Manuscript #589

1. Title: RAS Polymorphisms and the Progression of Atherosclerosis  
   Short Title: RAS polymorphisms and IMT progression

2. Writing Group:  
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3. Main Study Questions:  
   Is progression of atherosclerosis, defined by the progression of B-mode ultrasound  
   measured IXT over 6-9 years of follow-up, associated with ACE I/D and AGT1-R A/C  
   polymorphisms?

4. Hypotheses:  
   1) Individuals with AGT1-R CC or AC genotypes have an increased progression of  
      carotid IMT than carriers of the homozygous AA carriers  
   2) Individuals with ACE DD or ID genotypes have an increased rate of progression of  
      carotid IMT compared to carriers of the II allele.  
   3) In individuals who carry the AGT1-R A/C genotype (CC or AC), the presence of the  
      ACE DD or ID genotypes is associated with an increased risk of  
      atherosclerosis progression, but not in carriers of the AA genotype of AGT1-R.

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 progression of  
   atherosclerosis will be measured as visit specific residual change IMT adjusted for the  
   baseline and time. These individuals will also be classified dichotomously as having  
   severe progression of atherosclerosis if the follow-up visit specific adjusted residual IMT  
   was (2) standard deviation above the predicted IMT at any follow-up visits; or less  
   progression of atherosclerosis for persons not meet the criteria described here. A working  
   definition will be developed in collaboration with Drs. Heiss and Chambless.  

   For all cohort members, server progression of IMT cases will be identified by comparing  
   the follow-up visit specific adjusted residual NT to the visit specific predicted IMT. At  
   any follow-up visit, if an individual's adjusted residual IMT becomes greater than or  
   equal to 2 standard deviation of the predicted IMT at the visit, she or he will be identified  
   as a case. In this process about 500 cases will be identified. The genotypes (ACE DD, ID,  
   and II, 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. Proportional hazards models will be used to estimate the association, and the effects will be expressed as Hazards Ratio and 95% CI. In the cohort representative sample, the associations between the two polymorphisms and the continuously measured IMT and IMT progression will be examined to investigate the pattern of associations. The interaction of these two polymorphisms will be tested.

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