1.a. Full Title: Sulfonylurea use and atrial dysrhythmia burden

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

2. Writing Group: Writing group members: Joshua Lader, MD; Saul Blecker, MD; Kunihiro Matsushita, MD; Glenn Fishman, MD; Elsayed Soliman, MD; Jonathan Newman, MD, MPH; Alvaro Alonso, MD; Laura Loehr, MD

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

First author: Joshua M Lader, MD
Address: The Leon H Charney Division of Cardiology
New York University School of Medicine
Smilow Building #801
550 First Avenue
New York, NY 10016

Phone: 212-263-4130 Fax: 212-263-4129
E-mail: Joshua.Lader@nyumc.org

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: Laura R Loehr, MD
Address: Cardiovascular Diseases Program,
137 E. Franklin Street, suite 306, Chapel Hill, NC
University of North Carolina
Chapel Hill, NC 27514-3628

Phone: 919-966-8275 Fax: 919-966-9800
E-mail: llloehr@email.unc.edu

3. Timeline: 
We aim to evaluate whether sulfonylurea use is associated with a lower burden of atrial dysrhythmia (premature atrial complexes). We are interested in studying this among participants in the Atherosclerosis Risk in Communities Study that had 48-hour Holter monitoring as part of an ancillary study. We anticipate that this analysis will take approximately one to two years.

4. Rationale:
K\textsubscript{ATP} channels were first discovered in the heart\textsuperscript{1} and are prominently expressed there. Gated by an elevated ATP/ADP ratio, these channels link cellular energetics to membrane excitability.\textsuperscript{1} They are composed of heteromultimers of the pore-forming inwardly rectifying K\textsuperscript{+} channel (Kir6.1 or Kir6.2) and ATP-binding cassette sulfonylurea receptor (SUR1 or SUR2) subunits arranged in a 4:4 ratio.\textsuperscript{2} The molecular composition and functional properties of K\textsubscript{ATP} channels vary in different tissues and species. In pancreatic \(\beta\)-cells, K\textsubscript{ATP} channels are composed of Kir6.2 and SUR1.\textsuperscript{3} These channels tightly couple intracellular glucose levels over a physiologic range to membrane potential, thereby modulating calcium influx and insulin exocytosis. In contrast, K\textsubscript{ATP} channels in ventricular myocytes are composed of Kir6.2 and SUR2A.\textsuperscript{4} These channels modulate action potential duration only during instances of extreme metabolic stress, such as myocardial ischemia, at which time activation is highly arrhythmogenic.\textsuperscript{5} In rodent species, K\textsubscript{ATP} channels in the atria are thought to consist of Kir6.2 and SUR1.\textsuperscript{6,7} Like those K\textsubscript{ATP} channels in the pancreas with identical molecular composition, dialysis of rodent atrial myocytes with low levels of MgATP yields spontaneous channel activation. These data suggest that due to differences in subunit composition, rodent atrial K\textsubscript{ATP} channels are markedly more sensitive than ventricular channels and may open and modulate atrial excitability during minor metabolic perturbations, a process that has been demonstrated to be extremely arrhythmogenic.\textsuperscript{8} Indeed, atrial K\textsubscript{ATP} channels have subsequently been implicated in arrhythmogenesis in a murine model of hypertension and a rat model of augmented \(\beta\)-adrenergic tone.\textsuperscript{9,10} In both studies, application of sulfonylureas prolonged atrial refractoriness and reduced arrhythmia inducibility.\textsuperscript{9,10}

Augmented \(\beta\)-adrenergic tone provides a common thread linking many of the disease states associated with atrial fibrillation, and there are data to suggest that K\textsubscript{ATP} channels may mediate this relationship. Exposure to PKA augments K\textsubscript{ATP} channel function in several pancreatic \(\beta\)-cell lines,\textsuperscript{11} as well as those in arterial smooth muscle and ventricular myocardium.\textsuperscript{12} Specifically, it is known that PKA phosphorylation of the serine at residue 372 of Kir6.2 increases K\textsubscript{ATP} channel activity. Similarly, PKA phosphorylation of the serine at residue 1571 of SUR1 aids in the maintenance of functional K\textsubscript{ATP} channels at the sarcolemmal membrane.\textsuperscript{13} Arakel and colleagues have recently described a process in murine ventricular cardiomyocytes whereby \(\beta\)-agonism results in translocation of a population of Kir6.2 and SUR1-containing K\textsubscript{ATP} channels to the cell membrane, a process that is associated with action potential shortening and completely abrogated by genetic deletion of the SUR1 subunit. We have recently described a similar process occurring in human atrial-like pluripotent stem cell-derived cardiomyocytes.\textsuperscript{14}

As sulfonylureas are antagonists of K\textsubscript{ATP} channels, a mediator of atrial arrhythmias in murine models and \(\beta\)-induced electrophysiological changes in human atrial-like cells, we...
hypothesize that their use will be associated with a decreased burden of atrial dysrhythmia, including premature atrial complexes.

5. **Main Hypothesis/Study Questions:**
We hypothesize that sulfonylurea use is associated with a lower burden of atrial dysrhythmia (including premature atrial complexes) 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 cross sectional study to compare the burden of atrial dysrhythmia (including premature atrial complexes) 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 dysrhythmia, including age, sex, race, smoking status, obesity, severity of diabetes, blood pressure, renal function, prevalent coronary heart disease, and prevalent heart failure.

**Inclusion criteria:** A subpopulation of the ARIC study from two study sites (Jackson, MS and Forsyth County, NC) was selected by stratified random sampling to participate in an ancillary study of 48-hour ambulatory electrocardiography monitoring. Of the 15,792 adults enrolled in the ARIC study, 1205 had Holter-monitoring performed as part of the ancillary study. We will examine the 320 who had both Holter-monitoring and type-2 diabetes at any visit during the study period. This includes 110 individuals with a glucose lowering regimen that includes a sulfonylurea at the time of monitoring, as well as 210 diabetics with a medical regimen not including a sulfonylurea.

**Exclusion criteria:** Participants with poor quality measures, defined as Holter recordings with >10% noise or <20 hours of Holter recording time, will be excluded. We will also exclude three participants with Holter transmission issues resulting in no Holter recording, and one participant that came to the visit but chose not to wear a monitor. We will also exclude participants with a paced rhythm on the 48-hour Holter monitor. Participants with unknown diabetes status, unknown use of sulfonylureas, or other relevant missing variables will be excluded.

**Baseline data:** Relevant socio-demographic data (age, sex, race/ethnicity, study site, menopausal status, education), as well as 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. These will be determined from visit 5. Medical regimens at the time of study will also be assessed.

**Primary outcome data:** Our main outcome variable will be premature atrial complex (PAC) burden as measured from 48 hour Holter monitoring. Other outcomes will include
observed atrial fibrillation (expressed as a categorical variable), the burden of this arrhythmia, as well as premature ventricular complex (PVC) burden.

We will define PAC and PVC separately as:
1. Log of the (total number of PAC/hours of recording time)
2. Log of the (total number of PVC/hours of recording time)
3. Percentage of counts: total number of ectopic beats divided by the total number of beats recorded during the length of Holter monitoring x 100
   a. % PACs = (number of PACs / number of QRS complexes) x 100
   b. % PVCs = (number of PVCs / number of QRS complexes) x 100

We will define AF burden as the percent of time in AF over the 48 hour period. Presence of AF and other cardiac arrhythmias will be evaluated as categorical variables.

**Secondary outcome data:** Mean QTc over the monitoring period will be evaluated.

**Data analysis:** We will examine the association between prevalence of sulfonylurea use among diabetics and presence of PAC, PVC, or AF using logistic regression and we will use multivariable linear regression to examine the association between sulfonylurea use and burden of PAC, PVC, or AF using inverse variance weighting with weights that account for the study’s complex sampling design and non-response.

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; blood pressure; renal function; prevalent coronary heart disease; and prevalent heart failure. 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. 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. 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  

___ 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.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)?


Al Rifai M, Schneider AL, Alonso A, Maruthur N, Parrinello CM, Astor BC, Hoogeveen RC, Soliman EZ, Chen LY, Ballantyne CM, Halushka MK, Selvin E. sRAGE,


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* 2012.08________)
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.