N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) and Risk of Hypertension in the Atherosclerosis Risk in Communities (ARIC) Study

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BACKGROUND
Brain natriuretic peptide (BNP) is released by the heart in response to ventricular and auricular wall stress. Release of BNP is traditionally considered part of the body’s protective mechanism against pressure overload by inducing vasodilatation and diuresis. More recent evidence demonstrates that BNP also promotes vessel wall stress and preliminary studies suggest that chronic increased levels may increase risk of hypertension. This study aimed to evaluate the prospective association of N-terminal BNP (NT-proBNP), a cleavage product of BNP, with risk of hypertension in the Atherosclerosis Risk in Communities cohort study.

METHODS
We conducted a prospective analysis of 3,798 middle-aged participants in the ARIC study without hypertension at baseline (1996–1998). Using Cox proportional hazards models, we characterized the association between NT-proBNP at baseline and newly diagnosed hypertension for a maximum of 14 years of follow-up (median = 9 years).

RESULTS
We observed 2,113 new hypertension cases over the follow-up period. Higher baseline NT-proBNP was independently associated with an increased risk of hypertension. Adjusted hazard ratios for incident hypertension in the highest quartile compared to the lowest quartile of NT-proBNP at baseline was 1.24 (95% CI: 1.08–1.42). Each log-unit increase in NT-proBNP was associated with an 8% increased risk of hypertension (95% CI: 1.03–1.13).

CONCLUSIONS
Persons with elevated NT-proBNP, even with normal blood pressure at baseline, were at increased risk of developing hypertension. Our results suggest that elevated circulating BNP might contribute to the development of hypertension in previously normotensive individuals.

Keywords: biological markers; blood pressure; brain natriuretic peptide; cohort; epidemiology; hypertension; risk factors.

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Brain natriuretic peptide (BNP) is released by the heart in response to hemodynamic stress. Elevated BNP levels are indicative of increased ventricular overload.1–3 BNP levels are also tied closely with left ventricular mass, are commonly used for diagnosing and staging congestive heart failure, and are associated with cardiovascular disease risk and mortality.2,4,5 Release of BNP occurs in response to ventricular and auricular wall stress and induces vasodilation (vascular smooth muscle relaxation and increased endothelial permeability) and diuresis.5,7 Counteracting these “anti-hypertensive” effects, BNP also promotes the release of norepinephrine,6 impacts sodium homeostasis,8,9 and may reflect the presence of slight volume expansion10; these factors may contribute to an increase in blood vessel pressure. Given the two opposing effects of BNP on blood pressure, cross-sectional studies have had limited ability to characterize the association between BNP and hypertension. Using N-terminal pro-brain natriuretic peptide (NT-proBNP), a stable cleavage product of pro-brain natriuretic peptide (BNP),11 previous studies document cross-sectional associations of elevated NT-proBNP with hypertension and elevated blood pressure.12–14 However, the prospective association of elevated BNP with development of hypertension is not well characterized, and could inform our understanding of the potential role of BNP in altering hypertension risk. Thus, the aim of this study was to evaluate the association of NT-proBNP with risk of hypertension in the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesized that baseline NT-proBNP levels would be positively associated with incident hypertension during 14 years of follow-up.

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METHODS

Study population

The ARIC Study is an ongoing community-based cohort of 15,792 adults who were aged 45–64 years at the initial examination, which took place from 1987 to 1989. ARIC participants were recruited from four US communities (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD).\textsuperscript{15} Participants completed three follow-up examinations, spaced approximately 3 years apart. NT-proBNP was measured at ARIC Visit 4 (1996–1998), the baseline for the present study. Details regarding the study population and data collection procedures in ARIC have been previously published.\textsuperscript{15}

Among the 11,656 ARIC participants who attended Visit 4, we excluded persons with prevalent diagnosed ($n = 5,628$, based on self-reported diagnosis or use of blood pressure-lowering medication) or undiagnosed ($n = 859$, based on measured blood pressure $\geq 140/90$ mm Hg at baseline) hypertension, history of coronary heart disease ($n = 138$), history of congestive heart failure ($n = 7$), history of stroke ($n = 24$), or who were missing hypertension status information or other variables used in analyses during the follow-up period ($n = 1,202$). The final analytic sample included 3,798 Black and White ARIC participants with a maximum follow-up time of 14 years (median $= 9$ years).

NT-proBNP

NT-proBNP was measured in stored plasma samples using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics). The lower limit of detection for this assay is 5 pg/ml and the coefficient of variation is 3.5–4.7%. Previous studies demonstrate the long-term stability of NT-proBNP.\textsuperscript{16}

Incident diagnosed hypertension

Incident, newly diagnosed hypertension was assessed during annual telephone calls though mid-2014 using the following interviewer-administered questions: “Since we last contacted you has a doctor said you had high blood pressure?”, “Has a doctor ever said you had high blood pressure?”, or “Did you take any medications during the past 2 weeks for high blood pressure?” Time of newly diagnosed hypertension used for analysis was the date when participants first reported diagnosis of or treatment for hypertension after previous documentation of no hypertension history.

Other variables of interest

Age, sex, race, current smoking status, current alcohol use, medical history information, and educational attainment were self-reported by participants at the baseline clinic examination during a structured interview. Previous diagnosed diabetes was defined as self-report of a physician diagnosis or use of diabetes medications. The examination included measurement of blood pressure, height and weight, waist circumference, and hip circumference using standardized methods. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. High-sensitivity C-reactive protein (hs-CRP) was measured using a standard assay previously described.\textsuperscript{15}

Statistical analysis

Baseline characteristics for the study population were calculated after stratifying by quartiles of NT-proBNP. We used Cox proportional hazards regression models to obtain hazard ratios (HRs) and their 95% confidence intervals for the association between baseline NT-proBNP (modeled as a continuous variable and in quartiles) and incident hypertension after adjustment for covariates, overall and stratified by baseline blood pressure status (normotensive vs. prehypertensive). For the continuous models, individuals with NT-proBNP below the limit of detection ($n = 317$) were assigned a value of 2.5 pg/ml ($0.5 \times$ the lower limit of detection). In analyses with NT-proBNP modeled according to quartiles, participants in the lower quartile served as the reference group. The proportional hazards assumption was confirmed by examining interactions between follow-up time and NT-proBNP.

Time of incident hypertension was defined as the first report of a diagnosis of hypertension or antihypertensive medication use. Participants were censored in the event of death or loss to follow-up. Participants who developed incident coronary heart disease, congestive heart failure, or stroke were censored in sensitivity analyses to address the potential effect of the development of these conditions on blood pressure. Previous research has documented inverse associations between NT-proBNP with obesity and diabetes\textsuperscript{17,18} and therefore we additionally conducted stratified analyses to examine the association of NT-proBNP with incident hypertension by BMI category and diabetes status at baseline. For stratified analyses, subgroup-specific quartiles were constructed. We formally evaluated for interactions of NT-proBNP with BMI category, diabetes status, sex, race, and age. All analyses were performed using Stata Statistical Software: Release 13.1 (College Station, TX: StataCorp LP).

RESULTS

At baseline, the mean age of the study population was 62 years. Fifty-percent percent of the cohort was male and 13% were of Black race/ethnicity. Individuals with higher NT-proBNP levels were older, more likely to be female, had lower BMI, and had a lower prevalence of diabetes (Table 1). Additionally, participants with elevated NT-proBNP had higher systolic blood pressure and lower diastolic blood pressure at baseline ($P$ for trend $< 0.05$). Over a median follow-up time of 9 years (maximum of 14 years), 2,113 participants (56% of the population) were newly diagnosed with hypertension. Of those that developed hypertension over the follow-up period, only 27% had pre-hypertension at baseline, 71% were overweight or obese (BMI $\geq 25$ kg/m$^2$), and 10% had a history of diabetes.

Individuals in the lowest quartile of NT-proBNP were at lowest risk for developing hypertension compared to those in
the upper quartiles (Table 2). The adjusted HRs for incident hypertension by increasing quartiles of NT-proBNP at baseline were 1 (reference), 1.10 (95% CI: 0.97–1.24), 1.08 (95% CI: 0.95–1.24), and 1.24 (1.08–1.42), respectively. The magnitude of association of NT-proBNP with hypertension risk did not differ among those who were normotensive compared to pre-hypertension at baseline (P-for-interaction = 0.35). Each log-unit increase in NT-proBNP was associated with an 8% increased risk of hypertension (95% CI: 1.03–1.13). The Figure 1 depicts the adjusted HRs from the restricted cubic spline models for newly diagnosed hypertension by baseline NT-propBNP value in the total ARIC population. The HR for individuals in the highest quartile compared to the lowest quartile of NT-proBNP was higher among individuals who were overweight or obese. However, there was no statistically significant interaction between NT-proBNP and BMI or diabetes status observed (Supplementary Tables 1 and 2, P-for-interaction = 0.32 and 0.72, respectively). NT-proBNP was most strongly associated with incident hypertension in those aged 60 years and younger (HR = 1.09, 95% CI: 1.02–1.17) compared to those older than 60 years (HR = 1.06, 95% CI: 0.99–1.13). However, the association of NT-proBNP with hypertension risk did not differ significantly by age (P-for-interaction = 0.71), sex (P-for-interaction = 0.73), or race (P-for-interaction = 0.71). Sensitivity analyses censoring incident nonfatal cases of coronary heart disease, congestive heart failure, or stroke yielded similar results (data not shown).

**DISCUSSION**

Less than 20% of hypertension cases occur in isolation; a majority of individuals with new diagnoses present with other cardiovascular-related comorbidities. Changes in cardiac structure—a consequence of increased pressure on the blood vessels and present even in normotensive individuals—may occur prior to and accelerate the development of hypertension. In a community-based population of adults, higher levels of NT-proBNP (>99.5 pg/ml) at baseline were associated with increased risk of newly diagnosed hypertension; this association was independent of major cardiovascular risk factors and was evident in those who
were normotensive as well as prehypertensive at baseline. Our findings support the hypothesis that increased concentrations of BNP may increase vessel wall stress, could serve as a marker for salt sensitivity, and/or could indicate subtle volume expansion and thus may contribute to the development of hypertension even among those with blood pressure in the normal range.\textsuperscript{13}

The literature on the association of BNP with hypertension is mixed. In a cross-sectional study of 202 participants with history of dyspnea, median NT-proBNP was approximately 60\% higher in individuals with diagnosed hypertension compared to those without hypertension (\(P < 0.01\)).\textsuperscript{13} A case-control study that included 48 African patients with hypertension and 20 normotensive participants found that the mean NT-proBNP concentration was nearly 20 times higher in the hypertensive group (229 pg/ml vs. 12 pg/ml, \(P = 0.001\)).\textsuperscript{22} Despite the strong cross-sectional associations observed in these two studies, a prospective analysis of 1,801 participants in the Framingham Offspring Study found that elevated plasma BNP was associated with an increased risk of worsening blood pressure after 4 years in men but not women.\textsuperscript{23} This is in contrast to the present report where we found no evidence that the association differed by sex (\(P\text{-for-interaction} = 0.78\)). It is possible that the short follow-up period and relatively few events contributed to the observed lack of association among women in the Framingham study; it may be that the effect of BNP on chronic blood pressure unfolds over a longer period of time. Indeed, among ARIC participants who developed hypertension, the mean time to incident hypertension from the measurement of NT-proBNP was 7 years.

In previous studies, increased BNP has been inversely associated with metabolic disorders such as diabetes and obesity because of its posited role in adipose and glucose metabolism.\textsuperscript{14,17,24} While this mechanism is yet to be confirmed, increased levels also result in potentially deleterious actions such as the release of norepinephrine, which is known to increase blood pressure.\textsuperscript{6} Furthermore, recent studies have shown that natriuretic peptides might also be involved in blood pressure regulation via natriuretic peptide precursor A (NPPA) and natriuretic peptide precursor B (NPPB) genes that contribute to between-individual variability in blood pressure.\textsuperscript{25}

Some limitations of our study should be considered in the interpretation of our results. Because we relied on self-report for the identification of new hypertension cases, we cannot rule out the possibility that some participants may be misclassified leading to an underestimate of hypertension in this cohort. However, self-reported diagnosis has been shown to have high specificity\textsuperscript{26,27} and under-ascertainment of cases would likely bias our results towards the null. Additionally, attenuated results were observed for subgroup analyses stratified by baseline hypertension status, BMI category, and diabetes status; these weaker association were likely due to small sample sizes compared to analyses pooling the entire study sample. Despite rigorous measurement of cardiovascular risk factors, we further cannot rule out the possibility of residual confounding in this observational study. Nonetheless, our study benefited from the large sample size, a long duration of follow-up, repeated assessment of hypertension status during follow-up, and standardized measurement of known hypertension risk factors.

Various risk factors predict the development of hypertension in middle-aged and older adults. These risk factors include age, race/ethnicity, family history, genetic factors, socioeconomic factors, obesity, inactivity and other lifestyle behaviors, and sleep apnea.\textsuperscript{28} Circulating BNP may independently contribute to the development of hypertension. In summary, individuals with elevated NT-proBNP levels are at increased risk for developing hypertension. While BNP release may reduce blood pressure as an acute compensatory response to cardiac preload by dilating the vessels and reducing peripheral resistance, high doses of BNP—and perhaps prolonged presence of elevated subclinical levels—may increase peripheral resistance.\textsuperscript{6} Over time, chronic exposure BNP in the circulation might contribute to the development of hypertension in previously normotensive individuals. Additional research is warranted to further elucidate potential biological mechanisms and to more fully evaluate the utility NT-proBNP measurement for risk stratification and hypertension prevention, and more directly for improving our understanding of the pathophysiology of hypertension.

\begin{table}[h]
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\begin{tabular}{|c|c|}
\hline
\textbf{Table 2. Hazard ratios (95\% CI) of the association of baseline NT-proBNP with incident diagnosed hypertension among ARIC participants without history of coronary heart disease, congestive heart failure, or hypertension (\(n = 3,798\))} & \\
\hline
\textbf{Ln-transformed NT-proBNP} & \\
\hline
\textbf{Overall} & 1.08 (1.03–1.13) \\
\hline
\textbf{Within baseline blood pressure categories} & \\
\hline
\textbf{Normotensive (\(n = 3,072\))} & 1.06 (1.01–1.12) \\
\hline
\textbf{Pre-hypertensive (\(n = 777\))} & 1.07 (0.98–1.18) \\
\hline
\textbf{NT-proBNP quartiles} & \\
\hline
\textbf{Overall} & \\
\hline
\textbf{Q1:} & \\
\hline
\textbf{Q2:} & \\
\hline
\textbf{Q3:} & \\
\hline
\textbf{Q4:} & \\
\hline
\hline
\textbf{Within baseline blood pressure categories} & \\
\hline
\textbf{Normotensive (\(n = 3,044\))} & \\
\hline
\textbf{Q1:} & 1 (reference) \\
\hline
\textbf{Q2:} & 1.10 (0.97–1.24) \\
\hline
\textbf{Q3:} & 1.08 (0.95–1.23) \\
\hline
\textbf{Q4:} & 1.24 (1.08–1.42) \\
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\end{tabular}
\end{table}

\textsuperscript{a}Adjusted for age, sex, race, clinic site, educational attainment, diabetes status, body mass index, waist-hip ratio, high sensitivity c-reactive protein, smoking status, and alcohol intake.

\textsuperscript{13}American Journal of Hypertension  28(10) October 2015  1265
SUPPLEMENTARY MATERIAL

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

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DISCLOSURE

Drs. Hoogeveen and Ballantyne have received grant support from Roche Diagnostics (and the National Institutes of Health) and are co-investigators on a provisional patent filed by Roche for use of biomarkers in heart failure prediction. Roche Diagnostics had no role in the study design, analysis, or presentation preparation. Drs. Selvin and Ballantyne have served on an advisory board for Roche and have a pending patent filed by Roche for use of biomarkers in heart failure. Dr. Selvin has a pending patent for use of biomarkers in heart failure for the National Institute on Aging. Dr. Ballantyne has served on an advisory board for Roche. Drs. Hoogeveen and Ballantyne have served on an advisory board for Roche Diagnostics (and the National Institutes of Health) and are co-investigators on a provisional patent filed by Roche for use of biomarkers in heart failure prediction. Roche Diagnostics had no role in the study design, analysis, or presentation preparation. Drs. Selvin and Ballantyne have served on an advisory board for Roche. Dr. Selvin has a pending patent for use of biomarkers in heart failure for the National Institute on Aging. Dr. Ballantyne has served on an advisory board for Roche.

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