ARIC Manuscript Proposal #2406

PC Reviewed: 8/12/14  Status: A  Priority: 2

SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title:  Repeatability of Ankle-Brachial Index in ARIC at Visit 5

b. Abbreviated Title (Length 26 characters): Repeatability of ABI

2. Writing Group:
Writing group members: Ada M Al-Qunaibet, Michelle L Snyder, David Couper, Hirofumi Tanaka, Susan Cheng, Kunihiro Matsushita, Mike Griswold, Aaron Folsom, and Gerardo Heiss, others welcome.

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

First author: Ada M Al-Qunaibet
Address: University of North Carolina at Chapel Hill
137 E. Franklin St., Suite 303
Chapel Hill, NC, USA 27514

Phone: 919-966-2392  Fax: 919-966-9800
E-mail: qunaibet@email.unc.edu

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: Gerardo Heiss
Address: University of North Carolina at Chapel Hill
137 E. Franklin St., Suite 400
Chapel Hill, NC, USA 27514

Phone: 919-962-3253  Fax: 919-966-9800
E-mail: gerardo_heiss@unc.edu

3. Timeline: Analysis is to start as soon as approval is obtained. We plan to complete the manuscript within three months from data analysis.

4. Rationale:
The ankle-brachial index (ABI), the ratio of the systolic blood pressure measured in the ankles and the arms, is a non-invasive tool used to assess peripheral arterial occlusive disease. Numerous studies have characterized an association of lower levels of ABI with atherosclerotic lesions in the lower extremities and in other arterial territories, as well as with subclinical atherosclerosis, clinical coronary artery disease, incident ischemic strokes, and recurrent strokes1-8. Furthermore, the ABI has been incorporated into risk prediction
equations to identify persons with moderate to high risk of cardiovascular morbidity and mortality\textsuperscript{2,4,6}.

Use of the ABI in clinical practice to assess peripheral arterial disease has been recommended\textsuperscript{8} based on the documented high sensitivity and specificity with clinical stenosis detected by imaging modalities as gold standard. The conventional documented method to measure ABI is the use of hand-held Doppler probes although its undesirable features are observer-dependent variability and the significant time invested in serially measuring systolic blood pressure at six sites. These considerations favored the introduction of oscillometric, automated devices for the acquisition of high quality ABI data in large-scale, multicenter studies such as The Atherosclerosis and Risk in Communities (ARIC) study. The agreement between Doppler-derived and oscillometric ankle pressures and ABI in healthy individuals and those with mild PAD has been acceptable in most studies.\textsuperscript{8} A major concern is potential overestimation of the leg pressure value with the oscillometric methods among severe peripheral artery disease cases, which may not be a significant concern in a community setting.\textsuperscript{8}

In Visit 5 ARIC used the (oscillometric) Colin VP-1000 Plus device to measure ABI, both for reasons of data quality and for efficiency of data acquisition. The validity of this device relative to the Doppler-based ABI has been documented\textsuperscript{9}, and was reported to be among the best performing devices in a meta-analysis of 25 studies comparing oscillometric devices vs. Doppler ABI,\textsuperscript{10} presumably due to the double cuff technology (one cuff to occlude arteries and another to detect oscillation) of this device. This system measures systolic pressure simultaneously in the upper and lower extremities; importantly, the average difference between the Doppler ABI value and the oscillometric ABI value when measured simultaneously is -0.02±0.02\textsuperscript{10}. Further, the efficiency of the procedure allowed for a repeat measurement separated by 5 minutes, thus reducing the variability by the square root of the number of measurements.

Several factors contribute to the within-subject ABI variability for a given method of ABI measurement and calculation, such as the observers (technicians) and the time elapsed between measurements, although these were reported to be of considerably smaller magnitude than the "biological" variability between subjects and between legs\textsuperscript{11}. To our knowledge, three studies have compared the reliability of the oscillometric method to the Doppler method in assessing ABI, and concluded that the oscillometric method is more reliable\textsuperscript{12-14}. Since the studies focused on the agreement between methods, they lacked a detailed evaluation of the reproducibility of the oscillometric device. Kollias et al. reported an intra-observer intra-class correlation coefficient of 0.92 for an oscillometric method of ABI using the Watch BP Office Device\textsuperscript{13}. Furthermore, the repeatability of ABI has been examined for the Dinamp 1846 SX,\textsuperscript{15-17} the oscillometric device used in ARIC prior to Visit 5. Weatherley et al estimated the reliability coefficient of ABI to be 0.61 (95\% confidence interval: 0.50, 0.70) in 119 individuals, based on a single measure of ankle and arm systolic blood pressure. The reliability coefficient of ABI increased to 0.70 when using an average of two arm and ankle
systolic blood pressures to calculate ABI. To our knowledge the repeatability of ABI using the Colin VP-1000 Plus, used in ARIC Visit 5, has not been examined in a multi-center, population based study.

The quality assurance protocol for ARIC’s Visit 5 examination included repeat measurements on a subset of participants attending Stage I that allows an evaluation of the repeatability of blood pressure measurements and of ABI performed by the Colin VP-1000 Plus. The aim of the proposed study is to characterize the 4-8 week repeatability of limb-specific systolic blood pressure and of ABI from Visit 5 of the ARIC study, to aid in the analysis and interpretation of ABI.

5. Main Hypothesis/Study Questions:

1. Quantify the repeatability of brachial and ankle systolic blood pressures measured bilaterally.
2. Quantify the repeatability of ABI.
3. Estimate the minimum number of ABI measurements needed to ‘correctly’ classify an individual as having PAD based on predefined clinical ABI cut points.

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 methodological limitations or challenges if present).

Study design:
This repeatability analysis will include a subset of ARIC Visit 5 participants from Stage I that were invited to participate in the Repeatability Study. Field center staff asked the first eligible participant seen each month if he/she were willing to return 4-8 weeks later to repeat the study visit. If the participant was not interested, the staff recruited the next eligible and willing participant for the Repeatability Study. The Repeatability Study included around 15 participants per field center (64 with PWV/ABI measurement; 11 Forsyth County, NC; 20 Jackson, MS; 14 Minneapolis, MN; 19 Washington County, MD). Trained technicians obtained PWV; ABI measurements following the same standardized ARIC PWV/ABI protocol and were blinded to the values from the original visit.

ABI was measured by the Omron Colin VP-1000 Plus system (Omron Co., Ltd., Komaki, Japan) following the ARIC Visit 5 home and field center procedures manual 2. The participant is asked to lie in a supine position with both arms resting a long side while bent 90 degrees at the elbows. Two ECG clips are attached on the inner side of both wrists, and adequately sized blood pressure cuffs are placed on both arms and ankles, and the blood pressure is measured simultaneously in the four limbs at least twice with a 2-5 minutes interval. Further detail of the procedure can be found in the ARIC Visit 5 home and field center procedures manual 2.

ABI is calculated by taking the ratio of the systolic blood pressure in the lower legs to the systolic blood pressure in the arms. The American Heart Association recommends using the higher systolic blood pressure of the right or left arm as the denominator to calculate the ABI bilaterally, and they recommend using the higher systolic blood pressure of the popliteal artery.
or dorsalis pedis artery to calculate the ABI for each leg. Clinically used ABI cut points are listed in the following table. The Colin VP-1000 Plus estimates ABI for each lower extremity as ABI = ankle systolic blood pressure / (higher of left and right arm systolic blood pressure). We will select the lowest ABI value from the lower extremities to place an individual into an ABI category.

<table>
<thead>
<tr>
<th>ABI value and range</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.40</td>
<td>Non-compressible arteries</td>
</tr>
<tr>
<td>1.00 – 1.40</td>
<td>Normal</td>
</tr>
<tr>
<td>0.90 – 1.00</td>
<td>Borderline</td>
</tr>
<tr>
<td>0.41 – 0.90</td>
<td>Mild to moderate diminished arterial supply</td>
</tr>
<tr>
<td>&lt; 0.40</td>
<td>Severely diminished arterial supply</td>
</tr>
</tbody>
</table>

Table 1. Reference cut points for ankle brachial index values.

**Other variables:** Age, gender, race, heart rate, systolic blood pressure, body mass index, smoking status, and use of antiarrhythmic or vasoactive medications.

**Inclusions:** All participants from the ARIC Visit 5 Repeatability Study that underwent the PWV/ABI measurement.

**Exclusions:** Missing information on ABI, and exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI ≥ 40 kg/m² and participants with major arrhythmias (based on ECG data for MN code 8-1-3, 8-3-1 or 8-3-2).

**Statistical Analysis:**

We will present means and standard deviations (SD) of ABI, brachial and ankle systolic blood pressure for both the right and left sides. If ABI has a skewed distribution, we will present medians and inter-quartile ranges and log transform variables for the analysis if there is a skewed distribution.

We will use a nested random-effects analysis of variance model to parse the variance of ABI into between-participant ($\sigma_p^2$), between-visit ($\sigma_{bv}^2$), and within visit-components ($\sigma_{wv}^2$). We assume that the means of the measures do not vary by visit or by order within visit, as previously described in the ECG repeatability analyses (ARIC MS# 894, 897, 2000, 2012).

To estimate the repeatability, the intra-class correlation coefficient (ICC) will be calculated by dividing the between-participant variance by the total variance [$\sigma_p^2/\sigma_{total}^2 = \sigma_p^2/\sigma_p^2+\sigma_{bv}^2+\sigma_{wv}^2$]. If ABI shows a skewed distribution, it will be log transformed for the ICC calculation since the confidence interval is sensitive to departures from normality. We will also calculate the standard error of measurement (SEM) as SEM = $\sqrt{\sigma_{bv}^2+\sigma_{wv}^2}$.

ABI is used to diagnose peripheral arterial disease (PAD) based on a cut point of 0.9. The agreement between- and within-visit in PAD diagnosis (ABI<0.9) will be examined using the Kappa (K) statistic, $K = (Po – Pe)/(1-Pe)$ where Po is the observed agreement and Pe is the expected agreement. We will also calculate 95% confidence intervals for the K statistic. We will use predefined levels of K statistic that have been reported in the literature to assess the level of agreement (Table 2). We do not expect to have many observations with an ABI of <0.9, due
to small sample size. Therefore, we will also conduct an analysis that categorizes ABI into quartiles, and calculate the agreement between- and within-visit using a weighted Kappa. The above analysis will be repeated for both right and left sides to measure agreement between sides.

To examine the use of repeated measurements in study design development and interpretation of results, we will estimate changes in ABI based on the variance and sample size for one- and two-sample study designs. We will calculate the minimal detectable change with 95% confidence (MDC95) between two time points for an individual that reflects true change above that of measurement error [MDC95 = SEM*√2*1.96]. For a two-sample study design, we will calculate the minimal detectable difference (MDD) between two measurements as MDD = [(√2*σ²_total)/N]*(t_α(df)+t_β(df)), using the MDD as a percent of the grand mean.

*Sensitivity analysis:* In a sensitivity analysis, we will investigate whether excluding participants using antiarrhythmic or vasoactive medications per the ARIC medication survey use (MSR Item 33.g) and/or specific medication codes in the ARIC database affects the repeatability estimates.

**Limitations:**
Peripheral arterial disease using ABI is available at only two time points, limiting the analysis to repeatability 4-8 weeks later. In addition, we will not be able to estimate the inter-observer and intra-observer variation.

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.csc.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)?
   - Reliability of the Ankle Brachial Index in ARIC and FHS (MS804); Eigenbrodt, M. L.
Ankle-brachial index and physical function and activity in older individuals: the Atherosclerosis Risk in Communities (ARIC) Study (MS2312); Kuni Matsushita

The association of kidney disease measures with arterial stiffness: The Atherosclerosis Risk in Communities (ARIC) Study (MS2241); Kuni Matsushita

Peripheral Arterial Disease as an Indicator of Enlarged Abdominal Aorta Diameters (MS2242); Ada Al-Qunaibet

Repeatability of Pulse Wave Velocity in ARIC (MS2309); Michelle L. Snyder

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/

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


22. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-174