ARIC Manuscript Proposal #1883

PC Reviewed: 12/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of Insulin Resistance with Incident Heart Failure: the Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:

Writing group members: Orly Vardeny, Stuart Burke, Amil Shah, Laura Loehr, Laura Rasmussen-Torvik, Elizabeth Selvin, Patty Chang, Davide Castagno, David Aguilar, Madoka Takeuchi, Scott Solomon

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

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3. Timeline: Analysis to begin immediately, First draft by June 2012

4. Rationale:

Diabetes increases the risk for developing heart failure .[1] Insulin resistance, with or without diabetes, has also been shown to elevate the incidence of heart failure .[2-4] Ingelsson et al examined rates of incident heart failure after 9 years, based on measures of insulin resistance at baseline in Swedish men 70 years or older at baseline.[5] In unadjusted Cox proportional hazard analysis, fasting glucose, fasting insulin, fasting proinsulin, homeostasis model assessment insulin resistance (HOMA-IR) index, and impaired two hour oral glucose tolerance test were associated with an increased incidence of heart failure. When the models were subsequently adjusted for presence of diabetes and established risk factors (prior acute myocardial infarction, hypertension, electrocardiographic left ventricular hypertrophy, smoking, and serum cholesterol) impaired two hour oral glucose tolerance test and fasting proinsulin remained associated with an increased incidence of heart failure. In another study of 20,810 Veteran Administration patients, fasting blood glucose levels between 110 and 125 mg/dl were associated with an increased incidence of heart failure.[6]

Two studies have investigated the relationship between hemoglobin A1c values and the incidence of heart failure in the Atherosclerosis Risk in Communities (ARIC) study cohort.[7,8] Both studies related hemoglobin A1c values collected at ARIC Visit 2 to incident heart failure (death from HF or hospitalization from HF), and one of the studies included patients without diabetes at baseline.[7] Hemoglobin A1c values greater than 5.5% were associated with higher incidence of heart failure. Previous work in ARIC has also described the relationship between obesity and incident HF.[9] While obesity and insulin resistance are strongly linked, recent evidence in smaller studies has suggested that obesity without insulin resistance may have different prognostic importance than obesity that is associated with insulin resistance.[10] These relationships have not been explored in large cohort populations.

We propose to investigate the relationship between insulin resistance and the incidence of heart failure, to explore interactions with BMI/obesity, and determine the prognostic value of insulin resistance relative to HbA1c. HOMA-IR, a measure of both the ability to produce insulin and sensitivity to insulin, can be calculated in ARIC from fasting insulin and glucose values, measured at Visits 1 & 4. In contrast to previous studies that have related insulin resistance to incident HF, the ARIC cohort is a large bi-ethnic sample and offers the potential to explore interactions between BMI and insulin resistance with respect to incident HF, and to determine the incremental value of insulin resistance over HbA1c, which has already been explored in this cohort.

5. Main Hypothesis/Study Questions:

We hypothesize that insulin resistance will be associated with an increased risk for incident heart failure, heart failure hospitalizations, and death from heart failure. We further hypothesize that insulin resistance may modify the relationship between obesity and incident heart failure such that non-insulin resistant obese patients will be at reduced risk compared with insulin-resistant obese patients.

Specific Aims:

1. **To assess the relationship between insulin resistance at Visit 1 and visit 4 and subsequent incident heart failure. We hypothesize that insulin resistance will be related to incident heart failure in non-diabetics and independent of diabetes.**
2. **To assess how insulin resistance modifies the relationship between obesity and incident heart failure. We hypothesize that the relationship between obesity and incident heart failure is attenuated in patients without insulin resistance.**
3. **To compare the predictive value of HOMA-IR versus HbA1c as a predictor of incident heart failure (Visit 2).**

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).

Subjects with prevalent heart failure at visit one will be excluded as defined as either participant reported medication use for heart failure or Gothenberg score=3 or missing. Subjects with diabetes at visit one, defined as those self-reporting diabetes, those with elevated fasting blood sugar>126 or blood glucose>200, or those on diabetes medications, will be excluded for the primary analyses. In a separate analysis, participants who develop diabetes and/or heart failure between visits 1 and visit 4 will be excluded, and subsequent incident heart failure will be assessed following visit 4.
Analysis methods:

Primary Exposure Variable:

- HOMA-IR will be calculated from fasting insulin and fasting glucose values at Visit 1 and visit 4 utilizing the following formula: (fasting insulin)*(fasting glucose mg/dl)/405[11]

- HOMA-IR values will be categorized in the following standard groups: < 2.5, 2.5 – 4.0, > 4.0[12, 13]

Primary Endpoint: Combined incident heart failure, including heart failure hospitalizations or heart failure-related death.

Analysis:

1. Baseline characterististics will be compared between categorical HOMA-IR values using test for trend
2. Categorical HOMA-IR values at visit one and visit 4 will be related to incident heart failure with COX regression analysis in univariate and multivariable models adjusting for known confounders as well as those that are apparent based on baseline characteristics. These will include (but not be limited to): prior myocardial infarction, smoking, hypertension, and elevated serum cholesterol at

visit one. We will also test for interactions with BMI as a continuous variable and obesity (BMI > 30) as a categorical variable.

3. The change in HOMA-IR between visit 1 and visit 4 will be related to subsequent incident heart failure with COX regression analysis as described in #2.
4. Additional analyses will be performed using incident diabetes and myocardial infarction as time varying covariates, as well as sensitivity analyses excluding patients who develop diabetes or suffer MI prior to development of HF.
5. We will compare the predictive value of HOMA-IR (insulin resistance) relative to Hemoglobin A1c at visit two (adjusting for covariates) by assessing change in the C-statistic and with net reclassification techniques. For this analysis, we will exclude subjects with prevalent diabetes and heart failure at or prior to visit two.

Limitations

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- Unknown confounders may exist that are not accounted for in analysis models
- Death from HF assessed by death certificate, which may not capture all events
- May be more difficult to identify cases of diet controlled diabetes to exclude from models and include in sensitivity analyses

References

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2. Paolisso G, De Riu S, Marrazzo G, et al. Insulin resistance and hyperinsulinemia in patients with chronic congestive heart failure. *Metabolism.* 1991;40:972-977.
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4. Swan JW, Anker SD, Walton C, et al. *Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure.* J Am Coll Cardiol. 1997;30:527-532.
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6. Nielson C, Lange T. Blood glucose and heart failure in nondiabetic patients. *Diabetes Care.* 2005;28:607-611
7. Matsushita K, Blecker S, Pazin-Filho A, et al. The association of hemoglobin A1c with incident heart failure amoung people without diabetes: the atherosclerosis risk in communities study. *Diabetes.* 2010;59:2020-2026.
8. Pazin-Filho A, Kottgen A, Bertoni AG, et al. HbA1c as a risk factor for heart failure in persons with diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetologica* 2008;51:2197-2204.
9. Loehr LR, Rosamond WD, Poole C et al. Association of multiple anthropometrics of overweight and obesity with incident heart failure: the Atherosclerosis Risk in Communities study. Circ Heart Fail. 2009;2(1):18-24.
10. Voulgari C, Tentolouris N, Dilaveris P et al. Increased Heart Failure Risk in Normal-Weight People With Metabolic Syndrome Compared With Metabolically

Healthy Obese Individuals. J Am Coll Cardiol 2011;58:1343–50.
11. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care.* 2002;25(7):1177-1184
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13. Qu H-Q, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB (2011) The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. PLoS ONE 6(6): e21041. doi:10.1371/journal.pone.0021041

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

__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 most closely related manuscript proposals are #1488, #1164, #1125, #1144, corresponding to the following publications:

Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, Selvin E. The association of hemoglobin a1c with incident heart failure among people without diabetes:

the atherosclerosis risk in communities study. **Diabetes**. 2010 Aug;59(8):2020-6. Epub 2010 May 18. PubMed PMID: 20484138; PubMed Central PMCID: PMC2911067. ARIC Manuscript Number: 1488

Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. HbA 1c as a risk factor for heart failure in persons with Diabetes: the Atherosclerosis Risk in Communities (ARIC) study. **Diabetologia**. 2008 Dec;51(12):2197-204. ARIC Manuscript Number: 1164

Loehr LR, Rosamond WD, Poole C, McNeill AM, Chang PP, Folsom AR, Chambless LE, Heiss G. Association of multiple anthropometrics of overweight and Obesity with incident heart failure: the Atherosclerosis Risk in Communities study. **Circ Heart Fail**. 2009 Jan;2(1):18-24. ARIC Manuscript Number: 1125

Deswal A, Bozkurt B, Rosamond W, Heiss G, Chambless L, Chang P, Loehr L, Ballantyne C, Shahar E, Deswal JC. The obesity paradox in heart failure. ARIC Manuscript Number: 1144.

Loehr LR, Rosamond WD, Poole C, McNeill AM, Chang PP, Deswal A, Folsom AR, Heiss G. The potentially modifiable burden of incident heart failure due to obesity: the atherosclerosis risk in communities study. Am J Epidemiol. 2010;172(7):781-9. ARIC Manuscript Number: 1342

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