Clinical and Biomarker Predictors of Expanded Heart Failure Outcomes in Patients With Type 2 Diabetes Mellitus After a Recent Acute Coronary Syndrome: Insights From the EXAMINE Trial

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Background—Improved heart failure (HF) risk stratification after a recent acute coronary syndrome may identify those who can benefit from therapies that reduce HF risk. We aimed to identify clinical and biomarker predictors for expanded HF outcomes in patients with type 2 diabetes mellitus after recent acute coronary syndrome.

Methods and Results—The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial was a multicenter, non-inferiority, double-masked, placebo-controlled study which randomized 5380 patients with type 2 diabetes mellitus after recent acute coronary syndrome to alogliptin or placebo. Baseline biomarkers were measured in 5154 patients: N-terminal pro-B-type natriuretic peptide and clinical variables enabled risk stratification for expanded HF outcomes.

Conclusions—Among patients with type 2 diabetes mellitus after recent acute coronary syndrome, the use of biomarkers such as N-terminal pro-B-type natriuretic peptide and clinical variables enables risk stratification for expanded HF outcomes.

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Key Words: biomarkers • heart failure • natriuretic peptide • risk stratification

Diabetes mellitus is one of the most prevalent comorbidities in patients with heart failure (HF) and patients with type 2 diabetes mellitus are at significantly increased risk for developing incident and recurrent HF.1–3 Furthermore, the burden of HF events and HF death remains substantially high in patients with type 2 diabetes mellitus and established cardiovascular disease,4,5 even in patients with optimally controlled background risk factors and glycemic control.6 Trials of oral anti-hyperglycemic therapies such as thiazolidinediones and select dipeptidyl peptidase-4 inhibitors have demonstrated a significantly increased risk of HF.7–9 Other clinical markers of worsening HF, such as increased use of loop diuretics and increased peripheral edema, were also seen in these studies.7,8 Emerging anti-hyperglycemic therapies such as sodium glucose cotransporter-2 inhibitors have demonstrated a reduction in the risk of HF in large
cardiovascular outcome trials.10–13 Biomarkers play an important role in the risk stratification for incident and recurrent HF.14 To date, there are limited data on the use of clinical variables and biomarkers for HF risk stratification in patients with type 2 diabetes mellitus after recent acute coronary syndrome (ACS). Improved HF risk stratification may help to identify patients with type 2 diabetes mellitus who are post ACS, who may benefit from therapies, such as sodium glucose cotransporter-2 inhibitors, that can reduce the risk of HF outcomes.

To address this knowledge gap, we evaluated whether clinical variables and biomarkers can improve risk stratification for expanded heart failure (HF) outcomes in patients with type 2 diabetes mellitus after recent acute coronary syndrome (ACS) in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial.

Research Design and Methods

EXAMINE Trial

The design, rationale, results, and details of the EXAMINE trial have been previously published.15–18 The data used for this analysis from the EXAMINE trial are currently not publicly available. Briefly, the EXAMINE trial was a multicenter, randomized, non-inferiority, double-masked, placebo-controlled, cardiovascular safety trial. Patients were eligible if they had type 2 diabetes mellitus, 15 to 90 days post ACS, glycated hemoglobin between 6.5% and 11% at the time of screening (or 7%–11% if they were taking insulin), and were receiving drugs other than a dipeptidyl peptidase-4 inhibitor or glucagon-like peptide 1 receptor agonist to treat diabetes mellitus. Patients were excluded if they had type 1 diabetes mellitus; end-stage renal disease and were receiving dialysis; New York Heart Association class IV HF; refractory angina; uncontrolled arrhythmias; significant valve disease; or severe uncontrolled hypertension. In total, 5380 patients with type 2 diabetes mellitus and an ACS event within 15–90 days (before enrollment) were randomly assigned to receive alogliptin or placebo, administered in a double-masked fashion, in addition to standard treatment. Overall, alogliptin was non-inferior to placebo for the primary outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The median follow-up was 597 days (interquartile range 361–792 days). The institutional review board or ethics committee at each participating institution reviewed and approved the trial. All patients randomized in the trial provided informed consent, including for the biomarker study.

Biomarker Measurements

The biomarker population included 5154 patients at baseline. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was measured in all available samples from the 6-month follow-up visit. At baseline, blood was drawn into EDTA-anticoagulated plastic tubes and plasma was isolated and frozen at −20°C to −80°C at the local sites until they were shipped to the central laboratory. Frozen samples were then shipped to the Biomarker Research/Thrombolysis in Myocardial Infarction Clinical Trials Laboratory (Brigham and Women's Hospital [Boston, MA]), and were stored at −80°C or colder. Biomarkers across pathophysiologic pathways were measured including biomarker of myocardial stretch (NT-proBNP, Roche Diagnostics, Indianapolis, IN), cardiac ischemia (high-sensitivity troponin I [Hs-Tnl, Abbott Laboratories]), atherogenesis (Adiponectin [R&D Systems, Minneapolis, MN]), inflammation (growth-differentiation-factor-15 [GDF-15; Roche Diagnostics, Minneapolis, MN, USA], and macrophage activation (galectin-3 [Gal-3, BG Medicine, Inc, Waltham, MA]). Details of these assays have been provided previously.19–22

Outcomes of Interest

The primary outcome of the present analysis was an expanded HF outcome consisting of the composite of cardiovascular death, HF hospitalization, initiation of loop diuretics, or NT-proBNP elevation during follow-up (measured at 6 months). The secondary outcome of interest was the composite of cardiovascular death or HF hospitalization.

Statistical Analysis

Baseline continuous variables are presented as median (25th, 75th percentile) and categorical variables as number/total non-missing (percentage) among patient with and without biomarkers. A baseline clinical model was derived using age, sex, systolic blood pressure at baseline, history of HF,
Table 1. Baseline Characteristics

| Characteristics | Biomarker Population (n=5154) | With Primary Outcome (n=837) | Without Primary Outcome (n=4543) |
|-----------------|-------------------------------|---------------------------|---------------------------------|
| **Demographics**|                               |                           |                                 |
| Age, y          |                               |                           |                                 |
| Mean±SD (n)     | 60.9±9.9                      | 63.2±10.0                 | 60.5±9.8                        |
| Median          | 61.0                          | 63.0                      | 60.0                            |
| Range (min, max)| (26.0, 91.0)                 | (38.0, 91.0)              | (26.0, 91.0)                    |
| Male            | 67.7% (3491)                  | 58.8% (492)               | 69.5% (3159)                    |
| **Race**        |                               |                           |                                 |
| American Indian or Alaska Native | 2.1% (106) | 2.6% (22) | 1.9% (88) |
| Asian           | 20.0% (1030)                  | 21.5% (180)               | 20.0% (909)                     |
| Black or African American | 3.9% (203) | 5.7% (48) | 3.7% (168) |
| Native Hawaiian or Other Pacific Islander | 0.2% (11) | 0.1% (1) | 0.2% (10) |
| White           | 73.0% (3760)                  | 68.6% (574)               | 73.4% (3335)                    |
| Multiracial     | 0.9% (44)                     | 1.4% (12)                 | 0.7% (33)                       |
| **Ethnicity**   |                               |                           |                                 |
| Hispanic or Latino | 28.4% (1465) | 29.4% (246) | 28.4% (1291) |
| Not Hispanic or Latino | 71.6% (3689) | 70.6% (591) | 71.6% (3252) |
| **Region**      |                               |                           |                                 |
| United States, Canada | 15.5% (800) | 16.1% (135) | 15.8% (718) |
| Mexico, Central/South America | 25.9% (1333) | 27.8% (233) | 25.5% (1160) |
| Western Europe, Australia, New Zealand, Middle East | 11.5% (595/5154) | 11.0% (92) | 11.5% (524) |
| Eastern Europe, Africa | 28.4% (1465) | 24.9% (208) | 28.6% (1300) |
| Asia/Pacific    | 18.6% (961)                   | 20.2% (169)               | 18.5% (841)                     |
| Current smoker  | 13.7% (705)                   | 11.9% (100)               | 14.0% (634)                     |
| **NYHA class**  |                               |                           |                                 |
| I               | 22.0% (317)                   | 22.1% (76)                | 22.1% (255)                     |
| II              | 57.7% (831)                   | 51.2% (176)               | 59.6% (689)                     |
| III             | 18.9% (273)                   | 24.7% (85)                | 17.2% (199)                     |
| IV              | 1.4% (20)                     | 2.0% (7)                  | 1.1% (13)                       |
| **BMI, kg/m²**  |                               |                           |                                 |
| Mean±SD (n)     | 29.5±5.6                      | 30.0±6.6                  | 29.4±5.4                        |
| Median          | 28.7                          | 29.2                      | 28.7                            |
| Range (min, max)| (15.6, 68.3)                 | (15.6, 67.2)              | (15.7, 68.3)                    |
| **Systolic BP, mm Hg** |                       |                           |                                 |
| Mean±SD (n)     | 129.1±16.6                    | 130.4±18.3                | 128.7±16.3                      |
| Median          | 130.0                         | 130.0                     | 130.0                           |
| Range (min, max)| (80.0, 202.0)                | (82.0, 195.0)             | (80.0, 202.0)                   |
| **Diastolic BP, mm Hg** |                   |                           |                                 |
| Mean±SD (n)     | 76.4±9.7                      | 75.9±10.4                 | 76.5±9.5                        |
| Median          | 78.0                          | 78.0                      | 78.0                            |
| Range (min, max)| (40.0, 122.0)                | (40.0, 110.0)             | (42.0, 122.0)                   |

Continued
### Table 1. Continued

| Characteristics                  | Biomarker Population (n=5154) | With Primary Outcome (n=837) | Without Primary Outcome (n=4543) |
|----------------------------------|------------------------------|-----------------------------|---------------------------------|
| Heart rate, bpm                  |                              |                             |                                 |
| Mean±SD (n)                      | 71.4±10.8                    | 72.9±11.9                   | 71.1±10.5                       |
| Median                           | 70.0                         | 72.0                        | 70.0                            |
| Range (min, max)                 | (40.0, 143.0)                | (44.0, 118.0)               | (40.0, 143.0)                   |
| Medical history                  |                              |                             |                                 |
| Hypertension                     | 83.3% (4291)                 | 90.0% (753/837)             | 81.8% (3716)                    |
| Myocardial infarction            | 88.0% (4534)                 | 91.2% (763/837)             | 87.4% (3971)                    |
| Coronary bypass surgery          | 12.8% (659)                  | 17.4% (146/837)             | 11.9% (542)                     |
| Peripheral arterial disease      | 9.5% (489)                   | 14.6% (122/837)             | 8.6% (392)                      |
| Congestive heart failure         | 28.0% (1442)                 | 41.1% (344/837)             | 25.5% (1157)                    |
| Laboratory Results               |                              |                             |                                 |
| eGFR, mL/min per 1.73 m²         |                              |                             |                                 |
| Mean±SD (n)                      | 70.9±21.4                    | 62.1±22.5                   | 72.6±20.8                       |
| Median                           | 71.1                         | 61.7                        | 72.9                            |
| Range (min, max)                 | (4.2, 186.1)                 | (5.0, 143.0)                | (4.2, 186.1)                    |
| Glycated hemoglobin (%)          |                              |                             |                                 |
| Mean±SD (n)                      | 8.0±1.1                      | 8.0±1.0                     | 8.0±1.1                         |
| Median                           | 7.9                          | 7.9                         | 7.9                             |
| Range (min, max)                 | (4.9, 12.8)                  | (5.8, 12.8)                 | (4.9, 12.7)                     |
| Total cholesterol, mg/dL         |                              |                             |                                 |
| Mean±SD (n)                      | 154.4±44.0                   | 161.7±48.5                  | 153.0±42.8                      |
| Median                           | 147.0                        | 152.0                       | 146.0                           |
| Range (min, max)                 | (58.0, 481.0)                | (59.0, 390.0)               | (58.0, 481.0)                   |
| HDL cholesterol, mg/dL           |                              |                             |                                 |
| Mean±SD (n)                      | 43.1±10.5                    | 43.1±11.1                   | 43.2±10.5                       |
| Median                           | 42.0                         | 42.0                        | 42.0                            |
| Range (min, max)                 | (11.0, 106.0)                | (18.0, 115.0)               | (11.0, 104.0)                   |
| LDL cholesterol, mg/dL           |                              |                             |                                 |
| Mean±SD (n)                      | 78.7±34.8                    | 85.2±38.3                   | 77.4±33.9                       |
| Median                           | 72.0                         | 78.0                        | 71.0                            |
| Range (min, max)                 | (2.0, 290.0)                 | (12.0, 250.0)               | (2.0, 290.0)                    |
| Triglycerides, mg/dL             |                              |                             |                                 |
| Mean±SD (n)                      | 164.5±104.4                  | 167.4±99.6                  | 164.0±104.7                     |
| Median                           | 141.0                        | 144.0                       | 140.0                           |
| Range (min, max)                 | (34.0, 1631.0)               | (46.0, 838.0)               | (34.0, 1631.0)                  |
| Hemoglobin, g/dL                 |                              |                             |                                 |
| Mean±SD (n)                      | 13.5±1.6                     | 12.9±1.7                    | 13.6±1.5                        |
| Median                           | 13.6                         | 13.0                        | 13.6                            |
| Range (min, max)                 | (7.2, 19.7)                  | (7.2, 18.7)                 | (7.2, 19.7)                     |
| BNP, pg/mL                       |                              |                             |                                 |
| Mean±SD (n)                      | 162.1±276.7                  | 307.8±422.8                 | 135.0±229.9                     |

Continued
### Table 1. Continued

| Characteristics                  | Biomarker Population (n=5154) | With Primary Outcome (n=837) | Without Primary Outcome (n=4543) |
|----------------------------------|------------------------------|-------------------------------|----------------------------------|
| Median                           | 75.8                         | 157.4                        | 66.4                             |
| Range (min, max)                 | (9.0, 3879.7)                | (9.0, 3879.7)                 | (9.0, 3633.1)                    |
| Sodium, mEq/L                    |                              |                               |                                  |
| Mean±SD (n)                      | 139.9±2.8                    | 139.7±3.0                    | 139.9±2.8 (4542)                 |
| Median                           | 140.0                        | 140.0                        | 140.0                            |
| Range (min, max)                 | (119.0, 153.0)               | (122.0, 150.0)               | (119.0, 153.0)                   |
| Potassium, mEq/L                 |                              |                               |                                  |
| Mean±SD (n)                      | 4.5±0.5                      | 4.5±0.5                      | 4.5±0.5                          |
| Median                           | 4.4                          | 4.5                          | 4.4                              |
| Range (min, max)                 | (2.6, 9.2)                   | (2.9, 7.5)                   | (2.6, 9.2)                       |
| WBC, K/cu mm                     |                              |                               |                                  |
| Mean±SD (n)                      | 7.4±2.4                      | 7.5±2.1                      | 7.3±2.4                          |
| Median                           | 7.1                          | 7.3                          | 7.1                              |
| Range (min, max)                 | (2.0, 97.4)                  | (2.7, 16.8)                  | (2.0, 97.4)                      |
| Platelet count, K/cu mm          |                              |                               |                                  |
| Mean±SD (n)                      | 232.6±71.5                   | 234.6±78.4                   | 232.0±69.9                       |
| Median                           | 223.0                        | 222.0                        | 223.0                            |
| Range (min, max)                 | (46.0, 833.0)                | (74.0, 833.0)                | (46.0, 744.0)                    |
| Baseline medications             |                              |                               |                                  |
| Diabetic agents                  | 98.9% (5099)                 | 98.7% (826)                  | 99.0% (4499)                     |
| Sulfonylureas                    | 46.4% (2393)                 | 44.9% (376)                  | 46.8% (2127)                     |
| Metformin                        | 66.2% (3412)                 | 57.0% (477)                  | 67.9% (3085)                     |
| Insulin                          | 29.9% (1540)                 | 38.0% (318)                  | 28.3% (1287)                     |
| Thiazolidinediones               | 2.4% (126)                   | 2.4% (20)                    | 2.4% (111)                       |
| Pioglitazone                     | 2.3% (116)                   | 2.0% (17)                    | 2.3% (104)                       |
| Rosiglitazone                    | 0.2% (10)                    | 0.4% (3)                     | 0.2% (7)                         |
| Antiplatelet agents              | 97.3% (5014)                 | 95.5% (799)                  | 97.6% (4433)                     |
| ASA                              | 90.9% (4683)                 | 88.8% (743)                  | 91.1% (4138)                     |
| Thieno                           | 80.4% (4146)                 | 77.7% (650)                  | 80.8% (3670)                     |
| Cholesterol lowering agents      | 92.1% (4745)                 | 89.4% (748)                  | 92.3% (4194)                     |
| Statin                           | 90.6% (4672)                 | 87.3% (731)                  | 91.0% (4135)                     |
| Fibrate                          | 5.2% (266)                   | 6.1% (51)                    | 5.0% (227)                       |
| Niacin                           | 1.0% (49)                    | 0.8% (7)                     | 0.9% (43)                        |
| Ezetimibe                        | 2.3% (117)                   | 2.7% (23)                    | 2.1% (97)                        |
| Beta blockers                    | 82.3% (4240)                 | 79.6% (666)                  | 82.4% (3745)                     |
| Renin-angiotensin system-blocking agents | 82.4% (4247) | 84.1% (704)                  | 81.6% (3707)                     |
| ACEI                             | 62.1% (3201)                 | 59.7% (500)                  | 62.1% (2823)                     |
| ARB                              | 22.2% (1145)                 | 26.8% (224)                  | 21.3% (966)                      |
| Diuretics                        | 37.4% (1929)                 | 49.6% (415)                  | 35.2% (1599)                     |
| Thiazide                         | 15.0% (771)                  | 17.8% (149)                  | 14.4% (653)                      |

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duration of diabetes mellitus, prior myocardial infarction, hypertension, hyperlipidemia, smoking, and estimated glomerular filtration rate (eGFR; based on variables used in prior analyses).5,16–19 The multivariable association of baseline variables and clinical outcomes were assessed using Cox proportional hazards regression models, reported as hazard ratio (HR) and 95% CI.

The association between individual biomarkers (hs-TnI, NT-proBNP, GDF-15, adiponectin, and Gal-3) and time to events was determined. Linearity testing was performed to assess the relationship between biomarker and end point. The net reclassification improvement index was presented with 95% bootstrap CI. Continuous net reclassification improvement was calculated as it is the most objective and versatile measure of improvement in risk prediction. CI’s come from 1000 bootstrap samples selected with replacement of the size equal to the number of observations in the original data set. The biomarker cut-offs in the present analysis were determined through a complement of existing literature and statistical consideration. The following values were used as cut-offs for elevated biomarkers: adiponectin, values in the 4th quartile (ranging from 20.5 to 115 ng/mL); HsTnI ≥16 ng/mL for female and ≥34 ng/L male participants; NTproBNP ≥450 pg/mL for patients aged <50 years, ≥900 pg/mL for patients aged 50 to 75 years and ≥1800 for patients aged ≥75 years; and GDF-15 ≥1800 pg/mL23–25 The C-index is presented for the clinical model and with the addition of biomarker dichotomized as elevated or not elevated. Data were analyzed using SAS version 9.4 software (SAS, Cary, North Carolina). Statistical significance was based on a P<0.05.

### Results

#### Baseline Demographics

Among patients with biomarkers values (n=5154), the median age was 61.0 years, 67.7% (n=3491) were men, 73.0% (n=3760) were white, 83.3% (n=4291) had a history of hypertension, and 28.0% (n=1442) had a baseline history of HF (Table 1). Median biomarker levels at baseline were: hs-TnI 9 ng/L; Gal-3 17 ng/mL; adiponectin 5.2 μg/mL; NT-proBNP 422 pg/mL; and GDF-15 1246 pg/mL. Patients with a primary end point, compared with those who did not experience the end point, were older (63.2 versus 60.5 years of age), less likely to be men (58.8% versus 69.5%), and had a greater burden of cardiovascular comorbidities (Table 1).

#### Association of Clinical Variables and Biomarkers With Outcomes

Median patient follow-up was 18 months. Using clinical variables alone, eGFR (per unit increase, HR 0.98, 95% CI 0.98–0.99) and history of HF (HR 1.65, 95% CI 1.42–1.91) were most frequent clinical variables associated with the primary outcome (by the Wald-square measure) (Figure S1; Table 2). In univariate analysis, each biomarker was individually associated with the primary outcome (Table S1). In the multivariable model with both clinical variables and biomarkers, NT-proBNP was the strongest variable (by the Wald-square measure) associated with the primary outcome (per log2 HR 1.24, 95% CI 1.18–1.31) followed by a history of HF (HR 1.42, 95% CI 1.39–1.45).

### Table 1. Associated of Clinical Variables and Biomarkers With Outcomes

| Variable                                      | Hazard Ratio (95%CI) | Wald $\chi^2$ | p Value |
|-----------------------------------------------|----------------------|---------------|---------|
| eGFR, mL/min per 1.73 m²                       | 0.98 (0.98, 0.99)    | 52.3          | <0.0001 |
| Heart failure                                 | 1.65 (1.42, 1.91)    | 43.9          | <0.0001 |
| Duration of diabetes mellitus                 | 1.02 (1.01, 1.03)    | 19.8          | <0.0001 |
| Hypertension                                  | 1.47 (1.15, 1.88)    | 9.4           | 0.002   |
| Myocardial infarction                         | 1.47 (1.15, 1.87)    | 9.4           | 0.002   |
| Men                                           | 0.81 (0.70, 0.95)    | 7.1           | 0.008   |
| Smoking status                                | 1.17 (0.94, 1.46)    | 2.0           | 0.2     |
| Age                                           | 1.00 (1.00, 1.01)    | 0.9           | 0.4     |
| Hyperlipidemia                                | 1.06 (0.89, 1.25)    | 0.4           | 0.5     |
| Systolic BP, mm Hg                            | 1.00 (1.00, 1.01)    | 0.1           | 0.8     |

BP indicates blood pressure; eGFR, estimate glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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[1] Sharma et al. (2023). Predictors of Expanded Heart Failure Outcomes. *Journal of the American Heart Association*. DOI: 10.1161/JAHA.119.012797
95% CI 1.22–1.65) (Figure S2; Table 3). eGFR no longer remained significantly associated with the primary outcome in the multivariable model. All other biomarkers except adiponectin were also associated with the primary outcome in the multivariable model: GDF-15 (per log2 HR 1.15, 95% CI 1.04–1.28); Gal-3 (per log2 HR 1.21, 95% CI 1.03–1.41), and hs-TnI (per log2 HR 1.04, 95% CI 1.00–1.09).

For the secondary outcome of the composite of cardiovascular death or HF hospitalization, in the multivariable model with only clinical variables, the most associated variables were a history of HF (HR 2.89; 95% CI 2.33–3.58) followed by eGFR (per unit increase HR 0.98; 95% CI 0.97–0.98) (Table S2). Similar to the primary outcome, each individual biomarker in the univariate analysis was associated with cardiovascular death or HF hospitalization (Table S1). In the multivariable analysis, a doubling of NT-proBNP was most associated with cardiovascular death or HF hospitalization (per log2 HR 1.45; 95% CI 1.34–1.57), followed by a history of HF (HR 2.20; 95% CI 1.76–2.76), a doubling of hsTnI (per log2 HR 1.10; 95% CI 1.04–1.16), and a doubling of GDF-15 (per log2 HR 1.22; 95% CI 1.05–1.41) (Table S3). The P-value for the Hosmer-Lemeshow Goodness of fit test is <0.001 for the baseline clinical model and clinical model with the biomarkers (as continuous and cut-offs).

**Risk Stratification for Outcomes**

Compared with the baseline clinical model, individual biomarkers improved the discrimination in risk prediction of the primary outcome (Table 4). NT-proBNP, when added to a base clinical model, was associated with the greatest increase in discrimination compared with other individual biomarkers (c-statistic from 0.66 to 0.71) (Table 4). When combined, all biomarkers increased the discrimination of the primary end point compared with the baseline model (c-statistic from 0.66 to 0.72) (Table 4). For the secondary end point of cardiovascular death or HF hospitalization, NT-proBNP, compared with other biomarkers, was associated with the largest increase in outcome discrimination (c-statistic from 0.75 to 0.82) (Table S4). When all biomarkers were combined with the clinical model, the outcome discrimination improved (c-statistic from 0.75 to 0.83) (Table S4).

**Discussion**

Improving risk stratification for HF outcomes in patients with type 2 diabetes mellitus is crucial given the emergence of therapies that may reduce the risk of incident and recurrent HF. While multi-biomarker approaches to risk stratification for HF outcomes have been demonstrated in HF populations, there are sparse data among patients with type 2 diabetes mellitus. We evaluated the role of a combined clinical variables and biomarkers to improve risk stratification for HF outcomes in patients with type 2 diabetes mellitus post ACS in the EXAMINE trial. Our results identified that biomarkers, especially NT-proBNP, were among the strongest parameters associated with future risk of expanded HF outcomes while a prior history of HF was the strongest clinical predictor. Use of both clinical variables and biomarkers improved risk stratification for expanded HF outcomes over a clinical model. Our results suggest that the use of biomarkers either alone (NT-proBNP) or in combination may improve identification of patients with type 2 diabetes mellitus after a recent ACS who are at increased for future HF events.

Initiation of loop diuretics among stable patients may reflect an attempt at management of water retention or worsening HF symptoms and may be considered a marker for future risk of HF. Similarly, elevations in natriuretic peptides also reflect an increased risk of HF events. Expanding the definition of HF to include these end points as a component of the composite outcome enables a more sensitive definition of HF. In a prior analysis of the EXAMINE study, an increased NT-proBNP at baseline was significantly associated with increased future risk of HF.

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**Table 3. Multivariable Clinical and Biomarker Predictors of the Composite Outcome of Cardiovascular Death, Heart Failure Hospitalization, Initiation of Loop Diuretics, or Elevated NT-proBNP During Follow-Up**

| Variable | Hazard Ratio (95% CI) | Wald $\chi^2$ | P Value |
|----------|-----------------------|--------------|---------|
| log$_2$ (NT-proBNP) | 1.24 (1.18, 1.31) | 67.4 | <0.0001 |
| Heart failure | 1.42 (1.22, 1.65) | 20.8 | <0.0001 |
| Hypertension | 1.63 (1.27, 2.09) | 14.5 | 0.0001 |
| Duration of diabetes mellitus | 1.01 (1.00, 1.02) | 8.2 | 0.004 |
| log$_2$ (GDF-15) | 1.15 (1.04, 1.28) | 7.2 | 0.007 |
| log$_2$ (Gal-3) | 1.21 (1.03, 1.41) | 5.5 | 0.02 |
| Male | 0.83 (0.71, 0.97) | 5.5 | 0.02 |
| log$_2$ (hsTnI) | 1.04 (1.00, 1.09) | 4.2 | 0.04 |
| Hyperlipidemia | 1.16 (0.97, 1.38) | 2.7 | 0.1 |
| Smoking status | 1.17 (0.93, 1.45) | 1.9 | 0.2 |
| Systolic BP, mm Hg | 1.00 (1.00, 1.01) | 0.7 | 0.4 |
| log$_2$ (adiponectin) | 1.04 (0.95, 1.14) | 0.7 | 0.4 |
| Age | 1.00 (0.99, 1.01) | 0.6 | 0.5 |
| eGFR, mL/min per 1.73 m$^2$ | 1.00 (0.99, 1.00) | 0.3 | 0.6 |
| Myocardial infarction | 1.01 (0.79, 1.30) | 0.01 | 0.9 |

The clinical model adjusted by age (continuous), sex, systolic blood pressure (continuous), history of heart failure, duration of diabetes mellitus, prior myocardial infarction, hypertension, hyperlipidemia, smoking, estimated glomerular filtration rate (continuous). BP indicates blood pressure; Gal-3, galectin-3; GDF-15, growth-differentiation-factor –15; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
predictors of expanded heart failure outcomes

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HF have been advocated in consensus guidelines.14 Among mechanisms to identify patients at risk for incident HF and recurrent hospitalization or cardiovascular death.

The results were seen consistently across the more traditional HF outcome composite of HF hospitalization or initiation of loop diuretics, or elevated NT-proBNP during follow-up.

Furthermore, the risk of future cardiovascular events remained persistently elevated when landmarked for elevated NT-proBNP at 6 months. Similar findings have been seen with serial measurements of hs-TnI in the EXAMINE trial21 and in community cohorts.28 In our analysis, the association of an elevated NT-proBNP at baseline with an increased future risk of cardiovascular death or HF hospitalization or initiation of loop diuretic is not unexpected. A prior study demonstrated that adiponectin (a marker of atherogenesis) was associated with increased risk of cardiovascular events in the EXAMINE trial.22 When evaluated in our multivariable model, adiponectin was not associated with expanded HF outcomes. However, our analysis identified that biomarkers associated with myocardial stretch (NT-proBNP), cardiac fibrosis (GDF-15),29,30 cardiac ischemia (hsTnI)31,32 and macrophage activation (Gal-3)33,34 are significantly associated with an increased risk of our expanded primary HF outcome; these results suggest that multiple pathophysiologic mechanisms may be playing a role in driving the development of HF in patients with type 2 diabetes mellitus post-ACS. The results were seen consistently across the more traditional HF outcome composite of HF hospitalization or cardiovascular death.

Using multiple biomarkers across pathophysiologic mechanisms to identify patients at risk for incident HF and recurrent HF have been advocated in consensus guidelines.14 Among 15,10 stable community participants with diabetes mellitus but without prevalent cardiovascular disease in the Atherosclerosis Risk in Communities study, both troponin T ≥14 ng/L (HR 1.96, 95% CI 1.57–2.46) and NT-proBNP >125 pg/mL (HR 1.61, 95% CI 1.29–1.99) were statistically associated with incident cardiovascular events (coronary heart disease, HF, or stroke).28 In post-ACS patients with type 2 diabetes mellitus, the risk of HF and recurrent ACS remains high yet there are limited data on strategies to optimize risk prediction.18,23 Our demonstration that among patients with type 2 diabetes mellitus post ACS, a multi-biomarker approach improves the risk stratification of expanded HF outcomes has significant therapeutic implications. For example, among higher risk patients, medications such as sodium glucose cotransporter-2 inhibitors that may reduce the risk of HF events can be initiated or intensified.

Gal-3 indicates galectin-3; GDF-15, growth-differentiation-factor -15; hs-CRP, high-sensitivity C-reactive protein; integration, discrimination index; IDI, integration discrimination index; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*The clinical model adjusted by age (continuous), sex, systolic blood pressure (continuous), history of heart failure, duration of diabetes mellitus, prior myocardial infarction, hypertension, hyperlipidemia, smoking, estimated glomerular filtration rate (continuous).

Cardiovascular death, myocardial infarction, or stroke.20

Table 4. Discrimination for the Composite Outcome of Cardiovascular Death, Heart Failure Hospitalization, Initiation of Loop Diuretics, or Elevated NT-proBNP During Follow-Up

| Models | c-Statistic | Change in c-Statistic | Continuous NRI (95% Bootstrap CI) | IDI (95% Bootstrap CI) |
|--------|-------------|-----------------------|-----------------------------------|-----------------------|
| Clinical model* | 0.66 | | | |
| Clinical model+hsTnI | 0.68 | 0.019 | 0.2914 (0.2054, 0.3705) | 0.0340 (0.0283, 0.0406) |
| Clinical model+NT-proBNP | 0.71 | 0.050 | 0.3854 (0.3037, 0.4721) | 0.0877 (0.077, 0.0976) |
| Clinical model+GDF-15 | 0.67 | 0.010 | 0.1521 (0.0631, 0.243) | 0.0183 (0.014, 0.0235) |
| Clinical model+Gal-3 | 0.67 | 0.009 | 0.1265 (0.0384, 0.2062) | 0.0162 (0.0123, 0.0204) |
| Clinical model+adiponectin | 0.67 | 0.010 | 0.1455 (0.0561, 0.2311) | 0.0091 (0.0062, 0.0129) |
| Clinical model+all biomarkers | 0.72 | 0.054 | 0.4097 (0.3245, 0.4963) | 0.0955 (0.0848, 0.1078) |
| Clinical model+hsTnI (by cut-offs) | 0.67 | 0.008 | 0.2380 (0.1559, 0.3231) | 0.0152 (0.0111, 0.0192) |
| Clinical model+NTproBNP (by cut-offs) | 0.69 | 0.028 | 0.4141 (0.3314, 0.4948) | 0.0487 (0.0421, 0.0553) |
| Clinical model+GDF-15 (by cut-offs) | 0.67 | 0.005 | 0.2485 (0.1571, 0.3316) | 0.0088 (0.0062, 0.0114) |
| Clinical model+Gal-3 (by cut-offs) | 0.67 | 0.004 | 0.1832 (0.0940, 0.2660) | 0.0057 (0.0039, 0.0079) |
| Clinical model+adiponectin (by cut-offs) | 0.67 | 0.005 | 0.2226 (0.1416, 0.3096) | 0.0067 (0.0042, 0.0095) |
| Clinical model+all biomarkers(by cut-offs) | 0.70 | 0.034 | 0.3996 (0.3159, 0.4867) | 0.0588 (0.0515, 0.0662) |

Gal-3 indicates galectin-3; GDF-15, growth-differentiation-factor -15; hs-CRP, high-sensitivity C-reactive protein; integration, discrimination index; IDI, integration discrimination index; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
from therapies such as mineralocorticoid receptor antagonists and sodium glucose cotransporter-2 inhibitors.

Limitations
The EXAMINE trial was composed of patients with type 2 diabetes mellitus who had a recent ACS; as such the results of our analysis may not be generalizable to other populations with type 2 diabetes mellitus. Additional measures of HF status such as left ventricular ejection fraction, a known prognostic marker in patients with diabetes mellitus, were not formally assessed. While the c-statistic improved from 0.66 to 0.70 for the model with biomarkers for the expanded HF outcome, the clinical utility of such an increase in discrimination remains unclear. The results from the P-value of calibration of the Hosmer-Lemeshow Goodness of Fit test highlight the challenges in model calibration for expanded HF outcomes. Nevertheless, EXAMINE may be an optimal setting to investi- gate this issue given the trial enrolled the highest proportion of patients with baseline HF (28%) of any cardiovascular safety trial of anti-hyperglycemic therapies, enriched cardiovascular risk given the requirement for a recent ACS, and collected robust biomarker data in >95% of enrolled patients.

Conclusions
Among stable patients with type 2 diabetes mellitus after recent ACS, combining clinical variables with biomarkers approach allows for risk stratification for a broad range of heart failure events. Given the emergence of anti-hyperglycemic therapies that reduce the risk of heart failure among patients with type 2 diabetes mellitus and established cardiovascular disease, future randomized studies evaluating the role of risk prediction using clinical factors and biomarkers to target these medical therapies are warranted. In settings where assaying multiple biomarkers is impractical, measurement of natriuretic peptides as a single biomarker may most inform risk of future HF events. Patients with type 2 diabetes mellitus and elevated natriuretic peptide concentrations or prior history of HF face particularly high risks of subsequent HF events and warrant closer monitoring.

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Supplemental Material
Table S1. Univariate association of individual biomarkers with heart failure outcomes.

| Biomarkers          | HF hospitalization or elevated NTproBNP during follow-up or initiation of loop diuretics or CV death | HF hospitalization or CV death |
|---------------------|--------------------------------------------------------------------------------------------------|-------------------------------|
|                     | Hazard ratio (95% CI)                                                                 | P value                      |
| Biomarker (continuous) |                                                                                                 |                               |
| log2 (hsTnI)        | 1.18 (1.15, 1.21)                                                                                 | <.0001                        |
| log2 (NTproBNP)     | 1.40 (1.35, 1.46)                                                                                 | <.0001                        |
| log2 (GDF15)        | 1.67 (1.55, 1.80)                                                                                 | <.0001                        |
| log2 (GAL3)         | 1.94 (1.74, 2.16)                                                                                 | <.0001                        |
| log2 (ADPN)         | 1.53 (1.42, 1.66)                                                                                 | <.0001                        |
| Biomarkers (by cut-offs) |                                                                                                 |                               |
| Elevated hsTnI      | 1.77 (1.52, 2.06)                                                                                 | <.0001                        |
| Elevated NTproBNP   | 2.61 (2.27, 3.00)                                                                                 | <.0001                        |
| Elevated GDF15      | 2.09 (1.81, 2.40)                                                                                 | <.0001                        |
| Elevated GAL3       | 1.96 (1.70, 2.26)                                                                                 | <.0001                        |
| Elevated ADPN       | 1.92 (1.66, 2.22)                                                                                 | <.0001                        |

ADPN: adiponectin; GaL-3: galectin-3; GDF-15: growth-differentiation-factor -15; hs-CRP: high sensitivity C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide.
Table S2. Multivariable clinical predictors for the composite of heart failure hospitalization or cardiovascular death.

| Variable                  | Hazard ratio(95%CI) | Wald $X^2$ | P value |
|---------------------------|---------------------|------------|---------|
| Heart failure             | 2.89 (2.33, 3.58)   | 94.3       | <.0001  |
| eGFR (ml/min/1.73m$^2$)  | 0.98 (0.97, 0.98)   | 50.9       | <.0001  |
| Myocardial infarction     | 3.43 (2.00, 5.88)   | 20.1       | <.0001  |
| Duration of diabetes      | 1.02 (1.01, 1.03)   | 10.5       | 0.0012  |
| age                       | 1.01 (1.00, 1.03)   | 5.1        | 0.0244  |
| Systolic BP (mmHg)        | 0.99 (0.99, 1.00)   | 3.8        | 0.0515  |
| Hyperlipidemia            | 1.23 (0.96, 1.57)   | 2.7        | 0.0985  |
| Hypertension              | 1.33 (0.93, 1.90)   | 2.4        | 0.1246  |
| Male                      | 0.91 (0.73, 1.13)   | 0.7        | 0.3933  |
| Smoking Status            | 1.16 (0.83, 1.62)   | 0.7        | 0.3965  |

eGFR: estimate glomerular filtration rate; BP blood pressure.
Table S3. Multivariable clinical variables and biomarkers for the outcome of heart failure hospitalization and cardiovascular death.

| Variable                  | Hazard ratio (95%CI) | Wald $X^2$ | P value |
|---------------------------|----------------------|------------|---------|
| log$_2$(NTproBNP)         | 1.45 (1.34, 1.57)    | 78.8       | <.0001  |
| Heart Failure             | 2.20 (1.76, 2.76)    | 47.2       | <.0001  |
| log$_2$(hsTnI)            | 1.10 (1.04, 1.16)    | 12.0       | 0.0005  |
| log$_2$(GDF15)            | 1.22 (1.05, 1.41)    | 7.0        | 0.0080  |
| Hyperlipidemia            | 1.41 (1.08, 1.83)    | 6.6        | 0.0103  |
| Hypertension              | 1.54 (1.07, 2.23)    | 5.3        | 0.0216  |
| Myocardial infarction     | 1.85 (1.06, 3.23)    | 4.7        | 0.0302  |
| Duration of diabetes      | 1.01 (1.00, 1.02)    | 2.9        | 0.0873  |
| log$_2$(GAL3)             | 1.18 (0.95, 1.47)    | 2.2        | 0.1411  |
| Systolic BP (mmHg)        | 1.00 (0.99, 1.00)    | 1.6        | 0.2122  |
| Age                       | 1.01 (1.00, 1.02)    | 1.3        | 0.2516  |
| Male                      | 0.90 (0.71, 1.13)    | 0.8        | 0.3642  |
| Smoking Status            | 1.16 (0.82, 1.63)    | 0.7        | 0.3959  |
| log$_2$(ADPN)             | 1.03 (0.90, 1.17)    | 0.2        | 0.6861  |
| eGFR (ml/min/1.73m$^2$)   | 1.00 (0.99, 1.01)    | 0.04       | 0.8306  |

ADPN: adiponectin; Gal-3: galectin-3; GDF-15: growth-differentiation-factor-15; eGFR: estimated glomerular filtration rate; hs-CRP: high sensitivity C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide.
### Table S4. Discrimination for the outcome of heart failure hospitalization or cardiovascular death.

| Models                                      | c-statistic | Change in c-statistic | Continuous NRI (95% Bootstrap CI) | IDI (95% Bootstrap CI) |
|---------------------------------------------|-------------|-----------------------|-----------------------------------|------------------------|
| Clinical model*                             | 0.75        |                       |                                   |                        |
| Clinical model + hsTnI                      | 0.78        | 0.036                 | 0.5778 (0.4562, 0.6992)           | 0.0708 (0.0527, 0.0921) |
| Clinical model + NTproBNP                   | 0.82        | 0.075                 | 0.6684 (0.5655, 0.7735)           | 0.1619 (0.1344, 0.1947) |
| Clinical model + GDF15                      | 0.76        | 0.016                 | 0.2066 (0.0818, 0.3356)           | 0.0305 (0.0181, 0.046)  |
| Clinical model + GAL3                       | 0.76        | 0.011                 | 0.2246 (0.1062, 0.3401)           | 0.0208 (0.0123, 0.0311) |
| Clinical model + ADPN                       | 0.76        | 0.015                 | 0.2644 (0.1422, 0.3887)           | 0.0132 (0.0037, 0.0236) |
| **Clinical model + All biomarkers**         | 0.83        | 0.082                 | 0.6994 (0.5924, 0.8101)           | 0.1747 (0.145, 0.2091)  |
| Clinical model + hsTnI (by cut-offs)        | 0.76        | 0.016                 | 0.4460 (0.3213, 0.5796)           | 0.0411 (0.0276, 0.0553) |
| Clinical model + NTproBNP (by cut-offs)     | 0.81        | 0.060                 | 0.9041 (0.7951, 1.0132)           | 0.1302 (0.1099, 0.1516) |
| Clinical model + GDF15 (by cut-offs)        | 0.76        | 0.010                 | 0.4195 (0.3013, 0.5416)           | 0.0168 (0.0094, 0.0239) |
| Clinical model + GAL3 (by cut-offs)         | 0.76        | 0.007                 | 0.3139 (0.1853, 0.4307)           | 0.0131 (0.0081, 0.019)  |
| Clinical model + ADPN (by cut-offs)         | 0.76        | 0.014                 | 0.4065 (0.2829, 0.5394)           | 0.0198 (0.0105, 0.0295) |
| **Clinical model + All biomarkers (by cut-offs)** | 0.82        | 0.068                 | 0.8276 (0.721, 0.9346)            | 0.1522 (0.1299, 0.1791) |

*The clinical model adjusted by age (continuous), sex, systolic blood pressure (continuous), history of heart failure, duration of diabetes, prior myocardial infarction, hypertension, hyperlipidemia, smoking, estimated glomerular filtration rate (continuous). ADPN: adiponectin; Gal-3: galectin-3; GDF-15: growth-differentiation-factor-15; hs-CRP: high sensitivity C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide.
Figure S1. Relative importance of clinical variables for the composite outcome of cardiovascular death, heart failure hospitalization, initiation of loop diuretics, or elevated NT-proBNP during follow-up.

eGFR estimated glomerular filtration rate. Variables with a p-value ≥0.05 for the association with the variable and outcome in multivariable analysis are not displayed. A higher $X^2$ score implies a stronger association with the outcome.
Figure S2. Relative importance of clinical variables and biomarkers for the composite outcome of cardiovascular death, heart failure hospitalization, initiation of loop diuretics, or elevated NT-proBNP during follow-up.

NT-proBNP N-terminal pro-B-type natriuretic peptide; GDF-15 growth-differentiation-factor-15; Gal-3 galectin-3. Variables with a p-value ≥0.05 for the association with the variable and outcome in multivariable analysis are not displayed. A higher $X^2$ score implies a stronger association with the outcome.