ARIC Manuscript Proposal # 2331

PC Reviewed: 3/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title: Prevalence of QTc interval-prolonging medications use in ARIC populations, and the subsequent risk of morbidity and mortality.

b. Abbreviated Title (Length 26 characters): Risk of QTc prolonging medications.

2. Writing Group: Khalid Alburikan, Jo Ellen Rodgers, James Tisdale, Emily Thudium, Elsayed Soliman, Carla Sueta, Anna Kucharska-Newton, Sally Stearns, Eric Whitsel; others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. KAA

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3. Timeline:

Analyses to start following receipt of ARIC Visit3-5 data. It is anticipated that results of this study will be submitted as an abstract for presentation at the American Heart Association Meeting in November 2014, with manuscript submission following shortly thereafter.

4. Rationale:

Sudden cardiac death (SCD) is a leading cause of death among adults over the age of 40 in the United States.[1] Observational studies suggest a majority of SCD cases are due to ventricular fibrillation.[2] However, precipitating events leading to ventricular fibrillation in an otherwise stable patient remain uncertain.

In the past decade, prolongation of the QT interval on an electrocardiogram (ECG) has been identified as one of the most frequent causes of medication restriction or withdrawal from the market.[3] Recently, the Federal Drug Administration (FDA) issued additional warnings and approved revised drug labeling for ondasetron and citalopram in response to the increasing evidence linking these medications with incidence of corrected QT (QTc) prolongation.[4,5] A lengthened QTc interval (> 500 msec or increase > 60 msec) translates to a prolonged action potential, which creates an electrophysiological environment that favors the development of cardiac arrhythmias, most notably torsade de pointes (TdP), a serious and often fatal arrhythmia. Therefore, QTc interval has been used as a surrogate marker for an increased risk of developing TdP.[6,7] Recently, prolonged QTc interval has also been linked to a twofold

increased risk of atrial fibrillation and threefold increased risk of stroke.[8,9] While the latter study did adjust for the use of QTc prolonging medications, the former study did not examine the association of QTc interval prolonging medications and these outcomes. And thus, the association between QTc prolonging medications and atrial fibrillation and stroke is unclear.

In addition to screening patients for single agents or concomitant therapies that may contribute to an increased QTc interval, patients may undergo extensive monitoring, such as ECG monitoring, when cardiovascular medications (e.g., select antiarrhythmic agents) known to prolong the QTc interval are initiated during hospitalization. Registry data, however, suggest non-cardiovascular QTc interval prolonging medications (e.g., antimicrobial agents, antipsychotics) are associated with up to a threefold increase in the risk of sudden cardiac death.[10] Several factors have been proposed to explain the increased risk of SCD with non-cardiovascular QTc prolonging medications: pharmacokinetic and pharmacodynamic drug interactions which may lead to an increase in drug exposure and lack of prescriber knowledge (select medications, combinations of therapies and other risk factors for QTc interval prolongation e.g., age, sex).[6] It is essential to gain a better understanding of the relative risks associated with cardiovascular and non-cardiovascular QTc interval prolonging medications including, the differential risk with select therapies as well as various combinations.

To date, cohort studies have demonstrated that approximately 10% of patients may be receiving prescriptions for one, if not two, potentially QTc interval prolonging medications and up to 5% may also receive a prescription for a potentially interacting medication.[11,12] This is concerning as several studies have demonstrated a two to three-fold increase in mortality with select QTc interval prolonging medications (e.g., erythromycin, antipsychotic agents).[13,14] However, relative contribution of prescribing multiple QTc interval prolonging medications on morbidity and mortality in patients with existing risk factors remains unknown.

The purpose of this manuscript proposal is to assess the appropriateness of prescribing of QTc interval-prolonging medications, specifically frequency of prescribing multiple QTc interval prolonging medications and use in high risk patients, and the association between appropriateness of prescribing and subsequent risk of morbidity and mortality. The relationship between degree of QTc interval prolongation and morbidity and mortality will also be assessed. Ultimately, we hope to identify the degree of QT interval prolongation associated with increased mortality in patients with varying degrees of risk. Tentatively, we expect to include up to 15,000 participants from visits 1-4 in our analysis, though for the longitudinal analysis, we do not expect to include people who only participated in Visit 1. At this time, to the best of our knowledge; no other study has reported the risks associated with QTc interval prolonging medications in a large population such as the ARIC population. We propose to use data from visits 1-4; specifically, ECG data, Medispan data and self-report medications. We will use files that Eric Whitsel has developed with cleaned medication codes to facilitate easy identification of QT-prolonging medications used.

Study Objectives:

The study will address the following objectives:

1. Report prevalence of prescribing of QTc interval-prolonging medications alone and in combination in the ARIC population.

2. Identify clinically relevant values of QTc interval across categories of QTc interval-prolonging medications in combination with several risk factor known for QTc interval prolongation. See Table-1 below for further clarification.

3. Examine the association of the use of QTc interval prolonging medications (alone or in combination with other QTc prolonging medication) with the risk of stroke, atrial fibrillation, and all-cause mortality as well as mortality due to sudden cardiac death (SCD).

4. Examine effect measure modification of the association of QTc interval prolonging medications with the risk of stroke atrial fibrillation, all-cause mortality and SCD by risk factor burden.

Table 1. Estimates of shift in mean QTc values in association with the use of QTc prolonging medications			
Exposure QT-Interval Prolonging		**Mean, median, range of QTc- interval *(msec)***	**△ Difference of mean observed QTc and normal QTc values *(msec)***
Number of Medication	Number of Risk Factors*		
1	0		
	1		
	≥ 2		
≥ 2	0		
	1		
	≥ 2		

** Risk factors are defined in the method section.*

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:

All ARIC cohort study participants with resting 12-lead ECG and a calculated QTc interval, who participated in visits 1-4 will be eligible for inclusion. Information concerning the QT interval, and heart rate (HR) will be collected. We will use a linear formula for rate corrected QT as recommended by a task force sponsored by professional organizations.[15] Specifically, we will setup a linear regression model with QT interval as the dependent variable and heart rate interval as the independent variable. Based on the beta-coefficient associated with heart rate, the following formula will be derived for heart rate adjusted QT (QTa): QTa = QT + beta coefficient*(heart rate-60).[15]

The exposure of interest is the use of QTc interval prolonging medications at the visits, as observed from the medication self-report. QTc interval-prolonging medications will be defined according to the AzCERT classifications, as noted in Appendix-1 (www.qtdrugs.org). Prior to categorizing the agent, AzCERT conducts a rigorous evaluation of every medication, including clinical and pharmacologic analyses. The medications contained within the AzCERT database reflect a consensus opinion of AzCERT's Scientific Advisory Board, which is comprised of internists, cardiologists, electrophysiologists, pharmacologists, and scientists. AzCERT maintains three lists of drugs known to prolong the QT interval: 1) drugs accepted to carry a definite risk of causing TdP (definite TdP risk), 2) drugs that prolong the QT interval and have been associated with TdP but lack substantial evidence for causing TdP (possible TdP risk), and 3) drugs that carry a risk of QT interval prolongation and/or TdP under certain conditions, such as drug overdose or co-administration with interacting drugs (conditional TdP risk).

Risk factors for QTc interval prolongation will be collected (See Table-2). Interacting medications are defined as any medications that may increase the risk of QTc interval prolonging medications exposure, by inhibiting its metabolism and/or elimination.

Table-2 Risk Factors for QTc Interval Prolongation
QTc interval > 500 msec
Advanced age > 65 years
Female gender
Bradycardia
Left ventricular systolic dysfunction
Concomitant use of an inhibitor of the cytochrome P-450 system

Outcomes:

For the first objective, to best describe the prescribing practices for QTc interval prolonging medication, we will identify patients receiving any single medication known for QTc interval prolongation, as well as patients receiving from 2 to 4 QTc interval prolonging medications (in any combination). Also, we will determine the number of risk factors for each participant, including the total number of potentially interacting medications.

For the second and third objectives we will use as a reference the expected gender-specific normal values of the QTc interval (< 460 msec for women and < 450 msec for men) to identify the difference potential increase in the observed QTc interval among participants with a single QTc interval prolonging medication, as well as participant reporting the use of a combinations of QTc prolonging medications with or without presence of risk factors. Through 2001, morbidity outcomes will include adjudicated stroke, atrial fibrillation (derived from ECG data and hospitalization records' ICD-9 codes), adjudicated sudden cardiac death defined as the death was characterized as a sudden, pulseless condition without a known non-cardiac cause, and all-cause mortality.

Analytical methods:

We will use descriptive analyses to report the most commonly used QTc-prolonging medications, combinations of QTc-prolonging medications, risk factors for QTc prolongation and subsequent effect on QTc interval. We will use various medications and risk factors combination (see table 1) to determine the magnitude of QTc interval prolongation.

Cox proportional hazard analysis will be utilized to examine the associations between QTc interval-prolonging medication use (as a dichotomous variable) and the risk of stroke, atrial fibrillation, SCD and all-cause mortality. Multinomial regression models will be used to account for competing risk of death. As previously described, prescribing of one if not two QTc-prolonging medications has been reported to be as high as 10%, and select QTc interval prolonging medications are associated with two to three-fold increase in risk of mortality.[11-14] In the population of ARIC study participants alive and non-missing at Visit 3 (12,877), we anticipate that at least 1,289 participants will have reported use of at least one QTc prolonging medication. We estimate that for those study participants we will have 80% power to detect a hazard ratio of at least 1.42 (α=0.05) if the event rate is at least 20%. The distribution of QTc interval prolonging medication use will dictate creation of meaningful categories of QTc prolonging medication use in combination with risk factor burden (see Table 1) and will inform final study power determinations for these additional subgroups

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? __x__ 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
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? ____ Yes __x__ No
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.

b. 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.

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Appendix-1

Generic Name	Brand Name	Therapeutic Use
Alfuzosin	Uroxatral®	Benign prostatic hyperplasia
Amantadine	Symmetrel®, Symadine®	Anti-infective/ Parkinson's Disease
Amiodarone	Cordarone®, Pacerone®, Nexterone®	abnormal heart rhythm
Amisulpride	Solian®, Supitac®, Soltus®, Amazeo®	Psychosis
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®	depression
Amoxapine	Asendin®, Amokisan®, Asendis®, Defanyl®, Demolox®, Moxadil®	Depression
Anagrelide	Agrylin®, Xagrid®	Thrombocythemia
Arsenic trioxide	Trisenox®	Leukemia
Atazanavir	Reyataz®	HIV/AIDS
Azithromycin	Zithromax®, Zmax®	bacterial infection
Bedaquiline	Sirturo®	Drug-resistant Tuberculosis
Bortezomib	Velcade®, Bortecad®	Multiple Myeloma,lymphoma
Bosutinib	Bosulif®	Leukemia
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®	sedation/ insomnia
Chloroquine	Aralen®	malaria infection
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	schizophrenia/ nausea
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	bacterial infection
Citalopram	Celexa®, Cipramil®	depression
Clarithromycin	Biaxin®, Prevpac®	bacterial infection
Clomipramine	Anafranil®	depression
Clozapine	Clozaril®, Fazaclo®, Versacloz®	schizophrenia
Cocaine	Cocaine	Topical anesthetic
Crizotinib	Xalkori®	Anti-cancer
Dabrafenib	Tafinlar®	Melanoma
Dasatinib	Sprycel®	Leukemia
Desipramine	Pertofrane®, Norpramine®	depression
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Sedation
Dihydroartemisinin+piperaquine	Eurartesim®	Malaria
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®	Allergic rhinitis, insomnia
Disopyramide	Norpace®	abnormal heart rhythm
Dofetilide	Tikosyn®	abnormal heart rhythm
Dolasetron	Anzemet®	nausea, vomiting
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®,	depression
Dronedarone	Multaq®	Atrial Fibrillation
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	anesthesia adjunct, nausea
Eribulin	Halaven®	metastatic breast neoplasias
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®,	bacterial infection; increase GI
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India),	Major depression/ Anxiety
Famotidine	Pepcid®, Fluxid®, Quamatel®	Peptic ulcer/ GERD
Felbamate	Felbatol®	seizure
Fingolimod	Gilenya®	Multiple Sclerosis
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	fungal infection
Fluoxetine	Prozac®, Sarafem®, Fontex®	depression
Foscarnet	Foscavir®	HIV/AIDS
Fosphenytoin	Cerebyx®, Prodilantin®	seizure
Furosemide (Frusemide)	Lasix®, Fusid®, Frumex®	Increase urine & salt loss
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,	Dementia, Alzheimer's
Gemifloxacin	Factive®	bacterial infection
Granisetron	Kytril®, Sancuso®, Granisol®	Nausea, vomiting
Halofantrine	Halfan®	malaria infection

Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®,	schizophrenia, agitation
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®,	Increase urine & salt loss
Ibutilide	Corvert®	abnormal heart rhythm
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Schizophrenia
Imipramine (melipramine)	Tofranil®	depression
Indapamide	Lozol®, Natrilix®, Insig®	Increase urine & salt loss
Isradipine	Dynacirc®	high blood pressure
Itraconazole	Sporanox®, Onmel®	fungal infection
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®	fungal infection
Lapatinib	Tykerb®, Tyverb®	breast cancer, metastatic
Levofloxacin	Levaquin®, Tavanic®	bacterial infection
Lithium	Eskalith®, Lithobid®	bipolar disorder
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®,	pain control, narcotic
Mirtazapine	Remeron	Depression
Moexipril/HCTZ	Uniretic®, Univasc®	high blood pressure
Moxifloxacin	Avelox®, Avalox®, Avelon®	bacterial infection
Nicardipine	Cardene®	high blood pressure
Nilotinib	Tasigna®	Leukemia
Norfloxacin	Noroxin®, Ambigram®	Bacterial infections
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®,	depression
Ofloxacin	Floxin®	bacterial infection
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Schizophrenia, bipolar
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®,	Nausea, vomiting
Oxytocin	Pitocin®, Syntocinon®	Labor stimulation
Paliperidone	Invega®, Xepilon®	Schizophrenia
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®	depression
Pasireotide	Signifor®	Cushings Disease
Pazopanib	Votrient®	Anti-cancer
Pentamidine	NebuPent®, Pentam®	pneumocystis pneumonia
Perflutren lipid	Definity®	Echocardiography
Pimozide	Orap®	Tourette's tics
Posaconazole	Noxafil®, Posamol®	Fungal infection
Procainamide (Oral off US	Pronestyl®, Procan®	abnormal heart rhythm
Promethazine	Phenergan®	nausea
Protriptyline	Vivactil®	depression
Quetiapine	Seroquel®	schizophrenia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-	abnormal heart rhythm
Quinine sulfate	Qualaquin®	Malaria or leg cramps
Ranolazine	Ranexa®, Ranozex®	chronic angina
Rilpivirine	Edurant®, Complera®, Eviplera®	HIV/AIDS
Risperidone	Risperdal®	schizophrenia
Ritonavir	Norvir®	HIV/AIDS
Saquinavir	Invirase®(combo)	HIV/AIDS
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®,	depression
Sevoflurane	Ulane®, Sojourn®	anesthesia
Solifenacin	VESIcare®	treatment of overactive bladder
Sorafenib	Nexavar®	Anti-cancer
Sotalol	Betapace®, Sotalex®, Sotacor®	abnormal heart rhythm
Sunitinib	Sutent®	Renal cell cancer, GIST
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Immune suppression
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	breast cancer
Telavancin	Vibativ®	Bacterial infection
Telithromycin	Ketek®	bacterial infection
Thioridazine	Mellaril®, Novoridazine®, Thioril®	schizophrenia
Tizanidine	Zanaflex®, Sirdalud®	Spasticity
Tolterodine	Detrol®, Detrusitol®	Bladder spasm
Toremifene	Fareston®	Anti-cancer
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®,	Depression, insomnia
Trimethoprim-Sulfa	Septra®, Bactrim®, Sulfatrim®, Biseptol®, Co-	bacterial infection
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	depression
Vandetanib	Caprelsa®	Thyroid cancer

Vardenafil	Levitra®	vasodilator
Vemurafenib	Zelboraf®	Anti-cancer
Venlafaxine	Effexor®, Efexor®	depression
Voriconazole	VFend®	anti-fungal
Vorinostat	Zolinza®	Lymphoma
Ziprasidone	Geodon®, Zeldox®	schizophrenia