Serial Measurement of Natriuretic Peptides and Cardiovascular Outcomes in Patients With Type 2 Diabetes in the EXAMINE Trial

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OBJECTIVE

Patients with type 2 diabetes are at increased risk of developing heart failure (HF). Enhanced recognition of patients at risk for HF would help guide therapeutic decisions.

RESEARCH DESIGN AND METHODS

We investigated the prognostic implications of changes in N-terminal B-type natriuretic peptide (NT-proBNP) concentration in patients with type 2 diabetes and ischemic heart disease who were enrolled in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, a phase 3b trial of alogliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor. Patients with type 2 diabetes and a recent acute coronary syndrome event were eligible. NT-proBNP was measured at baseline and 6 months. Cardiovascular (CV) death or hospitalization for HF was the end point of principal interest for this analysis.

RESULTS

We observed a strong graded relationship between increasing baseline and 6-month NT-proBNP concentration and the incidence of major CV events ($P < 0.001$). After adjusting for potential confounders, NT-proBNP at baseline was independently associated with the development of major CV events, in particular hospitalization for HF. Patients who had persistently high NT-proBNP ($P < 0.001$) or developed high NT-proBNP at 6 months ($P < 0.001$) were at a significantly higher risk for CV death/HF than those in whom NT-proBNP remained low at both time points or who had a high NT-proBNP value at baseline that subsequently declined to the low category. Absolute changes in NT-proBNP by 6 months were also strongly associated with subsequent outcomes. Treatment with a DPP-4 inhibitor did not meaningfully alter NT-proBNP concentrations ($P = 0.20$).

CONCLUSIONS

Serial monitoring of NT-proBNP in patients with type 2 diabetes and ischemic heart disease may be useful for identifying patients at highest risk for HF.

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Diabetes is associated with an increased risk of microvascular and macrovascular disease (1,2). In addition, heart failure (HF) has emerged as an increasingly important complication of diabetes. Patients with type 2 diabetes are almost twice as likely to develop HF as patients without diabetes (3), and almost half of patients with type 2 diabetes eventually are diagnosed with HF (4). In addition, some oral hypoglycemic agents increase the likelihood of developing HF, and HF itself has become a target for preventive pharmacotherapies in type 2 diabetes (5). Therefore, enhanced recognition of patients who are at risk for HF or who are in the early stages of development of HF is needed to potentially guide therapeutic decision making. Cardiovascular (CV) biomarkers may be useful for this purpose. B-type natriuretic peptide (BNP) and the N-terminal part of the precursor molecule proBNP (NT-proBNP), in particular, are established biomarkers of CV stress and have prognostic value with respect to HF and major CV events (6–9).

Inhibition of dipeptidyl peptidase 4 (DPP-4) activity is an established therapy to lower glucose in type 2 diabetes (10), and several clinical trials have studied its CV safety and efficacy (11,12). The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial was a phase 3b clinical outcomes trial that addressed the CV safety of the DPP-4 inhibitor alogliptin in patients with type 2 diabetes who were stabilized following an acute coronary syndrome (ACS) event (13,14). The relation between baseline BNP and outcomes with alogliptin in the EXAMINE trial has been reported (15). We expand those analyses in the current study, investigating the prognostic implications of changes in natriuretic peptide concentration over time in patients with type 2 diabetes and ischemic heart disease, as well as changes in BNP versus NT-proBNP with alogliptin; these are of interest because of the known role of DPP-4 in cleaving BNP1–32.

RESEARCH DESIGN AND METHODS

Study Population and Design

The full details of the design of the EXAMINE trial have been published (13). In brief, the EXAMINE trial was a double-blind, placebo-controlled, noninferiority trial in which patients (n = 5,380) with type 2 diabetes and an ACS event within 15–90 days before enrollment were randomized to treatment with alogliptin or placebo. Patients were eligible for the trial if they had type 2 diabetes, had 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 glucagon-like peptide 1 analog or a DPP-4 inhibitor to treat diabetes. Patients were excluded if they had type 1 diabetes; had end-stage renal disease and were receiving dialysis; or had New York Heart Association class IV HF, refractory angina, uncontrolled arrhythmias, significant valve disease, or severe uncontrolled hypertension.

Patients were randomly assigned to receive alogliptin or placebo, administered in a double-blind fashion, in addition to standard treatment, according to regional guidelines, for type 2 diabetes, CV risk factors, and HF. The types of additional medications and their uses were summarized previously (14,15). The patients were followed for a minimum of 1 day and a maximum of 1,253 days, with a median follow-up of 597 days (interquartile range [IQR] 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 Analysis

BNP and NT-proBNP were measured in all available baseline specimens from patients randomized in the EXAMINE trial. In addition, NT-proBNP was measured in all available samples from the 6-month follow-up visit. Because of the known effects of DPP-4 inhibitors on proteolysis of BNP, BNP was measured only in a subset of patients to enable a comparative analysis of the change in BNP versus NT-proBNP over time during treatment with alogliptin or placebo. Blood was drawn into EDTA-anticoagulated plastic tubes; plasma was isolated and frozen at −20 to −80°C at the local sites until they were shipped to the central laboratory. Frozen samples then were shipped from the central laboratory to the Biomarker Research/Thrombolysis in Myocardial Infarction (TIMI) Clinical Trials Laboratory at Brigham and Women's Hospital (Boston, MA), where they were maintained at −80°C or colder.

BNP was measured with an Architect i2000SR analyzer (Abbott Laboratories, Abbott Park, IL). This chemiluminescent immunoassay has a 10 pg/mL limit of quantitation and a reportable range of 10–5,000 pg/mL. Total imprecision was 8.0% at 88 pg/mL, 7.3% at 481 pg/mL, and 4.0% at 3,370 pg/mL. NT-proBNP was measured with a cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN) using an electrochemiluminescence immunoassay with a 5 pg/mL limit of detection and a reportable range of 5–35,000 pg/mL. Total imprecision of the assay was 2.5% at both 138 and 4,578 pg/mL.

End Points

The primary end point for the trial was the composite of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke. CV death or hospitalization for HF was the end point of principal interest for this analysis. An independent clinical events committee that was unaware of the treatment randomization adjudicated all components of the primary and secondary efficacy end points according to prespecified criteria that were based on the standardized definitions recommended by the U.S. Food and Drug Administration (14). The end point of HF was prospectively adjudicated, requiring hospitalization along with clinical evidence of and treatment for HF (16).

Statistical Analysis

We used the Wilcoxon rank sum test to compare continuous variables and the χ^2 test to compare categorical variables. Event rates at 24 months were estimated using Kaplan-Meier analysis unless otherwise noted. BNP and NT-proBNP were analyzed in the overall population at baseline. Patients were stratified according to quartiles of BNP and NT-proBNP. A sensitivity analysis was performed in the subset of patients who were enrolled at least 30 days after the qualifying ACS event.

The analysis of NT-proBNP concentrations at 6 months versus subsequent outcomes was restricted to those patients without a recurrent CV event (MI, stroke, hospitalization for unstable angina or HF) in the 30 days preceding the month 6 visit. Landmark analyses were performed starting at the month 6 visit through 24 months thereafter. A Cox proportional hazards model was used to assess the association between BNP and NT-proBNP and future CV events. The model adjusted for important potential confounders including age, sex, BMI, type of qualifying ACS event and time since the event, history of HF, hypertension, and estimated glomerular filtration rate (eGFR). Analyses were conducted using a prespecified NT-proBNP cut point of 400 pg/mL. An exploratory

receiver operating characteristics analysis also was performed. Alogliptin and placebo were compared using a Cox proportional hazards model that included geographic region and baseline renal function as prespecified stratifying variables. Analyses were performed using SAS (version 9.3).

RESULTS

Baseline Patient Characteristics

We evaluated baseline specimens from 5,224 patients. Median concentration of NT-proBNP was 420.4 pg/mL (IQR 154.1–1,084.0 pg/mL) at baseline. Baseline patient characteristics stratified by quartiles of NT-proBNP concentrations are shown in Table 1. Patients with higher concentrations of NT-proBNP were older, more likely to be female, and more likely to have a longer duration of diabetes, history of HF, history of a qualifying MI versus unstable angina, peripheral arterial disease, and lower eGFR. We found no association between quartiles of NT-proBNP and levels of glycated hemoglobin.

Baseline NT-proBNP and CV Outcomes

In this population of patients with type 2 diabetes and established coronary artery disease (CAD), a strong graded relationship was found between increasing NT-proBNP concentration from baseline and the incidence of major CV events, including HF ($P < 0.001$ for each end point; Fig. 1*A* and Supplementary Fig. 1). After adjusting for potential confounders, the concentration of NT-proBNP at baseline was independently associated with the development of a major CV event, in particular hospitalization for HF (Table 2). We found no significant excess risk of CV events with alogliptin versus placebo in any of the groups defined by NT-proBNP, including among high-risk patients in the fourth quartile (Supplementary Fig. 2).

6-Month NT-proBNP and CV Outcomes

Specimens were obtained from 4,367 patients at 6 months; 4,282 of these had baseline aliquots available. Concentrations of NT-proBNP at 6 months were significantly lower than those at baseline, with a median of 216.3 pg/mL (IQR 87.1–550.0 pg/mL). Nonetheless, a strong graded relationship existed between the 6-month NT-proBNP concentration and the incidence of major CV events (Fig. 1*B*); this risk was independent of potential confounders (Table 2).

Serial NT-proBNP and CV Outcomes

When stratified into low and high NT-proBNP cohorts based on a cut point of 400 pg/mL, patients who had persistently high NT-proBNP or in whom NT-proBNP became high at 6 months (1,399 subjects [33%]) were at a significantly higher risk of adverse outcomes than those in whom NT-proBNP remained low at both time points (1,966 subjects [46%]) or who had a high NT-proBNP at baseline but the value subsequently declined to the low category (917 subjects [21%]) (Fig. 2). An exploratory receiver operating characteristics analysis supported the prespecified cut point of 400 pg/mL as providing reasonable balance of specificity and sensitivity compared with post hoc alternatives (Supplementary Fig. 3).

The absolute change in NT-proBNP by 6 months was also strongly associated with subsequent outcome. Outcomes stratified by the absolute change in NT-proBNP are shown in Supplementary Fig. 4, revealing patients with an absolute increase in NT-proBNP >400 pg/mL have a markedly higher risk for CV death or HF. The relative change in NT-proBNP offered less useful discrimination, with the exception of hospitalization for HF (Supplementary Fig. 5).

Serial Assessment of BNP and NT-proBNP Stratified by Alogliptin Versus Placebo

By 6 months, the concentration of BNP decreased by a mean of 44.3 pg/mL in the alogliptin arm ($P < 0.0001$) and by 23.8 pg/mL in the placebo arm ($P = 0.047$). While the decrease from baseline was numerically greater in the alogliptin group, the decreases in the alogliptin and placebo groups were not statistically different ($P = 0.20$). In particular, BNP was not observed to have

Table 1—Baseline patient characteristics stratified according to NT-proBNP levels

Characteristics	Q1 (<154.1 pg/mL) (*n* = 1,306)	Q2 (154.1 to <420.4 pg/mL) (*n* = 1,306)	Q3 (420.4 to <1,084 pg/mL) (*n* = 1,306)	Q4 (≥1,084 pg/mL) (*n* = 1,306)	*P* value (trend)*
Age (years)	57.0 (51.0, 63.0)	60.0 (54.0, 67.0)	62.0 (55.0, 70.0)	64.0 (57.0, 71.0)	<0.001
Age ≥65 years	274 (21.0)	437 (33.5)	532 (40.7)	618 (47.3)	<0.001
Female	380 (29.1)	395 (30.2)	398 (30.5)	512 (39.2)	<0.001
Duration of diabetes (years)	5.8 (2.3, 11.1)	6.8 (2.6, 12.8)	7.4 (2.7, 14.5)	9.6 (3.6, 15.7)	<0.001
Glycated hemoglobin (%)	7.9 (7.1, 8.8)	7.8 (7.2, 8.7)	7.9 (7.1, 8.7)	7.9 (7.2, 8.7)	0.968
Current smoker	218 (16.7)	197 (15.1)	159 (12.2)	138 (10.6)	<0.001
Hypertension	1,103 (84.5)	1,088 (83.3)	1,061 (81.2)	1,094 (83.8)	0.147
Prior coronary intervention or CABG	920 (70.4)	935 (71.6)	909 (69.6)	796 (60.9)	<0.001
Peripheral artery disease	92 (7.0)	120 (9.2)	118 (9.0)	163 (12.5)	<0.001
History of HF	268 (20.5)	306 (23.4)	349 (26.7)	544 (41.7)	<0.001
Index inclusion ACS					<0.001
MI	778 (59.8)	973 (74.8)	1,112 (85.3)	1,164 (89.2)	
Unstable angina	524 (40.2)	328 (25.2)	191 (14.7)	141 (10.8)	
Time after index ACS to randomization (days)	49.0 (32.0, 67.0)	47.0 (31.0, 68.0)	43.0 (29.0, 64.0)	39.0 (27.0, 57.0)	<0.001
eGFR <45 mL/min/1.73 m^2	36 (2.8)	100 (7.7)	129 (9.9)	323 (24.7)	<0.001
eGFR (mL/min/1.73 m^2)	77.7 (67.6, 89.3)	73.4 (60.0, 86.7)	70.3 (56.1, 85.1)	60.1 (45.4, 74.9)	<0.001

Data are presented as the median (25th, 75th percentile) or the *n* (%). eGFR was calculated according to the MDRD equation. CABG, coronary artery bypass graft. *The trend *P* value for the median value was calculated by the Jonckheere-Terpstra test.

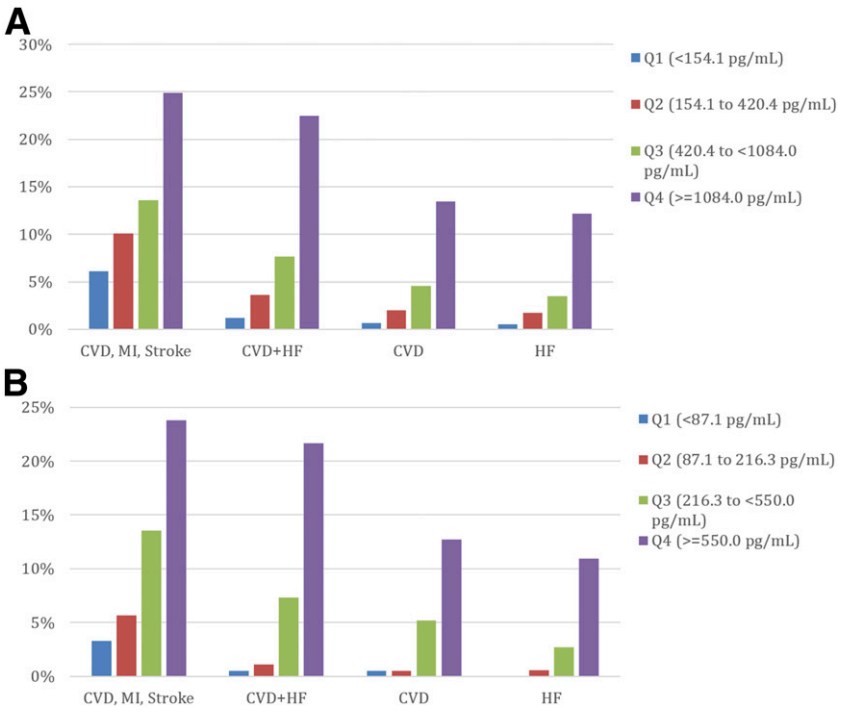

Figure 1—Rates of adverse outcomes by NT-proBNP quartiles (Q), determined through the use of Kaplan-Meier analysis. *A*: Outcomes at 24 months by baseline NT-proBNP quartiles. *B*: Outcomes at 30 months relative to enrollment by 6-month NT-proBNP quartiles. $P < 0.001$ for all trends. CVD, CV death.

increased (or to show a blunted decrease) in the presence of the DPP-4 inhibitor.

By 6 months, the mean absolute decrease in NT-proBNP concentration was 361 pg/mL in the alogliptin arm ($P <$ 0.001 vs. baseline) and 330 pg/mL in the placebo arm ($P < 0.001$), and it did not differ significantly between the two arms ($P = 0.49$) (Supplementary Table 1).

CONCLUSIONS

In this large, nested prospective study of patients with type 2 diabetes and established CAD with a recent ACS event, we observed a strong graded relationship between NT-proBNP, assessed at enrollment and at 6 months, and future CV outcomes. Moreover, we found that the change in NT-proBNP was associated with subsequent outcomes. In addition, in this randomized trial of a DPP-4 inhibitor, we did not observe significant differences in changes in BNP or NT-proBNP over 6 months between patients treated with alogliptin and those receiving the placebo.

Natriuretic Peptides and Outcomes in Established Ischemic Heart Disease and Diabetes

In this large population with established ischemic heart disease, both baseline and follow-up concentrations of NT-proBNP were significantly associated with adverse CV outcomes. By 6 months after randomization, the median NT-proBNP value had decreased significantly, to ~200 pg/mL, but remained similarly associated outcomes, in particular CV death and hospitalization for HF.

The concept of evaluating serial concentrations of BNP or NT-proBNP over time to assess the risk of adverse outcomes is well established in patients with a primary problem of HF (16–18). We previously proposed that serial measurements of natriuretic peptides may be useful in patients with ischemic heart disease (7,19–21). However, additional validation of this approach is needed in robustly sized studies such as this one. Moreover, alternative approaches to classifying the change in natriuretic peptide concentration, including relative, absolute, or categorical changes in this setting, have not been thoroughly explored. In this analysis of the prognostic association

Table 2—Adjusted hazard ratios for CV events stratified by baseline and 6-month NT-proBNP

		Q1	Q2	Q3	Q4
Baseline	Events (*n*)	<154.1 pg/mL	154.1–420.4 pg/mL	420.4 to <1,084.0 pg/mL	≥1,084.0 pg/mL
Patients per quartile (*n*)		1,306	1,306	1,306	1,306
CVD, MI, stroke	577	Referent (*n* = 65)	1.65 (1.21, 2.24) (*n* = 102)	2.44 (1.83, 3.25) (*n* = 141)	4.71 (3.60, 6.16) (*n* = 269)
CVD + HF	365	Referent (*n* = 12)	3.00 (1.56, 5.78) (*n* = 33)	7.48 (4.09, 13.68) (*n* = 77)	24.1 (13.5, 42.9) (*n* = 243)
CVD	212	Referent (*n* = 7)	2.95 (1.25, 6.98) (*n* = 19)	8.17 (3.72, 17.94) (*n* = 46)	23.5 (11.0, 50.2) (*n* = 140)
HF	182	Referent (*n* = 5)	3.27 (1.20, 8.92) (*n* = 15)	7.24 (2.84, 18.49) (*n* = 34)	29.3 (12.0, 71.5) (*n* = 128)
6 months		<87.1 pg/mL	87.1–216.3 pg/mL	216.3 to <550.0 pg/mL	≥550.0 pg/mL
Patients per quartile (*n*)		1,091	1,093	1,091	1,092
CVD, MI, stroke	353	Referent (*n* = 25)	1.67 (1.03, 2.73) (*n* = 46)	3.46 (2.22, 5.40) (*n* = 95)	6.23 (4.07, 9.55) (*n* = 187)
CVD + HF	215	Referent (*n* = 2)	3.88 (0.84, 18.0) (*n* = 9)	19.05 (4.64, 78.17) (*n* = 45)	53.26 (13.15, 215.75) (*n* = 159)
CVD	124	Referent (*n* = 2)	1.61 (0.29, 8.82) (*n* = 4)	11.56 (2.78, 48.18) (*n* = 30)	26.81 (6.56, 109.57) (*n* = 88)
HF	102	Referent (*n* = 0)	n/a (*n* = 5)*	n/a (*n* = 17)*	n/a (*n* = 80)*

Data are presented as the median (25th, 75th percentile), unless otherwise indicated, and are adjusted for age, sex, renal function, time from index ACS event, and history of HF. CVD, CV death; n/a, not available; Q, quartile. *No HF events occurred in the referent group and thus the hazard ratios cannot be reliably estimated. The raw event rates, estimated using Kaplan-Meier analysis, were 0%, 0.57%, 2.71%, and 10.95% for Q1, Q2, Q3, and Q4, respectively.

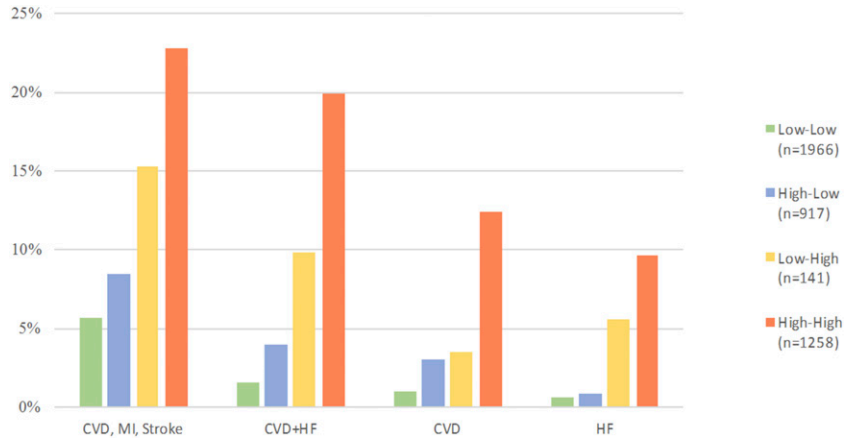

Figure 2—Rates for outcomes at 24 months, starting at 6 months and stratified by change in NT-proBNP category between baseline and 6 months, determined through the use of Kaplan-Meier analysis. (High and low categories included subjects with NT-proBNP concentrations ≥400 pg/mL and <400 pg/mL, respectively.) $P < 0.001$ for all trends. CVD, CV death.

with dynamic changes in NT-proBNP over 6 months, we found that an absolute increase in NT-proBNP by >400 pg/mL is associated with significantly heightened risk of CV events. In addition, a simple categorical framework for assessing serial NT-proBNP, with high and low categories including subjects with NT-proBNP concentrations ≥400 pg/mL and <400 pg/mL, respectively, showed a clear discrimination of risk and may be most practical for clinical practice, with a significant gradient of rates for all outcomes. Classification by relative changes in NT-proBNP seemed to be less useful across all CV outcomes in our cohort, although a relationship with HF was apparent.

These results lend additional support to the notion of using natriuretic peptides for serial monitoring of patients with diabetes and ischemic heart disease whose diseases are in a seemingly clinically stable phase. Such monitoring may prove useful as clinicians consider treatment for individual patients using new or established therapies that may adversely or positively affect the risk of incident HF events in patients with type 2 diabetes and known CV disease. The emergence of data demonstrating the efficacy of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide 1 agonists in modifying the risk for HF in patients with type 2 diabetes point toward the potential for the heightened clinical relevance of strategies for biomarker-based CV risk stratification in patients with type 2 diabetes (22,23).

Safety of Alogliptin in High-Risk Patients

Because a primary objective of the EXAMINE trial was to assess the CV safety of alogliptin therapy, we assessed CV outcomes with alogliptin compared with placebo in patients stratified by quartiles of NT-proBNP at baseline. We did not observe any significant adverse effect of alogliptin, including among the highest-risk patients, who were identified through the use of NT-proBNP. These results are analogous to our prior observations in patients stratified by BNP (15) and by cardiac troponin I (24).

DPP-4 Inhibition and Natriuretic Peptide Concentration

BNP is a known substrate of DPP-4 that cleaves the intact 32–amino acid BNP molecule between proline in position 2 and lysine in position 3. As a consequence, inhibitors of DPP-4 have the potential to increase the concentration of intact, immunoreactive BNP in the absence of increased underlying myocardial wall stress. Because such an effect could confound the diagnosis of HF, this theoretical concern has contributed to uncertainty as to whether some DPP-4 inhibitors increase the risk of developing HF. In this randomized study with serial measurement of both BNP and NT-proBNP, we were uniquely positioned to assess for this possible effect, which would have been expected to manifest as a discordant pattern of changes in BNP (i.e., an increase) with alogliptin compared with placebo. However, we found no meaningful difference in the pattern of change of BNP and NT-proBNP during treatment with alogliptin and placebo. Both biomarkers declined, with no difference found between patients treated with alogliptin versus those treated with placebo. This finding is supported by those of a recent study of the effect of DPP-4 inhibition on BNP and NT-proBNP levels measured by commercial immunoassays (25).

Limitations

Our study has several limitations. First, the EXAMINE trial included patients with diabetes who had a recent ACS, and therefore the specific risk estimates that we have described may not be applicable to other patient populations with chronic ischemic heart disease. Furthermore, few CV events occurred in patients with NT-proBNP in the three lower quartiles. In addition, we do not have data that would permit us to adjust for the severity of CAD and HF class.

Conclusion

Among patients with type 2 diabetes who were stable after a recent ACS event, NT-proBNP identified patients at high risk for adverse CV outcomes, in particular future HF. Absolute and categorical changes in NT-proBNP levels between baseline and 6 months were associated with adverse outcomes. Treatment with a DPP-4 inhibitor did not meaningfully alter BNP concentration. Our results point to the potential value of serial monitoring of natriuretic peptides in patients with type 2 diabetes who are at risk for HF and who may be candidates for therapies that ameliorate the risk of adverse CV outcomes, including HF, in this population.

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Author Contributions. P.J. performed NT-proBNP testing and cowrote the manuscript. W.B.W. chaired the steering committee of the EXAMINE trial, designed this study, and critically reviewed and edited the manuscript. C.P.C. designed this study and critically reviewed and edited the manuscript. Q.G. performed statistical analyses and reviewed the manuscript. D.A.M. designed this study, acquired data, and cowrote the manuscript. P.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented at Heart Failure 2018, Vienna, Austria, 26–29 May 2018.

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