ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #196

1. Title:
A Cross-Sectional Assessment of Carotid Arterial Wall Thickness and Age: A Combined Analysis of the CARDIA, ARIC, and CHS Cohorts

2. Writing Group:
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3. Background:
The primary goals of this manuscript are to: (1) describe the distribution of intimal-medial wall thickness (IMT) over a large age range, and (2) to present the relationship of IMT to cardiovascular risk factors over a large age range.

Both ARIC and CHS have recently reported a general description of the relationship of IMT and age (Howard, et. al, O'Leary, et. al respectively). The upper percentiles of IMT, which are likely to represent atherosclerosis, increase rapidly with age within the ARIC age range of 45 to 65. The mean IMT is detectably thicker in the CHS population than in ARIC, and again within the CHS population there is an increase in mean IMT with age.

The two primary reasons for presenting a combined analysis are: (1) an epidemiologically motivated effort to describe the distribution over the entire age range where it is pre-clinically and clinically manifest, and to describe the relationship of mean IMT to risk factors, and (2) a statistically motivated effort to increase the range of the primary independent variable (age) to allow a more precise estimation of these relationships. These goals are complementary. In addition, the sample size of the combined data set allows the description of this distribution to be presented by gender (and to a lesser extent, by race).

Secondly, the impact of major cardiovascular risk factors on clinical events may differ in the elderly population as compared to their younger counterparts (for example, Langer et. al's description of the declining impact of hypertension with age and Manolio et. al's description of the declining impact of lipids with age). While the CARDIA data is of insufficient size to assess the impact of risk factors (n=200), the ARIC and CHS data bases have frequently been individually employed for this purpose. Combining these two substantial data bases for the assessment of the impact of risk factors offers the opportunity to assess differential impact of factors with increasing age. There are a number of possible underlying mechanisms which may result in a differential effect of risk factors on IMT including: (1) a true biological differential effect, where participants change in their susceptibility to the underlying risk factor with age (potentially due to differences in exposure time to the risk factor), (2) a survivorship bias, where those participants with advanced atherosclerosis (who are susceptible to the risk factors) are removed from the analysis with increasing frequency with increasing age, or (3) methodological differences between ARIC and CHS. Admittedly, these cross-sectional analyses will not be able to distinguish between these effects. Most of these efforts have focused on clinical events, and little is known about differential risk factor effects on IMT.

Whether there are age-differential impacts of risk factors on IMT may be addressed within ARIC and CHS. However, the age range of ARIC is restricted to a relatively narrow age range (20 years), increasing the difficulty of detecting differential effects. While the CHS population has a open upper age range, there is a decreasing proportion of participants at the older age ranges, again making the analysis within the CHS population more difficult. The combination of these two studies allows for the opportunity for the powerful examination of this hypothesis.

There are, of course, methodological problems in these analyses. ARIC and CARDIA used very similar ultrasound scanning techniques, and where the images were measured by the same central laboratory; hence, differences between these studies is likely to be small. However, there are significant differences in the ultrasound methodology of the CHS and ARIC/CARDIA studies, but the studies share many of the same goals and techniques. The position of these studies in the scientific arena makes an understanding of the impact of the similarities and differences between the programs critical. This manuscript will also offer the opportunity to review systematically the similarities and differences in ultrasound measurements between the CHS and ARIC/CARDIA, for the benefit of a wide readership which is being exposed to the results of each of these three major NHLBI-supported studies in the absence of such a comparison.

Differences in CHS and ARIC/CARDIA ultrasound data exist at both the scanning and reading stages of processing, briefly:

Scanning **CHS.** Three views of the largest lesion in each ICA system, and one view of the CCA, are collected using a Toshiba device. Digital images are selected by the sonographer captured on diskette and on video tape for transfer to the reading center.

ARIC/CARDIA (first visit). Five (5) carotid images at specified views are evaluated in each carotid artery: three angles of the CCA, the bifurcation, and the ICA. Images are captured on videotape.

Reading **CHS.** The disks are reviewed, and at each of the selected images at systole the near wall, lumen, and far wall are digitized by drawing a smooth line over the boundaries. The readers collect data, and grade their confidence in the measurements from low to high.

ARIC/CARDIA. The tapes are transcribed by an automated system, and images at peak systole are recorded on optical disks. Measurements are of the near and far wall boundaries are made by digitizing 11 "slices" across the boundaries for each of the images. The readers are instructed to not record data if they do not have a high degree of confidence in the measurements.

The product of the two systems is that ARIC/CARDIA has data primarily describing the far wall, and has more missing data than CHS; however, the data is all measured with a high degree of confidence. Because ARIC has data primarily on the far wall, this paper will be restricted to that area.

4. Variables and plan of analysis:
Three steps are proposed in the analysis. First, unadjusted differences (for risk factors) in IMT between the ARIC and CHS studies will be examined. Secondly, the differential impact with increasing age of "major" cardiovascular risk factors on mean IMT will be investigated. Finally, the distribution of IMT will be described as a function of age and risk factors. Care will also be taken to evaluate differential IMT between the two studies after adjustment for risk factors.

Percentile regression techniques of Efron will be used to estimate selected percentiles (i.e., 10th, 25th, 50th, 75th, and 90th) of IMT as a function of age. In separate analyses using estimated IMT at the common and internal carotid arteries at the baseline examination, the discrete jump of IMT in each of the percentiles at age 65 (switch over between the studies) will be estimated. In addition, differences between ARIC and CHS in the slope of the relationship between age and IMT will be examined. To the extent that absence of a discrete jump between studies and differences in slope allow, the distribution of IMT, as described by estimated percentiles, will be described for the population above the age of 45. These analyses will be presented separately for race-sex strata. It is anticipated that piecewise models will be fit to each study (CARDIA, ARIC, CHS) as a function of age, and then the magnitudes of the jumps between studies and differences in slopes estimated. The goal the percentile regression is, for each of the percentiles estimated, to describe the magnitude of the discrete jumps between the studies and to describe differences in the slope with age across the three studies. It is assumed that models of the form:

$$IMT = B_0 + B_1A + B_2S_1 + B_3AS_1 + B_4S_2 + B_5AS_1$$

where A is age, S_1 is an indicator variable for ARIC (S_1 = 1 if ARIC or CHS, and 0 otherwise), and S_2 is an indicator variable for ARIC/CHS (S_2 = 1 if ARIC or CHS, 0 for CARDIA) will be employed. The jumps at ages 45 and 65 can then be estimated by adjusting the age to be centered at 45 and then 65.

Secondly, the impact of select major risk factors on mean IMT will be examined. Specifically, hypertension, diabetes, and cigarette smoking will be considered as categorical variables; and HDL, LDL, and fibrinogen will be considered as continuous variables. For each of these variables the effect for each study will be estimated, and differences between the study tested. The analysis will primarily focus on the effect of mean IMT using standard linear models; however, secondary analyses will examine the impact of these factors on the percentiles of IMT using Efron's technique. The evaluation of the differential impact of the risk factor with increasing age will be considered both as: (1) age-by-risk factor interactions, and (2) by analysis within age strata (5 or 10 year intervals depending on the sample size within the strata). Presentation will likely be by age strata, as it will allow a clearer interpretation to the clinical readership. The effect for each of these variables in each study will be estimated after adjustment for age, and differences in the magnitude of the impact of the between the studies tested (a study by risk factor interaction). At the first pass, the analysis will be restricted to the univariate analysis of each of these risk factors (after "adjustment" for study and age). Because of the relatively small size of the CARDIA data set, those data will be omitted from this analysis. It is anticipated that models of the form:

$$IMT = B_0 + B_1A + B_2R + B_3AR + B_4S + B_5AS + B_6RS + B_7ARS$$

will be employed, where A is the age of the participant, R is the risk factor under consideration, and S is a study indicator (S = 0 for ARIC and S = 1 for CHS). Attempts to simplify the model (remove interactions

and main effects will be formed in a backward stepwise manner (under hierarchical constraints). Definitions of risk factors in the two studies will be:

1) Age: These are sufficiently similar for use.
CHS: AGE01 (eligibility form question #1)
ARIC: V1AGE01 (Difference in years between birth & visit dates)

2) Smoking: These are sufficiently similar for use.
CHS: SMOKE (1 = never, 2 = former, 3 = current), defined by self reported answers to personal history form
questions 4 & 5:

4. Have you smoked more than 100 cigarettes or 5 packs of cigarettes in your lifetime?
5. Have you smoked cigarettes during the last 30 days?

ARIC: CIGT01 (1 = current, 2 = former, 3 = never), defined by self reported answers to home interview form
questions 28 & 30:

28. Have you ever smoked cigarettes (CODE "NO" IF LESS THAN 400 CIGARETTES IN A LIFETIME).
30. Do you now smoke cigarettes?

3) Hypertension: These are sufficiently similar for use after collapsing the "borderline" into normotensive for CHS.
CHS: HYPER (3 = hypertensive, 2 = borderline, 1 = normotensive)

Hypertensive if systolic bp greater than or equal to 160 or diastolic greater than or equal to 95 or (prior MD
diagnosis of hypertension and anti-hypertensive medication use) where we redefine borderline to be
normotensive.

ARIC: HYPERT06 (l = hypertensive, 0 = normotensive)

Hypertensive if systolic bp greater than or equal to 160 or diastolic greater than or equal to 95 or use of
anti-hypertensive medication

4) Diabetes: These are similar after recoding the IGT into normal for CHS.
CHS: DIABETES (3 = diabetic, 2 = impaired glucose tolerance, 1 = normal)

Diabetic if fasting glucose greater than or equal to 140 mg/dl or two hour post glucose load greater than or
equal to 200 mg/dl or medical history form question 7 (md told you that you had diabetes) is "Yes" or
phlebotomy insulin question 5 (are you diabetic and do you take insulin) is "Yes" or taking insulin or oral

hypoglycemic medication.

ARIC: DIABTS02 (1 = diabetic, 0 = normal)

Diabetic blood glucose greater than or equal to 200 mg/dl or fasting (8 hours or more) blood glucose greater than or equal to 140 mg/dl or home interview form question 10e (Has a doctor ever said you had diabetes (sugar in the blood)) is "Yes", or taking medications for diabetes or high blood sugar.

5) Body Mass: These are sufficiently similar for use.
CHS: BMI (weight (kg) / height squared (m))
ARIC: BMI01 ((weight (lbs) / 2.2) / (height (cm) / 100)^2)

6) HDL: These are sufficiently similar if units align.
CHS: HDL44 (units???)
ARIC: HDL01 (mg/dl) or HDLSIU02 (mmol/L)

7) LDL (calculated): These are sufficiently similar if units align.
CHS: LDL44 (units???)
ARIC: LDL02 (mg/dl) or LDLSIU02 (mmol/L)

8) FIBRINOGEN: These are sufficiently similar if units align.
CHS: FIB44 (units???)
ARIC: HEMA09 (units???)

Finally, the first analysis focusing on the distribution of IMT as a function of age will be repeated after adjustment for the major risk factors examined in the second step of the analyses. Similar techniques will be employed as these factors are added to regression equations.

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