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NT-proBNP changes and clinical outcomes in contemporary heart failure trials: A trial-level meta-regression analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 February 2026 and was last updated on 28 February 2026.

INTRODUCTION

Review question / Objective To re-examine the association between treatment-induced changes specifically in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and major clinical outcomes in recent, landmark phase 3 randomized controlled trials (RCTs) of chronic heart failure (HF). By assessing this trial-level association in the modern therapeutic era, this study aims to evaluate the true potential of NT-proBNP as a robust candidate intermediate endpoint that could provide supportive evidence for therapeutic efficacy and streamline future HF drug development.

Condition being studied Chronic heart failure.

METHODS

Participant or population Patients with chronic heart failure.

Intervention Pharmacological interventions for chronic heart failure.

Comparator Control treatments (e.g., placebo or active control) utilized in the included phase 3 RCTs.

Study designs to be included Phase 3 randomized controlled trials (RCTs).

Eligibility criteria Eligible studies are RCTs that met all of the following criteria: (1) adult patients with chronic HF were enrolled; (2) pharmacological interventions for chronic HF were evaluated; (3) baseline and post-treatment changes in NT-proBNP were reported; and (4) clinical outcomes, including all-cause mortality, cardiovascular death, or HF hospitalization, were reported.
Trials of acute HF, pilot studies, phase 2 trials, trials restricted to specific phenotypes (e.g., HF with anemia), and non-English language articles are excluded. We strictly restricted our analysis to phase 3 trials to ensure clinical comparability and

minimize heterogeneity in treatment effects across the included trials.

Information sources Chronic HF trials published until January 31, 2026, will be identified using PubMed and Scopus. The literature search will also be conducted by manual screening of reference lists of relevant reviews and retrieved articles.

Main outcome(s) The primary clinical outcomes of interest are all-cause mortality, cardiovascular death, and HF hospitalization.

Additional outcome(s) The composite of cardiovascular death and HF hospitalization.

Quality assessment / Risk of bias analysis The risk of bias for each included RCT will be assessed using the Cochrane Collaboration's Risk of Bias tool across seven domains. Two reviewers (HF and TG) will independently evaluate the studies. For incomplete outcome data, the risk of bias is defined as high for primary endpoints if the loss to follow-up is ≥ 5%. For NT-proBNP data, the risk is categorized as low (≥ 80% attainment), unclear (70–79%), or high (< 70%). Discrepancies will be resolved by consensus.

Strategy of data synthesis The associations between treatment-induced changes in NT-proBNP and treatment effects on the clinical outcomes will be assessed at the trial level using weighted random-effects meta-regression analyses conducted on the log HR scale. For the primary analysis, the treatment-induced change in NT-proBNP is calculated as the between-group difference in the percentage change from baseline to follow-up. As a secondary analysis, the between-group difference in changes based on geometric means will be utilized for trials where reported. Each trial will be plotted as a single point on a bubble plot and weighted by the inverse variance of the log HR. The coefficient of determination (R2) will be calculated to quantify the proportion of variability. Heterogeneity will be assessed using the I2 statistic and tau2. Values of I2 75% high. All analyses will be performed using Stata version 19, and a two-sided P value of <0.05 is considered statistically significant.

Subgroup analysis Not prespecified in this protocol..

Sensitivity analysis A leave-one-out sensitivity analysis will be performed to assess the influence of individual trials on the overall results of the meta-regression models.

Country(ies) involved Japan.

Keywords Heart failure; randomized; natriuretic peptide; meta-regression.

Contributions of each author
Author 1 - Hidekatsu Fukuta.
Author 2 - Toshihiko Goto.