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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**Support** - JSPS KAKENHI Grant Number 23K09577.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202620086**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 21 September 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 phase 3 randomized controlled trials (RCTs) that meet all of the following criteria: (1) adult patients with chronic heart failure were enrolled; (2) a pharmacological intervention for chronic heart failure was evaluated; (3) baseline and post-treatment NT-proBNP data sufficient to estimate the treatment effect on NT-proBNP were reported; and (4) at least one relevant clinical outcome, including all-cause mortality, cardiovascular death, heart failure hospitalization, or a composite of cardiovascular death and heart failure events, was reported.

Trials of acute heart failure, pilot studies, phase 2 trials, and non-English language articles are excluded. Trials enrolling clinically defined or phenotype-enriched chronic heart failure populations are not excluded solely on the basis of the enrolled phenotype, provided that the other eligibility criteria are fulfilled. The influence of phenotype-enriched trials will be examined in sensitivity analyses.

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 $\geq 5\%$. For NT-proBNP data, the risk is categorized as low ($\geq 80\%$ 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 clinical outcomes will be assessed at the trial or treatment-comparison level using weighted random-effects meta-regression analyses conducted on the log hazard ratio scale.

The treatment-induced change in NT-proBNP will be expressed using a relative change measure comparing the treatment and control groups. Where sufficient data are available, this will be calculated as the ratio of the relative change from baseline in the treatment group to that in the control group, and its natural logarithm will be used in the meta-regression analysis.

Each eligible trial or treatment comparison will contribute one data point. The coefficient of determination (R^2) will be calculated to quantify the trial-level association. Heterogeneity will be assessed using appropriate measures. A two-

sided P value of <0.05 will be considered statistically significant.

Subgroup analysis Exploratory subgroup analyses will be performed according to heart failure phenotype, including heart failure with reduced ejection fraction and heart failure with preserved or mildly reduced ejection fraction, when sufficient trials are available. These subgroup analyses were not prespecified in the original registration and will therefore be regarded as exploratory.

Sensitivity analysis Sensitivity analyses will include leave-one-out analyses to assess the influence of individual trials or treatment comparisons on the overall meta-regression results.

Additional exploratory sensitivity analyses will assess the robustness of the findings after exclusion of clinically or mechanistically distinct groups of trials. These analyses will include exclusion of phenotype-enriched trials and selected therapeutic classes, including SGLT2 inhibitors, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and selected renin-angiotensin system-targeting therapies. Additional analyses may also evaluate the influence of comparisons originating from the same parent trial or sharing a common control group.

Sensitivity analyses based on treatment class or heart failure phenotype were introduced during the ongoing analysis and were not prespecified in the original protocol; these analyses will therefore be considered exploratory.

Country(ies) involved Japan.

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

Contributions of each author

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