1. **Full Title:** Postural Blood Pressure Change and Incident Stroke, Coronary Heart Disease, and All-cause Mortality

2. **Abbreviated Title (Length 26 characters):** Postural BP and Mortality

3. **Writing Group (list individual with lead responsibility first):**

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4. **Timeline:** Begin preliminary analyses immediately, but finalize analyses after the release of the 1998 data update. Have a first draft of the manuscript within three months of the data release.

5. **Rationale:** Two ARIC Studies have shown that orthostatic hypotension (OH), a fall in diastolic blood pressure of at least 10 mm Hg or of systolic blood pressure of at least 20 mm Hg upon standing, is associated with an increased risk of coronary heart disease and stroke. Since both stroke and coronary heart disease constitute a large component of overall mortality, we expect that OH will also be associated with an increase in all-cause mortality.

While elevation of blood pressure/hypertension is a well-recognized contributor to both stroke and heart disease, only a few studies have evaluated postural increase in blood pressure as a cardiovascular risk factor. Three studies suggested that persons that have an exaggerated increase in blood pressure in response to standing may have characteristics that could place them at increased risk of cardiovascular disease outcomes. We, therefore, hypothesize that a marked increase in blood pressure on standing will be associated with an increased risk of stroke, coronary heart disease, and all-cause mortality compared to slight to moderate postural pressure changes. An exaggerated increase in blood pressure upon standing could contribute to stroke through several mechanisms. First, a rapid pressure increase could cause disruption of plaques resulting in embolism or could cause local intraplaque hemorrhage or thrombus formation resulting in a decrease in cerebral blood flow. Alternatively, a marked increase in postural blood pressure could contribute to stroke because it predisposes to atherosclerosis or because it is associated with other risk factors for cardiovascular disease. Similar mechanisms could contribute to coronary heart disease.
However, just as hypertension is a stronger risk factor for stroke than for coronary heart disease, postural pressure increase may be a stronger risk factor for stroke than for coronary heart disease.

A separate question is whether marked fluctuation in blood pressure upon standing and while standing (i.e. in the initial postural blood pressure change and subsequent changes in standing blood pressures) results in an increased risk of stroke. In particular, persons with a marked increase followed by a large fall in blood pressure could be predisposed to cerebral ischemia. The variability in blood pressures could potentially contribute to cerebral ischemia by resulting in instability of the normal cerebrovascular auto-regulation or because it is a marker of other risk factors or of autonomic dysfunction.

Because of the previously demonstrated associations and those we suggest above, we hypothesize there will be an U-shaped association between postural blood pressure change and these outcomes.

5. **Main Hypothesis/Study Questions:**
   
   An exaggerated decrease in blood pressure on standing will be associated with an increased risk for all-cause mortality while an exaggerated increase in blood pressure on standing will be associated with an increased risk for coronary heart disease, stroke, and all-cause mortality, either because of an association with other risk factors or because of an independent effect.
   
   1. Is OH, a fall in mean systolic blood pressure of at least 20 mm Hg or a fall in mean diastolic blood pressure of at least 10 mm Hg, associated with an increase in all-cause mortality relative to persons without OH in unadjusted analyses and after adjusting for cardiovascular and other risk factors. (The positive association of OH with stroke and CHD has already been published using ARIC data).
   
   2. Do persons with the largest postural blood pressure increase have an increased risk for the three outcomes relative to persons with less marked change (excluding persons with OH)? Do the associations remain after adjusting for cardiovascular risk factors?
   
   3. Is there a U-shaped association between postural blood pressure change and the three outcomes in unadjusted analyses and after adjusting for risk factors.
   
   4. Are persons with large fluctuations of blood pressure on standing (eg. those with an increase followed by a pressure drop or vice versa) at an increased risk of stroke in unadjusted and adjusted analyses compared to those with less marked fluctuations in blood pressure?

6. **Data (variables, time window, source, inclusions/exclusions):**

   Exclusions: ethnicity other than black or white, blacks from Minneapolis and Washington County, age younger than 45 or older than 64 at baseline, positive or unknown history of physician-diagnosed stroke or myocardial infarction or coronary heart disease at baseline, atrial fibrillation/flutter by ECG at baseline, use of medication for congestive heart failure or arrhythmias at baseline and missing blood pressure measurements that preclude calculation of postural blood pressure change.

   Visit 1 data: diastolic and systolic postural blood pressure changes, individual standing blood pressures, mean supine blood pressure, race, gender, age, center, education, systolic bp, diastolic
bp, antihypertensive medication use, diabetes status, smoking status, BMI, total cholesterol, smoking status, ethanol consumption, IMT, ECG measure for LVH, ABI, VWF, WBC, fibrinogen, prevalent CHD, history of stroke, history of chronic lung disease, use of medication for congestive heart failure, medication for arrhythmias, ECG evidence of arrhythmias, history of chronic lung disease, history of cancer.

Surveillance data: incident definite probable stroke by 1998 and follow-up time, incident coronary heart disease (hospitalized MI, definite fatal CHD, silent MI by ECG) and follow-up time, deadby98 and follow-up time.

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 ICTDER02 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

References: