Published in final edited form as:

Am J Cardiol. 2015 August 15; 116(4): 532–537. doi:10.1016/j.amjcard.2015.05.014.

Usefulness of B-type Natriuretic Peptides to Predict Cardiovascular Events in Women (From the Women's Health Study)

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Abstract

Natriuretic peptides are positively associated with incident cardiovascular disease (CVD), but data in women, particularly with regard to improvements in risk prediction, are sparse. We measured the N-terminal prohormone form of B-type natriuretic peptide (NT-proBNP) in 480 cases of incident CVD (myocardial infarction, stroke, and cardiovascular death) and a reference subcohort of 564 women from the Women's Health Study who were followed for a median (IQR) of 11.5 (7.3–13.4) years. Median (IQR) NT-proBNP concentrations were higher in women who developed CVD [81 ng/L (50–147)] than those who did not [64 ng/L (38–117); $P < 0.0001$]. For women in the highest as compared to the lowest quartile of NT-proBNP the risk of CVD was 65% higher after adjusting for established cardiovascular risk factors and kidney function (adjusted hazard ratio (aHR) 1.65, 95% CI 1.03–2.64, P -trend=0.03). When analyzed as a continuous variable, the aHR per 1-SD difference in Ln(NT-proBNP) was 1.22 (1.03–1.44; $P=0.02$). The per 1-SD change in Ln(NT-proBNP) appeared stronger for cardiovascular death (aHR 1.43, 95% CI 1.05–1.94, $P=0.02$) and stroke (aHR 1.24, 95% CI 1.03–1.50, $P=0.03$) than for myocardial infarction (aHR 1.09, 95% CI 0.87–1.37, $P=0.44$). When added to traditional risk covariables, NT-proBNP did not significantly improve the c-statistic (0.751 to 0.757; $P=0.09$), or net reclassification into $<5\%$, 5 to $<7.5\%$, and 7.5% 10-year CVD risk categories (0.014; $p=0.18$). In conclusion, in this prospective study of initially healthy women, NT-proBNP concentrations showed statistically significant association with incident CVD that was independent of traditional cardiovascular risk factors, but did not substantially improve measures of CVD risk prediction in this sample.

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Keywords

Prevention; Natriuretic peptides; risk factors

Introduction

B-type natriuretic peptides are widely used for the diagnosis of heart failure in patients presenting with shortness of breath.^{1–3} Natriuretic peptides also consistently associate with adverse cardiovascular events in stable patients with and without preexisting cardiovascular disease (CVD). However, the published data in primary prevention populations are largely derived from studies that include a small number of events among women,^{4–7} or excluded women altogether.^{8,9} Recently, we reported a strong relationship between the N-terminal prohormone fragment of B-type natriuretic peptide (NT-proBNP) and incident CVD in a cohort of women,¹⁰ but whether those findings extend to other populations of women is not known. In addition, a few studies have assessed whether natriuretic peptides might improve measures of CVD risk prediction in healthy populations,^{5,6,8,11} but only one has addressed that question specifically in women.¹⁰ We sought to address these issues by measuring NT-proBNP concentrations in a prospective case-cohort study of 480 cases of incident cardiovascular disease (myocardial infarction, stroke, or cardiovascular death) and a reference subcohort of 564 women from the Women's Health Study.

Methods

Women included in this study were enrolled in the Women's Health Study (WHS), a completed, randomized, double-blind, placebo-controlled 2×2 factorial trial of aspirin and vitamin E in the prevention of CVD and cancer. The WHS enrolled 39,876 female health professionals, 28,345 of whom provided a blood sample prior to randomization. Among these, 19,871 (70.1%) were fasting at the time of sample collection and were eligible for inclusion in this ancillary study. WHS participants have been followed continuously for the occurrence of CVD, a composite of non-fatal myocardial infarction, non-fatal stroke (ischemic and hemorrhagic) and cardiovascular death.

We utilized a case-cohort study design to efficiently address the study hypothesis. From 19,871 non-diabetic women with fasting blood samples, we first selected a random sample of CVD cases (n=465), and then chose 564 women for inclusion in the reference subcohort, which was frequency matched on age (5 year increments) and race with the selected CVD cases. Women who developed CVD during follow up were eligible for inclusion in the reference subcohort, and by chance 15 of the 564 women chose developed incident CVD during follow up. Thus, the final sample size of women with incident CVD was 480.

Plasma NT-proBNP was measured using an electrochemiluminescent assay provided by Roche Diagnostics (Indianapolis, IN). Plasma samples were also previously measured for total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (hsCRP), high sensitivity cardiac troponin T (Roche Diagnostics, Indianapolis, IN)¹² and creatinine.

Medians and proportions in the cases and reference subcohort were compared using the Wilcoxon rank-sum and chi-square tests, respectively. NT-proBNP concentrations were divided into increasing quartiles based on the distribution in the reference subcohort. Employing methods appropriate for a case-cohort sample, Cox proportional hazards models were used to test for association between baseline NT-proBNP and incident CVD.^{13–15} The risk per 1-SD unit of natural logarithm-transformed [Ln(NT-proBNP)] was also calculated. Models were adjusted for age, race, and aspirin assignment; those covariables plus traditional CVD risk factors (body mass index, current smoking, family history of MI, systolic blood pressure, total and high-density lipoprotein [HDL] cholesterol, and high-sensitivity C-reactive protein [hsCRP]). The last two models included age, race, aspirin, CVD risk factors, and estimated glomerular filtration rate (eGFR) with and without high-sensitivity cardiac troponin T.¹²

To directly compare the performance of risk prediction algorithms with and without NT-proBNP, we compared a model including the covariables used in the American College of Cardiology (ACC)/American Heart Association (AHA) 2013 pooled cohort atherosclerotic CVD risk model (age, race, systolic blood pressure, treatment for hypertension, smoking, and total and HDL cholesterol)¹⁶ and hemoglobin A1c and randomized aspirin assignment to the same model plus Ln(NT-proBNP). Diabetes was omitted from the model because none of the women included in this case-cohort had diabetes at baseline. We also compared a model using the Reynolds Risk Score covariables (age, race, systolic blood pressure, smoking, total and HDL cholesterol, family history of MI, hemoglobin A1C, and hsCRP)¹⁷ and randomized aspirin assignment to the same model plus Ln(NT-proBNP). We calculated c-statistics and integrated discrimination improvement (IDI), and then used the categorical net reclassification index (NRI) to determine if NT-proBNP improved our ability to classify women into 10-year CVD risk categories of <5%, 5 to <7.5%, and ≥7.5%. Sensitivity analyses were conducted with the previous 10-year risk thresholds of <5%, 5 to <10%, 10 to <20%, and ≥20%. Statistical tests of discrimination measures were performed using 1000 bootstrap samples.

The study was approved by the Brigham and Women's Hospital Institutional Review Board. Financial support for the measurement of NT-proBNP and high-sensitivity troponin T was provided by Roche Diagnostics. The sponsor had no role in the study design, collection, analysis, or interpretation of the data, in the writing of this report, or the decision to submit this article for publication.

Results

A total of 480 cases of incident CVD and 564 in the reference subcohort were included in analyses. The median (Q1–Q3) follow up for the population was 11.5 (7.3–13.4) years. The women who developed incident CVD had a higher prevalence of cardiovascular risk factors including hypertension, high cholesterol, and smoking (Table 1). Median (Q1–Q3) NT-proBNP concentrations at baseline were higher among women who had incident CVD than in those in the reference subcohort (Table 1).

Women with NT-proBNP concentrations in the highest quartile (≥ 117.4 ng/L) were at increased risk of incident CVD (Table 2). In risk factor adjusted models, the risk of incident CVD for women in the highest as compared to the lowest quartile of NT-proBNP was nearly 70% higher. These estimates remained largely unchanged after adjusting for renal function and high-sensitivity cardiac troponin T (hsTnT) (Table 2).

The association between NT-proBNP and incident CVD was consistent across a broad array of high- and low-risk subgroups, including age above or below 60 years, body mass index above or below 30, presence or absence of hypertension, and lipid and hsCRP concentrations (Figure). The association between NT-proBNP and the composite outcome appeared to be driven by its association with cardiovascular death and stroke (Table 3). The association with incident myocardial infarction did not appear to be as strong.

We observed modest, but non-significant improvements in the ability of models that used the AHA/ACC pooled cohort model covariables to discriminate after the addition of Ln(NT-proBNP) (Table 4). We observed a non-significant increase in the c-statistic (95% CI) to 0.757 (0.737–0.775) after the addition of Ln(NT-proBNP) to the ACC/AHA pooled cohort covariables ($P=0.09$). The changes in the NRI and IDI were not statistically significant. After the addition of Ln(NT-proBNP) to a model including the Reynolds Risk Score covariables, we observed a non-significant increase in the c-statistic (95% CI) to 0.758 (0.739–0.779) ($P=0.059$). No significant improvements were seen in the categorical NRI or the IDI after the addition of NT-proBNP. In a sensitivity analysis using the 10-year CVD risk categories of $<5\%$, 5 to $<10\%$, 10 to $<20\%$, and $\geq 20\%$, we again saw no significant improvement in the NRI after the addition of Ln(NT-proBNP) to either the ACC/AHA or Reynolds covariables.

Discussion

In this prospective cohort of healthy women, NT-proBNP concentrations were an independent predictor of the occurrence of a first major cardiovascular event. This association was consistent across a broad array of high- and low-risk subgroups, including those above and below the age of 60, with and without hypertension, abnormal lipids, a family history of heart disease, or obesity. However, in spite of this consistent, independent association, the addition of NT-proBNP led to only small, non-significant improvements in predicting 10-year cardiovascular risk, including the ability to classify women into 10-year cardiovascular risk categories of $<5\%$, 5 to $<7.5\%$, and $\geq 7.5\%$. The limited size of the sample, particularly of the reference subcohort, may have affected the power of our study to detect significant improvement.

The 480 cardiovascular events reported here represent a substantial increase in the overall number of incident cardiovascular events reported in women. The vast majority of those events (1,821) are from the Women's Health Initiative,¹⁰ and a small number of events were reported in other cohorts that include both men and women.^{4,7,18} The adjusted risk per 1-SD change in NT-proBNP in this study are comparable to that observed in the recently published data from the Women's Health Initiative.¹⁰

In this study, NT-proBNP was positively associated with cardiovascular death and stroke, but the association with incident myocardial infarction appeared to be somewhat weaker. The results for cardiovascular death and stroke parallel those observed in the Women's Health Initiative¹⁰ and in other cohorts that include men and women,^{4,7,18} The results for MI are also consistent with that seen in other cohorts.^{4,10} The biological mechanism of the relationship between natriuretic peptides and cardiovascular risk is not well understood. Natriuretic peptides are released into the circulation as a result of elevated ventricular wall stress, and they may serve as a sensitive indicator of that stress due to myocardial ischemia,^{19,20} neurohormonal activation, hypertension, left ventricular hypertrophy, or a combination of those factors. The relationship with stroke raises the possibility that natriuretic peptide concentrations somehow integrate risk attributable to hypertension as well as clinically silent atrial fibrillation.^{10,21,22}

We did not observe a significant change in the c-statistic, categorical NRI, or IDI when the NT-proBNP was added to the covariables included in either the AHA/ACC mixed cohort model,¹⁶ or the Reynolds Risk Score.¹⁷ While the lack of significant improvement in this study may appear to contradict recently published findings using different risk categories (10-year CVD risk of <5%, 5 to <10%, 10 to <20%, and ≥20%),¹⁰ the magnitude of the changes in the c-statistic and categorical NRI were similar in the two studies. The lack of significance in the present study could be related to the smaller number of events, the relatively small numbers in the reference subcohort, or to differences in the study populations.¹⁰

Strengths of our study include the prospective design and the relatively large number of incident cardiovascular events in a cohort of middle-aged women and who have been underrepresented in studies of novel markers of cardiovascular risk. In spite of the large number of events, however, we may still be underpowered to detect small improvements in risk reclassification, perhaps due to the small size of the reference subcohort. Nonetheless, these data do not support the routine use of NT-proBNP for CVD risk stratification.

Acknowledgments

The Women's Health Study was supported by grants HL-043851, HL-080467, and HL-099355 from the National Heart, Lung, and Blood Institute and CA-047988 from the National Cancer Institute, the Donald W. Reynolds Foundation (Las Vegas, NV), the Leducq Foundation (Paris, France), and the Doris Duke Charitable Foundation (New York, NY). This study was funded by an investigator-initiated award to Dr. Everett from Roche Diagnostics, Indianapolis, Indiana. Dr. Everett reports research support from Novartis, Basel, Switzerland. Dr. Ridker reports research grant support from Novartis, Basel, Switzerland, the NIH, and is listed as a co-inventor on patents held by Brigham and Women's Hospital on the use of inflammatory biomarkers in cardiovascular disease. Drs. Cook and Pradhan report research support from the NIH.

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Figure.

Adjusted hazard ratios and 95% confidence intervals (CI) for a first major cardiovascular event per 1-standard deviation (SD) increase in natural logarithm transformed NT-proBNP [Ln(NT-proBNP)] stratified by a number of key subgroups. A first major cardiovascular event is defined as the composite of myocardial infarction (MI), stroke, and cardiovascular death. Hazard ratios are adjusted for age, race, and aspirin assignment, body mass index, current smoking, family history of MI, systolic blood pressure, total and high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein and estimated glomerular filtration rate. The total N events may be less than 480 and N total less than 1044 if participants were missing information for a particular subgroup stratification variable. Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure. Units are years for age; kg/m² for BMI; mm Hg for SBP; mg/dL for cholesterol, HDL-C, and triglycerides; and mg/L for hsCRP.

Table 1

Baseline characteristics of the study population

Characteristic	CVD Cases* (n=480)	Reference Subcohort* (n=564)	P-value
Age (years)	61 (54–67)	57 (51–58)	0.06
White	457 (95%)	519 (92%)	-
BMI (kg/m ²)	25.0 (22.7–28.3)	25.6 (23.0–28.3)	0.42
Systolic blood pressure (mmHg)	135 (125–145)	125 (115–135)	<0.0001
Current smoker	109 (23%)	56 (10%)	<0.0001
Family history of MI	61 (13%)	68 (12%)	0.39
Alcohol use 1 drink per day	176 (37%)	225 (40%)	0.20
Exercise 1 times per week	177 (37%)	260 (46%)	0.002
Hypertension	228 (48%)	180 (32%)	<0.0001
Elevated cholesterol history	207 (43%)	191 (34%)	0.02
Hormone therapy use	167 (35%)	191 (34%)	0.62
Randomized aspirin use	223 (46%)	277 (49%)	0.37
High cholesterol treatment	30 (6%)	24 (4%)	0.38
Total cholesterol (mg/dL)	221 (197–249)	214 (188–240)	0.001
LDL cholesterol (mg/dL)	133 (112–156)	125 (107–149)	0.02
HDL cholesterol (mg/dL)	50.2 (41.4–60.1)	51.6 (43.0–62.1)	0.11
eGFR, (ml/min/1.73m ²)	45 (37–55)	47 (39–57)	0.07
hsCRP (mg/L)	2.7 (1.2–5.5)	2.2 (0.9–4.6)	0.004
NT-proBNP (ng/L)	81 (50–147)	64 (38–117)	<0.0001
ln(NT-proBNP)	4.4 (3.9–5.0)	4.2 (3.7–4.8)	<0.0001

* Numbers are N (%) for categorical variables and median (Q1–Q3) for continuous variables. Women selected for the reference subcohort who developed cardiovascular disease during follow up are included in both groups for calculation of the N (%) and medians (Q1–Q3), but were excluded from the analysis for statistical testing.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; MI, myocardial infarction; NT-proBNP, N-terminal prohormone Brain Natriuretic Peptide;

Table 2

Risk of incident cardiovascular disease according to baseline concentration of NT-proBNP

Model	Hazard Ratio (95% CI)				P-trend	Hazard Ratio (95% CI) per 1-SD of Ln(NT-proBNP)	P-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
NT-proBNP range (ng/L)	<37.8	37.8 to <64.3	64.3 to <117.4	117.4			
Age, race, aspirin-adjusted	1.0	1.17 (0.80–1.71)	1.33 (0.91–1.94)	1.40 (0.95–2.09)	0.08	1.21 (1.05–1.41)	0.01
CV risk factor adjusted*	1.0	1.28 (0.84–1.95)	1.66 (1.07–2.59)	1.69 (1.05–2.66)	0.02	1.23 (1.04–1.45)	0.02
CV risk factor + eGFR	1.0	1.28 (0.84–1.96)	1.69 (1.09–2.64)	1.65 (1.03–2.64)	0.03	1.22 (1.03–1.44)	0.02
CV risk factor + eGFR + hsTnT adjusted	1.0	1.26 (0.82–1.93)	1.69 (1.08–2.64)	1.65 (1.02–2.76)	0.03	1.21 (1.02–1.44)	0.03

* Cardiovascular disease (CVD) risk factor adjusted model is adjusted for age, race, body mass index, current smoking, family history of myocardial infarction, randomized aspirin assignment, and natural logarithm transformed systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and high sensitivity C-reactive protein.

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; hsTnT, high-sensitivity cardiac troponin T.

Table 3

Adjusted* risk of each of the components of the composite cardiovascular endpoint according to baseline concentration of NT-proBNP

Endpoint	Hazard Ratio (95% CI)				P-trend	Hazard Ratio (95% CI) per 1-SD of Ln(NT-proBNP)	P-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
Composite CV outcome (n=480)	1.0	1.28 (0.84–1.96)	1.69 (1.09–2.64)	1.65 (1.03–2.64)	0.03	1.22 (1.03–1.44)	0.02
CV Death (n=108)	1.0	0.95 (0.43–2.08)	1.26 (0.57–2.80)	1.62 (0.72–3.63)	0.17	1.43 (1.05–1.94)	0.02
Myocardial infarction (n=168)	1.0	1.37 (0.75–2.51)	1.78 (0.96–3.31)	1.31 (0.65–2.61)	0.34	1.09 (0.87–1.37)	0.44
Stroke (n=254)	1.0	1.45 (0.86–2.45)	1.97 (1.15–3.36)	1.97 (1.13–3.44)	0.01	1.24 (1.03–1.50)	0.03

* Models are adjusted for cardiovascular risk factors (age, race, body mass index, current smoking, family history of myocardial infarction, randomized aspirin assignment, and natural logarithm-transformed systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, high sensitivity C-reactive protein) and natural logarithm-transformed eGFR.

Table 4

Discrimination statistics for the American College of Cardiology (ACC)/American Heart Association (AHA) pooled cohort covariables and the Reynolds Risk Score (RRS) covariables before and after including NT-proBNP.

	ACC/AHA Covariables*	ACC/AHA Covariables + NT-proBNP	P-value	RRS Covariables [‡]	RRS + NT-proBNP	P-value
C-statistic (95% CI)	0.751 (0.732–0.770)	0.757 (0.737–0.775)	0.09	0.752 (0.733–0.772)	0.758 (0.739–0.779)	0.059
Categorical NRI (95% CI) [‡]	-	0.014 (–0.0033 – 0.036)	0.18	-	0.019 (–0.010 – 0.054)	0.27
IDI (95% CI)	-	0.000289 (–0.0013 – 0.0015)	0.68	-	0.00012 (–0.0019 – 0.0016)	0.89

* Age, race, aspirin assignment, current smoking, systolic blood pressure, treatment for hypertension, total and high-density lipoprotein cholesterol, hemoglobin A1c, and diabetes

[‡] Age, race, aspirin assignment, current smoking, systolic blood pressure, total and high-density lipoprotein cholesterol, hemoglobin A1c, family history of myocardial infarction, and high-sensitivity C-reactive protein

[‡] 10-year CVD risk categories of <5%, 5 to <7.5%, and 7.5%

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CI, confidence intervals; IDI, integrated discrimination improvement; NRI, net reclassification index;; RRS, Reynolds Risk Score