

**Manuscript Proposal Outline (Upload)**

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**Proposal Title: Association between 30-year predicted cardiovascular disease risk and incident hypertension.**

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1. **Overview**

Provide a brief overview of the proposal including the nature of the problem to be addressed, scientific relevance, objectives/aims, research question/hypotheses, and methods/analytical plan (**<250 words**):

The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends initiation of antihypertensive medication for adults with stage 1 hypertension, systolic BP of 130 to 139 mmHg or diastolic BP of 80 to 89 mmHg, and high cardiovascular disease (CVD) risk. In this guideline, the definition of high CVD risk included 10-year predicted atherosclerotic CVD (ASCVD) risk ≥10% using the Pooled Cohort Equations. In 2023, the American Heart Association published the PREVENT equations. Most US adults with stage 1 hypertension and 10-year predicted ASCVD risk ≥10% by the Pooled Cohort Equations have 10-year predicted total CVD risk <10% by the PREVENT equations and may not be recommended antihypertensive medication. In addition to equations for predicting 10-year total CVD risk, there are PREVENT equations to estimate 30-year total CVD risk. It may be reasonable to recommend antihypertensive medication for adults with stage 1 hypertension and high 30-year predicted total CVD risk if these individuals have a high incidence of stage 2 hypertension, systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or initiation of antihypertensive medication, and they have sub-clinical CVD. We propose to study the association between 30-year predicted total CVD risk using the PREVENT equations with the incidence of stage 2 hypertension among Jackson Heart Study participants. We hypothesize the incidence of stage 2 hypertension will increase progressively with higher 30-year predicted total CVD risk. In addition, we hypothesize that a high proportion of participants who develop stage 2 hypertension will have evidence of sub-clinical CVD, estimated by left ventricular hypertrophy at Visit 3.

1. **Background/Rationale**

Please include discussion on relevance of African Americans to the proposed topic (**<1000 words**).

In the United States, more cardiovascular disease (CVD) events are attributable to hypertension and uncontrolled blood pressure (BP) than any other CVD risk factor.1 Approximately 122 million Americans had hypertension in 2017-2020, defined as systolic BP ≥130 mm Hg or diastolic BP ≥ 80 mm Hg or use of antihypertensive medication, with a higher prevalence among African American adults compared to White adults.2 The higher prevalence of hypertension and uncontrolled BP among African American adults compared to white adults contributes to disparities in CVD.3 Clinical trial evidence has consistently demonstrated the benefits of antihypertensive medication and intensive BP lowering in reducing CVD risk and attenuating hypertension-related target organ damage among diverse populations,4,5 emphasizing the importance early detection, and proactive management approaches including timely antihypertensive treatment for CVD prevention. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) BP guideline recommended initiation of antihypertensive medication among individuals with stage 1 hypertension, defined as systolic BP of 130 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg, and high cardiovascular risk, defined by a history of CVD, age ≥ 65 years, diabetes, chronic kidney disease, and/or 10-year predicted atherosclerotic CVD (ASCVD) risk ≥10% using the Pooled Cohort Equations.6

In 2023, the AHA published the PREVENT equations, offering updated risk assessment tools for estimating 10- and 30-year predicted ASCVD or total CVD risk in contemporary populations.7 Compared to the Pooled Cohort Equations, the PREVENT equations were designed to estimate total CVD risk, in addition to ASCVD risk, among a wider age range (i.e., as young as age 30 years compared to 40 years for the Pooled Cohort Equations), over a longer time horizon including 30 years, and was validated in more diverse populations.7 Despite the high correlation between predicted 10-year ASCVD risk by the Pooled Cohort and PREVENT Equations, many adults with 10-year predicted ASCVD risk ≥10% by the Pooled Cohort Equations do not have 10-year predicted ASCVD or total CVD risk ≥10% when assessed using the PREVENT equations7 and may not be recommended to initiate antihypertensive medication. However, a high percentage of adults 30 to 60 years of age without hypertension with 10-year total CVD risk <10% have high (≥30%) 30-year total CVD risk estimated by the PREVENT equations. It has been suggested that initiation of antihypertensive medication may be reasonable for young adults with stage 1 hypertension if they have high long-term risk for CVD events given the high lifetime risk for progression to stage 2 hypertension (systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or initiation of antihypertensive medication), risk for end-organ damage, and ability of early treatment to prevent high BP levels. Therefore, it may be reasonable to recommend initiation of antihypertensive medication for adults with stage 1 hypertension and high 10-year or 30-year predicted risk if these individuals have a high incidence of stage 2 hypertension, and they have sub-clinical CVD when they develop stage 2 hypertension.

We propose to investigate the association between 30-year predicted total CVD risk, as estimated by the PREVENT equations, and the incidence of stage 2 hypertension among Jackson Heart Study (JHS) participants. We hypothesize a higher incidence of stage 2 hypertension will be present among participants with higher 30-year predicted total CVD risk. Furthermore, we hypothesize that a substantial proportion of participants who transition to stage 2 hypertension will have evidence of sub-clinical CVD, as indicated by left ventricular hypertrophy (LVH) during their assessment at Visit 3. By estimating the associations between long-term predicted total CVD risk, incidence of stage 2 hypertension, and subclinical CVD, this study has the potential to inform BP management and CVD prevention.

1. **Research Hypothesis**

1. Higher 30-year predicted total CVD risk using the PREVENT equations is associated with a higher incidence rate of stage 2 hypertension. We will test this hypothesis in the overall sample and stratified by 10-year PREVENT total CVD risk ≥ 10%.

2. Among participants who did not experience a CVD event between visit 1 and visit 3 and with 10-year predicted total CVD risk using the PREVENT equations < 10% at visit 1, higher 30-year predicted total CVD risk using the PREVENT equations at visit 1 is associated with higher left ventricular mass index and a higher prevalence of LVH at visit 3.

In exploratory analyses, we will test the hypotheses above in three subgroups based on the 2017 ACC/AHA guideline defined BP levels at visit 1: *normal BP* (systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg), *elevated BP* (systolic BP 120 to < 130 mm Hg and diastolic BP < 80 mm Hg), and *stage 1 hypertension* (systolic BP 130 to < 140 mm Hg with diastolic BP < 90 mm Hg or diastolic BP 80 to < 89 with systolic BP < 140 mm Hg).

1. **Inclusions/Exclusions**

We will include participants who were aged 30 to < 60 years at visit 1 as 30-year predicted total CVD risk using the PREVENT equations has been validated for adults in this age range.7 We will restrict the sample to participants who consented to CVD follow-up and did not have a history of CVD at visit 1 as 10- and 30-year total CVD risk is only recommended to be estimated for primary prevention. We will exclude participants without information on self-reported antihypertensive medication use and BP at visit 1 and will also exclude participants who did not have information on variables in the 10-year and 30-year total CVD PREVENT equations at visit 1. We will also exclude participants with values for the variables in the PREVENT equations at visit 1 that are outside the recommended range, i.e., total cholesterol < 130 or > 320 mg/dL, high-density lipoprotein cholesterol < 20 or > 100 mg/dL, systolic BP < 90 or > 200 mm Hg, or estimated glomerular filtration rate < 15 or > 140 ml/min/1.73m2. Last, we will restrict the sample to participants without stage 2 hypertension at visit 1 and with known hypertension status at either visit 2 or visit 3. We anticipate over 1,000 JHS participants will meet these criteria.

1. **Variable Definitions**

We will compute 10-year and 30-year risk for CVD using the base PREVENT equations, which include age, sex, high density lipoprotein (HDL) cholesterol, non-HDL cholesterol, systolic BP, diabetes status, current smoking status, estimated glomerular filtration rate, antihypertensive medication use, and statin use. We will compute estimated glomerular filtration rate using a validated equation based on serum creatinine that does not incorporate information about race.8 The base equations of PREVENT are being proposed for this analysis as they are most readily applied in clinical settings and there is little difference in these equations and equations that include additional components among people with stage 1 hypertension.

Incident stage 2 hypertension will be defined as being present at the first visit during follow up at which a participant has systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or self-reported antihypertensive medication use. Participants who do not develop stage 2 hypertension will be censored for the analysis of this outcome at the last visit they attended. We will use time between the date of visit 1 and the date of the earliest visit with stage 2 hypertension as the interval censored event time.

History of CVD at baseline will be defined by self-reported coronary heart disease, stroke, or heart failure prior to visit 1.

Incident total CVD will be defined by an adjudicated CHD or stroke event after baseline or heart failure starting in 2005, when adjudication for heart failure began.

Left ventricular mass (LVM) at visit 3 will be defined using cardiac image modeling parameters from the magnetic resonance imaging scans collected during visit 3 (some scans were conducted at the final phase of visit 2 – these will not be used). LVM index (LVMI) will be defined as LVM (g) / height (m2.7) and LVH will be defined as LVMI > 38 g/m2.7 for women, and > 45.1 g/m2.7 for men.9

1. **Statistical Analysis Plan and Methods**

All proposed analyses will be completed overall and in subgroups based on BP (normal BP, elevated BP, and stage 1 hypertension). Participant characteristics will be summarized using means for continuous and percentage for categorical variables. Medians with 25th and 75th percentiles will be presented instead of means for continuous variables that exhibit skew (e.g., predicted CVD risk is often skewed towards lower values). We will summarize the distribution of JHS participants included in the current analysis according to 10-year and 30-year total CVD risk using the PREVENT equations. Specifically, we will compute the proportion of participants with 10-year total CVD risk < 10% and ≥10%. Within the 10-year total CVD risk groups, we will additionally compute the proportion with 30-year total CVD risk <10%, 10% to <20%, 20% to <30%, and ≥30%. Next, for each of the 30-year risk categories, we will compute mean LVMI and the proportion of participants who developed stage 2 hypertension and LVH, separately.

Interval censored Cox regression models will be used to test whether 30-year predicted total CVD risk using the PREVENT equations at visit 1 is associated with incident stage 2 hypertension at visits 2 or 3. Linear regression will be used to test whether 30-year predicted CVD risk using the PREVENT equations at visit 1 is associated with LVMI at visit 3. Poisson regression with robust standard errors will be used to test whether 30-year predicted risk using the PREVENT equations at visit 1 is associated with LVH at visit 3. As predicted total CVD risk using the PREVENT equations is the primary independent variable, we will not include multivariable adjustment for variables (e.g., age) that are used to estimate predicted risk in these equations.

Inthe primary analyses, we will assume that 30-year predicted risk using the PREVENT equations at visit 1 has a linear relationship with the outcomes, i.e., incident stage 2 hypertension, LVMI and LVH. In secondary analyses, we will relax the assumption of linearity by using a categorical variable, i.e., 30-year predicted CVD risk using PREVENT <10%, 10% to <20%, 20% to <30%, and ≥30%, instead of continuous 30-year predicted CVD risk. These secondary analyses will perform the same hypothesis tests as the primary analyses.

A number of participants may have missing data for LVMI at visit 3. In the primary analysis, we will assume these data are missing completely at random and perform a complete case analysis. In a sensitivity analysis, we will assess how robust the complete case analysis is by performing multiple imputation and testing the same hypotheses. If multiple imputation leads to conflicting inferences compared to complete case analysis, we will note that data may not have been missing completely at random as a limitation and present the results with multiple imputation as the primary analysis.

1. **References (maximum 15)**

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