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Trial-level associations of treatment-induced changes in NT-proBNP, patient-reported health status, and exercise capacity with clinical outcomes in transthyretin amyloid cardiomyopathy: a systematic review and trial-level meta-regression protocol

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ADMINISTRATIVE INFORMATION

Support - JSPS KAKENHI Grant Number 23K09577.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100054**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 October 2026 and was last updated on 12 October 2026.

INTRODUCTION

Review question / Objective To compare trial-level associations between treatment-induced changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP), Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS), and 6-minute walk distance (6MWD) and treatment effects on all-cause mortality, cardiovascular (CV) death, and recurrent CV events in phase 3 randomized trials of disease-modifying therapies for transthyretin amyloid cardiomyopathy (ATTR-CM).

Rationale NT-proBNP, patient-reported health status, and exercise capacity are commonly used to assess treatment response in ATTR-CM. However, the extent to which treatment-induced changes in these measures correspond to treatment effects on major clinical events at the trial level is uncertain. Previous analyses in broader heart failure populations included heterogeneous disease phenotypes and interventions. A disease-

specific evaluation of phase 3 ATTR-CM trials can clarify the relative strengths and limitations of these associations.

Condition being studied Transthyretin amyloid cardiomyopathy (ATTR-CM), a progressive infiltrative cardiomyopathy caused by myocardial deposition of misfolded transthyretin amyloid fibrils and associated with heart failure, functional impairment, and an increased risk of death and CV events.

METHODS

Participant or population Adults with ATTR-CM enrolled in phase 3 randomized controlled trials of disease-modifying therapies.

Intervention Disease-modifying pharmacological therapies evaluated in eligible phase 3 ATTR-CM trials, including transthyretin stabilizers and transthyretin-targeted RNA therapeutics. Eligible

treatment groups included tafamidis, patisiran, acoramidis, vutrisiran, and eplontersen.

Comparator Placebo. For ATTR-ACT, the tafamidis 20-mg and 80-mg groups were combined for comparison with placebo.

Study designs to be included Phase 3 randomized, placebo-controlled trials of disease-modifying pharmacological treatments for ATTR-CM.

Eligibility criteria Trials will be eligible if they (1) enroll adults with ATTR-CM; (2) evaluate a disease-modifying treatment in a phase 3 randomized, placebo-controlled design; (3) report an extractable treatment-induced change in at least one of NT-proBNP, KCCQ-OS, or 6MWD; and (4) provide a treatment-effect estimate for at least one of all-cause mortality, CV death, or recurrent CV events. Phase 2 trials, nonrandomized studies, and studies without the required trial-level biomarker, functional, or clinical outcome data will be excluded. Outcome-specific analyses will include only trials with the corresponding available effect estimates.

Information sources PubMed was searched on September 30, 2026. Information has been collected from primary trial reports and supplementary appendices, relevant secondary analyses, and publicly available regulatory or health technology assessment documents. Source data will be checked and verified as needed during data analysis.

Main outcome(s) The main outcomes will be the trial-level associations between treatment-induced changes in NT-proBNP, KCCQ-OS, or 6MWD and treatment effects on (1) all-cause mortality, (2) CV death, and (3) recurrent CV events, including CV-related hospitalizations and urgent heart failure visits as defined in individual trials. Mortality treatment effects will be expressed as hazard ratios, and recurrent CV event effects as rate ratios. Each association will be summarized by weighted trial-level R^2 , the regression slope (β), and corresponding statistical inference.

Quality assessment / Risk of bias analysis Risk-of-bias assessments have been tabulated for random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases using a Cochrane domain-based approach. Incomplete outcome data have been evaluated separately for clinical outcomes, NT-proBNP, KCCQ-OS, and 6MWD. For response measures, observed-data

availability of at least 80% is considered low risk, 70–79% unclear risk, and less than 70% high risk where the denominator is available. Prespecified imputation and repeated-measures methods are considered when interpreting the judgments. Where the number of evaluable observations cannot be established, risk is classified as unclear. Trial-specific judgments will be verified before finalization.

Strategy of data synthesis Trial-level associations are being evaluated using random-effects meta-regression. Treatment effects on all-cause mortality and CV death will be modeled as log hazard ratios; treatment effects on recurrent CV events will be modeled as log rate ratios. The NT-proBNP predictor will be the natural logarithm of the treatment-to-placebo ratio of relative changes from baseline, $\ln(R)$, where $R = (\text{active follow-up} / \text{active baseline}) / (\text{placebo follow-up} / \text{placebo baseline})$, or the corresponding directly reported adjusted between-group relative-change ratio. KCCQ-OS and 6MWD predictors will be the between-group differences in change from baseline. Between-trial variance (τ^2) will be estimated by restricted maximum likelihood (REML). Weighted linear regressions will use inverse-variance weights $1/(\text{SE}^2 + \tau^2)$; weighted R^2 , β , and nominal P values will be reported. Given the small number of trials, modified Knapp–Hartung small-sample-corrected 95% confidence intervals and P values will also be calculated using a t distribution with $k - 2$ degrees of freedom and a variance scaling factor constrained to be at least 1. Nine predictor–outcome combinations will be assessed where data are available. Findings will be interpreted as exploratory and hypothesis-generating.

Subgroup analysis No subgroup meta-regression will be performed because the number of eligible phase 3 trials is expected to be small.

Sensitivity analysis No leave-one-out or trial-exclusion sensitivity analyses are planned because few trials are expected to contribute to each outcome-specific model. The effect of the small number of trials on statistical inference will instead be addressed by reporting modified Knapp–Hartung-adjusted 95% confidence intervals and P values alongside nominal weighted-regression results. This correction will not be described as a separate sensitivity analysis.

Country(ies) involved Japan.

Keywords ransthyretin amyloid cardiomyopathy; NT-proBNP; Kansas City Cardiomyopathy

Questionnaire; Six-minute walk distance; Meta-regression.

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