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Sustained Pre-hypertensive Blood Pressure and Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—The association between sustained pre-hypertension and AF has not been thoroughly examined.

Methods—This study included 5,311 participants (mean age 62 ± 10 years; 47% male; 42.9% non-whites) from the Multi-Ethnic Study of Atherosclerosis. Sustained exposure was based on 2 or more visits within the same blood pressure category (optimal: $<120/80$ mm Hg; pre-hypertension: $120\text{--}139/80\text{--}89$ mm Hg; hypertension: $140/90$ mm Hg or antihypertensive medication use) during visits 1, 2, and 3. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between blood pressure category and AF.

Results—Over a median follow-up of 5.3 years, 182 (3.4%) participants developed AF. Pre-hypertension and hypertension were associated with an increased risk of AF compared with participants who had optimal blood pressure (optimal: HR=1.0, referent; pre-hypertension: HR=1.8, 95%CI=1.004, 3.2; hypertension: HR=2.6, 95%CI=1.6, 4.4).

Conclusion—Sustained pre-hypertension is associated with an increased risk of AF.

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Keywords

blood pressure; atrial fibrillation; epidemiology; risk factors

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, with an increased prevalence among older individuals.¹ Established AF risk factors include heart failure, myocardial infarction, obesity, diabetes, an enlarged left atrium, and hypertension.^{2–4}

Population-based studies that have examined the association between blood pressure and AF have focused on blood pressure determinations from a single visit.^{2,3,5–9} In this framework, hypertension (e.g., >140/90 mm Hg) is clearly associated with an elevated risk for AF. However, evidence that sustained exposure to more modest levels of blood pressure, including pressure in the pre-hypertension range (systolic pressure 120–139 mm Hg), is associated with AF has not been thoroughly examined.^{4,7,8,10} This is due to the presumption that the effect of modest elevations in blood pressure on atrial structure and function is not as great or that a dose-response relationship does not exist in this range. Additionally, measurement error or temporal variation in blood pressure potentially results in the misclassification of persons as pre-hypertensive when in fact they more typically have optimal blood pressure.

An alternative approach is to consider the sustained exposure to blood pressure over time. Such an approach would help determine if extended exposure to modestly elevated blood pressure is associated with significant adverse consequences, such as AF, and also mitigate against measurement or biologic variability associated with single measurements. Therefore, the purpose of this study was to examine the sustained exposure to blood pressure level over time with incident AF in the Multi-Ethnic Study of Atherosclerosis (MESA). Determining whether blood pressures in the pre-hypertension range are associated with adverse consequences possibly will have significant implications for treatment recommendations which currently are limited to persons with hypertension.¹¹

METHODS

Study Design

Details of MESA have been described previously.¹² Briefly, between July 2000 and September 2002, 6,814 participants were recruited at 6 field centers in the United States (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Requirement for study participation included an age between 45 and 84 years and for participants not to have clinical cardiovascular disease at the time of study enrollment. The institutional review boards at each participating institution approved the study protocol and informed consent was obtained from all participants.

We examined the association between sustained blood pressure exposure between MESA visits 1, 2, and 3 (2000–2005) and incident AF. Participants were excluded if they met any of the following criteria: blood pressure measurements from MESA visits 1, 2, or 3 were missing, visit 1 baseline covariates were missing, AF was prevalent at visit 3, or data were missing regarding AF follow-up.

Blood Pressure Categorization

Blood pressure was measured during MESA visits 1, 2, and 3 using a standardized protocol. After the participant rested for 5 minutes in a seated position, blood pressure was recorded 3 separate times and the mean of the last 2 values was recorded for each visit. Optimal blood pressure was defined as blood pressure <120/80 mm Hg and no antihypertensive medication use. Pre-hypertension was defined as blood pressure between 120–139/80–89 mm Hg and no antihypertensive medication use. Hypertension was defined as blood pressure values ≥140/90 mm Hg or a history of at least 2 consecutive visits in which antihypertensive medication use was reported. The sustained exposure to each blood pressure level was based on 2 or more visits in the same category. A small number of participants (n=163, 3.1%) were noted to have different blood pressure categories at all 3 visits and these participants were categorized as pre-hypertensive based on the average blood pressure value across all visits.

Atrial Fibrillation

During follow-up phone calls every 9–12 months, participants were asked to identify hospitalizations, and medical records were obtained, including discharge diagnoses. Additionally, for participants enrolled in fee-for-service Medicare who were 65 years or older, Medicare claims data were used to identify inpatient AF cases. Incident AF was defined by International Classification of Disease Ninth Revision codes 427.31 or 427.32 and included permanent and non-permanent cases.

Baseline Characteristics

Participant characteristics collected during the initial MESA visit were used. Age, sex, race/ethnicity, income, and education were self-reported. Annual income was categorized into 2 levels (<\$20,000 versus ≥\$20,000). Similarly, education was categorized into “high school or less,” and “some college or more.” Smoking was defined as ever (e.g., current or former) and never smoker. Blood samples were obtained after a 12-hour fast and measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, and plasma glucose were used in this analysis. Diabetes was defined as fasting glucose values ≥126 mg/dL or the use of diabetes medications. Aspirin, statin, antihypertensive, and lipid-lowering medication use were self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Using baseline electrocardiogram data, left ventricular hypertrophy was defined by the Cornell criteria (R wave amplitude AV_L plus S wave amplitude V_3 ≥28 mm for men and ≥20 mm for women).¹³

Statistics

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean ± standard deviation. Statistical significance for categorical variables

was tested using the chi-square method and the Kruskal-Wallis procedure for continuous variables. Kaplan-Meier estimates were used to compute cumulative incidence of AF by blood pressure category and the differences in estimates were compared using the log-rank procedure.¹⁴ Follow-up time was defined from the time of visit 3 until a diagnosis of AF, death, loss to follow-up, or end of follow-up (December 31, 2010). Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between each blood pressure category and AF. Multivariable models were constructed with incremental adjustments using covariates from visit 1 as follows: Model 1 adjusted for age, sex, race/ethnicity, income, and education; Model 2 adjusted for Model 1 covariates plus smoking, diabetes, body mass index, total cholesterol, HDL-cholesterol, lipid-lowering medications, aspirin use, and left ventricular hypertrophy. Sensitivity analyses were conducted with adjustment for study visit 3 covariates, incident coronary heart disease, and incident heart failure, separately. The proportional hazards assumption was not violated in our analysis. Statistical significance was defined as $p < 0.05$. SAS[®] Version 9.3 (Cary, NC) was used for all analyses.

RESULTS

Of the 6,814 participants from the original MESA cohort, 58 participants had a diagnosis of AF before study enrollment. The majority of these cases were detected by Medicare linkage and only one case was present in the baseline electrocardiogram. Of those that remained, 6 participants with missing follow-up data and 943 participants whose follow-up ended before study visit 3 also were excluded, of which 118 developed AF. Additionally, 496 participants with missing baseline characteristics, blood pressure values, and hypertensive medication data across MESA visits were excluded. A total of 5,311 study participants (mean age 62 ± 10 years; 47% male; 57.1% whites; 19.8% blacks; 16.5% Hispanics; 6.6% Chinese-Americans) had complete data and were included in the final analysis.

A total of 1,612 (30%), 1,122 (21%), and 2,577 (49%) participants were categorized as having sustained blood pressure in the optimal, pre-hypertension, and hypertension range, respectively. The mean time between study visits 1 and 3 was 3.2 ± 0.30 years. Baseline characteristics by blood pressure category are shown in Table 1. The relationship between the initial blood pressure category and the cumulative blood pressure classification over all 3 visits is shown in Table 2. Among those with an initial blood pressure in the optimal range, 18.5% ultimately were classified as having sustained pre-hypertension or hypertension. Of those with an initial blood pressure in the pre-hypertension range, 34% were ultimately classified as having sustained blood pressures in the optimal or hypertension range. For participants who were initially classified as hypertension, 6.5% were reclassified as pre-hypertension.

Over a median follow-up of 5.3 years (interquartile range=4.8, 5.5), a total of 182 (3.4%) participants developed AF. A higher incidence of AF was observed among participants with sustained pre-hypertension (incidence rate ratio=2.7, 95%CI=1.5, 4.8) and sustained hypertension (incidence rate ratio=4.7, 95%CI=2.9, 7.7) compared with participants with sustained optimal blood pressure (referent). Unadjusted cumulative incidence curves for AF by blood pressure category are shown in Figure 1 (log-rank $p < 0.0001$).

In a multivariable Cox regression analysis, sustained exposures to pre-hypertension and hypertension were associated with an increased risk of AF compared with participants whose blood pressure remained in the optimal range (Table 3). Similar results were obtained when we used time-updated baseline covariates from study visit 3 (optimal: HR=1.0, referent; pre-hypertension: HR=2.0, 95%CI=1.1, 3.6; hypertension: HR=2.8, 95%CI=1.6, 4.7), and after adjusting for incident coronary heart disease (optimal: HR=1.0, referent; pre-hypertension: HR=1.9, 95%CI=1.1, 3.5; hypertension: HR=2.8, 95%CI=1.6, 4.7) and incident heart failure (optimal: HR=1.0, referent; pre-hypertension: HR=1.8, 95%CI=1.02, 3.4; hypertension: HR=2.7, 95%CI=1.6, 4.5).

DISCUSSION

In this analysis from MESA, sustained exposure to pre-hypertension was associated with an increased risk of AF compared with those whose blood pressures remained in the optimal range. As expected, participants who maintained hypertensive blood pressure or who were treated for hypertension also had an increased risk of AF.

The association between blood pressure and AF risk has been described extensively. Data from the Framingham Heart Study and Manitoba Follow-up Study have shown that men and women who have hypertension (defined by systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg or use of antihypertensive medications) are more likely to have AF than those with more optimal blood pressures.^{2,5} Similarly, systolic blood pressure per 10 mm Hg increase was associated with an increased AF risk in the Cardiovascular Health Study.³ These studies examined the association of blood pressure based on single measurements and did not examine the association of AF with varying levels of blood pressure across time.

Recently, several studies have attempted to define the risk of AF across varying levels of blood pressure and time. The lifetime risk of AF was shown to vary by blood pressure level from a single measurement in the Framingham Study.⁴ Similarly, an increased AF risk was observed among healthy Norwegian men with systolic blood pressure values between 128 and 138 mm Hg compared with men who had values <128 mm Hg from single measurements.⁷ Data from the Women's Health Initiative Study also showed that high-normal (e.g., 130 to 139 mm Hg) self-reported single blood pressure values are associated with an increased risk of AF.⁸ Interestingly, the reports from Norwegian men and the Women's Health Initiative Study described an association between high-normal blood pressure and AF using time-updated blood pressure values. However, both studies failed to report which participants remained within each respective blood pressure category over time (e.g., reclassification) and used the most recent blood pressure value from subsequent visits. In contrast, the current analysis attempted to appropriately group participants who remained in similar blood pressure categories over time to examine the risk of AF with sustained levels of blood pressure rather than merely relying on single measurements or time-updated values.

The results of the current study potentially provide more accurate information regarding the risk of AF associated with sustained exposure to blood pressure as we did not rely on single

measurements for categorization. Persons with pre-hypertension have a tendency to progress to hypertension, underscoring the importance of multiple measurements over time to appropriately categorize blood pressure level.¹⁵ Nonetheless, the results of the current study highlight an important aspect of AF epidemiology regarding blood pressure and AF risk; sustained exposure to pre-hypertension carries an inherent risk of AF above blood pressure that remains in the optimal range.

Several explanations for the association between elevated blood pressure and AF exist. Increases in left atrial diameter and blood pressure are directly related.¹⁶ Additionally, increased arterial stiffness as measured by pulse pressure is associated with AF.⁶ Potentially, persons with elevated blood pressure, including pre-hypertension, will develop enlarged left atria and arterial stiffness that correlates with fibrosis of the pulmonary veins, the origin of AF.¹⁷ Similarly, elevated blood pressure is associated with conditions that predispose to AF development, such as advanced age, diabetes, and coronary heart disease.² Therefore, it is plausible that pre-hypertension carries an increased risk for conditions that also increase one's risk for AF.¹⁸ However, our results remained significant after adjusting for these conditions in our multivariable models. Furthermore, participants with evidence of clinical cardiovascular disease were excluded from participation in MESA and this potential confounder was not accounted for in our main model. We subsequently incorporated this as a time-updated covariate and our findings were not materially altered.

Recent guidelines have made specific recommendations regarding the decision to initiate antihypertensive therapy. Largely, these recommendations were based on outcomes regarding overall mortality, cardiovascular disease-related mortality, cardiovascular disease outcomes (e.g., myocardial infarction, heart failure), and kidney function.¹¹ Due to the large burden that AF places on the healthcare system and future projections in the prevalence of AF, a careful examination of antihypertensive therapy recommendations and AF risk is warranted.¹

Our results should be interpreted in the context of several limitations. We attempted to categorize sustained exposure to blood pressure levels based on 3 consecutive visits in MESA. Although consistency in the blood pressure measurement protocol was required across study visits, misclassification remains a possibility. The identification of incident AF cases was ascertained from hospitalization discharge records and inpatient Medicare claims data using International Classification of Disease codes which possibly resulted in misclassification. However, this method has been reported to have adequate positive predictive value for identifying AF events.^{19,20} Potentially, non-permanent cases of AF were missed due to the intermittent nature of these cases (e.g., paroxysmal AF). Additionally, routine monitoring for AF (e.g., Holter monitors) was not performed in MESA and asymptomatic cases of AF possibly were missed. Although a small number of AF cases were found in the pre-hypertension group, these estimates likely are reduced due to the above reasons. Nonetheless, a significant result was found after rigorous multivariable adjustment. Furthermore, several potential confounders were included in our multivariable models that likely influenced the development of AF but residual confounding remains a possibility.

In conclusion, we have shown that sustained exposure to pre-hypertension possibly is associated with an increased risk of AF. Further research should examine the potential role of pharmacologic interventions and lifestyle modifications to lower blood pressure in individuals with pre-hypertension and if these interventions reduce the burden of AF in this population.

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Figure 1. Unadjusted Cumulative Incidence of AF (N=5,311)*

*Incidence curves are statistically different (log-rank $p < 0.0001$).

Table 1

Baseline Characteristics (N=5,311)

Characteristic	Optimal (n=1,612)	Pre-hypertension (n=1,122)	Hypertension (n=2,577)	P-value *
Age, mean $\pm$ SD (years)	57 $\pm$ 8.9	61 $\pm$ 9.8	65 $\pm$ 9.4	<0.0001
Male (%)	724 (45)	598 (53)	1,191 (46)	<0.0001
Race				
White (%)	740 (46)	450 (40)	897 (35)	
Black (%)	258 (16)	273 (24)	907 (35)	
Chinese-American (%)	258 (16)	137 (12)	266 (10)	
Hispanic (%)	356 (22)	262 (23)	507 (20)	<0.0001
Education, high school or less (%)	429 (27)	396 (35)	995 (39)	<0.0001
Annual income, <\$20,000 (%)	307 (19)	265 (24)	809 (31)	<0.0001
Current or former smoker (%)	718 (45)	535 (48)	1,191 (46)	0.26
Diabetes (%)	81 (5.0)	101 (9.0)	548 (21)	<0.0001
Body mass index, mean $\pm$ SD (kg/m ²)	26 $\pm$ 4.6	28 $\pm$ 5.2	29 $\pm$ 5.6	<0.0001
Total cholesterol, mean $\pm$ SD (mg/dL)	196 $\pm$ 35	197 $\pm$ 35	192 $\pm$ 35	<0.0001
HDL-cholesterol, mean $\pm$ SD (mg/dL)	52 $\pm$ 15	51 $\pm$ 15	51 $\pm$ 14	0.0059
Aspirin (%)	238 (15)	237 (21)	789 (31)	<0.0001
Lipid-lowering medications (%)	141 (8.8)	134 (12)	582 (23)	<0.0001
Left ventricular hypertrophy (%)	17 (1.0)	23 (2.1)	143 (5.6)	<0.0001

* Statistical significance for continuous data was tested using Kruskal-Wallis procedure and categorical data was tested using the Chi-square test.

HDL=high-density lipoprotein; SD=standard deviation.

Table 2

Reclassification of Participants over Time*

Visit 1 Classification	Cumulative Classification		
	Optimal	Pre-hypertension	Hypertension
Optimal	81.5%	15.1%	3.4%
Pre-hypertension	15.7%	66.0%	18.3%
Hypertension	0.0%	6.5%	93.5%

* Participants were reclassified using subsequent study blood pressure measurements and documentation of antihypertensive medications.

Bold values represent the percentage of participants who remained in the same blood pressure category between visits 1 and 3.

Table 3

Risk of Atrial Fibrillation (N=5,311)

Category	Events/#At risk	Incidence rate per 1000 person-years (95%CI)	Model 1* HR (95%CI)	P-value	Model 2† HR (95%CI)	P-value
Optimal	18/1,612	2.2 (1.4, 3.5)	1.0	-	1.0	-
Pre-hypertension	33/1,122	6.0 (4.3, 8.4)	1.9 (1.04, 3.3)	0.038	1.8 (1.004, 3.2)	0.048
Hypertension	131/2,577	10.5 (8.8, 12.4)	2.8 (1.7, 4.6)	<0.0001	2.6 (1.6, 4.4)	0.0003

* Adjusted for age, sex, race/ethnicity, income, and education.

† Adjusted for Model 1 plus smoking, diabetes, body mass index, total cholesterol, HDL-cholesterol, lipid-lowering medications, aspirin, and left ventricular hypertrophy.

CI=confidence interval; HDL=high-density lipoprotein; HR=hazard ratio; SD=standard deviation