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The Association of Five-Year Changes in the Levels of N-Terminal Fragment of the Prohormone Brain-Type Natriuretic Peptide (NT-proBNP) with Subsequent Heart Failure and Death in Patients with Stable Coronary Artery Disease: The Heart and Soul Study

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Coronary artery disease · NT-proBNP · Heart failure

Abstract
Background: The N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) is a powerful predictor of adverse outcomes in patients with coronary artery disease (CAD). However, little is known regarding the prognostic significance of longitudinal changes in NT-proBNP levels. ***Methods:*** We evaluated the ability of 5-year changes in NT-proBNP levels to predict subsequent heart failure (HF) hospitalization or cardiovascular (CV) death in 635 participants with stable CAD enrolled in the Heart and Soul Study. ***Results:*** The median (IQR) 5-year change in NT-proBNP was 50 pg/mL (–5 to +222). During an average of 4.0 ± 1.4 years follow-up (i.e., 9 years from the baseline measurement), there were 67 events. Participants with 5-year changes in the highest quartile (≥ 223 pg/mL increase in NT-proBNP) had an almost 4-fold greater risk of subsequent HF or CV death than those in the lowest quartile of ≤–5 pg/mL (HR 3.8; 95% CI 2.0–7.3; $p < 0.001$). This association remained strong after adjustment for demographic variables, comorbidities, left ventricular mass index, systolic and diastolic function, and baseline and follow-up NT-proBNP levels (HR 3.9; 95% CI 1.1–13.4; $p = 0.01$). ***Conclusion:*** Changes in NT-proBNP levels at 5 years predict subsequent HF or CV death in patients with stable CAD, independent of other prognostic markers, including baseline and follow-up NT-proBNP levels. A stable NT-proBNP level predicts a low risk of subsequent events.

Introduction

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and biologically active BNP are the 2 cleavage products of proBNP that are released into the circulation

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in response to left ventricular (LV) pressure and volume overload [1–4]. Elevated levels of NT-proBNP are associated with adverse cardiovascular (CV) outcomes in the setting of acute and chronic heart failure (HF) and stable coronary artery disease (CAD) [5–9].

In a cohort of community-dwelling adults, increases in NT-proBNP levels over the long-term were associated with adverse CV outcomes [10, 11]. Currently, however, it is not known whether long-term changes in levels of NT-proBNP predict subsequent adverse CV outcomes among patients with stable CAD. In this study, we sought to evaluate whether changes in NT-proBNP levels in participants with stable CAD over a 5-year period predicted an increased risk of subsequent HF hospitalization and CV-related mortality.

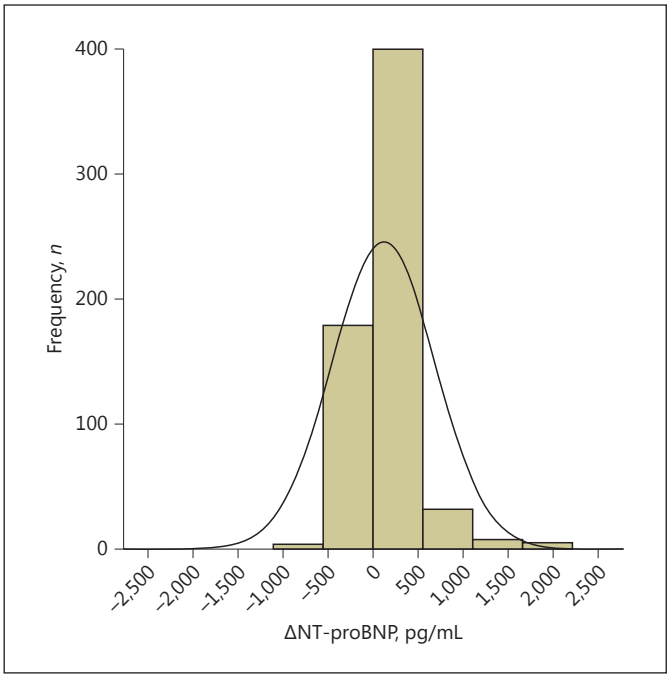

Fig. 1. Histogram showing the distribution of the 5-year change in NT-proBNP (ΔNT-proBNP) levels (pg/mL) with a superimposed normal curve.

Methods

Participants

The Heart and Soul Study was a prospective study of a large cohort of patients with stable CAD [12]. Patients were enrolled between September 2000 and December 2002 from various clinics within the San Francisco Bay area if they met at least 1 of the following criteria: (1) a history of myocardial infarction (MI), (2) at least 50% stenosis in ≥1 coronary vessel as confirmed by angiography, (3) evidence of exercise-induced ischemia by treadmill or nuclear testing, and (4) a history of coronary revascularization. Participants were excluded if they had had a MI in the 6 months prior to enrollment, deemed themselves unable to walk 1 block, or were planning to move out of the local area within 3 years. Participants underwent a baseline medical examination, filled out a medical questionnaire, and provided fasting blood samples. Surviving participants were followed up at 5 years with a repeat medical examination and blood work. Of 1,024 patients at enrollment, 635 with NT-proBNP levels measured at baseline and the 5-year follow-up were included in this study.

Predictor

The primary predictor was the change in plasma NT-proBNP levels over a 5-year period. Serum samples were collected, following a 12-h fast, at baseline and the 5-year follow-up. All samples were collected in EDTA-containing tubes, centrifuged, aliquoted, and stored at –70°C. NT-proBNP levels were measured using the Roche ElecSys 2010 proBNP assay (Roche Diagnostics, Indianapolis, IN, USA) [6]. The assay ranges from 5 to 35,000 pg/mL. The intra- and interassay coefficients of variation ranged, respectively, from 2.7 and 3.2% at NT-proBNP concentrations of 175 pg/mL to 1.8 and 2.3% at NT-proBNP concentrations of 4,962 pg/mL.

Outcomes

Our primary outcomes were HF hospitalization and CV-related death after the 5-year follow-up visit. The process by which information was collected and adjudicated has been described previously [9]. HF hospitalization was defined as signs and symptoms of HF requiring hospitalization. CV-related death was coded if 1 of these conditions was met: (1) following a death during a hospitalization for acute MI, and (2) following a death occurring within 1 h of the onset of terminal symptoms not explained by other etiologies. All outcomes were verified by 2 independent and blinded adjudicators, with the addition of a third in the event of a disagreement in outcome classification.

Covariates

Covariate data, including medical history, physical exam, and blood samples, were collected at baseline and the 5-year follow-up visit [13]. Serum lipid levels were measured following a 12-h fast. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation [14]. Transthoracic echocardiography, including 2-dimensional and Doppler imaging, was performed using the Acuson Sequoia ultrasound system (Siemens Medical Solutions USA, Inc., Mountain View, CA, USA). LV mass index was calculated by dividing LV mass, estimated by the truncated ellipsoid method, by body surface area [15]. Ejection fraction was calculated as (LV end-diastolic volume – LV end-systolic volume)/(LV end-diastolic volume). The LV diastolic function category was assigned using the American Society of Echocardiography guidelines, and diastolic dysfunction was defined as the presence of any of the following: impaired relaxation, pseudonormal filling, or restrictive filling [16].

Statistical Analysis

We modeled the 5-year change in NT-proBNP both as quartiles and as a linear variable. Demographic, laboratory, and echocardiographic values at the 5-year follow-up were compared across quar-

Table 1. Participant characteristics according to quartile of 5-year change in NT-proBNP levels

	Quartile I (n = 158)	Quartile II (n = 159)	Quartile III (n = 159)	Quartile IV (n = 159)	p value
5-Year change, pg/mL	–5	–5 to +50	50–222	>222	
Age, years	69±10	68±10	72±10	73±10	<0.001
Ethnicity					
White	103 (65)	94 (59)	93 (58)	93 (58)	0.55
Black	22 (14)	28 (18)	27 (17)	22 (14)	0.70
Other	33 (21)	37 (23)	39 (25)	44 (28)	0.56
Diabetes	40 (25)	39 (25)	44 (28)	61 (39)	0.02
Smoking	18 (12)	23 (15)	22 (14)	27 (17)	0.62
Male	128 (81)	127 (80)	131 (82)	134 (84)	0.76
A history of HF	28 (18)	15 (10)	22 (14)	51 (32)	<0.001
A history of MI	68 (44)	69 (44)	79 (51)	96 (61)	0.006
PCI or CABG	97 (61)	79 (51)	106 (68)	109 (69)	0.002
SBP, mm Hg	136±19	135±18	137±18	138±24	0.72
DBP, mm Hg	76±10	76±10	74±10	74±13	0.03
BMI	29±6	28±5	29±5	29±5	0.64
Medication at baseline					
β-Blocker	107 (68)	68 (43)	87 (55)	101 (64)	<0.001
ACEI/ARB	77 (49)	67 (42)	80 (50)	98 (62)	0.006
Statin	102 (65)	109 (69)	111 (70)	118 (74)	0.30
Aspirin	120 (76)	115 (73)	116 (73)	113 (71)	0.79
LDL, mg/dL	96±32	94±29	96±36	93±36	0.84
HDL, mg/dL	45±13	47±15	48±15	48±18	0.22
eGFR, mL/min/1.73 m^2	77±23	84±18	73±20	59±21	<0.001
LV mass index, g/m^2	90±27	83±22	92±25	106±32	<0.001
LV ejection fraction, %	64±10	64±8	63±9	56±14	<0.001
LV diastolic function					
Normal	63 (41)	81 (53)	70 (45)	39 (25)	<0.001
Mildly abnormal	63 (41)	56 (37)	56 (36)	76 (49)	0.07
Moderately abnormal	15 (10)	11 (7)	15 (10)	15 (10)	0.83
Severely abnormal	13 (8)	5 (3)	14 (9)	24 (16)	0.003
NT-proBNP, pg/mL					
Level at baseline (IQR)	105 (16–225)	29 (5–54)	66 (5–109)	135 (13–300)	0.001
Level at 5 years (IQR)	137 (59–281)	75 (41–145)	243 (155–324)	1,065 (641–1,950)	0.001
Change at 5 years (IQR)	–64 (–154 to –24)	16 (6–31)	108 (71–152)	600 (356–1,290)	<0.001

Values are expressed as n (%) or mean ± SD, or are otherwise indicated. HF, heart failure; MI, myocardial infarction; CABG, coronary artery bypass grafting; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; LV, left ventricular.

tiles of the 5-year NT-proBNP change, using the ANOVA for continuous variables and the χ^2 test for categorical variables. We used demographically adjusted and multivariable-adjusted Cox proportional-hazards models to evaluate the association of quartiles of the 5-year change in NT-proBNP with the HF hospitalization or CV-related death. Variables that differed across quartiles of the 5-year change in NT-proBNP level ($p < 0.05$) were included as covariates in the multivariable-adjusted models. The association between 5-year change in NT-proBNP level modeled as a linear variable and outcome was evaluated using demographically adjusted and multivariable-adjusted Cox proportional hazards models, with the predictor being the residual change score obtained by regressing the log-transformed 5-year NT-proBNP measures on the log-transformed baseline measures.

We compared C statistics of 5-year follow-up value of NT-proBNP versus 5-year change in NT-proBNP for the prediction of subsequent HF hospitalization or CV-related death by adding them each to a clinical model that included age, a history of HF, MI, coronary revascularization and diabetes, diastolic blood pressure, estimated glomerular filtration rate (eGFR), and LV mass index, ejection fraction, and diastolic function category. Event-free survival in each quartile of the 5-year change in NT-proBNP levels was compared using the Kaplan-Meier survival analysis. Data were analyzed using STATA v12.0 (StataCorp).

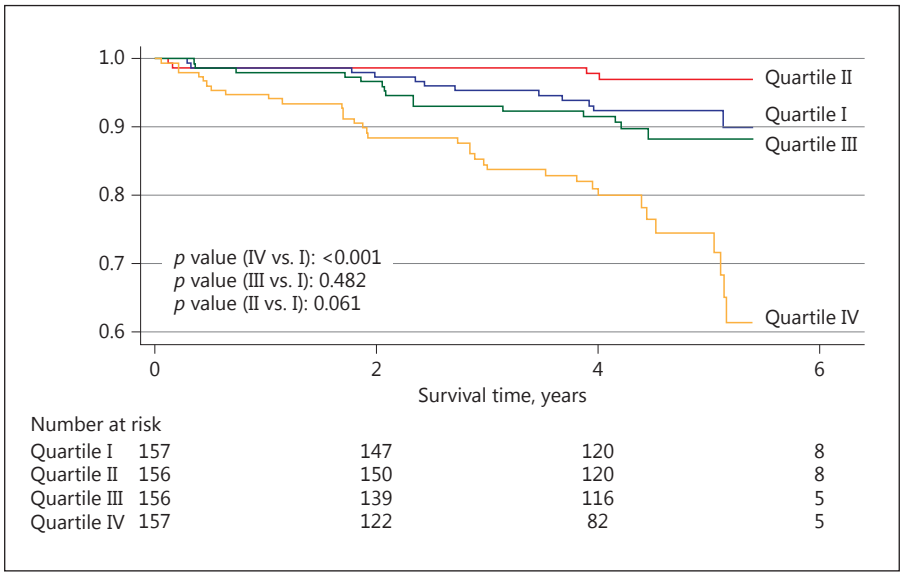

Fig. 2. Kaplan-Meier event-free survival curves by quartiles of the 5-year change in NT-proBNP levels.

Results

Among 635 participants, 5-year changes in NT-proBNP ranged from –16,971 to +17,321 pg/ml (Fig. 1). The baseline median NT-proBNP level of 66 pg/mL (IQR 5–142) increased to 226 pg/mL (IQR 90–551) at the 5-year follow-up. Participants with the greatest change in NT-proBNP levels were older and more likely to be diabetic, use a β-blocker or angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and were also more likely to have a history of HF, MI, and coronary revascularization at the 5-year follow-up (Table 1). They also had lower diastolic blood pressure, eGFR, and LV ejection fraction, a higher LV mass index, and a prevalence of abnormal diastolic function.

During 4.0 ± 1.4 years of follow-up after the 5-year visit, 39 participants were admitted for an HF exacerbation, and 45 participants died from CV-related causes. In total, 67 participants (10.6%) had HF exacerbation or CV-related death during the follow-up period.

Compared with the lowest quartile (a decrease of ≥5 pg/mL), participants in the highest quartile of the 5-year change in NT-proBNP level (an increase of ≥223 pg/mL) had worse survival free of HF or CV death (Fig. 2). In the unadjusted model, the highest quartile of NT-proBNP change was associated with a nearly 4-fold increased risk of HF or CV death (Table 2). Despite full adjustment for covariates, this magnitude of risk persisted. When modeled as a log-transformed linear variable in the residual score analysis, baseline-corrected changes in NT-proBNP level were predictive of HF or CV death (HR 1.42; 95% CI 1.11–1.81; $p = 0.005$). With full adjustment for covariates, it was no longer predictive of the combined outcome of HF or CV death (HR 1.21; 95% CI 0.86–1.69; $p = 0.27$) but remained predictive of CV death (HR 1.54; 95% CI 1.03–2.28; $p = 0.03$).

When added to a clinical model that included year 1 NT-proBNP level, neither the year 5 NT-proBNP nor the 5-year change in NT-proBNP substantially improved the prediction of HF hospitalization or CV-related death (*C* statistics: 0.84, 0.84, and 0.84, respectively).

Discussion

NT-proBNP level has been shown to be an independent predictor of adverse CV events in patients with stable CAD [9]. In this study, we sought to examine the association between 5-year change in NT-pro BNP level and the risk of subsequent HF hospitalization and CV-related death in patients with stable CAD. We found that the greatest 5-year change in NT-proBNP levels were associated with an increased risk of HF hospitalization or CV-related death, independent of traditional risk factors. This finding expands the literature by demonstrating the prognostic utility of serial NT-proBNP measurements among patients with stable CAD.

Single NT-proBNP levels are predictive of both short- and long-term mortality in patients with acute and chron-

Table 2. Association of quartiles of the 5-year change in NT-proBNP levels with HF and CV death

Change in NT-proBNP at 5 years, pg/mL	Quartile I	Quartile II			Quartile III			Quartile IV		
	≤5	−5 to +50			50–222			>222		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Unadjusted	Ref.	0.3	0.1–1.0	0.05	1.3	0.6–2.8	0.52	3.8	2.0–7.3	**<0.001**
Model 1	Ref.	0.6	0.2–2.2	0.10	2.0	0.9–4.3	0.10	3.4	1.8–6.5	**<0.001**
Model 2	Ref.	0.8	0.2–2.6	0.66	2.7	1.0–7.0	**0.04**	6.0	1.9–18.9	**<0.01**
Model 3	Ref.	0.7	0.2–2.5	0.62	2.5	1.0–6.6	0.06	6.2	1.9–19.8	**<0.01**
Model 4	Ref.	0.7	0.2–2.4	0.60	2.4	0.9–6.3	0.08	5.3	1.6–17.0	**<0.01**
Model 5	Ref.	0.7	0.2–2.5	0.61	2.4	0.9–6.4	0.08	5.1	1.6–16.6	**<0.01**
Model 6	Ref.	0.7	0.2–2.3	0.55	2.1	0.8–5.7	0.15	3.9	1.1–13.4	**<0.03**

Model 1: baseline NT-proBNP level. Model 2: + 5-year NT-proBNP level. Model 3: + age. Model 4: + a history of myocardial infarction, heart failure, coronary revascularization or diabetes prior to the 5-year follow-up. Model 5: + 5-year diastolic blood pressure and estimated glomerular filtration rate. Model 6: + 5-year LV mass index, ejection fraction, and diastolic function category. Ref., reference; HR, hazard ratio; CI, confidence interval. *p* values are given with reference to quartile I; *p* values in bold type represent statistically significant values.

ic CAD. The utility of NT-proBNP levels in predicting mortality among patients with CAD has been confirmed in several large-scale trials [17]. Among patients presenting with suspected acute coronary syndromes, those with the highest levels of NT-proBNP at admission were found to have a consistently elevated risk of death during a follow-up period of 40 months [18]. Moreover, we previously reported the association of NT-proBNP levels with adverse CV events among patients with stable CAD enrolled in the Heart and Soul Study [9].

The prognostic value of serial NT-proBNP levels was studied previously in a cohort of community-dwelling adults free from HF at baseline. DeFilippi et al. [11] found that increased levels of NT-proBNP over time predicted a higher risk of new-onset HF and CV-related death, independent of traditional risk factors and abnormalities on ECG and echocardiography. Our findings in patients with stable CAD are similar to those of deFilippi et al. [11] in that the prognostic value of NT-proBNP appeared to follow a threshold effect, whereby the greatest change in NT-proBNP had the most robust association with adverse clinical outcomes. We observed this threshold at a 5-year change in NT-proBNP levels of ≥223 pg/mL, which was similar to the threshold of ≥190 pg/mL found in the study by deFilippi et al. [11].

Our study supports possible future research examining changes in NT-proBNP levels for guiding treatment in patients with stable CAD in order to prevent HF or CV death. Percutaneous coronary intervention in patients with stable angina has been associated with decreased NT-proBNP levels immediately following revascularization [19]. Moreover, among patients with HF, treatment with standard pharmacologic therapy has been shown to decrease levels of NT-proBNP [20]. Several meta-analyses have shown improved mortality among patients treated for HF with the aim of reducing BNP and NT-proBNP levels [21–23]. Additionally, the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study examined whether the use of HF medications targeted toward decreasing NT-proBNP level to a prespecified goal after HF hospitalization had an effect on mortality [24]. While no clear mortality benefit was demonstrated in the intervention group, those patients who had an increase in NT-proBNP level after HF hospitalization were at a significantly increased risk of HF and CV-related death at up to 2 years of follow-up, a finding consistent with our results.

Our study had several limitations. Since the participants were mainly urban men with stable CAD, our findings may not be generalizable to different populations with other disease states, including those with a history of recent MI. Moreover, since HF was defined as HF requiring hospitalization, we may not have captured outpatient HF events. In addition, we had limited information on medication use at the 5-year follow-up evaluation. Finally, the number of patients at risk for HF or CV-related death was quite small. This is because there was a very high mortality rate among those participants in quartile 4 as well as differential follow-up times for some of our

participants. Participants were recruited into the Heart and Soul Study during a 2-year period, so the patients enrolled first had 2 more years of follow-up than those who enrolled last.

In summary, among patients with stable CAD, an increase in NT-proBNP level over the long-term is independently associated with an increased risk of subsequent HF hospitalization or CV death. This finding suggests that tracking changes in NT-proBNP levels may have clinical utility among patients with stable CAD, and it lends support for future research to evaluate NT-proBNP as a therapeutic target in patients with stable CAD.

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