1.a. Full Title: Enumerating the community burden of heart failure

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

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

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3. Timeline:
Analyses will begin once the manuscript proposal is approved.

4. **Rationale:**

Heart failure (HF) is a major and growing public health concern affecting approximately 5.8 million Americans.\(^1\) While the considerable morbidity and mortality attributed to HF can be greatly reduced by optimal treatment and clinical management,\(^2,\)\(^3\) almost one-half of those hospitalized for HF die within five-years after diagnosis.\(^4\) Importantly, there are indications that unrecognized ventricular dysfunction and HF are common in older adults,\(^5\) women, the obese, and persons with chronic obstructive pulmonary disease and type 2 diabetes.\(^6\)

Available estimates suggesting that HF is such a pressing public health problem are largely drawn at fixed points in time from closed cohorts, hospitalizations for decompensated HF, or medical care billing data. As a result, the extant picture of the population burden of HF and its temporal trends is manifestly incomplete, particularly for outpatient settings.

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

1. Estimate the reproducibility of self reported HF across annual follow up questionnaires.

2. Quantify the validity and predictive value of individual annual follow up questionnaire items that assess self-reported HF symptoms, signs and treatment for HF vs. (a) reports by a medical provider, (b) hospitalization discharge codes / validated HF hospitalizations and (c) Medicare claims data indicating HF.

3. Estimate the association of self-reported signs and symptoms associated with HF and measured on the annual follow up questionnaires with (a) hospitalizations and CMS claims data that list HF ICD-9- screening codes and (b) physician reported HF diagnosis / treatment for HF.

4. Estimate the association of physician diagnosed HF over the course of the ARIC cohort follow-up with (a) hospitalizations and CMS claims data that list HF ICD-9 codes and (b) physician reported HF diagnosis / treatment for HF.

5. Screen for HF by applying the Gothenburg criteria to data reported by the ARIC cohort members during annual follow-up calls, their physician visits, emergency department visits and hospitalizations, and the associated diagnoses.

6. Estimate the outpatient and inpatient prevalence of HF in ARIC cohort members using data provided by Aims 1-5, outpatient and inpatient CMS data, hospitalizations listing HF codes, and reports by participant’s treating physicians.

7. Characterize the transition from HF managed in outpatient settings to acute/decompensated HF events requiring hospitalization, including the associated precursors and correlates.

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).**
**Gothenburg score.** The Gothenburg score was introduced in 1987 as a HF screening tool.\(^7,8\) The score is derived from cardiac signs and symptoms, pulmonary signs and symptoms, and therapies for HF, and used to classify patients into four groups with increasing likelihood of having HF. For this study, we will construct Gothenburg scores using data from annual follow up questionnaires and the Physician Heart Failure form.

**Statistical methods.** Initially, we will examine the data by a) evaluating completeness, plausibility and the logical consistency of measured values; b) exploring univariate and bivariate distributions; and c) generating descriptive statistics for each sex-race-outcome stratum. Interval scale variables will be evaluated using both continuous and categorical parameterizations, with cut-points informed by clinical guidelines and percentile thresholds. Transformations will be used when indicated.

**Estimate the reproducibility, validity, and predictive value of individual phone interview questionnaire items vs. Physician Heart Failure data, hospitalization discharge codes, and CMS claims data (Aims 1-4).** Concordance between nominal HF indices will be examined using the kappa statistic. The following benchmarks will be used to characterize reliability: slight reliability, 0-0.2; fair reliability, 0.21-0.4; moderate reliability, 0.41-0.6; substantial reliability, 0.61-0.8; and almost perfect reliability, 0.81-1.0.\(^9\) We will also compare self-reported HF to indications from all available HRA forms in ARIC surveillance and self-reported HF indicators to items obtained from the PHF.

An outpatient Gothenburg score and score based on Stage I analyses will be derived using AFUL questionnaire items. Agreement between the HF scores, HF hospitalizations, CMS data, and self-reported HF will be assessed using the kappa statistic.

**Estimate the prevalence of outpatient HF (Aim 6).** Initially outpatient HF will be defined as either a physician-confirmed HF diagnosis or three Medicare HF outpatient codes (428.x, 402.x1, 404.x1, 404.x3) in any position within two years. Additional definitions of HF based on combinations of outpatient codes will be investigated as demonstrated by the literature.\(^10\) For comparison, the prevalence of inpatient HF will also be evaluated using validated HF events and combinations of Medicare HF inpatient codes. The annual prevalence of HF will be estimated in the combined population and by sex and race using Poisson regression adjusting for age.

**Characterize the transition into (chronic) HF, Aim 7.** We will investigate the feasibility of evaluating the natural history of HF with multi-state Markov models (MSM), the most commonly used models for describing the development for longitudinal data.\(^11\) The simplest MSM is a mortality model for survival analysis that describes two states, alive or dead, and only one transition. However, the “alive” state can be partitioned, as shown in Figure 13.E. Cox proportional hazard or Poisson models can be used to estimate the rate and probability of transitioning between the various states described in Figure 13.E as well as the mean time in a given state and life expectancy.
Transition probabilities are estimated several ways. For a non-parametric Markov model without covariates, cumulative incidence estimates (i.e. $P_j(s,t) = P(\text{in state } j \text{ at time } t \mid \text{in state } h \text{ at time } s)$) are obtained using the Aalen-Johansen estimator.\textsuperscript{11} Cox-type regression models estimate transition probabilities by product-integration of the intensities.\textsuperscript{12} Although estimates of $\lambda_4$, $\lambda_5$, and $\lambda_6$ are available in several populations, few studies have examined transitions from the healthy to outpatient HF ($\lambda_2$) or from outpatient HF to inpatient HF ($\lambda_1$) or death ($\lambda_3$) or considered the transition between all four states concurrently.

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.csec.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)?

This manuscript is related to #1282 (Heiss, Outpatient Surveillance of Heart Failure). Drs. Heiss and Rosamond are members of the writing group and have approved this proposal.

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  

____X__ A. primarily the result of an ancillary study (list number* _2008.17_ )

_____ 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.cscce.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


