Note to the Publications Committee: This proposal was originally submitted 09/10/03 and was approved by the Publications and Steering Committee as a priority 2. The author has resubmitted the proposal in response to your recommendations. Specifically, the ankle-brachial index values for diagnosis are revised in hypothesis one, as suggested by the committee. For review on the 11/21/03 Conference Call.

ARIC Manuscript Proposal # 962

1.a. Full Title: A cross-sectional evaluation of ankle-brachial index and hemostatic markers from the Atherosclerosis Risk in Communities Study cohort.

b. Abbreviated Title (Length 26 characters):

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

Analysis to begin August, 2003 with manuscript submission by October, 2003

4. Rationale:

Peripheral arterial disease (PAD) is a prevalent manifestation of atherosclerosis that affects the arterial supply to the lower extremities. PAD is easily diagnosed by a decreased ankle-brachial index (ABI), and is associated with leg symptoms in approximately half of the 8 to 12 million Americans who suffer from this disease.

PAD not only causes significant reductions in quality of life through impairment of ambulatory function, it is also associated with a significantly higher mortality rate due to systemic ischemic events, such as myocardial infarction and stroke. The pathologic lesion associated with PAD, the atherosclerotic plaque, is the same as that associated with coronary artery disease (CAD) and cerebrovascular disease (CVD). In active atherosclerotic lesions that lead to acute ischemic events, the pathologic process involves endothelial damage, inflammatory mediation, rupture of a weakened fibrotic cap leading to exposure of underlying intima and thrombogenic proteins, activation of hemostatic factors, and formation of a thrombus over the ruptured plaque.

Previous investigations have demonstrated that elevations of hemostatic markers, specifically von Willebrand factor, fibrinogen, and factor VIII, predict the presence of underlying CAD (1,2,3,4). They also predict an increased risk of future cardiac ischemic events and ischemic stroke. One study found that individuals with unstable angina had the greatest elevations in these markers, those with stable angina had lesser elevations, and those with asymptomatic CAD had the lowest marker levels (5). Prospective investigation in the ARIC study also

demonstrated this association and found that these hemostatic factors are markers of increased risk for cardiac and cerebral ischemic events (6,7).

Less investigation has been performed to evaluate the role that these hemostatic markers might play in individuals with PAD. The Edinburgh Artery Study showed an independent association between elevated fibrinogen and decreased ABI (8). The ADMIT trial also showed a correlation between these two variables (9). Little work has been done with vWF, factor VIII activity, or factor VII activity and PAD. Less investigation has been done concerning levels of C-reactive protein (CRP), tPA antigen, plasminogen activator inhibitor (PAI-1), D-dimer, beta-thromboglobulin, and soluble thrombomodulin (STM) and PAD.

Because PAD, CVD, and CAD are different clinical manifestations of the same disease process, it would be reasonable to assume that these hemostatic markers are elevated in individuals with decreased ABI's, and that there may be a step-wise relationship between low ABI values and hemostatic marker elevation. It could also be conjectured that individuals with claudication demonstrate greater marker elevation than individuals with asymptomatic PAD. ARIC measured several hemostatic factors at baseline or in a case-cohort subset but these data have not yet been analyzed.

References

1. Assman G, Cullen P, Heinrich J, Schulte H. Hemostatic variables in the prediction of coronary risk: results of the 8 year follow-up of healthy men in the Munster Heart Study (PROCAM). Prospective Cardiovascular Munster Study. *Israel J Med Sci.* 1996;32:364-370.
2. Jansson JH, Nilsson TK, Johnson O. von Willebrand factor in plasma: a novel risk factor for recurrent MI and death. *Br Heart J.* 1991;66:351-355.
3. Thompson SG, Kienast J, Pyke SDM, et al. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med.* 1995;332:635-641.
4. Wilhelmsen L, Svardsudd K, Korsan-Bengtsen K, et al. Fibrinogen as a risk factor for stroke and MI. *N Engl J Med.* 1984;311:501-505.
5. Bogaty P, Poirier P, Simard S, et al. Biological profiles in subjects with recurrent acute coronary events compared with subjects with long-standing stable angina. *Circulation.* 2001;103:3062-3068.
6. Folsom AR, Rosamund WD, Shahar E, et al. Prospective study of markers of hemostatic function with risk of ischemic stroke. *Circulation.* 1999;100:736-742.
7. Folsom AR, Wu KK, Rosamund WD, et al. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 1997;96:1102-1108.
8. Lowe GD, Fowkes FG, Dawes J, et al. Blood viscosity, fibrinogen, and activation of coagulation and leukocytes in peripheral arterial disease and the normal population in the Edinburgh Artery Study. *Circulation.* 1993;87:1915-1920.
9. Philipp CS, Cisar LA, Kim HC, et al. Association of hemostatic factors with peripheral vascular disease. *Am Heart J.* 1997;134:978-984.

5. Main Hypothesis/Study Questions:

1. To determine whether in the entire baseline sample, elevations in hemostatic factors (fibrinogen, von Willebrand factor, factor VIII activity, factor VII activity, and WBC count) are associated with decreased ankle-brachial index (<.90 in men, 0.85 in women), and to determine whether there is a dose response between hemostatic marker elevation and decreasing ABI.
2. To determine in the ARIC case-cohort sample whether BTG, CRP, tPA antigen, D-dimer, PAI-1, and STM are elevated in individuals with decreased ankle-brachial indices, and to determine whether there is a dose response between hemostatic factor levels and reduced ABI.

6. Data (variables, time window, source, inclusions/exclusions):

Inclusion: For hypothesis 1, we will use the full ARIC data set. For hypothesis 2, we will use the PAD case-cohort sample.

Exclusion: We plan to exclude participants with prevalent CHD or stroke, and people on anticoagulant medications (warfarin, heparin, etc.).

Covariates: Age, gender, race, smoking status and amount, waist to hip ratio, LDL, HDL, SBP, diabetes, blood pressure medications

Analysis: The primary measure of association will be the odds ratio looking at the diagnosis of PAD. For hypothesis 1, routine logistic regression will be used, with and without covariates. Dose-response examination will use mean hemostatic factors across levels of ABI (or vice-versa, prevalence of low ABI across quartiles of hemostatic factors). Analysis of hypothesis 2 will involve case-cohort sample weightings to compute odds ratios. Dose-response in odds ratios will be examined across quartiles of hemostatic factors.

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 ICTDER02 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
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

____X_ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

There are no known overlapping manuscript proposals. The laboratory committee requested that this paper be written.

11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.