1.a. Full Title: Seasonal variations in heart failure admissions

b. Abbreviated Title (Length 26 characters): Heart failure, seasonal

2. Writing Group:
   Writing group members: Lara C. Kovell, Stephen P. Juraschek, Patricia Chang, Edgar R. Miller III, Lisa Wruck, Wayne Rosamond, Stuart D. Russell, others welcome

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

First author:
Address: Lara C. Kovell, MD
   Department of Medicine
   1830 E. Monument St.
   Suite 9020
   Baltimore, Maryland 21287
   Phone: 410-955-7911
   Fax: 410-955-0374
   E-mail: lara@jhmi.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
   Name: Stuart D Russell, MD
   Address:
   Johns Hopkins University School of Medicine
   1800 Orleans Street, Zayed Tower 7125S
   The Johns Hopkins Hospital
   Baltimore, MD 21287
   Phone: (410) 955-5708
   Fax: (443)287-3180
   E-Mail: srussel4@jhmi.edu

3. Timeline: Data analysis to begin after approval of this manuscript proposal. First draft should be available by June, 2014.
4. **Rationale:**

Over 5.1 million Americans have heart failure (HF), a devastating disease associated with high morbidity, mortality, and cost. The estimated cost of HF was $32 billion in 2013 with projections predicting $70 billion by 2030, as the population ages and disease prevalence increases. Along with rising costs, the annual number of HF admissions has surpassed 1 million since 2000. Multiple precipitants for HF exacerbations, leading to hospitalization, are well known - including medication or dietary non-adherence, ischemia, arrhythmia, and infection. Less commonly considered are physical or environmental stressors leading to HF admission, including changes in ambient temperature. Previous studies have been done in other countries to demonstrate the impact of change in season on heart failure admissions, and have shown a higher rate of HF admissions in colder months. One study done in New Jersey emergency departments corroborated an increase in HF visits during colder months with a higher HF admission rate in warmer months. However, nationwide studies in the US have not been attempted to determine trends in this country.

The mechanism for this seasonal variation is unclear, though multiple hypotheses have been postulated. Some suggest it is the direct effect of the cold temperature, which causes peripheral vasoconstriction, increased heart rate and blood pressure. Another contributor is the increase in upper respiratory illnesses such as influenza in the winter. A winter peak has also been established in myocardial infarction, which also may contribute as ischemia precipitates HF exacerbations.

Given the diverse demographic composition of the Atherosclerosis Risk in Community [ARIC] Study, we seek to examine the effect of seasonal variation on hospitalizations and deaths due to HF and to examine possible contributors to this pattern.

5. **Main Hypothesis/Study Questions:**

**Primary study questions:**
1. To investigate the hospitalization rate and mortality rate by month and season to confirm the pattern of seasonal variation in heart failure admissions:
   a. Hospitalizations
   b. Length of hospital stay
   c. CHF-mortality
2. To characterize the co-morbidities, demographics, presenting vitals, lab abnormalities, echo findings associated with HF admissions

**Secondary study questions:**
1. To evaluate whether age, sex, race, and socioeconomic status modify the relationship between season and heart failure admissions
2. To examine factors precipitating admissions (e.g. pneumonia, non-compliance with medications, non-compliance with diet, angina, afib/aflutter) and whether these are associated with season.
Hypotheses:

1. Patients with HF have decreased reserve to deal with hemodynamic stressors. As the temperature decreases in the winter, HF patients will have more admissions due to the increased hemodynamic stress to their systems, including increased heart rate, blood pressure, decreased water loss, increased vasoconstriction and circulating catecholamine levels.

2. Patients with summer admissions will have more comorbidities and higher 28-day and 1-year mortality rates than those admitted in the winter

3. Lower SES patients will have more admissions in the winter

4. Elderly patients (>75 years old) will have increased mortality rates in the winter, due to the increase comorbidity associated with concomitant respiratory viruses.

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: Prospective analyses of data from the ARIC Study.

Inclusion/Exclusion:
We will include the community surveillance component from all four field centers, Forsyth County, North Carolina; Jackson, MS; northwest Minneapolis suburbs, Minnesota; Washington County, Maryland. Exclude those with acute MI as their primary diagnosis and those with incomplete hospital records.

Outcome:
HF hospitalizations identified through community-wide hospital surveillance via trained personnel. The following separate outcomes from the annual surveillance data will be examined in this proposed study:

1. Hospital admissions

2. All-cause mortality, ascertained through December 31st, 2010.

3. 28-day and 1-year mortality after HF admission

4. Length of stay

Other Variables of Interest:
Covariates will include gender (male or female), age (continuous), race (black or white), field center, body mass index (continuous), hypertension history (average SBP>140, DBP>90, or medication use), eGFR-CKDEPI creatinine equation
(continuous), ejection fraction (categorical), coronary heart disease (dichotomous), atrial fibrillation/Flutter (dichotomous), diabetes (dichotomous), stroke (dichotomous), depression (dichotomous), anemia (dichotomous), COPD (dichotomous), sleep apnea (dichotomous), education (dichotomous greater or less than high school), insurance status (dichotomous, yes or no), smoking status (current, former, and never), alcohol status (current, former, and never), mean monthly temperature by site, and diuretic use.

Precipitating factors: noncompliance with diet (dichotomous), noncompliance with medication (dichotomous), pneumonia (dichotomous), angina/myocardial infarction (dichotomous), atrial fibrillation/flutter (dichotomous)

Lab values: hemoglobin (continuous, g/dL), ProBNP (continuous, pg/mL), Troponin T (continuous, ng/mL), sodium (continuous, mEq/L), serum creatinine (continuous, mg/dl), BUN (continuous, mg/dL)

Discharge medications: ACE inhibitors, Angiotensin II receptor blockers, beta blockers, digitalis, diuretics, aldosterone blocker, statin, nitrates, hydralazine (all dichotomous)

Analysis Plan

Table 1: Population characteristics, by season
- age, sex, race
- BMI, EF, BP, HR
- HTN, DM, Afib, CAD, stroke, CKD, COPD, depression, anemia, sleep apnea
- smoking, alcohol status
- Length of stay
- precipitating factor for admission

Figure 1: HF admissions by month of the year
- overall
- 4 separate graphs for the 4 communities, with mean max and min monthly temperature

Figure 2: Mortality rates by month/season

Table 2/Forest Plot: Independent predictors of in-hospital mortality
- Age, gender, race
- Comorbidity - CHD, HTN, DM, CKD, Afib, etc
- Na < 135, EF < 35
- summer admission
- winter admission

Table 3: Discharge treatment by LV EF, stratified by season
- EF ≤ 35; EF > 35; no EF
- % on ACE inhibitors, ARBs, beta-blockers, digoxin, diuretics, aldosterone blocker, nitrates, hydralazine
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 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 _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](http://www.cscc.unc.edu/ARIC/search.php) ____ Yes _X_ 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)?

ARIC Publications on Heart Failure:

Aric Publications on Mortality:


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.cscc.unc.edu/aric/forms/](http://www.cscc.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