1.a. **Full Title:** Predicting risk in heart failure with preserved ejection fraction – a model based on clinical features at hospital presentation

b. **Abbreviated Title (Length 26 characters):** Predicting risk in HFPEF

2. **Writing Group:**

   Writing group members: Tonje Thorvaldsen, Sunil K Agarwal, Brian Lee Claggett, Patricia Chang, Wayne Rosamund, Scott Solomon, others welcome

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

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3. **Timeline:** This study analysis is to begin immediately with anticipated manuscript submission within 6 months.
4. **Rationale:**

Heart failure (HF) is the leading cause of hospital admissions among older adults in the US\(^1\). About 40-50\% of patients presenting with acute decompensated heart failure (ADHF) are estimated to have preserved ejection fraction (HFPEF)\(^2,3\). Prognosis in HF is grim, though highly variable between individuals. Several models for predicting survival in HF exist\(^4-8\), some of which are derived from clinical trials or single centers and thus maybe less applicable to the general HF population, some are restricted to patients with reduced ejection fraction (HFREF) and some are developed for ambulatory patients limiting the use in a hospital setting. The HF registries ADHERE, OPTIMIZE-HF and Get With The Guidelines Program have all developed risk predicting models for inhospital mortality for patients admitted with HF regardless of ejection fraction, identifying between 3-7 risk factors of importance\(^9-11\). Though the risk score from the latter study was validated for the subgroup of HFPEF patients, comprehensive inpatient risk-prediction models specifically developed for HFPEF patients are lacking.

Clinical features of HFPEF have been described in several studies\(^12,13\), compared to HFREF, these patients are more often older, female and overweight and they more commonly have a history of hypertension. Atrial fibrillation and chronic kidney disease may also be more prevalent in HFPEF patients\(^14\). Less is known about predictors of outcome among these patients. Decreased renal function and hypotension at admission seem to be strong predictors of mortality both in HFREF and HFPEF\(^15\).

No treatment has yet been shown to reduce mortality in HFPEF. A better insight in which factors relate to poor outcome may help targeting new treatment options. Moreover early risk assessment at the time of hospital presentation may guide clinicians in their decision making, identifying patients in need of more intensive monitoring and therapy.

We will use the Heart Failure Community Surveillance in the ARIC study to create a model for risk-prediction in patients with HFPEF presenting with ADHF.

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

Specific aim:

To create a model predicting risk in patients hospitalized with HFPEF based on clinical features and lab values at presentation. The threshold to define preserved ejection fraction will be set to ≥50\%.

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).**
This study will analyze events from the Heart Failure Community Surveillance in the ARIC study, including the years 2005 through 2012.

Events of ADHF, defined as definite or probable by the ARIC classification, with an EF $\geq 50\%$ will be included. Patients with a previous EF $< 50\%$ (normalized EF) will be excluded. We will analyze those events with current or previous information on EF.

Ejection fraction will be picked as the first non-missing value using the following order:

1) Current hospitalization: TTE, MRI, CT scan, radionuclide ventriculogram, Coronary angiography, Stress test, TEE
2) Previous hospitalization : same order as current hospitalization

All analyses will be weighted by the specified sampling fractions.

**Outcome variables:** Case fatality (CF) at 28 days and at 365 days.

**Potential covariates for the model:** Demographics (age, sex, race), health insurance status, vitals (BMI, systolic and diastolic blood pressure, heart rate), signs and symptoms at presentation/onset of ADHF (rales, jugular venous distension, edema, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, chest pain, cough), laboratory values (hemoglobin, sodium, creatinine, BUN, natriuretic peptides, troponins), previous medical history (smoking habits, anemia, atrial fibrillation/flutter, previous CHD/myocardial infarction, previous history of HF, incident or recurrent hospitalization for HF, stroke/TIA, depression, diabetes, dialysis, hypertension, COPD, sleep apnea, pulmonary hypertension, peripheral vascular disease, thyroid disease, ventricular arrhythmia), previous procedures (revascularization/CABG, defibrillator, pacemaker ), HF treatment prior to event (ACEi, ARB, betablockers, MRA, digoxin, statins, diuretics), , types of HF (ischemic, idiopathic/dilated), signs on chest x-ray (alveolar/pulmonary edema, cardiomegaly, congestion).

**Other variables of interest:** Center, hospital length of stay, imaging findings during hospitalization, in-hospital mortality, discharge diagnoses.

**Descriptive statistics:** Patient characteristics will be compared between those who died and those who survived at 28 and 365 days respectively. Categorical data will be displayed as percent frequencies and compared by $\chi^2$ or Fisher exact tests. Continuous data will be displayed as means ($\pm$SD) for normally distributed variables and medians (interquartile range) for variables with skewed distributions, comparison will be performed by Wilcoxon rank sum test or t-test as appropriate. The level of significance will be set to 5% and all p values will be 2-sided.

**Risk predicting model:**

We will build one model predicting 28 day CF and one predicting 365 day CF.
We will assess whether there are any significant differences in the relationship between each variable and short-term vs. long-term risk of death (28 days vs. 365 days).

Potential variables for the risk-predicting model will be defined based on review of literature, clinical relevance, risk predicting role in univariate analysis and availability in the Community Surveillance.

To select the final variables for the model we will use logistic regression with a stepwise selection process applying both forward and backward selection techniques.

Best fitting logistic regression models will be developed and performance measures of the model calculated. These will include goodness-of-fit statistics and c-statistics.

**Missing data:**
We intend to use variables which contain ≤3% missing data in the model. For categorical variables with more than 3% missing we will add the category “unknown” where “missing” will be included, in that way events with missing data can be included in the multivariable model.

We will consider a sensitivity analysis including the variables that are excluded from the main analysis because of missing data.

7.a. Will the data be used for non-CVD analysis in this manuscript?  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? 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.cscce.unc.edu/ARIC/search.php](http://www.cscce.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)?

#1551 Characteristics, treatment and outcome in heart failure with preserved vs. reduced ejection fraction: The Atherosclerosis Risk in Communities (ARIC) study

#2281 Race and gender differences in heart failure with preserved ejection fraction: Morbidity, Case Fatality, and their Determinants

We have been in contact with Sunil K Agarwal, first author of proposal #1551 and part of the writing group of proposal #2281 and our project will be in collaboration with him.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 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/

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

12. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. 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.* Apr 15 2008;101(8):1151-1156.