**ARIC Manuscript Proposal #2795**

**PC Reviewed: 7/12/16** **Status: A** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**: Atrial Fibrillation and the Risk of Cancer: the ARIC Study

**b. Abbreviated Title (Length 26 characters)**: AF and Cancer

**2. Writing Group**:
Writing group members:

Chetan Shenoy, Faye L. Norby, Anna E. Prizment, Elsayed Z. Soliman, Laura R. Loehr, Alvaro Alonso, Lin Y. Chen

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

**First author**:
Address: Chetan Shenoy, MBBS
Cardiovascular Division
Department of Medicine
University of Minnesota Medical School
420 Delaware Street SE, MMC 508
Minneapolis, MN 55455.

Phone: (612) 626-1391 Fax: (612) 626 4411
E-mail: cshenoy@umn.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: Lin Y. Chen, MD**,** MS
Address: Cardiac Arrhythmia Center, Cardiovascular Division,
Department of Medicine,
University of Minnesota Medical School,
420 Delaware Street SE, MMC 508,
Minneapolis, MN 55455.

Phone: 612-625-4401 Fax: 612-624-4937
E-mail: chenx484@umn.edu

**3. Timeline**: Statistical Analysis: 1 month
Manuscript Preparation: 2 months

## 4. Rationale:

Recent studies have suggested an increased risk of cancer in patients with AF (1-3). Shared risk factors and/or common systemic disease processes may explain this association. The elevated cancer risk has been demonstrated to persist beyond 1 year of AF diagnosis (3). However, these studies have limitations. The study by Guzetti et al. was a retrospective case-control study which does not allow reliable assessment of the temporality of the association between AF and cancer, given the potential latency of both diagnoses (1). The study by Ostenfeld et al. lacked an internal control group (2). Finally, the most recent study by Conen et al. was limited to female health professionals who were mostly white from the Women's Health Study (3).

Similarly, patients with cancers such as breast cancer and colorectal cancer have an increased risk of AF (2-9) and new-onset AF in patients with cancer is associated with an increased risk of short-term mortality (10). Inflammation may be the explanation for increased risk of AF in this population (11, 12).

ARIC provides a unique opportunity to examine the bidirectional associations between AF and cancer in a large, biracial prospective cohort study of both men and women. A better understanding of these associations could provide more insights into pathophysiology, prevention and detection of cancer and AF.

## 5. Main Hypothesis/Study Questions:

**Aim:** To evaluate the association of incident AF with the risk of incident cancer, and the association of incident cancer with the risk of incident AF.

**Hypothesis:** Incident AF will be significantly associated with an increased risk for cancer. Incident cancer will be significantly associated with an increased risk of AF.

## 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 Population: We will include all participants from the baseline visit (V1). We will exclude those with missing covariates and missing ECG data. We will also exclude participants with prevalent AF and/or cancer (excluding non-melanoma skin cancers) at the baseline visit.

AF Diagnosis – Exposure and outcome (separate analyses):
Incident AF determined from resting ECGs obtained during 5 study examinations and hospital discharge codes.

Cancer Diagnosis – Exposure and outcome (separate analyses):
Incident cancer through 2011 identified by linkage to the state cancer registries of MD, MN, MS, and NC and supplemented by active surveillance of the cohort.
Covariates:

Age, sex, race, study center, educational level, smoking (never, former, current), pack-years of smoking, alcohol consumption (non-drinker, >0 to <2drinks/day, ≥2 drinks/day), physical activity (poor, intermediate, ideal), body mass index, hypertension, hypercholesterolemia, diabetes mellitus, and incident cardiovascular events (myocardial infarction, heart failure, and stroke).

Statistical Analyses:

**Association of incident AF with the risk of incident cancer:**

Follow-up will be defined as time between the baseline exam until the date of cancer diagnosis, death, or end of follow-up, whichever occurs earlier. We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for the association of time-dependent AF with incident cancer.

Model 1: Age, sex, race, study center

Model 2: Model 1 + educational level, smoking (never, former, current), pack-years of smoking, alcohol consumption (non-drinker, >0 to <2drinks/day, ≥2 drinks/day), physical activity (poor, intermediate, ideal), body mass index, hypertension, hypercholesterolemia, diabetes mellitus, and incident cardiovascular events (myocardial infarction, heart failure, and stroke).

We will perform sex- and race-stratified analysis.

We will assess association with all cancer, and specific types of cancers: lung, colorectal, breast, and prostate cancer.

We will also perform analyses to test the association of AF with cancer at different lengths of follow-up after the diagnosis of AF (0-3 months, 3-12 months and beyond 12 months) to verify that a potential increased risk of cancer is not just due to ascertainment bias in patients newly diagnosed with AF.

**Association of incident cancer with the risk of incident AF:**

Follow-up will be defined as time between the baseline exam until the date of AF diagnosis, death, or end of follow-up, whichever occurs earlier. We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for the association of time-dependent cancer with incident AF.

Model 1: Age, sex, race, study center

Model 2: Model 1 + educational level, smoking (never, former, current), pack-years of smoking, alcohol consumption (non-drinker, >0 to <2drinks/day, ≥2 drinks/day), physical activity (poor, intermediate, ideal), body mass index, use of hypertension medications, systolic blood pressure, diastolic blood pressure, hypercholesterolemia, diabetes mellitus, and incident cardiovascular events (myocardial infarction, heart failure, and stroke).

We will perform sex- and race-stratified analysis.

We will also perform analyses to test the association of cancer with AF at different lengths of follow-up after the diagnosis of cancer (0-3 months, 3-12 months and beyond 12 months) to verify that a potential increased risk of AF is not just due to ascertainment bias in patients newly diagnosed with cancer.

**7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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 __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.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* _____)**

**_X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.12 AF ancillary study)**

*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.

**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 __X__ No.

**References:**


1. Guzzetti S, Costantino G, Vernocchi A, Sada S, Fundaro C. First diagnosis of colorectal or breast cancer and prevalence of atrial fibrillation. Internal and emergency medicine. 2008;3(3):227-31.
2. Ostenfeld EB, Erichsen R, Pedersen L, Farkas DK, Weiss NS, Sorensen HT. Atrial fibrillation as a marker of occult cancer. PLoS One. 2014;9(8):e102861.
3. Conen D, Wong JA, Sandhu RK, et al. RIsk of malignant cancer among women with new-onset atrial fibrillation. JAMA Cardiology. 2016.
4. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. Journal of the American College of Cardiology. 2014;63(10):945-53.
5. Klein Hesselink EN, Lefrandt JD, Schuurmans EP, et al. Increased Risk of Atrial Fibrillation After Treatment for Differentiated Thyroid Carcinoma. The Journal of clinical endocrinology and metabolism. 2015;100(12):4563-9.
6. O'Neal WT, Lakoski SG, Qureshi W, et al. Relation between cancer and atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke Study). Am J Cardiol. 2015;115(8):1090-4.
7. Cheng WL, Kao YH, Chen SA, Chen YJ. Pathophysiology of cancer therapy-provoked atrial fibrillation. International journal of cardiology. 2016;219:186-94.
8. Nouraie M, Kansal V, Belfonte C, et al. Atrial Fibrillation and Colonic Neoplasia in African Americans. PLoS One. 2015;10(8):e0135609.
9. Erichsen R, Christiansen CF, Mehnert F, Weiss NS, Baron JA, Sorensen HT. Colorectal cancer and risk of atrial fibrillation and flutter: a population-based case-control study. Internal and emergency medicine. 2012;7(5):431-8.
10. Lardaro T, Self WH, Barrett TW. Thirty-day mortality in ED patients with new onset atrial fibrillation and actively treated cancer. The American journal of emergency medicine. 2015;33(10):1483-8.
11. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108(24):3006-10.
12. Misialek JR, Bekwelem W, Chen LY, et al. Association of White Blood Cell Count and Differential with the Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study. PLoS One. 2015;10(8):e0136219.