1.a. Full Title: Anger proneness and markers of hemostatic function: Possible mechanisms for cardiovascular disease

b. Abbreviated Title (Length 26 characters): Anger and hemostatic function

2. Writing Group (list individual with lead responsibility first):
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3. Timeline:
   Data analyses completed: August 2001
   Manuscript to ARIC Publications/Steering Committee: December 2001
   Manuscript to journal: February 2002

4. Rationale: Studies in ARIC and elsewhere have reported a positive association between anger/hostility and coronary heart disease (CHD) (1-3), but the biologic mechanisms mediating this link are yet to be clarified. It is hypothesized that anger (a variant of psychological stress) may exert influence on CHD via an atherosclerotic or a thrombotic process (4, 3, 5). The potential role of the thrombotic process is the focus of the proposed analyses. The physiologic sequelae of anger that directly affects the cardiovascular system is the response of the sympathetic-adrenomedullary axis. Catecholamine secretion in response to heightened sympathetic arousal can “trigger” thrombosis by setting in motion a process that begins with plaque fissuring and ends in an occlusive thrombus (6-9). Three biochemical processes that are responsible for blood clotting include platelet adhesion and aggregation, plasma coagulation, and fibrin formation. The objective of the proposed study is to evaluate the contribution of these markers of hemostatic function to the anger-CHD association. The results may provide insight into the potential of the thrombotic process as a mediator of the anger-CHD link.
5. **Main Hypothesis/Study Questions:**

1) Each of the markers of hemostatic function (platelet activation, as measured by beta-thromboglobulin, platelet factor 4, and serum thromboxane B2; plasma coagulation, as measured by fibrinogen, Factor VII, Factor VIII, and von Willebrand factor antigen; and fibrinolytic activity, as measured by tissue plasminogen activator antigen) is significantly associated with the anger-CHD association, and suggests a mediating role.

**Analytic strategy:**
The study hypothesis will be tested using Cox regression analysis in which time to CHD event will be modeled as a function of trait anger. Change in the estimate criteria (comparing hazard ratios for anger with and without the hemostatic variable) will be used to evaluate the contribution of each hemostatic variable to the anger-CHD relation. Formal tests of interaction for age, race/ethnicity, sex, hypertension, diabetes, smoking, and aspirin use will be conducted.

6. **Data (variables, time window, source, inclusions/exclusions):**
- **Visit 1 variables:** prevalent CHD, race, sex, educational level, von Willebrand factor antigen, Factor VII, Factor VIII;
- **Case-control data:** fibrinopeptide A, beta-thromboglobulin, platelet factor 4, serum thromboxane B2, and tissue plasminogen activator antigen;
- **Visit 2 variables:** Spielberger Trait Anger Scale, age, aspirin use;
- **Events data:** CHD events through 1997.

While trait anger and the hemostasis variables were measured at different times, the proposed analyses are justified based on the definition of trait anger as a stable, enduring predisposition to experience frequent and intense anger.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes ___X__ No

b. If Yes, is the author aware that the file 1CTDER01 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ___ Yes ___ No

c. Will the DNA data be used in this manuscript? ___ Yes ___X__ No

d. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ___ Yes ___ No

**Literature Cited**


