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Selective serotonin reuptake inhibitors and intracerebral hemorrhage risk and outcome

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Abstract

Background and Purpose—Selective serotonin reuptake inhibitors have a well-established association with bleeding complications and conflicting reports on outcome after stroke. We sought to evaluate whether pre-ICH SSRI use increased ICH risk, and post-ICH SSRI use improved ICH outcome.

Methods—Through post-hoc analysis of the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study, SSRI use was categorized into no use, pre-ICH only, pre- and post-

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ICH use (termed “continuous”), and post-ICH only (termed “new”). Using multivariable modeling, associations were sought between pre-ICH SSRI use and ICH risk in the case-control set, and associations between post-ICH SSRI use and 3-month outcome were analyzed in the ICH case set. Exploratory analyses sought to assess influence of race/ethnicity in models.

Results—The final study cohort consisted of 2287 ICH cases and 2895 controls. Pre-ICH SSRI use was not associated with ICH risk (OR, 0.824;95%CI, 0.632- 1.074) nor potentiation of ICH risk with anticoagulant or antiplatelet use. New post-ICH SSRI use was associated with unfavorable modified Rankin Scale score at 3 months after ICH (OR,1.673; 95%CI,1.162-2.408; p=0.006) in multivariable analyses. Additional propensity score analysis indicated a similar trend but did not reach statistical significance (P=0.107). When stratified by race/ethnicity, multivariable modeling demonstrated reduced ICH risk with pre-ICH SSRI use in Hispanics (OR,0.513; 95%CI,0.301-0.875; p=0.014), but not non-Hispanic whites or black, and no associations between post-ICH SSRI use and 3-month outcome in any racial/ethnic group.

Conclusions—In a large multi-ethnic cohort, pre-ICH SSRI use was not associated with increased ICH risk but post-ICH SSRI use was associated with unfavorable 3-month neurological outcome after ICH.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01202864.

Keywords

intracerebral hemorrhage; selective serotonin reuptake inhibitors; risk; outcome; multivariable model

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of depression and other psychiatric disorders. However, inhibiting serotonin reuptake results in platelet dysfunction.[1] Observational studies have found associations between SSRIs and abnormal bleeding.[2, 3] Several studies also suggested increased risk for intracerebral hemorrhage (ICH) in patients treated with SSRIs, [4-7] though unconfirmed.[8, 9] Combined use of SSRI and other antiplatelets/anticoagulants has been associated with higher risk of ICH in some studies,[5] but not in others.[10] Thus, no consensus exists, inviting further study.

Further, SSRI use may affect ICH outcomes. In ischemic stroke, pre-stroke SSRI use has been associated with elevated 30-day mortality[11] and lower rates of discharge to home,[12] but these findings have not been reproduced.[13] Recent clinical trials found inconsistent efficacy of fluoxetine initiation after ischemic stroke for long-term motor recovery.[14, 15] However, little data exist to guide SSRI use in ICH.

The objectives of this study were to explore ICH risk and outcome with SSRI use in a large, prospective case-control study. We hypothesized that pre-ICH SSRI use increased ICH risk due to anti-platelet effects, but new post-ICH SSRI use improved neurological outcome after ICH.

Materials and Methods

Standard protocol approvals, registrations, and patient consents.

The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study[16] was approved by the institutional review boards of each enrolling institution. Informed consent was obtained from all enrolled participants or their legal representatives.

Data availability statement

ERICH study data, including interview, chart abstraction, and imaging findings for cases and controls, obtained through direct request from the ERICH study steering committee. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study population.

Described previously,[16] the ERICH study was a multicenter, prospective observational case-control study of ICH risk factors and outcomes which recruited 1,000 non-Hispanic white, 1,000 non-Hispanic black, and 1,000 Hispanic patients with spontaneous, primary ICH and the same number of matched ICH-free controls based on age, race/ethnicity, sex, and geographic location. Participants were enrolled from 19 US sites comprising 42 hospitals. Patients diagnosed with spontaneous ICH, who were over 18 years of age and resided within 50 miles of the recruiting center were eligible for the study. Cases of ICH due to malignancies, irreversible coagulopathy, dural venous sinus thrombosis, vascular malformations, aneurysms, tumors, or hemorrhagic conversion of recent ischemic stroke were not eligible for the study. All participants or designated proxies underwent a standardized data collection protocol including a personal interview and medical chart abstraction.

Antidepressant Use.

Using medical chart abstraction and patient/family interviews, all medications taken in the 2 weeks before ICH onset were recorded; for controls, 2 weeks before the interview, to avoid recall bias. Medications at discharge and the first follow-up (3 months) were also recorded. SSRI used for the current analysis included citalopram, escitalopram, fluoxetine, paroxetine, and sertraline, vilazodone, or vortioxetine. Serotonin and norepinephrine reuptake inhibitors (SNRI) use included desvenlafaxine, duloxetine, milnacipran, or venlafaxine. Serotonin antagonist and norepinephrine reuptake inhibitors (SARI) included trazodone. Norepinephrine–dopamine reuptake inhibitor (NDRI) included bupropion; tricyclics included amitriptyline, desipramine, doxepin, imipramine, or nortriptyline; and tetracyclic included mirtazapine. SSRI use was conceptualized as pre-ICH only, new post-ICH (at discharge and/or 3 months but not pre-ICH use); continuous (at pre-ICH and discharge and/or 3 months), and no SSRI use at any time point.

Covariates.

Data used in the present study included age, sex, race/ethnicity, body mass index (BMI), history of hypertension, diabetes mellitus, elevated cholesterol, history of heart diseases,

prior stroke, concurrent diagnosis of depression, smoking, heavy alcohol use (>14 drinks per week), illicit drug use, concurrent anticoagulant or antiplatelet use, newly diagnosed depression, presence of APOE e2/e4 alleles, and antidepressant use from pre-ICH through 3-months followup, initial Glasgow Coma Scale score, hematoma location and volume by computed tomography at diagnosis, presence of intraventricular hemorrhage, pre-ICH modified Rankin Scale (mRS), and mRS at discharge and 3-month follow-up. History of heart disease was defined as prior history of any cardiac disease. Smoking history was classified as current or former history of cigarette smoking. Illicit drug abuse included history of current or former use of marijuana, cocaine/crack, or other illegal substances. Anticoagulant use was defined as concurrent use of warfarin, heparin, low molecular weight heparin, or factor Xa inhibitors or direct thrombin inhibitor. Antiplatelet use was defined as concurrent use of aspirin or non-aspirin antiplatelet. New diagnosis of depression was defined as diagnosis during hospitalization without prior history of depression.

Outcomes.

Neurologic outcome at 3 months following ICH was assessed by telephone for mRS. A mRS ≥3 was defined as unfavorable outcome, and mRS <3 was considered favorable outcome.

Statistical analysis.

Descriptive statistics are given as mean (standard deviation) for continuous variables or number (percent) for categorical variables with t-test or chi-square, as appropriate, used for comparisons. For each outcome, a univariate analysis was performed by building a model with each individual variable as a predictor. Binary outcomes were modeled using logistic regression, while continuous outcomes were modeled using linear regression. Each variable found to have a p-value <0.15 for association with outcome in the univariate analysis was included in the initial multivariable model. Backwards selection based on Akaike Information Criterion was used to identify the final multivariable model. During model selection, SSRI use was forced into each model. Baseline and outcome characteristics of matched case-control design were analyzed as described above. ICH risk and 3-month outcome analyses were conducted using two different cohorts. ICH risk analyses used interview data in matched case-control design including ICH patients and non-ICH controls from the general population. ICH outcome analyses used interview and chart abstraction data from ICH cases. For the association of new post-ICH SSRI use and 3-month outcome, propensity score analyses were used by matching patients into the balanced, 1:1 ratio nearest neighbor approach (subjects with ICH). Exploratory analyses using the above statistical approaches sought to assess influence of race/ethnicity in our models.

Results

Pre-ICH SSRI use and risk of ICH.

For analyses, 2287 of 3000 ICH cases were used with 382 participants excluded due to lack of specific medications history and 331 patients for missing crucial variables. There were 2895 of 3000 controls used in analyses with 56 participants excluded due to lack of specific medications history and 49 for missing crucial variables (Supplemental Table I). Table 1 describes the study subjects stratified by pre-ICH SSRI use. Pre-ICH SSRI use was not

associated with overall ICH risk, but when stratified by ICH subtype, pre-ICH SSRI use was associated with decreased non-lobar ICH risk (Table 2). Models were adjusted for BMI, history of stroke, depression, heart disease, hypertension, high cholesterol, heavy alcohol use, or use of street drugs. Presence of apolipoprotein e2 and e4 alleles were included in lobar ICH models. Since SSRIs potentiate antiplatelet effects,[1] interaction terms between SSRI and antiplatelet/anticoagulant use were sought, but not found, for SSRI and antiplatelet use (odds ratio [OR], 1.147; 95%CI, 0.508-2.590, p=0.146) nor SSRI and anticoagulant use (OR, 1.201; 95%CI, 0.539- 2.680, p=0.148). Finally, no association was found between SSRI use and hematoma volume in separate multivariable modeling of patients with ICH (−2.7% difference in ICH volume; 95%CI, 24.81-25.85%), when controlling for the same covariates, despite known platelet interactions.[1]

SSRI use and 3-month outcome of ICH.

For outcome analyses, 1676 of 3000 ICH cases were used with 996 participants excluded due to lack of follow up mRS and 228 for missing crucial variables from the total ERICH cohort. Summary statistics for ICH cases analyzed as the outcome cohort stratified by SSRI use are shown in Table 3. No relationships were found between pre-ICH SSRI use (OR, 1.557; 95%CI, 0.535- 4.526, p=0.417) or continued SSRI use (OR, 1.498; 95%CI, 0.86-2.612; p=0.154) and 3-month unfavorable outcome. However, new, post-ICH SSRI use was associated with unfavorable outcome (mRS≥3) at 3 months after ICH, after adjustment for covariates (Table 4). Further, propensity score analysis was used to test the association between new, post-ICH SSRI use and 3-month outcome. Supplemental Table II contains the baseline and outcome characteristics for propensity score matched ICH patients with new, post-ICH SSRI use versus ICH patients without post-ICH SSRI use. Using the same covariates from the primary outcome model, multivariable modelling of propensity score matched ICH cases was similar with adjusted ORs of new, post-ICH SSRI use likely associated with unfavorable 3-month ICH outcome, though not statistically significant (OR, 1.376; 95%CI, 0.925-2.471; p=0.107).

Subgroup analyses by race/ethnicity.

For the subgroup analyses by race/ethnicity, pre-ICH SSRI use in the study cohort was stratified by race/ethnicity (Supplemental Table III). Adjusted ORs of lobar and non-lobar ICH risk stratified by racial/ethnic groups are presented in Supplemental Table IV. After adjusting for covariates, pre-ICH SSRI use was not associated with ICH risk for non-Hispanic white or black participants, but pre-ICH SSRI use in Hispanics was associated with reduced risk (OR, 0.513; 95%CI, 0.301-0.875; p=0.014). Subgroup analyses were carried out for lobar and non-lobar ICH. In Hispanic participants only, pre-ICH SSRI use was associated with reduced risk of non-lobar ICH (OR, 0.398; 95%CI, 0.210-0.753; p=0.005), but not lobar ICH after adjustment for APOE genotyping. Outcome models for new, post-ICH SSRI use were also stratified by race/ethnicity (Supplemental Table V). New, post-ICH SSRI use was not associated with 3-month ICH outcome in Hispanic, non-Hispanic black, or white participants, though each subgroups' adjusted ORs were consistent with our primary finding of new, post-ICH SSRI use associated with unfavorable 3-month outcome in the total cohort (non-Hispanic black, OR, 1.713; 95%CI, 0.896-3.276; p=0.104; Hispanic, OR, 1.392; 95%CI, 0.714-2.714; p=0.332; non-Hispanic White, 1.770; 95%CI, 0.900-3.480; p=0.098).

Discussion

In this large, multiethnic prospective case-control cohort of participants with ICH, significant associations between pre-ICH SSRI use and ICH risk were not found. Despite known pharmacology, no interaction term between pre-ICH SSRI and antiplatelet or anticoagulant medications were found for ICH risk, and pre-ICH SSRI use was not associated with hematoma volume. New post-ICH SSRI use was associated with unfavorable mRS at 3 months after ICH, while controlling for known covariates. Similarly, modeling using propensity score matching found comparable ORs, but was not statistically significant. Subgroup exploratory analyses stratified by race/ethnicity found pre-ICH SSRI use was associated with decreased ICH risk of non-lobar ICH for Hispanic patients, and new post-ICH SSRI use was not associated with worse outcome at 3 months after ICH in black, white or Hispanic patients.

The current findings for pre-ICH SSRI use and ICH risk are largely congruent with and build upon prior studies. However, prior studies were not specific to SSRIs,[8, 10, 17], inadequately controlled,[17] smaller samples,[8, 10, 17] or not focused on primary ICH.[8, 17] Our sample controlled for multiple known covariates of risk in a single case-control cohort, focused on primary ICH, and specifically analyzed SSRI use. However, other reports have demonstrated increased ICH risk with pre-ICH SSRI use, but again using smaller samples unable to control for many relevant covariates.[18, 19] Further, prior meta-analysis pre-ICH SSRI exposure with oral anticoagulants was associated with an increased risk of brain bleeding, though limited by studies not focused on primary ICH or lacking ICH-relevant medical history and physiologic data.[20] However, absence of significant effects for the interaction term between SSRI and antiplatelets/anticoagulants use in our analyses is supported by prior report.[10] Given the size and depth of ICH-specific data of the present sample, pre-ICH SSRI use is unlikely to increase risk of ICH, but if risk is increased, the effect size is likely to be small.

Implications of SSRI use after acute neurological injury are complex, as randomized control trial and meta-analysis data indicate different results between SSRI treatment after ischemic stroke and neurologic function in patients undergoing rehabilitation.[14,15,21] Association between post-ICH SSRI use and unfavorable 3-month neurological outcome in our study runs counter to prior publications.[22] Further, in our analyses, pre-ICH and continued SSRI use through the study period were not associated with unfavorable outcome, and subgroup analyses found no association between new, post-ICH SSRI use and unfavorable 3-month mRS in racial/ethnic subgroup analyses. However, despite lack of statistical significance, effect sizes in non-Hispanic white and black patients with ICH were consistent with the association of unfavorable outcome in the total study cohort, and lack of associations was likely related to sample size. Notably, a randomized controlled trial of fluoxetine for motor recovery after acute ICH is currently ongoing and may directly address the question of potential therapeutic effect of SSRIs after ICH.[23]

One advantage of the ERICH cohort is its ability to examine racial/ethnic differences in ICH. Exploratory findings from the present study suggested that Hispanic ethnicity may affect ICH risk in pre-ICH SSRI users, which we believe to be the first study to examine

such differences in ICH. Although no association between pre-ICH SSRI use and ICH risk was found in the total cohort, pre-ICH SSRI use was associated with reduced ICH risk in Hispanic patients, which appears to be primarily fueled by non-lobar location. Though hematoma location does not always confer ICH etiology,[24] no relationship was found between pre-ICH SSRI use and lobar ICH in blacks, whites, or Hispanics, after adjusting for APOE2 and APOE4 status. Our results should be interpreted cautiously due to the modest numbers of pre-ICH SSRI users in Hispanic and black patients in our cohort.

Separating SSRI effects from treated or untreated concomitant depression prior to or after ICH is difficult. [25-27] Post-stroke depression negatively effects stroke recovery.[22] Further, diagnostic and treatment rates of depression among blacks and Hispanic, though comparable, were far less than observed for whites.[28] Since the ERICH study was not designed to specifically address depression and treatment in ICH, detailed qualitative and quantitative measures of depression are outside the scope of this dataset. Further, timing of SSRI exposure around ICH ictus, regularity of SSRI use, and actual doses taken are unable to be determined in this study. These limitations should be considered within known SSRI pharmacodynamics, i.e., requiring several weeks to realize effects but lasting several months. While diagnosis of depression was included in outcome modeling, only 40 participants were newly diagnosed with depression during hospitalization for ICH, and post-discharge diagnoses of depression were not recorded. Finally, despite the large overall sample size, segmentation of SSRI use into pre-ICH only, pre- and post-ICH, or post-ICH only resulted in relatively small groups, limiting covariate inclusion. This limitation was even greater in the exploratory analyses of racial/ethnicity effects. Despite these limitations, the advantage of our study is the methodologically rigorous, large case-control structure specific to ICH and its ability to control for multiple confounders and explore various subpopulations (i.e., hematoma location, race/ethnicity, etc.).

In conclusion, pre-ICH SSRI use was not associated with ICH risk in our cohort. New, post-ICH SSRI use was associated with unfavorable 3-month neurological outcome, but these data cannot be used to advise on prescribing antidepressants in patients with depression after ICH. Further, These effects appear to vary across different race/ethnicities and ICH etiologies. The present data may be used to determine variability and potential effect size of SSRI use in ICH patients to power prospective studies in a variety of ICH populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

APOE	apolipoprotein E gene

BMI	body mass index
CI	confidence interval
ERICH	Ethnic/Racial Variations of Intracerebral Hemorrhage
GCS	Glasgow Coma Scale
IVH	intraventricular hemorrhage
mRS	modified Rankin Scale
NDRI	norepinephrine dopamine reuptake inhibitor
OR	odds ratio
SARI	serotonin antagonist and reuptake inhibitors
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

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Table 1.
Characteristics of ERICH controls and ICH cases stratified by pre-ICH SSRI use.

Significance was set at p< 0.05 using chi-square and t-test's as appropriate. Note: %, percent; APOE, apolipoprotein E allele; BMI, body mass index; ICH, intracerebral hemorrhage; n, number; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitors; NDRI, norepinephrine–dopamine reuptake inhibitor.

	No SSRI use (n=4830)	SSRI use (n=352)	Total (n=5182)	p-value
ICH, n (%)	2141 (44.3)	146 (41.5)	2287 (44.1)	0.299
Lobar ICH, n (%)	646 (19.4)	60 (22.6)	706 (19.6)	0.208
Non-lobar ICH, n (%)	1495 (35.7)	86 (29.5)	1581 (35.3)	0.030
Age, mean (SD), years	61.2 (14.1)	65.6 (12.4)	61.5 (14.0)	<0.001
Female, n (%)	1923 (39.8)	220 (62.5)	2143 (41.4)	<0.001
BMI, mean (SD)	29.3 (6.9)	30.0 (7.3)	29.4 (6.9)	0.149
Prior Stroke, n (%)	215 (4.5)	36 (10.2)	251 (4.8)	<0.001
Hypertension, n (%)	3046 (63.1)	248 (70.5)	3294 (63.6)	0.005
Diabetes, n (%)	1065 (22.0)	120 (34.1)	1185 (22.9)	<0.001
High Cholesterol, n (%)	2038 (42.2)	232 (65.9)	2270 (43.8)	<0.001
Heart Disease, n (%)	761 (15.8)	89 (25.3)	850 (16.4)	<0.001
Depression, n (%)	729 (15.1)	262 (74.4)	991 (19.1)	<0.001
Heavy Alcohol Use, n (%)	543 (11.2)	22 (6.3)	565 (10.9)	0.004
Prior Tobacco, n (%)	2479 (51.3)	203 (57.7)	2682 (51.8)	0.021
Current Tobacco Use, n (%)	904 (18.7)	50 (14.2)	954 (18.4)	0.035
Illicit Drug Use, n (%)	305 (6.3)	13 (3.7)	318 (6.1)	0.048
Non-Aspirin Antiplatelet Use, n (%)	204 (4.2)	31 (8.8)	235 (4.5)	<0.001
Aspirin Use, n (%)	1945 (40.3)	173 (49.1)	2118 (40.9)	0.001
Anticoagulant Use, n (%)	270 (5.6)	41 (11.6)	311 (6.0)	<0.001
SNRI Use, n (%)	92 (1.9)	4 (1.1)	96 (1.9)	0.302
SARI Use, n (%)	56 (1.2)	23 (6.5)	79 (1.5)	<0.001
NDRI Use, n (%)	33 (0.7)	22 (6.3)	55 (1.1)	<0.001
Tricyclic Antidepressant Use, n (%)	49 (1.0)	8 (2.3)	57 (1.1)	0.029
Tetracyclic Antidepressant Use, n (%)	16 (0.3)	4 (1.1)	20 (0.4)	0.019
Presence of APOE e2, n (%)	707(14.6)	49(13.9)	756(14.6)	0.713
Presence of APOE e4, n (%)	1371(28.4)	103(29.3)	1474(28.4)	0.725

Table 2.

Multivariable modeling of associations between pre-ICH SSRI use and ICH risk.

Regression models for ICH and subtypes were adjusted for the listed covariates. Presence of APOE2 and E4 alleles were included in lobar ICH models only. Significance was set at $p < 0.05$. Abbreviations: %, percent; APOE, apolipoprotein E; BMI, body mass index; CI, confidence interval; ICH, intracerebral hemorrhage; NDRI, norepinephrine–dopamine reuptake inhibitor; OR, odds ratio; SARI, Serotonin antagonist and reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Predictor	Any ICH		Lobar ICH		Non-lobar ICH	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
SSRI	0.824 (0.632, 1.074)	0.152	0.952 (0.669, 1.355)	0.785	0.724 (0.528, 0.992)	0.044
SNRI	0.480 (0.296, 0.778)	0.003	0.594 (0.313, 1.127)	0.111	0.387 (0.211, 0.713)	0.002
SARI	0.767 (0.46, 1.277)	0.308	1.080 (0.568, 2.053)	0.814	0.605 (0.320, 1.144)	0.122
NDRI	0.340 (0.16, 0.722)	0.005	0.201 (0.047, 0.851)	0.029	0.442 (0.191, 1.023)	0.057
Tricyclic	1.060 (0.596, 1.882)	0.843	1.394 (0.661, 2.938)	0.383	0.847 (0.425, 1.689)	0.637
Tetracyclic	1.194 (0.442, 3.224)	0.727	1.530 (0.498, 4.695)	0.458	0.757 (0.219, 2.615)	0.660
Antiplatelet	0.776 (0.682, 0.884)	<0.001	0.893 (0.739, 1.080)	0.244	0.717 (0.618, 0.831)	<0.001
Anticoagulant	2.491 (1.871, 3.315)	<0.001	2.445 (1.712, 3.491)	<0.001	2.543 (1.837, 3.520)	<0.001
BMI	0.983 (0.974, 0.991)	<0.001	0.967 (0.954, 0.981)	<0.001	0.989 (0.979, 0.999)	0.026
Prior Stroke	6.556 (4.57, 9.404)	<0.001	5.722 (3.706, 8.836)	<0.001	7.033 (4.801, 10.302)	<0.001
Depression	1.041 (0.878, 1.234)	0.646	1.247 (0.981, 1.587)	0.072	0.984 (0.810, 1.196)	0.87
Heart Disease	1.180 (0.985, 1.414)	0.073	1.384 (1.087, 1.764)	0.009	1.053 (0.852, 1.302)	0.631
Hypertension	3.614 (3.148, 4.151)	<0.001	2.246 (1.835, 2.749)	<0.001	4.635 (3.942, 5.449)	<0.001
High Cholesterol	0.533 (0.467, 0.608)	<0.001	0.655 (0.540, 0.795)	<0.001	0.503 (0.434, 0.584)	<0.001
Heavy Alcohol Use	1.680 (1.389, 2.031)	<0.001	1.257 (0.940, 1.681)	0.122	1.903 (1.546, 2.343)	<0.001
Illicit Drug Use	1.605 (1.250, 2.060)	<0.001	1.376 (0.931, 2.033)	0.109	1.778 (1.353, 2.336)	<0.001
APOE2 allele	N/A	N/A	1.232 (0.974, 1.559)	0.083	N/A	N/A
APOE4 allele	N/A	N/A	1.422 (1.177, 1.719)	<0.001	N/A	N/A

Table 3.
Characteristics of ERICH ICH cases stratified by SSRI use.

SSRI use was conceptualized as pre-ICH only, new post-ICH (up to 3 months post-ICH but not pre-ICH use); continuous (pre-ICH and up to 3 months post-ICH), and no SSRI use at any time point. Significance was set at $p< 0.05$ using one-way analysis of variance across SSRI use categories. Note: %, percentage; BMI, body mass index; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; ml, milliliter; mRS, modified Rankin Scale; NDRI, norepinephrine–dopamine reuptake inhibitor; SARI, Serotonin antagonist and reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

	No SSRI use (n=1332)	Pre-ICH use only (n=28)	New SSRI use (n=208)	Continuous SSRI use (n=108)	Total (n=1676)	p-value
Age, mean (SD), years	60.7 (13.4)	67.0 (11.9)	56.0 (13.6)	64.7 (12.7)	60.5 (13.5)	<0.001
Female, n (%)	530 (39.8)	16 (57.1)	79 (38.0)	66 (61.1)	691 (41.2)	<0.001
BMI, mean (SD)	29.5 (7.2)	28.5 (7.9)	29.6 (7.1)	29.5 (6.5)	29.5 (7.2)	0.618
Prior Stroke, n (%)	108 (8.1)	9 (32.1)	16 (7.7)	16 (14.8)	149 (8.9)	<.0001
Hypertension, n (%)	1036 (77.8)	21 (75.0)	161 (77.4)	89 (82.4)	1307 (78.0)	0.694
Diabetes, n (%)	326 (24.5)	13 (46.4)	43 (20.7)	44 (40.7)	426 (25.4)	<0.001
High Cholesterol, n (%)	518 (38.9)	22 (78.6)	60 (28.8)	67 (62.0)	667 (39.8)	<0.001
Heart Disease, n (%)	227 (17.0)	2 (7.1)	30 (14.4)	37 (34.3)	296 (17.7)	<0.001
Depression, n (%)	182 (13.7)	12 (42.9)	37 (17.8)	83 (76.9)	314 (18.7)	<0.001
Heavy Alcohol Use, n (%)	186 (14.0)	3 (10.7)	30 (14.4)	9 (8.3)	228 (13.6)	0.389
Current Tobacco Use, n (%)	660 (49.5)	18 (64.3)	107 (51.4)	64 (59.3)	849 (50.7)	0.112
Illicit Drug Use, n (%)	96 (7.2)	3 (10.7)	19 (9.1)	6 (5.6)	124 (7.4)	0.579
Non-Aspirin Antiplatelet Use, n (%)	70 (5.3)	4 (14.3)	14 (6.7)	14 (13.0)	102 (6.1)	0.003
Aspirin Use, n (%)	564 (42.3)	14 (50.0)	75 (36.1)	63 (58.3)	716 (42.7)	0.002
Anticoagulant Use, n (%)	120 (9.0)	6 (21.4)	13 (6.3)	27 (25.0)	166 (9.9)	<0.001
SNRI Use, n (%)	30 (2.3)	1 (3.6)	4 (1.9)	0 (0.0)	35 (2.1)	0.422
SARI Use, n (%)	7 (0.5)	3 (10.7)	0 (0.0)	10 (9.3)	20 (1.2)	<0.001
NDRI Use, n (%)	8 (0.6)	1 (3.6)	0 (0.0)	4 (3.7)	13 (0.8)	<0.001
Tricyclic Antidepressant Use, n (%)	19 (1.4)	2 (7.1)	2 (1.0)	0 (0.0)	23 (1.4)	0.034
Tetracyclic Antidepressant Use, n (%)	9 (0.7)	0 (0.0)	1 (0.5)	2 (1.9)	12 (0.7)	0.502
Admission GCS, mean (SD)	13.3 (3.0)	12.0 (3.8)	12.8 (3.1)	13.5 (2.8)	13.3 (3.1)	<0.001
Pre-ICH mRS ≥3, n (%)	71 (5.3)	4 (14.3)	4 (1.9)	21 (19.4)	100 (6.0)	<0.001
Initial GCS, mean (SD)	13.3 (3.0)	12.0 (3.8)	12.8 (3.1)	13.5 (2.8)	13.3 (3.1)	<0.001
Lobar, n (%)	937 (70.3)	20 (71.4)	149 (71.6)	65 (60.2)	1171 (69.9)	<0.001
Presence of IVH, n (%)	468 (35.1)	16 (57.1)	102 (49.0)	39 (36.1)	625 (37.3)	<0.001
ICH volume, mean (SD), mL	14.4 (16.5)	17.8 (22.3)	20.9 (21.8)	14.4 (18.1)	15.3 (17.5)	<0.001
Post-ICH mRS ≥3, n (%)	937 (70.3)	25 (89.3)	176 (84.6)	82 (75.9)	1220 (72.8)	<0.001
3-month mRS ≥3 , n (%)	649 (48.7)	22 (78.6)	134 (64.4)	72 (66.7)	877 (52.3)	<0.001

Table 4.

Multivariable model of association between new, post-ICH SSRI user and 3-month ICH outcome (mRS≥3) including *a priori* covariates.

Regression model was adjusted for the listed covariates. Significance was set at p< 0.05. Note: CI, confidence interval; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin score; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

Predictor	OR (95% CI)	p-value
New SSRI Use	1.601 (1.098-2.336)	0.015
Age (per year)	1.043 (1.032-1.054)	<0.001
Female	1.460 (1.139-1.870)	0.003
Prior Stroke	1.914 (1.240-2.956)	0.003
Diabetes	1.345 (1.018-1.777)	0.037
History of Depression	1.473 (1.074-2.021)	0.016
Post-ICH Depression	1.388 (0.647-2.978)	0.400
Pre-ICH mRS ≥3	5.743 (2.943-11.206)	<0.001
Discharge mRS ≥3	5.520 (4.078-7.472)	<0.001
Lobar Location	0.375 (0.274-0.512)	<0.001
ICH Volume (per mL)	1.042 (1.032-1.053)	<0.001
Presence of IVH	1.223 (0.948-1.577)	0.121
Initial GCS (per point increase)	0.890 (0.852-0.929)	<0.001