ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #325

1. Title: Lower Extremity Arterial Disease as an Independent Predictor of Incident Coronary Heart Disease

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3. Timeline:

July - October, 1995:	Initiation and completion of statistical analyses
October, 1995 - January, 1996:	Preparation of manuscript

4. Rationale:

The presence of lower extremity arterial disease (LEAD) has been shown in several studies to be a sentinel for total and cardiovascular mortality. Intermittent claudication (IC), the symptomatic expression of lower extremity arterial disease, is associated with a twofold to fourfold increase in mortality risk (1-8) and in incidence of fatal and non-fatal stroke (9). In studies using non-invasive methods to measure presence of pre-clinical LEAD, such as those using low ankle-brachial index (ABI) or venous occlusicmn plethysmography, relative risks between 2.5 and 6.6 have been reported for all-cause and coronary heart disease mortality (2,10-16). There is less information available on risk of CHD morbidity, though in a preliminary report describing hypertensive men and women, low ABI was associated with a doubling in risk in incident coronary heart disease morbidity and mortality, and a relative risk of 2.5 in cardiovascularfatal and nonfatal events (13).

Because many of the studies above were comprised of highly selected participants, such as persons referred to non-invasive laboratories for testing for LEAD (10,12,15), hypertensives (13), and women 65 years of age or older (11), the generalizability of these results to middle-aged populations is at issue.

5. Purpose:

The purposes of this study are to: (1) determine whether there is an association between baseline LEAD, defined by low ABI, and incident (fatal and non-fatal) CHD in the ARIC population; (2) explore the LEAD-incident CHD association using ABI values on an interval or continuous scale; and (3) determine whether LEAD is associated with all-cause mortality, and if so, describe the association in relation to the incident CHD mortality/LEAD association.

6. Data:

a) Exposure variable: Visit 1 ankle-brachial index
b) Outcome variables: Incident fatal and non-fatal coronary heart disease; All-cause mortality; Incident cases of symptomatic CHD, such as angioplasty, coronary
artery bypass graft surgery, Rose Questionnaire angina, "Silent" MI detected by ECG
c) Co-variables as possible confounders or effect modifiers, also at visit 1: Gender, race, center, triglycerides, waist-to-hip ratio, measures of socio-economic
status
d) Risk factors common to both CHD and LEAD: age, smoking, hypertension, cholesterol, diabetes, body

mass index

7. Analysis strategy:

Survival analysis (life table and/or Kaplan-Meier methodology) will be used to compare those with and without baseline LEAD, using ABI as a marker of LEAD. In addition, the survival experience along the range of low ABI, from very low, indicating severe disease, to values indicating moderate and mild disease will be examined. Proportional hazards assumptions will be examined, and if appropriate, Cox models will be constructed to consider covariates.

8. Feasibility:
An issue may be whether there are currently enough incident, fatal and nonfatal, CHD events. The formula below comparing two binomial proportions from two independent samples can be used to estimate power.

**Note: Statistical Formulas and tablesnot available on the web. Please contact the ARIC Student Assistant at the Collaborative Studies Coordinating Center (Phone: 919-962-3268) for a faxed copy of the formulas and tables.

There is adequate power (84%) to observe at least a 2.5-fold difference in those with and without LEAD using a minimum of 200 incident events, an estimate of the current number of CHD events in ARIC. Based on the large relative risks observed in earlier studies, with the caveat that several populations were highly selected, the current study seems feasible. Examination of this association based on ABI as a continuous variable is likely to have equivalent or greater power.