ARIC Manuscript Proposal #2703

1.a. Full Title: Sulfonylurea use and the risk of incident atrial fibrillation

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

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

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3. Timeline:
We aim to use the Atherosclerosis Risk in Communities (ARIC) database to evaluate whether sulfonylurea use is associated with a lower risk of developing incident atrial fibrillation. We anticipate that this analysis will take approximately one to two years.

4. **Rationale:**
Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and is a major risk factor for stroke, congestive heart failure and mortality.(1-3) Although remodeling in response to AF has been a subject of intense investigation,(4,5) relatively few studies have focused on the mechanisms responsible for the initiation of atrial tachyarrhythmias.

Many conditions associated with AF, including hypertension with left ventricular hypertrophy (6), dilated cardiomyopathy (7-9), clinical heart failure from severe valvular disease (10), and increasing age (11), are thought to be energetically-taxing to the myocardium. In response to metabolically-taxing states and the ensuing decreased ATP:ADP ratio, $K_{\text{ATP}}$ channels open and couple cellular metabolism with electrical activity. These channels were first discovered in the heart (12) and are expressed throughout the body in metabolically active cell types and are found in the sarcolemmal and mitochondrial membranes. Differences in the molecular composition of the channel determine its biophysical and pharmacological properties. The $K_{\text{ATP}}$ channel complex is composed of inward rectifier potassium channel (Kir6.x) and sulfonylurea receptor (SURx) subunits.(13) Recent studies have demonstrated atrial $K_{\text{ATP}}$ channel complexes are predominantly composed of Kir6.2 and SUR1 subunits, similar to those in the pancreas.(14,15) SUR1-containing $K_{\text{ATP}}$ channels are sensitive to small changes in the ATP:ADP ratio, with alterations in channel open-probability occurring over physiologic ranges. Moreover, activation of these channels in isolated atrial preparations has been shown to be pro arrhythmic.(16) Given these data, it is intriguing to speculate how this ion channel could contribute to electrophysiological remodeling associated with various metabolically-taxing cardiovascular disease states.

We have recently obtained data suggesting that $K_{\text{ATP}}$ channels play an important role in mediating the atrial electrophysiological consequences of hypertension.(17) Elevated blood pressure (BP) in our murine model was associated with a reduction in atrial effective refractory period (ERP) and APD, and augmented sarcolemmal $K_{\text{ATP}}$ channel density. These alterations were associated with increased atrial arrhythmia inducibility and were reversible with $K_{\text{ATP}}$ channel blockade using sulfonylureas. More recently, Kim and colleagues demonstrated that $K_{\text{ATP}}$ channel antagonism with sulfonylureas reversed the electrophysiologic changes and atrial arrhythmia susceptibility associated with acute β-adrenergic receptor activation.(18) The findings of these studies highlight the $K_{\text{ATP}}$ channel as a potential novel molecular mediator of atrial arrhythmogenesis, and raise the question as to whether sulfonylurea use could attenuate this process.

As sulfonylureas are antagonists of $K_{\text{ATP}}$ channels, a mediator of atrial arrhythmias in murine models, we hypothesize that their use will be associated with a decreased risk of the development of atrial fibrillation in humans.

5. **Main Hypothesis/Study Questions:**
We hypothesize that sulfonylurea use is associated with a lower risk of developing atrial fibrillation in diabetics from the Atherosclerosis Risk in Communities (ARIC) cohort.

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:** This will be a retrospective cohort study to compare the incidence of atrial fibrillation in patients with type-2 diabetes with a glucose lowering regimen that includes a sulfonylurea against those type-2 diabetics not taking a sulfonylurea. We will attempt to stratify patients by baseline characteristics that would also predispose to atrial fibrillation, including age, sex, race, smoking status, obesity, severity of diabetes (from glycated hemoglobin level, fasting serum glucose and insulin, and duration of diabetes), blood pressure, and renal function.

**Inclusion criteria:** Of the 15,792 adults enrolled in the ARIC study, we will examine those free of atrial fibrillation at their baseline visit who had type-2 diabetes at any visit during the study period.

**Exclusion criteria:** Participants with missing or non-readable ECGs, unknown prevalent AF status, prevalent AF or atrial flutter (based on the electrocardiograms and a 2 two-minute rhythm strip from the first visit), unknown diabetes status at any visit, unknown use of sulfonylureas, or other relevant missing variables at baseline will be excluded.

**Baseline data:** Relevant socio-demographic (age, sex, race/ethnicity, study site, menopausal status, education), body mass index, height, smoking history (status and pack-years), alcohol history, glycated hemoglobin level, brachial systolic and diastolic blood pressure (SBP and DBP, respectively), hypertension status, and renal function will be included for analysis. Baseline medical regimens will also be assessed.

**Covariate follow-up data:** Interval changes in SBP/DBP, hypertension status, diabetes status, body mass index, renal function, heart failure status, and smoking status will be included as covariates.

**Primary outcome data:** Our main outcome variable will be incident atrial fibrillation. AF events will be identified from: 1) ECGs performed during follow-up exams; 2) death certificates (ICD-9 code 437.3 or ICD-10 code I48); 3) hospital discharge records through the end of follow up. An AF diagnosis will be assigned if AF was listed as any cause of death (ICD-9 427.3 or ICD-10 I48). AF events identified during hospitalization for cardiac surgery will be excluded as these may not relate to the natural history of AF and persistent AF will be captured in subsequent hospitalization. The date of incident AF will be defined as the first visit when ECGs showed AF, hospital discharge coded as AF or death date when AF was listed as a cause of death, whichever occurred first.

**Secondary outcome data:** Secondary outcome variables will include myocardial infarction, stroke, or death.
Data analysis: Cox proportional hazards regression models will be used to estimate the hazard ratios and 95% confidence intervals of AF by sulfonylurea use. Each participant will contribute follow-up time from the date of diabetes diagnosis until the earliest of the following dates: AF event, death, loss to follow-up, or administrative censoring. Those with prevalent diabetes at the first visit will contribute follow-up time from this examination. Patients will contribute follow-up time to the sulfonylurea group only while identified as taking this class of medication.

The following additional analyses will be performed: stratified analyses by age; sex; race; smoking status (never, former, and current); obesity (body mass index); diabetes severity (estimated by glycated hemoglobin level at visit 2, fasting serum glucose and insulin levels from visit 2, and self-reported duration of diabetes from visit 4); blood pressure; and renal function. All analyses will be conducted with SAS version 9.2 (SAS Institute Inc, Cary, NC). Two-sided values of P<0.05 for main effects and P<0.2 for interactions will be considered statistically significant.

Methodologic limitations: The primary limitation to the proposed study is one of power. We estimate that less than 700 individuals were taking sulfonylureas at any of the first four visits. From previously published data characterizing the ARIC cohort, we know that approximately 13.3% develop incident AF and 11.6% have diabetes.(19) Assuming that the world of patients taking sulfonylureas completely resides within the world of people with diabetes suggests an enrollment ratio of approximately 0.64. Based on the previously published association of diabetes with AF in the ARIC cohort (HR 1.35), we expect approximately 300 patients in the diabetic cohort to develop atrial fibrillation.(20) With these approximations, the study we propose would be powered to detect a 30% relative risk reduction for the development of atrial fibrillation, which is a significantly more modest effect than we might expect from our murine model.(17) Alternatively, it is conceivable that this study will not be adequately powered to answer our clinical question, resulting in Type 2 error. Another limitation to the proposed study is confounding by indication for sulfonylurea therapy; this limitation is intrinsic to any study evaluating secondary effects of medication use in a retrospective fashion. We propose to mitigate this confounding by stratification by diabetes severity (using glycated hemoglobin, fasting glucose and insulin levels from visit 2, as well as self-reported duration of diabetes from visit 4). Nevertheless, it is possible that diabetics receiving sulfonylureas are different from those receiving other hypoglycemic agents in other unmeasured variables. Other limitations to the study are intrinsic to any observational analysis, including confounding by other unforeseen parameters.

References:


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 __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.cscce.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? ____ Yes  ___X__ 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/

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.