Clinical Outcomes of Concomitant Use of Warfarin and Selective Serotonin Reuptake Inhibitors

A Multidatabase Observational Cohort Study

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Abstract:

Background: Patients treated with warfarin are often coprescribed selective serotonin reuptake inhibitors (SSRIs) for coexisting depression. Some SSRIs are potent CYP2C9 inhibitors that may increase warfarin plasma concentrations and the risk of bleeding. We aimed to examine the effect of the putative CYP2C9-mediated warfarin-SSRI interaction on clinical outcomes.

Methods: We conducted an observational cohort study among warfarin initiators who had a subsequent SSRI prescription in 5 US claims databases. Patients were followed for up to 180 days as long as they were exposed to both warfarin and their index SSRI groups. Cox regression models were used to estimate hazard ratios and 95% confidence intervals for bleeding events, ischemic or thromboembolic events, and mortality comparing patients treated with SSRIs that are potent CYP2C9 inhibitors (fluoxetine, fluvoxamine) with those treated with other SSRIs after propensity score matching.

Findings: The eligible cohort comprised 52,129 patients. Hazard ratios were 1.14 (95% confidence interval [CI], 0.94–1.38) for bleeding events, 1.03 (95% CI, 0.87–1.21) for ischemic or thromboembolic events, and 0.90 (95% CI, 0.72–1.14) for mortality. Results were consistent across individual component outcomes, different warfarin stabilization periods, and subgroup analyses.

Conclusions: Patients concomitantly treated with warfarin and SSRIs that are potent CYP2C9 inhibitors had comparable rates of bleeding events, ischemic or thromboembolic events, and mortality as did patients cotreated with warfarin and other SSRIs, although small but potentially meaningful effects on bleeding cannot be completely excluded. SSRI inhibition of CYP2C9 does not appear to affect major safety or effectiveness outcomes of warfarin treatment in clinical practice, where patients may be closely monitored.

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Depression imposes a profound public health burden given its high lifetime prevalence and its association with severe disability.[1,2] Depression and anxiety often coexist with cardiovascular diseases, atrial fibrillation, and thromboembolic disorders.[3–5] As compared with those without depression, patients with depression are at a 1.5-times higher risk of coronary heart disease and a 1.7-times higher risk of stroke.[6,7] The interplay between depression and cardiovascular and cerebrovascular disease is complex. As compared with those without a prior myocardial infarction (MI), patients with a prior MI have a 5- to 7-fold increased risk of anxiety and depressive disorders.[8] Patients with a prior stroke have a 4-fold higher risk of depression than do those without a prior stroke.[9] Thus, it is common for patients to receive anticoagulant and antidepressant therapy concomitantly. Despite the introduction of new oral anticoagulants, warfarin remains the most widely used anticoagulant in the world and selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants.[10,11]

In terms of pharmacological mechanisms, warfarin has the intended effect of inhibiting blood coagulation,[12,13] and SSRIs can impair platelet aggregation.[14–16] Thus, there is the potential for a pharmacodynamic interaction that can result in higher risk of bleeding and potentially lower risk of ischemic events when both drugs are used together. In addition, warfarin undergoes extensive metabolism through cytochrome P450 (CYP) enzymes, mainly via CYP2C9.[17,18] Previous in vitro studies using human liver microsomes showed that, among SSRIs, fluvoxamine and fluoxetine have the lowest inhibition constants (*Ki*) and the highest inhibitory capability when interacting with CYP2C9 substrates.[19,20] By inhibiting CYP2C9, both SSRIs that are identified as potent inhibitors of CYP2C9 may further increase warfarin plasma concentrations.[17–20] A number of studies have assessed the pharmacodynamic effects of concomitant use of warfarin and SSRIs on bleeding risk and have found higher rates of bleeding events associated with concomitant use of warfarin and SSRIs as compared with use of warfarin alone.[21–25] However, these studies have not examined whether the use of SSRIs that are potent inhibitors of CYP2C9 further increases bleeding risk via additional pharmacokinetic interaction as compared with other SSRIs.

We examined the effect of the putative pharmacokinetic interaction between warfarin and SSRIs that are potent inhibitors of CYP2C9 on bleeding events, ischemic or thromboembolic events, and all-cause mortality. We hypothesized that if the pharmacokinetic interaction is clinically important, patients treated with warfarin who receive SSRIs that are potent inhibitors of CYP2C9 would have an increased risk of bleeding events and

possibly a lower risk of ischemic or thromboembolic events as compared with those who receive SSRIs that are not potent inhibitors of CYP2C9.

MATERIALS AND METHODS

Data Source and Source Population

We identified eligible patients from 5 US databases covering the years 1994 to 2013: (1) the Optum Research Database (Optum; July 1, 2004 to December 31, 2013); (2) the Medicaid Analytic eXtract database (MAX; July 1, 2000 to December 31, 2010); (3) pharmacy claims data from the Pharmaceutical Assistance Contract for the Elderly (PACE) program linked to Medicare claims data for beneficiaries in Pennsylvania (July 1, 1994, to December 31, 2005); (4) pharmacy claims data from the Pharmaceutical Assistance for the Aged and Disabled (PAAD) program linked to Medicare claims data for beneficiaries in New Jersey (July 1, 1995 to December 31, 2005); and (5) pharmacy claims data from stand-alone Medicare Part D plans or retiree drug plans administered by CVS CareMark linked to Medicare claims data (CareMark; July 1, 2005, to December 31, 2008). These data sources include information on demographic and enrollment records, inpatient and outpatient diagnoses and procedures, outpatient pharmacy dispensing, and death information. This study was approved by the institutional review board of the Brigham and Women's Hospital.

Study Population and Study Drugs

From each database, we identified patients who initiated warfarin and had a subsequent SSRI prescription during warfarin treatment. Warfarin initiation was defined as the first warfarin prescription dispensing during the study period with no dispensing for warfarin, dabigatran, rivaroxaban, or apixaban in the preceding 180 days. To ensure availability of sufficient data to capture baseline covariates, we excluded patients with less than 180 days of continuous enrollment before warfarin initiation, allowing gaps in enrollment of up to 31 days. We also excluded those with prior SSRI prescriptions with days' supply that overlapped the warfarin initiation date or those with SSRI prescriptions on the warfarin initiation date, those who received both SSRI groups on the index date (defined below), and those younger than 18 years in Optum and MAX or younger than 65 years in PACE, PAAD, and CareMark on the index date.

Warfarin discontinuation was defined using a grace period of up to 7 days between the end of one prescription and the start date of the next prescription, if any. The index date was defined as the date of the first SSRI prescription during warfarin treatment. SSRIs were classified as those that are potent CYP2C9 inhibitors (fluoxetine, fluvoxamine) or those that are not potent CYP2C9 inhibitors (paroxetine, sertraline, citalopram, escitalopram).

Outcomes and Follow-Up

The outcomes of interest were composite bleeding events, composite ischemic or thromboembolic events, and all-cause mortality. Composite bleeding events were defined as the first hospitalization for upper gastrointestinal (GI) bleeding, lower GI bleeding, hemorrhagic stroke, major urogenital bleeding, or other types of major bleeding. Composite ischemic or thromboembolic events were defined as the first hospitalization for acute MI, ischemic stroke, systemic embolism, transient ischemic attack, or venous thromboembolism. We defined each outcome using validated claims-based algorithms with positive predictive values of 88% for upper GI bleeding,[26] 67% to 100% for lower GI bleeding,[27] 80% to 86% for hemorrhagic stroke,[28] 75% to 100% for major urogenital bleeding,[27] 80% to 100% for other types of major bleeding,[27] 88% to 94% for acute MI,[26,29] 90% for ischemic stroke,[28] 77% for transient ischemic attack,[30] and 72% for venous thromboembolism.[31,32] *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for the outcomes are provided in Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A418.[26–32] To examine the effect on individual bleeding and ischemic or thromboembolic events, we also conducted analyses of each outcome separately.

Patients were followed for up to 180 days from their first day of concomitant warfarin and SSRI treatment (index date) to the earliest of the following: outcome occurrence, warfarin discontinuation, SSRI treatment discontinuation or change, death, disenrollment from the health insurance program, or the end of data in the respective database. Similar to warfarin, SSRI treatment discontinuation was defined using a grace period of up to 7 days between the end of one prescription and the date of the next prescription, if any. SSRI treatment change (switch or addition) was defined as a dispensation of a drug in the other SSRI group.

Covariate Assessment and Adjustment

We measured a large number of potential baseline confounders including age on the index date, sex, and the calendar year of the index date. We assessed the length of warfarin use prior to SSRI treatment, gaps in warfarin use, number of international normalized ratio (INR) tests performed, and the use of potentially interacting drugs between the warfarin initiation date and the SSRI index date. We assessed individual comorbidities using inpatient and outpatient diagnosis codes and the use of various medications from outpatient pharmacy dispensing claims, which we measured during 2 periods: (1) the 180 days before warfarin initiation and (2) the period between warfarin initiation and the SSRI index date, which is of variable length for different patients and the length of which was included as a covariate. We calculated the combined comorbidity score, which comprises 20 clinical conditions,[33] using data from the 180 days before warfarin initiation to the SSRI index date. Measures of resource utilization included the number of hospital admissions, outpatient visits, and nursing home stays in the 180 days preceding the index date. Table S2, Supplemental Digital Content 1, http://links.lww.com/JCP/A418, provides more detailed covariate information.

Statistical Analysis

Using the covariates mentioned previously, we estimated baseline propensity scores (PSs) using logistic regression models to predict the probability of receiving SSRIs that are potent CY2C9 inhibitors versus SSRIs that are not potent CYP2C9 inhibitors. Because we had many more patients treated with SSRIs that are not potent CYP2C9 inhibitors, we conducted variable ratio matching (up to 10 patients who received SSRIs that are not potent inhibitors to each patient who received a potent inhibitor) using a nearest-neighbor algorithm with a maximum matching caliper of 0.01 on the PS scale.[34] We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) in the 1:10 variable-ratio–matched cohort. To account for the variable-ratio matching, the Cox model was stratified on matching ratio.[34] Variable-ratio matching produces covariate balance within matched sets but not marginally in the overall matched population.[34] We therefore randomly sampled 1 individual using an SSRI that is not a potent CYP2C9 inhibitor from each set of patients matched to an individual using potent CYP2C9

inhibitors. We examined whether adequate balance in covariates was achieved between treatment groups using standardized differences[35] in this sample.

We identified study cohorts, extracted information on variables, fit PS models, and performed PS matching separately within each database. We fit separate Cox proportional hazards regression models in each database to obtain database-specific estimates. Furthermore, we computed standardized differences across the databases for each variable using pooled means and SDs. We pooled the 1:10 variable-ratio–matched cohorts from the 5 databases and used Cox models, stratified on matching ratios, to estimate summary HRs and 95% CIs.[36]

Sensitivity and Subgroup Analyses

To assess the impact of using different warfarin stabilization periods, we conducted sensitivity analyses by restricting the analyses to those patients who had at least 7, 14, 28, or 56 days of continuous warfarin use before receiving SSRIs. In practice, physicians may carefully monitor prothrombin time and adjust warfarin doses accordingly after prescribing SSRIs. Given that information about warfarin dose adjustment is not available in the databases, we indirectly estimated warfarin mean daily dose using strength of warfarin and quantities and days' supply dispensed with each prescription. We compared warfarin mean daily dose between treatment groups. We also included warfarin mean daily dose before SSRI exposure as an additional variable in the PS model and estimated HRs for each outcome. As patients may discontinue warfarin or SSRI treatment if an interaction is suspected, we also used warfarin or SSRI treatment discontinuation as proxies for minor outcomes that do not result in hospitalization.

We conducted subgroup analyses to examine potential effect measure modification by several characteristics, including age (≥65 and <65 years), sex, and whether patients had histories of GI ulcer or bleeding, MI, or stroke. We used the PS estimated from the total study population in each database to rematch patients within each subgroup of interest.[37]

RESULTS

Baseline Characteristics

The eligible cohort comprised 52,129 warfarin initiators who also received SSRIs during their warfarin therapy across the 5 databases; 8011 (15%) received SSRIs that are potent CYP2C9 inhibitors, and 44,118 (85%) received SSRIs that are not potent CYP2C9 inhibitors (Fig. 1 and Table S3, Supplemental Digital Content 1, http://links.lww.com/JCP/A418). Sertraline (27%) was the most commonly used SSRI, followed by escitalopram (20%), paroxetine (19%), citalopram (18%), fluoxetine (15%), and fluvoxamine (<1%). The mean age of the cohort was 54 (SD, 12) years, and 28% were male (Table 1 and Tables S4a–S4e, Supplemental

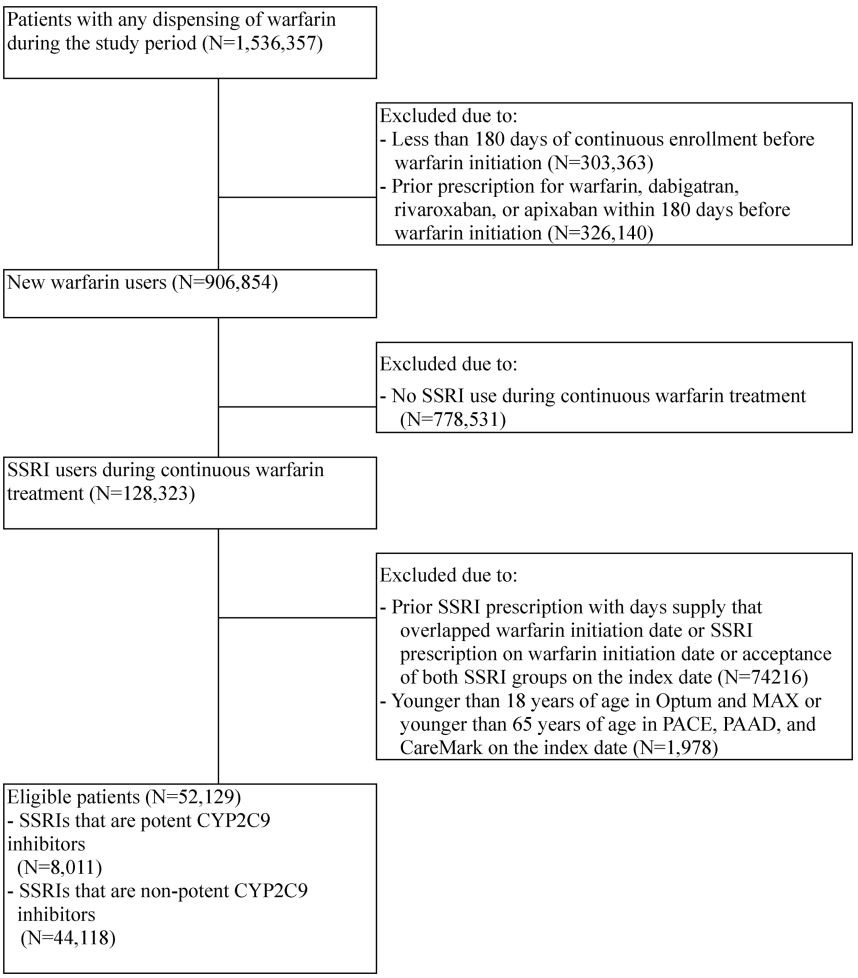

FIGURE 1. Flowchart of the study cohort assembly.

TABLE 1. Selected Baseline Characteristics by SSRI Group*

	Before Matching			After Matching		
	Total Study Cohort (n = 52,129)			Matched Study Cohort (n = 49,881)		
Characteristics	Potent CYP2C9 Inhibitors (n = 8011)	Other SSRIs (n = 44,118)	Standardized Difference	Potent CYP2C9 Inhibitors (n = 8000) n = 8000†	Other SSRIs (n = 41,881) n = 8000†	Standardized Difference
Age, mean (SD), y	54.28 (11.94)	57.45 (12.04)	−0.26	54.25 (11.95)	54.24 (12.47)	0.00
Male, %	28.26	31.89	−0.08	28.26	27.88	0.01
Variables measured between warfarin initiation and the SSRI index date						
Length of warfarin use, mean (SD), d	39.32 (70.95)	44.82 (83.97)	−0.07	39.2 (70.51)	38.86 (65.84)	0.00
No. of INR tests, mean (SD)	2.21	2.27	−0.01	2.18 (4.73)	2.24 (4.65)	−0.01
Drugs that may decrease INR or anticoagulant effectiveness, %	0.34	0.59	−0.04	0.30	0.36	−0.01
Drugs that may increase INR or risk of bleeding, %	39.81	42.6	−0.06	39.80	40.09	−0.01
Variables measured in the 180 d before warfarin initiation, %						
Hypertension	49.83	55.10	−0.11	49.81	49.89	0.00
Recent acute MI	2.62	3.14	−0.03	2.62	2.54	0.01
Unstable angina	3.13	3.24	−0.01	3.14	3.07	0.00
Coronary artery disease	25.74	30.84	−0.12	25.70	25.48	0.01
Atrial fibrillation	20.66	26.38	−0.14	20.62	20.79	0.00
Valve replacement	1.88	2.11	−0.02	1.89	1.96	−0.01
Congestive heart failure	20.36	24.54	−0.10	20.34	21.1	−0.02
Hemorrhagic stroke	0.46	0.64	−0.03	0.46	0.58	−0.02
Ischemic stroke	7.62	9.29	−0.06	7.61	7.53	0.00
Transient ischemic attack	4.23	5.38	−0.06	4.23	4.41	−0.01
Peripheral vascular disease	5.82	7.36	−0.06	5.83	5.64	0.01
Venous thromboembolism	27.75	26.71	0.02	27.76	27.42	0.01
Hyperlipidemia	25.68	30.30	−0.11	25.69	25.74	0.00
Diabetes	27.09	28.09	−0.02	27.10	27.51	−0.01
PUD/upper GI bleeding	20.20	20.66	−0.01	20.17	19.80	0.01
ACEIs/ARBs	33.63	37.25	−0.08	33.65	33.52	0.00
β-Blockers	32.49	37.29	−0.10	32.48	32.84	−0.01
CCBs	21.79	24.07	−0.05	21.78	21.37	0.01
Other antihypertensive drugs	35.07	35.82	−0.02	35.05	34.96	0.00
Antiplatelet drugs	7.39	9.17	−0.06	7.40	7.61	−0.01
Injectable anticoagulants‡	17.90	17.12	0.02	17.92	17.39	0.01
Lipid-lowering agents	29.31	31.82	−0.05	29.31	29.50	0.00
Antidiabetic drugs	20.86	21.27	−0.01	20.86	21.36	−0.01
Gastroprotective agents	38.97	37.86	0.02	38.97	38.62	0.01
Cox-2 NSAIDs	8.39	8.22	0.01	8.40	8.18	0.01
Nonselective NSAIDs	23.13	21.07	0.05	23.13	23.30	0.00
Glucocorticoids	16.78	17.24	−0.01	16.78	17.35	−0.02
Antidepressants§	24.48	20.71	0.09	24.46	24.15	0.01
Variables measured between warfarin initiation and the SSRI index date, %						
Hypertension	21.11	26.58	−0.13	21.11	20.39	0.02
Recent acute MI	0.20	0.35	−0.03	0.20	0.19	0.00
Unstable angina	0.43	0.72	−0.04	0.43	0.43	0.00
Coronary artery disease	11.06	14.92	−0.12	11.03	10.53	0.02
Atrial fibrillation	14.51	18.7	−0.12	14.50	14.45	0.00
Valve replacement	¶	0.06	−0.03	¶	¶	0.00
Congestive heart failure	9.23	11.68	−0.08	9.19	9.07	0.00

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TABLE 1. *(Continued)*

Characteristics	Before Matching: Total Study Cohort (n = 52,129)			After Matching: Matched Study Cohort (n = 49,881)		
	Potent CYP2C9 Inhibitors (n = 8011)	Other SSRIs (n = 44,118)	Standardized Difference	Potent CYP2C9 Inhibitors (n = 8000) n = 8000†	Other SSRIs (n = 41,881) n = 8000†	Standardized Difference
Hemorrhagic stroke	¶	0.15	−0.01	¶	0.15	−0.02
Ischemic stroke	3.28	3.82	−0.03	3.28	3.10	0.01
Transient ischemic attack	1.40	1.86	−0.04	1.37	1.40	0.00
Peripheral vascular disease	1.60	2.01	−0.03	1.60	1.47	0.01
Venous thromboembolism	16.19	15.20	0.03	16.20	15.93	0.01
Hyperlipidemia	9.30	11.57	−0.08	9.29	9.28	0.00
Diabetes	16.77	17.69	−0.02	16.77	16.73	0.00
PUD/upper GI bleeding	5.15	6.24	−0.05	5.14	5.37	−0.01
ACEIs/ARBs	20.07	22.46	−0.06	20.05	20.81	−0.02
β-Blockers	18.96	23.28	−0.11	18.96	19.70	−0.02
CCBs	12.09	13.84	−0.05	12.08	11.70	0.01
Other antihypertensive drugs	21.99	23.62	−0.04	21.99	21.52	0.01
Antiplatelet drugs	2.47	3.49	−0.06	2.47	2.59	−0.01
Injectable anticoagulants‡	7.89	8.00	<0.01	7.90	7.98	0.00
Lipid-lowering agents	17.77	20.17	−0.06	17.77	17.49	0.01
Antidiabetic drugs	13.57	13.90	−0.01	13.56	13.44	0.00
Gastroprotective agents	22.70	24.13	−0.03	22.69	22.76	0.00
Cox-2 NSAIDs	3.39	3.56	−0.01	3.39	3.62	−0.01
Nonselective NSAIDs	5.96	5.36	0.03	5.97	6.50	−0.02
Glucocorticoids	6.22	6.83	−0.03	6.20	6.52	−0.01
Antidepressants§	14.93	13.19	0.05	14.93	14.67	0.01
Variables measured from 180 d before warfarin initiation to the SSRI index date						
Combined comorbidity score, mean (SD)	2.47 (2.58)	2.90 (2.81)	−0.16	2.46 (2.58)	2.51 (2.61)	−0.02
Variables measured in the 180 d before the SSRI index date						
No. of physician visits, mean (SD)	6.78 (6.56)	7.00 (6.61)	−0.03	6.78 (6.56)	6.83 (6.39)	−0.01
No. of hospitalizations, mean (SD)	1.22 (1.35)	1.28 (1.46)	−0.04	1.22 (1.35)	1.24 (1.47)	−0.01
No. of nursing home stay, mean (SD)	1.55 (5.19)	2.10 (6.10)	−0.10	1.55 (5.19)	1.54 (4.92)	0.00

*Presenting as summary estimates for mean, SD, and standardized difference across databases.

†One user of potent CYP2C9 inhibitors: 1 randomly sampled user of other SSRIs in each matched subset.

‡Anticoagulants other than warfarin, dabigatran, rivaroxaban, and apixaban.

§Antidepressants other than SSRIs.

¶Cell with a number <11.

ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; Cox, cyclooxygenase; GI, gastrointestinal; INR, International normalized ratio; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PUD, peptic ulcer disease.

Digital Content 1, http://links.lww.com/JCP/A418). Before matching, patients treated with SSRIs that are potent CYP2C9 inhibitors were younger and were less likely to have had a diagnosis of hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, and hyperlipidemia and to have used β-blockers than patients treated with SSRIs that are not potent inhibitors. Patients treated with SSRIs that are potent CYP2C9 inhibitors also had a lower combined comorbidity score and were less likely to have had prior nursing home stays.

After PS matching, a total of 49,881 patients (8000 patients treated with SSRIs that are potent CYP2C9 inhibitors and 41,881 patients treated with SSRIs that are not potent CYP2C9 inhibitors; 96% of the total study cohort) were included in the analysis (Table S3, Supplemental Digital Content 1, http://links.lww.com/JCP/A418). Propensity score matching reduced observed differences in baseline characteristics between treatment groups (Table 1 and Tables S4a–S4e, Supplemental Digital Content 1, http://links.lww.com/JCP/A418).

Follow-Up and Outcomes

During a mean follow-up of 52 days of concomitant warfarin and SSRI exposure, we observed a total of 822 composite

TABLE 2. Follow-up and Outcome Event Rates by SSRI Group

	Before Matching						After Matching					
	Total Study Cohort (n = 52,129)						Matched Study Cohort (n = 49,881)					
	Potent CYP2C9 Inhibitors (n = 8011)			Other SSRIs (n = 44,118)			Potent CYP2C9 Inhibitors (n = 8000)			Other SSRIs (n = 41,881)		
Outcome	No. of Events	Person-Days at Risk	Crude Incidence (per 1000 Person-Days)*	No. of Events	Person-Days at Risk	Crude Incidence (per 1000 Person-Days)*	No. of Events	Person-Days at Risk	Adjusted Incidence (per 1000 Person-Days)†	No. of Events	Person-Days at Risk	Adjusted Incidence (per 1000 Person-Days)†
Composite bleeding events	125	391,499	0.33	697	2,296,289	0.34	124	390,953	0.33	626	2,171,430	0.29
Composite ischemic or thromboembolic events	175	390,340	0.39	994	2,283,511	0.34	175	389,780	0.39	927	2,158,767	0.39
All-cause mortality	86	394,909	0.24	680	2,313,795	0.37	86	394,349	0.23	593	2,187,347	0.30

*Data were pooled using random-effects meta-analysis.
†Data were weighted by the matching ratio and were pooled using random-effects meta-analysis.

TABLE 3. Hazard Ratios Comparing Use of SSRIs That Are Potent CYP2C9 Inhibitors Versus Use of SSRIs That Are Not Potent CYP2C9 Inhibitors, by Composite Outcomes

	Crude HR	HR After PS Matching (95% CI)
Composite bleeding events	1.05 (0.87–1.27)	1.14 (0.94–1.38)
Composite ischemic or thromboembolic events	0.98 (0.84–1.15)	1.03 (0.87–1.21)
All-cause mortality	0.76 (0.61–0.95)	0.90 (0.72–1.14)

bleeding events, 1169 composite ischemic or thromboembolic events, and 766 deaths. Most patients were censored because of warfarin discontinuation (55%), followed by SSRI treatment discontinuation (33%). There was no material difference in mean follow-up durations between SSRI treatment groups (49 [SD, 43]days for SSRIs that are potent CYP2C9 inhibitors vs 52 [SD, 46]days) for SSRIs that are not potent CYP2C9 inhibitors). Crude and adjusted incidence rates of composite outcomes and all-cause mortality for each treatment group are presented in Table 2 and Table S5, Supplemental Digital Content 1, http://links.lww.com/JCP/A418.

The crude HRs comparing SSRIs that are potent CYP2C9 inhibitors to SSRIs that are not potent CYP2C9 inhibitors were 1.05 (95% CI, 0.87–1.27) for bleeding events, 0.98 (95% CI, 0.84–1.15) for ischemic or thromboembolic events, and 0.76 (95% CI, 0.61–0.95) for mortality (Table 3 and Table S6, Supplemental Digital Content 1, http://links.lww.com/JCP/A418). After PS matching, the adjusted HRs were 1.14 (95% CI, 0.94–1.38), 1.03 (95% CI, 0.87–1.21), and 0.90 (95% CI, 0.72–1.14), respectively. Adjusted HRs for individual bleeding and individual ischemic or thromboembolic events are shown in Table 4. We did not find significant differences across individual outcomes, although a numerically higher HR with a wide CI was observed for the upper GI bleeding (HR, 1.30; 95%CI, 0.74–2.28).

Sensitivity and Subgroup Analyses

Results of analyses restricting to patients with at least 7, 14, 28, or 56 days of continuous warfarin use before the SSRI index

TABLE 4. Hazard Ratios Comparing Use of SSRIs That Are Potent CYP2C9 Inhibitors Versus Use of SSRIs That Are Not Potent CYP2C9 Inhibitors, by Individual Outcomes

Individual Outcome	HR After PS Matching (95% CI)
Bleeding events	
Upper GI bleeding	1.30 (0.74–2.28)
Lower GI bleeding	1.06 (0.77–1.44)
Hemorrhagic stroke	0.73 (0.26–2.07)
Major urogenital bleeding	1.10 (0.64–1.88)
Other major bleeding	1.21 (0.91–1.61)
Ischemic or thromboembolic events	
Ischemic stroke	1.16 (0.74–1.81)
Acute MI	1.17 (0.64–2.12)
Systemic embolism	1.18 (0.81–1.73)
Transient ischemic attack	—*
Venous thromboembolism	0.98 (0.80–1.19)

*Unable to be calculated because of zero events in the group of SSRIs that are potent CYP2C9 inhibitors in all 5 databases but was accounted for in the composite ischemic or thromboembolic events.

TABLE 5. Results of Sensitivity Analyses Requiring Minimum Warfarin Use Before SSRI Initiation

Time Lengths From Warfarin Initiation to the SSRI Index Date	≥7 d	≥14 d	≥28 d	≥56 d
	HR After PS Matching (95% CI)			
Composite bleeding events	1.20 (0.96–1.51)	1.12 (0.85–1.48)	0.87 (0.58–1.32)	0.84 (0.46–1.55)
Composite ischemic or thromboembolic events	1.02 (0.84–1.24)	1.02 (0.81–1.29)	1.01 (0.74–1.39)	0.80 (0.48–1.34)
All-cause mortality	0.97 (0.75–1.25)	0.98 (0.73–1.33)	0.67 (0.42–1.05)	0.80 (0.43–1.50)

date were not materially different from the primary results (Table 5). Warfarin mean daily dose before the SSRI index date (5.6 [SD, 3.4] mg/d) was slightly higher than that after the SSRI index date (5.1 [SD, 3.3] mg/d). However, there was no apparent difference by treatment group before or after the index date (Table S7, Supplemental Digital Content 1, http://links.lww.com/JCP/A418). Additional controlling for warfarin mean daily dose before the index date yielded similar results to those from the primary analysis (Table S8, Supplemental Digital Content 1, http://links.lww.com/JCP/A418). We did not observe a difference in warfarin or SSRI treatment discontinuation between SSRI exposure groups (Table S9, Supplemental Digital Content 1, http://links.lww.com/JCP/A418).

Subgroup analyses did not reveal differential effects across subgroups of age, sex, and histories of GI or ulcer bleeding, MI, and stroke, although a significantly higher risk of composite bleeding events was observed among females (adjusted HR, 1.28; 95% CI, 1.03–1.59) (Fig. 2).

DISCUSSION

In this large-scale, multidatabase cohort study, we found comparable rates of composite bleeding events, composite ischemic or thromboembolic events, and death between patients concomitantly treated with warfarin and SSRIs that are potent CYP2C9 inhibitors and those concomitantly treated with warfarin and SSRIs that are not potent CYP2C9 inhibitors. Results were consistent across individual component outcomes, sensitivity analyses, and subgroup analyses. Although potent CYP2C9 inhibitors represented only 15% of SSRI exposures in our study, they may be more commonly used in other countries.[38–40] Our findings provide reassurance that, beyond a potential pharmacodynamic interaction between warfarin and SSRIs, SSRIs that inhibit CYP2C9 do not further affect warfarin outcomes. However, numerically small but potentially meaningful effects on bleeding (especially upper GI bleeding) cannot be completely excluded.

A number of studies have examined whether concomitant use of warfarin and SSRIs is associated with a greater risk of hemorrhagic complications.[21–25] Several observational studies have suggested that as compared with use of warfarin alone concomitant use of warfarin and SSRIs is associated with higher risk of various bleeding events ranging from 1.1-fold to 3.5-fold increases.[21–24] However, not all of these studies disentangled the individual effects of warfarin and SSRIs, each of which can increase bleeding risk,[12–16] and none attempted to determine whether certain SSRIs also produce a pharmacokinetic interaction with warfarin through CYP2C9 inhibition in addition to the potential pharmacodynamic interaction.

By comparing outcomes between patients treated with warfarin and SSRIs that are potent and that are not potent CYP2C9 inhibitors, we were able to directly assess the clinical impact of the putative pharmacokinetic interaction under the assumption that the pharmacodynamic interaction between warfarin and the SSRIs was the same between the 2 SSRI groups. Although laboratory studies suggest in vitro interactions between warfarin and drugs that inhibit CYP2C9,[19,20] we did not observe differences in major clinical outcomes between SSRIs that are potent versus not potent CYP2C9 inhibitors. There are several possible explanations for this discrepancy. First, in clinical practice, close INR monitoring and frequent warfarin dose adjustment usually occur in response to changes in INR, especially during the first few weeks of treatment. If patients who received SSRIs that are potent CYP2C9 inhibitors experience an increase in INR, it is possible that the warfarin dose might have been adjusted accordingly. In sensitivity analyses, indirectly estimated warfarin mean daily dose was not materially different between treatment groups. Also, controlling for warfarin mean daily dose prior to SSRI exposure yielded similar results to those form the main analysis. Nevertheless, because we do not have direct measures of INR in the databases, we cannot determine the extent to which close INR monitoring explains our results. Second, humans might have compensatory mechanisms that maintain homeostasis among drugs and metabolic enzymes. For example, previous in vitro experiments have observed that modulation of CYP3A4 levels may influence the activity of CYP2A9.[41,42] In the case of warfarin and CYP2C9 inhibition, it is possible that other enzymes that metabolize warfarin, or CYP2C9 itself, might be up-regulated, which would normalize warfarin plasma concentrations and limit changes in clinical outcomes. However, further studies targeting warfarin-related metabolic pathways, including CYP2C9, CYP1A2, CYP2C19, and CYP3A4,[17,18] are needed.

Our study has a number of strengths. Because of their large size and ability to follow patients longitudinally, electronic health care databases that capture information about routine health service utilization play an important role in assessing the clinical impact of drug-drug interactions. Although screening for potential drug-drug interactions is an essential aspect of drug development and regulatory approval, these studies do not assess whether pharmacokinetic interactions result in meaningful clinical outcomes in the real world. Moreover, as compared with individuals enrolled in pharmacokinetic studies, patients in routine care are more likely to have multiple chronic conditions and receive multiple treatments, which increases the likelihood of drug-drug interactions.[43,44] In addition, we used data from 5 large databases that cover geographically, socioeconomically, and clinically diverse populations, which facilitates the generalizability of our findings.

However, there are important limitations of administrative health care data and of our study that must be considered when interpreting our results. First, pharmacy claims data provide accurate information about the prescriptions that patients fill, but they do not necessarily reflect whether and when patients consume the medications, which can lead to exposure misclassification. While we would expect this misclassification to be nondifferential between our exposure groups, this could lead to a bias toward the null. Second, the databases that we used do not contain measures of prothrombin time (eg, INR values), information about warfarin dose adjustment, and data about whether patients were stabilized on warfarin therapy at the time of receiving SSRI treatment. As

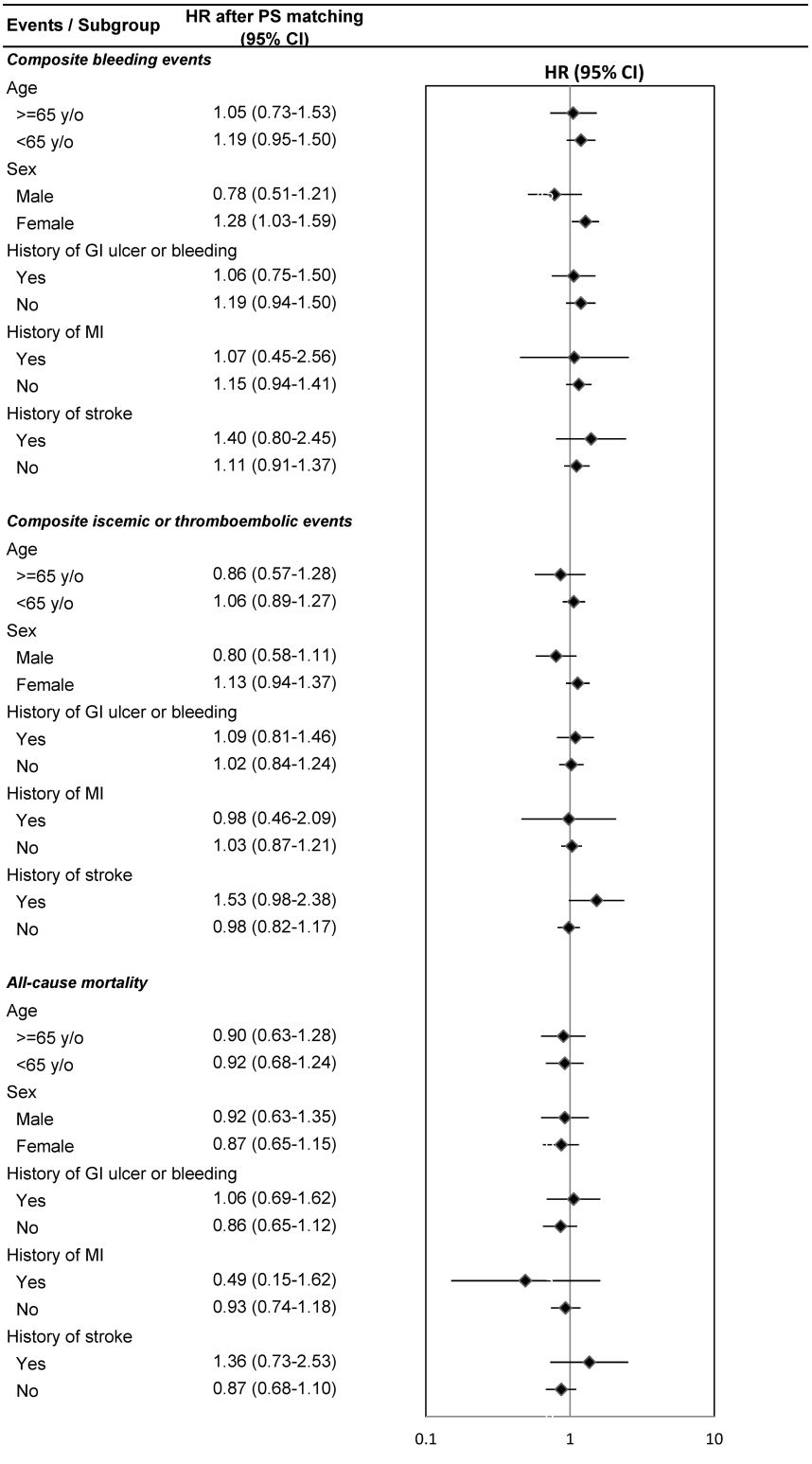

FIGURE 2. Results of subgroup analyses comparing use of SSRIs that are potent CYP2C9 inhibitors versus use of SSRIs that are not potent CYP2C9 inhibitors.

mentioned previously, careful monitoring and immediate warfarin dose adjustments in response to changes in INR would limit the impact of a pharmacokinetic interaction. Our sensitivity analyses that restricted patients to those with at least 7, 14, 28, or 56 days of continuous warfarin use before SSRI treatment yielded similar results to the main analysis. While these analyses may partially eliminate the influence of the warfarin stabilization period on the null findings, the HR did drop monotonically with increasing lengths of warfarin stabilization periods. Nevertheless, without data on INR values and warfarin dose adjustment, we cannot fully detertmine their impact on the results. Third, although we used 5 data sources across different health care systems, our findings were mostly driven by the Optum and MAX databases, which accounted for 80% of the sample size. In addition, although we observed a significantly higher risk of bleeding events among women when comparing warfarin and SSRIs that are potent CYP2C9 inhibitors to warfarin and SSRIs that are not potent CYP2C9 inhibitors, this is the only statistically significant result out of the many subgroup analyses. Therefore, the possibility that this is a chance finding cannot be ruled out. Further research focusing on a sex-specific effect would be helpful to elucidate this finding. We also recognize that power was limited for the evaluation of differential treatment effects across subgroups and individual components of the outcomes. Fourth, although we believe that our design, in which all patients initiated warfarin and subsequently initiated an SSRI, and our PS-matched analysis substantially limited the opportunity for confounding to influence our results, as in all observational studies, we cannot rule out the possibility of unmeasured confounding, because CYP2C9 genotypes or risk factors such as smoking, diet, over-the-counter medication use, and body mass index are not available in claims data. Finally, given that the mean follow-up duration was short in this study, further studies quantifying the long-term clinical impacts of concomitant use of warfarin and SSRIs are warranted.

In conclusion, this multidatabase cohort study suggested comparable rates of bleeding and ischemic or thromboembolic outcomes between patients concomitantly treated with warfarin and SSRIs that are potent CYP2C9 inhibitors and those concomitantly treated with warfarin and SSRIs that are not potent CYP2C9 inhibitors, where patients may be closely monitored.

AUTHOR DISCLOSURE INFORMATION

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