Association of Antidepressant Type with the Risk of Cardiovascular Disease in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

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BACKGROUND: Antidepressant medications (AD's) are associated with autonomic dysfunction which is linked with future risk of (CVD) cardiovascular disease. However, it is not clear if certain AD's types are associated with more CVD than others. We hypothesized that selective serotonin reuptake inhibitors (SSRI) are associated with reduced hazards of Atrial Fibrillation (AF), Heart Failure (HF), Myocardial Infarction (MI) and Ischemic Stroke (IS) as compared to other AD medications (non-SSRI).

METHODS AND RESULTS: We studied 2027 participants from the Atherosclerosis Risk in Communities (ARIC) Study (mean age 63 ± 10 years; 29% men; 78% white) who self-reported AD use during one of the ARIC five visits (1987 through 2013). Exposure to SSRI vs non-SSRI was determined. Participants were followed up to 2016 for a median of 13.5 years. A total of 329, 366, 198 and 1345 events for AF, HF, MI and IS, respectively, were identified in this ARIC subset. Using multivariable Cox regression models to adjust for sociodemographic and clinical risk factors, SSRI was not significantly associated with hazards of AF, HF, MI and IS, when compared to non-SSRI medications [hazard ratio (HR)= 1.11, 95% confidence interval (95%CI) (0.8-8 1.40), HR= 0.93, 95%CI 0.72- 1.20, HR= 0.91, 95%CI, 0.65-1.27 HR= 1.02, 95%CI, (0.67-1.56), respectively.]

CONCLUSION: In a community-based sample of individuals initiating AD's, type of AD was not associated with statistically different hazards of CVD outcomes including AF, HF, MI and IS. These results do not provide evidence supporting the use of a particular AD over another in relation to CVD risk

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I. CHAPTER I: LITERATURE REVIEW AND BACKGROUND

MAJOR DEPRESSIVE DISORDER AND THE NEED FOR ANTIDEPRESSANTS

Major depressive disorder (MDD) is a common illness worldwide, with more than 300 million people affected, according to the World Health Organization (WHO). MDD is associated with disability and increasing healthcare expenditures. The lifetime prevalence of MDD has been rising consistently reaching to approximately 15% with projected lifetime risk at age 75 years of 25%.[1] Pharmacological and psychological treatments are available; however, due to multiple factors, Antidepressant (AD) medications are used more frequently than psychological interventions.

MDD is also recognized as a leading cause of disability, with substantially rising prevalence since 1990, due to several factors implicated in this rise. Along with this rise, the economic burden of depressive disorders in the USA alone is quite significant and estimated to be more than US$210 billion, with approximately, 50% attributable to workplace cost. This shows that depression poses a substantial burden on health systems in both developed as well as developing countries, with emphasis on the need to properly treat patients, and improve overall mental health.

ANTIDEPRESSANTS MEDICATIONS

AD's have been a mainstay of treatment since clinically introduced in the 1950s. There is a consistently increasing trend in AD use in the United States (U.S.) A recent report from the National Health and Nutrition Examination Survey (NHANES) has pointed to the growing use of

antidepressants in the U.S. where almost 13 percent of people age 12 and over in 2011-2014 used antidepressants in the past month, up from just under 8 percent in 1999-2002.[2] More recently, the rise of AD use has been attributed to the increase in the AD long-term use.[3, 4] Regardless of the reason for increased use, this trend raises concerns regarding potential harm and tolerability of these medications. Furthermore, this underscores the importance of understanding the long terms health risk of AD use, particularly, cardiovascular-related health outcomes.

AD are often grouped into various classes of drugs with slightly different mechanisms of action. Since their introduction in 1958, Tricyclic Antidepressants (TCA) were the first-line treatment for depression for about 30 years,[5, 6] until the Selective Serotonin Reuptake Inhibitors (SSRI) were introduced.[7] Monoamine Oxidase Inhibitors (MOA-I) and Serotonin and Norepinephrine Reuptake Inhibitors SNRIs and trazodone are less commonly used AD medications. Other less common AD's indications include generalized anxiety disorder, obsessive-compulsive disorder, insomnia, complex regional pain, fibromyalgia, alcohol withdrawal and neuropathic pain.

Studies have found that most if not all AD's are more effective than placebo in treating depression, their safety profile may vary according to different AD types. In fact, there is a long-standing debate and concerns about the relative efficacy and tolerability of AD types. Some studies have reported that SSRI may not be protective from certain health outcomes as compared to TCA and SSRI might be associated with a higher risk of fractures and hyponatremia.[8, 9] Others have reported the opposite.[10, 11]

ANTIDEPRESSANTS AND CHRONIC DISEASE RISK

AD's utilization is associated with increased risks for chronic diseases. A recent study found that widespread utilization of antidepressants may be contributing to long-term increased risk

of weight gain at the population level with a strong temporal association between AD use and weight gain.[12] This raises concerns regarding the increased risks of obesity and its associated multiple morbidities and future cardiovascular risks that might be associated with AD's use.[13] However, it is important to notice that AD's differ modestly in their propensity to contribute to weight gain.[14, 15] More importantly, it is unclear if this differential weight gain translates to metabolic disturbance and differential cardiovascular risk.

The effects of the AD's on the cardiovascular system may extend beyond metabolic disturbances and weight gain. Serotonin is implicated in cardiovascular physiology as it is normally released by activated platelets, causing enhanced platelet aggregation[16], and is implicated in vascular tone modulation.[17] A functional polymorphism of the serotonin transporter SLC6A4 which is considered to be the only mechanism for serotonin uptake into platelets is associated with an increased risk of premature myocardial infarction (MI).[18] A high expression of serotonin transporter genotype was also found to be protective of ischemic stroke.[19] SSRIs with high affinity for the serotonin transporter have been shown to decrease platelet activity in patients with coronary artery disease.[20, 21] On a population level, greater serotonin transporter affinity was found to be associated with reduced odds of MI among subjects using SSRI.[22]

PROBLEM STATEMENT:

Different antidepressant medications are associated differential CVD risk including risks for MI, Heart Failure (HF), Atrial Fibrillation (AF) and Stroke.

A few population-based observational studies indicated an increased risk of stroke, Atrial Fibrillation (AF) and CV events associated with selective serotonin reuptake inhibitors (SSRI) and

tricyclic antidepressants (TCA) compared with those who are not using AD's [23, 24]. For example, Jerrel et al have found that among children and adolescents, patients who were exposed to SSRIs and weight-inducing antidepressants had a higher risk of incident cardiovascular events, when compared to a random sample of children not using AD's. [25] In contrast, other studies have demonstrated protective effects for ADs against CVD risk. Santangelo et al have shown that sertraline and citalopram are associated with reduction in CVD events among geriatric population with depression as compared to those who are not receiving treatment [26]. Similarly, in depressed patients who experienced an acute MI, Taylor et al have reported that the use of SSRIs might reduce subsequent cardiovascular morbidity and mortality[27]. Furthermore, Zuidersma et al reported that among post MI patients, antidepressant use was associated with improved survival even though it was not related to CVD risk [28].Other studies have shown that TCA as compared to SSRI might be associated with excess CVD risk [10, 29].

We have shown previously that AD's may alter left atrial electrophysiology through affecting P-terminal force (PTFV1).[30] Given that PTFV1 is a known marker for AF, stroke and Heart Failure (HF) [31, 32], this may indicate that ADs could influence the risk of AF, stroke and HF. However, it is unclear if those effects are driven by certain type of AD medications. Therefore, we seek to study the relative association of antidepressant type with the risk of CVD in the community using the Atherosclerosis Risk in Communities (ARIC) study.

PURPOSE STATEMENT

Further assessments of AD-type and relative CVD risk could provide an understanding of potential health benefits or harm associated with SSRI as compared TCA medications or other AD medications. This may have implications on the long-term effects of different AD types and CVD

risk. More specifically, this may help inform the decision of AD type in patients who amay be at higher risk of CVD. Additionally, this may help clinicians decide on changing AD type for those who develop certain cardiovascular risk factors or event cardiovascular events. This will also help guide future observational studies and clinical trials looking at the potential cardiovascular outcomes of subjects with depression treated with different types of AD's.

This analysis will focus on the assessment of different cardiovascular endpoints (MI, HF, Stroke and AF) among subjects using AD.

II. CHAPTER II: METHODOLOGY

The ARIC study is designed to investigate the etiology and natural history of atherosclerosis, the etiology of clinical atherosclerotic diseases, and variation in cardiovascular risk factors, medical care and disease by race, gender, location, and date.

Study Population:

The ARIC study is a mostly biracial prospective epidemiologic prospective cohort study conducted in four U.S. communities: Washington County, Maryland; Jackson, Mississippi; selected Minneapolis suburbs, Minnesota; and Forsyth County, North Carolina.[33] It aims at identifying the risk factors and investigating the etiology and outcomes of atherosclerosis. Approximately 4,000 individuals aged 45-64 from a defined population in their community were recruited from each ARIC center. In total, baseline examination was completed in 15,792 individuals (55% women, 27% blacks). Participants were then followed-up regularly every three years until 1998, with the first exam (baseline, visit 1) occurring in 1987-89, the second (visit 2) in 1990-92, the

third (visit 3) in 1993-95, and the fourth (visit 4) in 1996-98. Participants who survived underwent a fifth exam (visit 5) in 2011-13 and a sixth exam (visit 6) in 2016-17. Study participants provided written informed consent at baseline and each following visit and the study has been approved by Institutional Review Boards at the participating institutions. For this analysis, we included individuals who participated in any of the five visits and have used SSRI or TCA. Of these, we excluded participants with missing information or prevalent MI, HF, Stroke and AF. or had missing information. We also excluded non-white subjects from Minnesota and Maryland centers, and those of race other than white or black from North Caroline center.

Assessment of AD Use

Study participants were asked to bring all medications, vitamins, and supplements taken in the 2 weeks prior to each study visit. All medication names were transcribed and coded.. Each AD medication was categorized according to the type; SSRI, TCA and atypical AD's. Given that the number of subjects using atypical AD's was relatively low during each visit, we grouped TCA with atypical AD's and considered them as one category (non-SSRI).

Use of SSRI vs non-SSRI was assessed during each study visit. Subjects were categorized to primary exposure, SSRI or non-SSRI according to the first type of AD used regardless if they changed AD type during any of the subsequent visits. Subjects initiated SSRI and non-SSRI for the first time were considered in the non-SSRI group.

Determination of Incident HF, MI and stroke

HF, MI, and stroke were defined based on adjudicated cases following standard ARIC definitions. HF definition was derived based on the Gothenburg criteria at visit 1 and from HF-related

hospitalizations during follow-up [34]. MI was defined based on self-reported physician diagnosis of MI at baseline or evidence of old MI on ECG and events adjudicated during the follow-up [35].

The incidence date of CVD (MI, HF, AF, stroke) was defined as the date of each type of event or the date of out of hospital death if that is the first manifestation of CVD. Follow-up was available through December 31, 2016.

For this study, we included definite and probable ischemic stroke events. Ischemic stroke was ascertained via cohort follow-up, active surveillance of hospitalizations and linkage with registries through December 31, 2016. Trained personnel abstracted hospital records, and events were adjudicated by committee review.[36]

Determination of Incident AF

We used three methods to determine AF cases in the ARIC cohort. First, 12-lead electrocardiograms (ECGs) were obtained during study exams, and data were transmitted electronically to the ARIC ECG reading center at EPICARE (Wake Forest School of Medicine, Winston-Salem, NC). Second, trained abstractors collected information from participants' hospitalization identified by follow-up phone calls and surveillance of local hospitals, including all discharge codes. If the ICD-9-CM codes 427.31 (AF) or 427.32 (atrial flutter) (or ICD-10-CM I48.xx after October 2015) were listed in any given hospitalization, then AF was deemed as present. We excluded AF cases related to open cardiac surgery. Last, AF was identified from death certificates if ICD-9 427.3 or ICD-10 I48 were listed as any reason of death. A detailed description and validity of this approach has been previously published.[37]

Assessment of Covariates

We considered relevant demographic covariates that were measured in visit 1 through visit 5: sex, age, race, study center and education at baseline. Information regarding sex, race, age, education, smoking and alcohol and use of medications were self-reported. Age was defined as the age at the study visit where a participants first self-reported AD use. Sex and race were ascertained at visit 1. Level of education was categorized as grade school, high school but no degree, high school graduate, vocational school, college and graduate school, as reported at Visit 1.

We considered clinical covariates that are relevant to CVD risk. Systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, alcohol drinking status, diabetes history, use of antihypertensive medications, use of aspirin medications, Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) levels. In visits 1 through 3 and in visit 5, SBP and DBP were measured 3 times respectively and the mean of the last 2 measurements was used for our analysis, while only 2 measurements were taken at visit 4. Diagnosis of diabetes was defined as the use of antidiabetic medication, or a self-reported physician diagnosis of diabetes, fasting blood glucose ≥126 mg/dl.

Statistical Analysis

Categorical variables were assessed using Chi-square test. Students t-test was used to examine continuous variables with normal distribution and Wilcoxon median test for non-parametric variables. Table 1 was constructed by obtaining unadjusted estimates of relevant covariates for participants using SSRI's and non-SSRI's (including TCA and atypical AD's).

We used Cox proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (95%CI) of each CVD outcome (AF, MI, HF and stroke) considering AD-type as the primary exposure (SSRI vs non-SSRI). Start of follow-up was the date of the visit in which AD medication use was recorded for the first time, end of follow up was defined as date of the specific CVD occurrence, December 31, 2016, death, or lost to follow-up, whichever occurred earlier. We treated individuals based on their first exposure and independently of their subsequent change in AD type (similar to an intention-to-treat approach). Proportional hazard assumption was checked using Schoenfeld residuals. Models were stratified to accommodate covariates that violate proportional hazard assumption. Follow up time was quantified based on the median follow up time for subjects not experiencing the event of interest (censored observation).[38]

Minimally adjusted models considered age, race-center, sex and level of education. Further adjustments for clinical comorbidities considered clinical covariates and included cigarettes smoking, ETOH use, BMI, hypertension, diabetes, systolic blood pressure (SBP), diastolic blood pressure (DBP) and year of AD initiation. Covariate values corresponded to the time of AD initiation. Subjects who used SSRI and non-SSRI in the same time period were considered as non-SSRI. AF models were stratified by center as this variable did not satisfy the proportional hazard assumption. HF models were stratified by diabetes as this variable did not satisfy the proportional hazard assumption. Stroke models were stratified by age category as this variable did not satisfy the proportional hazard assumption.

III. CHAPTER III: RESULTS

Descriptive Statistics:

Of the 15,792 participants in the ARIC cohort, a total of 2027 (13%) of them had used at least an SSRI or TCA or other antidepressant medications during one of the 5 visits. Of these, 944 (46.6%) had started using SSRI only, whereas the remaining 1083 (53.4%) subject started other AD medications (mainly TCA). Mean age± standard deviation (SD) for the sample at the time of AD initiation was 63±10, 589 participants (29%) were male, and 447 (78%) white.

Table 1 compares the baseline characteristics for participants enrolled in the study according to their exposure to AD type. Participants using SSRI were older, less likely to use antihypertensive medications and less likely to have initiated AD treatment prior to 1994. There was a temporal trend of increased use of SSRI over TCA over the years of follow up. All other covariates were relatively similar between the two groups. Figure 1 represent the number of ARIC participants starting AD by type across each visit.

Subjects were followed for a median of 14 to15.8 years. A total of 329, 366, 198 and 134 events for AF, HF, MI and stroke were recorded for this subsample.

AD type and incidence of AF

Over a median follow up of 14.2 years, 329 subjects experienced had an event of interest (AF) in this ARIC sample. As outlined in Table 2, in our minimally adjusted model; after adjustment for sex, age, race, center and level of education, SSRI's (as compared to non-SSRI's) were not associated with a statistically different hazards of AF Hazard ration. (HR) (HR= 1.11, 95% CI, 0.84, 1.41). The association remained essentially the same after further adjustment for BMI, cigarette smoking, ETOH use, antihypertensive medications, SBP, DBP, diabetes and the calendar year of initiation of ADs (HR= 1.10, 95%CI (0.84, 1.41). When considering stratified models to evaluate for sex (male vs female) and race (African American vs whites) specific effects, the association remained the same (Table 3).

AD type and incidence of HF

Over a median follow up of 15.8 years, 366 participants developed HF in this ARIC sample. In our minimally adjusted model; after adjustment for sex, age, race, center and level of education, SSRI's (as compared to non-SSRI's) were not associated with a statistically different hazards of HF (HR= 0.90, 95% CI, 0.72, 1.14). The association remained non-significant despite further adjustment for BMI, cigarette smoking, ETOH use, antihypertensive medications, SBP, DBP, diabetes and the year of diagnosis (HR= 0.90, 95%CI 0.72, 1.20). When considering stratified models to evaluate for sex (male vs female) and race (African American vs whites) specific effects, the association remained the same (Table 4).

AD type and incidence of MI

Over a median follow up of 14.9 years, 198 participants experienced at least one MI event in this ARIC sample. In our minimally adjusted model; after adjustment for sex, age, race, center and level of education, SSRI's (as compared to non-SSRI's) were not associated with a statistically different hazards of MI (HR= 0.80, 95% CI, 0.60, 1.11). The association remained non-significant despite further adjustment for BMI, cigarette smoking, ETOH use, antihypertensive medications, SBP, DBP, diabetes and the year of diagnosis (HR= 0.90, 95%CI 0.65, 1.27). When considering stratified models to evaluate for sex (male vs female) and race (African American vs whites) specific effects, the association remained the same (Table 5).

Assessment of Stroke Hazards

Over a median follow up of 14 years, 134 subjects experienced at least one IS event in this ARIC sample. In our minimally adjusted model; after adjustment for sex, age, race, center and level of

education, SSRI's (as compared to non-SSRI's) were not associated with a statistically different hazards of IS (HR= 0.90, 95% CI, 0.59, 1.24). The association remained non-significant despite further adjustment for BMI, cigarette smoking, ETOH use, antihypertensive medications, SBP, DBP, diabetes and the year of diagnosis (HR= 0.90, 95%CI 0.67, 1.56). When considering stratified models to evaluate for sex (male vs female) and race (African American vs whites) specific effects, the association remained the same (Table 6)).

IV. DISCUSSION

The findings of this analysis provide evidence that SSRI and non-SSRI are associated with relatively similar hazards of AF, HF, MI and IS in a community-based cohort. Additionally, we have also observed that approximately 13% of the ARIC cohort have used AD at the start of the study or during follow up. These results do not support the presence of a protective effect of SSRI as compared to other AD medications regarding the outcomes of AF, HF, MI and IS.

TCA's medications are well-known to cause tachycardia and autonomic dysfunction leading to orthostatic hypotension.[39, 40] This observation is particularly important given that tachycardia has been linked to increased risks of coronary heart disease and death in the NHANES as well as other studies.[41-43] We therefore may doubt if this TCAs effects on heart rate may not carry a significant long-term risk of CVD, particularly HF and MI, as compared to SSRI. However, it is also worth mentioning that we evaluated for chronic CVD disease risks in this study and thus acute cardiovascular compromise, including sudden cardiac death, has not been studied in this sample which has been a concern according to some studied.[44, 45]

Despite the increasing pattern of SSRI use we observed in this community sample, the hazards of AF, HF, MI and IS remained comparable to those who were taking non-SSRI medications. This may indicate that clinicians while selecting AD type should primarily focus on psychiatric indications rather than reducing cardiovascular risk profile. However, it might be possible that our community sample did not include many of those who are receiving higher doses of TCA's or those with who have severe cardiovascular dysfunction. Nonetheless, clinicians must still make treatment decisions for this patient on a case-by-case basis, considering the type and severity of psychiatric condition as well as the type and severity of cardiovascular disease and the established cardiovascular effects of the various antidepressant medications.

Our study is subject to certain limitations. First, antidepressants were not categorized by dose and thus it was not possible to evaluate dose dependent effects of SSRI or non-SSRI. Second, the information on AD use being restricted to self-reported information from clinic visits which is subjected to misclassification bias. However, this misclassification is likely to be non-differential with regards to AD type and thus we expect bias to be toward the null. Third, the study lacks details on important psychological factors, including, depressive symptoms and a diagnosis of depression. However, we were able to minimize this confounding by limiting our study to those who were already taking AD. Third, the lack of time-dependent information regarding the use of AD medications may have limited our ability to establish a clear time-dependent exposure to SSRI vs non-SSRI. Finally, it is essential to note that our sample was predominantly composed of white and females which may limit the generalizability of our results.

Previous studies that have shown that AD's are associated with autonomic modulations demonstrated by reduced HR variability.[46] At the same time, cardiac autonomic dysfunction has been associated with increase AF risk in a large population based cohort.[47] Increased activation of atrial 5-hydroxytryptamine receptors has been linked to increasing risk of adverse cardiovascular events, particularly, AF[23, 24]. But our study findings do not support a differential association of SSRI vs non-SSRI on incident AF or other CVD outcomes.

In conclusion, in a community sample of subjects using AD's, we found that subjects who used SSRI and non-SSRI were relatively at similar risks of AF, HF, MI and stroke. This calls for further studies to determine if certain AD's medications are more protective than others with regards to adverse cardiovascular events.

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VI. TABLES

Table 1. Baseline characteristics of the ARIC cohort study at the time of SSRI vs other antidepressants initiation.

	SSRI	Other Antidepressants
N (%)	944 (46.6%)	1083 (53.4%)
Clinical variables		
Age, mean ± SD, years	70 (10.5)	59.8 (8.7)
Sex, women, %	767 (70.8%)	671 (71.1%)
Race, AA, %	155 (16.4%)	22 (30%)

BMI, mean ± SD, kg/m2	29.2 (6.3)	28.6 (6.1)
SBP, mean ± SD, mmHg	123.9 (18.6)	123.1 (18.6)
DBP, mean ± SD, mmHg	70.8 (9.9)	72.8 (10.9)
Smoking Status		
Current smoker, %	237 (25.1)	290 (26.8%)
Former smoker, %	289 (30.7%)	332 (30.7%)
Never smoker, %	417 44.2%)	460 (42.5%)
Drinking Status		
Current drinker, %	551 (58.6%)	534 (49.5%)
Former drinker, %	179 (19%)	254 (23.6%)
Never drinker, %	211 (22.4%)	290 (26.9%)
HTN treatment, %	278 (29.5%)	463 (42.8%)
Diabetes, %	187 (20.7%)	246 (23%)
MI history, %	22 (2.3%)	15 (1.4%)
HF history, %	32 (3%)	25 (2.7%)

AF history, %	58 (6.1%)	23 (2.1%)
Initiation After 1994, %	779 (82.5%)	412 (38%)
BMI: body mass index, AA: African American, SBP: systolic blood pressure, DBP: diastolic blood pressure, MI: myocardial infarction, HF: Heart failure, AF: Atrial fibrillation, MI: Myocardial infarction.		

Table 2. Association of AD type and incident CVD.

	AF	HF	MI	Stroke
# events	329	366	198	135
SSRI	135	137	68	45
No SSRI	194	229	130	90
Median Follow-up (years)	14.2	15.8	14.9	14.9
	HR (95%CI)			
Model 1	1.11 (0.88, 1.4)	0.91 (0.72,1.14)	0.81 (0.6, 1.11)	0.85 (0.59, 1.24)
P-Value	0.40	0.47	0.18	0.40
Model 2	1.09 (0.84, 1.41)	0.93 (0.72, 1.20)	0.91 (0.65, 1.27)	1.02 (0.67, 1.56)
P-Value	0.51	0.58	0.57	0.91

Model 1= Model adjusted for age, sex, race/center, and education, Model 2= Model 1+ adjustment for BMI, cigarette smoking, Alcohol use, antihypertensive medications, diabetes and the year of diagnosis.

Abbreviations: AF: Atrial Fibrillation, HF: Heart Failure, MI: Myocardial Infarction, Stroke: ischemic stroke, CI: confidence interval, HR: Hazard ration.

Table 3. Association of AD type and incident AF by Sex and Race.

	Female (n=1322)	Male (n=527)	White (n=1467)	AA (n-=424)
# events	218	111	266	63
	HR (95%CI)			
Model 1	1.06 (0.79, 1.41)	1.23 (0.82, 1.85)	1.18 (0.92, 1.53)	0.69 (0.37, 1.29)
P-Value	0.72	0.32	0.20	0.24
Model 2	1.06 (0.77, 1.45)	1.35 (0.83, 2.22)	1.22 (0.92, 1.63)	0.71 (0.36, 1.42)
P-Value	0.39	0.23	0.17	0.33

Model 1= model adjusted for age, center, and education (stratified by sex or race). Model 2= Model 1+ adjustment for BMI, cigarette smoking, Alcohol use, antihypertensive medications, diabetes, statin, aspirin, previous MI, previous HF and year of treatment visit (stratified by sex or race).

Abbreviations: AF: Atrial Fibrillation, HF: Heart Failure, MI: Myocardial Infarction, Stroke: ischemic stroke, CI: confidence interval, HR: Hazard ration.

Table 4. Association of AD type and incident HF by Sex and Race.

	Female (n=1322)	Male (n=527)	White (n=1467)	AA (n-=353)
# events	243	117	262	98
HR (95%CI)				
Model 1	0.96 (0.72, 1.26)	0.74 (0.49, 1.12)	1.04 (0.80, 1.35)	0.62 (0.37, 1.04)
P-Value	0.76	0.15	0.78	0.07
Model 2	0.91 (0.67, 1.23)	0.87 (0.53, 1.41)	1.08 (0.81,1.46)	0.56 (0.31, 1.00)
P-Value	0.53	0.56	0.59	0.05

Model 1= model adjusted for age, center, and education (stratified by sex or race). Model 2= Model 1+ adjustment for BMI, cigarette smoking, Alcohol use, antihypertensive medications, diabetes, statin, aspirin, previous MI, and year of treatment visit (stratified by sex or race).

Abbreviations: AF: Atrial Fibrillation, HF: Heart Failure, MI: Myocardial Infarction, Stroke: ischemic stroke, CI: confidence interval, HR: Hazard ration.

Table 5. Association of AD type and incident MI by Sex and Race.

	Female (n=1322)	Male (n=527)	White (n=1467)	AA (n=353)
# events	128	70	154	44
HR (95%CI)				
Model 1	0.83 (0.57, 1.21)	0.71 (0.41, 1.21)	0.88 (0.63, 1.24)	0.54 (0.25, 1.18)
P-Value	0.33	0.20	0.48	0.12
Model 2	1.05 (0.66, 1.66)	0.84 (0.44 1.59)	1.06 (0.70, 1.59)	1.08 (0.39, 3.00)
P-Value	0.84	0.59	0.80	0.88

Model 1= model adjusted for age, center, and education (stratified by sex or race). Model 2= Model 1+ adjustment for BMI, cigarette smoking, Alcohol use, antihypertensive medications, diabetes, statin, aspirin, LDL, HDL and year of treatment visit (stratified by sex or race).

Abbreviations: AF: Atrial Fibrillation, HF: Heart Failure, MI: Myocardial Infarction, Stroke: ischemic stroke, CI: confidence interval, HR: Hazard ration, LDL= Low Density Lipoprotein. HDL= High Density Lipoprotein

Table 6. Association of AD type and incident Stroke by Sex and Race.

	Female (n=1322)	Male (n=527)	White (n=1467)	AA (n=353)
# events	97	38	94	41
HR (95%CI)				
Model 1	0.81 (0.52, 1.25)	0.98 (0.47, 2.02)	0.88 (0.57, 1.35)	0.69 (0.32, 1.49)
P-Value	0.34	0.95	0.55	0.88
Model 2	1.12 (0.65, 1.92)	1.37 (0.54, 3.49)	1.182 (0.70, 2.00)	1.14 (0.42, 3.08)
P-Value	0.68	0.51	0.53	0.80

Model 1= model adjusted for age, center, and education (stratified by sex or race). Model 2= Model 1+ adjustment for BMI, cigarette smoking, Alcohol use, antihypertensive medications, diabetes, statin, aspirin, LDL, HDL and year of treatment visit (stratified by sex or race).

Abbreviations: AF: Atrial Fibrillation, HF: Heart Failure, MI: Myocardial Infarction, Stroke: ischemic stroke, CI: confidence interval, HR: Hazard ration, LDL= Low Density Lipoprotein. HDL= High Density Lipoprotein

VII. FIGURES:

Figure 1. ARIC study visits and the number of participants starting antidepressants across each visit by type (SSRI vs non-SSRI) with arrows width correlating with the number of participants.