INPLASY

Efficacy of Disease-Modifying Monotherapy and Combination Therapy for Transthyretin Amyloid Cardiomyopathy: Systematic Review and Meta-Analysis of Phase 3 Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202690037

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 September 2026 and was last updated on 8 September 2026.

INTRODUCTION

Review question / Objective In adults with ATTR-CM enrolled in phase 3 placebo-controlled randomized trials, what is the efficacy of disease-modifying therapy (transthyretin stabilizers or silencers) compared with placebo on all-cause mortality, 6-minute walk distance (6MWD), Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score and N-terminal pro–B-type natriuretic peptide (NT-proBNP), and does this efficacy differ between patients treated with monotherapy and patients treated in combination with a background transthyretin stabilizer?

Condition being studied Transthyretin amyloid cardiomyopathy, both wild-type (ATTRwt) and hereditary/variant (ATTRv) disease.

METHODS

Participant or population Inclusion: Only high-quality phase 3 randomized controlled trials (RCTs) investigating disease-modifying medications for ATTR-CM were included.
Exclusion: Non-randomized trials, including case-control studies, cohort studies, post-hoc analyses of RCTs, and phase 1 or 2 randomized trials investigating ATTR-CM. Studies investigating conditions other than ATTR-CM.

Intervention Disease-modifying agents for ATTR-CM, including stabilizers, silencers, or depleters.

Comparator Placebo.

Study designs to be included Randomized controlled trials.

Eligibility criteria Inclusion: Only high-quality phase 3 randomized controlled trials (RCTs)

investigating disease-modifying medications for ATTR-CM were included.
Exclusion: Non-randomized trials, including case-control studies, cohort studies, post-hoc analyses of RCTs, and phase 1 or 2 randomized trials investigating ATTR-CM. Studies investigating conditions other than ATTR-CM.

Information sources PubMed, MEDLINE, Embase and the Cochrane Library will be searched.

Main outcome(s) All-cause mortality at the longest available follow-up in each trial, analysed from event counts in each randomized arm.

Quality assessment / Risk of bias analysis The Cochrane risk-of-bias tool for randomized trials is applied by two reviewers independently across the five domains (randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result). Certainty of evidence for each outcome in each cohort is rated using GRADE.

Strategy of data synthesis Analyses are performed in three prespecified cohorts: (A) the overall randomized population; (B) the monotherapy stratum, defined by the absence of a transthyretin stabilizer at randomization; (C) the combination stratum, defined by ongoing transthyretin stabilizer use at randomization.

A random-effects model would be employed in the meta-analysis to compare pooled data from disease-modifying medications versus placebo.

Subgroup analysis The stabilizers and silencers based on different drug mechanisms, and monotherapy and combination therapy will be used to do the subgroup analysis.

Sensitivity analysis A fixed-effects model would be employed as sensitivity analysis.

Country(ies) involved Taiwan; United States of America; Italy.

Keywords transthyretin amyloid cardiomyopathy; disease-modifying therapy; transthyretin stabilizer; transthyretin silencer; meta-analysis; randomized controlled trialtransthyretin amyloid cardiomyopathy; disease-modifying therapy; transthyretin stabilizer; transthyretin.

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