Serial Assessment of High-Sensitivity Cardiac Troponin and the Effect of Dapagliflozin in Patients with Heart Failure with Reduced Ejection Fraction: An Analysis of the DAPA-HF Trial

Running title: *Berg et al.; Serial Assessment of Cardiac Troponin in DAPA-HF*

David D. Berg, MD, MPH[1]; Kieran F. Docherty, MBChB[2]; Naveed Sattar, FMedSci[2]; Petr Jarolim, MD, PhD[3]; Paul Welsh, PhD[2]; Pardeep S. Jhund, MBChB[2]; Inder S. Anand, MD, DPhil[4]; Vijay Chopra, MD[5]; Rudolf A. de Boer, MD, PhD[6]; Mikhail N. Kosiborod, MD[7]; Jose C. Nicolau, MD, PhD[8]; Eileen O'Meara, MD[9]; Morten Schou, MD, PhD[10]; Ann Hammarstedt, MD, PhD[11]; Anna-Maria Langkilde, MD, PhD[11]; Daniel Lindholm, MD, PhD[11]; Mikaela Sjöstrand, MD, PhD[11]; John J.V. McMurray, MD[2]; Marc S. Sabatine, MD, MPH[1]; David A. Morrow, MD, MPH[1]

[1]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland; [3]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]University of Minnesota, Minneapolis, MN; [5]Max Superspeciality Hospital, Saket, New Delhi, India; [6]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands ; [7]Saint Luke's Mid America Heart Institute, University of Missouri, Kansas City, MO; [8]Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil; [9]Department of Cardiology, Montreal Heart Institute and Université de Montréal, Montreal, Canada; [10]Department of Cardiology, Herlev and Gentofte University Hospital, Herlev, Denmark; [11]AstraZeneca, Goteborg, Sweden.

Address for Correspondence:

David D. Berg, MD, MPH
TIMI Study Group
Brigham and Women's Hospital
60 Fenwood Road, Suite 7022
Boston, MA 02115
Tel : 617-278-0145
Fax: 617-734-7329
Email: dberg1@bwh.harvard.edu

*This article is published in its accepted form, it has not been copyedited and has not appeared in an issue of the journal. Preparation for inclusion in an issue of ***Circulation*** involves copyediting, typesetting, proofreading, and author review, which may lead to differences between this accepted version of the manuscript and the final, published version.
**This work was presented AHA Scientific Sessions 2021, November 13-November 15, 2021.
***This manuscript was sent to Dr. Allan Jaffe, Guest Editor for review by expert referees, editorial decision, and final disposition.

Abstract

Background: Circulating high-sensitivity cardiac troponin T (hsTnT) predominantly reflects myocardial injury, and higher levels are associated with a higher risk of worsening heart failure (HF) and death in patients with HF with reduced ejection fraction (HFrEF). Less is known about the prognostic significance of changes in hsTnT over time, the effects of dapagliflozin on clinical outcomes in relation to baseline hsTnT levels, and the effect of dapagliflozin on hsTnT levels.
Methods: DAPA-HF was a randomized, double-blind, placebo-controlled trial of dapagliflozin (10 mg daily) in patients with NYHA class II-IV symptoms and left ventricular ejection fraction ≤40% (median follow-up = 18.2 months). hsTnT (Roche Diagnostics) was measured at baseline in 3,112 patients and at 1 year in 2,506 patients. The primary endpoint was adjudicated worsening HF or cardiovascular death. Clinical endpoints were analyzed according to baseline hsTnT and change in hsTnT from baseline to 1 year. Comparative treatment effects on clinical endpoints with dapagliflozin vs. placebo were assessed by baseline hsTnT. The effect of dapagliflozin on hsTnT was explored.
Results: Median baseline hsTnT concentration was 20.0 (25^{th}-75^{th} percentile, 13.7 to 30.2) ng/L. Over 1 year, 67.9% of patients had a ≥10% relative increase or decrease in hsTnT concentrations, and 43.5% had a ≥20% relative change. A stepwise gradient of higher risk for the primary endpoint was observed across increasing quartiles of baseline hsTnT concentration (adjusted hazard ratio [aHR] Q4 vs. Q1, 5.10; 95% CI, 3.67-7.08). Relative and absolute increases in hsTnT over 1 year were associated with higher subsequent risk of the primary endpoint. The relative reduction in the primary endpoint with dapagliflozin was consistent across quartiles of baseline hsTnT (p-interaction = 0.55), but patients in the top quartile tended to have the greatest absolute risk reduction (absolute risk difference, 7.5%; 95% CI, 1.0% - 14.0%). Dapagliflozin tended to attenuate the increase in hsTnT over time compared to placebo (relative least squares mean reduction, -3% [-6% to 0%]; p=0.076).
Conclusions: Higher baseline hsTnT and greater increase in hsTnT over 1 year are associated with worse clinical outcomes. Dapagliflozin consistently reduced the risk of the primary endpoint, irrespective of baseline hsTnT levels.
Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique Identifier: NCT03036124.

Key Words: heart failure, clinical trials, cardiac troponin, biomarkers, sodium-glucose cotransporter-2 inhibitors

Non-standard Abbreviations and Acronyms

ARR = absolute risk reduction
CEC = clinical events committee
DAPA-HF = Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure
EMPEROR-Reduced = EMPagliflozin outcomE tRial in patients with chrOnic hearRt failure with Reduced ejection fraction
GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca - Heart Failure
hsTnT = high-sensitivity cardiac troponin T
KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire - total symptom score
LoQ = limit of quantitation
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
SGLT2i = sodium-glucose cotransporter 2 inhibitor
TIMI = Thrombolysis in Myocardial Infarction
URL = upper reference limit
Val-HeFT = Valsartan Heart Failure Trial
VICTORIA = VerICiguaT glObal study in subjects with heart failure with Reduced ejectIon frAction

Clinical Perspective

What is new?

- In this biomarker substudy of patients with heart failure with reduced ejection fraction (HFrEF) from the DAPA-HF trial, increases in high-sensitivity cardiac troponin T (hsTnT) over a one-year time interval were highly predictive of subsequent risk of worsening heart failure and cardiovascular death.
- The effect of dapagliflozin on the primary endpoint was consistent irrespective of baseline hsTnT concentration with no evidence of attenuated treatment benefit in those with very high hsTnT concentrations.

What are the clinical implications?

- In patients with HFrEF, even modest increases in cardiac troponin over the course of a year provide robust prognostic information about subsequent risk of clinical deterioration.
- Serial measurement of cardiac troponin may provide objective assessment of clinical trajectory, which might in turn be used to inform clinical decision-making.

Introduction

Chronic release of disrupted myofibrillar elements, including cardiac troponin, occurs in patients with chronic heart failure (HF) even in the absence of clinically evident coronary artery disease.[1] Multiple mechanisms may contribute to myocardial injury in HF, including subendocardial ischemia, hemodynamic stress, altered calcium handling, neurohormonal activation, and inflammation.[2, 3] Notably, in patients with chronic HF, both the presence and magnitude of cardiac troponin elevation are strong predictors of adverse clinical outcomes, including death and hospitalization.[4-6] However, less is known about the prognostic significance of changes in cardiac troponin over time in this patient population. Moreover, the interaction between cardiac troponin concentration and the efficacy of established and emerging HF therapies may be relevant to personalizing management of chronic HF.

In the DAPA-HF (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) trial, treatment with the sodium-glucose cotransporter 2 inhibitor (SGLT2i) dapagliflozin significantly reduced cardiovascular death or worsening HF in ambulatory patients with HF with reduced ejection fraction (HFrEF) (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.65-0.85; $p<0.001$).[7] Since cardiac troponin identifies patients with HFrEF at elevated cardiovascular risk, it may be useful for stratifying the efficacy of HF therapies like dapagliflozin according to disease severity. Given concerns about a potential attenuation of treatment benefit of SGLT2i in patients with more advanced HF, as reflected by New York Heart Association (NYHA) functional class, understanding this relationship is of particular interest for this pharmacotherapeutic class.[8] In a recent analysis of high-sensitivity cardiac troponin T (hsTnT) measured at baseline in the EMPEROR-Reduced trial, the effect of empagliflozin on cardiovascular death or hospitalization for heart failure was generally consistent irrespective of

baseline hsTnT concentration when hsTnT was modeled categorically but appeared to be attenuated in patients with higher hsTnT concentrations when hsTnT was modeled continuously.[9]

Because of serial blood sampling conducted during the trial, DAPA-HF is an ideal cohort for defining the prognostic performance of cardiac troponin in a well-characterized population of ambulatory patients with HFrEF. Moreover, DAPA-HF provides the opportunity to assess the relationship between changes in cardiac troponin over time and important HF endpoints. Finally, this nested prospective biomarker study affords an opportunity to evaluate the efficacy of dapagliflozin on clinical endpoints in relation to circulating cardiac troponin concentration and the effect of dapagliflozin on cardiac troponin over time.

Methods

Study Population

DAPA-HF was a multinational, randomized, double-blind, placebo-controlled trial of the SGLT2i dapagliflozin (10 mg daily) in 4,744 patients with HFrEF followed for a median of 18.2 months. The study enrolled patients with NYHA functional classes II-IV and a left ventricular ejection fraction (LVEF) ≤40%, who in the view of the investigators were optimally treated with pharmacological and device therapy according to local guidelines.

Study participants were also required to have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/ml, or ≥400 pg/ml if hospitalized for HF within the previous 12 months. Patients with atrial fibrillation or atrial flutter were required to have an NT-proBNP concentration ≥900 pg/ml, irrespective of prior HF hospitalization. Notable exclusion criteria included HF hospitalization in the 4 weeks prior to enrollment, myocardial infarction

(MI) or coronary revascularization in the 3 months prior to enrollment, and estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73 m^2 (or rapidly declining kidney function). A full list of inclusion and exclusion criteria has been reported.[10]

Participation in a prospective biomarker substudy was offered to all enrolled patients in countries where regulations allowed. The ethics committee at each participating institution approved the protocol. Written informed consent was obtained from all patients. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussion.

Biomarkers

Venous blood samples were collected on the day of randomization and at 12 months. Samples were collected in EDTA anticoagulant tubes and isolated plasma was stored at −20°C or colder until shipped on dry ice to the central repository, where it was stored at −80°C or colder until thawed for analysis. hsTnT was measured (TIMI Clinical Trials Laboratory, Boston, MA) with an Elecsys immunoassay on the Cobas e 601 (Roche Diagnostics). The limit of quantitation (LoQ) of the assay is 6 ng/L and the 99th percentile upper reference limit (URL) used in our laboratory is 14 ng/L. For this analysis, patients with hsTnT concentrations <6.0 ng/L were assigned a value of 3.0 ng/L (i.e., half the LoQ). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured in a central laboratory (Covance) using an Elecsys immunoassay (Roche Diagnostics) during conduct of the trial.

Clinical endpoints

The primary endpoint in the trial was the composite of worsening HF (unplanned HF hospitalization or urgent HF visit resulting in intravenous therapy for HF) or cardiovascular death, whichever occurred first. Secondary endpoints for the present analysis included the

occurrence of HF hospitalization or cardiovascular death, HF hospitalization, cardiovascular death, sudden cardiac death, death due to heart failure or cardiogenic shock, all-cause mortality, total HF hospitalizations and cardiovascular death, the slope of change from baseline in eGFR over time, and change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS). Due to the small number of clinical events occurring beyond one year of follow-up, only the primary endpoint was assessed in the landmark analyses described below. All events were centrally adjudicated by a blinded clinical events committee (CEC) using standard definitions.

Statistical analyses

Baseline characteristics were summarized according to baseline hsTnT concentration (stratified as greater than or equal to, or less than the median). Categorical variables are shown as counts and percentages, and continuous variables as means (standard deviations) or medians (25^{th}-75^{th} percentiles), as appropriate. Differences in the baseline characteristics were evaluated with the Pearson χ^2 test for categorical variables and student T test or Wilcoxon rank sum test for continuous variables, as appropriate.

Time-to-event endpoints were analyzed according to baseline hsTnT concentration using Cox proportional hazards models, stratified according to type 2 diabetes mellitus (T2DM) status, history of HF hospitalization, and treatment-group assignment as fixed-effect factors as described in the trial statistical analysis plan. In the models for all-cause mortality, history of HF hospitalization was not included. Adjusted estimates of the association between baseline hsTnT were assessed using Cox models that included age, sex, eGFR, LVEF, baseline NT-proBNP (log-transformed), and principal cause of heart failure (i.e., ischemic vs. non-ischemic) as additional covariates. These analyses were performed with hsTnT modeled both as a categorical

variable (quartiles) and continuous variable (log-transformed based on the right-skewed distribution; hazard ratios [HR] reported per 1 integer unit). The proportional hazards assumption was confirmed to be valid by examining log(-log(Survival)) plots. The adjusted association between baseline hsTnT (log-transformed) and risk of the primary endpoint is also displayed using an adjusted restricted cubic spline. In addition, incidence of the primary endpoint is described according to categorical subgroups defined by baseline quartiles of hsTnT and baseline quartiles of NT-proBNP. The slope of change in eGFR over time was examined using a repeated-measures mixed-effect model, adjusting for baseline value, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient with an unstructured covariance structure as previously described.[11] KCCQ-TSS outcomes are reported as the proportions of patients with a clinically important improvement (i.e., increase in KCCQ-TSS ≥5 points) and clinically important deterioration (i.e., decrease in KCCQ-TSS ≥5 points) in symptoms from baseline to 8 months. These data were analyzed according to baseline hsTnT quartiles using a logistic regression model according to methods previously described.[12] Total (including recurrent) events were analyzed using a semiparametric proportional-rates model. These univariable and multivariable analyses were repeated with the use of absolute hsTnT values at 12 months, as well as absolute and relative change in hsTnT values from randomization to 12 months. Patients who experienced an MI or worsening HF episode within 30 days prior to the 12-month blood draw were excluded from those analyses (n=23). Since there are no established thresholds for change in hsTnT concentration in this setting, we evaluated continuous relationships and several absolute and relative change thresholds according to the distribution of the hsTnT data. Analogous to the baseline hsTnT data, the relationships of both 12-month hsTnT concentration and change in hsTnT concentration to subsequent risk of the primary endpoint are

displayed using adjusted restricted cubic splines. In addition, the relationship of change in NT-proBNP concentration from baseline to 8 months to subsequent risk of the primary endpoint was displayed using an adjusted restricted cubic spline, and the incidence of the primary endpoint was described according to categorical subgroups defined by ≥20% increase in hsTnT, ≥20% increase in NT-proBNP, neither, or both. All analyses using the 12-month hsTnT concentration or change in hsTnT concentration are landmark analyses beginning at the 12-month post-randomization visit.

To test for heterogeneity in the treatment effect of dapagliflozin vs. placebo on the primary and secondary endpoints according to baseline hsTnT quartiles, a randomized treatment-by-baseline hsTnT quartile interaction term was included as a covariate in each of the models described above. The effect of dapagliflozin on the primary endpoint was also examined according to continuous hsTnT as a fractional polynomial. To compare absolute differences in the treatment effect of dapagliflozin vs. placebo on the primary endpoint according to baseline hsTnT, absolute risk reduction (ARR) was calculated by subtracting the event rates in patients randomized to dapagliflozin from the event rates in patients randomized to placebo across each baseline hsTnT quartile.

The difference between randomized treatment groups in the change in hsTnT from baseline to 12 months was analyzed using an analysis of covariance model with treatment-group assignment as a fixed-effect factor and baseline hsTnT as a covariate. Results are reported as the ratio of geometric means with 95% confidence intervals.

Results

Distribution of troponin values

Baseline hsTnT values were available in 3,112 patients, and 12-month values were available in 2,506 patients. The median baseline hsTnT concentration was 20.0 (25^{th}-75^{th} percentile, 13.7 to 30.2) ng/L (Supplemental Figure I). More than 98% of patients had a baseline hsTnT ≥6 ng/L and nearly three-fourths had a baseline hsTnT level above the 99^{th} percentile URL (hsTnT ≥14 ng/L). The median hsTnT concentration at 12 months was 19.5 (13.0 to 29.7) ng/L (Supplemental Figure I). Descriptive statistics of the distributions of hsTnT at baseline and 12 months stratified by treatment arm are summarized in Supplemental Table I.

Among patients with available samples at both timepoints and no MI or worsening HF episode within 30 days prior to the 12-month visit (n=2,400), the median change in hsTnT from baseline to 12 months was small (+0.31; 95% CI, -2.77 to +3.61 ng/L). However, examination of the distribution of changes in hsTnT from baseline to 12 months indicates that hsTnT increased or decreased in the majority of patients. Specifically, 67.9% had a ≥10% relative change and 43.5% had a ≥20% relative change in hsTnT. Considering absolute concentrations, 64.7% had a ≥2 ng/L change and 29.3% had a ≥6 ng/L change in hsTnT (Supplemental Figure II).

Baseline characteristics

Baseline characteristics stratified by median baseline hsTnT are summarized in Table 1. Baseline characteristics of patients in the biomarker substudy vs. full trial cohort and of patients with serial samples vs. baseline samples only are summarized in Supplemental Table II and Supplemental Table III, respectively. Patients with higher baseline hsTnT values were older, were more likely to be male, and had a higher prevalence of atrial fibrillation and T2DM (each $p<0.001$). Higher baseline hsTnT values were associated with worse baseline functional status,

as evidenced by lower KCCQ-TSS scores and a higher proportion of patients with NYHA class III-IV symptoms (each $p<0.001$). Baseline hsTnT was positively correlated with NT-proBNP (Spearman correlation coefficient [r] = 0.36; $p<0.001$) and inversely correlated with eGFR (r = -0.35; $p<0.001$).

Relationship of cardiac troponin and clinical endpoints

Over a median follow-up of 18.2 months, there was a stepwise gradient of higher risk for the primary endpoint across increasing quartiles of baseline hsTnT concentration (Q1: 6.3%; Q2: 13.9%; Q3: 22.4%; Q4: 31.2%; p-trend <0.001; Figure 1). In adjusted models, the relationship between baseline hsTnT and risk of cardiovascular death or worsening HF remained highly significant, with a >3-fold higher risk between the top and bottom quartiles (adjusted HR 3.44; 95% CI, 2.46-4.82; Table 2). The risk gradient was also observed for all secondary endpoints, including in the adjusted models (p-trend <0.001 for all; Table 2 and Supplemental Figure III). The relationships between continuous baseline hsTnT and clinical endpoints are shown in Supplemental Table IV and Supplemental Figure IV.

When baseline hsTnT and NT-proBNP were analyzed collectively, there was a significant gradient of risk for the primary endpoint across increasing quartiles of baseline hsTnT within each quartile of baseline NT-proBNP (p-trend <0.01 for each). Moreover, there was >10-fold difference in risk between patients in the highest quartile of both hsTnT and NT-proBNP as compared to those in the bottom quartile of both hsTnT and NT-proBNP (43.7% vs. 4.3%; adjusted HR 12.53, 95% CI 6.75-23.25; Figure 2).

Examining hsTnT concentrations at a fixed timepoint of 12 months post-randomization, there was a continued graded relationship between hsTnT concentration and subsequent risk of the primary endpoint, including in adjusted analyses (Supplemental Figure V).

Prognostic significance of change in cardiac troponin over 12 months

The change in troponin over time was evaluated using the $\log_2$-transformed ratios of 12-month hsTnT concentration to baseline concentration, which was analyzed as a continuous variable using adjusted restricted cubic splines. Increases in hsTnT concentration over time (ratios >0) were significantly associated with higher subsequent risk of the primary endpoint, whereas decreases over time (ratios <0) were associated with only a non-significant trend towards lower subsequent risk of the primary endpoint (Figure 3). Based on the adjusted restricted cubic spline, 20%, 50%, and 100% increases in circulating hsTnT were associated with HRs of 1.64 (95% CI 1.25-2.24), 2.29 (95% CI 1.46-3.58), and 2.43 (95% CI 1.57-3.78), respectively, for subsequent risk of the primary endpoint.

When analyzed categorically according to either relative or absolute change from baseline, there was a consistent pattern of higher subsequent risk of the primary endpoint with increasing hsTnT concentration over the first year (Figure 3). Notably, in patients with lower baseline hsTnT values (i.e., below the median), increases in hsTnT were associated with higher risk and decreases in hsTnT appeared to be associated with lower risk of the primary endpoint. In contrast, in patients with higher baseline hsTnT values (i.e., above or at the median), risk increased with increases in hsTnT but did not appear to diminish with decreases in hsTnT (Supplemental Figure VI).

Finally, increases in NT-proBNP concentration from baseline to 8 months were also significantly associated with higher subsequent risk of the primary endpoint (Supplemental Figure VII). Furthermore, patients with ≥20% increases in both hsTnT (from baseline to 12 months) and NT-proBNP (from baseline to 8 months) had higher subsequent rates of the primary

endpoint than did patients with a ≥20% increase in only one biomarker (Supplemental Figure VII).

Efficacy of dapagliflozin as a function of baseline troponin

In the overall trial cohort (n=4,744), dapagliflozin reduced the primary endpoint by 26% (HR 0.74, 95% CI 0.65-0.85).[7] Among patients with available baseline hsTnT data (n=3,112), dapagliflozin reduced the primary endpoint by 23% (HR 0.77, 95% CI 0.65-0.91). The relative treatment effect of dapagliflozin vs. placebo was consistent across baseline concentrations of hsTnT, both when analyzed according to quartiles (p-interaction = 0.55) and as a continuous variable (p-interaction = 0.29) (Figure 4). Furthermore, there was no heterogeneity in the relative treatment effect of dapagliflozin vs. placebo for any of the secondary endpoints (Supplemental Table V). Owing to their higher baseline risk, patients in the top quartile of baseline hsTnT concentration appeared to experience the greatest numeric ARR in the primary endpoint (absolute risk difference, 7.5%, 95% CI 1.0% - 14.0%; Figure 4).

Effect of dapagliflozin on cardiac troponin over 12 months

There was a non-significant trend towards attenuation of the increase in hsTnT from baseline to 12 months in patients treated with dapagliflozin vs. placebo (relative least squares mean reduction, -3% [-6% to 0%]; p=0.076).

Discussion

In this biomarker substudy of patients with HFrEF from the DAPA-HF trial, nearly all patients had detectable myocardial injury and approximately three-quarters had a baseline hsTnT concentration that exceeded the 99th percentile URL (hsTnT ≥14 ng/L). We found a strong, stepwise increase in the risk for key cardiovascular endpoints with higher baseline concentration

of hsTnT. Additionally, we found that the majority of patients with HFrEF had dynamic hsTnT concentrations over 1 year, and that greater increase in hsTnT over 1 year was associated with higher risk for the primary endpoint of cardiovascular death or worsening heart failure. Reassuringly, the effect of dapagliflozin on the primary endpoint was consistent irrespective of baseline hsTnT concentration with no evidence of attenuated treatment benefit in those with very high hsTnT concentrations. Finally, we found that dapagliflozin tended to attenuate increase in hsTnT over time (p=0.076), suggesting possible diminution of myocardial injury with SGLT2 inhibition.

Cardiac troponin in the assessment of heart failure patients

Current guidelines strongly recommend (class I) measurement of cardiac troponin in hospitalized HF patients and in patients with specific cardiomyopathies (e.g., amyloidosis), but only weakly endorse their potential value (class IIb) in patients with chronic HF.[13, 14] Our findings add to the evidence base supporting a potential role for hsTnT testing in ambulatory patients with HFrEF. Specifically, our results in this large, well-characterized population extend prior work showing a direct monotonic relationship between circulating cardiac troponin concentration and risk of important clinical endpoints, including cardiovascular death and worsening heart failure, in ambulatory patients with HFrEF.[5, 6] Our results also further prior work showing that the prognostic value of cardiac troponin is independent of and incremental to the prognostic value of natriuretic peptides with respect to forecasting future risk of adverse HF events.[15, 16]

Importantly, our results demonstrate that changes in hsTnT over a one-year time interval are also highly predictive of subsequent risk in patients with chronic HF. Prior analyses have explored the association of serial changes in cardiac troponin with clinically important outcomes; however, all of these studies have either been in small cohorts[17] or have focused on short-term

changes in cardiac troponin, either over the course of days during HF hospitalization[18, 19] or over the course of several months in ambulatory HF patients.[20] Among patients enrolled in the Val-HeFT and GISSI-HF trials, for example, short-term changes in hsTnT (i.e., over 3-4 months) were associated with adverse HF events. Building on these previous analyses, our study is the first large analysis to demonstrate that changes in hsTnT over a longer time horizon are highly predictive of risk of cardiovascular death and worsening HF events in ambulatory patients with HFrEF, even in a well-treated contemporary cohort. Moreover, we describe the combined prognostic significance of increases in both hsTnT and NT-proBNP over time, underscoring the complementary nature of assessing these two biomarkers serially.

These findings have several implications. First, they reinforce the prognostic value of cardiac troponin in ambulatory patients with HFrEF. Second, they provide strong evidence that even modest increases in cardiac troponin over the course of a year provide robust prognostic information about subsequent risk of clinical deterioration, perhaps by offering insight into myocardial disease progression. Third, they suggest that serial measurement of cardiac troponin may provide objective assessment of clinical trajectory, which might in turn be used to inform clinical decision-making. Continued research in this area could ultimately show that changes in cardiac troponin might represent an appropriate trigger for adding second-line medical therapies beyond the four pillars of contemporary pharmacological management of HFrEF (i.e., beta-blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, SGLT2i). Alternatively, changes in troponin may be shown to be an appropriate trigger to refer a patient for consideration of advanced heart failure therapies. These hypotheses warrant further investigation in future work.

Efficacy of dapagliflozin as a function of baseline troponin

Evaluating the associations of hsTnT with clinical outcomes in the context of the DAPA-HF trial also allowed us to assess whether there was a differential response to treatment with dapagliflozin according to disease severity as reflected by hsTnT. By analogy, in the VICTORIA trial, there was diminished efficacy of vericiguat in HFrEF patients with very high NT-proBNP concentrations, and no apparent benefit when circulating NT-proBNP concentration exceeded 8,000 pg/ml.[21] A similar question has been raised about SGLT2i based on a meta-analysis of the DAPA-HF and EMPEROR-Reduced trials, in which there appeared to be heterogeneity in the treatment effect of SGLT2i between patients with NYHA class II (greater effect) vs. III-IV symptoms (lesser effect).[8]

An analysis examining the efficacy of empagliflozin in EMPEROR-Reduced in relation to baseline hsTnT concentration demonstrated that although all patients appeared to benefit from empagliflozin, the magnitude of relative risk reduction was potentially diminished in patients with higher hsTnT concentrations when hsTnT was modeled continuously.[9] In our analysis, there was no apparent attenuation in the treatment benefit of dapagliflozin with higher hsTnT (p-value for randomized treatment-by-baseline hsTnT interaction term = 0.29). Considering the results of the EMPEROR-Reduced and DAPA-HF hsTnT analyses collectively, a reasonable interpretation is that there is most likely a consistent relative treatment benefit of SGLT2i across the spectrum of disease severity reflected by circulating hsTnT. Furthermore, owing to the higher risk in patients with very high hsTnT levels, the absolute treatment benefit of SGLT2i is likely largest in this group.

Effect of dapagliflozin on cardiac troponin over 12 months

Although there was general trend of increasing hsTnT over 12 months among patients in the DAPA-HF trial, dapagliflozin showed a trend towards attenuating the rise in hsTnT, reflecting a possible reduction in myocardial injury over time. While the difference in the rise of hsTnT between treatment groups was small, even minor changes in hsTnT over this time period were prognostically significant in our study. This observation suggests possible directions for exploring the mechanisms of cardiovascular protection provided by SGLT2i, which remains an area of active investigation. Although this is the first large study to suggest a trend towards reduction in circulating hsTnT with SGLT2i in patients with HFrEF, previous studies have shown similar modest reductions in hsTnT with SGLT2i in other populations, including patients with T2DM.[22] It is possible that any blunting of myocardial injury over time may be a reflection of the favorable hemodynamic effects and reverse left ventricular remodeling that has been observed in mechanistic studies.[23-25] Whether any effect of SGLT2i on hsTnT levels is causally related to the clinical benefits of SGLT2i or is simply an epiphenomenon cannot be established within the construct of a cardiovascular outcomes trial.

Study Limitations

Our study should be considered in the context of several limitations. First, DAPA-HF did not enroll patients with HF with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF); thus, the observed trends in this analysis cannot be extrapolated across the LVEF spectrum. Second, patients with an eGFR $\leq$30 ml/min/1.73 m^2 were excluded from the DAPA-HF trial. Since hsTnT concentrations are affected by impaired renal clearance, the cut points used in this study for baseline hsTnT concentration and for change in hsTnT concentration over time may not apply to patients with advanced renal disease. Third, because all

events occurring prior to the 12-month study visit were necessarily excluded from the landmark analyses, our power was diminished for analyses leveraging the serial hsTnT data. Finally, because venous blood samples were only available at baseline and 12 months, we could not directly compare the prognostic significance of short- to intermediate-term vs. long-term changes in hsTnT.

Conclusions

In this biomarker substudy of the DAPA-HF trial, nearly all patients had detectable myocardial injury at the time of study enrollment, and the majority had dynamic circulating hsTnT concentrations over 12 months. Higher baseline hsTnT values and greater increases in hsTnT values over 1 year were associated with worse clinical outcomes, including cardiovascular death and worsening HF. The effect of dapagliflozin on the primary endpoint was consistent irrespective of baseline hsTnT concentration with absolute risk reductions that range up to 7.5% over a median of 18 months in those with highest risk identified by hsTnT. Finally, there was a non-significant trend of attenuated rise in hsTnT over 12 months in patients treated with dapagliflozin.

Sources of Funding

The DAPA-HF trial was funded by AstraZeneca. D.D.B. is supported by Harvard Catalyst KL2/CMeRIT (National Institutes of Health, National Center for Advancing translational Sciences grant UL 1TR002541).

Disclosures

D.D.B. has received research grant support to his institution from AstraZeneca and Pfizer, and consulting fees from AstraZeneca. K.F.D.'s employer, the University of Glasgow, has been remunerated by AstraZeneca for working on the DAPA-HF trial; K.F.D reports personal fees from AstraZeneca and Eli Lilly outside the submitted work. N.S. has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp and Dohme, Novo Nordisk, Novartis, Sanofi, and Pfizer; and has received grant support from Boehringer Ingelheim. P.Ja. has received research support from Abbott Laboratories, Amgen Inc., AstraZeneca, Daiichi Sankyo, Inc., Eisai, Inc., GlaxoSmith Kline, Merck & Co., Inc., Regeneron Pharmaceuticals, Inc., Roche Diagnostics Corp., Siemens Healthineers, Takeda Global Research and Development Center, and Waters Technologies Corp., and consulting fees from Roche Diagnostics. P.W. reports grant income from Roche Diagnostics, Astrazeneca, Boehringer Ingelheim, and Novartis outside the submitted work. P.S.J.'s employer, the University of Glasgow, has been remunerated by AstraZeneca for working on the DAPA-HF trial and the DELIVER trial; P.S.J. reports speakers and advisory board fees from AstraZeneca, speakers and advisory board fees from Novartis, and advisory board fees and grants from Boehringer Ingelheim. I.A. reports consulting fees from Boehringer Ingelheim and IQVIA related to work on clinical events committee during the conduct of the study, and personal/consulting fees from ARCA, Amgen, Boston Scientific

Corporation, Novartis, LivaNova, and Zensun. V.C. has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novartis. R.A.d.B. has received research grants and/or fees to his institution (UMCG) from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche outside the submitted work, and speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche, outside the submitted work. M.N.K. has received grant and research support from AstraZeneca, grants and honoraria from Boehringer-Ingelheim, and honoraria from Sanofi, Amgen, Novo Nordisk, Merck (Diabetes), Janssen, Bayer, Novartis, Eli Lilly, and Vifor Pharma. J.C.N. has received grant/research support from Amgen, Astrazeneca, Bayer, Esperion, CLS Behring, Dalcor, Daiichi Sankyo, Janssen, Novartis, NovoNordisk, Sanofi, and Vifor, and honoraria or consulting fees from Daiichi Sankyo, Novartis, Sanofi, and Servier. E.O. reports serving as a consultant and speaker for AstraZeneca, Bayer, Boehringer Ingelheim and Novartis; steering committee and national lead investigator contracts between her institution (Montreal Heart Institute Research Center) and American Regent, AstraZeneca, Cytokinetics, Merck, and Novartis; clinical trial participation with Amgen, Abbott, American Regent, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eidos, Novartis, Merck, Pfizer, and Sanofi. M.Sc. has received lecture fees from Boehringer Ingelheim, Novartis, AstraZeneca and Novo Nordisk. A.H., A-M.L., D.L., and M.Sj. are employees of AstraZeneca. J.J.V.M. is supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217; his employer, Glasgow University, has received payment for his work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, GlaxoSmithKline, Novartis, Pfizer, Theracos; and he has received personal lecture fees from the Corpus, Abbott, Hikma, Sun Pharmaceuticals, and Medscape. M.S.S. reports research grant support through Brigham and

Women’s Hospital from Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Daiichi Sankyo, Eisai, Intarcia, Medicines Company, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, and Takeda, and consulting for Althera, Amgen, Anthos Therapeutics, AstraZeneca, Bristol-Myers Squibb, CVS Caremark, DalCor, Dr. Reddy’s Laboratories, Dyrnamix, Esperion, IFM Therapeutics, Intarcia, Janssen Research and Development, Medicines Company, MedImmune, Merck, and Novartis. D.A.M. reports grants to the TIMI Study Group from Abbott Laboratories, Amgen, Anthos Therapeutics, AstraZeneca, BRAHMS, Eisai, GlaxoSmithKline, Medicines Co., Merck, Novartis, Pfizer, Roche Diagnostics, Quark, Siemens, and Takeda, and consultant fees from InCardia, Merck & Co, Novartis, and Roche Diagnostics. D.D.B., M.S.S., and D.A.M. are members of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Anthos Therapeutics, ARCA Biopharma, AstraZeneca, Bayer, Daiichi-Sankyo, Eisai, Intarcia, Ionis Pharmaceuticals, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Roche, Siemens Healthcare Diagnostics, The Medicines Company, and Zora Biosciences.

Supplemental Material

Supplemental Tables I - V

Supplemental Figures I - VII

References

1. Missov E, Calzolari C and Pau B. Circulating cardiac troponin I in severe congestive heart failure. *Circulation*. 1997;96:2953-2958.
2. De Boer RA, Pinto YM and Van Veldhuisen DJ. The imbalance between oxygen demand and supply as a potential mechanism in the pathophysiology of heart failure: the role of microvascular growth and abnormalities. *Microcirculation*. 2003;10:113-126.
3. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM and Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56:1071-1078.
4. Horwich TB, Patel J, MacLellan WR and Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833-838.
5. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation*. 2007;116:1242-1249.
6. Aimo A, Januzzi JL, Jr., Vergaro G, Ripoli A, Latini R, Masson S, Magnoli M, Anand IS, Cohn JN, Tavazzi L, et al. Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure: An Individual Patient Data Meta-Analysis. *Circulation*. 2018;137:286-297.
7. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381:1995-2008.
8. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020;396:819-829.
9. Packer M, Januzzi JL, Ferreira JP, Anker SD, Butler J, Filippatos G, Pocock SJ, Brueckmann M, Jamal W, Cotton D, et al. Concentration-dependent clinical and prognostic importance of high-sensitivity cardiac troponin T in heart failure and a reduced ejection fraction and the influence of empagliflozin: the EMPEROR-Reduced trial. *Eur J Heart Fail*. 2021;23:1529-1538.
10. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail*. 2019;21:665-675.
11. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Bohm M, Chopra V, de Boer RA, Desai AS, Ge J, et al. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. *Circulation*. 2021;143:298-309.
12. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, et al. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. *Circulation*. 2020;141:90-99.
13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017 ACC/AHA/HFSA Focused Update of the

2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137-e161.
14. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.
15. Rorth R, Jhund PS, Kristensen SL, Desai AS, Kober L, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Packer M, et al. The prognostic value of troponin T and N-terminal pro B-type natriuretic peptide, alone and in combination, in heart failure patients with and without diabetes. *Eur J Heart Fail*. 2019;21:40-49.
16. Pocock SJ, Ferreira JP, Gregson J, Anker SD, Butler J, Filippatos G, Gollop ND, Iwata T, Brueckmann M, Januzzi JL, et al. Novel biomarker-driven prognostic models to predict morbidity and mortality in chronic heart failure: the EMPEROR-Reduced trial. *Eur Heart J*. 2021; ehab579.
17. Miller WL, Hartman KA, Burritt MF, Grill DE and Jaffe AS. Profiles of serial changes in cardiac troponin T concentrations and outcome in ambulatory patients with chronic heart failure. *J Am Coll Cardiol*. 2009;54:1715-1721.
18. O'Connor CM, Fiuzat M, Lombardi C, Fujita K, Jia G, Davison BA, Cleland J, Bloomfield D, Dittrich HC, Delucca P, et al. Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study. *Circ Heart Fail*. 2011;4:724-732.
19. Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, Fracassi F, Bordonali T, Milani P, Danesi R, et al. The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. *Eur J Heart Fail*. 2007;9:776-786.
20. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi F, Maggioni AP, Tavazzi L, Tognoni G, Cohn JN, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation*. 2012;125:280-288.
21. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, Butler J, Lam CSP, Ponikowski P, Emdin M, et al. N-Terminal Pro-B-Type Natriuretic Peptide and Clinical Outcomes: Vericiguat Heart Failure With Reduced Ejection Fraction Study. *JACC Heart Fail*. 2020;8:931-939.
22. Januzzi JL, Jr., Butler J, Jarolim P, Sattar N, Vijapurkar U, Desai M and Davies MJ. Effects of Canagliflozin on Cardiovascular Biomarkers in Older Adults With Type 2 Diabetes. *J Am Coll Cardiol*. 2017;70:704-712.
23. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF, et al. Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). *Circulation*. 2021;143:516-525.
24. Nassif ME, Qintar M, Windsor SL, Jermyn R, Shavelle DM, Tang F, Lamba S, Bhatt K, Brush J, Civitello A, et al. Empagliflozin Effects on Pulmonary Artery Pressure in Patients With Heart Failure: Results From the EMBRACE-HF Trial. *Circulation*. 2021;143:1673-1686.
25. Mullens W, Martens P, Forouzan O, Dauw J, Vercammen J, Luwel E, Ceyssens W, Kockaerts V, Ameloot K and Dupont M. Effects of dapagliflozin on congestion assessed by remote pulmonary artery pressure monitoring. *ESC Heart Fail*. 2020;7:2071-2073.

Tables

Table 1. Baseline characteristics according to baseline hsTnT concentration.

	hsTnT <Median (<20.0 ng/L) N=1,554	**hsTnT ≥Median (≥20.0 ng/L) N=1,558**	**p-value**
hsTnT (ng/L), median (IQR)	13.7 (10.4-16.6)	30.1 (24.2-41.5)	
Age (years), mean (SD)	65.3±10.4	69.1±10.1	<0.001
Female sex, n (%)	442 (28.4)	235 (15.1)	<0.001
Race, n (%)			
Asian	313 (20.1)	263 (16.9)	
Black	32 (2.1)	55 (3.5)	0.011
White	5 (0.3)	7 (0.4)	
Other	1,204 (77.5)	1,233 (79.1)	
Geographic region, n (%)			
Asia/Pacific	304 (19.6)	257 (16.5)	
Europe	891 (57.3)	877 (56.3)	0.005
North America	226 (14.5)	293 (18.8)	
South America	133 (8.6)	131 (8.4)	
NYHA class, n (%)			
II	1,151 (74.1)	996 (63.9)	<0.001
III	400 (25.7)	555 (35.6)	
IV	3 (0.2)	7 (0.4)	
Heart rate (bpm), mean (SD)	70.6±10.9	71.1±11.5	0.22
SBP (mmHg), mean (SD)	122.4±15.3	122.4±16.1	0.94
LVEF, median (IQR)	31.8±6.5	30.6±7.0	<0.001
NT-proBNP (pg/mL), median (IQR)			
Patients with atrial fibrillation	1596.3 (1121.2-2344.2)	2434.9 (1430.1-4139.2)	<0.001
Patients without atrial fibrillation	1033.2 (646.0-1710.8)	1672.5 (962.8-3162.9)	<0.001
KCCQ-TSS, median (IQR)	80.2 (62.5-93.8)	76.0 (57.3-90.6)	<0.001
BMI (kg/m^2), mean (SD)	28.5±6.1	28.6±5.8	0.70
Principal cause of HF, n (%)			
Ischemic	887 (57.1)	960 (61.6)	0.008
Non-ischemic	560 (36.0)	480 (30.8)	
Unknown	107 (6.9)	118 (7.6)	
Medical history, n (%)			
Hospitalization for HF	670 (43.1)	743 (47.7)	0.010
Atrial fibrillation	586 (37.7)	683 (43.8)	<0.001
Type 2 diabetes mellitus	528 (34.0)	770 (49.4)	<0.001
Estimated GFR ($ml/min/1.73m^2$)			
Mean (SD)	70.7±18.1	59.5±17.7	<0.001
<60 $ml/min/1.73m^2$, n (%)	441 (28.4)	823 (52.8)	<0.001
Device therapy, n (%)			
ICD/CRT-D	437 (28.1)	539 (34.6)	<0.001
CRT-P/CRT-D	105 (6.8)	155 (9.9)	<0.001
Medical treatments, n (%)			
ACEI/ARB	1,295 (83.3)	1,258 (80.7)	0.060
ARNI	184 (11.8)	193 (12.4)	0.64
Beta-blocker	1,498 (96.4)	1,482 (95.1)	0.078

MRA	1,121 (72.1)	1,094 (70.2)	0.24
Diuretic	1,261 (81.1)	1,377 (88.4)	<0.001
Digoxin	188 (12.1)	292 (18.7)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; bpm, beats per minute; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; HF, heart failure; hsTnT, high-sensitivity troponin T; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; kg, kilograms; L, liter; LVEF, left ventricular ejection fraction; m^2, meters-squared; min, minute; ml, milliliters; mmHg, millimeters of mercury; MRA, mineralocorticoid receptor antagonist; ng, nanograms; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SBP, systolic blood pressure.

Table 2. Clinical endpoints by quartiles of baseline hsTnT concentration.

Endpoint, n (%)	Quartile of Baseline hsTnT Concentration				p-value
	Q1 <13.7 (N=779)	**Q2 13.7-<20.0 (N=778)**	**Q3 20.0-<30.2 (N=777)**	**Q4 ≥30.2 (N=778)**	
Primary endpoint	49 (6.3)	108 (13.9)	174 (22.4)	243 (31.2)	<0.001
Adjusted HR (95% CI)	Referent	1.99 (1.42, 2.81)	2.90 (2.09, 4.03)	3.44 (2.46, 4.82)	
Hospitalization for HF	36 (4.6)	61 (7.8)	107 (13.8)	155 (19.9)	<0.001
Adjusted HR (95% CI)	Referent	1.49 (0.98, 2.26)	2.31 (1.55, 3.42)	2.71 (1.81, 4.05)	
Cardiovascular death	17 (2.2)	61 (7.8)	111 (14.3)	134 (17.2)	<0.001
Adjusted HR (95% CI)	Referent	3.17 (1.84, 5.46)	4.98 (2.95, 8.42)	4.70 (2.75, 8.05)	
Sudden cardiac death	9 (1.2)	29 (3.7)	38 (4.9)	55 (7.1)	<0.001
Adjusted HR (95% CI)	Referent	2.93 (1.38, 6.26)	3.40 (1.61, 7.22)	4.00 (1.87, 8.57)	
Death due to HF or CS	2 (0.3)	11 (1.4)	37 (4.8)	38 (4.9)	<0.001
Adjusted HR (95% CI)	Referent	4.26 (0.94, 19.35)	10.7 (2.53, 45.2)	7.56 (1.74, 32.8)	
CV death or hosp for HF	49 (6.3)	107 (13.8)	173 (22.3)	237 (30.5)	<0.001
Adjusted HR (95% CI)	Referent	1.97 (1.40, 2.78)	2.87 (2.07, 4.00)	3.31 (2.36, 4.64)	
Total hospitalizations for HF and CV deaths	80 (6.7)	145 (12.4)	265 (23.6)	373 (33.9)	<0.001
Adjusted RR (95% CI)	Referent	1.57 (1.07, 2.30)	2.47 (1.70, 3.58)	2.66 (1.82, 3.86)	
Death from any cause	26 (3.3)	72 (9.3)	131 (16.9)	160 (20.6)	<0.001
Adjusted HR (95% CI)	Referent	2.42 (1.54, 3.81)	3.86 (2.50, 5.97)	3.78 (2.41, 5.91)	
eGFR slope, ml/min/1.73 m^2, adjusted mean (95% CI)	-1.64 (-2.15, -1.12)	-1.73 (-2.26, -1.21)	-1.50 (-2.04, -0.95)	-2.78 (-3.34, -2.22)	0.005
KCCQ-TSS					
≥5-point improvement, %	57.1 (53.5, 60.7)	54.3 (50.7, 57.9)	51.3 (47.4, 55.2)	52.3 (48.6, 56.0)	
Adjusted OR (95% CI)	Referent	1.04 (0.92-1.19)	0.90 (0.79-1.03)	0.91 (0.80-1.03)	
≤5-point deterioration, %	25.4 (22.2, 28.6)	28.2 (24.9, 31.4)	30.9 (27.5, 34.3)	31.8 (29.3, 35.2)	
Adjusted OR (95% CI)	Referent	0.94 (0.82-1.09)	1.10 (0.95-1.26)	1.18 (1.02, 1.37)	

Event rates for time-to-event endpoints are reported as n/N. Event rates for total hospitalizations for HF and cardiovascular deaths are reported per 100 patient-years. KCCQ-TSS outcomes are reported as the proportion of patients with clinically important improvement or deterioration. Cox proportional hazards models were stratified according to type 2 diabetes mellitus (T2DM) status, history of HF hospitalization, and treatment-group assignment as fixed-effect factors, and adjusted for age, sex, eGFR, LVEF, NT-proBNP (log-transformed), and principal cause of heart failure (ischemic vs. non-ischemic) as covariates. The slope of change in eGFR over time was examined using a repeated-measures mixed-effect model. KCCQ-TSS data were analyzed using a logistic regression model. Total events were analyzed using a semiparametric proportional-rates model. CI indicates confidence interval; CS, cardiogenic shock; CV, cardiovascular; HF, heart failure; HR, hazard ratio; hsTnT, high-sensitivity cardiac troponin T; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; OR, odds ratio; RR, rate ratio.

Figure Legends

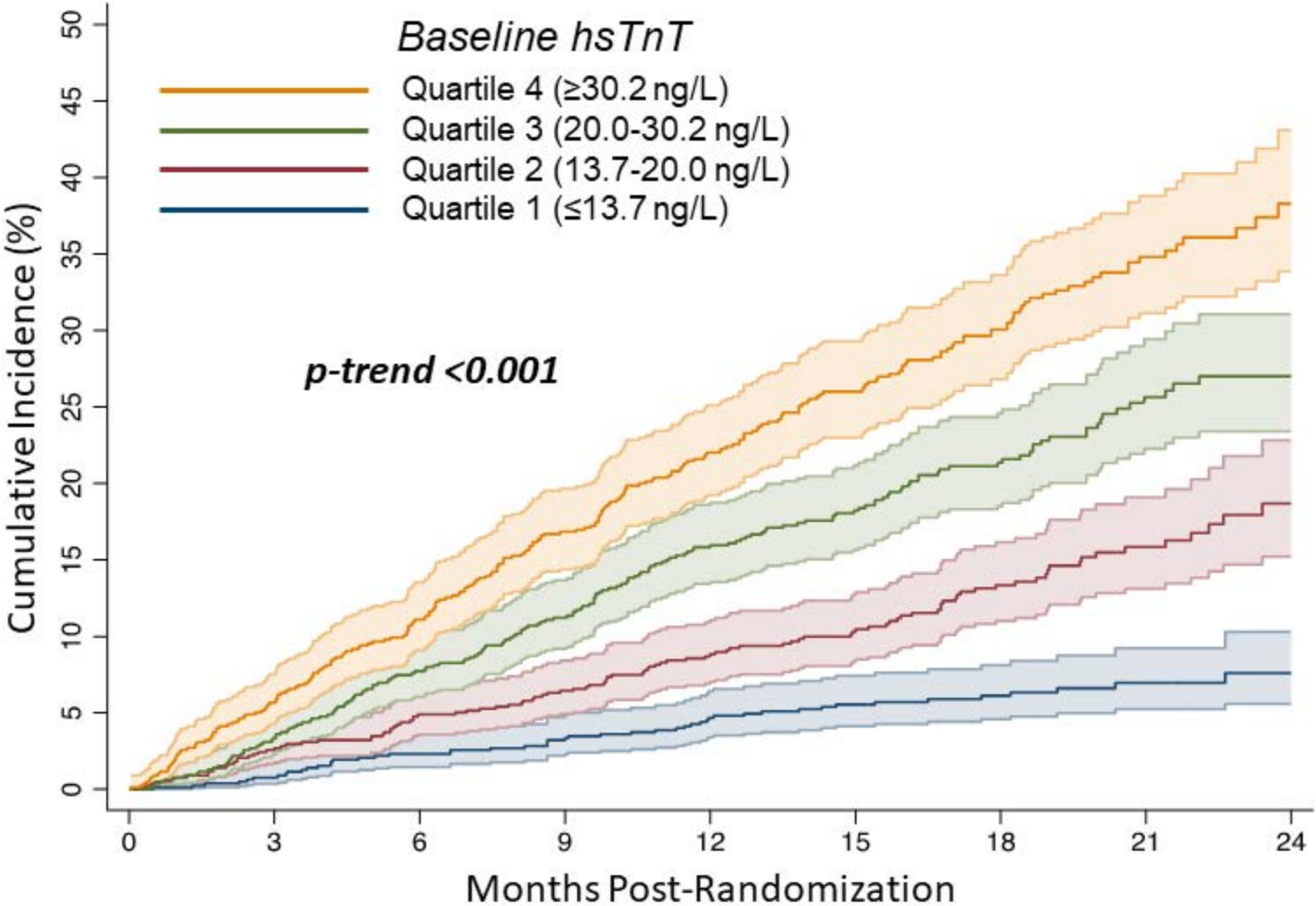
Figure 1. Cumulative incidence of the primary endpoint by quartile of baseline hsTnT concentration. The primary endpoint was a composite of worsening heart failure (unplanned heart failure hospitalization or urgent heart failure visit resulting in intravenous therapy for heart failure) or cardiovascular death. The shaded areas represent 95% confidence intervals of the Kaplan-Meier estimates. hsTnT indicates high-sensitivity cardiac troponin T; ng/L, nanograms per liter.

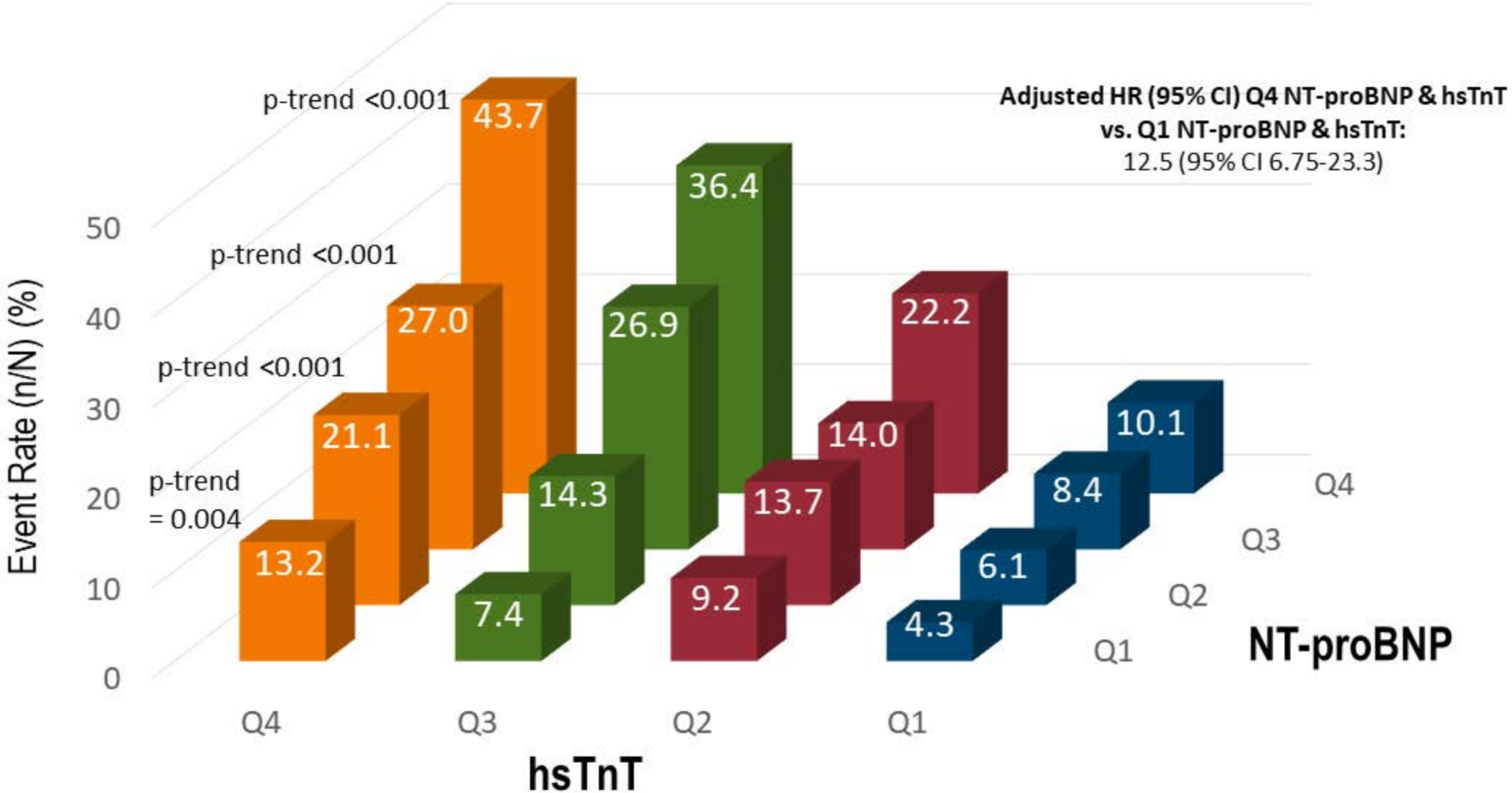
Figure 2. Incidence of the primary endpoint by quartile of baseline hsTnT concentration and baseline NT-proBNP concentration. The quartile cut points for hsTnT were <13.7 ng/L (Q1), 13.7-20.0 ng/L (Q2), 20.0-30.2 ng/L (Q3), ≥30.2 ng/L (Q4). The quartile cut points for NT-proBNP were <857 pg/ml (Q1), 857-1,437 pg/ml (Q2), 1,438-2,649 pg/ml (Q3), and ≥2,650 pg/ml (Q4). Event rates (n/N) are reported through the end of trial follow-up. hsTnT indicates high-sensitivity cardiac troponin T; ng/L, nanograms per liter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pg/ml, picograms per milliliter.

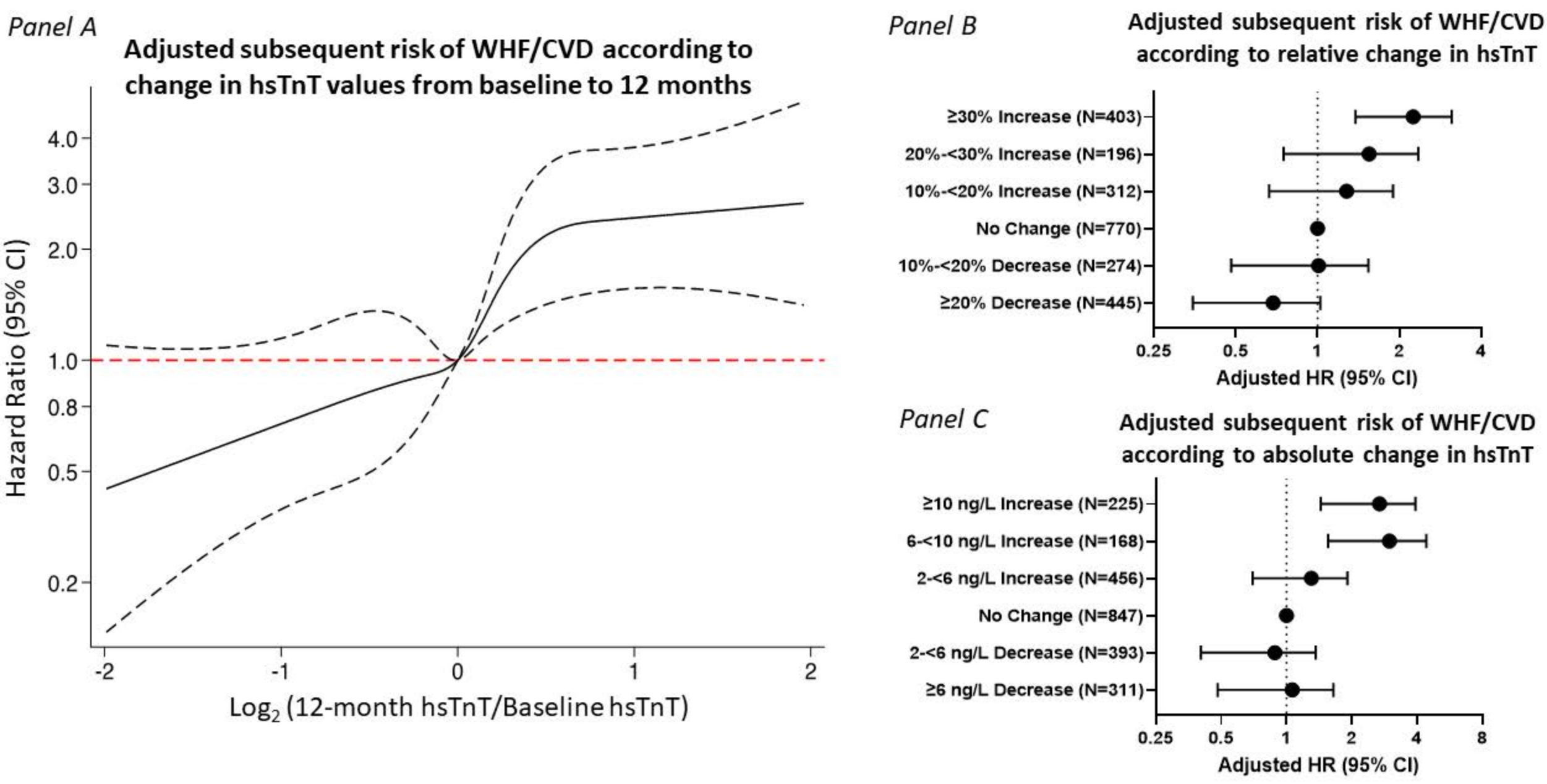
Figure 3. Subsequent risk of the primary endpoint according to change in hsTnT concentration from baseline to 12 months. Analyses are performed from a landmark of the 12-month study visit. Multivariable models include randomized treatment, prior HF hospitalization, age, sex, eGFR, LVEF, baseline NT-proBNP (log-transformed), principal cause of HF, baseline hsTnT, and are stratified by diabetes status at baseline. Hazard ratios for the primary endpoint according to the $\log_2$-transformed ratio of 12 month to baseline hsTnT were modeled using adjusted restricted cubic spline analysis (*Panel A*). The referent hazard is the hazard for patients with no

change in hsTnT. The dotted lines represent 95% confidence intervals of the hazard ratio estimates. A value of 1.0 on the x-axis represents a doubling in hsTnT from baseline to 12 months. Hazard ratios for the primary endpoint according to relative (*Panel B*) and absolute (*Panel C*) categorical changes are shown. CI indicates confidence interval; CVD, cardiovascular death; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; hsTnT, high-sensitivity cardiac troponin T; LVEF, left ventricular ejection fraction; ng/L, nanograms per liter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHF, worsening heart failure.

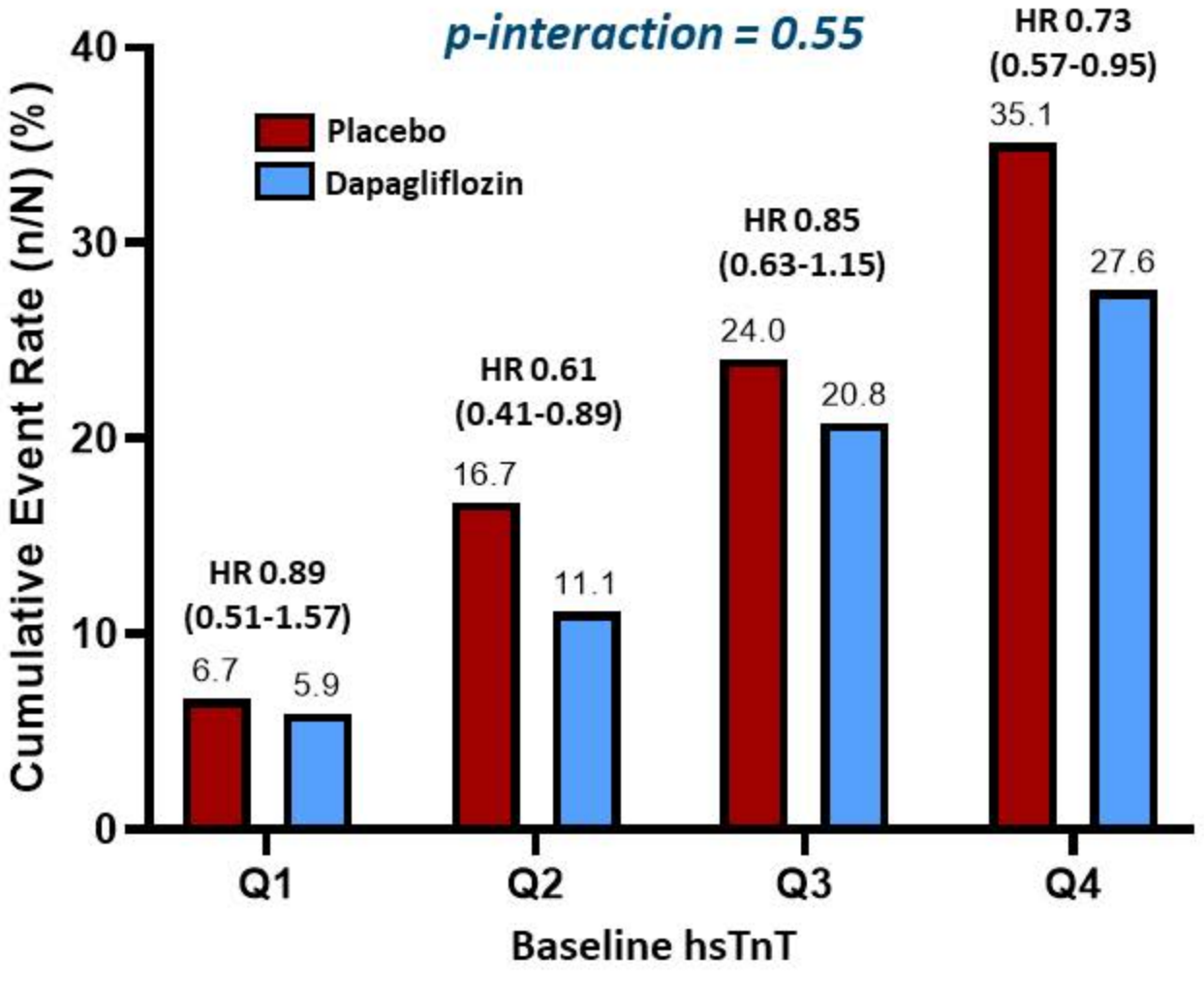
Figure 4. Treatment effect of dapagliflozin by baseline hsTnT concentration. There was a consistent relative treatment effect of dapagliflozin vs. placebo across quartiles of baseline hsTnT (*Panel A*). Patients in the top quartile had the greatest absolute treatment benefit. There was also a consistent relative treatment effect of dapagliflozin vs. placebo irrespective of baseline hsTnT when modeled continuously using fractional polynomial analysis (*Panel B*). The gray area represents 95% confidence intervals of the hazard ratio estimates. CI indicates confidence interval; HF, heart failure; HR, hazard ratio; hsTnT, high-sensitivity cardiac troponin T; ln, natural logarithm; ng/L, nanograms per liter.


Baseline hsTnT
Quartile 4 (≥30.2 ng/L)
Quartile 3 (20.0-30.2 ng/L)
Quartile 2 (13.7-20.0 ng/L)
Quartile 1 (≤13.7 ng/L)
p-trend <0.001
Cumulative Incidence (%)
0
5
10
15
20
25
30
35
40
45
50
0
3
6
9
12
15
18
21
24
Months Post-Randomization


Adjusted HR (95% CI) Q4 NT-proBNP & hsTnT vs. Q1 NT-proBNP & hsTnT:
12.5 (95% CI 6.75-23.3)
p-trend <0.001
p-trend <0.001
p-trend <0.001
p-trend = 0.004
43.7
36.4
27.0
26.9
22.2
21.1
14.0
14.3
13.7
10.1
8.4
6.1
13.2
7.4
9.2
4.3
Event Rate (n/N) (%)
0
10
20
30
40
50
Q4
Q3
Q2
Q1
hsTnT
Q4
Q3
Q2
Q1
NT-proBNP


Panel A
Adjusted subsequent risk of WHF/CVD according to change in hsTnT values from baseline to 12 months
Hazard Ratio (95% CI)
4.0
3.0
2.0
1.0
0.8
0.5
0.2
-2
-1
0
1
2
Log2 (12-month hsTnT/Baseline hsTnT)
Panel B
Adjusted subsequent risk of WHF/CVD according to relative change in hsTnT
≥30% Increase (N=403)
20%-<30% Increase (N=196)
10%-<20% Increase (N=312)
No Change (N=770)
10%-<20% Decrease (N=274)
≥20% Decrease (N=445)
0.25
0.5
1
2
4
Adjusted HR (95% CI)
Panel C
Adjusted subsequent risk of WHF/CVD according to absolute change in hsTnT
≥10 ng/L Increase (N=225)
6-<10 ng/L Increase (N=168)
2-<6 ng/L Increase (N=456)
No Change (N=847)
2-<6 ng/L Decrease (N=393)
≥6 ng/L Decrease (N=311)
0.25
0.5
1
2
4
8
Adjusted HR (95% CI)

Panel A



Panel B