SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND RISK OF NON-CARDIOEMBOLIC ISCHEMIC STROKE: A NESTED CASE-CONTROL STUDY

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ABSTRACT

Background and Purpose: Multiple studies have reported that the use of selective serotonin reuptake inhibitors (SSRIs) is associated with an increased risk of ischemic stroke; however, this finding may be the result of a confounding by indication. We examined the association using different approaches to minimize such potential bias.

Methods: A nested case-control study was carried out in a Spanish primary health-care database (BIFAP) over the study period 2001-2015. Cases were patients sustaining an ischemic stroke with no sign of cardioembolic or unusual etiology. For each case, up to five matched controls (for exact age, sex, and index date) were randomly selected. Antidepressants were divided in 6 pharmacological subgroups according to their mechanism of action. The current use of SSRIs (use within a 30-day window prior to index date) was compared to non-use, past use (beyond 365 days) and current use of other antidepressants through a conditional logistic regression model to obtain adjusted odds ratios (AORs) and 95% confidence intervals (95%CI). Only initiators of SSRIs and other antidepressants were considered.

Results: A total of 8,296 cases and 37,272 matched controls were included. Of them, 255 (3.07%) were current users of SSRIs among cases and 834 (2.24%) among controls, yielding an AOR of 1.14 (95%CI:0.97-1.34) as compared to non-users, 0.94 (95%CI:0.77-1.13) as compared to past-users and 0.74 (95%CI:0.58-0.93) as compared to current users of other antidepressants. No relevant differences were found by duration (≤1year, >1year), sex, age (<70, ≥70 years old) and background vascular risk.

Conclusions: The use of SSRIs was not associated with an increased risk of non-cardioembolic ischemic stroke. On the contrary, as compared to other antidepressants, SSRIs appeared to be protective.

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NON-STANDARD ABBREVIATIONS AND ACRONYMS

AD-NE:Antidepressants with a predominant inhibition of the noradrenergic reuptake

AMI:Acute Myocardial Infarction

AORs:Adjusted Odds Ratios

BMI:body mass index

CI:confidence intervals

ICD-9-CM:International Classification of Diseases, version 9, Clinical Modification

ICPC-2:International Classification of Primary Care, version 2

MICE:multiple imputation by chained equations models

NaSSAs:Noradrenergic α-2 receptor antagonists with specific serotonergic antagonism

NE:norepinephrine

PCP:primary care physicians

SARIs:Serotonin receptor antagonists with serotonin reuptake inhibition

SNRIs:Serotonin-norepinephrine reuptake inhibitors

SSRI:Selective Serotonin Recapture Inhibitors

TACs-SER:Tricyclic antidepressants with a preferential inhibitory action on the reuptake of serotonin

TIA:transient ischemic attack

INTRODUCTION

The relationship between the use of selective serotonin reuptake inhibitors (SSRIs), the most widely prescribed antidepressants, and ischemic stroke has been a matter of controversy for the last two decades, with many studies suggesting an increased risk[1-5], while a few showing a decreased risk[6-7] or a neutral effect[8]. These findings seem to be a pharmacological paradox as SSRIs have a recognized antiplatelet effect[9] and one should expect a risk reduction, similar to the one found for acute myocardial infarction (AMI)[10-19]. Such discrepancies can be attributed to several factors: 1)depression itself has been reported to be a risk factor for stroke[20,21], and this may result in a confounding by indication when users of antidepressants are compared to non-users, as most studies did; 2)some studies pooled SSRIs with other antidepressants, as if they all had the same pharmacological profile[22]; 3)none of the studies distinguished between the two main pathophysiological types of ischemic stroke: cardioembolic vs non-cardioembolic, when it may not be reasonable to expect the same effect of SSRIs on both types; and 4)the inclusion of prevalent users in the analysis[23].

In the present study we aimed to assess the association of SSRIs and five other antidepressant subgroups with ischemic stroke of probable non-cardioembolic origin, trying to overcome the aforementioned problems by using different methodological approaches.

PATIENTS AND METHODS

The dataset are available at: https://github.com/saromar/SSRI-stroke

Study design

We carried out a nested case-control study using BIFAP[24], a Spanish population-based database containing fully anonymized primary care medical information, including outpatient

prescriptions (Expanded Methods in the Data Supplement). We identified a study cohort of 3,757,621 patients aged between 40 and 99 years without any previous record of cancer or stroke and at least one-year registry with their primary care physician (PCP) over the study period 2001-2015. Once patients fulfilled these criteria, they were followed-up until the occurrence of a stroke (any type), death, 100 years of age or end of the study period, whichever came first.

Selection of cases and controls

We identified all potential stroke cases using specific codes and free text associated with the diagnosis (see Expanded Methods in the Data Supplement for details). For each case, the index date was established as the recorded date of stroke diagnosis. Once the cases were identified, a second validation procedure was carried out to establish the most probable pathophysiological subtype: cardioembolic and non-cardioembolic using the free text associated with the diagnosis. Additionally, records of atrial fibrillation, use of class IC or class III antiarrhythmics, use of oral anticoagulants, or mitral valve prosthesis/stenosis, either before or within three months after the event, were used as supporting information for cardioembolic stroke. All cases with a probable cardioembolic origin were excluded, thus focusing the analysis on non-cardioembolic ischemic events, including both large and small (or lacunar) vessel disease, as both share an arterial wall involvement associated with vascular risk factors. We also excluded from the analysis strokes of unusual origin, such as vasculitis, arterial dissection or cocaine abuse. From the primary cohort, five controls were selected per each case individually matched for exact age, sex, and index date (density sampling). Finally, we excluded prevalent users of antidepressants (those patients with recorded prescriptions of any antidepressant before start date) from both cases and controls, in order to focus on initiators of antidepressants ("new user design")[23].

Exposure definition

Antidepressants were subclassified in 6 subgroups according to their mechanism of action[10,25]: 1)Selective Serotonin Reuptake Inhibitors (SSRIs); 2)Serotonin-norepinephrine reuptake inhibitors (SNRIs); 3)Tricyclic antidepressants (TCAs) with a preferential inhibitory action on the reuptake of serotonin (SER)[26,27]; 4) Serotonin receptor antagonists with serotonin reuptake inhibition (SARIs); 5) Noradrenergic α-2 receptor antagonists with specific serotonergic antagonism (NaSSAs); 6)Antidepressants with a predominant inhibition of the noradrenergic reuptake (AD-NE)[26-27] (see Expanded Methods in the Data Supplement for a detailed description of individual drugs included in each group). Mono-amine-oxydase inhibitors and agometaline were excluded due to their low use. Bupropion was also excluded as it was mostly used for smoking cessation. For some analyses, SNRIs, TCAs-SER, NaSSAs and AD-NE were grouped as NonSSRIs-nonSARIs.

Patients were classified as "current users" when they had recorded prescriptions for the drug(s) of interest and the last one lasted until a time window of 30 days prior to the index date; "recent users" when the last recorded prescription ended between 31 and 365 days prior to the index date; "past users" when the last recorded prescription ended beyond 365 days prior to the index date; and non-users when there were no records of prescriptions for the drug of interest before the index date.

In order to reduce confounding by indication, we took "past users of any antidepressant" as the main category of reference for all antidepressant subgroups. Additionally, we also took "non-users" for comparison with previous studies, and "current users of other antidepressants

different from SSRIs and SARIs" when specifically assessed the association of stroke with SSRIs or SARIs.

Among current users, the duration of treatment was measured as "continuous duration" using only consecutive prescriptions (accepting a maximum of 60-day gap between the end of supply of a previous prescription and the start of the next one). Treatment duration was stratified into two groups, less than or equal to one year and greater than one year.

Potential confounding factors

The following variables were selected as potential confounding factors using expert criteria: 1)number of visits to the PCP in the year prior to the index date (as a general indicator of comorbidity); 2)lifestyle factors: body mass index (BMI), smoking status and alcohol abuse (recorded as such by the PCP); 3)depression (any recorded diagnosis before the index date); 4)comorbidities (any time before the index date): ischemic heart disease (including history of myocardial infarction or angina pectoris, including the use of nitrates as an indicator of angina), heart failure, transient ischemic attack (TIA), peripheral artery disease, hypertension, diabetes (recorded as such and/or use of glucose-lowering drugs), dyslipidemia (recorded as such and/or use of lipid-lowering drugs), chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney failure and hyperuricemia (asymptomatic and gout); and 5)recorded use of the following drugs in the 30 days prior to the index date: antiplatelet drugs, non-steroidal anti-inflammatory drugs, paracetamol, metamizole, opioids, corticosteroids, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium-channel blockers, beta-blockers, alfa-blockers, diuretics, proton pump inhibitors, H2-receptor antagonists, benzodiazepines and antipsychotics.

Statistical analysis

Conditional logistic regression models were built to assess the association between use of different antidepressant subgroups and incident ischemic stroke of non-cardioembolic origin. Adjusted Odds Ratios (AORs) and the corresponding 95% confidence intervals (CI) were calculated by including the main exposure plus the potential confounders described above. We only obtained the AORs when there were at least 5 exposed cases.

We also explored whether there was an interaction with some important variables such as sex, age (stratified as less than 70 years and equal to or greater than 70 years) and background vascular risk. The latter was divided in three categories[28]: 1) Group 1: established vascular disease (high-risk): those with a history of ischemic heart disease (AMI or angina pectoris), TIA, peripheral arterial disease or diabetes (included here because diabetes has been reported to have a risk equivalent to ischemic heart disease[29]); 2) Group 2: one or more vascular risk factors (intermediate-risk): those with a history of hypertension, dyslipidemia, chronic renal failure, current smoking or BMI > 30 kg/m2 (and none of the conditions mentioned in the first point); 3) Group 3: no known vascular risk factor or disease (low-risk). Statistical interaction was evaluated using the Altman and Bland test[30].

We had explicit missing values for BMI (36.0%) and smoking (50.8%). For the rest of variables, we assume that the lack of recording was equivalent to lack of such characteristic. To address such missing values we used the missing-indicator method, as we checked that the distribution of missing values did not vary across main exposure categories[31]. Nonetheless, in a sensitivity analysis we also ran multiple imputation by chained equations models (MICE)[32].

We conducted all analyses using STATA version 15/SE (StataCorp. College Station, Texas. 77845, USA).

Ethical approval

The Research Ethics Committee of the University Hospital Príncipe de Asturias approved the study on 26 January, 2021 and granted a waiver for the informed consent.

RESULTS

We initially identified 14,374 valid cases of ischemic stroke. After excluding 4,780 cases (33.3%) of probable cardioembolic origin and 52 (0.4%) labelled as stroke of other origin, we retained 9,542 cases (66.4%), of non-cardioembolic origin, and randomly sampled 47,710 controls individually matched with cases for sex, age and index date. For the new-user analysis, we further excluded 1,232 cases (12.9%) and 5059 (10.6%) controls who had recorded prescriptions of antidepressants before the start date, as well as 14 (0.1%) cases and 5379 (11.3%) controls who were left unmatched. The final sample was made up of 8,296 cases and 37,272 matched controls (mean ratio 1 to 4.5) (figure 1). The median follow-up time was 3.3 years (range:1.6-6.2) for cases and 2.9 years (range:1.4-5.4) for controls.

The characteristics of cases and controls are shown in table 1. As expected, cases presented a higher prevalence of cardiovascular comorbidities, risk factors and comedication than controls.

Among controls, we examined the prevalence at index date of comorbidities, risk factors and comedication among current users of SSRIs and compared them with non-users, past-users and current users of nonSSRIs-nonSARIs. As postulated, past users and current users of nonSSRIs-nonSARIs were more comparable with current users of SSRIs than non-users (Figure I in the Data Supplement).

There were 255 (3.07%) current users of SSRIs among cases and 834 (2.24%) among controls, yielding a crude OR of 1.43 (95%CI:1.24-1.66) and an AOR of 1.14 (95%CI:0.97-1.34) as compared to non-users, and 0.97 (95%CI:0.81-1.16) and 0.94 (95%CI:0.77-1.13), respectively, as compared to past-users (Table 2). As compared to non-users most antidepressants subgroups showed a statistically significant increased risk (Table 2).

When current users of SSRIs or SARIs were compared to current users of nonSSRIs-nonSARIs, the AORs were 0.74 (95%CI:0.58-0.93) and 0.72 (95%CI:0.49-1.04), respectively (Table 3). In figure 2 we show how the AORs for SSRIs changed when different strategies to control for confounding by indication were employed: adjustment for depression, and change of the reference group (past-users as or current-users of other antidepressants).

The results of duration among current users of different subgroups as compared to past-users are shown in Table I in the Data Supplement. An increased risk can be reasonably excluded for SSRIs either in short or long-term treatments. No trend was observed either with SARIs. Of note, during the first year of treatment we found a significant increased risk associated with TCAs-SER (AOR=1.72;95%CI:1.07-2.77) and a similar trend for SNRIs (AOR=1.46;95%CI:0.96-2.20).

Current use of SSRIs was not associated with an increased risk of non-cardioembolic ischemic stroke in any subgroup of patients when compared to past-users, by sex, age and background vascular risk (figure 3) (see Table II in the Data Supplement for other subgroups).

The association of current users of different individual agents as compared to past users is shown in Table III in the Data Supplement.

The use of MICE models to address missing values of smoking and BMI did not materially change the results of the main analysis (Table IV in the Data Supplement).

DISCUSSION

In this nested case-control study we found that the current use of SSRIs was associated with an increased risk of ischemic stroke of non-cardioembolic origin when they were compared to non-users of antidepressants, but such increased risk disappeared when past users of antidepressants were employed as the comparator and turned into a reduced risk when they were compared with current users of other antidepressants (nonSSRIs-nonSARIs). These results show the importance of confounding by indication that may have affected most studies performed thus far in this area and how the selection of a more comparable group (either previous users or active comparators) can help to circumvent this bias. No increased risk with SSRIs was found in any of the subgroups of patients examined (by sex, age, and background vascular risk), or with short or prolonged durations, which reinforces the safety of these drugs concerning the risk of non-cardioembolic ischemic stroke, even in high-risk populations. The data of other pharmacological subgroups, with the exception of SARIs, are not as reassuring as those of SSRIs: antidepressants with a predominant noradrenergic reuptake inhibition profile could be associated with an increased risk; and TCAs and SNRIs may be associated with an increased risk during the first year of treatment.

Two recent meta-analyses have assessed the association of SSRIs with cerebrovascular events (any stroke) and both concluded that the use of SSRIs as compared to non-use was associated with an increased risk ranging from 1.24 (95%CI:1.15-1.34)[33] to 1.41 (95%CI:1.13-1.69)[34]. In the latter, when the analysis was restricted to patients with depression, a lower but still

significant increased risk was found (RR=1.21; 95%CI:1.02-1.40)[34]. Only Biffi et al[33] provided specific estimates for ischemic stroke including 3 studies and totaling 4,281 cases, being the pooled RR of 1.15 (95%CI:0.98-1.36), but no distinction was made between the two main pathophysiological types of ischemic stroke (cardioembolic vs. non-cardioembolic). Both meta-analyses also provided information for TCAs, with a pooled RR ranging from 1.06 (0.96-1.17) for any cerebrovascular disease (4 studies)[33] to 1.08 (95%CI:0.93-1.22) for any stroke (9 studies)[34]. No specific information was provided for the association of TCAs with ischemic stroke. Further, TCAs were not separated according to the predominant amine whose reuptake is inhibited (serotonin vs norepinephrine). Neither did they provide information for other pharmacological subgroups. Two more recent studies, not included in the meta-analyses, reached different results. Douros et al[7] compared current users of antidepressants depending on their affinity for the 5-HT transporter [27] and found a moderate reduced risk of ischemic stroke (RR=0.88;95%CI:0.80-0.97) associated with the so-called "strong" inhibitors (including duloxetine, fluoxetine, paroxetine and sertraline) as compared to "weak" inhibitors (including mianserin, mirtazapine, nefazodone, reboxetine, agomelatine and viloxazine), while no reduction (RR=0.98; 95%CI:0.92-1.04) was observed when current use of "strong" inhibitors were compared to "intermediate" inhibitors (citalopram, escitalopram, fluvoxamine and venlafaxine). Glymour et al[21], after a careful analysis accounting for depression as time-varying confounder, did not find either an increased risk of stroke with SSRIs (OR=0.98; 95%CI:0.80-1.20), though they did not distinguish between ischemic and hemorrhagic stroke.

In this context, our study have some remarkable novelties: 1)we focused our analysis on non-cardioembolic ischemic stroke in order to maximize the potential preventive effect of SSRIs, as these drugs have been reported to exert a moderate antiplatelet effect[9] and it is expected that on cardioembolic strokes should have a weaker effect, if any; 2)the number of cases included

was much larger than any of the individual studies included in the meta-analysis by Biffi et al[33] and even doubled the overall number of cases of the pooled analysis; only the study by Douros et al[7] (not included in the meta-analysis) was larger than ours (N=15,860), but they did not separate out cardioembolic strokes (supposed to be at least one third of all ischemic stroke cases) and they also included TIAs; 3)we classified antidepressants in different classes based on a more precise mechanism of action[10], which is a more meaningful approach than a classification based on the chemical structure or the "generation" of the antidepressants when we are to assess their respective effects; 4)we compared current users of SSRIs with past users of any antidepressant or with current users of other antidepressants in order to reduce the confounding by indication; 5)we provide estimates for 6 pharmacological classes of antidepressants and 11 individual drugs; and 6)all analyses were performed in new users to avoid a prevalent-user bias.

Overall, our data suggest that SSRIs are not associated with an increased risk of non-cardioembolic ischemic stroke, and as compared to other antidepressants may even be protective. This is not in accordance with most studies published until now, nor with the meta-analyses commented before, but we think that the discrepancy may be explained by methodological issues. Most published studies compared current users of SSRIs with non-users. When we did the same, we found a 21% increased risk (or 14% when depression was included in the model), closer to the estimates provided by the aforementioned meta-analyses[33-34]. On the contrary, when we compared with past users we found an neutral effect, and when compared to other antidepressants (nonSSRIs-nonSARIs), we found a 26% reduced risk, similar to that found by Douros et al[7], who used weak inhibitors of the serotonin reuptake as comparators. Interestingly, Glymour et al[21] estimated in 24% the magnitude of the confounding by indication which is about the excess risk detected in the meta-analyses mentioned above. In

sum, when confounding by indication is properly discounted, a preventive effect of SSRIs is revealed as compared to other antidepressants. We did not observe an increased risk of SSRIs in any subgroup of patients by age, sex or background vascular risk (even in patients at high risk), which suggest that SSRIs are the safest antidepressants in patients at vascular risk and should be the first-choice antidepressants in them.

The results with SARIs (trazodone) deserve a comment. Their main mechanism of action is the antagonism of the 5-HT_{2A} receptor which mediates in platelets the pro-aggregatory effect induced by serotonin. So, it is conceivable that by blocking this receptor, SARIs could present an antiplatelet effect. In our previous study on AMI[10] we observed a remarkable reduced risk associated with the use of SARIs, similar to the one found with SSRIs. In the present study, results did not reach statistical significance and, then, we cannot conclude that the use of SARIs is associated with a reduced risk, but at least an increased risk can be ruled out, which is reassuring taking into account that trazodone is widely used in the elderly at low doses (100 mg or lower) for its hypnotic properties[35], mainly due to the antagonism on H_1 receptors[36].

The increased risk associated with TCA-SER and SNRI during the first year of treatment, should be further studied, as we cannot rule out the possibility of a residual confounding by indication (in case these drugs were more prescribed for severe cases).

The present study has a number of limitations. First, as in any observational study, unknown or unmeasured factors may have caused some residual confounding; this possibility should be less probable in the comparison of SSRIs with past users or current users of other antidepressant; interestingly, in these comparisons the crude analysis gave almost identical results than the full-adjusted analysis. Second, the possibility exists that some ischemic stroke

cases were not captured and that cases considered cardioembolic could be non-cardioembolic and vice versa, though we consider that the likelihood of this misclassification might be low after the extensive validation carried out; at any rate, as researchers who performed the case validation were blinded to drug exposure, such potential misclassification of cases should have been non-differential with respect to the exposure; it is well-known that a non-differential misclassification of the event would tend the measure of association towards the null[37], and then it cannot be argued as an explanation of the protective results found with SSRIs as compared to other antidepressants. Third, we did not distinguish between large and small vessel disease among non-cardioembolic strokes; although this can be considered a limitation, we should bear in mind that both share an arterial wall involvement associated with risk factors and both benefit from antiplatelet therapy as secondary prevention; thus, the expected effect of SSRIs on them should be similar. Fourth, though all prescriptions are filled through the computer and then completely recorded, treatment adherence by patients cannot be assured. Fifth, as multiple comparisons were made, the possibility exists that some results may be explained by chance.

SUMMARY

Many studies in the past have reported an increased risk of ischemic stroke associated with the use of SSRIs. According to our results this positive association can be explained by several methodological factors, in particular the confounding provoked by the indication itself. When this bias is properly controlled for using an active comparator group (other antidepressants), SSRIs are shown to be protective.

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DISCLOSURES

FdA has received unrestricted research grants from Sanofi-Pasteur for a research project different from this one.

SUPLEMENTAL MATERIALS

Expanded Methods

Online Tables I-IV

Online Figure I

Data Set

References 10, 24-27

STROBE checklist

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FIGURE LEGENDS

Figure 1. Flow chart of patient selection.

Abbreviations: PCPs: primary care physicians.

Figure 2: Risk of non-cardioembolic ischemic stroke origin associated with the use of SSRIs as compared to: 1)non-users of antidepressants without adjustment for depression, 2)non-users of antidepressants with adjustment for depression, 3)past users of antidepressants, and 4)current users of NonSSRIs-nonSARIs.

Abbreviations: AOR: Adjusted odds ratio, CI: Confidence Interval; SARIs: Serotonin receptor Antagonists with serotonin Reuptake Inhibition, SSRIs: Selective Serotonin Recapture Inhibitors

Figure 3: Risk of non-cardioembolic ischemic stroke associated with the current use of SSRIs as compared to past use of any antidepressant and current use of nonSSRIs-nonSARIs, by sex, age and background vascular risk.

Abbreviations: AOR: Adjusted odds ratio; CI: Confidence Interval; SARIs: Serotonin receptor Antagonists with serotonin Reuptake Inhibition; SSRIs: Selective Serotonin Recapture Inhibitors.

Table 1. Characteristics of cases and controls.

	Cases(%) N=8296	Controls(%) N=37272	Non-adjusted OR* (95%CI)
Age; mean(±SD)	73.5(±12.8)	73.2(±12.8)	-
Men	4628(55.79)	21801(58.49)	-
Visits (last 12 months)			
Up to 5	1775(21.40)	11624(31.19)	1(Ref.)
6-15	3305(39.84)	14199(38.10)	1.59(1.49-1.69)
16-24	1826(22.01)	6429(17.25)	1.99(1.85-2.15)
25+	1390(16.76)	5020(13.47)	1.98(1.82-2.15)
BMI kg/m^2			
Up to 24.9	1121(13.51)	4907(13.17)	1(Ref.)
25-29	2438(29.39)	10853(29.12)	1.00(0.92-1.08)
30-34	1447(17.44)	6131(16.45)	1.05(0.96-1.14)
35-39	422(5.09)	1586(4.26)	1.16(1.02-1.32)
40+	110(1.33)	388(1.04)	1.22(0.97-1.52)
Unknown	2758(33.24)	13407(35.97)	0.91(0.84-0.98)
Smoking			
Never smoking	2513(30.29)	11553(31.00)	1(Ref.)
Current smoker	1517(18.29)	4685(12.57)	1.66(1.54-1.80)
Past smoker	538(6.49)	2107(5.65)	1.29(1.16-1.44)
Unknown	3728(44.94)	18927(50.78)	0.92(0.87-0.98)
Alcohol abuse	255(3.07)	620(1.66)	1.98(1.70-2.30)
Ischemic heart disease			

AMI	416(5.01)	1379(3.70)	1.46(1.30-1.63)
Angor pectoris[†]	624(7.52)	2276(6.11)	1.28(1.16-1.40)
Heart failure	348(4.19)	1499(4.02)	1.02(0.90-1.15)
TIA	397(4.79)	770(2.07)	2.38(2.10-2.70)
PAD	400(4.82)	920(2.47)	2.05(1.82-2.32)
Hypertension	5014(60.44)	18865(50.61)	1.53(1.45-1.61)
Diabetes[‡]	2476(29.85)	6959(18.67)	1.89(1.79-2.00)
Dyslipidemia[§]	3535(42.61)	14241(38.21)	1.21(1.15-1.27)
COPD	700(8.44)	2715(7.28)	1.21(1.11-1.33)
Rheumatoid arthritis	62(0.75)	290(0.78)	0.93(0.70-1.22)
Chronic kidney failure	433(5.22)	1326(3.56)	1.49(1.33-1.67)
Hyperuricemia			
Asymptomatic	602(7.26)	2761(7.41)	1.00(0.91-1.09)
Gout	396(4.77)	1568(4.21)	1.18(1.06-1.33)
Current use of			
Antiplatelet drugs	2136(25.75)	5817(15.61)	2.08(1.96-2.21)
Paracetamol	1263(15.22)	5686(15.26)	1.06(0.98-1.14)
Metamizole	376(4.53)	1308(3.51)	1.38(1.23-1.56)
NSAIDs	787(9.49)	3445(9.24)	1.08(0.99-1.18)
Opioids	345(4.16)	1339(3.59)	1.18(1.04-1.33)
Corticosteroids	175(2.11)	623(1.67)	1.28(1.08-1.51)
ACEIs	1639(19.76)	6414(17.21)	1.28(1.20-1.36)
ARBs	1377(16.60)	5374(14.42)	1.22(1.14-1.31)
CCBs	1196(14.42)	4364(11.71)	1.34(1.25-1.44)

Beta-Blockers	846(10.20)	3213(8.62)	1.24(1.14-1.34)
Alfa-Blockers	212(2.56)	801(2.15)	1.24(1.06-1.44)
Diuretics	1087(13.10)	4548(12.20)	1.13(1.05-1.22)
PPIs	2393(28.85)	9135(24.51)	1.32(1.24-1.40)
H_2-receptor antagonists	199(2.40)	600(1.61)	1.51(1.28-1.78)
Benzodiazepines	1373(16.55)	5600(15.02)	1.14(1.06-1.22)
Antipsychotics	319(3.85)	742(1.99)	2.02(1.77-2.32)

Abbreviations: ACEIs: Angiotensin Converting Enzyme Inhibitors; AMI: Acute Myocardial Infarction; ARBs: Angiotensin II-Receptor Blockers; BMI: Body Max Index; CCBs: Calcium-channel blockers; CI: Confidence Interval; COPD: chronic obstructive pulmonary disease; NSAIDs: Non-steroidal Anti-inflammatory Drugs; OR: Odds ratio; PAD: Peripheral Artery Disease; PPI: Proton-pump inhibitors; SD: Standard Deviation; TIA: Transient Ischemic Attack.

*Adjusted only for matching factors (age, sex, and calendar year).

†Recorded as such, and/or when patients were using nitrates.

‡Recorded as such, and/or when patients were using glucose-lowering drugs.

§Recorded as such, and/or when patients were using lipid-lowering drugs.

Table 2. Risk of non-cardioembolic ischemic stroke associated with the current use of different antidepressant subgroups as compared to: non-users or past users.

	Cases(%) N=8296	**Controls(%) N=37272**	***As compared to non-users***		***As compared to past users***	
			Non-adjusted OR[*] (95%CI)	**Adjusted OR[†] (95%CI)**	**Non-adjusted OR[*] (95%CI)**	**Adjusted OR[†] (95%CI)**
Non users	7157(86.27)	33828(90.76)	1(Ref.)	1(Ref.)	0.68 (0.60-0.76)	0.82 (0.72-0.94)
Current users of						
Any antidepressant	529(6.38)	1521(4.08)	1.62(1.46-1.80)	1.28(1.13-1.45)	1.10(0.94-1.28)	1.05(0.89-1.24)
SSRIs	255(3.07)	834(2.24)	1.43(1.24-1.66)	1.14(0.97-1.34)	0.97(0.81-1.16)	0.94(0.77-1.13)
SNRIs	62(0.75)	151(0.41)	1.93(1.43-2.61)	1.47(1.07-2.02)	1.30(0.95-1.80)	1.21(0.87-1.68)
TCAs-SER	41(0.49)	92(0.25)	2.09(1.45-3.03)	1.74(1.18-2.57)	1.41(0.96-2.08)	1.43(0.96-2.14)
SARIs	57(0.69)	163(0.44)	1.61(1.19-2.19)	1.11(0.80-1.53)	1.09(0.79-1.51)	0.91(0.65-1.29)
NASSAs	58(0.70)	164(0.44)	1.63(1.21-2.21)	1.45(1.05-1.99)	1.10(0.80-1.52)	1.19(0.85-1.66)
AD-NE	5(0.06)	4(0.01)	5.28(1.40-19.87)	3.64(0.94-14.10)	3.56(0.94-13.49)	2.99(0.77-11.65)
Concomitant use	51(0.61)	113(0.30)	2.11(1.51-2.95)	1.63(1.14-2.34)	1.43(1.00-2.03)	1.34(0.93-1.95)
- *Including SSRIs/SARIs*	42(0.51)	94(0.25)	2.10(1.45-3.03)	1.66(1.12-2.45)	1.42(0.96-2.08)	1.36(0.91-2.04)

- *Other combinations*	9(0.11)	19(0.05)	2.19(0.98-4.88)	1.53(0.68-3.46)	1.48(0.66-3.32)	1.26(0.55-2.86)
Recent users	232(2.80)	729(1.96)	1.50(1.29-1.74)	1.23(1.04-1.45)	1.01(0.84-1.22)	1.01(0.83-1.23)
Past users	378(4.56)	1194(3.20)	1.48(1.31-.167)	1.22(1.06-1.39)	1(Ref.)	1(Ref.)

Abbreviations: AD-NE: Antidepressants with a predominant noradrenergic re-uptake inhibition; CI: Confidence Interval; NASSAs: Noradrenergic α-2 receptor antagonists with Specific Serotonergic antagonism; OR: Odds ratio; SARIs: Serotonin receptor Antagonists with serotonin Reuptake Inhibition; SSRIs: Selective Serotonin Recapture Inhibitors; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; TCAs-SER: Tricyclic Antidepressants with a preferential inhibitory action on the reuptake of Serotonin.

*Adjusted only for matching factors (age, sex, and calendar year).

†Adjusted for matching factors (age, sex, and calendar year) plus all variables shown in table 1.

Table 3. Risk of non-cardioembolic ischemic stroke associated with the current use of SSRIs or SARIs as compared to current use of nonSSRIs-nonSARIs.

	Cases(%) N=8296	Controls(%) N=37272	Non-adjusted OR* (95%CI)	Adjusted OR† (95%CI)
Non users	7157(86.27)	33828(90.76)	0.53(0.44-0.63)	0.65(0.53-0.79)
Current use of:				
NonSSRIs-nonSARIs	175(2.11)	430(1.15)	1(Ref.)	1(Ref.)
SSRIs	255(3.07)	834(2.24)	0.76(0.60-0.95)	0.74(0.58-0.93)
SARIs	57(0.69)	163(0.44)	0.85(0.60-1.21)	0.72(0.49-1.04)
SARIs+SSRIs	10(0.12)	27(0.07)	0.92(0.44-1.96)	0.77(0.35-1.69)
SSRIs with others	26(0.31)	56(0.15)	1.13(0.68-1.86)	1.18(0.70-2.00)
SARIs with others	6(0.07)	11(0.03)	1.47(0.53-4.14)	1.36(0.47-3.96)
Recent users	232(2.80)	729(1.96)	0.79(0.63-1.00)	0.80(0.63-1.01)
Past users	378(4.56)	1194(3.20)	0.78(0.63-0.97)	0.79 (0.63-0.98)

Abbreviations: AD-NE: Antidepressants with a predominant noradrenergic re-uptake inhibition; CI: Confidence Interval; NASSAs: Noradrenergic α-2 receptor antagonists with Specific Serotonergic antagonism; OR: Odds ratio; SARIs: Serotonin receptor Antagonists with serotonin Reuptake Inhibition; SSRIs: Selective Serotonin Recapture Inhibitors; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; TCAs-SER: Tricyclic Antidepressants with a preferential inhibitory action on the reuptake of Serotonin.

*Adjusted only for matching factors (age, sex, and calendar year).

†Adjusted for matching factors (age, sex, and calendar year) plus all variables shown in table 1.