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Increasing NT-proBNP Precedes The Development of Arterial Hypertension: The Multi-Ethnic Study Of Atherosclerosis

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Abstract

Background—Longitudinal associations between the aminoterminal pro B-type natriuretic peptide (NT-proBNP) and incident hypertension are lacking.

Methods—We tested associations between baseline NT-proBNP (bNT-proBNP) and also change in NT-proBNP (NT-proBNP) (visit 3 NT-proBNP – bNT-proBNP; 3.2 years apart) with incident hypertension (systolic blood pressure ≥ 140 and/or diastolic BP ≥ 90 mmHg or taking anti-hypertensive medications). Incident hypertension was evaluated in 5596 individuals in the Multi-Ethnic Study of Atherosclerosis (MESA) without hypertension at baseline (53% females, age

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Disclosures

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range 45 – 84 years without overt cardiovascular disease) and followup for 9.5 years and in a subgroup (1550) who had bNT-proBNP <100 pg/mL and no hypertension at visit 3. Incident hypertension was regressed (proportional hazards) on quintiles of bNT-proBNP (range) 1) reference <19.2, 2) 19.3 – 40.8, 3) 40.9 – 70.9, 4) 71 – 135.2 and 5) >135.5 and also on NT-proBNP categories (reference < –10, –10 – 10, >10 – 50 and >50 pg/mL). Hazard ratios (HRs) were adjusted for age, race, sex, education, diabetes, obesity, LV mass/height, SBP and DBP, IL-6, salt intake, estimated glomerular filtration rate and exercise.

Results—Compared to the reference category, HRs (95% CI) for incident hypertension compared to the first quintile of bNT-proBNP were 1.47 (1.13–1.93), 1.57 (1.18–2.09), 1.52 (1.12–2.06) and 2.36 (1.62–3.41). HRs for incident hypertension by categories of NT-proBNP from 3.2 to 9.5 years followup were 0.98 (0.62 – 1.56), 1.13 (0.72 – 1.79) and 1.82 (1.07 – 3.12).

Conclusion—The development of hypertension tended to be preceded by elevated levels of bNT-proBNP or a substantial positive NT-proBNP.

Keywords

hypertension; incidence; NT-proBNP; change in NT-proBNP; subclinical atherosclerosis; risk factor

Introduction

Cross-sectional reports have shown a positive association between B-type natriuretic peptide (BNP) and blood pressure in both normotensive and hypertensive individuals [1, 2]. Conversely, the cross-sectional Olmsted County Study [3] found that pre-hypertensive individuals had lower BNP and also lower levels of the biologically inactive amino terminal-pro B-type natriuretic peptide (NT-proBNP) than normotensive or hypertensive subjects. This U-shaped relationship between NT-proBNP and blood pressure categories suggested that low NT-proBNP could be predictive of higher blood pressure values and the development of future hypertension. However, the Framingham Heart Study demonstrated a positive association between BNP and progression of blood pressure in men, but not in women [4], inconsistent with this hypothesis.

Furthermore, BNP was not associated with incident hypertension in either the Jackson Heart Study [5] or the Framingham Heart Study over a followup period of 3 and 5 years, respectively [4]. In the Multi-Ethnic Study of Atherosclerosis (MESA), participants free of overt cardiovascular disease at baseline were followed for 10 years and NT-proBNP was measured at baseline and at visit 3 (3.2 years later). The longer followup time and the use of NT-proBNP, which is more stable and has a longer half-life than BNP [6], by the MESA study, may provide a more optimal setting to predict future hypertension. Therefore, MESA provides an opportunity to test the longitudinal association between baseline levels and change in NT-proBNP (NT-proBNP) with the development of hypertension.

We hypothesized that prehypertensive individuals have lower NT-proBNP values than normotensives cross-sectionally at baseline, as was observed by Macheret et al. [3]. Further, we hypothesized a U-shaped relationship between baseline NT-proBNP and incident hypertension in normotensives, where low and high NT-proBNP levels increase the risk of

future hypertension and intermediate values are neutral or protective against the development of future hypertension. We also predicted that in those individuals with NT-proBNP within the physiological range (<100 pg/mL) [7] both a large negative and a large positive NT-proBNP associate with incident hypertension, while intermediate changes do not.

Methods

Study sample

MESA was designed to understand subclinical cardiovascular disease and its progression in a multiethnic cohort [8]. Between July 2000 and August 2002, 6814 men and women of white, black, Hispanic or Chinese race/ethnicity, who were 45–85 years of age and free of overt cardiovascular disease, were recruited from portions of 6 US communities. Table 1 describes the number of participants by followup time. Cross-sectional analysis included 5596 participants with measured NT-proBNP at baseline with and without hypertension. Longitudinal analysis included only those individuals without hypertension at baseline and with measured NT-proBNP ($n = 2925$). Further subanalysis on this latter group was performed on those with measured NT-proBNP at visit 1 and 3, with baseline NT-proBNP <100 pg/mL and without hypertension at visit 1 ($n = 1980$) and then in those without hypertension at visit 3 ($n = 1555$), Table 1. Clinical examinations occurred at baseline and at visit 2–5, on average 1.6, 3.2, 4.8 and 9.5 years later. The institutional review boards at all participating centers approved the study and written informed consent was obtained from every participant before data collection.

Laboratory Measures and Data Collection

Resting seated heart rate and blood pressure was measured 3 times using a Dinamap model pro 100 automated oscillometer (Critikon, Tampa, FL) at each visit. The last two measurements were averaged for analysis. In baseline cross-sectional analyses, blood pressure was defined hierarchically by Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure (JNC7) [9] categories: $<110/75$ (reference), $110 - 119/75 - 79$, $120 - 129/80 - 84$, $130 - 139/85 - 89$ (pre-hypertension), or $140/90$ mmHg (all untreated) or treated with antihypertensive medication, regardless of blood pressure.

All participants self-reported age, sex and race/ethnicity, highest education, daily physical activity (MET-min/week), and medical and dietary histories. Medication containers were examined at each examination for medication inventory. Height and weight were measured wearing light clothing and no shoes. Body mass index (BMI) was $\text{weight (kg)}/\text{height}^2$ (meters). Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$.

Blood samples were drawn following an 8 hour fast and sent to central laboratories at the Universities of Vermont (Burlington, VT) and Minnesota (Minneapolis, MN). Serum glucose was measured by the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, New York). Serum NT-proBNP was measured at the VA San Diego Health Care System using an ElecSys 2010 analyzer (Roche Diagnostics, Indianapolis, IN) with intra-

assay and interassay coefficients of variation of 1.3% and 4.8%, respectively [10]. Serum creatinine levels were used to estimate glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) formula [11]. IL-6 was measured by ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS human IL-6 immunoassay; R&D Systems, Minneapolis, Minnesota) and highly sensitive C-reactive protein (hsCRP) was determined using the BNII nephelometer (N High Sensitivity CRP, Dade Behring Inc, Deerfield, IL).

Definition of hypertension, metabolic syndrome and diabetes

Incident hypertension was systolic blood pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg or antihypertensive medication use ever during followup among people initially free of hypertension. Diabetes was defined as fasting glucose ≥ 126 mg/dL (≥ 7 mmol) or history of diabetic medication. Metabolic syndrome was defined according to the Adult Treatment Panel III report [12].

Subclinical disease and imaging protocols

Subclinical CVD was defined by the presence of carotid plaque, left ventricular hypertrophy or coronary artery calcium >0 . Carotid plaque was defined as a more than 25% diameter narrowing estimated from Doppler recordings of peak-systolic velocities [13]. Coronary artery calcium (CAC) was determined with electron beam or multi-detector computed tomography (CT) [14]. Left ventricular mass was determined using cardiac MR images [15] and left ventricular hypertrophy (LVH) defined as a left ventricular mass corrected by height above the 95th percentiles by gender; 52 and 49 g/m for males and females, respectively. Left ventricular diastolic wall distensibility (DWD), larger values of which DWD indicate more distensible ventricles, was estimated from left ventricular wall thickness at end systole and end diastole measured using cardiac MRI, determined at 6 different segments averaged across 3 cross sectional slices acquired at the base, middle and apex of the left ventricle (LV), as [16]

$$DWD = (ESWT - EDWT) / ESWT,$$

where ESWT indicates end systolic wall thickness and EDWT indicates end diastolic wall thickness. DWD indicates the reduction in left ventricular wall thickness during diastole as a fraction of the left ventricular wall thickness during systole.

Statistical analysis

NT-proBNP was log transformed; the mean transform was exponentiated to estimate the geometric mean. Change (visit 3 – baseline) in NT-proBNP (Δ NT-proBNP) was expressed as the median (range) in its natural scale.

Linear regression analyses assessed the cross-sectional association between NT-proBNP and blood pressure categories, with adjustment in model 1 for age, sex and race, and in model 2 adding highest education achieved, diabetes, obesity (BMI > 30 kg/m²), baseline systolic and diastolic blood pressures, left ventricular mass/height, use of added table salt, eGFR,

IL-6, and total intentional exercise (MET-min/week). NT-proBNP was used as the dependent variable to replicate the prior analysis ⁶, which showed lower NT-proBNP in individuals with pre-hypertension.

In the prospective analysis, Cox proportional hazards models estimated hazard ratios (HRs) for incident hypertension regressed on quintiles of baseline NT-proBNP in individuals without baseline hypertension.

Hazard ratios (HRs) for incident hypertension were also regressed on NT-proBNP for individuals with baseline NT-proBNP <100 pg/mL; based on the following prediction categories of NT-proBNP: <-10, -10 – 9.99, 10 – 50 and ≥ 50 pg/mL. The median value of NT-proBNP was 10 pg/mL, which we used as a cutoff to select categories of no substantial NT-proBNP (<-10 to <10 pg/mL), large decrease <-10 pg/mL, an intermediate category 10 and <50 pg/mL, and an upper category ≥ 50 pg/mL, representing those with NT-proBNP above the third quartile. Given non-linear associations, categories rather than continuous NT-proBNP were used to flexibly describe the shape of association and test the hypothesis that low levels of NT-proBNP were associated with incident hypertension. Linear and quadratic associations regressing incident hypertension on baseline NT-proBNP or NT-proBNP as continuous variables were also performed.

HRs for incident hypertension regressed on NT-proBNP were evaluated during two time periods. The first time period was concurrent with NT-proBNP change, i.e., baseline to visit 3 (3.2 years) incidence regressed on NT-proBNP, excluding baseline hypertensives. The second period was prospective, i.e., incidence starting at visit 3 to visit 5 (6.5 years), regressed on NT-proBNP (baseline to visit 3), excluding visit 3 hypertensives. HRs were adjusted as in model 1 and model 2. Significance was set at $p < 0.05$. Statistical analysis used PC-SAS version 9.3 by SAS Institute Inc., Cary, NC.

Results

Baseline characteristics

Table 2 shows baseline characteristics by blood pressure categories. NT-proBNP adjusted for age, race and gender was greater in those with hypertension, 59.8 pg/mL (95% CI: 57.6, 62.2) at baseline than in those without, 43.6 pg/mL (95% CI: 42.0, 45.2), $p < 0.0001$. Compared to individuals in the optimal BP category, the proportion of males, blacks, obese and diabetics was higher in the pre-hypertensive category, ($p < 0.0001$). Age, heart rate, height corrected left ventricular end diastolic volume and left ventricular mass and IL-6 increased as a function of blood pressure categories ($p < 0.0001$), while eGFR decreased ($p < 0.0001$). Individuals in the high BP category were more likely to be current smokers, on cholesterol lowering medications and diabetic. Physical activity and added salt table was not different by BP categories, $p = 0.2$.

Among those without baseline hypertension (Table 3), individuals with higher NT-proBNP tended to be female, white, older, nonsmokers and thinner, and to have subclinical cardiovascular disease, and higher IL-6 (Table 3). There was no difference in systolic blood pressure across quintiles and diastolic blood pressure was lower at the highest quintile of

NT-proBNP. However, in hypertensive individuals diastolic blood pressure was not associated with baseline NT-proBNP, data not shown. It is important to notice that the prevalence of metabolic syndrome and diabetes were greatest in the lowest quintile of NT-proBNP.

Figure 1 shows the nonlinear cross-sectional association between the adjusted NT-proBNP levels as a dependent variable and blood pressure categories. NT-proBNP levels adjusted for model 1 and 2 were ~12% lower in the pre-hypertensive category than in those individuals with optimal blood pressure (<110/75 mmHg), $p < 0.02$. Furthermore, NT-proBNP levels adjusted for model 1 and 2 in individuals with hypertension were higher than those in the optimal and the pre-hypertensive category, $p < 0.0001$. NT-proBNP followed a quadratic association with BP categories, (p value < 0.0003).

Figure 2 shows a quadratic association between NT-proBNP and left ventricular DWD adjusted for age, race and sex, $p < 0.0001$, ($n = 3747$). Left ventricular DWD had a positive association with cardiac index and with ejection fraction showing linear coefficients (SE) of 0.04 (0.001) and 0.006 (0.0001) $p < 0.0001$, respectively. These data suggest that higher DWD values are related to better LV function and lower levels may indicate diastolic dysfunction.

Baseline NT-proBNP and incident hypertension

Incident hypertension over 9.5 years of followup occurred in 41.2% ($n = 1206/2925$). HRs for incident hypertension adjusted for age, race and sex increased by 25% between the first and second quintile, but did not further increase substantially until NT-proBNP reach values > 135 pg/mL (Figure 3). These association were strengthened with additional adjustment (model 2), with small but significant increases in risk of incident hypertension when NT-proBNP values were between 19 and 135 pg/mL and substantial increase in HRs at NT-proBNP values > 135 pg/mL (Figure 3). Using NT-proBNP as a continuous variable, HRs increased by 0.25 (0.05) for every SD increase in NT-proBNP (model 1), $p < 0.0001$ and HRs increased by 0.27 (0.08) for every SD increase in NT-proBNP (model 2), $p = 0.0007$. Quadratic associations were not significant (data not shown). Adding hsCRP to model 2 or restricting to prehypertensives (data not shown) did not substantially alter these findings. In addition, further adjusting model 2 for carotid plaque and CAC > 0 did not substantially change the HRs for incident hypertension. No interaction was seen with metabolic syndrome, obesity or diabetes (data not shown).

Although no significant interactions with demographic variables were observed between baseline NT-proBNP and hypertension, the distribution of individuals by gender, race and age category varied markedly among quintiles of NT-proBNP. Therefore we examined the association of baseline NT-proBNP with incident hypertension in demographic subgroups to see whether they were consistent with the overall analysis shown in Figure 3. HRs for incident hypertension over 9.5 years of followup regressed on baseline NT-proBNP 135.5 vs < 19.2 pg/mL were more variable than in the overall analysis (consistent with reduced sample sizes) but were consistent in direction with the overall analysis, ranging across demographics from 2.00 to 5.19 (Table 4) for age category < 65 vs ≥ 65 years; for men vs women; and for whites, Hispanics, Chinese, and African Americans.

NT-proBNP and HRs for incident hypertension baseline to visit 3

In this time period, 21.5% (425/1980) hypertension-free participants with baseline NT-proBNP <100 pg/mL developed hypertension. Among these 1980 participants, 14% (n=277) of participants had NT-proBNP $\geq$ 50 pg/mL, while 17% (n=334) had a negative change of $\geq$ -10.2 pg/mL or more. Incident hypertension was associated with change in NT-proBNP when adjusted for model 1. But when using the more extended model 2 neither linear nor quadratic fits were associated with incident hypertension, (Table 4).

NT-proBNP and HRs for incident hypertension: visit 3 to visit 5

From visit 3 to visit 5, 26% (406/1555) of participants with baseline NT-proBNP <100 pg/mL and not hypertensive by visit 3 developed hypertension. HRs for incident hypertension increased over categories of NT-proBNP (model 1) for those individuals not hypertensive at visit 3 and followed until visit 5 (6.3 years), $p = 0.07$. This association strengthened in model 2, where there was a 63% increase in the risk of future hypertension in those whose NT-proBNP $\geq$ 50 pg/mL vs those who decreased by $\geq$ -10.2 pg/mL or more. Among the 1980 participants, those with NT-proBNP $\geq$ 50 pg/mL, 38% (n=103/277) had carotid plaque and 43% (118/277) had CAC >0. These prevalences were higher than in those with NT-proBNP of $\geq$ -10.2 pg/mL or more: 26% (n=86/331) had coronary plaque and 32% (106/335) had CAC >0. NT-proBNP was unrelated to presence of LVH. Further adjusting model 2 for carotid plaque and CAC >0 did not substantially change the HRs for incident hypertension. A quadratic association was observed between NT-proBNP and incident hypertension, but only when adjusting in model 2, $p = 0.01$ (Table 4).

HRs for incident hypertension over 6.3 years of followup after visit 3 regressed on NT-proBNP $\geq$ 50 vs $\leq$ -10 pg/mL were mostly consistent with the overall analysis. For age category <65 vs $\geq$ 65 years hazard ratios ranged from 1.99 to 1.51 (model 2 of Table 3). However, NT-proBNP was associated with incident hypertension in women, but not in men ($p=0.04$). With regard to race, the association of NT-proBNP with incident hypertension was not significantly different among the 4 race/ethnicity groups, although hazard ratios differed, consistent with substantially reduced samples sizes in each race/ethnic group.

Discussion

This study shows that NT-proBNP predicted hypertension over 9.5 years of followup, particularly among participants whose NT-proBNP was $\geq$ 135 pg/mL at baseline. Furthermore, restricting to hypertension-free individuals with baseline NT-proBNP levels not considered to significantly increase the risk of future CVD [17] or all-cause mortality [18] (i.e., <100 pg/mL) a NT-proBNP $\geq$ 50 pg/mL over 3.2 years was associated with a 82% increased risk of incident hypertension in the following 6.3 years. Furthermore, the presence of carotid plaque and CAC >0 at baseline appeared to precede a substantial increase in NT-proBNP.

Lack of association between low levels of NT-proBNP and incident hypertension

Our cross-sectional findings agreed with the cross-sectional analysis by Macheret et al. [3] in which pre-hypertensive individuals had low NT-proBNP levels. The association between low NT-proBNP levels and incident hypertension had been postulated based on the observation that individuals with a mutation that raises BNP have less risk of developing hypertension than individuals without it [19]. In addition, the blood pressure lowering physiological functions of natriuretic peptides and successful treatment of an individual with resistant hypertension with subcutaneous BNP [20] supported the hypothesis that the contrary, low levels of NT-proBNP, could lead to hypertension. However, in our longitudinal analysis neither low baseline NT-proBNP (<19.3 pg/mL) nor a decrease in NT-proBNP (>-10 pg/mL) over 3.2 years predicted incident hypertension. In agreement with our findings, a BNP knockout mouse model did not have higher blood pressure values compared to wild type mice with normal BNP levels [21]. Although insulin resistance, metabolic syndrome and diabetes are more frequent at the lowest quintile of baseline NT-proBNP and these are risk factors for hypertension, our longitudinal findings do not support the concept that low NT-proBNP levels elevate the risk of incident hypertension.

Elevated baseline NT-proBNP and a substantial positive NT-proBNP increase the risk of developing hypertension

The positive association between NT-proBNP and incident hypertension observed in our study extends the findings of the Jackson Heart Study [5] and the Framingham Study [4]. In the Jackson Heart Study, baseline BNP levels predicted blood pressure increase, but did not predict incident hypertension. Similarly, in Framingham, baseline BNP levels was associated with progression of blood pressure, but only in males. The longer follow-up time by our study and the use of NT-proBNP instead of BNP, are factors that can contribute to the difference in results between studies. In addition, these associations were generally consistent across different age categories, gender and racial and ethnic groups. It is important to note the small increase in hypertension risk below NT-proBNP 135 pg/mL. To this extent our findings agree with Macheret et al. [3], that when NT-proBNP is <135 pg/mL, natriuretic peptides seems to be able to maintain blood pressure values below hypertensive levels. However, at values >135 pg/mL, this capacity seems to be lost, leading to a progressive rise in blood pressure and the development of hypertension.

The 82% increase in the risk of incident hypertension preceded by a NT-proBNP 50 pg/mL in people with NT-proBNP initially <100 pg/mL is a novel finding and highlights the notion that a substantial increase in NT-proBNP should be a risk factor to consider when predicting future hypertension. Eggers et al. [22] reported that in 70 year olds followed for 8 years, those who had a NT-proBNP 100% of their baseline values had an increase in all cause and CVD mortality when compared to those who had less increase or a decrease in NT-proBNP [22]. In our study, the median baseline NT-proBNP value for individuals who had an increase of 50 pg/mL was 44 pg/mL and the median NT-proBNP after that 3.2-year period was 73.8 pg/mL. Therefore, with an average yearly increase in NT-proBNP of ~23 pg/mL it would take close to 4 years for NT-proBNP to reach levels that would substantially increase the risk of future hypertension (i.e., 135 pg/mL) and to exceed the levels that are associated with an increased mortality in hypertensive subjects (>134 pg/mL)

[18]. These findings indicate that a substantial NT-proBNP (i.e., 23 pg/mL per year) would be an earlier marker for risk of hypertension than a single value.

Risk factors related to increases in NT-proBNP

A substantial rise in NT-proBNP could be due to the presence of left ventricular diastolic dysfunction as evidenced by the elevated levels of NT-proBNP in individuals with low levels of left ventricular DWD. Associations of NT-proBNP with IL-6 [23] and carotid plaque in individuals with NT-proBNP <100 pg/mL and no hypertension suggests that the rise in NT-proBNP may be preceded by the combined presence of left ventricular dysfunction and subclinical atherosclerosis along with an inflammatory process. In support of this hypothesis, we showed that the presence of carotid plaque and CAC at baseline was positively associated with an increase in NT-proBNP 3.2 years later. Furthermore, data from the MESA population showed that cIMT is positively associated with systolic and diastolic ventricular dysfunction [23], and cross sectionally CAC is positively associated with IL-6 [24] and both ventricular dysfunction and IL-6 can independently elevate NT-proBNP [25, 26]. Collectively, these data support our hypothesis that subclinical CVD and inflammation precede an increase in NT-proBNP.

Potential biological mechanisms for the association between NT-proBNP and the development of hypertension

These findings are in line with the notion that within a range (<100 pg/mL) variations in NT-proBNP reflect the physiological responses to regulate blood pressure. Instead, values 100 pg/mL reflects the influence of pathological process on the production of NT-proBNP [7]. In this regard, prolonged stimulation of natriuretic peptides synthesis can lead to: 1) chronically elevated natriuretic peptides blood levels, which may induce a state of desensitization of natriuretic peptide receptors [27, 28] and 2) alterations in the post-translational maturation process with the release of biologically inactive natriuretic peptides [29, 30]. Additionally, an increased clearance of natriuretic peptides, seen in obese individuals with hypertension can also impair the physiological effects of natriuretic peptides [31]. Interestingly, diastolic blood pressure is inversely associated with NT-proBNP, but only in non-hypertensive individuals. The fact that this association is not observed in hypertensive individuals suggests that the response to natriuretic peptides is different between hypertensives and non-hypertensive individuals. These combined or individual mechanisms can potentially impair the capacity of the renal and cardiovascular system to respond to volume and pressure loads, which could lead to the development of hypertension [32, 33].

Strength and limitations

A major strength of this study is the measurement of NT-proBNP at two different times in a large, well-characterized cohort of participants free of CVD at baseline and the long follow up time of nearly 10 years. One limitation is that BNP was not measured in our study. BNP and NT-proBNP are assumed to exist on an equimolar basis, but because they are cleared from circulation at different rates and through different mechanisms, the ratio BNP to NT-proBNP is different than 1 and should not be used interchangeably [34]. However, our

results agree with other studies that have used only BNP. No substantial interactions with demographics were observed, although the small number of individuals at visit 3 free of hypertension and with NT-proBNP < 100 pg/mL does not allow us to state conclusively if the association between NT-proBNP and incident hypertension follows similar patterns between gender and among race/ethnic groups.

Conclusions

Results from this analysis finds that elevated baseline levels (≥ 135 pg/mL) increased the risk of developing hypertension. In addition, in those with baseline NT-proBNP < 100 pg/mL a substantial rise (≥ 23 pg/mL/year) in NT-proBNP was also predictive of incident hypertension. The substantial increase in the risk of developing hypertension only after NT-proBNP exceeds or changes above a certain rate is consistent with the presence of a threshold value above which NT-proBNP reflects the inability of natriuretic peptides to regulate blood pressure.

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Figure 1.

Cross-sectional analysis at baseline. Dip in NT-proBNP levels observed in pre-hypertensive BP categories.

Values are back transformed geometric means $\pm$ 95% CI. Model 1 adjusted for age, race and gender. Model 2 = model 1 + highest level of education, presence of diabetes, presence of obesity (BMI > 30 kg/m²), left ventricular end diastolic volume, heart rate categories $<$ or $>$ then 60 beats per minute, left ventricular mass/height, add table salt, estimated glomerular filtration rate, IL-6, and total intentional exercise in MET-min/week. * indicates that NT-proBNP is lower in category c than in categories a, b, d and e for both model 1 and 2, $p < 0.02$.

Figure 2.

NT-proBNP values as a function of left ventricular diastolic wall distensibility.

NT-proBNP values are back transformed geometric means $\pm$ 95% CI. Quadratic model adjusted for age, race and sex, $p < 0.0001$.

Figure 3.

Hazard ratios for incident hypertension according to quintiles of NT-proBNP concentrations. Prospective analysis using baseline NT-proBNP and any incident high blood pressure at exams 2–5 (9.7 yr followup), N=2925.

Hazard ratios $\pm$ 95% CI. Models 1 and 2 covariates are described in Methods and in the footnote to Table 2. Bar represents the hazard ratio reference line. p values for trend for linear associations regressed on NT-proBNP as a continuous variable for model 1 < 0.0001 and model 2 = 0.0007. Quadratic associations were not significant.

Table 1

Description and number of participants by followup time from the MESA study cohort.

Followup time	n	Blood pressure category excluded	NT-proBNP measured	NT-proBNP values included
Cross sectional	5596	None	Visit 1	All values
Visit 1 to visit 5 (9.5 years)	2925	Hypertensive at baseline	Visit 1	All values
Visit 1 to visit 3 (3.2 years)	1980	Hypertensive at baseline	Visit 1 and 3	< 100 pg/mL at baseline
Visit 3 to visit 5 (6.3 years)	1555	Hypertensive at or before visit 3	Visit 1 and 3	< 100 pg/mL at baseline

From an initial cohort of 6814 men and women without overt cardiovascular disease. Value of NT-proBNP < 100 pg/mL reflects a value that does not represent an increased risk of cardiovascular disease.

Table 2

Demographic characteristics of 5596 individuals by blood pressure categories at baseline in the Multi-Ethnic Study of Atherosclerosis.

	Blood pressure categories (mmHg)						p
	<110/75	<120/80	<130/85	<140/90	≥140/90	HBP med	
	5596	1079	890	629	524	650	1824
NT-proBNP, pg/mL, Median (Range)	43.7 (4.9– 1632)	39.3 (4.9– 1545)	42.4 (4.9– 1274)	52.6 (4.9– 1832)	76.7 (4.9– 3460)	69.2 (4.9– 11699)	
Age, years	56.5 (0.3)	59.2 (0.3)	61.2 (0.4)	63.9 (0.4)	66.8 (0.4)	66.5 (0.2)	<0.0001
Female %	52.8	44.7	40.5	47.3	47.1	52.7	<0.0001
Race							<0.0001
White, %	39.2	44.2	39.5	37.0	34.8	36.2	
Black, %	26.3	18.4	18.6	23.4	24.0	29.7	
Chinese, %	12.2	16.9	13.3	14.2	15.4	12.4	
Hispanic, %	22.4	24.1	28.7	25.4	25.8	21.8	
Smokers, %	12.5	16.8	16.4	12.3	10.4	10.0	<0.0001
Statin use, %	14.8	8.2	7.9	10.7	9.9	24.7	<0.0001
Diabetes, %	12.5	4.1	8.2	8.2	10.0	21.2	<0.0001
Obese, %	28	13.7	31.3	27.9	29.4	35	<0.0001
Education level, %	81.3	85.7	82.0	81.1	77.2	79.0	0.02
Heart rate, bpm	61.5 (0.3)	63.5 (0.36)	65 (0.4)	65.6 (0.5)	66 (0.4)	64.8 (0.2)	<0.0001
LV end diastolic volume, mL	120.3 (1)	124.2 (1.1)	124.5 (1.3)	127.5 (1.4)	129.5 (1.3)	130.6 (0.7)	<0.0001
LV mass/height, g/cm	32.7 (0.3)	34.1 (0.3)	35.7 (0.3)	36.8 (0.4)	39.3 (0.4)	39.0 (0.2)	<0.0001
Added table salt, %	20.7	22.7	22.5	20.7	19.3	13.2	<0.0001
IL-6, pg/mL	1.40 (0.04)	1.44 (0.04)	1.46 (0.05)	1.56 (0.05)	1.59 (0.05)	1.70 (0.03)	<0.0001
eGFR, mL/min	78.7 (0.5)	78.4 (0.5)	79.7 (0.6)	79.8 (0.6)	78.8 (0.6)	76.0 (0.3)	<0.0001
Physical activity, MET- min/week	1665 (75)	1588 (80)	1553 (94)	1637 (101)	1388 (92)	1501 (51)	0.2

Mean (SE) values adjusted for age, race and gender (except when age, race or gender was the dependent variable). Blood pressure categories defined according to the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7). High Blood Pressure (HBP) Med = individuals on antihypertensive medications. Smokers = percent of current smokers.

Statin use = percent of individuals on statin medication. Education = % who finished high school or higher. Obese = body mass index ≥ 30 kg/m², bpm = beats per minute, LV = left ventricle, Added table salt = % of individuals that added salt often or always. IL-6 = interleukin-6. eGFR = estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, IL-6 = Interleukin 6. MET = metabolic equivalent units.

Table 3

General characteristics of 2925 participants without hypertension by quintiles of NT-proBNP level at baseline.

pg/mL, median (range)	Quintiles of baseline NT-proBNP				
	8.6 (4.9 – 19.2)	28.9 (19.3 – 40.8)	53.7 (40.9 – 70.9)	95.4 (71 – 135.2)	213.9 (135.5 – 1832)
n	770	676	598	537	344
p					
Age, years	53.9 (0.3)	57.7 (0.3)	60.6 (0.4)	63.3 (0.4)	67.8 (0.5)
Females, %	26.6	43.2	59.5	69.3	71.2
Race					
White, %	25.1	41.1	45.3	52.5	61.3
Black, %	27.5	18.8	15.6	12.3	11.3
Chinese, %	20.5	13.8	15.9	13.4	7.6
Hispanic, %	26.9	26.3	23.2	21.8	19.8
Smokers, %	18.2	14.9	13.6	12.7	12.2
Metabolic syndrome, %	23.1	24.3	19.3	19.7	17.2
Diabetes, %	9	8.3	4.4	5.0	6.4
Education level, %	83.4	84.3	84.0	81.6	82.9
Obesity, %	31.0	26.9	21.9	19.4	18.3
L VH, %	1.0	2.3	1.3	1.22	4.7
Carotid plaque, %	26.2	31.0	31.1	36.0	40.2
CAC >0, %	33.6	38.3	40.3	43.4	52.9
SBP, mmHg	115.0 (0.5)	115.0 (0.5)	115.0 (0.5)	114.5 (0.6)	114.7 (0.7)
DBP, mmHg	69.7 (0.3)	69.8 (0.3)	69.2 (0.3)	68 (0.4)	66.4 (0.5)
Added table salt, %	21.4	20.5	21.1	24.0	19.9
HOMA-IR	3.26 (0.30)	2.56 (0.29)	1.96 (0.31)	1.73 (0.34)	1.55 (0.44)
IL-6, pg/mL	1.34 (0.04)	1.36 (0.04)	1.31 (0.05)	1.46 (0.05)	1.67 (0.06)
eGFR, mL/min	80.8 (0.5)	81.2 (0.5)	82.2 (0.5)	81.7 (0.6)	81.6 (0.7)
Physical activity, MET-min/wk	1584 (91.2)	1538 (88.9)	1611 (94.3)	1757 (102.6)	1746 (132.3)
p					
					0.5

NT-proBNP values are median (range). Values are mean (SE) adjusted for age (except when age was the dependent variable), race and gender. Obesity = body mass index > 30 kg/m², LVH = left ventricular hypertrophy define as g/m >95th percentile, 52 and 49 g/m for males and females, respectively. Carotid plaque = a more than 25% diameter narrowing, CAC = coronary artery calcium Agatston score > 0, SBP = systolic blood pressure, DBP = diastolic blood pressure, Added table salt = % of individuals that added salt often or always. Education = finished high school or higher. Homeostatic model assessment insulin resistance (HOMA-IR). eGFR = glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, IL-6 = Interleukin 6, MET = metabolic equivalent units minutes/week.

Hazard ratios for incident hypertension by categories of change () in NT-proBNP from baseline to visit 3 in 1980 individuals with NT-proBNP 100 pg/mL at baseline examination and in the subset of 1555 of these people who did not develop hypertension by visit 3.

Table 4

	NT-proBNP, pg/mL, median (range)					p for quadratic association
	-22.8 (-76.4 – -10.1)	0.50 (-10 – 9.95)	23.4 (10 – 49.9)	73.8 (50.1 – 3750)		
Baseline NT-proBNP, pg/mL, median (25th percentile, 75th percentiles)	56.8 (37.6 – 76.1)	21.4 (8.1 – 40.6)	27.5 (12.7 – 47.6)	44.2 (21.9 – 63.4)		
Incidence of hypertension						
Baseline to visit 3, n/N, (%)	56/334 (17)	116/662 (18)	154/707 (22)	99/277 (36)		
Model 1 (HR 95% CI)	1	1.06 (0.77 – 1.47)	1.28 (0.95 – 1.75)	2.17 (1.57 – 3.04)		< 0.0001
Model 2 (HR 95% CI)	1	0.80 (0.5 – 1.29)	1.07 (0.71 – 1.67)	1.18 (0.73 – 1.94)		0.7
Visit 3 to visit 5, n/N, (%)	60/278 (22)	133/546 (24)	158/553 (29)	55/178 (31)		
Model 1 (HR 95% CI)	1	1.06 (0.77 – 1.47)	1.28 (0.95 – 1.75)	2.17 (1.57 – 3.04)		0.07
Model 2 (HR 95% CI)	1	0.98 (0.62 – 1.56)	1.13 (0.72 – 1.79)	1.82 (1.07 – 3.12)		0.01

n/N indicates number of participants that developed hypertension/total number of participants in that category of NT-proBNP, % is the proportion of participants that developed hypertension for that category of NT-proBNP. Model 1 was adjusted for age, race and gender and model 2 = model 1 + highest level of education achieved, presence of diabetes and obesity based on BMI > 30 kg/m², diastolic and systolic blood pressure, left ventricular mass/height, reported amount of added table salt, estimated glomerular filtration rate, IL-6 and total intentional weekly exercise. Baseline to visit 3 indicates follow-up of non-hypertensive individuals from baseline to visit 3 (3.2 years) concurrent with NT-proBNP. Visit 3 to visit 5 follows non-hypertensive individuals at visit 3 up to visit 5 (6.3 years) for incidence of hypertension subsequent to NT-proBNP.