ALLHAT-related Study Proposal Outline

Please complete the following items with as much detail as possible. The proposal length should not exceed 4 single-spaced pages, excluding table shells, questionnaires and data collection forms.

1. Title: Determinants and sequelae of visit-to-visit variability in blood pressure

2. Principal investigator and co-investigators: Paul Muntner (PI), Suzanne Oparil (Co-investigator), Donna Arnett (Co-investigator), ALLHAT CTC and Steering Committee members are invited to participate

3. Background:

The prognostic value of blood pressure is mainly based on the method of obtaining measurements in a clinic setting, typically averaged over several visits(1). Usual blood pressure, which cannot be measured with total precision, is considered to be the most important component of blood pressure(2). It is used as a marker for adverse outcomes (e.g., cardiovascular disease and end-stage renal disease) and for assessing the benefits of antihypertensive drugs. Visit-to-visit variability (VVV) of blood pressure is often dismissed as random fluctuation and is thought to be a limitation of measuring blood pressure in the office setting(3). However, data are challenging the paradigm of “usual” BP hypothesis which states that average blood pressure levels over a period of time are of primary importance in the pathogenesis of cardiovascular disease. In several recent studies, a strong association has been identified between VVV of blood pressure and the incidence of cardiovascular disease(4-7). Additionally, recent evidence suggests that VVV of blood pressure is reproducible and not a random phenomenon(8).

Few data are available on risk factors for high VVV of blood pressure(2). Given its strong association with adverse outcomes, there is a need to better understand the correlates of VVV. Many of the studies of VVV of blood pressure have been conducted in white populations(4). Few published data are available on VVV of blood pressure in African-Americans and Hispanics, groups with usual higher blood pressure levels in the general US population(9). Also, many patients do not take their antihypertensive medications as prescribed and these individuals are at increased risk for uncontrolled hypertension and cardiovascular disease(10-12). It seems plausible that low medication adherence may lead to higher levels of VVV of blood pressure. One proposed mechanism for increased VVV of blood pressure is arterial stiffness(13;14). The association of genotypes with mean blood pressure levels and arterial stiffness has been evaluated in several prior studies(15;16). However, genetic factors associated with VVV of blood pressure are less well studied.

The aim of the proposed study is to examine determinants of VVV of BP as well as outcomes associated with higher levels of VVV of blood pressure among participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT was large, double-blind, randomized controlled trial designed to determine whether cardiovascular disease incidence and mortality differed between persons randomized to take a diuretic-based (represented by chlorthalidone) anti-hypertensive drug regimen compared to regimens based on drugs from three alternative classes: a calcium channel blockers (amlodipine), an ACE inhibitors (lisinopril), and an alpha adrenergic blocker (doxazosin)(17).
total of 42,418 study participants were recruited at 623 clinical sites across the United States and Canada between February 1994 and January 1998. Overall, there was no difference in the primary outcome of interest (fatal coronary heart disease and non-fatal myocardial infarction) but the incidence of heart failure was lower in the diuretic group compared to the calcium channel blocker and ACE inhibitor groups and the incidence of stroke and a combined cardiovascular disease outcome were lower in the diuretic group compared to the ACE inhibitor group(18). ALLHAT provides a unique setting with standardized blood pressure measurements at set time periods as well as data on the frequency of missing antihypertensive medication doses, genotypes, and rigorous collection of outcomes over a long follow-up period.

4. Objectives

- To evaluate the effects of (1) Race-ethnicity, (2) Different antihypertensive medication drug classes, (3) Missing antihypertensive medication doses, and (4) Genetic profiles on VVV in blood pressure.
- To determine the relationship between VVV in blood pressure and CHD, stroke and ESRD.
- To conduct mediation analyses to determine whether higher VVV in blood pressure explains the association between antihypertensive medication class, medication adherence, race-ethnicity, and genetics and outcomes including CHD, stroke and ESRD.

5. Methods

A. Participants in the analysis (inclusion and exclusion criteria):

All ALLHAT participants with blood pressure measurements from study visits conducted 3, 6, 9 and 12 months following randomization will be included in the proposed analysis. Participants who withdrew from the study prior to the 12 month study visit will be excluded. Additionally, for the analysis of outcomes, individuals who have a CHD, stroke or ESRD event prior to their 12 month study visit will be excluded.

B. Participating clinical centers

Participants from all clinical centers will be included in the analyses. No new data are being collected and this study relies on data collected as part of the main ALLHAT study. As described in detail below, all of the data to be analyzed reside with the CTC. Therefore, there will be no additional burden on the clinical centers resulting from the proposed study. Participants from all clinical centers will be included in the analyses. No new data are being collected and this study relies on data collected as part of the main ALLHAT study. As described in detail below, all of the data to be analyzed reside with the CTC. Therefore, there will be no additional burden on the clinical centers resulting from the proposed study.

C. Procedures for and timing of supplementary data collection if any (laboratory studies, outcomes)

No supplementary data are being collected for the proposed ancillary study.

D. ALLHAT variables needed for ALLHAT-related study (including baseline, follow-up and outcomes data)

The following variables are being requested for the proposed analyses:
Age, race, sex, education history of cardiovascular disease, diabetes, LDL-cholesterol, HDL-cholesterol, left ventricular hypertrophy, body mass index, estimated glomerular filtration rate, aspirin use, estrogen use (all from baseline), randomization assignment for both the blood pressure and statin trials of ALLHAT, additional blood pressure lowering drugs being taken by ALLHAT participants during follow-up, blood pressure measurements at baseline, 3, 6, 9 and 12 months post-randomization, medication adherence data at visits conducted at 3, 6, 9 and 12 months post-randomization, clinical outcomes (coronary heart disease, stroke and end-stage renal disease and date of event). Additionally, we request use of genotype data from GENHAT from the 43 variants genotyped in the full GenHAT cohort.

E. Table shells (append)

Due to the large number of analyses proposed in this grant proposal, we have not prepared table shells. Table shells for analyses will be provided as requested.

F. Statistical analysis, sample size calculation and location of ALLHAT-related study analysis (local vs. CC)

We request that the analyses be performed at the University of Alabama at Birmingham. Given the large sample size and long term follow up of ALLHAT participants, statistical power is available to detect small but clinically important effect sizes for the current analyses. For example, assuming a CHD event rate of 1.35% per year (per the ALLHAT study protocol) and 12 years of follow-up data for outcomes, with 40,000 ALLHAT study participants, we will have 90% statistical power to detect a hazard ratio for mortality of 1.12 comparing the highest to lowest quintile of VVV of blood pressure. For ESRD, a less common outcome, we assumed a 0.125% annual event rate and will have 90% statistical power to detect a hazard ratio of 1.42 comparing the highest to lowest quintile of VVV. For studies of the determinants of VVV in blood pressure, we will be able to detect small differences in VVV. As an example, we calculated the minimal detectable difference in VVV in blood pressure for individuals deemed to be not adherent versus their counterparts who are adherent to antihypertensive medication during follow-up. We assumed that 5% of ALLHAT participants were not adherent to their antihypertensive medication regimen (e.g., 5% took <90% of their prescribed doses) during the initial 12 months post-randomization - statistical power will be available to detect small differences if a higher percentage of participants were not adherent. Assuming the within-person across study visit standard deviation for VVV is 14 mmHg, 90% statistical power is available to detect a difference in VVV of 1.1 mmHg. Statistical power will be available to detect similarly small VVV in blood pressure differences by race/ethnicity and genotype. Finally, as a substantial number of ALLHAT participants received step two or three medications (or other antihypertensive medications) during the first year of follow-up (18;19), analyses of drug classes and change in VVV in blood pressure will be evaluated for all participants as well as those remaining on monotherapy through the initial year following randomization. Statistical power of 90% will be available to detect a difference in VVV of 0.9 mmHg comparing participants on monotherapy with Lisinopril or Chlorthalidone (or Chlorthalidone versus Amlodipine or Lisinopril versus Amlodipine).

7. Expected Conclusions

Based on the work of Rothwell, we anticipate that higher levels of VVV in blood pressure will be associated with increased rates of stroke(7). Fewer data are available on the effects of
VVV in blood pressure on CHD and ESRD incidence. Nonetheless, given the proposed mechanisms for VVV of blood pressure on stroke, it is plausible to expect that higher VVV will be associated with increased risk for CHD and ESRD. Missing doses of antihypertensive medication is associated with an increased risk for stroke and mortality. We hypothesize that low adherence, defined by missing antihypertensive medication doses, will result in blood pressure fluctuations and higher VVV in blood pressure. Additionally, given proposed mechanisms underlying higher levels of VVV of blood pressure, we expect African-Americans to have higher VVV of blood pressure. Finally, to our knowledge, there are no data examining the genetic underpinnings of VVV in blood pressure. While VVV in blood pressure may be partially explained by age and environmental factors, there may also be a genetic component. We hypothesize that certain genotypes associated with blood pressure levels will be associated with VVV in blood pressure(20). These genotypes will provide insight into the mechanisms underlying high levels of VVV in blood pressure.

8. References


(2) Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010; 375(9718):938-948.


9. Feasibility of the study

A. Required assistance from the CTC

Although Drs. Muntner, Oparil and Arnett are quite familiar with ALLHAT and GENHAT, we plan to collaborate with members of the CTC to conduct the proposed study. Effort from the CTC will include coordinating activities, data manuscript and support for the data analysis. As noted below, through grant funding, the CTC will be reimbursed for their effort

B. Confidentiality and other human subjects issues

This study involves secondary analysis of data collected for ALLHAT. All of the data to be
analyzed reside at the CTC. Furthermore, all data are de-identified. Therefore, we anticipate no informed consent/human subject issues.

C. Anticipated impact on ALLHAT participants, clinics, and labs

None – as no new data will be collected we anticipate no impact on participants/clinics.

11. Cost estimate and proposed funding mechanism (include date of planned submission and expected review date)

We propose submitting an R01 grant application to NHLBI for funding. We will work with the CTC to address the statistical and administrative costs associated with the proposed analyses. These costs will be covered in the R01 grant. We anticipate a grant submission for October 2010 with a planned review in February 2011.

Please submit completed proposals to:
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