HELIOS·B

Influence of Disease-Modifying Therapy on the Effectiveness of Vutrisiran in Transthyretin Cardiac Amyloidosis

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Introduction

HELIOS-B: A randomised, double-blind study in patients with ATTR-CM

Background

- The siRNA vutrisiran reduced all-cause mortality and recurrent CV events in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) in the HELIOS-B trial
- Patterns of use of concomitant disease-modifying therapy (including tafamidis and HF therapies) during the trial, and whether such background therapy modifies the treatment effect of vutrisiran, remains uncertain

Objectives

- Describe baseline use and post-randomisation initiation (‘drop-in’) of concomitant therapies: tafamidis, SGLT2i, MRA, beta-blockers, ACE/ARB/ARNI
- Characterize temporal prescribing patterns across the trial population during follow-up
- Evaluate whether background therapy modifies the effect of vutrisiran on the primary composite endpoint (ACM + recurrent CV events)

Abbreviations: ACE, angiotensin-converting enzyme; ACM, all-cause mortality; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; siRNA, small interfering ribonucleic acid. **Reference**: Fontana M, et al. *N Engl J Med.* 2025;392:33–44.

Study Design & Methods

HELIOS-B

Patient Population (N=654)

- ATTR-CM: variant or wild-type
- Symptomatic HF
- NYHA class ≤III; 6-MWT ≥150 m; eGFR ≥30 mL/min/1.73 m², NT-proBNP limits at BL[a]
- 40% of patients on tafamidis and 77% on any HF medication at BL

1:1 RANDOMISATION

Vutrisiran SC q3M 25 mg

or

Placebo SC q3M

Primary Endpoint
Composite of ACM and recurrent CV events during the DB period

Vutrisiran SC q3M 25 mg

- Calculated baseline use and post-randomisation initiation rates for tafamidis, SGLT2i, MRA, beta-blockers, and ACE/ARB/ARNI in the vutrisiran and placebo arms
- Used time-updated LWYY models to examine whether concomitant medication use modified vutrisiran's treatment effect on the primary composite endpoint
  - Baseline use and drop-in of each medication class were incorporated as time-varying covariates
  - Evidence of treatment effect modification was assessed by the p value for the treatment-by-medication interaction term

[a]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation). **Abbreviations:** 6-MWT, 6-minute walk test; ACEi, angiotensin-converting enzyme inhibitor; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BL, baseline; CV, cardiovascular; DB, double-blind; eGFR, estimated glomerular filtration rate; HF, heart failure; LWYY, Lin-Wei-Yang-Ying; MRA, mineralocorticoid receptor antagonist; pt-yrs, patient-years; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; q3M, every 3 months; SGLT2i, sodium-glucose cotransporter-2 inhibitor. **Reference**: Fontana M, et al. *N Engl J Med.* 2025;392:33–44.

Baseline Use and Initiation Rates for Tafamidis and HF Therapies

- Concomitant therapy common at baseline (40% on tafamidis and 77% on any HF medication)
- SGLT2i and MRA demonstrated the most rapid uptake
- HF therapy initiation rate nominally higher in placebo arm

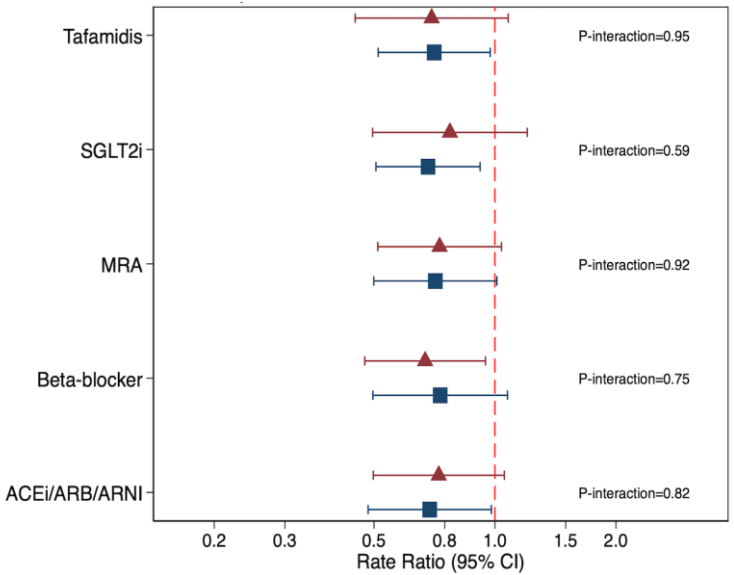
	Baseline Use in Overall Population	Drop-in Therapy in Eligible Population			
		Vutrisiran		Placebo	
Therapy	n/N (%)	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)
Tafamidis	259/654 (39.6)	43/196 (21.9)	9.7	41/199 (20.6)	9.3
Initiation due to disease progression		10		15	
Initiation for other reasons, including potential clinical benefit		33		26	
SGLT2i	21/654 (3.2)	102/316 (32.3)	14.3	114/317 (36.0)	16.7
Initiation due to disease progression		37		39	
Initiation for other reasons, including potential clinical benefit		65		75	
MRA	230/654 (35.2)	73/220 (33.2)	14.9	74/204 (36.3)	16.9
Beta-blocker	288/654 (44.0)	38/190 (20.0)	8.5	40/176 (22.7)	10.9
ACEi/ARB/ARNI	302/654 (46.2)	16/181 (8.8)	3.6	21/171 (12.3)	5.5
Any HF medication	503/654 (76.9)	168/322 (52.2)	27.6	183/325 (56.3)	32.4

Data are presented as n/N (%) where n represents the number of drop-in events and N represents the eligible population. For tafamidis, SGLT2i, MRA, beta-blocker, and ACEi/ARB/ARNI, the eligible population is defined as patients not on that specific medication class at baseline. For any HF medication, the eligible population is defined as patients on <4 HF medication classes at baseline. Drop-in of any HF medication refers to initiation of any additional HF medication post-baseline.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; pt-yrs, patient-years; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Treatment Effect of Vutrisiran on All-Cause Death and Recurrent Cardiovascular Events by Concomitant Therapy Use

Treatment effect remains **consistent** regardless of background therapy with tafamidis or heart failure medications



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Conclusions

1. Concomitant disease-modifying and HF therapies were common at baseline, and initiation of new therapies, particularly SGLT2i and MRA, was substantial during follow-up
2. Tafamidis drop-in for disease progression was low, but nominally higher among placebo-treated patients. HF medication drop-in was nominally higher in the placebo group
3. Vutrisiran's treatment benefit on all-cause mortality and recurrent CV events was consistent regardless of background tafamidis or HF therapies
4. These findings support the efficacy of vutrisiran across the spectrum of contemporary ATTR-CM pharmacotherapy and provide evidence for its use alongside other disease-modifying and guideline-directed HF therapies in clinical practice

We thank the patients, their families, investigators, staff, and all collaborators for their participation in HELIOS-B

Abbreviations: ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.