1. Full Title: Association of prothrombin gene variant (nt20210a) with risk of CHD: the ARIC Study
   Abbreviated Title (Length 26): Prothrombin polymorphism and MI

2. Writing Group (list individual with lead responsibility first):
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3. Timeline:
   Measurement of PROTHROMBIN gene polymorphism is in progress in the ARIC CRS and CHD incident events as approved by the CC.
   Preliminary analysis 07/98
   Manuscript preparation 09/98
   Circulation to co-authors 10/98
   Submission to journal 11/98

4. Rationale:
   A number of genetic risk factors for the development of CHD has been identified in the past. Some of these represent polymorphism in genes of proteins that are associated with the process of blood clotting (1-4). Recently, it has been shown that a polymorphism in the 3’ untranslated region of the gene coding for human prothrombin (G or A at nt20210) leads to elevated plasma prothrombin levels and is associated with an increased risk of venous thromboembolism (5). Prothrombin is the precursor protein of the serine protease thrombin, which is the main enzyme in the blood clotting cascade (6) and a potent activator of platelets. In addition, it has been shown that thrombin acts as a potent mitogen leading to propagation of atherosclerosis and thus might very well be involved not only in venous but also in arterial thrombosis.
Although the majority of reports agree that the heterozygous prothrombin genotype is associated with venous thrombosis, Arruda et al (7) recently reported the increased prevalence of mutated allele in a small selected arterial disease group when compared to controls and Watzke et al (8) showed increased prevalence in 98 patients with CHD compared to healthy newborns. On the contrary, Ferraresi et al (9) found no association with artery disease. Since data are still controversial and keeping in mind the crucial position of thrombin in the hemostatic system we believe that it deserve further investigation and that ARIC provides a opportunity to addressing this question. At present, it is unknown what impact G2021 OA substitution has on prothrombin function, but the possibility that polymorphism is an additional predictor of early MI deserves investigation. We propose to determine the frequency of prothrombin gene variant (nt20210A) in the ARIC CHD cases and cohort random samples and its association with incident MI cases.

5. Main Hypothesis:
Presence of 20210 A allele of the prothrombin gene is associated with an increased risk for incident CHD.

6. Data (variables, time window, source, inclusions/exclusions):
Data will be sent to the CC and also analyzed locally by Dr Chul Ahn, with supervision from the CC.

REFERENCES:
8. Wat_ke HH, Schuttrumpf J, Graf S et al. Increased prevalence of a polymorphism in
the gene coding for human prothrombin in patients with coronary heart
genotype is associated with early venous thrombosis in inherited
thrombophilias and is not increased in frequency in artery disease. Arterioscler Thromb
Vasc Biol 1997;17:2418-2422.