ARIC Manuscript Proposal #2363

PC Reviewed: 5/13/14   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a.   Full Title: Association between plasma testosterone and the incidence of ischemic stroke and ischemic changes on brain MRI in the Atherosclerosis Risk In Communities (ARIC) cohort study

  b. Abbreviated Title (Length 26 characters): T and CVA

2.   Writing Group:
    Writing group members: Reshmi Srinath, MD; Sherita Hill Golden, MD, MHS; Kathryn A. Carson, ScM; Rebecca F. Gottesman, MD PhD; Adrian Dobs, MD, MHS

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __RS__ **[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).
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3.   Timeline: Data analysis will begin immediately with expected completion within 12 months.

4.   Rationale:
The overall goal of this proposal is to understand the relationship between testosterone level and risk of ischemic stroke and cerebrovascular disease associated changes on brain MRI. Cross-sectional observational studies in men have demonstrated that low testosterone is associated with increased all-cause mortality and cardiovascular mortality (Malkin et al. Heart 2010). We also know that low testosterone level is prevalent in up to 30% of the male population over the age of 60 and that levels decline with age(Harman et al. JCEM 2001). Low testosterone may cause elevated vascular risk mechanistically since it is associated with lipid abnormalities, insulin resistance, obesity and pro-atherogenic changes on the vasculature. A prospective case cohort study from France of ~500 men over the age of 65 suggested a J-shaped association between serum testosterone and risk of ischemic cardiovascular events including ischemic stroke (Soisson et al. Maturitas 2013). While another longitudinal cohort study of ~3700 community dwelling elderly men in Australia found a significant U-shaped association between serum total testosterone and all-cause mortality and a similar but nonsignificant association between testosterone and clinical cardiovascular events (Yeap BB et al. JCEM Jan 2014).

   We will use frozen samples from men in the ARIC cohort to look at the distribution of serum testosterone in males and to document the association with ischemic cerebrovascular events and associated brain MRI changes. Given the recent growth in therapeutic testosterone options the timing is ideal to consider the role of testosterone levels in ischemic stroke and cerebrovascular disease.

5.   Main Hypothesis/Study Questions: Low serum testosterone is associated independently with ischemic stroke risk and ischemic changes on brain MRI

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 cohort study, using ARIC visit 4 as baseline
Inclusion criteria: male> or equal to age 55 at visit 4, no prior history of coronary heart disease or ischemic stroke at baseline (ARIC Visit 4), no prior exposure to exogenous testosterone or exposure during the course of the study based on review of medications performed at baseline and follow up visits.
Exclusion criteria: females, males <age 55, known prior history of coronary disease or ischemic stroke at baseline (ARIC Visit 4), exposure to exogenous testosterone prior to or during the course of the study as assessed by review of medications performed at baseline and follow up visits.

Data to be collected: Plasma samples were requested from frozen samples taken from participants during visit 4(1996-1999). We have limited our analysis to those samples taken from males before 1030 AM with sufficient volume for laboratory analysis(>0.5 cc). Plasma total testosterone using liquid chromatography mass spectrophotometry was performed in 2012 by Dr. Shallender Bhasin (Boston University, Boston, MA).

Primary outcome: Incidence of ischemic stroke (adjudicated as definite or probable) with annual surveillance through at least 2010. Our other outcome is evidence on brain MRI of white matter hyperintensities, lacunar or other ischemic infarcts at visit 5.

Other covariates: Age, race/center, smoking status, adiposity (waist circumference, body-mass index), fasting LDL, triglycerides, HDL, diabetes status, fasting glucose, use of anti-lipid medications, hypertension status.

Analysis:
>   -Correlation analyses and chi-square tests will be used to determine the association between morning plasma testosterone and the following measures: age, race/center, smoking status, adiposity (waist circumference, body-mass index), fasting LDL, triglycerides, HDL, diabetes status, fasting glucose, use of anti-lipid medications, hypertension status.
>   -Survival analyses will be used to assess the relationship between morning plasma testosterone and incidence of ischemic stroke. Multivariable regression analysis will be adjusted for all covariates listed above.
>   -Linear and logistic regression models will be used to determine the association between morning plasma testosterone and white matter hyperintensities, lacunar or other ischemic infarcts on brain MRI at visit 5.
>   -When methods are finalized to analyze change/incidence of lacunar or other infarcts and progression of white matter hyperintensities between visit 3 and visit 5, we will consider evaluating this in a separate analysis.

Data analysis will be conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC)

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"?

    __x__ 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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes ____ No

11.b. If yes, is the proposal
  A. primarily the result of an ancillary study (list number* 2008.01, 2011.02)
  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:

Harman SM, Metter EJ, Tobin JD et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinology Metabolism* 2001;86:724-731.

Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: A review. *Maturitas* 69(2011): 322-337.

Makinen Juuso, Jarvisalo M et al. Increased carotid atherosclerosis in andropausal middle-aged men. *Journal of the American College of Cardiology* 2005; 45:1603-8.

Malkin CJ et al. Low serum testosterone and increased mortality in men with coronary heart disease. *Heart* 2010;96:1821-1825.

Soisson, Veronique et al. A J shaped association between plasma testosterone and risk of ischemic arterial event in elderly men: the French 3C cohort study. *Maturitas* 75(2013):282-288.

Yeap BB et al. In older Men an optimal plasma testosterone is associated with reduced all-cause mortality and higher DHT with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *JCEM* 99(2014):E9-E18)