Original article

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Association of change in 5-year N-terminal fragment of the prohormone brain-type natriuretic peptide with left ventricular structure and function in stable coronary disease

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Aims **We sought to characterize the association between long-term changes in the N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) and changes in left ventricular (LV) structure and function in patients with stable coronary artery disease.**

Methods **We included 593 participants without significant valvular disease enrolled in the Heart and Soul Study. We evaluated the association of 5-year change in NT-proBNP (ΔNT-proBNP) with changes in echocardiography-determined LV ejection fraction (LVEF), LV systolic dysfunction (LVSD; LVEF < 50%), LV mass index, incident LV hypertrophy (LVH) (LV mass index >102 g/m^2 for men and >88 g/m^2 for women), and LV diastolic dysfunction (LVDD) using linear and logistic regression.**

Results **Over 5 years, the prevalence of LVH declined from 36 to 32% ($P < 0.001$), the prevalence of LVDD increased from 11 to 14% ($P = 0.035$), mean LVEF decreased from 63 ± 9% to 62 ± 10% ($P = 0.07$), and the prevalence of LVSD increased from 9 to 11% ($P = 0.12$). Compared with the lowest ΔNT-proBNP quartile (≥8 ng/l decrease) the highest quartile (>218 ng/l increase) had significantly more incident LVH and LVSD ($P < 0.001$ for both), with a trend toward increased incidence of LVDD. In logistic regression models adjusted for demographics, cardiac comorbidities, baseline LV structure and function, medication use, kidney function, and baseline NT-proBNP, log-transformed ΔNT-proBNP was associated only with incident LVSD (odds ratio 2.48×10^6, 95% confidence interval $224.53 - 2.73 \times 10^{10}$, $P = 0.002$).**

Conclusion **A ΔNT-proBNP is independently associated with incident LVSD in patients with stable coronary artery disease. This suggests that a long-term rise in NT-proBNP levels may warrant evaluation for incident LVEF less than 50%.**

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Keywords: left ventricular ejection fraction, N-terminal fragment of the prohormone brain-type natriuretic peptide, stable coronary artery disease

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Introduction

Circulating levels of the N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) are associated with left ventricular (LV) hypertrophy (LVH), diastolic dysfunction (LVDD), and systolic dysfunction (LVSD) in multiple populations.[1–4] However, the associations of long-term changes in NT-proBNP with changes in LV structure and function in stable coronary artery disease (CAD) have not been evaluated, and no evidence-based surveillance strategy exists for patients with known stable ischemic CAD.[5] Further understanding of the relationship between changes in NT-proBNP level and the progression of cardiac disease may facilitate monitoring and potentially guide use of available secondary prevention or therapeutic strategies in patients with elevated risk. We evaluated the association of 5-year changes in NT-proBNP (ΔNT-proBNP) with changes in LV structure and function in 593 outpatients with stable CAD enrolled in the prospective Heart and Soul Study.

Methods

The Heart and Soul Study is a prospective cohort study evaluating the impact of psychosocial factors on cardiovascular outcomes. The study methods have been previously described in detail.[6] Participants were enrolled between 2000 and 2002 from two Veterans' Affairs hospitals, an academic medical center, and nine public health clinics in the San Francisco area. All participants had CAD defined by either a history of myocardial infarction (MI), angiographic evidence of at least 50% stenosis in a coronary vessel, evidence of inducible ischemia by treadmill electrocardiography or nuclear perfusion stress imaging, or a history of coronary revascularization. Patients were excluded if they were unable to walk more than one block, had a history of acute coronary syndrome within the prior 6 months, or intended to move out of the local area within 3 years. We further limited analysis to the 593 participants with both baseline and 5-year NT-proBNP levels measured, and without echocardiography-determined moderate or severe mitral or aortic

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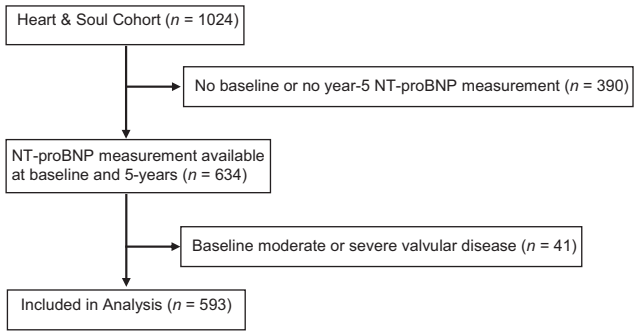
Fig. 1



Flowchart of patients included and excluded from analysis.

regurgitation or stenosis (Fig. 1). The institutional review boards at the University of California San Francisco, the San Francisco Veterans Affairs Medical Center, the Veterans Affairs Palo Alto Healthcare System, and the Community Health Network of San Francisco approved this protocol. All participants provided written informed consent. The investigation was performed in accordance with the Declaration of Helsinki.

Fasting blood samples were drawn while patients continued their prescribed medications. Plasma samples were collected and stored in aliquots at −70 °C. A commercial assay with detectable range from 5 to 35 000 ng/l was used to measure NT-proBNP (Elecsys proBNP; Roche Diagnostics, Indianapolis, Indiana, USA). The intra-assay and interassay coefficients of variation were 2.7 and 3.2%, respectively, at an NT-proBNP concentration of 175 ng/l, and 1.8 and 2.3%, respectively, at an NT-proBNP concentration of 4962 ng/l. The assayer was blinded to all other results including echocardiography and prior NT-proBNP measurements. ΔNT-proBNP was calculated as the difference between 5-year and baseline NT-proBNP levels.

A complete resting two-dimensional echocardiogram and Doppler ultrasound examination was performed with an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, California, USA) at baseline and at the 5-year follow-up visit. LV end-diastolic and end-systolic volumes were approximated using the modified bi-plane methods of discs, with LV ejection fraction (LVEF) calculated as (end-diastolic volume − end-systolic volume)/end-diastolic volume. The truncated ellipsoid method was used to estimate LV mass, which was indexed to BSA.[7] Mitral inflow *E* and *A* wave velocities, *E* wave deceleration time, and the ratio of pulmonary venous systolic-to-diastolic flow velocity time integral were used to group LV diastolic function into categories of 'normal', 'mild dysfunction' defined by an *E*/*A* ratio 0.75 or less with systolic dominant pulmonary vein flow, 'moderate dysfunction' defined by an *E*/*A* ratio at least 0.75 and less than 1.5 with diastolic dominant pulmonary vein flow, or 'severe dysfunction' defined by an *E*/*A* ratio at least 1.5 with diastolic dominant pulmonary vein flow.[8] LVDD was defined by moderate or severe LVDD. LVH was defined by a calculated LV mass index (LVMI) more than 102 g/m^2 for men and more than 88 g/m^2 for women.[9] LVSD was defined by LVEF less than 50%. All echocardiograms were interpreted by a single expert reader (N.B.S.) who was blinded to all other results including NT-proBNP measurements and prior echocardiography.

Self-reported age, sex, ethnicity, past medical history, and smoking status were assessed by questionnaire at study baseline and at the 5-year follow-up visit. Medication use at baseline was recorded from prescriptions provided by patients but was not reliably recorded after trial enrollment. Estimated glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[10]

NT-proBNP levels below the lower limit of detection were entered as 5 ng/l. ΔNT-proBNP were normally distributed and analyzed in quartiles. Differences in participant characteristics were compared using Chi-square tests for categorical variables and one-way analysis of variance for continuous variables. We used demographically and multivariable-adjusted linear regression models to generate regression coefficients (β) and 95% confidence intervals (CI) to evaluate the association of ΔNT-proBNP with change in LVEF and LVMI. We used demographically multivariable-adjusted binary logistic regression to calculate odds ratios (ORs) and evaluate the association of ΔNT-proBNP with incident LVH, LVSD, and LVDD in the subset of patients without LVH, LVSD, and LVDD at baseline, respectively. We adjusted for age, year 5 medical history including hypertension, history of MI, history of percutaneous coronary intervention, history of coronary artery bypass grafting, history of heart failure, baseline medication use, baseline echocardiographic findings including LVEF, LVMI, and diastolic dysfunction category, baseline and year 5 GFR, and baseline NT-proBNP values. ΔNT-proBNP was natural log-transformed for all regression analyses. All analyses were performed using IBM SPSS version 20.0 (IBM Corp. Armonk, NY, USA).

Results

Our study included 593 participants with stable CAD and without significant valve disease enrolled in the Heart and Soul Study (Fig. 1). The participants were predominantly men, white, and elderly (Table 1). The baseline demographic characteristics were similar to those previously reported for the overall Heart and Soul Study cohort.[11] By year 5, hypertension and previous MI were present in more than half of participants. Over 5 years, the mean LVMI, the prevalence of LVH, and the mean LVEF decreased, whereas the prevalence of LVSD and the prevalence of LVDD increased.

Table 1 Baseline and year 5 demographic, clinical, and echocardiographic characteristics by 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide quartile

		Quartiles of ΔNT-proBNP (ng/l)				
Variable	Whole cohort, $n=593$	1 (≤−8.1), $n=151$	2 (−8.0 to 48.3), $n=153$	3 (48.4–218), $n=149$	4 (>218), $n=140$	*P* value*
Age, year 5 (years)	71 ± 15	69 ± 15	68 ± 14	73 ± 15	73 ± 15	<0.001
Men	482 (81%)	123 (82%)	122 (80%)	118 (79%)	119 (85%)	0.58
Race/ethnicity						0.24
White	353 (60%)	103 (68%)	86 (56%)	83 (56%)	81 (58%)	
Black	97 (16%)	20 (13%)	29 (19%)	26 (17%)	22 (16%)	
Hispanic	71 (12%)	14 (9%)	24 (16%)	19 (13%)	14 (10%)	
Asian	54 (9%)	9 (6%)	9 (6%)	17 (11%)	19 (14%)	
Other	18 (3%)	5 (3%)	5 (3%)	4 (3%)	4 (3%)	
SBP, year 5 (mmHg)	136 ± 20	136 ± 19	136 ± 18	136 ± 18	138 ± 24	0.87
DBP, year 5 (mmHg)	75 ± 11	76 ± 10	77 ± 9	74 ± 10	74 ± 12	0.09
BMI, year 5 (kg/m^2)	29 ± 6	30 ± 6	28 ± 6	29 ± 5	28 ± 5	0.11
Medical history, year 5						
Hypertension	443 (76%)	116 (77%)	105 (70%)	109 (74%)	113 (82%)	0.05
Diabetes mellitus	170 (29%)	42 (28%)	35 (23%)	44 (30%)	49 (36%)	0.11
Myocardial infarction	292 (50%)	70 (47%)	66 (43%)	73 (50%)	83 (60%)	0.049
PCI	255 (44%)	77 (51%)	55 (37%)	67 (46%)	56 (41%)	0.07
CABG	211 (36%)	49 (32%)	37 (24%)	58 (40%)	67 (49%)	<0.001
Heart failure	104 (18%)	27 (18%)	13 (9%)	20 (14%)	44 (32%)	<0.001
Medication use, baseline						
Aspirin	467 (79%)	122 (81%)	120 (78%)	121 (81%)	104 (74%)	0.46
Beta-blocker	342 (58%)	106 (70%)	64 (42%)	83 (56%)	89 (64%)	<0.001
ACEi/ARB	300 (51%)	77 (51%)	63 (41%)	75 (50%)	85 (61%)	0.01
Diuretic	153 (26%)	34 (23%)	27 (18%)	29 (20%)	63 (45%)	<0.001
Statin	408 (69%)	99 (66%)	103 (67%)	106 (71%)	100 (71%)	0.63
Estimated GFR, baseline (ml/min)	74 ± 20	74 ± 21	83 ± 17	75 ± 17	62 ± 20	<0.001
Estimated GFR, year 5 (ml/min)	74 ± 22	76 ± 23	84 ± 18	75 ± 21	59 ± 21	<0.001
Serum creatinine, baseline (mg/dl)	1.09 ± 0.56	1.13 ± 0.90	0.97 ± 0.19	1.02 ± 0.20	1.24 ± 0.55	<0.001
Serum creatinine, year 5 (mg/dl)	1.24 ± 0.64	1.20 ± 0.42	1.09 ± 0.23	1.16 ± 0.28	1.53 ± 1.14	<0.001
NT-proBNP, baseline (pg/ml)	321 ± 870	551 ± 1564	98 ± 118	199 ± 346	448 ± 546	<0.001
NT-proBNP, year 5 (pg/ml)	533 ± 1024	244 ± 348	114 ± 121	311 ± 353	1540 ± 1683	<0.001
LVEF, baseline (%)	63 ± 9	63 ± 8	64 ± 7	63 ± 8	60 ± 11	<0.001
LVEF, year 5 (%)	62 ± 10	63 ± 9	64 ± 9	64 ± 9	57 ± 13	<0.001
ΔLVEF (%)	−0.4 ± 9.3	0.6 ± 8.8	−0.2 ± 8.7	0.5 ± 7.9	−2.6 ± 11.2	0.01
LVMI, baseline (g/m^2)	96 ± 24	95 ± 24	88 ± 17	95 ± 25	106 ± 26	<0.001
LVMI, year 5 (g/m^2)	92 ± 27	89 ± 27	84 ± 22	91 ± 24	103 ± 32	<0.001
ΔLVMI (g/m^2)	−5 ± 26	−6 ± 26	−6 ± 23	−5 ± 22	−3 ± 32	0.76
LVH, baseline	208 (36%)	52 (25%)	37 (18%)	48 (23%)	71 (34%)	<0.001
LVH, year 5	181 (32%)	42 (23%)	31 (17%)	38 (21%)	70 (39%)	<0.001
LVSD, baseline	52 (9%)	13 (9%)	7 (5%)	9 (6%)	23 (17%)	0.002
LVSD, year 5	66 (11%)	10 (7%)	10 (7%)	13 (9%)	33 (24%)	<0.001
LVDD, baseline	55 (11%)	23 (18%)	10 (7%)	9 (7%)	13 (11%)	0.02
LVDD, year 5	71 (14%)	18 (14%)	15 (11%)	17 (13%)	21 (22%)	0.12

ACEi, angiotensin converting enzyme inhibitor; ANOVA, analysis of variance; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; PCI, percutaneous coronary intervention. * *P* values by ANOVA for continuous variables and by Chi-square test for categorical variables.

The median ΔNT-proBNP was 48.3 ng/l (interquartile range −8.1, 218). Participant age, a history of MI, coronary artery bypass grafting, and heart failure all increased significantly across ΔNT-proBNP quartiles (Table 1). Medication use among the quartiles was variable. Levels of baseline and year 5 GFR and of baseline and year 5 NT-proBNP increased across ΔNT-proBNP quartiles. In the highest ΔNT-proBNP quartile, baseline and year 5 LVMI were significantly greater, baseline and year 5 LVEF were lower, and the decrease in LVEF greater. The prevalence of LVH at baseline and year 5 was significantly higher in highest quartile of ΔNT-proBNP, as was the prevalence of LVSD. However, LVDD varied significantly across quartiles of ΔNT-proBNP at baseline but not at year 5.

In unadjusted and multivariable-adjusted linear regression models, ΔNT-proBNP as a continuous variable was not significantly associated with ΔLVMI or ΔLVEF (Table 2).

In contrast, incident LVH, LVDD, and LVSD were higher in the highest quartiles of ΔNT-proBNP (Fig. 2). Compared with the lowest quartile, the highest quartile of ΔNT-proBNP had significantly higher incidence of LVH and LVSD in univariate analysis ($P<0.001$ for both), with a trend toward an increase in incident LVDD ($P=0.18$). However, in multivariable-adjusted logistic regression models including demographics, cardiac comorbidities, parameters of baseline LV structure and function, and laboratory values

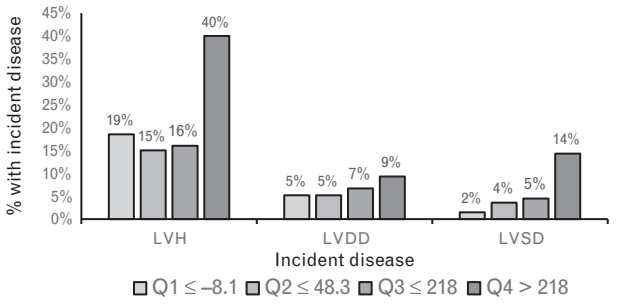
Table 2 Association of natural log-transformed 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide with Δ left ventricular ejection fraction and Δ left ventricular mass index by multivariable linear regression analysis

	ΔLVEF (%)			ΔLVMI (g/m^2)		
Model	β	95% CI	*P* value	β	95% CI	*P* value
Model 1[a]	−10	−30 to 9	0.31	26	−20 to 74	0.27
Model 2[b]	−9	−28 to 11	0.39	27	−20 to 75	0.27
Model 3[c]	−6	−33 to 21	0.66	56	−14 to 126	0.12
Model 4[d]	−1	−29 to 27	0.93	48	−24 to 120	0.19
Model 5[e]	−1	−29 to 27	0.94	37	−35 to 108	0.31

β per 1-unit change in natural log-transformed ΔNT-proBNP. ΔNT-proBNP, 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide; CI, confidence interval; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index. [a] Adjusted for age. [b] Adjusted for age and year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure. [c] Adjusted for age, year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure, and baseline echocardiographic left ventricular ejection fraction, left ventricular mass index, and left ventricular diastolic dysfunction. [d] Adjusted for age, year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure, baseline echocardiographic left ventricular ejection fraction, left ventricular mass index, and left ventricular diastolic dysfunction, year 5 GFR, and log-transformed baseline NT-proBNP. [e] Adjusted for age, year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure, baseline echocardiographic left ventricular ejection fraction, left ventricular mass index, and left ventricular diastolic dysfunction, year 5 creatinine, log-transformed baseline NT-proBNP, and baseline medications.

including baseline NT-proBNP, log-transformed ΔNT-proBNP as a continuous variable was significantly associated only with incident LVSD (OR 2.48×10^6, 95% CI $224.53–2.73 \times 10^{10}$, $P = 0.002$), whereas associations with incident LVH (OR 623.35, 95% CI $0.13–2.99 \times 10^6$, $P = 0.14$) and LVDD (OR 3.42, 95% CI 0.11–102.83, $P = 0.48$) were not statistically significant (Table 3).

Fig. 2



Percentage of participants with incident left ventricular hypertrophy, left ventricular diastolic dysfunction, and left ventricular systolic dysfunction per quartile of 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide. Quartile of 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide in ng/l. Chi-square *P* value for quartile 1 versus quartile 4: $P < 0.001$ (incident left ventricular hypertrophy), $P = 0.18$ (incident left ventricular diastolic dysfunction), and $P < 0.001$ (incident left ventricular systolic dysfunction). LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction.

Discussion

In stable CAD, increases in NT-proBNP level over 5 years were independently associated with the development of LVSD. Though there is also an additional association with incident LVH, this association does not remain statistically significant after multivariable adjustment. Our findings extend those from other cardiovascular conditions to stable CAD and suggest that long-term change in NT-proBNP level may serve as a useful adjunct for screening patients with stable CAD for functional cardiac deterioration.

Although associations between changes in NT-proBNP measurements and LV structure and function in patients with stable CAD have not been previously reported, similar associations between change in brain-type natriuretic peptide (ΔBNP) or ΔNT-proBNP values and LV parameters have been demonstrated in other cardiovascular conditions. In patients with heart failure and reduced ejection fraction enrolled in the Valsartan in Heart Failure Trial, increases in 4-month and 12-month ΔBNP after enrollment was associated with persistent or worsening LV dilation and less improvement in LVEF compared with decreases in ΔBNP.[12] In similar patients in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction trial, elevated ΔBNP at 43 weeks was associated with LV dilation and decreased LVEF, and increasing ΔBNP was associated with worsening LVEF in the Beta-Blocker Evaluation of Survival Study.[13,14] In patients with asymptomatic moderate or severe aortic stenosis, increases in ΔBNP greater than 29 ng/l over a mean of 22 months of follow-up were associated with worsening diastolic dysfunction and lack of LVEF augmentation with exercise.[15,16]

Identification of patients with LV structural and functional abnormalities is clinically helpful as such individuals are at elevated risk for adverse outcomes. Although best characterized in the case of heart failure with reduced ejection fraction, in which the degree of reduction in LVEF and the extent of increase in LV mass are associated with increased risk of hospitalization and mortality, this relationship has been broadly described.[17] In over 4000 patients from the Framingham cohort, compared with patients with echocardiographically normal LVs, those with asymptomatic decreased LVEF had close to five-times the risk of progression to symptomatic heart failure as well as an increased risk of mortality.[18] Other community-based cohorts have reached similar conclusions and demonstrated that even severe systolic or diastolic dysfunction can initially lay unrecognized in the absence of screening.[19,20] Furthermore, in the Heart and Soul Study population studied here, LV structural and functional derangements including abnormalities in LVEF, LVMI, and LVDD have all been associated with subsequent heart failure hospitalization and other major adverse cardiovascular events.[21,22] Thus, identifying patients with LV abnormalities selects a population at elevated risk; such

Table 3 Association of natural log-transformed 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide with incident left ventricular hypertrophy, left ventricular diastolic dysfunction, and left ventricular systolic dysfunction by multivariable logistic regression analysis

	Incident LVH			Incident LVDD			Incident LVSD		
Model	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Model 1[a]	103.48	$0.58-1.86\times10^{4}$	0.08	0.47	0.16–1.39	0.17	2751.93	$13.90-5.45\times10^{5}$	0.003
Model 2[b]	158.68	$0.88-2.87\times10^{4}$	0.06	0.41	0.13–1.28	0.12	1174.49	$3.69-3.74\times10^{5}$	0.02
Model 3[c]	1991.43	$0.52-7.68\times10^{6}$	0.07	0.42	0.13–1.34	0.14	5.06×10^{5}	$76.28-3.36\times10^{6}$	0.003
Model 4[d]	705.15	$0.16-3.06\times10^{6}$	0.12	5.94	0.22–162.89	0.29	3.80×10^{6}	$405.94-3.6\times10^{10}$	0.001
Model 5[e]	623.35	$0.13-2.99\times10^{6}$	0.14	3.42	0.11–102.83	0.48	2.48×10^{6}	$224.53-2.73\times10^{10}$	0.002

ΔNT-proBNP, 5-year change N-terminal fragment of the prohormone brain-type natriuretic peptide; CI, confidence interval; GFR, glomerular filtration rate; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; OR, odds ratio per 1-unit change in natural log-transformed ΔNT-proBNP. [a] Adjusted for age. [b] Adjusted for age and year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure. [c] Adjusted for age, year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure, and baseline echocardiographic left ventricular ejection fraction, left ventricular mass index, and left ventricular diastolic dysfunction. [d] Adjusted for age, year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure, baseline echocardiographic left ventricular ejection fraction, left ventricular mass index, and left ventricular diastolic dysfunction, year 5 GFR, and log-transformed baseline NT-proBNP. [e] Adjusted for age, year 5 hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and heart failure, baseline echocardiographic left ventricular ejection fraction, left ventricular mass index, and left ventricular diastolic dysfunction, year 5 creatinine, log-transformed baseline NT-proBNP, and baseline medications.

individuals may then be candidates for appropriate therapies to delay progression of their cardiovascular disease according to the most recent societal guidelines.[23]

Nevertheless, although the conceptual framework has been clearly established, the utility of population-based screening with NT-proBNP remains incompletely characterized and only two clinical trials have suggested a benefit. The STOP-HF trial screened patients with cardiovascular risk factors using BNP and treated those with BNP levels more than 50 ng/l using a multifaceted intervention with echocardiography and cardiology referral.[24] In this small cohort with a low event rate, there was a significant reduction in follow-up LVSD with BNP testing, and nonsignificant decreases in heart failure incidence and hospitalizations for cardiovascular events. In the PONTIAC trial, patients with diabetes mellitus but without cardiac disease were screened using NT-proBNP.[25] Patients with NT-proBNP levels more than 125 ng/l were randomized to care by diabetes 'care units' or to cardiology outpatient clinics with the goal of rapid augmentation of renin–angiotensin system antagonists and beta-blockers. The PONTIAC intervention increased use of renin–angiotensin system antagonists and was associated with concomitant decreases in death and hospitalization after 2 years. Both STOP-HF and PONTIAC assert that an NT-proBNP screening strategy can help select high risk patients for therapeutic interventions. Our current work suggests that patient selection for such an intervention may also be aided by incorporating known changes in NT-proBNP levels over time, a screening criterion that was not included by either of these trials. Our data also advocate further investigation into surveillance routines for patients with stable CAD to appropriately prevent poor outcomes in this at-risk patient group.

Thus, the approximately 10% increased risk of progression to LVEF less than 50% associated with an increase in NT-proBNP of 100 ng/l over 5 years is likely to be clinically useful for three potential purposes: first, for identification of patients with incident structural heart disease without signs or symptoms of heart failure (stage B heart failure) as described in this study; second, to assist in diagnosis of patients with structural heart disease with symptoms of heart failure (stage C heart failure); and third, to assist in prognosis; in addition to the risk associated with LV structural and functional changes, in the Valsartan Heart Failure Trial, 4-month change in NT-proBNP added prognostic information for New York Heart Association class III–IV heart failure.[23,26]

Limitations to this work include that only change in NT-proBNP was analyzed as a predictor, whereas many clinicians use only BNP. We chose to focus on NT-proBNP because of its previously demonstrated predictive superiority to BNP for cardiovascular events in the Heart and Soul Study population.[11] We only had baseline and year 5 levels of NT-proBNP; although it would have been interesting to see how the levels fluctuated in the intermediate period, we sought to find the association of ΔNT-proBNP with change in LV structure and function. In addition, the study population was composed primarily of older white urban men with stable CAD, limiting the generalizability of the findings to alternative populations. Stable CAD, as defined in Methods section, captures a heterogeneous population; this affects the generalizability of the findings, both positively and negatively. Symptomatology was not analyzed as part of this investigation; thus, it is unclear if increases in ΔNT-proBNP monitoring would capture primarily symptomatic or asymptomatic changes in LV systolic function. We chose not to include left atrial bi-plane volume as a marker of LV diastolic function in our analysis as it was not available for many participants and including it would further limit the number of study participants who could be included. Finally, there was limited information regarding medication use by participants at year 5 of follow-up, and thus, multivariable models could not be adjusted completely.

In conclusion, in stable CAD, 5-year ΔNT-proBNP level is independently associated with incident LVSD but not with LVDD or LVH. These findings suggest that long-term change in NT-proBNP level may serve as a useful adjunct for screening patients with stable CAD for functional cardiac deterioration.

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Conflicts of interest

There are no conflicts of interest.

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