ARIC Manuscript Proposal #2757

PC Reviewed: 5/10/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Can the risk of intracranial hemorrhage be predicted in patients treated with statins, antiplatelets, and anticoagulants? The Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters):

Predictors of intracranial bleed

2. Writing Group:
Writing group members:

Richa Sharma (first author), Rebecca Gottesman (senior author), Kunihiro Matsushita, Cliff Jack, Michael Griswold, Thomas Mosley, Myriam Fornage, Others welcome

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

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3. Timeline:
We anticipate completion of analysis and preparation of results after 12 months.

4. Rationale:

Many patients are prescribed a statin (simvastatin, pravastatin, lovastatin, rosuvastatin, atorvastatin), an antiplatelet medication (aspirin, clopidogrel, dipyridamole), an anticoagulant (warfarin, dabigatran, rivaroxaban, apixaban), or a combination of these, for a variety of indications such as cardiac (e.g. coronary artery disease), cerebral (e.g. stroke prevention), and systemic (e.g. deep venous thrombosis). There are generally clear guidelines about when to start these medications for most common indications such as the CHADS2VASC score and atrial fibrillation[1]. However, what is less well understood is whether the long-term risks of hemorrhagic complications from these medications, particularly intracranial hemorrhage (ICH) and cerebral microbleeds (CMB), are the same in all individuals.

Cerebral microbleeds are defined as hemorrhages <5mm in size and located near vessels affected by hypertensive arteriopathy or cerebral amyloid angiopathy (CAA). Though these may be individually subclinical, their accumulation can lead to cognitive decline. CAA occurs in nearly half of the elderly population and in up to 80-90% in patients with Alzheimer's.[2, 3] Among patients with a diagnosis of CAA and greater CMB count, there is a 5.27-fold increased hazard of ICH.[2] Therefore, it is critical to assess the risk of developing CAA and ICH in patients who are exposed to possible risk factors such as the medications of interest.

The mechanism of possible risk of intracranial hemorrhage in patients on an antiplatelet or anticoagulant therapy is intuitive since these medications are designed to target receptors resulting in platelet dysfunction and clotting inhibition. With regards to statins, lower cholesterol levels have been shown in prior epidemiologic studies to be associated with intracranial hemorrhage.[4-6] Furthermore, the SPARCL trial demonstrated a higher risk of hemorrhagic stroke among patients who received atorvastatin for secondary stroke prevention compared to patients who did not receive this medication.[7] Thus, these medications which are routinely prescribed may be increasing the risk of intracranial hemorrhage in certain patients.

There are a number of models in the literature that predict the risk of hemorrhage, including the HAS-BLED[8], ATRIA[9], and HEMORR2HAGES[10] scores; these scores use parameters such as hypertension, renal disease, liver disease, stroke history, prior major bleed, age, medications, and alcohol usage to determine an individual's risk of hemorrhage. However, these scores address the risk of any type of bleed, not specifically ICH, nor do they evaluate whether these factors are particularly important in increasing hemorrhage risk on individuals on statins, antiplatelet or anticoagulant medications. The Hemorrhage Risk Stratification score is an online application which determines the risk of hemorrhagic transformation of an acute ischemic stroke in patients with an indication for anticoagulation based on age, stroke volume, and renal function[11]. This model only included patients with acute ischemic infarcts and evaluated the risk of hemorrhagic conversion.

With regards to cerebral microhemorrhages, there have been no studies dedicated to determining the relationship between statin use and CMB. A small, single-center prospective cohort study showed that recurrent lobar hemorrhages were associated with

aspirin usage.[12] The Rotterdam Scan Study was a cross-sectional study of an elderly population free of dementia in the Netherlands which demonstrated patients antiplatelet use was more prevalent in patients with cerebral microbleeds, but no association between anticoagulant use and cerebral microhemorrhages.[13] There is a need to clarify the risk of use of these medications and CMB.

There has been a national emphasis on focusing research about clinical management to precision, or personalized medicine. One individual on an anticoagulant may have an ICH whereas another similarly aged person may not. Understanding how various factors in that individual's medical history, genetic makeup, and environment/ behavior might influence that risk can ultimately help guide clinical decision-making. Thus, there is a practical need for a model derived from a large, longitudinal cohort which takes into account clinical characteristics, cognitive performance, laboratory data, and relevant genetic polymorphisms to predict the long-term risk of ICH in patients taking a certain statin, antiplatelet, or anticoagulant such that the predicted risk may inform decision-making at the individual level.

5. Main Hypothesis/Study Questions:

a.) Our primary hypothesis is thatrisk of ICH will be increased by use of statins, antiplatelet, or anticoagulant medication compared to those taking neither, and that the risk of ICH from these medications can be predicted by a risk score (propensity score) combining demographic, clinical, genetic, serologic, and cognitive data.

b.) A secondary hypothesis will explore the same question, with an individual's risk of CMB as the outcome. We hypothesize that risk of CMB will be increased in participants taking any statins, antiplatelet, or anticoagulant, and that the risk of CMB will be predictedby a risk score combining demographic, clinical, genetic, serologic, cognitive, and imaging markers. We also hypothesize that the number of CMBs will be strongly associated with the same factors in the presence of statins, antiplatelet, or anticoagulant use.

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).

Baseline Characteristics, Exposures, and Outcomes of Interest*:*
Clinical, laboratory, and genetic from ARIC will be combined in a model to evaluate risk of hemorrhage among individuals on statin, antiplatelet, or anticoagulant medications. Clinical data from the baseline visit (visit 1) that we plan to use to control for their potential confounding effects will include age, gender, race, smoking history, history of hypertension, history of hyperlipidemia, history of diabetes, history of coronary artery disease, history of atrial fibrillation, GFR, prior adjudicated ischemic stroke, and prior intracranial hemorrhage. Cognitive evaluations were conducted as part of ARIC visit 2, and we will use global Z-scores as a covariate. There are laboratory data available in ARIC visit 1 which we will account for including hemoglobin, prothrombin time,

activated partial thromboplastin time, and platelet count which will be relevant. There are also other markers of coagulopathy in the database including plasminogen activator inhibitor-1 associated with fibrinolysis, platelet glycoproteins, and homocysteine. Finally, we plan to evaluate the following genes: beta amyloid precursor protein APP gene (associated with familial cerebral amyloid angiopathy)[14], APOE *ε2* and ε4 (associated with sporadic cerebral amyloid angiopathy)[15], Notch3 (associated with CADASIL)[16], COL4A1 (encodes type IV collagen of blood vessels)[17], CYPC9*3, CYP2C9 (warfarin metabolism)[18], VKORC1 (vitamin K epoxide reductase complex subunit-1)[19], CYP2C19 (clopidogrel metabolism)[20], P2Y1 (aspirin resistance)[21], P2Y12 (clopidogrel resistance)[22], LIMK1(associated with ICH)[23], and CYP3A4(associated with subarachnoid hemorrhage)[23] as these have been correlated with bleeding risk in patients who are on antiplatelets or anticoagulants in the literature.

We will also explore time-varying covariates and covariate status closer in proximity to the event, either ICH or MRI signaling of CMB.

The exposures of this study will be medications of interest. These are statins (simvastatin, lovastatin, pravastatin, rosuvastatin, atorvastatin), antiplatelet (aspirin, clopidogrel, dipyramidole) and/or anticoagulant (warfarin, low molecular weight heparin, fondaparinaux, dabigatran, rivaroxaban, apixaban (we anticipate minimal to no use of these newer anticoagulants). Medication usage will be reviewed from each visit, through any incident ICH for the ICH analysis, and through and including visit 5, for the microbleed analysis. We will also use the annual follow-up phone call data to update the use of these three drugs for a time-varying analysis.

There are approximately **150 patients** in ARIC with adjudicated ICH as of the end of 2012. In the subset of participants from ARIC-NCS with 3T brain MRI (**1958** patients), T2* gradient echo imaging was performed. These have been rated and reviewed to determine the presence, location, and number of hemosiderin deposits (CMBs) in the brain. About one-third of these patients had CMBs.

Design and Analysis: The analysis will include all participants in the ARIC study with available data from at least one visit on medication use,[24] although we will also explore antiplatelet or anticoagulant use as a time-varying exposure in those participants (the majority) with medication information from most if not all visits. All statistical analyses will be performed in SAS 9.3. Participants will be considered by exposure to these medications of interest, defined as using statins, antiplatelets, or anticoagulants at any point during followup from ARIC visit 1. Outcome will be evaluated as time-to-event through an adjudicated ICH (at any point in followup) or as a binary event as a CMB (from 2011-2013 MRI). Univariate analyses will be performed to outline the baseline characteristics of the cohort. If sample size allows, we will stratify patients into groups defined by medication type.

Creation of risk score/ propensity score: We will create a logistic regression model evaluating the risk of any ICH, incorporating factors described in previous risk models or otherwise recognized in the literature to increase ICH risk, using a propensity score approach. Clinical, laboratory, and genetic variables will be tested, as described above. The use of medications will not be evaluated at this point. The most parsimonious model

will be selected via backward elimination. The overall discriminative capacity of the model will be ascertained by a concordance index capturing the area under the curve of a receiver operating curve, and we will confirm balance of the propensity score model. Then, the predicted propensity score values will be binned into quintiles for use for the primary analyses.

Analysis of ICH Outcome: Because the primary focus of the study is how the above risk score will modify the relationship between statin/antiplatelet/ anticoagulant use, each, and ICH (hypothesis 1) and between statin/antiplatelet/ anticoagulant use, each, and CMB (hypothesis 2), the primary analyses will evaluate, as independent variables, in separate models for each medication category as well as in a model where use of any of these medications is combined into a single variable (any medication usage in this group versus no medication usage in this group), statin/anticoagulant/ antiplatelet use X propensity score quintile interaction terms. If possible, we would also like to use annual follow-up phone call data to update the three drugs for time-varying analysis. For hypothesis 1, where the outcome of interest is any ICH, we will build a Cox proportional hazard regression model to calculate the hazard rate of an ICH. We will also consider creating a propensity score for use of statins and/or anti platelet or anticoagulant medications which will be incorporated into the final model as an adjustment covariate.

Analysis of Cerebral Microbleed Outcome: Given that MRIs were only performed during one cross-sectional time period, 2011-2013, for hypothesis 2, a logistic regression will be used to determine the risk of the presence of CMB, with focus on the same statin/ antiplatelet/ anticoagulant X propensity score quintile interaction term described above. Also, a similar analysis will be performed with the cumulative use of statin/antiplatelet/anticoagulant use (medication-years) as the interaction term instead. The association between the number of CMBs and the proposed independent variables will be evaluated in an ordinal logistic regression.

Limitations: This will not be a randomized controlled study, thus precluding the ability to determine causality. There will not be any pathologic correlate with the radiographic findings of cerebral microbleeds in the dataset. We also acknowledge that power will be limited given the relatively small number of hemorrhages. We have chosen to do a propensity score in order to minimize concerns about inadequate power with many covariates. Finally, it would be ideal to measure the risk of intracranial hemorrhage in patients with existing and recognizable CMB taking a medication of interest, but we only have one time point thus far which includes MRI with GRE sequencing.

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 ICTDER03 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 ICTDER 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?

__x__ 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"?

__x__ 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)?

Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, Woodward M, Longstreth WT, Psaty BM, Shlipak MG et al. 2014. **Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts.** Stroke. 45(7):1925-31

Ferket BS, van Kempen BJH, Wieberdink RG, Steyerberg EW, Koudstaal PJ, Hofman A, Shahar E, Gottesman RF, Rosamond W, Kizer JR et al. 2014. **Separate prediction of intracerebral hemorrhage and ischemic stroke.**. Neurology. 82(20):1804-12.

Folsom AR, Yatsuya H, Mosley TH, Psaty BM, Longstreth WT. 2012. **Risk of intraparenchymal hemorrhage with magnetic resonance imaging-defined leukoaraiosis and brain infarcts.**. Ann Neurol. 71(4):552-9.

Morrison AC, Bare LA, Luke MM, Pankow JS, Mosley TH, Devlin JJ, Willerson JT, Boerwinkle E. 2008. **Single nucleotide polymorphisms associated with coronary heart disease predict incident ischemic stroke in the atherosclerosis risk in communities study.**.Cerebrovasc Dis. 26(4):420-4.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

_X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.06 (ARIC-NCS)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. 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.
Understood.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

REFERENCES:

1. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272
2. Hosmer DW, Lemeshow S. *Applied logistic regression*. New York: Wiley; 1989.
3. Hosmer DW, Lemeshow S. *Applied logistic regression*. New York: Wiley; 2000.
4. Iso H, Jacobs DR, Jr., Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *The New England journal of medicine*. 1989;320:904-910
5. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the honolulu heart program. *Stroke; a journal of cerebral circulation*. 1989;20:1460-1465
6. Lee SH, Bae HJ, Yoon BW, Kim H, Kim DE, Roh JK. Low concentration of serum total cholesterol is associated with multifocal signal loss lesions on gradient-echo magnetic resonance imaging: Analysis of risk factors for multifocal signal loss lesions. *Stroke; a journal of cerebral circulation*. 2002;33:2845-2849
7. Stroke Prevetion by Aggressive Reduction in Cholestrol Levels I, Karam JG, Loney-Hutchinson L, McFarlane SI. High-dose atorvastatin after stroke or transient ischemic attack: The stroke prevention by aggressive reduction in cholesterol levels (sparcl) investigators. *Journal of the cardiometabolic syndrome*. 2008;3:68-69
8. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (has-bled) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest*. 2010;138:1093-1100
9. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: The atria (anticoagulation and risk factors in atrial fibrillation) study. *Journal of the American College of Cardiology*. 2011;58:395-401
10. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: Results from the national registry of atrial fibrillation (nraf). *American heart journal*. 2006;151:713-719
11. Marsh EB, Llinas RH, Hillis AE, Gottesman RF. Hemorrhagic transformation in patients with acute ischaemic stroke and an indication for anticoagulation. *European journal of neurology : the official journal of the European Federation of Neurological Societies*. 2013;20:962-967
12. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2010;75:693-698
13. Vernooij MW, Haag MD, van der Lugt A, Hofman A, Krestin GP, Stricker BH, et al. Use of antithrombotic drugs and the presence of cerebral microbleeds: The rotterdam scan study. *Archives of neurology*. 2009;66:714-720
14. Greenberg SM, Shin Y, Grabowski TJ, Cooper GE, Rebeck GW, Iglesias S, et al. Hemorrhagic stroke associated with the iowa amyloid precursor protein mutation. *Neurology*. 2003;60:1020-1022
15. McCarron MO, Nicoll JA. Apolipoprotein e genotype and cerebral amyloid angiopathy-related hemorrhage. *Annals of the New York Academy of Sciences*. 2000;903:176-179
16. Lian L, Li D, Xue Z, Liang Q, Xu F, Kang H, et al. Spontaneous intracerebral hemorrhage in cadasil. *The journal of headache and pain*. 2013;14:98
17. Gould DB, Phalan FC, van Mil SE, Sundberg JP, Vahedi K, Massin P, et al. Role of col4a1 in small-vessel disease and hemorrhagic stroke. *The New England journal of medicine*. 2006;354:1489-1496
18. International Warfarin Pharmacogenetics C, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *The New England journal of medicine*. 2009;360:753-764
19. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of vkorc1 haplotypes on transcriptional regulation and warfarin dose. *The New England journal of medicine*. 2005;352:2285-2293

20. Darweesh SK, Leening MJ, Akoudad S, Loth DW, Hofman A, Ikram MA, et al. Clopidogrel use is associated with an increased prevalence of cerebral microbleeds in a stroke-free population: The rotterdam study. *Journal of the American Heart Association*. 2013;2:e000359
21. Fabre JE, Nguyen M, Latour A, Keifer JA, Audoly LP, Coffman TM, et al. Decreased platelet aggregation, increased bleeding time and resistance to thromboembolism in p2y1-deficient mice. *Nature medicine*. 1999;5:1199-1202
22. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding complications with the p2y12 receptor antagonists clopidogrel and ticagrelor in the platelet inhibition and patient outcomes (plato) trial. *European heart journal*. 2011;32:2933-2944
23. Yamada Y, Metoki N, Yoshida H, Satoh K, Kato K, Hibino T, et al. Genetic factors for ischemic and hemorrhagic stroke in japanese individuals. *Stroke; a journal of cerebral circulation*. 2008;39:2211-2218
24. The atherosclerosis risk in communities (aric) study: Design and objectives. The aric investigators. *American journal of epidemiology*. 1989;129:687-702