

CRITICAL APPRAISAL

Combination Stabilizer and Silencer Therapy in ATTR-CM: Insights from CARDIO-TTRansform

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The clinical trajectory of transthyretin amyloid cardiomyopathy (ATTR-CM) is driven by a structural cascade in which native transthyretin (TTR) protein tetramers dissociate into misfolded monomers and eventually form cardiotoxic amyloid fibrils¹. This cascade can occur from a point mutation in the *TTR* gene rendering it unstable, also known as variant ATTR-CM, or by an age-related process of unknown etiology and non-mutated *TTR* gene, also known as wild-type ATTR-CM¹. Two distinct drug classes now slow this process. Tetramer stabilizers, including tafamidis and acoramidis, bind circulating TTR and prevent its dissociation into amyloidogenic monomers^{2,3}. TTR silencers, including both the small interfering RNA (siRNA) vutrisiran and the antisense oligonucleotide (ASO) eplontersen, reduce hepatic synthesis directly at the messenger RNA level, lowering the substrate available to dissociate and misfold^{4,5}.

Tafamidis, acoramidis, and vutrisiran have previously been tested in efficacy trials for ATTR-CM, each meeting their primary endpoints as compared with placebo. Eplontersen is the latest TTR-targeted therapy to be evaluated in ATTR-CM, studied in the CARDIO-TTRansform trial largely in the context of background TTR stabilizer therapy, which represents a key component of the current standard of care. At randomization, more than half of participants were already receiving a TTR stabilizer, and among those not receiving a stabilizer at baseline, over half initiated one during the trial. Although the primary endpoint was not met, CARDIO-TTRansform demonstrated important treatment effects in the monotherapy population, and its overall findings are nuanced and warrant careful interpretation^{6,7}. This manuscript provides a critical appraisal of CARDIO-TTRansform and the evolving context of combination TTR stabilizer and silencer therapy, with the goal of informing clinical decision-making in the rapidly changing field of ATTR-CM.

CARDIO-TTRANSFORM: STUDY DESIGN, POPULATION, AND RESULTS

CARDIO-TTRansform was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of eplontersen compared with placebo in participants with ATTR-CM. The study enrolled 1,432 patients across 130 sites in 20

countries and is the largest treatment trial conducted in ATTR-CM to date. Participants were randomized 1:1 to eplontersen 45 mg or placebo, administered subcutaneously every four weeks for up to 140 weeks, on top of locally available standard of care, which included unrestricted use of TTR stabilizers⁸.

The population's age, sex distribution, race, and genotype were broadly similar to the previous treatment trials (Table 1)^{6,8}. Disease severity in CARDIO-TTRansform tracked ATTRIBUTE-CM and HELIOS-B with a comparable mix of patients by baseline New York Heart Association (NYHA) class, National Amyloidosis Centre (NAC) stage, Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) scores, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The major difference between CARDIO-TTRansform and the other trials was the concomitant medications used. Stabilizers were used in 81% of the population by the end of the study: 57% at baseline, and 57% of the remainder initiated one during the course of the trial. Moreover, more patients in CARDIO-TTRansform were on sodium-glucose cotransporter 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists (MRAs) relative to previous trials, the mainstays of modern heart failure therapy in ATTR-CM⁶. No prior ATTR-CM outcomes trial has enrolled patients with this degree of background therapy already in place.

The primary endpoint was a composite of cardiovascular mortality and recurrent cardiovascular clinical events through week 140. Secondary endpoints were tested in a prespecified hierarchical order: change from baseline in six-minute walk test (6MWT) distance, change in KCCQ-OS score, total recurrent cardiovascular events, all-cause mortality, the primary endpoint restricted to the subgroup already on a stabilizer at baseline, and cardiovascular mortality⁸.

CARDIO-TTRansform did not meet its primary composite endpoint; through week 140, there were 381 events in 210 of the 715 patients assigned to eplontersen versus 392 events in 231 of the 717 assigned to placebo (rate ratio 0.89; 95% CI 0.73 to 1.09; *P* = .277). Baseline stabilizer use modified the treatment effect (*P* for interaction = .017). In those on a baseline TTR stabilizer, the rate ratio was 1.14 (95% CI 0.85 to 1.53) while the rate ratio was 0.71 (95% CI 0.54 to 0.93) in those in the eplontersen monotherapy

TABLE 1
Clinical Characteristics of Active-arm Treated Patients Across ATTR-CM Drug Trials

	ATTR-ACT (tafamidis) n = 264	ATTRIBUTE-CM* (acoramidis) n = 421	HELIOS-B* (vutrisiran) n = 326	CARDIO-TTRransform* (eplontersen) n = 715
Enrollment Period	Dec 2013-Aug 2015	Apr 2019-Oct 2020	Dec 2019-Aug 2021	Mar 2020-Jul 2023
Age, years	75 (46-88)	77.4 ± 6.5	77.0 (45-85)	76.2 ± 7.2
Sex				
Female	8.7%	8.8%	8.3%	11.0%
Male	91.3%	91.2%	91.7%	89.0%
Race				
White	79.9%	87.4%	85.0%	88.7%
Black	14.0%	4.8%	7.1%	7.6%
Genotype				
ATTRwt	76.1%	90.3%	88.7%	85.0%
ATTRv	23.9%	9.7%	11.3%	15.0%
NYHA Class				
I	9.1%	12.1%	15.0%	11.7%
II	61.4%	69.6%	76.7%	71.2%
III	29.5%	18.3%	8.3%	17.1%
NAC stage				
1	45.1%	57.2%	63.8%	60.7%
2	36.0%	31.8%	30.7%	29.2%
3	18.9%	10.9%	5.5%	10.1%
6MWT, m	350.6 ± 121.3	361.2 ± 103.7	372.0 ± 103.7	350.5 ± 95.2
KCCQ-OS, points	67.3 ± 21.4	71.7 ± 19.4	73.0 ± 19.4	72.5 ± 19.8
NT-proBNP, pg/mL	2995.5 (1752-4862)	2326 (1332-4019)	2021 (1138-3312)	2068 (1323-3563)
Tafamidis use				
Baseline	N/A	0%	39.9%	57.3%
Drop-in*	N/A	14.9%	13.5%	24.3%
All-Cause Mortality	29.5% at 30 months	19.3% at 30 months	15.6% at 33-36 months	15.5% at 32 months

Data are presented as mean ± standard deviation, median (range or interquartile range), or percentage. *Drop-in TTR stabilizer use was allowed after 12 months in ATTRIBUTE-CM, not actively planned within the first 12 months in HELIOS-B, and allowed at any time in CARDIO-TTRransform. ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant/hereditary ATTR amyloidosis; ATTRwt, wild-type ATTR amyloidosis; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; N/A, not applicable; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 6MWT, six-minute walk test.

group. In the overall study population, secondary endpoints showed favorable effects of eplontersen vs placebo including 6MWT distance (19.7 m; 95% CI 9.9 to 29.6), KCCQ-OS score (4.0 points; 95% CI 2.0 to 6.0), and all-cause mortality (hazard ratio 0.78; 95% CI 0.61 to 0.99). Because the primary endpoint was not met, every endpoint below it in the prespecified hierarchy should be considered nominal. Finally, the safety profile did not differ meaningfully from placebo⁷.

EFFICACY OF EPLONTERSEN MONOTHERAPY

For patients newly diagnosed with ATTR-CM, the current treatment choices include tafamidis, acoramidis, or vutrisiran. Treatment is almost always initiated with a single agent; combination therapy so far has been both untested and costly. When considering regulatory approval of another up-front agent for this disease, we should examine the eplontersen monotherapy population. At week 140, this group had a nominally significant 29% lower rate of the composite endpoint of cardiovascular mortality and recurrent cardiovascular events compared with placebo as well as favorable

effects on 6MWT distance (difference vs placebo 29.9 m; 95% CI 14.3 to 45.5) and KCCQ-OS score (7.6 points; 95% CI 4.2 to 11.0)⁷. While we need to remember that the overall trial was negative for the primary endpoint, the prespecified monotherapy findings are encouraging.

Comparison of the four agents from clinical trial data is nearly impossible due to differences in eras, inclusion/exclusion criteria, baseline disease severity, concomitant TTR stabilizer therapy, choice of endpoints, and the influence of COVID-19 on enrollment and follow-up. Nevertheless, the closest comparison we can achieve is by looking at the all-cause mortality curves in the monotherapy populations across all four trials (**Figure 1A**). The three therapies studied in the modern era (acoramidis, vutrisiran, and eplontersen) have closely aligned mortality curves. Therefore, much of the differences in survival percentages seen among the trials are likely related to more modern heart failure management of ATTR-CM and combination therapy in the silencer trials, rather than major differences in drug potency. Compared with HELIOS-B, CARDIO-TTRransform enrolled more patients on baseline tafamidis (57.2% vs 39.6%), had roughly twice the rate of stabilizer drop-in during

follow-up (24.3% vs 12.8%), and had substantially higher use of SGLT2 inhibitors (18.5% vs 3.2%) and MRAs (43.2% vs 35.2%) at baseline⁶. ATTR-ACT is the outlier, but it was conducted in an era before ATTR-CM was widely recognized when diagnosis required biopsy confirmation rather than non-invasive bone scintigraphy, no disease-modifying therapy existed, and contemporary heart failure therapies were not yet available.

COMPARISON BETWEEN SILENCERS

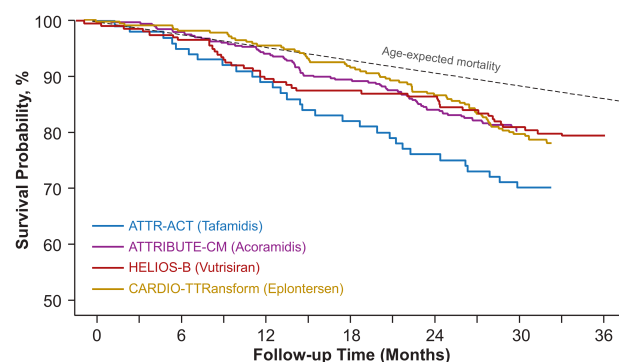
While the HELIOS-B and CARDIO-TTRransform trials differ in meaningful ways, a prespecified trial-level meta-analysis pooled data from both trials ($n = 2,086$) in an effort to compare the efficacy of the two silencers⁹. The primary endpoint was harmonized to the HELIOS-B definition of all-cause death and recurrent cardiovascular events. Results revealed a 20% reduction with gene silencing (rate ratio 0.80; 95% CI 0.69 to 0.94; $P = .006$) with no significant heterogeneity between trials ($I^2 = 15.4\%$; P for heterogeneity = .28)⁹. Concordance held across every other outcome examined including all-cause death, time to first death or cardiovascular event, 6MWT distance, and KCCQ-OS score.

The difference in TTR knockdown between agents is difficult to compare due to multiple issues: different assays used (enzyme-linked immunosorbent assay [ELISA] vs electrochemiluminescence immunoassay [ECLIA]), different baseline characteristics including proportion with variant disease where baseline TTR levels are lower, different dosing intervals between agents (every 3 months vs monthly) leading to variations in peak/trough levels, different measurement statistics (observed mean vs steady-state mean vs least-squares mean vs median), different baseline therapies, and the relative importance of percent knockdown from baseline vs absolute TTR level. To analyze knockdown without the influence of background and drop-in stabilizer use, the NEURO-TTRransform and HELIOS-A trials evaluated both therapies in polyneuropathy – eplontersen reduced serum TTR by a least-squares mean of 81.7% (observed median 85.0%, absolute mean trough 3.66 mg/dL) at week 65⁵, while vutrisiran produced a mean steady-state trough reduction of 81.0% (observed median 86.2%, absolute steady-state mean 3.94 mg/dL) through 18 months¹⁰.

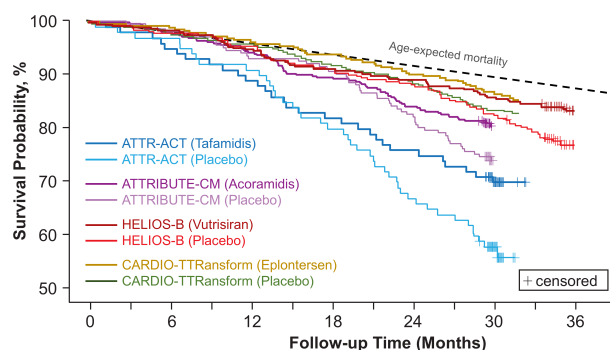
The apparent difference in TTR reduction between CARDIO-TTRransform and HELIOS-B was likely influenced in part by background TTR stabilizer use. Stabilizers increase circulating TTR concentrations despite concurrent silencing therapy; consequently, differences in baseline and subsequent stabilizer use can influence the observed TTR levels and percentage change from baseline. In HELIOS-B, serum TTR in the placebo group remained relatively stable through month 30 (−1.7%), such that the mean steady-state trough reduction of 78.8% from baseline was similar in magnitude to the placebo-corrected reduction. By contrast, in CARDIO-TTRransform, serum TTR increased in the placebo group as patients initiated stabilizer therapy. Consequently, the observed mean reduction from baseline at week 140 was 69.7%, corresponding to a least-squares mean placebo-corrected reduction of 77.2% (post hoc on-treatment placebo-corrected reduction 79.4%).

FIGURE 1

A Time to All-Cause Mortality – Monotherapy Treatment



B Time to All-Cause Mortality - Overall



Time to all-cause mortality among drug trials in ATTR-CM. Survival curves restricted to the monotherapy arm for ATTR-ACT (tafamidis), ATTRIBUTE-CM (acoramidis), HELIOS-B (vutrisiran), and CARDIO-TTRransform (eplontersen) superimposed in the same graph (Panel A). Survival curves for the treatment and placebo arms of ATTR-ACT, ATTRIBUTE-CM, HELIOS-B, and CARDIO-TTRransform superimposed in the same graph (Panel B). Population age-expected mortality is also depicted and based on the Social Security actuarial life table (4.1% mortality hazard per year based upon 2019 life table for median age of 77 years with 91% males, not accounting for cohort aging over 36 months). Survival curves for the three agents studied in the modern era (acoramidis, vutrisiran, and eplontersen) are closely aligned. Curves were truncated at differing follow-up duration based on prespecified time points in each drug trial.

The effect of combination stabilizer/silencer therapy on serum TTR levels is complicated and not currently well understood. There is a concept from light chain amyloidosis that the lower the amyloidogenic protein the better the outcomes; this has not been adequately studied in ATTR, particularly in the setting of stabilizer therapies that actually increase TTR protein levels. The field would benefit from standardization of assays and statistical methods used to measure knockdown, and a deeper dive using available data from these trials to better elucidate the differences in knockdown between current and future agents.

COMBINATION TTR STABILIZER AND SILENCER THERAPY

Stabilizers and silencers act at different steps of the same pathway. Stabilizers bind the TTR tetramer and slow its dissociation, while silencers lower how much TTR is produced by the liver. Both reduce the pool of misfolded, amyloidogenic protein reaching the heart. As successive trials enrolled a larger proportion of patients

already taking a stabilizer, the incremental benefit from a second agent grew smaller. This raises the possibility of a ceiling effect for therapies directed at the amyloid precursor protein since modern era treatment is bringing patients closer to their age-adjusted life expectancy and leaving less residual risk to modify (**Figure 1B**).

In the pooled meta-analysis, when gene silencing was added to patients on a baseline TTR stabilizer, there was no incremental benefit on the primary endpoint (rate ratio 0.97; 95% CI 0.77 to 1.23). There was also no treatment group where combination therapy seemed to benefit this primary endpoint after examining results by age, NYHA class, NT-proBNP, and variant status. Baseline NAC stage was not tested, yet both trials showed a benefit in NAC stage 1 with combination therapy suggesting that combination therapy may be more beneficial in earlier stage patients. Secondary endpoints such as all-cause mortality (hazard ratio 0.67; 95% CI 0.48 to 0.93) and 6MWT distance (14.2 m; 95% CI 3.7 to 24.7 m) showed benefit in the combination therapy group. Recurrent cardiovascular events and change in KCCQ-OS score directionally favored combination therapy but did not meet statistical significance⁹.

There is some nuance to interpreting these data. First, a recurrent-event model counts every hospitalization a living patient accrues, so a therapy that keeps patients alive longer can be penalized on total event burden even while lowering mortality. A win ratio or joint frailty model would be additive to help answer the question. Second, patients prescribed stabilizers at baseline were meaningfully different from those who were not; they were younger, had longer disease duration, lower NAC stage, lower NT-proBNP, better functional status, and by definition had already survived a period on therapy. A lower-risk stratum accrues fewer events, which reduces power. Tafamidis was also essentially the only stabilizer used, so these data may not apply to acoramidis. Third, common wisdom assumed that patients with variant ATTR-CM would benefit more from combination therapy due to more rapid progression and destabilizing mutations that may accelerate tetramer dissociation beyond the stability provided by tafamidis. Somewhat surprisingly, there was actually a trend towards worsening in the primary endpoint with combination therapy in the variant population. In the pooled analysis confined to patients already on a stabilizer, the rate ratio in variant disease was 1.39 (95% CI 0.98 to 1.99) compared with 0.90 (95% CI 0.73 to 1.10) in wild-type disease (*P* for heterogeneity = .035), directionally consistent in both trials (1.38 in CARDIO-TTRtransform and 1.51 in HELIOS-B)⁹. This may be due to a true lack of benefit or to the small number of variant patients in these trials, but highlights that combination therapy in variant disease should not be presumed beneficial on mechanistic grounds alone. Fourth, the assumption that patients with advanced disease would benefit from combination therapy was also not borne out in the meta-analysis.

FUTURE DIRECTIONS

CARDIO-TTRtransform's results arrive amid a new horizon of ATTR-CM trials that will face the same challenge of baseline disease-modifying therapy. Cliramtug and coramitug, monoclonal

antibodies designed to deplete existing amyloid fibrils, are now being tested in the phase 3 DepleTTR-CM (NCT06183931) and CLEOPATTR (NCT07207811) trials, respectively^{11,12}. Immutrin and other companies are also developing TTR protein depleters. Nexiguran ziclumeran (nex-z), a CRISPR-based gene-editing therapy that permanently reduces hepatic TTR production (90% at 12 months)¹³, is currently enrolling participants in the phase 3 MAGNITUDE (NCT06128629) trial. Nucleosiran, a next generation siRNA, reduces serum TTR levels by over 96% at day 29 after the first dose¹⁴, and is being tested in the phase 3 TRITON (NCT07052903) trial. While the depleters benefit from a different mechanism of action, nex-z and nucleosiran will help to answer the question of whether deeper TTR suppression is additive to baseline TTR stabilization. As stabilizer use continues to increase in newly diagnosed ATTR-CM, it is very important to consider how these new and ongoing drug trials are designed, powered, and eventually interpreted. Finally, given the extreme financial expense of all these therapies, the cost-effectiveness of adding additional agents will have to be decided by government entities and insurers. Sample size can always be increased until a small incremental benefit becomes statistically detectable; the more difficult question is whether an effect of that size is worth the cost of a second agent at the current price points.

CONCLUSION

CARDIO-TTRtransform was the largest trial in ATTR-CM, and its results are nuanced and require careful interpretation. Treating this trial as a negative study risks discarding a drug that appears to benefit patients as a first-line monotherapy treatment. The mechanism of gene silencing with an ASO is not ineffective; rather, the addition of this gene silencer to baseline tafamidis does not appear to provide much incremental benefit with respect to the combined endpoint of mortality and cardiovascular events. Future studies and substudies of these pivotal trials should investigate why combination therapy appears to reduce all-cause mortality without a corresponding reduction in recurrent cardiovascular events. Additionally, stronger TTR silencers or fibril depleters may add incremental benefit on top of stabilizers, but trials that enroll an unrestricted-stabilizer population will keep answering a question about marginal benefit while hoping to answer one about mechanism and efficacy. The bar is high: stabilizer therapy combined with contemporary heart failure management has moved ATTR-CM a long way since ATTR-ACT, and patients enrolled in these trials are now living closer and closer to their age-adjusted life expectancy.

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– original draft, writing – review & editing. Sperry: conceptualization, visualization, writing – original draft, writing – review & editing.

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