Vutrisiran Is Associated With Preservation of Intrinsic Capacity and Healthy Ageing in Patients With Transthyretin Amyloidosis With Cardiomyopathy: Post Hoc Analysis of HELIOS-B

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Background and Objectives

Background

- Ongoing accumulation of amyloidogenic TTR protein in the heart leads to ATTR-CM, resulting in progressive heart failure and reduced survival.[1,2] ATTR-CM occurs predominantly in **older individuals** with patients commonly experiencing **multisystem involvement and decline in functional capacity**[3,4]
- **Intrinsic Capacity (IC)** is the composite of an individual's physical and mental capacities and a key determinant of healthy ageing in older adults[5,6]
- The **ICOPE framework** is a **World Health Organization (WHO)** initiative to **slow the decline in IC** and functional status in the rapidly ageing global population and provides a screening tool to detect early and clinically meaningful declines across six domains of IC[6–8]
- In the phase 3 HELIOS-B study of patients with ATTR-CM, vutrisiran, an RNAi therapeutic inhibiting hepatic TTR synthesis, significantly reduced the risk of **all-cause mortality and recurrent CV events** vs placebo. The impact of vutrisiran on IC has not been assessed[9–11]

World Health Organization

ICOPE

INTEGRATED CARE FOR OLDER PEOPLE

Objective

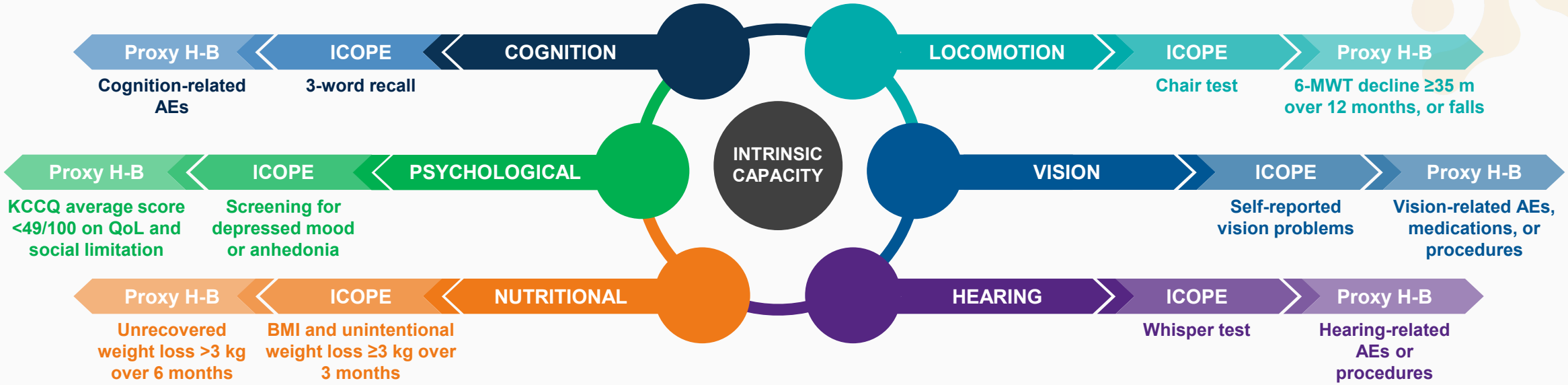
- To assess the **impact of vutrisiran on healthy ageing** using the six domains of IC aligned with the ICOPE framework

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; IC; Intrinsic Capacity; ICOPE, Integrated Care for Older People; RNAi, RNA interference; TTR, transthyretin; WHO, World Health Organization.

References: 1. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 2. Nativi-Nicolau et al. *ESC Heart Failure* 2021;8:3875–84; 3 Guijarro et al. *JACC Adv* 2025;4:102354; 4. Grodin & Goyal. *JACC CardioOncol* 2025;7:279–81; 5. WHO. ICOPE Handbook, 2024. https://www.who.int/publications/i/item/9789240103726 (accessed 22 May 2026); 6. WHO Guideline, 2017. https://who.int/publications/i/item/9789241550109 (accessed 22 May 2026); 7. Liu et al. *Geriatric Nurs* 2025;66:103698; 8. Cesari et al. *J Gerontol A Biol Med Sci* 2018;73:1653–60; 9. AMVUTTRA®. US Prescribing Information. Alnylam. 2025. https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf (accessed 22 May 2026); 10. AMVUTTRA®. Summary of Product Characteristics. Alnylam. 2025. https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf. (accessed 22 May 2026); 11. Fontana et al. *New Engl J Med* 2025;392:33–44.

Methods

- Post hoc analyses of patients in HELIOS-B with ATTR-CM, who were randomised to vutrisiran 25 mg Q3M or placebo over a 33–36-month double-blind period[1]
- Establishment of proxies in HELIOS-B, aligned with six IC domains, from the ICOPE framework[2-4]



Abbreviations: 6-MWT, 6-minute walk test; AE, adverse event; BMI, body mass index; IC, intrinsic capacity; ICOPE, Integrated Care for Older People; KCCQ, Kansas City Cardiomyopathy Questionnaire Overall Summary; Q3M, every 3 months; QoL, quality of life.

References: 1. Fontana et al. *New Engl J Med* 2025;392:33–44; 2. WHO. ICOPE Handbook, 2024. https://www.who.int/publications/i/item/9789240103726 (accessed 22 May 2026); 3. WHO Guideline, 2017. https://who.int/publications/i/item/9789241550109 (accessed 22 May 2026); 4. Cesari et al. *J Gerontol A Biol Med Sci* 2018,73:1653–60.

Baseline Characteristics Were Balanced Between Arms

HELIOS-B

Baseline Characteristics

	Overall Population		Monotherapy Population[a]		Baseline Tafamidis Subgroup	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=129)	Vutrisiran (n=130)
Age at randomisation, years						
Median (range)	76.0 (46–85)	77.0 (45–85)	76.0 (53–85)	77.5 (46–85)	75.0 (46–85)	77.0 (45–85)
<80 years, n (%)	238 (72.6)	221 (67.8)	138 (69.3)	121 (61.7)	100 (77.5)	100 (76.9)
≥80 years, n (%)	90 (27.4)	105 (32.2)	61 (30.7)	75 (38.3)	29 (22.5)	30 (23.1)
Vision impairment, n (%)	128 (39.0)	110 (33.7)	61 (30.7)	56 (28.6)	67 (51.9)	54 (41.5)
Hearing impairment, n (%)	21 (6.4)	24 (7.4)	9 (4.5)	11 (5.6)	12 (9.3)	13 (10.0)
Cognition impairment, n (%)	9 (2.7)	13 (4.0)	4 (2.0)	6 (3.1)	5 (3.9)	7 (5.4)
Locomotion impairment-falls, n (%)	1 (0.3)	1 (0.3)	0	1 (0.5)	1 (0.8)	0
6-MWT distance, metres, mean (SD)	377.1 (96.3)	372.0 (103.7)	372.8 (98.1)	362.7 (102.7)	383.8 (93.5)	386.1 (104.0)
Psychological state impairment, n (%)	64 (19.5)	62 (19.0)	45 (22.6)	44 (22.4)	19 (14.7)	18 (13.8)
Nutritional state impairment, n (%)	NA	NA	NA	NA	NA	NA
Weight, kg, mean (SD)	81.1 (14.4)	80.5 (13.7)	79.6 (13.9)	79.0 (12.8)	83.3 (15.0)	82.8 (14.6)
mBMI, kg/m^2 x g/L median (IQR)	1210.9 (1098.5–1333.5)	1183.8 (1082.7–1306.1)	1206.1 (1094.9–1324.1)	1188.7 (1087.3–1335.2)	1214.7 (1100.8–1336.0)	1174.5 (1074.5–1291.3)

[a]The monotherapy group includes patients who had no tafamidis use at baseline.

Abbreviations: 6-MWT, 6-minute walk test; IQR, interquartile range; mBMI, modified body mass index; SD, standard deviation.

Vutrisiran Reduced Decline in Intrinsic Capacity

Primary Outcome: Change From Baseline in Composite IC Score Across Six Functional Domains

For each domain of IC score: 1 = no impairment, 0 = impairment; composite IC score range 0–6 (higher scores = less impairment)[1,2]

Mean (SEM)	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=129)	Vutrisiran (n=130)
Baseline score	5.32 (0.04)	5.36 (0.04)	5.40 (0.05)	5.40 (0.05)	5.19 (0.07)	5.29 (0.06)
End of double-blind period	3.78 (0.07)	4.20 (0.06)	3.86 (0.08)	4.28 (0.08)	3.67 (0.11)	4.09 (0.11)
Change from baseline	**–1.54 (0.06)**	**–1.15 (0.05)**	**–1.54 (0.08)**	**–1.12 (0.07)**	**–1.53 (0.09)**	**–1.20 (0.09)**
OR for decline (95% CI)[a] *P*-value	**0.48** (0.36, 0.63) *P*<0.0001		**0.43** (0.30, 0.62) *P*<0.0001		**0.55** (0.35, 0.87) *P*=0.0099	

Consistent across key subgroups, including tafamidis-treated patients

Overall Population: 25% less decline from baseline IC score and 52% reduction in the risk of decline

[a]Regression model based on an ordinal regression model including treatment group, type of ATTR amyloidosis, age group, NYHA class and baseline NT-proBNP as covariates.

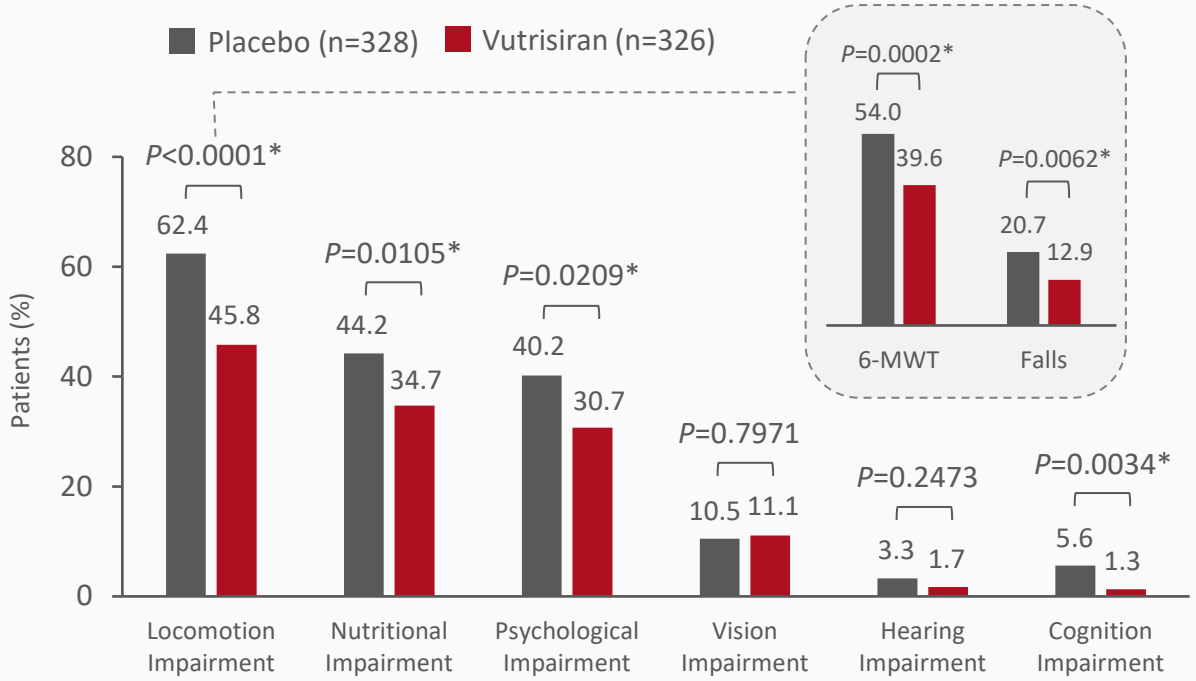
Abbreviations: CI, confidence interval; IC, intrinsic capacity; NYHA, New York Hear Association; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; OR, odds ratio; SEM, standard error of mean.

References: 1. WHO. ICOPE Handbook, 2024. https://www.who.int/publications/i/item/9789240103726 (accessed 22 May 2026); 2. WHO Guideline, 2017. https://who.int/publications/i/item/9789241550109 (accessed 22 May 2026).

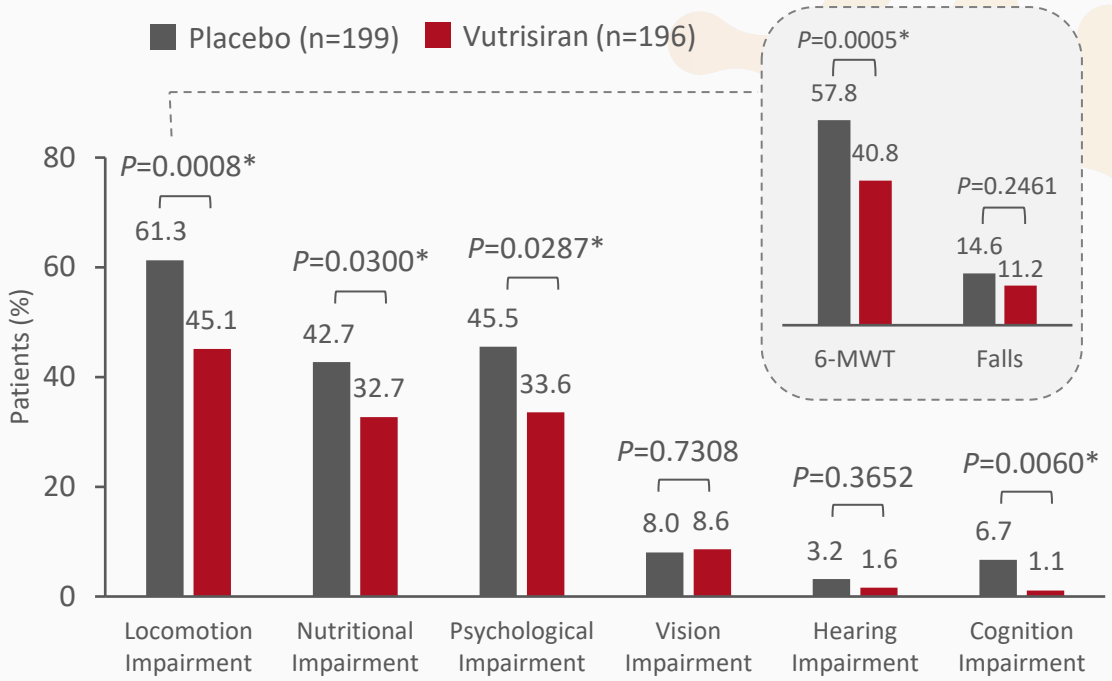
Vutrisiran Preserved Most Intrinsic Capacity Domains vs Placebo

Secondary Outcome: Proportion of Patients With New Occurrences of Impaired IC Domains During the Double-Blind Period

Overall Population



Monotherapy Population



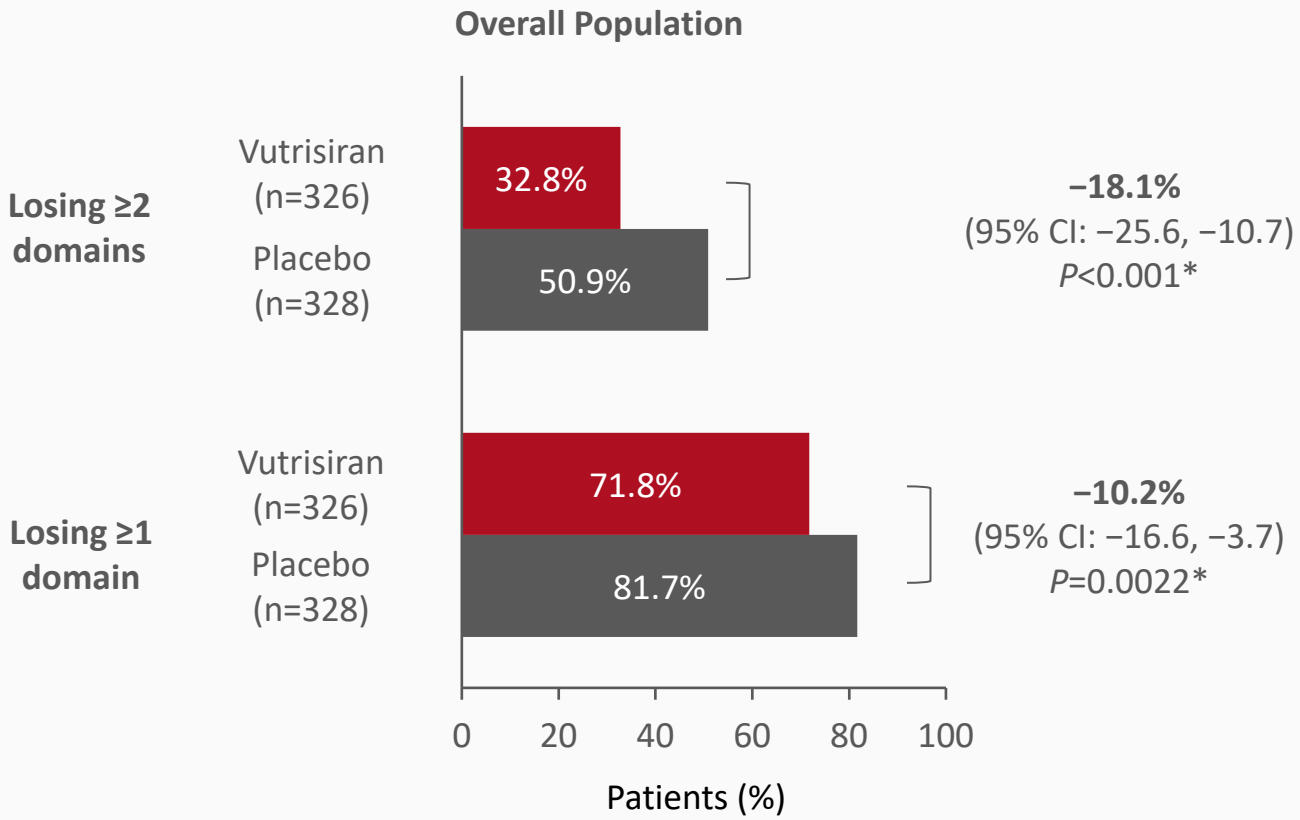
- Vutrisiran also significantly improved **locomotion impairment in the baseline tafamidis subgroup** (*P*=0.006) relative to placebo, with numerical improvements in all other domains

*Indicates statistical significance (P<0.05).

Abbreviations: 6-MWT, 6-minute walk test; IC, intrinsic capacity.

Fewer Patients Experience Multi-Domain Decline With Vutrisiran

Secondary Outcome: Proportion of Patients With a Decline in ≥1 or ≥2 IC Domains During the Double-Blind Period[a]



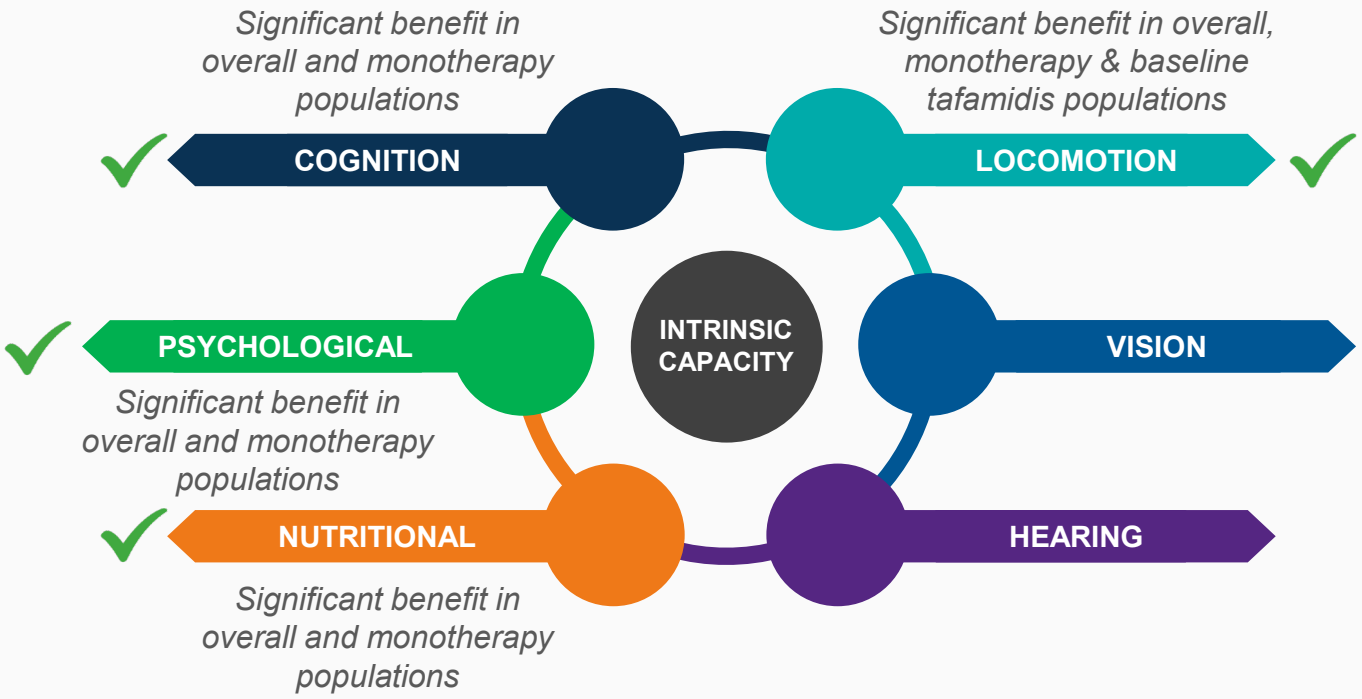
With vutrisiran, in the overall population:

- **18.1% fewer patients experienced a decline in ≥2 domains**
- **10.2% fewer patients experienced a decline in ≥1 domain**

[a]Differences between placebo and vutrisiran groups presented as adjusted treatment differences (95% CI). *Indicates statistical significance (P<0.05).

Abbreviations: CI, confidence interval; IC, intrinsic capacity.

Summary of Vutrisiran Impact on Intrinsic Capacity



- Vutrisiran contributes to the preservation of IC across multiple domains in patients with ATTR-CM
- This evidence supports the benefits of vutrisiran beyond survival and cardiac outcomes
- Further studies are required to determine if the benefits of vutrisiran represent a direct effect on IC or are a consequence of its benefits on cardiomyopathy and QoL[1–3]
- Limits: post hoc nature of the analysis and use of unvalidated proxies

✓ = significant benefit in IC domain with vutrisiran vs placebo

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Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; IC, Intrinsic Capacity; QoL, quality of life.

References: 1. Fontana et al. *New Engl J Med* 2025;392:33–44; 2. Fontana et al. *J Am Coll Cardiol* 2025;85:753–61; 3. Jering et al. *Nat Med* 2025;31:3560–568.