










ORIGINAL RESEARCH

# Risk Estimates of Imminent Cardiovascular Death and Heart Failure Hospitalization Are Improved Using Serial Natriuretic Peptide Measurements in Patients With Coronary Artery Disease and Type 2 Diabetes

Emil Wolsk , MD, PhD\*; Brian Claggett , PhD\*; Rafael Diaz , MD; Kenneth Dickstein, MD, PhD; Hertz C. Gerstein, MD; Lars Køber, MD; Eldrin F. Lewis, MD, MPH; Aldo P. Maggioni , MD; John J. V. McMurray , MD, PhD; Jeffrey L. Probstfield , MD; Matthew C. Riddle, MD; Scott D. Solomon , MD; Jean-Claude Tardif , MD; Marc A. Pfeffer , MD, PhD

**BACKGROUND:** Baseline and temporal changes in natriuretic peptide (NP) concentrations have strong prognostic value with regard to long-term cardiovascular risk stratification. To increase the clinical utility of NP sampling for patient management, we wanted to assess the incremental predictive value of 2 serial NP measurements compared with a single measurement and provide absolute risk estimates for cardiovascular death or heart failure hospitalization (HFH) within 6 months based on 2 serial NP measurements.

**METHODS AND RESULTS:** Consecutive NP samples obtained from 5393 patients with a recent coronary event and type 2 diabetes enrolled in the ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide) trial were used to construct best logistic regression models with outcome of cardiovascular death or HFH (136 events). Absolute risk estimates of cardiovascular death or HFH within 6 months using either BNP (B-type natriuretic peptide) or NT-proBNP (N-terminal pro-BNP) serial measurements were depicted based on the concentrations of 2 serial NP measurements. During the 6-month follow-up periods, the incidence rate ( $\pm 95\%$  CIs) of cardiovascular death or HFH for patients was 14.0 (11.8–16.6) per 1000 patient-years. Risk prediction depended on NP concentrations from both prior and current sampling. NP sampling 6 months apart improved the predictive value and reclassification of patients compared with a single sample (AUROC [Area Under the Receiver Operating Characteristic curve]: BNP,  $P=0.003$ . NT-proBNP,  $P<0.0001$ ), with a majority of moderate-risk patients (6-month risk between 1% and 10%) being reclassified on the basis of the second NP sample.

**CONCLUSIONS:** Serial NP measurements improved prediction of imminent cardiovascular death or HFH in patients with coronary artery disease and type 2 diabetes. The absolute risk estimates provided may aid clinicians in decision-making and help patients understand their short-term risk profile.

**Key Words:** BNP ■ ELIXA ■ heart failure ■ natriuretic peptides ■ risk stratification

See Editorial by Miller et al.

Correspondence to: Brian Claggett, PhD, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, 02115 MA.  
E-mail: bclaggett@bwh.harvard.edu

\*E. Wolsk and B. Claggett are co-first authors.

For Sources of Funding and Disclosures, see page 8.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## CLINICAL PERSPECTIVE

### What Is New?

- This study illustrates how risk prediction of imminent cardiovascular death or heart failure hospitalization is improved by incorporating information from 2 consecutive measurements of natriuretic peptides.
- Furthermore, absolute risk estimates are provided for any given 2 measurements of natriuretic peptides.

### What Are the Clinical Implications?

- The study provides absolute risk estimates for cardiovascular death or heart failure hospitalization within 6 months for any 2 given concentrations of natriuretic peptides, aiding clinicians in decision-making and helping patients understand their short-term risk profile.

## Nonstandard Abbreviations and Acronyms

|            |                               |
|------------|-------------------------------|
| <b>HFH</b> | heart failure hospitalization |
| <b>NP</b>  | natriuretic peptides          |

**N**atriuretic peptides (NP) have been shown to be strong predictors of cardiovascular mortality and morbidity. The primary clinical utility of NP measurements is to support or exclude a heart failure (HF) diagnosis in patients presenting with dyspnea.<sup>1</sup> Beyond diagnostic use, both baseline and temporal changes in NP concentrations have a strong predictive value with regard to long-term cardiovascular risk stratification in various populations, including patients with diabetes<sup>2,3</sup> and HF.<sup>4,5</sup> Higher baseline NP concentrations or NP that change from lower to higher concentrations are associated with an increased risk of cardiovascular outcomes and the opposite holds true, ie, lower or decreasing NP levels are associated with better outcomes.<sup>2-4,6,7</sup> As NP concentrations reflect left heart filling pressures,<sup>8</sup> serial NP measurements could provide information about short-term dynamic changes in left heart filling pressures and hence could serve as a strong predictive biomarker for risk of imminent cardiovascular death and heart failure hospitalization (HFH) in patients with diabetes with or without HF.<sup>4,9</sup> However, the association of changes in NP concentrations with the risk of cardiovascular events have mostly been reported as relative risks (eg, hazard ratio), which are not easily used in clinical practice.<sup>10</sup> To increase the clinical utility of serial

NP sampling for patient management, we wanted to assess the incremental predictive value of 2 serial NP measurements compared with a single measurement, and provide absolute risk estimates for cardiovascular death or HFH within 6 months based on the concentrations of 2 serial NP measurements (ie, BNP [B-type natriuretic peptide] or NT-proBNP [N-terminal pro-BNP]) in patients with a recent coronary event and type 2 diabetes (T2D) enrolled in the ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide) trial; NCT01147250.

## METHODS

The design and primary findings of ELIXA have been published.<sup>11,12</sup> Data and study materials will not be made publicly available to other researchers. The study was approved by the appropriate national and institutional regulatory and ethics boards. All the patients provided written informed consent. In summary, 6068 patients with T2D and an index acute coronary event occurring within 180 days before screening were included in the study. The objective of the trial was to assess the efficacy and safety of lixisenatide, a glucagon-like peptide-1 receptor agonist, with respect to cardiovascular morbidity and mortality. In this randomized, double-blind, placebo-controlled trial, patients were enrolled between 2010 and 2013 and followed for a median of 25 months. Key exclusion criteria were an age <30 years, an estimated glomerular filtration rate of <30 mL per minute per 1.73 m<sup>2</sup> of body-surface area, a glycosylated hemoglobin level of <5.5% or >11.0%, or an inability to provide written informed consent.

All cardiovascular events were reported to a centralized and independent adjudication committee who classified events according to pre-specified definitions.<sup>11</sup> For our analysis, the primary end point was cardiovascular death or HFH.

Sampling of BNP and NT-proBNP was performed at baseline (randomization) and at month 6, 18, and 24 after randomization. Samples were collected and analyzed at a core laboratory (Covance Central Laboratory Services, Meyrin, Switzerland). The triage BNP assay was used to analyze BNP. The intra-assay coefficient of variation was 1.1% to 3.1%. The inter-assay coefficient of variation was 1.8% to 6.6%. The Immulite NT-proBNP assay was used to analyze NT-proBNP. The intra-assay coefficient of variation was 2.3% to 5.4%. The inter-assay coefficient of variation was 4.0% to 6.4%. Baseline NP samples from 5925 patients (98%) were available for analyses. Samples were available from 5507 patients at month 6, from 4930 patients at month 18, and from 2947 patients at month 24. For our analyses, patients

were included if they had at least 1 pair of NP (both BNP and NT-proBNP) samples obtained 6 months apart (month 0–6 and/or month 18–24) with no intervening HFH and whose status was known within a 6-month window starting from the second measurement of NP. As the pre-scheduled visits during the entire follow-up included 2 separate periods with 6-month paired samples (period 1, months 0–6; period 2, months 18–24) followed by a 6-month follow-up, an individual patient could contribute to the analysis with up to 2 periods (Figure S1). Both patients with and without a history of HF before randomization were included in this analysis. If a patient with no history of HF at randomization experienced a non-fatal HFH before month 18, patients were re-classified as having a history of HF during the second observation period.

### Statistical Analysis

Baseline characteristics were compared using t tests or rank-sum tests for continuous variables, as appropriate, or  $\chi^2$  tests for categorical variables (region, race, albuminuria). Numerical values are reported as mean $\pm$ SD or median [interquartile range]. Incidence rates were estimated as the number of events occurring during the specified time interval divided by the total patient-time at risk during that interval. CIs were estimated using Poisson regression. As natriuretic peptide concentrations were right-skewed, natriuretic peptide values were natural log-transformed. BNP and NT-proBNP were considered separately. For each NP, logistic regression models with NP concentrations were used to estimate the probability of cardiovascular death or HFH within 6 months, using the baseline sample alone (prior NP) or also including the current sample (current NP). Best model fit was obtained testing both linear, quadratic, cubic, and interaction terms. The best model was chosen based as the one producing the smallest akaike information criterion among the candidate models. As individual patients could contribute with up to 2 observations periods, standard errors were estimated using patient-level clustering in regression models. A visual heat map of the absolute risk of cardiovascular death or HFH within 6 months was constructed using information from absolute concentrations of NP. To estimate changes in AUROC (Area Under the Receiver Operating Characteristic curve) and Net Reclassification Index, the base model (prior NP value) was compared with the base model+current NP sample included (*roccomp* and *incrisk* packages, STATA). Reclassification was reported both as a continuous variable (Net Reclassification Index) and according to pre-selected risk categories (>1%, 1%–2.5%, 2.5%–5%, 5%–10%, >10%) risk of cardiovascular death or HFH within 6 months.

Variables known to affect NP concentrations were identified from the literature (ie, history of HF, glomerular filtration rate, age, and body mass index) and included in the best models for sensitivity analysis.<sup>2,13</sup> *P* values <0.05 were considered statistically significant. All data analyses were conducted using STATA version 14 (College Station, TX). The graphical output was created using R statistical freeware (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

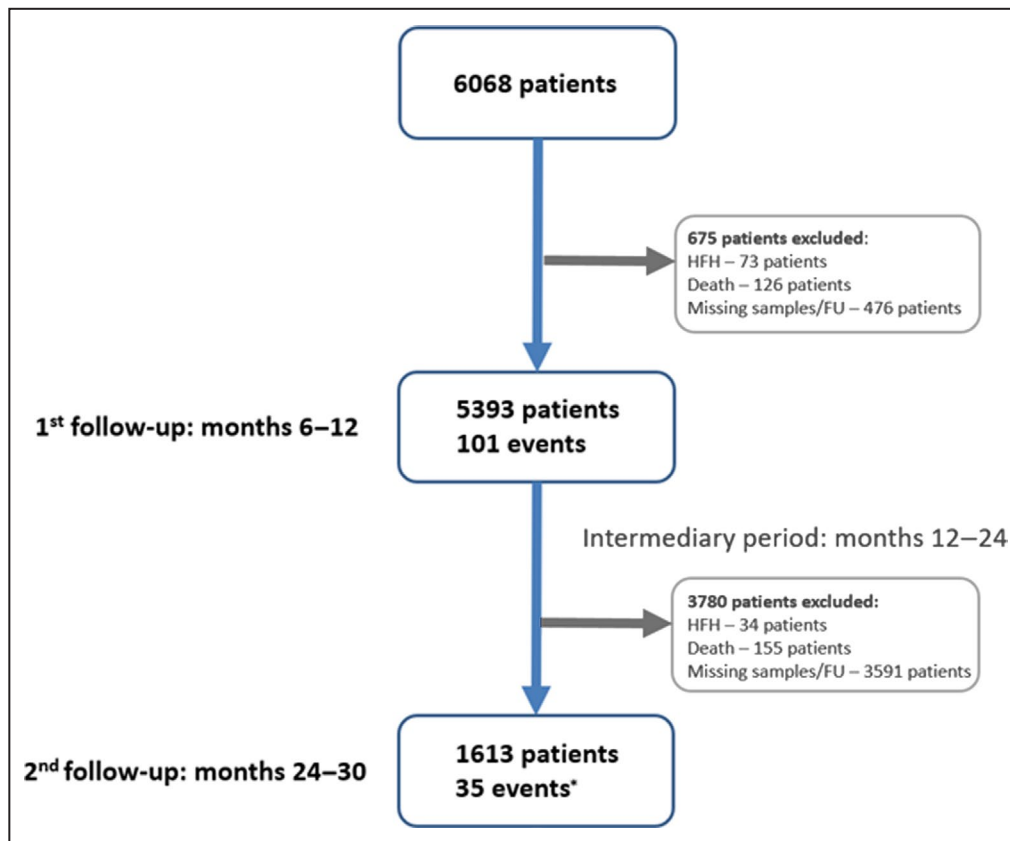
### Baseline Characteristics

Of 5393 patients with at least 1 set of paired NP samples (prior+current), 1518 of these patients contributed an additional 6-month observation period for analysis, totaling 6911 paired samples with 6-month follow-up, see consort Figure 1 for more details. Patients who were omitted from primary analyses because of missing paired NP samples and/or follow-up of 6 months (*n*=675) are characterized in Table S1. Of our included population (*n*=5393), 134 patients (2.5%) experienced a total of 136 events during the 2 6-month follow-up periods. Of these, 101 occurred during the first observation period, and 35 occurred during the second observation period.

Baseline characteristics of patients are listed in Table 1. Of the 5393 patients included, the 134 patients that experienced cardiovascular death or HFH during the 6-month follow-up periods were significantly older and had more cardiovascular risk factors, including history of HF, longer duration of T2D and more diabetic complications (neuropathy, lower estimated glomerular filtration rate, increased albuminuria) compared with those who did not experience any events during the entire trial (data not shown). Furthermore, the baseline concentrations of NP were higher in patients who experienced the primary outcome during follow-up (No events: BNP, 89 [44, 179] pg/mL; NT-proBNP, 255 [102, 636] pg/mL. Events: BNP, 310 [142, 664] pg/mL; NT-proBNP, 1214 [545, 3300] pg/mL; *P*<0.0001 for both NP). The NP values in paired samples (prior+current) were found to be highly correlated (Spearman rho=0.72 for BNP, 0.81 for NT-proBNP).

### Risk of Cardiovascular Death or HFH Within 6 Months From Last NP Sampling

During the 6-month follow-up periods, the incidence rate ( $\pm$ 95% CIs) of cardiovascular death or HFH for patients was 14.0 (11.8, 16.6) per 1000 patient-years (PY). In patients without a history of HF, the risk was 10.0 (7.0, 12.6) per 1000 PY, and in patients with a history of HF it was 28.2 (21.8, 36.4) per 1000 PY.



**Figure 1. Flowchart of study.**

Patients included in analysis during a follow-up period had to have paired natriuretic peptides samples in relationship to the specific period. FU indicates follow-up; HFH, heart failure hospitalization; and NP, natriuretic peptides. \*2 events were repeat events in the same individuals.

### Predictive Value of Current Versus Paired (Prior and Current) NP Sampling

The prior NP sample was significantly associated with outcome of cardiovascular death or HFH within 6 months using either NT-proBNP ( $P < 0.0001$ ) or BNP ( $P < 0.0001$ ). Using the prior NP value to predict the primary outcome between 6 and 12 months after it was obtained yielded the following AUROC values: BNP, 0.792 (0.747, 0.837); NT-proBNP, 0.784 (0.739, 0.829). Incorporation into the model of a second NP sample (current) obtained 6 months after the prior sample significantly improved the predictive value for both BNP (0.836 [0.795, 0.877],  $P = 0.003$ ), and NT-proBNP (0.840 [0.800, 0.881],  $P < 0.0001$ ), such that patients with greater NT-proBNP increases over the course of 6 months were at higher risk for subsequent cardiovascular death and HFH (Figure 2). A sensitivity analysis of AUROC values using single versus 2 serial measurements with differing follow-up times (3, 6, 12 months), showed that the predictive value of NP measurements decreased as follow-up was extended (Table S2).

Figure 2 depicts a heat map of the absolute risk estimates of cardiovascular death or HFH within

6 months using either BNP or NT-proBNP serial measurements.

The reclassification of patients after adding a prior NP sample to the base model was summarized both as continuous Net Reclassification Index (BNP, 58% [28%, 87%]; NT-proBNP, 60% [33%, 86%]) and according to risk categories. When patients were grouped according to preselected risk categories (<1%, 1%–2.5%, 2.5%–5%, 5%–10%, >10% risk of cardiovascular death or HFH within 6-months), patients in the range of 1% to 10% risk gained the largest incremental value of paired sampling (Tables 2 and 3). These patients accounted for 50% of all patients.

### Modifying the Predictive Value of Serial NP Sampling According to History of HF

Having a history of HF was a risk factor for 6-month cardiovascular death or HFH risk. For a given NP concentration, patients with history of HF were found to be at increased risk of events (BNP model: odds ratio, 1.4 [CI, 1.0–2.1],  $P = 0.047$ . NT-proBNP model: odds ratio, 1.3 [CI, 0.9–1.9];  $P = 0.135$ ). History of HF did not modify

**Table 1. Baseline Characteristics of All Patients (n=5393) Included in the Study**

|                                      |                |
|--------------------------------------|----------------|
| Age, y                               | 60.2±9.6       |
| Men                                  | 3762 (70%)     |
| BMI, kg/m <sup>2</sup>               | 30.1±5.7       |
| SBP, mm Hg                           | 129±17         |
| DBP, mm Hg                           | 77±10          |
| Heart rate, bpm                      | 70±10          |
| Current smoker                       | 613 (11%)      |
| Former smoker                        | 2449 (45%)     |
| Prior MI (before index ACS)          | 1179 (22%)     |
| Prior HF                             | 1190 (22%)     |
| Prior AF                             | 316 (6%)       |
| Prior stroke                         | 282 (5%)       |
| Prior CABG                           | 324 (8%)       |
| Hypertension                         | 4097 (76%)     |
| COPD                                 | 224 (4%)       |
| ACS type at index                    |                |
| STEMI                                | 2399 (44%)     |
| NSTEMI                               | 2047 (38%)     |
| UAP                                  | 942 (17%)      |
| Insulin use                          | 2070 (38%)     |
| Duration of diabetes, yr             | 9±8            |
| Albuminuria_group                    |                |
| No albuminuria                       | 4082 (76%)     |
| Microalbuminuria                     | 982 (18%)      |
| Macroalbuminuria                     | 329 (6%)       |
| HbA1c, %                             | 7.6±1.3        |
| eGFR, mL/min per 1.73 m <sup>2</sup> | 76±21          |
| NT-proBNP, pg/mL                     | 313 [123, 784] |
| BNP, pg/mL                           | 103 [48, 208]  |

ACS indicates acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; STEMI, ST-segment elevation MI; and UAP, unstable angina pectoris.

the relationships between NP and outcomes. Figure 3A and 3B depict the absolute risk estimates of cardiovascular death or HFH within 6 months for NT-proBNP serial measurements in patients without and with a history of HF, respectively. Diagrams of absolute risk estimates of cardiovascular death or HFH within 12 months using BNP or NT-proBNP serial measurements in patients without and with a history of HF were also generated (Figure S2A and S2B). Use of HF medication at baseline differed depending on history of HF (Table S3).

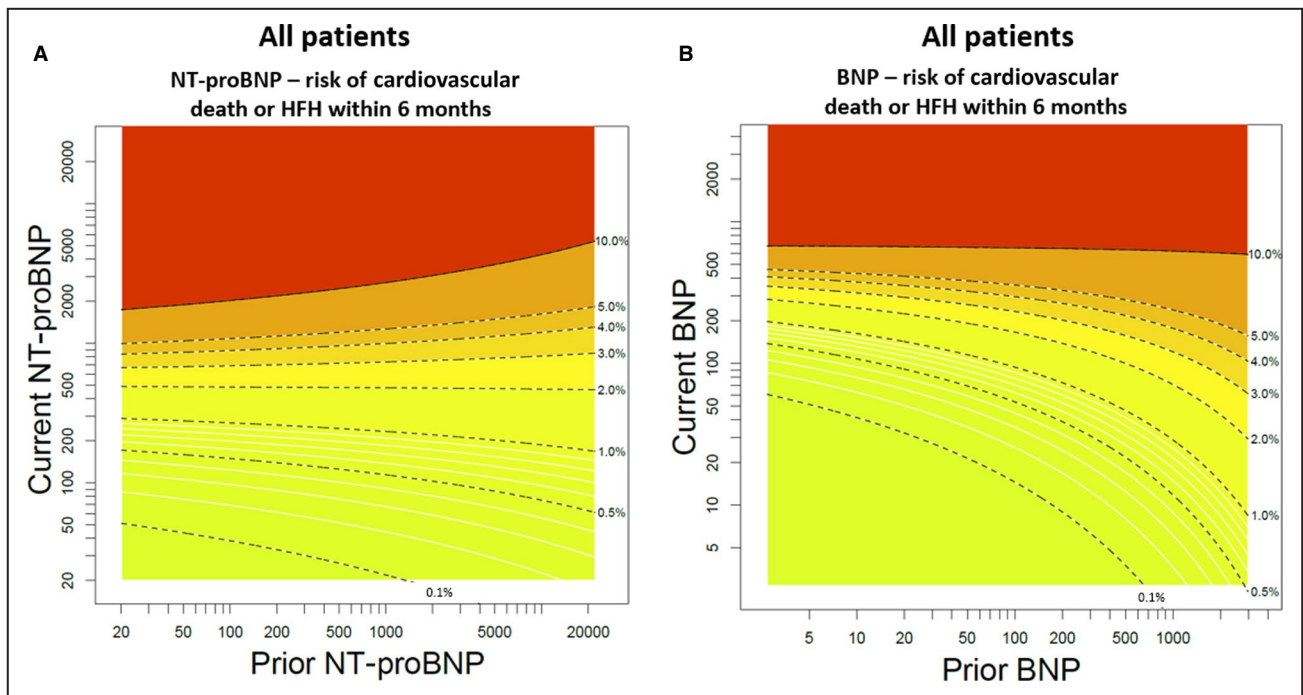
## DISCUSSION

In this study, we took advantage of regularly scheduled measurements of BNP and NT-proBNP to learn

the value of single compared with 2 serial NP measurements to predict imminent cardiovascular death or HFH. We found that the predictive value of a single sample of both BNP and NT-proBNP (prior) was highly predictive of imminent cardiovascular death or HFH. Knowing the change in either BNP or NT-proBNP concentrations over 6 months further refined prediction of this outcome. A visual heat map of the absolute risk of cardiovascular death or HFH within 6 months was constructed using information from absolute concentrations to aid clinicians with disease management and help patients understand their short-term risk profile based on serial NP concentrations.

Earlier studies have convincingly shown the strong predictive value of NP to predict long-term cardiovascular risk.<sup>2,4,7,14,15</sup> In a sub-study of the A to Z trial which included patients with a recent coronary event, patients with an increase in BNP to ≥80 pg/mL 4 months after their coronary event, had >4-fold higher risk of the composite end point of death or HF during a 2-year follow-up, compared with patients with BNP <80 pg/mL.<sup>7</sup> In a post-hoc analysis of the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) and PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Nephrilysin Inhibitor with Angiotensin-Converting-Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, patients with HF who experienced subsequent HFH or death had a greater antecedent increase or lack of decrease in NP compared with patients without these events.<sup>4,5</sup> However, data are sparse on the association of NP concentrations and short-term absolute risk of HFH in ambulatory patients, as well as comparative data on the predictive value of single versus serial NP sampling in this context. In addition, the bulk of evidence pertains to patients with HF, not patients with diabetes at high risk of cardiovascular outcomes (±HF).

Conventional biomarkers such as weight and heart rate may change preceding imminent HFH in patients with established HF. However, noticeable weight changes are only evident ≈1 week before HFH,<sup>16</sup> and even large increases in heart rate confer only moderate increases in risk of subsequent cardiovascular death or HFH.<sup>17</sup> This limits their clinical utility to identify patients at risk of imminent cardiovascular death or HFH and guide modifications in patient management. In contrast, our data showed high predictive ability of a single NP sample to predict cardiovascular death or HFH (AUROC: BNP, 0.792; NT-proBNP, 0.784), supporting recently published data from the ALTITUDE (Aliskiren in Type 2 Diabetes Using Cardiorenal Endpoints) trial.<sup>3</sup> Despite these high receiver operating characteristic values using a single NP sample, adding information from a subsequent sample obtained 6 months after was able to further refine the risk estimates (ΔAUROC:



**Figure 2.** Risk of cardiovascular death or heart failure hospitalization in all patients within the following 6 months using both a prior and a current NT-proBNP (A) or BNP (B) concentration.

Dotted lines represent percentage risk of events at various natriuretic peptide concentrations. Yellow color: risk of cardiovascular death or HFH 0% to 4.9%. Orange color: risk of cardiovascular death or HFH 5% to 9.9%. Red color: risk of cardiovascular death or HFH ≥10%. BNP indicates B-type natriuretic peptide; HFH, heart failure hospitalization; and NT-proBNP, N terminal pro-B-type natriuretic peptide.

BNP +0.04, NT-proBNP +0.06). Overall, more than half of patients were reclassified using serial NP measurements, compared with a single measurement. We observed that adding current NP information to a prior sample, most prominently reclassified patients in the risk range of 1% to 10% of cardiovascular death or HFH within 6 months. Patients at the lowest end of the risk spectrum (ie, <1%) were at such low risk, that adding information from a current sample did not have any clinical significance in risk assessment. These data support the use of NP to monitor patients at moderate-high risk of cardiovascular death or HFH and indicates that using NP sampling over time provides a valid

dynamic risk assessment in this group of patients. As this was not an interventional study, we cannot infer whether patient monitoring using our risk estimates could translate into clinical benefits.

Previous attempts to use NP to monitor clinical status of patients with HF and modify treatment have been ambiguous with regards to outcomes of cardiovascular death or HFH,<sup>18–21</sup> in contrast to the positive results from the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial that used direct and daily measurements of pulmonary artery pressure to intensify treatment.<sup>22,23</sup> The

**Table 2.** Reclassification of Patients into Predefined Risk Categories Following the Addition of a Current NT-proBNP Sample to a Prior Sample Obtained 6 Months Earlier

| Prior sample only | Current and prior sample |              |              |             |           | Total       |
|-------------------|--------------------------|--------------|--------------|-------------|-----------|-------------|
|                   | <1% risk                 | 1%–2.5% risk | 2.5%–5% risk | 5%–10% risk | >10% risk |             |
| <1% risk          | 3132 (95%)               | 123 (4%)     | 19 (1%)      | 10 (0%)     | 5 (0%)    | 3289 (48%)  |
| 1%–2.5% risk      | 1150 (55%)               | 703 (34%)    | 163 (8%)     | 55 (3%)     | 27 (1%)   | 2098 (30%)  |
| 2.5%–5% risk      | 113 (12%)                | 358 (38%)    | 282 (30%)    | 135 (14%)   | 48 (5%)   | 936 (14%)   |
| 5%–10% risk       | 9 (2%)                   | 59 (13%)     | 113 (26%)    | 130 (29%)   | 130 (29%) | 441 (6%)    |
| >10% risk         | 0 (0%)                   | 5 (3%)       | 17 (12%)     | 27 (18%)    | 98 (67%)  | 147 (2%)    |
| Total             | 4404 (64%)               | 1248 (18%)   | 594 (9%)     | 357 (5%)    | 308 (4%)  | 6911 (100%) |

Number of subjects are shown in the table. NT-proBNP indicates N-terminal pro-brain natriuretic peptide.

**Table 3. Reclassification of Patients into Predefined Risk Categories Following the Addition of a Current BNP Sample to a Prior Sample Obtained 6 Months Earlier**

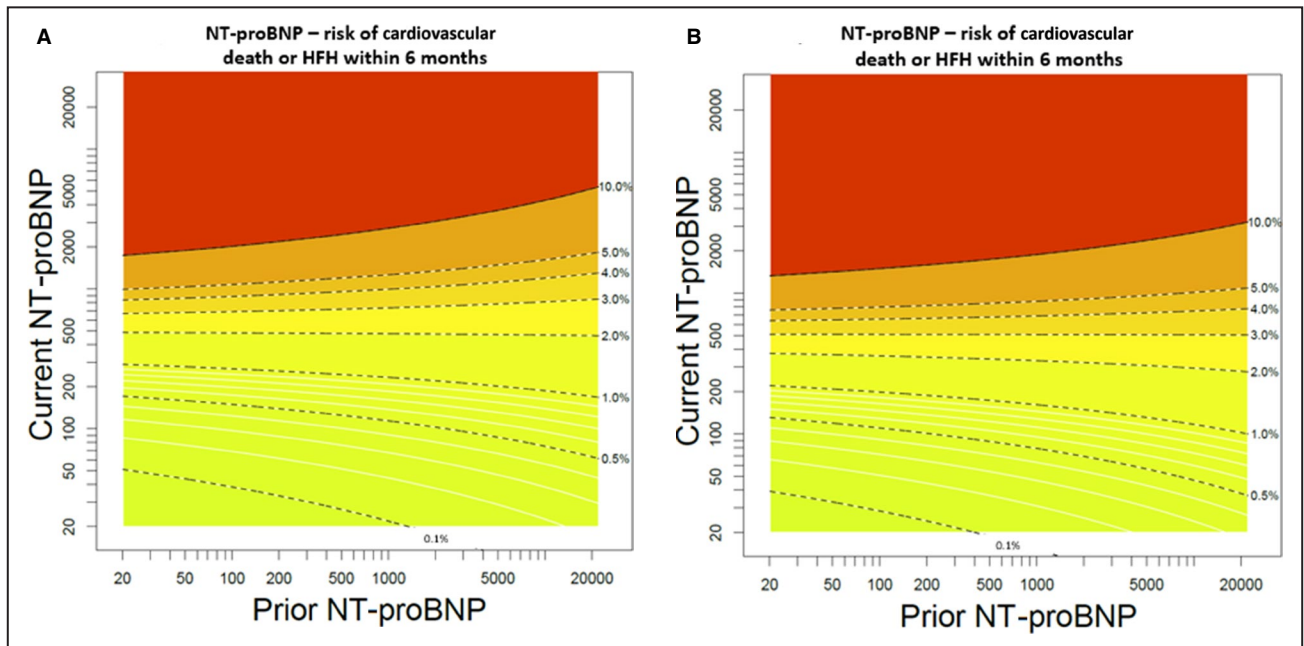
| Prior sample only | Current and prior sample |              |              |             |           | Total       |
|-------------------|--------------------------|--------------|--------------|-------------|-----------|-------------|
|                   | <1% risk                 | 1%–2.5% risk | 2.5%–5% risk | 5%–10% risk | >10% risk |             |
| <1% risk          | 2996 (91%)               | 252 (8%)     | 43 (1%)      | 8 (0%)      | 5 (0%)    | 3304 (48%)  |
| 1%–2.5% risk      | 904 (44%)                | 790 (38%)    | 294 (14%)    | 72 (3%)     | 11 (1%)   | 2071 (30%)  |
| 2.5%–5% risk      | 80 (8%)                  | 291 (31%)    | 355 (37%)    | 186 (20%)   | 41 (4%)   | 953 (14%)   |
| 5%–10% risk       | 10 (2%)                  | 48 (11%)     | 100 (23%)    | 183 (44%)   | 88 (21%)  | 429 (6%)    |
| >10% risk         | 0 (0%)                   | 2 (1%)       | 8 (5%)       | 44 (29%)    | 100 (65%) | 154 (2%)    |
| Total             | 3990 (58%)               | 1383 (20%)   | 800 (12%)    | 493 (7%)    | 245 (4%)  | 6911 (100%) |

Number of subjects are shown in the table. BNP indicates B-type natriuretic peptide.

differences in outcomes may be attributable to better temporal hemodynamic information obtained from an indwelling pressure gauge, and perhaps patient selection (eg, only NYHA class 3 patients in the CHAMPION trial). Another factor in differences in outcomes could be the treatment algorithms applied in trials using NP concentrations. Many studies used pre-specified cut-off concentrations (eg, NT-proBNP <1000 pg/mL) as a treatment target,<sup>19,21</sup> and hence individual treatment intensification was primarily pursued if NP levels exceeded the cut-off. Our data suggests that patients may still be at high risk of cardiovascular death and HFH despite having lower concentrations than the cut-off used in the trials if their NP concentrations rise

over a 6-month period (patient from ELIXA trial: NT-proBNP 300 → 990 pg/mL=6% risk of cardiovascular death or HFH within 6 months). The value of using 2 serial NP measurements was consistent irrespective of whether the follow-up period was restricted to 3, 6, or 12 months. When depicting the risk for cardiovascular death and HFH, it was evident that most of the predictive information was provided by the current sample. We believe that increasing the sampling interval beyond 6 months may diminish the incremental value provided by the addition of a prior NP sample.

Another feature of our cohort was that it included patients with and without HF. The event rate for cardiovascular death and HFH in patients with HF was ≈2- to 3-fold



**Figure 3. Risk of cardiovascular death or heart failure hospitalization within the following 6 months using both a prior and a current NT-proBNP concentration in patients without (A) and with (B) a history of heart failure.**

Dotted lines represent percentage-risk of events at various natriuretic peptide concentrations. Yellow color: risk of cardiovascular death or HFH 0% to 4.9%. Orange color: risk of cardiovascular death or HFH 5% to 9.9%. Red color: risk of cardiovascular death or HFH ≥10%. BNP indicates B-type natriuretic peptide; HFH, heart failure hospitalization; and NT-proBNP, N terminal pro-B-type natriuretic peptide.

higher than in patients without HF. Whereas the vast majority of knowledge pertaining to NP is related to patients with HF,<sup>4,14,15,24</sup> it is known that NP also has predictive value in patients without HF.<sup>9,25</sup> In accordance, we found no interaction with regard to history of HF indicating that NP changes are predictive of cardiovascular death and HFH irrespective of HF status but the magnitude of change in NP confers different risk depending on HF status.<sup>9</sup>

Our study also examined whether BNP and NT-proBNP were equally predictive of cardiovascular death and HFH. Although both NP were highly predictive of the primary end point, the change of NT-proBNP had additional value compared with BNP, and slightly more patients were reclassified with NT-proBNP. It has been shown that there are significant fluctuations in NP over time in stable patients.<sup>26</sup> When viewing paired samples of both BNP and NT-proBNP in our patients, it was apparent that serial measurements of NT-proBNP were better correlated, as has also been shown before.<sup>27,28</sup> Perhaps the lower variability in NT-proBNP makes relevant pre-event changes in this biomarker more easily identifiable from that of biological variability.

## Limitations

Our study obtained information about the history of HF at randomization. Information pertaining to the details of the HF history such as number of prior HFH, changes in (HF) medication, etc. were not the primary focus of the ELIXA trial and hence is not available in this post hoc analysis. This also limits our ability to associate changes in NP with temporal changes in medication for all patients.

Although our sampling frequency of NP surpasses that of most trials, further insights into the temporal relationship of changes in NPs and events may have been lost because of the interval between samples. Our heat maps were constructed from our models but lack CIs, which should be noted when assessing the risk estimates of patients. Furthermore, patients with estimated glomerular filtration rate <30 mL/min per 1.73 m<sup>2</sup> were excluded from this study, which should be noted, as renal function is shown to affect levels of NPs.<sup>13</sup>

Our study design allowed us to investigate changes in BNP and NT-proBNP in patients with coronary artery disease and T2D. However, we cannot infer that these changes will also be evident in patients without diabetes as diabetes itself may affect NP levels.<sup>25,29</sup> Extrapolation of the findings to other populations should be done cautiously. Although NP concentrations proved predictive of imminent cardiovascular events, we acknowledge that other biomarkers may be independently associated with outcomes and further modify the risk estimates provided in this study.

We did not have access to patient cohorts with serial NP measurements with a sufficient number of events to use as a validation cohort.

## CONCLUSIONS

Serial NP measurements improved prediction of imminent cardiovascular death or HFH in patients with coronary artery disease and T2D. The absolute risk estimates provided may aid clinicians in decision-making and further help patients understand their short-term risk profile.

## ARTICLE INFORMATION

Received February 17, 2021; accepted December 13, 2021.

### Affiliations

Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (E.W., B.C., S.D.S., M.A.P.); Department of Cardiology, Herlev-Gentofte Hospital, Herlev, Denmark (E.W.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); University of Bergen, Stavanger University Hospital, Stavanger, Norway (K.D.); Division of Endocrinology & Metabolism, McMaster University, Hamilton, ON, Canada (H.C.G.); Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (L.K.); Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, CA (E.F.L.); Research Center of the Italian Association of Hospital Cardiologists, Florence, Italy (A.P.M.); Maria Cecilia Hospital, GVM Care & Research, Cotignola, RA, Italy (A.P.M.); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.M.); Division of Cardiology, University of Washington Medical Center, Seattle, WA (J.L.P.); Division of Endocrinology, Oregon Health and Science University, Portland, OR (M.C.R.); and Montreal Heart Institute, Université de Montréal, Montreal, Canada (J.T.).

### Sources of Funding

None.

### Disclosures

E.W. reports speaker fees from Orion Pharma, Novartis Healthcare, Boehringer-Ingelheim, Merck. B.C. has received consulting fees for Amgen, Biogen, Corvia, Myokardia, and Novartis. R.D. has received a research grant from Sanofi for the ELIXA trial and reports speaker fees from Sanofi, Astra, Novo Nordisk, Eli Lilly, as well as research grants from Amarin, Amgen, Population Health Research Institute, and Montreal Heart Research Center. K.D. served on the Executive Committee for the ELIXA study. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care and reports research grants from Eli Lilly, AstraZeneca, Merck, Novo Nordisk, and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, Sanofi, and Kowa. L.K. reports speaker fees from Novartis, AstraZeneca, Novo, and Boehringer, outside this work. E.F.L. received research funding for conduct of the ELIXA study. A.P.M. reports personal fees for participation in study committees sponsored by Bayer, Fresenius, Novartis outside the present work. J.J.V.M. reports payments to their employer, Glasgow University, for their work on clinical trials, consulting, and other activities: Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cytokinetics, DalCor, GSK, Novartis, Pfizer, Theracos, and personal lecture fees: Abbott, Hickma, Sun Pharmaceuticals, Servier. M.C.R. has received research funding through Oregon Health & Science University: Eli Lilly, Novo Nordisk, AstraZeneca, and honoraria for consulting: Adocia, AstraZeneca, Eli Lilly, GlaxoSmithKline, Intercept, Novo Nordisk, Sanofi, Theracos. SDS has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Respicardia, Sanofi Pasteur, Theracos, and has consulted for Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau. J-C.T. has received research grants from Amarin, Astra-Zeneca, DalCor, Esperion, Ionis, RegenXBio, Sanofi and Servier; honoraria from DalCor, Sanofi, and Servier; holds minor equity



interest in DalCor; and is an author of a patent on pharmacogenomics-guided CETP inhibition. M.A.P. receives research support from Novartis, serves as a consultant for AstraZeneca, Corvidia, DalCor, GlaxoSmithKline, Novartis, Novo Nordisk, Pharmascience, and Sanofi, and has equity in DalCor. J.L.P. has no disclosures to report.

## Supplemental Material

Tables S1–S3

Figures S1–S2

## REFERENCES

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128
- Wolsk E, Claggett B, Pfeffer MA, Diaz R, Dickstein K, Gerstein HC, Lawson FC, Lewis EF, Maggioni AP, McMurray JVV, et al. Role of B-type natriuretic peptide and N-terminal prohormone BNP as predictors of cardiovascular morbidity and mortality in patients with a recent coronary event and type 2 diabetes mellitus. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.116.004743
- Malachias MVB, Jhund PS, Claggett BL, Wijkman MO, Bentley-Lewis R, Chaturvedi N, Desai AS, Haffner SM, Parving H-H, Prescott MF, et al. NT-proBNP by itself predicts death and cardiovascular events in high-risk patients with type 2 diabetes mellitus. *J Am Heart Assoc*. 2020;9:e017462. doi: 10.1161/JAHA.120.017462
- Zile MR, Claggett BL, Prescott MF, McMurray JVV, Packer M, Rouleau JL, Swedberg K, Desai AS, Gong J, Shi VC, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2016;68:2425–2436. doi: 10.1016/j.jacc.2016.09.931
- Yan RT, White M, Yan AT, Yusuf S, Rouleau JL, Maggioni AP, Hall C, Latini R, Afzal R, Floras J, et al. Usefulness of temporal changes in neurohormones as markers of ventricular remodeling and prognosis in patients with left ventricular systolic dysfunction and heart failure receiving either candesartan or enalapril or both. *Am J Cardiol*. 2005;96:698–704. doi: 10.1016/j.amjcard.2005.04.048
- Squire IB, O'Brien RJ, Demme B, Davies JE, Ng LL. N-terminal proatrial natriuretic peptide (N-ANP) and N-terminal pro-B-type natriuretic peptide (N-BNP) in the prediction of death and heart failure in unselected patients following acute myocardial infarction. *Clin Sci Lond Engl*. 1979;2004(107):309–316. doi: 10.1042/CS20040087
- Morrow DA, de Lemos JA, Blazing MA, Sabatine MS, Murphy SA, Jarolim P, White HD, Fox KAA, Califf RM, Braunwald E, et al. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. *JAMA*. 2005;294:2866–2871. doi: 10.1001/jama.294.22.2866
- Rademaker MT, Charles CJ, Melton IC, Richards AM, Frampton CM, Siou J, Qu F, Eigler NL, Gutfinger D, Troughton RW. Monitoring of heart failure: comparison of left atrial pressure with intrathoracic impedance and natriuretic peptide measurements in an experimental model of ovine heart failure. *Clin Sci Lond Engl*. 1979;2011(120):207–217. doi: 10.1042/CS20100388
- Wolsk E, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber L, Lawson FC, Lewis EF, Maggioni AP, McMurray JVV, et al. Increases in natriuretic peptides precede heart failure hospitalization in patients with a recent coronary event and type 2 diabetes mellitus. *Circulation*. 2017;136:1560–1562. doi: 10.1161/CIRCULATIONAHA.117.029503
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, 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. doi: 10.1161/CIR.0000000000000509
- Bentley-Lewis R, Aguilar D, Riddle MC, Claggett B, Diaz R, Dickstein K, Gerstein HC, Johnston P, Køber LV, Lawson F, et al. Rationale, design, and baseline characteristics in Evaluation of LIXisenatide in Acute Coronary Syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. *Am Heart J*. 2015;169:631–638.e7. doi: 10.1016/j.ahj.2015.02.002
- Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247–2257. doi: 10.1056/NEJMoa1509225
- Vickery S, Price CP, John RJ, Abbas NA, Webb MC, Kempson ME, Lamb EJ. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis*. 2005;46:610–620. doi: 10.1053/j.ajkd.2005.06.017
- Lindahl B, Lindbäck J, Jernberg T, Johnston N, Stridsberg M, Venge P, Wallentin L. Serial analyses of N-terminal pro-B-type natriuretic peptide in patients with non-ST-segment elevation acute coronary syndromes: a Fragmin and fast Revascularisation during In Stability in Coronary artery disease (FRISC)-II substudy. *J Am Coll Cardiol*. 2005;45:533–541. doi: 10.1016/j.jacc.2004.10.057
- Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, Tognoni G, Cohn JN. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). *J Am Coll Cardiol*. 2008;52:997–1003. doi: 10.1016/j.jacc.2008.04.069
- Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation*. 2007;116:1549–1554. doi: 10.1161/CIRCULATIONAHA.107.690768
- Vazir A, Claggett B, Jhund P, Castagno D, Skali H, Yusuf S, Swedberg K, Granger CB, McMurray JVV, Pfeffer MA, et al. Prognostic importance of temporal changes in resting heart rate in heart failure patients: an analysis of the CHARM program. *Eur Heart J*. 2015;36:669–675. doi: 10.1093/eurheartj/ehu401
- Schou M, Gustafsson F, Videbaek L, Andersen H, Toft J, Nyvad O, Ryde H, Fog L, Jensen JCH, Nielsen OW, et al. Adding serial N-terminal pro brain natriuretic peptide measurements to optimal clinical management in outpatients with systolic heart failure: a multicentre randomized clinical trial (NorthStar monitoring study). *Eur J Heart Fail*. 2013;15:818–827. doi: 10.1093/eurjhf/hft037
- Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA*. 2009;301:383–392. doi: 10.1001/jama.2009.2
- McLellan J, Heneghan CJ, Perera R, Clements AM, Glasziou PP, Kearley KE, Pidduck N, Roberts NW, Tyndel S, Wright FL, et al. B-type natriuretic peptide-guided treatment for heart failure. *Cochrane Database Syst Rev*. 2016;12:CD008966. doi: 10.1002/14651858.CD008966.pub2
- Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Mark DB, Piña IL, Passmore G, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;318:713–720. doi: 10.1001/jama.2017.10565
- Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet Lond Engl*. 2016;387:453–461. doi: 10.1016/S0140-6736(15)00723-0
- Givertz MM, Stevenson LW, Costanzo MR, Bourge RC, Bauman JG, Ginn G, Abraham WT; CHAMPION Trial Investigators. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017;70:1875–1886. doi: 10.1016/j.jacc.2017.08.010
- Anand IS, Fisher LD, Chiang Y-T, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN; Investigators V-H. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2003;107:1278–1283. doi: 10.1161/01.CIR.0000054164.99881.00
- Gori M, Gupta DK, Claggett B, Selvin E, Folsom AR, Matsushita K, Bello NA, Cheng S, Shah A, Skali H, et al. Natriuretic peptide and high-sensitivity troponin for cardiovascular risk prediction in diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetes Care*. 2016;39:677–685. doi: 10.2337/dc15-1760

- 
26. Meijers WC, van der Velde AR, Muller Kobold AC, Dijck-Brouwer J, Wu AH, Jaffe A, de Boer RA. Variability of biomarkers in patients with chronic heart failure and healthy controls. *Eur J Heart Fail.* 2017;19:357–365. doi: 10.1002/ejhf.669
  27. Schou M, Gustafsson F, Nielsen PH, Madsen LH, Kjaer A, Hildebrandt PR. Unexplained week-to-week variation in BNP and NT-proBNP is low in chronic heart failure patients during steady state. *Eur J Heart Fail.* 2007;9:68–74. doi: 10.1016/j.ejheart.2006.05.001
  28. O'Hanlon R, O'Shea P, Ledwidge M, O'Loughlin C, Lange S, Conlon C, Phelan D, Cunningham S, McDonald K. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. *J Card Fail.* 2007;13:50–55. doi: 10.1016/j.cardfail.2006.09.003
  29. Peng Q, Hu W, Su H, Yang Q, Cheng X. Levels of B-type natriuretic peptide in chronic heart failure patients with and without diabetes mellitus. *Exp Ther Med.* 2013;5:229–232. doi: 10.3892/etm.2012.760

# Supplemental Material

**Table S1. Baseline characteristics of patients included vs. excluded from the study.**

|                                     | Patients excluded (n=675) | Patients included (n=5393) |          |
|-------------------------------------|---------------------------|----------------------------|----------|
|                                     |                           |                            | P-values |
| <b>Age (years)</b>                  | 60.9 ± 10.0               | 60.2 ± 9.6                 | 0.09     |
| <b>Male</b>                         | 444 (66.1%)               | 3762 (69.8%)               | 0.05     |
| <b>BMI (kg/m<sup>2</sup>)</b>       | 30.6 ± 5.9                | 30.1 ± 5.7                 | 0.03     |
| <b>SBP (mmHg)</b>                   | 130.3 ± 17.8              | 129.5 ± 17.2               | 0.24     |
| <b>DBP (mmHg)</b>                   | 76.9 ± 11.2               | 77.1 ± 9.9                 | 0.53     |
| <b>Heart rate (bpm)</b>             | 71.8 ± 10.2               | 69.9 ± 10.4                | <0.001   |
| <b>Current smoker</b>               | 96 (14.3%)                | 613 (11.4%)                | 0.03     |
| <b>Former smoker</b>                | 296 (44.1%)               | 2449 (45.4%)               | 0.52     |
| <b>Prior MI (before index ACS)</b>  | 209 (31.1%)               | 1179 (21.9%)               | <0.001   |
| <b>Prior HF</b>                     | 210 (31.3%)               | 1194 (22.1%)               | <0.001   |
| <b>Prior AF</b>                     | 58 (8.6%)                 | 345 (6.4%)                 | 0.03     |
| <b>Prior stroke</b>                 | 47 (7.0%)                 | 282 (5.2%)                 | 0.06     |
| <b>Prior CABG</b>                   | 82 (12.2%)                | 424 (7.9%)                 | <0.001   |
| <b>Hypertension</b>                 | 535 (79.6%)               | 4097 (76.0%)               | 0.04     |
| <b>COPD</b>                         | 44 (7.2%)                 | 230 (4.2%)                 | <0.001   |
| <b>ACS type at index</b>            |                           |                            | <0.001   |
| <b>STEMI</b>                        | 267 (39.9%)               | 2399 (44.5%)               |          |
| <b>NSTEMI</b>                       | 299 (44.7%)               | 2047 (38.0%)               |          |
| <b>UAP</b>                          | 99 (14.8%)                | 942 (17.5%)                |          |
| <b>Insulin use</b>                  | 303 (45.1%)               | 2070 (38.4%)               | <0.001   |
| <b>Duration of diabetes (years)</b> | 10.5 ± 9.1                | 9.1 ± 8.1                  | <0.001   |

|                             |                      |                      |        |
|-----------------------------|----------------------|----------------------|--------|
| <b>albuminuria_group</b>    |                      |                      | <0.001 |
| <b>No albuminuria</b>       | 447 (66.5%)          | 4082 (75.7%)         |        |
| <b>Microalbuminuria</b>     | 165 (24.6%)          | 982 (18.2%)          |        |
| <b>Macroalbuminuria</b>     | 60 (8.9%)            | 329 (6.1%)           |        |
| <b>HbA1c (%)</b>            | 7.8 ± 1.3            | 7.7 ± 1.3            | 0.15   |
| <b>eGFR (ml/min/1.73m2)</b> | 72.9 ± 21.6          | 76.3 ± 21.3          | <0.001 |
| <b>BNP (pg/ml)</b>          | 120.0 [56.0, 237.0]  | 97.0 [47.0, 199.0]   | <0.001 |
| <b>NT-proBNP (pg/ml)</b>    | 326.0 [113.0, 819.0] | 286.7 [112.0, 728.0] | <0.001 |

**Table S2. The predictive ability of current natriuretic peptide measurements added to prior natriuretic peptide measurements depending on differences in follow-up time.**

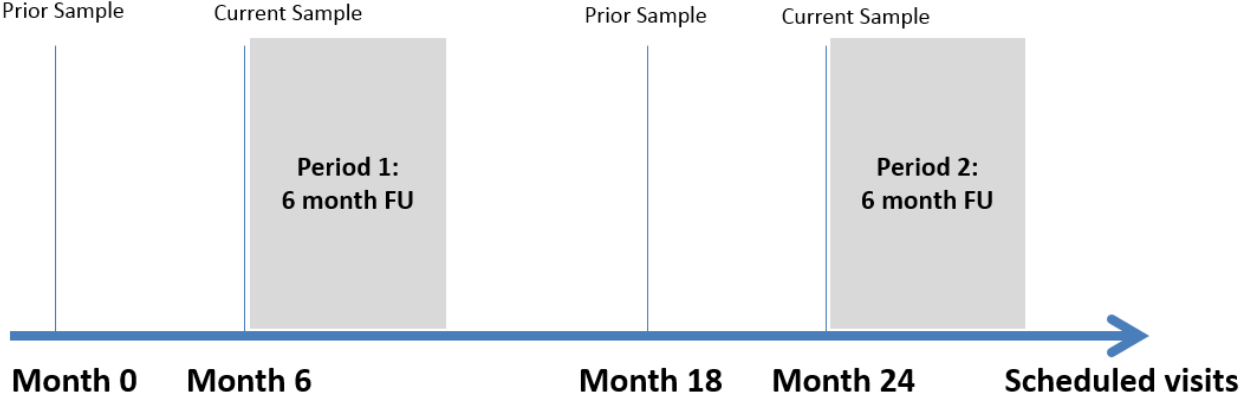
| Follow-up period              |           | AUROC      |                 |        | p value |
|-------------------------------|-----------|------------|-----------------|--------|---------|
|                               |           | Prior only | Prior + Current | Delta  |         |
| <b>3 months (90 events)</b>   | NT-proBNP | 0.803      | 0.853           | +0.050 | 0.02    |
|                               | BNP       | 0.804      | 0.856           | +0.052 | 0.02    |
| <b>6 months (136 events)</b>  | NT-proBNP | 0.784      | 0.840           | +0.056 | 0.0001  |
|                               | BNP       | 0.792      | 0.836           | +0.044 | 0.003   |
| <b>12 months (240 events)</b> | NT-proBNP | 0.768      | 0.818           | +0.050 | <0.0001 |
|                               | BNP       | 0.775      | 0.809           | +0.034 | 0.002   |

- All models adjust for history of heart failure

**Table S3. Heart failure medication at baseline in patient with and without a history of heart failure.**

|                                    | <b>Patients with no heart failure at baseline (n=4199)</b> | <b>Patients with heart failure at baseline (n=1194)</b> |         |
|------------------------------------|--|---|---------|
|                                    |  |   | P-value |
| <b>ACE inhibitor/AT2rb</b>         | 3556 (84.7%)   | 1049 (87.9%)  | 0.006   |
| <b>Beta-blockers</b>               | 3510 (83.6%)   | 1053 (88.2%)  | <0.001  |
| <b>Potassium-sparing diuretics</b> | 423 (10.1%)  | 340 (28.5%)   | <0.001  |
| <b>Diuretics</b>                   | 1360 (32.4%)   | 729 (61.1%)   | <0.001  |

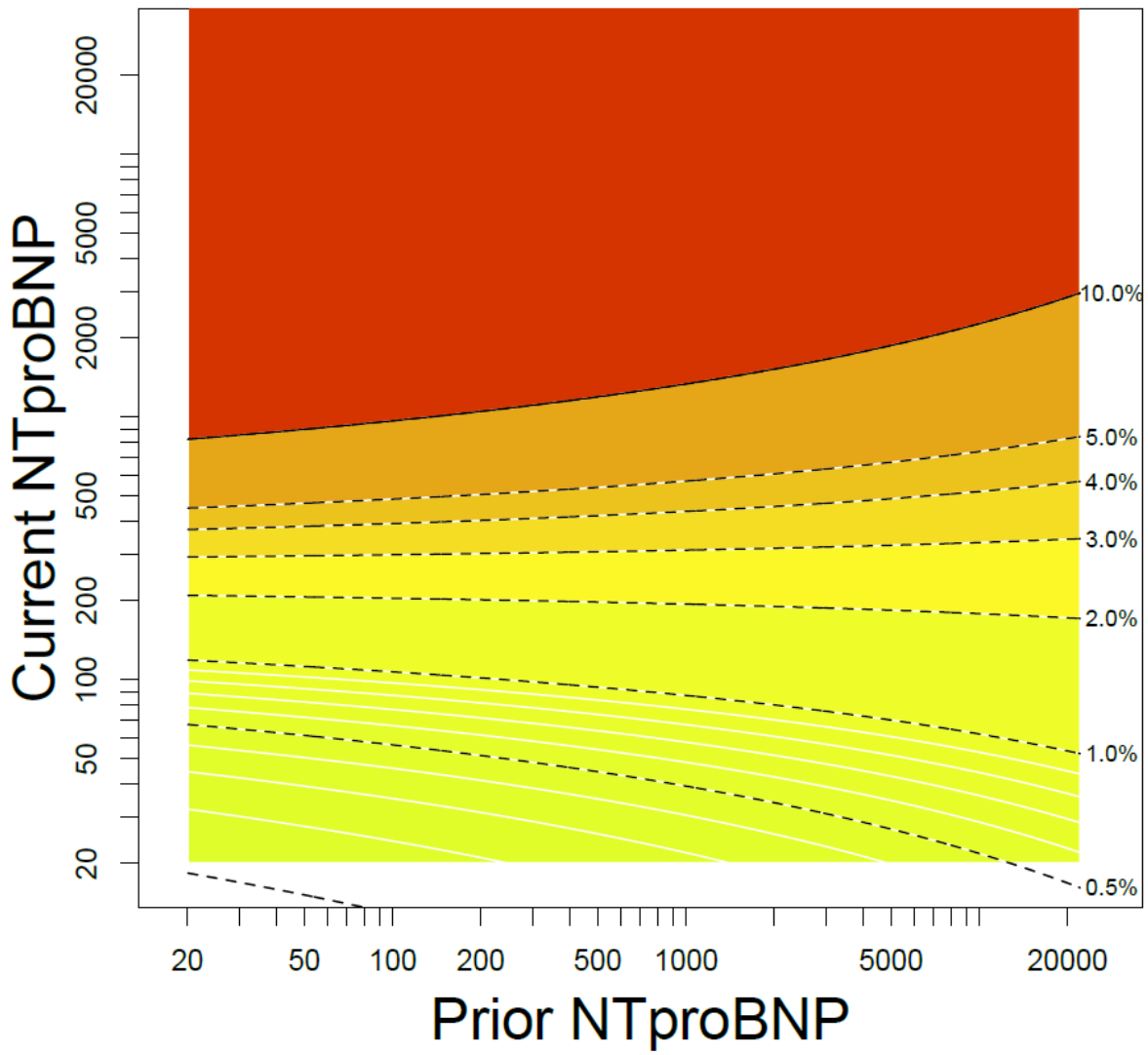
**Figure S1. Sampling and study design.**





**Figure S2 A. Risk of cardiovascular death or heart failure hospitalization within the following 12 months in patients with no history of heart failure using both a prior and a current NT-proBNP concentration.**

**NTproBNP: 365-day risk of CV Death + HF**



**Figure S2 B. Risk of cardiovascular death or heart failure hospitalization within the following 12 months in patients with a history of heart failure using both a prior and a current NT-proBNP concentration.**

