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Gene Silencer Therapy in Transthyretin Amyloid Cardiomyopathy
A Meta-Analysis of Outcomes Trials

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IMPORTANCE Gene-silencing therapies reduce hepatic transthyretin (TTR) production and have been evaluated in phase 3 trials in TTR amyloid cardiomyopathy (ATTR-CM). However, differences in trial design and background therapies have limited assessment of the overall treatment effect and its consistency according to baseline TTR stabilizer use.

OBJECTIVE To assess the effect of TTR gene-silencing therapies in patients with ATTR-CM.

DATA SOURCES AND STUDY SELECTION PubMed was searched through June 15, 2026, for randomized, placebo-controlled, phase 3 outcome trials of gene-silencing therapies in ATTR-CM.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Fixed-effects meta-analysis estimated rate ratios (RRs) or hazard ratios (HRs) with 95% CIs.

MAIN OUTCOMES AND MEASURES The prespecified primary outcome was the composite of all-cause mortality and recurrent cardiovascular events. Secondary outcomes included all-cause mortality, cardiovascular death, time to first primary outcome, functional capacity (6-minute walk distance), and health status (Kansas City Cardiomyopathy Questionnaire–Overall Summary Score).

RESULTS A total of 2 studies (HELIOS-B and CARDIO-TTRansform) met the inclusion criteria and included 2086 patients with ATTR-CM. The studies included 1902 men with a median age of 77 years (range for HELIOS-B, 45-85 years; for CARDIO-TTRansform, 41-91 years). Gene-silencing therapy reduced the primary end point by 20% (RR, 0.80; 95% CI, 0.69-0.94; *P* = .006), with no heterogeneity between trials (*P* for heterogeneity = .28). Gene-silencing therapy also reduced the risk of all-cause death (HR, 0.74; 95% CI, 0.61-0.91) and time to first all-cause death or cardiovascular events (HR, 0.77; 95% CI, 0.67-0.89) compared with placebo. Gene silencers preserved 6-minute walk distance (placebo-corrected difference, +22.2 m; 95% CI, 14.3-30.0) and Kansas City Cardiomyopathy Questionnaire–Overall Summary Score (+4.5; 95% CI, 2.7-6.2), with no evidence of between-trial heterogeneity. Treatment effects on primary end points differed according to baseline stabilizer use, with significant benefits observed among patients not receiving background stabilizer therapy (RR, 0.69; 95% CI, 0.57-0.85) and no significant incremental benefit observed for those receiving concomitant stabilizer at baseline (RR, 0.97; 95% CI, 0.77-1.23; *P* for heterogeneity = .03). Similar heterogeneity was observed for functional capacity and health status.

CONCLUSIONS AND RELEVANCE The findings from this meta-analysis support TTR gene silencing for ATTR-CM. The attenuated benefit observed for patients receiving concomitant TTR stabilizer therapy may reflect residual differences in case mix, disease duration, or magnitude of TTR suppression or a true ceiling on additional benefit of gene silencing in the setting of background TTR stabilization.

TRIAL REGISTRATION PROSPERO registration: CRD420261421656. ClinicalTrials.gov Identifier: HELIOS-B, NCT04153149; and CARDIO-TTRansform, NCT04136171

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Supplemental content

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized and historically underdiagnosed cause of progressive heart failure and premature death in older adults.[1] Characterized by deposition of amyloid fibrils composed of misfolded TTR protein within the myocardium, ATTR-CM leads to restrictive physiology, arrhythmias, and progressive impairment in functional capacity and quality of life. Although advances in noninvasive imaging have enabled diagnosis earlier in the disease course, patients continue to experience substantial morbidity, recurrent hospitalizations, and reduced survival, underscoring the need for therapies that greatly modify disease natural history.[2]

Among emerging disease-modifying strategies, TTR gene silencing represents a particularly compelling therapy. By reducing hepatic production of both wild-type and variant TTR, gene-silencing therapies decrease the supply of circulating precursor protein available for ongoing amyloid fibril formation and subsequent tissue deposition. This upstream mechanism contrasts with TTR stabilization, which prevents tetramer dissociation but does not reduce circulating TTR concentration. Two large pivotal phase 3 cardiovascular (CV) outcomes trials have evaluated the gene-silencing strategy in ATTR-CM: HELIOS-B,[3] investigating vutrisiran, and CARDIO-TTRansform,[4] evaluating eplontersen. The HELIOS-B trial met its primary end point and demonstrated reduction in all-cause death and CV events, whereas the CARDIO-TTRansform trial missed its primary end point of reducing CV death and CV events. Direct comparison between these trials is challenging. Differences exist in trial design, eligibility criteria, disease severity at enrollment, background use of TTR stabilizers, end point definitions, follow-up duration, and analytic approaches. These distinctions are particularly relevant because the ATTR-CM population with a diagnosis today differs substantially from that enrolled in earlier studies, reflecting increasing disease awareness, earlier diagnosis, and evolving standards of supportive heart failure care. Consequently, observed event rates and treatment effects may be influenced not only by therapeutic intervention but also by changes in patient characteristics and clinical management.[5]

Furthermore, increasing use of combination therapy with gene silencers and TTR stabilizers raises important questions regarding the consistency and magnitude of incremental benefit associated with TTR suppression in patients receiving contemporary background treatment.[6] Individual trials may be insufficiently powered to address certain clinically important outcomes, particularly all-cause mortality, and differences in trial methodology may obscure common therapeutic signals. A systematic synthesis of available evidence therefore has the potential to provide a more precise estimate of the effects of TTR silencing on survival, CV events, functional status, and patient-reported outcomes while exploring the consistency of treatment benefit across differing trial populations and treatment backgrounds.

We conducted a prespecified meta-analysis of the 2 pivotal, randomized, placebo-controlled, phase 3, gene-silencing, CV outcomes trials in ATTR-CM, HELIOS-B and CARDIO-TTRansform. Using harmonized end point definitions where feasible and prespecified approaches to address between-trial heterogeneity, we sought to quantify the effects of TTR suppression on mortality, CV events, functional capacity, health status, and safety outcomes and to determine whether the clinical benefits of gene silencing are consistent across studies conducted in an evolving therapeutic landscape.

Key Points

Questions Do transthyretin gene-silencing therapies improve outcomes in transthyretin amyloid cardiomyopathy, and are benefits modified by baseline transthyretin stabilizer use?

Findings In this meta-analysis of 2 randomized trials including 2086 patients, transthyretin gene-silencing therapies improved clinical outcomes overall, with evidence of treatment heterogeneity according to baseline transthyretin stabilizer use: significant benefit for patients not receiving stabilizers but not in those receiving them.

Meaning These findings support transthyretin gene silencing for transthyretin amyloid cardiomyopathy and suggest that treatment benefit may vary according to concomitant transthyretin stabilizer therapy.

Methods

Search Strategy and Selection Criteria

We performed a prespecified meta-analysis of 2 randomized, placebo-controlled trials evaluating gene silencers in patients with ATTR-CM (CARDIO-TTRansform and HELIOS-B). The designs of both studies have been previously reported.[3,7] To identify any additional eligible studies, the systematic search was conducted independently by 2 authors (Y.H. and M.V.) using the prespecified search string and study quality following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Disagreements were resolved by the senior author (S.D.S.). Two authors (Y.H. and M.V.) systematically searched PubMed for randomized, placebo-controlled, phase 3 outcome trials evaluating gene-silencing therapies in ATTR-CM that were published up to June 15, 2026. Eligibility was restricted to randomized trials designed and powered to evaluate clinical outcomes as the primary end point. Bias of identified studies was similarly rated independently by 2 authors (Y.H. and M.V.). The prespecified search strategy, registered in PROSPERO, is provided in the eMethods in Supplement 3 and no additional eligible trials were identified (**Figure 1**). Data from the CARDIO-TTRansform trial, which were unpublished at the analysis, were included through collaboration with the trial steering committee, using individual participant-level data. For HELIOS-B, published aggregate data were used whenever available, and for outcomes that were not publicly reported, treatment effect estimates were generated from individual participant-level trial data with the permission of the sponsor. Outcome data were extracted or estimated independently by 2 authors (Y.H. and B.L.C.), and discrepancies were resolved by consensus.

Outcomes and Subgroups

The primary end point of the meta-analysis was prespecified as the composite of all-cause mortality and recurrent CV events during the double-blind period, corresponding to the primary end point of HELIOS-B. Cardiovascular events were based on trial-specific adjudicated definitions. HELIOS-B defined CV events broadly as all CV hospitalizations and urgent heart failure visits, whereas CARDIO-TTRansform defined CV events as CV hospitalizations due to heart failure exacerbation, myocardial infarction, stroke, transient ischemic attack, or arrhythmia in addition to urgent heart failure visits. Secondary end points included all-cause mortality during the double-blind period, CV death during the double-blind period, and time to first composite of all-cause death or CV events. All these outcomes were adjudicated by masked clinical end points committees in both trials.

Treatment effects on functional capacity and health status were assessed with the 6-minute walk distance and the Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS; range, 0-100, with higher scores indicating better health status), respectively.

The effects of gene silencers on clinical outcomes, functional capacity, and health status were evaluated in the overall population and in key prespecified subgroups according to baseline use of TTR stabilizer therapy. The effect of gene silencers on the primary end point was further examined across 4 prespecified subgroups defined in HELIOS-B: age (<75 vs ≥75 years), ATTR type (wild-type vs hereditary), New York Heart Association functional class (I/II vs III), and N-terminal pro-brain natriuretic peptide levels (>2000 pg/mL vs ≤2000 pg/mL).

Select adverse events, including any adverse events, serious adverse events, and adverse events leading to treatment discontinuation, were collated from HELIOS-B and CARDIO-TTRansform but were not directly compared or meta-analyzed due to differences in data capture and event definitions across trials.

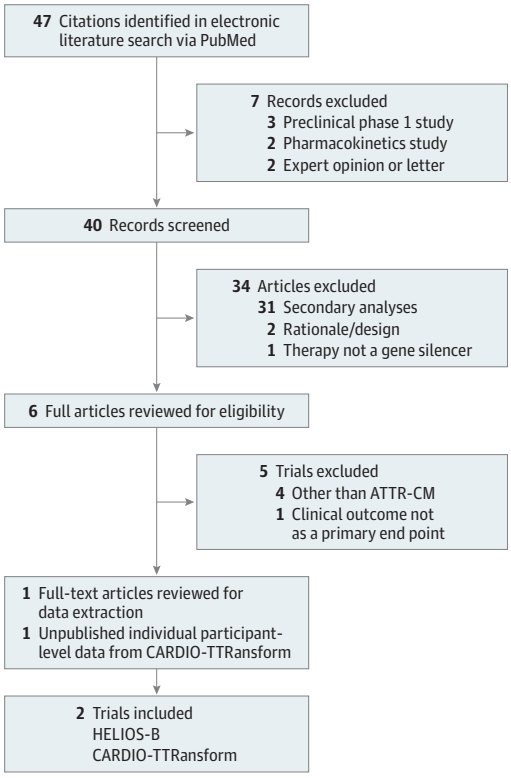
Statistical Analysis

All effect estimates were extracted as point estimates with corresponding 95% CIs. For time to first event outcomes, hazard ratios derived from Cox proportional hazards models were included. For recurrent-event outcomes, rate ratios derived from the semiparametric proportional rates model of Lin et al[8] were included. Trial-specific treatment effects were estimated using the prespecified covariate-adjusting models for each trial.

To evaluate functional capacity and health status, changes from baseline in 6-minute walk distance and KCCQ-OSS were analyzed using an analysis of covariance model at week 140 in CARDIO-TTRansform and a mixed-effects model for repeated measures at month 30 in HELIOS-B.[3,7]

Efficacy analyses were based on the intention-to-treat population and included all randomly assigned and treated participants. Trial-specific treatment effects were pooled using fixed-effect inverse-variance meta-analysis to estimate the overall effect of gene silencers vs placebo for each outcome and prespecified subgroup. Between-trial heterogeneity was assessed with Cochran *Q* test. Differences in treatment effects between subgroup levels were also assessed with Cochran *Q* test for subgroup differences.

Figure 1. Flow Diagram of Trials Included in Meta-Analysis



ATTR-CM indicates transthyretin amyloid cardiomyopathy.

The protocol for the meta-analysis of the CARDIO-TTRansform (Supplement 1) and HELIOS-B (Supplement 2) trials was preregistered with PROSPERO (CRD420261421656) before unmasking of the CARDIO-TTRansform trial results. All trials were assessed as high quality with a low risk of bias across the 2 trials (eTable 1 in Supplement 3). All participants provided written consent, and the study protocols were approved by the institutional review boards at all participating sites. Meta-analysis calculations were performed with Stata version 18.0 (StataCorp). All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

Trial Selection and Characteristics

Overall, 2086 participants were enrolled from 2 randomized, placebo-controlled trials evaluating eplontersen (CARDIO-TTRansform; n = 1432) and vutrisiran (HELIOS-B; n = 654). The trial designs were broadly similar, with minor differences in the eligibility criteria and primary end point definitions (**Table**).

Across both trials, respectively, the median age was 77 years, 1297 (91%) and 605 (93%) participants were men, 1221 (85%) and 578 (88%) had wild-type ATTR-CM, and 997 (70%) and 508 (78%) were in New York Heart Association class II. Baseline use of concomitant TTR stabilizer therapy (all tafamidis) was more common in CARDIO-TTRansform than in HELIOS-B (819 [57%] vs 259

Table. Key Study Design Elements, Baseline Characteristics, and Background Medical Therapy of CARDIO-TTRansform and HELIOS-B

	CARDIO-TTRansform (n = 1432)	HELIOS-B (n = 654)
Study design		
Comparison	Eplontersen vs placebo	Vutrisiran vs placebo
Enrollment period	Mar 2020-Jul 2023	Dec 2019-Aug 2021
Sites	130 sites in 20 countries	87 sites in 26 countries
Key eligibility criteria		
Age, y	18-90	18-85
NYHA class/UK NAC stage[a,b]	Excluded if NYHA class IV	Excluded if NYHA class IV or NYHA class III and NAC stage 3
NT-proBNP, pg/mL	≥600 (≥1200 in AF) No upper limit	>300 (>600 in AF) <8500
6-min walk distance, m[c]	≥100	≥150
Concomitant stabilizer use	No restriction	Tafamidis-naive patients were required to have no active plans to initiate treatment within 1 y of enrollment but could begin tafamidis if the investigator considered it necessary
End point		
Primary efficacy end point	Composite of CV death and recurrent CV events	Composite of all-cause death and recurrent CV events
Study duration	Up to 32.2 mo (mortality follow-up extended to 36.8 mo)	33-36 mo (mortality follow-up extended to 42 mo as an extension study)
Patient demographics		
Age, median (range), y	77 (41-91)	77 (45-85)
Men, No. (%)	1297 (90.6)	605 (92.5)
Women, No. (%)	135 (9.4)	49 (7.5)
Body mass index, mean (SD)	26.6 (4.1)	27.0 (3.7)
Race, No. (%)[d]		
Asian	35 (2.4)	37 (5.7)
Black	111 (7.8)	47 (7.2)
Other or not reported or multiple	15 (1.0)	18 (2.8)
White	1271 (88.8)	552 (84.4)
Time since ATTR diagnosis, median (range), y	0.8 (0-11.3)	0.9 (0-11.1)
Disease severity, No. (%)		
NYHA class[a]		
I	192 (13.4)	84 (12.8)
II	997 (69.6)	508 (77.7)
III	243 (17.0)	62 (9.5)
UK NAC stage[b]		
1	896 (62.6)	437 (66.8)
2	401 (28.0)	187 (28.6)
3	135 (9.4)	30 (4.6)
TTR genotype, No. (%)		
Wild-type ATTR	1221 (85.3)	578 (88.4)
Variant ATTR[e]	211 (14.7)	76 (11.6)
Val122Ille	130 (61.6) [n = 211]	49 (64.5) [n = 76]
Ille68Leu	18 (8.5) [n = 211]	2 (2.6) [n = 76]
Thr60Ala	14 (6.6) [n = 211]	7 (9.2) [n = 76]
Val30Met	28 (13.3) [n = 211]	6 (7.9) [n = 76]
Functional status		
6-min walk distance, mean (SD), m[c]	352.2 (96.2)	374.6 (100.0)
KCCQ-OSS, mean (SD)[f]	72.6 (19.9)	72.6 (19.7)
Laboratory markers		
NT-proBNP, median (IQR), pg/mL	2025 (1297-3466)	1920 (1100-3206)
Troponin, median (IQR), ng/mL[g]	0.050 (0.035-0.069)	0.067 (0.043-0.106)
eGFR, median (IQR), mL/min/1.73 m^2	60.2 (49.0-73.5)	65 (53-81)
Echocardiographic parameters		
LVEF, mean (SD), %	55.9 (9.8)	55.8 (12.5)
LV stroke volume, mean (SD), mL	56.7 (17.3)	52.3 (17.8)
LV wall thickness, mean (SD), mm	18.3 (2.9)	18.2 (2.7)
LV global longitudinal strain, mean (SD), %	−14.5 (3.1)	−14.0 (3.5)
E/e' ratio, mean (SD)	15.5 (6.8)	15.1 (6.5)
Comorbidities, No. (%)		
AF	907 (63.3)	393 (60.1)
Hypertension	907 (63.3)	388 (59.3)
Diabetes mellitus	244 (17.0)	111 (17.0)
Concomitant medications, No. (%)		
Tafamidis at baseline	819 (57.2)	259 (39.6)
Duration of tafamidis before randomization, median (range), mo	9.0 (0.0-92.0)	10.8 (1.1-65.5)
Stabilizer initiation during double-blind period, No. (%)	341 (23.8)	84 (12.8)
Time from randomization to stabilizer initiation, median (IQR), d	479 (239-684)	531 (372-852)
SGLT2i at baseline, No. (%)	265 (18.5)	21 (3.2)
MRAs at baseline, No. (%)	618 (43.2)	230 (35.2)

(continued)

Table. Key Study Design Elements, Baseline Characteristics, and Background Medical Therapy of CARDIO-TTRansform and HELIOS-B (continued)

	CARDIO-TTRansform (n = 1432)	HELIOS-B (n = 654)
β-Blockers at baseline, No. (%)	614 (42.9)	288 (44.0)
ACEi/ARB/ARNi at baseline, No. (%)	591 (41.3)	302 (46.2)
Loop diuretics at baseline, No. (%)	1243 (86.8)	507 (77.5)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ARNi, angiotensin-receptor–neprilysin inhibitors; ATTR, transthyretin amyloidosis; CV, cardiovascular; eGFR, estimated glomerular filtration rate; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire–Overall Summary Score; LV, left ventricular; LVEF, LV ejection fraction; MRA, mineralocorticoid receptor antagonist; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro–brain natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

SI conversion factor: to convert troponin to µg/L, multiply by 1.0. Body mass index is calculated as weight in kilograms divided by height in meters squared.

[a] New York Heart Association functional class was categorized as follows: class I, no limitation in physical activity (least affected); class II, mild limitation of physical activity, with symptoms occurring during ordinary activities; class III, substantial limitation of physical activity, with symptoms developing during less than ordinary activities; and class IV, symptoms present at rest or with any physical activity (most affected).

[b] National Amyloidosis Centre stage was categorized as follows: stage 1 (least severe), NT-proBNP level less than or equal to 3000 pg/mL and eGFR greater than or equal to 45 mL/min/1.73 m^2; stage 2, NT-proBNP level greater than 3000 pg/mL or eGFR less than 45 mL/min/1.73 m^2; and stage 3 (most severe), NT-proBNP level greater than 3000 pg/mL and eGFR less than 45 mL/min/1.73 m^2.

[c] A farther distance walked indicates better function.

[d] Race was self-reported based on fixed categories in both trials. Other in CARDIO-TTRansform included Brown, Caribbean, Cypriot, Hispanic, Jewish, Latino, and Lebanese. Other in HELIOS-B included Jewish and Mestizo.

[e] *V122I* is the most common TTR variant in the United States. *I68L* has been reported primarily in Italy. *T60A* is the most common ATTR variant in Ireland. *V30M* is endemic in Portugal, Sweden, Brazil, and Japan.

[f] Scores range from 0 to 100, with higher scores indicating better health status.

[g] Troponin T in CARDIO-TTRansform and troponin I in HELIOS-B.

[40%]). Baseline characteristics between patients with baseline stabilizer and those without it (defined as monotherapy population) are provided in eTable 2 in Supplement 3. Baseline use of sodium-glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists was also higher in the more recent CARDIO-TTRansform trial (Table).

Median follow-up was 2.7 years in CARDIO-TTRansform and 3.0 years in HELIOS-B. At the end of the double-blind period, mean reductions from baseline in trough serum TTR concentration were 81.0% (95% CI, 79.0%-83.0%) with vutrisiran in HELIOS-B and 71.9% (95% CI, 70.2%-73.7%) with eplontersen in CARDIO-TTRansform.

Clinical Outcomes

Gene silencers significantly reduced the composite of all-cause death and recurrent CV events (20% reduction; rate ratio, 0.80; 95% CI, 0.69-0.94; $P = .006$), without evidence of heterogeneity between trials ($I^2 = 15.4\%$; P for heterogeneity by Cochran Q test = .28) (**Figure 2**). The benefits were consistent for all-cause death (hazard ratio, 0.74; 95% CI, 0.61-0.91) and time to first all-cause death or CV events (hazard ratio, 0.77; 95% CI, 0.67-0.89) (Figure 2) compared with placebo.

There was significant heterogeneity in the treatment effect of gene silencers on the primary end point according to baseline stabilizer use (rate ratio, 0.69 [95% CI, 0.57-0.85] without baseline stabilizer therapy vs 0.97 [95% CI, 0.77-1.23] with baseline stabilizer therapy; P for heterogeneity = .03) (**Figure 3**), whereas there was no statistical evidence of heterogeneity for all-cause death, CV death, or time to first all-cause death or CV events (Figure 3).

Treatment effects on the primary end point were attenuated in patients with baseline N-terminal pro-brain natriuretic peptide concentrations greater than 2000 pg/mL compared with those with concentrations of 2000 pg/mL or less (P for heterogeneity = .007). There was no evidence of treatment-effect heterogeneity across the other prespecified subgroups, including age, ATTR disease type, and New York Heart Association class (**Figure 4**).

Among patients receiving baseline stabilizer therapy, there was a suggestion of treatment-effect heterogeneity by ATTR disease type (variant vs wild-type). Among patients not receiving stabilizer therapy, there was a suggestion of heterogeneity by age and baseline N-terminal pro-brain natriuretic peptide concentrations (eFigures 1 and 2 in Supplement 3).

Functional Capacity and Health Status

Compared with placebo, gene silencers preserved functional capacity and health status, as assessed by the 6-minute walk distance (placebo-corrected difference, +22.2 m; 95% CI, 14.3-30.0) and KCCQ-OSS (+4.5; 95% CI, 2.7-6.2), respectively, with no evidence of heterogeneity between trials (**Figure 5**). For both outcomes, treatment effects were attenuated in patients receiving baseline stabilizer therapy compared with those not receiving it (P for heterogeneity = .04 for 6-minute walk distance; P for heterogeneity <.001 for KCCQ-OSS).

Safety Outcomes

Safety outcomes were analyzed descriptively because of differences in event ascertainment and reporting between the 2 trials. Overall rates of serious adverse events and treatment discontinuation were similar between the gene silencer and placebo groups. No new safety signals were identified in either trial irrespective of baseline stabilizer use (eTable 3 in Supplement 3).

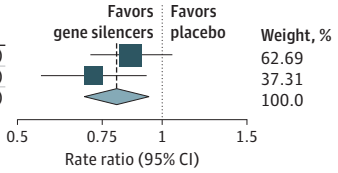
Discussion

In this trial-level meta-analysis of 2 pivotal randomized trials in ATTR-CM, HELIOS-B and CARDIO-TTRansform, gene silencing of TTR favorably modified a range of clinically meaningful outcomes, including all-cause mortality, recurrent CV events, functional capacity, and health-related quality of life. These benefits were driven predominantly by patients not taking TTR stabilizer therapy at baseline, whereas no apparent incremental benefit was observed for patients already receiving background stabilizers. These data confirm the substantial clinical efficacy of gene silencing as monotherapy for patients

Figure 2. Forest Plot of Treatment Effects on Clinical Outcomes in Overall Cohort

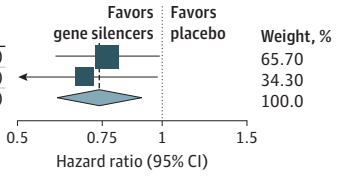
A All-cause death and recurrent CV events (primary end point)

Study	Total No. of events: Gene silencer	Placebo	Rate ratio (95% CI)	Weight, %
CARDIO-TTRansform	406	433	0.86 (0.71-1.05)	62.69
HELIOS-B	251	332	0.72 (0.56-0.93)	37.31
Heterogeneity: I^2 = 15.4%, P = .28			0.80 (0.69-0.94)	100.0



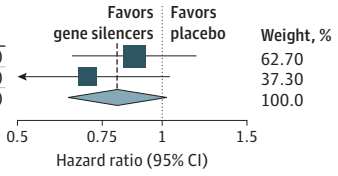
B All-cause death

Study	No. with event/No. of patients (%): Gene silencer	Placebo	Hazard ratio (95% CI)	Weight, %
CARDIO-TTRansform	111/715 (16)	130/717 (18)	0.77 (0.60-0.99)	65.70
HELIOS-B	56/326 (17)	75/328 (23)	0.69 (0.49-0.98)	34.30
Heterogeneity: I^2 = 0.0%, P = .62			0.74 (0.61-0.91)	100.0



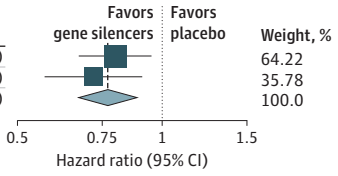
C CV death

Study	No. with event/No. of patients (%): Gene silencer	Placebo	Hazard ratio (95% CI)	Weight, %
CARDIO-TTRansform	85/715 (12)	86/717 (12)	0.88 (0.65-1.18)	62.70
HELIOS-B	44/326 (13)	58/328 (18)	0.70 (0.48-1.04)	37.30
Heterogeneity: I^2 = 0.0%, P = .36			0.81 (0.64-1.02)	100.0



D Time to first all-cause death or CV events

Study	No. with event/No. of patients (%): Gene silencer	Placebo	Hazard ratio (95% CI)	Weight, %
CARDIO-TTRansform	225/715 (31)	256/717 (36)	0.80 (0.67-0.95)	64.22
HELIOS-B	125/326 (38)	159/328 (48)	0.72 (0.57-0.91)	35.78
Heterogeneity: I^2 = 0.0%, P = .48			0.77 (0.67-0.89)	100.0



Primary end point was a composite of all-cause death and recurrent cardiovascular (CV) events.

with ATTR-CM and question the additional clinical benefit of combining currently available gene-silencing therapies with stabilizers. The safety profiles of both gene-silencing agents were reassuring, with no excess of serious adverse events or treatment discontinuation in either trial.

A key finding of this meta-analysis was the marked attenuation of the aggregate treatment effect in patients receiving background stabilizer therapy compared with those receiving monotherapy across all clinically relevant end points, with no convincing evidence of incremental clinical benefit beyond stabilizer therapy alone. Given that TTR stabilizers reduce TTR tetramer dissociation and thereby limit the supply of amyloidogenic monomers available for fibril formation[9,10] and that silencers reduce the amount of TTR upstream, these therapies work within the same pathophysiologic pathway such that reductions in circulating TTR achieved with currently available gene-silencer therapies may be redundant or may simply be insufficient to provide additional clinical benefit for patients receiving background stabilizers.

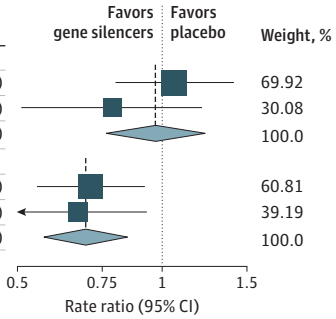
Despite the lack of statistical heterogeneity between trials in this meta-analysis, there may still be important differences between the pharmacologic effects of each of the gene-silencing therapies or the trials that evaluated them. Data from the earlier HELIOS-B trial suggested that among patients in the relatively small subgroup treated with background stabilizers, there was potential incremental benefit with vutrisiran. However, the more recent and substantially larger CARDIO-TTRansform trial demonstrated neutral findings in this subgroup and contributed greater statistical weight to this meta-analysis. The possibility that the resulting combined estimates thus may obscure important differences between the trials cannot be ruled out.

These results should not be interpreted as definitive evidence that gene-silencing therapies could not provide incremental clinical benefit on top of background stabilizers or that all gene-silencing therapies will have equivalent efficacy when administered on a background of stabilizers. Whether deeper TTR suppression translates into incremental clinical benefit

Figure 3. Forest Plot of Treatment Effects on Clinical Outcomes in the Baseline Stabilizer and Monotherapy Population

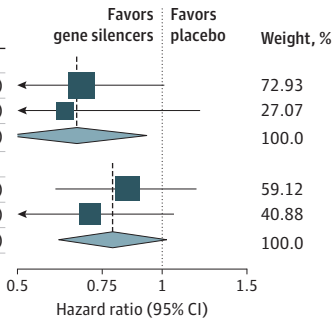
A All-cause death and recurrent CV events (primary end point)

Study	Total No. of events: Gene silencer	Placebo	Rate ratio (95% CI)	Weight, %
Baseline stabilizer				
CARDIO-TTRansform	216	189	1.06 (0.80-1.41)	69.92
HELIOS-B	96	121	0.79 (0.51-1.21)	30.08
Heterogeneity: I^2 = 19.6%, P = .27			0.97 (0.77-1.23)	100.0
Monotherapy population				
CARDIO-TTRansform	190	244	0.71 (0.55-0.92)	60.81
HELIOS-B	155	211	0.67 (0.49-0.93)	39.19
Heterogeneity: I^2 = 0.0%, P = .78			0.69 (0.57-0.85)	100.0
Heterogeneity between groups: P = .03				



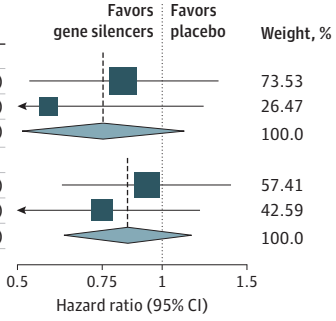
B All-cause death

Study	No. with event/No. of patients (%): Gene silencer	Placebo	Hazard ratio (95% CI)	Weight, %
Baseline stabilizer				
CARDIO-TTRansform	44/410 (11)	59/409 (14)	0.68 (0.46-1.01)	72.93
HELIOS-B	15/130 (12)	23/129 (18)	0.63 (0.33-1.20)	27.07
Heterogeneity: I^2 = 0.0%, P = .84			0.67 (0.48-0.93)	100.0
Monotherapy population				
CARDIO-TTRansform	67/305 (22)	71/308 (23)	0.85 (0.60-1.18)	59.12
HELIOS-B	41/196 (21)	52/199 (26)	0.71 (0.47-1.06)	40.88
Heterogeneity: I^2 = 0.0%, P = .51			0.79 (0.61-1.02)	100.0
Heterogeneity between groups: P = .43				



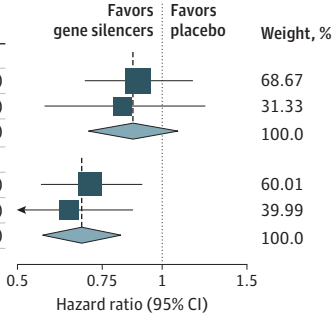
C CV death

Study	No. with event/No. of patients (%): Gene silencer	Placebo	Hazard ratio (95% CI)	Weight, %
Baseline stabilizer				
CARDIO-TTRansform	36/410 (9)	40/409 (10)	0.83 (0.53-1.31)	73.53
HELIOS-B	11/130 (8)	19/129 (15)	0.58 (0.27-1.22)	26.47
Heterogeneity: I^2 = 0.0%, P = .42			0.75 (0.51-1.11)	100.0
Monotherapy population				
CARDIO-TTRansform	49/305 (16)	46/308 (15)	0.93 (0.62-1.39)	57.41
HELIOS-B	33/196 (17)	39/199 (20)	0.75 (0.47-1.20)	42.59
Heterogeneity: I^2 = 0.0%, P = .50			0.85 (0.62-1.15)	100.0
Heterogeneity between groups: P = .64				



D Time to first all-cause death or CV events

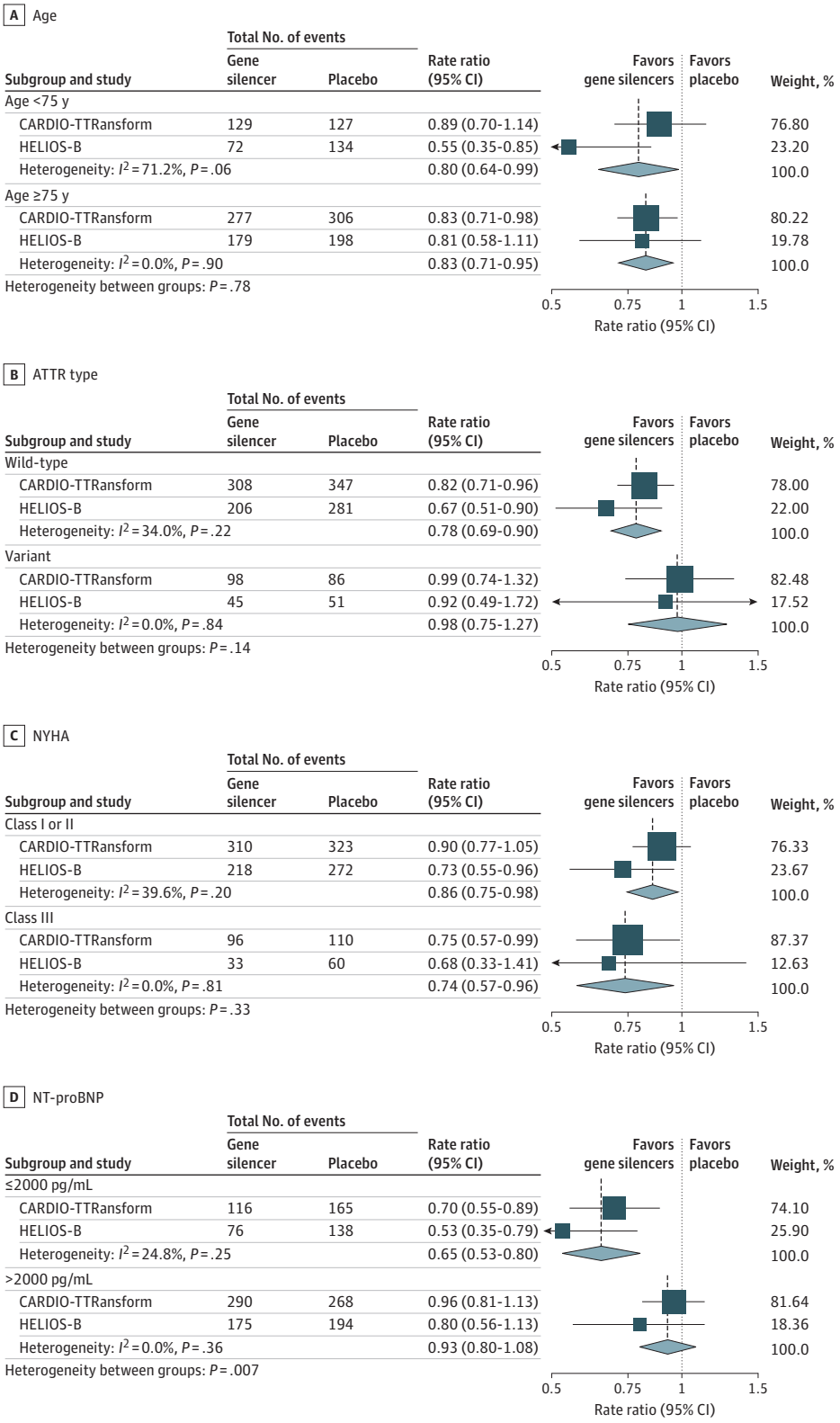
Study	No. with event/No. of patients (%): Gene silencer	Placebo	Hazard ratio (95% CI)	Weight, %
Baseline stabilizer				
CARDIO-TTRansform	111/410 (27)	118/409 (29)	0.89 (0.69-1.16)	68.67
HELIOS-B	49/130 (38)	54/129 (42)	0.83 (0.57-1.23)	31.33
Heterogeneity: I^2 = 0.0%, P = .77			0.87 (0.70-1.08)	100.0
Monotherapy population				
CARDIO-TTRansform	114/305 (37)	138/308 (45)	0.71 (0.56-0.91)	60.01
HELIOS-B	76/196 (39)	105/199 (53)	0.64 (0.48-0.87)	39.99
Heterogeneity: I^2 = 0.0%, P = .60			0.68 (0.56-0.82)	100.0
Heterogeneity between groups: P = .09				



Monotherapy population indicates patients without baseline stabilizer therapy. CV indicates cardiovascular.

will be directly tested in trials assessing next-generation therapies capable of producing substantially greater and more durable reductions in circulating TTR, in which almost all patients will be receiving background stabilizer therapy.

Figure 4. Forest Plot of Treatment Effects on Primary End Point Among Major Subgroups

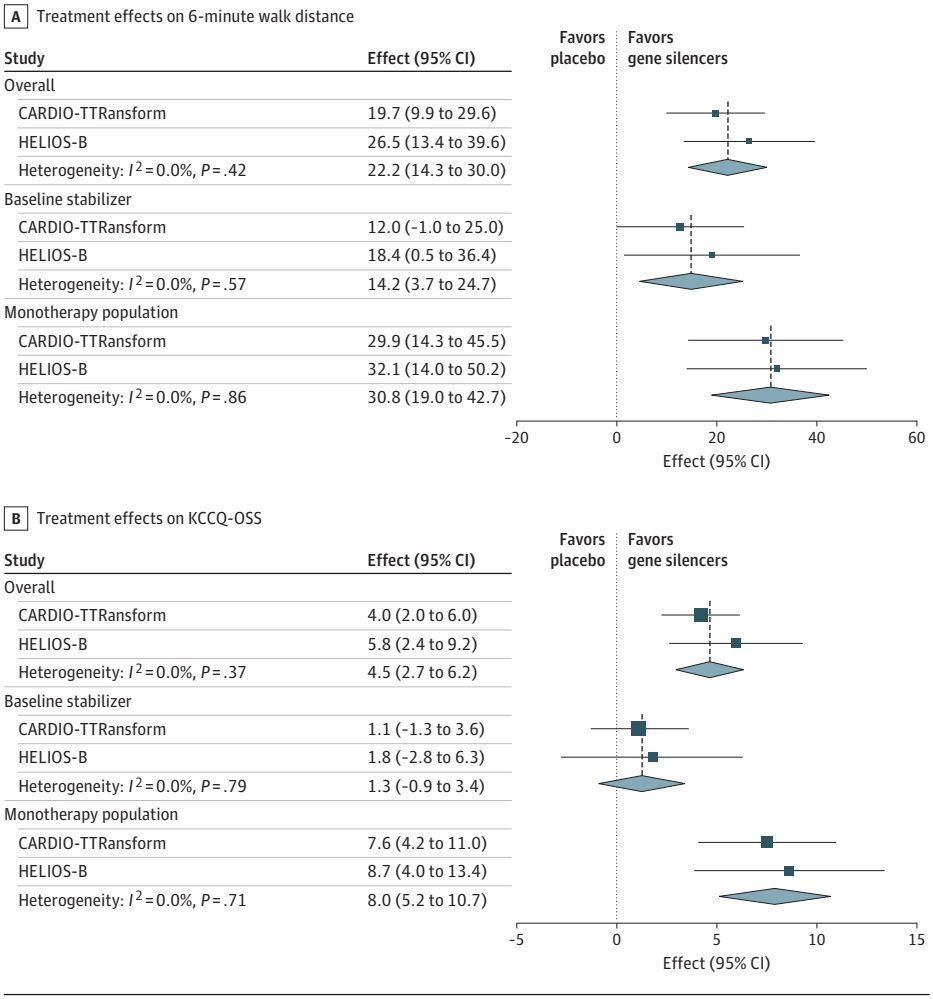


Primary end point was a composite of all-cause death and recurrent cardiovascular (CV) events. ATTR indicates transthyretin amyloidosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; and NYHA, New York Heart Association.

Limitations

This meta-analysis has several limitations. First, it relied on aggregated trial-level data and used trial-specific covariate adjustments; therefore, it could not account for patient-level heterogeneity or apply uniform adjustment for baseline risk across studies. Second, although subgroup analyses according

Figure 5. Forest Plot of Treatment Effects on 6-Minute Walk Distance and Kansas City Cardiomyopathy Questionnaire–Overall Summary Score (KCCQ-OSS)



A longer distance walked for the 6-minute walk distance indicates better functional capacity. Scores for the KCCQ-OSS range from 0 to 100, with higher scores indicating better health status. Monotherapy population indicates patients without baseline stabilizer therapy.

to baseline TTR stabilizer use were prespecified, neither HELIOS-B nor CARDIO-TTRansform was powered to definitively evaluate the incremental benefit of combination therapy. Consequently, the subgroup estimates, particularly those from HELIOS-B, should be interpreted with appropriate caution. Third, differences in eligibility criteria, duration from diagnosis, racial distribution, end point definitions, duration of follow-up, rates of stabilizer initiation during follow-up, and background medical therapy contributed to residual between-trial heterogeneity and limited the precision with which treatment effects could be compared across studies. Fourth, tafamidis was the only stabilizer available at trial enrollment, limiting the generalizability of these results to the broader class of stabilizer therapies. Fifth, differences in the use of contemporary heart failure therapies, including sodium-glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists, between HELIOS-B and CARDIO-TTRansform may also have influenced the observed treatment effects and complicate interpretation of subgroup findings.

Conclusions

Gene-silencing therapies are effective disease-modifying treatments for ATTR-CM, reducing mortality and CV events and preserving functional capacity and health-related quality of life. However, the current randomized evidence does not demonstrate incremental clinical benefit from combining currently available gene-silencing therapies with stabilizers compared with stabilizer therapy alone. Ongoing studies of next-generation gene-silencing and genome-editing therapies will determine whether achieving deeper and more sustained TTR suppression translates into additional clinical benefit beyond that achievable with TTR stabilizer therapy alone.

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