1.a. Full Title

The Natural History of Pre-Hypertension

b. Abbreviated Title

‘Pre-hypertension Progression’

2. Writing Group

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3. Time Line

Obtain data set: May 2004
Begin statistical analysis: May 2004
Complete statistical analysis: August 2004
Complete manuscript: December 2004

4. Rationale/ Background
The Seventh Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 1 has recently designated a new category of blood pressure, pre-hypertension. It is defined by systolic blood pressure (SBP) in the range 120-139 mm Hg or a diastolic blood pressure (DBP) 80-89 mm Hg. Individuals with blood pressure in the pre-hypertension range, previously considered normal, are now recommended for a minimum of close follow-up and lifestyle modification, and possibly, drug intervention.

Individuals with pre-hypertension will swell the ranks of those targeted for blood pressure modification by another 25 to 30 million in the United States; worldwide, the number may be several-fold higher. As such, the societal impact of individuals with pre-hypertension will be great. Yet important questions about the natural history of pre-hypertension are not fully answered 2. For example, what is the rate of progression to hypertension? Does pre-hypertension regress to lower levels of blood pressure? What are the risk factors associated with progression to hypertension, and with regression to lower levels of blood pressure? Are there important subgroups of individuals, minorities, individuals with diabetes mellitus, individuals with renal insufficiency, others, in whom the risk of developing hypertension is elevated? Such epidemiological information would be useful for clinicians advising individual patients, for investigators planning intervention studies, and for policy advisors determining allocation of government resources.

Previous investigations in the ARIC cohort have examined novel and traditional risk factors for incident hypertension; factors associated with incident hypertension include elevated alcohol consumption 3, an elevated ratio of polyunsaturated to saturated plasma fatty acids 4, arterial stiffness 5, orthostatic hypotension 6, low socioeconomic status 7, weight gain 8, and retinal arteriolar narrowing 9. Other ARIC investigations have demonstrated a weak or minimal association of variables such as magnesium 10 or fibrinogen 11 with incident hypertension. In addition, weight loss was associated with the remission of hypertension 12. Finally, additional studies examining the relationship of ethnicity (MS# 457), physical activity (MS # 459), insulin (MS # 423) with incident hypertension have been withdrawn (for unclear reasons).

These previous studies in ARIC provide us with important information for covariable adjustment for our planned analysis. Our proposed investigation may have some overlap with the previous studies in terms of variables being analyzed, but will not overlap in terms of the primary objectives, namely characterizing the newly-defined JNC category of individuals with pre-hypertension.

In summary, given the novelty/newness of the pre-hypertension category and its potential public health implication, it is important to focus on this group of individuals with blood pressure between 120/80 to 139/89 mm Hg. There are gaps in the research literature addressing this newly defined group of clinical interest. Most published research addresses blood pressure as a continuous measure or as hypertensive vs. non-hypertensive. We propose to address this deficiency in the literature by focusing on the pre-hypertension category, splitting it into high-normal blood pressure (130/85 – 139/89) and normal blood pressures (120/80 – 129/84) based on JNC 6 recommendations, and determining whether blood pressure increases more rapidly over time in the high-normal blood pressure group than in those with normal or optimal blood pressure.
5. **Main Hypothesis**

Optimal, normal, and high normal levels of blood pressure will progress to levels of blood pressure consistent with the current definitions of hypertension over time. It is intuitive that individuals with high-normal blood pressures would develop hypertension more quickly than those having lower baseline blood pressures. In this proposal, we will test if the corresponding risk of progression to hypertension is greater in the high-normal group than in the normal group, and verify that the optimal group has the lowest risk of developing hypertension. Although this is mentioned as the first analysis, it is simply to set the stage for the primary analysis. We will investigate the rate of change in blood pressure over time for each of the three baseline blood pressure groups (optimal, normal and high-normal), hypothesizing that the rate of change in blood pressure over time will be greatest among individuals with high-normal blood pressure. Based on the findings of our earlier study (ARIC Proposal # 865), we also propose the following secondary hypotheses: (1) the risk of progressing to hypertension (as well as the rate of change in blood pressure) is greater among African Americans than among whites, for each blood pressure group even after adjustment for baseline blood pressure and other covariates discussed in the background paragraphs and (2) the risk of progressing to hypertension (as well as the rate of change in blood pressure) is greater among individuals with diabetes mellitus than among non-diabetics, even after adjustment for baseline blood pressure and other covariates discussed in the background paragraphs.

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

ARIC cohort visit 1 blood pressure, age, race, gender, prevalence of hypertension, systolic blood pressure, diastolic blood pressure, alcohol consumption, prevalence of CHD, medication use variables, insulin, glucose, cholesterol, LDL, HDL, triglycerides, vWF, BMI, diabetic status, smoking status, physical activity level, education level, (other marker of socioeconomic status) and follow-up time.

Incident hypertension over nine years of follow-up, Visits 2-4 (according to current ARIC definitions)

Exclusions: hypertension, race other than black or white, individuals with prevalent CHD/CVD (because of the likelihood of using medications that lower blood pressure).

Analysis summary: Tests for the homogeneity of baseline characteristics among each comparison group (optimal, normal, and high-normal groups) will be performed. We will cross-tabulate hypertension status at baseline (high-normal, normal and optimal) and during follow-up (ever hypertensive during follow-up, else ever high-normal, else normal, else optimal if optimal throughout). This will ascertain only incident events (hypertensives) and provide crude overview of disease progression. The Kaplan-Meier estimates will be used to compute the cumulative incidence of hypertension, stratified according to initial blood pressure category. We will determine gender specific, and race specific cumulative incidences of hypertension. In addition, the proportionality of hazards over time will be also examined for each group. Multivariate Cox proportional hazards models will be constructed to evaluate the association between initial blood
pressure (high normal, normal and optimal) and the risk of incident hypertension, adjusting other risk factors. To minimize residual confounding, continuous blood pressure levels at baseline will be controlled in addition to the trichotomized blood pressure group. Corrections for measurement errors in baseline blood pressure (as continuous variable) and misclassification (as categorical variable) will be incorporated because it is well known that blood pressure exhibits not so high repeatability. Finally, due to serious uncertainty about the exact time of endpoint, we will repeat regression analyses using logistic regression and survival analysis suited for interval-censored data as a confirmatory purpose.

To test the equality of the rates of progression, we will try random (or mixed) effects models with blood pressures as repeated outcomes and time (allowing up to cubic terms) and starting blood pressure and blood pressure groups as covariates. Again, further corrections for measurement errors (and misclassification) will be considered.

The above analysis will be repeated in the following subgroups: African-Americans, individuals with renal insufficiency, and individuals with diabetes mellitus, and important interactions by blood pressure group will be examined.

All analyses will be done with SAS software (SAS Institute, Cary, N.C.). Two sided p-values will be used as criteria to assess statistical significance.

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 ICTDER02 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 ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html

_____ Yes  ____X__ No  See background paragraphs for potential overlap.
References


