A Systematic Literature Review of Studies Evaluating Clinical Outcomes in Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

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Objective

- To systematically identify clinical trials in patients with ATTR-CM and provide an overview of the available evidence on treatment efficacy and safety.

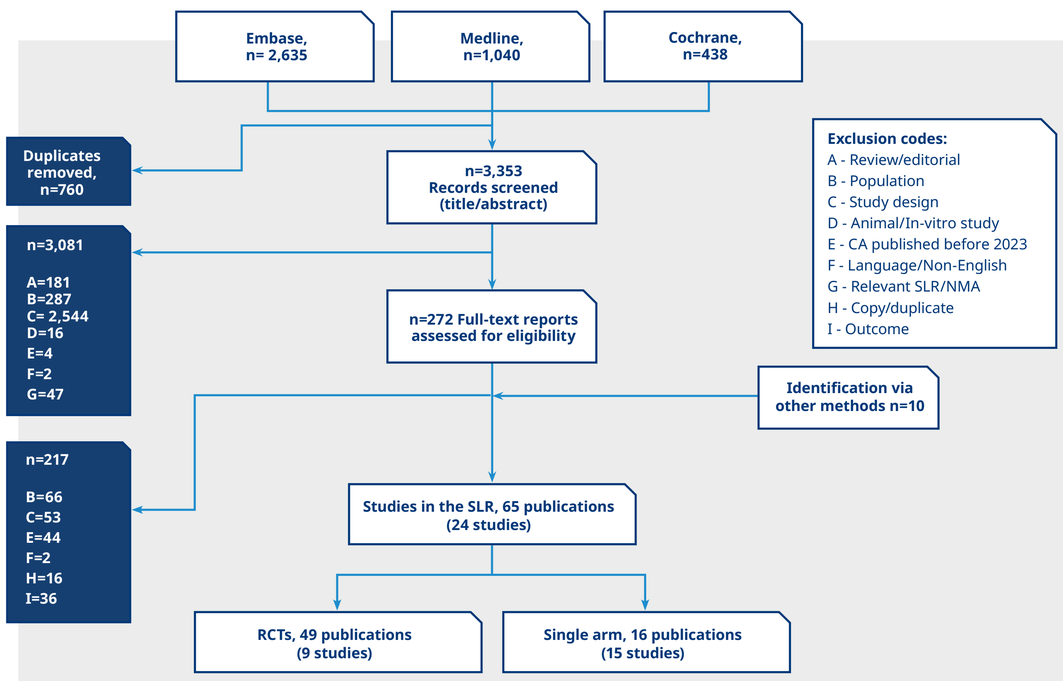
Introduction

- ATTR-CM is a rare, progressive, and often underdiagnosed condition caused by deposition of misfolded transthyretin protein as amyloid fibrils in the myocardium, leading to progressive cardiac dysfunction.[1]
- Although disease-modifying therapies and supportive care are available, substantial unmet need remains, particularly for therapies that can meaningfully alter disease progression.[1]
- Comparative efficacy and safety evidence across ATTR-CM treatments remains fragmented and inconsistently reported.

Methods

- The systematic literature review (SLR) was conducted in accordance with guidance from the Cochrane Collaboration,[2] the Centre for Reviews and Dissemination,[3] and the National Institute for Health and Care Excellence (NICE),[4] with reporting in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.
- Embase, MEDLINE, and the Cochrane Library were searched from database inception to February 2026; grey literature, including conference proceedings, was searched from 2023 onwards.
- Eligible studies were randomised controlled trials (RCTs) and single-arm clinical trials in patients with ATTR-CM, with no restriction by trial phase.
- Outcomes included composite clinical endpoints, mortality, hospitalisations, disease progression, functional capacity, cardiac biomarkers, patient-reported outcomes (PROs), and safety.
- Title/abstract and full-text screening were conducted by two independent reviewers; data extraction was conducted by one reviewer and independently verified by a second reviewer.
- The quality of RCTs and observational studies was assessed using the NICE single technology appraisal user guide[5] and the Downs and Black quality checklist,[6] respectively.

Figure 1. PRISMA flow diagram of study selection



Abbreviations: CA, conference abstract; NMA, network meta-analysis; OLE, open-label extension; RCT, randomised controlled trial; SLR, systematic literature review.

Results

Evidence base

- Sixty-five publications reporting 24 studies were included, comprising 49 publications from 9 RCTs and 16 publications from 15 single-arm studies (**Figure 1**).
- Multiple disease-modifying and supportive therapies were evaluated; tafamidis (n=4 studies), acoramidis (n=3), and doxycycline-based regimens (n=3) were among the most frequently studied interventions.

Clinical efficacy

- Placebo-controlled RCTs demonstrated favourable effects of several disease-modifying therapies across composite clinical outcomes (**Figure 2A**), mortality (**Figure 2B**), CV-related hospitalisation and event outcomes (**Figure 2C**), functional capacity (**Figure 3A**) and cardiac biomarkers (**Figure 3B**).[7-12]
- Other placebo-controlled RCT evidence not highlighted in **Figure 2** and **Figure 3** was heterogeneous in terms of patient populations, interventions, outcomes assessed, and follow-up durations.[13-15]
- Disease progression outcomes were heterogeneous and assessed using different definitions, limiting cross-study interpretation.[7,10,16]
  - In APOLLO-B, the odds of no disease progression at 12 months numerically favoured patisiran vs placebo (OR: 1.4; 95% CI: 0.77–2.55).[7,17]
  - In ATTRibute-CM, stable or improved disease at 30 months was reported in 52.1% of patients receiving acoramidis vs 43.1% receiving placebo.[10,18]
  - No clinical progression of cardiac involvement was reported at 12 months in a single-arm study of doxycycline plus tauroursodeoxycholic acid.[16]

Patient-reported outcomes

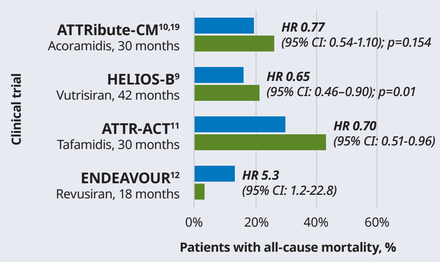
- Kansas City Cardiomyopathy Questionnaire (KCCQ)-based measures were the most commonly reported PROs (n=13 studies). In placebo-controlled RCTs, KCCQ-OS outcomes favoured active treatment versus placebo (**Figure 4**);[7-12,14,15,20-24] at 36 months, declines from baseline were smaller with vutrisiran (–9.7 vs –15.5) versus placebo; similarly, at 30 months, smaller declines were observed with acoramidis (–11.5 vs –21.4) and tafamidis (–3.9 vs –14.6) versus placebo, while patisiran was associated with a small improvement at 52 weeks (+0.3 vs –3.4 with placebo).[7,9-11]

Figure 2. Clinical outcomes generally favoured active treatment versus placebo, with revusiran in ENDEAVOUR a notable exception[7,9-11,†]

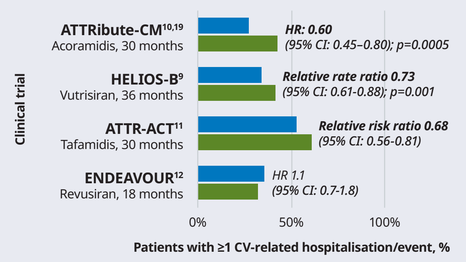
A) Composite clinical outcomes generally favoured active treatment versus placebo[7,9-11]

Trial	Outcome definition	Treatment comparison	Follow-up	Effect estimate	Interpretation
ATTRibute-CM[10]	Death from any cause, CV-related hospitalisation, change from baseline in NT-proBNP, and change from baseline in 6MWT	Acoramidis vs placebo	30 months	**Win ratio 1.8** (95% CI: 1.4–2.2); p<0.001	Favoured acoramidis
HELIOS-B[9]	Death from any cause and recurrent CV events (defined as hospitalisations for CV causes or urgent visits for HF)	Vutrisiran vs placebo	33–36 months	**HR 0.72** (95% CI: 0.56–0.93); p=0.01	Favoured vutrisiran
ATTR-ACT[11]	All-cause mortality and frequency of CV-related hospitalisations (hierarchical primary endpoint)	Tafamidis vs placebo	30 months	**Win ratio 1.70** (95% CI: 1.26–2.29); p<0.001	Favoured tafamidis
APOLLO-B[7]	Death from any cause, frequency of CV events, and change from baseline in 6MWT over 12 months	Patisiran vs placebo	52 weeks	**Win ratio 1.27** (95% CI: 0.99–1.61)	Not statistically significant

B) All-cause mortality was generally lower with active treatment than placebo, except with revusiran in ENDEAVOUR[9-12,19,‡,§]



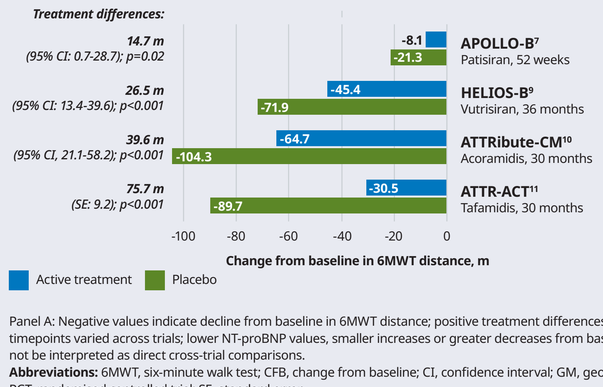
C) CV-related hospitalisation and event outcomes favoured acoramidis, vutrisiran and tafamidis versus placebo[9-12,19,‡,§,¶]



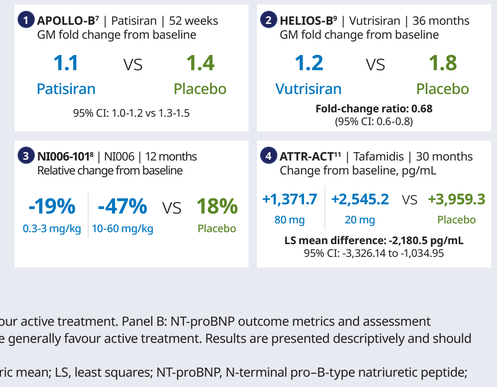
†Values are reported to up to two decimal places where available in the source publications.
‡Bold indicates statistically significant treatment effects (p<0.05 and/or 95% CI excluding the null value).
§Revusiran was evaluated in ENDEAVOUR, which was terminated early; not all planned efficacy endpoints were analysed.
¶CV-related endpoint definitions and effect measures varied across trials. ATTRibute-CM and ENDEAVOUR assessed time to first CV-related hospitalisation; HELIOS-B assessed recurrent CV events (CV hospitalisations and urgent HF visits); ATTR-ACT assessed the annualised frequency of CV-related hospitalisations. Effect estimates should not be directly compared across trials.
Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; NR, not reported; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RCT, randomised controlled trial.

Figure 3. Disease-modifying therapies generally slowed but did not fully prevent deterioration in functional capacity, while cardiac biomarker outcomes favoured active treatment versus placebo[7-11]

A) Decline in 6MWT distance occurred in both groups but was consistently smaller with active treatment[7,9-11]



B) NT-proBNP outcomes generally favoured active treatment versus placebo across trials[7-9,11]

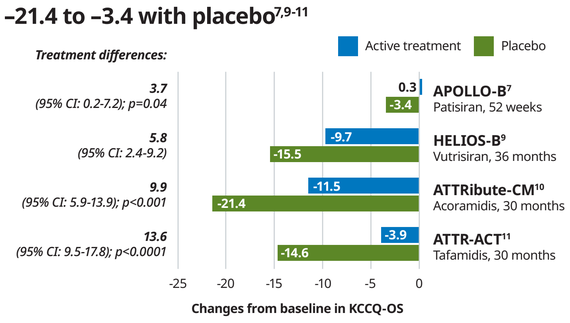


Panel A: Negative values indicate decline from baseline in 6MWT distance; positive treatment differences favour active treatment. Panel B: NT-proBNP outcome metrics and assessment timepoints varied across trials; lower NT-proBNP values, smaller increases or greater decreases from baseline generally favour active treatment. Results are presented descriptively and should not be interpreted as direct cross-trial comparisons.
Abbreviations: 6MWT, six-minute walk test; CFB, change from baseline; CI, confidence interval; GM, geometric mean; LS, least squares; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RCT, randomised controlled trial; SE, standard error.

Safety

- High adverse event rates were observed across both active-treatment and placebo groups (63.0%–100% vs 85.0%–98.9%, respectively), with the reported ranges also including studies not shown in Table 1; fatigue, dizziness, falls, and pain were among the most commonly reported AEs.[7-14] Table 1 presents AE data from key trials.
- Serious adverse event rates were similar to or lower with active treatment than placebo in most RCTs (0%–75.6% vs 12.0%–79.1%, respectively), with the reported ranges also including studies not shown in Table 1; revusiran in ENDEAVOUR was a notable exception (59.3% vs 51.5%, respectively) (**Table 1**).[7-14]

Figure 4. KCCQ-OS change from baseline ranged from –11.5 to 0.3 with active treatment versus –21.4 to –3.4 with placebo[7,9-11]



Positive values indicate improvement and negative values indicate deterioration from baseline. Treatment differences are LS mean differences where reported.
Abbreviations: CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; LS, least squares; RCT, randomised controlled trial.

Table 1. Adverse events were common across treatment groups, and the incidence of serious adverse events was generally similar or lower with active treatment[7,9-12]

Trial, intervention, timepoint	≥1 adverse event, % of patients		≥1 serious adverse event, % of patients	
	Active Treatment	Placebo	Active Treatment	Placebo
APOLLO-B[7] patisiran 52 weeks	91.0	94.0	34.0	35.0
ENDEAVOUR[12] revusiran 18 months	97.1	93.9	59.3	51.5
HELIOS-B[9] vutrisiran 36 months	99.0	98.0	62.0	67.0
ATTRibute-CM[10] acoramidis 30 months	98.1	97.6	54.6	64.9
ATTR-ACT[11] tafamidis 30 months	98.5	98.9	75.4	79.1

Conclusions

- Placebo-controlled RCTs demonstrated benefits with several disease-modifying therapies across clinical, functional, biomarker, and patient-reported outcomes, with active treatments slowing deterioration in functional capacity and health status versus placebo in several trials.
- Despite these relative benefits, declines from baseline in functional capacity and patient-reported health status generally persisted with active treatments, indicating residual disease burden.
- No head-to-head RCTs comparing active treatments were identified; comparative RCT evidence was limited to placebo-controlled trials.
- Overall, these findings support clinical benefit with current disease-modifying therapies but highlight a substantial unmet need for treatments that halt or reverse ATTR-CM disease progression.

References

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