1. Title:

Antihypertensive therapy and the risk of carotid intimal-medial thickness progression: the Atherosclerosis Risk in Communities (ARIC) Study

2. Writing Group:

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3. Timeline:

May begin immediately upon approval.

4. Rationale:

Clinical trials of antihypertensive therapy have demonstrated a reduction in stroke, particularly among older individuals with isolated systolic hypertension.\textsuperscript{1-4} The mechanism for this reduction is likely multifactorial, including a reduction in blood pressure. However, some have suggested that antihypertensive medications may have properties that reduce atherosclerosis, and hence stroke, through mechanisms other than lowering blood pressure.\textsuperscript{5}

In the rat model, angiotensin converting enzyme inhibitors and t-type calcium channel antagonists have been demonstrated to decrease neointimal formation in the carotid artery after vascular endothelial injury.\textsuperscript{6-8} Investigation of humans with carotid atherosclerosis searching for disruption in laminar blood flow, a possible precursor to endothelial injury, have found that the beta-blocker metoprolol improves laminar flow significantly through its effects on heart rate, while nifedipine causes disruption of laminar flow by increasing heart rate.\textsuperscript{9}

With the advent of B mode carotid ultrasonography, evaluation of the intermediary for stroke, carotid intimal-medial wall thickness, is easy to perform. This method of carotid wall assessment is safe and has proven reliability.\textsuperscript{10} With this technique, some clinical trials of antihypertensive therapy have examined the relationship between intimal-medial wall thickness and antihypertensive agents.\textsuperscript{11-15}
Results of completed clinical trials have revealed mixed results, likely a result of different study populations, protocols, duration, and study medication. A substudy from The Systolic Hypertension in the Elderly Program (SHEP) revealed significantly higher rate of carotid intimal-medial wall progression in the control group compared to those on active treatment (31% vs. 14% progression; p=0.02). In a study of diabetics randomized to the angiotensin converting enzyme inhibitor fosinopril, carotid intimal-medial wall progression was again significantly less in the treated group (4.3% in treated vs. 15.1%). This again was demonstrated in the Verapamil in Hypertension and Atherosclerosis Study (VHAS) when both treatment with verapamil and chlorthalidone caused regression of carotid intimal-medial wall thickness, with significantly greater reduction in wall thickness by verapamil. However, in the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS), no difference was found between isradipine and hydrochlorothiazide for carotid intimal-medial wall progression.

To our knowledge, no prospective cohort study to date has examined the relationship between antihypertensive therapy and carotid intimal-medial wall progression. Compared to clinical trials, performing a cohort study is important for several reasons. First, external validity would be superior for a population-based sample compared to previous and ongoing clinical trials. Second, multiple antihypertensive classes could be examined in this relationship. Third, subgroups could possibly be identified that may particularly benefit from a certain medication class.

5. **Main Hypotheses:**

   a) Among hypertensive individuals, antihypertensive therapy is associated with a slower progression or perhaps regression of carotid intimal-medial wall thickness.
   
   b) After adjustment for blood pressure, changes in carotid intimal-medial wall thickness will differ by antihypertensive medication class.

6. **Design:**

   Prospective cohort study of hypertensive individuals (N=3,804), examining for carotid artery intimal-medial wall progression over 3 years of follow-up.

7. **Data:**

   Baseline variables will include age, race, sex, education, blood pressure, waist-to-hip ratio, BMI, smoking, alcohol use, HDL, LDL, triglycerides, diabetes, antihypertensive medication class (ACE inhibitor, beta-blocker, calcium channel antagonist, and thiazide diuretic), antihyperlipidemic medications, and carotid intimal-medial wall thickness. Follow-up data will include visit 2 carotid intimal-medial wall thickness. Secondary outcome measures will include transient ischemic attack and stroke.
8. **Main analysis:**

Multiple linear regression analysis with change in carotid intimal-medial wall thickness as the outcome and antihypertensive medication class as the independent variables of interest. Difficulties with baseline medication data include duration of medication use, changes in therapy, and multiple medication use. We will attempt to address duration of use and changes in therapy by using visit 2 as baseline and assessing initiation and changes of antihypertensive medication from visit 1. To address the issue of multiple medication use, we will examine the relationship initially using monotherapy categories, therefore eliminating the effect of other potential antihypertensive medications. We will perform other analyses adjusting for other antihypertensive medications. Other known medications that may impact on intimal-medial wall thickness, such as antihyperlipidemic medications, will be included in the analyses. Secondary analyses of transient ischemic attack and stroke will be performed by multiple logistic regression using the same models as in the multiple linear regression analysis.

**Reference List**


