Antidepressant Use and Risk of Incident Cardiovascular Morbidity and Mortality Among Postmenopausal Women in the Women's Health Initiative Study

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Abstract

Background: Antidepressants are commonly prescribed medications, but their effect on cardiovascular morbidity and mortality remains unclear.

Methods: Prospective cohort study of 136 293 community-dwelling postmenopausal women in the Women's Health Initiative (WHI). Women taking no antidepressants at study entry and who had at least 1 follow-up visit were included. Cardiovascular morbidity and all-cause mortality for women with new antidepressant use at follow-up (n=5496) were compared with those characteristics for women taking no antidepressants at follow-up (mean follow-up, 5.9 years).

Results: Antidepressant use was not associated with coronary heart disease (CHD). Selective serotonin reuptake inhibitor (SSRI) use was associated with increased stroke risk (hazard ratio [HR],1.45, [95% CI, 1.08-1.97]) and all-cause mortality (HR,1.32 [95% CI, 1.10-1.59]). Annualized rates per 1000 person-years of stroke with no antidepressant use and SSRI use were 2.99 and 4.16, respectively, and death rates were 7.79 and 12.77. Tricyclic antidepressant (TCA) use was associated with increased risk of all-cause mortality (HR,1.67 [95% CI, 1.33-2.09]; annualized rate, 14.14 deaths per 1000 person-years). There were no significant differences between SSRI and TCA use in risk of any outcomes. In analyses by stroke type, SSRI use was associated with incident hemorrhagic stroke (HR, 2.12 [95% CI, 1.10-4.07]) and fatal stroke (HR, 2.10 [95% CI, 1.15-3.81]).

Conclusions: In postmenopausal women, there were no significant differences between SSRI and TCA use in risk of CHD, stroke, or mortality. Antidepressants were not associated with risk of CHD. Tricyclic antidepressants and SSRIs may be associated with increased risk of mortality, and SSRIs with increased risk of hemorrhagic and fatal stroke, although absolute event risks are low. These findings must be weighed against quality of life and established risks of cardiovascular disease and mortality associated with untreated depression.

ANTIDEPRESSANTS ARE AMONG the most widely prescribed medications in the United States. From 2001 through 2003, more than 10% of participants in the population-based National Comorbidity Survey–Replication study were treated with antidepressants, and the percentage was higher among women and older participants.[1] This prevalence represents a more than 5-fold increase over the 1990-1992 period and was particularly pronounced among less severely depressed individuals. Similar trends have been observed in European countries.[2]

While depression is an independent risk factor for cardiovascular morbidity and mortality,[3–5] the effects of antidepressant use on these outcomes is less clear. Formerly first-line therapy, tricyclic antidepressants (TCAs) have now become second-line treatments, in part because of their potential for cardiotoxic effects. Selective serotonin reuptake inhibitors (SSRIs) have supplanted TCAs as first-line treatments, in part owing to their relative safety in overdose. Moreover, because of the platelet-aggregating effects of serotonin, the blockade of serotonin reuptake and secondary depletion of platelet serotonin with SSRI use might have protective effects against ischemic cardiovascular events.[6–8] In this regard, observational studies of the medical risks of antidepressants have had mixed results.[9–13]

Importantly, little is known about antidepressant safety among older women, a group at increased risk of both depression and cardiovascular disease. Therefore, we examined the prospective association between new antidepressant use and cardiovascular morbidity and

mortality in a large cohort of postmenopausal women who participated in the Women's Health Initiative (WHI).[14–19]

METHODS

The WHI consisted of 3 overlapping clinical trials (CTs) and a longitudinal cohort observational study (OS) conducted in 40 US clinical centers with the aim of investigating risk factors for several chronic diseases in 161 608 postmenopausal women aged 50 to 79 years. Women were enrolled from 1993 through 1998 and observed for incident events. Details of the study design and baseline characteristics are reported elsewhere.[14–19]

Recruitment into the WHI was mostly through mass mailings to age-eligible women using voter registration, motor vehicle, and commercial lists. Exclusion criteria included having a condition that would prevent study participation owing to drug dependency or mental illness. At the baseline visit, subjects completed questionnaires on medical and psychosocial characteristics. The first follow-up clinic visit for OS participants was at 3 years and for CT participants at 1 year after baseline and took place from 1997 through 2001 for OS and 1995 through 1999 for CT participants. The first follow-up visit constituted the start of follow-up in our analyses. The protocol and consent were approved by the participating centers' institutional review boards, and all women gave written informed consent.

Medication use was assessed at baseline and at the first follow-up visit for all participants. Women were asked to bring all medications to the clinic in their original bottles, and drug information was entered into a medications database derived from the Master Drug Data Base (MDDB; Medi-Span, Indianapolis, Indiana). Use of antidepressants was classified into the 4 mutually exclusive categories of SSRIs, TCAs, other or multiple antidepressants, or none. Use of trazodone, which is typically used adjunctively in low doses to promote sleep, was not an exclusion criterion for the SSRI and TCA categories: 72 women were taking an SSRI with trazodone, and 3 women were taking a TCA with trazodone.

The analytic cohort consisted of women who were taking no antidepressants at baseline and who completed at least 1 follow-up visit (N=136 293). Of these, 74 324 were in the OS and 61 969 were in a CT (Figure 1). New antidepressant use was defined as use of no antidepressant medication at baseline and use of 1 of the categories of antidepressants at the first follow-up visit.

Depression, as described in more detail elsewhere,[5] was measured at baseline and first follow-up visit using an 8-item screening instrument developed for the Medical Outcomes Study[20] that incorporates 6 items about depressive symptoms from the Center for Epidemiologic Studies Depression Scale[21] and 2 items from the Diagnostic Interview Schedule.[22] The scale score is based on a logistic regression prediction equation using a weighted combination of responses to these 8 items. This screening instrument has been validated against direct interview assessments in primary care and mental health patients.[20] A cut point of 0.06 demonstrated good sensitivity (89%) and specificity (95%) for detecting presence of a depressive disorder in the past month in both the primary care and mental health populations[20] and was used to define a positive depression finding in our sample.

In a prior study of WHI OS cohort participants,[23] the 0.06 cut point exhibited a negative predictive value of 99% for current major depression or dysthymia compared with the gold standard, a psychiatrist-administered semistructured clinical interview (the structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]) (*DSM-IV*). However, the positive predictive value was only 20%, indicating that most women in this low-prevalence population classified as depressed would not meet criteria for *DSM-IV* depression by psychiatric interview, though they may have had subsyndromal symptoms. For lifetime major depression and dysthymia, the negative predictive value was 81%, and the positive predictive value was 52%.

End points were ascertained from medical history update questionnaires mailed annually to OS participants and semiannually to CT participants. Intensive investigation by telephone follow-up obtained additional details from medical records, laboratories, and death certificates. Potential cardiovascular outcomes were centrally adjudicated by trained physicians, and stroke outcomes by neurologists.[24] Stroke was defined as the rapid onset of a persistent neurologic deficit attributed to an obstruction lasting longer than 24 hours without evidence for other causes, unless death supervened or there was a demonstrable lesion compatible with acute stroke on a computed tomographic or magnetic resonance imaging scan. Strokes were classified as ischemic or hemorrhagic based on results of brain imaging studies. For death events, communication with proxy respondents and/or National Death Index searches were conducted.

Occurrences considered *events* for this research were (1) the first occurrence of coronary heart disease (CHD), defined as fatal plus nonfatal myocardial infarction (MI) or death due to definite or possible CHD; (2) fatal or nonfatal stroke; and (3) all-cause mortality occurring after the first follow-up visit. Cox proportional hazards models used the time to event for these outcomes, with start time being the first follow-up visit and censoring occurring either when an event took place or at the time of the last available medical update form.

Baseline characteristics were compared among those with no new antidepressant use and those with new use of the various categories of antidepressants. Annualized rates for the combined OS and CT cohorts and for each cohort separately, as well as by age group, were calculated by dividing the number of events after the first follow-up visit by years to the event or to the last follow-up contact for those with no event. This number was multiplied by 1000 to get the annualized rate per 1000 person-years. Hazard ratios (HRs) associated with SSRI or TCA use compared with no use of antidepressants were obtained from Cox proportional hazards models. Analyses combining OS and CT cohorts were stratified by WHI treatment arm, and we allowed the baseline hazard function to vary by treatment arm. This approach to combining cohorts has been previously used in WHI.[25] We also compared events among users of SSRIs to those among users of TCAs. Interactions between antidepressant use and depression, aspirin use, migraine, statin use, hormone use, systolic blood pressure, and age were examined by including the interaction terms in the models. In adjusted Cox proportional hazards models, individuals were excluded for missing data on any covariate.

To address potential confounding by indication, we obtained a propensity score from a logistic regression model to predict any new antidepressant use from demographic, lifestyle, risk factor, and comorbidity variables measured at baseline. Thus these propensity scores were a weighted composite of the individual covariates for each person. The C statistic was 0.72, indicating a moderate ability of the variables included in the model to discriminate new use of antidepressants. Propensity scores were used in 2 ways: (1) we stratified on decile of propensity probability in the Cox regressions (STRATA statement in SAS software, version 9.1; SAS Institute Inc, Cary, North Carolina); and (2) we matched those taking antidepressants with controls taking no antidepressants by propensity probability. This yielded a matched subset of 8408 participants. We repeated this procedure for propensity to be taking SSRIs and taking TCAs. The matched groups were balanced on race and/or ethnicity, education, income, region of the country, having seen a care provider in the past year, life events, smoking, alcohol intake, physical activity, hormone use, body mass index, systolic and diastolic blood pressure, treatment for hypertension, high cholesterol level requiring treatment with pills, diabetes treatment, aspirin, hysterectomy, history of stroke or MI at baseline, and history of cardiovascular disease at baseline. The new antidepressant use group differed slightly in age and had more self-reported migraine, depression, and use of nonsteroidal anti-inflammatory drugs (NSAIDs), all of which characteristics were controlled for in the Cox models.

We present 5 Cox regression models: (1) unadjusted; (2) adjusted for multiple potential confounders; (3) stratified on propensity and adjusted for multiple potential confounders; (4) sensitivity analysis using model 3 and excluding those subjects with a history of MI or stroke; and (5) analyses of groups matched on propensity score. When reporting HRs, we use those from model 3 unless otherwise noted.

Based on graphical approaches and goodness of fit tests, we detected no violations of the assumption of proportional hazards. All analyses were done using SAS software, version 9.1. Results with $P<.05$ (2-tailed) were considered statistically significant. No adjustment was made for multiple comparisons, and we present nominal 95% confidence intervals (CIs). For SSRIs in the fully adjusted models, power was 80% at a 2-tailed significance level of .05 to detect HRs of 1.51 for CHD, 1.59 for stroke, and 1.33 for death; the corresponding HRs for TCAs were 1.80 (CHD), 1.94 (stroke), and 1.51 (death).

RESULTS

Of the 161 808 women enrolled in the WHI, 84% (n=136 293) were not taking any antidepressants at baseline and had at least 1 follow-up visit. Four percent (n=5496) were taking some antidepressant at the next follow-up visit, of whom 55.3% (n=3040) were taking only SSRIs; 27.1% (n=1490), TCA only; and 17.6% (n=966) another antidepressant or multiple antidepressants, which might have included an SSRI or TCA. For the combined CT and OS cohort, mean (SD) follow-up after the first follow-up visit was 5.86 (1.73) years (maximum, 10.8 years). For the CT women, follow-up after the first annual visit was 7.14 (1.41) years, and for the OS women, follow-up after the third-year visit was 4.80 (1.17) years.

Comparison of baseline characteristics of women with no new antidepressant use vs those with new use (Table 1) revealed that the subjects in the new use cohort were younger, had more life events in the past year, had higher levels of several cardiovascular risk factors, were more likely to have a history of migraine headache, were more likely to be undergoing hormone therapy, and were more likely to be taking aspirin or NSAIDs.

Among the analytic cohort, there were 6262 deaths, 2357 strokes, and 2983 CHD events during follow-up. Annualized rates for death, stroke, or CHD were higher for women with new antidepressant use than for those without in both the CT and OS cohorts and in each age group (Table 2).

New use of either SSRIs or TCAs was not significantly associated with the risk of CHD (Table 3). However, in unadjusted models, SSRI use was associated with a 40% higher risk of stroke (HR, 1.40 [95% CI, 1.09-1.80]). Hazard ratios were similar in models adjusted for multiple confounders and in propensity analyses, including matched analyses. Use of SSRIs compared with no antidepressant use was associated with a 32% higher relative risk of all-cause death in the adjusted model stratified on propensity score (95% CI, 1.10-1.59). The HR for TCA use was 1.67 (95% CI, 1.33-2.09). In other analyses (not shown), models additionally controlling for antianxiety agents and sensitivity analyses excluding those with treated diabetes mellitus, high cholesterol requiring treatment with pills, or current smoking did not substantively change these associations. There were no significant interactions between antidepressant use and age, migraine headache, or aspirin or NSAID use. Among women treated with antidepressants, there were no significant differences between SSRIs and TCAs for any events. The fully adjusted HR comparing SSRI with TCA was 1.17 (95% CI, 0.75-1.81) for CHD, 1.20 (95% CI, 0.76-1.87) for stroke, and 1.03 (95% CI, 0.79-1.33) for death.

Of the 2357 strokes occurring after the first follow-up visit, 1518 were adjudicated as ischemic, 392 as hemorrhagic, 273 as other type, and 174 as unknown type. There were 1907 nonfatal strokes, 445 stroke deaths, and 5 stroke cases in which the patient died of unknown or missing cause. Of the 445 stroke deaths, 134 involved ischemic strokes, 134 hemorrhagic, 24 other, and 153 unknown stroke type. Excess risk of stroke with SSRIs was largely for hemorrhagic stroke (HR, 2.12; 95% CI, 1.10-4.07) (Table 4). The risk of ischemic stroke associated with new SSRI use did not reach statistical significance (HR, 1.21; 95% CI, 0.80-1.83). The use of SSRIs and the use of TCAs were both associated with an increased risk of all fatal strokes (HR, 2.10; 95% CI, 1.15-3.81 and HR, 2.56; 95% CI, 1.26-5.26, respectively). However, SSRIs appeared to convey a higher risk of death from hemorrhagic stroke ($HR_{hemorrhagic\ stroke\ death}$, 2.04; 95% CI, 0.74-5.61) than from ischemic stroke ($HR_{ischemic\ stroke\ death}$, 1.00; 95% CI, 0.24-4.11). There were no significant interactions for hemorrhagic stroke between use of SSRIs and use of statins or aspirin.

To further explore the sensitivity of our results to the timing of depression assessment, we calculated HRs for any new antidepressant use among those above and below the cut point for depression at baseline and, separately, at first follow-up visit. The risk of stroke and death was elevated whether the baseline or follow-up depression score was used (Figure 2).

We examined the distributions of causes of death by antidepressant type and did not observe any clear association between antidepressant classes and cause of death (Table 5).

COMMENT

Our results indicate that among postmenopausal women, antidepressant use is associated with increased risk of all-cause mortality and, for SSRI users, stroke (particularly, hemorrhagic stroke). To our knowledge, this is the largest study of the association between antidepressant use and cardiovascular morbidity and mortality among older women. Compared with women with no antidepressantuse, those using SSRIs had a 45% increased relative risk of incident stroke and 32% increased risk of death in models stratified on propensity and adjusted for multiple covariates. The risk of death was similarly increased among TCA users. We did not observe any significant differences in risk between SSRI and TCA users, which suggests that among women whose symptoms were believed to require treatment, neither class of antidepressant was associated with greater risk. Consistent with prior evidence that SSRIs may increase the risk of abnormal bleeding due to their antiplatelet effects, we observed a significantly increased hazard for hemorrhagic stroke among SSRI users compared with nonusers, though absolute risks were small.

A key question is whether the association between antidepressant use and cardiovascular morbidity and mortality is truly related to drug exposure or to underlying differences in other cardiovascular risk factors, including depression, among the exposed groups. In this study, we found adverse effects of antidepressant use despite controlling for traditional cardiovascular risk factors and the propensity to be taking an antidepressant. Depression is an established risk factor for cardiovascular morbidity and mortality[3–5] and has been associated with an increased risk of stroke[4] and increased mortality following stroke and MI.[26,27] We found no significant difference in risk of stroke or death between those using SSRIs and those using TCAs, despite their different therapeutic mechanisms, which raises the possibility that residual confounding by depression could account for part of the excess risk.

We attempted to address residual confounding due to depression by exploring multiple ways of removing the variance attributable to depression. Antidepressant exposure was associated with the excess in analyses that (1) controlled for depression at baseline and/or follow-up visits and (2) included depression as a continuous score at both baseline and follow-up as covariates in our fully adjusted models. If residual confounding were operative, we might expect an association with CHD rather than stroke because there were more CHD outcomes, and the association between depression and CHD is better established. Prior evidence from the WHI OS cohort[5] demonstrated that the baseline depression screen predicted cardiovascular death and all-cause mortality, which suggests that this measure is sensitive to the morbidity and mortality effects of depression.

The depression screen used in the present study has been used extensively in previous epidemiologic studies[20,28–30] and has demonstrated good sensitivity and specificity for detecting major depression and dysthymia in primary care samples.[31] Nevertheless, this depression screen was not designed as a diagnostic assessment and has psychometric

limitations.[23] Thus, we cannot entirely rule out residual confounding. If our observation of increased risk with antidepressant use is attributable to such confounding, our results would at least imply that antidepressant treatment in a community sample of postmenopausal women does not remove the cerebrovascular and mortality risks associated with depressive symptoms.

Consistent with several previous studies,[13,32,33] we did not observe an association between antidepressant use and CHD. In 1 study of union health plan members,[9] an increased risk of MI was associated with TCA (but not SSRI) use. However, the mean age of this cohort was approximately 45 years, substantially younger than the WHI women. Our results also contrast with several studies that have suggested a protective effect of SSRIs on risk of MI.[12,33] A Danish case-control study of first-time hospitalization for MI[33] found a modest protective effect of SSRIs but only among individuals with a history of cardiovascular disease. Another case-control study of first MI cases[12] found a protective effect for SSRIs with a high affinity for the serotonin transporter but no effect for non-SSRI antidepressants. A study using the United Kingdom General Practice Research Database (GPRD)[13] reported a reduced risk of MI among SSRI users but no effect of non-SSRI antidepressants. However, recent past use of SSRIs (discontinued within the past month) was associated with an increased risk of MI. In contrast, a larger study using GPRD data (61% male)[10] found an increased risk of MI for both SSRI use (odds ratio [OR], 1.49; 95% CI, 1.43-1.56) and TCA use (OR, 1.41; 95% CI, 1.37-1.45). In that study, risk was elevated primarily within 28 days of exposure to the antidepressant for both SSRIs and TCAs but was not increased with more prolonged use.

In contrast to our findings for CHD, we observed an increased risk of stroke with antidepressant use, largely attributable to hemorrhagic stroke, consistent with the antiplatelet effects of SSRIs. Of 5 previous studies,[4,26,34–36] only 1[36] found evidence of increased risk of stroke among antidepressant users. In the GPRD database,[34] there was no association between use of SSRIs and risk of intracranial hemorrhage. However, this study had limited power, with only 7 SSRI users among 65 cases. A larger registry-based Danish case-control study also did not find an effect of SSRI use on stroke risk,[35] although there was a nonsignificant increased risk of hemorrhagic stroke (OR, 2.4; 95% CI, 0.9-6.2) among individuals taking both SSRIs and NSAIDs. No increased risk of hemorrhagic stroke was found in another study of 2441 cases of intracranial hemorrhage and 1776 controls.[37] A prospective study of Framingham Heart Study participants[4] found no association between antidepressant treatment and stroke, although the analyses did not distinguish type of antidepressants or stroke. The only prior study to find a link between antidepressants and stroke analyzed 1086 cases of depression and stroke and 6515 controls identified through a medical claims database.[36] An increased risk of cerebrovascular events was seen with use of SSRIs (HR, 1.24; 95% CI, 1.07-1.44), TCAs (HR, 1.34; 95% CI, 1.10-1.62), and other antidepressants (HR, 1.43; 95% CI, 1.21-1.69). Discrepancies between our results and those of prior studies may be due to differences in methodology, sample characteristics, or power considerations.

The association between antidepressants and all-cause mortality in our study is notable because this outcome has not been widely examined in prior studies. The distribution of

causes of death did not indicate any category that accounted for this excess risk. Thus, it remains unclear from our data whether antidepressants have a causal effect on mortality or are merely a marker of increased risk from other causes (eg, residual depressive symptoms) that may not have been fully controlled.

If antidepressants do contribute to stroke and mortality, the pathogenesis could be multifactorial and might vary by drug class. Tricyclic antidepressants have potential cardiac toxic effects that could increase the risk of fatal MI, stroke, and sudden death, including orthostatic hypotension, reduced heart rate variability, and QT interval prolongation.[38] Preclinical studies suggest that both TCAs and SSRIs have calcium-channel blocking activity in cardiac myocytes and antagonize voltage-gated ion channels.[39,40] Like TCAs, SSRIs and serotonin-norepinephrine reuptake inhibitors appear to have effects on cardiac conduction and negative inotropic effects.[39] Also, SSRIs have other effects relevant to cardiovascular outcomes. First, blockade of the serotonin transporter by SSRIs can deplete platelet serotonin levels and interfere with thrombus formation.[41] This has been linked to bleeding complications[42,43] and could contribute to the association between SSRI use and hemorrhagic stroke observed in our study. Second, serotonin has vasoconstrictive effects on larger cerebral arteries; proserotonergic effects of SSRIs could exacerbate stroke risk, although, despite sporadic reports of cerebral vasospasm associated with serotonergic medications,[44] there is little direct evidence for this.[45,46] Finally, small studies have found that SSRIs can be associated with adverse effects on a number of cardiovascular risk factors, including reduced heart rate variability, and increases in pulse pressure, C-reactive protein levels, and serum cholesterol levels.[47,48]

Our results should be considered in light of several limitations. First, this was an observational study and not a randomized trial of antidepressant use. Second, our analyses of multiple outcomes followed by post hoc analyses of stroke subtype may have incurred a risk of type I error. In addition, available data did not permit us to determine precise dosages or medication adherence. Nevertheless, variability in antidepressant exposure might be expected to obscure rather than spuriously produce a relationship between antidepressant use and cardiovascular outcomes.

It should also be noted that we measured exposure (new use of antidepressant) at the first follow-up visit. It is possible that individuals treated only between baseline and first follow-up would be classified as unexposed. This could bias the observed effect estimates toward the null, making our results conservative.

Our exposure definition also does not capture new use of antidepressants after the start of follow-up. A more stringent statistical analysis might treat antidepressant use as a time-dependent variable, since it is probable that antidepressant use changed during follow-up. However, treating antidepressant use as a time-dependent variable was not possible in the combined cohort because in the WHI OS cohort,[14–19] antidepressant use was measured only at baseline and the start of follow-up. Thus, our results should be interpreted with great caution. Nevertheless, exposure misclassification during follow-up would likely produce bias toward the null hypothesis.

Furthermore, while the depression screen used herein has been shown to predict cardiovascular morbidity and mortality in this sample,[5] it may be less sensitive or specific than a clinician diagnosis of depression. If the increased risks we observed are attributable to residual confounding by depressive symptoms, our results suggest that antidepressant treatment does not neutralize the effects of depression on stroke and mortality among postmenopausal women. Overall, the interpretation and implications of our results must be placed in the context of the observational nature of these analyses, the imperfect measurement of depression, and the known risks associated with depression. Finally, this sample comprised predominantly white older women, and inferences to other populations must be drawn cautiously.

In this prospective study of antidepressant use and incident cardiovascular morbidity and mortality among postmenopausal women, we observed increased risks of all-cause mortality in association with incident use of any antidepressants. The most commonly used antidepressants, SSRIs, were also associated with incident stroke and, in particular, hemorrhagic stroke. Although these results raise concerns about adverse effects of antidepressants, it is important to note that depression itself has been implicated as a risk factor for CHD, stroke, early death, and other adverse outcomes. In addition, inadequately treated depression is associated with substantial disability, impairments in quality of life, and health care costs.[49] Nevertheless, our results suggest that physicians should be vigilant about controlling other modifiable cardiovascular risk factors in women taking antidepressants. Further research is needed to clarify the risk-benefit ratio of antidepressant use among older women.

After acceptance of the manuscript for this article, we became aware of a recent report by Whang et al[50] that also found no relationship between antidepressant use and CHD but found a significant association with sudden cardiac death. As in our study, the possibility of residual confounding by depression cannot be ruled out.

Financial Disclosure:

Funding/Support:

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Women's Health Initiative Memory Study

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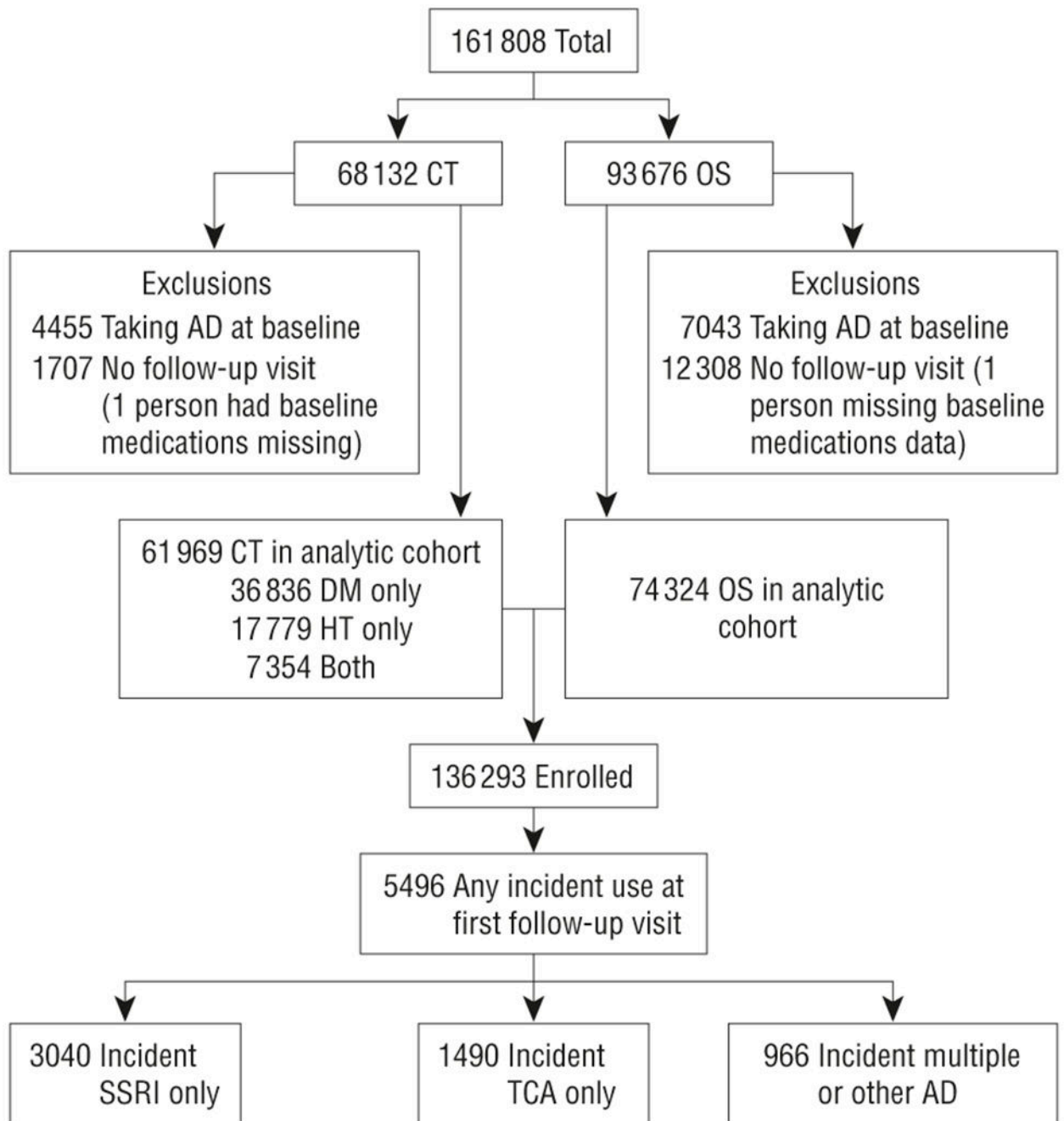
Figure 1.
Diagram depicting derivation of analytic cohort. AD indicates antidepressant; CT, clinical trial; DM, diabetes mellitus; HT, hypertension; OS, observational study; SSRI, selective serotonin reuptake inhibitor; and TCA, tricyclic antidepressant.
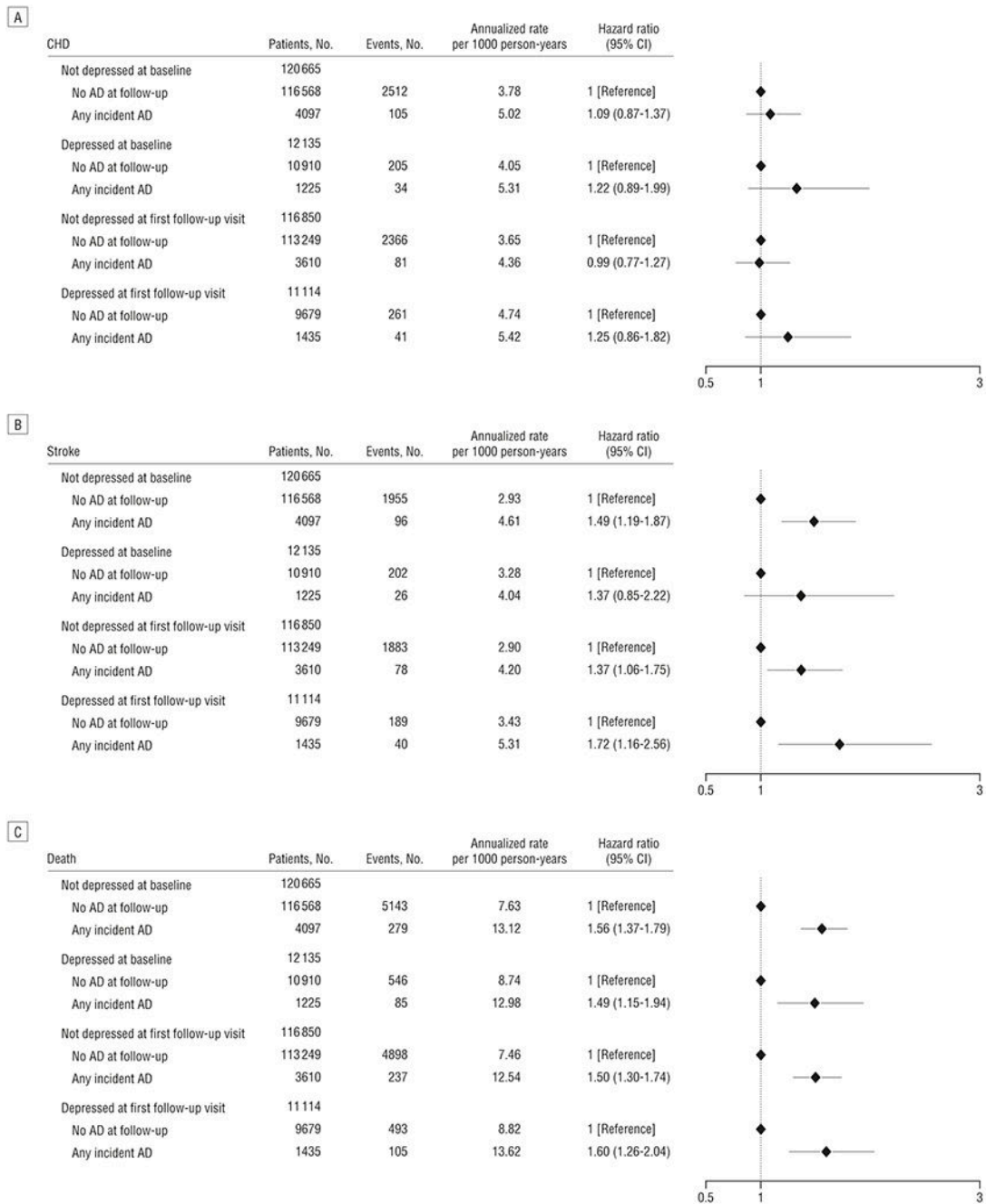
Figure 2.
Hazard ratios for coronary heart disease (CHD) (A), stroke (B), and all-cause mortality
(C). All panels compare antidepressant users and nonusers stratified by depression status
at baseline and first follow-up and adjusted for age, race, income, log of depression
screen score at baseline and follow-up, systolic blood pressure, high cholesterol level
requiring treatment with pills, hypertension treatment, smoking status, physical activity,
body mass index, alcohol use, diabetes treatment, history of myocardial infarction or stroke,
hormone therapy use, migraine headaches, aspirin or nonsteroidal anti-inflammatory use,

and decile of propensity for any incident antidepressant use. AD indicates antidepressant; CI, confidence interval.

Table 1.

Baseline Characteristics of Women's Health Initiative[14–19] Clinical Trial and Observational Study Participants Who Were Not Taking ADs at Baseline and Had at Least 1 Follow-up Visit

Characteristic	Participants, No.[a]	Participants, %			Participants, %		
		No Incident AD Use (n = 130 797)	Any Incident AD Use (n = 5496)	P Value	Incident SSRI Only (n = 3040)	Incident TCA Only (n = 1490)	Incident Other or Multiple AD (n = 966)
All	136 293	100	100		100	100	100
Age, y				<.001			
50-59	44 486	32.42	37.97		39.51	31.21	43.58
60-69	61 994	45.65	41.65		40.46	44.16	41.51
70-79	29 813	21.94	20.38		20.03	24.63	14.91
Race/ethnicity				<.001			
American Indian or Alaskan Native	543	0.40	0.42		0.43	0.60	0.10
Asian or Pacific Islander	3736	2.80	1.27		1.05	1.74	1.24
Black or African American	12 087	9.01	5.55		5.30	7.38	3.52
Hispanic/Latino	5097	3.73	3.98		4.11	4.09	3.42
White, not of Hispanic origin	112 969	82.70	87.45		87.86	84.90	90.06
Other	1527	1.12	1.02		0.82	1.07	1.55
Education				.04			
0-8 y or some high school	6623	4.84	5.24		5.07	6.11	4.45
High school diploma–some college	74 081	54.30	55.60		54.67	58.66	53.83
College graduate or postgraduate	54 606	40.13	38.54		39.64	34.50	41.30
Income, $				.01			
<20 000	20 107	14.69	16.27		14.57	20.13	15.63
20 000-49 999	57 247	42.02	41.56		42.01	40.94	41.10
50 000	50 054	36.76	35.92		36.88	32.82	37.68
Do not know	3516	2.59	2.40		2.50	2.48	1.97
Region				<.001			
Northeast	31 499	23.21	20.69		23.22	18.39	16.25
South	34 533	25.11	30.71		31.41	26.85	34.47
Midwest	30 075	22.12	20.74		19.31	23.49	21.01

Characteristic	Participants, No. [a]	Participants, %				Participants, %		
		No Incident AD Use (n = 130 797)	Any Incident AD Use (n = 5496)	P Value	Incident SSRI Only (n = 3040)	Incident SSRI Only (n = 3040)	Incident TCA Only (n = 1490)	Incident Other or Multiple AD (n = 966)
West	40 186	29.55	27.86		26.05	31.28	28.26
Current care provider				<.001			
No	8476	6.33	3.60		3.55	3.22	4.35
Yes	126 523	92.72	95.47		95.79	95.37	94.62
Life events in the past year, No.				<.001			
0	28 992	21.44	17.36		16.58	19.26	16.87
1 or 2	72 699	53.48	50.09		48.95	51.95	50.83
3 or 4	26 252	19.05	24.20		25.43	21.88	23.91
5	5589	4.01	6.15		6.71	4.83	6.42
Smoking status				<.001			
Never smoked	69 849	51.51	45.11		44.74	48.12	41.61
Past smoker	56 015	40.92	45.40		46.58	42.82	45.65
Current smoker	8774	6.37	8.10		7.24	7.58	11.59
Alcohol use				<.001			
Nondrinker	14 594	10.77	9.22		8.26	11.14	9.32
Past drinker	23 819	17.27	22.49		21.94	24.50	21.12
<1 Drink/mo	16 826	12.34	12.41		12.96	11.01	12.84
<1 Drink/wk	28 041	20.56	20.96		20.82	21.28	20.91
From 1 to <7 drinks/wk	35 737	26.34	23.45		24.57	21.48	22.98
7 drinks/wk	16 317	12.02	10.74		10.76	9.93	11.90
Physical activity				<.001			
No activity	19 590	14.25	17.36		17.63	15.77	18.94
Some activity of limited duration	52 307	38.37	38.46		38.72	39.73	35.71
From 2 to <4 episodes/wk	23 334	17.13	16.87		16.84	16.71	17.18
4 Episodes/wk	34 363	25.29	23.42		23.22	22.68	25.16
Hormone use				<.001			
Never used hormones	45 180	33.68	20.61		21.68	20.87	16.87
Past hormone user	30 663	22.53	21.82		22.70	21.48	19.57
Current hormone user	56 362	40.80	54.60		52.63	54.36	61.18

Characteristic	Participants, No.[a]	No Incident AD Use (n = 130 797)	Any Incident AD Use (n = 5496)	P Value	Incident SSRI Only (n = 3040)	Incident TCA Only (n = 1490)	Incident Other or Multiple AD (n = 966)
Weight status, BMI				<.001			
Underweight, <18.5	1157	0.85	0.91		0.99	0.74	0.93
Normal, 18.5-24.9	47 316	34.82	32.30		30.46	32.95	37.06
Overweight, 25.0-29.9	47 154	34.66	33.19		33.29	33.76	31.99
Obesity I, 30.0-34.9	24 745	18.10	19.51		19.97	19.33	18.32
Obesity II, 35.0-39.9	9824	7.18	7.88		8.68	6.64	7.25
Extreme obesity III, 40	4955	3.58	4.95		5.26	5.37	3.31
Systolic blood pressure, mm Hg				.49			
120	52 678	38.66	38.34		38.98	34.63	42.03
120-140	55 657	40.81	41.56		42.24	41.21	39.96
>140	27 854	20.46	20.00		18.72	24.09	17.70
Diastolic blood pressure, mm Hg				.29			
<90	126 956	93.14	93.47		93.65	92.75	94.00
90	9207	6.77	6.40		6.25	7.11	5.80
Hypertension/treatment status				<.001			
Never hypertensive	86 391	63.62	57.71		58.42	53.49	62.01
Untreated hypertensive	10 230	7.47	8.26		8.09	8.19	8.90
Treated hypertensive	32 033	23.26	29.39		28.82	32.62	26.19
High cholesterol requiring treatment with pills				<.001			
No	110 549	81.23	78.33		79.01	74.83	81.57
Yes	17 417	12.62	16.54		16.12	18.46	14.91
Treatment status for diabetes				<.001			
No	130 840	96.10	93.69		94.57	90.47	95.86
Yes	5342	3.83	6.15		5.30	9.19	4.14
Aspirin				<.001			
No	105 748	77.69	75.22		75.26	75.10	75.26
Yes	30 545	22.31	24.78		24.74	24.90	24.74
NSAIDs except aspirin				<.001			
No	111 465	82.12	73.82		75.36	71.07	73.19

Characteristic	Participants, No.[a]	Participants, %			Participants, %		
		No Incident AD Use (n = 130 797)	Any Incident AD Use (n = 5496)	P Value	Incident SSRI Only (n = 3040)	Incident TCA Only (n = 1490)	Incident Other or Multiple AD (n = 966)
Yes	24 828	17.88	26.18		24.64	28.93	26.81
Migraine				<.001			
No	114 644	89.92	81.88		82.64	79.93	82.40
Yes	13 322	10.08	18.12		17.36	20.07	17.60
Depression at baseline				<.001			
No	120 665	89.12	74.55		71.61	82.42	71.64
Yes	12 135	8.34	22.29		25.36	14.09	25.26
History of myocardial infarction before first follow-up visit				<.001			
No	132 970	97.63	95.96		96.18	95.64	95.76
Yes	3323	2.37	4.04		3.82	4.36	4.24
History of stroke before first follow-up visit				<.001			
No	134 319	98.62	97.02		96.88	97.25	97.10
Yes	1974	1.38	2.98		3.13	2.75	2.90

Abbreviations: AD, antidepressant; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic AD.

[a]Numbers in categories may not add to full cohort because of missing values for some variables.

Table 2.

Cardiovascular Events and Annualized Rates by Women's Health Initiative[14-19] Cohort, AD Use at Start of Follow-up, and Age[a]

AD Status	Participants, No.	CHD		Stroke		Death	
		Events, No.	Annualized Rate[b]	Events, No.	Annualized Rate[b]	Events, No.	Annualized Rate[b]
All Cohorts (Observational Study and Clinical Trials)							
No AD at follow-up	130 797	2843	3.81	2232	2.99	5881	7.79
Incident SSRI	3040	73	4.73	64	4.16	201	12.77
Incident TCAs	1490	41	5.18	39	4.92	114	14.14
Incident other or multiple ADs	966	26	5.38	22	4.55	66	13.42
	136 293	2983		2357		6262	
Observational Study Cohort Only							
No AD at follow-up	70 497	1184	3.61	9866	3.00	3018	9.08
Incident SSRI	2153	43	4.45	42	4.38	153	15.54
Incident TCAs	958	26	6.00	24	5.52	69	15.56
Incident other or multiple ADs	716	17	5.26	15	4.64	47	14.31
	74 324	1270		9947		3287	
Clinical Trials Cohort							
No AD at follow-up	60 300	1659	3.97	1246	2.98	2863	6.77
Incident SSRI	887	30	195.19	22	793.79	48	8.15
Incident TCAs	532	15	4.19	15	4.19	45	12.40
Incident other or multiple ADs	250	9	5.63	7	4.36	19	11.63
Clinical Trials Cohort by Age Group, y							
50-59							
No AD at follow-up	42 399	396	1.53	268	1.04	830	3.20
Any incident AD	2087	35	3.02	20	1.73	76	6.49
Incident SSRI	1201	19	2.85	7	1.05	40	5.93
Incident TCAs	465	7	2.62	6	2.27	21	7.83
Incident other or multiple ADs	421	9	4.03	7	3.11	15	6.60
60-69							

AD Status	Participants, No.	CHD		Stroke		Death	
		Events, No.	Annualized Rate [b]	Events, No.	Annualized Rate [b]	Events, No.	Annualized Rate [b]
No AD at follow-up	59 705	1233	3.67	965	2.87	2382	7.01
Any incident AD	2289	55	4.79	50	354.35	148	12.65
Incident SSRI	1230	31	5.10	32	5.29	73	11.82
Incident TCAs	658	14	4.05	10	2.86	44	12.42
Incident other or multiple ADs	401	10	5.15	8	4.12	31	15.64
70-79							
No AD at follow-up	28 693	1214	8.01	999	6.58	2669	17.18
Any incident AD	1120	50	9.75	55	10.83	157	29.53
Incident SSRI	609	23	8.57	25	9.44	88	31.26
Incident TCAs	367	20	8.04	23	6.65	49	17.49
Incident other or multiple ADs	144	7	10.68	7	10.87	20	30.07

Abbreviations: AD, antidepressant; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] All cohort members had no antidepressant use at baseline and also had at least 1 follow-up visit.

[b] Per 1000 person-years.

Table 3.

Hazard Ratios for Cardiovascular Events and All-Cause Mortality Associated With Antidepressant Use [a]

Statistical Analysis	Events, No./Participants in Analysis, No. [b]	Hazard Ratio (95% Confidence Interval)		
		SSRI	TCA	OM
MI or CHD Death				
Model 1, unadjusted	2982/135 516	1.28 (1.01-1.61)	1.37 (1.01-1.90)	1.48 (1.00-2.17)
Model 2, adjusted for potential confounders [c]	2198/105 256	1.10 (0.83-1.48)	1.00 (0.69-1.44)	1.23 (076-1.99)
Model 3, stratified by propensity decile and adjusted for covariates assessed at start of follow-up [d]	1981/95 511	0.95 (0.70-1.29)	1.13 (0.77-1.65)	1.19 (0.74-1.93)
Model 4, as in model 3 but excluding those with Hx stroke or MI [e]	1703/92 605	0.88 (0.62-1.24)	1.05 (0.68-1.62)	1.3 (0.76-2.21)
Model 5, matched group analyses adjusted for covariates assessed at start of follow-up [f]	Varying [g]	0.74 (0.49-1.11)	1.02 (0.59-1.77)	1.30 (0.57-2.94)
Stroke				
Model 1, unadjusted	2357/135 666	1.40 (1.09-1.80)	1.66 (1.21-2.28)	1.54 (1.01-2.35)
Model 2, adjusted for potential confounders [c]	1762/105 403	1.55 (1.16-2.07)	1.31 (0.90-1.90)	1.88 (1.19-2.97)
Model 3, stratified by propensity decile and adjusted for covariates assessed at start of follow-up [d]	1595/95 643	1.45 (1.08-1.97)	1.35 (0.90-2.03)	1.80 (1.14-2.85)
Model 4, as in model 3 but excluding those with Hx stroke or MI [e]	1451/92 603	1.39 (1.00-1.91)	1.27 (0.80-2.00)	1.97 (1.21-3.19)
Model 5, matched group analyses adjusted for covariates assessed at start of follow-up [f]	Varying [g]	1.36 (0.88-2.10)	1.35 (0.71-2.59)	1.32 (0.66-2.60)
Death				
Model 1, unadjusted	6262/136 212	1.57 (1.36-1.81)	1.78 (1.48-2.15)	1.65 (1.30-2.11)
Model 2, adjusted for potential confounders [c]	4525/105 788	1.61 (1.35-1.91)	1.58 (1.27-1.97)	1.58 (1.17-2.14)
Model 3, stratified by propensity decile and adjusted for covariates assessed at start of follow-up [d]	4060/95 984	1.32 (1.10-1.59)	1.67 (1.33-2.09)	1.36 (0.99-1.86)
Model 4, as in model 3 but excluding those with Hx stroke or MI [e]	3649/92 660	1.30 (1.06-1.59)	1.61 (1.25-2.07)	1.45 (1.04-2.03)
Model 5, matched group analyses adjusted for covariates assessed at start of follow-up [f]	Varying [g]	1.37 (1.03-1.82)	1.37 (0.96-1.98)	1.42 (0.87-2.32)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; DBP, diastolic blood pressure; Hx, history of; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; OM, another or multiple antidepressants; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] All analyses for combined observational study and clinical trial cohorts are stratified by study arm.

[b] The numbers vary depending on adjustment because those with missing values in any covariate are omitted from the Cox regression models.

[c]Model 2 is adjusted for the following potential confounders assessed at the baseline screening visit: age, race, income, high cholesterol level requiring treatment with pills, smoking status, physical activity, alcohol intake, treatment for diabetes, log of baseline depression score. Model 2 is also adjusted for the following variables assessed at the start of follow-up: SBP, BMI, log of depression score, hormone use, migraine or bad headache, aspirin or NSAID use, history of stroke or MI.

[d]Model 3 is stratified by decile of propensity to be taking any new antidepressant at the start of follow-up and adjusted for the following covariates assessed at the first follow-up visit: SBP, BMI, log of depression, hormone use, migraine or bad headache, aspirin or NSAID use, and history of stroke or MI.

[e]Model 4 is stratified by propensity decile and adjusted for the same covariates as in model 3 but excludes those with a history of stroke or MI prior to the start of follow-up.

[f]Model 5 involves analyses of matched groups adjusted for the following covariates assessed at the start of follow-up: SBP, log depression score, BMI, hormone use, migraine or bad headache, aspirin or NSAID use, history of MI or stroke.

[g]Numbers vary because separate propensity matchings were done for each antidepressant. For CHD, the numbers were SSRI, 107/4130; TCA, 55/2084; and OM, 30/1411. For stroke, the numbers were SSRI, 89/4125; TCA, 40/2088; and OM, 37/1412. For death, the numbers were SSRI, 211/4162; TCA, 129/2100; and OM, 85/1530. The following variables entered in the propensity logistic: age, race/ethnicity, education, income, physical activity, region of the country, having current health care provider, having last medical visit within past year, alcohol use, smoking, self-reported general health, life events, social functioning, social support, emotional well-being, hormone use, hysterectomy, having been diagnosed as having diabetes ever, being treated for diabetes, having high cholesterol level requiring treatment pills, BMI, waist to hip ratio, SBP, DBP, treatment for hypertension, history of cancer, pulmonary embolism, congestive heart failure, and history of MI, stroke, transient ischemic attack, angina, or revascularization.

Table 4.

Hazard Ratios and 95% Confidence Intervals[a] for Ischemic and Hemorrhagic Strokes and for Stroke Mortality for Incident Use of Ans Compared With No Use

New Use of AD	Ischemic Stroke (n = 1026/95 074)[b]	Hemorrhagic Stroke (n = 271/94 319)[b]	All Fatal Strokes (n = 288/94 336)[b]
SSRI	1.21 (0.80-1.83)	2.12 (1.10-4.07)	2.10 (1.15-3.81)
TCA	1.04 (0.59-1.85)	1.11 (0.35-3.48)	2.56 (1.26-5.26)
OM	1.67 (0.92-3.05)	1.18 (0.29-4.78)	1.98 (0.73-5.40)

Abbreviations: AD, antidepressant; BMI, body mass index; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; OM, another or multiple antidepressants; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic AD.

[a]Cox regression analyses are stratified on treatment arm and on decile of propensity to be taking any new AD and adjusted for the following variables assessed at the start of follow-up: hormone use, log of depression screen score, BMI, history of MI or stroke, systolic blood pressure, migraine or bad headaches, aspirin or NSAID use.

[b]Total reported as number of events/number of participants in the analysis.

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Table 5.

Cause of Death as a Percentage of Total Number of Deaths in Each Medication Category

Incident Use	Total Deaths, No.	Proportion of Total Deaths, %						
		Stroke	CVD[a]	Cancer	Suicide	Other Traumatic	Other or Unknown
No AD	5881	7.28	22.3	44.43	0.17	2.58	23.21
No AD among depressed	546	7.14	23.44	41.21	0.00	2.38	25.82
No AD among nondepressed	5143	7.31	22.13	45.09	0.17	2.64	22.65
SSRI	201	7.96	18.41	38.31	1.00	1.49	32.84
TCA	114	10.53	21.05	33.33	0.88	1.75	32.46
OM	66	6.06	30.31	33.33	1.52	3.03	25.76

Abbreviations: AD, antidepressant; CHD, coronary heart disease; CVD, cardiovascular disease; OM, another or multiple antidepressants; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic AD.

[a]Cardiovascular disease includes CHD, pulmonary embolism, and other or unknown CVD.