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Effect of Selective Serotonin Reuptake Inhibitors on Bleeding Risk in Patients with Atrial Fibrillation Taking Warfarin

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Abstract

Selective serotonin reuptake inhibitor (SSRI) medications have been linked to increased bleeding risk, however, the actual association between warfarin, SSRI exposure, and bleeding risk has not been well-established. We studied the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) cohort of 13,559 adults with atrial fibrillation (AF), restricted to the 9186 patients contributing follow-up time while taking warfarin. Exposure to SSRIs and tricyclic antideprssants (TCAs) were assessed from pharmacy database dispensing data. The main outcome was hospitalization for major hemorrhage. Results were adjusted for bleeding risk and time in an INR range ≥ 3. We identified 461 major hemorrhages during 32,888 person-years of follow-up, 45 events during SSRI use, 12 during TCA only use, and 404 without either medication. Hemorrhage rates were higher during periods of SSRI exposure compared with periods on no antidepressants (2.32 per 100 person-years vs. 1.35 per 100 person-years, $p \leq 0.001$) and did not differ between TCA exposure and no antidepressants (1.30 per 100 person-years on TCAs, $p = 0.93$). After adjusting for bleeding risk and time in INR range > 3, SSRI exposure was associated with an increased rate of hemorrhage compared with no antidepressants (adjusted relative risk 1.41, 95% CI: 1.04-1.92, p=0.03), whereas TCA exposure was not (adjusted relative risk 0.82, 95% CI: 0.46-1.46, p=0.50). In conclusion, SSRI exposure was associated with higher major hemorrhage risk in patients on warfarin and this risk should be considered when selecting antidepressant treatments in those patients.

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Keywords

Anticoagulation; atrial fibrillation; warfarin; bleeding risk

Introduction

Antidepressant medications are commonly used medications, with a prevalence of 10-15% use among adults in the United States.[1] Selective serotonin reuptake inhibitors (SSRIs) are considered a first-line pharmacologic therapy for depression and several other conditions, and are widely prescribed due to relatively favorable side-effect profiles.[2] However, there is some evidence that SSRIs may increase bleeding risk, particularly upper gastrointestinal hemorrhage.[3-8] Serotonin plays a role in platelet aggregation, and it has been suggested that SSRIs block platelet reuptake of serotonin and therefore inhibit the ability of platelets to aggregate.[9-11] Drug information guides warn about a potential interaction between warfarin and SSRIs.[12] However, the actual relation between warfarin, SSRI exposure, and bleeding risk has not been well characterized. Previous studies have not controlled for other factors that may influence warfarin-associated bleeding risk, and have not accounted for anticoagulation intensity in patients taking concomitant SSRIs and warfarin. To address these issues, we tested the association between SSRI exposure and major hemorrhage events in patients taking warfarin for atrial fibrillation (AF) using data from a large, community-based cohort of patients with diagnosed AF.

Methods

The AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study is a cohort of 13,559 adults enrolled in Kaiser Permanente Northern California with diagnosed AF between July 1, 1996, and December 31, 1997 and followed for a median 6 years.[13, 14] Patients with prior valve repair or replacement, mitral stenosis, perioperative AF that was transient, or recent hyperthyroidism were excluded.[14]

Demographic and clinical data on individuals were obtained from automated clinical databases using condition-specific International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes and disease registries.[13, 14] Clinical and laboratory databases were used to calculate an ATRIA bleeding risk score for each patient. The ATRIA bleeding risk index is a validated risk tool based on 5 clinical variables (anemia, severe renal disease, age, prior bleeding, and hypertension) and predicts the likelihood of warfarin-associated major hemorrhage.[15] We did not have information on non-prescription medications such as aspirin or NSAIDs. Exposure to prescription antiplatelet medications (clopidogrel and ticlopidine) was determined from searching the pharmacy database.

The current study focused on the 9186 patients who were exposed to warfarin during the study period. Longitudinal warfarin exposure was determined using a previously validated algorithm based on serial pharmacy dispensings and outpatient INR measurements.[13, 14] Measurements of the INR were obtained from health plan outpatient laboratory databases. The proportion of time spent within specific INR ranges (<2.0, 2.0-3.0, and > 3.0) was determined using a modified linear interpolation method.[2, 18]

Exposure to SSRIs was defined as receipt of one or more of the following FDA-approved medications during the study period based on information for dispensed prescriptions found in health plan pharmacy databases: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. We also included venlafaxine, a serotonin and norepinephrine inhibitor, because of reported similarities in bleeding effects.[12] Longitudinal exposure, duration, and timing of SSRI exposure was determined by the date of dispensation and number of medication days supplied between serial prescriptions using previously described methods.[13, 14]

We also searched for exposure to tricyclic antidepressants (TCAs), medications that are often used for similar indications as SSRIs but have not been linked to hemorrhage risk. Specifically, we searched for amitriptyline, desipramine, doxepin, imipramine, nortiptyline, protriptyline, and trimipramine. Longitudinal exposure was assessed in the same way as for SSRIs.

We searched for hospitalizations for incident major hemorrhages occurring on warfarin. Primary ICD-9 diagnosis codes for extracranial hemorrhages (gastrointestinal, genitourinary, retroperitoneal) or primary and secondary diagnoses of intracranial hemorrhage (including intracerebral, subarachnoid, or subdural) were identified from computerized databases based on previously validated algorithms.[13, 14] Medical records for all potential hemorrhagic events then underwent validation through medical chart review using a formal review protocol by a clinical outcomes committee.[13] All events included must have been either during warfarin exposure or within 5 days of preceding warfarin exposure. Major hemorrhages were defined as bleeding events that were fatal, required ≥ 2 units of transfused blood, or hemorrhage into a critical anatomic site (e.g. intracranial, retroperitoneal, or intraocular that impairs vision).[14] Reviewers also collected information about exposure to aspirin in patients presenting with hemorrhage.[13]

The analysis was restricted to periods of on-warfarin exposure. Descriptive statistics were used to summarize the patient characteristics during exposure to SSRIs, TCAs, or neither medication. Multivariable Poisson regression models were developed to compare rates of major hemorrhage during periods of concomitant SSRI and warfarin exposure to periods of warfarin exposure alone, adjusting for ATRIA bleeding risk score and proportion of follow-up time in an INR range ≥ 3. A generalized estimating equations approach was used to adjust for periods where individual patients could be exposed multiple times to warfarin. We also performed similar analyses examining the rates of hemorrhage on concomitant TCA and warfarin use. Analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). The institutional review boards at each participating institution approved the study.

Results

A total of 9186 patients with AF in the cohort took warfarin, with 32,888 person-years of follow-up time on warfarin available for analysis. The median duration of warfarin use was 3.5 years [interquartile range: 1.2 to 6.0 years]. Clinical characteristics of the patients, weighted by the length of follow-up, are presented in Table 1. Because anticoagulated

patients could discontinue warfarin and subsequently resume therapy at a later time, individual patients could contribute multiple periods on warfarin; 2790 patients (30%) had >1 period on warfarin and 709 patients (8%) had >2 periods on warfarin.

Among patients on warfarin, 1743 patients had concomitant use of at least one SSRI (1939 person-years of simultaneous SSRI and warfarin exposure). The SSRIs used were paroxetine (51.6% of SSRI users), fluoxetine (49.4%), sertraline (13.9%), venlafaxine (4.6%), citalopram (3.8%), and fluvoxamine (0.5%).

The INR could be interpolated for 86.3% of the total warfarin-exposed time, and 65.5% of the interpolated person-years were in a therapeutic INR range of 2 - 3. SSRI and TCA exposure was associated with a greater proportion of time spent in an INR ≥ 3 compared to not being on these agents (12.3% for SSRIs, 11.9% for TCAs, and 10.3% for neither, $p<0.001$). The mean ATRIA bleeding risk score during periods of SSRI exposure was higher than on no antidepressants (2.99 vs. 2.45, $p<0.001$). A higher mean bleeding risk score was also observed during TCA exposure compared to no antidepressants (2.73 vs. 2.45, $p<0.001$).

We identified 461 validated incident warfarin-associated major hemorrhages during follow-up. Of these events, 45 events occurred during SSRI use (16 intracranial, 29 extracranial), 12 events during TCA-only use (5 intracranial, 7 extracranial), and 404 events during periods where neither medication was used (165 intracranial, 239 extracranial).

Unadjusted rates of major hemorrhage were higher during periods of SSRI exposure compared with periods when patients were not on antidepressants (2.32 per 100 person-years vs. 1.35 per 100 person-years, $p<0.001$). The rates of hemorrhage for patients taking fluoxetine, paroxetine, and sertraline were similar (2.26, 2.46, and 2.47 per 100 person years, respectively). In contrast, rates of hemorrhage during TCA-only exposure were not significantly different from rates on no antidepressant use (1.30 per 100 person-years on TCAs vs. 1.35 per 100 person-years on none, $p =0.94$).

In a multivariable model adjusting for ATRIA bleeding risk score and time in INR range ≥ 3, SSRI exposure was significantly associated with an increased risk for major hemorrhage compared with no antidepressants (adjusted rate ratio = 1.41, 95% CI: 1.04-1.92) while TCA exposure was not associated with increased hemorrhage risk (Table 2). Essentially the same effects were seen for both intra- and extracranial hemorrhages although the heightened risk with SSRI exposure was not statistically significant in these subgroup analyses.

Among the 461 patients who developed hemorrhage events, the proportion of patients with chart-documented aspirin use at the time of event did not differ among patients taking SSRIs, TCAs, or no antidepressants. Of the 43 patients with hemorrhage on SSRIs, 6 patients had documented aspirin use (14.0%), compared to 2 out of 11 patients on TCAs (18.2%) and 39 out of 383 (10.2%) in those on neither antidepressant ($p=0.66$ and 0.43, respectively) Only 0.3% of the total person-years on warfarin indicated concomitant exposure to other antiplatelet agents (clopidogrel and ticlopidine) and there were no significant differences in the proportion of clopidogrel or ticlopidine use across SSRI, TCA, or neither categories (0.3% use in all groups, $p=0.72$).

INR level at the time of major hemorrhage event was < 2 in 17.8% of the SSRI group, 8.3% of the TCA group, and 15.1% of the neither medication group. INRs > 3.0 at time of event were present in 53.3% of the SSRI group, 33.3% of the TCA group, and 36.9% of the neither medication group.

Discussion

SSRI exposure was associated with a higher risk of major hemorrhage in patients taking warfarin for AF, and this association was not accounted for by differences in baseline predicted bleeding risk. Patients taking SSRIs were more likely to have an INR > 3 at the time of bleeding presentation, but did not have a greater proportion of supratherapeutic INRs overall while taking warfarin. We did not observe an increased hemorrhage risk in patients taking tricyclic antidepressants, suggesting an increased bleeding risk may be unique to SSRI antidepressants.

One potential mechanism of how SSRIs may increase bleeding risk could be related to the essential role of serotonin in the ability of platelets to aggregate.[16, 17] Platelets do not synthesize their own serotonin and therefore rely on reuptake of serotonin from the plasma, a process that is blocked by SSRIs.[10] Analyses comparing the blood of patients on and off SSRI treatment have shown the former to have significantly lower concentrations of platelet serotonin.[11]

Several prior studies have found an association between SSRI use and increased bleeding risk, although data amongst patients taking warfarin has been scarce.[3, 5, 7, 8, 18, 19] One study of older patients found a mild increase in upper gastrointestinal bleeding risk in patients taking antidepressants with potent SSRI effects (relative risk of 1.1).[20] Data on the risk of combining SSRI and warfarin has been limited and mostly from case-control analyses that did not account for potential confounders of bleeding risk.[21-23] A study by Teichert et al. showed that users of SSRIs were more likely to be over-anticoagulated, although our analysis found a significant association even after controlling for supratherapeutic INRs.[24] Labos et al. reported that patients taking antiplatelet agents had significant increases in bleeding risk among those patients taking aspirin, clopidogrel, or both along with an SSRI when compared to their non-SSRI taking counterparts.[25] Recent evidence has suggested improved physical and psychological outcomes in patients treated with SSRIs after stroke.[26] However, the potential in improving outcomes may need to be balanced by increased rates of bleeding.[27, 28] Since prevention of ischemic stroke is the main indication for the use of warfarin in patients with AF, the risks and benefits of SSRIs use in anticoagulated patients with stroke need to be carefully considered.

Our study has several limitations. Although we used a validated bleeding risk prediction score to control for potential differences in bleeding risk, there may have been additional or unmeasured confounding factors. We did not have measures of depression, frailty, or indication for SSRI or TCA. Information on aspirin exposure was not available except for those patients who developed hemorrhage, and although we found no significant differences in aspirin use between SSRI users and non-users, differential aspirin or NSAID use in the entire cohort may have led to differences in hemorrhage rates. We do not know why more

patients on SSRIs who had a bleeding event presented with supratherapeutic INRs; however, the overall proportion of INRs > 3 did not differ between SSRI users and other patients.

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Table 1

Clinical Characteristics of Patients with Atrial Fibrillation on Warfarin Taking Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), or neither class of medication

	Neither Med	TCA	SSRI
Total follow-up time (person years)	30,028	921	1,939
	% person-years or mean		
Age ≥ 75 years	53.2	54.4	55.1
Female sex	40.7	59.1	52.7
Hypertension	60.8	71.0	64.5
Diabetes mellitus	19.9	33.8	27.6
Congestive heart failure	36.7	45.8	43.0
Coronary artery disease	32.5	42.4	36.8
History of gastrointestinal bleeding	6.8	9.4	10.2
History of intracranial hemorrhage	0.5	1.1	1.1
History of other bleeds	2.7	3.7	3.2
$CHADS_2$ stroke risk score			
0	10.7	5.4	7.4
1	27.6	18.0	22.5
2	32.5	34.3	28.6
3	18.4	21.6	24.4
4	7.3	12.8	12.2
5	3.0	4.9	5.9
6	0.6	0.3	1.9
ATRIA bleeding risk score			
Low risk (0 – 3 points)	38.9	33.7	32.3
Intermediate risk (4 points)	44.4	42.6	42.8
High risk (5 – 10 points)	16.7	23.7	24.9
ATRIA bleeding risk score (mean)	2.45	2.73	2.99

Table 2

Rate ratios of all major hemorrhage, intracranial hemorrhage, and extracranial hemorrhage among anticoagulated patients taking Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), or neither class of medication

		Unadjusted Rate Ratio [95% CI]	Adjusted Rate Ratio* [95% CI]
All Major Hemorrhage	SSRI exposure	1.73 [1.27-2.35]	1.41 [1.04-1.92]
	TCA exposure	0.98 [0.55-1.73]	0.82 [0.46-1.46]
	Neither	Referent	Referent
Intracranial hemorrhage	SSRI exposure	1.50 [0.90-2.51]	1.36 [0.82-2.28]
	TCA exposure	0.99 [0.41-2.40]	0.92 [0.38-2.23]
	Neither	Referent	Referent
Major extracranial hemorrhage	SSRI exposure	1.88 [1.28-2.76]	1.47 [0.998-2.15]
	TCA exposure	0.96 [0.45-2.03]	0.76 [0.36-1.62]
	Neither	Referent	Referent

*Analyses adjusted for ATRIA bleeding risk score and time in INR range ≥ 3.0