

ARIC Manuscript Proposal #2694

PC Reviewed: 1/12/16
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Short-term prognostic impact of cardio-ankle vascular index (CAVI) in community-dwelling older adults

b. Abbreviated Title (Length 26 characters): CAVI in older adults

2. Writing Group:

Writing group members: Kunihiro Matsushita, Shoshana H. Ballew, Hirofumi Tanaka, Gerardo Heiss, and Josef Coresh, others welcome

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name:
Address:

3. Timeline:

This ancillary study will basically use existing data, and we anticipate to complete the project in 1 to 2 years depending on number of clinical outcomes of interest (see "Statistical Analyses" below).

4. Rationale:

Increased arterial stiffness (or reduced compliance) has been found to be an independent predictor of mortality and cardiovascular disease.¹ Although several parameters of arterial stiffness have been proposed and explored, carotid-femoral PWV is in general considered the standard measurement of central artery stiffness.¹ In this context, the American Heart Association has listed a new parameter of arterial stiffness, cardio-ankle vascular index (CAVI), with a few unique properties in their recent scientific statement.² CAVI is based on the arterial stiffness parameter β and reportedly not affected by changes in blood pressure during measurement.³ CAVI reflects stiffness of various arteries including aorta, femoral artery, popliteal artery and tibial artery.³ Indeed, several studies have demonstrated a close link of CAVI to cardiovascular risk factors and the presence of atherosclerosis.⁴ Moreover, CAVI does not

require probes for carotid and femoral arteries and is more easily measurable compared to carotid-femoral PWV.

However, unlike carotid-femoral PWV,⁵ to our knowledge, no studies have assessed whether CAVI can predict future adverse health outcomes, limiting its ability as a parameter of arterial stiffness in clinical practice and research. In this context, using data of heart-ankle PWV measured at visit 5 of the Atherosclerosis Risk in Communities (ARIC) Study during 2011 and 2013 and implementing algorithm behind CAVI, we will be able to “calculate” CAVI. Therefore, using this approach, we will assess whether CAVI will predict future adverse outcomes such as total mortality and cardiovascular outcomes and contrast its prognostic value with that of other arterial stiffness parameter such as carotid-femoral PWV, brachial-ankle PWV, and femoral-ankle PWV. Contrasting these different parameters regarding their prognostic values would be important since age-related stiffening, as well as the risk factor profile associated with arterial stiffness, differ between the central – elastic – arteries and the peripheral – predominantly muscular – arteries.⁶

5. Main Hypothesis/Study Questions:

The main aim is to assess whether CAVI is associated with clinical outcomes and if so whether its prognostic value is similar to or greater than that of other arterial stiffness parameters, i.e., carotid-femoral PWV, brachial-ankle PWV, and femoral-ankle PWV.

We hypothesize that CAVI will be associated with future adverse health outcomes and its association is similar to that of other PWV parameters.

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

Analyses will include all black and white participants at visit 5 with data on heart-ankle PWV. Using a conversion algorithm provided from Fukuda Denshi, CAVI will be calculated from heart-ankle PWV measured at ARIC visit 5. PWV parameters were measured with OMRON VP-1000 plus by certified technicians at ARIC visit 5 among 4,948 participants.

Exclusions

Race/ethnicity other than black or white

Participants with missing data on heart-ankle PWV at visit 5

Exclusions for tonometry data quality (body mass index [BMI] ≥ 40 kg/m², major arrhythmias [Minnesota code 8-1-3, 8-3-1, and 8-3-2], Minnesota code 8-1-2 with evidence of biased PWV waveforms, aortic aneurysms, abdominal aorta ≥ 5 cm, history of aortic or peripheral revascularization or aortic graft, aortic stenosis, moderate or greater aortic regurgitation)

Exposure Variables at Visit 5

- CAVI calculated from heart-ankle PWV and systolic and diastolic blood pressures
- Carotid-femoral PWV, brachial-ankle PWV, heart-ankle PWV, carotid-heart PWV, and femoral-ankle PWV, central pulse pressure, and augmentation index for contrast (“other arterial stiffness parameters”)

Traditional risk factors at Visit 5

- Demographics: age, sex, race, education
- Medical history/comorbidities: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, stroke, or peripheral artery disease), hypercholesterolemia, hypertension, diabetes mellitus
- Laboratory/vital/lifestyle measures: cholesterol levels (total, HDL, LDL), triglycerides, glucose levels, kidney function and damage markers, heart rate, systolic blood pressure, diastolic blood pressure, ankle brachial index, body mass index, smoking and drinking status
- Medications: antihypertensive medications, cholesterol-lowering medications, glucose lowering medication, and antiplatelet

Outcome Variables:

- All-cause mortality
- Cardiovascular mortality
- Coronary heart disease
- Heart failure
- Stroke
- Peripheral artery disease

Statistical Analyses

We will first summarize baseline characteristics according to CAVI and the other arterial stiffness parameters (e.g., their quartiles). Also, we will evaluate correlations between those measures of arterial stiffness. Subsequently, we will quantify the association of CAVI with adverse outcomes using Cox proportional hazards models. CAVI and the other arterial stiffness parameters will be modeled as their quartiles and as continuous variables (1-SD as a linear term or spline terms, as appropriate). We will also evaluate whether these stiffness parameters can improve prediction statistics (calibration, discrimination, and reclassification) beyond traditional cardiovascular risk factors. We will repeat the analysis in several key demographic and clinical subgroups to evaluate the robustness of our findings.

As of the end of 2012, there were 81 cases of cardiovascular outcomes or deaths during median follow-up time of 280 days. By April 2016, we anticipate to have outcomes through 2013 and anticipate a total of ~180 events. With 180 events, we will be able to detect hazard ratio of 1.52 per 1-SD increment of cardio-ankle vascular index (CAVI) with statistical power of 80%. This effect size is comparable to relative risk of 1.47 reported for aortic pulse wave velocity (PWV) in a meta-analysis.⁷ In case, event accrual is slower than our projection, we will update the results using outcomes through 2014, which should be available no later than April 2017.

Limitations

As stated in the prior section, we anticipate having adequate numbers of outcomes of interest for the overall analysis, although we would need to carefully our results from the mix of fatal and non-fatal cardiovascular events of various kinds. Due to relatively short follow-up time, statistical power can be an issue for some subgroup analyses. Some PWV measurements were not collected due to technical errors, participant factors and scheduling conflicts in some ARIC

participants. As with all observational studies, we cannot rule out the possibility of residual confounding.

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 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? 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.cscce.unc.edu/ARIC/search.php>

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)?

To our knowledge, there are no ARIC proposals for CAVI and the other arterial stiffness parameters and their associations with mortality and cardiovascular outcomes after Visit 5.

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* 2015.28)**
 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/>

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.csc.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References

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