1.a. Full Title: Blood Pressure and Risk of Myocardial Infarction in Washington County, MD

b. Abbreviated Title (Length 26 characters): Blood Pressure & First MI

2. Writing Group (list individual with lead responsibility first):
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3. Timeline:
   August 1, 2000 – December 31, 2001

4. Rationale:
   Acute myocardial infarction accounts for the majority of coronary heart disease (CHD), the current leading cause of death and a major source of morbidity in the United States. Numerous observational and randomized, controlled studies have confirmed an independent association of elevated baseline systolic (SBP) and diastolic (DBP) blood pressures with subsequent CHD. However, only a handful of prospective studies has addressed the role of change in blood pressure over time, therefore, the patterns of blood pressure change that are most strongly associated with CHD risk and the relative predictive value of earlier versus more recent blood pressure levels remain unclear.

   Furthermore, the relative importance of DBP, SBP, mean arterial blood pressure (MAP), and pulse pressure (PP) in CHD risk has not been fully elucidated. Increased pulse pressure is thought to reflect age-related arterial stiffening and is hypothesized to predispose to myocardial ischemia and infarction by simultaneously increasing the workload of the heart and decreasing coronary perfusion. While a small body of evidence suggests a potentially stronger predictive role for PP compared to other blood pressure indices among middle-aged and older individuals, confirmatory studies are needed. And, whereas the risks of severe isolated systolic hypertension are well-documented, the cardiovascular disease risks posed by Stage 1 ISH (140 < SBP ≤ 160 mm Hg and DBP < 90) have not been well characterized.

   The proposed prospective cohort study promises to shed light on the relative roles of commonly used blood pressure indices in risk of myocardial infarction, and therefore has tremendous clinical and public health relevance. Evidence from a large population based prospective study of the risks posed by Stage 1 Isolated systolic hypertension will help justify randomized trials of
anti-hypertensive therapy for persons with blood pressure in this range. Similarly, confirmation of the predictive value of pulse pressure has important implications for cardiovascular disease risk assessment among middle-aged and older individuals, as current hypertension guidelines do not consider potential risks associated with highly discordant systolic and diastolic pressures. Finally, clarification of the risks associated with different patterns of blood pressure change over time, and with blood pressure levels from earlier in life, may ultimately aid clinicians in identifying those patients most at risk and in need of intervention.

5. **Main Hypothesis:**
The goal of the proposed study is to examine risks of incident myocardial infarction associated with blood pressure in a population-based sample, and specifically,
1) To estimate the prevalence of and risks associated with isolated systolic hypertension.
2) To assess the value of pulse pressure in determining risk.
3) To determine the patterns of change in blood pressure that are most strongly associated with risk and evaluate the relative predictive value of earlier versus later blood pressure measurements.

The following hypotheses will be evaluated:
1) Stage 1 Isolated Systolic Hypertension confers increased risk of incident MI
2) Increased pulse pressure is associated with increased risk of MI
3) Increases in pulse pressure over time are associated with increased risk of MI
4) Incident hypertension between 1974 and 1989, as ascertained in 1989, is associated with increased risk of MI compared to sustained hypertension from 1974 to 1989.

6. **Data (variables, time window, source, inclusions/exclusions):**
The proposed study will have a prospective cohort design.

**Data Sources:**
The study population will consist of the approximately 24,655 residents of Washington County, MD who in 1989 participated in a campaign known as Clue II, in which participants completed a brief health survey, underwent a blood draw and had their blood pressure measured. Follow-up of the Clue II Cohort is conducted from the Training Center for Public Health Research in Washington County, which tracks vital status of cohort members by regularly monitoring county death certificates and searching obituaries. Additionally, follow-up questionnaires have been mailed to cohort members in 1996 and 1998. A subset of 8,395 Clue II cohort members also participated in a similar campaign in 1974 known as Clue I, and therefore have blood pressure measurements from both time points.

To obtain data on hospitalized incident MI in the cohort, linkage of the Clue II cohort to the Atherosclerosis Risk in Communities (ARIC) Surveillance program in Washington County, MD is proposed. The proposed linkage would be conducted by staff at the Training Center for Public Health Research, and would utilize the following personal identifiers: first name, last name, middle initial, birth name, date of birth, gender, and race. ARIC Surveillance data from 1987 through 1998 would be requested for linkage. A total of approximately 520 definite or probable first MI events is expected to be identified in the Clue II cohort as a result of linkage.

In addition, given that ARIC Surveillance has ascertained only an 84% sample of hospital discharges containing the ICD-9 code for acute MI (410) among men since 1994, it is proposed that excluded hospital discharges with an ICD-9 code of 410 among male Clue II cohort
members be recovered in order to increase ascertainment of MI in the cohort. In the proposed recovery project, excluded hospital discharge lists (falling on dates divisible by 6) would be retrieved from storage at the ARIC Surveillance Washington County Field Center and compared to a list of age-eligible male Clue II cohort using the personal identifiers listed above in order to identify excluded hospital discharges with an ICD-9 code of 410 among Clue II males. Once the excluded discharges among Clue II males were identified, trained abstractors from ARIC Surveillance would abstract relevant hospital records, and the discharges would be classified according to ARIC Surveillance criteria for hospitalized myocardial infarction. The recovery project would yield approximately 30 definite or probable first MI events in the Clue II cohort. The data linkage and MI recovery projects together are expected to require one year to complete.

**Variables:**

In both Clue I (1974) and Clue II (1989), blood pressure was measured by a nurse who took three seated readings using a standard mercury sphygmomanometer after participants had been at rest. In Clue II, the last of the three readings was recorded, and in Clue I the lowest reading was recorded. Self-reported use of anti-hypertensive medications was collected in both Clue I and Clue II.

Cardiovascular disease risk factors and other variables available for assessment as confounders or effect modifiers include age, sex, smoking status, hormone use, education, and marital status from both Clue I and Clue II health surveys, as well as self reported height and weight and total cholesterol from Clue II. Baseline diabetes status was not assessed in either Clue I or Clue II.

**Inclusions/Exclusions:**

The cohort will be limited to those who were age-eligible for ARIC surveillance from 1989 through 1998, who have non-missing baseline blood pressure measurements, and who have not been lost to follow-up. Additionally, to remove prevalent MI cases from the cohort, cohort members with self-reported (on a Clue II follow-up questionnaire) or ARIC-identified history of MI prior to 1989 will be excluded. MI Cases will consist of cohort members who were identified by ARIC Surveillance as having suffered a definite or probable first MI during follow-up. For the analyses of change in blood pressure, the study population will be limited to members of the Clue II Cohort who were also members of the Clue I Cohort, because they have blood pressure measurements from both 1974 and 1989.

Survival analysis will be used to analyze the data in order to account for differential amounts of follow-up time within the cohort. Cox regression will be used for crude and multivariate modeling.

Addressing the study’s first aim, sex- and age-specific estimates of the prevalence of isolated systolic hypertension will be calculated and risks of MI associated with isolated systolic hypertension will be estimated, stratifying by age and sex. For the study’s second aim, the associations of pulse pressure and the other blood pressure indices with MI will be estimated, stratifying by age, sex and use of anti-hypertensive therapy, and risk estimates will be compared.

With regard to the study’s third specific aim, the fifteen year change in blood pressure indices and hypertension status will be calculated and the risks associated with different patterns of blood pressure change will be compared. Additionally, the risks associated with blood pressure levels in 1974 and 1989 will be estimated and compared.
7.a. Will the data be used for non-CVD analysis in this manuscript?   ____ Yes   __X__ No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?   ____ Yes   ____ No
(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?   ____ Yes   __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = “No use/storage DNA”?   ____ Yes   ____ No