ARIC Manuscript Proposal #1708

PC Reviewed: 10/12/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Anthropometric measures of the calf for the assessment of incident CHD risk in the ARIC study

b. Abbreviated Title (Length 26 characters): **Calf measures, risk assessment**

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _GB_ **[please confirm with your initials electronically or in writing]**

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3. **Timeline**: Analysis to start as soon as approval obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the analysis and manuscript preparation will take place within one year from approval of the proposal.

4. **Rationale**: Anthropometric measures of the waist and hip are inexpensive to obtain and yet strongly associated with cardiovascular risk factors and with incident CHD events. According to the Adult Treatment Panel III (ATP III) released by the National Cholesterol Education Program, waist circumference (WC) is one of five screening variables to identify patients with metabolic syndrome (MS). The ATP III guidelines clearly favor WC over body mass index (BMI) which highlights the central importance of abdominal obesity for MS. However, WC cutoff points differ significantly with ethnicity and gender suggesting that ratios may be preferable. The results of the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study indicate that waist-to-height ratio identifies coronary risk more strongly than waist circumference, waist-to-hip ratio or BMI (Heart 2010;96:136-140). Recent studies have shown that calf circumference (CC) is inversely related with carotid plaques (Stroke 2008;39:2958) and it's association is stronger when compared with the waist-to-hip ratio. We propose to investigate various anthropometric measures including waist/hip, waist/height, waist/calf, a set of calf-based ratios (1) calf circumference; 2) calf-girth-to-hip ratio; 3) calf-girth-to-waist ratio; 4) calf-girth-to-height ratio; and 5) (calf girth * height)/waist ratio) and evaluate which of the measures has the strongest association with sub-clinical atherosclerosis and clinically manifest atherosclerosis (coronary heart disease, stroke, PAD) in the ARIC study.

5. **Main Hypothesis/Study Questions**:
   Hypothesis:

1. Calf girth and/or ratios involving the calf girth are associated with prevalent and incident PAD and CHD.
2. Calf girth and/or ratios involving the calf girth are associated with carotid intima media thickness (CIMT) and/or plaque presence.
3. Calf girth and/or ratios involving the calf girth will have a stronger association with CHD and PAD than waist and hip-based ratios or BMI.

Questions to be addressed in a step wise manner:

a. Do calf girth and/or calf to waist/hip/height ratios provide a stronger association with PAD and CHD than traditional anthropometric measures in the ARIC study?

b. Are ratios involving the calf girth associated with carotid intima media thickness and/or plaque presence?
c. Does the calf girth to waist/hip/height ratios have stronger association with prevalent and incident CHD and PAD in the ARIC study?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

After standard exclusions and excluding individuals with no calf/waist/hip measurements, missing CIMT/ plaque information, missing ankle brachial index (ABI) information and those missing prevalent CHD information, we will perform the following analyses.

A) Compute the following calf-based anthropometric measurements (available at baseline):
   1) Calf girth (circumference of the right calf)
   2) Calf-girth-to-hip ratio
   3) Calf-girth-to-waist ratio
   4) Calf-girth-to-height ratio
   5) (Calf girth * height)/waist

B) Analyze the relationship at the baseline ARIC visit between the four calf-based measures 1) calf circumference; 2) calf-girth-to-hip ratio; 3) calf-girth-to-waist ratio; 4) calf-girth-to-height ratio; and 5) (calf girth * height)/waist ratio with:
   1) Carotid plaque
   2) Mean distal common carotid intima-media-thickness
   3) Ankle brachial index (relationship with PAD - ABI was measured at the 4 exams and during hospitalization follow-ups)
   4) Prevalent CHD
   5) Metabolic syndrome

All the calf girth to waist/hip/height ratios analyses presented will be done using the proposed anthropometric measures as both continuous variables, possibly non-linear, and as stratified as calf girth to waist/hip/height ratios >75^{th} percentile, 25^{th} to 75^{th} percentile and <25^{th} percentile. The calf girth to waist/hip/height ratios will be age, sex and race specific. For ABI analysis, association with calf girth of same leg will be performed.

C) Analyze incident events

Crude rates and hazard ratios for total and incident events will be analyzed with and without adjustment for cardiovascular risk factors (age, race, gender, diabetes, total cholesterol, BMI). Cardiovascular disease events include fatal or nonfatal myocardial infarction or coronary heart disease death, PAD, stroke, and coronary revascularization.

Models will be examined for incident events (ARIC participants with cardiovascular disease, myocardial infarction will be excluded from baseline). Interactions between each

anthropometric measure will be tested for statistical significance. Hazard ratios will be represented as point estimates (95% confidence intervals). We will compare different models after adjusting for all covariates (standardized per 1 standard deviation). We will use the area under curve (AUC) from the receiver operating characteristics (ROC) as measure of merit for comparing different models.

Details of the analysis plan:

1. Define and compute the calf-based measures upon the selection of all eligible ARIC participants.

2. Determine at baseline the association of 1) calf circumference; 2) calf-girth-to-hip ratio; 3) calf-girth-to-waist ratio; 4) calf-girth-to-height ratio; and 5) (calf girth * height)/waist ratio with traditional risk factors (TRF), CIMT and plaque measures.

3. Describe and analyze the observed incident CHD events for the 5 calf-based measurements.

4. Using a Cox proportional hazards model, the 10-year predicted CHD risk of the study participants will be calculated using a model with TRF alone and then by adding 1) calf circumference; 2) calf-girth-to-hip ratio; 3) calf-girth-to-waist ratio; 4) calf-girth-to-height ratio; and 5) (calf girth * height)/waist ratio to TRF, CIMT, and plaque. Participants will be categorized into the various risk groups (<5%, 5-10%, 10-20% and >20% 10 year CHD risk)

5. Determine and compare the predictivity of all models using the AUC. Identify the *best* calf-based ratio based on the hazards models computed in step 4.

6. Analyze the relationship of the change over time of the *best* calf-based measurement with the progression of PAD and CHD (using Framingham and ARIC risk scores).

7. Categorize ARIC participants based on the *best* calf-based measurement and their respective carotid plaque amounts and CIMT into various risk groups for CHD risk assessment.

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://www.cscc.unc.edu/ARIC/search.php

___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)?

MS# 59B; MS# 343A; MS# 1177;

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _x___ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. 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.