# Concomitant Anticoagulant and Antidepressant Therapy in Atrial Fibrillation Patients and Risk of Stroke and Bleeding

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**We aimed to quantify the effects of antidepressant (AD) use in oral anticoagulant (OAC)-treated patients with atrial fibrillation (AF). Using the Stockholm Healthcare database, we analyzed AF patients initiated with an OAC. Outcomes were severe bleeds and strokes and were analyzed using Cox models. We included 17,210 patients claiming warfarin and 13,385 claiming a non–vitamin K OAC. The number of patients that claimed an AD during follow-up was 4,303. Concomitant OAC and AD use was associated with increased rates of severe bleeds (4.7 vs. 2.7 per 100 person-years) compared with OAC treatment alone (adjusted hazard ratio (aHR) 1.42, confidence interval (CI): 1.12–1.80), but not significantly associated with increased stroke rates (3.5 vs. 2.1 per 100 person-years, aHR 1.23, CI: 0.93–1.62). No significant differences in risks were observed between different OAC classes or different AD classes. In conclusion, concomitant use of an OAC and an AD is associated with an increased bleeding risk.**

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Antidepressants have been associated with both increased bleeding and stroke risk. In patients with atrial fibrillation, oral anticoagulants are used to prevent stroke, but they increase the bleeding risk.

### WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In patients with atrial fibrillation, is the combined use of antidepressants with oral anticoagulant therapy associated with increased bleeding and stroke risk, compared with monotherapy with oral anticoagulants?

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Atrial fibrillation patients receiving antidepressants together with oral anticoagulants had a 42% increased risk for severe bleeds compared with patients receiving only oral anticoagulants, or an excess of 1.1 bleeds per 100 person-years. The effect of the combination was less clear regarding the risk for stroke.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ A critical consideration for the need of an antidepressant is recommended when it is combined with oral anticoagulant therapy. Careful follow-up in patients receiving this combination is warranted.

Antidepressants (ADs) are among the most frequently prescribed medications for a variety of psychiatric indications, especially depression and anxiety.[1] Almost all ADs share the feature of having a direct influence on serotonin neurotransmission by influencing serotonin levels and serotonin receptor signaling.[2] Besides the beneficial effects on a patient's well-being, serotonin inhibition also affects platelet function.[3,4] By decreasing platelet serotonin or inhibiting serotonin receptors, platelet aggregation may become compromised, which results in impaired hemostasis.[4,5] Numerous studies have reported on the increased bleeding risk that is associated with AD use.[6–8] Several studies have reported an increased risk for ischemic stroke in patients receiving ADs as well.[7,9–11] It is hypothesized that ADs cause vasoconstriction in cerebral arteries due to serotonergic activation, causing an increased risk for ischemic stroke.[12,13] However, it cannot be ruled out that this observed association is due to confounding by indication, since depression is a known risk factor for stroke.[11,14]

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In patients with atrial fibrillation (AF), treatment with oral anticoagulants (OACs) is effective in reducing the risk of having a stroke, but also increases the risk of having a severe bleed.[15–17] Since OACs in general, and especially non–vitamin K antagonist oral anticoagulants (NOACs), are widely used in clinical practice,[18,19] there is need for a deeper understanding of their potential drug–drug interactions to further optimize antithrombotic treatment. The interaction with ADs is of key importance since both bleeding and stroke risks might be influenced. The combination of vitamin K antagonists such as warfarin and ADs has been studied previously, and is associated with an approximately 30% increased risk for severe bleeds.[20–23] However, neither the stroke risk for any combination of OACs and ADs nor the risk for severe bleeding with the combination of NOACs and ADs have been studied before.

The aim of the present study was therefore to assess the effects of combined use of different ADs with OAC therapy in the NOAC era on both bleeding and stroke risk in patients with AF.

## RESULTS

A total of 134,016 patients had a diagnosis code for AF in the Stockholm healthcare database (Vårdanalysdatabasen, VAL). Of these, 30,595 received a new prescription for any OAC within the study period and were included in the cohort, 17,089 with warfarin, and 13,506 with a NOAC. A total of 4,303 (14.1%) of these patients claimed a prescription for an AD during the year of follow-up, yielding 2,226 person-years of current AD treatment, and 22,860 person-years of no current AD treatment.

AD use occurred slightly more often in the NOAC-treated group (13.5% with warfarin vs. 14.8% with a NOAC) and selective serotonin reuptake inhibitors (SSRIs) were the most commonly used ADs (61.0%). **Table 1** shows the baseline characteristics of the cohort. Patients receiving an AD during follow-up were older (75.6 vs. 73.1 years of age (mean)), more often female (58% vs. 42%), had more comorbidities, and used more comedication compared with the patients not receiving an AD.

A total of 712 severe bleeds and 551 strokes occurred during the year of follow-up (**Table 2**). The most frequently occurring type of bleed was a gastrointestinal bleed (GIB) (50.9%), and ischemic strokes accounted for 63.5% of the composite stroke endpoint.

### Bleeding risk

The incidence rate (IR) of severe bleeds during person-time with current AD use was 4.7 per 100 person-years, compared with 2.7 per 100 person-years during person-time without current AD use. After adjustment, this yielded an adjusted hazard ratio (aHR) of 1.42 (1.12–1.80) (**Table 2**). Based on the adjusted IR of severe bleeds per 100 person-years we estimated a risk difference of 1.1 bleeds per 100 person-years during concomitant AD use (**Figure 1**).

**Table 2** also shows the aHR for different types of bleeds; both GIBs (aHR 1.42; 1.02–1.98) and other severe bleeds (aHR 1.75; 1.09–2.79) were significantly increased. The risk of intracranial bleeds was not associated with AD use (aHR 1.09; 0.66–1.80).

In the separate models for warfarin and NOAC users, we found similar results as in the main model. Both for NOAC and warfarin users the risk was increased, but nonsignificant in warfarin users (aHR 1.29; 0.92–1.81). When checking for an interaction in the model, this was nonsignificant ($P = 0.730$), meaning no statistically significant difference in risk between warfarin and NOACs.

### Stroke risk

The IR of the stroke endpoint during AD use was 2.5 per 100 person-years, compared with 2.1 per 100 person-years during episodes without AD use (**Figure 1**). After adjustment, this yielded an aHR of 1.23 (0.93–1.62) (**Table 2**). The aHR was 1.31 (0.89–1.93) in NOAC-treated patients and 1.12 (0.75–2.24) in warfarin-treated patients. The secondary outcome ischemic stroke was not significantly increased.

### Stratified analyses

Analyses stratified on sex, age-group, type of AD (i.e., SSRI, tricyclic antidepressant, or other), or AD use in the year prior to inclusion yielded no statistically significant different results in any subgroup, i.e., there were no significant interactions (**Table 3**). Stratification based on OAC class (i.e., NOAC or warfarin) yielded a $P$ for interaction of 0.730 for severe bleeds and 0.201 for the stroke endpoint, indicating no different effects in the two OAC classes (aHRs shown in **Table 2**).

### Sensitivity analyses

**Propensity score matching.** Using propensity score matching, 3,802 patients receiving an AD during follow-up were matched to the same number of patients not receiving an AD. Baseline characteristics after matching were almost identical, and all standardized mean differences were below 0.1, indicating successful matching (**Table S2**).

For severe bleeds, the results were similar as with the main analysis (**Table S3**). For stroke, the model yielded an HR of 1.47 (1.08–2.02).

**Falsification endpoint.** The composite falsification endpoint of acute upper respiratory infection, influenza, and pneumonia showed an aHR of 1.08 (0.78–1.48) in the Cox regression model, showing no indication of residual confounding in this analysis (**Table S4**). None of the subgroup analyses showed any significantly increased risk.

**Former users and never users.** Comparing person-time of current use with person-time for individuals who never used an AD yielded similar results as the main analyses: an increased risk for severe bleeds and not for stroke.

Comparing person-time of former users of ADs with person-time of nonusers yielded nonsignificant aHRs of 1.11 (0.73–1.69) for severe bleeds and 0.59 (0.33–1.07) for stroke, showing no indication for residual confounding (**Table S5**).

**Exposure definitions.** Using different exposure definitions of AD treatment (i.e., using the defined daily dose) to create exposure periods, and including a 20% grace period for noncompliance yielded similar results as the main analysis (**Table S6**).

**Table 1 Baseline characteristics**

| | Baseline cohort | |
|---|---|---|
| | Patients without AD | Patients with AD |
| *n* | 26,291 | 4,304 |
| Age at index, years (mean (SD)) | 73.09 (11.1) | 75.62 (10.8) |
| Female | 10,957 (42%) | 2,499 (58%) |
| Warfarin treatment | 14,789 (56%) | 2,300 (53%) |
| NOAC treatment | 11,502 (44%) | 2,004 (47%) |
| Reduced dose NOAC treatment | 3447 (13%) | 823 (19%) |
| Years since first AF date (mean (SD)) | 1.65 (3.1) | 1.75 (3.2) |
| Valvular AF | 334 (1%) | 67 (2%) |
| AD class | | |
| SSRI | N/A | 2,625 (61%) |
| TCA | N/A | 487 (11%) |
| Other[a] | N/A | 1,192 (28%) |
| Antidepressant use in year prior to inclusion | 548 (2%) | 3,218 (75%) |
| Concomitant drug use | | |
| Aspirin | 11,525 (44%) | 2,014 (47%) |
| NSAID | 3,177 (12%) | 620 (14%) |
| Clopidogrel | 1,120 (4%) | 284 (7%) |
| Other antiplatelets | 562 (2%) | 156 (4%) |
| Corticosteroids | 2,035 (8%) | 419 (10%) |
| Diuretics | 6,999 (27%) | 1,445 (34%) |
| Beta blocker | 14,963 (57%) | 2,617 (61%) |
| Calcium channel blocker | 7,002 (27%) | 1,157 (27%) |
| RAAS inhibitor | 12,333 (47%) | 2,073 (48%) |
| Lipid lowering agent | 8,105 (31%) | 1,503 (35%) |
| Antidiabetic drug | 3,093 (12%) | 582 (14%) |
| Gastro protective agent | 4,795 (18%) | 1,368 (32%) |
| Comorbidities | | |
| Anemia < 3 months | 344 (1%) | 80 (2%) |
| Major bleeding < 3 months | 153 (1%) | 34 (1%) |
| Stroke/TIA/embolism < 3 months | 1,652 (6%) | 394 (9%) |
| Anemia 3–12 months | 380 (1%) | 105 (2%) |
| Major bleeding 3–12 months | 180 (1%) | 55 (1%) |
| Stroke/TIA/embolism 3–12 months | 422 (2%) | 148 (3%) |
| Anemia ≥ 12 months | 2,939 (11%) | 762 (18%) |
| Major bleeding ≥ 12 months | 1,447 (6%) | 427 (10%) |
| Stroke/TIA/embolism ≥ 12 months | 2,424 (9%) | 747 (17%) |
| Alcoholism | 1,065 (4%) | 384 (9%) |
| Hypertension | 17,689 (67%) | 3,223 (75%) |
| Abnormal liver function | 613 (2%) | 119 (3%) |
| Renal disease | 2,041 (8%) | 498 (12%) |
| Heart failure | 5,996 (23%) | 1,280 (30%) |
| Diabetes | 4,780 (18%) | 961 (22%) |
| Vascular disease | 7,047 (27%) | 1,415 (33%) |
| Cancer | 5,596 (21%) | 1,104 (26%) |
| COPD | 2,382 (9%) | 651 (15%) |
| ≥2 Falls | 2,954 (11%) | 803 (19%) |
| Dementia, delirium, or other mental disorders due to known physiological condition | 995 (4%) | 556 (13%) |
| Mental disorder due to psychoactive substance use | 1,518 (6%) | 519 (12%) |
| Schizophrenia | 139 (1%) | 79 (2%) |
| Mood disorder | 1655 (6%) | 1,993 (46%) |
| Anxiety | 2,397 (9%) | 1,516 (35%) |
| Behavioral syndromes | 2,218 (8%) | 814 (19%) |
| Disorder in personality and behavior | 52 (0%) | 40 (1%) |
| Unspecified mental disorder | 116 (0%) | 63 (1%) |
| Year of index date | | |
| 2011 | 2,172 (8%) | 286 (7%) |
| 2012 | 4,517 (17%) | 617 (14%) |
| 2013 | 3,487 (13%) | 494 (11%) |
| 2014 | 6,305 (24%) | 1,059 (25%) |
| 2015 | 5,016 (19%) | 935 (22%) |
| 2016 | 4,794 (18%) | 913 (21%) |

Baseline characteristics of patients receiving an antidepressant during follow-up and patients not receiving an antidepressant during follow-up.
AD, antidepressant; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone-system; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TIA, transient ischemic attack.
[a]Other antidepressants are bupropion, duloxetine, mianserin, mirtazapine, and moclobemide.

**Censoring.** Censoring the patients when they received antiplatelet therapy or nonsteroidal anti-inflammatory drug therapy yielded similar results as the main analysis (**Table S6**).

## DISCUSSION

In the current population-based cohort study, we found an increased risk for severe bleeds in OAC-treated AF patients with concomitant AD therapy. We found a nonsignificant trend toward an increased risk of stroke. The observed risks were similar for NOAC and warfarin treatment and for the different ADs (i.e., SSRI, tricyclic antidepressant (TCA), or other ADs). Increases in bleeding risk were significant for GIBs and other severe bleeds, but not for intracranial bleeds. Sensitivity analyses added to the robustness of our findings and showed no indication for residual and unmeasured confounding. However, in a sensitivity analysis using propensity score matching, the stroke risk was significantly increased.

### Study strengths

This is to our knowledge the first study to investigate both stroke and bleeding risk when combining ADs with OACs,

**Table 2 Number of events and the results from the Cox regression**

| | | Number of outcomes | | | |
|---|---|---|---|---|---|
| | | AD nonusers | AD users | Adjusted HR (95% ) | Risk difference |
| All OAC | Person-years | 22,860 | 2,226 | — | — |
| Bleeds | Severe bleed | 607 | 105 | 1.42 (1.12–1.80) | 1.1 |
| | GIB | 309 | 54 | 1.42 (1.02–1.98) | 0.6 |
| | Intracranial bleed | 160 | 23 | 1.09 (0.66–1.80) | 0.1 |
| | Other severe bleed | 138 | 28 | 1.75 (1.09–2.79) | 0.5 |
| Strokes | TIA/ischemic stroke/ unspecified | 474 | 77 | 1.23 (0.93–1.62) | 0.5 |
| | Ischemic stroke | 298 | 52 | 1.29 (0.92–1.81) | 0.4 |
| NOAC | Person-years | 10,305 | 1,084 | — | — |
| Bleeds | Severe bleed | 253 | 55 | 1.58 (1.12–2.21) | 1.4 |
| | GIB | 142 | 29 | 1.32 (0.83–2.10) | 0.4 |
| | Intracranial bleed | 57 | 8 | 1.02 (0.45–2.34) | 0.0 |
| | Other severe bleed | 54 | 18 | 3.02 (1.62–5.64) | 1.1 |
| Strokes | TIA/ischemic stroke/ unspecified | 199 | 42 | 1.31 (0.89–1.93) | 0.6 |
| | Ischemic stroke | 132 | 28 | 1.25 (0.78–2.02) | 0.3 |
| Warfarin | Person-years | 12,555 | 1,142 | — | — |
| Bleeds | Severe bleed | 354 | 50 | 1.29 (0.92–1.81) | 0.8 |
| | GIB | 167 | 25 | 1.57 (0.97–2.54) | 0.8 |
| | Intracranial bleed | 103 | 15 | 1.08 (0.58–2.01) | 0.1 |
| | Other severe bleed | 84 | 10 | 1.02 (0.49–2.12) | 0.0 |
| Strokes | TIA/ischemic stroke/ unspecified | 275 | 35 | 1.12 (0.75–2.24) | 0.3 |
| | Ischemic stroke | 166 | 24 | 1.35 (0.83–2.19) | 0.5 |

Number of events per treatment group, adjusted hazard ratios, and absolute risk difference of bleeds and stroke. Hazard ratios adjusted age, sex, OAC class, year of inclusion, years since AF (atrial fibrillation) diagnosis, and comorbidities and comedication as presented in **Table 1**.
AD, antidepressant; aHR, adjusted hazard ratio; CI, confidence interval; GIB, gastro intestinal bleed; NOAC, non–vitamin K oral anticoagulant; OAC, oral anticoagulant; TIA, transient ischemic attack.

as well as describing bleeding risk when combining ADs with NOACs. We addressed a clinically relevant research question for which evidence has been very limited so far. Both AF and OAC and AD use are increasing,[1,24–26] which will result in higher numbers of patients receiving this combination. A major strength of this study is the completeness of the VAL database, which contains full healthcare coverage of an entire healthcare region, resulting in high external validity of our findings. The other major strength of this study is the robustness of our design. We used different approaches to test our hypotheses and validated our results by several sensitivity analyses and additional tests to check for residual confounding. The sensitivity analyses yielded similar results, and additional tests all showed no signs of major residual confounding, which supports the validity of our results.

### Study limitations

Our study has some limitations. First, this is an observational study, and despite all efforts, one can never completely rule out unmeasured confounding. Depression is a known risk factor for stroke and could act as a confounder, even after adjusting for it, since diagnoses for depression might be lacking. There is no evidence that depression is a risk factor for severe bleeds, and therefore these results are not potentially biased by depression as confounder. Second, one is never sure whether a patient actually takes the medication as prescribed. Sensitivity analyses by defining AD treatment episodes in different ways yielded similar results, but uncertainty still exists whether patients took their prescribed medication at the time of an event. Third, we used a conservative approach in defining outcomes, especially for strokes. With that, we avoid misclassification, but also probably underestimate the incidence of strokes. Fourth, the VAL database lacks information on lifestyle factors, such as smoking.

### Previous studies

Previous studies have reported an approximate 30% increase in the risk for severe bleeds when combining warfarin treatment with ADs.[20–23] Our study confirmed these findings and showed a similarly increased risk when combining ADs with NOACs. Contrasting to previous work, we found a similarly increased risk for all AD classes, while others found an increased risk only for SSRIs in combination with warfarin. There is, however, evidence

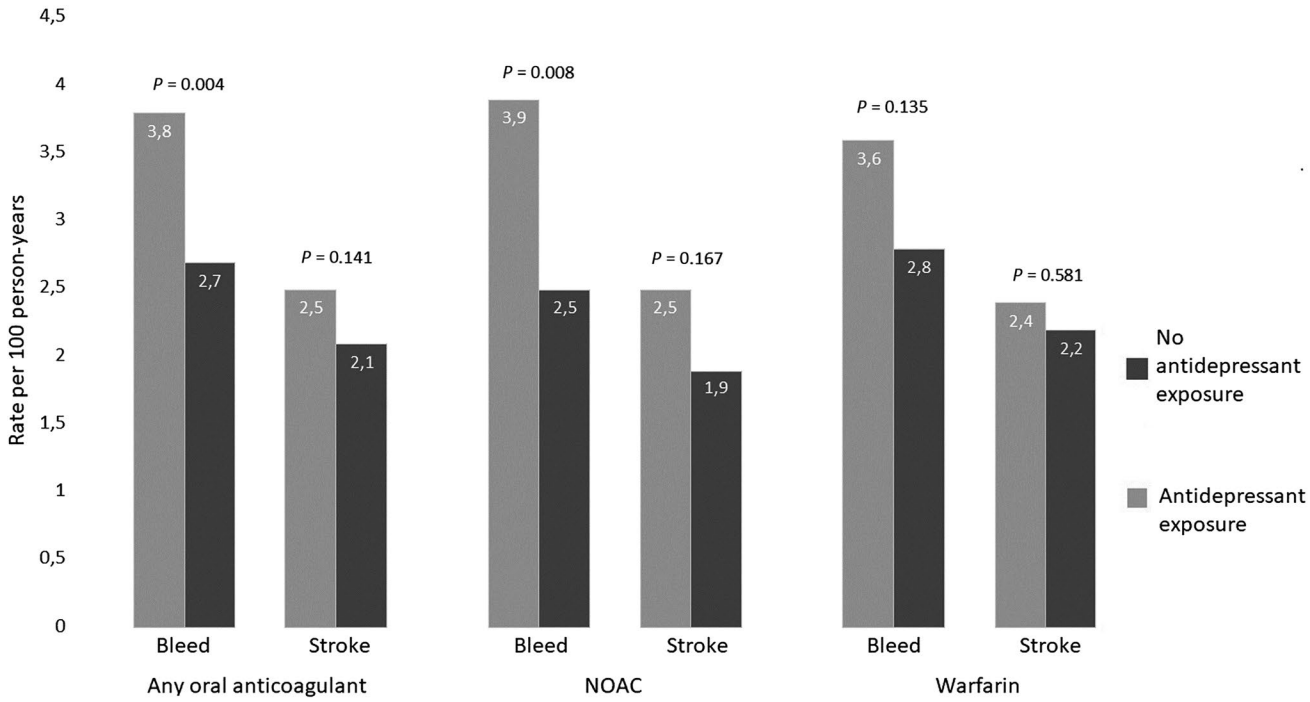


**Figure 1** Rates of stroke and bleed per 100 person-years after adjustment for confounders for patients with concomitant antidepressant use and for patients with anticoagulant therapy alone. Rates are shown for all oral anticoagulants and stratified for non–vitamin K oral anticoagulants and warfarin. NOAC, non–vitamin K oral anticoagulant.

**Table 3 Results from the Cox regression, stratified by sex, age, antidepressant class, and prior AD use**

| | Bleed | | Stroke | |
|---|---|---|---|---|
| | Adjusted HR (95% CI) | *P* for interaction | Adjusted HR (95% CI) | *P* for interaction |
| Sex | | | | |
| Male | 1.57 (1.07–2.32) | 0.578 | 1.53 (0.97–2.40) | 0.668 |
| Female | 1.40 (0.98–2.00) | | 1.37 (0.91–2.08) | |
| Age | | | | |
| <80 | 1.46 (1.00–2.12) | 0.940 | 1.35 (0.87–2.09) | 0.623 |
| ≥80 | 1.48 (1.03–2.13) | | 1.52 (1.00–2.32) | |
| AD class | | | | |
| SSRI | 1.30 (0.90–1.88) | 0.393 | 1.13 (0.73–1.75) | 0.085 |
| TCA | 1.53 (0.74–3.17) | | 1.44 (0.58–3.60) | |
| Other[a] | 1.73 (1.17–2.55) | | 1.92 (1.25–2.95) | |
| AD use in year prior to index date | | | | |
| Yes | 1.89 (1.14–3.15) | 0.382 | 1.28 (0.88–1.88) | 0.110 |
| No | 1.50 (1.09–2.08) | | 2.04 (1.18–3.52) | |

Adjusted hazard ratios for severe bleeds and stroke risk, stratified by sex, age (<80 and ≥80 years of age), antidepressant class, and prior antidepressant use. Other antidepressants are: bupropion, duloxetine, mianserin, mirtazapine, and moclobemide. Hazard ratios adjusted age, sex, OAC class, year of inclusion, years since AF diagnosis, and comorbidities and comedication as presented in Table 1.

AD, antidepressant; aHR, adjusted hazard ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Other antidepressants are bupropion, duloxetine, mianserin, mirtazapine, and moclobemide.

suggesting an increased bleeding risk independent of AD class in patients in general,[7,8] or in patients on concomitant nonsteroidal anti-inflammatory drug treatment.[27] One recent meta-analysis of observational studies showed an increased bleeding risk for mirtazapine and bupropion, both of which have very little or no influence on the serotonin transporter.[28] For mirtazapine, it is hypothesized the 5HT-2A receptor affinity increases the risk for bleeding,[29] as serotonin-mediated enhancement of platelet activation in whole blood is mediated by 5HT-2A receptors.[30] For bupropion, it is hypothesized that the effects on dopamine and

noradrenaline neurotransmission increase the risk for bleeding.[28] These findings are supported by the new insights from our study and suggest that TCAs or other antidepressants are not safer alternatives to SSRIs in OAC-treated patients.

We are, to our knowledge, the first to report on the association between concomitant OAC and AD use regarding the risk of suffering ischemic stroke. Studies have shown an increased risk for ischemic stroke with AD use in general, but this was without concomitant OAC treatment.[7,9–11] Our data suggests an increased risk of stroke when combining OACs and ADs, and in the propensity score matched model this increase was statistically significant. A study in another larger database may confirm these signals. Depression appears to increase the risk of suffering stroke,[14] but it is noteworthy that AD treatment may counterbalance the beneficial effects of OAC treatment in the prevention of stroke in AF patients.

We found no difference in the results with warfarin or NOAC treatment strategies or for different AD classes. Therefore, we cannot recommend any combination to be the safest should a patient have indications for both treatments. We have shown an increased risk for severe bleeds in all patients, and therefore increased awareness is recommended when prescribing any of the studied combinations. A critical consideration for the need of an AD is recommended when it is combined with OAC therapy.

### Conclusion

In this study of a complete healthcare region we found that AD use in OAC-treated AF patients was associated with an increased risk for severe bleeds. In addition, we found suggestions of an increased risk for stroke that merit further investigations. We found no differences between OAC treatment strategies or between different AD classes. Increased awareness and careful follow-up of patients receiving this combination is warranted.

## METHODS

### Data source

For this population-based cohort study, we used the VAL database, which is the Stockholm Healthcare Database, containing pseudonymized information on all 2.3 million inhabitants in the Stockholm region.[31,32] The individual-level information consists of data regarding demographics, medical information, and prescription claims. This gives the opportunity to have complete healthcare data for follow-up of all inhabitants in the region.

The medical information in VAL covers both primary and secondary care, and diagnoses and interventions are registered as International Classification of Diseases, Tenth Revision (ICD-10) codes. Data for primary care have been available since 2003, and for secondary care since 1993. Information is available on migration and death for all individuals. Data from different databases are linked through a unique Personal Identification Number.[33] The VAL database is updated monthly, and we had data available until December 2017 at the time of data extraction.

In the database, prescription claims data contain drugs claimed in any pharmacy in Sweden and are derived from the national prescribed drug registry and registered as Anatomical Therapeutic Chemical Classification System codes.[34] Data on claimed drugs are available in the VAL database from July 2010. The drug information registered consists of amounts, dosages, expenditures, reimbursement, age, and gender of the patient, copayment, and prescriber categories.

The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2).

### Patient selection

From the VAL database, we selected all patients with a diagnosis code for atrial fibrillation (I48) from 2003 until 2016. Validation studies have shown a positive predictive value of 97% for this diagnosis.[35] Among the AF patients, we selected all patients with a new prescription for either a NOAC or warfarin from July 2011 until the end of 2016. We defined a prescription as a new prescription if the patient had no prescription for any OAC during the year prior to inclusion. The date of the first prescription of the OAC was considered the index date.

### Follow-up and censoring

After inclusion, we followed patients for a maximum of one year during the study period, which was from July 2011 until December 2017. During this year of follow-up, patients remained in the cohort as long as they claimed new prescriptions for a NOAC or warfarin. If they did not claim their previously prescribed OAC, we censored the patients at the estimated end of the duration covered by the last claimed prescription. Follow-up ended when a patient claimed a prescription for another oral anticoagulant class (i.e., switch from warfarin to NOAC or vice versa), when a patient experienced an outcome of interest (for ICD-10 codes see **Table S1**), when a patient emigrated from the county, or when a patient died.

### Exposure definition

We included all claims for an AD from the index date until the end of follow-up to identify treatment episodes with ADs during follow-up. We looked for AD prescriptions 1 year prior to the index date to identify potential AD treatment episodes that overlapped the index date. We defined a treatment episode from the claim of an AD prescription until the calculated end of the treatment period, and these periods were considered current use periods. We calculated this using the number of pills claimed and the common dose for the antidepressant. We classified ADs into three classes: SSRIs, TCAs, and other ADs. For Anatomical Therapeutic Chemical Classification System codes, see **Table S1**.

### Outcome definitions

For bleeding risk, we assessed the occurrence of a severe bleed, using ICD-10 codes as described in **Table S1**. We included the first registration of a bleed requiring acute somatic care in inpatient or outpatient hospital-based care, starting from the day after inclusion in the cohort.[36,37] The primary outcome was the occurrence of any severe bleed. Secondary outcomes were GIB, intracranial hemorrhage, and other severe bleeds (**Table S1**). Validation studies have shown a positive predictive value of 95.5% and sensitivity of 100% for these diagnoses.[36]

For stroke risk, we assessed the occurrence of a composite endpoint of a transient ischemic attack (TIA), ischemic stroke, and unspecified stroke using ICD-10 codes as described in **Table S1** as primary outcome. We included the first registration in acute somatic inpatient care starting from the day after inclusion in the cohort. Only the primary or first secondary diagnosis was used as has been previously done.[37,38] The secondary outcome was the occurrence of ischemic stroke. Validation studies have shown a positive predictive value of 98.6% for the combined stroke/TIA diagnosis and a sensitivity of 93.5%.[39]

### Comedication and comorbidity definition

We defined baseline drug use as claims in the six months prior to the index date (**Table 1**). We included claims of drugs that are known to influence the risk for bleeding and/or stroke, as they can introduce confounding. In addition, we assessed whether patients had AD prescription in the year

prior to inclusion. We also included comorbidities registered in the database before inclusion of the patient (**Table 1**). For anemia, a prior bleed, and a prior stroke/TIA/embolism, we also specifically assessed diagnoses recorded in the 3 months before inclusion and the year before inclusion to further identify high-risk patients. Finally, we calculated the years between the first AF diagnosis and index date for each patient.

### Statistical analyses

We used descriptive statistics to present baseline characteristics and to calculate IRs per 100 person-years. We used a Cox proportional hazards model to calculate HRs with 95% confidence intervals (CIs) and to control for potential confounders. The primary outcomes, severe bleed and stroke, were analyzed in separate models. We used the aHR to calculate an adjusted IR in patients on current AD treatment in order to estimate an adjusted risk difference. To test to the robustness of our findings, we conducted several sensitivity analyses, including a propensity score matched analysis.

SAS Enterprise Guide 7.1 was used for all statistical analyses (SAS Institute Inc., Cary, NC).

**Cox proportional hazards model**. We used a Cox proportional hazards model to assess the association between current AD use and risk for severe bleed and stroke compared with patients without current AD use. In the models, we adjusted for age, sex, OAC class (i.e., warfarin or NOAC), year of inclusion, years since AF diagnosis, baseline medication, and comorbidities as presented in **Table 1**. We used age and years since AF diagnosis as continuous variables. In the model, AD use was included as a time-dependent variable, and we compared person-time with AD treatment to person-time without current AD treatment.

Besides the main model, which included any OAC treatment, we constructed two models, one with only warfarin users and one with only NOAC users. In the NOAC model, we also included a variable for the dose of the NOAC (i.e., standard or reduced). These models were analyzed similarly to the main analyses to gain insight in potential differences between NOACs and warfarin.

**Stratified analyses**. We tested for significant interaction terms and conducted stratified analyses to assess if an association was modified by the following prespecified subgroups; gender, age <80 or ≥80 years, type of AD (SSRI, TCA, other), AD use in the year prior to inclusion, and type of OAC (NOAC or warfarin).

### Sensitivity analyses

**Propensity score matching**. In order to further address potential confounding, we calculated propensity scores for the probability of receiving an AD during the year of follow-up. To calculate the propensity score, we performed a logistic regression conditional on age, gender, OAC class, year of inclusion, years since AF diagnosis, and baseline medication and comorbidities as presented in **Table 1**. With the Greedy matching algorithm (http://bioinformaticstools.mayo.edu/research/gmatch/), we matched each patient receiving an AD during follow-up to one patient not receiving an antidepressant during follow-up, based on the propensity score. Matching was done using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. We considered matching successful if the standardized mean difference for all covariates was below 0.1.

We also used propensity score matching to analyze the risks in different OAC treatment groups. For this, we conducted separate matching procedures for the two OAC treatment groups. When matching NOAC patients, we also included a variable for the dose of the NOAC (i.e., standard or reduced) in the logistic regression to calculate the propensity score.

**Falsification endpoint**. We analyzed a falsification endpoint to assess whether our results could be due to residual and unmeasurable confounding.[40,41] We used a composite endpoint of acute upper respiratory infection, influenza, and pneumonia, registered in secondary inpatient or outpatient care, and requiring acute somatic care (i.e., all ICD-10 codes starting with J0 and J1). ADs are not believed to increase the risk for these diseases, but they could be related to residual and unmeasurable confounding (e.g., socioeconomic status, lifestyle factors, etc.). We analyzed the composite falsification endpoint with the same definitions as the main analyses, with the assumption of similar confounders for the falsification endpoint as for the study endpoints.

**Former users and never users**. We conducted sensitivity analyses by comparing person-time of current AD use with never-use person-time (i.e., person-time from patients never receiving an AD during follow-up). We also compared never-use person-time with former-use person-time (i.e., the unexposed person-time after an AD prescription has ended, but before follow-up has ended).

With this analysis, we can assess potential residual confounding due to unknown confounders that are more frequently present in AD users, regardless of receiving an AD at that time.

**Exposure definitions**. We used alternative definitions for the AD exposure since this definition can influence the results. We constructed AD treatment episodes with a grace period for noncompliance of 20% and by calculating the expected treatment duration using the defined daily dose.

**Censoring**. We added two additional censoring moments in the main Cox model with all patients. First, we censored patients when they claimed a prescription for any antiplatelet agent; second, we censored patients when they claimed a prescription for any nonsteroidal anti-inflammatory drug, since antiplatelet and nonsteroidal anti-inflammatory drug therapy influence the risk for both stroke and bleeds.[42]

### SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

**Supplementary Tables:** Tables S1–S6.


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### CONFLICT OF INTEREST

J.J.K. reports personal fees from Boehringer Ingelheim, outside of the submitted work; O.K. reports grants from GSK, grants from Lygature, personal fees from Roche, outside the submitted work; all other authors declared no competing interests for this work.

### AUTHOR CONTRIBUTIONS

J.J.K., B.W., A.K.M.-T., O.H.K., P.H., and T.F. wrote the manuscript; J.J.K., T.F., A.K.M.-T., and P.H. designed the research; J.J.K., B.W., and T.F. performed the research; J.J.K. and T.F. analyzed the data; O.H.K. contributed new reagents/analytical tools.




1. Hemels, M.E., Koren, G. & Einarson, T.R. Increased use of antidepressants in Canada: 1981–2000. *Ann. Pharmacother.* **36**, 1375–1379 (2002).
2. Tatsumi, M., Groshan, K., Blakely, R.D. & Richelson, E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur. J. Pharmacol.* **340**, 249–258 (1997).

3. Halperin, D. & Reber, G. Influence of antidepressants on hemostasis. *Dialogues Clin. Neurosci.* **9**, 47–59 (2007).
4. Skop, B.P. & Brown, T.M. Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. *Psychosomatics* **37**, 12–16 (1996).
5. Serebruany, V.L. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? *Am. J. Med.* **119**, 113–116 (2006).
6. de Abajo, F.J., Rodríguez, L.A. & Montero, D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* **319**, 1106–1109 (1999).
7. Coupland, C., Dhiman, P., Morriss, R., Arthur, A., Barton, G. & Hippisley-Cox, J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* **343**, d4551 (2011).
8. Meijer, W.E.E., Heerdink, E.R., Nolen, W.A., Herings, R.M.C., Leufkens, H.G.M. & Egberts, A.C.G. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch. Intern. Med.* **164**, 2367–2370 (2004).
9. Smoller, J.W. *et al*. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the women's health initiative study. *Arch. Intern. Med.* **169**, 2128–2139 (2009).
10. Trifirò, G., Dieleman, J., Sen, E.F., Gambassi, G. & Sturkenboom, M.C.J.M. Risk of ischemic stroke associated with antidepressant drug use in elderly persons. *J. Clin. Psychopharmacol.* **30**, 252–258 (2010).
11. Shin, D., Oh, Y.H., Eom, C.-S. & Park, S.M. Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. *J. Neurol.* **261**, 686–695 (2014).
12. Singhal, A.B., Caviness, V.S., Begleiter, A.F., Mark, E.J., Rordorf, G. & Koroshetz, W.J. Cerebral vasoconstriction and stroke after use of serotonergic drugs. *Neurology* **58**, 130–133 (2002).
13. Molaie, M. Serotonin syndrome presenting with migrainelike stroke. *Headache* **37**, 519–521 (1997).
14. Pan, A., Sun, Q., Okereke, O.I., Rexrode, K.M. & Hu, F.B. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* **306**, 1241–1249 (2011).
15. Hart, R.G., Pearce, L.A. & Aguilar, M.I. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Intern. Med.* **146**, 857–867 (2007).
16. Ruff, C.T. *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* **383**, 955–962 (2014).
17. Connolly, S.J. *et al*. Apixaban in patients with atrial fibrillation. *N. Engl. J. Med.* **364**, 806–817 (2011).
18. Komen, J., Forslund, T., Hjemdahl, P., Andersen, M. & Wettermark, B. Effects of policy interventions on the introduction of novel oral anticoagulants in Stockholm: an interrupted time series analysis. *Br. J. Clin. Pharmacol.* **83**, 642–652 (2016).
19. Huisman, M.V. *et al*. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. *J. Am. Coll. Cardiol.* **69**, 777–785 (2017).
20. Quinn, G.R. *et al*. Effect of selective serotonin reuptake inhibitors on bleeding risk in patients with atrial fibrillation taking warfarin. *Am. J. Cardiol.* **114**, 583–586 (2014).
21. Cochran, K.A., Cavallari, L.H., Shapiro, N.L. & Bishop, J.R. Bleeding incidence with concomitant use of antidepressants and warfarin. *Ther. Drug Monit.* **33**, 433–438 (2011).
22. Schalekamp, T., Klungel, J.H., Souverein, P.C. & de Boer, A. Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. *Arch. Intern. Med.* **168**, 180–185 (2008).
23. Schelleman, H., Brensinger, C.M., Bilker, W.B. & Hennessy, S. Antidepressant-Warfarin interaction and associated gastrointestinal bleeding risk in a case-control study. *PLoS One* **6**, e21447 (2011).
24. Pratt, L.A., Brody, D.J. & Gu, Q. Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014 Key Findings Data from the National Health and Nutrition Examination Survey. <https://www.cdc.gov/nchs/data/databriefs/db283_table.pdf#2> (2011). Accessed August 20, 2018.
25. Chugh, S.S. *et al*. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* **129**, 837–847 (2014).
26. Krijthe, B.P. *et al*. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur. Heart J.* **34**, 2746–2751 (2013).
27. Shin, J.-Y. *et al*. Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. *BMJ* **351**, h3517 (2015).
28. Na, K.-S., Jung, H.-Y., Cho, S.-J. & Cho, S.-E. Can we recommend mirtazapine and bupropion for patients at risk for bleeding?: A systematic review and meta-analysis. *J. Affect. Disord.* **225**, 221–226 (2018).
29. Anttila, S.A.K. & Leinonen, E.V.J. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev.* **7**, 249–264 (2001).
30. Li, N., Wallén, N.H., Ladjevardi, M. & Hjemdahl, P. Effects of serotonin on platelet activation in whole blood. *Blood Coagul. Fibrinolysis* **8**, 517–523 (1997).
31. Forslund, T., Wettermark, B., Wändell, P., von Euler, M., Hasselström, J. & Hjemdahl, P. Risk scoring and thromboprophylactic treatment of patients with atrial fibrillation with and without access to primary healthcare data: experience from the Stockholm health care system. *Int. J. Cardiol.* **170**, 208–214 (2013).
32. Forslund, T., Wettermark, B., Wändell, P., von Euler, M., Hasselström, J. & Hjemdahl, P. Risks for stroke and bleeding with warfarin or aspirin treatment in patients with atrial fibrillation at different CHA(2)DS(2)VASc scores: experience from the Stockholm region. *Eur. J. Clin. Pharmacol.* **70**, 1477–1485 (2014).
33. Ludvigsson, J.F., Otterblad-Olausson, P., Pettersson, B.U. & Ekbom, A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur. J. Epidemiol.* **24**, 659–667 (2009).
34. Wettermark, B. *et al*. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol. Drug Saf.* **16**, 726–735 (2007).
35. Smith, J.G., Platonov, P.G., Hedblad, B., Engström, G. & Melander, O. Atrial fibrillation in the Malmö diet and cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur. J. Epidemiol.* **25**, 95–102 (2010).
36. Friberg, L. & Skeppholm, M. Usefulness of Health Registers for detection of bleeding events in outcome studies. *Thromb. Haemost.* **116**, 1131–1139 (2016).
37. Forslund, T., Wettermark, B., Andersen, M. & Hjemdahl, P. Stroke and bleeding with non-vitamin K antagonist oral anticoagulant or warfarin treatment in patients with non-valvular atrial fibrillation: a population-based cohort study. *Europace.* **20**, 420–428 (2017).
38. Friberg, L., Skeppholm, M. & Terént, A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J. Am. Coll. Cardiol.* **65**, 225–232 (2015).
39. Ludvigsson, J.F. *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* **11**, 450 (2011).
40. Prasad, V. & Jena, A.B. Prespecified falsification end points: can they validate true observational associatons?. *JAMA* **309**, 241–242 (2013).
41. Dusetzina, S.B., Brookhart, M.A. & Maciejewski, M.L. Control outcomes and exposures for improving internal validity of nonrandomized studies. *Health Serv. Res.* **50**, 1432–1451 (2015).
42. Kent, A.P. *et al*. Concomitant oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. *J. Am. Coll. Cardiol.* **72**, 255–267 (2018).