Manuscript #590

1. Title: RAS Polymorphisms and the Development of LEAD  
   Short Title: RAS polymorphisms and LEAD

2. Writing Group:  
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3. Main Study Questions:  
   Is the risk of incident LEAD, measured by ABI changed from > 0.9 to < 0.90 after an  
   average of 7.5 years of follow-up, associated with ACE I/D and AGT1-R A-C  
   polymorphisms?

4. Hypotheses:  
   1) Individuals with the ACE DD or ID genotypes are more likely to develop incident  
      LEAD compared to carriers of the n allele  
   2) Individuals with the AGT1-R CC or AC genotypes are more likely to develop incident  
      LEAD than carriers of the AA 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  
      developing LEAD, but not in carriers of the AA genotype of AGT1-R.

5. Analytic Approach:  
   The cohort representative sample described in MS proposal land their genotype data will  
   be used as the comparison group for this manuscript. The lower extremity arterial  
   atherosclerosis will be measured as ankle and brachial systolic blood pressure ratio  
   (ABI). Persons with baseline ABI S 0.90, indicative of prevalent LEAD, will be excluded  
   from this comparison group during the analysis for this manuscript (not for others). The  
   ABI value S 0.90 at either Visit 3 or Visit 4 will be used to identify persons who become  
   an incident LEAD in this group.

   All baseline LEAD free (ABI > 0.90) cohort participants who had at least one ABI  
   measure during either Visit 3 or Visit 4 will be the pool for the incident LEAD cases.  
   From this cohort, participants who had follow-up ABI measure < 0.9 in either Visit 3 or  
   Visit 4 will be identified as incident cases. In this process, we anticipate to identify 500  
   cases of incident LEAD from the entire cohort. The genotypes (ACE DD, ID, and 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 model will be used to estimate the association, and the effects will
be expressed as Hazards Ratio and 95% CI. The interaction of these two polymorphisms will be tested.

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