

**Manuscript Proposal Outline (Upload)**

**Instructions:** Use a font size of 11 points or larger with at least one-half inch margins (top, bottom, left, and right) for all pages. Note: Supplemental materials such as table shells must be uploaded separately.

1. **Proposal Title:**
2. **Lead Author:**
3. **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. Among adults with stage 1 hypertension, most with 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. 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 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 when they develop stage 2 hypertension. 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 higher left ventricular mass index 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 (2017-2020) have hypertension, defined as systolic BP ≥130 mm Hg or diastolic BP ≥ 80 mm Hg, with a higher prevalence among African American compared to White adults.2 Disparities in hypertension contribute to disparities in CVD.3 Clinical trial evidence has consistently demonstrated the benefits of pharmacological BP control in reducing adverse cardiovascular events and attenuating hypertension-related target organ damage among diverse populations,4,5 emphasizing the importance of timely intervention, early detection, and proactive management approaches for CVD prevention and health equity. The introduction of the 2017 American College of Cardiology/American Heart Association (ACC/AHA) BP guideline was a pivotal milestone in hypertension management, advocating for proactive 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 heightened cardiovascular risk, as determined by a 10-year predicted atherosclerotic CVD (ASCVD) risk ≥10% using the Pooled Cohort Equations.6

In 2023, the AHA published the PREVENT equations, offering novel risk assessment tools for estimating 10- and 30-year predicted ASCVD or total CVD risk.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 (as young as age 30- compared to 40- years), a longer-term (30-year risk), and more diverse population.7 Despite high correlation between predicted 10-year ASCVD risk by the Pooled Cohort and PREVENT Equations, many adults classified as high risk by the Pooled Cohort Equations do not meet the threshold of ≥10% 10-year predicted ASCVD or total CVD risk when assessed using the PREVENT equations7 and may not be recommended antihypertensive medication. Further, a high percentage of adults 30 to 79 years of age without hypertension could have low (<10%) 10-year total CVD risk and high (≥30%) 30-year total CVD risk. To optimize cardiovascular health outcomes, 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, systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or initiation of antihypertensive medication, 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 assessed by the PREVENT equations, and the incidence of stage 2 hypertension among Jackson Heart Study participants. We hypothesize that as the 30-year predicted total CVD risk increases, the incidence of stage 2 hypertension increases. Furthermore, we hypothesize that a substantial proportion of participants who transition to stage 2 hypertension will exhibit evidence of sub-clinical CVD, as indicated by elevated left ventricular mass index during their assessment at Visit 3. By estimating these associations between long-term CVD risk, hypertension progression, and subclinical CVD burden, this study will inform more refined strategies and thresholds for hypertension 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.

2a. Higher 30-year predicted total CVD risk using the PREVENT equations at visit 1 is associated with increased risk for incident CVD events.

2b. 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 left ventricular hypertrophy (LVH) at visit 3.

In exploratory analyses, we will test the four hypotheses above in three subgroups based on 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 has been validated for adults in this age range.7 We will restrict our sample to participants who consented to CVD follow-up and had no history of CVD at visit 1. 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 CVD PREVENT equations at visit 1. Furthermore, we will exclude participants with values for the variables in the PREVENT equations at visit 1 that are outside the recommended range. Last, we will restrict the sample to include 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 equation, which use age, 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 and cystatin C that does not incorporate information about race.

Stage 2 hypertension will be defined as having systolic BP > 140 mm Hg, diastolic BP > 90 mm Hg, or self-reported antihypertensive medication use. Incident stage 2 hypertension will be defined by stage 2 hypertension status at visits 2 and 3. 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 will be defined by self-reported coronary heart disease or stroke prior to visit 1.

1. **Statistical Analysis Plan and Methods**

Participant characteristics will be summarized using means for continuous and percentage for categorical variables, overall and in subgroups based on BP (normal BP, elevated BP, and stage 1 hypertension). 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%. Among the participants with 10-year total CVD risk < 10%, we will 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 the proportion of participants who developed stage 2 hypertension, CVD, 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. Cox regression models will be applied to test whether 30-year predicted CVD risk using the PREVENT equations at visit 1 is associated with incident CVD. Linear regression will be used to test whether 30-year predicted CVD risk using the PREVENT equations at visit 1 is associated with left ventricular mass 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 left ventricular hypertrophy 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.

Inour 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, CVD, LVMI and LVH. In secondary analyses, we will model a non-linear relationship using a natural cubic spline. These secondary analyses will perform the same hypothesis tests as the primary analyses.

A number of participants may have missing data for left ventricular mass at visit 3. In our 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)**

1. Cheng S, Claggett B, Correia AW, Shah AM, Gupta DK, Skali H, Ni H, Rosamond WD, Heiss G, Folsom AR, et al. Temporal Trends in the Population Attributable Risk for Cardiovascular Disease. *Circulation*. 2014;130:820-828. doi: doi:10.1161/CIRCULATIONAHA.113.008506

2. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, et al. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. *Circulation*. 2023;147:e93-e621. doi: doi:10.1161/CIR.0000000000001123

3. Fiscella K, Holt K. Racial disparity in hypertension control: tallying the death toll. *Annals of family medicine*. 2008;6:497-502. doi: 10.1370/afm.873

4. Group SR. A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine*. 2015;373:2103-2116.

5. Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, Bosch J, Sussex B, Probstfield J, Yusuf S. Reduction of Cardiovascular Risk by Regression of Electrocardiographic Markers of Left Ventricular Hypertrophy by the Angiotensin-Converting Enzyme Inhibitor Ramipril. *Circulation*. 2001;104:1615-1621. doi: doi:10.1161/hc3901.096700

6. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127-e248. doi: 10.1016/j.jacc.2017.11.006

7. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, et al. Development and Validation of the American Heart Association’s PREVENT Equations. *Circulation*. 2024;149:430-449. doi: doi:10.1161/CIRCULATIONAHA.123.067626