1.a. Full Title: Pleiotropic Effects of Statins

b. Abbreviated Title (Length 26 characters): Pleiotropic Effects

2. Writing Group:
   Writing group members: Michael Domanski (NHLBI), Aaron Folsom, Christie Ballantyne, Xin Tian (NHLBI), Vandana Sachdev (NHLBI), Sean Coady (NHLBI); Eliot Peyster (NHLBI)

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

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3. Timeline: The analysis will be done at NHLBI and will proceed as soon as the proposal is approved.

4. Rationale: The therapeutic benefit of statin lowering of LDL is well established. The question of whether statins reduce coronary events by mechanisms other than lipid lowering has received considerable attention. Indeed, statins appear to improve endothelial function, possibly by improving nitric oxide availability,\(^1,2\)
The West of Scotland Coronary Prevention Group (WOSCOPS) compared event rates in pravastin- and placebo-treated patients whose LDL levels during the study were 140 to 180 mg/dL and found that event rates were reduced in the pravastatin-treated patients, after adjusting for cholesterol and triglyceride levels\(^3\), suggesting the possibility of a non-LDL-lowering benefit. On the other hand, after adjusting for apolipoprotein B and A1 levels, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) study showed no such difference\(^4\). Meta-regression analysis of the available studies by Davidson et al, comparing percent change in total cholesterol to percent change in adverse cardiovascular events, suggests that the degree of lipid lowering fully accounts for event reduction\(^2\).

When compared to older studies, the earlier than expected reduction of adverse events in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)\(^5\) and (PROVE-IT) trials has been taken to suggest pleiotropic effects. However, these patients had acute coronary syndromes and the reasonableness of comparing these patients to those in older studies that entered stable, chronic patients is questionable.

The presence or absence of pleiotropic effects is an important one. If there are effects that are dependent on the specific molecule used to reduce LDL, then each statin would have to be individually vetted against clinical endpoints. If the LDL achieved were the determinant of risk, rather than the molecule used for treatment, then any generic statin (or, for that matter, other drug) that safely achieves the desired LDL level could be used.

We propose to perform an analysis (see below) to look for evidence of pleiotropic effects in the ARIC cohort.

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

*Study question:* Is clinical outcome (MI, stroke, or cardiovascular death) altered by statins, independent of their LDL lowering effect? That is, do the data suggest that there are so-called “pleiotropic” effects?

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

Data: Prevalent coronary heart disease (history of MI, MI by ECG, coronary revascularization), prevalent stroke (self-report), indicator for Statin medication brought to clinic, indicators for Beta Blocker or Ace Inhibitor medication brought to clinic, systolic blood pressure, self-reported use of medications for high blood pressure, diabetes (126 mg/dL cutpoint), LDL cholesterol, HDL cholesterol, total cholesterol, education, family history of cardiovascular disease, any form of health insurance, fasting indicator (8 hour), current smoking, age, race, sex, and follow-up data through 2002 for hospitalized MI or fatal CHD death and fatal/nonfatal stroke.

Since statin use was minimal at visit 1 (less than 1%), risk factors will be collected from visits 2-4 with follow-up data through 2002. Examination data will be excluded if the subject was nonfasting or missing data for statin use or a covariate. Prevalent disease will be included as a dichotomous covariate (Yes/No).

The main analysis will pool exams 2-4 to create data organized as person-exams. Follow-up will extend from exam to exam so that the risk factor profile will be updated at each attended exam. For each attended exam, a maximum follow-up of five years will be used to limit the influence of possible interventions during follow-up. To account for the multiple observations per subject, hazard ratios will be estimated using a multiplicative hazards regression model (a form of time dependent analysis where the entire risk factor profile is updated at each exam). The main outcome will be the first hospitalized MI or fatal CHD event that occurs for the subject, and a secondary outcome will include fatal/nonfatal stroke. Note that if an incident event occurs between exam 1 and the first exam included in the analysis, then the subject will be regarded as having prevalent disease and the first event (if any) will actually be the first recurrent event. The base model will include use of statins plus traditional CVD risk factors and subsequent analyses will add education, family history and presence/absence of health insurance as covariates.

Since the vast majority of ARIC participants were not on statins, there is the possibility that results could be weighted too heavily toward non-statin users. A second analysis will be conducted excluding subjects in whom NCEP guidelines do not recommend any cholesterol intervention (either dietary or pharmacologic).
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

__________________  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)?
No proposal appeared to be reasonably related.

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.