ARIC Manuscript Proposal # 3001

1.a. Full Title: The Impact of the Severity, Duration and Longitudinal Changes in the Metabolic Syndrome on the Risk of Incident Heart Failure.

b. Abbreviated Title (Length 26 characters): Metabolic Syndrome and HF


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

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3. **Timeline:** We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. **Rationale:**

Heart failure is a major and growing public health challenge given its high prevalence, morbidity, mortality and associated medical costs. Heart failure incidence approaches 10 in 1000 in those over the age of 65 and on average the lifetime risk of congestive heart failure is 1 in 5 for both men and women [1, 2]. There are currently nearly 6 million HF patients in the U.S. and approximately half of those diagnosed with heart failure die within 5 years of their diagnosis [2]. Furthermore, by 2030, the prevalence of heart failure is expected to increase to 8 million [3]. Management of patients with heart failure (HF) also poses a significant financial burden on society with an estimated annual cost of 53.1 billion by 2030, with most of those costs linked to hospitalization of heart failure patients [4]. Given these significant burdens associated with HF, there is a growing emphasis on identifying individuals at increased HF risk that may benefit from targeted preventive therapies. One such subgroup is those individuals with the metabolic syndrome (MS).

MS is diagnosed by having three of the following cluster of cardiovascular (CV) risk factors: elevated blood pressure, hyperglycemia, low HDL-cholesterol, elevated triglycerides, and abdominal obesity [5]. Metabolic syndrome is highly prevalent, being found in a third of U.S. adults [6] and up to 29% of children with obesity [7]. In prospective analyses, the presence of MS has been associated with a 2.5-fold higher risk of heart failure [8] and a 1.5-fold increase in risk of all-cause mortality [9]. In clinical guidelines, those with MS have therefore been categorized as a group at high risk for HF. However, several aspects of the relationship between MS and HF have not been characterized, including the impact of the severity and duration of MS and changes in MS components over time on the likelihood of developing HF.

We will therefore evaluate how the severity, duration and changes in MS over time influence HF risk within the prospective, community-based Atherosclerosis Risk in Communities (ARIC) study. With serial measures of metabolic risk factors and extended continuous surveillance for HF events within a diverse and broadly representative population, ARIC is well-suited to provide novel insights regarding this research question.

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

**Aims:**

1) To evaluate whether a longer duration of having the metabolic syndrome components is associated with an increased incidence of congestive heart failure.
2) To determine whether an increase in the number of metabolic syndrome components over time is associated with an increase in the incidence of congestive heart failure.

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: This will be a prospective analysis examining the association between changes in metabolic syndrome components over time and the development of incident heart failure. We will utilize visit 4 participants without HF or coronary heart disease (CHD) and examine the association between MS changes from visit 1 through visit 4 with the risk of incident HF occurring after visit 4.

Exposures: The primary exposure will be metabolic syndrome components as defined by the AHA/NHLBI criteria [Abdominal obesity (male waist > 40 in; female waist > 35 in), Triglycerides >= 150 mg/dL or on TG lowering therapy, HDL cholesterol (male < 40; female < 50) or on HDL improvement therapy, Blood pressure >=130/=85 or on BP therapy and Fasting glucose >= 100 mg/dL or on glucose lowering therapy]. We will examine various metrics including presence or absence of MS at each study visit; the number of MS components at each visit; changes (increase or decrease) in the number of MS components over time and the duration of MS.

Outcomes: The primary outcome is the development of incident heart failure occurring after visit 4 and through December 31, 2013. Incident heart failure will be defined as HF hospitalization or death as determined from hospital discharge coding and death certificates. We will perform additional analyses utilizing only adjudicated HF cases (from 1/1/2005 onwards) with further testing done after the adjudicated HF cases have been stratified by type [heart failure with reduced ejection fraction v. heart failure with preserved ejection fraction].

Exclusions: We will exclude those with DM, HF or CHD (given that ischemia is a principle mechanism for the development of heart failure and is associated with MS) at or prior to visit 4. We will also exclude those with missing data on MS components at any of the study visits (from visit 1 to visit 4) and the small number of participants that are not categorized as black or white.

Covariates: Age, sex, race, socio-economic status, smoking status, alcohol use, educational level, occupation and total cholesterol, measured at Visit 4.

In sensitivity analyses, we may also adjust for hs-CRP, hs-cTnT and NT-proBNP as assessed at visit 4.
Main Analyses: We will evaluate the association between changes in MS components over time and the risk of incident heart failure using the analytic steps below.

1) We will perform univariate comparison of demographics, lifestyle factors and clinical characteristics among those with and without MS at visit 4.

2) We will construct Cox regression models, adjusted for the covariates listed above, to evaluate the association between the presence of MS at Visit 4 and the risk of HF after Visit 4.

3) We will construct Cox models to assess the associations of the number of MS components at each of the first 4 study visits (Visits 1, 2, 3 and 4) and the risk of HF occurring after Visit 4. We will also assess the association of each individual metabolic syndrome factor (abdominal obesity, low HDL, elevated TG, hyperglycemia and elevated blood pressure) with incident HF.

4) We will construct cross-categories of the presence and absence of MS at Visit 1 and Visit 4, creating 4 groups: 1) MS absent at Visits 1 and 4; 2) MS present at Visit 1 and absent at Visit 4; 3) MS absent at Visit 1 and present at Visit 4; 4) MS present at Visits 1 and 4. Using group 1 as the reference, we will assess the association of each subgroup with the risk of incident HF after Visit 4.

5) We will assess the association between the duration of MS (from Visits 1 through 4) with the risk of HF occurring after Visit 4. MS will be coded as 0 or 1 at each visit and the product of the presence of MS and the length of time between visits (in years), summed for each visit interval, will be used to determine duration of MS.

6) Among those without MS at Visit 1 (<3 components), we will assess the impact of progression or stability in MS components from visits 1 through 4 on HF risk after Visit 4. We will categorize changes in MS components as: 1) 0 components at Visits 1 and 4 (reference); 2) no MS by Visit 4, with stable number of MS components (stable 1 or 2 components at Visits 1 and 4); 3) no MS by Visit 4, with mild progression in MS components (progression from 0 to 1 or 2, or from 1 to 2, from Visit 1 to 4); 4) progression to MS by Visit 4, with 3 MS components; 5) progression to MS by Visit 4, with 4 or 5 components. We will assess the associations of each subgroup with incident HF risk. In additional sensitivity analyses, we will create subgroups for the limited number of individuals who decreased in the number of metabolic syndrome components from Visits 1 to 4.

7) We will assess the risk of incident HF after Visit 4 per increase in MS component from Visit 1 to 4 among those without metabolic syndrome at Visit 1.

8) We will perform analyses stratified by race and gender and test for interactions between metabolic syndrome changes and these demographic subgroups on the risk of incident HF.
9) Additional analyses will be also performed using adjudicated heart failure cases. These cases will be subdivided by the type of heart failure (heart failure with reduced ejection fraction or heart failure with preserved ejection fraction).

Sensitivity Analysis:

- In sensitivity analyses, we will additionally adjust for hs-CRP, hs-cTnT and NT-proBNP
- In sensitivity analyses, we may also adjust for incident CHD occurring before the onset of HF, as a time-varying covariate.

Limitations:

- There is the likelihood for some residual confounding in our efforts to evaluate the relationship between the number of metabolic syndrome components and the how they change over time and the development of HF.
- The use of hospitalization and discharge codes for the diagnosis of incident HF may have resulted in some misclassification.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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  ____ 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.cscu.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)?

The association of Insulin Resistance with Incident Heart Failure: the Atherosclerosis Risk in Communities (ARIC) study. ARIC Proposal Number: 1883

Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) Study. ARIC Proposal Number: 1125

The association of hemoglobin A1c with incident heart failure among persons without diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. ARIC Proposal Number: 1488

Does cardiac troponin T help identify subjects with metabolic syndrome at higher risk of cardiovascular events? An analysis from the ARIC study. ARIC Proposal Number: 2319

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.
Reference List


