Comparative Efficacy of Vutrisiran and Acoramidis in Transthyretin Amyloid Cardiomyopathy: A Matching-Adjusted Indirect Comparison

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Conclusions

- Vutrisiran showed numerically lower rates of all-cause mortality and the all-cause mortality/cardiovascular hospitalization composites relative to acoramidis; the differences were not statistically significant
- Vutrisiran and acoramidis had comparable outcomes on assessments of functional capacity, quality of life and biomarkers

Introduction

- Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, fatal disease caused by deposition of misfolded transthyretin (TTR) as amyloid in the heart
- Vutrisiran, an RNAi therapeutic that decreases TTR production, and acoramidis, a TTR stabilizer, are both approved therapies for ATTR-CM in multiple jurisdictions
  - Vutrisiran lowered the risk of death from any cause and recurrent cardiovascular events, and slowed decline in functional capacity (6MWT) and quality of life (KCCQ-OS), relative to placebo in the phase 3 HELIOS-B trial (NCT04153149)
  - Acoramidis improved a four-component hierarchical outcome of ACM, CVH, NT-proBNP and 6MWT, and slowed decline in 6MWT and KCCQ-OS, relative to placebo in the phase 3 ATTRibute-CM trial (NCT03860935)
- In the absence of randomized, head-to-head trials, indirect treatment comparisons (ITCs) can help assess the comparative efficacy of vutrisiran versus acoramidis in ATTR-CM

Objective

To estimate the comparative efficacy of vutrisiran versus acoramidis in patients with ATTR-CM

Endpoints assessed in the ITC

- All-cause mortality, over each trial's prespecified follow-up period (HELIOS-B: up to 42 months; ATTRibute-CM: 30 months)
- Composite outcomes over each trial's prespecified follow-up period (HELIOS-B: 33–36 months; ATTRibute-CM: 30 months)
  - Composite of ACM and recurrent CVH events
  - Composite of ACM or first CVH event
- Change from baseline in 6MWT at Month 30
- Change from baseline in KCCQ-OS at Month 30
- Change from baseline in NT-proBNP at Month 30

Table 1. Trial populations

	HELIOS-B (vutrisiran)[1]	ATTRibute-CM (acoramidis)
Trial design	Phase 3, randomized, double-blind trial of vutrisiran (25 mg once every three months) versus placebo for up to 36 months	Phase 3, randomized, double-blind trial of acoramidis (800 mg twice daily) versus placebo for 30 months
Trial eligibility criteria	**Key inclusion criteria:** • 18-85 years • History of HF with ≥ 1 prior HF hospitalization or clinical evidence of HF • End-diastolic interventricular septal wall thickness > 12 mm • Baseline NT-proBNP > 300 ng/L and < 8500 ng/L, or > 600 ng/L and < 8500 ng/L for patients with permanent or persistent AF • 6MWT ≥ 150 m • Karnofsky performance status ≥ 60% • Not on tafamidis at baseline and not planning to initiate tafamidis within 12 months[2] **Key exclusion criteria:** • NYHA class IV and NYHA class III with NAC stage 3 • eGFR <30 mL/min/1.73 m^2	**Key inclusion criteria:** • 18-90 years • History of HF with ≥ 1 prior hospitalization for HF or clinical evidence of HF or HF symptoms that require/required ongoing treatment with diuretic • Interventricular septum or left-ventricular wall thickness ≥ 12 mm • Baseline NT-proBNP ≥ 300 pg/mL and < 8500 pg/mL • 6MWT ≥ 150 m • Not on tafamidis within 14 days before dosing and not planning to start within 12 months[2] **Key exclusion criteria:** • NYHA class IV • eGFR <15 mL/min/1.73 m^2
Analysis population and sample size	HELIOS-B monotherapy population • Vutrisiran n = 196 • Placebo n = 199	mITT population of ATTRibute-CM[3] • Acoramidis n = 409 • Placebo n = 202

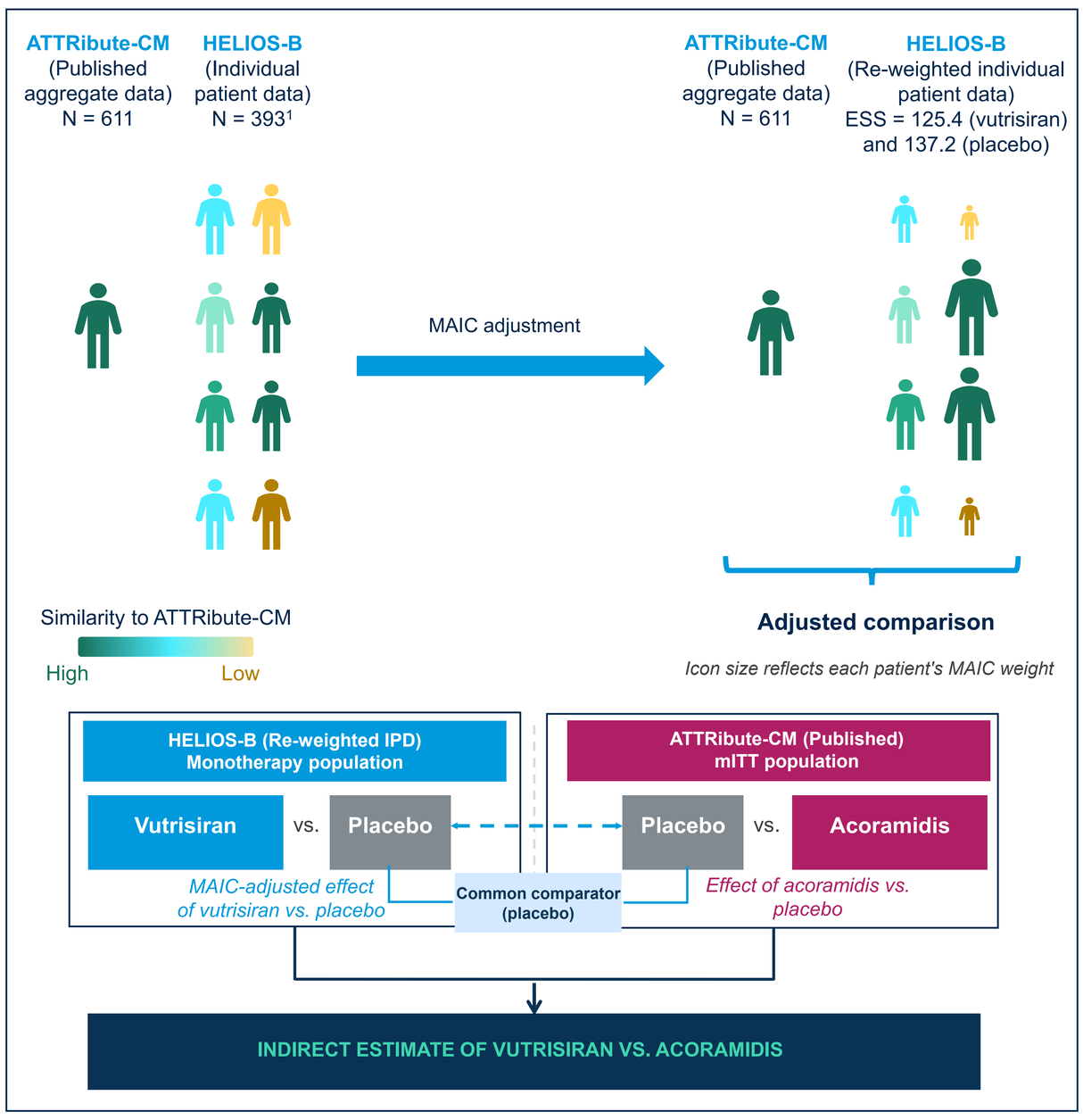
Notes:
[1] HELIOS-B data cut-offs: 22 Nov 2024 for all-cause mortality and 8 May 2024 for all other endpoints.
[2] Tafamidis drop-in (i.e., initiation of tafamidis ≥12 months post-baseline) was allowed at investigators' discretion in both trials. Proportions of tafamidis drop-in: HELIOS-B monotherapy population, 21.5% (vutrisiran 22.4%, placebo 20.6%); ATTRibute-CM, 17.5% (acoramidis 14.9%, placebo 22.8%).
[3] In ATTRibute-CM, 21 patients with stage 4 kidney disease were excluded from the primary analysis, resulting in a modified intention-to-treat population of 611 patients.

Methods

Anchored matching-adjusted indirect comparisons

- Matching adjusted indirect comparisons (MAIC) were used to reweight individual patient data from the HELIOS-B monotherapy population to match published aggregate data on baseline characteristics of ATTRibute-CM trial arms
- Baseline characteristics considered as potential effect modifiers and adjusted between trials were: Age; ATTR genotype (wtATTR vs. hATTR); NYHA class (I/II vs. III); NAC disease stage (1-2 vs. 3), NT-proBNP, 6MWT, KCCQ-OS and eGFR
- ITC estimates were based on comparison of MAIC-weighted outcome models for the vutrisiran versus placebo effect in the HELIOS-B monotherapy population to published results for the acoramidis versus placebo effect from ATTRibute-CM. Bootstrapping was used to estimate confidence intervals for ITC estimates

Figure 1. Anchored matching-adjusted indirect comparisons



Note:
[1] One patient in the vutrisiran arm and one in the placebo arm were excluded from the MAIC for missing baseline KCCQ-OS score used in matching.

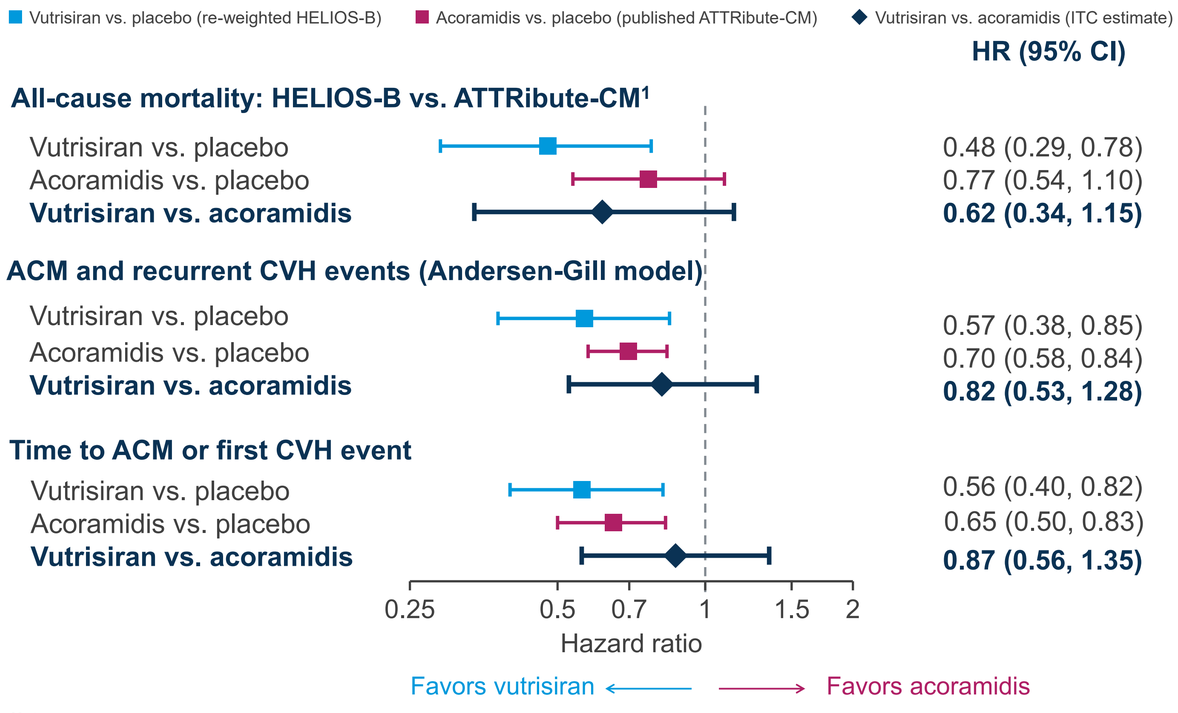
Results

Table 2. Baseline characteristics were balanced after adjustment

	HELIOS-B (before adjustment)		Populations informing the outcome comparison: HELIOS-B (after adjustment)		ATTRibute-CM	
	Vutrisiran (N = 195[1])	Placebo (N = 198[1])	Vutrisiran (ESS = 125.4)	Placebo (ESS = 137.2)	Acoramidis (N = 409)	Placebo (N = 202)
Age, years *	76.3 (6.8)	75.5 (6.4)	77.0 (6.0)	77.0 (5.8)	77.0 (6.5)	77.0 (6.7)
Male, %	90.8	91.9	92.4	91.3	91.4	89.6
Region: US, %	2.6	0.5	2.4	0.3	18.8	20.8
ATTR type: wild-type, % *	88.2	87.4	90.5	90.1	90.5	90.1
NYHA class III, % *	4.6	9.1	17.1	14.4	17.1	14.4
NAC disease stage 3, % *	7.7	3.0	11.0	10.4	10.9	10.4
6MWT, m *	362.9 (103.0)	373.1 (98.3)	361.2 (101.6)	348.4 (98.4)	361.2 (103.7)	348.4 (93.6)
KCCQ-OS score *	70.3 (20.2)	69.9 (20.8)	71.5 (20.7)	70.3 (20.4)	71.5 (19.4)	70.3 (20.5)
NT-proBNP, pg/mL *	2,883 (2,048)	2,414 (1,851)	2,865 (1,946)	2,650 (1,940)	2,865 (2,150)	2,650 (1,900)
eGFR, mL/min/1.73 m^2 *	67.3 (23.2)	69.9 (20.6)	62.0 (19.5)	63.0 (19.9)	62.0 (17.4)	63.0 (17.5)
Time since diagnosis, years	1.03 (1.28)	1.17 (1.28)	1.07 (1.30)	1.18 (1.30)	1.20 (1.20)	1.10 (1.20)
Body mass index	27.2 (3.7)	27.0 (3.6)	26.9 (3.8)	27.2 (3.5)	27.1 (3.8)	27.0 (3.7)

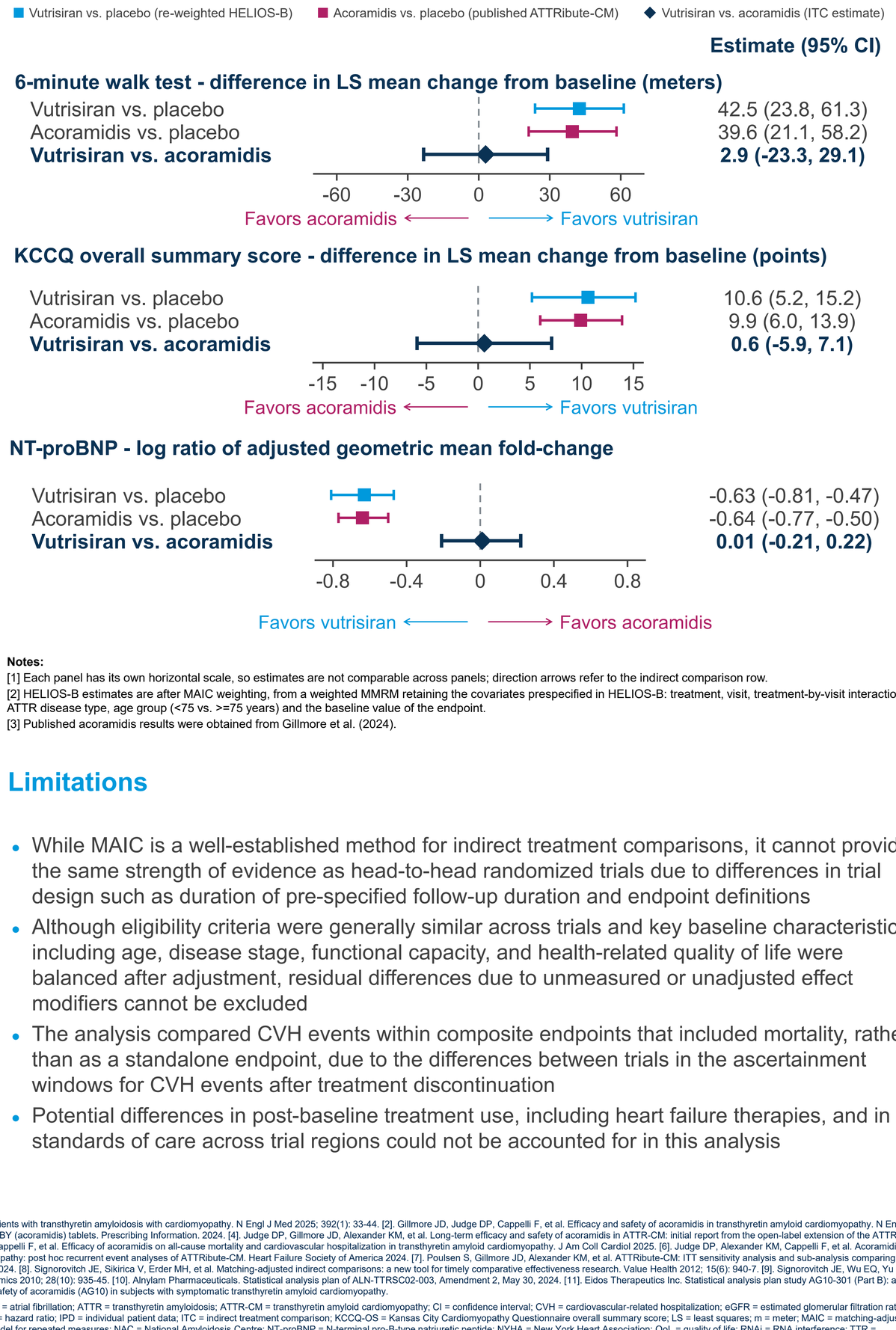
Notes:
[1] One patient in the vutrisiran arm and one in the placebo arm were excluded from the MAIC for missing baseline KCCQ-OS score used in matching.
[2] Values are mean (standard deviation) for continuous characteristics and percentages for categorical characteristics.
[3] Asterisks denote a matching factor in MAIC.
[4] Characteristics not used for matching, most notably enrollment region, remain imbalanced.

Figure 2. Vutrisiran showed numerically lower hazards of all-cause mortality and mortality/CVH composites compared to acoramidis



Notes:
[1] For comparison of all-cause mortality, the pre-specified HELIOS-B analysis based on follow-up for mortality from approximately 33 to 42 months is compared to the prespecified 30-month ATTRibute-CM analysis of the full randomized population.
[2] Heart transplantation and mechanical circulatory support device placement (left-ventricular assist device in HELIOS-B, cardiac mechanical assist device in ATTRibute-CM) were treated as death in both trials.
[3] HELIOS-B estimates are after MAIC weighting, from weighted Cox proportional hazards and weighted modified Andersen-Gill models, each retaining the covariates prespecified in HELIOS-B: treatment arm, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA class and age group.
[4] Published acoramidis results were obtained from the U.S. prescribing information for acoramidis, Poulsen et al. (2024) and Judge et al. (2024).

Figure 3. Comparable results were observed in functional, QoL, and biomarker endpoints at month 30



Notes:
[1] Each panel has its own horizontal scale, so estimates are not comparable across panels; direction arrows refer to the indirect comparison row.
[2] HELIOS-B estimates are after MAIC weighting, from a weighted MMRM retaining the covariates prespecified in HELIOS-B: treatment, visit, treatment-by-visit interaction, ATTR disease type, age group (<75 vs. >=75 years) and the baseline value of the endpoint.
[3] Published acoramidis results were obtained from Gillmore et al. (2024).

Limitations

- While MAIC is a well-established method for indirect treatment comparisons, it cannot provide the same strength of evidence as head-to-head randomized trials due to differences in trial design such as duration of pre-specified follow-up duration and endpoint definitions
- Although eligibility criteria were generally similar across trials and key baseline characteristics including age, disease stage, functional capacity, and health-related quality of life were balanced after adjustment, residual differences due to unmeasured or unadjusted effect modifiers cannot be excluded
- The analysis compared CVH events within composite endpoints that included mortality, rather than as a standalone endpoint, due to the differences between trials in the ascertainment windows for CVH events after treatment discontinuation
- Potential differences in post-baseline treatment use, including heart failure therapies, and in standards of care across trial regions could not be accounted for in this analysis

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If you are seeking additional scientific information related to Alnylam therapeutics, non-US HCPs should contact medinfo@alnylam.com. US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com.

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Abbreviations: 6MWT = 6-minute walk test; ACM = all-cause mortality; AF = atrial fibrillation; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; CI = confidence interval; CVH = cardiovascular-related hospitalization; eGFR = estimated glomerular filtration rate; ESS = effective sample size; hATTR = hereditary ATTR; HF = heart failure; HR = hazard ratio; IPD = individual patient data; ITC = indirect treatment comparison; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire overall summary score; LS = least squares; m = meter; MAIC = matching-adjusted indirect comparison; mITT = modified intention-to-treat; MMRM = mixed model for repeated measures; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; QoL = quality of life; RNAi = RNA interference; TTR = transthyretin; wtATTR = wild-type ATTR.