ARIC Manuscript Proposal # 3357

1.a. Full Title: Trends in Heart Failure Hospitalization Before and After Stroke

b. Abbreviated Title (Length 26 characters): Heart Failure and Stroke

2. Writing Group:
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   Others welcome

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

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3. Timeline: We anticipate that a manuscript will be ready for submission 1 year after we receive the data.

4. Rationale:
Heart failure imposes a significant burden on individuals in terms of morbidity and mortality as well as health care costs and quality of life. In the United States, 6.5 million individuals are currently living with heart failure. (Benjamin et al. 2018) The lifetime risk of incident heart failure ranges from 20-45% in those 45 years and older (Benjamin et al. 2018) The five-year survival rate following diagnosis is 50%. (Yancy et al. 2013) Recent trends in the United States have seen a modest decline in heart failure incidence and longer survival. (Benjamin et al. 2018) This has contributed to higher prevalence of heart failure in the population. In the year 2014, there were 900,000 hospital discharges with a primary diagnosis of heart failure. The annual estimated cost of heart failure will be 69.7 billion by the year 2030. (Benjamin et al. 2018)

7.2 million Americans (2.7% prevalence) over the age of 19 have had a stroke. (Benjamin et al. 2018) Annually, 795,000 Americans have a stroke, with a little over three quarters of these being incident strokes. (Benjamin et al. 2018) Heart failure and stroke share common risk factors. Hypertension, diabetes, coronary heart disease, valvular heart disease, heart rhythm disorders, and elevated cholesterol are associated with both diseases. (Meschia et al. 2014, Benjamin et al. 2018) Additionally, lifestyle factors including physical inactivity, diet, smoking as well as obesity and central adiposity are also associated with increased risk of heart failure and stroke. (Meschia et al. 2014, Benjamin et al. 2018)

There are sex differences in the risk of heart failure and stroke. Men have a higher risk of heart failure and women have a higher risk of stroke. (Yancy et al. 2017, Benjamin et al. 2018) When considering heart failure subtypes by ejection fraction, black men have the highest rates of heart failure with reduced ejection fraction whereas white women have the highest rates of heart failure with preserved ejection fraction. (Benjamin et al. 2018)

Previous research has demonstrated an association between heart failure and stroke. (Abdul-Rahim et al. 2015, Agarwal et al. 2014, Alberts et al. 2010, Chen et al. 2017) A systematic review found stronger associations between stroke and heart failure with reduced ejection fraction (HFrEF). The association between heart failure and stroke has been observed in individuals with and without atrial fibrillation. (Kim and Kim 2018) Additionally, following a stroke, individuals may be at elevated risk of hospital readmission for cardiovascular events, including myocardial infarction, dysrhythmias, and heart failure. (Lakshminarayan et al. 2011) There was a significant increase in the risk of heart failure admissions one year after a stroke (HR = 1.8, CI = 1.3-2.7, p < 0.001). (Lakshminarayan et al. 2011) One gap in the literature on the risk of post-stroke heart failure is that prior works did not differentiate between heart failure subtypes or examine interactions with sex.

The aim of this proposal is to examine the associations between i) stroke and incident heart failure; and ii) stroke and risk of heart failure hospitalization. We will examine these two endpoints separately because although heart failure is primarily managed in the outpatient setting, stroke patients may be less able to manage medications and accomplish self-care. This could lead to additional hospital admissions for heart failure exacerbation or decompensation that would not have otherwise occurred. These analyses will examine potential interactions by sex. If power permits, we will also examine the associations within heart failure subtypes.

ARIC is an ideal data source for these analyses because of its multi-decade longitudinal follow up as well as adjudicated stroke and heart failure outcomes. Recognition of stroke as a risk factor for heart failure could help identify high-risk individuals and have important implications on the prediction and management of heart failure and forestall hospital admissions in stroke survivors.
5. Main Hypothesis/Study Questions:

Aim 1: What is the time course of incident heart failure in stroke survivors? When is the stroke survivor at highest risk of diagnosis of heart failure?

Aim 2: What is the time course of heart failure hospitalization in stroke survivors? When is the stroke survivor at highest risk of a heart failure hospitalization?

Aim 3: Do the associations between stroke and either incident heart failure or heart failure hospitalization vary by sex?

Aim 4 (exploratory): Does the association between stroke and incident heart failure vary by heart failure subtype?

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: The primary analysis will include ARIC participants who had an adjudicated ischemic stroke (N = approximately 600) and matched stroke-free controls. Controls will be matched 4:1 on sex, race, and age within two years.

Exclusion criteria: We will exclude individuals who reported a stroke or incident heart failure prior to visit 2. Hence, participants will have to have no past history of HF or stroke at the time of their visit 2. For aim 3, we will exclude individuals without ejection fraction data.

Independent variable: Incident stroke will be defined as adjudicated definite and probable ischemic strokes and intraparenchymal hemorrhages that occurred following visit 2 (1987-1989). Hospitalizations and deaths of ARIC participants were identified during annual follow up. A trained nurse abstracted medical records. Strokes were identified and categorized using a computer algorithm based on the National Survey of Stroke. Strokes were reviewed by a physician and disagreements between the algorithm and physician were resolved by a second physician. (Rosamond et al. 1999) We did not include subarachnoid hemorrhages since these are often due to rupture of aneurysm or other structural vascular malformations rather than a sequela of traditional vascular risk factors.

Dependent variable: Heart failure hospitalization will be defined as probable or possible acute decompensated or chronic stable heart failure. Medical records were reviewed for evidence of heart failure and, if present, trained staff completed a detailed abstraction. Abstracted records were reviewed and classified by two physicians. A third physician reviewer resolved disagreements. For aim 3, heart failure with preserved ejection fraction (HFpEF) will be defined as a left ventricular ejection fraction (LVEF) ≥ 45%. Ejection fraction will be identified using the heart failure abstraction forms.
Covariates: age, race, sex, hypertension, diabetes, myocardial infarction (MI), dyslipidemia, treatment for hypertension and diabetes, smoking status, body mass index, and health insurance type at visit 2. For aim 3, sex will be ascertained through self-report.

Analysis plan:

Primary analysis: We will examine baseline characteristics at visit 2 among ARIC participants with and without incident stroke using means and standard deviations for continuous variables and counts and percent for categorical variables. IQR will be used for skewed variables.

We will use Cox proportional hazards regression to examine the relationship between stroke and heart failure. Incident heart failure and index heart failure hospitalization will be examined separately. Extended Cox regression will be utilized if the proportional hazards assumption is not met. We will test for bias due to competing risk of mortality by using Fine and Grey extended Cox. For aims 1 and 2, we will first run a crude model, followed by a second model adjusting for relevant comorbidities (hypertension, diabetes, MI, dyslipidemia, treatment for hypertension and diabetes), and a third model adding smoking status, body mass index, and health insurance type. For aim 3, we will stratify by sex. For aim 4, if there are sufficient cases of incident heart failure with preserved and reduced ejection fraction, we will assess the risk of incident heart failure by subtype. Because these results may be biased due to the competing risks of the two subtypes of heart failure, we will run these models using Fine and Grey extended Cox regression.

We will conduct sensitivity analysis for the heart failure subtype specific analyses using cutoffs of < 40% for HFrEF and > 50% for HFpEF. All tests will be conducted in SAS using 2-tailed tests with a p-value < 0.05 considered statistically significant.

Limitations: Adjudication of stroke and heart failure in ARIC will reduce but not eliminate misclassification of the exposure and outcome. The secondary analysis may be limited by survival bias and confounding due to age.

References


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? _____ 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 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](http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html)

   _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)?

   #1701: Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study
   
   #2679: Neurocognitive function and quality of life in heart failure: the ARIC study.
   
   # 1265r: Common Allele on Chromosome 9p21 and Risk of Heart Failure, Stroke, and Atherosclerosis in The Atherosclerosis Risk in Communities (ARIC) Study

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 [https://www2.cscc.unc.edu/aric/approved-ancillary-studies](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](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.