ARIC Manuscript Proposal # 1551

PC Reviewed: 9/8/09                  Status: A                  Priority: 2
SC Reviewed: __________            Status: ____             Priority: ____

1.a. Full Title: Characteristics, treatment and outcome in heart failure with preserved vs. reduced ejection fraction: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): HFpEF vs. HFrEF

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

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3. Timeline:
Following approval of this manuscript by the ARIC Publications Committee this work will lead to manuscript within 15 months.
4. **Rationale:**

Heart Failure (HF) is a major public health problem in the US [1]; while it has grim prognosis (30% mortality at one year) [2], its treatment cost exceeds those for both coronary artery disease and cancer combined and requires about 5.4% of the total US health care cost [3].

Symptomatic HF patients are categorized into those with predominantly reduced left ventricular systolic function vs. those with preserved (symptoms attributed to diastolic dysfunction) because of possible prognostic and therapeutic differences between them [4]. Furthermore, there is no standard definition of diastolic dysfunction. It is mostly a diagnosis of exclusion of systolic heart failure (ejection fraction >50%) in the presence of symptoms of cardiac congestion [4]. Also, the thresholds used for defining ‘preserved’ ejection fraction varies across studies [4].

Recent studies exploring heart failure with preserved ejection fraction (HFpEF) suggest that an average of 50% HF cases based on Framingham criteria [5], and 30% or more with clinical criteria based diagnosis may have ejection fractions greater than 50% [6]. ACC/AHA guidelines attribute 20-40% of the HF to be diastolic in nature [7]. Similarly, almost half of the patients hospitalized for HF had an ejection fraction of ≥ 40% [8]. While, the incidence of HFrEF may be declining due to better management, particularly reperfusion therapy, the incidence of HFpEF may be rising [9] Further, HFpEF prevalence might have been underestimated in the absence of effective diagnostic tools i.e., patients with HFpEF may have been ascribed to other co-morbidities, which exist with high frequency in the elderly [10].

Patients with HFpEF tend to be older, to be female, and to have a history of hypertension more commonly than heart failure with reduced ejection fraction (HFrEF) [8, 11, 12]. Among patients admitted with HFpEF a lower proportion had diabetes, coronary artery diseases, and hyperlipidemia; whereas a higher proportion had lung disease, and atrial fibrillation. [6] Further, obesity is strongly associated with diastolic dysfunction, possibly through intermediaries such as pulmonary hypertension, right heart dysfunction [13], and LVD [14] mediated through sleep apnea and other pathways, finally leading to HF since ventricles are interdependent (Bernheim and reverse Bernheim phenomenon).

Despite its high burden and the economic cost of diastolic HF (or HFpEF) there is a paucity of clinical trials providing clues for its optimal treatment [4]. Importantly, there may be differences in the ways patients with these two entities are cared for. Bursi et al. show lower prescription of ACE inhibitors and beta blockers to HFpEF patients despite evidence of beneficial effect of ACEI in this population [15]. Also, results from large hospital based data from Canada show that patients with a preserved ejection fraction were less likely to receive primary care from a cardiologist and were less likely to have had a cardiology consultation than patients with a reduced ejection fraction [6]. Such differences could account for some of the poor outcome seen among HFpEF patients [6].

Heart failure patients with a preserved ejection fraction had complication rates similar to those of patients with a reduced ejection fraction, including similar rates of cardiac arrest, acute coronary syndrome, renal failure, and admission to the ICU or coronary care unit [6]. The survival among HFpEF is poor, with six months mortality rates similar (16%) in patients with HFrEF and HFpEF [15], with the latter probably having slightly better survival [9]. Additionally, although there is a decrease in mortality rates after diagnosis of HFrEF; the same is not seen for HFpEF [16]. In the Framingham Heart
Study, although the mortality at 6.2 years was more than four times that of matched controls in both HFpEF and HFrEF, the overall mortality rate among HFpEF was lower. However, a large cohort of patients admitted with HF showed no statistical differences in mortality at 30 days or one year among those with ejection fraction >50% as compared to those with EF< 40%[6]. Senni et al. reviewed 13 smaller studies examining the outcomes of patients with heart failure and found that 6 of the 13 studies did not show a significant difference in mortality between the two sub-entities[17].

Lastly, little is known about the risk predictors of mortality among patients with HFpEF. A recent study suggested that history of ischemic heart disease, a history of dilated cardiomyopathy, and non-sinus rhythm are independent predictors of in-hospital mortality in these patients[18]. Also, diabetes was seen to have a stronger adverse effect (cardiovascular morbidity and hospital readmissions) among HFpEF than HFrEF patients [19].

The above mentioned studies defined the presence of heart failure using various criteria including Framingham, International Classification of Diseases (ICD) discharge codes, or rarely clinical judgment. However, the proportion and case fatality of HFpEF and HFrEF, may differ when different HF classification schema are used and requires an examination. Similarly, differences in the characteristics and treatment between HFpEF vs. HFrEF using a contemporary classification (i.e. “ARIC criteria”) are worth examination. Similarly, an exploration of potential predictors of case fatality among HFpEF and HFrEF groups (defined using “ARIC criteria”) from the available abstracted elements will be examined.

5. Main Hypothesis/Study Questions:
The study questions below will explore the impact of HF classification schema and ejection fraction thresholds to define HF, and preserved EF, respectively. The criteria to be used to define HF are: Framingham, Boston, NHANES, and ARIC, and the thresholds of ejection fraction to define preserved HF are ≥ 40 and ≥ 50%.

1. To estimate the proportion of hospitalized HF patients, and case fatality with reduced vs. preserved ejection fraction using two aforementioned ejection fraction thresholds and the above mentioned (n =4) HF classification criteria.

2. To compare the clinical and socio-demographic differences of patients admitted with acute heart failure (HF) with preserved vs. reduced ejection fraction using ‘ARIC criteria’ to define HF and ≥ 50% threshold to define preserved function.

3. To evaluate the differences in the in-hospital care received by HF patients with preserved vs. reduced ejection fraction using ‘ARIC criteria’ to define HF and ≥ 50% threshold to define preserved function.

4. To estimate the differences in, and predictors of case fatality among HF patients with preserved vs. reduced ejection fraction using ‘ARIC criteria’ to define HF and ≥ 50% threshold to define preserved function through 2007.
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).

A computer classification of HF events (n = 3851) using several criteria (Framingham, Boston, NHANES, and Gothenburg) is in place. Also, classification of events using “ARIC criteria” for the year 2005 (n= 1285) and year 2006 (n=1555) is almost complete. The Coordinating Center is about to release closed cohorts file (including all deaths through 2006) and mortality data through 2007 may be available by mid year.

Proportion of HF patients with preserved function will be reported for each of the four HF criteria and using two ejection fraction thresholds. Assuming an annual death rate of >20% among patients admitted with HF, there will be more than 500 deaths at one year following hospitalization. Survival analysis using Cox regression models will be done to model time to death, and also time to readmission for the cohort (repeated events, with robust variance adjustment) contrasting the HFpEF with HFrEF defined using four HF criteria and two ejection fraction thresholds.

Descriptive statistics will be reported for characteristics (socio-demographics, clinical signs and symptoms present, comorbidities, imaging findings, and laboratory values including BNP) and medical care (use of various diagnostic tests, and in-hospital treatment) contrasting HFpEF with HFrEF (HF defined using “ARIC criteria” and using a threshold of ≥ 50% to define preserved function).

Predictors of mortality will be identified using backward elimination in Cox regression model for each of the HFrEF and HFpEF subgroup separately (HF defined using “ARIC criteria” and a threshold of ≥ 50% to define preserved function).

Ejection fraction value will be picked in following hierarchy: current hospitalization echocardiogram, current hospitalization ventriculogram/magnetic resonance, previous hospitalization echocardiogram, previous hospitalization ventriculogram/magnetic resonance, missing. For those with missing the characteristics will be described as a separate category.

7. a. Will the data be used for non-CVD analysis in this manuscript? No

8.a. Will the DNA data be used in this manuscript? 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.

No overlaps found.
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)?

MP#1331 Comparison of Hospitalized Heart Failure Diagnostic Criteria

Other proposals looking at risk factors of HF:
MP#922 Alcohol consumption and risk of congestive heart failure
MP#890B Plasma Fatty Acid Composition and Incidence of Heart Failure in Middle Aged Adults
MP#1118 Kidney Function as a Risk Factor for Incident Heart Failure
MP#1125 Diabetes, obesity and insulin resistance as risk factors for incident hospitalized HF
MP#1144 The Obesity Paradox in Heart Failure.
MP#1160 Life Course Socioeconomic Exposures and Heart Failure.
MP# 1164 Hemoglobin A1c as a Risk Factor for HF Hospitalization among Persons with Diabetes.
MP#1197 Albuminuria as a Predictor of Incident Heart Failure Hospitalization and Mortality.
MP#1232 ECG Abnormalities Preceding Heart Failure: Estimation and Prediction
MP#1276 Exhaustion and risk for congestive heart failure.
MP#1342 The preventable burden of heart failure due to obesity and hypertension.
MP#1377 Relationship between pulmonary disease, lung function and incident hospitalized heart failure.

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/

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:


11. Sweitzer, N.K., et al., Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol, 2008. 101(8): p. 1151-6.


