ARIC Manuscript Proposal # 1688

PC Reviewed: 9/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Diabetes, glucose homeostasis and risk of subsequent atrial fibrillation: the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Diabetes and atrial fibrillation

2. Writing Group:
Rachel R. Huxley, Alvaro Alonso, Faye Lopez, Kristian B. Filion, Sunil K. Agarwal, Laura Loehr, Elsayed Z. Soliman, James Pankow, Elizabeth Selvin

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

First author: Rachel Huxley
Address: Div of Epidemiology & Community Health
University of Minnesota
1300 S 2nd St, suite 300. Minneapolis, MN 55454
Phone: 952-250-1730 Fax: 612-624-0315
E-mail: rhuxley@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: **Alvaro Alonso**
Address: Div of Epidemiology & Community Health
University of Minnesota
1300 S 2nd St, suite 300. Minneapolis, MN 55454
Phone: 612-626-8597 Fax: 612-624-0315
E-mail: alonso@umn.edu

3. Timeline:
Data analysis – 3 months
First draft of the manuscript – 3 months

4. Rationale:

Atrial fibrillation (AF) is one of the most frequently sustained cardiac arrhythmia seen in clinical practice, affecting an estimated 2.2 million Americans [1]. Individuals with AF

have between two to seven times the risk of stroke compared with unaffected individuals; moreover, AF doubles the rate of cardiovascular disease mortality and all-cause mortality [2,3]. AF is more prevalent in whites than in African Americans [4, 5], although the reasons for this racial difference remain unknown.

Aside from age, established risk factors for AF include heart failure and valvular heart disease, and some cardiovascular risk factors such as elevated blood pressure, obesity, thyroid dysfunction and smoking [3]. In addition to these risk factors, observational studies have also reported on the association between type-2 diabetes and AF but with equivocal results [3,6-9]. The discrepancies in study findings may be due in part to one or more of the following methodological limitations: smaller effect size and event rates thus limited power, exposure misclassification, under-ascertainment of AF, and competing risk of death.

The ongoing uncertainty as to the relationship between diabetes and AF is one of the primary reasons underlying this current proposal. In addition, previous studies have largely been restricted to predominantly white populations and there are currently no data pertaining to the association in African-Americans. Moreover, few of the earlier studies were able to adjust for possible confounders such as body mass index and prior cardiac disease, which may have resulted in an overestimation in the magnitude of previously reported associations. For example, unpublished data from a recently conducted meta-analysis indicate that the summary estimate from those studies that were age- and sex-adjusted only was substantially greater compared with the estimate from those studies that were able to adjust for a range of possible confounders: RR 1.70 (95% CI: 1.29 - 2.22) versus RR 1.24 (95% CI: 1.06 - 1.44; p = 0.053), respectively (Huxley et al. *submitted for review)*.

Finally, few studies have been able to examine the relationships between other measures of glucose homeostasis, namely impaired fasting glucose and HbA1c, with incident AF in persons with and without diabetes. In the one case-control study that has examined the association between HbA1c levels and AF, individuals with diabetes and HbA1c levels greater than 9% had double the risk of AF compared with those diabetics with HbA1c levels less than 7% [10]. If these findings can be replicated in a prospective analysis, then such information may contribute to the early detection of those individuals most at risk of AF.

The ARIC study provides an excellent for a prospective study of the association between diabetes and incident AF in both whites and African-Americans with a specific focus on measures of glucose homeostasis including HbA1c, which previously has not been well documented. Further, information on a large number of socio-demographic, physiological, and biochemical risk factors will enable adjustment for known and unknown confounders allowing a more accurate estimate of the association to be determined.

5. Main Hypothesis/Study Questions:

i. To determine the risk of AF among individuals with type-2 diabetes compared with non-diabetic individuals.

ii. To investigate the continuous associations between levels of fasting blood glucose (FBG) and HbA1c with incident AF in those individuals without a history of diagnosed diabetes.

iii. To examine the relationship between fasting insulin level and incident AF in those without a history of diagnosed diabetes.

iv. To determine whether there are significant differences by race and gender in the above associations

We hypothesize that diabetes will be an independent risk factor for development of AF and that measures of glucose homeostasis (fasting glucose and HbA1c) will be independently associated with incident AF, even among persons without diabetes.

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).

We will assess the association between measures of glucose homeostasis and AF risk using a longitudinal data analysis approach. Visit 2 will be the baseline for these analyses as HbA1c was only measured at this visit. For the third objective, namely, the relationship between fasting insulin level and incident AF, visit 4 will be the baseline (insulin was not measured at previous study visits).

Exclusions
The following individuals will be excluded from all analyses:

- Those with missing or unreadable ECGs at visit 1 or 2
- Those with prevalent AF at visit 2 (defined as AF by ECG in visit 1 or 2, or AF hospitalization between visits 1 and 2)
- Those with missing variables for any of the covariates
- Those with non-fasting blood samples

Sensitivity analyses

1. The first sensitivity analysis is in regards to objective 1. The main analysis between type-2 diabetes and incident AF will include all individuals with type-2 diabetes (both diagnosed and undiagnosed) and a secondary analysis will consider individuals with undiagnosed diabetes as a separate category.

2. The second sensitivity analysis concerns objectives two and three; the main analysis will exclude those with a previous diagnosis of type-2 diabetes and a secondary analysis will also exclude those with undiagnosed diabetes

Exposure

Study participants with a FBG <100 mg/dL, a HbA1c < 5.7%, no use of antidiabetic medication, and no history of physician-diagnosed diabetes will be considered to have an optimal level of blood glucose and will be considered to be non-diabetics. Individuals with a FBG 100-125 mg/dL or HbA1c 5.7-6.4%, no use of antidiabetic medication, and no history of physician-diagnosed diabetes will be considered to have sub-optimal glucose profile. Those with FBG ≥126 mg/dL or HbA1c ≥ 6.5% or use of antidiabetic medication or history of physician-diagnosed diabetes will be categorized as diabetic. In addition to examining the risk of AF by diabetes status, associations between markers of glucose homeostasis (i.e., FBG, HbA1c and fasting insulin) with incident AF will also be examined.

Outcome

Incident cases of AF identified in the follow-up through the end of 2007 from three sources: ECGs done at study visits, presence of AF ICD9 (427.31 or 427.32) code in a hospital discharge, or AF listed as any cause of death. Hospitalizations with AF associated with cardiac surgery will not be considered events. Date of AF incidence will be the earliest of any AF diagnosis.

Statistical analysis

Means and standard deviations (SD) for the continuous variables and percentages for the categorical variables will be obtained separately for men and women and for white and African-American participants. We will determine the age- and gender-standardized prevalence of diabetes pre-diabetes and the age- and gender-standardized incidence of AF for both diabetes and pre-diabetes, separately in Whites and African-Americans. Associations between diabetes, pre-diabetes, FBG, HbA1c and fasting insulin with the incidence of AF will be estimated using time-dependent Cox proportional hazards models. Separate analyses will be conducted in men and women and in Whites and African-Americans, and models will adjust for age, study site, education, income, prior history of cardiovascular disease, body mass index (BMI), systolic blood pressure, total cholesterol, HDL-cholesterol, smoking, physical activity, and alcohol consumption. We will explore the assumption of proportional hazards adding to the model an interaction term between follow-up time and exposure of interest, computing Schoenfeld residuals, and by inspection of the log(-log[survival function]) curves.

We will also examine the continuous association between HbA1c levels with incident AF using Cox models with adjustment for the same covariates as before. Spline regression analysis will be used to model dose-response relationships between FBG, fasting insulin and HbA1c with incident AF.

The above analyses will be repeated in a sensitivity analysis after excluding those individuals with a prior history of cardiovascular disease.

Limitations

In our primary analysis, the main concern is that misclassification may exist in outcome ascertainment although preliminary analyses suggest a positive predictive value of ~90% for AF diagnosis done through hospital discharge codes, implying a limited amount of misclassification [4]. Additional limitations include residual confounding and misclassification of the exposure at baseline and due to their time-varying nature.

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

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.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)?

MS #1488 (Matsushita) HbA1c and HF in non-diabetes

MS #1539 (Selvin) HbA1c and microvascular disease
MS #1627 (Huxley) Low risk factor profile and AF
MS #1667 (Lopez) Lipid profile and AF
MS #1674 (Agarwal) Lung function, COPD, and AF

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

X A. primarily the result of an ancillary study (list number* 2006.15 and 2008.12)

___ 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.

6. References

1. A.S. Go, E.M. Hylek and K.A. Phillips *et al.*, Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, *JAMA* **285** (2001), pp. 2370–2375.
2. W. Rosamond, K. Flegal and K. Furie *et al.*, Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, *Circulation* **117** (2008), pp. e25–e146.
3. E.J. Benjamin, P.A. Wolf and R.B. D'Agostino *et al.*, Impact of atrial fibrillation on the risk of death: the Framingham Heart Study, *Circulation* **98** (1998), pp. 946–952. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study.
4. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ and Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) study American Heart Journal 2009; 158:111-117.
5. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care 2009; 32:1851-56.
6. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997; 96:2455–61.
7. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. J Intern Med. 2001; 250:382-9.

8. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002;113:359–64.
9. Agmon Y, Khandheria BK, Meissner I, et al. Association of atrial fibrillation and aortic atherosclerosis: a population-based study. Mayo Clin Proc. 2001; 76:252-9.
10. Dublin S, Glazer NL, Smith NL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med. 2010; 25:853-8.

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