ORIGINAL RESEARCH

Selective Serotonin Reuptake Inhibitors and Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: An Analysis From the ROCKET AF Trial

Gene R. Quinn, MD, MS, MPH; Anne S. Hellkamp, MS; Graeme J. Hankey, MD; Richard C. Becker, MD; Scott D. Berkowitz, MD; Günter Breithardt, MD; Maurizio Fava, MD; Keith A. A. Fox, MB, ChB; Jonathan L. Halperin, MD; Kenneth W. Mahaffey, MD; Christopher C. Nessel, MD; Manesh R. Patel, MD; Jonathan P. Piccini, MD, MHS; Daniel E. Singer, MD

***Background*—**There is concern that selective serotonin reuptake inhibitors (SSRIs) substantially increase bleeding risk in patients taking anticoagulants.

***Methods and Results*—**We studied 737 patients taking SSRIs in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Embolism and Stroke Trial in Atrial Fibrillation) trial of rivaroxaban compared with warfarin for the prevention of stroke/systemic embolism in patients with atrial fibrillation. These patients were propensity score matched 1:1 to 737 patients not taking SSRIs. The primary outcome measure was major and nonmajor clinically relevant bleeding events, the principal safety outcome in ROCKET AF. Over a mean 1.6 years of follow-up, the rate of major/nonmajor clinically relevant bleeding was 18.57 events/100 patient-years for SSRI users versus 16.84 events/100 patient-years for matched comparators, adjusted hazard ratio (aHR) of 1.16 (95% confidence interval [CI], 0.95–1.43). The aHRs were similar in patients taking rivaroxaban (aHR 1.11 [95% CI, 0.82–1.51]) and those taking warfarin (aHR 1.21 [95% CI, 0.91–1.60]). For the rarer outcome of major bleeding, the aHR for SSRI users versus those not taking SSRIs was 1.13 (95% CI, 0.62–2.06) for rivaroxaban; for warfarin, the aHR was higher, at 1.58 (95% CI, 0.96–2.60) but not statistically significantly elevated.

***Conclusions*—**We found no significant increase in bleeding risk when SSRIs were combined with anticoagulant therapy, although there was a suggestion of increased bleeding risk with SSRIs added to warfarin. While physicians should be vigilant regarding bleeding risk, our results provide reassurance that SSRIs can be safely added to anticoagulants in patients with atrial fibrillation.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT00403767. **(*J Am Heart Assoc*. 2018;7: e008755. DOI: 10.1161/JAHA.118.008755.)**

Key Words: anticoagulation • atrial fibrillation • bleeding risk • rivaroxaban • selective serotonin reuptake inhibitors

Treatment with oral anticoagulants, including warfarin and non–vitamin K antagonist oral anticoagulants, significantly decreases the risk of ischemic stroke in patients with atrial fibrillation (AF), but also increases the risk of bleeding.[1,2] The risk of bleeding on oral anticoagulants depends on multiple patient factors, including the use of concomitant medications. Because of their relatively favorable side-effect profiles, selective serotonin reuptake inhibitors (SSRIs) are recommended by guidelines as first-line therapy for depressive and anxiety disorders, particularly in the

From the Smith Center for Outcomes Research, Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA (G.R.Q.); Harvard Medical School, Boston, MA (G.R.Q., M.F., D.E.S.); Alaska Heart and Vascular Institute, Anchorage, AK (G.R.Q.); Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (A.S.H., M.R.P., J.P.P.); Medical School, The University of Western Australia, Crawley, Australia (G.J.H.); University of Cincinnati College of Medicine, Cincinnati, OH (R.C.B.); Bayer U.S. LLC, Parsippany, NJ (S.D.B.); Department of Cardiovascular Medicine, Hospital of the University of Münster, Germany (G.B.); Department of Psychiatry (M.F.), and Division of General Internal Medicine (D.E.S.), Massachusetts General Hospital, Boston, MA; University of Edinburgh and Royal Infirmary of Edinburgh, United Kingdom (K.A.A.F.); Mount Sinai School of Medicine, New York, NY (J.L.H.); Department of Medicine, Stanford University, Stanford, CA (K.W.M.); Janssen Research & Development, Raritan, NJ (C.C.N.).

Correspondence to: Daniel E. Singer, MD, Division of General Internal Medicine, 100 Cambridge St., 16th Floor, Massachusetts General Hospital, Boston, MA, 02114. E-mail: desinger@mgh.harvard.edu

Received January 25, 2018; accepted June 14, 2018.

Clinical Perspective

What Is New?

- Patients with atrial fibrillation may also have anxiety and/or depression.
- As a result, patients may be prescribed selective serotonin reuptake inhibitors (SSRIs) as well as anticoagulants.
- Given the platelet inhibitory effects of SSRIs, there is concern that the addition of SSRIs to anticoagulants may substantially raise the risk of bleeding.
- We assessed whether SSRIs increased the risk of bleeding in the ROCKET AF randomized trial of rivaroxaban versus warfarin in patients with atrial fibrillation.
- We found no strong evidence that SSRIs raised the risk of major plus nonmajor clinically relevant bleeding events when combined with anticoagulants overall, nor with either rivaroxaban or warfarin, individually.
- There was a suggestion that SSRIs added to warfarin might increase the risk of major bleeds, but this finding was not statistically significant.

What Are the Clinical Implications?

- There are patients with atrial fibrillation taking anticoagulants to prevent stroke, for whom SSRIs are indicated.
- While physicians should be vigilant regarding bleeding risk, our results provide reassurance that SSRIs can be safely added to anticoagulants in patients with atrial fibrillation.

elderly.[3–5] As a result, SSRIs may be prescribed along with oral anticoagulants in patients with AF, a condition particularly common in older individuals.[6] A concern is that SSRIs have been linked to increased risk of bleeding.[7–16] Indeed, the product information for SSRIs includes a warning about possible increased bleeding risk.[17] This increase in bleeding risk is thought to be due to serotonin's role in platelet aggregation, which is inhibited by SSRIs, as well as to a direct decrease in platelet adhesion to both collagen and fibrinogen.[11,18–20] Further, SSRIs inhibit the cytochrome P450 metabolic pathway, potentially increasing warfarin's effect.[21–23] Several studies have reported that the combination of warfarin and SSRIs leads to an increased risk of major hemorrhage.[24–28] No study has yet examined the possible drug-drug interaction between SSRIs and non–vitamin K antagonist oral anticoagulants. In the current study, we use the experience of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Embolism and Stroke Trial in Atrial Fibrillation) (NCT00403767) randomized trial[29] to assess whether SSRIs increased the risk of bleeding in both patients treated with the factor Xa inhibitor rivaroxaban and those treated with warfarin, adjusted to achieve a target international normalized ratio (INR) of 2.5 (range, 2.0–3.0).

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The methodology and results of the ROCKET AF trial have been described in detail.[29,30] Briefly, ROCKET AF was a multicenter, international, double-blind, double-dummy, noninferiority randomized trial comparing fixed-dose rivaroxaban (20 mg once daily, or 15 mg once daily in patients with creatinine clearance of 30–49 mL/min) with adjusted-dose warfarin (target INR, 2.5; range, 2.0–3.0) for the prevention of stroke (ischemic or hemorrhagic) or systemic embolism.

Patient Population

Complete inclusion and exclusion criteria for ROCKET AF have been published.[29] Briefly, patients with electrocardiographically documented nonvalvular AF at moderate to high risk for stroke were recruited at 1178 participating sites in 45 countries. Patients in ROCKET AF were seen at study entry, 2 and 4 weeks, and then monthly during follow-up. At these visits, patients were asked to describe their medications, which could have included SSRIs. There were too few patients who took serotonin and norepinephrine reuptake inhibitors (SNRIs) or trazodone to study the effects of these agents. To focus on SSRIs, we excluded patients who took an SNRI but did not take an SSRI (n=119), took both an SSRI and an SNRI but started the SNRI first (n=5), took trazodone but did not take an SSRI at any time (n=63), or took both trazodone and an SSRI but took trazodone first (n=7). We included 9 patients who took an SNRI and 21 patients who took trazodone concurrently with an SSRI for whom the SSRI was started first or concurrently with the other agent. This resulted in 737 patients taking an SSRI at any time during the trial. Our safety (bleeding rate) analyses excluded patients who did not receive their randomized study anticoagulant: 2 in the SSRI group and 1 in the matched no-SSRI group. This resulted in 734 matched pairs. As in the original ROCKET AF trial report, our efficacy analyses excluded 17 SSRI-using patients from one Good Clinical Practice–violating site, resulting in analyses of 720 matched pairs.

Exposure

Patients were considered to be taking an SSRI if their medication record listed "selective serotonin reuptake inhibitors," including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. SNRIs included desvenlafaxine, duloxetine, or venlafaxine.

Patients must have been taking the SSRI medication for a minimum of 14 consecutive days to be considered in the medication group. During follow-up, interruptions of ≤7 days

were ignored. Changes from 1 type of SSRI to another were considered a continuation of SSRI therapy. Patients who took more than 1 type of SSRI were counted in the category of the SSRI taken for the largest proportion of time.

Outcomes

This study's primary outcome was the safety composite of major and nonmajor clinically relevant (NMCR) bleeding events, the ROCKET AF trial's primary safety outcome. The secondary end point was major bleeding alone. Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration ≥2 g/dL, transfusion of ≥2 units of whole blood or packed red blood cells, or permanent disability. NMCR bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact with a physician, temporary interruption of study drug, pain, or impairment of daily activities. Intracranial hemorrhage alone is not included as a separate outcome because there were too few events. Safety end points were measured between first dose of study drug (warfarin or rivaroxaban) until 2 days after the last dose of study drug.

We also report on the efficacy outcome of stroke (ischemic or hemorrhagic) and non–central nervous system (CNS) systemic embolism, as defined in the ROCKET AF protocol.[29,30] Stroke could be either ischemic or hemorrhagic and was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours and was not due to another identifiable cause. Brain imaging (computed tomography or magnetic resonance imaging) was recommended for all suspected strokes, and this was performed in 79% of patients with stroke in the current matched-pair analysis. Non-CNS embolism was defined as an abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms. Efficacy end points were measured from the time of randomization to study termination. Occurrence of end point events was assessed at each follow-up visit and via notification between study visits. All outcome events were adjudicated by a clinical end points committee whose members were blinded to patient assignment to warfarin or rivaroxaban.

Statistical Analysis

For the current analysis, 2 populations from the ROCKET AF trial were used. For the primary comparison of bleeding rates, we analyzed the on-treatment group of patients consisting of patients randomly assigned to warfarin or rivaroxaban who received at least 1 dose of the assigned study drug. For comparison of the rates of stroke and systemic embolism, we used an intention-to-treat approach, including all randomized patients regardless of exposure to the study drug. All baseline summaries are based on the intention-to-treat populations. Categorical variables are presented as counts (percentages), and continuous variables are presented as medians (25th and 75th percentiles). Continuous variables were compared with Wilcoxon rank-sum tests, and categorical variables were compared with Pearson chi-square tests.

Patients taking SSRIs were matched 1:1 to those not taking SSRIs using a propensity score. The propensity model used multiple logistic regression, with the dependent variable being an indicator of patient use of an SSRI at any time during the study, and included the independent baseline variables of age, sex, race (white, black, Asian, or other), body mass index, geographic region (North America, Western Europe/Australia/New Zealand/South Africa, and Latin America versus Eastern Europe and East Asia/India), systolic blood pressure, type of AF, time since AF diagnosis, congestive heart failure, prior myocardial infarction, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, prior stroke or transient ischemic attack, and history of anxiety or depression. For continuous predictors, restricted cubic splines were used to accommodate nonlinearity. This model generated an estimated probability and corresponding *logit* ($\log_e[p/(1-p)]$) of being an SSRI patient for each patient. Patients were then matched 1:1 using a caliper width of 0.20*(standard deviation of the logit).[31] Matching at ratios of >1 non-SSRI:1 SSRI patient resulted in poor balance of covariates between groups. Balance of covariates included in the propensity score between matched groups was assessed by the standardized difference, which is the absolute difference in means (or proportions) divided by the average standard deviation.

Event rates (events per 100 patient-years) were generated for all end points. Only the first event for each patient was included in the analysis. Patients who were on an SSRI for only part of the follow-up period contributed event-free time to both SSRI and no-SSRI groups; any event that occurred was counted toward the medication group the patient was in at the time. When an event occurred on the same day as the medication was started or the first day on which it was stopped, the event was credited to the *prior* group. SSRI and no-SSRI groups were compared using Cox proportional hazards models including SSRI in each model as a time-dependent covariate, allowing patients to change group over time. Model standard errors used a robust sandwich covariance matrix to account for any possible

dependency within matched pairs.[32] Hazard ratios (with 95% [CIs]) for each comparison, with *P* values, were generated from the Cox models. Safety and efficacy models were adjusted for predictors of outcomes previously identified in the full ROCKET AF cohort. The proportional hazards assumption for SSRI was met for all models.

INR test values via study-supplied point-of-care devices[29] were available for 755 patients, including 388 patients in the SSRI group and 367 patients in the matched no-SSRI group. Patients in analyses involving INR values may not have had a matched patient with INR values available. Time in therapeutic range for the INR of 2.0 to 3.0 was calculated using the Rosendaal method.[33] In this subset of warfarin patients, a sensitivity model examined the association of SSRI versus no-SSRI with major or NMCR bleeding, with and without INR measurement included in the model as a time-dependent covariate.

The Duke Clinical Research Institute (Durham, NC) coordinated the trial, managed the database, and performed the primary analysis, independent of the sponsors. The study complies with the Declaration of Helsinki and was approved by the Duke Institutional Review Board and ethics committees at each participating site. All patients provided written informed consent. The members of an international executive committee designed the trial and were responsible for overseeing the conduct of the study and all subanalyses. Dr Daniel Singer had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Results

In the ROCKET AF trial, 737 patients (5.2%) took SSRIs at any time during follow-up, including 504 taking SSRIs at entry to the study. Forty-seven percent (n=345) of patients taking SSRIs were randomly allocated to rivaroxaban treatment and 53% randomly allocated to warfarin. The median duration of SSRI use was 16.7 months (25th, 75th: 10.3, 24.0), and 81.3% of patients remained on an SSRI at the end of the study. The most commonly used SSRI was citalopram (28% of SSRI users), followed by sertraline (24%), fluoxetine (18%), escitalopram (17%), and paroxetine (12%), with fluvoxamine (0.9%) uncommonly used. Nineteen SSRI users started SSRIs after the patient had discontinued their assigned anticoagulant.

In the overall ROCKET AF patient population, there were multiple clinical and demographic differences between SSRI users and nonusers (Table 1). SSRI users were older, more likely to be female, more likely to be white, much more likely to have come from North America, and more likely to have diabetes mellitus, but less likely to have heart failure. Congestive heart failure, hypertension, age 75 or greater, diabetes, and prior stroke times 2 ($CHADS_2$) scores were very similar. At entry into the trial, a larger proportion of SSRI users were experienced vitamin K antagonist users and fewer were taking aspirin on a chronic basis. One-to-one propensity score matching resulted in excellent balance of covariates with standardized differences of <10% on all variables included in the propensity score model (Table 2). There was also very good balance across the full range of baseline characteristics (Table 2). The notable remaining statistically significant differences were a slightly higher mean creatinine clearance and a higher proportion with prior vitamin K antagonist use in SSRI users.

The average follow-up on treatment for safety outcomes for patients on SSRIs was 1.6 years for both patients on SSRIs and the matched SSRI nonusers. The rate of major/NMCR bleeding was 18.57 events per 100 patient-years versus 16.84 events per 100 patient-years for matched comparators, with an adjusted hazard ratio (aHR) of 1.16 (95% CI, 0.95–1.43). The aHR for the much less common end point of major bleeds was 1.37 (95% CI, 0.94–1.99) (Table 3). Event rates stratified by rivaroxaban versus warfarin are presented in Table 4. The aHRs for SSRI versus no-SSRI exposure for safety outcomes in patients taking rivaroxaban (aHR, 1.11 [95% CI, 0.82–1.51] for major/NMCR bleeds and 1.13 [95% CI, 0.62–2.06] for major bleeds) were similar to those in patients taking warfarin (aHR, 1.21 [95% CI, 0.91–1.60] for major/NMCR bleeds and 1.58 [95% CI, 0.96–2.60] for major bleeds), with no evident interaction of effect (Table 5). There were relatively few efficacy events among the matched pairs. The aHR for all stroke and non-CNS embolism, SSRI/no-SSRI, was 1.23 with a wide CI (0.76–2.00) and for ischemic stroke alone was 1.20 (0.69–2.09) (Table 3). For stroke/non-CNS embolism, the point estimate aHR for SSRI versus no-SSRI was higher among patients randomized to rivaroxaban (aHR, 1.61) than among patients randomized to warfarin (aHR, 1.09), but the CIs were wide and highly overlapping and the test for interaction was statistically nonsignificant (Table 5). This was similarly true for the more limited efficacy outcome of ischemic stroke. Among the matched pairs, the effect of rivaroxaban versus warfarin was also not significantly different among SSRI users and their nonuser comparators. The aHR for rivaroxaban versus warfarin for major/NMCR bleeds was 0.99 (95% CI, 0.72–1.35) for patients taking SSRI versus 1.07 (95% CI, 0.83–1.38) for the no-SSRI comparators. For stroke/non-CNS embolism, the aHR of rivaroxaban versus warfarin was 0.74 (95% CI, 0.33–1.68) among patients taking SSRIs and 0.50 (95% CI, 0.24–1.03) among no-SSRI comparators (interaction *P*=0.44) (Table 5).

Among patients taking warfarin, the time in therapeutic range was 61% for patients taking SSRIs versus 60% for the no-SSRI matched group. The time above the upper limit of the target INR of 3.0 was 15% in the SSRI group and 14% for

Table 1. Baseline Characteristics for Patients Classified by SSRI Use at Any Time

Variable	SSRI at Any Time (n=737)	No SSRI at Any Time (n=13 333)	*P* Value
Randomized to rivaroxaban, no. (%)	345 (47%)	6695 (50%)	0.072
Age, median (25th, 75th), y	75 (67, 79)	73 (65, 78)	<0.0001
Female, no. (%)	389 (53%)	5188 (39%)	<0.0001
Race, no. (%)			
White	671 (91%)	11 027 (83%)	<0.0001
Black	13 (2%)	164 (1%)	
Asian	29 (4%)	1748 (13%)	
Other	24 (3%)	394 (3%)	
Region			
East Asia	24 (3%)	1451 (11%)	<0.0001
India	5 (1%)	262 (2%)	
Eastern Europe	80 (11%)	5410 (41%)	
Western Europe/ Australia/ New Zealand	140 (19%)	2024 (15%)	
South Africa	25 (3%)	218 (2%)	
Latin America	150 (20%)	1714 (13%)	
North America	313 (42%)	2254 (17%)	
Type of AF			
Persistent	575 (78%)	10 818 (81%)	0.10
Paroxysmal	151 (20%)	2327 (17%)	
New onset	11 (1%)	188 (1%)	
Time since AF diagnosis, median (25th, 75th), y	3.7 (1.1, 7.8)	3.2 (0.9, 7.1)	0.010
$CHADS_2$ score, mean (SD)	3.5 (1.0)	3.5 (0.9)	0.082
$CHADS_2$ score, no. (%)			
1		3 (<1%)	
2	93 (13%)	1735 (13%)	
3	303 (41%)	5837 (44%)	
4	216 (29%)	3824 (29%)	
5	106 (14%)	1676 (13%)	
6	19 (3%)	258 (2%)	
Presenting characteristics, median (25th, 75th),			
BMI, kg/m^2	28.8 (25.4, 33.3)	28.1 (25.1, 31.9)	0.0002
Systolic BP, mm Hg	129 (118, 140)	130 (120, 140)	<0.0001
Diastolic BP, mm Hg	78 (70, 82)	80 (70, 86)	<0.0001
Heart rate, beats/min	72 (65, 81)	76 (68, 86)	<0.0001
CrCl,* mL/min	66 (51, 88)	67 (52, 87)	0.62
Baseline comorbidities, no. (%)			
Prior stroke or TIA	398 (54%)	6980 (52%)	0.38
Hypertension	665 (90%)	12 067 (91%)	0.80
Diabetes mellitus	332 (45%)	5259 (39%)	0.0025
Prior myocardial infarction	138 (19%)	2289 (17%)	0.28
Congestive heart failure	407 (55%)	8402 (63%)	<0.0001
Peripheral arterial disease	56 (8%)	766 (6%)	0.037
COPD	101 (14%)	1358 (10%)	0.0023
Anxiety or depression	231 (31%)	247 (2%)	<0.0001
Medications, no. (%)			
Prior VKA use	574 (78%)	8156 (61%)	<0.0001
Prior chronic aspirin use	226 (31%)	4910 (37%)	0.0007
ACE inhibitor/ ARB at baseline	525 (71%)	9914 (74%)	0.059
β Blocker at baseline	485 (66%)	8625 (65%)	0.54
Digitalis at baseline	272 (37%)	5125 (38%)	0.41
Diuretic at baseline	469 (64%)	7899 (59%)	0.018
Nonsteroidal anti-inflammatory at baseline	72 (10%)	467 (4%)	<0.0001

*Calculated using the Cockcroft-Gault equation.
ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; $CHADS_2$, Congestive heart failure, hypertension, age 75 or greater, diabetes, and prior stroke times 2; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack; VKA, vitamin K antagonist.

the no-SSRI group. Among patients taking warfarin with INR data, the aHR (SSRI/no-SSRI) for major/NMCR bleeding was almost identical with (aHR, 1.20 [95% CI, 0.90–1.58]) or without (aHR, 1.20 [95% CI, 0.90–1.59]) INR as a time-varying covariate in the model.

Table 2. Baseline Characteristics for Patients Who Used an SSRI at Any Time and Their Matched No-SSRI Cohort

Variable	SSRI at Any Time (n=737)	No SSRI at Any Time (n=737)	*P* Value
Randomized to rivaroxaban, % (no.)	47% (345)	50% (365)	0.30
Age,* median (25th, 75th), y	75 (67, 79)	75 (68, 79)	0.32
Female,* no. (%)	389 (53%)	382 (52%)	0.72
Race,* no. (%)			
White	671 (91%)	650 (88%)	0.28
Black	13 (2%)	13 (2%)	
Asian	29 (4%)	40 (5%)	
Other	24 (3%)	34 (5%)	
Region,* no. (%)			
East Asia	24 (3%)	35 (5%)	0.11
India	5 (1%)	3 (<1%)	
Eastern Europe	80 (11%)	81 (11%)	
Western Europe/ Australia/ New Zealand	140 (19%)	174 (24%)	
South Africa	25 (3%)	18 (2%)	
Latin America	150 (20%)	154 (21%)	
North America	313 (42%)	272 (37%)	
Type of AF, no. (%)			
Persistent	575 (78%)	587 (80%)	0.65
Paroxysmal*	151 (20%)	142 (19%)	
New onset	11 (1%)	8 (1%)	
Time since AF diagnosis, median (25th, 75th), y*	3.7 (1.1, 7.8)	4.1 (1.3, 8.2)	0.26
$CHADS_2$ score, mean (SD)	3.5 (1.0)	3.5 (1.0)	0.79
$CHADS_2$ score, no. (%)			
1			0.50
2	93 (13%)	93 (13%)	
3	303 (41%)	318 (43%)	
4	216 (29%)	193 (26%)	
5	106 (14%)	105 (14%)	
6	19 (3%)	28 (4%)	
Presenting characteristics, median (25th, 75th)			
BMI,* kg/m^2	28.8 (25.4, 33.3)	28.6 (25.1, 32.5)	0.20
Systolic BP,* mm Hg	129 (118, 140)	130 (120, 140)	0.72
Diastolic BP, mm Hg	78 (70, 82)	78 (70, 82)	0.92
Heart rate, bpm	72 (65, 81)	75 (64, 85)	0.097
CrCl,† mL/min	66 (51, 88)	62 (48, 83)	0.010
Baseline comorbidities, no. (%)			
Prior stroke or TIA*	398 (54%)	397 (54%)	0.96
Hypertension*	665 (90%)	668 (91%)	0.79
Diabetes mellitus*	332 (45%)	325 (44%)	0.71
Prior myocardial infarction*	138 (19%)	135 (18%)	0.84
Congestive heart failure*	407 (55%)	399 (54%)	0.68
Peripheral arterial disease	56 (8%)	55 (7%)	0.92
COPD*	101 (14%)	94 (13%)	0.60
Anxiety or depression*	231 (31%)	230 (31%)	0.96
Medications, no. (%)			
Prior VKA use	574 (78%)	540 (73%)	0.039
Prior chronic aspirin use	226 (31%)	245 (33%)	0.29
ACE inhibitor/ARB at baseline	525 (71%)	546 (74%)	0.22
Beta blocker at baseline	485 (66%)	477 (65%)	0.66
Digitalis at baseline	272 (37%)	279 (38%)	0.71
Diuretic at baseline	469 (64%)	449 (61%)	0.28
Nonsteroidal anti-inflammatory at baseline	72 (10%)	57 (8%)	0.17

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; $CHADS_2$, Congestive heart failure, hypertension, age 75 or greater, diabetes, and prior stroke times 2; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack; VKA, vitamin K antagonist.

*Variables included in the propensity score, see Methods.

†Calculated using the Cockcroft-Gault equation.

Discussion

In our current analysis from the ROCKET AF randomized trial, we assessed the risk of major plus NMCR bleeding due to the addition of SSRIs to anticoagulants for patients with AF. To reduce confounding, we used a propensity score matched analysis with additional adjustment for potential confounders in Cox regression models. Our study provides estimates of

Table 3. Efficacy and Safety End Points by SSRI Use (Matched Cohorts)

Outcomes	SSRI Events/100 Patient-years (Total Events)	No SSRI Events/100 Patient-years (Total Events)	SSRI vs No SSRI	
			HR* (95% CI)	*P* Value
Safety outcomes				
Major/NMCR bleeding	18.57 (159)	16.84 (242)	1.16 (0.95, 1.43)	0.15
Major bleeding	5.61 (48)	4.11 (59)	1.37 (0.94, 1.99)	0.10
Efficacy outcomes				
Stroke/non-CNS embolism	2.64 (27)	2.31 (37)	1.23 (0.76, 2.00)	0.40
Ischemic stroke	2.15 (22)	1.74 (28)	1.20 (0.69, 2.09)	0.51

CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; NMCR, nonmajor clinically relevant; SSRI, selective serotonin reuptake inhibitor.
*The safety end point models used the safety population and were adjusted for age; sex; geographic region; prior stroke or transient ischemic attack; anemia; prior gastrointestinal bleed; chronic obstructive pulmonary disease; diastolic blood pressure; creatinine clearance (calculated using the Cockcroft-Gault equation); platelets; albumin; prior acetylsalicylic acid, vitamin K antagonist, or thienopyridine; baseline nonsteroidal anti-inflammatory drug; and randomized anticoagulant treatment. Efficacy end point models used the intention-to-treat population and were adjusted for age, sex, geographic region, body mass index, paroxysmal atrial fibrillation, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease (myocardial infarction, peripheral artery disease, or carotid occlusive disease), congestive heart failure, hypertension, chronic obstructive pulmonary disease, diastolic blood pressure, creatinine clearance (calculated using the Cockcroft-Gault equation), heart rate, abstinence from alcohol use, baseline nonsteroidal anti-inflammatory drug, and randomized anticoagulant treatment.

SSRI effect when combined with the non–vitamin K antagonist oral anticoagulant rivaroxaban, as well as with a standard warfarin regimen aimed at an INR target of 2.5 (range, 2.0–3.0). The aHR for major/NMCR bleeds was 1.16 (95% CI, 0.95–1.43) among patients taking either trial anticoagulant. When examined according to allocated anticoagulant, the aHR was 1.21 (95% CI, 0.91–1.60) for patients taking warfarin and 1.11 (95% CI, 0.82–1.51) for those taking rivaroxaban, with no significant interaction between taking SSRIs and type of anticoagulant. For the much less common outcome of major bleeding, the aHR was a nonsignificant 1.37 (95% CI, 0.94–1.99) with aHRs of 1.13 (95% CI, 0.62–2.06) for patients assigned to rivaroxaban and 1.58 (95% CI, 0.96–2.60) for patients assigned to warfarin, but with a nonsignificant test for interaction. If SSRIs conferred an additional anticoagulant effect, we might expect a reduced rate of stroke/non-CNS embolism among SSRI users. In fact, we observed a small, statistically nonsignificant increase in the rate of efficacy events in patients taking SSRIs, although the precision of this estimate was limited by the small number of events. Finally, viewing the results from the alternate perspective, there was no significant difference due to SSRI status in the comparison of rivaroxaban versus warfarin.

In at least 1 study, SSRIs were found to increase the risk of exceptionally high INR values, perhaps reflecting inhibition of the cytochrome P450–mediated metabolism of warfarin.[34] However, a recent large pharmacoepidemiologic study of SSRIs and warfarin found no evidence that bleeding risk was associated with strength of SSRI inhibition of cytochrome P450 2C9.[23] We also saw no evidence of SSRIs augmenting warfarin's effect. The time in therapeutic range and the percentage of time of an INR >3.0 among warfarin users on SSRIs were essentially the same as those values among warfarin users not on SSRIs. Further, inclusion of time-updated INR values had no effect on the hazard ratios generated by our Cox regression models.

Our results should be viewed in the context of prior studies. In a large community-based observational AF cohort, we previously found an adjusted relative risk for major hemorrhage of 1.41 (95% CI, 1.04–1.92) with the addition of SSRIs to warfarin.[26] Several studies using large national databases have reported that concomitant use of SSRIs with vitamin K antagonists increased the risk of hospitalized

Table 4. Efficacy and Safety End Point Event Rates by SSRI Use and Randomized Warfarin vs Rivaroxaban (Matched Cohorts)

Outcomes	Events/100 Patient-years (Total Events)			
	SSRI Rivaroxaban	No SSRI Rivaroxaban	SSRI Warfarin	No SSRI Warfarin
Safety outcomes				
Major/NMCR bleeding	18.47 (72)	16.87 (124)	18.66 (87)	16.81 (118)
Major bleeding	4.62 (18)	3.94 (29)	6.43 (30)	4.27 (30)
Efficacy outcomes				
Stroke/non-CNS embolism	1.94 (9)	1.49 (12)	3.23 (18)	3.12 (25)
Ischemic stroke	1.51 (7)	0.99 (8)	2.69 (15)	2.50 (20)

CNS indicates central nervous system; NMCR, nonmajor clinically relevant; SSRI, selective serotonin reuptake inhibitor.

Table 5. Adjusted Comparisons of Efficacy and Safety End Points by SSRI Use and Randomized Warfarin vs Rivaroxaban (Matched Cohorts)

Outcomes	*P* Value for Interaction of SSRI and Treatment	Rivaroxaban Patients	Warfarin Patients	SSRI Patients	No SSRI Patients
		SSRI vs No SSRI HR (95% CI)	SSRI vs No SSRI HR (95% CI)	Rivaroxaban vs Warfarin HR (95% CI)	Rivaroxaban vs Warfarin HR (95% CI)
Safety Outcomes					
Major/NMCR bleeding	0.69	1.11 (0.82, 1.51)	1.21 (0.91, 1.60)	0.99 (0.72, 1.35)	1.07 (0.83, 1.38)
Major bleeding	0.40	1.13 (0.62, 2.06)	1.58 (0.96, 2.60)	0.69 (0.38, 1.25)	0.96 (0.58, 1.61)
Efficacy outcomes					
Stroke/non-CNS embolism	0.44	1.61 (0.71, 3.64)	1.09 (0.60, 1.96)	0.74 (0.33, 1.68)	0.50 (0.24, 1.03)
Ischemic stroke	0.41	1.72 (0.64, 4.61)	1.04 (0.53, 2.02)	0.71 (0.29, 1.77)	0.43 (0.18, 1.01)

Models are the same as in Table 3, with the addition of a term for the interaction between SSRI use and randomized treatment. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; NMCR, nonmajor clinically relevant; SSRI, selective serotonin reuptake inhibitor.

bleeding events by roughly 30% to 70%, and a recent nested case-control study from the United Kingdom Clinical Practice Datalink found an odds ratio of 1.73 (95% CI, 0.89–3.39) for intracranial hemorrhage in patients taking warfarin when SSRIs were added.[15,24,25,27] Although the CIs overlapped to varying degrees, our point estimate hazard ratio, SSRI versus no-SSRI, of 1.16 was smaller than those previously reported and close to the null value of 1.0.

Our study has several notable limitations and strengths. The use of SSRIs in ROCKET AF was driven by clinical judgment and not randomized allocation. However, because SSRIs are not usually included as a major interacting drug with vitamin K antagonists or rivaroxaban, there is reduced concern about "confounding by contraindication." Moreover, our propensity score matched approach resulted in a good balance of observed potential confounders. Still, in any nonrandomized assessment of drug effect, there may be residual confounding. As part of a large randomized trial, our study benefited from the careful prospective data collection, close follow-up, and formal adjudication of bleeding events by a committee blinded to oral anticoagulant assignment. In a formal sense, however, our results are not necessarily generalizable beyond the types of patients we analyzed in ROCKET AF. Although the end point of major/NMCR bleeding events is not as clinically important as major bleeding events alone, major/NMCR bleeding events were the primary safety outcome of the ROCKET AF trial and provide a more statistically powerful assessment of SSRI effect. Studies have reported that bleeding risk with SSRIs was associated with degree of inhibition of serotonin reuptake.[24] We had too few users of strong and weaker serotonin reuptake inhibitors to test this effect. More generally, we assessed SSRIs as a class and cannot assess the effect of individual SSRI agents.

In conclusion, we did not find a significantly increased risk of bleeding among patients in ROCKET AF assigned to either warfarin or rivaroxaban anticoagulant therapy who also took SSRIs. Both anticoagulants and SSRIs are used among predominantly older patients with AF, and their concurrent use is not uncommon. In general, our findings provide some reassurance that the addition of SSRIs to oral anticoagulants does not substantially increase the risk of bleeding. This reassurance has to be tempered somewhat, given the modestly elevated, but statistically nonsignificant, aHR for major bleeding we observed for the addition of SSRIs to warfarin and the upper bound of the hazard ratio CI.

Sources of Funding

Dr Quinn was supported by the Harvard Medical School Fellowship in Patient Safety and Quality (Boston, MA). Dr Singer was supported, in part, by the Eliot B. and Edith C. Shoolman Fund of Massachusetts General Hospital (Boston, MA).

Disclosures

Dr Hankey has served on a speaker's bureau for Bayer HealthCare Pharmaceuticals. Dr Becker has received consulting fees/honoraria from Boehringer Ingelheim, Daiichi-Sankyo, and Portola, and research support from AstraZeneca. Dr Berkowitz is an employee of Bayer U.S. LLC. Dr Breithardt has received consulting fees/honoraria from Bayer HealthCare, J & J, BMS/Pfizer, MSD, Boehringer Ingelheim, Portola, and Sanofi Aventis. Dr Fava has received research support from Alkermes, Inc, Johnson & Johnson, Axsome, Acadia Pharmaceuticals, Cerecor, Lundbeck Inc, Neuralstem, Otsuka, Taisho, Marinus Pharmaceuticals, BioHaven, Takeda, Vistagen, Relmada Therapeutics Inc, and Stanley Medical Research Institute (SMRI), and has equity holdings in Compellis and Psybrain, Inc. Dr Fox has received consulting fees/honoraria from AstraZeneca, Bayer, Janssen, Merck & Co. Inc, and Sanofi Aventis/Regeneron, and research support from Eli Lilly and GlaxoSmithKline. Dr Halperin has received consulting fees/honoraria from Bayer

HealthCare Pharmaceuticals, Boehringer Ingelheim, Medtronic Inc, Ortho-McNeil-Janssen Pharmaceuticals Inc, and Pfizer. Dr Mahaffey has received consulting fees/honoraria from Eli Lilly, ACC, AstraZeneca, BAROnova, Bayer, Bio2 Medical, Boehringer Ingelheim, Bristol-Myers Squibb, Cubist, Elsevier (AHJ), Epson, Forest, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Mt. Sinai, Myokardia, Omthera, Portola, Purdue Pharma, Springer Publishing, The Medicines Company, Vindico, and WebMD, and research support from Amgen, Boehringer Ingelheim, Daiichi-Sankyo, Johnson & Johnson, Medtronic, St. Jude, and Tenax, and has ownership interest in BioPrint Fitness. Dr Nessel is an employee of Janssen Research & Development. Dr Patel has received consulting fees/honoraria from Bayer Healthcare, Genzyme, Medscape—theheart.org, and Merck, and research support from AHRQ, AstraZeneca, Janssen, Johnson & Johnson, Maquet, NHLBI, and PCORI. Dr Piccini has received consulting fees/honoraria from Johnson & Johnson, Medtronic, and Spectranetics, and research support from ARCA Biopharma, Boston Scientific, Gilead Sciences Inc, Johnson & Johnson, Resmed, and St. Jude Medical. Dr Singer has consulted for Boehringer Ingelheim, Bristol-Myers Squibb, CVS Health, Johnson & Johnson, Medtronic, Merck, and Pfizer, and has received research support from Boehringer Ingelheim, Bristol-Myers Squibb, and Medtronic. The remaining authors have no disclosures to report.

References

1. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449–1457.
2. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e44S–e88S.
3. Pratt LA, Brody DJ, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. *NCHS Data Brief*. 2011;(76):1–8.
4. Chemali Z, Chahine LM, Fricchione G. The use of selective serotonin reuptake inhibitors in elderly patients. *Harv Rev Psychiatry*. 2009;17:242–253.
5. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2008;149:725–733.
6. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375.
7. de Abajo FJ, Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ*. 1999;319:1106–1109.
8. Kharofa J, Sekar P, Haverbusch M, Moomaw C, Flaherty M, Kissela B, Broderick J, Woo D. Selective serotonin reuptake inhibitors and risk of hemorrhagic stroke. *Stroke*. 2007;38:3049–3051.
9. de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry*. 2008;65:795–803.
10. Meijer WEE, Heerdink ER, Nolen WA, Herings RMC, Leufkens HGM, Egberts ACG. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch Intern Med*. 2004;164:2367–2370.
11. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging*. 2011;28:345–367.
12. Roose SP, Rutherford BR. Selective serotonin reuptake inhibitors and operative bleeding risk: a review of the literature. *J Clin Psychopharmacol*. 2016;36:704–709.
13. Laporte S, Chapelle C, Caillet P, Beyens M-N, Bellet F, Delavenne X, Mismetti P, Bertoletti L. Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: a meta-analysis of observational studies. *Pharmacol Res*. 2017;118:19–32.
14. Auerbach AD, Vittinghoff E, Maselli J, Pekow PS, Young JQ, Lindenauer PK. Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery. *JAMA Intern Med*. 2013;173:1075–1081.
15. Mortensen JK, Larsson H, Johnsen SP, Andersen G. Post stroke use of selective serotonin reuptake inhibitors and clinical outcome among patients with ischemic stroke: a nationwide propensity score-matched follow-up study. *Stroke*. 2013;44:420–426.
16. Andrade C, Sharma E. Serotonin reuptake inhibitors and risk of abnormal bleeding. *Psychiatr Clin North Am*. 2016;39:413–426.
17. Lexapro Highlights of Prescribing Information. Available at: https://www.allergan.com/assets/pdf/lexapro_pi. Accessed July 3, 2017.
18. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B. Paroxetine decreases platelet serotonin storage and platelet function in human beings. *Clin Pharmacol Ther*. 2000;68:435–442.
19. Reikvam A-G, Hustad S, Reikvam H, Apelseth TO, Nepstad I, Hervig TA. The effects of selective serotonin reuptake inhibitors on platelet function in whole blood and platelet concentrates. *Platelets*. 2012;23:299–308.
20. Hallbäck I, Hägg S, Eriksson AC, Whiss PA. In vitro effects of serotonin and noradrenaline reuptake inhibitors on human platelet adhesion and coagulation. *Pharmacol Rep*. 2012;64:979–983.
21. Bykov K, Schneeweiss S, Donneyong MM, Dong Y-H, Choudhry NK, Gagne JJ. Impact of an interaction between clopidogrel and selective serotonin reuptake inhibitors. *Am J Cardiol*. 2017;119:651–657.
22. Andrade C. Selective serotonin reuptake inhibitor drug interactions in patients receiving statins. *J Clin Psychiatry*. 2014;75:e95–e99.
23. Dong Y-H, Bykov K, Choudhry NK, Donneyong MM, Huybrechts KF, Levin R, Schneeweiss S, Gagne JJ. Clinical outcomes of concomitant use of warfarin and selective serotonin reuptake inhibitors: a multidatabase observational cohort study. *J Clin Psychopharmacol*. 2017;37:200–209.
24. Renoux C, Vahey S, Dell'Aniello S, Boivin J-F. Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. *JAMA Neurol*. 2017;74:173–180.
25. Schelleman H, Brensinger CM, Bilker WB, Hennessy S. Antidepressant-warfarin interaction and associated gastrointestinal bleeding risk in a case-control study. *PLoS One*. 2011;6:e21447.
26. Quinn GR, Singer DE, Chang Y, Go AS, Borowsky LH, Udaltsova N, Fang MC. Effect of selective serotonin reuptake inhibitors on bleeding risk in patients with atrial fibrillation taking warfarin. *Am J Cardiol*. 2014;114:583–586.
27. Schalekamp T, Klungel OH, Souverein PC, de Boer A. Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. *Arch Intern Med*. 2008;168:180–185.
28. Wallerstedt SM, Gleerup H, Sundström A, Stigendal L, Ny L. Risk of clinically relevant bleeding in warfarin-treated patients–influence of SSRI treatment. *Pharmacoepidemiol Drug Saf*. 2009;18:412–416.
29. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
30. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J*. 2010;159:340–347.e1.
31. Rosenbaum P, Rubin D. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Stat*. 1985;39:33–38.
32. Lee EW, Wei LJ, Amato DA, Leurgans S. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. *Survival analysis: State of the art*. 1992;211:237–247.
33. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236–239.
34. Teichert M, Visser LE, Uitterlinden AG, Hofman A, Buhre PJ, Straus S, De Smet PAGM, Stricker BH. Selective serotonin re-uptake inhibiting antidepressants and the risk of overanticoagulation during acenocoumarol maintenance treatment. *Br J Clin Pharmacol*. 2011;72:798–805.