Antidepressants and the risk of hemorrhagic stroke in the elderly: A nested case-control study

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Abstract

Background and Purpose: Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed in the elderly due to a more favorable risk profile than other antidepressants (ADs). However, SSRIs are associated with an increased risk of gastro-intestinal bleeding, while evidence on the risk of hemorrhagic stroke (HS) is limited. Therefore, we compared the risk of HS associated with use of ADs in the elderly.

Methods: Based on data from the German Pharmacoepidemiological Research Database (GePaRD), a case-control study matched on age, sex, and health insurance provider, nested in a cohort of incident users of ADs ≥ 65 years was performed. Cases were identified from hospital discharge diagnoses. Exposure was identified from outpatient prescriptions. Multivariable conditional logistic regression was used to estimate adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Based on 4,059 cases and 40,590 controls, an increased risk of HS was found in current use of SSRIs (OR 1.39; 95% CI 1.22–1.58), selective serotonin and noradrenaline reuptake inhibitors (1.69; 1.35–2.11), noradrenergic and specific serotonergic antidepressants (1.44; 1.22–1.69), and of noradrenaline reuptake inhibitors (3.81; 1.54–9.43) compared to tri- and tetracyclic antidepressants. An increased risk of HS was seen in patients with a high baseline risk of bleeding and in patients with depression. The risk of HS varied between individual ADs.

Conclusion: Our study shows that use of medication inhibiting serotonin and/or noradrenaline reuptake increases the risk of HS in patients aged 65 years and older and that the risk varies across individual ADs.

Key Points

- Risk for hemorrhagic stroke is increased in elderly users of selective serotonin reuptake inhibitors, selective serotonin and noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants and noradrenaline reuptake inhibitors compared to tri- and tetracyclic antidepressants and varies across individual antidepressants
- Risk is higher in patients with depression and a higher baseline risk of bleeding, but for some AD classes, risks are also elevated in patients with a low baseline risk of bleeding.

1. INTRODUCTION

In patients aged 65 years or older, antidepressants (ADs), especially tri- and tetracyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), are frequently prescribed for the treatment of depressive disorders [1]. SSRIs are usually preferred to TCAs due to a more favorable risk profile in the treatment of the elderly [2, 3]. However, over the past two decades, studies have shown that the use of SSRIs is associated with an increased risk of gastro-intestinal and other bleeding events [4-6]. One of the most serious bleeding events is hemorrhagic stroke (HS), which has a high fatality, especially within the first 30 days after diagnosis [7, 8]. Depending on the damage caused to the brain, patients might never fully recover, leading to disability and associated high costs and loss of quality of life [9].

Several studies examined the risk of HS [10-12] or intracranial hemorrhage [13-16] associated with the use of SSRIs. However, Douros et al. showed in their systematic review that most of these studies suffered from methodological problems (e.g., inclusion of prevalent users rather than incident users) or lack of power [17]. They summarized that no firm conclusions could be drawn based on the existing studies and that further research was needed [17], although some studies indicate an increased risk of HS associated with the use of ADs [16, 12, 18, 19]. We addressed the methodological issues by performing a case-control analysis in a cohort of more than 700,000 incident AD users and selecting TCAs as active comparator and focused on older patients. The aim of the study was to compare the risk of HS between different classes of AD as well as between individual agents.

2. MATERIALS AND METHODS

2.1. Data Source

This study is based on data from the German Pharmacoepidemiological Research Database (GePaRD). GePaRD is based on claims data from four statutory health insurance providers

(SHIs) in Germany and currently includes information on more than 20 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on all reimbursable outpatient drug dispensations and all reimbursable outpatient (i.e., from general practitioners and specialists) and inpatient diagnoses and services. Diagnoses are coded according to the International Classification of Diseases, 10th revision, German modification (ICD-10 GM). Per data year, there is information on approximately 17% of the general population and all geographical regions of Germany are represented. Methodological assessment and validation studies have shown the applicability of GePaRD for pharmacoepidemiological research and GePaRD has been used for various pharmacoepidemiological studies [20-22].

2.2. Study Design and Setting

The study was conducted as a case-control study nested in a population-based cohort of incident AD users between January 1st, 2005 and December 31st, 2011. An incident user design was selected to avoid bias related to the depletion of susceptibles and under-ascertainment of early adverse effects [23]. To enter the cohort, patients had to (i) be aged 65 years or older, (ii) be insured continuously for at least 365 days before cohort entry, and (iii) to receive their first outpatient AD prescription after 365 days without a prescription for an AD. Patients with a history of HS were not excluded. Cohort entry was the first day all criteria were fulfilled. Cohort exit was defined as (i) interruption of the insurance status for more than three days or end of insurance including death, (ii) end of the study period or (iii) the occurrence of HS, whichever came first.

2.3. Case Definition and Control Selection

Cases of HS were identified by main hospital discharge diagnoses indicating subarachnoid bleeding, intracerebral bleeding or non-traumatic intracranial bleeding not coded as epidural

or subdural (ICD-10 GM codes I60, I61, and I62.9). In sensitivity analyses, two more specific case definitions were used excluding (i) cases without imaging procedures performed two days before to two days after the index day or (ii) cases with an acute traumatic brain injury (ICD-10 GM S06) in the 30 days before the index day. In the second sensitivity analysis, we also excluded controls with an acute traumatic brain injury in the 30 days before the index day.

The index day was set to the admission date of the respective hospitalization. Up to ten controls were matched to each case by sex, year of birth (+/- 1 year), and SHI using risk set sampling with time in cohort as the time axis. The date resulting in the same time of follow-up as for the respective case was designated as the index date of the control. Eligible patients hospitalized for any reason at the index date of the case were not at risk of being hospitalized for HS and thus excluded from the set of potential controls. Cases were eligible to be selected as a control before their index day and controls could be selected more than once [24].

2.4. Exposure Definition

Dispensations of ADs were identified through the Anatomical Therapeutic Chemic Classification System (ATC) code N06A and classified regarding to their proposed mode of action: TCAs, SSRIs, monoamine oxidase inhibitors (MAOs), selective serotonin noradrenalin reuptake inhibitors (SSNRIs), noradrenalin reuptake inhibitors (NARIs), noradrenergic and specific serotonergic antidepressant (NaSSAs), Hypericum St. John's wort and homeopathic ADs (Herbal), and other ADs (other). As in previous studies [22, 25], supply was estimated as the amount of defined daily doses (DDDs) of the dispensation plus an additional 150% of the DDD to account for lower dosage and lack of compliance in the elderly [26, 27]. In sensitivity analyses supply was estimated as (i) number of DDDs and (ii) four times the number of DDDs (= adding 300% of the DDDs). Taking into consideration the long half-life of several ADs, the end of the exposure period was defined as the end of supply plus 30 days carry-over-

period. Based on the period between the end of the exposure period of the last dispensation and the index day, exposure status was defined as (i) current if the exposure period overlapped index day, (ii) recent if the exposure period ended 1 to 30 days before index day, and (iii) past if the exposure period ended more than 30 days before index day. Current users of two or more ADs of different classes (class-level analysis) or of individual agents (agent-level analysis) were assigned to the separate category multiple use.

2.5. Assessment of Potential Confounders

Comorbidities including risk factors for HS were obtained from in- and outpatient diagnoses in the 365 days before cohort entry. History of medication serving as a proxy for severity of disease and overall health status was retrieved from outpatient drug dispensation data in the 365 days before cohort entry. Additionally, use of potential confounding drugs was assessed by searching for dispensations of the respective drugs with supplies overlapping the index day.

To identify patients with a high risk of bleeding and to assess possible effect modification by the baseline bleeding risk, the HAS-BLED-score by Pisters et al. [28] was calculated using patient information at cohort entry. Information on the international normalized ratio is not available in GePaRD and was therefore not used for the calculation.

2.6. Statistical Analysis

Conditional logistic regression was used to estimate matched and adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs), comparing current, recent, and past use of AD classes to current use of TCAs and current use of individual agents to current use of amitriptyline. TCAs and amitriptyline were chosen as reference, as they have not been associated with bleeding events thus far and represented the most frequently prescribed ADs in the underlying cohort [29].

Risk factors of HS as well as co-morbidities, co-medications, indicators of life-style habits and indicators of overall health status were taken into account as potential confounders. Pre-defined confounders e.g. a history of HS, congestive heart failure, use of antiarrhythmic drugs or antihypertensive drugs at baseline were always included in the model. A backward selection procedure (Wald test p-value < .05 for staying in the model) was used to select further relevant covariates. In a sensitivity analysis, a full model, including all potential confounders, was calculated. Additionally, stratified analyses were performed for HAS-BLED score ≥ 3 (yes/no), diagnosis of depression (yes/no), and diagnosis of depression but no diagnosis of cancer or pain (yes/no). All statistical analyses were conducted using SAS 9.3.

3. RESULTS

Overall, 714,444 incident AD users were included. During the study period, 4,059 cases of HS were observed. The mean time between cohort entry and onset of stroke was 832 days (SD: 648). The overall incidence rate (IR) of HS in the cohort was 1.7 (CI 1.6–1.7) per 1,000 person-years (PYs), with the highest (unadjusted) IR seen in patients starting use of an SSRI (2.3, 2.2–2.4) and the lowest in patients starting use of a TCA (1.5, 1.4–1.5).

All 4,059 cases could be matched to 10 controls. About two thirds (67.5%) of the cases were female and the median age was 78 years (25%–75% quantile 73–83 years). Overall, risk factors of HS and other comorbidity were a bit more frequent in cases, while use of drugs other than ADs at index day was more frequent in controls (see Table 1).

Compared to current TCA use, an elevated risk for HS was seen for current use of SSRIs (adjusted OR 1.39; 95% CI 1.22–1.58), SSNRIs (1.69; 1.35–2.11), NaSSAs (1.44; 1.22–1.69), and NARIs (3.81; 1.54–9.43), whereas a lower risk was seen in current use of MAO (0.55; 0.28–1.05, see Table 2). The ORs were similar when the more specific case definitions were applied, considering only cases with imaging procedures for diagnosis (sensitivity analysis 1)

or only cases (and controls) without traumatic brain injury in the 30 days before index day (sensitivity analysis 2; for both analyses see Table 3).

For SSRIs, SSNRIs, NaSSAs and NARIs, an increased risk of HS compared to TCA use was seen in current users with a high baseline risk of bleeding, i.e., a HAS-BLED score value of 3 or more (see Electronic Supplement 1). An increased risk of HS was also observed in current users of SSRIs, SSNRIs, NaSSAs and NARIs with a low baseline risk of bleeding.

In patients with depression, an increased risk of HS was seen for current use of SSRIs, SSNRIs, NaSSAs and NARIs compared to TCAs (see Electronic Supplement 2). By restricting the analysis further to patients with a diagnosis of depression but no diagnosis of cancer or pain, an increased risk was observed for SSRIs, SSNRIs, NARIs and NaSSA.

The estimated effects were robust to changes of the definition of supply in all AD classes presented, except for NARIs where the estimate was smaller when the supply was estimated as the numbers of DDDs only. Results of these sensitivity analyses are shown in Electronic Supplement 3.

Compared to current use of amitriptyline, a higher risk for HS was seen in current use of the TCAs amitriptylinoxide (OR 2.55, 95% CI 1.36–4.77), clomipramine (1.88, 0.93–3.79), maprotiline (3.23, 1.75–6.00), and nortriptyline (3.46, 1.66–7.24), the SSRIs escitalopram (2.12, 1.49–3.01) and citalopram (1.30; 1.07-1.57), the SSNRI venlafaxine (2.17, 1.59–2.95), the NaSSA mirtazapine (1.24, 1.01–1.52), and the NARI reboxetine (3.07, 1.21–7.77). Lower risks of HS were seen for current use of the TCAs doxepine (0.62, 0.49–0.79) and trimipramine (0.50, 0.37–0.67), the SSRI paroxetine (0.71, 0.49–1.04), and the MAO moclobemide (0.46, 0.21–1.00). Figure 1 shows the risk of HS in current use of individual antidepressants compared to amitriptyline.

4. DISCUSSION

In this large population-based study including more than 700,000 incident elderly users of ADs, we showed that current use of SSRIs (1.39; 1.22–1.58), SSNRIs (1.69; 1.35–2.11), NaSSAs (1.44; 1.22–1.69), and NARIs (3.81; 1.54–9.43), i.e., ADs inhibiting serotonin and/or noradrenaline reuptake, was associated with an increased risk of HS compared to current use of TCAs. Further investigations revealed that the risk varied across individual ADs. Taking into account a wide range of co-morbidities, use of co-medications, and other potential confounding factors the highest risk estimate was seen for the TCA amitriptylinoxide and the NARI reboxetine, but also the widely used TCAs clomipramine, nortriptyline, and maprotiline and the SSRI escitalopram were associated with a two-fold higher risk of HS. Despite the observed increases in risk, HS remains a rare event with 4,059 cases among 714,444 new users of ADs (0.57%) and IRs ranging between 1.5 and 2.3 per 1,000 PYs. It also still remains a less frequent event than e.g. gastro-intestinal bleedings [18].

The results are in line with Renoux et al. who observed in the general adult population a relative risk of intracranial hemorrhage of 1.17 for SSRIs compared to TCAs [16], the systematic review by Douros et al. also focusing on the general adult population [17] and Lee at al. [30] who observed a hazard ratio of 1.17 for SSNRIs compared to SSRIs. Comparison to other studies is hampered by the inclusion of prevalent users [13, 31, 18] and other methodological problems [17]. Regarding individual agents, we identified only one study that investigated the risk of stroke in the elderly. However, as the authors of that study were not able to distinguish between ischemic and hemorrhagic stroke, leading to the possibility that the majority of identified cases of stroke were ischemic and not hemorrhagic, comparison is difficult [32].

As in all observational studies confounding by indication is of concern, especially as ADs are not only used for the treatment of depression but also for other indications such as (cancer related or neuropathic) pain [33]. Additionally, indications may overlap, for example sleep

disturbances are commonly associated with depression in the elderly. To account for different indications and resulting possible differences in dosage, we adjusted for depression as well as potential other indications. Furthermore, we examined the risk of HS in more homogeneous group of patients with a diagnosis of depression and the even further restricted group of patients with depression but no diagnosis of pain or cancer. In these analyses the estimated effects were larger for SSRIs, SSNRIs and NaSSA, indicating that the higher risks seen for these AD classes cannot only be explained by confounding by indication. However, the risks were smaller for NARI, suggesting some confounding by indication for this drug class.

Even though we have seen a lower risk of HS for the MAO tramylcypromine and for MAO overall compared to amitriptyline/TCA use, these effects are most likely due to the selected population of MAO users. MAOs are contraindicated in patients with cardiovascular diseases in general and specifically in patients with atrial hypertension. Additionally, dietary restrictions apply to avoid a critical increase in blood pressure which can occur under use of MAOs when patients consume tyramine-containing foods (e.g., cheddar cheese) [34, 35].

The results presented for the individual agents seem to be at odds with the main analysis but can be explained by the weight the individual agents have in the class of TCAs and SSRIs. Out of 9,136 cases and controls using TCAs at index day, 75 used amitriptylinoxide, 101 used clomipramine, 61 used imipramine, 140 used maprotiline and 45 used nortriptyline compared to 2,769 users of amitriptyline. In the 6,009 users of SSRIs, 345 used fluoxetine, 70 used fluvoxamine and 671 used paroxetine. This indicates that the effect seen for SSRIs in the main analysis was mainly driven by citalopram (3,551 patients) and escitalopram (547 patients). As confounding by indication or severity is potentially more problematic in analyses comparing individual agents, the differences between individual drugs with small numbers of users must be interpreted with caution.

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The higher risks of HS for ADs inhibiting the reuptake of serotonin are to be expected, as serotonin is an agent influencing the coagulation process and lack of serotonin or at least a lower level of serotonin in the platelets prolongs coagulation time [36]. Differences in the risk of HS or other bleeding events might be explained by differences in the strength of serotonin reuptake inhibition. However, even within the group of ADs with a high degree of serotonin reuptake inhibition (in this study: clomipramine, fluoxetine, paroxetine, sertraline and duloxetine) a high variability in the risk of bleeding events was observed [6]. Additionally, Renoux et al. [16] reported relatively small effects of 1.25 (1.01-1.54) for the group of strong inhibitors vs. weak inhibitors and 1.13 (0.93-1.37) for intermediate inhibitors vs. weak inhibitors. These results might be partly explained by confounding by indication or severity, but at least indicate that the degree of serotonin reuptake inhibition does not seem to be the only explaining factor for an increased risk of HS in use of ADs.

Regarding exposure assessment, advantages of claims data are that patients had to receive the drug and pay the co-payment, that information on AD exposure is precise in terms of dispensing date and drug product and that recall bias can be ruled out. Contrariwise, information on the treatment pattern, actual dosage, and on adherence to therapy is not available and the duration of supply had to be estimated. Therefore, misclassification of exposure may have occurred. Further, adding 150% of the supply to the DDDs to account for low dose and compliance plus another 30 days to account for the long half-life of some of the ADs might be an overestimation of exposed time. However, the observed risks of HS did not change in the sensitivity analyses regarding the definition of supply and reflecting different assumptions on dose taken and overall adherence, indicating that is not likely that misclassification of exposure had a considerable impact on the results.

Misclassification of the outcome was probably not am important issue in our study. In Germany, hospital main discharge diagnoses are considered to have high validity since they are

based on all information relevant to diagnosis (including laboratory tests and imaging results) during the in-hospital stay and are subject to regular inspection. Nevertheless, we performed two sensitivity analyses excluding (i) patients without an imaging within two days of the index day and (ii) patients with a traumatic brain injury 30 days before the HS, which both yielded similar results as the main analysis, indicating that the effect of outcome misclassification on the results seems to be negligible. This is in line with a sensitivity analysis using imaging procedures in a previous GePaRD-based study on subarachnoid bleedings in antithrombotic users, where excluding patients without imaging procedures did not change the results either, supporting the validity of discharge diagnoses [37]. Please note that patients who were excluded in the sensitivity analyses might have had an imaging procedure that was not coded or performed outside of the time window of ±2 days.

Even though adjustment for potentially confounding concomitant use of drugs such as antithrombotic drugs was performed, under-adjustment for these drugs might have occurred as concomitant use was defined as a supply which overlapped the index day. It might, however, have been the case that this window was too strict.

Due to the nature of the database, information on lifestyle factors like smoking, exercising, and diet, which are potential confounding factors for the occurrence of HS [38-40] are not included. Further, as GePaRD only holds information on medication reimbursed by the SHIs, information on the use of over-the-counter medication like non-steroid anti-inflammatory drugs and acetylic-salicylic acid is missing. However, both lifestyle factors and use of over-the-counter medication are associated with several diagnoses and use of prescription drugs. By adjusting for a variety of covariates including these diagnoses and drugs, the results were indirectly also adjusted — at least in part — for the underlying lifestyle factors and use of over-the-counter medication.

A major strength of this study is its design, which addresses the methodological issues discussed by Douros et al. We nested our case-control analysis in a cohort of more than 700,000 incident users of ADs and thus avoided biases caused by the depletion of susceptibles and time-dependent hazard functions [23]. Further, we chose an active comparator design and adjusted for many potential confounders and potential indications in the multivariable analysis to minimize confounding by indication. The large sample size of 4,059 cases and 40,590 controls allowed us to investigate potential effect modification by the baseline bleeding risk and depression and to assess the risk of HS for individual agents.

5. CONCLUSION

In summary, our study shows that use of medication inhibiting serotonin and/or noradrenaline reuptake increases the risk of HS in patients aged 65 years and older and that the risk varies across individual ADs. HS remains a rare event, but physicians should carefully weigh benefits and risks when prescribing AD to the elderly.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

Wiebke Schäfer, Bianca Kollhorst, and Tania Schink are working at the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The studies and the resulting publications are not influenced by the pharmaceutical industry.

Christina Princk currently works at the Governmental Institute of Public Health of Lower Saxony, Hanover, Germany, and has no conflicts of interest that are directly relevant to the content of this study.

Ethical approval

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved SHIs, the German Federal (Social) Insurance and the Senator for Science, Health and Consumer Protection in Bremen as their responsible authorities approved the use of the data for this study. Informed consent for studies based on GePaRD is not required by law and according to the Ethics Committee of the University of Bremen these studies are exempt from institutional review board review.

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450 # TABLES

451 **Table 1.** Characteristics of cases with hemorrhagic stroke and matched controls

	Cases (n=4,059)	Controls (n=40,590)	Adjusted OR* (95% CI†)
Female	2,738 (67.5%)	27,380 (67.5%)	
Median age at index date (Q1–Q3)	78 (73–83)	78 (73–83)	
History of			
Depression‡	2,224 (54.8%)	21,392 (52.7%)	1.19 (1.10–1.29)
Intracerebral, intracranial or sub-arachnoid bleeding‡	456 (11.2%)	538 (1.3%)	5.02 (34.22–5.97)
Gastrointestinal bleedings‡	81 (2.0%)	535 (1.3%)	2.22 (1.66–2.97)
Congestive heart failure‡	941 (23.2%)	7,637 (18.8%)	1.23 (1.11–1.36)
Hypertension‡	3,207 (79.0%)	31,232 (76.9%)	0.95 (0.86–1.04)
Ischemic stroke and transient ischemic attack (TIA)‡	1,011 (24.9%)	4,449 (11.0%)	1.80 (1.61–2.01)
Myocardial infarction‡	234 (5.8%)	2,808 (6.9%)	0.90 (0.76–1.08)
Coronary heart disease‡	1,347 (33.2%)	13,311 (32.8%)	1.11 (1.01–1.22)
Vascular diseases‡, [1]	1,373 (33.8%)	11,520 (28.4%)	1.34 (1.23–1.47)
Cancer	867 (21.4%)	8,312 (20.5%)	0.84 (0.76-0.92)
Pain	2,126 (52.4%)	21,847 (53.8%)	1.41 (1.31–1.53)
Dementia	1,159 (28.5%)	6,610 (16.3%)	1.24 (1.08–1.42)
Cardiac arrhythmia	1,347 (33.2%)	12,262 (30.2%)	1.26 (1.16–1.37)
Epilepsy	1,387 (34.2%)	10,338 (25.5%)	1.92 (1.76-2.09)
Other neurological disorders[2]	380 (9.4%)	1,196 (2.9%)	1.51 (1.27–1.78)
Parkinson's disease and movement disorders	1,201 (25.6%)	10,589 (26.1%)	1.14 (1.04-1.25)
Renal diseases	710 (17.5%)	6,009 (14.8%)	--§

COPD	948 (23.4%)	10,799 (26.2%)	0.91 (0.83–1.00)
Diabetes	1,277 (31.5%)	10,954 (27.0%)	1.20 (1.11–1.31)
Obesity	527 (13.0%)	6,161 (15.2%)	--§
Signs for malnutrition (fluid and electrolyte deficit and deficiency anemia)	722 (19.0%)	4,875 (12.01%)	1.21 (1.08–1.35)
Drug use at baseline			
Angiotensin II receptor blockers	1,071 (26.4%)	10,339 (25.5%)	--§
Calcium channel inhibitors	1,967 (51.5%)	16,629 (41.0%)	1.54 (1.41–1.67)
Diuretics	1,373 (33.8%)	13,488 (33.2%)	--§
Vasodilators	976 (24.1%)	11,168 (27.5%)	--§
Other antihypertensive drugs[3]	2,484 (61.2%)	23,588 (58.1%)	--§
Glucocorticosteroids	1,098 (27.1%)	13,164 (32.4%)	1.25 (1.14–1.36)
Antidementive drugs	683 (16.8%)	3,539 (8.7%)	1.68 (1.43–1.96)
Drug use at index date			
Acetylic-salicylic acid‡, 4	28 (0.7%)	1,153 (2.8%)	0.25 (0.15–0.40)
Antithrombotic agents‡, 5	1,106 (27.2%)	20,460 (50.4%)	0.33 (0.30–0.36)
Non-steroidal anti-inflammatory drugs‡	438 (10.8%)	24,712 (60.9%)	0.06 (0.06–0.07)

*OR: Odds Ratio; †CI: Confidence Interval; ‡ a priori variable, always included into the model; § variable removed by backward selection; [1] defined as peripheral vascular disease, stenosis of the carotid artery, venous thromboembolism and valvular diseases; [2]includes Huntington's disease (G10), hereditary ataxia (G11), spinal muscular atrophy (G12), systemic atrophies (G13), postpolio syndrome (G14), drug-induced chorea (G25.4), other chorea (G25.5), degeneration of nervous system due to alcohol (G31.2), other specified and unspecified degenerative diseases of nervous system (G31.8 and G31.9), other degenerative disorders of nervous system in diseases classified elsewhere (G32), multiple sclerosis (G35), other acute disseminated demyelination (G36), other demyelinating diseases of central nervous system (G37), speech disturbances not elsewhere classified (R47) and convulsions not elsewhere classified (R56);[3] C02K; [4] as analgesic or antipyretic (N02BA01); [5] ATC group B01A antithrombotic agents, i.e. vitamin K antagonists (B01AA), Heparin (B01AB), platelet aggregation inhibitors (B01AC), enzymes (B01AD), direct thrombin (B01AE) and factor Xa inhibitors (B01AF) (=NOACs), and other antithrombotic agents (B01AX)

Table 2. Matched and adjusted odds ratios for the risk of hemorrhagic stroke in current antidepressant use compared to current TCA use

	Matched OR		Adjusted OR Main analysis (n cases: 4,059)	
Class of AD (N cases/controls)	OR	CI[†]	OR	CI
TCA (723/8,413)	1.00 (Ref).	- (Ref).	1.00 (Ref).	- (Ref).
SSRI (800/5,209)	1.79	1.61–2.00	**1.39**	**1.22–1.58**
SSNRI (139/1,271)	1.24	1.02–1.51	**1.69**	**1.35–2.11**
NaSSA (354/2,629)	1.56	1.37–1.79	**1.44**	**1.22–1-69**
NARI (11/26)	5.45	2.68–11.08	**3.81**	**1.54–9.43**
MAO (12/220)	0.64	0.35–1.14	0.55	0.28–1.05

Adjusted for the variables listed in Table 1; OR: Odds Ratio; AD: antidepressant; CI: Confidence Interval; TCA: tri- and tetracyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; SSNRI: selective serotonin noradrenaline reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressant; NARI: noradrenaline reuptake inhibitor; MAO: monoamine oxidase inhibitor; estimates for use of multiple and other ADs as well as herbal ADs are not presented as these drugs are only reimbursed in very selected patients and numbers were very small.

Table 3. Adjusted odds ratios for the risk of hemorrhagic stroke in current antidepressant use compared to current TCA use: sensitivity analysis regarding the case definition

	Adjusted OR Sensitivity 1*			Adjusted OR Sensitivity 2†		
Class of AD	N cases/controls	OR	CI	N cases/controls	OR	CI
TCA	618/7,123	1.00 (Ref).	- (Ref).	702/8,172	1.00 (Ref).	- (Ref).
SSRI	669/4,329	**1.37**	**1.19–1.57**	778/5,073	**1.53**	**1.08–2.17**
SSNRI	117/1,105	**1.58**	**1.25–2.01**	137/1,248	**2.66**	**1.44–4.93**
NaSSA	299/2,218	**1.43**	**1.20–1.71**	343/2,554	1.40	0.90–2.17
NARI	9/21	**3.75**	**1.38–10.20**	10/26	3.63	0.36-36.56
MAO	9/188	0.47	0.22–0.98	12/212	0.93	0.20–4.43

Adjusted for the variables listed in Table 1; OR: Odds Ratio; AD: antidepressant; CI: Confidence Interval; TCA: tri- and tetracyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; SSNRI: selective serotonin noradrenaline reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressant; NARI: noradrenaline reuptake inhibitor; MAO: monoamine oxidase inhibitor; *: only cases with imaging procedures two days before to two days after the index day; †: exclusion of cases with a diagnosis of traumatic brain injury within 30 days before the index day.

FIGURES

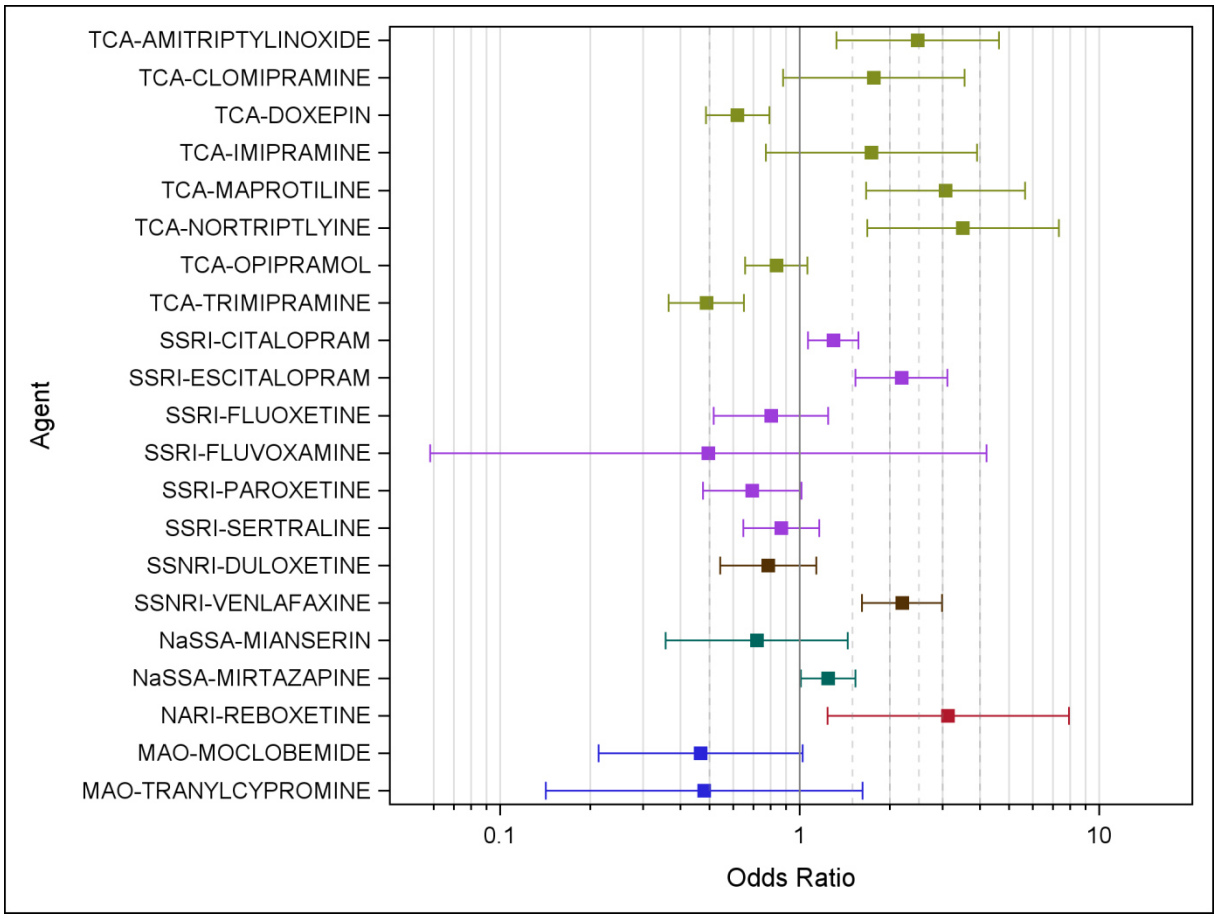

Fig. 1. Forest plot: risk of hemorrhagic stroke in current use of individual antidepressive agents **compared to current use of amitriptyline** (only individual drugs with at least one exposed case and control each are displayed)