ARIC Manuscript Proposal # 1172

PC Reviewed: _06/_19_/06	**Status: ____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lp-PLA_2 and hs-CRP as Predictors of Ischemic Stroke

b. Abbreviated Title (Length 26 characters): Lp-PLA_2 and Risk of Stroke by ROC Analysis

2. Writing Group:

Writing group members: CM Ballantyne, R Hoogeveen, H Bang, G Heiss, LE Chambless, J Coresh, H Ni, A Folsom, R Sharrett, E Boerwinkle

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

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3. Timeline: start summer of 2006. CSCC analysis

4. Rationale: ARIC has produced stroke prediction models using ROC analysis. Since Lp-PLA_2 is independent of traditional risk markers, Lp-PLA_2 and hs-CRP may improve the prediction of stroke. Hypertension is known to be an important risk factor for stroke, and there are national guidelines for treatment of stroke (JNC7: Chobanian AV et al. *JAMA* 2003;289:2560–2572). National guidelines (Pearson TA et al. *Circulation* 2003;107:499–511) have recommended that hs-CRP may be useful in improving risk assessment in patients with moderate risk (10–20% over 10 years) who may be considered borderline in regard to choice of therapy, and a common approach in evaluating potential risk factors has been to examine whether predictivity in improved in intermediate-risk patients. However, because primary care physicians typically do not calcuate 10-year Framingham risk, another approach that might be more clinically relevant despite having more limited power is to perform exploratory analyses in selected subgroups.

5. Main Hypothesis/Study Questions:

(1) Does Lp-PLA_2 or hs-CRP add to stroke prediction beyond traditional risk factors already identified in ARIC? The rationale for this question is straightforward as many previous studies in ARIC have examined whether addition of new risk markers improves risk assesssment beyond established risk assessment equations or algorithms. In addition, the editorial to ARIC manuscript #940 requested this analysis. (2) Does Lp-PLA_2 or hs-CRP measurement improve risk prediction in individuals who are classified by nationally recognized clinical guidelines as at increased risk but for whom there are no clear therapy recommendations, particular individuals with "prehypertension" or "metabolic syndrome"? The second question will examine whether the measurement of additional markers may be useful in clinical practice to improve risk assessment in patients who are thought to be at "borderline" increased risk for stroke. Despite several decades of educational efforts and recommendations by national guidelines such as the NCEP ATP III (Expert Panel on Evaluation, Detection, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486–2497), the vast majority of physicians do not routinely use quantitative risk assessment tools to determine a patient's 10-year risk for CHD or stroke. Most physicians are aware that individuals with stage 1 or higher hypertension and diabetes are at increased risk for stroke, and these individuals routinely receive both lifestyle and pharmacotherapies such as antihypertensive medications, statins, and aspirin that have been shown to reduce risk for stroke. JNC7 has designated SBP of 120–139 mm Hg or DBP of 80–89 mm Hg as "prehypertension." The recommendation for such patients is lifestyle modification, but there is no recommendation for antihypertensive drug therapy unless there are also "compelling indications" such as chronic kidney disease or diabetes, in which case drugs are recommended to lower blood pressure to <130/80 mm Hg (Chobanian AV et al. *JAMA* 2003;289:2560–2572). The ATP III guidelines and more recent AHA/NHLBI guidelines (Grundy SM et al. *Circulation* 2005;112:2735–2752) have used clinical criteria to identify individuals with a clustering of risk factors who are said to have "metabolic syndrome." These individuals are also targeted for lifestyle modification without clear recommendation for interventions (statin, antihypertensive medications, aspirin) unless merited by an individual risk factor. Because physicians routinely identify patients as having "prehypertension" or "metabolic syndrome" but do *not* routinely quantitatively assess 10-year risk for stroke or other cardiovascular events, we believe that it would be clinically important to determine whether newer biomarkers improve risk assessment in populations that are routinely identified.

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 methodologic limitations or challenges if present).

The main independent variable is Lp-PLA_2, and other independent variables are the "traditional risk markers" previously elucidated. The nested case–cohort evaluated for Lp-PLA_2 should be examined in the whole cohort, and we will also determine whether there are significant increases in the AUC for prehypertensives (SBP 120–139 mm Hg) and/or hypertensives (SBP ≥140 mm Hg). A similar approach would be used for patients with metabolic syndrome and/or diabetes. Analysis will start by reproducing ARIC's previous "basic" risk model in a case–cohort (tertile) subset. Then, we will test whether adding Lp-PLA_2 and hs-CRP in either continuous or categorical ROC analysis contributes to further increase in the AUC. For categorical analysis, evaluation of a suitable cutpoint, e.g., top tertile (high) versus bottom two tertiles (not high) should be idenitifed. The CART analysis would also be conducted. Recognizing the limited power for examining the primary hypothesis, we will also examine secondary, exploratory hypotheses in selected subgroups.

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)? Prediction of ischemic stroke risk in ARIC" and "Lp-PLA_2, hs-CRP, and risk of incident ischemic stroke in ARIC"

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. primiarly 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.