.

**Table 3** Clinical outcomes according to age categories (monotherapy population)

| Outcome | <75 years | | | 75 to <80 years | | | ≥80 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vutrisiran (*n* = 73) | Placebo (*n* = 80) | HR or RR (95% CI) | Vutrisiran (*n* = 48) | Placebo (*n* = 57) | HR or RR (95% CI) | Vutrisiran (*n* = 75) | Placebo (*n* = 62) | HR or RR (95% CI) | Interaction *p*-value |
| Composite primary outcome | | | | | | | | | | |
| All-cause mortality and recurrent cardiovascular events | 42 events [22.1/100py] | 76 events [38.2/100py] | RR 0.56 (0.34–0.92) | 39 events [31.0/100py] | 46 events [31.6/100py] | RR 0.93 (0.46–1.89) | 74 events [41.2/100py] | 89 events [61.6/100py] | RR 0.64 (0.37–1.10) | 0.78 |
| Components of the composite primary outcome | | | | | | | | | | |
| Recurrent cardiovascular events | 32 events [16.8/100py] | 61 events [30.6/100py] | RR 0.53 (0.31–0.90) | 31 events [24.6/100py] | 38 events [26.1/100py] | RR 0.94 (0.46–1.94) | 56 events [31.2/100py] | 66 events [45.7/100py] | RR 0.64 (0.33–1.25) | 0.70 |
| Secondary outcomes | | | | | | | | | | |
| All-cause mortality (up to 42 months) | 12 (16%) [5.3/100py] | 21 (26%) [8.8/100py] | HR 0.55 (0.27, 1.12) | 9 (19%) [6.1/100py] | 14 (25%) [7.9/100py] | HR 0.62 (0.26–1.48) | 23 (31%) [11.0/100py] | 28 (45%) [16.2/100py] | HR 0.63 (0.36–1.10) | 0.77 |
| Difference (95% CI) | | | | | | | | | | |
| KCCQ-OSS change from baseline to month 30 | +9 (+2, +16) | | | +7 (−2, +15) | | | +14 (+7, +22) | | | 0.36 |
| 6MWT distance change from baseline to month 30 | +34 (+9, +58) | | | +41 (+10, +72) | | | +25 (−4, +53) | | | 0.64 |

6MWT, 6-min walk test; CI, confidence interval; HR, hazard ratio; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire overall summary score; py, patient-years; RR, rate ratio.

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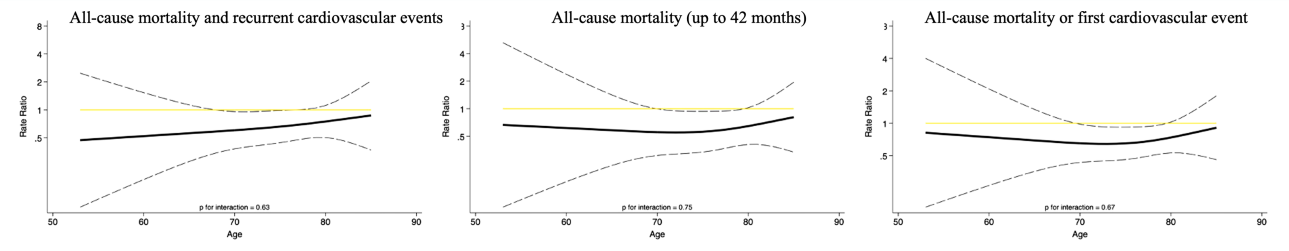


**Figure 2** Cubic spline models for primary composite, all-cause mortality and composite of all-cause mortality or first cardiovascular event in the overall population. Cubic spline models show the estimated treatment effect of vutrisiran versus placebo across the continuous spectrum of age for three outcomes: the primary composite of all-cause mortality and recurrent cardiovascular events up to 36 months (left), all-cause mortality up to 42 months (middle), and a composite based on time-to-first-event (all-cause mortality or first cardiovascular event; right). The solid black line represents the estimated hazard ratio for treatment effect at each age, and dashed lines indicate the 95% confidence interval. The horizontal yellow line denotes the line of no effect (hazard ratio 1.0). Interaction *p*-values are provided for each outcome, testing whether the treatment effect varies by age.

**Table 4 Safety of vutrisiran by age categories**

| | <75 years | | 75 to <80 years | | ≥80 years | | |
|---|---|---|---|---|---|---|---|
| | **Placebo (*n* = 134)** | **Vutrisiran (*n* = 123)** | **Placebo (*n* = 103)** | **Vutrisiran (*n* = 98)** | **Placebo (*n* = 91)** | **Vutrisiran (*n* = 105)** | **Interaction *p*-value** |
| Any treatment-emergent AE | 131 (97.8) | 121 (98.4) | 102 (99.0) | 97 (99.0) | 90 (98.9) | 104 (99.0) | 0.86 |
| Any treatment-emergent SAE | 87 (64.9) | 72 (58.5) | 67 (65.0) | 66 (67.3) | 66 (72.5) | 63 (60.0) | 0.53 |
| Any treatment-emergent AE leading to treatment discontinuation | 3 (2.2) | 5 (4.1) | 6 (5.8) | 3 (3.1) | 4 (4.4) | 2 (1.9) | 0.19 |
| Any treatment-emergent SAE leading to treatment discontinuation | 3 (2.2) | 3 (2.4) | 3 (2.9) | 1 (1.0) | 4 (4.4) | 1 (1.0) | 0.21 |

Data are expressed as *n* (%).
AE, adverse event; SAE, serious adverse event.

## Limitations

The results of this age-stratified analysis should be interpreted in the overall context of the HELIOS-B trial. Although this was a prespecified analysis, the trial was not powered for definitive comparisons within individual age groups. The smaller numbers of patients and events within individual strata limit the precision of subgroup estimates, and apparent variability in hazard ratios, particularly in the 75–79 and ≥80 year groups, likely reflect random variation rather than true differences in treatment effect. Importantly, there was no evidence of statistical heterogeneity in treatment effect by age.

Additionally, as in other ATTR-CM trials, eligibility criteria excluded patients with significant frailty or advanced comorbidities (such as NYHA class IV symptoms), meaning that the study population represents an older but selected group, which may affect the generalizability of the study findings.

# Conclusion

In conclusion, this prespecified age-stratified analysis of HELIOS-B demonstrates that the clinical benefits of vutrisiran extend across the full age spectrum, including patients aged ≥80 years. Vutrisiran treatment led to a consistent reduction in death and cardiovascular events, preservation of functional status, and maintenance of quality of life, with a favourable safety profile. These findings reinforce that age alone should not be a barrier to offering effective disease-modifying therapies for ATTR-CM, and support the use of vutrisiran in elderly patients, who represent a substantial and growing proportion of the affected population.

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**Conflict of interest**: B.C. has personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, Rocket, Valo, and has served on a data safety monitoring board for Novo Nordisk. P.G.P. has received speaker fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; has received consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Neurimmune, Novo Nordisk, and Pfizer; and has

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