1.a. Full Title: Plasma triglycerides and risk of stroke incidence and mortality in the ARIC study.
   b. Abbreviated Title (Length 26 characters): Triglycerides and stroke

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

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3. Timeline:

   4 months:
   • Literature review – 2 weeks
   • Outline paper – 1 week
   • Data analysis – 6 weeks
   • Write manuscript – 4 weeks
   • Review and edit paper – 4 weeks

4. Rationale:

   Previous epidemiologic studies could not show a consistent association between high triglycerides and an increased risk of ischemic stroke. This failure to detect a significant relationship between stroke and triglycerides may be due to several factors:
- The inverse relationship between triglycerides and high density lipoproteins (HDL) as well as the possible interactions between triglycerides and both HDL and LDL-C\(^4\) would have masked the possible association between triglycerides and stroke when adjusting for these lipoproteins.
- In most previous studies the authors did not make a distinction between hemorrhagic and non-hemorrhagic stroke, which – considering the different risk factors for both entities – could have biased their results towards the null.
- In addition, the changing lipid profiles seen in higher ages could have attenuated an underlying association in some of these studies.\(^3\)

Recent evidence from randomized clinical trials suggests that lowering triglyceride levels with fibrates can decrease the risk of an ischemic stroke and transient ischemic attacks (TIA) in patients with preexisting CHD.\(^4,5\) The nature of these study populations limits the inferences about the association in the general population. We would therefore like to look at the ARIC cohort in order to enhance our knowledge about the external validity of the findings of these clinical trials, and particularly to assess possible interactions between triglycerides and other lipid components. In addition, given the possible associations between triglycerides and abnormalities of the clotting system\(^6\), it would be important to examine the association with ischemic strokes while stratifying for underlying atherosclerosis (based on IMT).

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

   We will try to focus on two main objectives:

   1. To assess the interactions between triglycerides and both LDL-C and HDL with regard to incident (and fatal, if the sample size is not sufficient) ischemic strokes, as suggested by the recent analyses of results from the Bezafibrate Infarction Prevention (BIP) study
   2. To assess the relationship between triglycerides and ischemic strokes while stratifying for IMT.

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

   Cox proportional hazard regression analysis will be utilized to investigate the effect of triglycerides on stroke incidence and mortality.

   **Dependent variable:** Stroke incidence and mortality, IMT

   **Independent variable:** triglyceride levels (at baseline)

   **Covariates:** Visit 1: age, race, center, LDL, HDL, IMT, prevalent CHD and stroke, current smoking, former smoking, hypertension, BMI, waist-hip ratio, sporting activity, diabetes mellitus, fibrinogen, left ventricular hypertrophy, atrial fibrillation, white blood cell count, socioeconomic information, dietary factors, endarterectomy, alcohol consumption, presence of myocardial infarction, medication
The minimal model will include age, race, center, and sex. The extended model will include all other possible confounders.

**Inclusion/Exclusion:** Exclusions are individuals with prevalent strokes and CHD.

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/csc/ARIC/stdy/studymem.html](http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html)

_____  Yes  _____XX**___ No

**Manuscripts No. 421 is a possible overlap. In this paper, the association between triglycerides and stroke was weak. However, #421 did not address the issue of interactions with HDL and LDL-C, or the effect of underlying subclinical atherosclerosis.**

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2 Prospective studies collaboration. Cholesterol, diastolic blood pressure and stroke: 13,000 strokes in 45,000 people in 45 prospective cohorts. Lancet 1995; 346:1647-1653.
5 Bloomfield Rubins H et al. Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men with Low Levels of High-Density Lipoprotein Cholesterol. NEJM 1999/341:410-8