ARIC Manuscript Proposal #2083

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

1.a. Full Title: Differences in the Impacts of Traditional Cardiovascular Risk Factors on Coronary Artery Disease and Stroke between Japan and US

b. Abbreviated Title (Length 26 characters): CVD predictors in Japan and US

2. Writing Group:
Writing group members:
Yuichiro Yano, MD, Kunihiro Matsushita, MD, PhD; Yingying Sang, MS; Shizukiyo Ishikawa, MD, PhD; Kazuomi Kario, MD, PhD; Aaron Folsom, MD, PhD; George L. Bakris, MD; Kazunori Kayaba MD, PhD; Yoshikazu Nakamura MD, PhD, Eiji Kajii MD, PhD, and Josef Coresh, MD, PhD; others welcome.

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

First author: Yuichiro Yano, MD
Address: American Society of Hypertension Comprehensive Hypertension Center, Department of Medicine, University of Chicago Medicine, 5841 S. Maryland Ave., MC 1027, Chicago, IL 60637, USA., Tel.: (773) 702-7936
E-mail: yyano@jichi.jp

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: Kunihiro Matsushita, MD, PhD
Address: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street (Rm W6017), Baltimore, MD 21205
Phone: (443) 287-8766  Fax: (443) 683-8358
E-mail: kmatsush@jhsph.edu

3. Timeline:
Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 3 months.
4. Rationale:

Coronary artery disease (CAD) and stroke are leading causes of mortality worldwide and account for over 30% of all deaths. In addition to their impacts on mortality, both CAD and stroke substantially affect quality of life. Due to the ageing of the population, their burden is expected to further increase. Thus, the prevention of these cardiovascular diseases (CVD) should be a public health priority.

There is a global variation in the relative burdens of CAD and stroke. Asian countries have greater mortality and morbidity from stroke compared with CAD, whereas the opposite is true in Western countries. The reasons for the variation are not well understood. High blood pressure (BP), advanced age, and heavy alcohol use are stronger predictors for stroke than for CAD, whereas dyslipidemia, diabetes mellitus, and smoking are more strongly linked to CAD. Therefore, the differences in the distribution of the traditional cardiovascular risk factors or their contributions to increased risk of CAD and stroke across regions have been considered to account for.

In terms of distribution of risk factors, in Japan, a country with a higher incidence of stroke than CAD, the circulating cholesterol levels have been lower compared with Western population. However, a recent report demonstrates that total cholesterol levels among Japanese are getting closer to those in the US during the past 20 years. Similarly, previous international collaboration studies showed no difference in BP values between Japan and Western countries.

Also, it is possible that traditional cardiovascular risk factors contribute to the risk of CAD and stroke differently across racial groups or regions, but data on this aspect are scarce. The INTERHEART study, a large, international, standardized, case-control study, indicated that there was a regional variation in the relative impacts of traditional risk factors (e.g., smoking, hypertension, and diabetes) on CAD events. Similarly, a regional variation has been reported for risk factors of stroke in the Asia-Pacific Cohort Studies Collaboration, e.g., higher impact of BP in Asian populations than in Australia or New Zealand. However, to our knowledge, no studies have simultaneously assessed the respective impacts of several traditional cardiovascular risk factors on stroke and CAD simultaneously in Asian and Western countries.

Therefore, using the combined database with two population-based cohort studies from the US (Atherosclerosis Risk in Communities [ARIC] Study) and Japan (Jichi Medical School [JMS] Study), we will comprehensively compare the strength of the association of key traditional cardiovascular risk factors in the Framingham CVD prediction tool (i.e., age, sex, smoking, hypertension, dyslipidemia, and diabetes) with CAD and stroke between the US and Japan. ARIC study will provide a great opportunity to compare whites and blacks separately with Japanese.
5. **Main Hypothesis/Study Questions:**

**Hypothesis 1:**
The impacts of traditional risk factors on CAD and stroke differ between Japanese and blacks and whites in the US. For example, we hypothesize a steeper association between BP and stroke in Japanese compared with blacks and whites in the US, and a steeper association between serum cholesterol and CAD in US populations compared with Japanese.

**Hypothesis 2:**
The incidence rate of CAD and stroke differs substantially in two cohorts (higher stroke incidence rate in Japanese than in US populations, and higher CAD rate in the US than in Japan)

**Hypothesis 3:**
The distribution of traditional risk factors differs between US and Japan.

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:** Prospective collaborative study using data from ARIC and JMS.

**Inclusions:**
**ARIC study:**
All black and white ARIC participants with data on traditional risk factors (i.e., age, sex, smoking, information about use of antihypertensive drugs, BP, serum total cholesterol, high-density lipoprotein cholesterol [HDL-C], and diabetic status) at visit 2. We will use visit 2 data (1990-92) to align with JMS (1992-93) regarding calendar year of baseline. Those with history of CVD at visit 2 will be excluded from the analysis.

**JMS study:**
All subjects who had data of traditional risk factors and did not have history of CVD at baseline (N~10,000).

**Exclusions:**
Individuals those with pre-existing CAD or stroke and missing data on the traditional risk factors at baseline in both studies.
Race/ethnicity other than whites or blacks in ARIC study,
**Exposure:** We focused on traditional risk factors for CAD and stroke included in the Framingham CVD prediction tool.\textsuperscript{13}

1. **Age and sex**
   The age range is 18-90 years in JMS and 46-70 years in ARIC at baseline for this study. Although we will first investigate all eligible participants from two cohorts, given that age is a potent risk factor for CVD, we will repeat the analysis in participants aged 46-70 years to match age range in both cohorts. We will primarily incorporate age and gender as predictors in prediction models but also test their potential interactions with other traditional risk factors.

2. **BP**
   **ARIC study:**
   Certified technicians measured three systolic and diastolic BP with participants in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer. The average of the second and third readings was recorded.

   **JMS-cohort:**
   The systolic BP and diastolic BP at baseline were measured using a fully automated and validated upper arm cuff-oscillometric device, the BP203RV-II (Nippon Colin). Blood pressure was measured once after resting for 5 minutes while seated.

3. **Lipid parameters**
   **ARIC study:**
   Total cholesterol and HDL-C were determined using enzymatic methods. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.

   **JMS-cohort:**
   Total cholesterol was measured using an enzymatic method (Wako; interassay coefficient of variation [CV], 1.5% for total cholesterol). HDL-C was measured using the phosphotungstate precipitation method (Wako; interassay CV, 1.9%). LDL-C was calculated using the Friedewald equation.

4. **Smoking status**
   **ARIC study:** At baseline a self-administered questionnaire asked for information about smoking status (never, past, and current).

   **JMS-cohort:** Ditto.
5. diabetes

**ARIC study:**
The serum glucose level was measured by means of the hexokinase method. Diabetes will be defined according to a standard definition based on glucose measurements (fasting glucose ≥126 mg/dl or non-fasting glucose ≥200 mg/dL), a self-reported diagnosis of diabetes, or medication use.

**JMS-cohort**
Blood glucose was measured via an enzymatic method (Kanto Chemistry; interassay CV, 1.9%). Diabetes will be defined according to a standard definition based on glucose measurements (fasting glucose ≥126 mg/dl or non-fasting glucose ≥200 mg/dL), a self-reported diagnosis of diabetes, or medication use.

**Outcome Incidence of CAD and stroke:**

**ARIC study:**
ARIC investigators conduct continuous, comprehensive surveillance for all cardiovascular disease-related hospitalizations and deaths in the four communities. All potential cardiovascular events are adjudicated using published criteria. We defined incident CAD as a definite or probable myocardial infarction, or definite coronary death. Stroke included definite or probable cases defined as sudden or rapid onset of neurologic symptoms that lasted for 24 h or led to death in the absence of another cause.

**JMS cohort:**
JMC cohort assessed definitive or probable myocardial infarction, stroke (ischemic and hemorrhagic), sudden death, and death (cause of death can be almost assessed). Angina and TIA were not included. The details of how to defined CVD events are described in the previous published data. Briefly, the definition of myocardial infarction is based on based on MONICA CRITERIA. Stroke is defined as sudden onset of a neurological deficit persisting for ≥24 hours in the absence of any other disease that could account for the symptoms. Sudden death is defined as unexplained sudden death within 24 hours of the abrupt onset of symptoms.

**Other variables of interest and covariates:**

**Statistical Analysis Plan:**
All statistical analyses will be performed with Stata version 12.1 (Stata Corp) at Johns Hopkins. Comparisons of baseline clinical parameters between Japanese, blacks and whites will be performed using the ANOVA with normal distribution or Kruskal–Wallis test for
variables with skewed distribution, and categorical parameters were compared with the chi-squared test.

Then, to assess whether the impacts of traditional risk factors on CAD and stroke differ across three racial groups, we will incorporate their interaction terms with traditional risk factors in Cox proportional hazards models. We will also conduct a test of difference in coefficients for traditional risk factors obtained from stratified analyses according to three racial groups. Traditional risk factors will be models as categorical variables as well as continuous variables when applicable. We will use the following categories: age ≤45 years, 46-50 years, 51-55 (ref), 56-60, 61-65 years, 66-70, and >70 years; systolic BP <120 mm Hg (ref), 120-139 mm Hg, 140-159 mm Hg, and ≥160 mm Hg; diastolic BP <80 mm Hg (ref), 80-89 mm Hg, 90-99 mm Hg, ≥100 mm Hg; total cholesterol <160 mg/dL (ref), 160-239 mg/dL, 240-279 mg/dL, and ≥280 mg/dL; HDL-C <35 mg/dL, 35-44 mg/dL, 45-49 mg/dL, 50-59 mg/dL (ref), and ≥60 mg/dL, diabetes yes vs. no (ref); smoking current vs. former/never (ref). For continuous predictors, we will calculate HR per 10 years for age, per 10 mmHg for BP, and per 10 mg/dL for lipids.

**Limitations:**
(i) As with any observational study, we will not be able to rule out the possibility of residual confounding. In particular, some unmeasured variables such as lifestyle (e.g., diet and physical activity) and sociodemographic factors (e.g., incomes and education) are important confounders. (ii) JMS cohort did not assess what type of antihypertensive drugs was used in hypertensive patients at baseline. Type of lipid-lowering therapy, including statin, was also not assessed in JMS cohort. However, the introduction of the first statin in Japan is 1989. Consequently, it is unlikely that this limitation would have change our inferences substantially. (iii) Available medications might vary between two countries. (iv) JMS cohort has ~400 cases and ~80 cases of incident stroke and CAD, respectively. Thus, the results, particularly for CHD, needs to be interpreted carefully in light of limited statistical power.

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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  
___ 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

___ 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)?

Although there are several ARIC proposals investigating the associations between traditional risk factors and stroke and CAD, there are no proposals comparing these associations between ARIC and Asian cohorts.

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.
References.


