ARIC Manuscript Proposal #2022

PC Reviewed: 10/9/12 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Peripheral arterial disease and risk of incident heart failure in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): **PAD and heart failure**

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

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:

Peripheral arterial disease (PAD) is a marker for increased risk of all cause and cardiovascular mortality.[1-7] The presence of PAD is also associated with an increased risk of morbidity from atherosclerotic disease, such as myocardial infarction and stroke.[8-10] However, the relationship between PAD and heart failure has been relatively unexplored.

Among patients with prevalent heart failure, PAD is associated with increased risk of cardiovascular death or heart failure hospitalization.[11, 12] Heart failure patients with PAD also had lower baseline exercise capacity, lesser response to exercise training, and worse outcomes.[13] Few studies have addressed the association between PAD and incident HF. In the Cardiovascular Health Study of elderly Americans, an ankle brachial index (ABI) <0.9 was associated with an increased risk for heart failure in those without prevalent CHD (RR 1.61, 95%CI 1.14-2.29), although this was not the case in those with prevalent CHD (1.28, 95% CI 0.90-1.82).[4] In a secondary analysis of the Heart Outcomes Prevention Evaluation (HOPE), incidence rates for HF were higher in those with clinical evidence of PAD or ABI <0.9 as compared to those with normal ABI.[14] However, the Cardiovascular Health Study specifically evaluated an elderly population and the HOPE study recruited patients with known cardiovascular disease or several cardiovascular risk factors. Thus, the association between PAD and incident HF in a middle aged, lower risk, community dwelling bi-racial has not been evaluated.

Proposed mechanisms for the association between PAD and HF include increased atherosclerotic CAD, left ventricular hypertrophy, and vascular stiffness. Previous studies from ARIC have demonstrated that an ABI < 0.9 is a marker of atherosclerosis,[15,16] however, the association between PAD and cardiovascular outcomes and mortality is present even in those without coronary artery disease or when adjusting for prevalent coronary heart disease. Furthermore, in the Multi Ethnic Study of Atherosclerosis (MESA) abnormal ABI has been demonstrated to be associated with higher LV mass by cardiac magnetic resonance imaging even in the absence of other atherosclerotic disease.[17] In two cross sectional analyses of patients referred for PAD evaluation, echocardiography demonstrated a higher prevalence of left ventricular dysfunction among those with PAD as compared to those without, even in those without comorbid CAD.[18, 19] Together these data suggest that the association of PAD with adverse cardiovascular outcomes, in at least some patients, may be attributable to non atherosclerotic pathways. Indeed, vascular stiffness as measured by pulse pressure, and even when controlling for CAD, is an important contributor to the development of heart failure.[20] This association may be mediated by induction of cardiac hypertrophy as well impairments in coronary blood flow, precipitating ischemia even in the absence of epicardial coronary artery disease.[21]

The ARIC study offers a unique opportunity to explore the relationship between PAD and incident heart failure in a bi-racial middle aged community cohort. As well, the ARIC study allows for evaluation of whether the relationship between PAD and incident HF is modified by atherosclerotic CAD, left ventricular hypertrophy, vascular stiffness, in addition to gender and race.

5. Main Hypothesis/Study Questions:

Main Objectives:

1) Describe the relationship between ankle brachial index and incident heart failure
2) Describe the relationship between peripheral arterial disease and incident heart failure

3) Assess for effect modification by coronary artery disease, left ventricular hypertrophy, vascular stiffness, gender, and/or race on the relationship between peripheral arterial disease and incident 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).

This will be a longitudinal study of ARIC cohort participants beginning at visit 1 in whom ankle brachial index was measured.

Study population

To be included in the analysis the participant must have undergone measurement of ankle brachial index at visit 1 with available data regarding prevalent and incident heart failure status. Exclusion criteria include:

- Prevalent or missing HF status at visit 1. (Prevalent HF at visit 1 will be defined by stage 3 Gothenburg Criteria or use of HF medications).
- Missing HF status in follow up
- Missing information regarding ankle brachial index and/or PAD status at visit 1
- Missing covariate data (BMI, diabetes, hypertension, prevalent CHD, prior stroke, smoking status, alcohol status, systolic BP, diastolic BP, glucose, left ventricular hypertrophy by ECG, total cholesterol)
- Non African-American, Non White participants in ARIC as well as African Americans in the Minneapolis and Washington County cohorts.

Exposure and covariates

Participants will be categorized according to ankle brachial index ≤ 0.90, 0.90-<1.0, 1.0-<1.10, 1.11 to 1.40, > 1.40. Additionally, participants will also be categorized according to presence or absence of peripheral arterial disease based upon ABI < 0.9, intermittent claudication (roseic03), prior carotid endarterectomy (phea07c), prior non-coronary arterial revascularization (phea07e), prior lower extremity balloon angioplasty (phea09b).

Clinical characteristics and outcomes (incident HF) will be compared between categories of ABI and PAD, based upon data variables collected at visit 1. In particular, clinical variables to be evaluated include: age, sex, race, Rose claudication, hypertension, use of antihypertensive medications, diabetes mellitus, coronary artery disease, interim myocardial infarction, lipid levels, smoking status, body mass index, blood pressure, electrocardiographic left ventricular hypertrophy, sport index, arterial stiffness assessed via pulse pressure, and renal function/chronic kidney disease.

Outcome

The primary outcome of interest will be incident heart failure, defined as the first hospitalization with an ICD-9 code of 428.xx on the discharge summary or death with heart failure listed as the primary cause on the death certificate. The follow up period will be defined as the time elapsed from the visit 1 date to the date of incident HF, date of last contact for those lost to follow-up, or December 31, 2009. A secondary outcome will be the composite of death or heart failure over the same follow up period described above.

Statistical analyses:

Categorical variables will be compared via $\chi 2$ or Fischer exact test, while continuous data will be compared between groups via a non parametric trend test. P values < 0.05 will be considered significant. Incidence rates for heart failure will be calculated as number of events divided by person time at risk and will be stratified by race and category of ABI or presence of PAD. Time to event analysis will be performed according to the Kaplan Meier method with the log-rank test used to assess for differences. Univariate and multivariate hazard ratios for incident heart failure will be estimated using Cox proportional hazards regression, stratified by race. Effect modification by race, gender, coronary artery disease, left ventricular hypertrophy, physical activity, and arterial stiffness will also be tested. Sensitivity analyses excluding those participants with prevalent coronary artery disease at baseline will also be performed. Inclusion of incident PAD as a time varying covariate into regression models will also be performed. We will also perform these analysis using ABI as a continuous variable.

Limitations

ABI was measured on a single lower extremity and therefore this may reduce the sensitivity for identifying PAD. Additionally, ABI will only be assessed at visit 1 and thus the association between ABI and incident heart failure would not take into account the ABI at the time of incident HF event. Incident HF will be defined from ICD-9 codes from hospitalization discharge summaries that were not further adjudicated. However, this definition has been previously validated and utilized in ARIC. Arterial stiffness as assessed by pulse pressure may be less accurate than those of pulse wave velocity, however, PWV measures were not available during ARIC visit 1.

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)?

1) Timothy P. Murphy, Rajoo Dhangana, Michael J. Pencina, Ralph B. D'Agostino Sr. Ankle–brachial index and cardiovascular risk prediction: An analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis 220 (2012) 160–167.

2) Beth D Weatherley, Jeanenne J Nelson, Gerardo Heiss, Lloyd E Chambless, A Richey Sharrett, F Javier Nieto, Aaron R Folsom and Wayne D Rosamond. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987–2001. *BMC Cardiovascular Disorders* 2007, **7**:3.

3)Yang EY, Rubin J, Selvin E, Sharrett AR, Virani SS, Boerwinkle E, Coresh J, Ballantyne CM, Nambi V. The association between arterial stiffness and incident heart failure and microvascular disease – an analysis from the ARIC Study. *In this analysis the authors propose to assess the association between vascular stiffness (as measured by carotid distensibility at visit 2) and incident heart failure. This differs from our analysis, where we will use pulse pressure as a surrogate for vascular stiffness to examine whether this modifies the relationship between peripheral arterial disease and incident heart failure.*

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/

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.

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