ARIC Manuscript Proposal # 3308

PC Reviewed: 12/11/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: New Diagnosis of Intracerebral Hemorrhage and the Risk of Subsequent Ischemic Stroke and Acute Myocardial Infarction

b. Abbreviated Title (Length 26 characters): **ICH and Arterial Thrombosis**

2. Writing Group:
Writing group members: Hooman Kamel, Ivan Diaz, Emily Levitan, Mitchell S.V. Elkind, Virginia Howard, George Howard, Monika Safford, Rebecca Gottesman, W.T. Longstreth Jr., and any others recommended by the committee.

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

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3. Timeline: Proposed Start Date: 01/01/2019; Proposed End Date: 12/31/2020

Study is funded by **NIH/NINDS K23NS105948 (**PI: Murthy), Expiration 02/28/2023

4. Rationale:

Intracerebral hemorrhage (ICH) accounts for 15-25% of all strokes in the U.S (Andaluz, 2009). Although it is the deadliest stroke type and often leads to severe disability, survivors of ICH do show substantial recovery during the months and years after the event (Hemphill, 2009). Among survivors, the burden of ICH is further compounded by incident ischemic stroke and acute myocardial infarction (MI), which are independently associated with 5-fold higher odds of death or disability (Garg, 2012). Therefore, prevention of further brain injury and worsened disability is a vital consideration in this vulnerable population. The majority of ICH patients have risk factors that are common to other ischemic cerebrovascular and cardiovascular diseases. As a result, these patients have a considerable risk for ischemic stroke and MI (Hanger, 2007). In fact, rates of clinical stroke in the first year after ICH are estimated to be 2-5% (Hill, 2000; Zia, 2009), while MI occurs in about 3-6% of ICH patients (Butler, 1998; Nielsen, 2015).

Prior studies of stroke and MI after ICH have not included control groups with rigorous adjustment for vascular risk factors and comorbidities, and thus the degree of stroke/MI risk after ICH remains unclear. In a preliminary study of Medicare patients, we found a significant association between ICH and subsequent risk of ischemic stroke or acute MI at the end of the first month (hazard ratio [HR], 6.7; 95% confidence interval, 4.9-8.6). The risk continued to remain elevated at the end of 6 months (HR, 2.4; 95% CI, 1.2-3.8). Notable limitations of prior studies including ours include the lack of data on premorbid use and resumption of antithrombotic medications and selection bias from the inclusion of only patients older than 66 years. These limitations underline the need for performing a similar study with more comprehensive data and better generalizability. Therefore, we propose a cohort study using data from 4 large epidemiological studies: REGARDS, the Cardiovascular Health Study (CHS), Atherosclerosis Risk in Communities (ARIC), and the Northern Manhattan Study (NOMAS) with prospectively adjudicated stroke and MI outcomes to evaluate this risk in those with and without ICH.

5. Main Hypothesis/Study Questions:

We aim to determine whether a new diagnosis of intracerebral hemorrhage is independently associated with subsequent ischemic stroke and acute myocardial infarction.

Hypothesis: A new diagnosis of intracerebral hemorrhage increases the risk of subsequent stroke and acute myocardial infarction, independent of traditional stroke risk factors.

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).

Study Design: We propose a cohort study of patient-level data from the REGARDS, CHS, ARIC, and NOMAS studies.

Study Subjects: All participants in the respective studies will be included.

Measurements, Outcomes, and Covariates: Our time-dependent predictor variable will be any new diagnosis of ICH. Patients who do not survive the first 30 days will be excluded from the analysis. Our primary outcome will be any adjudicated ischemic stroke or MI. Secondary outcomes will include ischemic stroke alone and MI alone. Ischemic stroke will include only clinically symptomatic cases. Diffusion-restricted lesions on brain MRI in ICH patients will not be counted as stroke for our study.

Our covariates will be as age, sex, race, income, education level, systolic blood pressure, antihypertensive drug therapy, diabetes mellitus, atrial fibrillation, smoking status, body mass index, congestive heart failure, chronic kidney disease, and antithrombotic medication use, collected at the time of study enrollment.

Data elements requested: age, sex, race, income, education level, systolic blood pressure, antihypertensive drug therapy, diabetes mellitus, atrial fibrillation, valvular heart disease, smoking status, body mass index, congestive heart failure, and chronic kidney disease, dates of occurrence of new ischemic strokes, MI and ICH, antithrombotic medication use if available, and mortality.

Brief Analysis Plan and Methods: We will use survival analysis to compare the risk of stroke/MI in those with and without ICH. Time of entry will be defined as the date of the enrollment visit for each study. New diagnoses of ICH will be modeled as a time-dependent covariate. Follow-up will be censored on last follow-up date or when patients experience the primary outcome, withdraw from the study, or die. In the proposed study, we plan to obtain data on vascular comorbidities at baseline (study enrollment). We concur that the covariates change over time, but also realize that logistically it may be difficult to capture this accurately over time, and across the different study populations. To navigate this issue, we propose to use Marginal Structural Models (MSMs). MSMs are a new class of causal models for the estimation, from observational data, of the causal effect of a time-dependent exposure in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables (Robins 2000). To account for possible unobserved baseline differences in the 4 study populations, we will adjust by a categorical variable indicating the source study. We will use a targeted minimum loss based estimation approach (Neugebauer 2007) for the marginal structural model. Based on our pilot data, we anticipate that the proportional hazards assumption will be violated, with a much stronger association in the first 6 months after ICH and a lesser or null association beyond this point. Our marginal structural model will include time-dependent effects and interactions with ICH, which will allow us to compute time-specific hazard ratios. Standard errors and confidence intervals will be computed using the bootstrap. Given that marginal structural models have lower power than the equivalent Cox models, if time-varying confounding does not cause bias, we will use a Cox model to get more precise estimates.

Sensitivity analyses: We would ideally like to exclude patients who experience an MI or ischemic stroke prior to ICH. However, given concerns over having an adequate number of ICH cases, we decided to be conservative in our main analysis. We will perform additional sensitivity

analyses after excluding these patients. It is also possible that the heightened risk of ischemic stroke and MI after ICH may be related to discontinuation of antithrombotic medications. However, there is a paucity of published literature on this topic. We propose to account for antiplatelet medications in our MSM as a covariate. Should there be any concern for residual confounding, then we propose to perform additional sensitivity analyses excluding patients on antithrombotic medications, assuming we have adequate power.

Power Estimation: The collective cohort from the four studies will include 50,000 participants with about 300 ICH patients who survived beyond 30 days. Using a highly conservative 6% combined event rate for ischemic stroke and MI (Soliman 2014, O'Neal 2015), we will have greater than 90% power to detect a HR of 3.0 with an α of 0.05 (Cox's Proportional Hazards Model command in PASS v13). While we acknowledge that the proposed statistical analysis is different from the analysis used to compute the above power, we believe this power calculation is a useful and informative approximation. Calculating the power for the proposed marginal structural model is not currently possible due to the absence of preliminary data to estimate the probability distributions required to compute the variance in the marginal structural model.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

Yes

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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

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.

References:

1. Andaluz, N. and M. Zuccarello (2009). "Recent trends in the treatment of spontaneous intracerebral hemorrhage: analysis of a nationwide inpatient database." J Neurosurg 110(3): 403-410.
2. Butler, A. C. and R. C. Tait (1998). "Restarting anticoagulation in prosthetic heart valve patients after intracranial haemorrhage: a 2-year follow-up." Br J Haematol 103(4): 1064-1066.
3. Hanger, H. C., T. J. Wilkinson, N. Fayez-Iskander and R. Sainsbury (2007). "The risk of recurrent stroke after intracerebral haemorrhage." J Neurol Neurosurg Psychiatry 78(8): 836-840.
4. Hemphill, J. C., 3rd, D. C. Bonovich, L. Besmertis, G. T. Manley and S. C. Johnston (2001). "The ICH score: a simple, reliable grading scale for intracerebral hemorrhage." Stroke 32(4): 891-897.
5. Hemphill, J. C., 3rd, M. Farrant and T. A. Neill, Jr. (2009). "Prospective validation of the ICH Score for 12-month functional outcome." Neurology 73(14): 1088-1094.
6. Hill, M. D., F. L. Silver, P. C. Austin and J. V. Tu (2000). "Rate of stroke recurrence in patients with primary intracerebral hemorrhage." Stroke 31(1): 123-127.
7. Garg, R. K., S. M. Liebling, M. B. Maas, A. J. Nemeth, E. J. Russell and A. M. Naidech (2012). "Blood pressure reduction, decreased diffusion on MRI, and outcomes after intracerebral hemorrhage." Stroke 43(1): 67-71.
8. Nielsen, P. B., T. B. Larsen, F. Skjoth, A. Gorst-Rasmussen, L. H. Rasmussen and G. Y. Lip (2015). "Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study." Circulation 132(6): 517-525.

9. Neugebauer, R., van der Laan, M. (2007). "Nonparametric causal effects based on marginal structural models." Journal of Statistical Planning and Inference 137(2): 419-434.
10. O'Neal, W. T., W. T. Qureshi, S. E. Judd, J. F. Meschia, V. J. Howard, G. Howard and E. Z. Soliman (2015). "Heart rate and ischemic stroke: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study." Int J Stroke 10(8): 1229-1235.
11. Robins, J. M., M. A. Hernan and B. Brumback (2000). "Marginal structural models and causal inference in epidemiology." Epidemiology 11(5): 550-560.
12. Soliman, E. Z., M. M. Safford, P. Muntner, Y. Khodneva, F. Z. Dawood, N. A. Zakai, E. L. Thacker, S. Judd, V. J. Howard, G. Howard, D. M. Herrington and M. Cushman (2014). "Atrial fibrillation and the risk of myocardial infarction." JAMA Intern Med 174(1): 107-114.
13. Zia, E., G. Engstrom, P. J. Svensson, B. Norrving and H. Pessah-Rasmussen (2009). "Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage." Stroke 40(11): 3567-3573.