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Target Organ Complications and Prognostic Significance of Alerting Reaction: Analysis from the Dallas Heart Study

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Abstract

Objective—Noninvasive BP measurement often triggers a transient rise in BP, known as an alerting reaction. However, the prevalence and prognostic significance of the alerting reaction has never been assessed in the general population.

Methods—We evaluated the association between the alerting reaction and left ventricular mass (LVM) by magnetic resonance imaging and urinary-albumin-to-creatinine ratio (UACR) in the Dallas Heart Study, a large population sample of 3,069 subjects. Participants were categorized into 4 groups based on levels of consecutive BP: 1.normal 1st BP and average 3rd to 5th (avg3-5) BP of <140/90 mmHg (control group), 2.high 1st BP of ≥140/90 mmHg and normal (avg3-5) BP (HN), 3.normal 1st BP and high (avg3-5) BP, and 4.high 1st to 5th BP. Then, associations between BP categories with incident cardiovascular outcomes (coronary heart disease, stroke, atrial fibrillation, heart failure, and cardiovascular death) over a median follow-up period of 9.4 years were assessed.

Results—The sample-weighted prevalence of isolated hypertension during the first BP measurement was 9.6%. Presence of an alerting reaction was independently associated with increased LVM, UACR, cardiovascular events after adjustment for traditional cardiovascular risk factors and baseline BP (adjusted HR 1.24, 95%CI 1.07-1.43).

Conclusions—Our study indicated that the alerting reaction is independently associated with increased cardiovascular and renal complications.

Keywords

Blood pressure measurement; systemic hypertension; prognosis; cardiovascular events; target organ damage

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Conflicts of Interest: None

Introduction

Blood pressure (BP) measurement by healthcare professionals often induces an immediate rise, which may lead to overdiagnosis of hypertension [1-3]. The transient initial rise in BP, known as an *alerting reaction*, is proposed to be related to overactivation of sympathetic nervous system when patients encounter physicians or nurses in the medical environment [4]. The alerting reaction has been identified in both normotensive and hypertensive men and women [5]. However, the prevalence of an alerting reaction has never been determined in any large scale population. Furthermore, the prognostic significance of an alerting reaction has never been assessed in the general population, particularly among individuals of African descent, the ethnic group with the highest risk of hypertensive target organ damage.

Accordingly, we determined the extent of target organ complications and cardiovascular prognosis associated with an alerting reaction in participants of the Dallas Heart Study (DHS), a probability-based population sample of Dallas County adults. The presence or absence of an alerting reaction was determined based on the first BP and the average level of the 3rd to 5th (avg3-5) BP during the same clinic visit in all subjects.

Methods

Study Population

The DHS is a multi-ethnic probability-based population sample of Dallas County residents ages 18-65 years, established in 2000, as previously described [6,7]. This study was designed to oversample African Americans, the ethnic population with highest burden of hypertension. All participants in the DHS provided written informed consent, and the UT Southwestern Medical Center Institutional Review Board approved the study. During the clinic visit (n=3,069), 5 serial blood pressure (BP) measurements were taken in the seated position using a validated automatic oscillometric device (Series #52,000, Welch Allyn, Inc., Arden, North Carolina) [8], each separated by 1 min. Then, participants underwent detailed cardiovascular phenotyping by magnetic resonance imaging (MRI) during this visit [9,10].

Variable Definitions

Race/Ethnicity was self-reported. High BP was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg. Subjects were categorized into 4 groups based on the first (1st) BP and (avg3-5) BP values: 1. Normal 1st BP and normal (avg3-5) BP (NN or control group), 2. High 1st BP and normal (avg3-5) BP (HN or isolated BP elevation during the first measurement), 3. Normal 1st BP and high (avg3-5) BP (NH), 4. High 1st BP and high (avg3-5) BP (HH or sustained hypertension group).

Two continuous variables were created to assess the magnitude of BP change during the alerting reaction; Δ alerting BP = 1st BP minus (avg3-5) BP and alerting ratio = Δ alerting BP divided by (avg3-5) BP. A sensitivity analysis was conducted using the mean of first and second (avg1-2) BP, rather than 1st BP alone, to determine Δ alerting BP and alerting ratio and assess their association to target organ complications and cardiovascular events.

Outcome Measures

Left ventricular mass was measured by MRI as previously described [9,10]. Urinary albumin and creatinine were measured in the first morning void urine sample, and the UACR was calculated in mg/g for each participant as previously described [11]. Mortality data were queried from the National Death Index (NDI) through December 2010. Cardiovascular death was defined by *International Statistical Classification of Diseases, 10th Revision* codes I00-I99. Two overlapping approaches were used to capture non-fatal cardiovascular (CV) events occurring after enrollment as previously described [9]. First, a detailed health survey regarding interval cardiovascular events was administered annually to study participants. Second, quarterly tracking was performed for hospital admissions using the Dallas-Fort Worth Hospital Council Data Initiative Database, a consortium of all acute-care hospitals in Dallas County. Primary clinical source documents were reviewed for all suspected non-fatal cardiovascular events and were independently adjudicated by an endpoint committee blinded to all study data. Adjudicated CV events included unstable angina, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, stroke, transient ischemic attack, cerebrovascular revascularization, hospitalization for atrial fibrillation or heart failure, and cardiovascular death. Follow-up data for both fatal and nonfatal events were complete through December 31, 2010.

Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR) or mean with standard deviation, as appropriate, and categorical variables are presented as proportions. To account for sampling strategy and non-participation, sample weighting was used to determine the prevalence of alerting reaction in Dallas County residents [7]. For all other analyses evaluating associations within the DHS cohort, no sample weighting was used. The Kruskal-Wallis test was used to compare differences in LVM indexed by Body Surface Area (LVM/BSA) and urine albumin-to-creatinine ratio (UACR) among the NN, HN, NH, and HH groups. Wilcoxon rank-sum tests were used for pairwise comparisons. A linear regression was used to assess the associations between Δ alerting BP and alerting ratio with LVM/BSA and UACR after adjustment for age, gender, BMI, ethnicity, diabetes, total cholesterol level, (avg3-5) BP, smoking and alcohol use in all participants.

Associations of HN, NH, and HH groups, Δ alerting BP and alerting ratio with composite CV events (adjudicated CV events and CV death) was assessed by multivariable Cox proportional hazards regression. Subjects with a history of cardiovascular disease at baseline were excluded from these analysis (n=227). The analyses were performed adjusting for age, sex, race, body mass index, diabetes, history of tobacco use, total cholesterol, history of alcohol use and treatment for hypertension. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and Prism version 6 (GraphPad, La Jolla, CA).

Results

During the clinic visit of the DHS, systolic and diastolic BP fell progressively across the 5 measurements. BP reduced from the first to third measurements by 2.6±6.3/1.8±3.9mmHg. Additional BP decline from the 3rd to the 5th measurements was more attenuated

(0.9±5.9/0.5±3.7mmHg, p<0.001 vs. reduction from 1st to 3rd measurement for both systolic and diastolic BP, Figure 1), suggesting presence of an alerting reaction during the first two BP measurements. There were no significant changes in heart rate during serial BP measurement. The sample-weight adjusted prevalence of isolated BP elevation during the first measurement (HN) was 9.6%. Baseline characteristics are shown in table 1. Participants in the HN group were more likely to be obese, older, African American, on antihypertensive medications, and have higher heart rate, alerting ΔBP, alerting ratio, total cholesterol levels and diabetes mellitus than the control group (table 1).

Both alerting ΔBP and alerting ratio were significantly correlated with LV mass index in untreated men and in both treated and untreated women after adjustment for age, race, and BMI, avg3-5BP, fasting plasma glucose, total cholesterol level, triglyceride level, waist circumference, heart rate, smoking, and alcohol (Table 2). Both alerting ΔBP and alerting ratio were significantly correlated with UACR in untreated men but not in treated men or women.

Furthermore, we found that LVMI and UACR were significantly higher in the HN group compared to NN group after adjustment for mean diastolic BP 3-5, age, sex, race, and BMI, fasting plasma glucose, total cholesterol level, triglyceride level, waist circumference, heart rate, smoking, and alcohol use (figure 2B and 2D) among the untreated population. When baseline systolic BP (average SBP3-5) was introduced in the model in addition to relevant variables, UACR remained significantly higher in the HN compared to the NN group (fig 2C), suggesting increased subclinical renal and cardiovascular damage in individuals with high alerting reaction, independent of baseline BP. LVM/BSA in the HN group were not significantly different from the NN group in the treated and untreated population when all relevant variables and average SBP3-5 were included in the model. However, the LVMI in the HN, HH, and NN groups were significantly higher than the NH group in both treated and untreated population after adjustment for SBP (figure 2A and supplemental Figure S1).

To determine prognostic significance of an alerting reaction, we determine association between alerting ΔBP as well as alerting ratio and the composite cardiovascular events over a median follow-up period of 9.4 years (IQR 9.0-9.8, Table 3). Two hundred and five composite cardiovascular events were recorded, including 127 all cause deaths and 49 cardiovascular deaths. Among the untreated population (n = 2,201), 122 composite events were recorded (77 in men and 45 in women). To avoid confounding influence of antihypertensive treatment and higher baseline BP in the HN group, Δ alerting BP and alerting ratio were entered in the linear regression model which included systolic BP beyond the alerting phase (avg3-5 BP). We also found that Δ alerting BP were associated with cardiovascular events independent of (avg3-5) SBP, fasting plasma glucose, total cholesterol level, triglyceride level, waist circumference, heart rate, smoking, and alcohol (HR 1.24, 95% CI 1.07-1.43, p < 0.01, Table 3) while the association with alerting ratio tended to be significance (HR 1.01, 0.99-1.03), p = 0.09). Analysis of sex-specific data showed that both Δ alerting BP and alerting ratio were significantly associated with cardiovascular events in men but not in women (Table 3).

Hazard ratios (HR) for cardiovascular events in subjects in the HN group during the follow-up are presented in Table 4 and Kaplan–Meier survival curves in figure 3. Among the treated and untreated male population, the HN group experienced higher composite cardiovascular outcomes compared to the NN group (HR 1.88 [95% CI, 1.03-3.41, p=0.04, Table 4), after adjustment for age, BMI, ethnicity, heart rate, fasting plasma glucose, serum triglyceride, and waist circumference, total cholesterol level, smoking and alcohol. After mean SBP is included in the model in addition to all relevant variables (model 3), the association was no longer significant (p = 0.13). The association of alerting reaction with composite CV events was consistent in all subgroups (all p-interaction >0.1, Figure 4).

Sensitivity Analysis

When DBP was used to determine presence of alerting reaction instead of SBP, both Δ alerting BP and alerting ratio remained significantly correlated with LVM/BSA, and UACR after adjustment for covariates (supplemental Table S1). Both Δ alerting BP and alerting ratio were also significant predictors of cardiovascular events independent of (avg3-5) DBP, age, sex, BMI, heart rate, ethnicity, fasting plasma glucose, total cholesterol level, serum triglyceride level, smoking and alcohol use (supplemental Table S2).

When (avg1-2) SBP, rather than the 1st SBP alone, was used to determine presence or absence of alerting reaction, both Δ alerting BP and alerting ratio remained significantly correlated with LVM/BSA, and UACR after adjustment for covariates (supplemental Table S3). Similarly, both Δ alerting BP and alerting ratio were significant predictors of cardiovascular events independent of (avg3-5) SBP, age, sex, BMI, heart rate, ethnicity, fasting plasma glucose, total cholesterol level, serum triglyceride level, smoking and alcohol use (supplemental Table S4).

Discussion

The major findings of our study are three fold. First, isolated hypertension during the first BP measurement is common, occurring in almost 10% of the general population, and is more prevalent in older adults with cardiovascular risk factors, particularly in African Americans. Second, presence of an alerting reaction is independently associated with increased risk of target organ complications. Third, presence of an alerting reaction is associated with increased risk for cardiovascular events compared to the control group with sustained normotension, independent of traditional cardiovascular risk factors.

Our study underscores the importance of measuring and analyzing multiple office BP measurements to verify the presence of sustained hypertension and identify transient BP elevation related to an alerting reaction. Currently, hypertension guidelines have provided inconsistent recommendation regarding methods of clinic BP assessment [12-14]. While the American Heart Association and the American Society of Hypertension advocate averaging BP from at least 2 office BP measurements [13,14], the Canadian Hypertension Education Program prefers mean BP of the second and third measurement after discarding the first office BP reading [12]. In our multiethnic study cohort, presence of an alerting reaction was associated with a phenotype that represented a higher cardiovascular risk than subjects with sustained normotension. Although at a lower risk than the group with sustained

hypertension, the group with an alerting reaction demonstrated evidence of increased cardiac hypertrophy and subclinical renal injury. Furthermore, an alerting reaction was associated with increased cardiovascular event rate compared to the control group. Sex-specific analysis, however, suggested that female subjects are less susceptible to develop subclinical renal injury and adverse cardiovascular events associated with an alerting reaction. Nevertheless, association between an alerting reaction and increased left ventricular mass remained significant in the female subgroup. Thus, our supports the concept that first BP reading carries important prognostic information and should not be discarded when determining ones BP status.

Our results differ from Woodiwiss et al [15] study that demonstrated no difference between single and multiple BP readings to predict target organ damage. Similarly, a previous analysis from the Third National Health and Nutrition Examination Survey (NHANES III) did not show association between standard deviation of 3 BP readings obtained within the same visit and cardiovascular mortality [16]. However, neither study addressed the alerting reaction specifically and less sensitive methods, including applanation tonometry and echocardiography, were used to assess arterial stiffness and left ventricular mass.

Our study represents the first which demonstrated prognostic significance of an alerting reaction in a multiethnic population in the United States. Although overall BP was higher in the subjects with an alerting reaction compared to the control group, the magnitude of increase in BP during the first and second measurement compared to the third to fifth measurement remained associated with target organ complications and cardiovascular outcome when both BP variables were simultaneously entered in the model. Similar results were observed when the ratio of alerting reaction based on (avg1-2) relative to (avg3-5) BP measurement was entered in the continuous model. Although the HN group displayed the highest alerting ΔBP and alerting ratio among the 4 groups, there was an overlap in the magnitude of the alerting reaction among the HH, HN, and NN groups, all of which were associated with alerting ratio above 1 as shown in Table 1. Thus, our data suggest that the alerting reaction is not all or none phenomenon, which may explain failure to demonstrate higher cardiovascular events in the HN group after adjustment for mean BP in our final model of the Cox analysis (model 3).

Precise mechanisms underlying the alerting reaction are unknown but previous studies have implicated the role of the sympathetic nervous system. Elevated heart rate in the alerting reaction group provided support for this hypothesis. Furthermore, participants with alerting reaction exhibited multiple factors known to be associated with increased sympathetic nerve activity at rest, including African American race/ethnicity [17], obesity [18,19], older age [20], and insulin resistance [21,22]. These factors alone or in combination may predispose to heightened sympathetic activation during BP cuff inflation. Palatini et al [23] found that BP changes during a doctor's visit were associated with higher urinary epinephrine levels and BP changes during a public speech. Subsequent studies using direct measurement of sympathetic nerve activity with direct microneurography technique showed that cuff inflation elicited marked sympathetic activation, particularly when obtained by physicians [4,24]. Presence of high alerting reaction in our study are likely to reflect presence of white coat effect or white coat hypertension. However, lack of confirmation by elevated BP at

repeated clinic visits in conjunction with normal out-of-office BP in the absence of health care professionals in our study limits our ability to directly infer alerting reaction to WCH. Furthermore, many previous studies demonstrated that the magnitude of rise in BP during the alerting reaction was shown to bear either no correlation or weak correlation with the difference between daytime ambulatory BP and office BP [23,25,26], suggesting differences in pathophysiologic processes.

Our study is limited by its observational design, which limits our ability to establish a causal role between alerting reaction with cardiovascular complications. It is well known that sympathetic nervous system contributes to both pathogenesis of hypertension and long term prognosis of patients with cardiovascular diseases [27-29]. Thus, it is possible that overactivation of sympathetic nervous system observed in individuals with alerting reaction contributes to their adverse cardiovascular outcomes. We determined the presence of alerting reaction based on only 5 clinic BP measurements and it is unknown if BP will further decline with more BP measurements over time. Unlike changes in BP, we also did not observe reduction in the heart rate from the first to fifth BP measurement. Because each BP measurement was separated by 1 minute, we cannot exclude the possibility that episodes of transient rise in the heart rate of 30-45 sec or less were not captured with our method. Our study is also limited to be representative of population in the Dallas County and may not be applicable to all other populations.

Conclusion

Our study suggested a relatively common pattern of transient BP elevation associated with cuff inflation in almost 10% of the general population, which was independently associated with increased LV hypertrophy, renal injury and adverse cardiovascular events. Further studies are needed to confirm these findings and identify an effective strategy to minimize cardiovascular risks associated with an alerting reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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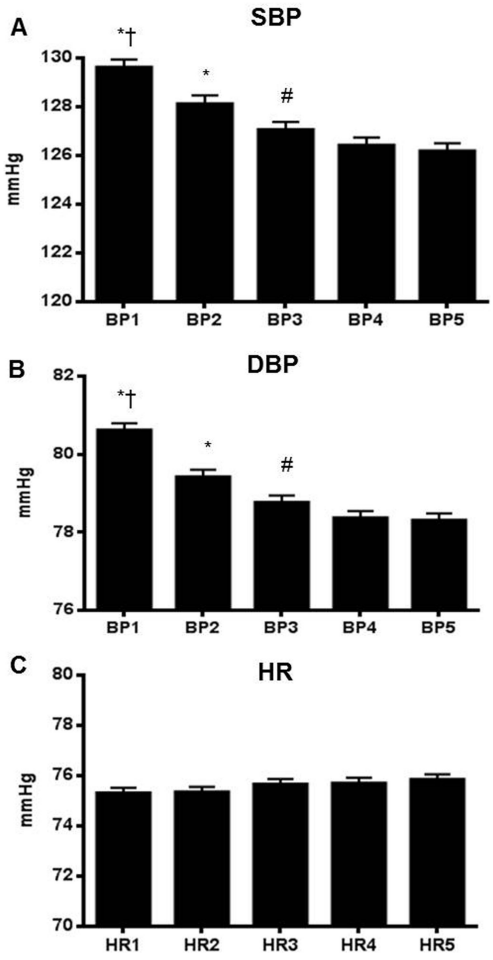

Figure 1.

Serial average systolic blood pressure (A), diastolic blood pressure (B) and heart rate (C) values of 5 separate measurements during clinic visit in the Dallas Heart Study.

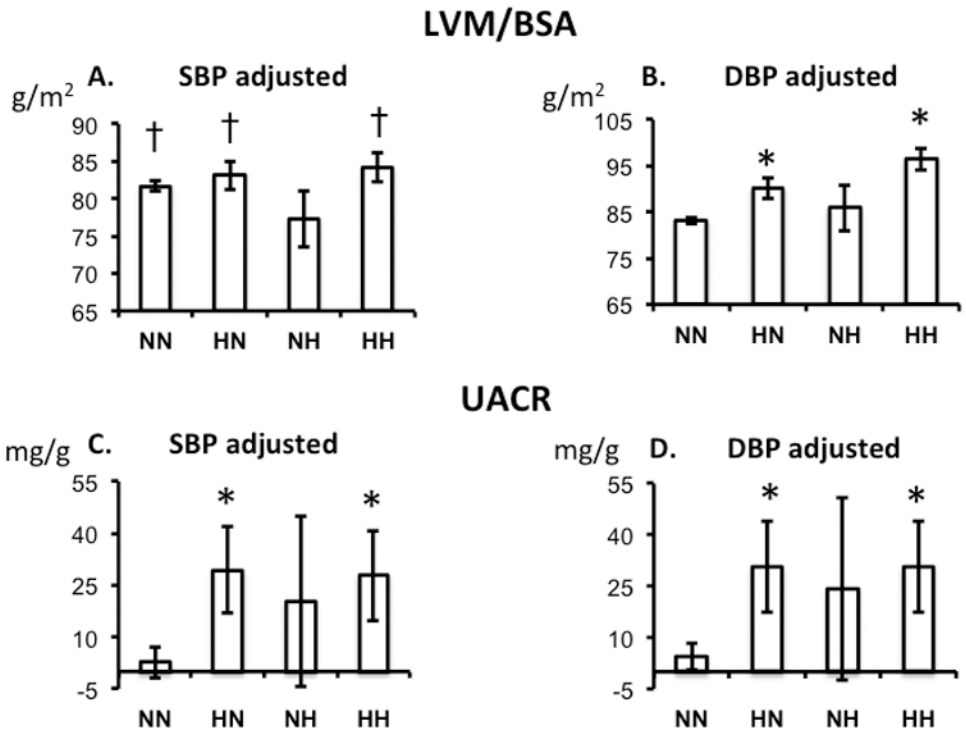

Figure 2.

Left ventricular mass indexed by body surface area (LVM/BSA) and UACR of the untreated participants after adjustment for relevant variables (age, BMI, ethnicity, sex, fasting plasma glucose, total cholesterol level, triglyceride level, waist circumference, heart rate, smoking, and alcohol use) plus avg 3-5 SBP (A and C) and after adjustment for relevant variables plus avg 3-5 DBP (B and D) among the 4 different BP groups. * $p<0.01$ vs. NN Group, †$p<0.01$ vs. HN group.

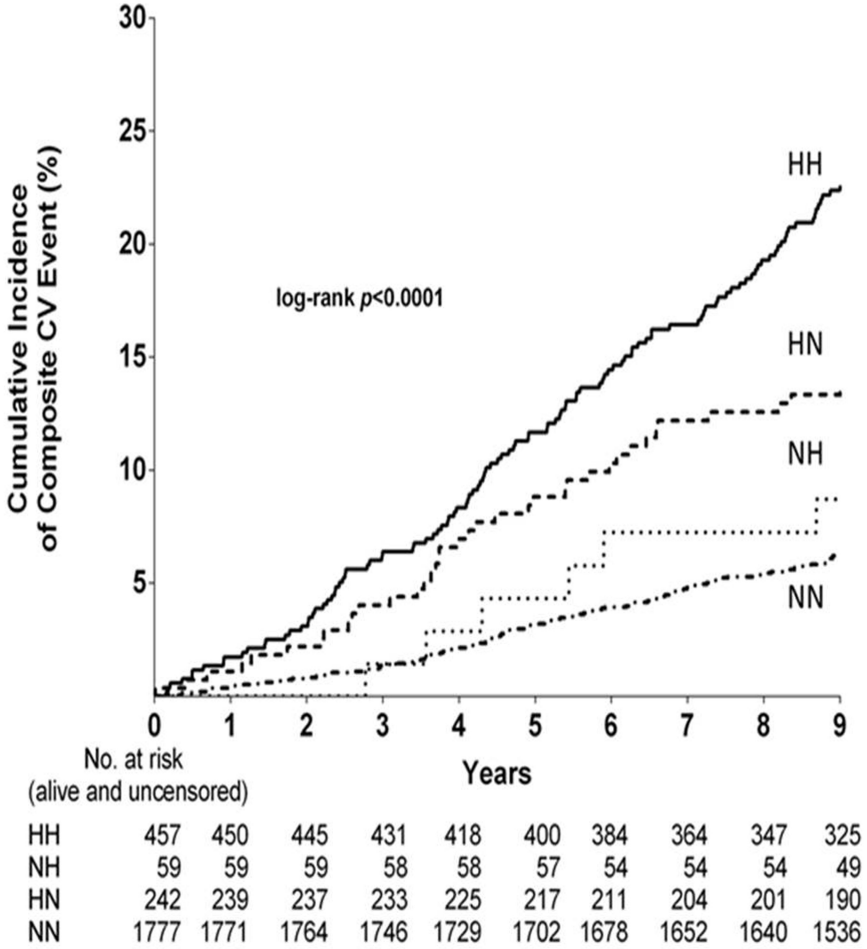

Figure 3.

Kaplan Meier curve shows cumulative Incidence of composite cardiovascular events among four blood pressure groups during follow up period.

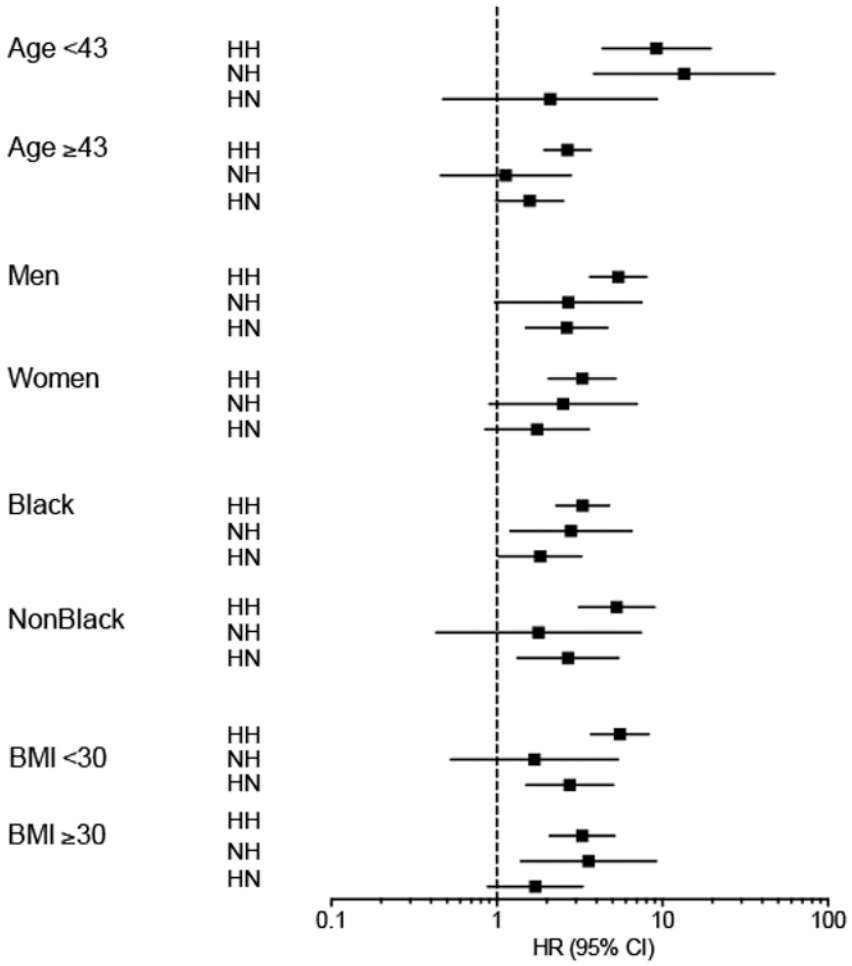

Figure 4.

Hazard ratio of composite cardiovascular events among BP categories according to different clinical characteristics.

Table 1
Baseline Characteristics of Subjects Based on BP Categories

	Control (NN) (n=2119)	Initially high then normal (HN) (n=298)	Initially normal then high (NH) (n=76)	Sustained Hypertension (HH) (n=576)
Age	42.7 ± 9.6	47.7 ± 9.1 *	48.8 ± 9.4 *	49.3 ± 9.0 *
Male (%)	44.9%	43.2%	43.4%	45.5%
1st Systolic BP (mmHg)	120 ± 11	141± 7 *	134 ± 4 *	157 ± 18 *†‡
(Avg3-5) Systolic BP (mmHg)	117 ± 11	133 ± 6 *	140 ± 6 *	155 ± 16 *†‡
1st Diastolic BP (mmHg)	75 ± 8	88 ± 7 *	83 ± 5 *	94 ± 10 *†‡
(Avg3-5)Diastolic BP (mmHg)	74 ± 8	82 ± 6 *	85 ± 7 *	92 ± 9 *†‡
Alerting ratio ** (median, IQR)	1.02 (0.99,1.05)	1.08 (1.04, 1.13) *†‡	0.92 (0.88-0.96) *	1.02 (0.99-1.05) ‡
Alerting ΔBP (mmHg) **	2 ± 6	12 ± 10 *†‡	-13 ± 11 *	4 ± 9 *
Heart rate (bpm)	75 ± 11	78 ± 12 *	76 ± 12	78 ± 13 *
White (%)	33.9%	32.6%	34.2%	19.8% *†‡
African Americans (%)	43.8%	55.3% *	53.9 % *	70.1% *†
Hispanics (%)	19.9%	11.4% *	9.2% *	8.7% *
Other Ethnicity (%)	2.3%	0.7%	2.6%	1.4%
Treatment of Hypertension (%)	14%	38% *	34% *	39% *
BMI (kg/m^2)	29.6 ± 6.5	33.3 ± 7.2 *	31.5 ± 9.1	33.2 ± 8.4 *
Waist Circumference (cm)	96.2 ± 15.8	105.9 ± 16.5 *	103.7 ± 18.7 *	106.5 ± 16.9 *
Diabetes (%)	7.9%	18.4% *	25% *	20.8% *
Fasting plasma glucose (mg/dL)	98.1 ± 34.7	110.4 ± 48.6 *	117.1 ± 67.0 *	115.1 ± 58.8 *
Total cholesterol (mg/dL)	178.8 ± 38.5	189.03 ± 37.8 *	183.6 ± 35.5	185.4 ± 45.9 *
Triglyceride (mg/dL)	120.4 ± 108.9	138.8 ± 108.9 *	140.8 ± 73.4 *	137.0 ± 117.2 *‡
Alcohol Use (%)	64%	64%	71%	63%
Tobacco use (%)	27.8%	23.5%	23.7%	32.2% *†

* p<0.01 vs. NN,

† p<0.01 vs. HN Group,

‡ p<0.05 vs. NH Group.

BMI indicates body mass index. Data presented as percentage or mean with standard deviation.

** Alerting Ratio = (1st SBP - (avg3-5) SBP)/(avg3-5) SBP, Alerting ΔBP = 1st SBP- (avg3-5) SBP

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Table 2

Multivariable Linear Regression Model Describing Association of Δ Alerting BP and Alerting Ratio with LVM index and UACR among treated and untreated population.

Untreated Participants *								
	Untreated Females (n = 1,171)				**Untreated Males (n = 1,030)**			
	LVM/BSA		**UACR**		**LVM/BSA**		**UACR**	
Variable	**Standardized Estimate**	**P Value**	**Standardized Estimate**	**P Value**	**Standardized Estimate**	**P Value**	**Standardized Estimate**	**P Value**
†ΔAlerting BP (10mmHg increase)	0.06	**0.01**	0.03	**0.2**	0.14	**<0.01**	0.08	**<0.01**
† Alerting Ratio	0.06	**0.02**	0.04	**0.1**	0.13	**<0.01**	0.08	**<0.01**
Treated Participants *								
	Treated Females (n = 300)				**Treated Males (n = 209)**			
	LVM/BSA		**UACR**		**LVM/BSA**		**UACR**	
Variable	**Standardized Estimate**	**P Value**	**Standardized Estimate**	**P Value**	**Standardized Estimate**	**P Value**	**Standardized Estimate**	**P Value**
†ΔAlerting BP (10mmHg increase)	0.17	**<0.01**	0.06	0.26	0.08	0.26	0.12	0.07
† Alerting Ratio	0.17	**<0.01**	0.06	0.33	0.07	0.32	0.09	0.21

*Adjusted for age, race, and BMI, (avg3-5) SBP, fasting plasma glucose, total cholesterol level, triglyceride level, waist circumference, heart rate, smoking, and alcohol.

†Alerting ΔBP = 1st SBP - (avg3-5) SBP,

†Alerting Ratio = (1st SBP - (avg3-5) SBP)/(avg3-5) SBP

Table 3

10-Year Adjusted Hazard Ratio for Composite CV Events of Alerting Ratio and Δ Alerting BP

All Untreated Participants (122 composite events)*			
Model 1	**Hazard Ratio**	**CI**	**P value**
† Δ Alerting BP (10 mmHg increase)	1.21	1.05-1.39	**<0.01**
* Alerting Ratio	1.18	1.03-1.36	**0.02**
Model 2			
† Δ Alerting BP (10 mmHg increase)	1.20	1.04-1.39	**0.01**
† Alerting Ratio	1.17	1.01-1.35	**0.03**
Model 3			
*Δ Alerting BP (10 mmHg increase)	1.24	1.07-1.43	**<0.01**
† Alerting Ratio	1.01	0.99-1.03	0.09
Untreated Males (77 composite events) ‡			
Model 1	**Hazard Ratio**	**CI**	**P value**
† Δ Alerting BP (10 mmHg increase)	1.28	1.07-1.53	**<0.01**
* Alerting Ratio	1.27	1.06-1.53	**<0.01**
Model 2			
† Δ Alerting BP (10 mmHg increase)	1.29	1.08-1.55	**<0.01**
† Alerting Ratio	1.28	1.06-1.54	**<0.01**
Model 3			
† Δ Alerting BP (10 mmHg increase)	1.30	1.09-1.56	**<0.01**
* Alerting Ratio	1.33	1.10-1.60	**<0.01**
Untreated Females (45 composite events)‡			
Model 1	**Hazard Ratio**	**CI**	**P value**
† Δ Alerting BP (10 mmHg increase)	1.09	0.85-1.41	0.49
* Alerting Ratio	1.07	0.82-1.41	0.6
Model 2			
† Δ Alerting BP (10 mmHg increase)	1.08	0.83-1.40	0.56
† Alerting Ratio	1.06	0.80-1.40	0.66
Model 3			
*Δ Alerting BP (10 mmHg increase)	1.11	0.86-1.44	0.41
† Alerting Ratio	1.12	0.84-1.5	0.42

† Alerting ΔBP = 1st SBP - (avg3-5) SBP, Alerting Ratio = 1st SBP - (avg3-5) SBP)/(avg3-5) SBP

* Model 1: age, sex, race, heart rate, and BMI, Model 2: Model 1+, fasting plasma glucose, serum triglyceride, and waist circumference, total cholesterol level, smoking and alcohol, Model 3: Model 2+ avg3-5 SBP

[≠]Model 1: age, race, heart rate, and BMI, Model 2: Model 1+, fasting plasma glucose, serum triglyceride, and waist circumference, total cholesterol level, smoking and alcohol, Model 3: Model 2+ avg3-5 SBP

Table 4
10-Year Adjusted Hazard Ratio for Composite CV Events by BP Groups

Among Treated and Untreated Male Participants (121 composite events)			
Model 1	**Hazard Ratio**	**95% CI**	**P value**
NN	1.00		
HN	1.93	1.08-3.45	**0.03**
NH	2.23	0.79-6.25	0.13
HH	2.77	1.81-4.22	**<0.01**
Model 2:			
NN	1.00		
HN	1.88	1.03-3.41	**0.04**
NH	2.47	0.87-6.97	0.08
HH	2.61	1.70-3.99	**<0.01**
Model 3:			
NN	1.00		
HN	1.59	0.86-2.93	0.13
NH	1.75	0.59-5.12	0.30
HH	1.44	0.75-2.78	0.27
Among Treated and Untreated Female Participants (84 composite events)			
Model 1	**Hazard Ratio**	**95% CI**	**P value**
NN	1.00		
HN	1.18	0.56-2-46	0.66
NH	1.43	0.50-4.05	0.50
HH	1.97	1.20-3.25	**<0.01**
Model 2:			
NN	1.00		
HN	0.97	0.46-2.07	0.95
NH	0.94	0.31-2.77	0.90
HH	1.54	0.92-2.58	0.10
Model 3:			
NN	1.00		
HN	0.79	0.37-1.72	0.55
NH	0.53	0.16-1.82	0.31
HH	0.78	0.34-1.80	0.56
Among Untreated Male Participants (77 composite events)			
Model 1	**Hazard Ratio 10 mmHg Increase**	**95% CI**	**P value**
NN	1.00		
HN	1.52	0.70-3.33	0.29
NH	0.75	0.10-5.52	0.77
HH	2.56	1.61-2.75	**<0.01**

Among Treated and Untreated Male Participants (121 composite events)			
Model 1	**Hazard Ratio**	**95% CI**	**P value**
Model 2:			
NN	1.00		
HN	1.35	0.59-3.10	0.48
NH	0.99	0.13-7.36	0.77
HH	2.45	1.45-4.17	**<0.01**
Model 3:			
NN	1.00		
HN	1.24	0.53-2.88	0.63
NH	0.82	0.11-6.33	0.85
HH	1.77	0.78-4.05	0.18
Among Untreated Female Participants (composite 45 events)			
Model 1	**Hazard Ratio 10 mmHg Increase**	**95% CI**	**P value**
NN	1.00		
HN	0.60	0.14-2.57	0.49
NH	2.40	0.70-8.19	0.16
HH	2.35	1.19-4.65	0.01
Model 2:			
NN	1.00		
HN	0.52	0.12-2.28	0.38
NH	2.02	0.59-6.95	0.27
HH	1.66	0.80-3.44	0.17
Model 3:			
NN	1.00		
HN	0.42	0.09-1.88	0.26
NH	1.28	0.33-4.99	0.72
HH	10.82	0.24-2.72	0.74

Model 1: Model 1: age, race, heart rate and BMI
Model 2: Model 1+, fasting plasma glucose, serum triglyceride, and waist circumference, total cholesterol level, smoking and alcohol
Model 3: Model 2+ avg3-5 SBP