ARIC Manuscript Proposal #2460

PC Reviewed: 11/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ___**

1.a. Full Title: **Prevalence of Sub-Clinical Infarctions by Brain MRI in Patients with Heart Failure who are At High Risk of Undiagnosed Atrial Fibrillation**

b. Abbreviated Title (Length 26 characters): **Undiagnosed AF in CHF**

2. Writing Group: (alphabetical): Lin Yee Chen, Rebecca Cogswell, Rebecca F. Gottesman, Scott Solomon, Alvaro Alonso, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. RJC

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3. Timeline: Statistical analysis: 2 months
Manuscript preparation: Part 1: 2 months, Part 2: 2 months

4. Rationale:

There are currently 6 million Americans with Heart failure (HF), and this number is projected to increase to 8.5 million by 2030.[1] Heart failure has been associated with accelerated cognitive decline, however the exact mechanism of this decline remains unclear.[2] While atrial fibrillation is a common co-morbidity in this patient group,[3,4] it is unknown how many patients have undiagnosed paroxysmal atrial fibrillation. Evidence is emerging that atrial fibrillation is associated with cognitive impairment or dementia even in individuals without a history of clinical stroke.[5] In addition, it has been recently demonstrated that by the time atrial fibrillation is diagnosed, subclinical brain infarctions can be detected by MRI along with measureable cognitive deficits.[6] Presence of these infarctions by brain MRI in patients with heart failure without a diagnosis of atrial fibrillation would suggest that atrial fibrillation is being missed. It may be that undiagnosed atrial fibrillation is responsible for some of the cognitive impairment observed in the heart failure population.

In this study, we propose to analyze whether a clinical diagnosis of heart failure is associated with the presence of subclinical infarcts by brain MRI in patients without a history of atrial fibrillation. We will also assess whether these subclinical infarcts are associated with the presence of mild cognitive impairment or dementia. This analysis will be performed first in patients with heart failure with preserved ejection fraction (HFpEF) and then be repeated in patients with heart failure with reduced ejection fraction (HFrEF).

Our overarching hypothesis is that undetected atrial fibrillation is common in the heart failure population, and failure to detect this is leading to subclinical brain infarcts and cognitive decline. If subclinical infarcts are detected in patients without atrial fibrillation, this would suggest that increased heart rhythm surveillance and earlier anticoagulation treatment may be needed. This would be the first step towards creating a change in clinical practice which has a large potential public health benefit.

5. Main Hypothesis/Study Questions

Part 1: Heart Failure with Preserved Ejection Fraction (HFpEF)

Aim #1: To assess whether cohort subjects with HFpEF and no documented atrial fibrillation (AF) have a burden of subclinical infarcts (SCIs) similar to patients with documented AF.

Hypothesis #1:
Cohort subjects with a diagnosis of HFpEF and no prior AF will have a similar number of SCI as those with documented AF (whether with or without HFpEF), which will be higher than cohort subjects without HFpEF or AF.

Aim #2: Evaluate the association between HFpEF and cognitive function as mediated through the presence of subclinical brain infarcts.

Hypothesis #2:
Cohort subjects with HFpEF, no AF but who have SCIs detected by brain MRI will have similar cognitive scores to subjects with HFpEF and AF. These cognitive scores will be lower than the other test groups (no HFpEF/no AF, no HFpEF/AF, HFpEF/noAF/no SCIs).

Part 2. Heart Failure with Reduced Ejection Fraction (HFrEF)

Aim #1: To assess whether cohort subjects with HFrEF and no documented atrial fibrillation (AF) have a burden of subclinical infarcts (SCIs) similar to patients with documented AF.

Hypothesis #1:
Cohort subjects with a diagnosis of HFrEF and no prior AF will have a similar number of SCI as those with documented AF (whether with or without HFrEF), which will be higher than cohort subjects without HFrEF or AF.

Aim #2: Evaluate the association between HFrEF and cognitive function as mediated through the presence of subclinical brain infarcts.

Hypothesis #2:
Cohort subjects with HFrEF, no AF but who have SCIs detected by brain MRI will have similar cognitive scores to subjects with HFpEF and AF. These cognitive scores will be lower than the other test groups (no HFrEF/no AF, no HFrEF/yes AF, HFrEF/no AF/no SCI).

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).

Part 1: HFpEF

Study Design
This is a **cross-sectional study** using data from visit 5/ARIC-NCS (2011-13) of the Atherosclerosis Risk in Communities Study. The number of subclinical infarcts detected by brain MRI will be compared among the following groups:

1) HFpEF, atrial fibrillation
2) HFpEF, no atrial fibrillation
3) No CHF, atrial fibrillation
4) No CHF, no atrial fibrillation

Study population:
Cohort subjects from visit 5/ARIC-NCS (2011-13) of the Atherosclerosis Risk in Communities Study.

Inclusion Criteria: Subjects with the following data from visit 5 will be included: echocardiogram with a measurable ejection fraction, brain MRI and cognitive testing. In addition, subjects will need to have complete data regarding incident heart failure and previous or current atrial fibrillation up to the time of visit 5.

Exclusion criteria

1. History of a permanent pacemaker implanted
    a. Rational: these patients will not have undiagnosed atrial fibrillation
2. Severe aortic stenosis (AVA < 1.0 cm^2) at the visit 5 echocardiogram
    a. Rationale: these patients do not have HFpEF
3. Diagnosis of Alzheimer's prior to visit 5
4. Patients on hemodialysis at visit 5 (these patient represent a different population, and HFpEF cannot be diagnosed in the presence of end stage renal disease)
5. Prior open heart surgery
    a. Rational: these patients have another mechanism for the presence of subclinical brain infarcts via cardiopulmonary bypass
6. Prior stroke
    a. Defined as any hospital discharge for stroke prior to visit 5

Variable definitions:

Primary Predictor:
HFpEF, defined as EITHER:

1) Incident adjudicated HF admission based on ARIC Mortality and Morbidity Classification Committee with an ejection fraction ≥ 50 % at the time of the hospitalization.

2) Prevalent HFpEF at visit 5 as defined by stage 3 or manifest HF according to Gothenburg criteria or the use of medications for HF at visit 5 AND left ventricular ejection fraction ≥ 50%.

Atrial fibrillation (dichotomous variable)
Presence of atrial fibrillation will be defined by either of the following:
1) A hospital discharge record showing an ICD-9 code of 427.31 (Atrial fibrillation)
2) Atrial fibrillation detected by ECG performed during any ARIC study visit

Outcome (Aim 1)
Subclinical cerebral infarcts (SCIs)
SCIs will be defined as the total number of focal, non-mass lesions ≥ 3 mm that are bright on T2 and proton density, and dark on T1 images.

Covariates
Baseline variables: age, race, hypertension, diabetes, hypercholesterolemia, smoking (never, former, current), coronary artery disease.

The following variables will be tested for interaction:

Treatment with:

1) warfarin
2) statin
3) ASA

Statistical plan (Aim 1): Multivariate linear regression, cross-sectional analysis.

The four groups will be treated as a categorical variable in the multivariate analysis. Additionally the groups will be tested individually against No CHF/no A fib as the reference group.

The following baseline echocardiographic variables (LA volume indexed (mL/m^2), LA diameter (cm), IVS diameter (mm) as well as nt-bnp (continuous and categorical) will be tested in a logistic regression model along with HFpEF to assess for the odds of having any subclinical infarcts (dichotomous outcome).

Outcome (Aim 2) Neurocognitive function

1) Z-scores from 3 neuropsychological tests: Delayed Word Recall (DWR) Test, Digit Symbol Substitution (DSS) Test, and Word Fluency (WF) Test, as well as a global cognitive scores derived from these tests

2) Cognitive function as defined as normal, mild cognitive impairment or dementia by the ARIC neurocognitive committee from comprehensive neurologic testing at visit 5.

Covariates
Baseline variables: age, race, gender, level of education, occupation, hypertension, diabetes, hypercholesterolemia, smoking (never, former, current), coronary artery disease, myocardial infarction, body mass index.

Statistical plan (Aim 2): Multivariate linear regression, cross sectional analysis.

For Aim 2, there will be 5 comparison groups:

1) HFpEF, atrial fibrillation
2) HFpEF, no atrial fibrillation, no SCIs
3) HFpEF, no atrial fibrillation, yes SCIs
3) No CHF, atrial fibrillation
4) No CHF, no atrial fibrillation

The five groups will be treated as a categorical variable in the multivariate analysis. To test the association between HFpEF and cognitive function, separate models will be run for each cognitive test (DWR, DSS, and WF) and the global cognitive scores.

The models will consist of CHF status (time-dependent), a term for the interaction of CHF x time, and covariates: age, race, gender, educational level, occupation, current smoking, body mass index, hypertension, diabetes, coronary heart disease or myocardial infarction, as well as interactions between time and covariates.

To be tested as a mediator: subclinical cerebral infarcts (SCIs)

Part 2: Heart Failure with Reduced Ejection Fraction
The above protocol will be repeated substituting HFrEF for HFpEF. The only difference in the design and analysis plan is the exclusion criteria.

Exclusion criteria:

1. History of an ICD or pacemaker implanted
    a. Rational: these patients will not have undiagnosed atrial fibrillation
2. Previous diagnosis of Alzheimer's prior to visit 5
3. Prior open heart surgery
4. Prior stroke
    a. Defined as any hospital discharge for stroke prior to visit 5.

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/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)?

#1739: AF and Cognitive Decline – Chen
#1740: AF and Dementia – Chen

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* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1999.01 – ARIC MRI Study**,** 2008.12 AF ancillary study**)**

*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.

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

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2. Gottesman RF, Grega MA, Bailey MM, et al. Association between hypotension, low ejection fraction and cognitive performance in cardiac patients. *Behavioural neurology.* 2010;22(1-2):63-71.
3. Redfield MM, Borlaug BA, Lewis GD, et al. PhosphdiesteRasE-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure (RELAX) trial: rationale and design. *Circulation. Heart failure.* Sep 1 2012;5(5):653-659.
4. Vukasovic RJ, Castro GP, Sepulveda ML, et al. [Characteristics of heart failure with preserved ejection fraction: results of the Chilean national registry of heart failure, ICARO]. *Revista medica de Chile.* May 2006;134(5):539-548.
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6. Chen LY, Lopez FL, Gottesman RF, et al. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. *Stroke; a journal of cerebral circulation.* Sep 2014;45(9):2568-2574.