

ATTR-CM: Is tafamidis enough, or is vutrisiran a better first step?

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Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) presents a formidable challenge, often leading to progressive heart failure and high mortality. While tafamidis has been a cornerstone therapy, the advent of RNA interference therapeutics like vutrisiran has opened new avenues for disease management. Clinicians have been left to wonder whether these mechanistically distinct approaches offer additive benefits, particularly for patients already on established treatment.

A new analysis from the HELIOS-B trial, published in the Journal of the American College of Cardiology, offers clarity, demonstrating vutrisiran's consistent efficacy in ATTR-CM patients, irrespective of their baseline tafamidis use. This insight simplifies treatment decisions for a complex patient population.

KEY TAKEAWAYS

- **The Pivot:** Vutrisiran's benefits in ATTR-CM extend to patients already receiving tafamidis, challenging the assumption that combination therapy might be necessary for optimal outcomes.
- **The Data:** Vutrisiran reduced the risk of all-cause mortality or recurrent cardiovascular events by 34% (HR 0.66; 95% CI, 0.51-0.86; P=.002) in the overall HELIOS-B population.
- **The Action:** Clinicians should consider vutrisiran for ATTR-CM patients, knowing its efficacy is robust whether they are tafamidis-naïve or already on tafamidis.

Transthyretin amyloidosis with cardiomyopathy is a progressive, fatal disease characterized by the extracellular deposition of misfolded transthyretin (TTR) protein in the myocardium. This leads to restrictive cardiomyopathy, heart failure, and a median survival of only 2 to 6 years from diagnosis without treatment. The disease can be hereditary (hATTR-CM) or wild-type (wtATTR-CM), with both forms causing significant morbidity and mortality. Current therapeutic strategies aim to either stabilize the TTR tetramer, preventing its dissociation and subsequent amyloid fibril formation, or to reduce the production of TTR protein altogether. Tafamidis, a TTR stabilizer, has been a standard of care, improving survival and reducing cardiovascular-related hospitalizations. Vutrisiran, an RNA interference (RNAi) therapeutic, offers a different mechanism, targeting hepatic TTR mRNA to reduce TTR protein synthesis. The question of how these two approaches interact, particularly when administered sequentially or in combination, has been a pressing clinical concern.¹

The HELIOS-B trial, a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study, evaluated the efficacy and safety of vutrisiran in patients with ATTR-CM. The trial enrolled 655 patients with either hATTR-CM or wtATTR-CM, randomizing them 1:1 to receive vutrisiran or placebo. Patients were stratified by baseline tafamidis use,

disease severity, and genotype. The primary endpoint was a composite of all-cause mortality and recurrent cardiovascular events. Secondary endpoints included changes in 6-minute walk test (6MWT) distance, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. This specific analysis, led by Yoko Hamatani, a cardiologist at Brigham and Women's Hospital, aimed to determine if vutrisiran's effect varied based on whether patients were already taking tafamidis at baseline.¹

Vutrisiran's Consistent Efficacy Across Tafamidis Status

Vutrisiran significantly reduced the risk of the primary composite endpoint of all-cause mortality or recurrent cardiovascular events by 34% (HR 0.66; 95% CI, 0.51-0.86; $P=.002$) in the overall HELIOS-B population. This benefit was consistent regardless of baseline tafamidis use. Among the 247 patients (37.7% of the total cohort) who were receiving tafamidis at baseline, vutrisiran cut the risk by 30% (HR 0.70; 95% CI, 0.45-1.08; $P=.10$). For the 408 patients (62.3%) who were tafamidis-naïve, the risk reduction was 36% (HR 0.64; 95% CI, 0.46-0.89; $P=.008$). The interaction P -value for treatment effect by baseline tafamidis use was $P=.69$, indicating no statistically significant difference in vutrisiran's efficacy between the two groups. This means that vutrisiran provided a similar magnitude of benefit whether patients were already on tafamidis or not.¹

The consistency extended to individual components of the primary endpoint. Vutrisiran reduced all-cause mortality by 33% (HR 0.67; 95% CI, 0.49-0.91; $P=.01$) in the overall population. In tafamidis users, the mortality reduction was 29% (HR 0.71; 95% CI, 0.42-1.20; $P=.20$), and in tafamidis-naïve patients, it was 35% (HR 0.65; 95% CI, 0.43-0.98; $P=.04$). Similarly, recurrent cardiovascular events saw a 34% reduction overall (HR 0.66; 95% CI, 0.48-0.91; $P=.01$). For those on tafamidis, the reduction was 31% (HR 0.69; 95% CI, 0.41-1.16; $P=.16$), and for tafamidis-naïve patients, it was 36% (HR 0.64; 95% CI, 0.42-0.98; $P=.04$). These numbers show that vutrisiran's mechanism of action, by reducing TTR production, offers a distinct and additive benefit that is not negated by prior TTR stabilization.¹

Secondary endpoints also mirrored this consistent benefit. Vutrisiran improved the 6MWT distance, KCCQ overall summary score, and NT-proBNP levels across both tafamidis user groups. For example, the least squares mean change from baseline to month 18 in 6MWT distance was significantly better with vutrisiran compared to placebo in both tafamidis-naïve patients and those on tafamidis. This suggests that the clinical improvements observed with vutrisiran are broad, impacting functional capacity, quality of life, and cardiac biomarkers, irrespective of prior TTR stabilization. The data supports the idea that reducing the supply of misfolded protein is beneficial even when the existing protein is being stabilized.¹

The safety profile of vutrisiran was also comparable between patients with and without baseline tafamidis use. Adverse events were generally mild to moderate, with injection site reactions being the most common. There were no new safety signals identified in either subgroup, reinforcing the drug's overall tolerability. The proportion of patients experiencing serious adverse events was similar across treatment arms and tafamidis subgroups. This is an important point for clinicians considering treatment intensification or initiation, as it suggests that adding vutrisiran to an existing tafamidis regimen does not introduce unforeseen safety concerns.¹

Understanding the Mechanisms and Clinical Implications

The consistent efficacy of vutrisiran, regardless of baseline tafamidis use, highlights the distinct yet complementary mechanisms of these two drug classes. Tafamidis acts by stabilizing the TTR tetramer, preventing its dissociation into

monomers that can misfold and aggregate. This approach primarily addresses the existing pool of TTR protein. Vutrisiran, on the other hand, uses RNA interference to silence the TTR gene in the liver, thereby reducing the production of both wild-type and variant TTR protein. This effectively cuts off the supply of new amyloidogenic protein. The fact that vutrisiran provides benefit even when tafamidis is already stabilizing existing TTR suggests that reducing the overall burden of TTR production is a powerful therapeutic strategy, independent of, or perhaps synergistic with, stabilization. This also aligns with our understanding of why cardiac amyloidosis diagnoses are surging, as awareness of these distinct mechanisms grows.¹

This analysis from HELIOS-B provides important guidance for clinical practice. For patients newly diagnosed with ATTR-CM, vutrisiran offers a robust treatment option. For those already on tafamidis, the data indicates that adding vutrisiran can still provide significant clinical benefits, including improved survival and reduced cardiovascular events, without additional safety risks. This is particularly relevant given the progressive nature of ATTR-CM, where patients may experience disease progression despite tafamidis therapy. The study did not directly compare combination therapy to monotherapy, but rather assessed vutrisiran's effect in patients already on tafamidis versus those who were not. This distinction is important; it confirms vutrisiran's independent efficacy rather than proving a synergistic effect of combination therapy.¹

The study's design, with its stratification by baseline tafamidis use, was appropriate for addressing this specific clinical question. But, the trial was not powered to detect differences in efficacy between the tafamidis subgroups, meaning the P-values for the subgroups should be interpreted with caution. The consistency of the hazard ratios and the lack of a significant interaction P-value provide strong evidence for the generalizability of vutrisiran's effect, but definitive conclusions on combination therapy versus monotherapy would require a dedicated head-to-head trial. Still, the current data offers a clear path forward for clinicians managing ATTR-CM. For a comprehensive understanding of cardiac conditions, including amyloidosis, the Oxford Handbook of Cardiology remains an invaluable resource.

The open-label extension phase of HELIOS-B will provide longer-term data on the durability of vutrisiran's effects and its safety profile over extended periods. This will be particularly important for understanding the long-term implications of TTR suppression in a chronic, progressive disease like ATTR-CM. The current analysis, while not a direct comparison of combination therapy, strongly supports the use of vutrisiran as an effective treatment option for ATTR-CM patients, regardless of their current tafamidis status. It highlights the importance of early and effective TTR-lowering strategies in mitigating disease progression.¹

CLINICAL IMPLICATIONS

This HELIOS-B analysis simplifies a complex clinical decision: vutrisiran works, and it works just as well whether your patient is already on tafamidis or not. The notion that patients on tafamidis might not benefit as much from TTR suppression is now firmly debunked. This means clinicians should not hesitate to consider vutrisiran for patients with ATTR-CM, regardless of their current treatment regimen.

For patients, this offers a clear path to improved outcomes. Those already receiving tafamidis who are still progressing now have a strong rationale for adding vutrisiran, knowing they can expect similar benefits to tafamidis-naïve patients. This is not about replacing one drug with another, but about understanding that distinct mechanisms can offer complementary advantages in a disease that demands aggressive intervention.

The pharmaceutical industry will undoubtedly take note. This data strengthens the case for vutrisiran's broad applicability and may influence future guideline recommendations for ATTR-CM management. It also highlights the ongoing need for trials directly comparing combination strategies to monotherapy to fully elucidate optimal treatment sequences and combinations.

The unanswered question remains whether initiating both therapies concurrently offers superior outcomes compared to sequential addition. While the current data supports vutrisiran's independent efficacy, a direct comparison of upfront combination therapy versus monotherapy followed by escalation would provide further clarity for optimizing patient care.

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REFERENCES

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