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RESEARCH ARTICLE

Baseline characteristics of patients with transthyretin amyloid cardiomyopathy in the CARDIO-TTRansform trial of eplontersen

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Abstract

Aims

Eplontersen is an antisense oligonucleotide that suppresses hepatic production of circulating transthyretin (TTR) by targeting *TTR* mRNA. We present baseline data from an ongoing trial, CARDIO-TTRansform, evaluating eplontersen in patients with TTR amyloid cardiomyopathy (ATTR-CM) and compare findings across previous ATTR-CM trials.

Methods and results

We evaluated 1432 patients enrolled in CARDIO-TTRansform from March 2020 to July 2023 who received ≥1 dose of study intervention (eplontersen or placebo) and had ≥1 post-baseline measurement. Mean (standard deviation) age was 76.4 (7.1) years; 9.4% were female; 88.8% were White. A total of 211 (14.7%) patients had hereditary/variant ATTR-CM (ATTRv-CM); Val122Ile (p.Val142Ile) was the most common genotype ($n = 130$). Patients spanned New York Heart Association functional classes I ($n = 192$), II ($n = 997$), and III ($n = 243$); 62.6% were National Amyloidosis Centre disease stage 1. Median (interquartile range) N-terminal pro-B-type natriuretic peptide was 2025 (1296–3465) pg/ml; $n = 51$ measured >8500 pg/ml. Median (interquartile range) high-sensitivity troponin T was 50 (35–69) pg/ml and mean left ventricular ejection fraction was 55.7% (9.7%). At baseline, 57.2% were on TTR stabilizer; 18.4% were on sodium-glucose co-transporter-2 inhibitors.

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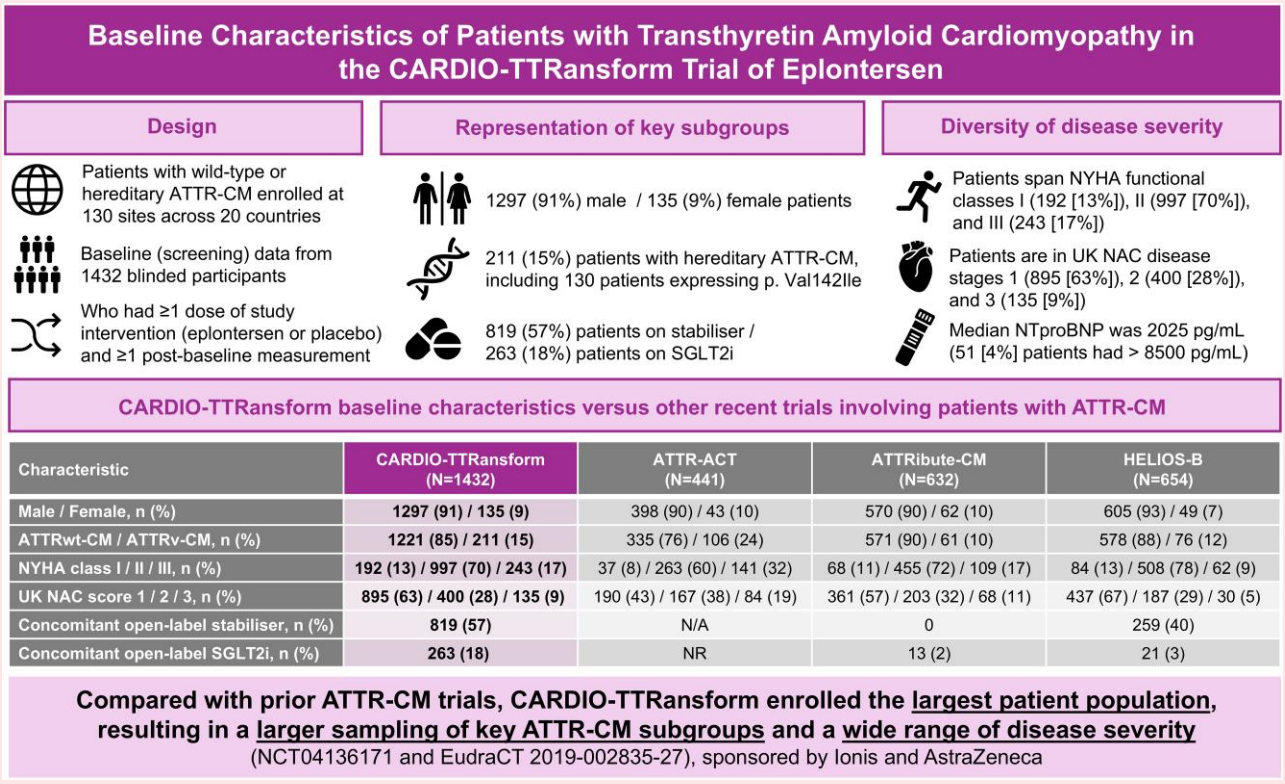
Conclusion The baseline characteristics of CARDIO-TTRansform were consistent with previous ATTR-CM trials; however, CARDIO-TTRansform evaluated patients with a wide range of disease severity and receiving the contemporary standard of care for ATTR-CM. Overall, blinded baseline data suggest that CARDIO-TTRansform provides a unique opportunity to determine the clinical benefits of eplontersen in a contemporary setting and in clinically relevant subgroups of patients with ATTR-CM.

Trial registration number NCT04136171

Graphical Abstract



Compared with prior ATTR-CM trials, CARDIO-TTRansform enrolled the largest patient population, resulting in a larger sampling of key ATTR-CM subgroups and a wide range of disease severity. ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, hereditary/variant ATTR-CM; ATTRwt-CM; wild-type ATTR-CM; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association Functional Classification; SGLT2i, sodium-glucose cotransporter protein inhibitor

Keywords Amyloidosis • Cardiomyopathy • Heart failure • Transthyretin • Eplontersen • ATTR-CM

Introduction

Transthyretin (ATTR) amyloidosis is a progressive, systemic, and life-threatening disease caused by the destabilization of the transthyretin (TTR) tetramer, leading to its dissociation into free misfolded monomers that aggregate into insoluble amyloid fibril deposits.[1–3] In transthyretin amyloid cardiomyopathy (ATTR-CM), the deposition of these amyloid fibrils in the myocardial extracellular matrix drives a structural cardiac remodelling process characterized by concentric wall thickening and progressive systolic and diastolic dysfunction.[2–4] Together, these changes contribute to a decline in cardiac performance in patients, resulting in exercise intolerance, decreased quality of life, higher rates of heart failure-associated hospitalization, and increased mortality.[1,5,6]

There are two types of ATTR-CM, hereditary or variant ATTR-CM (ATTRv-CM), which occurs as a result of variants in the *TTR* gene, and wild-type ATTR-CM (ATTRwt-CM), which is non-hereditary and is postulated to occur as a result of misfolding and deposition of wild-type TTR as an acquired pathogenic process associated with ageing.[1,2]

Within the past decade, there have been considerable advances in the management of ATTR-CM.[7,8] Current ATTR treatments can be broadly categorized into two types: therapies that stabilize the tetrameric structure of the TTR protein to prevent monomer formation and misfolding, and therapies that silence the gene that produces the

TTR protein by binding and degrading *TTR* messenger RNA (mRNA).[7–12] Despite existing heart failure therapies, considerable unmet clinical need remains for these ATTR-CM patients with respect to mortality and morbidity.[1]

Eplontersen is a novel TTR silencer that is under investigation for the treatment of ATTR-CM. As an antisense oligonucleotide utilizing a GalNaC ligand for liver-targeted drug delivery[13,14] eplontersen inhibits hepatic TTR protein production by binding *TTR* mRNA and mediating degradation of the sense TTR strand through the recruitment of ribonuclease H1.[13,14]

Eplontersen is currently approved for the treatment of hereditary ATTR amyloidosis with polyneuropathy based on results from the Phase 3 NEURO-TTRansform trial, which showed significant improvement across multiple disease-relevant outcomes among patients who received eplontersen as compared with those in an external placebo group.[14] The clinical benefits of eplontersen for ATTR amyloidosis with polyneuropathy imply that eplontersen has the potential to benefit patients with ATTR-CM as well.

Here, we describe the baseline demographics and clinical characteristics of patients enrolled in an ongoing clinical trial, CARDIO-TTRansform (NCT04136171; EudraCT No. 2019-002835-27), evaluating the efficacy and safety of eplontersen in patients with ATTR-CM, and compare our findings to published baseline data from three other randomized, placebo-controlled, fixed-duration outcomes trials of approved TTR stabilizer or gene silencing therapies involving patients with ATTR-CM. By characterizing key differences in patient profiles across trials, we can identify gaps in the clinical evidence that enable a more nuanced interpretation of how different therapies affect outcomes for ATTR-CM.

Methods

Study design

CARDIO-TTRansform is an ongoing Phase 3, global, double-blind, placebo-controlled trial comparing the efficacy and safety of eplontersen (45 mg once every 4 weeks) versus placebo in patients with either ATTRwt-CM or ATTRv-CM. Enrolment occurred at 130 study sites across 20 countries from March 2020 to July 2023, with a study treatment period of up to 140 weeks. Eligible patients were randomized 1:1 to receive eplontersen or placebo, with stratification by baseline New York Heart Association (NYHA) class (I/II vs III), TTR genotype (wild-type vs variant), 6-min walk test (6MWT) distance (≤350 m vs >350 m), and TTR stabilizer use at randomization (yes vs no). Full details of the CARDIO-TTRansform study design have been previously described.[15]

Inclusion and exclusion criteria

Table 1A provides a summary of inclusion and exclusion criteria for CARDIO-TTRansform as well as three other placebo-controlled Phase 3 studies involving patients with ATTR-CM: ATTR-ACT (tafamidis),[9] ATTRibute-CM (acoramidis),[10] and HELIOS-B (vutrisiran).[11] Briefly, CARDIO-TTRansform enrolled adults ≥18–90 years of age diagnosed with ATTR-CM and mild or moderate heart failure (NYHA functional class I–III and a history of at least one heart failure-associated hospitalization or signs and symptoms requiring loop diuretic therapy). The presence of ATTR amyloid deposits was confirmed by an endomyocardial or extracardiac biopsy (i.e. positive for Congo red staining) or by grade 2 or 3 cardiac uptake on 99m-technetium scintigraphy, confirmed by single-photon emission computed tomography imaging, in the absence of renally adjusted abnormal serum-free light chain ratio or monoclonal proteins detected on serum and urine immunofixation. Patients were required to have confirmed cardiac involvement based on a screening echocardiogram with left ventricular wall thickness >12 mm, have an N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration ≥600 pg/ml (or ≥1200 pg/ml if in atrial fibrillation), and have a minimum 6MWT distance of >100 m at screening.

Exclusion criteria for CARDIO-TTRansform included having alanine aminotransferase or aspartate aminotransferase >2.0 times the upper limit of normal (ULN), total bilirubin ≥2.0×ULN, platelets count below 125×10^9/L, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 (<45 mL/min/1.73 m^2 in France, Spain, and Denmark), and a urine protein creatinine ratio ≥750 mg/g, as well as being the recipient of a liver or heart transplant and/or left ventricular assist device. Patients previously treated with other TTR gene silencers were also excluded.

Open-label concomitant use of TTR stabilizer, as well as sodium-glucose cotransporter 2 (SGLT2) inhibitors and other heart failure therapies, was not an exclusion criterion at screening and was allowed at any time during the double-blind period of the trial without restriction, if clinically indicated and locally available.

Planned efficacy analyses

Primary efficacy analysis details for CARDIO-TTRansform, as well as ATTR-ACT,[9] ATTRibute-CM,[10] and HELIOS-B,[11] are summarized in *Table 1B*. Full efficacy analyses and statistical testing hierarchy details for CARDIO-TTRansform have been previously described.[15] Briefly, the CARDIO-TTRansform primary analysis will compare the composite endpoint of cardiovascular-related death and recurrent cardiovascular events up to 140 weeks of treatment using an Andersen–Gill method. Secondary endpoints, in order of testing hierarchy, include changes in 6MWT distance and Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score, recurrent cardiovascular clinical events, all-cause mortality, the composite endpoint of cardiovascular-related death and recurrent cardiovascular events in a subgroup of patients receiving TTR stabilizer at baseline, and CV mortality.

Baseline data collection and statistical methodology

Detailed baseline data were collected from patients in CARDIO-TTRansform at screening and before randomization. Baseline assessments included demographics and clinical characteristics, ATTR-CM-specific medical history, concomitant medications, vital signs, NYHA functional classification, 6MWT distance and KCCQ-OS scores, echocardiographic parameters, and laboratory values.[15]

All CARDIO-TTRansform baseline demographic and clinical data are reported descriptively and in the overall, blinded full analysis population. Continuous variables are presented as means with standard deviations (SD) or medians with ranges or interquartile ranges (IQR) specified. Categorical variables are presented as percentages. Similar baseline data from ATTR-ACT,[9] ATTRibute-CM,[10] and HELIOS-B[11] clinical trials were extracted from published works for comparison.

CARDIO-TTRansform study ethics

The study is being conducted according to the guidelines of the International Conference on Harmonization and in accordance with the Declaration of Helsinki and all applicable regulatory requirements. All participants provided written informed consent prior to assessment of eligibility and participation in the study. The study protocol and any current protocol amendments have been approved by the local institutional review boards and ethics committees.

Results

Baseline demographics and characteristics of patients in CARDIO-TTRansform

A total of 1432 patients with ATTR-CM were enrolled at 130 CARDIO-TTRansform study sites across 20 countries between March 2020 and July 2023, received at least one dose of study intervention (eplontersen or placebo), and had at least one post-baseline efficacy measurement (*Figure 1*).

Enrolment data, along with baseline demographics and clinical characteristics of the blinded CARDIO-TTRansform population at randomization, are presented in *Table 2*. These are shown alongside

Table 1 Summary of (A) inclusion/exclusion criteria and (B) efficacy endpoint analysis details across trials involving patients with ATTR-CM

A

	CARDIO-TTRansform (*N* = 1432)	ATTR-ACT (*N* = 441)[9]	ATTRibute-CM (*N* = 632)[10]	HELIOS-B (*N* = 655)[11]
Age, years	≥18 to 90, inclusive	≥18 to ≤90	≥18 to ≤90	≥18 to 85, inclusive
History of heart failure	≥1 heart failure-associated hospitalization or signs and symptoms of heart failure requiring loop diuretic therapy	≥1 prior hospitalization for heart failure or clinical evidence of heart failure manifesting in signs or symptoms of volume overload or elevated intracardiac pressures requiring a diuretic for improvement	≥1 previous hospitalization for heart failure, signs and symptoms of volume overload, or heart failure that resulted in diuretic treatment	≥1 previous hospitalization for heart failure or clinical evidence of heart failure, with signs and symptoms of volume overload or elevated intracardiac pressures warranting diuretic treatment
LV wall thickness, mm	>12 (via echocardiogram)	>12 (via echocardiogram)	≥12 (via echocardiogram or CMR)	>12 (via echocardiogram)
NT-proBNP, pg/ml	≥600 (≥1200 if patient has atrial fibrillation); no upper limit	≥600; no upper limit	≥300 to <8500	>300 (>600 if patient has atrial fibrillation) to <8500
NYHA class/UK NAC stage	Exclude if class IV	Exclude if class IV	Exclude if class IV	Exclude if class IV, or class III if also UK NAC stage 3
eGFR, ml/min/1.73 m^2	≥30	>25	≥15, ≥30 for the primary analyses	≥30
6MWT distance, metres	≥100	>100	≥150	≥150
Open-label concomitant stabilizer use	No restrictions	N/A	Patients could initiate tafamidis after 12 months of blinded study therapy	Tafamidis-naïve patients were required to have no active plans to initiate treatment within one year of enrolment, but could begin tafamidis if the investigator considered it to be necessary

B

	CARDIO-TTRansform (*N* = 1432)	ATTR-ACT (*N* = 441)[9]	ATTRibute-CM (*N* = 632)[10]	HELIOS-B (*N* = 655)[11]
Primary efficacy endpoint/s	Composite of CV death and recurrent CV events	Two-step hierarchical: All-cause mortality followed by frequency of CV-related hospitalizations	Four-step hierarchical: first death from any cause, followed by CV-related hospitalizations, then change from baseline in NT-proBNP, then change from baseline in 6MWT distance	Composite of all-cause death and recurrent CV events
Statistical method for primary efficacy endpoint	Recurrent events Andersen Gill (LWYY)	Finkelstein–Schoenfeld	Finkelstein–Schoenfeld	Recurrent events Andersen Gill (LWYY)
Study duration for endpoint analyses	Up to 140 weeks (up to 160 weeks for CV and all-cause mortality)	30 months	30 months	33 to 36 months (up to 42 months for mortality as an extension study)

6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LWYY, Lin–Wei–Yang–Ying; LV, left ventricular; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

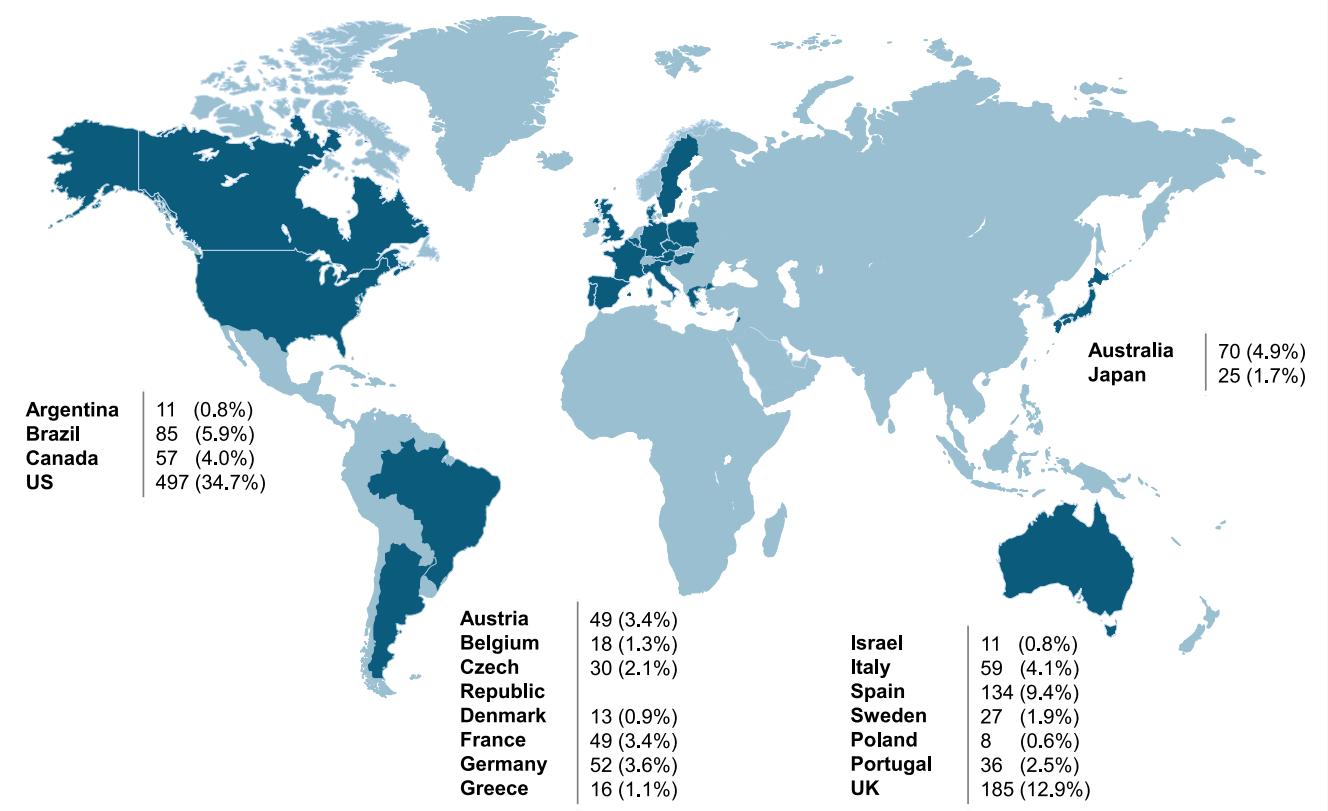


Figure 1 Patients enrolled across the 130 study sites in the CARDIO-TTRansform trial and included the full analysis population ($N = 1432$) by country of origin

corresponding data from other ATTR-CM trials (ATTR-ACT,[9] ATTRibute-CM,[10] and HELIOS-B[11]).

The mean (SD) age of patients in CARDIO-TTRansform was 76.4 (7.1) years, and patients ranged from 41 to 91 years of age; 9.4% ($n = 135$) of patients were female. Mean (SD) modified body mass index was 1117.6 (186.5) g/L × kg/m^2. Most patients (88.8% [$n = 1271$]) were White, while 7.8% ($n = 112$) were Black; 7.3% ($n = 105$) were of Hispanic or Latino ethnicity.

Patients reported a median (range) duration of ATTR-CM symptoms of 1.6 (0.1–24.4) years before enrolment and had been diagnosed with ATTR-CM a median of 0.8 (0–11.3) years prior. Overall mean (SD) 6MWT distance was 352.2 (96.3) m and mean KCCQ-OS score was 72.6 (19.9). Most patients had some limitations on physical activity, with 69.6% ($n = 997$) of patients categorized as NYHA functional class II and 17.0% ($n = 243$) as class III. The most common UK NAC disease stage was 1 (62.6%, $n = 895$), followed by 2 (28.0%, $n = 400$), and 3 (9.4%, $n = 135$). Overall, proportions of participants by NYHA class and NAC stage were balanced across regions.

Most patients (85.3% [$n = 1221$]) had ATTRwt-CM. Among the 14.7% ($n = 211$) of patients with ATTRv-CM, 61.6% had variant Val122Ile (p.Val142Ile, $n = 130$).

Median NT-proBNP (IQR) was 2025 (1296–3465) pg/ml, with 51 patients having levels over 8500 pg/ml. Median high-sensitivity troponin T concentration was 50 (35–69) pg/ml. Mean (SD) eGFR was 61.5 (16.3) ml/min/1.73 m^2, with nearly half of patients (49% [$n = 701$]) below 60 ml/min/1.73 m^2. The mean (SD) left ventricular ejection fraction was 55.7% (9.7%), stroke volume was 56.3 (17.5) ml, and left ventricular wall thickness was 18.3 (3.0) mm. Patients had a mean global longitudinal strain of −13.5% (3.0%) and lateral E/e′ ratio of 15.5 (6.9).

Most patients in CARDIO-TTRansform had cardiac comorbidities at baseline. The majority (63.1% [$n = 904$]) had atrial fibrillation or flutter, 19.1% ($n = 273$) had a permanent pacemaker, and 8.0% ($n = 115$) had an implanted cardiac defibrillator. Other comorbidities included diabetes mellitus (17.0% [$n = 244$]) and a history of hypertension (63.3% [$n = 906$]).

Commonly prescribed concomitant medications included diuretics (88.8% [$n = 1272$] of patients, including 1229 on loop diuretics), anticoagulants (60.7% [$n = 869$]), beta-adrenergic blockers (42.4% [$n = 607$]), mineralocorticoid receptor antagonists (42.3% [$n = 606$]), and agents acting on the renin-angiotensin system (40.9% [$n = 585$]). Additionally, 18.4% ($n = 263$) and 57.2% ($n = 819$) of patients were receiving SGLT2 inhibitors and TTR stabilizers at baseline, respectively. The mean (SD) duration of TTR stabilizer use prior to Study Day 1 was 12.6 (12.0) months.

Comparison of CARDIO-TTRansform patient baseline characteristics with those of patients in prior ATTR-CM trials

Patients in CARDIO-TTRansform had several points of similarity with patients evaluated in recent ATTR-CM trials (*Table 2*). Baseline demographic and clinical characteristics such as age range, sex ratio, and race were similar across all trials. However, the greater sample size of CARDIO-TTRansform resulted in higher absolute numbers of female patients, Black patients, and those with ATTRv-CM than have previously been evaluated. Baseline disease/symptom severity varied across ATTR-CM trials, with CARDIO-TTRansform having a similar or higher proportion of patients with severe symptoms (categorized as NYHA III and UK NAC stage 3) than in ATTRibute-CM and HELIOS-B, and a

Table 2 **Study enrolment details, and baseline demographics and clinical characteristics in patients in the full analysis population of the CARDIO-TTRansform trial and in patients evaluated in other ATTR-CM trials**

	CARDIO-TTRansform (*N* = 1432)	ATTR-ACT (*N* = 441)[9]		ATTRibute-CM (*N* = 632)[10,b]		HELIOS-B (*N* = 655)[11]	
	Overall population (*N* = 1432)	Pooled Tafamidis[a] (*N* = 264)	Placebo (*N* = 177)	Acoramidis (*N* = 421)	Placebo (*N* = 211)	Vutrisiran (*N* = 326)	Placebo[c] (*N* = 328)
Enrolment dates	March 2020–July 2023	December 2013–August 2015		April 2019–October 2020		December 2019–August 2021	
Countries, *n*	20	13		18		26	
Sites, *n*	130	48		104		87	
Characteristic							
Age, years	Mean (SD): 76.4 (7.1) Median (range): 77 (41–91)	Mean: 74.5 (7.2) Median: 75 (46–88)	Mean: 74.1 (6.7) Median: 74 (51–89)	Mean: 77.4 (6.5)	Mean: 77.1 (6.8)	Median: 77.0 (45–85)	Median: 76.0 (46–85)
Male, *n* (%)	1297 (90.6%)	241 (91.3%)	157 (88.7%)	384 (91.2%)	186 (88.2%)	299 (91.7%)	306 (93.3%)
Female, *n* (%)	135 (9.4%)	23 (8.7%)	20 (11.3%)	37 (8.8%)	25 (11.8%)	27 (8.3%)	22 (6.7%)
Modified BMI, g/L × kg/m^2	Mean (SD): 1117.6 (186.5)	Mean: 1058.8 (173.8)	Mean: 1066.4 (194.4)	NR	NR	Median (IQR): 1183.8 (1082.7–1306.1)	Median: 1210.9 (1098.5–1333.5)
Race, *n* (%)							
White	1271 (88.8%)	211 (79.9%)	146 (82.5%)	368 (87.4%)	187 (88.6%)	277 (85.0%)	275 (83.8%)
Black	112 (7.8%)	37 (14.0%)	26 (14.7%)	20 (4.8%)	10 (4.7%)	18 (5.5%)	19 (5.8%)
Asian	35 (2.4%)	13 (4.9%)	5 (2.8%)	10 (2.4%)	3 (1.4%)	23 (7.1%)	24 (7.3%)
Other or not reported	10 (0.7%)	3 (1.1%)	0	23 (5.5%)	11 (5.2%)	8 (2.5%)	10 (3.0%)
Multiple	4 (0.3%)	NR	NR	NR	NR	NR	NR
Ethnicity, *n* (%)							
Hispanic or Latino	105 (7.3%)	NR	NR	NR	NR	NR	NR
Duration of ATTR-CM, median (range)							
Duration between symptom onset and enrolment, years	1.6 (0.1–24.4)	NR	NR	NR	NR	NR	NR
Duration between diagnosis and enrolment, years	0.8 (0–11.3)	NR	NR	NR	NR	0.9 (0–11.1)	1.0 (0–10.8)
Functional test scores, mean (SD)							
6MWT distance, metres	352.2 (96.3)	350.6 (121.3)	353.3 (126.0)	362.8 (103.5); *n* = 409[b16]	351.5 (93.8); *n* = 202[b16]	372.0 (103.7)	377.1 (96.3)
KCCQ-OS score	72.6 (19.9)	67.3 (21.4)	65.9 (21.7)	71.7 (19.4); *n* = 409[b16]	70.5 (20.7); *n* = 202[b16]	73.0 (19.4)	72.3 (19.9)

Continued

Table 2 *Continued*

	CARDIO-TTRansform (*N* = 1432)	ATTR-ACT (*N* = 441)[9]		ATTRibute-CM (*N* = 632)[10,b]		HELIOS-B (*N* = 655)[11]	
	Overall population (*N* = 1432)	Pooled Tafamidis[a] (*N* = 264)	Placebo (*N* = 177)	Acoramidis (*N* = 421)	Placebo (*N* = 211)	Vutrisiran (*N* = 326)	Placebo[c] (*N* = 328)
NYHA functional class, *n* (%)							
I	192 (13.4%)	24 (9.1%)	13 (7.3%)	51 (12.1%)	17 (8.1%)	49 (15.0%)	35 (10.7%)
II	997 (69.6%)	162 (61.4%)	101 (57.1%)	293 (69.6%)	162 (76.8%)	250 (76.7%)	258 (78.7%)
III	243 (17.0%)	78 (29.5%)	63 (35.6%)	77 (18.3%)	32 (15.2%)	27 (8.3%)	35 (10.7%)
UK NAC disease stage, *n* (%)							
1	895 (62.6%)	119 (45.1%)[17]	71 (40.1%)[17]	241 (57.2%)	120 (56.9%)	208 (63.8%)	229 (69.8%)
2	400 (28.0%)	95 (36.0%)[17]	72 (40.7%)[17]	134 (31.8%)	69 (32.7%)	100 (30.7%)	87 (26.5%)
3	135 (9.4%)	50 (18.9%)[17]	34 (19.2%)[17]	46 (10.9%)	22 (10.4%)	18 (5.5%)	12 (3.7%)
TTR genotype, *n* (%)							
Wild-type	1221 (85.3%)	201 (76.1%)	134 (75.7%)	380 (90.3%)	191 (90.5%)	289 (88.7%)	289 (88.1%)
Hereditary (variant)	211 (14.7%)	63 (23.9%)	43 (24.3%)	41 (9.7%)	20 (9.5%)	37 (11.3%)	39 (11.9%)
Val122Ile (p.Val142Ile)	130 (61.6%)	38 (60.3%)[18]	23 (53.5%)[18]	24/39 (61.5%)	12/19 (63.2%)	24 (64.9%)	25 (64.1%)
Ile68Leu (p.Ile88Leu)	18 (8.5%)	9 (14.3%)[18]	4 (9.3%)[18]	NR	NR	0	2 (5.2%)
Thr60Ala (p.Thr80Ala)	14 (6.6%)	6 (9.5%)[18]	6 (14.0%)[18]	3/39 (7.7%)	2/19 (10.5%)	2 (5.4%)	6 (15.4%)
Val30Met (p.Val50Met)	28 (13.3%)	3 (4.8%)[18]	6 (14.0%)[18]	1/39 (2.6%)	0	4 (10.8%)	2 (5.1%)
Blood biomarkers, median (IQR)							
NT-proBNP, pg/ml	2025 (1296–3465)	2996 (1752–4862)	3161 (1864–4825)	2326 (1332–4019)	2306 (1128–3754)	2021 (1138–3312)	1801 (1042–3082)
>8500, *n* (%)	51 (3.6%)	NR	NR	N/A	N/A	N/A	N/A
Troponin, pg/ml	High-sensitivity troponin T: 50 (35–69)	Troponin I: 140 (90–200)	Troponin I: 140 (80–190)	NR	NR	Troponin I: 72 (45–116)	Troponin I: 65 (41–106)
Renal function							
eGFR, ml/min/1.73 m^2	Mean (SD): 61.5 (16.3) Median (IQR): 60.3 (49.0–73.5)	Mean: 57.5 (17.3)[17]	Mean: 55.6 (16.8)[17]	Mean: 61 (18)	Mean: 61 (19)	Median: 64 (50–81)	Median: 65 (53–81)
<60, *n* (%)	701 (49.0%)	154 (58.3%)[17]	110 (62.1%)[17]	NR	NR	NR	NR
<45, *n* (%)	229 (16.0%)	60 (22.7%)[17]	47 (26.6%)[17]	65/409[b] (15.9%)[16]	29/202[b] (14.4%)[16]	NR	NR

Continued

Table 2 *Continued*

	CARDIO-TTRansform (*N* = 1432)	ATTR-ACT (*N* = 441)[9]		ATTRibute-CM (*N* = 632)[10,b]		HELIOS-B (*N* = 655)[11]	
	Overall population (*N* = 1432)	Pooled Tafamidis[a] (*N* = 264)	Placebo (*N* = 177)	Acoramidis (*N* = 421)	Placebo (*N* = 211)	Vutrisiran (*N* = 326)	Placebo[c] (*N* = 328)
Echocardiography parameters, mean (SD)							
LVEF, %	55.7 (9.7)	48.4 (10.3)	48.6 (9.5)	NR	NR	55.6 (12.7)[19]	55.9 (12.4)[19]
LV stroke volume, ml	56.3 (17.5)	45.8 (16.1)	45.1 (16.9)	NR	NR	50.7 (16.3)[19]	53.8 (19.0)[19]
LV wall thickness, mm	18.3 (3.0)	17.0 (3.9)	16.7 (4.1)	NR	NR	18.2 (2.6)[19]	18.2 (2.7)[19]
Global longitudinal strain, %	−13.5 (3.0)	−9.3 (3.5)	−9.4 (3.6)	NR	NR	−14.0 (3.5)[19]	−14.0 (3.5)[19]
E/e′ ratio	Lateral: 15.5 (6.9)	Lateral (*n* = 176[a]): 17.1 (7.7) Septal (*n* = 176[a]): 24.8 (11.0)[20]	Lateral: 17.2 (7.8) Septal: 24.2 (10.4)[20]	NR	NR	Lateral: 14.8 (6.7) Septal: 20.5 (7.9)[19]	Lateral: 15.3 (6.3) Septal: 21.1 (8.3)[19]
Co-morbidities, *n* (%)							
Atrial fibrillation	904 (63.1%)	93/176[a] (52.8%)[20]	89 (50.3%)[20]	236/409[b] (57.7%)[16]	117/202[b] (57.9%)[16]	197 (60.4%)[19]	196 (58.8%)[19]
Permanent pacemaker	273 (19.1%)	13 (4.9%)	12 (6.8%)	77/409[b] (18.8%)[16]	38/202[b] (18.8%)[16]	NR	NR
Implanted cardiac defibrillator	115 (8.0%)	16 (6.1%)	9 (5.1%)	NR	NR	NR	NR
History of hypertension	906 (63.3%)	145 (54.9%)	84 (47.5%)	NR	NR	185 (56.7%)[19]	187 (57.0%)[19]
Diabetes mellitus	244 (17.0%)	20 (7.6%)	13 (7.3%)	NR	NR	56 (17.2%)[19]	55 (16.8%)[19]
Type 1	5 (0.3%)	NR	NR	NR	NR	NR	NR
Type 2	239 (16.7%)	NR	NR	NR	NR	NR	NR
Concomitant medications, *n* (%)							
Diuretics (any)	1272 (88.8%)	175 (66.3%)	123 (69.5%)	357 (84.8%)[21]	179 (84.8%)[21]	NR	NR
High-ceiling (loop) diuretic (azosemide, furosemide, bumetanide, torsemide, ethacrynic acid)	1229 (85.8%)	NR	NR	323 (76.7%)[21]	164 (77.7%)[21]	261 (80.1%)	259 (79.0%)
Anticoagulants/antithrombotics	869 (60.7%) (anticoagulants)	105 (39.8%) (antithrombotics)	72 (40.7%) (antithrombotics)	339 (80.5%)[21] (antiplatelet/ anticoagulants)	168 (79.6%)[21] (antiplatelet/ anticoagulants)	NR	NR
Beta-adrenergic blockers	607 (42.4%)	76 (28.8%)	53 (29.9%)	189 (44.9%)[21]	94 (44.5%)[21]	NR	NR
MRAs	606 (42.3%)	NR	NR	143 (34.0%)[21]	72 (34.1%)[21]	NR	NR
Agents acting on the renin-angiotensin system	585 (40.9%)	69 (26.1%)	48 (27.1%)	183 (43.5%)[21]	87 (41.2%)[21]	NR	NR
ACEis	241 (16.8%)	NR	NR	83 (19.7%)[21]	46 (21.8%)[21]	NR	NR
ARBs	345 (24.1%)	NR	NR	100 (23.8%)[21]	41 (19.4%)[21]	NR	NR
ARNIs	82 (5.7%)	NR	NR	12 (2.9%)[21]	7 (3.3%)[21]	NR	NR

Continued

Table 2 *Continued*

	CARDIO-TTRansform (*N* = 1432)	ATTR-ACT (*N* = 441)[9]		ATTRibute-CM (*N* = 632)[10,b]		HELIOS-B (*N* = 655)[11]	
	Overall population (*N* = 1432)	**Pooled Tafamidis[a] (*N* = 264)**	**Placebo (*N* = 177)**	**Acoramidis (*N* = 421)**	**Placebo (*N* = 211)**	**Vutrisiran (*N* = 326)**	**Placebo[c] (*N* = 328)**
SGLT2i	263 (18.4%)	NR	NR	8 (1.9%)[21]	5 (2.4%)[21]	10 (3.1%)	11 (3.0%)
Patients initiating post-baseline (drop-ins)	Ongoing	NR	NR	35 (8.3%)[21]	28 (13.3%)[21]	102 (31.3%)	114 (35.0%)
TTR stabilizer, open label	819 (57.2%) (all tafamidis)	N/A	N/A	0	0	130 (39.9%) (all tafamidis)	129 (39.0%) (all tafamidis)
Duration of TTR stabilizer use prior to Study Day 1, months	Mean (SD): 12.6 (12.0) Median (Range): 9.0 (0.1–92.0)	N/A	N/A	N/A	N/A	Median (Range): 9.2 (1.1–65.3)	Median (Range): 11.3 (1.1–65.5)
Patients initiating post baseline (drop-ins)	Ongoing	N/A	N/A	61/409[b] (14.9%) only permitted after 12-month visit[21]	46/202[b] (22.8%) only permitted after 12-month visit[21]	44 (13.5%) (all tafamidis)	41 (12.5%) (all tafamidis)
GLP-1 receptor agonist	10 (0.7%)	NR	NR	4 (1.0%)[21]	2 (0.9%)[21]	NR	NR
Outcomes, *n* (%)							
All-cause mortality	Ongoing	30 months: 78 (29.5%)	30 months: 76 (42.9%)	30 months: 79/409[b] (19.3%)[16]	30 months: 52/202[b] (25.7%)[16]	42 months: 60 (18.4%)	42 months: 85 (25.9%)

Modified BMI was defined as the product of serum albumin concentration (g/L) and conventional BMI (kg/m^2).
UK NAC stages were defined as: Stage 1, NT-proBNP ≤3000 pg/ml and eGFR ≥45 ml/min/1.73 m^2; Stage 2, NT-proBNP >3000 pg/ml or eGFR <45 ml/min/1.73 m^2; Stage 3, NT-proBNP >3000 pg/ml and eGFR <45 ml/min/1.73 m^2.
NYHA Classes categories were defined as: Class I, no limitation of physical activity; Class II, slight limitation of physical activity, with ordinary activity causing symptoms; Class III, marked physical limitations, with less-than-ordinary activity causing symptoms; Class IV: symptoms at rest or with any activity.
6MWT, 6-minute walk test; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ATTR-CM, transthyretin amyloid cardiomyopathy; BMI, body mass index; DB, double-blind; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; N/A; not applicable; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NR, not reported; NYHA, New York Heart Association; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TTR, transthyretin.
[a]Pooled tafamidis data are listed from all patients in the ATTR-ACT study who were randomized to receive either 80 mg tafamidis or 20 mg tafamidis (*N* = 264). Some baseline measurements were available only for patients who received tafamidis 80 mg only (*n* = 176).
[b]Data are listed, where available, from the overall randomized population (*N* = 632). Some baseline measurements were available only from the modified intention-to-treat population (*N* = 614; acoramidis *n* = 409, placebo *n* = 202) which included all the patients who had undergone randomization, received at least one dose of acoramidis or placebo, had at least one efficacy evaluation after baseline, and had eGFR >30 ml/min/1.73 m^2.
[c]Reported baseline and mortality data from HELIOS-B omit one patient in the placebo group (originally N = 329) who was randomized but withdrew before dosing.

lower proportion than ATTR-ACT. CARDIO-TTRansform had a higher cardiovascular comorbidity burden than all other trials, with a higher proportion of patients reporting a history of atrial fibrillation, permanent pacemakers, implanted cardiac defibrillators, and a history of hypertension. Baseline use of both TTR stabilizer and SGLT2 inhibitors was also considerably higher in CARDIO-TTRansform compared with patients in other studies.

Discussion

The ongoing, global, Phase 3 CARDIO-TTRansform trial has enrolled the largest and most clinically diverse cohort of patients with ATTR-CM to date and thus has the potential to provide definitive evidence for the effectiveness of eplontersen therapy in ATTR-CM. When compared to other recent ATTR-CM clinical trials, CARDIO-TTRansform includes a higher number of female patients, Black patients, and patients with ATTRv-CM.[9–11] CARDIO-TTRansform patients also had a higher cardiovascular comorbidity burden than those included in previous trials, and presented with a wide spectrum of disease severity at baseline. Additionally, patients enrolled in CARDIO-TTRansform had a notably higher use of TTR stabilizer and SGLT2 inhibitors than that recorded in previous trials, reflecting the rapid uptake of guideline-directed therapies in routine clinical practice.[22,23] Collectively, these baseline data suggest that CARDIO-TTRansform is positioned to evaluate the efficacy of eplontersen across a population that closely reflects the real-world ATTR-CM population, including a large number of patients treated with TTR stabilizer and those with advanced disease.

Comparing CARDIO-TTRansform across the two other contemporary ATTR-CM trials, several of the differences in baseline characteristics and disease severity observed are likely attributable to differences in inclusion and exclusion criteria.[9–11] HELIOS-B excluded NYHA class III patients who were in UK NAC stage 3 (NT-proBNP >3000 pg/ml and eGFR <45 ml/min/1.73 m^2), whereas CARDIO-TTRansform applied no such restriction. Both HELIOS-B and ATTRibute-CM also imposed upper NT-proBNP thresholds (<8500 pg/ml), while CARDIO-TTRansform allowed enrolment without an upper biomarker limit and included 51 participants >8500 pg/mL. Functional eligibility criteria also differed, with CARDIO-TTRansform using a lower 6MWT threshold (≥100 vs ≥150 m). Taken together, these allowed for the inclusion of more functionally impaired patients in CARDIO-TTRansform, which addresses an important historical evidence gap limiting our understanding of such patients. However, given the differences in study design, study centres utilized, and periods of data collection in the studies outlined in this publication, it should also be noted that the variability observed in patients' baseline demographics and clinical characteristics may also have been influenced by additional factors.

While broadly comparable use of concomitant medications was observed across all evaluated trials, patients in CARDIO-TTRansform had notably higher baseline TTR stabilizer and SGLT2 inhibitor use, and, unlike patients in HELIOS-B and ATTRibute-CM, had no restrictions on the initiation of concomitant open-label TTR stabilizer in the double-blind period. The higher uptake of SGLT2 inhibitors in CARDIO-TTRansform is consistent with accumulating data from retrospective analyses and large registries supporting their role in ATTR-CM.[24]

The differences in baseline characteristics between CARDIO-TTRansform and other contemporary trials compared with ATTR-ACT likely reflect the period in which the trials were conducted. ATTR-ACT was conducted before widespread adoption of the non-invasive diagnostic pathway,[25] when ATTR-CM was typically recognized only at later stages of the disease's natural history and confirmed by cardiac biopsy.[26] Patients enrolled in ATTR-ACT, therefore, had substantially more advanced disease and a higher proportion of ATTRv-CM than patients in more recent studies, including CARDIO-TTRansform. This is reflected in the higher proportion of patients with NYHA class III and UK NAC stage 3 disease, and data suggesting the presence of more advanced biomarker abnormalities, poorer nutritional status, and more pronounced echocardiographic dysfunction at baseline. In contrast, patients enrolled in the three most contemporary trials are likely to have benefitted from increased awareness, earlier diagnosis, and use of non-invasive diagnostic pathways, ultimately leading to enrolment of patients with less advanced disease.[9–11]

Overall, the inclusion strategy used in CARDIO-TTRansform resulted in the enrolment of a broad spectrum of patients who are representative of the contemporary real-world therapeutic environment of ATTR-CM. As such, CARDIO-TTRansform is uniquely positioned to address several pivotal unanswered questions in ATTR-CM. First, as the largest ATTR-CM trial conducted to date, it provides the strongest opportunity thus far to not only provide key evidence of the effectiveness of eplontersen, but also to assess its efficacy in patients with advanced disease. Prior trials included only small numbers of NYHA class III patients, whereas CARDIO-TTRansform enrolled 243 such individuals, the largest cohort with advanced disease studied in any randomized ATTR-CM outcomes trial. Second, the trial evaluates eplontersen in the context of contemporary clinical practice, characterized by widespread use of TTR stabilizer and SGLT2 inhibitors, including at baseline. As these treatments have been shown to be efficacious at reducing both cardiovascular hospitalizations and mortality in patients with ATTR-CM,[9,22–24] it is likely that event rates in this contemporary study population may be reduced compared with prior ATTR-CM trials. However, given the large size of CARDIO-TTRansform, this study represents a unique opportunity to better understand if there is a benefit of eplontersen in addition to standard of care, reflecting real-world practice patterns; CARDIO-TTRansform includes a secondary endpoint testing the treatment effect of the primary endpoint in patients who are receiving baseline TTR stabilizer. Third, CARDIO-TTRansform incorporates key differences in primary endpoint structure. The use of cardiovascular mortality rather than all-cause mortality, together with the inclusion of urgent heart failure visits alongside cardiovascular hospitalizations, may more accurately describe the cardiovascular benefits of the investigational therapy compared with prior trial designs. Fourth, due to its larger sample size CARDIO-TTRansform includes the highest number of female patients and patients of Black or African ancestry enrolled in any ATTR-CM outcomes trial to date.[9–11] It is important that this trial enrolled a diverse population, particularly in light of the recognized differences in diagnosis, disease expression, and outcomes in these populations.[27] For example, there continues to be delayed diagnosis and a lack of clinical data in female patients with ATTR-CM. Some recent evidence suggests that use of a single, non-indexed wall thickness threshold in echocardiography may contribute to delays in diagnosis, as females are less likely than males to meet the diagnostic cut-off. This may also limit their inclusion in clinical trials.[28,29] It is therefore imperative that additional clinical data are collected in this underserved population to address the unmet need for greater understanding of treatment outcomes and responses in female patients and to facilitate the ultimate goal of reducing the under-diagnosis and underrepresentation of female patients in ATTR-CM clinical trials.

In summary, CARDIO-TTRansform is the largest ATTR-CM trial to date. Blinded baseline data suggest that CARDIO-TTRansform has enrolled a diverse study population, spanning a wide range of disease severity and receiving the contemporary standard of care for ATTR-CM, including widespread use of TTR stabilizer. Thus, its design provides a unique opportunity to determine the clinical benefits of eplontersen in a contemporary setting and in clinically relevant subgroups of patients with ATTR-CM.

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Declarations

Disclosure of Interest

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Data Availability

Data requests from qualified researchers will be considered once all three of the following criteria are met: (1) 12 months from marketing approval of the study drug in both the United States and European Union; (2) 18 months from conclusion of the study; and (3) 6 months from the publication of this article. For additional information, visit https://vivli.org/ourmembers/ionis.

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Ethical Approval

Ethical Approval was not required.

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