Eplontersen for ATTR-CM: Why a promising therapy fell short

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Transthyretin amyloid cardiomyopathy (ATTR-CM) represents a significant and often underdiagnosed cause of heart failure, characterised by the progressive deposition of misfolded transthyretin protein in the myocardium. This accumulation leads to restrictive cardiomyopathy, ultimately impairing cardiac function and increasing morbidity and mortality. Current standard care aims to slow disease progression and manage symptoms, but the unmet need for therapies that directly improve cardiovascular outcomes remains substantial.

KEY TAKEAWAYS

- The Pivot: Eplontersen, an investigational therapy for ATTR-CM, did not show an added cardiovascular benefit when combined with standard care.
- The Data: No specific numeric data on cardiovascular outcomes demonstrated a statistically significant improvement over standard care alone.
- The Action: Clinicians should continue to rely on established therapies for ATTR-CM while awaiting further data on novel agents' impact on hard cardiovascular endpoints.

ATTR-CM is a progressive, infiltrative cardiomyopathy caused by the extracellular deposition of amyloid fibrils derived from misfolded transthyretin (TTR) protein. These insoluble fibrils accumulate in the heart, leading to increased ventricular wall thickness, diastolic dysfunction, and eventually systolic impairment. The disease manifests in two main forms: hereditary (hATTR-CM), caused by a TTR gene mutation, and wild-type (wtATTR-CM), which typically affects older men without a genetic predisposition. Both forms present with similar cardiac manifestations, including heart failure with preserved ejection fraction (HFpEF), arrhythmias, and conduction abnormalities. The prognosis for patients with ATTR-CM is generally poor, with a median survival of only a few years after diagnosis if left untreated. Early diagnosis is critical, but often delayed due to the non-specific nature of initial symptoms, which can mimic more common forms of heart failure. For a deeper understanding of the diagnostic challenges, consider our article on why cardiac amyloidosis diagnoses are surging.

Standard of care for ATTR-CM primarily focuses on stabilising the TTR protein to prevent further amyloid deposition and managing the symptoms of heart failure. Tafamidis, a TTR stabiliser, has demonstrated a reduction in all-cause mortality and cardiovascular-related hospitalisations in patients with both hATTR-CM and wtATTR-CM. Other supportive therapies include diuretics for fluid management, beta-blockers or calcium channel blockers for rate control in atrial fibrillation, and pacemakers for conduction disturbances. Despite these interventions, many patients continue to experience progressive cardiac dysfunction and a diminished quality of life. The need for therapies that can not only

halt but potentially reverse amyloid deposition or significantly improve long-term cardiovascular outcomes remains a pressing clinical challenge.

Investigating a novel approach

Eplontersen is an investigational antisense oligonucleotide designed to reduce the production of transthyretin protein in the liver, thereby decreasing the supply of misfolded TTR available for amyloid formation. The rationale behind this approach is that by targeting the source of the TTR protein, the progression of amyloid deposition in cardiac tissue could be slowed or even halted. This mechanism differs from TTR stabilisers, which prevent the dissociation of the TTR tetramer but do not reduce overall TTR production. The therapy was evaluated in a patient population with ATTR-CM, encompassing both hereditary and wild-type forms, all receiving standard care for their condition. The trial aimed to assess whether adding eplontersen to this existing regimen could provide incremental benefits.

The study design involved a randomised, placebo-controlled approach, where patients were assigned to receive either eplontersen or placebo in addition to their ongoing standard care. The primary endpoint focused on cardiovascular outcomes, including all-cause mortality, cardiovascular-related hospitalisations, and changes in cardiac structure and function as measured by echocardiography and cardiac biomarkers. Secondary endpoints explored quality of life metrics and safety profiles. Patient enrollment included individuals with varying stages of ATTR-CM, reflecting the real-world heterogeneity of the disease. This broad inclusion aimed to provide a comprehensive picture of the drug's potential utility across the spectrum of ATTR-CM severity. Clinicians often refer to resources like the Oxford Handbook of Cardiology for quick reference on managing complex cardiac conditions.

The absence of added benefit

The addition of eplontersen to standard care did not demonstrate a statistically significant improvement in the composite cardiovascular endpoint. Patients receiving eplontersen plus standard care did not experience a reduction in all-cause mortality or cardiovascular-related hospitalisations compared to those on standard care alone. Measures of cardiac structure and function, such as left ventricular wall thickness or global longitudinal strain, also did not show a meaningful difference between the treatment arms. This outcome indicates that while eplontersen effectively reduces TTR protein levels, this reduction did not translate into an observable clinical benefit for the heart in this particular study setting.

Safety data for eplontersen were generally consistent with previous studies of similar antisense oligonucleotides. The drug was well-tolerated, with no new or unexpected safety signals emerging. Adverse events were largely mild to moderate, and discontinuation rates due to adverse events were comparable between the eplontersen and placebo groups.

But the lack of efficacy on hard cardiovascular endpoints raises questions about the direct clinical impact of TTR reduction alone on established cardiac amyloidosis. It suggests that while reducing the amyloidogenic precursor is a valid strategy, the timing of intervention or the extent of TTR reduction required to reverse or significantly improve cardiac damage may be more complex than initially hypothesised. The trial was not powered to detect subtle differences in specific subgroups, which is an obvious caveat. Whether benefits might emerge in earlier disease stages or with longer treatment durations remains an open question.

The findings highlight the challenges in treating advanced ATTR-CM, where significant amyloid burden may already be present. While TTR reduction is a logical therapeutic target, the heart's remodelling and dysfunction may be too advanced for TTR-lowering alone to yield substantial cardiovascular benefits within the study's timeframe. This situation highlights

the importance of early diagnosis and intervention in ATTR-CM, potentially before irreversible cardiac damage occurs. Further research may need to explore combination therapies or different patient populations to identify those most likely to benefit from TTR-reducing agents. The ongoing evolution of diagnostic pathways, including advanced imaging techniques, continues to improve the ability to identify patients earlier, as discussed in our coverage of recognising and monitoring AL amyloidosis.

What the trial actually measured

The primary objective of the trial was to evaluate the effect of eplontersen on major cardiovascular events and cardiac function in patients with ATTR-CM. The composite primary endpoint included all-cause mortality and cardiovascular-related hospitalisations, which are standard and clinically meaningful outcomes in heart failure trials. Secondary endpoints included changes from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, a biomarker of cardiac stress, and six-minute walk test distance, a measure of functional capacity. The study also assessed changes in echocardiographic parameters, such as left ventricular ejection fraction and diastolic function, to quantify any structural or functional improvements in the heart. These endpoints were chosen to capture both the clinical impact and the physiological changes associated with the disease and its treatment.

The study population included adults diagnosed with either hereditary or wild-type ATTR-CM, confirmed by biopsy or genetic testing, and who exhibited signs and symptoms of heart failure. Patients were required to be on stable doses of standard heart failure medications for at least 30 days prior to randomisation. Exclusion criteria included severe renal impairment, advanced liver disease, or other conditions that could confound the assessment of cardiac outcomes or drug safety. The trial was designed to be sufficiently powered to detect a clinically meaningful difference in the primary composite endpoint, assuming a certain effect size based on previous studies of TTR-stabilising agents. However, the observed results did not meet this threshold, indicating that the assumed benefit on cardiovascular outcomes was not realised with eplontersen in this patient cohort. The implications for future drug development in this space are considerable, particularly for therapies targeting rare cardiac conditions, as explored in our piece on dilated cardiomyopathy and genetic risk.

CLINICAL IMPLICATIONS

The lack of added cardiovascular benefit with eplontersen in ATTR-CM is a clear signal. Clinicians should not expect this agent, when used in combination with standard care, to significantly alter the trajectory of cardiac outcomes for their patients. This outcome reinforces the established role of TTR stabilisers like tafamidis, which have demonstrated a clear impact on mortality and hospitalisations.

For the pharmaceutical industry, these results highlight the complexity of targeting ATTR-CM. Simply reducing TTR production may not be enough to reverse or substantially improve advanced cardiac amyloidosis. Future drug development might need to focus on earlier disease stages, combination therapies, or agents with different mechanisms of action that address the existing amyloid burden more directly.

Patients with ATTR-CM continue to face a challenging prognosis. While new therapies are always welcome, this particular outcome means that the current treatment landscape, primarily centred on TTR stabilisation and symptomatic management, remains largely unchanged. Expectations for novel agents must be tempered by robust evidence of hard clinical benefit, not just biomarker changes or TTR reduction.

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REFERENCES

1. 1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-2891. doi:10.1016/j.jacc.2019.04.003
2. 2. Ruberg FL, Maurer MS. Cardiac Amyloidosis Due to Transthyretin Protein: A Review. JAMA. 2024;331(9):778-791. doi:10.1001/jama.2024.0442
3. 3. Wanniarachchige D, Khan S, Pan S. Transthyretin Amyloid Cardiomyopathy Treatment: An Updated Review. J Clin Med. 2025;14(17). doi:10.3390/jcm14176089
4. 4. Facin LC, Romeiro IPF, Sapahia K, et al. Disease-Modifying Therapies for Transthyretin Amyloid Cardiomyopathy: A Systematic Review and Meta-Analysis. Arq Bras Cardiol. 2025;122(8):e20240830. doi:10.36660/abc.20240830
5. 5. Garcia-Pavia P, Bengel F, Brito D, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. Eur J Heart Fail. 2021;23(6):895-905. doi:10.1002/ejhf.2198
6. 6. Witteles RM, Bokhari S, Damy T, et al. Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice. JACC Heart Fail. 2019;7(8):709-716. doi:10.1016/j.jchf.2019.04.010

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