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ORIGINAL RESEARCH

# Cardiovascular Biomarkers and Heart Failure Risk in Stable Patients With Atherothrombotic Disease: A Nested Biomarker Study From TRA 2°P-TIMI 50

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**BACKGROUND:** Patients with stable atherothrombotic disease vary in their risk of developing heart failure (HF). Circulating cardiovascular biomarkers may improve HF risk assessment and identify patients who may benefit from emerging HF preventive therapies.

**METHODS AND RESULTS:** We measured high-sensitivity cardiac troponin I and BNP (B-type natriuretic peptide) in 15 833 patients with prior myocardial infarction, ischemic stroke, or peripheral artery disease from the TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50) trial, excluding patients with recent myocardial infarction (<30 days). Biomarkers were categorized using a priori cut points. Hospitalization for HF (HHF) end points were adjudicated with blinded structured review of serious adverse events. Associations between biomarkers and HHF outcomes were adjusted for sex and independent clinical risk predictors of HHF in our cohort (age ≥75, prior HF, type 2 diabetes mellitus, polyvascular disease, body mass index, anemia, chronic kidney disease, hypertension). Baseline high-sensitivity cardiac troponin I and BNP each identified a significant graded risk of HHF independent of clinical risk predictors, including in the subgroups of patients with and without type 2 diabetes mellitus and with and without prior HF. Patients with both high-sensitivity cardiac troponin I ≥5 ng/L and BNP ≥100 pg/mL had the highest HHF event rates. When added to a multivariable Cox regression model with clinical risk predictors (C-index 0.88; 95% CI, 0.85–0.90), BNP (C -index 0.92; 95% CI, 0.90–0.93), and high-sensitivity cardiac troponin I (C-index 0.90; 95% CI, 0.88–0.92) each significantly improved the prognostic performance of the model (both $P_{LRT}$<0.001).

**CONCLUSIONS:** Biomarkers of myocardial injury and hemodynamic stress are independent predictors of HHF risk in patients with stable atherothrombotic disease, with and without prior HF and/or type 2 diabetes mellitus.

**REGISTRATION:** URL: https://www.clinicaltrials.gov; Unique identifier: NCT00526474.

**Key Words:** atherosclerosis ■ biomarkers ■ heart failure

The prevalence of heart failure (HF) is increasing globally,[1,2] and it is now estimated that 1 in 5 people will develop HF during their lifetime.[3] The trend of rising HF prevalence has been attributed to improved treatment of patients with HF and myocardial infarction leading to longer survival from these diseases and to a rising population burden of risk factors for HF including type 2 diabetes mellitus (T2DM) and obesity,[4,5] particularly among younger individuals.[6] Recognizing this growing public health burden, recent

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## CLINICAL PERSPECTIVE

### What Is New?

- Biomarkers of myocardial injury and hemodynamic stress are powerful and independent predictors of risk of hospitalization for heart failure in patients with stable atherothrombotic disease, with consistent prognostic performance in patients with and without type 2 diabetes mellitus and with and without prior heart failure.
- Simultaneous assessment of both high-sensitivity troponin I and BNP (B-type natriuretic peptide) identifies patients at particularly high risk of incident and recurrent hospitalization for heart failure.

### What Are the Clinical Implications?

- Assessment of high-sensitivity troponin I and BNP may be helpful for identifying patients with atherothrombotic disease who may benefit most from heart failure preventive interventions.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **HHF** | hospitalization for heart failure |
| **hsTnI** | high-sensitivity troponin I |
| **SGLT2** | sodium-glucose cotransporter-2 |
| **T2DM** | type 2 diabetes mellitus |

HF guidelines have placed increasing emphasis on HF prevention.[7]

Among those at greatest risk for developing HF are patients with established atherosclerotic cardiovascular disease (ASCVD) and patients with T2DM. To reduce HF risk in patients with ASCVD, lifestyle modifications and pharmacotherapy aimed at controlling ASCVD risk factors (eg, antihypertensives) are recommended.[7,8] In addition, among patients with ASCVD and T2DM, sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as an option to reduce the risk of future and recurrent HF events.[9–11] Further, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial of patients with established HF with reduced ejection fraction, the SGLT2 inhibitor dapagliflozin robustly decreased HF risk in patients with and without T2DM.[12] The clinical efficacy of these novel agents in reducing future and recurrent HF events has ushered in a new era of HF prevention and highlighted the importance of new tools for HF risk stratification.

Prior studies have suggested that circulating biomarkers of cardiovascular disease, including high-sensitivity cardiac troponin[13,14] and natriuretic peptides,[15] may help to identify patients with stable coronary artery disease who are at increased risk of developing HF. Nevertheless, there are limited data on the collective prognostic value of high-sensitivity cardiac troponin and natriuretic peptides for HF risk assessment, particularly in patients with ASCVD and T2DM. We therefore designed a nested biomarker study to evaluate the performance of a high-sensitivity troponin I (hsTnI) assay in combination with a BNP (B-type natriuretic peptide) assay for predicting risk of hospitalization for HF (HHF) in patients with stable atherothrombotic disease in a well-characterized cohort from a large, multinational clinical trial.

## METHODS

### Study Population

The TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events -Thrombolysis in Myocardial Infarction 50) trial was a multinational, randomized, placebo-controlled trial of the protease-activated receptor-1 antagonist vorapaxar in 26 449 stable patients with atherothrombotic disease. More than two-thirds (n=17 779) of patients were enrolled based on a history of myocardial infarction within the previous 2 weeks to 12 months. Major exclusion criteria included a planned revascularization procedure, history of bleeding diathesis, and active hepatobiliary disease. The median follow-up time was 30 months (25th–75th percentile, 24–36 months). The ethics committee at each participating center 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 discussions.

This biomarker substudy in TRA 2°P-TIMI 50 was a nested prospective study that was conducted in all countries where the logistics of sample collection permitted. Of the 26 449 patients enrolled in the TRA 2°P-TIMI 50 trial, 19 429 had an available baseline serum sample for the measurement of hsTnI and/or BNP. To avoid any potential confounding related to persistent increases in hsTnI concentrations owing to recent myocardial infarction, we excluded patients who had a myocardial infarction in the 30 days before enrollment (n=3596), leaving 15 833 patients for this analysis.

### Biomarkers

Baseline blood samples were collected in EDTA anticoagulant tubes, and isolated plasma was stored at –20°C or colder until shipped to the central laboratory on dry ice, where it was stored at –70°C or colder until thawed for analysis at the TIMI Clinical Trials Laboratory (Boston, MA). BNP and hsTnI were measured using

chemiluminescent magnetic microparticle immunoassays (Abbott ARCHITECT). Levels of hsTnI were categorized according to the following previously reported cut points: <2 ng/L (limit of detection), 2 to <5, 5 to 26, and >26 ng/L (99th percentile upper reference limit). BNP levels were categorized according to the following prespecified cut points: <50, 50 to <100, 100 to 200, and >200 pg/mL.

## Clinical End Points

HF events leading to or prolonging hospitalization were reported in the TRA 2°P-TIMI 50 trial by local site investigators as serious adverse events. We retrospectively adjudicated HHF end points with blinded structured review of serious adverse events using established definitions. For this analysis, we included patients meeting criteria for "definite" or "probable" HHF (Data S1).

## Statistical Analysis

Baseline characteristics were summarized according to a priori biomarker categories. Differences in the baseline characteristics between biomarker strata were evaluated with the Pearson $\chi^2$ test for categorical variables and Kruskal-Wallis test for continuous variables. Cumulative HHF event rates at 3 years were calculated for each prespecified individual biomarker category using the Kaplan-Meier method, and trends were compared using the log-rank test. Adjusted estimates of the association between individual biomarkers and HHF were calculated using multivariable Cox models with the biomarker as an independent variable along with sex and established independent clinical risk predictors of HHF in our cohort (age ≥75, prior HF, T2DM, number of vascular beds with atherosclerotic disease [ie, polyvascular disease], body-mass index, anemia, chronic kidney disease, and hypertension). Cumulative HHF event rates were also described according to categorical subgroups defined by high (≥100 pg/mL) versus low (<100 pg/mL) baseline BNP level and high (≥5 ng/L) versus low (<5 ng/L) baseline hsTnI level and compared using the log-rank test.

Multivariable analyses using Cox regression modeling were performed to assess the prognostic performance of the independent clinical risk predictors alone and the clinical risk predictors in combination with the biomarkers (individually and collectively). Discriminatory performance was assessed using Harrell's C-index. The predictive performance of these models was compared using the likelihood ratio test.

We performed 2 subgroup analyses: (1) in patients with T2DM (n=4089) versus without T2DM (n=11 742); and (2) in patients with prior HF (n=1229) versus no prior history of HF (n=14 603) to evaluate the performance of the biomarkers in identifying recurrent and incident HHF risk.

All statistical analyses were performed with SAS System v9.4 (SAS Institute Inc., Cary, NC, USA).

# RESULTS

## Patient Population

The median baseline hsTnI and BNP values among the 15 833 patients in the nested biomarker analysis were 4.9 ng/L (25th–75th percentiles, 2.9–9.3 ng/L) and 35.7 ng/L (25th–75th percentiles, 16.6–77.3 ng/L), respectively. The baseline characteristics of this cohort are summarized according to a priori categories of BNP and hsTnI in Tables 1 and 2, respectively and are compared to the overall trial cohort in Table S1. The mean age was 62±11 years and 25% were women. Twenty-six percent of patients had T2DM and 8% had a prior history of HF. Among patients with available data, nearly two-thirds had a normal left ventricular ejection fraction (ie, ≥55%).

## Biomarkers and Risk of HF

Baseline hsTnI and BNP each identified a significant gradient of risk of HHF (Figure 1). The 3-year Kaplan-Meier (KM) event rates of HHF were 0.1%, 0.6%, 2.4%, and 5.6% in patients with hsTnI <2, 2 to <5, 5 to 26, and >26 ng/L, respectively (*P*-trend<0.001). Similarly, the 3-year KM event rates of HHF were 0.4%, 1.6%, 3.5%, and 10.9% in patients with BNP <50, 50 to <100, 100 to 200, and >200 pg/mL, respectively (*P*-trend<0.001). After adjusting for the effects of the independent clinical risk predictors, hsTnI and BNP remained independently associated with risk of HHF (adjusted *P*-trend<0.001 for each). Moreover, patients with elevated baseline levels of both hsTnI (≥5 ng/L) and BNP (≥100 pg/mL) had significantly higher rates of HHF than patients with elevated hsTnI or elevated BNP alone (*P*<0.001 for each) (Figure 2).

Collectively, the independent clinical risk predictors yielded a C-index of 0.88 (95% CI, 0.85–0.90) for the prediction of HHF risk. Adding BNP to the independent clinical risk predictors significantly improved the prognostic performance of the model for predicting HHF events (C-indices 0.92 [95% CI, 0.90–0.93] versus 0.88 [95% CI, 0.85–0.90]; $P_{LRT}$<0.001). Similarly, adding hsTnI to the independent clinical risk predictors modestly but significantly improved the prognostic performance of the model (C-index 0.90 [95% CI, 0.88–0.92] versus 0.88 [95% CI, 0.85–0.90]; $P_{LRT}$<0.001).

## Subgroup Analyses

In the subgroup of patients with T2DM (n=4089), baseline hsTnI and BNP each identified a significant gradient of HHF risk that was similar to the overall

**Table 1. Baseline Characteristics Stratified by Prespecified BNP Categories**

| Variable | BNP <50 (N=9784), % | BNP 50 to <100 (N=3218), % | BNP 100–200 (N=1810), % | BNP >200 (N=993), % | *P* Value |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age, median (25th–75th), y | 59 (52–66) | 64 (57–72) | 67 (60–74) | 69 (61–76) | <0.0001 |
| Female sex | 22.9 | 27.3 | 30.1 | 30.8 | <0.0001 |
| White race | 83.5 | 86.9 | 85.6 | 84.2 | <0.0001 |
| Body mass index, median (25th–75th), kg/m$^2$ | 28 (25–31) | 27 (25–30) | 27 (25–30) | 27 (24–30) | <0.0001 |
| Other comorbidities | | | | | |
| Current smoker | 24.1 | 16.7 | 14.6) | 14.3 | <0.0001 |
| Hypertension | 67.7 | 72.0 | 76.6 | 79.8 | <0.0001 |
| Diabetes mellitus | 23.7 | 26.4 | 31.7 | 33.7 | <0.0001 |
| Prior myocardial infarction | 60.2 | 75.3 | 77.9 | 82.8 | <0.0001 |
| Prior heart failure | 3.8 | 8.3 | 15.5 | 31.1 | <0.0001 |
| Baseline left ventricular ejection fraction <55% | 27.9 | 42.9 | 53.1 | 69.6 | <0.0001 |
| Cerebrovascular disease | 31.6 | 20.4 | 20.9 | 19.2 | <0.0001 |
| Coronary artery disease | 66.3 | 83.1 | 87.6 | 92.5 | <0.0001 |
| Peripheral artery disease | 23.4 | 25.6 | 31.0 | 34.2 | <0.0001 |
| Baseline estimated glomerular filtration rate <60 mL×min$^{-1}$×1.73×m$^{-2}$ | 11.5 | 18.6 | 27.3 | 40.3 | <0.0001 |
| Baseline medication use | | | | | |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker | 69.2 | 74.1 | 76.3 | 77.6 | <0.0001 |
| Beta blocker | 56.7 | 75.4 | 79.8 | 83.7 | <0.0001 |

BNP indicates B-type natriuretic peptide.

biomarker cohort, though notably, the HHF event rates were higher among patients with T2DM (3-year KM event rates 0.3%, 1.4%, 5.0%, and 9.3% in patients with hsTnI <2, 2 to <5, 5–26, and >26 ng/L, respectively [*P*-trend<0.001]; 3-year KM event rates 0.9%, 3.8%, 6.2%, and 18.5% in patients with BNP <50, 50–<100, 100–200, and >200 pg/mL, respectively [*P*-trend<0.001]). After adjusting for the effects of the independent clinical risk predictors, hsTnI and BNP remained independently associated with risk of HHF (adjusted *P*-trend<0.001 for each) (Figure 3). Similar to the full cohort, patients with T2DM with elevated baseline levels of both hsTnI (≥5 ng/L) and BNP (≥100 pg/mL) had significantly higher rates of HHF than patients with elevated hsTnI or elevated BNP alone (*P*<0.001 for each) (Figure 4). Adding BNP to the independent clinical risk predictors significantly improved the prognostic performance of the model for predicting HHF events (C-index 0.87 [95% CI, 0.84–0.90] versus 0.82 [95% CI, 0.78–0.86]; $P_{LRT}$<0.001). Similarly, adding hsTnI to the independent clinical risk predictors significantly improved the prognostic performance of the model (C-index 0.85 [95% CI, 0.81–0.88] versus 0.82 [95% CI, 0.78–0.86]; $P_{LRT}$<0.001) (Table 3).

We also performed a subgroup analysis in patients with no prior history of HF (n=14 603) to assess the performance of clinical characteristics and serum biomarkers for predicting *incident* HHF. In this subgroup, baseline hsTnI and BNP again identified a significant gradient of HHF risk, though not surprisingly, the HHF event rates were lower (3-year KM event rates 0.1%, 0.3%, 1.2%, and 2.2% in patients with hsTnI <2, 2 to <5, 5–26, and >26 ng/L, respectively [*P*-trend<0.001]; 3-year KM event rates 0.2%, 0.7%, 2.2%, and 5.2% in patients with BNP <50, 50–<100, 100–200, and >200 pg/mL, respectively [*P*-trend<0.001]). After adjusting for the effects of the independent clinical risk predictors, hsTnI and BNP remained independently associated with risk of HHF (*P*-trend<0.001 for each) (Figure 3). As in the full cohort, patients with no prior history of HF with elevated baseline levels of both hsTnI (≥5 ng/L) and BNP (≥100 pg/mL) had significantly higher rates of HHF than patients with elevated hsTnI or elevated BNP alone (*P*<0.001 for each) (Figure 4). Adding BNP and hsTnI to the independent

**Table 2. Baseline Characteristics Stratified by Prespecified hsTnI Categories**

| Variable | hsTnI <2 (N=1604), % | hsTnI 2 to <5 (N=6439), % | hsTnI 5–26 (N=6637), % | hsTnI >26 (N=1153), % | *P* Value |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age, median (25th–75th), y | 57 (50–64) | 61 (54–69) | 63 (55–71) | 61 (54–69) | <0.0001 |
| Female sex | 42.3 | 26.9 | 20.1 | 20.7 | <0.0001 |
| White race | 87.9 | 85.3 | 83.8 | 79.3 | <0.0001 |
| Body mass index, median (25th–75th), kg/m$^2$ | 27 (24–30) | 27 (25–31) | 28 (25–31) | 28 (25–31) | <0.0001 |
| Other comorbidities | | | | | |
| Current smoker | 23.9 | 23.1 | 18.9 | 16.4 | <0.0001 |
| Hypertension | 61.3 | 69.6 | 73.2 | 71.2 | <0.0001 |
| Diabetes mellitus | 20.4 | 24.4 | 27.4 | 32.5 | <0.0001 |
| Prior myocardial infarction | 47.3 | 58.7 | 76.1 | 84.4 | <0.0001 |
| Prior heart failure | 1.7 | 3.8 | 11.4 | 17.7 | <0.0001 |
| Baseline left ventricular ejection fraction <55% | 16.1 | 26.0 | 46.9 | 58.7 | <0.0001 |
| Cerebrovascular disease | 41.2 | 31.6 | 21.3 | 18.6 | <0.0001 |
| Coronary artery disease | 53.9 | 66.3 | 83.2 | 89.6 | <0.0001 |
| Peripheral artery disease | 23.8 | 26.6 | 25.0 | 23.2 | 0.0122 |
| Baseline estimated glomerular filtration rate <60 mL×min$^{-1}$×1.73×m$^{-2}$ | 7.4 | 12.6 | 21.3 | 24.6 | <0.0001 |
| Baseline medication use | | | | | |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker | 58.0 | 68.7 | 76.1 | 79.7 | <0.0001 |
| Beta blocker | 50.7 | 60.6 | 70.7 | 74.8 | <0.0001 |

hsTnI indicates high-sensitivity troponin I.

clinical risk predictors each significantly improved the prognostic performance of the model for predicting HHF events (BNP: C-index 0.89 [95% CI, 0.86–0.92] versus 0.81 [95% CI, 0.77–0.85]; $P_{LRT}$<0.001; hsTnI: C-index 0.85 [95% CI, 0.81–0.88] versus 0.81 [95% CI, 0.77–0.85]; $P_{LRT}$<0.001) (Table 3).

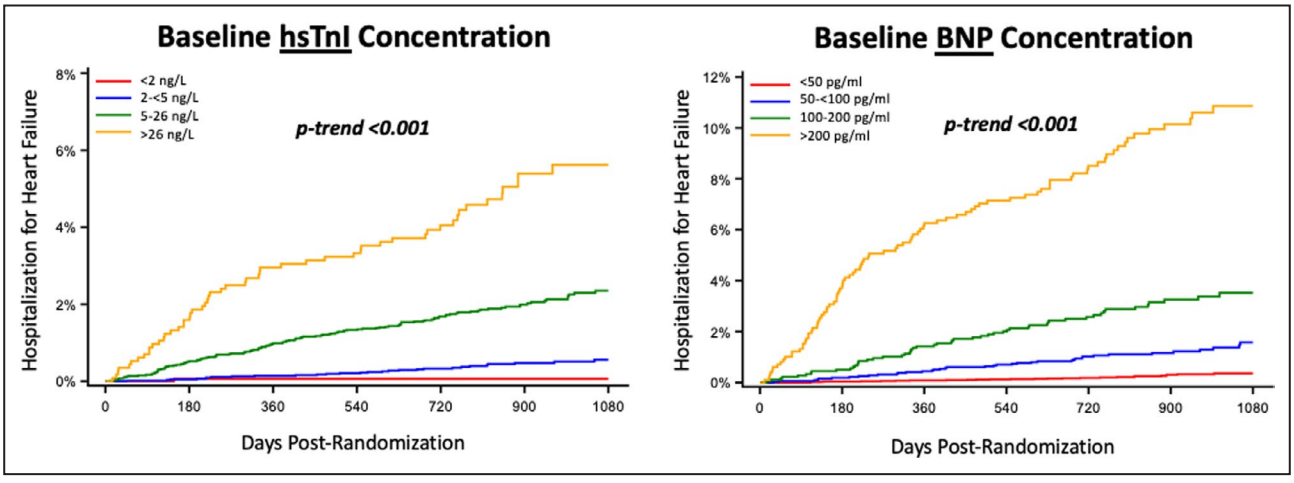


**Figure 1. Kaplan-Meier estimates of hospitalization for heart failure by baseline biomarker concentration (n=15 833).**
High-sensitivity troponin I and B-type natriuretic peptide each identified a significant gradient of risk of hospitalization for heart failure. BNP indicates B-type natriuretic peptide; and hsTnI, high-sensitivity troponin I.

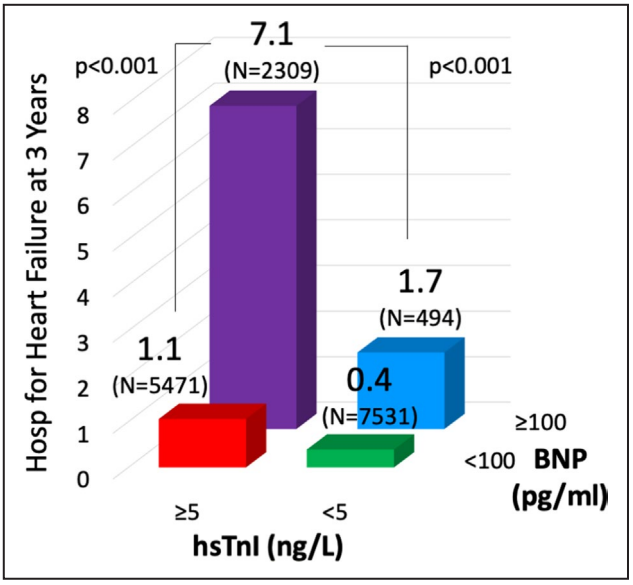


**Figure 2. Hospitalization for heart failure event rates at 3 years stratified by high-sensitivity troponin I and B-type natriuretic peptide (n=15 805).**
Heart failure events are shown as Kaplan-Meier estimates. Patients with elevated baseline levels of both hsTnI (≥5 ng/L) and BNP (≥100 pg/mL) had significantly higher rates of hospitalization for heart failure than patients with elevated hsTnI or elevated BNP alone. BNP indicates B-type natriuretic peptide; and hsTnI, high-sensitivity troponin I.

## DISCUSSION

In this nested prospective biomarker analysis from the TRA 2°P-TIMI 50 trial, we found that biomarkers of myocardial injury (hsTnI) and hemodynamic stress (BNP) robustly identified patients with stable atherothrombotic disease who are at increased of risk of developing HF. Importantly, these findings extended to subgroups of patients with and without T2DM and with and without a prior history of HF, underscoring their broad utility for HF risk prediction. In the context of increasing focus on HF prevention, and intense interest in defining populations most likely to benefit from HF preventive therapies (ie, SGLT2 inhibitors), these data suggest that well-established and widely available biomarkers of cardiovascular disease may be important tools for HF risk stratification and clinical decision-making.

### Atherosclerotic Cardiovascular Disease and Heart Failure

ASCVD is the most common cause of HF globally, accounting for nearly two-thirds of all HF syndromes.[16] Moreover, the risk of HF in patients with ASCVD is exaggerated in patients with atherosclerosis involving multiple vascular beds (ie, peripheral arterial disease and cerebrovascular disease). The traditional view of the progression from ASCVD to HF is that patients with epicardial coronary disease develop acute coronary syndromes resulting in ischemic myocardial necrosis.[17] Following a significant myocardial infarction, a neurohormonal cascade is activated that leads to progressive adverse left ventricular remodeling and dysfunction (ie, ischemic cardiomyopathy), culminating in a syndrome of HF with reduced ejection fraction.[17] Mounting evidence from the past decade suggests that an alternative pathway to ischemic HF is mediated by coronary microvascular dysfunction, in which endothelial dysfunction results from inflammation and altered expression of endothelial nitric oxide synthase. This more often occurs in patients with multiple comorbidities (eg, T2DM, obesity, chronic kidney disease) and typically manifests with a syndrome of HF with preserved ejection fraction.

Detection of persistent subclinical chronic myocardial injury with the use of hsTnI in patients with apparently stable atherothrombotic disease can provide important pathophysiologic insights into the progression from ASCVD to HF. In addition, detection of subclinical hemodynamic stress (which may be related to ischemic myocardial remodeling) with the use of BNP offers another pathobiologic benchmark in the transition from ASCVD to HF. The strong independent associations between increased concentrations of hsTnI and BNP and the risk of incident and recurrent HHF build on previous studies supporting the robust prognostic performance of these biomarkers.[13,15] In addition, we demonstrate that simultaneous assessment of both hsTnI and BNP using simple dichotomous thresholds identifies patients at particularly high HHF risk. These data suggest that a multimarker approach may be able to discriminate HF risk more fully.

### Clinical Implications

In addition to providing incremental prognostic information to standard risk tools, biomarkers should ideally have actionable clinical implications. Although this application was not directly tested in this analysis, these data suggest that hsTnI and BNP may be helpful adjunctive tools for identifying patients with atherothrombotic disease who may benefit most from HF preventive interventions. For example, a natriuretic peptide-based screening strategy has previously been shown to reduce incident left ventricular dysfunction and HF in stable patients with multiple cardiovascular risk factors.[18] Because patients with existing atherothrombotic disease have an even higher risk of incident or recurrent HF, an analogous biomarker-based screening and prevention strategy has enormous therapeutic potential in this population.

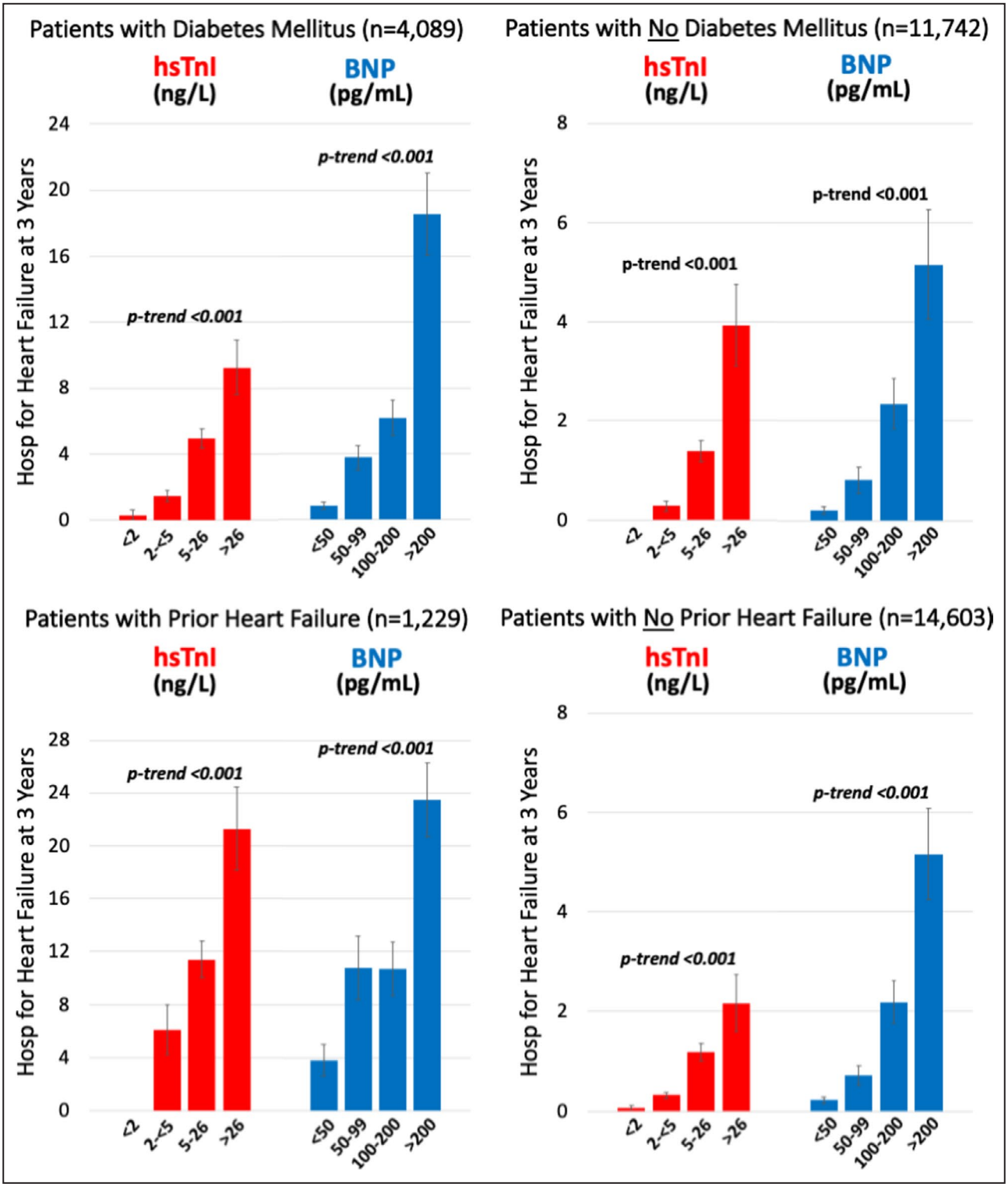


**Figure 3. Cardiovascular biomarkers and hospitalization for heart failure at 3 years in the subgroups of patients with diabetes mellitus and patients with no prior history of heart failure.**
High-sensitivity troponin I and B-type natriuretic peptide each identified a significant gradient of risk of hospitalization for heart failure in the subgroups of patients with diabetes mellitus and patients with no prior history of heart failure. The vertical scales are different in each subgroup owing to major differences in the absolute event rates. SE bars are shown. BNP indicates B-type natriuretic peptide; and hsTnI, high-sensitivity troponin I.

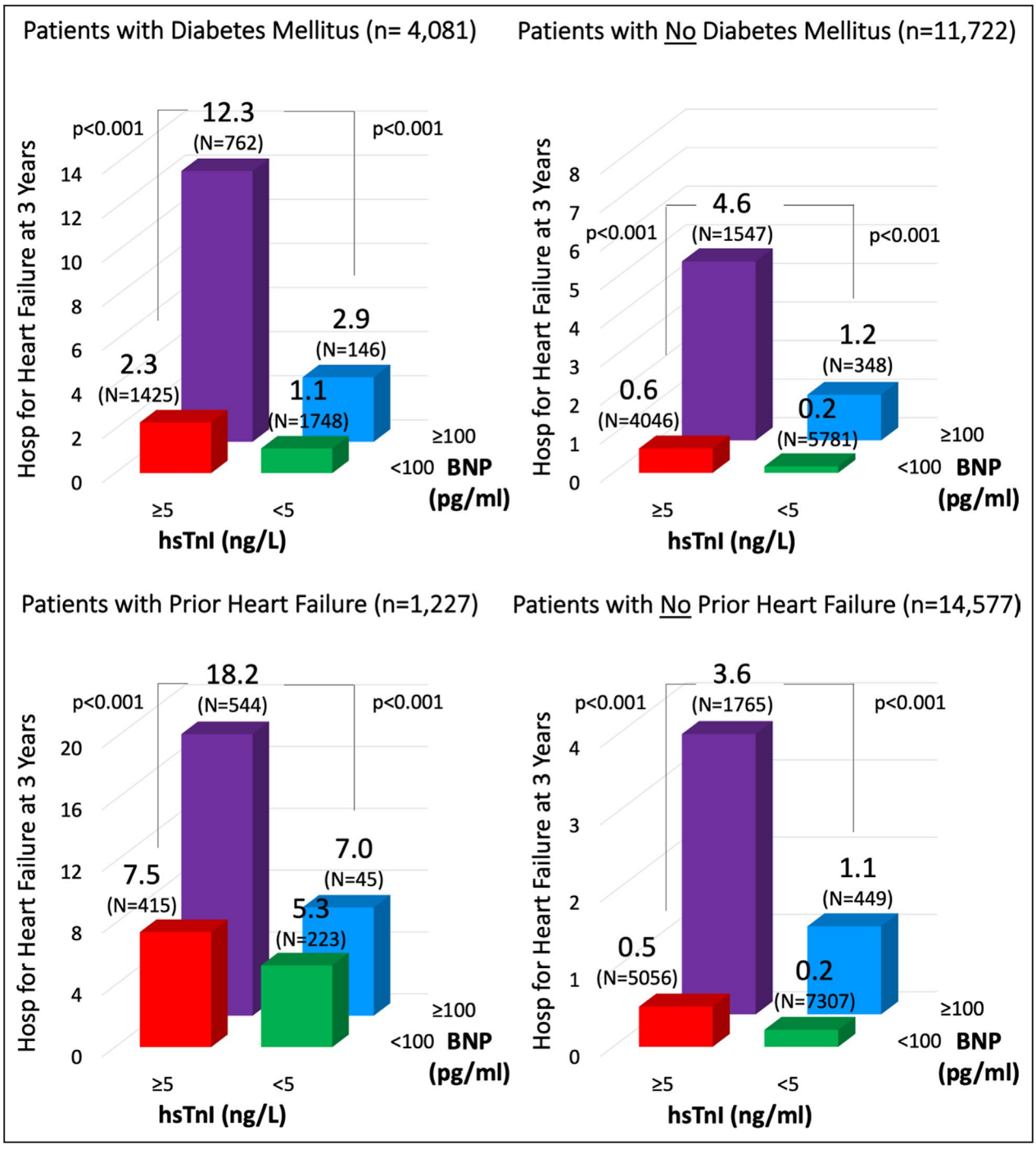


**Figure 4. Hospitalization for heart failure event rates at 3 years stratified by high-sensitivity troponin I and B-type natriuretic peptide in the subgroups of patients with diabetes mellitus and patients with no prior history of heart failure.** Heart failure events are shown as Kaplan-Meier estimates. Patients with elevated baseline levels of both hsTnI (≥5 ng/L) and BNP (≥100 pg/mL) had significantly higher rates of hospitalization for heart failure than patients with elevated hsTnI or elevated BNP alone. The vertical scales are different in each subgroup owing to major differences in the absolute event rates. BNP indicates B-type natriuretic peptide; and hsTnI, high-sensitivity troponin I.

The potential clinical implications of our results are particularly intriguing given the emergence of SGLT2 inhibitors for the treatment and prevention of HF. SGLT2 inhibitors have been specifically shown to reduce the risk of HHF in patients with T2DM with or without prior HF[9–11] and in patients with HF with reduced ejection fraction with or without T2DM.[12] In the present analysis, hsTnI and BNP, both individually and collectively, identified a significant gradient of HHF risk in each of these clinically relevant groups. Because the cost of

**Table 3. Comparison of Predictive Models for Heart Failure**

| Risk Model | Harrell's C-Index (95% CI) |
|---|---|
| All patients (n=15 586) | |
| Clinical risk predictors | 0.88 (0.85–0.90) |
| Clinical risk predictors and hsTnI | 0.90 (0.88–0.92) |
| Clinical risk predictors and BNP | 0.92 (0.90–0.93) |
| Clinical risk predictors and both hsTnI and BNP | 0.92 (0.91–0.94) |
| Patients with type 2 diabetes mellitus (n=4024) | |
| Clinical risk predictors | 0.82 (0.78–0.86) |
| Clinical risk predictors and hsTnI | 0.85 (0.81–0.88) |
| Clinical risk predictors and BNP | 0.87 (0.84–0.90) |
| Clinical risk predictors and both hsTnI and BNP | 0.88 (0.85–0.91) |
| Patients without type 2 diabetes mellitus (n=11 562) | |
| Clinical risk predictors | 0.86 (0.82–0.91) |
| Clinical risk predictors and hsTnI | 0.90 (0.86–0.93) |
| Clinical risk predictors and BNP | 0.92 (0.90–0.95) |
| Clinical risk predictors and both hsTnI and BNP | 0.93 (0.91–0.95) |
| Patients with prior history of heart failure (n=1216) | |
| Clinical risk predictors | 0.71 (0.67–0.76) |
| Clinical risk predictors and hsTnI | 0.75 (0.71–0.80) |
| Clinical risk predictors and BNP | 0.77 (0.73–0.81) |
| Clinical risk predictors and both hsTnI and BNP | 0.78 (0.75–0.82) |
| Patients with no prior history of heart failure (n=14 370) | |
| Clinical risk predictors | 0.81 (0.77–0.85) |
| Clinical risk predictors and hsTnI | 0.85 (0.81–0.88) |
| Clinical risk predictors and BNP | 0.89 (0.86–0.92) |
| Clinical risk predictors and both hsTnI and BNP | 0.90 (0.87–0.92) |

The clinical risk predictors include age ≥75, sex, prior heart failure, type 2 diabetes mellitus, polyvascular disease, body mass index, anemia, chronic kidney disease, and hypertension. BNP indicates B-type natriuretic peptide; and hsTnI, high-sensitivity troponin I.

SGLT2 inhibitors may be prohibitive in certain clinical settings, our data suggest that biomarker-based risk stratification may be a cost-effective strategy for identifying patients who are likely to benefit most from these HF preventive therapies. BNP and hsTnI also demonstrated a significant gradient of risk in patients with atherothrombotic disease *without* either T2DM or prior HF; although this population represents an exciting new frontier for HF prevention, the efficacy of SGLT2 inhibitors in this population remains unknown.

## Limitations

There are several limitations to this analysis. First, all patients included in this analysis were enrolled in a clinical trial, so these data may not be fully representative of a nontrial population of patients with stable atherothrombotic disease. Second, we did not assess left ventricular ejection fraction as part of the end point adjudication, so we are not able to comment on whether these biomarkers perform similarly for the prediction of HF with reduced ejection fraction and HF with preserved ejection fraction events. Finally, analyses of the selected subgroups have reduced statistical power; nevertheless, the biomarker-based risk gradients were remarkably consistent across groups.

## CONCLUSIONS

Biomarkers of myocardial injury (hsTnI) and hemodynamic stress (BNP) are powerful and independent predictors of HHF risk in patients with stable atherothrombotic disease, including in those with and without T2DM and with and without prior HF. Simultaneous assessment of both hsTnI and BNP identifies patients at particularly high risk of incident and recurrent HHF, among whom HF preventive therapies warrant investigation.

## ARTICLE INFORMATION

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## Supplementary Material

**Data S1**
**Table S1**

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# SUPPLEMENTAL MATERIAL

**Data S1.**

**Supplemental Methods. Hospitalization for Heart Failure (HHF) Endpoint Definitions.**

*Definite Hospitalization for Heart Failure (HHF)*: meets all listed criteria

1) Hospitalization ≥24 hours (or change in date if admission/discharge times not documented) ***or*** urgent/unscheduled office or emergency department visit
2) Diagnosis of heart failure (HF) by site investigator
3) Has ≥1 of the following HF symptoms:
    a. **Dyspnea** – dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough in supine position, tachypnea
    b. **Fatigue**
    c. **Reduced exercise tolerance**
    d. **Symptoms relating to decreased end-organ perfusion** – worsening cerebral, renal, liver, abdominal/gastrointestinal, or peripheral circulatory function manifested by symptoms such as dizziness, lightheadedness, syncope, confusion, altered mental status, restlessness, decline in cognitive state, nausea, vomiting, abdominal pain, abdominal fullness, abdominal discomfort or abdominal tenderness, cold clammy extremities, discoloration of extremities or lips, jaundice, pain in extremities, reduced urine output, darkening of urine color, chest pain, and/or palpitations
    e. **Other symptoms of volume overload** – swelling of lower extremities; swelling or indentation of pressure marks in areas of fluid accumulation such as the legs, ankles, or lower back; an increase in abdominal girth, right-sided abdominal fullness, discomfort, or tenderness; an increase in body weight; oozing and development of skin breakdown in lower extremities.
4) Has ≥2 of the following HF physical exam findings:
    a. **Elevated jugular venous pressure and/or positive hepatojugular reflux**
    b. **Lung auscultation suggesting pulmonary edema** – Crackles, rales, crepitations, or narrative states that pulmonary edema was found on physical exam
    c. **Peripheral edema** – double-count as "other symptom of volume overload", and vice versa
    d. **Abdominal distention or ascites** – double-count as "other symptom of volume overload", and vice versa
    e. **S3 gallop**
    f. **Weight gain** – double-count as "other symptom of volume overload", and vice versa
    g. **Report of pulmonary edema with no radiographic or auscultatory evidence cited** – assumed to be pulmonary crackles

    ***or***

    Has ≥1 HF physical exam finding and ≥1 of the following non-physical exam objective findings of HF:

    a) **Radiographic evidence of pulmonary edema** – chest radiograph or other imaging modality such as computed tomography or magnetic resonance imaging with evidence of pulmonary venous or alveolar congestion, interstitial or pulmonary edema, bilateral pleural effusions, or cephalization of venous flow
    b) **Elevated natriuretic peptides** - Serum B type natriuretic peptide (BNP) ≥ 100 pg/mL or NT-proBNP ≥ 300 pg/mL

c) **Invasive evidence of HF** - Right heart catheterization demonstrating elevated cardiac filling pressures and/or reduced cardiac index

5) Died within 48 hours of admission (*not* on comfort measures only) ***or*** received one of the following HF treatments:
    a. **Intravenous diuretic**
    b. **Intensified oral diuretic therapy** – increase in oral diuretic dose or addition of another oral diuretic (may be counted as HF treatment only if patient was hospitalized). For this analysis, diuretic therapy of unspecified route of administration was counted as "intensified oral diuretic therapy."
    c. **Intravenous vasoactive therapy** – inotrope, vasodilator, or vasopressor
    d. **Mechanical fluid removal** – ultrafiltration, hemofiltration, dialysis
    e. **Mechanical circulatory support** – intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart

*Probable HHF*: meets all listed criteria

1) Hospitalization ≥24 hours (or change in date if admission/discharge times not documented) ***or*** urgent/unscheduled office or emergency department visit
2) Diagnosis of HF by site investigator
3) Has ≥1 physical exam ***or*** non-physical exam objective finding of HF (see *Definite HHF* criteria)
4) Died within 48 hours of admission (*not* on comfort measures only) ***or*** received HF treatment (see *Definite HHF* criteria), where digoxin also counts as treatment
5) Does not meet criteria for *Definite HHF*

*Possible HHF*: meets all listed criteria

1) Hospitalization ≥24 hours (or change in date if admission/discharge times not documented) ***or*** urgent/unscheduled office or emergency department visit
2) Diagnosis of HF by site investigator ***or*** has ≥1 HF symptom (see *Definite HHF* criteria) ***or*** has HF symptom(s) not otherwise specified
3) Died within 48 hours of admission (*not* on comfort measures only) ***or*** received HF treatment, where digoxin also counts as treatment ***or*** has ≥1 HF physical exam finding ***or*** has ≥1 non-physical exam objective finding of HF (see *Definite HHF* criteria)
4) Does not meet criteria for *Definite HHF*, *Probable HHF*, or *HHF excluded*

*HHF not excluded*: meets all listed criteria

1) Hospitalization ≥24 hours (or change in date if admission/discharge times not documented) ***or*** urgent/unscheduled office or emergency department visit
2) Diagnosis of HF by site investigator ***or*** has ≥1 HF symptom (see *Definite HF* criteria) ***or*** has HF symptom(s) not otherwise specified
3) Does not meet criteria for *Definite HHF*, *Probable HHF*, *Possible HHF*, or *HHF excluded*

*HHF excluded*: meets ≥1 of the listed criteria

1) Site investigator made no HF diagnosis ***and*** made an alternative diagnosis

2) No HF diagnosis or symptoms (see *Definite HHF* criteria) are reported (including HF symptom[s] not otherwise specified)
3) Admitted for elective placement of implantable cardioverter-defibrillator but without other HF treatment, physical exam findings, non-physical exam objective findings, or new/worsening symptoms (see *Definite HHF* criteria)

**Table S1. Baseline characteristics of patients included in the biomarker substudy and overall trial population of TRA 2°P-TIMI 50.**

| Variable | Biomarker Substudy (n=15,833), % | Overall Population (n=26,449), % |
|---|---|---|
| *Demographics* | | |
| Age, mean (SD) | 61.5 (10.8) | 60.9 (10.9) |
| Female sex | 25.1 | 23.9 |
| White race | 84.5 | 87.3 |
| Body-mass index, median ($25^{th}$-$75^{th}$), $kg/m^2$ | 27 (25 – 31) | 28 (25 – 31) |
| | | |
| *Other Comorbidities* | | |
| Current smoker | 20.9 | 20.8 |
| Hypertension | 70.4 | 68.7 |
| Diabetes mellitus | 25.8 | 25.4 |
| Prior myocardial infarction | 66.7 | 72.4 |
| Prior heart failure | 7.8 | 7.8 |
| Baseline LVEF | | |
| ≥55% | 62.9 | 60.4 |
| 45-54% | 23.2 | 24.9 |
| 35-44% | 10.2 | 10.8 |
| <35% | 3.8 | 3.9 |
| Cerebrovascular disease | 27.3 | 23.7 |
| Coronary artery disease | 73.9 | 78.3 |
| Peripheral artery disease | 25.4 | 22.1 |
| Baseline eGFR <60 $mL*min^{-1}*1.73*m^{-2}$ | 16.6 | 15.6 |
| | | |
| *Baseline medication use* | | |
| ACE Inhibitor or ARB | 71.5 | 74.0 |
| Beta blocker | 64.9 | 68.8 |
| | | |
| *Serum biomarkers* | | |
| BNP | | |
| <50 pg/mL | 61.9 | 57.9 |
| 50-99 pg/mL | 20.4 | 21.3 |
| 100-200 pg/mL | 11.5 | 13.0 |
| >200 pg/mL | 6.3 | 7.7 |
| hsTnI | | |
| <2 ng/L | 10.1 | 8.9 |
| 2-<5 ng/L | 40.7 | 37.5 |
| 5-26 ng/L | 41.9 | 43.9 |
| >26 ng/L | 7.3 | 9.7 |

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; eGFR = estimated glomerular filtration rate; hsTnI = high-sensitivity troponin I; $kg/m^2$ = kilograms per meter squared; LVEF = left ventricular ejection fraction; ng/L = nanograms per liter; pg/mL = picograms per milliliter.