ORIGINAL RESEARCH

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

Abhinav Sharma, MD, PhD; Muthiah Vaduganathan, MD, MPH; João Pedro Ferreira, MD, PhD; Yuyin Liu, MSc; George L. Bakris, MD; Christopher P. Cannon, MD; William B. White, MD; Faiez Zannad, MD, PhD

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: NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity troponin I, adiponectin, growth-differentiation-factor-15, and galectin-3. Our primary outcome was cardiovascular) death, HF hospitalization, elevated NT-proBNP during follow-up, or loop diuretics initiation. The association between clinical variables, biomarkers, and outcomes were assessed using Cox regression models. In the study population, the median age was 61.0 years, 67.7% were men, and 28.0% had baseline HF (median follow-up was 18 months). In multivariable analyses, NT-proBNP had the strongest association with the primary outcome (per $\log_2$, hazard ratio 1.24; Wald χ^2 67.4; $P<0.0001$) followed by a prior HF history (hazard ratio 1.42; Wald χ^2 20.8; $P<0.0001$). A model with clinical variables and biomarkers allowed for risk prediction for expanded HF outcomes (C-statistic=0.72). Discrimination results were similar for cardiovascular death or HF hospitalization.

Conclusions—Among patients with type 2 diabetes mellitus after recent acute coronary syndrome, the use 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

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Accompanying Tables S1 through S4 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012797

Correspondence to: Abhinav Sharma, MD, PhD, McGill University Health Centre, 1001 Decarie Blvd, Montreal, Quebec, Canada. E-mail: sabhinav@stanford.edu

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Clinical Perspective

What Is New?

- Prognostication for heart failure events remains challenging among patients with type 2 diabetes mellitus who are post-acute coronary syndrome.
- Natriuretic peptides and a clinical history of heart failure are the strongest predictors of future heart failure events.

What Are the Clinical Implications?

- NT-proBNP (N-terminal pro-B-type natriuretic peptide) combined with clinical variables should be considered when risk stratifying patients with type 2 diabetes mellitus post-acute coronary syndrome for future heart failure events.

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-TnI, 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 NTproBNP 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/m^2			
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 m^2			
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)

Continued

Table 1. Continued

Characteristics	Biomarker Population (n=5154)	With Primary Outcome (n=837)	Without Primary Outcome (n=4543)
Loop	17.5% (901)	23.9% (200)	16.3% (740)
Nitrates	32.6% (1678)	38.7% (324)	31.6% (1435)
Calcium channel blockers	22.4% (1153)	27.4% (229)	21.3% (968)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker ASA, aspirin; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA New York Heart Association; WBC, white blood cell count.

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 is 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. CIs 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 7.94 to 63.48 μg/mL); Gal-3 values in the 4th quartile (ranging from 20.5 to 115 ng/mL); HsTnI ≥16 ng/L 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/mL.[23–25] 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 $\log_2$ HR 1.24, 95% CI 1.18–1.31) followed by a history of HF (HR 1.42,

Table 2. Association of Clinical Variables With 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 χ^2	*P* Value
eGFR, mL/min per 1.73 m^2	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.

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 $\log_2$ HR 1.15, 95% CI 1.04–1.28); Gal-3 (per $\log_2$ HR 1.21, 95% CI 1.03–1.41), and hs-TnI (per $\log_2$ 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 NTproBNP was most associated with cardiovascular death or HF hospitalization (per $\log_2$ 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 $\log_2$ HR 1.10; 95% CI 1.04–1.16), and a doubling of GDF-15 (per $\log_2$ 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).

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 χ^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.

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,[14] 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 ellitus 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.[7,8,18] 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.[26,27] In a prior analysis of the EXAMINE study, an increased NT-proBNP at baseline was significantly associated with increased future risk of

Table 4. Discrimination for the Composite Outcome of 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.
*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] 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 trial[21] 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 1510 stable community participants with diabetes mellitus but without prevalent cardiovascular disease in the Atherosclerosis Risk in Communities study, both troponin T $\geq$14 ng/L (HR 1.96, 95% CI 1.57–2.46) and NTproBNP >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. Other therapies such as thiazolidinediones can potentially also be avoided among higher HF risk patients. In addition, natriuretic peptides (the biomarker that was identified with the greatest risk of HF events in our multi-marker model) has for the first time been added to the HF guidelines to be considered in screening for patients at risk for development of HF.[14,35] Our data support these recommendations; while clinical variables can be useful to risk stratify for clinical outcomes,[36,37] patients with elevated natriuretic peptide concentrations should be carefully monitored for potential development of HF, especially after exposure to therapies such as thiazolidinediones. Furthermore, natriuretic peptides may further stratify for individuals who may have increased benefit

from therapies such as mineralocorticoid receptor antagonists[38] 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,[39] 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 investigate this issue given the trial enrolled the highest proportion of patients with baseline HF (28%) of any cardiovascular safety trial of anti-hyperglycemic therapies,[40] 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 are 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	Hazard ratio (95% CI)	P value
Biomarker (continuous)				
log2 (hsTnI)	1.18 (1.15, 1.21)	<.0001	1.30 (1.26, 1.35)	<.0001
log2 (NTproBNP)	1.40 (1.35, 1.46)	<.0001	1.80 (1.70, 1.90)	<.0001
log2 (GDF15)	1.67 (1.55, 1.80)	<.0001	2.08 (1.89, 2.29)	<.0001
log2 (GAL3)	1.94 (1.74, 2.16)	<.0001	2.36 (2.07, 2.69)	<.0001
log2 (ADPN)	1.53 (1.42, 1.66)	<.0001	1.90 (1.70, 2.12)	<.0001
Biomarkers (by cut-offs)				
Elevated hsTnI	1.77 (1.52, 2.06)	<.0001	2.76 (2.25, 3.39)	<.0001
Elevated NTproBNP	2.61 (2.27, 3.00)	<.0001	6.02 (4.84, 7.49)	<.0001
Elevated GDF15	2.09 (1.81, 2.40)	<.0001	3.02 (2.47, 3.69)	<.0001
Elevated GAL3	1.96 (1.70, 2.26)	<.0001	2.75 (2.25, 3.36)	0.0012
Elevated ADPN	1.92 (1.66, 2.22)	<.0001	2.93 (2.39, 3.58)	0.0002

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

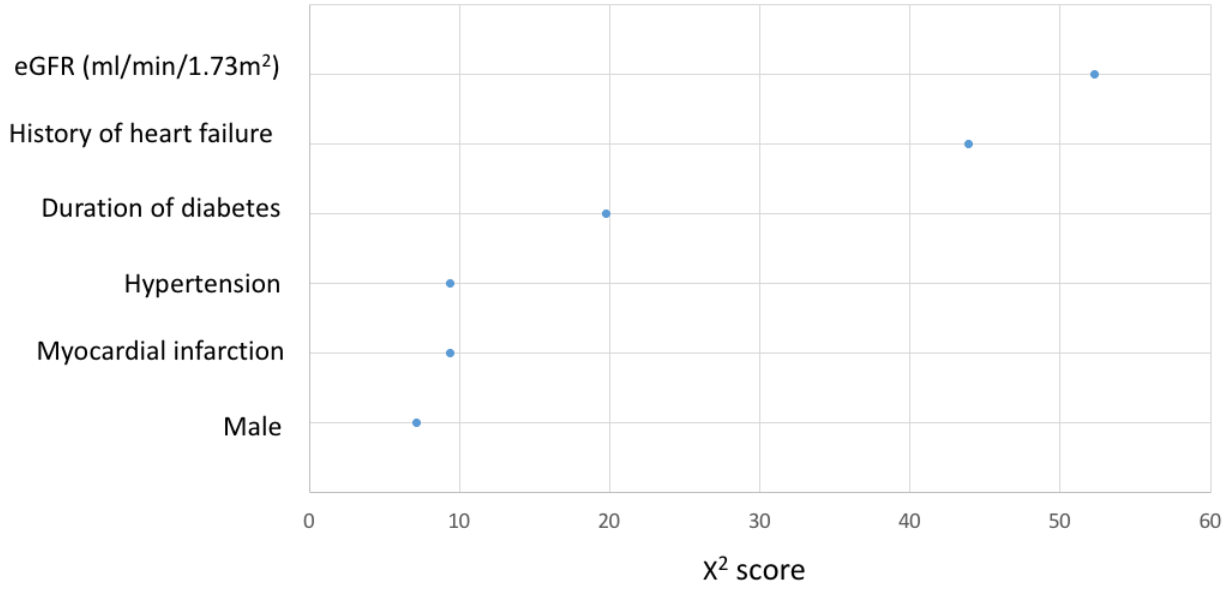
ADPN: adiponectin; Gal-3: galectin-3; GDF-15: growth-differentiation-factor -15; eGFR estimated glomerular filtration rate; hs-CRP: high sensitivity C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

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)

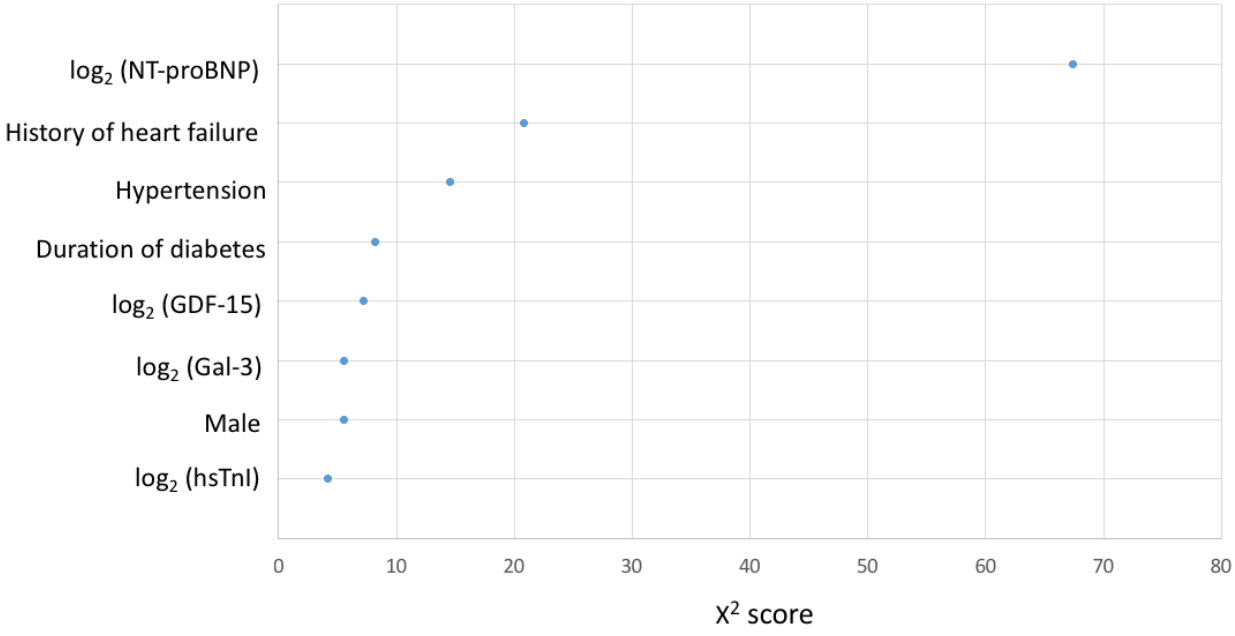
*The clinical model adjusted by age (continuous), sex, systolic blood pressure (continuous), history of heart failure, duration of diabetes, prior myocardial infarction, hypertension, hyperlipidemia, smoking, estimated glomerular filtration rate (continuous). ADPN: adiponectin; Gal-3: galectin-3; GDF-15: 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.