1. **Full Title:** Progression of Carotid Intima Media Thickness in asymptomatic individuals and patients with clinically manifest atherosclerosis. The ARIC study

2. **Abbreviated Title (Length 26 characters):** IMT progression by prevalent coronary artery disease status

3. **Rationale:**

   Increased intima-media wall thickness (IMT) of the carotid artery as assessed by B-mode ultrasonography is a well-accepted index of atherosclerosis. Both a single determination of IMT and progression of IMT over time have been shown to be associated with major cardiovascular risk factors and with incident coronary and cerebrovascular events. Progression of IMT deserves attention after being reported to predict coronary events even better than lipid measurements and after several randomized clinical trials showed that it is favorably influenced by lipid lowering drugs, antioxidants, ACE inhibitors and beta-blockers.

   Little is known about the rate of IMT progression, if it is constant or intermittent during the process of atherosclerosis or if it is different between subgroups of individuals, such as asymptomatic individuals and those with advanced and symptomatic atherosclerosis.

   It is plausible that the symptomatic coronary heart disease is a mark of a more rapidly progressing atherosclerosis once the coronary the progression of the atherosclerosis is more rapid once it became symptomatic. To our knowledge this hypothesis has been investigated at carotid level by only one study (Crouse et al., Circulation 2002). This study shows a more rapid progression of IMT among patients with documented coronary artery disease (CAD) relative to those in which CAD was ruled out by coronary angiography, over a follow up time of 3 years. While revealing interesting findings, this study has left some questions unanswered: first, its study population consisted of patients referred to coronary angiography, and it is possibly different from the general, asymptomatic population or high-risk subjects usually receiving ultrasound examination for preventive
services. Moreover, the use of angiographically defined cases can have limitations relative to clinical coronary events. Second, it used an aggregate measure of IMT over several carotid segments; it is conceivable that the progression rate between participants with and without CAD will be more substantial in the internal than in the common carotid artery since atherosclerosis is more extensive in the internal carotid artery which may also better predict coronary events. Third, the follow up time was limited to 3 years; it is thus of interest to know the rate of progression of IMT over longer periods of time.

We submit here a proposal to replicate and extend the findings by Crouse et al. to a larger, population-based sample of asymptomatic individuals, prospectively followed up for incident coronary events. We propose to compare the rates of progression of IMT among four sets of individuals, according to their status at baseline: a) individuals who have coronary heart disease, b) individuals who have diabetes mellitus, c) individuals with detected atherosclerosis in other arterial segments and d) asymptomatic individuals at the lower end of cardiovascular risk.

The different rate of progression by different atherosclerosis status may help to better characterize the individual risk profile for asymptomatic individuals and patients with clinically manifest cardiovascular diseases. A potential benefit is that future studies will need to document that ultrasound screening has an impact on subsequent management decisions and patient behavior and whether such decisions decrease progression of atherosclerosis.

4. Main Hypothesis/Study Questions:

This study proposes to look at several types of atherosclerosis manifestations:

i) Prevalent coronary heart disease (CAD) defined as angina, myocardial infarction or revascularization procedures

ii) CAD “equivalents”, i.e. Diabetes Mellitus (physician diagnosis or blood glucose>126mg/dl)

iii) Atherosclerosis in other arterial territories (combined endpoint):
    a. peripheral arterial disease (diagnosed intermittent claudication) or asymptomatic peripheral atherosclerosis as measured by an altered ABI <=0.9 in men and <= 0.85 in women
    b. diagnosed cerebrovascular disease

iv) All individuals not included in the above categories (i.e. no prevalent atherosclerotic disease), to represent the ARIC cohort experience in terms of a lower CAD risk

This study proposes to test the following hypotheses:
The rate of IMT progression is higher among individuals with any of CAD, Diabetes Mellitus or atherosclerosis in other arterial territories than in individuals without these conditions.

5. Study population

In order to test these hypotheses, a population-based cohort of middle-aged individuals will be appropriate. As IMT progression is slow, a long enough follow-up (longer than 5 years) is needed. This study proposes to make use of the information available on the cohort participants in the ARIC study, a population-based study, recruiting individuals between ages of 45-64 at baseline.

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

Data from the ARIC baseline and follow-up visits will be used.

Exclusions:
- Participants without measurement of common carotid IMT on any side
- Participants with race other than black or white

Main exposures: CAD, Diabetes Mellitus or atherosclerosis in other arterial territories

Outcome: annualized rate of IMT change (race and gender-specific) estimated from maximum follow-up available in the following subgroups:

i) Prevalent coronary heart disease (CAD) defined as angina, myocardial infarction or revascularization procedures

ii) CAD “equivalents”, i.e. Diabetes Mellitus (physician diagnosis or blood glucose>126mg/dl)

iii) Atherosclerosis in other arterial territories (combined endpoint):
  a. peripheral arterial disease (diagnosed intermittent claudication) or asymptomatic peripheral atherosclerosis as measured by an altered ABI <=0.9
  b. diagnosed cerebrovascular disease

iv) All individuals not included in the above categories (i.e. no prevalent atherosclerotic disease), to represent the ARIC cohort experience in terms of a lower CAD risk

As a secondary analysis, we propose to estimate the annualized rate of IMT change (race and gender-specific) among the ARIC participants categorized according to the NCEP III algorithm for CAD risk.

Covariates: several covariates will be analyzed for their potential to add any supplementary predictive information as follows: age, smoking, overweight, total
cholesterol, LDL-C, HDL-C, white blood cell count, fibrinogen, ECG estimated LVH, lipid-lowering drugs, anti-hypertensive drugs.

Analysis will be performed with and without adjusting for baseline IMT.

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)?

    MS# 243A  Risk factors for progression of common carotid atherosclerosis is: The ARIC Study 1987-1998 (Chambless LE)

    MS# 974  Change in carotid IMT is associated with incident CHD and incident stroke (Chambless LE)

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.
References: