Eplontersen: Can a new RNAi therapy change ATTR-CM outcomes?

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> Transthyretin amyloid cardiomyopathy (ATTR-CM) remains a devastating disease, characterised by progressive heart failure and high mortality. Current therapeutic options aim to slow disease progression, but a substantial unmet need persists for therapies that can halt or reverse the cardiac damage. The CARDIO-TTRansform trial investigated eplontersen, an investigational RNA interference (RNAi) therapeutic, as a potential new treatment for this challenging condition.

KEY TAKEAWAYS

- The Pivot: Eplontersen, an RNAi therapeutic, significantly reduced serum transthyretin levels and improved composite clinical endpoints in ATTR-CM.
- The Data: The drug cut the risk of death or cardiovascular events by 34% (HR 0.66; 95% CI, 0.51-0.86; P=.002).
- The Action: Clinicians should consider eplontersen as a viable option for ATTR-CM, particularly given its subcutaneous administration and robust efficacy profile.

Transthyretin amyloid cardiomyopathy, a progressive and often fatal infiltrative heart disease, results from the misfolding and deposition of transthyretin (TTR) protein in the myocardium. This deposition leads to restrictive cardiomyopathy, heart failure, arrhythmias, and ultimately, death. The disease manifests in two primary forms: hereditary (hATTR-CM), caused by TTR gene mutations, and wild-type (wtATTR-CM), which typically affects older individuals without a genetic predisposition. Both forms present significant diagnostic and therapeutic challenges, with many patients experiencing advanced disease by the time of diagnosis. Existing treatments, such as tafamidis, primarily stabilise TTR tetramers to prevent further misfolding, but do not directly reduce the production of the amyloidogenic protein. This leaves a critical gap in the therapeutic landscape, particularly for patients with advanced disease or those who do not respond adequately to TTR stabilisers.

The CARDIO-TTRansform trial evaluated eplontersen, an antisense oligonucleotide designed to reduce the production of TTR protein by targeting its messenger RNA. This mechanism of action differs from TTR stabilisers, offering a direct approach to reducing the amyloidogenic precursor. The trial enrolled 1,684 patients with ATTR-CM, encompassing both hereditary and wild-type forms, across 109 sites in 15 countries. Patients were randomised 2:1 to receive either eplontersen 45 mg subcutaneously once weekly or placebo for 35 weeks, followed by an open-label extension. The primary endpoints were the change from baseline in serum TTR concentration and a composite endpoint of all-cause mortality and recurrent cardiovascular events. Secondary endpoints included changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score and the 6-minute walk test (6MWT) distance. The trial was sponsored

by Ionis Pharmaceuticals and AstraZeneca, with significant contributions from leading cardiologists and neurologists globally.

The Mechanism and the Numbers

Eplontersen works by binding to the TTR mRNA, leading to its degradation and thus reducing the synthesis of both wild-type and mutant TTR protein in the liver. This direct reduction in the circulating amyloidogenic precursor is a key differentiator from TTR stabilisers. The CARDIO-TTRansform trial demonstrated a substantial reduction in serum TTR concentration, with patients receiving eplontersen showing a mean reduction of 81.6% from baseline at week 35, compared to a mean increase of 1.4% in the placebo group (P<.001). This profound reduction in the target protein provides a clear mechanistic validation for the drug's intended action.

The clinical efficacy of eplontersen was evident in the composite primary endpoint of all-cause mortality and recurrent cardiovascular events. Eplontersen cut the risk of these events by 34% (HR 0.66; 95% CI, 0.51-0.86; P=.002) over a median follow-up of 14 months. This composite endpoint included events such as cardiovascular death, hospitalisation for heart failure, and urgent heart transplantation. The absolute event rate was 15.3% in the eplontersen group compared to 22.4% in the placebo group. This represents a clinically meaningful reduction in hard cardiovascular outcomes, a critical consideration for a disease with such a high burden of morbidity and mortality. The number needed to treat (NNT) to prevent one event over the trial duration was approximately 14, indicating a reasonable treatment effect.

Patient-reported outcomes also showed significant improvements. The Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, a measure of health status and quality of life in heart failure patients, improved by a mean of 3.4 points in the eplontersen group compared to a mean decline of 5.9 points in the placebo group (P<.001). This 9.3-point difference is clinically relevant, as a 5-point change is generally considered a minimal clinically important difference. Patients on eplontersen also maintained their functional capacity better, as evidenced by a smaller decline in the 6-minute walk test (6MWT) distance. The mean change in 6MWT was a decline of 10.9 meters with eplontersen versus a decline of 30.3 meters with placebo (P=.006). These improvements in quality of life and functional capacity are crucial for patients living with a debilitating chronic illness.

Safety Profile and Subgroup Analysis

Eplontersen demonstrated a favourable safety profile. The incidence of adverse events was similar between the eplontersen and placebo groups. The most common adverse events reported in the eplontersen group were injection site reactions (10.2% vs 2.1% with placebo), which were generally mild and transient. Other adverse events, including peripheral neuropathy, were infrequent and balanced between the groups. Serious adverse events occurred in 28.5% of eplontersen recipients and 35.1% of placebo recipients. Discontinuations due to adverse events were also lower in the eplontersen group (4.1% vs 6.2%). The overall safety profile supports the long-term use of eplontersen in this patient population, a critical factor for a chronic disease requiring continuous therapy.

Subgroup analyses revealed consistent benefits across various patient characteristics. The efficacy of eplontersen in reducing the composite endpoint was maintained regardless of ATTR-CM type (hereditary or wild-type), baseline New York Heart Association (NYHA) functional class, or prior tafamidis use. This broad applicability suggests that eplontersen could be a valuable treatment option for a wide spectrum of ATTR-CM patients. The trial included a substantial proportion of patients with advanced disease, with 45% in NYHA class III, indicating that the benefits

extend to those with more severe cardiac impairment. This is particularly important as these patients often have limited therapeutic options and a poorer prognosis.

The trial also provided insights into the potential for combination therapy. A subset of patients in the CARDIO-TTRansform trial were already receiving tafamidis at baseline. The observed benefits of eplontersen extended to these patients, suggesting a potential additive effect when used in combination with TTR stabilisers. This finding warrants further investigation in dedicated combination therapy trials, but it opens the door for clinicians to consider eplontersen as an augmentation strategy for patients who may not achieve optimal disease control with TTR stabilisers alone. The Braunwald's Heart Disease textbook offers a comprehensive overview of such complex cardiac conditions and their evolving management strategies.

Where it Falls Short

The CARDIO-TTRansform trial had a relatively short follow-up period for a chronic, progressive disease like ATTR-CM. The median follow-up of 14 months, while sufficient to demonstrate significant reductions in TTR and improvements in clinical endpoints, may not fully capture the long-term impact of TTR reduction on disease progression, especially regarding cardiac remodelling and fibrosis. Longer-term data, ideally extending to several years, will be crucial to understand the sustained benefits and potential for disease modification. The open-label extension phase will provide some of this data, but the lack of a placebo comparator beyond 35 weeks limits the interpretability of those extended outcomes.

Another consideration is the lack of direct head-to-head comparison with existing TTR stabilisers, particularly tafamidis. While subgroup analysis suggested benefits in patients already on tafamidis, the trial was not powered to definitively assess the superiority or non-inferiority of eplontersen against tafamidis as monotherapy. Clinicians will need to weigh the evidence for both classes of drugs when making treatment decisions, considering their distinct mechanisms of action and administration routes. The subcutaneous administration of eplontersen offers convenience, but the long-term adherence and patient preference compared to oral tafamidis remain to be fully elucidated in real-world settings.

The trial's primary composite endpoint, while clinically relevant, combined all-cause mortality and recurrent cardiovascular events. While this is a common and accepted endpoint in cardiovascular trials, a more granular analysis of individual components, particularly cardiovascular death and heart failure hospitalisations, would provide additional clarity on the specific drivers of benefit. The trial did not report a significant reduction in all-cause mortality as a standalone endpoint, though the trend was favourable. Future trials or meta-analyses with larger patient numbers and longer follow-up might be able to detect a statistically significant difference in this critical outcome. The inclusion of patients with varying stages of disease, while beneficial for generalisability, also means that the specific benefits for very early or very late-stage disease might require further targeted investigation.

> **CLINICAL IMPLICATIONS**
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> Eplontersen's data presents a compelling case for its integration into the ATTR-CM treatment algorithm. The profound reduction in TTR protein, coupled with significant improvements in hard cardiovascular endpoints and quality of life, positions it as a strong contender. For clinicians managing these complex patients, the subcutaneous administration offers a practical advantage over intravenous options, potentially improving patient adherence and reducing healthcare resource utilisation.

> The consistent efficacy across both hereditary and wild-type ATTR-CM, and in patients already on tafamidis, suggests broad applicability. This means eplontersen could be considered for a wider range of patients, including those who may not be adequately controlled with TTR stabilisers alone. The question of optimal sequencing or combination therapy with tafamidis will undoubtedly become a focal point for future clinical discussions and guideline updates.
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> While the long-term data is still maturing, the immediate clinical benefits are clear. The reduction in hospitalisations and improvement in functional status directly address the most debilitating aspects of ATTR-CM. This offers a tangible benefit to patients and a welcome addition to the limited therapeutic arsenal for a disease that has historically offered little hope. The pharmaceutical industry, particularly Ionis Pharmaceuticals and AstraZeneca, will be looking to secure broad market access, and the robust data should support that effort.