



Transthyretin Stabilizers, Silencers, Gene Editing and Amyloid Depleters in Transthyretin Amyloidosis: A Systematic Review and Meta-Analysis of Randomized and Pivotal Clinical Trials

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Abstract

Background: Transthyretin amyloidosis (ATTR) occurs as a hereditary (variant) form, which presents as polyneuropathy, cardiomyopathy or a mixed phenotype, and as a wild-type form, which presents predominantly as cardiomyopathy. Four therapeutic classes are approved or in late-stage development: tetramer stabilizers, TTR silencers, gene editing and amyloid depleters. This review quantifies their efficacy and safety.

Methods: PubMed/MEDLINE, Embase, Cochrane CENTRAL, trial registries and congress proceedings were searched to 30 September 2026 (PRISMA 2020). Randomized and pivotal externally controlled phase 3 trials were eligible. Estimates were pooled with Paule–Mandel random-effects models; certainty was graded with GRADE. The protocol was not registered and screening was performed by one reviewer.

Results: Twelve pivotal trials (4,713 participants) and three early-phase trials were included. Active therapy reduced all-cause mortality in ATTR cardiomyopathy (pooled HR 0.73 (95% CI 0.62–0.85); $I^2 = 0\%$), with equivalent estimates for stabilizers and silencers; including the terminated revusiran trial ENDEAVOUR the estimate was 0.82 (95% CI 0.52–1.30). The composite of death and cardiovascular events was reduced (0.75 (95% CI 0.63–0.89)). Silencer monotherapy reduced composite events (0.69 (95% CI 0.56–0.85)); added to a background stabilizer the estimate was 0.98 (95% CI 0.69–1.40). In hereditary polyneuropathy, silencers attenuated neuropathy progression (mNIS+7 –26.9 points (95% CI –41.0 to –12.9); concurrently randomized trials only).

Conclusions: Stabilizers and silencers reduce mortality in ATTR-CM by approximately one quarter; incremental benefit of adding a silencer to an established stabilizer is not demonstrated. Estimates are sensitive to inclusion of the terminated revusiran trial. In polyneuropathy, the licensing of diflunisal extends the approved indications of the stabilizer class. Gene editing and amyloid depleters remain investigational.

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Introduction

Transthyretin (TTR) is a 127-amino-acid homotetrameric plasma protein synthesized predominantly by the liver that transports thyroxine and retinol-binding protein. Dissociation of the tetramer into monomers is the rate-limiting step of amyloidogenesis; misfolded monomers and oligomers aggregate into fibrils that deposit in peripheral nerves, myocardium and other tissues [1,2]. Two disease forms

are distinguished. Hereditary (variant) ATTR (ATTRv) is an autosomal dominant disorder caused by more than 130 pathogenic TTR variants with variable penetrance and a genotype-dependent spectrum ranging from length-dependent sensorimotor and autonomic polyneuropathy (ATTRv-PN) to cardiomyopathy (ATTR-CM) and mixed phenotypes. Wild-type ATTR (ATTRwt) is an age-related cardiomyopathy that predominantly affects men older than 70 years [1,3]. The global prevalence of ATTRv-PN was estimated at approximately 10,000 patients [4]. ATTR-CM is substantially more frequent: ATTRwt was identified in 13% of patients hospitalized for heart failure with preserved ejection fraction and increased left ventricular wall thickness [5], and the p.Val142Ile (V122I) variant is carried by 3–4% of individuals of African ancestry [6]. In the multicentre TRAM study conducted in Germany, Austria and Switzerland, 1.1% of 5,141 patients with polyneuropathy and/or cardiomyopathy of no obvious aetiology carried a pathogenic TTR variant [7]; the successor programme has characterized the first 3,167 participants [8]. Untreated ATTR-CM has a median survival of approximately 2–6 years from diagnosis, stratified by NT-proBNP and estimated glomerular filtration rate [9,10]. Therapeutic development has progressed through four mechanistic stages. Orthotopic liver transplantation, introduced in 1990, removes the source of variant TTR and was the first disease-modifying option for early-onset p.Val50Met (V30M) disease [11]. Kinetic stabilizers (tafamidis, diflunisal, acoramidis) bind the thyroxine-binding sites of the tetramer and reduce dissociation; diflunisal, long used off-label, obtained an EU marketing authorization as Attrogy on 17 July 2025 for stage

1 and stage 2 ATTRv-PN [12]. Silencers reduce hepatic TTR synthesis by RNA interference (patisiran, vutrisiran) or antisense oligonucleotides (inotersen, eplontersen). Investigational approaches comprise next-generation silencers with extended dosing intervals, single-dose in vivo CRISPR-Cas9 editing of TTR, and monoclonal antibodies that target misfolded TTR to promote phagocytic clearance of deposited amyloid [1,13,14]. Existing fibrils additionally act as templates that accelerate further fibril formation (amyloid seeding), which provides a rationale for combining substrate reduction with deposit removal [15]. Approved agents are summarized in Table 1.

Three developments require an updated quantitative synthesis. The CARDIO-TTRansform trial of eplontersen in ATTR-CM, the largest trial in the field (n = 1,432), did not meet its primary endpoint, and a prespecified analysis showed effect modification by background stabilizer therapy [16,17]. Diflunisal, previously used off-label, became the sixth agent licensed for ATTRv-PN in the European Union, an indication extension within the stabilizer class rather than a new mechanism [12,18]. In parallel, amyloid-depleter antibodies and CRISPR-based editing have entered phase 3. The objectives of this review were (i) to pool efficacy and safety data from randomized and pivotal trials across phenotypes, (ii) to compare stabilizer and silencer effects and quantify the interaction between silencers and background stabilizers, and (iii) to provide a structured overview of approved and investigational therapies including phenotype, genotype, population, sample size, endpoints and trial duration.

Table 1: Approved TTR-directed therapies (status 30 September 2026).

Agent (brand)	Class / mechanism	Route and dose	Regulatory status (EU / US)	Pivotal trials
Tafamidis (Vyndaqel®, Vyndamax®)	Kinetic stabilizer (thyroxine-binding site)	Oral; 20 mg meglumine (PN); 61 mg free acid / 80 mg meglumine (CM) once daily	ATTRv-PN stage 1: EU 2011. ATTR-CM (wt/v): US 2019, EU 2020	Fx-005 [19]; ATTR-ACT [20]
Acoramidis (Attruby®, Beyontra®)	Kinetic stabilizer (mimics protective p.Thr139Met variant)	Oral; 800 mg acoramidis HCl (712 mg) twice daily	ATTR-CM (wt/v): US 11/2024, EU 02/2025	ATTRIBUTE-CM [21,22]
Diflunisal (Attrogy®)	Kinetic stabilizer; salicylic acid derivative with NSAID activity	Oral; 250 mg twice daily	ATTRv-PN stage 1 and stage 2: EU 17/07/2025 (Purpose Pharma); EU orphan designation. Off-label before 2025	Berk et al. 2013 [12,23,24]
Patisiran (Onpatro®)	siRNA in lipid nanoparticle	IV 0.3 mg/kg every 3 weeks; premedication required	ATTRv-PN: US/EU 2018. ATTR-CM: US complete response letter 10/2023	APOLLO [25]; APOLLO-B [26]
Vutrisiran (Ammvutra®)	GalNAc-conjugated siRNA	SC 25 mg every 3 months	ATTRv-PN: US 06/2022, EU 09/2022. ATTR-CM: US 03/2025, EU 2025	HELIOS-A [27]; HELIOS-B [28]
Inotersen (Tegsedi®)	2'-MOE antisense oligonucleotide	SC 284 mg inotersen (300 mg inotersen sodium) weekly; platelet and renal monitoring	ATTRv-PN: EU/US 2018. UK: marketing ceased, NICE guidance withdrawn (2026). EU: marketing cessation from 01/12/2026; withdrawal of authorization planned	NEURO-TTR [29,30]
Eplontersen (Wainua®, Wainzua®)	GalNAc-conjugated antisense oligonucleotide	SC 45 mg every 4 weeks (autoinjector)	ATTRv-PN: US 12/2023, EU 2025. ATTR-CM: phase 3 primary endpoint not met (2026)	NEURO-TTRansform [31]; CARDIO-TTRansform [16]
Liver transplantation	Removal of variant TTR source	Surgical	Established for early-onset p.Val50Met ATTRv-PN; largely replaced by drug therapy	[11]

Note: Registration numbers are given in Tables 2, 3 and 6. Abbreviations: CM, cardiomyopathy; GalNAc, N-acetylgalactosamine; IV, intravenous; MOE, methoxyethyl; NSAID, non-steroidal anti-inflammatory drug; PN, polyneuropathy; SC, subcutaneous; siRNA, small interfering RNA; v, variant; wt, wild-type. Approval dates refer to first authorization for the respective indication.

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Methods

Protocol and reporting

The review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [32]. Eligibility criteria, outcomes and analysis methods were defined before data extraction. The protocol was not registered.

Information sources and search strategy

PubMed/MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched from inception to 30 September 2026 without language restriction. ClinicalTrials.gov, the EU Clinical Trials Register/Clinical Trials Information System, European Public Assessment Reports, US prescribing information and abstracts of the European Society of Cardiology, American Heart Association, American College of Cardiology, Heart Failure Association, International Society of Amyloidosis and Peripheral Nerve Society meetings (2018–2026) were screened. The search combined disease terms, class terms and substance names, the last including discontinued and terminated agents: ("transthyretin" OR "ATTR" OR "familial amyloid polyneuropathy") AND ("transthyretin stabili*" OR "gene silenc*" OR "antisense" OR "RNA interference" OR "siRNA" OR "gene editing" OR "amyloid deplet*" OR "monoclonal antibody" OR "tafamidis" OR "acoramidis" OR "diflunisal" OR "doxycycline" OR "tauroursodeoxycholic" OR "tolcapone" OR "patisiran" OR "vutrisiran" OR "revusiran" OR "ALN-TTRSC" OR "inotersen" OR "eplontersen" OR "nucresiran" OR "nexiguran ziclumeran" OR "NTLA-2001" OR "cliramitug" OR "ALXN2220" OR "NI006" OR "coramitug" OR "NNC6019" OR "PRX004" OR "AT-02") AND ("randomized" OR "randomised" OR "trial"). The class terms were added specifically to capture agents whose development has been discontinued and which are therefore unlikely to be retrieved by substance name alone. Database-specific strings including MeSH and Emtree terms, search dates and per-database yields are provided as Supplementary Table S1. Reference lists of included trials and reviews were hand-searched, and the complete ClinicalTrials.gov set of interventional phase 3 studies in ATTR amyloidosis was screened against the eligibility criteria.

Eligibility criteria

Population: adults with ATTRv-PN, ATTR-CM (wild-type or variant) or mixed phenotype. **Interventions:** any TTR-directed therapy (stabilizer, silencer, gene editing, amyloid depleter). **Comparator:** placebo, either concurrent or external (placebo arm of a preceding randomized trial of the same sponsor, as accepted by regulatory authorities). **Outcomes:** as defined in Section 2.5.

Designs: phase 3 randomized controlled trials (RCTs) and pivotal externally controlled phase 3 trials for quantitative synthesis; phase 1-2 trials of novel classes for narrative synthesis. Observational studies, uncontrolled open-label extensions (used descriptively only) and trials of supportive heart-failure therapy were excluded. Trials of agents whose development has been discontinued were eligible and were assessed individually; reasons for exclusion from quantitative synthesis are stated in Section 3.1.

Study selection and data extraction

Records were screened by title and abstract, followed by full-text assessment. Data were extracted into a standardized form and verified against primary publications, supplementary appendices, regulatory documents and registry entries: design, randomization ratio, sample size, genotype distribution, phenotype and key inclusion criteria, New York Heart Association (NYHA) class, background stabilizer use, treatment duration, primary and secondary endpoints, effect estimates with 95% confidence intervals (CI) and adverse events.

Outcomes

For ATTR-CM, the primary outcome was all-cause mortality (ACM). Secondary outcomes were the composite of death and cardiovascular (CV) events as defined in each trial, change in 6-minute walk distance (6MWD), change in Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS) and safety. For ATTRv-PN, the primary outcome was change in the modified Neuropathy Impairment Score +7 (mNIS+7); the secondary outcome was change in Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) score. Estimates were taken at the longest prespecified time point at which a randomized comparison was reported. For HELIOS-B this is the 42-month analysis of ACM, which includes vital status after transition to the open-label extension and is therefore randomized but not fully double-blind; the 36-month double-blind analysis was used in a sensitivity analysis [28]. For CARDIO-TTTransform, ACM through week 140 is reported separately for patients with and without baseline stabilizer therapy [17]. Because these are strata of one trial and differ systematically in age, disease duration and stage, they were combined into a single trial-level estimate by inverse-variance weighting for the primary analysis; the stratum-level analysis is reported separately in Section 3.5. Each trial therefore contributes one unit to each pooled estimate.

Risk of bias and certainty of evidence

Risk of bias was assessed with the Cochrane RoB 2 tool for RCTs [33] and with ROBINS-I for externally controlled trials [34]. Certainty of evidence per outcome was graded with the GRADE approach [35].

Statistical analysis

Hazard ratios (HR) and rate ratios (RR) were log-transformed; standard errors were derived from reported 95% CI. For ENDEAVOUR, mortality was entered as a risk ratio calculated from the crude on-treatment death proportions (18/140 versus 2/66), with its standard error derived from the event counts; this estimate was used only in the sensitivity analysis, in which it was pooled with the hazard and rate ratios of the other trials. Mean differences were pooled on the original scale; where only an exact P value was reported, the standard error was derived from the corresponding normal deviate. Random-effects models with the Paule–Mandel estimator of between-trial variance were used, because the DerSimonian–Laird estimator [36] underestimates between-trial variance when few trials are pooled, whereas the Paule–Mandel estimator [37] performs better in this setting [38]. Heterogeneity was quantified with Cochran Q, I^2 and τ^2 [39]. For outcomes with three or more trials, the Hartung–Knapp–Sidik–Jonkman correction, in its modified form with the variance scaling factor truncated at 1, was applied as a prespecified sensitivity analysis and is reported alongside the primary interval [40,41]; at two trials the correction is not interpretable and was not applied. Prespecified subgroup comparisons were therapeutic class (stabilizer versus silencer) and, for silencers, baseline stabilizer use (monotherapy versus add-on); differences were tested with a z-test on pooled log estimates, which is low-powered with two trials per group and is therefore reported alongside the within-trial interaction test of CARDIO-TTRansform. Three limitations of the pooled estimates were handled explicitly. First, the composite outcome combines a hazard ratio for time to first event (ATTRibute-CM) with rate ratios for recurrent events (HELIOS-B, CARDIO-TTRansform); these estimate different parameters, so an analysis restricted to the recurrent-event rate ratios is reported. Second, HELIOS-A and NEURO-TTRansform used the placebo arms of APOLLO and NEURO-TTR as external controls, so these control participants would contribute twice to a pool containing all four trials; the primary neuropathy analysis is therefore restricted to the two concurrently randomized trials, and the four-trial estimate is reported as a secondary analysis with this dependency stated. Third, the mNIS+7 versions differ between sponsors (range 0–304 points in Alnylam trials; 0–346.3 points in Ionis trials), and NIS+7 as used in the diflunisal trial is a further, non-equivalent scale; cross-scale comparisons are descriptive only. Further sensitivity analyses comprised fixed-effect models, leave-one-out analyses and inclusion of the terminated ENDEAVOUR trial. Funnel-plot assessment was not performed (fewer than 10 trials per outcome); publication and reporting bias were instead assessed qualitatively within GRADE on the basis of trial registration, availability of results for terminated programmes and sponsor involvement. Analyses were performed in Python 3.11 (NumPy 1.26, SciPy 1.11) using standard formulae; the

analysis script is provided as Supplementary File S2. Two-sided $P < 0.05$ defined statistical significance.

Results

Study selection and characteristics

Database searching, registry screening and hand-searching yielded 1,097 records; after removal of 211 duplicates, 886 records were screened by title and abstract and 839 were excluded, 47 full texts were assessed and 32 were excluded with reasons (PRISMA 2020 flow diagram, Supplementary Figure S1; per-database yields and search dates, Supplementary Table S1). Fifteen trials met the inclusion criteria: six pivotal trials in ATTR-CM (3,726 participants) [16,20,21,26,28,42], six pivotal trials in ATTRv-PN (987 participants) [19,23,25,27,29,31] and three early-phase trials of novel classes (180 participants) [14,43,44]. Characteristics of the pivotal trials and of the two early-phase amyloid-depleter trials are shown in Tables 2 and 3; the phase 1 trial of nexiguran ziclumeran [44] is summarized in Section 3.9 and Table 6. One eligible trial was identified that is absent from previous syntheses in this field. ENDEAVOUR (NCT02319005) randomized 206 patients with hereditary ATTR-CM2:1 to the GalNAc-conjugated siRNA revusiran ($n = 140$) or placebo ($n = 66$) and was terminated after a median of 6.71 months because of a mortality imbalance: 18 of 140 patients (12.9%) on revusiran and 2 of 66 (3.0%) on placebo died during the on-treatment period, corresponding to a risk ratio of 4.24 (95% CI 1.01–17.75); no causative mechanism was identified and the programme was discontinued [42]. ENDEAVOUR meets every stated eligibility criterion and is therefore reported in Table 2 and in the flow diagram. It was excluded from the primary quantitative synthesis on three grounds: median exposure of 6.71 months is incompatible with the 30- to 42-month horizon of the other trials; termination was event-driven, so the mortality estimate is conditioned on the stopping rule; and revusiran is not a current or candidate therapy. The exclusion is nevertheless not neutral, and the estimates with ENDEAVOUR included are reported as a sensitivity analysis in Section 3.3. A phase 3 trial of doxycycline plus tauroursodeoxycholic acid (NCT03481972, $n = 102$) was excluded because the combination is not a TTR-directed therapy within the definition of Section 2.3 and no peer-reviewed report of results was available. ATTR-CM populations were older (mean age 72–77 years), predominantly male ($\geq 90\%$) and, with the exception of ENDEAVOUR, predominantly wild-type (approximately 76% in ATTR-ACT to 90% in ATTRibute-CM). Background stabilizer use increased across trial eras: none in ATTR-ACT, drop-in permitted after month 12 in ATTRibute-CM, 25% in APOLLO-B, 40% in HELIOS-B (capped by protocol) and 57% in CARDIO-TTRansform, where a further 57% of patients without baseline stabilizer started one during follow-up [17]. Placebo-arm ACM declined from 42.9%

over 30 months in ATTR-ACT to 25.7% over 30 months in ATTRibute-CM [20,21]. ATTRv-PN trials enrolled patients with Coutinho stage 1–2 disease; the proportion carrying p.Val50Met ranged from approximately 43% (APOLLO) to 100% (Fx-005).

Risk of bias

Risk-of-bias judgements are shown in Table 4. Two of the four cardiomyopathy trials contributing to the primary outcome were rated at some concerns because of stabilizer drop-in during follow-up, and the overall judgement follows

the RoB 2 algorithm, under which any domain at some concerns precludes an overall rating of low. The diflunisal trial was at high risk of bias because of attrition. ENDEAVOUR was rated at some concerns because termination for a mortality imbalance makes the reported estimate conditional on the stopping rule. Both externally controlled trials (HELIOS-A, NEURO-TTRansform) were at serious risk of bias on ROBINS-I, driven by confounding from the use of a historical placebo population and by open-label outcome assessment.

Table 2: Trials in ATTR cardiomyopathy: design, population, genotype, endpoints and results. Rows 1–6 are pivotal phase 3 trials; rows 7–8 are early-phase trials reported narratively.

Trial (ref.)	Agent vs comparator; randomization	n	Genotype	Phenotype / key inclusion	Background stabilizer	Duration	Primary endpoint	Key results (active vs placebo)
ATTR-ACT (NCT01994889) [20]	Tafamidis 80 mg or 20 mg vs placebo; 2:1:2	441	wt 76%, v 24%	ATTR-CM, NYHA I–III, NT-proBNP ≥ 600 pg/mL, 6MWD > 100 m	None (by design)	30 mo	Hierarchical ACM, then CV hospitalization (Finkelstein–Schoenfeld)	Primary P < 0.001 . ACM 29.5% vs 42.9%; HR 0.70 (0.51–0.96). CVH RR 0.68 (0.56–0.81). 6MWD +75.7 m; KCCQ-OS +13.7 at 30 mo
ATTRibute-CM (NCT03860935) [21,22]	Acoramidis 800 mg BID vs placebo; 2:1	632 (611 mITT)	wt 90%, v 10% (p.Val142Ile n = 35)	ATTR-CM, NYHA I–III, eGFR ≥ 15 mL/min/1.73 m ²	Tafamidis drop-in permitted after month 12	30 mo	Hierarchical: ACM, CVH frequency, NT-proBNP, 6MWD (win ratio)	Win ratio 1.8 (1.4–2.2). ACM 19.3% vs 25.7%; HR 0.77 (0.54–1.10). ACM or first CVH HR 0.64 (0.50–0.83). 6MWD +39.6 m; KCCQ-OS +9.9
HELIOS-B (NCT04153149) [28]	Vutrisiran 25 mg q12w vs placebo; 1:1	655	wt $\approx 88\%$, v $\approx 12\%$	ATTR-CM, NYHA I–III (77.6% NYHA II); NT-proBNP upper limit applied at screening	40% tafamidis at baseline (cap)	Up to 36 mo; ACM to 42 mo	ACM + recurrent CV events (overall and monotherapy)	Overall HR 0.72 (0.56–0.93); monotherapy HR 0.67 (0.49–0.93); on tafamidis HR 0.79 (0.51–1.21). ACM HR 0.65 (0.46–0.90). 6MWD +26.5 m; KCCQ-OS +5.8
APOLLO-B (NCT03997383) [26]	Patisiran 0.3 mg/kg q3w IV vs placebo; 1:1	360	wt $\approx 80\%$, v $\approx 20\%$	ATTR-CM, NYHA I–III	25% tafamidis at baseline	12 mo	6MWD change	6MWD +14.7 m (0.7–28.7); KCCQ-OS +3.7 (0.2–7.2). Outcome composites not significant; US complete response letter
CARDIO-TTRansform (NCT04136171) [16,17]	Eplontersen 45 mg q4w SC vs placebo; 1:1	1,438 enrolled; 1,432 randomized and treated	wt and v (stratified)	ATTR-CM, NYHA I–III, NT-proBNP ≥ 600 pg/mL, no upper limit; 9.4% women	57% at baseline; 57% drop-in among others	140 wk	CV death + recurrent CV events	RR 0.89 (0.73–1.09), P = 0.28. ACM + CV events RR 0.86 (0.71–1.04). No stabilizer: RR 0.71 (0.54–0.93); on stabilizer: RR 1.14 (0.85–1.53); P interaction 0.017

ENDEAVOUR (NCT02319005) [42]	Revusiran 500 mg SC daily for 5 days then weekly vs placebo; 2:1	206	Hereditary (variant) ATTR only	ATTRv-CM, NYHA I–III	Not applicable (era before stabilizer approval)	Terminated; median exposure 6.71 mo	Co-primary: 6MWD and serum TTR change	Terminated for mortality imbalance: 18/140 (12.9%) vs 2/66 (3.0%) deaths on treatment; risk ratio 4.24 (1.01–17.75). No adverse effect on echocardiographic parameters, biomarkers or hospitalization; no causative mechanism identified; programme discontinued
Coramitug phase 2 (NCT05442047) [43]	Coramitug 10 or 60 mg/kg IV q4w vs placebo; 1:1:1	104	wt 87.5%, v 12.5%	ATTR-CM, NYHA II–III, IVS ≥ 12 mm	84% tafamidis, 7% silencer	52 wk	Co-primary: NT-proBNP and 6MWD change	NT-proBNP ratio 0.52 (0.35–0.78) at 60 mg/kg; 6MWD +13.5 m (–29.6 to 56.5), not significant
NI006 phase 1 (NI006-101) [14]	NI006 (clirmitug) 0.3–60 mg/kg IV q4w vs placebo; 2:1	40	wt and v	ATTR-CM, NYHA I–III	Permitted	4 mo + 8 mo open-label	Safety, pharmacokinetics	Reduction of cardiac scintigraphic tracer uptake and ECV at ≥ 10 mg/kg; no drug-related serious adverse events

Note: Values in parentheses are 95% CI. ENDEAVOUR is reported for completeness and is excluded from the primary quantitative synthesis (see Section 3.1). ACM, all-cause mortality; BID, twice daily; CV, cardiovascular; CVH, cardiovascular hospitalization; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; IVS, interventricular septum; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary (points); mITT, modified intention-to-treat; q3w/q4w/q12w, every 3/4/12 weeks; 6MWD, 6-minute walk distance; v, variant; wt, wild-type.

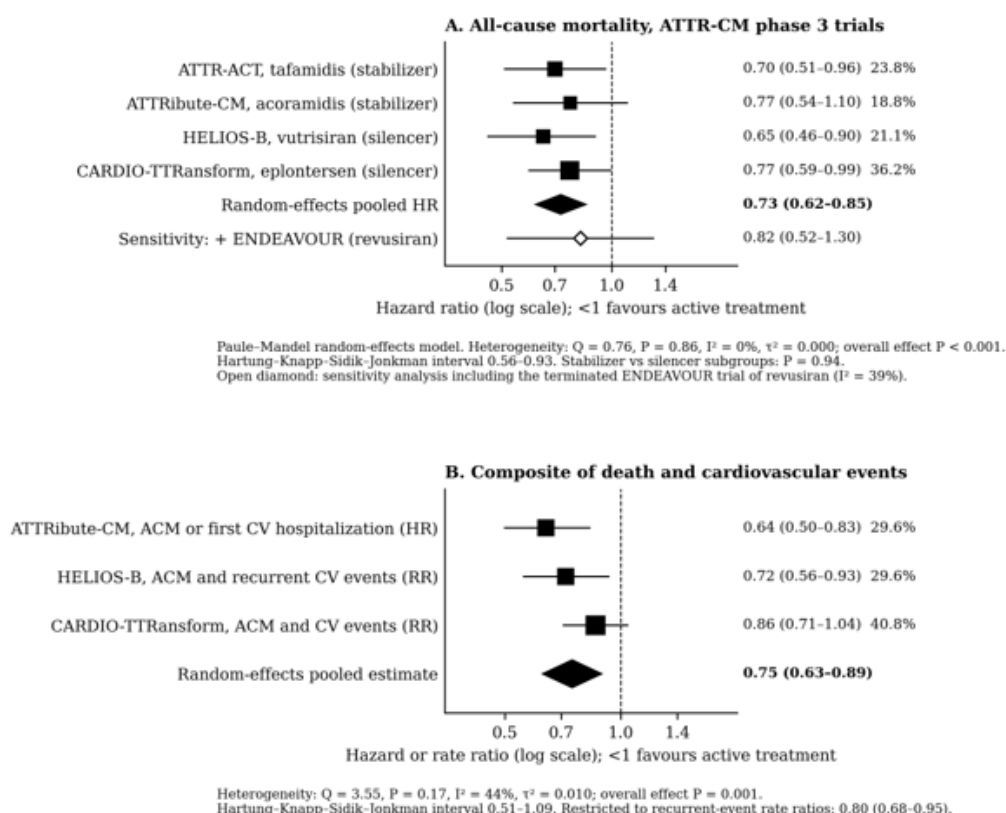


Figure 1: Random-effects meta-analyses in ATTR cardiomyopathy. (A) All-cause mortality; one unit per trial, CARDIO-TTRransform entered as the inverse-variance combination of its two baseline-stabilizer strata at week 140, HELIOS-B at 42 months; the open diamond is the sensitivity analysis including ENDEAVOUR. (B) Composite of death and cardiovascular events as defined in each trial. Squares are proportional to weight; horizontal lines are 95% CI; diamonds are pooled estimates.

All-cause mortality in ATTR-CM

Four phase 3 trials contributed one unit each (3,160 participants). Active TTR-directed therapy reduced ACM (pooled HR 0.73 (95% CI 0.62–0.85); $P < 0.001$) without detectable heterogeneity ($Q = 0.76$, $P = 0.86$, $I^2 = 0\%$, $\tau^2 = 0$) (Figure 1A). The Hartung–Knapp–Sidik–Jonkman interval was 0.56–0.93. Stabilizers (ATTR-ACT, ATTRibute-CM; 0.73 (95% CI 0.58–0.92)) and silencers (HELIOS-B, CARDIO-TTRansform; 0.72 (95% CI 0.59–0.89)) yielded equivalent estimates (P for subgroup difference = 0.94). In leave-one-out analyses the pooled estimate ranged from 0.70 to 0.75, and all four estimates excluded unity. Long-term extension of ATTR-ACT showed persistent survival benefit with continuous versus delayed tafamidis [45]. Three features of this estimate limit its interpretation. First, including the terminated ENDEAVOUR trial, in which revusiran was associated with excess mortality, moves the pooled estimate to 0.82 (95% CI 0.52–1.30) with $I^2 = 39\%$ and $P = 0.40$; for the silencer subgroup alone the estimate becomes 1.06 (95% CI 0.37–3.03) with $I^2 = 69\%$. The grounds for excluding ENDEAVOUR from the primary analysis are stated in Section 3.1, but the sensitivity analysis shows that the consistency of the primary estimate rests on that exclusion. Second, the

HELIOS-B 42-month estimate includes vital status after transition to open-label vutrisiran; with the 36-month double-blind estimate (HR 0.69 (95% CI 0.49–0.98)) in place of the 42-month estimate, the pooled HR is 0.74 (95% CI 0.63–0.86; $I^2 = 0\%$; Hartung–Knapp–Sidik–Jonkman interval 0.57–0.95) [28]. Third, the CARDIO-TTRansform contribution is the inverse-variance combination of its two randomized strata (HR 0.84, 0.60–1.18 without baseline stabilizer and 0.68, 0.46–1.01 with baseline stabilizer; combined 0.77 (95% CI 0.59–0.99)) [17].

Composite outcomes, cardiovascular events, functional capacity and quality of life

The composite of death and CV events (three trials, 2,719 participants) was reduced (0.75 (95% CI 0.63–0.89); $I^2 = 44\%$; Hartung–Knapp–Sidik–Jonkman interval 0.51–1.09) (Figure 1B). The three estimates are not equivalent measures: ATTRibute-CM reports a hazard ratio for time to first event, whereas HELIOS-B and CARDIO-TTRansform report rate ratios for recurrent events. Restricted to the two recurrent-event rate ratios the pooled estimate was 0.80 (95% CI 0.68–0.95) ($I^2 = 17\%$). CV hospitalization was reduced by tafamidis (RR 0.68, 0.56–0.81) and acoramidis

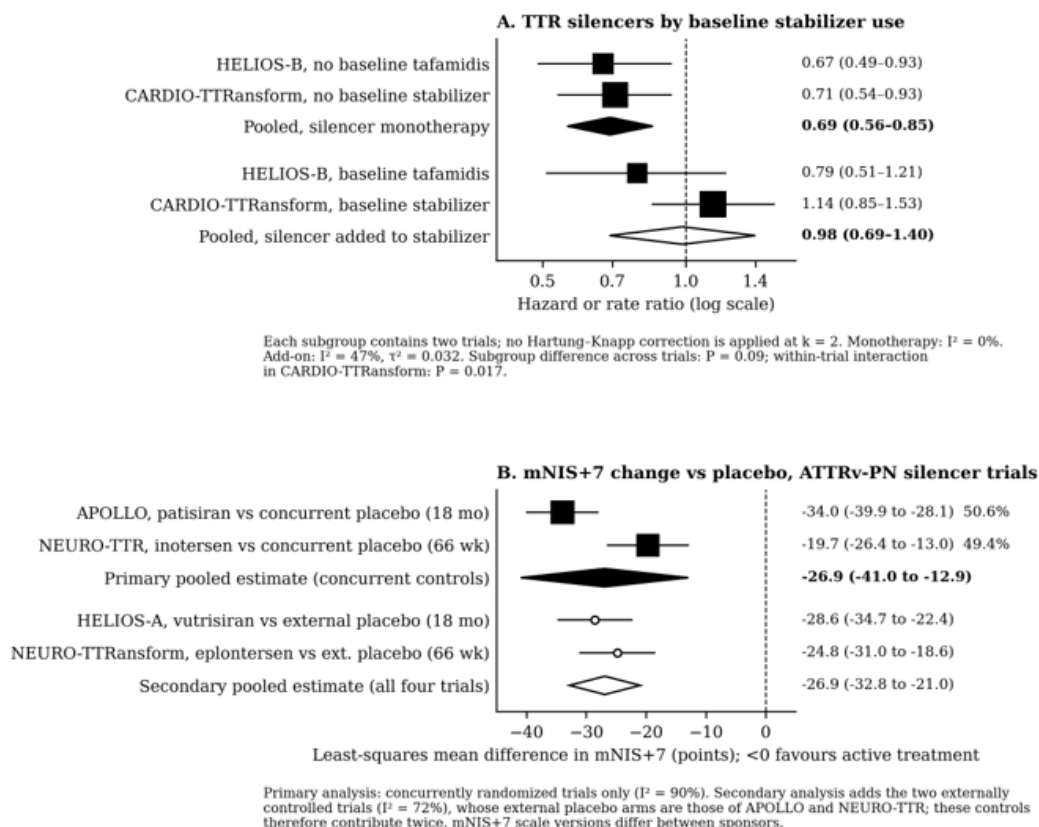


Figure 2: (A) TTR silencers in ATTR cardiomyopathy by baseline stabilizer use; primary composite endpoints (HELIOS-B: all-cause mortality and recurrent CV events; CARDIO-TTRansform: CV mortality and recurrent CV events). Open diamond: silencer added to stabilizer. (B) Change in mNIS+7 versus placebo in ATTRv-PN silencer trials. The primary estimate is restricted to the concurrently randomized trials; HELIOS-A and NEURO-TTRansform used the placebo arms of APOLLO and NEURO-TTR as external controls, so those participants contribute twice to the secondary four-trial estimate. HELIOS-A standard error derived from the exact P value.

(first CVH HR 0.60, 0.45–0.80; annualized frequency 0.22 vs 0.45) [20,22]. Across five trials, 6MWD decline was attenuated by 34.5 m (95% CI 13.2–55.7; $I^2 = 88\%$) and KCCQ-OS decline by 7.1 points (3.2–10.9; $I^2 = 84\%$); both intervals widen substantially under the Hartung–Knapp–Sidik–Jonkman correction (6MWD 4.4–64.6 m; KCCQ-OS 1.6–12.5 points), which is the appropriate reading given the heterogeneity. That heterogeneity reflects follow-up duration (12 months in APOLLO-B versus 30 months in ATTR-ACT) and background stabilizer use: in CARDIO-TTRansform, 6MWD differed by 29.9 m (14.3–45.5) without and by 12.0 m (–1.0 to 25.0) with baseline stabilizer [17].

Silencers with and without background stabilizer

Two outcome trials reported silencer effects by baseline stabilizer use (Figure 2A). Without baseline stabilizer, the pooled estimate for the primary composite was 0.69 (95% CI 0.56–0.85) ($I^2 = 0\%$). With baseline stabilizer (tafamidis in all cases), the pooled estimate was 0.98 (95% CI 0.69–1.40) ($I^2 = 47\%$). Each subgroup contains two trials, so no small-sample correction was applied and the across-trial test is low-powered: $P = 0.09$. The within-trial interaction test of CARDIO-TTRansform, which is the better-powered comparison, gave $P = 0.017$ across 1,432 patients [17]. Serum TTR on eplontersen at week 140 was similar in both strata (median 6.5 and 7.1 mg/dL), which places the effect modification downstream of TTR lowering [17]. In HELIOS-B, the composite of CV death and recurrent CV events in patients on baseline tafamidis was RR 0.78 (0.50–1.22) [28]; the slightly different value in Table 2 (HR 0.79, 0.51–1.21) is the corresponding estimate for the trial primary composite of all-cause mortality and recurrent CV events [28].

The mortality strata point in the opposite direction and this must be stated. For ACM at week 140, CARDIO-TTRansform reported HR 0.84 (0.60–1.18) without and 0.68 (0.46–1.01) with baseline stabilizer — that is, the more favourable estimate in the stratum in which no benefit was seen on the primary composite [17]. The two results are not contradictory in a strict sense: they are different endpoints with different event counts, both stratum estimates include unity, and the authors of the primary analysis attribute the pattern to patients with advanced cardiac involvement surviving longer while remaining susceptible to recurrent events, as previously observed with tafamidis in NYHA class III [17,20]. The conclusion of this review that silencer benefit is concentrated in patients without a stabilizer therefore applies to the composite and functional endpoints, for which the interaction was formally tested, and not to all-cause mortality, for which no interaction was demonstrated ($P = 0.44$) [17]. Combination therapy in the reverse sequence (stabilizer added to an established silencer) has not been tested in randomized trials.

Neuropathy outcomes in ATTRv-PN

In the two concurrently randomized silencer trials (APOLLO, NEURO-TTR; 397 participants), the pooled mNIS+7 mean difference versus placebo was –26.9 points (95% CI –41.0 to –12.9; $I^2 = 90\%$) and the Norfolk QOL-DN difference –16.5 points (–25.7 to –7.3; $I^2 = 76\%$) (Figure 2B). Adding the two externally controlled trials gives –26.9 points (–32.8 to –21.0; $I^2 = 72\%$) and –18.5 points (–22.8 to –14.2; $I^2 = 46\%$). The point estimates are almost unchanged, but the four-trial intervals are narrower than the data support, because the external control arms are the placebo arms of the two concurrently randomized trials and therefore contribute twice; the four-trial estimates are reported for completeness and are not used for inference. Improvement of mNIS+7 relative to baseline occurred in 56% of patisiran-treated and 48% of vutrisiran-treated patients versus 4% on placebo [25,27]. Stabilizers were tested only in early-stage disease and on a different scale, so no numerical comparison with the silencer estimates is possible. Tafamidis did not meet the co-primary endpoint in the intention-to-treat population of Fx-005 [19]. Diflunisal reduced progression of NIS+7 — a scale that is not equivalent to mNIS+7 — by an adjusted least-squares mean difference of 16.3 points over 24 months (observed means +8.2 versus +26.3 points), with concordant benefit on NIS, NIS-LL, the Kumamoto score and the SF-36 physical component [23]. This trial supported the EU marketing authorization of diflunisal as Attrogy on 17 July 2025 for stage 1 and stage 2 ATTRv-PN [12,24]. A network meta-analysis of pharmacological interventions in ATTRv-PN ranked both stabilizers below the silencers and did not separate diflunisal from tafamidis [46].

Safety

Serious adverse events did not differ from placebo for tafamidis, acoramidis, vutrisiran and eplontersen [16,20,21,28]. Acoramidis caused an early, non-progressive decrease in estimated glomerular filtration rate [21]. Patisiran requires premedication; infusion-related reactions occurred in 19% of APOLLO participants [25]. Inotersen caused thrombocytopenia (3%, including one fatal intracranial haemorrhage) and glomerulonephritis (3%), requiring weekly platelet and regular renal monitoring [29]; NICE withdrew its guidance after the manufacturer ceased marketing in the United Kingdom [47], and in the European Union marketing ceases from 1 December 2026, with withdrawal of the marketing authorization planned from the same date, for commercial reasons and explicitly not because of manufacturing, quality or safety concerns [30]. Eplontersen showed no thrombocytopenia or glomerulonephritis signal [31]. Silencers reduce serum retinol through loss of the TTR–retinol-binding protein complex, and vitamin A supplementation is required by the product information of each agent [18]. As an analgesic and anti-inflammatory

Table 3: Pivotal trials in hereditary ATTR polyneuropathy: design, population, genotype, endpoints and results.

Trial (ref.)	Agent vs comparator; randomization	n	Genotype	Phenotype / key inclusion	Duration	Primary endpoint	Key efficacy results	Safety signals
Fx-005 (NCT00409175) [19]	Tafamidis 20 mg vs placebo; 1:1	128	p.Val50Met 100%	Early-stage (stage 1) ATTRv-PN	18 mo	Co-primary: NIS-LL responders; Norfolk QOL-DN	Responders 45.3% vs 29.5% (P = 0.068, ITT); 60.0% vs 38.1% (P = 0.041, efficacy-evaluable)	Comparable to placebo
Diflunisal, Attrogy (NCT00294671) [12,23]	Diflunisal 250 mg BID vs placebo; 1:1	130	Mixed; p.Val50Met ≈50%	ATTRv-PN, Coutinho stage 1–2	24 mo	NIS+7 change	NIS+7 +8.2 vs +26.3 points (observed means); adjusted least-squares mean difference 16.3 (P < 0.001); benefit also in NIS, NIS-LL, Kumamoto score and SF-36 physical score. Substantial attrition	Renal function, fluid retention, gastrointestinal bleeding (NSAID class); adverse events comparable to placebo
APOLLO (NCT01960348) [25]	Patisiran 0.3 mg/kg IV q3w vs placebo; 2:1	225	39 variants; p.Val50Met 43%	ATTRv-PN, NIS 5–130	18 mo	mNIS+7 (0–304) change	mNIS+7 –34.0 (–39.9 to –28.1); 56% improved vs 4%. Norfolk –21.1 (–27.2 to –15.0)	Infusion-related reactions 19%; vitamin A decrease
NEURO-TTR (NCT01737398) [29]	Inotersen 284 mg SC weekly (300 mg inotersen sodium) vs placebo; 2:1	173 enrolled; 172 analysed	p.Val50Met ≈52%	ATTRv-PN, stage 1–2, NIS 10–130	66 wk	mNIS+7 (lonis) and Norfolk QOL-DN change	mNIS+7 –19.7 (–26.4 to –13.0); Norfolk –11.7 (–18.3 to –5.1)	Thrombocytopenia 3% (1 fatal intracranial haemorrhage); glomerulonephritis 3%
HELIOS-A (NCT03759379) [27]	Vutrisiran 25 mg SC q12w vs patisiran reference; 3:1; external placebo (APOLLO, n = 77)	164	p.Val50Met ≈44%	ATTRv-PN, NIS 5–130	18 mo (primary 9 mo)	mNIS+7 change vs external placebo	mNIS+7 –28.6 at 18 mo (48% improved vs 4%); Norfolk –21.0	Injection-site reactions (mild); vitamin A decrease
NEURO-TTRransform (NCT04136184) [31]	Eplontersen 45 mg SC q4w vs inotersen reference; 6:1; external placebo (NEURO-TTR, n = 60)	168	p.Val50Met majority	ATTRv-PN, stage 1–2	66 wk (85 wk total)	Serum TTR, mNIS+7 and Norfolk QOL-DN change	mNIS+7 –24.8 (–31.0 to –18.6); Norfolk –19.7 (–25.6 to –13.8)	No thrombocytopenia or glomerulonephritis signal; vitamin A decrease

Note: Values in parentheses are 95% CI; mean differences are least-squares differences versus placebo (negative values favour active treatment). mNIS+7, modified Neuropathy Impairment Score +7; NIS-LL, NIS–lower limbs; Norfolk QOL-DN, Norfolk Quality of Life–Diabetic Neuropathy; ITT, intention-to-treat; NSAID, non-steroidal anti-inflammatory drug.

agent, diflunisal is given at 500–1,000 mg/day in two divided doses for osteoarthritis and rheumatoid arthritis and, for mild to moderate pain, as a 1,000 mg loading dose followed by 500 mg every 12 hours; maintenance doses above 1,500 mg/day are not recommended [48]. At these doses it carries the established NSAID risks of gastrointestinal bleeding, ulceration and perforation, renal impairment, fluid retention and oedema, and cardiovascular thrombotic events [48]. Attrogy is licensed for ATTRv-PN at 250 mg twice daily (500 mg/day), at the lower end of this dose range [12], and in the pivotal trial adverse events did not differ between the diflunisal and placebo groups [23]. The non-steroidal anti-inflammatory drug class risks (renal dysfunction,

fluid retention, bleeding) nevertheless require assessment in patients with cardiac involvement [3,12,23]. The most consequential safety observation in the field remains the terminated ENDEAVOUR trial, in which revusiran was associated with 12.9% versus 3.0% on-treatment mortality without an identified mechanism [42]. In the phase 3 MAGNITUDE programme of nexiguran ziclumeran, grade 4 transaminase elevation with increased bilirubin in one participant led to a clinical hold on 29 October 2025, lifted on 27 January 2026 (MAGNITUDE-2) and 2 March 2026 (MAGNITUDE) with additional exclusion criteria [49]. The amyloid depleters coramitug and clirmitug showed no drug-related serious adverse events in phase 1–2 [14,43].

Table 4: Risk-of-bias assessment: RoB 2 for randomized trials (panel A), ROBINS-I for externally controlled trials (panel B).

Trial	Randomization	Deviations from intended intervention	Missing outcome data	Outcome measurement	Selective reporting	Overall
A. Randomized trials (RoB 2)						
ATTR-ACT	Low	Low	Low	Low	Low	Low
ATTRibute-CM	Low	Some concerns (tafamidis drop-in after month 12)	Low	Low	Low	Some concerns
HELIOS-B	Low	Low (drop-in balanced, capped by protocol)	Low	Low	Low	Low
APOLLO-B	Low	Low	Low	Low	Low	Low
CARDIO-TTRansform	Low	Some concerns (stabilizer drop-in in 57% of the no-stabilizer stratum)	Low	Low	Low	Some concerns
ENDEAVOUR	Low	Low	Some concerns (early termination)	Low	Some concerns (estimate conditional on stopping rule)	Some concerns
Fx-005	Low	Low	Some concerns (withdrawals for transplantation)	Low	Low	Some concerns
Diflunisal (Berk 2013)	Low	Low	High (attrition)	Low	Low	High
APOLLO	Low	Low	Low	Low	Low	Low
NEURO-TTR	Low	Low	Low	Low	Low	Low
Trial	Confounding	Selection of participants	Classification of interventions	Deviations / missing data	Outcome measurement	Overall
B. Externally controlled trials (ROBINS-I; selective reporting low in both)						
HELIOS-A	Serious (external placebo arm from APOLLO)	Moderate (differing eligibility windows)	Low	Low	Moderate (open-label assessment)	Serious
NEURO-TTRansform	Serious (external placebo arm from NEURO-TTR)	Moderate (differing eligibility windows)	Low	Low	Moderate (open-label assessment)	Serious

Certainty of evidence

Certainty was moderate for all-cause mortality in ATTR-CM and for the composite and neuropathy outcomes, and low for the functional outcomes (6MWD, KCCQ-OS) and for silencers as monotherapy and added to a background stabilizer (Table 5). The rating for all-cause mortality was downgraded for risk of bias, because two of the four contributing trials are at some concerns, and the publication-bias domain was

rated serious for no outcome but was explicitly considered: results of the terminated revusiran programme are published, the registered phase 3 trials in the field have reported, and all included trials were registered before enrolment, but every included trial is sponsor-funded and the primary estimate depends on a defensible exclusion of the one trial with an adverse mortality result.

Table 5: Summary of findings and GRADE certainty.

Outcome	Trials (participants)	Pooled effect (95% CI)	I ²	Certainty	GRADE domains
ACM, ATTR-CM	4 trials (3,160)	HR 0.73 (0.62–0.85)	0%	Moderate	Risk of bias –1 (two trials at some concerns, stabilizer drop-in); inconsistency not serious; indirectness not serious; imprecision not serious; publication bias not serious but estimate sensitive to exclusion of ENDEAVOUR
Death + CV events, ATTR-CM	3 trials (2,719)	0.75 (0.63–0.89)	44%	Moderate	Indirectness –1 (hazard ratio for first event pooled with recurrent-event rate ratios; differing composite definitions); other domains not serious
6MWD, ATTR-CM	5 trials (3,520)	MD +34.5 m (13.2–55.7)	88%	Low	Inconsistency –1 (I ² 88%, differing follow-up); imprecision –1 (small-sample-corrected interval 4.4–64.6 m)
KCCQ-OS, ATTR-CM	5 trials (3,520)	MD +7.1 (3.2–10.9)	84%	Low	Inconsistency –1 (I ² 84%); imprecision –1 (small-sample-corrected interval 1.6–12.5)
Silencer monotherapy, composite	2 trial strata (1,008)	0.69 (0.56–0.85)	0%	Low	Risk of bias –1 (subgroup-based; stabilizer drop-in in 57%); imprecision –1 (two strata, no small-sample correction possible)
Silencer added to stabilizer, composite	2 trial strata (1,079)	0.98 (0.69–1.40)	47%	Low	Inconsistency –1 (I ² 47%, opposite point estimates); imprecision –1 (interval includes clinically relevant benefit and harm)
mNIS+7, ATTRv-PN	2 concurrently randomized trials (397)	MD –26.9 (–41.0 to –12.9)	90%	Moderate	Inconsistency –1 (I ² 90%, differing scale versions and agents); other domains not serious
Norfolk QOL-DN, ATTRv-PN	2 concurrently randomized trials (397)	MD –16.5 (–25.7 to –7.3)	76%	Moderate	Inconsistency –1 (I ² 76%); other domains not serious

Note: All ratings start at high (randomized evidence); no upgrading was applied. HR, hazard ratio; for CARDIO-TTRansform and recurrent-event analyses the estimate is a rate ratio; MD, mean difference. Negative mNIS+7 and Norfolk QOL-DN values and positive 6MWD and KCCQ-OS values favour active treatment. The externally controlled trials HELIOS-A and NEURO-TTRansform are not included in the neuropathy rows because their control arms are those of APOLLO and NEURO-TTR (Section 3.6).

Investigational therapies

Six programmes are in active clinical development (Table 6). Nucleoside, a next-generation GalNAc-siRNA dosed twice yearly, is evaluated in TRITON-CM, an event-driven trial expanded to approximately 1,750 patients, and in TRITON-PN [50,51]. Nexiguran ziclumeran achieved a mean serum TTR reduction of approximately 90% after a

single infusion in phase 1, sustained over at least 12 months in ATTR-CM [13,44]. Two depleter antibodies are in phase 3 outcome trials: clirimitug (ALXN2220, formerly NI006) in DepleTTR-CM [52] and coramitug in CLEOPATTRA [53]. In the phase 2 coramitug trial, 84% of participants were on tafamidis; NT-proBNP decreased by 48% versus placebo at 60 mg/kg without a significant 6MWD effect over 52 weeks [43].

Table 6: TTR-directed therapies in active clinical development (phase 3 programmes and the phase 1 pan-amyloid depleter AT-02), and the completed CARDIO-TTRansform programme for reference (registry status 1 October 2026).

Agent (code; sponsor)	Class / mechanism; administration	Phase / trial	Population	n (planned)	Primary endpoint	Status	Available clinical data
Nucresiran (ALN-TTRsc04; Alnylam)	GalNAc-siRNA, next-generation silencer; SC twice yearly	Phase 3 TRITON-CM (NCT07052903); TRITON-PN	ATTR-CM wt/v incl. background stabilizer; ATTRv-PN	≈1,750 (CM)	ACM + CV events (CM)	Recruiting; primary completion estimated 05/2030 [50,51]	Phase 1: deep and durable TTR reduction; sponsor-reported median knockdown ≈95%
Nexiguran ziclumeran (nex-z, NTLA-2001; Intellia)	LNP-delivered CRISPR-Cas9 in vivo TTR knockout; single IV infusion	Phase 3 MAGNITUDE (NCT06128629, CM); MAGNITUDE-2 (NCT06672237, PN)	ATTR-CM wt/v; ATTRv-PN	≈1,200 (CM); ≈60 (PN)	CV death + CV events (CM); mNIS+7 and serum TTR (PN)	Clinical hold 10/2025 (grade 4 liver injury); lifted 01/2026 (PN) and 03/2026 (CM) [49]	Phase 1 (PN n = 6 initial; CM n = 36): mean TTR reduction ≈90%, sustained ≥12 months [13,44]
Cliramitug (ALXN2220, NI006; Alexion/AstraZeneca, Neurimmune)	Human IgG1 against misfolded TTR; macrophage-mediated amyloid depletion; IV q4w	Phase 3 DepleTTR-CM (NCT06183931)	ATTR-CM wt/v on standard of care	1,181 (2:1)	ACM + CV events	Recruitment complete; primary completion 06/12/2027 [52]	Phase 1 (n = 40): reduced cardiac tracer uptake and ECV [14]
Coramitug (NNC6019, PRX004; Novo Nordisk)	Humanized IgG1 against misfolded TTR; IV q4w	Phase 3 CLEOPATTRA (NCT07207811)	ATTR-CM	1,280	CV outcomes	Recruiting; primary completion 29/06/2029 [53]	Phase 2 (n = 104): NT-proBNP ratio 0.52 (0.35–0.78); 6MWD not significant [43,61]
Acoramidis (ACT-EARLY; BridgeBio)	Kinetic stabilizer; oral	Phase 3 ACT-EARLY (NCT06563895) [60]	Asymptomatic carriers of pathogenic TTR variants	587	Time to onset of ATTR-CM or ATTR-PN	Randomized, double-blind, placebo-controlled; primary completion 10/2031 [60]	Not yet reported
AT-02 (Attralus)	Humanized IgG1 fused to a pan-amyloid binding peptide; pan-amyloid removal; IV	Phase 1 AT02-001 (NCT05521022), three parts, with phase 2 open-label extension	Healthy volunteers and systemic amyloidosis (ATTR and AL)	Up to 150 participants with systemic amyloidosis across AT02-001 and the open-label extension	Safety, tolerability, pharmacokinetics	Dose escalation; EU orphan designation for ATTR and AL (2024)	Not yet reported
Eplontersen in ATTR-CM (Ionis/AstraZeneca)	GalNAc-ASO; SC q4w	Phase 3 CARDIO-TTRansform (NCT04136171)	ATTR-CM wt/v	1,438 enrolled; 1,432 randomized and treated	CV death + recurrent CV events	Completed 2026; primary endpoint not met; included in this synthesis, listed here for comparison [16]	RR 0.89 (0.73–1.09); monotherapy stratum RR 0.71 (0.54–0.93) [17]

Note: ASO, antisense oligonucleotide; ECV, extracellular volume; LNP, lipid nanoparticle; other abbreviations as in Tables 1–3. ClinicalTrials.gov registration numbers are given for every trial in Tables 2, 3 and 6; the NI006 phase 1 trial is identified by its sponsor protocol number. Sample sizes and status are taken from the ClinicalTrials.gov records cited in the respective row, accessed 1 October 2026; where a planned sample size is given by the sponsor rather than the registry, this is stated. The final row is a completed programme included in the quantitative synthesis and is shown here for comparison.

Citation: Arndt Rolfs, Christian Tanislav, Ameen Al-Refai, Volha Skrahina. Transthyretin Stabilizers, Silencers, Gene Editing and Amyloid Depleters in Transthyretin Amyloidosis: A Systematic Review and Meta-Analysis of Randomized and Pivotal Clinical Trials. Archives of Clinical and Biomedical Research. 10 (2026): 395-411.

Discussion

Principal findings

This meta-analysis includes all phase 3 outcome trials in ATTR-CM reported through September 2026, including CARDIO-TTRansform and the terminated revusiran trial ENDEAVOUR. Four findings emerge. First, TTR-directed therapy reduces all-cause mortality in ATTR-CM by about 27% among the four current programmes, without detectable heterogeneity; the estimate is attenuated and the consistency is lost when ENDEAVOUR is added, so the result holds for the therapies in current use and not for TTR-directed therapy as an undifferentiated class. Second, stabilizers and silencers produce equivalent mortality effects in indirect comparison. Third, on the composite and functional endpoints the benefit of silencers is concentrated in patients not receiving a stabilizer, while the pooled estimate for silencers added to tafamidis is centred on the null; for all-cause mortality no such interaction was demonstrated. Fourth, in ATTRv-PN, silencers attenuate or reverse neuropathy progression.

Stabilization versus silencing

Both classes reduce the flux of amyloidogenic monomer: stabilizers by lowering the dissociation rate of the tetramer, silencers by lowering substrate concentration, with placebo-adjusted reductions of approximately 80% or more in the pivotal trials [25,27,31]. Neither class removes established deposits. The near-identity of the pooled mortality estimates for the two classes is consistent with a shared downstream mechanism. No head-to-head trial exists, and differences in trial era, background therapy, disease severity and follow-up preclude a ranking. Across trials, benefit emerged earlier in less advanced disease; in ATTR-ACT, survival curves separated after approximately 18 months and patients in NYHA class III had more CV hospitalizations on tafamidis, whereas the HELIOS-B primary endpoint separated after approximately 6 months in a population with lower NT-proBNP [20,28]. Current guidance recommends tafamidis for ATTR-CM with NYHA class I–II symptoms [54,55]; the subsequent approvals of acoramidis and vutrisiran extend the choice of first-line therapy. Selection between classes in practice follows phenotype (neuropathy favours silencers), route and adherence, monitoring requirements, renal function, cost and access.

Combination therapy

The central new finding is the interaction between silencer effect and background stabilizer. In CARDIO-TTRansform, eplontersen reduced the primary composite by 29% in patients without a stabilizer and had no effect in the 819 patients on tafamidis, despite similar serum TTR suppression in both strata [17]. HELIOS-B showed a point estimate favouring vutrisiran in the tafamidis stratum with wide confidence intervals [28]. The pooled add-on estimate is centred on

unity, which is compatible with a ceiling effect of combined substrate reduction and stabilization, although the across-trial subgroup test at two trials per group has little power and the within-trial interaction test of CARDIO-TTRansform ($P = 0.017$) carries the inferential weight. Four constraints apply: the evidence is subgroup-based; baseline stabilizer users differed systematically (younger, longer disease duration, less advanced stage); 57% of patients without baseline stabilizer started one during CARDIO-TTRansform, which biases the monotherapy estimate towards the null [17]; and the interaction was demonstrated for the composite and functional endpoints but not for mortality, where the stratum estimates run in the opposite direction (Section 3.5). The data do not support routine addition of a silencer to an established stabilizer in ATTR-CM. Combination remains a rational option in mixed phenotypes with progressive neuropathy, where silencers carry independent evidence.

Stabilizers in polyneuropathy after the licensing of diflunisal

Diflunisal is the oldest TTR stabilizer with randomized evidence and was used off-label in ATTRv-PN for more than a decade. Its EU marketing authorization in July 2025 is an indication extension within an established class rather than a new mechanism, but it has two practical consequences. Tafamidis is licensed in the European Union for Coutinho stage 1 only, and acoramidis has not been studied in polyneuropathy [18,56]; diflunisal is therefore the only stabilizer with an approved indication covering stage 2. In addition, dosage, product quality, pharmacovigilance and reimbursement are now defined, which removes the practical barrier of prescribing an unapproved analgesic in a progressive orphan disease. Neither point implies comparative efficacy: the German expert consensus continues to recommend a second-generation silencer as first-line therapy for most patients with symptomatic ATTRv-PN and to regard stabilizers as a bridging option with immediate switch on any sign of progression, and an indirect comparison does not separate diflunisal from tafamidis [18,46]. Although Attrogy is given at 250 mg twice daily, at the lower end of the analgesic and anti-inflammatory dose range of diflunisal [12,48], and adverse events did not differ from placebo in the pivotal trial [23], the NSAID class risks — renal dysfunction, fluid retention and gastrointestinal bleeding — require assessment and monitoring, particularly in patients with cardiac involvement [12,23]. A second setting is patients who progress despite adequate TTR suppression by a silencer. Adding a stabilizer is mechanistically plausible, because tetramer dissociation is concentration-dependent and tetramers become more dissociation-prone at the low TTR concentrations produced by silencing [57]; under silencer therapy the drug-to-target ratio therefore shifts in favour of the stabilizer. Retrospective cohort data report that a substantial proportion of patients receive stabilizer plus silencer without an identified safety signal [58], and the German consensus

considers combination justified in severely progressive cases after multidisciplinary review [18]. This sequence is the reverse of the one tested in CARDIO-TTRansform, where a silencer was added to patients already on a stabilizer, and the negative result there does not transfer to it. No randomized trial has tested stabilizer add-on in either phenotype. A placebo-controlled add-on trial in patients with ATTRv-PN progressing under a second-generation silencer, with mNIS+7 and Norfolk QOL-DN as endpoints and prespecified renal and gastrointestinal monitoring, would close this gap; any of the licensed stabilizers could serve, with the approved stage-2 indication favouring diflunisal. Until such data exist, combination remains an individual decision taken in a specialized centre [3,18].

Declining event rates and trial design

Placebo-arm mortality fell from 42.9% (ATTR-ACT) to 25.7% (ATTRIBUTE-CM) over 30 months [20,21]. Contributing factors are earlier diagnosis by bone scintigraphy, lower NT-proBNP at enrolment, the entry of sodium-glucose cotransporter 2 inhibitors into heart failure with preserved ejection fraction [59] and background disease-modifying therapy. The consequences are larger and longer trials (CARDIO-TTRansform 1,432 patients over 140 weeks; TRITON-CM expanded to approximately 1,750 patients) [16,51], recurrent-event and hierarchical endpoints, and growing interest in validated surrogates (serum TTR, NT-proBNP, extracellular volume, scintigraphic uptake). Where an approved disease-modifying therapy is reimbursed, placebo-controlled monotherapy designs are increasingly difficult to justify, and future trials of novel agents will test add-on effects on top of an active standard of care, for which the CARDIO-TTRansform result sets a demanding benchmark.

Genotype and phenotype

ATTR-CM trials enrolled predominantly ATTRwt; ATTRv subgroups were small, and p.Val142Ile carriers of African ancestry are under-represented relative to the carrier frequency in that population, which limits genotype-specific inference [6,21]. In ATTRIBUTE-CM, the treatment effect on the composite of death or first CV hospitalization was consistent across subgroups including genotype [22]. ATTRv-PN trials were dominated by p.Val50Met; late-onset and non-p.Val50Met genotypes with mixed cardiac and neurological involvement are the populations in which silencers offer dual-organ benefit. Genetic testing is indicated in every patient with ATTR-CM [3]; it identifies ATTRv, enables cascade testing of relatives and defines candidates for pre-symptomatic surveillance and for the ACT-EARLY prevention trial, whose primary endpoint is the time to onset of either cardiomyopathy or polyneuropathy [60]. Screening programmes in unexplained polyneuropathy and cardiomyopathy yield a diagnostic rate of approximately

1% [7,8], which supports systematic genetic testing in these populations.

Novel modalities

In vivo CRISPR-Cas9 editing offers permanent TTR reduction after a single dose [13,44]. Irreversibility, the hepatotoxicity signal in MAGNITUDE and the need for long-term surveillance of off-target effects define the benefit-risk evaluation [49]. Amyloid depleters address the component of disease that no approved therapy targets. Phase 1 data for clirimitug and phase 2 data for coramitug show biomarker and imaging effects consistent with deposit removal, without functional benefit at 52 weeks [14,43]. Outcome data from DepleTTR-CM and CLEOPATTRA will determine whether deposit removal adds clinical benefit to substrate control. Given the CARDIO-TTRansform result, the deleter class represents the most plausible route to incremental benefit in patients already on a stabilizer.

Limitations

The analysis is based on aggregate data; individual participant data were not available, and extracted estimates were verified against primary publications and supplementary appendices but not recomputed from source data. Composite endpoints, follow-up durations and analysis methods differ between trials, and the composite pool mixes a first-event hazard ratio with recurrent-event rate ratios. The HELIOS-B 42-month mortality estimate includes vital status after transition to open-label treatment. The primary neuropathy estimate rests on two trials with I^2 of 90%, and the four-trial estimate contains dependent control arms. The exclusion of ENDEAVOUR is defensible but consequential, as Section 3.3 shows. With four or fewer trials per outcome, between-trial variance is estimated imprecisely whichever estimator is used, and the Hartung-Knapp-Sidik-Jonkman intervals should be read as the conservative bound. Study selection and data extraction were performed by a single reviewer; no second reviewer independently screened or extracted, which is a departure from standard systematic review methodology, and the protocol was not registered. Funnel-plot analysis was not feasible and publication bias was assessed qualitatively only. Information on pipeline programmes derives from registries and sponsor communications and was not independently verified beyond the cited records.

Conclusions

Among the therapies in current use, TTR stabilizers and silencers reduce all-cause mortality in ATTR cardiomyopathy by approximately one quarter, with equivalent effects between classes; the estimate is attenuated when the terminated revusiran trial is included. Silencers are effective as monotherapy; added to an established stabilizer, incremental benefit on composite and functional endpoints is not demonstrated. In hereditary polyneuropathy, silencers

attenuate or reverse neuropathy progression and remain first-line; the European licensing of diflunisal extends the approved indications of the stabilizer class to Coutinho stage 2. Stabilizer add-on in patients progressing under a silencer is untested and warrants a randomized trial. CRISPR-based editing and amyloid depleters are investigational; phase 3 outcome trials will report from 2027 onwards.

Declarations

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Conflicts of interest: A.R. is managing director of RCV GmbH (Arcensus) and RareGenetix GmbH, co-founder and chief executive officer of subrosa OmicsAI AG, founder and former chief executive officer of CENTOGENE, and investigator of the TRAM studies. A.R. has received no honoraria, consulting fees or research support from Purpose Pharma. V.S. is an employee of RareGenetix GmbH and investigator of the TRAM studies. A.A.-R. is affiliated with Tahleel Consultation Company LLC, Damman, Saudi Arabia. C.T. declares no conflicts of interest. No author has any advisory relationship with Purpose Pharma, the marketing authorization holder of diflunisal.

Author contributions: A.R. conceived the review, performed the search, data extraction and analyses, and wrote the manuscript. C.T. and A.A.-R. contributed to data interpretation and critical revision. V.S. supervised the work and critically revised the manuscript. All authors approved the submitted version.

Ethics approval and consent: Not applicable (analysis of published aggregate data).

Data availability: All data are derived from published sources cited in this article. The analysis script that reproduces every pooled estimate, heterogeneity statistic and sensitivity analysis reported here is provided as Supplementary File S2; the data extraction sheet is available from the corresponding author on request.

Supplementary material: Supplementary Table S1, database-specific search strings, search dates and per-database yields; Supplementary Figure S1, PRISMA 2020 flow diagram; Supplementary File S1, completed PRISMA 2020 checklist; Supplementary File S2, analysis script (Python).

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