Manuscript #587

1. Title: RAS Polymorphisms and Arterial Stiffness
   Short Title: RAS Polymorphisms and Arterial Stiffness

2. Writing group:
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3. Main Study Questions:
   Are indices of arterial stiffness associated with ACE I/D and AGT1-R A  C
   polymorphisms at the population level?

4. Hypotheses:
   1) Individuals with the AGT1-R CC or AC genotypes have stiffer carotid arteries
      compared to individuals with the AA genotype.
   2) Individuals with the ACE DD or ID genotypes have stiffer carotid arteries compared to
      individuals with the II genotype.
   3) These associations are not modified by the interaction of these two polymorphisms.
   4) These associations are not modified by the use of ACE inhibitor preparations.

5. Analytic Approach:
   The cohort representative sample described in MS proposal 1 and their genotype data will
   be used as the comparison group for this manuscript. The arterial stiffness will be
   measured as pressure adjusted carotid arterial diameter change during cardiac cycles, as
   proposed for the ARIC study. These individuals will also be classified dichotomously as
   having stiffer carotid arteries or less stiffer arteries using a cut point correspondent to 5th
   percentile of the arterial diameter change distribution generated from the entire ARIC
   cohort participants.

   All cohort members with pressure adjusted diameter change below the 5th percentile cut
   point will be identified as cases with stiffer carotid arteries. In this process about 500
   cases will be identified. The genotypes (ACE DD, X, and ID, AGT1-R CC, AC, AA) for
   these individuals will be identified.

   A standard case-cohort analysis approach will be used to test the hypotheses listed above.
   Logistic regression models will be used to estimate the association, and the effects will be
   expressed as odds ratio and 95% CI. In the cohort representative sample, the associations
   between the two polymorphisms and the continuously measured blood pressure adjusted
   arterial stiffness will be examined to investigate the pattern of associations. The
interaction of these two polymorphisms will be tested. The interaction of ACE inhibitor usage with each of these two polymorphisms will be tested.

Other covariates to be controlled for include age, ethnicity/center, sex, education levels, conventional CVD risk factors, diabetes, and hypertension.