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

2. Writing group:
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3. Main Study Questions:
   Do ACE I/D and AGT1-R A C polymorphisms interact with each other in the
development of incident CHD over 6 years of follow-up?

4. Hypotheses:
   1) Individuals with the AGT1-R CC or AC genotypes have an increased risk of
developing incident CHD.
   2) Individuals with the ACE DD or ID genotypes have an increased risk of developing
   incident CHD.
   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 CHD, but not in carriers of the AA genotype of AGT1-R.

5. Analytic Approach:
The ARIC official cohort representative sample (n=985) selected for the purpose of a
series of case-cohort studies and special assays will be used as the comparison group for
all the manuscripts focus on the ACE VD and AGT1-R polymorphisms. Their incident
CHD status will be identified.
All cohort participants identified as incident CHD (using the ARIC criteria, including
procedures and “silent MI by ECG) will be included into the "incident CHD case" group.
The surveillance data for the cohort member up to 1997 will be used to identify these
cases.

The genotypes (ACE DD, ID, and IL AGT1-R CC, AC, AA) for these individuals will be
identified.

Note: Genotype of ACE I/D polymorphism has been performed on the cohort
representative sample and individuals who developed incident CHD up to
1993. For these participants, only the AGTI-R A C polymorphism needs to be assessed.

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. The interaction 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, blood pressure and hypertension.