1. Full Title:  Angiotensinogen promotor polymorphism predicts the occurrence of atherosclerosis, PAD and Incident CHD and stroke.
   Abbreviated Title:  AGT-6 and ischemia

2. Writing Group:
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3. Timeline:
   Measurement of the AGT-6 promotor polymorphism is complete in all groups accept the stroke cases and controls. Measurement of the AGT-6 polymorphism will be carried out following distribution of the stroke case/control lists. I hope to have a draft manuscript for internal circulation by January, 1999.

4. Rationale:
   Angiotensinogen is the source of the vasoactive hormone angiotensin 11, the core effector molecule of the renin-angiotensin system. Inoue et al (JCI 99: 17861797, 1997) reported a polymorphism in the angiotensinogen gene promotor (position 6 from the transcription start site) that is associated with altered angiotensinogen levels and essential hypertension. Detailed in vitro transcription assays demonstrated that the polymorphism effects AGT promotor function. To our knowledge there are no published reports of the association between the AGT -6 promotor polymorphism and atherosclerosis or CHD. Therefore, we propose to determine the association of the AGT -6 promotor polymorphism with various ischemic diseases using the ARIC study's "simultaneous batch" and stroke case/control groups.

5. Main Issues/Hypotheses to be addressed:
   a) Ability of the AGT -6 promotor polymorphism to predict carotid artery disease case status (as measured by wall thickness), both individually and after considering the predictive ability of traditional risk factors, especially blood pressure and essential hypertension. Note: Inclusion of the Black supplement
   b) Ability of the AGT -6 promotor polymorphism to predict PAD case status (as measured by a reduced ankle-arm index), both individually and after considering the predictive ability of traditional risk factors, especially blood pressure and essential hypertension.
   c) Ability of the AGT-6 promotor polymorphism to predict incident CHD case status, both individually and after considering the predictive ability of traditional risk factors, especially blood pressure and essential hypertension.
   d) Ability of the AGT -6 promotor polymorphism to predict incident stroke case status, both individually and
after considering the predictive ability of traditional risk factors, especially blood pressure and essential hypertension. Subgroup analyses will consider both subclinical and clinical stroke, and stroke subtypes.

6. Data:
ARIC’s incident CHD cases, PAD cases and carotid disease cases will be compared to the synthetic cohort random sample. The stroke cases will be compared to the stroke controls. Obviously, the primary dependent variables are case statuses. Independent variables include, but are not limited to the AGT -6 promotor polymorphism and the vector of traditional risk factors, such as age, sex, BMI, plasma lipids, hypertension status, etc.