

ARIC Manuscript Proposal # 1863

PC Reviewed: 11/8/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Development and validation of prediction models for hemorrhagic and ischemic stroke in the Rotterdam Study, Cardiovascular Health Study, and Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

Prediction of stroke subtypes

2. Writing Group:

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

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3. Timeline:

4 weeks data preparation, 4 weeks data analysis, 12 weeks writing

4. Rationale:

Multiple atherosclerotic risk factors that influence stroke risk are well established and can be used to estimate an individual's stroke incidence over a 5 to 10-year time period.¹⁻⁴ However, these risk predictions apply to ischemic stroke only or to a combined endpoint of ischemic and hemorrhagic stroke. In addition, these were all developed using standard Cox regression modeling. Standard survival analysis will generally overestimate the cumulative incidence because it fails to regard those who die of non-stroke causes as ineligible for development of stroke events. Methods to adjust for competing risks are now increasingly being used for cardiovascular risk prediction.⁵⁻⁶

Simultaneous prediction of stroke subtypes (e.g. any, hemorrhagic, ischemic stroke) may be valuable for several reasons. First, the predictors for the different stroke subtypes may vary or may have different weights.⁷⁻⁹ Consequently, the likely effects of modifying predictors can vary for stroke subtypes. Second, for some preventive

interventions, a difference in efficacy has been demonstrated across stroke subtypes. For example, aspirin decreases the occurrence of ischemic stroke events, whereas it increases the risk of an intra-cerebral bleeding.¹⁰ Therefore, decision-making for aspirin therapy can be improved by predicting these two stroke subtypes at the same time. Finally, a more refined communication of the risk of stroke to the individual and the public can be facilitated.

5. Main Hypothesis/Study Questions:

The aim of this project is to develop and validate separate prediction models for estimation of the 10-year cumulative incidences of hemorrhagic, ischemic and any stroke within different geographical regions. The research hypothesis that will be tested is the assumption that effects of predictors will differ between stroke types, making separate prediction models necessary. An additional hypothesis that will be explored is the assumption that predictor effects will not differ between the cohorts, and that differences in risk between cohorts can be explained by variation in baseline risk.

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 study design is a pooled prospective study. We will use data from three population-based cohort studies: the Rotterdam Study, representing a middle-aged and elderly European population, the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study, which will be combined and represent the middle-aged and elderly US population. Prediction models for 10-year stroke subtype risks will be derived from a merged dataset with stratified baseline risks for US and European subjects.

The subjects eligible for these analyses are study participants who did not have prior stroke, did not use anticoagulation, and did not have atrial fibrillation at baseline. The outcomes of interest are defined as: time to fatal/non-fatal stroke event with specification for subtype (intracerebral hemorrhage, ischemic stroke, unspecified stroke); and time to death by other causes than the event of interest. Subarachnoid hemorrhages were excluded as these are not atherosclerotic of origin. The following cardiovascular risk factors that are measured at the baseline visit will be considered as the potential predictors: age; sex; current smoking; systolic blood pressure; diastolic blood pressure; blood pressure lowering treatment; history of cardiovascular disease other than stroke; diabetes mellitus (defined as: fasting glucose ≥ 126 mg/dL (7 mmol/L) or non-fasting glucose ≥ 200 mg/dL (11.1 mmol/L) or self-reported use of diabetes medications); total cholesterol; high-density lipoprotein cholesterol; body mass index; waist-to-hip ratio; race (black/white); estimated glomerular filtration rate using serum creatinine.

(This file ICTDER03 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 ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 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.cscce.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)?

Potential overlap exists with:

Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2004;160:259-69.

This study also uses established risk factors and a 10-year time horizon for prediction of stroke. It however only considers ischemic stroke and does not take into account the competing risk of death by other causes than ischemic stroke.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☐ Yes ☒ 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.cscce.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.

References

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