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B-Type Natriuretic Peptides Improve Cardiovascular Disease Risk Prediction in a Cohort of Women

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ABSTRACT

BACKGROUND Although N-terminal pro-B-type natriuretic peptide (NT-proBNP) has a strong relationship with incident cardiovascular disease (CVD), few studies have examined whether NT-proBNP adds to risk prediction algorithms, particularly in women.

OBJECTIVES This study sought to evaluate the relationship between NT-proBNP and incident CVD in women.

METHODS Using a prospective case-cohort within the WHI (Women's Health Initiative) observational study, we selected 1,821 incident cases of CVD (746 myocardial infarctions, 754 ischemic strokes, 160 hemorrhagic strokes, and 161 other cardiovascular [CV] deaths) and a randomly selected reference cohort of 1,992 women without CVD at baseline.

RESULTS Median levels of NT-proBNP were higher at study entry among incident cases (120.3 ng/l [interquartile range (IQR): 68.1 to 219.5 ng/l]) than among control subjects (100.4 ng/l [IQR: 59.7 to 172.6 ng/l]; $p < 0.0001$). Women in the highest quartile of NT-proBNP (≥140.8 ng/l) were at 53% increased risk of CVD versus those in the lowest quartile after adjusting for traditional risk factors (1.53 [95% confidence interval (CI): 1.21 to 1.94]; p for trend <0.0001). Similar associations were observed after adjustment for Reynolds Risk Score covariables (1.53 [95% CI: 1.20 to 1.95]; p for trend <0.0001); the association remained in separate analyses of CV death (2.66 [95% CI: 1.48 to 4.81]; p for trend <0.0001), myocardial infarction (1.39 [95% CI: 1.02 to 1.88]; p for trend = 0.008), and stroke (1.60 [95% CI: 1.22 to 2.11]; p for trend <0.0001). When added to traditional risk covariables, NT-proBNP improved the c-statistic (0.765 to 0.774; $p = 0.0003$), categorical net reclassification (0.08; $p < 0.0001$), and integrated discrimination (0.0105; $p < 0.0001$). Similar results were observed when NT-proBNP was added to the Reynolds Risk Score.

CONCLUSIONS In this multiethnic cohort of women with numerous CV events, NT-proBNP modestly improved measures of CVD risk prediction. (J Am Coll Cardiol 2014;64:1789–97) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

hsCRP = high-sensitivity C-reactive protein

IDI = integrated discrimination improvement

NP = natriuretic peptide

NRI = net reclassification improvement

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RRS = Reynolds Risk Score

Assays for B-type natriuretic peptides (NPs) have gained widespread acceptance as tools for diagnosis and risk stratification in patients experiencing shortness of breath and chest pain (1-3). NPs also have demonstrated consistent association with adverse cardiovascular (CV) outcome in stable patients with and without established cardiovascular disease (CVD) (4). However, few studies conducted in general populations have analyzed the association of NPs with CVD, specifically in women, and only a handful have comprehensively examined whether NPs improve clinical risk prediction in the general populations (5-8).

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Women have higher levels of NPs than men (5,9-13), and yet they have a lower absolute risk for CVD than men of similar age and risk factor burden (14). Obesity is also well known to affect NP levels in both whites and blacks (15,16), and differential patterns of adipose tissue in men and women may alter the relationship between NPs and CVD, as has been observed for other CVD risk markers (17). Reportedly, NP concentrations are lower in blacks than whites (18,19). In fact, although the relationship between NPs and CV risk appears consistent across several studies including general populations, many studies include only men (6,20), report the number of CVD events in women but do not report the association between NPs and CVD in women and men separately (7,11), or have too few events in women to analyze (13). Data on the relationship between NPs and CVD in women of nonwhite race/ancestry are even scarcer.

To better understand the relationship between NPs and CV risk in a broad population of women, we constructed a prospective, case-cohort study within the multiethnic Women's Health Initiative (WHI), and measured N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations at baseline in 1,821 women who subsequently had a major CV event (myocardial infarction [MI], stroke, or CV death) and a reference cohort of 1,992 women. We then tested whether the addition of NT-proBNP concentrations to traditional CVD risk markers, such as those included in the Framingham CVD score (21) or Reynolds Risk Score (RRS) (22), improved our ability to predict CV risk.

METHODS

STUDY POPULATION. This study includes participants in the WHI observational study (WHI-OS) and the WHI extension study. The WHI-OS is a multiethnic cohort of 93,676 post-menopausal women, aged 50 to 79 years at recruitment, who were enrolled between 1994 and 1998 at 40 sites across the United States. The racial/ethnic composition of the WHI-OS is representative of U.S. women in the included age groups. Of the 93,676 women in the WHI-OS, 71,872 had no prior history of MI, stroke, peripheral artery disease, venous thromboembolism, or cancer. Of those, 60,890 had baseline blood samples available for analysis.

Baseline information on medical history, health behaviors, and blood pressure (BP) measurements were collected by the WHI-OS clinical centers. Information on diabetes, smoking, family history of CVD, and medication use were self-reported.

OUTCOMES. The primary endpoint for this study was a composite of major CVD, defined as the occurrence of nonfatal MI, nonfatal stroke, or CV death. Chronic heart failure (HF) was not included as part of the primary CV endpoint. CVD outcomes were self-reported and physician-verified via review of cardiac biomarkers, electrocardiograms, and medical records as previously described (23). Coronary heart disease was defined as nonfatal MI and coronary death, and stroke was defined as a fatal or nonfatal persistent neurologic deficit of at least 24-h duration that was sudden in onset and compatible to obstruction or rupture of a cerebral artery. Strokes were classified as ischemic or hemorrhagic on the basis of brain imaging reports. Deaths were classified on the basis of death certificates, autopsy reports, and medical records.

SAMPLE SELECTION. A prospective case-cohort design was employed. A total of 2,000 women with incident CVD were selected for inclusion. We first included all incident cases among black (n = 200), Hispanic (n = 53), and Asian/Pacific Islander (n = 55) women, as well as 55 cases from women of unknown or other race/ethnicity groups. The remaining 1,637 cases were randomly selected from among 2,370 cases of incident CVD in white women. A reference cohort of approximately 2,000 women was selected using the same eligibility criteria and frequency matched by race/ethnicity and age (in 5-year groups). Women who developed CVD during follow-up were eligible to be selected as reference cohort members, but women who had prevalent CVD at enrollment, including transient ischemic attack, HF, or CV surgery, or who had no valid measurement of NT-proBNP (n = 2) were excluded from both the case and reference groups. After these exclusions, the final sample included 1,821 cases of CVD and a reference cohort of 1,992 women, of whom 132 were also cases.

LABORATORY ANALYSIS. Plasma samples were collected and stored centrally at −70°C and assayed for NT-proBNP, total cholesterol, high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hsCRP), and glycated hemoglobin A1c (the latter only among patients with diabetes) in a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program. NT-proBNP was measured using an electrochemiluminescent immunoassay from Roche Diagnostics (Indianapolis, Indiana).

STATISTICAL ANALYSIS. We estimated means and proportions in both the cases and the reference cohorts in a crude analysis. Overall population characteristics were estimated using inverse probability weights in PROC SURVEYMEANS and SURVEYFREQ in SAS version 9.2 (SAS Institute, Cary, North Carolina) to reflect the sampling in the total WHI cohort. Because the numbers in the full sample were known, our stratified sampling enabled us to mimic or recapture the characteristics of the full WHI cohort using reweighting by sampling frequency. The numbers of women among the cases and reference cohort who were above the age-specific NT-proBNP thresholds for acute HF in patients with dyspnea (>900 ng/l for ages 50 to 75 years and >1,800 ng/l for ages >75 years) were compared using the chi-square test (3). Cox proportional hazards models were used to test the association of NT-proBNP with incident CVD in all women, regardless of race/ethnicity. Previously described methods for proportional hazards regression in case-cohort samples, with appropriate weighting, were used (24–26). Using quartiles derived from all women selected for the reference cohort, the association of NT-proBNP with the composite CV outcome was tested in a series of adjusted models. The risk per 1-SD unit in Ln-transformed NT-proBNP (Ln-NT-proBNP) also was calculated. The first model, called the "multivariable model," was adjusted for age and race/ethnicity as well as underlying conditions and medication use (prior diabetes, angina, statin use, and current and past hormone therapy). We then constructed a "multivariable plus traditional risk factor" model that adjusted for covariables from the multivariable model above, plus the traditional risk markers that are included in the Adult Treatment Panel III risk model (27), the Framingham CVD risk score (21), and the American College of Cardiology/American Heart Association 2013 pooled cohort atherosclerotic CVD risk model (28): current smoking; the natural logs of systolic BP, total cholesterol, and HDL-C; and treatment for high BP. We also constructed a "Reynolds Risk Score" model that adjusted for covariables included in the multivariable model plus the variables in the RRS: current smoking; the natural logs of systolic BP, total cholesterol, HDL-C, and hsCRP; family history of premature MI; and glycated hemoglobin A1c among women with diabetes (22). In sensitivity analyses, body mass index (BMI) was included with the other covariables in the multivariable plus traditional risk factor and RRS models. We repeated the adjusted proportional hazards analysis for CV death, incident fatal/nonfatal MI, incident fatal/nonfatal stroke, and in analyses stratified by baseline characteristics. The Bonferroni-corrected p value for evidence of statistically significant interaction in the stratified analysis was $p < 0.00278$ ($p = 0.05/18$ tests).

To directly compare the performance of the multivariable plus traditional risk factor model and RRS model with and without NT-proBNP, we calculated the c-statistics for each model and the integrated discrimination improvement (IDI) (29). To determine whether NT-proBNP improved our ability to classify women into 10-year CVD risk categories of <5%, 5% to <10%, 10% to <20%, and ≥20%, we calculated the net reclassification improvement (NRI) (28). Survival methods were used throughout (30,31), and measures were reweighted to reflect the distribution in the overall cohort. Statistical tests of discrimination measures were performed using bootstrap samples. We also performed sensitivity analyses by including diabetes, angina, statin use, and current and past hormone therapy with the RRS covariables.

RESULTS

A total of 1,821 women who developed CVD during follow-up met the criteria for inclusion as cases, whereas 1,992 women met criteria for inclusion in the reference cohort. In total, there were 746 fatal/nonfatal MIs, 754 fatal/nonfatal ischemic strokes, 160 fatal/nonfatal hemorrhagic strokes, and 161 other CV deaths. The median follow-up time was 9.9 years (interquartile range: 8.0 to 11.6 years).

The study population's baseline characteristics presented both as crude analyses and in analyses reweighted to reflect sampling from the WHI population are displayed in **Table 1**. As anticipated, women who developed CVD during follow-up had higher BMIs, systolic BP, and hsCRP, and lower HDL-C levels. These women were also more likely to be current smokers, use loop diuretics, and have diabetes, a history of angina, or family history of premature MI. In both crude and reweighted analyses, NT-proBNP levels were significantly higher

TABLE 1 Comparisons of Baseline Characteristics of CVD Cases and Random Cohort, in the Sample and Reweighted to the Total WHI Cohort

	Crude			Reweighted to Population		
	Cohort (n = 1,992)	Cases (n = 1,821)	p Value	Cohort	Cases	p Value
Age, yrs	67.7 ± 0.2	67.8 ± 0.2	0.11	62.7 ± 0.04	67.9 ± 0.03	<0.001
Race/ethnicity						
Black	204 (10.2)	186 (10.2)	0.96	4,207 (7.2)	186 (7.6)	0.61
White	1,622 (81.4)	1,489 (81.8)	0.65	49,410 (84.7)	2,106 (86.4)	0.12
Hispanic	57 (2.9)	50 (2.8)	0.99	2,044 (3.5)	50 (2.1)	0.02
Asian	54 (2.7)	50 (2.8)	0.77	1,749 (3.0)	50 (2.1)	0.05
Other race/unknown race	55 (2.8)	46 (2.5)	0.48	914 (1.6)	46 (1.9)	0.51
Height, cm	160.9 ± 0.2	160.8 ± 0.2	0.78	161.5 ± 0.3	160.9 ± 0.1	0.095
Weight, kg	70.0 ± 0.3	72.2 ± 0.4	<0.0001	72.0 ± 0.6	72.1 ± 0.4	0.85
BMI, kg/m^2	26.9 ± 0.1	27.9 ± 0.1	<0.0001	27.3 ± 0.2	27.8 ± 0.1	0.057
Current smoking	96 (4.8)	161 (8.8)	<0.0001	3,310 (5.7)	207 (8.5)	0.009
Hormone therapy						
Current	830 (41.7)	719 (39.6)	0.12	27,986 (48.0)	977 (40.1)	<0.0001
Past	286 (14.4)	276 (15.2)	0.53	7,051 (12.1)	375 (15.4)	0.013
Blood pressure, mm Hg						
Systolic	129.7 ± 0.4	135.5 ± 0.4	<0.0001	126.3 ± 0.5	135.3 ± 0.4	<0.0001
Diastolic	74.3 ± 0.2	75.8 ± 0.2	<0.0001	74.8 ± 0.3	75.7 ± 0.2	0.012
Antihypertensive medication use	529 (26.6)	658 (37.7)	<0.0001	13,091 (22.5)	909 (37.3)	<0.0001
Total cholesterol, mg/dl	230.9 ± 1.0	228.0 ± 1.0	0.047	231.0 ± 1.5	228.4 ± 1.0	0.17
HDL, mg/dl	56.8 ± 0.4	51.1 ± 0.4	<0.0001	56.6 ± 0.5	51.1 ± 0.4	<0.0001
Cholesterol-lowering medication	178 (8.9)	176 (9.7)	0.55	4,359 (7.5)	236 (9.7)	0.037
Statin use	161 (8.0)	134 (7.4)	0.30	3,921 (6.7)	180 (7.4)	0.54
Loop diuretic use	48 (2.4)	71 (3.9)	0.002	1,188 (2.0)	92 (3.8)	0.006
hsCRP, mg/l*	2.3 (1.0–5.0)	3.0 (1.4–4.9)	<0.0001	2.4 (1.0–5.2)	3.0 (1.3–6.0)	<0.0001
Diabetes	93 (4.7)	189 (10.4)	<0.0001	2,151 (3.7)	238 (9.8)	<0.0001
HbA1c (if diabetic)	7.4 (0.2)	7.9 (0.1)	0.013	7.5 (0.2)	7.9 (0.1)	0.0099
Angina	55 (2.8)	83 (4.6)	0.004	1,314 (2.3)	112 (4.6)	0.0007
Family history of early MI	352 (17.7)	483 (22.1)	0.0002	11,413 (19.6)	552 (22.7)	0.042
NT-proBNP, pg/ml	100.4 (59.7–172.6)	120.3 (68.1–219.5)	<0.0001	82.7 (50.9–140.8)	122.4 (69.4–219.7)	<0.0001
Abnormal NT-proBNP†	17 (0.9)	49 (2.7)	<0.0001	312 (0.5)	65 (2.7)	<0.0001

Values are mean ± SE, n (%), or median (interquartile range). *Test is based on natural logs. †NT-proBNP >900 ng/l for ages 50 to 75 years and >1,800 ng/l for ages >75 years.

BMI = body mass index; CVD = cardiovascular disease; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; WHI = Women's Health Initiative.

among women who developed incident CVD (each $p < 0.0001$). In total, there were 8 cases with NT-proBNP concentrations above the age-specific cut points used to diagnose HF in patients with dyspnea (3) compared with only 1 in the reference cohort ($p = 0.004$) (**Table 1**).

The relationship between NT-proBNP levels and baseline characteristics of the reference cohort are displayed in Online Table 1. Increasing levels of NT-proBNP were associated with increasing age, systolic BP, and HDL-C; increased antihypertensive and hormone therapy use; and lower levels of BMI and hsCRP. No significant relationship was observed between NT-proBNP levels and total cholesterol, current smoking, diabetes, angina, loop diuretic use, or family history of premature MI. We observed a higher proportion of white women in the higher quartiles of NT-proBNP and the opposite pattern for black women (each $p < 0.0001$).

Increasing levels of NT-proBNP showed a positive relationship with incident CVD (**Table 2**) that remained significant after adjusting for covariables included in the traditional risk factor or RRS models. For example, relative to the women in the lowest quartile of NT-proBNP, women in the highest quartile were at 53% increased risk of CVD after adjusting for either the traditional risk factor covariables (hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.21 to 1.94; p for trend <0.0001) or the RRS covariables (HR: 1.53; 95% CI: 1.20 to 1.95; p for trend <0.0001). A linear increase in CVD risk was observed for women in the third and fourth quartiles relative to the first quartile, but the second quartile did not clearly fit this pattern (**Table 3**). Adding BMI or loop diuretic use to

TABLE 2 Association of NT-proBNP With Incident CVD

	Hazard Ratio (95% CI) by Quartile of NT-proBNP						
	Quartile 1 <50.9 ng/l	Quartile 2 50.9–<82.7 ng/l	Quartile 3 82.7–<140.8 ng/l	Quartile 4 ≥140.8 ng/l	p Value for Trend	Hazard Ratio (95% CI) per 1-SD* Unit Increase in Ln-NT-proBNP	p Value
Age and race/ethnicity adjusted	1.00	0.91 (0.72–1.14)	1.18 (0.95–1.45)	1.55 (1.26–1.92)	<0.0001	1.36 (1.26–1.48)	<0.0001
MV adjusted†	1.00	0.93 (0.74–1.17)	1.28 (1.03–1.59)	1.62 (1.30–2.02)	<0.0001	1.39 (1.28–1.51)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.92 (0.71–1.17)	1.29 (1.02–1.63)	1.53 (1.21–1.94)	<0.0001	1.37 (1.25–1.49)	<0.0001
MV + RRS adjusted§	1.00	0.94 (0.73–1.21)	1.29 (1.01–1.64)	1.53 (1.20–1.95)	<0.0001	1.36 (1.24–1.49)	<0.0001

*The SD of natural logarithm transformed NT-proBNP is 0.838. †Multivariable (MV)-adjusted model is adjusted for age and race/ethnicity, prior diabetes, angina, statin use, and current and past hormone therapy. ‡MV + traditional risk factor model is adjusted for the covariables in the MV model, plus current smoking and the natural logs of systolic blood pressure, total and HDL cholesterol, and blood pressure treatment. §MV + Reynolds Risk Score (RRS) model: adjusted for the covariables in the MV model, plus current smoking, the natural logs of systolic blood pressure, total and HDL cholesterol, hsCRP, family history of premature MI, and HbA1c among women with diabetes.

CI = confidence interval; Ln = Ln-transformed; other abbreviations as in Table 1.

the multivariable models presented in Table 2 did not change the relationship between NT-proBNP and incident CVD (data not shown).

When CV deaths and coronary and cerebrovascular events were considered separately, NT-proBNP was associated with both any CV death and fatal/nonfatal MI and fatal/nonfatal stroke (Table 3). The risk of CV death was more than 2.5 times higher for those in the highest quartile of NT-proBNP relative to those in the lowest quartile, even after adjusting for the RRS covariables (HR: 2.66; 95% CI: 1.48 to 4.81; p for trend <0.0001). Relative to those in the lowest quartile, these women were also at increased risk of fatal/nonfatal MI in models adjusted for traditional risk factor covariables (HR: 1.41; 95% CI: 1.05 to 1.89; p for trend = 0.004) and RRS covariables (HR: 1.39; 95% CI: 1.02 to 1.88; p for trend = 0.008). The risk of fatal/nonfatal stroke was also increased, with an HR of 1.60 (95% CI: 1.21 to 2.09; p for trend <0.0001) after adjustment for traditional risk factor covariables and an HR of 1.60 (95% CI: 1.22 to 2.11; p for trend <0.0001) after adjusting for RRS covariables. Further adjustment for BMI did not alter these risk estimates substantially (data not shown).

Associations between NT-proBNP concentrations and incident CVD stratified by a number of subgroups are displayed in Online Table 2. In general, the adjusted association between Ln-NT-proBNP and incident CVD was consistent across subgroups. The increase in the risk of incident CVD per 1-SD unit of Ln-NT-proBNP among past hormone therapy users (HR: 1.71; 95% CI: 1.00 to 2.91; p = 0.049) appeared to be larger than among current (HR: 1.41; 95% CI: 1.17 to 1.70; p = 0.0003) or never users

TABLE 3 Association of NT-proBNP With Cardiovascular Mortality, Incident Fatal and Nonfatal MI, and Incident Fatal and Nonfatal Stroke

	Hazard Ratio (95% CI) by Quartile of NT-proBNP						
	Quartile 1 <50.9 ng/l	Quartile 2 50.9–<82.7 ng/l	Quartile 3 82.7–<140.8 ng/l	Quartile 4 ≥140.8 ng/l	p Value for Trend	Hazard Ratio (95% CI) per 1-SD* Unit Increase in Ln-NT-proBNP	p Value
Cardiovascular mortality							
MV adjusted†	1.00	0.84 (0.42–1.68)	1.79 (0.99–3.24)	2.95 (1.67–5.20)	<0.0001	1.95 (1.65–2.31)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.81 (0.40–1.62)	1.78 (0.98–3.26)	2.82 (1.57–5.05)	<0.0001	1.89 (1.59–2.26)	<0.0001
MV + RRS adjusted§	1.00	0.82 (0.41–1.66)	1.81 (0.99–3.32)	2.66 (1.48–4.81)	<0.0001	1.80 (1.51–2.14)	<0.0001
MI (fatal and nonfatal)							
MV adjusted†	1.00	0.95 (0.70–1.27)	1.25 (0.94–1.65)	1.48 (1.12–1.96)	<0.0001	1.33 (1.21–1.47)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.94 (0.69–1.28)	1.25 (0.93–1.67)	1.41 (1.05–1.89)	0.004	1.28 (1.16–1.42)	<0.0001
MV + RRS adjusted§	1.00	0.97 (0.70–1.33)	1.26 (0.93–1.70)	1.39 (1.02–1.88)	0.008	1.26 (1.13–1.40)	0.0002
Stroke (fatal and nonfatal)							
MV adjusted†	1.00	0.95 (0.72–1.25)	1.21 (0.93–1.57)	1.72 (1.33–2.22)	<0.0001	1.40 (1.28–1.53)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.93 (0.70–1.25)	1.22 (0.93–1.61)	1.60 (1.21–2.09)	<0.0001	1.35 (1.22–1.48)	<0.0001
MV + RRS adjusted§	1.00	0.95 (0.71–1.27)	1.21 (0.92–1.60)	1.60 (1.22–2.11)	<0.0001	1.34 (1.22–1.48)	<0.0001

*The SD of natural logarithm transformed NT-proBNP is 0.838. †MV-adjusted model is adjusted for age, race/ethnicity, prior diabetes, angina, statin use, and current and past hormone therapy. ‡MV + traditional risk factor model is adjusted for the covariables in the MV model plus current smoking and the natural logs of systolic blood pressure, total and HDL cholesterol, and blood pressure treatment. §MV + RRS model is adjusted for the covariables in the MV model, plus current smoking, the natural logs of systolic blood pressure, total and HDL cholesterol, hsCRP, family history of premature MI, and HbA1c among women with diabetes.

Abbreviations as in Tables 1 and 2.

(HR: 1.28; 95% CI: 1.09 to 1.50; p = 0.003), but these apparent differences did not reach statistical significance (p for interaction = 0.03) after correcting for the number of comparisons (Bonferroni-corrected p < 0.00278).

When NT-proBNP was added to the multivariable plus traditional risk factor CVD prediction algorithm, we observed a small but statistically significant improvement in the c-index, with a difference in c-statistics of 0.009 (95% CI: 0.009 to 0.010; p = 0.0004) and improved classification of women into 10-year CVD risk categories of <5%, 5% to <10%, 10% to <20%, and ≥20% (NRI 0.059 [95% CI: 0.030 to 0.089]; p < 0.0001) (**Table 4**). Statistically significant improvements in the category-less NRI and IDI were also observed (**Table 4**). When NT-proBNP was added to an algorithm including the RRS covariates, we observed a small but statistically significant improvement in the c-index (difference 0.009; 95% CI: 0.005 to 0.013; p = 0.0001) and improved classification of women into the same 10-year CVD risk categories (NRI 0.033 [95% CI: 0.002 to 0.062]; p = 0.03) (**Table 4**). Both the category-less NRI and IDI showed statistically significant improvements after adding NT-proBNP to the RRS covariates (**Table 4**). Reclassification tables, weighted by cohort sampling, are displayed in Online Table 3 (for the multivariable plus traditional risk factor model) and Online Table 4 (for the RRS). When reweighted to reflect the sampling of the WHI-OS, the addition of NT-proBNP to the traditional risk factor covariables would reclassify 7,036 women, 4,246 (60%) correctly, of a possible 58,216 women. The addition of NT-proBNP to the RRS would reclassify 6,283 women (of 58,216), 5,209 (82.9%) correctly.

In sensitivity analyses that added prior diabetes, angina, statin use, and current and past hormone therapy to the RRS covariables used in the primary reclassification analysis, these results did not differ substantially (Online Table 5).

DISCUSSION

In this prospective case-cohort study, which included more than 1,800 cases of incident CVD in women, we observed a positive association between baseline NT-proBNP concentrations and the occurrence of a first major CV event, defined as an MI, stroke, or CV death (**Central Illustration**). Although a number of studies have reported this relationship in primary prevention or general populations, this study is the first to conduct a detailed evaluation of this relationship in women. This association was evident for CV mortality, fatal/nonfatal MI, and fatal/nonfatal stroke, and was consistent across a number of high- and low-risk subgroups. Finally, we observed that NT-proBNP concentrations, when added to the covariables included in either the traditional risk factor or RRS risk prediction algorithms, significantly improved our ability to identify women at increased risk of developing CVD in this multiethnic population (**Central Illustration**).

We believe these results are of scientific and clinical relevance for various reasons. First, the approximately 1,800 CV events included in this study represent the largest number of events used to evaluate NPs in a primary prevention population, regardless of the participants' sex. By comparison, a 2009 meta-analysis of NPs and CVD gathered approximately 1,000 events in primary prevention populations (4). Second, although there is consistent epidemiologic evidence that NP levels associate with future CV events in general populations, most of the published studies include few events in women (11–13), or women were not included in the study population (6,20). Women are known to have higher

TABLE 4 Changes to 10-Year CVD Risk Prediction Statistics After Adding NT-proBNP to Existing Risk Prediction Models

	MV + Traditional Risk Factor Covariables			RRS Covariables		
	MV + Traditional Risk Factor	MV + Traditional Risk Factor + NT-proBNP	p Value*	RRS	RRS + NT-proBNP	p Value†
C-statistic	0.770 (0.760–0.779)	0.779 (0.769–0.789)	0.0004	0.768 (0.757–0.776)	0.776 (0.765–0.785)	0.0001
Net reclassification improvement	–	0.059 (0.030–0.089)	<0.0001	–	0.033 (0.002–0.062)	0.03
Category-less net reclassification improvement	–	0.103 (0.020–0.183)	0.02	–	0.097 (0.013–0.19)	0.03
Integrated discrimination improvement	–	0.0102 (0.0055–0.016)	0.0001	–	0.0080 (0.0039–0.012)	0.0002

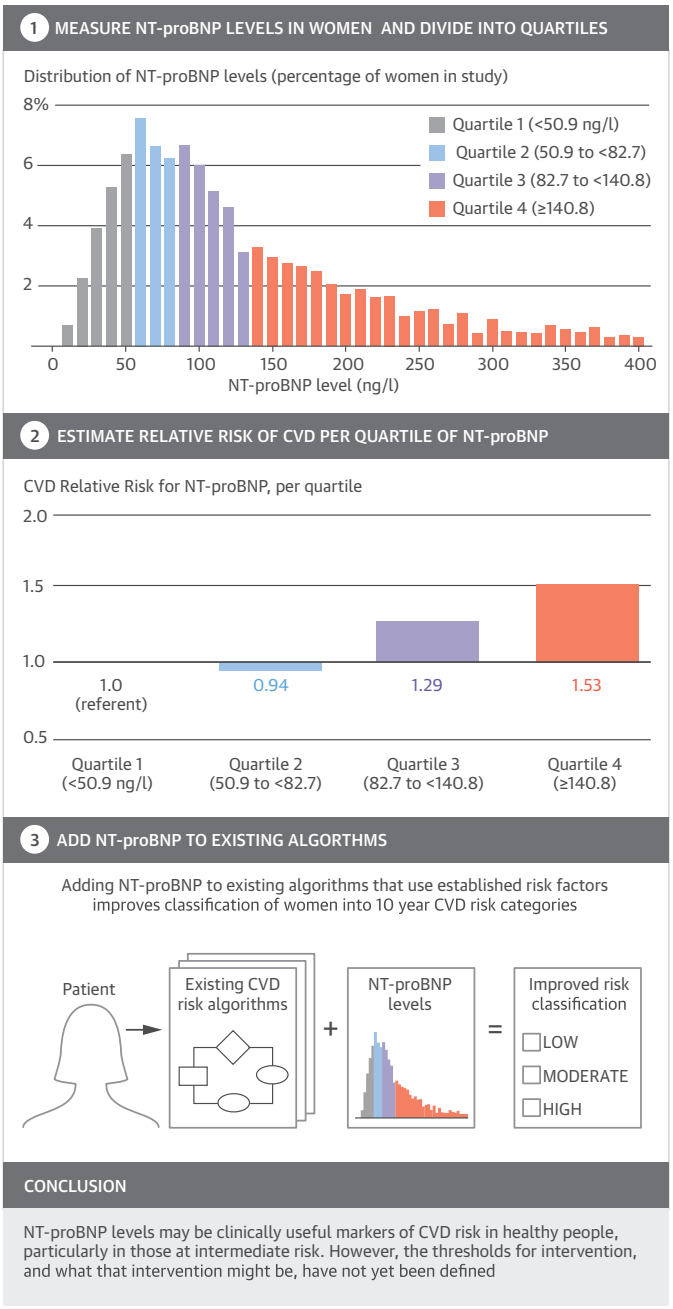
Values in parentheses are 95% CI. *Comparison of the performance of MV + traditional risk factor covariables + NT-proBNP concentrations versus MV + traditional risk factor covariables without NT-proBNP concentrations. The MV and traditional risk factor covariables were age, race/ethnicity, prior diabetes, angina, statin use, current or past hormone therapy, current smoking, and the natural logs of systolic blood pressure, total and HDL cholesterol, and blood pressure treatment. †Comparison of the performance of RRS covariables + NT-proBNP concentrations to RRS performance without NT-proBNP concentrations. The RRS covariables were age, race/ethnicity, current smoking, the natural logs of systolic blood pressure and total and HDL cholesterol, hsCRP, family history of premature MI, and HbA1c among women with diabetes.

Abbreviations as in **Tables 1 and 2**.

baseline concentrations of NPs than men (5,11–13) and yet have a lower risk of CVD at a given age and risk factor burden, as well as a lower lifetime risk of CVD (14,32). Despite these differences, women in our study who had NT-proBNP concentrations in the highest quartile (≥140.0 ng/l) were at more than 50% increased risk for the composite CV outcome when compared with those in the lowest quartile, even after adjusting for race and other important covariables included in established risk models.

These results are also consistent with prior work that has examined the association of NPs and CV endpoints that exclude HF and/or atrial fibrillation (4). Indeed, we observed significant associations between NT-proBNP and CV death from any cause, as well as MI and stroke, an observation that again is consistent with prior work in other cohorts (4,11–13,33). The mechanism of the association between NPs and incident CVD is not known, although it seems likely that NPs are measuring a component of CV risk that is either different from or incompletely accounted for by traditional CVD risk markers. Higher NT-proBNP concentrations may be evidence of subclinical myocardial ischemia (34,35), ventricular wall stress, neurohormonal activation, hypertension, or other conditions. The consistency of the association with NT-proBNP and incident stroke raises the possibility that elevated concentrations may identify individuals with unrecognized and/or silent atrial fibrillation, who might then be at high risk of cardioembolic stroke, as was hypothesized in a recently published study from the ARIC (Atherosclerosis Risk in Communities) cohort (33). We also note that the vast majority of women in the WHI had NT-proBNP concentrations well below the threshold that would prompt consideration of HF in patients with dyspnea (3).

Finally, we observed that adding NT-proBNP to traditional risk factors and the RRS improves CVD risk prediction in this multiethnic cohort of women. Only a handful of studies have tested the ability of NPs to improve CV risk prediction in primary prevention cohorts. The results have been mixed, with some reporting improvements alone or in combination with other markers (5,6,8,36) and others reporting no improvement (7). Because women have a lower prevalence of CVD for a given age distribution, and because traditional risk factors have superior risk prediction performance for women than men, even biomarkers with an independent association with CVD (such as NT-proBNP) may not improve upon the performance of existing risk prediction algorithms (37). Despite these challenges, in our study, NT-proBNP offered small but statistically significant



CENTRAL ILLUSTRATION Improving CVD Risk Prediction in Women by Adding NT-proBNP Levels to Existing Algorithms

N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were measured in 1,821 women with incident cardiovascular disease (CVD) (746 myocardial infarction, 754 ischemic stroke, 160 hemorrhagic stroke, and 161 cardiovascular death) and a randomly selected reference subcohort of 1,992 women without CVD at baseline. **(1)** The distribution of NT-proBNP concentrations in the reference subcohort. **(2)** The risk of the combined cardiovascular endpoint (myocardial infarction, stroke, or cardiovascular death) according to increasing quartiles of NT-proBNP. **(3)** The addition of NT-proBNP to traditional risk factors in risk prediction algorithms, which leads to modest but statistically significant improvements in the ability to predict 10-year cardiovascular disease risk.

improvements in the c-statistic, the categorical NRI, the continuous NRI, and the IDI when added to the traditional risk factor and RRS covariables. Although it is difficult to compare improvements in model performance across populations, we observed improvements in the c-statistic for major CV events that are similar in magnitude to those seen for cardiac troponin in the ARIC study (38) and close but somewhat smaller than those achieved with a multimarker score in a European cohort and in the Framingham Heart Study (8,36). The improvements are smaller than those seen with coronary calcium scans in the MESA (Multi-Ethnic Study of Atherosclerosis) (39).

Although statistically significant, the improvements in measures of risk prediction we observed with NT-proBNP were relatively modest. NPs may merit consideration as useful markers of CVD risk in those for whom a decision to begin preventive statin therapy is otherwise unclear, much like other adjunctive measures of CV risk (40). However, the therapeutic response to an elevated NP level in an otherwise healthy individual is not clear. Although using NPs as a tool to identify those who might benefit from statins would be one possible clinical strategy, no trial has tested this approach. Indeed, elevated NP levels may identify abnormalities in other biological pathways that are best addressed with other classes of agents rather than statins. For example, a recent trial of aggressive renin angiotensin and beta-blockade as compared with standard care in patients with type 2 diabetes and an elevated NT-proBNP (>125 ng/l) suggested a benefit for aggressive care (41).

STUDY STRENGTHS AND LIMITATIONS. Strengths of our study include its prospective nature, inclusion of a large number of women from a multiethnic cohort, and a large number of CV events. Limitations include the fact that the generalizability of our findings may be limited to women and the absence of any measures of renal function in the WHI. Although renal function is likely to be a confounder of the relationship between NT-proBNP and incident CVD, we note that measures of renal function are not included as risk predictors in the Adult Treatment Panel III, the Framingham CVD risk score, the 2013 American College of Cardiology/American Heart Association pooled cohort model, or in the RRS, despite having been considered for inclusion in the latter (21,22,27,28).

CONCLUSIONS

NT-proBNP showed a positive association with MI, stroke, and CV death in this large, prospective, case-cohort study with more than 1,800 first CV events. This association was observed for both fatal and nonfatal coronary and cerebrovascular events, when considered separately, and was consistent across several subgroups. Finally, when we added NT-proBNP to risk prediction models using traditional risk factors or the RRS covariables, we saw consistent, statistically significant improvements in the models' ability to correctly classify women into 10-year categories of CV risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Measurement of plasma NP levels can help identify HF among patients with dyspnea. In healthy men and women, NP levels correlate with risks of future MI, stroke, and CV death.

TRANSLATIONAL OUTLOOK: Additional work is needed to define the risk prediction thresholds for blood levels of specific NPs and to identify preventive interventions that improve CV outcomes for those with NP levels above those thresholds.

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KEY WORDS biomarkers, multiethnic, prevention, risk prediction

APPENDIX For supplemental tables, please see the online version of this article.