

ARIC Manuscript Proposal # 3326

PC Reviewed: 5/14/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Use of Medications with Cardiovascular Adverse Effects and Incident Cardiovascular Disease Among Statin Users

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

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

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3. Timeline:

1. Obtain IRB approval
2. Submit ARIC manuscript proposal
3. Submit ARIC data access proposal
4. Access ARIC data
5. Conduct analyses and draft manuscript
6. Publish manuscript

4. Rationale:

Many commonly used medications have the potential for cardiovascular adverse effects, including myocardial infarction, ischemic stroke, heart failure, QT prolongation and sudden cardiac death. We performed a preliminary analysis of the ARIC cohort using the BIOLINCC to examine whether and how the use of multiple medications with major adverse cardiovascular event (MACE) adverse effects (myocardial infarction, ischemic stroke and/or sudden cardiac death) is associated with an increased risk of cardiovascular disease and/or death among older adults. We found that among a primary prevention cohort without prevalent CVD and not treated with CVD medications, the risk of incident cardiovascular events increases with the number of medications with MACE adverse effects used. Specifically, the use of 1-2 (HR 1.56 [CI 1.10, 2.2]) or 3 or more (HR, 2.34 [CI 1.59, 3.47]) MACE medications was associated with significantly higher cardiovascular risk when compared to non-users. This relationship was not observed with the use of medications without MACE adverse effects.

Despite the insights provided by this prior work, it leaves several questions unanswered. First, we do not incorporate information on several cardiovascular risk factors, including both clinical and subclinical (e.g. heart failure, QT prolongation, CRP, Troponin, Coronary Artery Calcium (CAC) score, carotid intima media thickness (cIMT)). Second, we limit our analyses to medications with MACE adverse effects and therefore do not know whether and how medications with other CV risks, including QT prolongation and heart failure, may influence our findings. Finally, our analyses do not focus on statin users. Focusing on statins is of clinical and public health importance because statins are widely and increasingly used in the primary prevention of CVD. Despite the growing burden of polypharmacy and the widespread use of statins, however, there is limited information on whether and how the concurrent use of statins and additional medications with known cardiovascular adverse effects is associated with increased cardiovascular risk.

Thus, we propose to perform an analysis of the restricted access ARIC dataset, focusing on older individuals using statins. Through such a focus, we are selecting for a group of individuals at elevated cardiovascular risk, where any impact of adverse cardiovascular effects from medications may be especially likely to be discerned. This information is important because the concurrent use of statins in specific drug combinations may nullify the proven cardiovascular and survival benefits of statins. We will determine whether and how differences in the concurrent use of statins with impact the effectiveness of statins in the prevention of incident cardiovascular events (coronary heart disease, including fatal and nonfatal myocardial infarction and fatal and nonfatal stroke) and all-cause mortality. Our *central hypothesis* posits that the concurrent use of statins and medications with cardiovascular risk is associated with an increased risk for cardiovascular events. This analysis will generate fundamental new knowledge of interest to clinicians, patients, regulators and manufacturers alike.

5. Main Hypothesis/Study Questions:

Study Question:

What is the association between the concurrent use of medications with the potential adverse cardiovascular effects (overall and by type of adverse effect) and the risk of incident cardiovascular events (overall and by type of CV event) among older adult statin users without prevalent CVD?

Main Hypothesis: The concurrent use of medications with the potential for adverse cardiovascular effects is associated with increased cardiovascular risk among statin users not treated with cardiovascular medications at cohort entry.

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: Prospective cohort analysis in the ARIC Study with baseline defined at cohort entry at first statin use during annual follow up [AFU], 2006-2011)

Cohort Selection:

Participants who participated in AFU (form versions L and M, n=10,613) were assessed for eligibility. Participants that did not participate in Visit 4 (n=1,517), had prevalent CVD (n=792), did not initiate a statin (n=3,787), and had used CV medications at cohort entry (n=2,676 [see Appendix C]) were excluded. This resulted in a study population of 1,841 participants who used at least one statin in AFU (Figure 2). Participants enter the cohort at their first reported statin use in AFU (2006-2011) and are followed up until cohort exit.

- Inclusion
 - Participants are eligible for the study if they participate in ARIC AFU form versions L and M (from 2006-2011).
 - Participants who use statins at least once during the cohort period (AFU 2006-2011) will enter the cohort at their first reported statin use during AFU.
- Exclusion
 - Participants who did not participate in visit 4
 - Participants with prevalent cardiovascular disease, including coronary heart disease (CHD), cardiac ischemia, cerebrovascular ischemia, or heart failure prior to the first annual follow up (form version L) will be excluded.
 - Prevalent CHD is an ARIC variable available in visit 4 and is based on self-report of prevalent CHD at visit 1 and through adjudicated events thereafter.
 - Prevalent cardiovascular disease has also been identified through ARIC adjudicated event variables or, when adjudicated variables are not available, ICD-9 codes associated with hospitalization discharge events prior to AFU (Table 2).
 - Participants concurrently using cardiovascular medications at cohort entry (based on the first reported statin use during AFU).
 - A list of cardiovascular medications are provided in Appendix C.
 - Participants will exit the cohort on the day of their incident CV event or death, when they are lost to follow-up (LFU), or at the end of study follow up.

Table 1. Summary of Cohort Selection Criteria

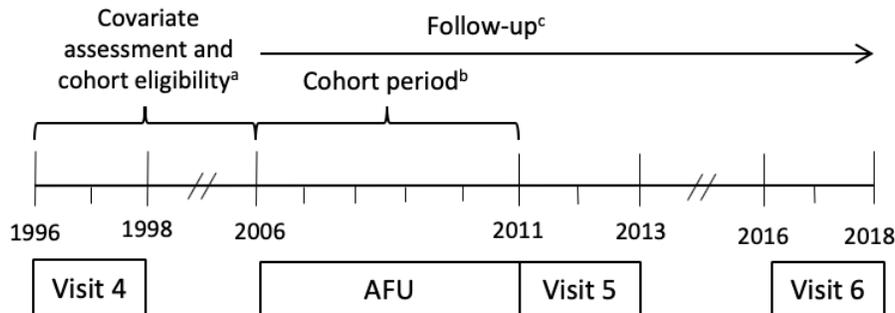
Criteria	Description
Eligibility	<ul style="list-style-type: none"> Participants are eligible for the study if they participate in ARIC AFU form versions L and M (from 2006-2011)
Exclusion	<ul style="list-style-type: none"> History of cardiovascular disease prior to AFU^a (including prevalent CHD, cardiac ischemia, cerebrovascular ischemia, or heart failure) Participant did not participate in visit 4 Participant used a CV medication at cohort entry
Cohort Entry ^b	<ul style="list-style-type: none"> Date of first reported statin use in AFU, participants will be followed up from this date until cohort exit (see below)
Cohort Exit ^b	<ul style="list-style-type: none"> Participants will exit the cohort <ul style="list-style-type: none"> - Following their incident cardiovascular event or death, - If they are lost to follow-up, or - At the end of study follow up

Abbreviations: AFU, annual follow-up; CHD, coronary heart disease

^a Prevalent CHD will be identified through the ARIC variable available in visit 4 and is based on self-report of prevalent CHD at visit 1 and through adjudicated events thereafter. Prior cardiovascular disease has also been identified through ICD-9 codes associated with hospitalization discharge events prior to AFU (listed in Table 2).

^b Please refer to “Cohort Entry and Exit” under *Summary of Data Analysis* for further clarification.

Figure 1. Study timeline.

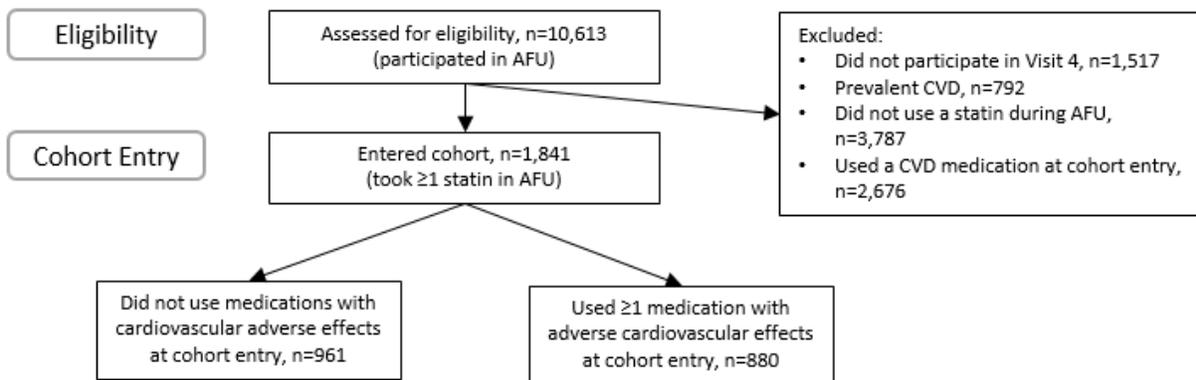


^a Participants were excluded from the cohort if they had a history of cardiovascular disease prior to cohort entry, or if they did not participate in Visit 4.

^b Participants enter cohort upon first statin use during AFU and are followed up through subsequent study visits. Cohort entry date is the date of first statin use.

^c Participants are followed up from the date of cohort entry until (1) they have an event, (2) are lost to follow up, or (3) reach the end of study follow-up (event free).

Figure 2. Sample size



Exposure

The use of prescription medications that have a potential for adverse cardiovascular effects will be identified using Micromedex (Truven Health Analytics). A similar approach was used by Dr. Qato for a recent publication focusing on the use of multiple medications with depression listed as an adverse effect on their FDA-approved label.¹ Medications with major adverse cardiovascular effects or MACE (*myocardial infarction, ischemic stroke, cerebrovascular accident, transient ischemic attack, cerebral ischemia, cardiac death, cardiac arrest*), or *QT prolongation* listed as common or serious adverse effects are defined as having a potential for adverse cardiovascular effects. The list of medications with cardiovascular adverse effects is included in Appendix A and the list of medications with QT prolongation adverse effects is included in Appendix B. We plan to ascertain a similar list for medications that have heart failure as a potential adverse effect and add these to our exposure definition. **Cardiovascular drugs indicated for the treatment of cardiovascular disease are listed in Appendix C and will be excluded. Therefore we will limit our exposure to the use of non-cardiovascular medications with adverse cardiovascular effects.**

Recent medication use (≤ 2 weeks) was collected at visit 4, annual follow up (AFU, forms L and M), visit 5, and visit 6. The number of medications with adverse cardiovascular effects will be identified based on medication name and therapeutic class, tallied, and modeled as both a time-fixed (based on cohort entry) and time-varying exposure.

Outcome

Three outcomes will be evaluated for this analysis: (1) incident cardiovascular (CV) event, (2) all-cause mortality, and (3) a combined CV event and/or all-cause mortality. Incident CV event that represent a composite of fatal or non-fatal myocardial infarction (MI), fatal or non-fatal ischemic stroke, cardiac death, cardiac arrest, or heart failure. CV events will be identified using adjudicated ARIC variables when available (e.g. HF, MI and ischemic stroke) and International Classification of Diseases, Ninth Revision (ICD-9) codes from hospitalization

¹ Qato DM, Ozenberger K, Olsson M. Prevalence of Prescription Medications With Depression as a Potential Adverse Effect Among Adults in the United States. *JAMA*. 2018 Jun 12;319(22):2289-2298. doi: 10.1001/jama.2018.6741. PubMed PMID: 29896627.

discharges when adjudicated variables are not available (Table 2). CV events will be considered fatal if death occurred on the same day as the event.

Table 2. ICD-9 Codes and ARIC Variables included as event determination

Event Description	ICD-9 Description	ICD-9 Codes	ARIC Variable	ARIC Dataset
All-Cause Mortality			dthdate_days	cevtps14
Coronary Heart Disease	Other acute and subacute forms of ischemic heart disease	411.8X		
	Coronary atherosclerosis, Chronic ischemic heart disease (unspecified)	414.XX		
MI ^{2 3}			cmidx: Validated MI variable, “probable” and “definite” MIs are added to the MI/CHD variable.	cevtps14
Ischemic Stroke ^{4 5 6 7}			inisc14: adjudicated definite/probable incident ischemic stroke tia21: adjudicated TIA stroke21: adjudicated stroke (it is unclear whether this is just ischemic stroke or adjudicated stroke) stia21: stroke or TIA	incps14
Cardiac Arrest ⁸	Cardiac arrest	427.5		
Sudden Death ⁹	Sudden death cause unknown	798	sudth1: sudden death w/in 1 hour	cevtps14
	Other ill-defined and unknown causes of morbidity and mortality	799	sudth24: sudden death w/in 24 hours	
Revascularization ¹⁰			celb08d: “Was coronary revasc performed?”	
Heart Failure ¹¹ (Note: Heart failure ICD-9 codes are used in our exclusion criteria. Adjudicated variables will	Rheumatic heart failure (congestive)	398.91	chfdiag: “ARIC adjudicated HF diagnosis”	hfcoccp14
	Hypertensive heart disease (with heart failure)	402.01, 402.11, 402.91		

² Shah, N. H., LePendu, P., Bauer-Mehren, A., Ghebremariam, Y. T., Iyer, S. V., Marcus, J., ... & Leeper, N. J. (2015). Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PloS one*, 10(6), e0124653. [https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124653]

³ http://www.icd9data.com/2014/Volume1/390-459/410-414/410/default.htm

⁴ Goldstein, L. B. (1998). Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke*, 29(8), 1602-1604. [https://www.ahajournals.org/doi/pdf/10.1161/01.str.29.8.1602]

⁵ Jones, S. A., Gottesman, R. F., Shahar, E., Wruck, L., & Rosamond, W. D. (2014). Validity of hospital discharge diagnosis codes for stroke: the Atherosclerosis Risk in Communities Study. *Stroke*, 45(11), 3219-3225. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290877/]

⁶ Chambless, L. E., Heiss, G., Shahar, E., Earp, M. J., & Toole, J. (2004). Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *American journal of epidemiology*, 160(3), 259-269. [https://academic.oup.com/aje/article/160/3/259/58851]

⁷ Rosamond, W. D., Folsom, A. R., Chambless, L. E., Wang, C. H., McGovern, P. G., Howard, G., ... & Shahar, E. (1999). Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*, 30(4), 736-743. [http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.566.3622&rep=rep1&type=pdf]

⁸ http://www.icd9data.com/2014/Volume1/390-459/420-429/427/427.5.htm

⁹ Corona, G., Rastrelli, G., Silverii, A., Monami, M., Sforza, A., Forti, G., ... & Maggi, M. (2013). The identification of prediabetes condition with ARIC algorithm predicts long-term CV events in patients with erectile dysfunction. *The journal of sexual medicine*, 10(4), 1114-1123. [https://onlinelibrary.wiley.com/doi/epdf/10.1111/jsm.12066]

¹⁰ Kalbaugh, C. A., Kucharska-Newton, A., Wruck, L., Lund, J. L., Selvin, E., Matsushita, K., ... & Loehr, L. (2017). Peripheral artery disease prevalence and incidence estimated from both outpatient and inpatient settings among medicare fee-for-service beneficiaries in the atherosclerosis risk in communities (ARIC) study. *Journal of the American Heart Association*, 6(5), e003796. [https://www.ahajournals.org/doi/full/10.1161/JAHA.116.003796]

¹¹ Rosamond, Wayne D., Patricia P. Chang, Chris Baggett, Anna Johnson, Alain G. Bertoni, Eyal Shahar, Anita Deswal, Gerardo Heiss, and Lloyd E. Chambless. "Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria." *Circulation: Heart Failure* 5, no. 2 (2012): 152-159. [https://www.ncbi.nlm.nih.gov/pubmed/22271752]

Event Description	ICD-9 Description	ICD-9 Codes	ARIC Variable	ARIC Dataset
<i>be used in event determination.)</i>	Hypertensive heart and chronic kidney disease (with heart failure)	404.01, 404.03, 404.13, 404.93, 404.91		
	Acute pulmonary heart disease	415, 415.1X		
	Chronic pulmonary heart disease	416.9		
	Cardiomyopathy (Other primary cardiomyopathies)	425.4		
	Heart failure	428.XX		

Table 3. Summary of covariates that will be included in adjusted models or through stratification.

Description	Covariates (categorization)	ARIC Study Visit (when collected) ^a
Demographic variables and Participant Characteristics	<ul style="list-style-type: none"> • Race (black/white) • Sex (male/female) • ARIC study center • Educational attainment • Insurance coverage • Family income in previous 12 months • Age (years) 	Visit 4, except for Age which will be collected at Cohort Entry (in AFU)
Modifiable Risk Factors	<ul style="list-style-type: none"> • Body Mass Index^a (BMI, <25 kg/m², 25 to <30 kg/m², and ≥30 kg/m²) • Cigarette smoking (current use, former use, or never use) • Alcohol consumption (current use, former use, or never use) 	Visit 4, Visit 5, Visit 6
Comorbid Conditions	<ul style="list-style-type: none"> • Diabetes^c (yes/no) • Hypertension^d (yes/no) 	Visit 4, Visit 5, Visit 6
Kidney Function	<ul style="list-style-type: none"> • Chronic Kidney Disease (yes/no) • Estimated glomerular filtration rate (eGFR, mL/min/1.73 m²) (continuous) • Albumin creatinine ratio (ACR, mg/g) (continuous) 	Visit 4, Visit 5, Visit 6
Medication Use	<ul style="list-style-type: none"> • Aspirin use (yes/no, modeled as time-varying) 	AFU, Visit 5, and Visit 6
Biomarkers of Subclinical CVD	<ul style="list-style-type: none"> • CRP • Troponin • Coronary Artery Calcium (CAC) score • Carotid intima media thickness (cIMT) 	Visit 4 (except for CAC, which is captured at Visit 5)
CVD Risk Measures	<ul style="list-style-type: none"> • Total cholesterol/high-density lipoprotein (HDL-C) (continuous) • 10-year CVD risk score^e (continuous) 	Visit 4, Visit 5, Visit 6

Other Heart Measures	<ul style="list-style-type: none"> • QT interval • Heart Rate 	Visit 4, Visit 5, Visit 6
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Abbreviations: CVD, cardiovascular disease; BMI, body mass index

^a Variables collected at multiple time-points will be modeled as time-varying based on when they are collected.

^b BMI is defined as weight [kilograms (kg)] divided by height [meters (m)] squared

^c Diabetes is based on the definition that includes recent antidiabetic medication use, a fasting (≥ 8 hours) blood glucose level of ≥ 126 mg/dL, or a nonfasting glucose of ≥ 200 mg/dL

^d Hypertension is identified by ARIC “Definition 5” and identified through self-report, recent antihypertensive medication use, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg

^e 10-year CVD risk score variable included in ARIC dataset were calculated by pooled cohort equations

Summary of Data Analysis

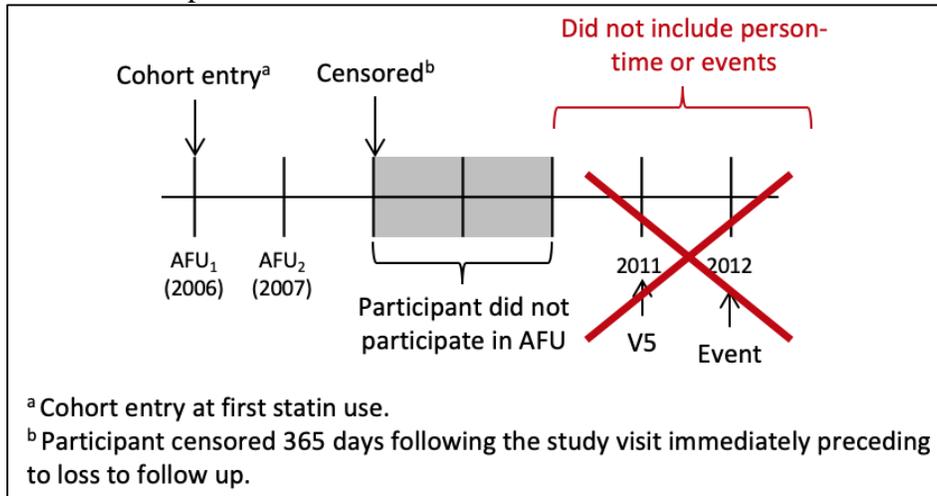
Descriptive statistics will be used to evaluate participant characteristics of the total sample and by use of medications with adverse cardiovascular effects at cohort entry. Cox proportional hazards regression models will be used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of incident CV events and all-cause mortality with the use of medications with adverse cardiovascular effects. Competing risks will be evaluated through cause-specific hazards, where three different models will be analyzed. These three models include modeling three different primary outcomes: (1) incident CV event, (2) all-cause mortality, and (3) a combined CV event or all-cause mortality. Death from a cause that is not related to CV disease is considered a competing risk for CV events because it prevents participants from a CV event later. The proportional hazards assumption will be tested using Schoenfeld Residuals. There will be two primary analyses:

1. Intention-to-treat analysis: Participants in the statin cohort will be grouped based on the number of medications with and those without adverse cardiovascular effects (non-use, 1-2 medications with cardiovascular adverse effects, and ≥ 3 medications with cardiovascular adverse effects) at cohort entry. This will be a time-fixed exposure based on medication use at cohort entry. We will also use propensity scores to match these 3 groups.
2. Time-varying analysis: Exposure to medications with adverse cardiovascular effects will be modeled as a time-varying exposure (Figure 4). The number of medications that do not have cardiovascular adverse effects will also be modeled as time-varying covariate in the same model.

Cohort Entry and Exit

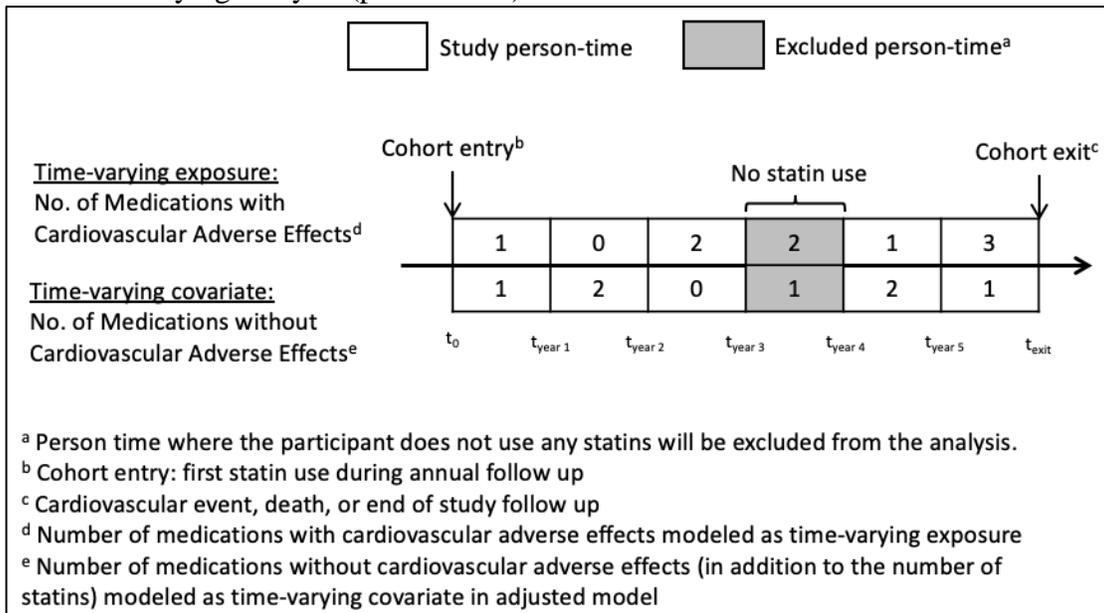
Participants will enter the cohort following the first use of statin during annual follow up (AFU). Participants will exit the cohort following their incident event, at loss to follow-up (LFU), or at the end of the study period (Figure 1). Participants will be considered LFU if more than 1 year passes between study visits and will be censored at 1-year after the last study visit (Figure 3).

Figure 3. Loss to follow up



For our time-varying analyses, we will restrict the person-time to periods of current exposure to statin medications. Current use is defined as the person-time following the study visit where the participant reported medication use. Person-time where participants do not report the use of statin medications will be excluded from the analysis (Figure 4).

Figure 4. Time-varying analysis (person-time)



Multiple sensitivity analyses will be conducted and will include:

1. Time-varying analyses among statin users that did not concurrently use at least one medication with adverse cardiovascular effects at cohort entry. Exposure to medications without cardiovascular adverse effects will be modeled as time-varying (serves as negative control).
2. We will exclude participants that used cholesterol lowering drugs prior to AFU form version L. Therefore, our cohort in this sensitivity analysis will include new-users of statins.
3. Ever-users of medications with adverse cardiovascular effects will be compared to never-users (i.e., participants that have never been exposed to medications with cardiovascular adverse effects).
4. Duration of use of medications with cardiovascular adverse effects (current and non-current). This will allow us to investigate the risk among individuals who take medications with cardiovascular adverse effects by recency of use.
5. Stratification / subgroup analyses: diabetes status (at Visit 4), hypertension (at Visit 4), gender, race, age at cohort entry (<65 years, 65 to 74 years, ≥ 75 years), aspirin ever-use, and 10-year CV risk score (<5%, 5 to <10%, and $\geq 10\%$).

Anticipated Methodologic Limitations/Challenges

The primary limitation in this analysis is the frequency where medication exposure is collected. We are addressing this limitation by considering participants with >1 year between study time points as lost to follow up and censoring them at the last known time point. Furthermore, there is a potential for healthy user and survival bias that is associated with this type of analysis. A participant must have survived to the beginning of study follow up (i.e., AFU form version L) and entry into the cohort in order to contribute person-time to the analysis. Finally, we have a long baseline eligibility period (8 to 10 years) between visit 4 and the first AFU (form version L) where medication information is collected and study follow up begins. This may result in misclassified covariates (e.g., diabetes, hypertension, and BMI). In order to address confounding by indication, participants treated with a CVD medication at cohort entry will be excluded. To address additional potential bias, we are incorporating inverse-treatment probability weights in addition to propensity score matching.

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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

___ 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)?

Alburikan, K. A., Aldemerdash, A., Savitz, S. T., Tisdale, J. E., Whitsel, E. A., Soliman, E. Z., ... & Rodgers, J. E. (2017). Contribution of medications and risk factors to QTc interval lengthening in the atherosclerosis risk in communities (ARIC) study. *Journal of evaluation in clinical practice*, 23(6), 1274-1280.

Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. (2016). Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA internal medicine*, 176(2), 238-246.

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 <https://www2.csc.c.unc.edu/aric/approved-ancillary-studies>

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.csc.c.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.

Appendix A. List of Medications with Potential Major Adverse Cardiovascular Events (MACE) Identified for Inclusion in the Study. Cardiovascular Drugs with MACE Adverse Effects that are listed in Appendix C will be excluded.

A. Medications cardiovascular adverse effects with a black-box warning (n=104)

1. Antiarrhythmic (Dronedaron, Flecainide, Phenytoin, Propafenone, Quinidine)
2. Antipsychotics (Aripiprazole, Clozapine, Fluoxetine/Olanzapine, Haloperidol, Iloperidone, Loxapine, Lurasidone, Mesoridazine, Olanzapine, Perphenazine, Perphenazine/Amitriptyline, Quetiapine, Risperidone, Thioridazine, Trifluoperazine)
3. Bronchodilators (Salmeterol, Tiotropium)
4. CNS Stimulants (Amphetamine, Amphetamine/Dextroamphetamine, Dextroamphetamine, Methamphetamine)
5. COX2 Inhibitors (Celecoxib, Rofecoxib)
6. Hormone/Hormone Modifiers^a (Conjugated Estrogens, Conjugated Estrogens/Medroxyprogesterone, Dienogest/Estradiol, Esterified Estrogens, Esterified Estrogens/Methyltestosterone, Estradiol, Estradiol/Levonorgestrel, Estradiol/Medroxyprogesterone, Estradiol/Norethindrone, Estradiol/Norgestimate, Estradiol/Testosterone, Estropipate, Ethinyl Estradiol, Ethinyl Estradiol/Desogestrel, Ethinyl Estradiol/Drospirenone/Levonorgestrel, Ethinyl Estradiol/Drospirenone, Ethinyl Estradiol/Ethinodiol, Ethinyl Estradiol/Etonogestrel, Ethinyl Estradiol/Levonorgestrel, Ethinyl Estradiol/Norelgestromin, Ethinyl Estradiol/Norethindrone, Ethinyl Estradiol/Norethindrone Acetate, Ethinyl Estradiol/Norgestimate, Ethinyl Estradiol/Norgestrel)
7. Narcotic Analgesics (Buprenorphine, Buprenorphine/Naloxone, Codeine, Fentanyl, Hydrocodone, Hydrocodone/Ibuprofen, Hydromorphone, Meperidine, Methadone, Morphine, Oxycodone, Oxycodone/Ibuprofen, Oxymorphone, Phenylephrine/Codeine, Phenylephrine/Hydrocodone, Propoxyphene, Pseudoephedrine/Codeine, Pseudoephedrine/Hydrocodone)
8. NSAIDs (Diclofenac, Diclofenac/Misoprostol, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meclofenamate, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin)
9. Thyroid Hormones (Levothyroxine, Levothyroxine/Liothyronine, Liothyronine)
10. Other (Chlorpromazine, Dabigatran, Danazol, Diflunisal, Dihydroergotamine, Epoetin Alfa, Immune Globulin, Interferon A2b/Ribavirin, Interferon Alfa2a, Interferon Alfa2b, Naproxen/Sumatriptan, Ribavirin, Salsalate)

B. Medications cardiovascular adverse effects with no black-box warning (n=168)

1. Anorexiant (Phentermine, Sibutramine¹)
2. Antiarrhythmic (Digoxin, Diltiazem², Dofetilide, Lidocaine, Sotalol)

3. Antidepressants (Amitriptyline, Citalopram, Clomipramine³, Desipramine³, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine³, Maprotiline, Nortriptyline, Paroxetine⁴, Protriptyline, Trimipramine)
4. Antidiabetic (Glimepiride, Glimepiride/Rosiglitazone, Repaglinide, Rosiglitazone)
5. Antigout (Allopurinol)
6. Antihypertensives^b (Amiloride, Amlodipine, Amlodipine/Telmisartan, Captopril, Enalapril, Felodipine, Isradipine, Losartan, Nicardipine, Nifedipine, Nisoldipine, Perindopril, Quinapril, Ramipril, Telmisartan, Trandolapril, Trandolapril/Verapamil, Verapamil)
7. Antiparkinsons (Carbidopa/Levodopa, Carbidopa/Levodopa/Entacapone, Pergolide, Selegiline)
8. Antipsychotics (Ziprasidone)
9. Anxiolytics, Sedatives, Hypnotics (Buspirone, Doxepin³, Zolpidem)
10. Bronchodilators (Albuterol, Albuterol/Ipratropium, Arformoterol, Formoterol⁵, Ipratropium⁶, Theophylline^{7,8})
11. CNS Stimulants (Atomoxetine, Benzphetamine, Dexmethylphenidate, Diethylpropion, Lisdexamfetamine, Methylphenidate, Phendimetrazine)
12. Corticosteroids (Betamethasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisone, Triamcinolone)
13. COX2 Inhibitors (Valdecoxib)
14. Hormone/Hormone Modifiers^a (Calcitonin, Etonogestrel, Levonorgestrel, Medroxyprogesterone, Testosterone)
15. Muscle Relaxants (Baclofen, Cyclobenzaprine, OnabotulinumtoxinA)
16. Narcotic Analgesics (Naloxone, Tramadol)
17. NSAIDs (Indomethacin/Betamethasone)
18. PDE-I (Sildenafil^{9,10}, Tadalafil, Vardenafil)
19. Proton-Pump Inhibitors (Dexlansoprazole)
20. Smoking Cessation (Bupropion, Nicotine¹¹, Varenicline)
21. Thyroid Hormones ([Desiccated] Thyroid¹²)
22. Other (Abacavir/Lamivudine, Abiraterone, Acitretin, Adalimumab, Alfuzosin, Almotriptan, Anagrelide, Anastrozole, Apixaban, Bicalutamide, Bortezomib, Capecitabine, Cevimeline, Cilostazol, Ciprofloxacin, Cisplatin^{13,14}, Colesevelam, Colestipol, Cyclosporine, Darbepoetin Alfa, Denosumab, Desmopressin, Dipyridamole, Docetaxel, Doxazosin, Eletriptan, Ephedrine¹⁵, Eplerenone, Ergotamine¹⁶⁻¹⁸, Erlotinib, Etravirine, Febuxostat, Fosamprenavir, Frovatriptan, Glatiramer, Goserelin, Granisetron, Guanfacine, Hydralazine, Infliximab, Interferon Gamma1b, Isoniazid PZA/Rifampin, Isosorbide Mononitrate, Isotretinoin, Leflunomide, Letrozole, Leuprolide, Lopinavir/Ritonavir, Maraviroc, Memantine, Minoxidil¹⁹⁻²¹, Mirabegron, Misoprostol, Moxifloxacin, Naltrexone, Naratriptan, Octreotide, Omalizumab, Ondansetron, Peginterferon Alfa2a, Pentoxifylline,

Phenylephrine/Ephedrine, Phenylephrine²², Prazosin²³, Pseudoephedrine²⁴⁻²⁶, Raloxifene, Rivastigmine, Rizatriptan, Sorafenib, Sumatriptan, Tacrolimus, Tamoxifen, Tegaserod, Trastuzumab, Tretinoin, Zolmitriptan)

^a Hormones/Hormone Modifiers: anabolic steroids, contraceptives, and sex hormones

^b Antihypertensives: antihypertensive combinations, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, calcium channel blockers, and diuretics

Appendix B. List of Medications with QT Prolongation and/or Torsades de Pointes

A. Medications that cause QT Prolongation and/or Torsades de Pointes (n=224)

1. Antiarrhythmics (Amiodarone, Dextromethorphan-Quinidine, Disopyramide, Dofetilide, Dronedaronone, Flecainide, Procainamide, Propafenone, Quinidine, Sotalol)
2. Antidepressants (Amitriptyline, Citalopram, Clomipramine, Desipramine, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Mirtazapine, Nortriptyline, Paroxetine, Sertraline, Trazodone, Trimipramine, Venlafaxine)
3. Antiemetics (Chlorpromazine, Diphenhydramine, Domperidone, Granisetron, Metoclopramide, Ondansetron, Palonosetron, Perphenazine, Promethazine)
4. Anti-Infectives
 - a. Macrolides (Azithromycin, Clarithromycin, Erythromycin, Telithromycin)
 - b. Quinolones (Ciprofloxacin, Gatifloxacin, Gemfloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Sparfloxacin)
 - c. Other (Amantadine, Atazanavir, Chloroquine, Efavirenz, Fluconazole, Hydroxychloroquine, Itraconazole, Ketoconazole, Lopinavir-Ritonavir, Metronidazole, Nelfinavir, Piperacillin-Tazobactam, Posaconazole, Quinine, Saquinavir)
5. Antihypertensives (Moexipril-HCTZ, Isradipine, Nifedipine, Bendroflumethiazide, Furosemide, Hydrochlorothiazide, Indapamide, Metolazone, Torsemide)
6. Antihyperlipidemics (Probucol)
7. Antineoplastics (Bortezomib, Capecitabine, Dasatinib, Fluorouracil, Lapatinib, Leuprolide, Sorafenib, Sunitinib, Tamoxifen)
8. Antipsychotics (Aripiprazole, Asenapine, Clozapine, Haloperidol, Iloperidone, Lithium, Mesoridazine, Olanzapine, Paliperidone, Pimozide, Quetiapine, Risperidone, Ziprasidone)
9. Anxiolytics, Sedatives, Hypnotics (Chloral hydrate, Doxepin, Hydroxyzine)
10. H₂ Antagonists (Cimetidine, Famotidine)
11. Muscle Relaxants (Tizanidine)
12. Narcotic Analgesics (Buprenorphine, Hydrocodone, Methadone, Tramadol)
13. PDE-I (Vardenafil)
14. Proton-Pump Inhibitors (Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole)

15. Other (Anagrelide, Astemizole, Cilostazol, Cisapride, Donepezil, Felbamate, Fingolimod, Galantamine, Loperamide, Memantine, Papaverine, Ranolazine, Solifenacin, Tacrolimus, Terfenadine, Tetrabenazine, Tolterodine)
16. Therapeutic class not specified in Multum database (Abarelix, Aclarubicin, Amisulpride, Amphotericin B, Amsacrine, Apalutamide, Apomorphine, Arseinc Trioxide, Artemether-Lumefantrine, Artesimol-Piperaquine, Bedaquiline, Bendamustine, Benperidol, Bepridil, Betrixaban, Bosutinib, Cabozantinib, Ceritinib, Clofazimine, Clotiapine, Crizotinib, Cyamemazine, Dabrafenib, Degarelix, Delamanid, Deutetrabenazine, Dexmedetomidine, Dolasetron, Droperidol, Eliglustat, Encorafenib, Eperisone, Epirubicin, Eribulin mesylate, Ezogabine, Flupentixol, Garenoxacin, Glasdegib, Halofantrine, Hydroquinidine, Ibogaine, Ibutilide, Inotuzumab, Ivabradine, Ketanserin, Lacidipine, Lenvatinib, Levomepromazine, Levomethadyl acetate, Levosulpiride, Lofexidine, Melperone, Midostaurin, Mifepristone, Mirabefron, Necitumumab, Nilotinib, Nusinersen, Osimertinib, Oxaliplatin, Oxytocin, Panobinostat, Pasireotide, Pazopanib, Pentamidine, Perflutren lipid, Pilsicainide, Pimavanserin, Pipamperone, Primaquine, Propofol, Prothipendyl, Ribociclib, Rilpivirine, Romidepsin, Roxithromycin, Sertindole, Sevoflurane, Sulpiride, Sultopride, Telaprevir, Telavancin, Terlipressin, Terodiline, Thioridazine, Tiapride, Tipiracil-Trifluridine, Toremfene, Tropisetron, Valbenazine, Vandetanib, Vemurafenib, Voriconazole, Vorinostat, Zotepine, Zuclopenthixol)

Source of list of medications with QT-Prolongation: <https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf>

^a Antihypertensives include: antihypertensive combinations, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, calcium channel blockers, and diuretics

Appendix C. Cardiovascular Drugs with an Indication for the Treatment of Cardiovascular Disease

1. Agents for Hypertensive Emergencies
2. Agents for Pulmonary Hypertension
3. Aldosterone Receptor Antagonists
4. Antiadrenergic Agents (Centrally Acting and Peripherally Acting)
5. Anticoagulants
6. Antiplatelets
7. Antianginal Agents
8. Antiarrhythmic Agents
9. Anticholinergic Chronotropic Agents
10. Antihypertensive Combinations
11. Beta-Adrenergic Blocking Agents
12. Calcium Channel Blocking Agents
13. Inotropic Agents
14. Miscellaneous Cardiovascular Agents
15. Peripheral Vasodilators
16. Renin Inhibitors
17. Vasodilators
18. Vasopressors