ORIGINAL RESEARCH

Association of Antidepressant Medication Type With the Incidence of Cardiovascular Disease in the ARIC Study

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***Background*—**The association of antidepressant medication type with the risk of cardiovascular disease (CVD) is unclear. We hypothesized that selective serotonin reuptake inhibitors (SSRIs) are associated with lower risks of CVD events relative to tricyclics and other non-SSRI antidepressants.

***Methods and Results*—**We studied 2027 participants from the ARIC (Atherosclerosis Risk in Communities) study (mean age 63±10 years; 29% men; 78% white) treated with antidepressants at some time between 1987 and 2013. Antidepressant usage was confirmed by participants bringing pill bottles to study visits. CVD events in the study sample were identified, including atrial fibrillation, heart failure, myocardial infarction, and ischemic stroke. Hazard ratios were used to compare CVD events adjusted for sociodemographic and clinical risk factors in SSRIs users (47%) versus non-SSRI users. Participants were followed from antidepressant initiation up to 2016 for a median of 13.5 years. We identified 332 atrial fibrillation, 365 heart failure, 174 myocardial infarction and 119 ischemic stroke events. CVD risk was similar for SSRIs and non-SSRI antidepressant users (hazard ratio, 1.10; 95% CI, 0.86–1.41 for atrial fibrillation; hazard ratio, 0.98; 95% CI, 0.77–1.25 for heart failure; hazard ratio, 0.91; 95% CI, 0.64–1.29 for myocardial infarction; and hazard ratio, 1.07; 95% CI, 0.70–1.63 for ischemic stroke).

***Conclusions*—**SSRI use was not associated with reduced risk of incident CVD compared with non-SSRI antidepressant use. These results do not provide evidence supporting the use of SSRIs compared with tricyclics and other non-SSRI antidepressants in relation to CVD risk. **(*J Am Heart Assoc*. 2019;8:e012503. DOI: 10.1161/JAHA.119.012503.)**

Key Words: antidepressant • atrial fibrillation • depression

Antidepressants are among the most commonly prescribed medications in the United States, prescribed to ≈15% of adults; however, questions about potential cardiovascular effects with long-term use persist.[1–7] Prescriptions of antidepressants have risen over the past 2 decades,[8] largely driven by the rising incidence of depression among US adults and the advent of the selective serotonin reuptake inhibitors (SSRIs),[9] which were found to have fewer short-term side effects than the older generation of tricyclic antidepressants (TCAs).[9–11] Population-based observational studies indicated an increased risk of cardiovascular disease (CVD), including stroke, atrial fibrillation (AF), and other cardiovascular events in patients using antidepressant medications including SSRIs and TCA compared with those not using antidepressants.[12,13] Studies of the effects of antidepressants on CVD events in patients with major depression and CVD are conflicting, with some studies but not others showing reduced risk of CVD events.[14–17] The findings that SSRIs have certain effects like reduction in platelet aggregation that may confer reduced CVD risk suggest a potential relative benefit of SSRIs over other antidepressants.[3,18] However, evidence for a differential CVD risk for SSRIs compared with tricyclics and other classes of non-SSRI antidepressants is limited.

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Clinical Perspective

What Is New?

- Antidepressant medication type (serotonin reuptake inhibitor versus non–serotonin reuptake inhibitor) was not associated with long-term risk of future cardiovascular disease in a community-based sample of antidepressant users.

What Are the Clinical Implications?

- Lack of adverse cardiovascular outcomes by type of antidepressant should allay concerns about use of non–serotonin reuptake inhibitor antidepressants in patients who do not respond to serotonin reuptake inhibitors or have unacceptable side effects related to their use.

In this study, we compared the relative CVD risk of different classes of antidepressants in participants of the ARIC (Atherosclerosis Risk in Communities) study, a community-based cohort, during a 26-year study period. Specifically, we addressed CVD risk associated with SSRIs compared with TCAs and other antidepressants. We hypothesized that SSRI usage would be associated with lower risk of CVD events, including myocardial infarction (MI), heart failure (HF), ischemic stroke, and AF, when compared with non-SSRI antidepressant usage.

Methods

The data, analysis, and study materials are not available to other researchers for purposes of reproducing the results or replicating the analysis due to human subject restrictions. Interested investigators may contact the ARIC Study Center at the University of North Carolina to request access to ARIC Study data.[19]

Study Population

The ARIC study is a prospective cohort study mostly of black and white men and women conducted in 4 communities in the United States: Washington County, Maryland; Jackson, Mississippi; selected Minneapolis suburbs, Minnesota; and Forsyth County, North Carolina.[20] Approximately 4000 individuals aged 45 to 64 were recruited from each ARIC community between 1987 and 1989. In total, the baseline examination was completed in 15 792 individuals (55% women, 27% blacks). Participants were then invited to take part in clinic visits every 3 years until 1998, with the second exam (visit 2) in 1990 to 1992, the third (visit 3) in 1993 to 1995, and the fourth (visit 4) in 1996 to 1998. Additional exams were conducted in 2011 to 2013 (visit 5) and 2016 to 2017 (visit 6). In addition to the clinic exams, participants have taken part in follow-up phone calls (annually before 2012; twice yearly since) and have been continuously surveilled for hospitalizations and death. 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 first 5 visits and reported use of antidepressants at any of the visits. Of these, we excluded participants with prevalent MI, HF, stroke or AF, at the first visit of which antidepressant medication use was recorded, or had missing information on CVD prevalence or other covariates. We also excluded nonwhite subjects from the Minnesota and Maryland centers, and those of race other than white or black.

Assessment of Antidepressant Exposure

Study participants were asked to bring all medications, vitamins, and supplements taken in the 2 weeks before each study visit. All medication names were transcribed and coded. Each antidepressant medication was categorized according to the class: SSRIs, TCAs, and other antidepressants, including monoamine oxidase inhibitors, serotonin and norepinephrine reuptake inhibitors, and others. The number of subjects using antidepressants other than SSRIs or TCAs during visits 1 through 5 was 27, 21, 36, 57, and 58, respectively. Given that this group was quite heterogenous and sparse, we grouped them with TCAs in a single category (non-SSRI).

In the primary analysis, participants were categorized as SSRI or non-SSRI users according to the type of the first antidepressant used regardless of whether they changed antidepressant class during any of the subsequent visits. Because we hypothesize that non-SSRIs are associated with increasing risk of CVD, participants who had joint use of SSRIs and non-SSRIs (n=83) were included in the non-SSRI group.

Ascertainment of Incident HF, MI, Ischemic Stroke, and AF

MI and ischemic stroke were defined on the basis of adjudicated cases following standard ARIC definitions using information collected via cohort follow-up and active surveillance of hospitalizations. Trained personnel abstracted hospital records and identified relevant *International Classification of Diseases, Ninth Revision (ICD-9)* codes, and events were adjudicated by committee review. Prevalent MI and stroke were defined on the basis of self-reported physician diagnosis at baseline exam and when they reported at a date before reporting antidepressant medication use. Prevalent MI was also identified if there was evidence of an old MI on the baseline ECG. Incident MI[21] and

ischemic stroke[22] events were classified by adjudication committees, according to ARIC protocols. Prevalent HF was derived on the basis of the Gothenburg criteria at visit 1, and incident HF from HF-related hospitalizations during follow-up.[23] Finally, prevalent AF was defined according to 12-lead ECGs obtained at the baseline exam. Incident AF was defined according to ECG findings during later study exams, hospital discharge codes continuously during the follow-up, and death certificates. We excluded AF cases related to open cardiac surgery. A detailed description and validity of this approach has been previously published.[24] Follow-up was administratively censored on December 31, 2016.

Assessment of Covariates

Information on sex, race, age, education, smoking, and alcohol use were self-reported. Age was defined as the age at the study visit where a participant was first categorized as an antidepressant user. Sex, race, and education 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. Use of medication was also assessed at each study visit by asking participants to bring any medications they had used over the preceding 2 weeks.

We considered clinical covariates relevant to CVD risk: systolic blood pressure, diastolic blood pressure, smoking status, alcohol drinking status, diabetes mellitus history, use of aspirin medications, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol levels, antihypertensive medications, and statin use. At each visit with >1 systolic blood pressure and diastolic blood pressure measurement, we used the mean of the last 2 measurements. Diagnosis of diabetes mellitus was defined as the use of antidiabetic medications, a self-reported physician diagnosis of diabetes mellitus, fasting blood glucose ≥126 mg/dL, or a nonfasting blood glucose ≥200 mg/dL. Blood lipids were measured at each visit using standard methods. The vital exhaustion questionnaire, which measures chronic psychological overburdening[25–27] and has been linked to various CVD end points,[28–30] was administered at visit 2. For analysis, scores were categorized into quartiles, based on the distribution observed in our analytic sample.

Statistical Analysis

Means and standard deviations and proportions were used to describe the characteristics of the population by SSRI use status. We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs of each CVD outcome separately (AF, MI, HF, and ischemic stroke) considering antidepressant class as the primary exposure (SSRI versus non-SSRI). Start of follow-up was the date of the visit in which antidepressant medication use was recorded for the first time, while 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, independent of subsequent changes in antidepressant use, similar to an intention-to-treat approach. The proportional hazard assumption was checked using Schoenfeld residuals. In instances in which there was evidence that the proportional hazards assumption had been violated, we explored models that were stratified by follow-up time. Follow-up time was stratified on the basis of the median follow-up time for subjects not experiencing the event of interest (censored observation).[31]

Minimally adjusted models included as covariates age, race/center, sex, and level of education. A second model additionally adjusted for cigarette smoking, alcohol use, body mass index (BMI), diabetes mellitus, systolic blood pressure, diastolic blood pressure, the use of antihypertensive medications, aspirin use, and calendar year of antidepressant initiation. Covariate values corresponded to the time of the first visit during which antidepressant use was reported. Further adjustments for high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and statin use was considered in the MI and stroke models. A third model additionally adjusted for quartiles of vital exhaustion score (visit 2). We also performed a sensitivity analysis to explore the influence that changing antidepressant therapy had on our results; specifically, we censored follow-up at the time of reporting use of a different class of antidepressant or stopped taking antidepressants. Additionally, we performed analyses using antidepressant class as time-dependent exposure by considering person-time of continued reported use of antidepressants, while excluding person-time when antidepressant use was no longer reported. Moreover, we used the Fine and Gray model to see if our results change if we considered mortality as a competing risk.[32] Finally, analyses were conducted testing an interaction between calendar year of reporting antidepressant use and antidepressant class using the cutoff of 1994, as this year was the median year of reporting antidepressant use in the cohort. Similarly, we tested the interaction between the age of first antidepressant reported use and antidepressant class using the cutoff of 62 years, as this age was the median age of reporting antidepressant use in the cohort. This analysis was repeated using study visits 1 through 4 while omitting visit 5 because of the time difference between visits 4 and 5.

Results

Of the 15 792 participants in the ARIC cohort, 2027 (13%) were taking an antidepressant during at least 1 of the 5 visits.

Of these, 944 (47%) had started using SSRIs only, whereas the remaining 1083 (53%) participants started other antidepressant medications (mainly TCAs). Mean age± SD for the sample at the time of antidepressant first reported use was 63±10 years; 589 participants (29%) were male and 447 (78%) white.

Table 1 shows the baseline characteristics for participants enrolled in the study according to their antidepressant type use after excluding 8 subjects with missing information on education and alcohol use. Participants using SSRIs were older, less likely to use antihypertensive medications, and less likely to have initiated antidepressant treatment before 1994. There was a temporal trend of increased use of SSRIs over non-SSRIs over the years of follow-up. The distribution of all other covariates was relatively similar between the 2 groups. The Figure represents the number of ARIC participants reporting antidepressant use by class across each visit.

Antidepressant Class and Incident CVD

We excluded 81, 89, 84, and 62 subjects with prevalent AF, HF, MI, and ischemic stroke, respectively, at the time of the first recorded use of antidepressants. A total of 332 participants were diagnosed with incident AF over a median of 13.4 years, 365 with incident HF over a median of 13.6 years, 174 with incident MI over a median of 13.5 years, and 119 with incident ischemic stroke over a median of 14.5 years. In a minimally adjusted model, SSRIs (as compared with non-SSRIs) were not associated with statistically different hazards of AF (HR, 1.10; 95% CI, 0.84–1.41), HF (HR, 0.95; 95% CI, 0.76–1.19), MI (HR, 0.90; 95% CI, 0.65–1.27), or ischemic stroke (HR, 0.90; 95% CI, 0.59–1.24) (Table 2). The association remained essentially the same after further adjustment for BMI, cigarette smoking, alcohol use, antihypertensive medications, systolic blood pressure, diastolic blood pressure, diabetes mellitus, and the calendar year of initiation of antidepressants, while including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and statin use in MI and stroke models (while excluding 102 subjects with missing low-density and high-density lipoprotein data). Further adjustment by vital exhaustion questionnaire score did not change our results meaningfully (Table 2, Model 3). Additionally, results remained similar when we used the Fine and Gray model to adjust for the competing risk of mortality (Table 2, Model 5).

We also performed sensitivity analyses by using class of antidepressant as a time-dependent exposure or censoring participants when they stopped antidepressant use or switched to a different type of antidepressant. Results remained similar (Table 3). Finally, the association of antidepressant class with CVD did not differ by calendar year or by the age of first antidepressant reported use (Tables 4 and 5).

Table 1. Baseline Characteristics of the ARIC Cohort Study at the Time of SSRI vs Non-SSRI Antidepressant Medication Initiation (n=2027)

	SSRI (n=944)	Other Antidepressants (n=1083)
Age, y*	70 (10.5)	59.8 (8.7)
Sex, women, %	71.1	70.8
Race, black, %	16.4	27.0
BMI, kg/m^2*	29.2 (6.3)	28.6 (6.1)
SBP, mm Hg*	123.9 (18.6)	123.1 (18.6)
DBP, mm Hg*	70.8 (9.9)	72.8 (10.9)
Current smoker, %	13.5	21.1
Current alcohol drinker, %	47.8	43.1
HTN treatment, %	62.6	57.3
Diabetes mellitus, %	19.8	23.7
MI history, %	5.8	2.7
HF history, %	5.5	3.4
AF history, %	6.1	2.1
Vital exhaustion, median (IQR)†	13 (6–21)	14 (8–22)
Initiation after 1994, %	82.5	38.0

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities study; BMI, body mass index; DBP, diastolic blood pressure; HF, heart failure; HTN, hypertension; IQR, interquartile range; MI, myocardial infarction; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor.
*Continuous variable given as mean (SD).
†Continuous variable given as median (IQR).

Discussion

This study did not show a reduced risk of CVD with SSRI usage compared with use of TCAs and other non-SSRI antidepressants. Specifically, there were no differences in incidence of AF, HF, MI, and ischemic stroke across classes of antidepressants (SSRI versus non-SSRI) over 26 years in a study sample in which at least 13% were prescribed antidepressants at some point during the study. These results do not support the presence of a protective effect of SSRIs as compared with other antidepressant medications for CVD.

TCA medications are well known to cause tachycardia and autonomic dysfunction, leading to orthostatic hypotension and ECG changes in a dose-dependent manner.[1,4] This observation is particularly important given that tachycardia has been linked to increased risks of coronary heart disease and death in many studies.[33–35] Cohen et al[36] have found that receiving a TCA prescription is associated with an increased risk of MI as compared with other antidepressants; however, this study was limited by the risk of information bias attributable to using an administrative database to determine exposure and the limited duration of follow-up. Other reports

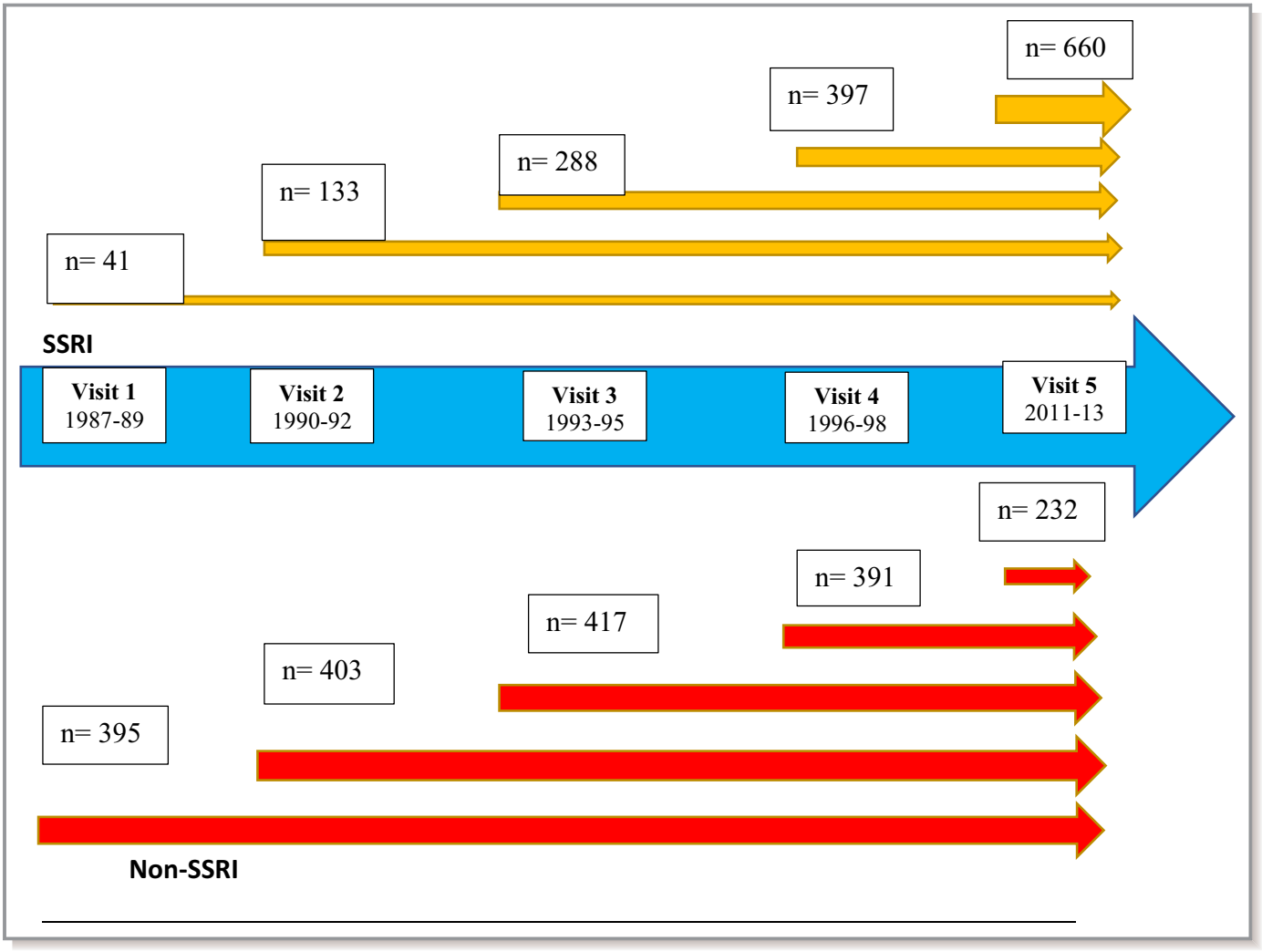

Figure. ARIC study visits and the number of participants starting antidepressants across each visit by class (SSRI vs non-SSRI) with arrows width weighted by the number of participants (n=2027). ARIC indicates Atherosclerosis Risk in Communities study; SSRI, selective serotonin reuptake inhibitor.

have suggested that both SSRIs and TCAs are associated with autonomic changes,[37] which were linked with increased AF risk in a large population-based cohort.[38] Additionally, increased activation of serotonin receptors has been associated with higher risk of adverse cardiovascular events, particularly AF.[12,13] In summary, based on the findings of the current study as well as other reports in the literature, there is not good evidence to support a differential association of SSRIs versus non-SSRIs on CVD events. We did not, however, compare CVD risk in patients taking all antidepressants with those not taking antidepressants.

Antidepressants have a number of effects that may affect the risk of CVD. Some antidepressants are associated with weight gain and metabolic disturbances.[39] SSRIs act by blocking the serotonin transporter and therefore reuptake of serotonin into the neuron, resulting in an increase in serotonin in the synapse. Serotonin is released by activated platelets, causing enhanced platelet aggregation,[40] and is implicated in modulation of vascular tone.[41] A functional polymorphism of the serotonin transporter was also associated with a higher risk of premature MI.[42] A high expression of the serotonin transporter genotype was also associated with lower risk of ischemic stroke.[43] SSRIs with high affinity for the serotonin transporter have been shown to decrease platelet activity in patients with coronary artery disease.[44,45] A case-control study also reported that odds of MI were lower among users of antidepressants with high serotonin transporter affinity, all of which were SSRIs.[46] In summary, although there are biological reasons why SSRI use may be beneficial for CVD events, the current study does not support this conclusion.

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 SSRIs or non-SSRIs. Second, the information on antidepressant use was

Table 2. Associations of Antidepressant Medication Types With Incident CVD in the ARIC Cohort (n=2027 Overall, Excluding Prevalent Cases in Each Analysis; n=81 AF; n=89 HF; n=84 MI; and n=62 Ischemic Stroke)

Outcomes				
	AF	HF	MI	Ischemic Stroke
Number of events				
Total	332	365	174	119
SSRI	136	137	62	43
Non-SSRI	196	228	112	76
Median follow-up, y	13.4	13.6	13.5	14.5
HR (95% CI) for SSRIs Compared With Non-SSRIs*				
Model 1[†]	1.10 (0.83–1.47)	0.95 (0.76–1.19)	0.81 (0.60–1.11)	0.85 (0.59–1.24)
Model 2[‡]	1.10 (0.86–1.41)	0.98 (0.77–1.25)	0.91 (0.64–1.29)	1.07 (0.70–1.63)
Model 3[§]	1.11 (0.86–1.42)	1.03 (0.80–1.32)	0.88 (0.61–1.26)	1.12 (0.82–1.74)
Model 4[‖]	1.07 (0.82–1.41)	1.05 (0.81– 1.36)	0.82 (0.56–1.19)	1.07 (0.70–1.63)
Model 5[¶]	1.10 (0.85–1.40)	0.90 (0.70–1.17)	0.83 (0.61–1.15)	0.91 (0.62–1.35)

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; HF, heart failure; HR, hazards ratio; LDL, low-density lipoprotein; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.
*HRs are for associations of using SSRIs compared with non-SSRIs, with each outcome.
[†]Adjusted for age, sex, race/center, and education.
[‡]Additional adjustment for BMI, cigarette smoking, alcohol use, antihypertensive medications, diabetes mellitus, and the year of diagnosis (HDL, LDL, statins use for MI and stroke model).
[§]Additional adjustment for vital exhaustion questionnaire scores (quartiles).
[‖]Additional adjustment for BMI, cigarette smoking, alcohol use, antihypertensive medications, diabetes mellitus (HDL, LDL, statins use for MI and stroke models), and the year of diagnosis while omitting visit 5.
[¶]Fine and Gray model adjusted for BMI, cigarette smoking, alcohol use, antihypertensive medications, diabetes mellitus (HDL, LDL, statin use for MI and stroke models), and the year of diagnosis, while considering mortality as a competing risk.

restricted to assessment of medication containers at the time of clinic visits. This could be subject to misclassification bias if medications were not counted correctly because of unwillingness of the participants to share information on antidepressant use or for other reasons. However, there is no reason to believe that this would affect one antidepressant class more than another. Third, the study lacks details on severity of depression and a diagnosis of depression. The only related measure available in the entire cohort was vital exhaustion, which is likely insufficient to account for

Table 3. Association of Antidepressant Medication Type With Incident CVD in the ARIC Cohort Study, by Censoring Subjects Who Stopped or Changed Antidepressant Medication Type During Any of the Visits and While Considering Antidepressant Reports as a Time-Dependent Exposure

Outcomes				
	AF	HF	MI	Ischemic Stroke
No. of events, time-adjusted	212	250	117	82
Median follow-up, y	5.1	5.1	5.1	5.1
No. of events, time dependent	231	276	140	100
Median follow-up, y	5.2	5.2	5.2	5.4
HR (95% CI)*				
Censored analysis	1.22 (0.89–1.66)	0.96 (0.72–1.28)	0.95 (0.62–1.44)	1.14 (0.70–1.88)
Time-dependent analysis	1.20 (0.91–1.59)	1.04 (0.81–1.35)	1.13 (0.78–1.64)	1.04 (0.67–1.62)

Censored analysis: Censoring subjects when they stop using or change antidepressant type. Time-dependent analysis: Considered subjects changing antidepressant class and those who stopped and restarted antidepressant use at a later study visit. Model adjusted for age, sex, race/center, education, BMI, cigarette smoking, alcohol use, antihypertensive medications, diabetes mellitus, and the year of diagnosis. (HDL, LDL, statins use for MI and stroke model). AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.
*HR for each outcome comparing use of SSRIs to non-SSRIs.

Table 4. Association of Antidepressant Medication Type With Incident CVD Considering Antidepressant Type by Period of Reported Use (Before 1994, After 1994) in the ARIC Cohort Study

Outcomes				
	AF	HF	MI	Ischemic Stroke
No. of events, total	332	365	174	119
Median follow-up, overall (y)	13.4	13.6	13.5	14.5
Before 1994, y	21.4	21.6	22.4	22.2
After 1994, y	5.4	5.4	5.3	5.2
HR (95% CI)*				
SSRI vs non-SSRI, on or prior to 1994	0.99 (0.67–1.45)	1.14 (0.79–1.63)	0.66 (0.37–1.16)	0.75 (0.39–1.45)
SSRI vs non-SSRI, after 1994	1.20 (0.87–1.67)	0.89 (0.65–1.21)	1.16 (0.72–1.86)	1.52 (0.81–2.86)
P value for interaction†	0.44	0.31	0.13	0.13

Model=adjustment for vital exhaustion questionnaire, BMI, cigarette smoking, alcohol use, antihypertensive medications, diabetes mellitus, and the year of diagnosis. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.
*HR for each outcome comparing the exposure of using SSRI medications as compared with non-SSRI medications.
†SSRI-by-year interaction *P* value.

depression severity. Although antidepressants are most commonly used for the treatment of depression, they are prescribed for other conditions as well.[47] Thus, unmeasured confounding attributable to differential prevalence of depression among antidepressant users might have biased our results. We attempted to minimize this confounding by adjusting for vital exhaustion questionnaire scale scores obtained during the second visit. In addition, although we considered propensity-score matched analysis, we decided against pursuing this approach, as it would limit our sample size and limit the strength of our conclusions. Fourth, the lack of precise data regarding the time of antidepressant initiation may have limited our ability to establish a clear time-dependent exposure to SSRIs versus non-SSRIs. However, we performed a sensitivity analysis to handle antidepressant use as a time-dependent exposure, and the results remained similar. Fifth, our sample was predominantly composed of white and female participants, which may limit the generalizability of our results. Finally, it is also worth mentioning that this analysis does not address the association of medication class with cardiovascular complications or sudden cardiac death happening soon after initiating antidepressants, which has been a concern for TCAs in some prior studies.[48,49] Strengths of the current study include the lower risk of information bias by having subjects bring their own medication containers rather than using prescription databases or

Table 5. Association of Antidepressant Medication Type With Incident CVD Considering Antidepressant Type by the Age of Participants When Antidepressant Use was First Reported (≤62 Years vs >62 Years) in the ARIC Cohort Study

Outcomes				
	AF	HF	MI	Ischemic Stroke
No. of events, total	332	365	174	119
Median follow-up, overall (y)	13.4	13.6	13.5	14
Age ≤62, y	20.1	20.2	20.8	20.9
Age >62, y	4.8	4.9	4.9	4.9
HR (95% CI)*				
SSRI vs non-SSRI, age ≤62	1.09 (0.79–1.50)	1.00 (0.73–1.37)	0.90 (0.58–1.41)	0.76 (0.42–1.36)
SSRI vs non-SSRI, age >62	1.16 (0.82–1.65)	1.02 (0.72–1.43)	0.93 (0.56–1.54)	1.65 (0.88–3.10)
P-value for interaction†	0.78	0.96	0.94	0.06

Model=adjustment for vital exhaustion questionnaire, BMI, cigarette smoking, alcohol use, antihypertensive medications, diabetes mellitus, and the year of diagnosis. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.
*HR for each outcome comparing the exposure of using SSRI medications as compared with non-SSRI medications.
†SSRI-by-age interaction *P* value.

self-reporting. Moreover, our study included a follow-up time of 14 years, which is longer than most other observation studies.

In conclusion, in a community sample of ARIC participants using antidepressants, our results do not provide evidence to suggest the existence of a marked difference in CVD risks among subjects using SSRIs and non-SSRIs, for the events of MI, HF, AF, and ischemic stroke. These findings should give confidence in prescribing non-SSRI antidepressants for patients who may not respond to SSRIs or have unacceptable side effects related to their use. Given the high prevalence of depression in the United States, this could have important clinical implications.

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Disclosures

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