

ARIC Manuscript Proposal #2923

PC Reviewed: 02/13/17
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Prospective study of the association between endogenous testosterone and incidence of atrial fibrillation

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __DB__ [**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:

A draft manuscript will be ready to submit for Publications Committee Review in spring 2017.

4. Rationale:

Atrial fibrillation (AF) is a commonly observed chronic arrhythmia and its prevalence has increased significantly over time⁸. The prevalence tends to increase with age and is higher in men than in women. Evidence exists that the risks of stroke, congestive heart failure (CHF), and cognitive dysfunction are higher in patients with AF, indicating the importance of AF as a public health concern^{5,8,9}.

Endogenous sex hormones, like testosterone, have many different effects on the body, including: sexual stimulation, metabolism, and development of various cardiovascular diseases and cancers. The mechanisms of aging-induced AF have not been fully elucidated³. However, data from the Framingham Heart Study identified a significant interaction between age and testosterone. They concluded testosterone and estradiol are associated with incident AF in a cohort of older men⁴. A case control study found that men with lone AF had significantly lower testosterone levels than those without lone AF (38 ng/dl, $p = 0.005$)². Research on testosterone in humans mainly focuses on men⁶. There often isn't comparable research on women.

Men have a 1.5-fold higher risk of developing AF compared with women after adjustment for age and other confounding factors⁵. However, among those in the Framingham Heart Study, women with new-onset of AF were found to have a higher relative risk of mortality 1.9 (95% CI, 1.5-2.2) than men with new-onset of AF 1.5 (95% CI, 1.2-1.8)⁷. Few data are available on the risk of adverse events associated with incident AF among large populations, particularly among middle-aged women¹⁰. Thus, analyzing the association of atrial fibrillation and testosterone in women is warranted.

There are early studies to suggest that testosterone replacement therapy in men with low testosterone levels may improve metabolic status by lowering blood sugar and HbA1C in men with type-2 diabetes, reducing abdominal girth, ameliorating features of the metabolic syndrome, all of which protect the cardiovascular system¹. Although testosterone replacement is a different issue, further investigation on the potential association between endogenous testosterone and AF may be relevant to the ongoing debate about whether testosterone replacement therapy is an appropriate cardiovascular disease preventive strategy for those with low testosterone levels.

With this sample size and number of expected events for the men in this sample, we anticipate being able to detect a hazard ratio of 1.2 or higher when comparing the 75th percentile vs. the 25th percentile of the male testosterone range. With this sample size and number of expected events for the women in this sample, we anticipate being able to detect a hazard ratio of 1.1 or higher when comparing the 75th percentile vs. the 25th

percentile of the female testosterone range. Both of these calculations use an alpha of 0.05 and power of 0.8.

ARIC also measured sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEAS). Although we have no specific hypotheses about these being associated with atrial fibrillation, we will also examine their association with AF in passing.

5. Main Hypothesis/Study Questions:

Question: Is there an independent inverse association between endogenous testosterone and incident atrial fibrillation for men and women?

Hypothesis: Low testosterone levels are associated with higher risk of incident atrial fibrillation.

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).

Design: Prospective study beginning at ARIC visit 4.

Exclusion criteria: Prevalent atrial fibrillation, missing testosterone levels.

Exposures: Endogenous testosterone measured at visit 4 - modeled as a continuous variable and/or in quintiles (if not normally distributed). Secondary: SHBG and DHEAS.

Outcome: Time to incident atrial fibrillation after visit 4, determined from hospital records, ARIC visit 5 ECGs, and death certificates.

Covariates: Main AF risk factors as published by ARIC (age, sex, race/ethnicity, BMI, SBP and medications, diabetes, smoking status, eGFR, prevalent CHD, and prevalent heart failure). Additionally, women will be stratified by HRT use and separate analyses will be conducted for each group.

Analysis: Examine sex-specific associations of AF and testosterone with covariates (with women stratified by HRT use). The main analysis will be to use sex-specific Cox proportional hazards models to calculate hazard ratios and adjust for the main AF risk factors, as noted above.

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 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.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)?

There is no overlap:

2234. Relationship between serum testosterone and the incidence of preclinical and clinical cardiovascular disease in men in the Atherosclerosis Risk In Communities (ARIC) cohort study

2805 Galectin-3 and Atrial Fibrillation Incidence

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 by Hoogeveen and Ballantyne on sex hormones. Not sure what number.)

*ancillary studies are listed by number at <http://www.csc.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, approved manuscripts using 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.

Sources:

1. Bain, Jerald. "Testosterone and the Aging Male: To Treat or Not to Treat?" *Maturitas* 66.1 (2010): 16-22. Web. 18 Nov. 2016.
2. Jiangtao, Lai, Dongchen Zhou, Shudong Xia, Yunpeng Shang, Lihong Want, Liangrong Zheng, and Jianhua Zhu. "Reduced Testosterone Levels in Males with Lone Atrial Fibrillation." *Clinical Cardiology* 32.1 (2009): 43-46. Web. 18 Nov. 2016.
3. Liu, Tong, Michael Shehata, Guangping Li, and Xunzhang Wang. "Androgens and Atrial Fibrillation: Friends or Foes?" *International Journal of Cardiology* 145.2 (2010): 365-67. Web. 18 Nov. 2016.
4. Magnani, J. W., C. B. Moser, J. M. Murabito, L. M. Sullivan, N. Wang, P. T. Ellinor, R. S. Vasan, E. J. Benjamin, and A. D. Coviello. "Association of Sex Hormones, Aging, and Atrial Fibrillation in Men: The Framingham Heart Study." *Circulation: Arrhythmia and Electrophysiology* 7.2 (2014): 307-12. Web. 18 Nov. 2016.
5. Wolf, Philip A., Emelia J. Benhamin, Albert J. Belanger, William B. Kannel, Daniel Levy, and Ralph B. D'agostino. "Secular Trends in the Prevalence of Atrial Fibrillation: The Framingham Study." *American Heart Journal* 131.4 (1996): 790-95. Web. 7 Dec. 2016.
6. Anders, Sari M. Van, Jeffrey Steiger, and Katherine L. Goldey. "Effects of Gendered Behavior on Testosterone in Women and Men." *Proceedings of the National Academy of Sciences* 112.45 (2015): 13805-3810. Web. 7 Dec. 2016.
7. Benjamin, E. J., P. A. Wolf, R. B. D'agostino, H. Silbershatz, W. B. Kannel, and D. Levy. "Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study." *Circulation* 98.10 (1998): 946-52. Web. 7 Dec. 2016.

8. Go, Alan S., Elaine M. Hylek, Kathleen A. Phillips, Yuchiaio Chang, Lori E. Henault, Joe V. Selby, and Daniel E. Singer. "Prevalence of Diagnosed Atrial Fibrillation in Adults." *Jama* 285.18 (2001): 2370. Web. 7 Dec. 2016.

9. Miyasaka, Y., ME. Barnes, and BJ. Gersch. "Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence." *Circulation* 114.2 (2006): 119-25. Web. 7 Dec. 2016.

10. Conen, David, Claudia U. Chae, and Robert J. Glynn. "Risk of Death and Cardiovascular Events in Initially Healthy Women With New-Onset Atrial Fibrillation." *Jama* 305.20 (2011): 2080. Web. 7 Dec. 2016.