Impact of an Interaction Between Clopidogrel and Selective Serotonin Reuptake Inhibitors

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Clopidogrel is a pro-drug that requires activation by the cytochrome P450 (CYP) enzyme system. Patients receiving clopidogrel are often treated with selective serotonin reuptake inhibitors (SSRIs) for co-existing depression. SSRIs that inhibit the CYP2C19 enzyme have the potential to reduce the effectiveness of clopidogrel. Using 5 US databases (1998 to 2013), we conducted a cohort study of adults who initiated clopidogrel while being treated with either an SSRI that inhibits CYP2C19 (fluoxetine and fluvoxamine) or a noninhibiting SSRI. Patients were matched by propensity score and followed for as long as they were exposed to both clopidogrel and the index SSRI group (primary analysis) or for 180 days after clopidogrel initiation (sensitivity analysis). Outcomes included a composite ischemic event (myocardial infarction, ischemic stroke, or a revascularization procedure) and a composite major bleeding event (gastrointestinal bleed or hemorrhagic stroke). The final propensity score−matched cohort comprised 9,281 clopidogrel initiators on CYP2C19-inhibiting SSRIs and 44,278 clopidogrel initiators on a noninhibiting SSRIs. Compared with those treated with a noninhibiting SSRI, patients on a CYP2C19-inhibiting SSRI had an increased risk of ischemic events (hazard ratio [HR] 1.12; 95% confidence interval [CI] 1.01 to 1.24), which was more pronounced in patients ≥65 years (HR 1.22; 95% CI 1.00 to 1.48). The HR for major bleeding was 0.76 (95% CI 0.50 to 1.17). In conclusion, the findings from this large, population-based study suggest that being treated with a CYP2C19-inhibiting SSRI when initiating clopidogrel may be associated with slight decrease in effectiveness of clopidogrel. **(Am J Cardiol 2017;119:651−657)**

Antiplatelet agents are the cornerstone of treatment in acute coronary syndrome, and although newer antiplatelet agents have recently become available, clopidogrel remains the most widely used prescription antiplatelet. Clopidogrel is a pro-drug that undergoes a 2-stage activation process, which is mediated by several cytochrome P450 (CYP) hepatic enzymes.[1] CYP2C19 is involved in both activation steps, raising concern that drugs that inhibit CYP2C19 might reduce clopidogrel's effectiveness,[2,3] although the clinical impact of such interactions has not been widely demonstrated.[4,5] Since up to 40% of patients with coronary artery disease are affected by depression,[6−9] many patients receiving antiplatelet therapy are often also treated with a serotonin selective reuptake inhibitor (SSRI).[9,10] Two SSRI agents, fluoxetine and fluvoxamine, are potent inhibitors of CYP2C19.[11,12] Although several studies have found attenuated laboratory response to clopidogrel in the presence of CYP2C19-inhibiting SSRIs,[13,14] no population-based study has examined whether SSRIs that are potent inhibitors of CYP2C19 affect clinically relevant outcomes of clopidogrel treatment. Given the lack of firm evidence about the clinical impact of this potential interaction, we examined ischemic and hemorrhagic outcomes related to clopidogrel in subjects exposed to SSRIs at the time of clopidogrel initiation in a large cohort of patients in the United States.

Methods

Data for this study were derived from 5 US databases: a commercial health insurance database (Optum Research Database), a Medicaid database (Medicaid Analytic eXtract [MAX]), and 3 Medicare databases that linked Medicare Parts A and B data to pharmacy claims data from (1) Medicare Part D plans or retiree drug plans administered by CVS Caremark, a large national pharmacy benefit manager (Caremark); (2) pharmacy assistance program in New Jersey (Pharmaceutical Assistance to the Aged and Disabled); and (3) pharmacy assistance program in Pennsylvania (Pharmaceutical Assistance Contract for the Elderly). Combined, the data sources covered the period from 1998 (following clopidogrel approval in the United States) through the end of 2013 and ∼100 million subjects. The Institutional Review Board of the Brigham and Women's Hospital approved this study and granted a waiver of consent. Data use agreements were in place.

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See page 656 for disclosure information.

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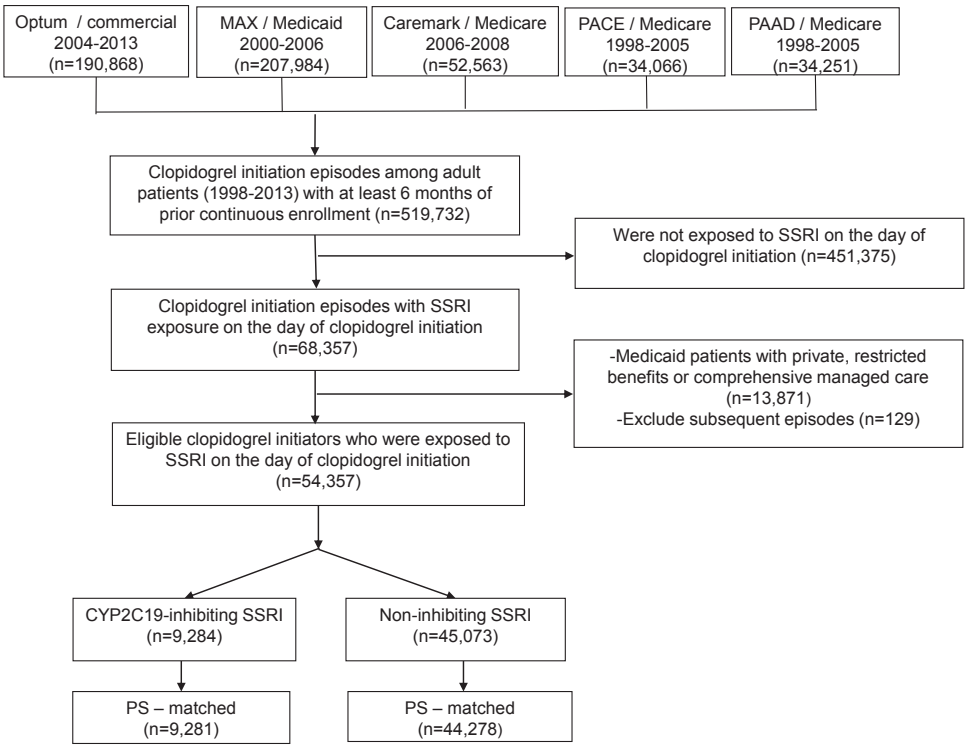

Figure 1. Patient flow chart. MAX = Medicaid Analytic eXtract; PAAD = Pharmaceutical Assistance to the Aged and Disabled; PACE = Pharmaceutical Assistance Contract for the Elderly.

We identified a cohort of patients ≥18 years who initiated clopidogrel from January 1, 1998, to December 31, 2013, while being treated with an SSRI. Initiation was defined as a new (index) prescription for clopidogrel with no prescription for any antiplatelet drug (clopidogrel, prasugrel, ticagrelor, cilostazol, or ticlopidine) in the preceding 6 months. Treatment with an SSRI was defined as having had a prescription for an SSRI before the clopidogrel index date with the days' supply overlapping the clopidogrel index date. Patients were required to have continuous insurance coverage for at least 6 months before clopidogrel initiation. Given the potential for incomplete Medicaid claims for patients in the MAX database who are also enrolled in Medicare (i.e., "dual eligibles"), managed care plans, restricted benefits plans, or private Medicaid insurance,[15] we excluded Medicaid beneficiaries ≥65 years and those who were enrolled in any of the earlier mentioned plans either on the index date or at any time during the preceding 6 months (Figure 1). SSRI prescriptions that overlapped with clopidogrel initiation were used to classify patients into either inhibiting SSRI or noninhibiting SSRI exposure groups. Inhibiting SSRIs were fluoxetine and fluvoxamine. Citalopram, escitalopram, paroxetine, and sertraline were the noninhibiting SSRIs.[11,12] Continuous exposure was assessed using prescription days' supply allowing for a 7-day grace period between serial prescriptions.

The primary effectiveness outcome was a composite ischemic end point comprising acute myocardial infarction (MI), ischemic stroke, and coronary revascularization procedure (coronary artery bypass grafting, stenting, or percutaneous transluminal coronary angioplasty [PTCA]). The primary safety outcome was a composite bleeding event end point, comprising hospitalizations for major upper gastrointestinal bleed and hemorrhagic stroke. Secondary outcomes included the individual components of the primary composite outcomes. All outcomes were assessed using validated claims-based algorithms (Supplementary Data). Previous validation studies found positive predictive values of 94% for MI,[16] 96% for ischemic stroke,[17] 95% for stenting,[18] 96% for PTCA,[18] 98% for coronary artery bypass grafting,[18] 88% for gastrointestinal bleeds,[19] and 89% for hemorrhagic stroke.[20] We also examined all-cause mortality. Because mortality data are incomplete in Medicaid data, we assessed mortality only in the subgroup of patients ≥65 years.

In the primary analysis, patients were followed for as long as they were exposed to both clopidogrel and their index SSRI group. Patients were censored at the first occurrence of an event of interest, death, disenrollment from the health plan, end of the database-specific study period (2013 for Optum, 2008 for Caremark, 2006 for MAX, and 2005 for Pharmaceutical Assistance Contract for the Elderly and Pharmaceutical Assistance to the Aged and Disabled), or discontinuation of either clopidogrel or their SSRI exposure group, defined as the end of days supply (plus additional 7 days to account for variation in adherence), whichever came first. Follow-up was also censored on a dispensing of another antiplatelet agent or of an SSRI in the other exposure group (an inhibiting SSRI for a patient in the noninhibiting group and vice versa). In addition, Medicaid patients were censored when they turned 65 or when enrolled in private, restricted benefits, or comprehensive medical managed care plans.

Table 1
Baseline characteristics of study patients

Patient characteristic	SSRI Exposure groups			
	Before PS matching		After PS matching	
	Inhibiting SSRI (n = 9,284)	Non-inhibiting SSRI (n = 45,073)	Inhibiting SSRI (n = 9,281)	Non-inhibiting SSRI (n = 9,281 out of 44,278*)
Age (years), mean ± SD	59.1 ± 12.2	61.7 ± 13.6	59.1 ±12.1	59.2 ± 12.6
Women	6139 (66.1%)	29139 (64.6%)	6136 (66.1%)	6166 (66.4%)
Type of insurance				
Commercial	3120 (33.6%)	14562 (32.3%)	3119 (33.6%)	3119 (33.6%)
Medicaid	4594 (49.5%)	19661 (43.6%)	4594 (49.5%)	4594 (49.5%)
Medicare	1570 (16.9%)	10850 (24.1%)	1568 (16.9%)	1568 (16.9%)
Year of clopidogrel initiation				
1998-2001	1464 (15.8%)	5096 (11.3%)	1462 (15.8%)	1420 (15.3%)
2002-2005	4434 (47.8%)	21543 (47.8%)	4433 (47.8%)	4495 (48.4%)
2006-2009	2507 (27.0%)	13902 (30.8%)	2507 (27.0%)	2476 (26.7%)
2009-2013	879 (9.5%)	4532 (10.1%)	879 (9.5%)	890 (9.6%)
Region				
Midwest	2134 (23.0%)	9496 (21.1%)	2134 (23.0%)	2147 (23.1%)
Northeast	2060 (22.2%)	12226 (27.1%)	2058 (22.2%)	2031 (21.9%)
South	3889 (41.9%)	18503 (41.1%)	3889 (41.9%)	3892 (41.9%)
West	1135 (12.2%)	4546 (10.1%)	1135 (12.2%)	1144 (12.3%)
Atrial fibrillation	669 (7.2%)	4482 (9.9%)	668 (7.2%)	631 (6.8%)
Atherosclerosis	157 (1.7%)	789 (1.8%)	157 (1.7%)	160 (1.7%)
Coronary artery disease	5769 (62.1%)	28261 (62.7%)	5767 (62.1%)	5735 (61.8%)
Congestive heart failure	1790 (19.3%)	9736 (21.6%)	1789 (19.3%)	1751 (18.9%)
Diabetes	3642 (39.2%)	17921 (39.8%)	3640 (39.2%)	3641 (39.2%)
Prior hemorrhagic stroke	39 (0.4%)	228 (0.5%)	39 (0.4%)	35 (0.4%)
Hyperlipidemia	4820 (51.9%)	24145 (53.6%)	4819 (51.9%)	4802 (51.7%)
Hypertension	6585 (70.9%)	33441 (74.2%)	6583 (70.9%)	6595 (71.1%)
Prior MI	1160 (12.5%)	5576 (12.4%)	1160 (12.5%)	1194 (12.9%)
Prior ischemic stroke	1139 (12.3%)	6143 (13.6%)	1137 (12.3%)	1094 (11.8%)
Recent (within 2 prior weeks) MI	875 (9.4%)	4051 (9.0%	875 (9.4%)	917 (9.9%)
Recent (within 2 prior weeks) CABG	51 (0.5%)	196 (0.4%)	51 (0.5%)	49 (0.5%)
Recent (within 2 prior weeks) PCI	2235 (24.1%)	9821 (21.8%)	2234 (24.1%)	2256 (24.3%)
Peptic ulcer disease	2098 (22.6%)	10831 (24.0%)	2098 (22.6%)	2094 (22.6%)
Peripheral vascular disease	1021 (11.0%)	5848 (13.0%)	1020 (11.0%)	1036 (11.2%)
Prior TIA	1250 (13.5%)	6449 (14.3%)	1250 (13.5%)	1245 (13.4%)
Unstable angina	1463 (15.8%)	6411 (14.2%)	1463 (15.8%)	1488 (16.0%)
Prior upper GI bleeding	94 (1.0%)	502 (1.1%)	94 (1.0%)	87 (0.9%)
Venous thromboembolism	253 (2.7%)	1493 (3.3%)	253 (2.7%)	255 (2.7%)
Combined comorbidity score, mean ±SD	1.7 ± 2.2	1.9 ± 2.4	1.7 ± 2.2	1.7 ± 2.2
Prior medications				
ACE Inhibitor or ARB	5256 (56.6%)	26375 (58.5%)	5254 (56.6%)	5199 (56.0%)
Beta blocker	4976 (53.6%)	25188 (55.9%)	4974 (53.6%)	4986 (53.7%)
Calcium channel blocker	2911 (31.4%)	15097 (33.5%)	2910 (31.4%)	2879 (31.0%)
Other antihypertensive agent	4646 (50.0%)	22360 (49.6%)	4645 (50.0%)	4644 (50.0%)
H2 receptor antagonists	1270 (13.7%)	5783 (12.8%)	1270 (13.7%)	1257 (13.5%)
Proton pump inhibitors	3866 (41.6%)	18877 (41.9%)	3864 (41.6%)	3849 (41.5%)
Other gastroprotective agent	267 (2.9%)	1341 (3.0%)	267 (2.9%)	255 (2.7%)
Statin	5508 (59.3%)	27096 (60.1%)	5507 (59.3%)	5474 (59.0%)
Other lipid-lowering agent	1509 (16.3%)	7812 (17.3%)	1509 (16.3%)	1529 (16.5%)
Non-selective NSAID	2256 (24.3%)	10412 (23.1%)	2255 (24.3%)	2291 (24.7%)
COX 2 inhibitor	1510 (16.3%)	6642 (14.7%)	1509 (16.3%)	1493 (16.1%)
Warfarin	744 (8.0%)	4019 (8.9%)	742 (8.0%)	745 (8.0%)
Concomitant inhibitor	1341 (14.4%)	6737 (14.9%)	1340 (14.4%)	1337 (14.4%)
Concomitant NSAID	1760 (19.0%)	7517 (16.7%)	1758 (18.9%)	1720 (18.5%)
Concomitant oral anticoagulant	442 (4.8%)	2482 (5.5%)	440 (4.7%)	449 (4.8%)
Health care utilization, mean ± SD				
Number of distinct prescription medications	15.4 ± 7.5	15.3 ± 7.4	15.4 ± 7.5	15.3 ± 7.5
Number of hospitalizations	0.9 ± 1.2	1.0 ± 1.2	0.9 ± 1.2	0.9 ± 1.1
Number of outpatient physician visits	9.3 ± 7.6	9.6 ± 7.9	9.3 ± 7.6	9.3 ± 7.7

(*continued*)

Table 1
(*continued*)

Patient characteristic	SSRI Exposure groups			
	Before PS matching		After PS matching	
	Inhibiting SSRI (n = 9,284)	Non-inhibiting SSRI (n = 45,073)	Inhibiting SSRI (n = 9,281)	Non-inhibiting SSRI (n = 9,281 out of 44,278*)
Number of days hospitalized	5.2 ± 9.6	5.8 ± 10.8	5.2 ± 9.6	5.2 ± 9.5
Number of days in a nursing home	7.2 ± 32.8	8.6 ± 34.8	7.2 ± 32.8	7.6 ± 33.8

Patient characteristics with prevalence <0.1 are not reported. See Supplementary Table 1a for all characteristics and standardized differences.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; COX = cyclooxygenase; GI = gastrointestinal; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; PS = propensity score; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; TIA = transient ischemic attack.

* Since variable ratio propensity score matching produces covariate balance within a matched set, but not marginally, one non-inhibiting SSRI-exposed patient along with their corresponding inhibiting SSRI-exposed patient was randomly sampled from each matched set.

Co-morbidities, other medications, and health care utilization were measured during the 6-month baseline period preceding each patient's clopidogrel initiation date. Exposure to concurrent drugs was defined by whether a patient had an active prescription for a drug on the clopidogrel initiation date. Propensity score (PS) matching was used to account for measured differences between the exposure groups. Propensity scores were estimated using logistic regression predicting the exposure to inhibiting versus noninhibiting SSRIs as a function of all the covariates. Because the cohort included many more patients exposed to noninhibiting SSRIs than patients exposed to inhibiting SSRIs, variable ratio (1 inhibiting to up to 10 noninhibiting) matching was performed within each database using a nearest-neighbor algorithm with a maximum caliper of 0.025. Because variable ratio matching produces covariate balance within a matched set, but not marginally in the overall matched population, we randomly sampled 1 non-inhibiting SSRI-exposed patient from each matched set along with their corresponding inhibiting SSRI-exposed patient and compared covariate distributions within this random sample to assess covariate balance achieved by PS matching.[21] We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). To account for the variable ratio matching, the Cox model was stratified by the matching ratio. Analyses were conducted in each data source separately and then in the pooled data set stratifying on the database. We also assessed treatment effects in subgroups of patients <65 and ≥65 years.

In a sensitivity analysis, we used an intention-to-treat (ITT) approach where patients were followed for a maximum of 180 days from clopidogrel initiation, regardless of whether they discontinued one or both drugs or switched to other treatments. This analysis was performed to account for potential differential censoring between exposure groups but has its own limitations because of greater exposure misclassification.[22]

Results

Of the 519,732 eligible clopidogrel initiations, 68,357 (13.2%) had concurrent SSRI exposure on clopidogrel initiation date. The final PS-matched cohort included 9,281 clopidogrel initiators treated with an inhibiting SSRI (97.5% with fluoxetine and 2.5% with fluvoxamine) and 44,278 initiators who were treated with a noninhibiting SSRI (34.0% with sertraline, 29.5% with paroxetine, 18.7% with escitalopram, and 17.8% with citalopram; Figure 1). The baseline characteristics were well balanced between the 2 exposure groups before and after PS matching (Table 1; see Supplementary Table 1a for standardized differences and Supplementary Tables 1b to 1f for database-specific patient characteristics). The mean age of patients was 59 years, and 66% were women.

The average follow-up for concomitant exposure to both clopidogrel and an SSRI was 80 days. Neither the duration of follow-up nor the reasons for censoring differed between exposure groups. The majority of patients were censored because of discontinuation of the index SSRI exposure group (57%); 36% were censored because of clopidogrel discontinuation. For the primary outcome of any ischemic event, 450 events were observed during 1,950 person-years of follow-up in the group exposed to inhibiting SSRIs and 1,965 events during 9,381 person-years of follow-up in the group exposed to noninhibiting SSRIs, yielding an HR of 1.12 (95% CI 1.01 to 1.24). For the individual components, patients on inhibiting SSRIs had a higher risk of undergoing a stent procedure (HR 1.18; 95% CI 1.04 to 1.34) and PTCA (HR 1.17; 95% CI 1.01 to 1.34). For the composite bleeding outcome, there were 25 events during 2,042 years of follow-up in the group exposed to inhibiting SSRIs and 169 events during 9,764 years of follow-up in the group exposed to noninhibiting SSRIs (HR 0.76; 95% CI 0.50 to 1.17; Table 2).

Results of the ITT analysis were qualitatively similar to those of the primary analysis although effect sizes were smaller (HR 1.08; 95% CI 0.99 to 1.17 for any ischemic event; Supplementary Table 2). Database-specific results are presented in the online data supplement (Supplementary Table 3 and Figures 1 and 2).

In patients ≥65 years, initiation of clopidogrel while treated with an inhibiting SSRI was associated with a 22% increase in risk of any ischemic event (95% CI 1.00 to 1.48), a 39% increase in risk of stenting (95% CI 1.08 to 1.78), and a 38% increase in PTCA (95% CI 1.05 to 1.81) (Figure 2, Supplementary Table 4). There were no meaningful

Table 2
Effects of exposure to clopidogrel plus inhibiting SSRI as compared to clopidogrel plus non-inhibiting SSRI

Outcome	Inhibiting SSRI (N = 9,281)		Non-inhibiting SSRI (N = 44,278)		HR (95% CI)
	Events, No.	Rate / 1000 PYs	Events, No.	Rate / 1000 PYs	
Any Ischemic	450	230.81	1965	209.47	1.12 (1.01-1.24)
Myocardial Infarction	50	24.56	263	26.97	0.97 (0.71-1.32)
Ischemic Stroke	52	25.52	295	30.26	0.94 (0.70-1.27)
Stent	305	155.04	1237	130.67	1.18 (1.04-1.34)
PTCA	250	125.94	1018	106.67	1.17 (1.01-1.34)
CABG	40	19.60	184	18.84	1.02 (0.72-1.44)
Any Bleeding event	25	12.25	169	17.31	0.76 (0.50-1.17)
Hemorrhagic Stroke	*	2.45	41	4.19	0.68 (0.27-1.74)
Upper GI Bleeding	20	9.79	128	13.11	0.79 (0.49-1.27)

Events and rates are from the variable ratio propensity score-matched cohort. HRs are adjusted for a database and matching ratio.

CABG = coronary artery bypass grafting; CI = confidence intervals; GI = gastrointestinal; HR = hazard ratio; PTCA = percutaneous transluminal coronary angioplasty; PYs = person years; SSRI = selective serotonin reuptake inhibitor.

* As per Centers for Medicare and Medicaid Services cell size suppression policy, cell sizes are too small for display (<11).

differences in risk of either ischemic or bleeding events in patients <65 years. Results were similar in ITT analyses, with slightly attenuated increases in risk for any ischemic events in patients ≥65 years (Supplementary Figure 3 and Table 5). There was no effect on all-cause mortality among the patients ≥65 years in either as-treated (HR 0.78; 95% CI 0.57 to 1.07) or ITT (HR 0.95; 95% CI 0.79 to 1.13) analyses.

Discussion

In this large PS-matched cohort study of 53,559 patients from 5 databases comprising geographically and demographically diverse populations, initiation of clopidogrel while being treated with a CYP2C19-inhibiting SSRI (fluoxetine or fluvoxamine) versus a noninhibiting SSRI was associated with a small increased risk of ischemic events. The increased risk was more pronounced in patients ≥65 years. However, we did not observe an increase in all-cause mortality in these patients.

These findings are compatible with what is known about the pharmacokinetics of clopidogrel. Clopidogrel is a prodrug that requires 2 sequential metabolic conversions.[1] Medications that inhibit CYP2C19, a key enzyme involved in both oxidative steps, can reduce the conversion of clopidogrel to its active metabolite, thereby reducing the concentration of the active antiplatelet agent in the blood. Several studies have reported that concomitant administration of clopidogrel and a CYP2C19-inhibiting SSRI leads to reduced platelet reactivity[13,14]; however, these studies were conducted in a small number of healthy volunteers and the extent to which reduced platelet reactivity produces a clinically significant reduction in the effectiveness of clopidogrel in patients with acute coronary syndrome is not known. To our knowledge, ours is the first study to evaluate the impact of the pharmacokinetic clopidogrel-SSRI interaction on clinical outcomes in a large nationwide cohort and to provide direct real-world evidence that CYP2C19-inhibiting SSRIs may reduce the effectiveness of clopidogrel.

The increased risk for the outcome of any ischemic event appears to be attributable to the effect of the clopidogrel-SSRI interaction on rates of revascularization (stent and PTCA), whereas no increase in the rate of MI was observed. Although this finding requires further investigation, recent studies reported a much higher increased risk of stent thrombosis than other cardiovascular events, including MI, among subjects carrying a CYP2C19 reduced function allele.[23,24] Given that the exposure groups were well balanced on cardiovascular risk factors at baseline in our study, and the choice of a particular SSRI agent is not driven by patients' cardiovascular prognosis, it is unlikely that the observed effect on the rates of revascularization is because of residual confounding, although we cannot completely exclude this possibility. In addition, the increase in risk was more pronounced in the elderly. Although the effect of age on enzyme inhibition has not been well characterized, a reduced CYP2C19 activity with age has been demonstrated,[25,26] which, coupled with possible decreased clearance of the inhibiting drug,[27] might have made elderly patient more susceptible to the effects of the interaction.

Several limitations of the present study should be noted. Administrative claims data do not provide information on clinical parameters, such as smoking, angiographic characteristics, or CYP2C19 genotype, which could affect the outcomes. However, we likely substantially reduced confounding by the choice of comparator group, given that all patients were clopidogrel initiators and all were treated with an SSRI. Indeed, the measured baseline characteristics were well balanced even before PS matching and we expect that unmeasured characteristics, such as CYP2C19 genotype, aspirin use, or smoking, would also be balanced because they likely do not contribute to the choice of a particular SSRI agent. Propensity score matching likely further reduced the potential for confounding.[28] As pharmacy claims data provide accurate information about drugs dispensed to patients, but do not provide information on whether patients actually consume the medications, misclassification of exposure is possible. However, we do not expect misclassification to be differential between exposure groups; therefore, if present, it likely biased the results toward the null, producing a more conservative estimate of the true effect.[29]

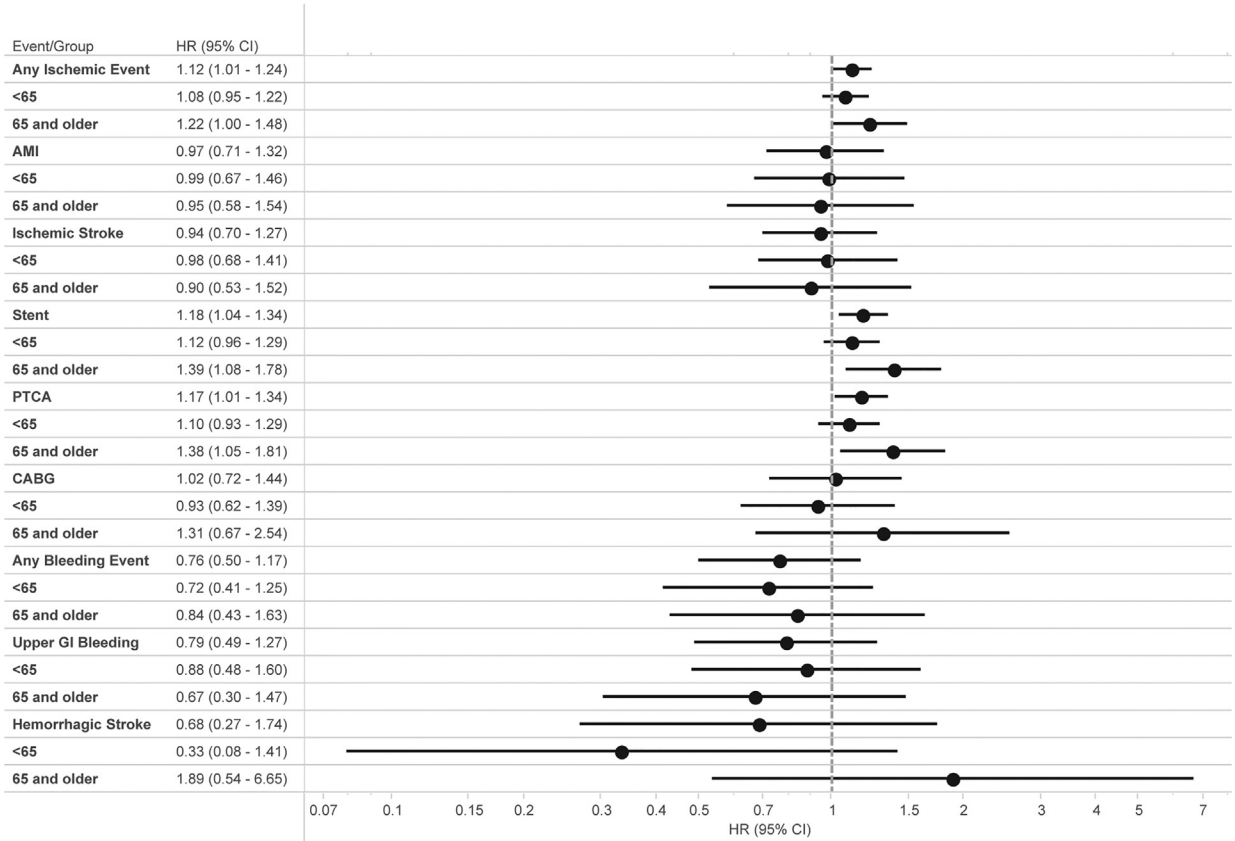

Figure 2. Hazard ratios for study outcomes stratified by age. AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; GI = gastrointestinal; PTCA = percutaneous transluminal coronary angioplasty.

The relatively short duration of follow-up is another limitation; however, it reflects the treatment patterns as they occur in routine care. Most patients were censored because of discontinuation of SSRI, which could have indicated a decision to stop the therapy by a treating physician or the lack of adherence to chronic depression medications among clopidogrel-treated patients. The ITT analysis that extended follow-up to 180 days regardless of discontinuation or treatment changes yielded similar results, although the effects were smaller, which is expected because of increased exposure misclassification with ITT analyses. In addition, not all databases had complete mortality information, which precluded us from analyzing mortality among all patients. In the databases with complete death information (Optum and Medicare), no cause of death was available. Therefore, we could not assess cardiovascular mortality as an outcome.

Last, the absolute magnitude of the effect observed in our study is small and, despite the narrow CI that excluded the null, a chance finding cannot be completely ruled out. Further research is needed to confirm our findings. Our results suggest that for most patients, the interaction does not appear to manifest in untoward clinical outcomes, although we did observe a >30% increase in revascularization procedures in patients ≥65 years. Because many SSRIs with similar antidepressant activity and side-effect profiles are available, every additional event can be easily prevented by selecting a non−CYP2C19-inhibiting SSRI.

In conclusion, the findings from this large nationwide investigation suggest that being treated with a CYP2C19-inhibiting SSRI when initiating treatment with clopidogrel may be associated with a small increased risk of ischemic events, especially in older (≥65 years of age) adults. Given that not all SSRIs inhibit CYP2C19, treatment with a noninteracting SSRI during treatment with clopidogrel should be the preferred option.

Disclosures

Dr. Schneeweiss is consultant to WHISCON, LLC., Newton, Massachusetts, and to Aetion, Inc., New York, New York, a software manufacturer of which he also owns equity. He is the principal investigator of investigator-initiated grants to the Brigham and Women's Hospital from Novartis, Basel, Switzerland, Genentech, San Francisco, California, and Boehringer Ingelheim, Ingelheim am Rhein, Germany, unrelated to the topic of this study. Dr. Gagne is the principal investigator of a grant from Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, to the Brigham and Women's Hospital for unrelated work. He is a consultant to Aetion Inc., New York, New York, and to Optum, Inc., Waltham, Massachusetts. Dr. Bykov is supported by an unrestricted training grant from Takeda, Cambridge, Massachusetts to Harvard T.H. Chan School of Public Health. The other authors have no conflicts of interest.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.10.052.

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