Drug Saf (2015) 38:1075–1082
DOI 10.1007/s40264-015-0328-2

SHORT COMMUNICATION

Selective Serotonin Reuptake Inhibitor Use and Perioperative Bleeding and Mortality in Patients Undergoing Coronary Artery Bypass Grafting: A Cohort Study

Joshua J. Gagne[1] · Jennifer M. Polinski[2] · Jeremy A. Rassen[3] · Michael A. Fischer[1] · John D. Seeger[1] · Jessica M. Franklin[1] · Jun Liu[1] · Sebastian Schneeweiss[1] · Niteesh K. Choudhry[1]

Published online: 19 July 2015

Abstract

Introduction Several small studies have reported inconsistent findings about the safety of selective serotonin reuptake inhibitors (SSRIs) among patients undergoing coronary artery bypass grafting (CABG). We sought to investigate post-CABG bleeding and mortality outcomes related to antidepressant exposure.

Methods We identified patients who underwent CABG between 2004 and 2008 in the Premier Perspective Comparative Database. We determined whether they received SSRIs, other antidepressants, or no antidepressants on any pre-CABG hospital day and used Cox proportional hazards models to compare bleeding and mortality rates among the exposure groups while adjusting for potential confounders based on administrative data, pre-CABG charge codes, and discharge diagnosis codes.

Results We identified 132,686 eligible patients: 7112 exposed to SSRIs, 1905 exposed to other antidepressants, and 123,668 unexposed. As compared with no exposure, neither SSRIs (hazard ratio [HR] 0.98; 95 % confidence interval [CI] 0.90–1.07) nor other antidepressants (HR 1.11; 95 % CI 0.96–1.28) increased major bleeds, and neither SSRIs (HR 0.93; 95 % CI 0.80–1.07) nor other antidepressants (HR 0.84; 95 % CI 0.62–1.14) increased mortality. Both SSRIs (HR 1.14; 95 % CI 1.10–1.18) and other antidepressants (HR 1.11; 95 % CI 1.03–1.19) were associated with a slight increase in receipt of one or more packed red blood cell (pRBC) units, but neither were associated with substantial increases in receipt of three or more pRBC units (HR 1.06; 95 % CI 0.96–1.17 for SSRIs; HR 1.09; 95 % CI 0.91–1.31 for other antidepressants).

Conclusion In this large cohort study, neither SSRIs nor other antidepressants were associated with elevated rates of major bleed, or in-hospital mortality.

Key Points

Several small studies have reported inconsistent findings about the safety of selective serotonin reuptake inhibitors among patients undergoing coronary artery bypass grafting.

In this study of 132,686 patients, neither selective serotonin reuptake inhibitors nor other antidepressants were associated with elevated rates of major bleed, or in-hospital mortality.

1 Introduction

Depressive symptoms have been associated with adverse health outcomes among patients undergoing coronary artery bypass grafting (CABG) [1]. Some authors recommend prophylactic antidepressant treatment among patients undergoing cardiac surgery [2], and the use of antidepressants in patients with acute coronary syndromes is increasing [3]. However, use of selective serotonin

✉ Joshua J. Gagne
jgagne1@partners.org

[1] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA, USA

[2] CVS Health, Woonsocket, RI, USA

[3] Aetion, Inc., New York, NY, USA

reuptake inhibitors (SSRIs), the most commonly prescribed antidepressant medication class in the USA, may increase patients' propensity to bleed [4, 5]. Serotonin enhances platelet activation induced by adenosine diphosphate and thrombin [6], and SSRIs can deplete serotonin in platelets by up to 95 % [7].

While epidemiologic studies have found associations between SSRIs and various bleeding events [8, 9], including gastrointestinal bleed [10, 11], few have examined whether SSRI exposure increases patients' bleeding risk during cardiac surgery, and those that have been conducted have been small studies and have reported inconsistent findings [12–16]. Perioperative blood loss and the need for blood transfusion in patients undergoing CABG are associated with an increased risk of postoperative morbidity and mortality [17]. It is therefore critical to understand whether perioperative SSRI use increases bleeding risk and mortality in these patients. Therefore, we sought to evaluate the association between SSRI exposure and bleeding events in a large US-representative cohort of patients undergoing CABG.

2 Methods

2.1 Data Source

We used data from the Premier Perspective Comparative Database, which collects hospital administrative data for all inpatients from approximately 400 hospitals, which comprises approximately one-sixth of all hospitalizations in the USA. The data contain a record of daily charges for all medications, procedures, and diagnostic tests during each patient's hospitalization, as well as patient demographic and hospital characteristics, discharge diagnoses, and discharge status, including death. The data are audited, verified, and validated before being made available for research purposes. This database has been used in many studies to evaluate health outcomes in relation to drug use [18–24].

2.2 Patients

Consistent with prior studies, we used International Classification of Diseases, 9th Revision, Clinical Modification procedure codes 36.1x and 36.2x to identify patients who underwent CABG between 1 January 2004 and 31 December 2008 [22]. These codes have been found to have very high sensitivity and specificity in identifying patients who undergo CABG [25]. In order to measure pre-CABG exposure to antidepressants, we excluded patients who underwent CABG on the day of hospital admission. Additionally, we excluded patients who also underwent valve repair during their index CABG.

2.3 Exposures

We determined whether patients received an antidepressant on one or more hospital days prior to CABG. We separately classified patients as exposed to SSRIs (i.e., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) or other antidepressants (i.e., clomipramine, doxepin, imipramine, amoxapine, desipramine, maprotiline, nortriptyline, protriptyline, duloxetine, mirtazapine, nefazodone, trazodone) on any day prior to CABG. We excluded from the other antidepressants group those patients exposed to bupropion, since it is commonly used for smoking cessation. To reduce exposure misclassification, we excluded those exposed to either venlafaxine or desvenlafaxine because these drugs inhibit reuptake of serotonin more than other non-SSRI antidepressants, but not to the same degree as the other SSRIs, which are highly selective for serotonin [26]. We also excluded patients exposed to both SSRIs and other antidepressants prior to CABG. Patients with no in-hospital antidepressant exposure prior to CABG served as the referent group.

2.4 Outcomes

We determined whether patients experienced a post-operative bleeding event requiring transfusion or died during the hospital stay. We defined a primary composite post-CABG bleeding endpoint as transfusions of three or more units of packed red blood cells (pRBCs) on a single day following the CABG date, any transfusion of platelets, fresh frozen plasma or cryoprecipitate following the CABG date, or an upper or lower gastrointestinal (GI) bleed. We defined GI bleed as one or more charge codes for esophagogastroduodenoscopy on any hospital day following the CABG day plus one or more diagnosis codes for GI bleed. In secondary analyses, we examined each individual outcome separately. We also assessed transfusion of one or more unit of pRBCs on a single day as a separate outcome.

2.5 Covariates

We used hospital charge codes, diagnosis codes, procedure codes, and physician service claims to identify potential confounders at the patient, surgery, and hospital levels. We focused on identifying covariates that may be related to bleeding or mortality or that may be proxies for other variables related to these outcomes. Specifically, we identified patients' age, sex, marital status, and year of hospitalization from administrative data. We used charge codes

recorded before the day of CABG to determine whether patients had received aldosterone agonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, anti-arrhythmic medications (amiodarone, dronedarone, sotalol, procainamide, propafenone), aspirin, beta-blockers, calcium channel blockers, clopidogrel, digoxin, dipyridamole, direct renin agonists, fibrates, oral or intravenous corticosteroids, H2-blockers, heparin, loop diuretics, medications to treat chronic obstructive pulmonary diseases, nicotine-replacement therapy, oral hypoglycemic agents, proton pump inhibitors, vitamin K, statins, thiazide diuretics, or warfarin. We used diagnosis codes to determine whether patients had had a previous CABG, previous percutaneous coronary intervention, or end-stage renal disease upon hospital admission. We identified whether the hospital admission was urgent or emergent. We categorized hospitals according to their geographic region (i.e., midwest, northeast, south, or west), whether they were urban or rural, and whether they were teaching hospitals as defined in their accreditation by the Association of American Medical College. We estimated the annualized volume of CABG surgeries performed at each hospital by dividing the total number of CABG patients for each hospital during the study time period by the number of years that each hospital had performed one or more CABG procedures.

2.6 Statistical Analysis

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) comparing postoperative bleeding rates among patients exposed to SSRIs and to other antidepressants against those with no pre-operative antidepressant exposure. We estimated two separate multivariable Cox models for each outcome. The first included all covariates listed above, measured during the 2 days prior to CABG (measured on hospital day 1 only for those who underwent CABG on hospital day 2), to standardize the covariate assessment period for all patients. The second model included the same covariates measured over all hospital days before surgery. We stratified all models by hospital day of CABG.

In a post hoc exploratory analysis, we examined additional definitions of the pRBC transfusion outcome. In particular, we examined whether exposure to SSRIs or other antidepressants were associated with receipt of one or more units of pRBCs and, separately, whether they were associated with receipt of two or more units of pRBCs.

3 Results

We identified 132,686 eligible patients who underwent CABG during our study period. The majority ($n = 123{,}669$; 93 %) did not receive an antidepressant prior to CABG, while 5 % ($n = 7112$) were exposed to SSRIs and 1 % ($n = 1905$) were exposed to other antidepressants (Table 1). The most common SSRI exposures were to sertraline ($n = 2091$; 29 % of all SSRI exposures), escitalopram ($n = 1600$; 22 %), and paroxetine ($n = 1476$; 21 %). The most common other antidepressant exposures were to trazodone ($n = 726$; 38 % of all other antidepressant exposures), duloxetine ($n = 459$; 24 %), and mirtazapine ($n = 223$; 12 %). Antidepressant-exposed patients were more commonly female (47 % for SSRIs and 42 % for other antidepressants vs. 28 % for no antidepressant exposure) and were more likely to have other drug exposures recorded on hospital days preceding CABG (e.g., proton pump inhibitors 55 % for SSRIs, 50 % for other antidepressants, and 37 % for no antidepressant exposure).

The incidence of major bleed was 5.7 % ($n = 7580$) in the overall cohort and 3644 (2.8 %) patients died during the index hospitalization (Table 2). The most commonly occurring bleeding-related event was transfusion of pRBCs. As compared with no exposure, neither SSRIs (HR 0.98; 95 % CI 0.80–1.07) nor other antidepressants (HR 1.11; 95 % CI 0.96–1.28) increased major bleeding risk in the primary multivariable adjusted model (Table 3). Neither SSRIs nor other antidepressants were associated with substantially elevated rates of any of the individual outcomes comprising the composite bleeding endpoint. Results were nearly identical for the two multivariable models across all component bleed outcomes.

In the post hoc exploratory analysis, in which we examined additional definitions of the pRBC transfusion outcome, both SSRIs (HR 1.14; 95 % CI 1.10–1.18) and other antidepressants (HR 1.11; 95 % CI 1.03–1.19) were associated with elevated rates of transfusion of one or more pRBC units and with transfusion of two or more pRBC units (HR 1.15; 95 % CI 1.10–1.21 for SSRIs; HR 1.15; 95 % CI 1.05–1.26 for other antidepressants; Fig. 1).

Compared with non-treated patients, the risk of mortality was similar for users of SSRIs (HR 0.93; 95 % CI 0.80–1.07) and other antidepressants (HR 0.84; 95 % CI 0.62–1.14) and did not materially differ in the second multivariable-adjusted model that included covariates measured over all pre-CABG hospital days.

Table 1 Demographic, surgical, hospital, and clinical characteristics of patients undergoing coronary artery bypass grafting by pre-surgical antidepressant administration

Characteristic	SSRI ($n = 7112$)	Other AD ($n = 1905$)	No AD ($n = 123,669$)
Patient demographic characteristics			
Age, mean (SD)	64.4 (11.0)	65.1 (10.7)	65.9 (11.1)
Female	3370 (47.4)	792 (41.6)	35,068 (28.4)
Race			
Black	346 (4.9)	107 (5.6)	9121 (7.4)
White	5705 (80.2)	1480 (77.7)	89,581 (72.4)
Other	1061 (14.9)	318 (16.7)	24,967 (20.2)
Marital status			
Single	776 (10.9)	215 (11.3)	13,943 (11.3)
Married	3818 (53.7)	1018 (53.4)	71,592 (57.9)
Widowed	1039 (14.6)	242 (12.7)	13,322 (10.8)
Divorced	668 (9.4)	170 (8.9)	8523 (6.9)
Other	811 (11.4)	260 (13.7)	16,289 (13.2)
Hospital and surgery characteristics			
Year of CABG			
2003	391 (5.5)	92 (4.8)	6151 (5.0)
2004	1516 (21.3)	290 (15.2)	25,245 (20.4)
2005	1219 (17.1)	267 (14.0)	23,493 (19.0)
2006	1329 (18.7)	363 (19.1)	24,317 (19.7)
2007	1258 (17.7)	379 (19.9)	21,962 (17.8)
2008	1166 (16.4)	430 (22.6)	20,180 (16.3)
2009	233 (3.3)	84 (4.4)	2321 (1.9)
Admission type			
Urgent/emergent	5297 (74.5)	1353 (71.0)	88,436 (71.5)
Elective	1779 (25.0)	541 (28.4)	34,593 (27.8)
Unknown	36 (0.5)	11 (0.6)	640 (0.5)
Hospital day of CABG			
2	1028 (14.5)	468 (25.6)	37,007 (29.9)
3	1274 (17.9)	320 (16.8)	23,028 (18.6)
4	1115 (15.7)	290 (15.2)	18,424 (14.9)
5	982 (13.8)	230 (12.1)	14,311 (11.6)
6+	2713 (38.2)	597 (31.3)	30,899 (25.0)
Teaching hospital	4361 (61.3)	1155 (60.6)	72,639 (58.7)
Rural hospital	611 (8.6)	161 (8.5)	9670 (7.8)
Number of hospital beds, mean (SD)	544.9 (228.5)	520.6 (218.9)	534.5 (222.8)
Region			
Midwest	1057 (14.9)	309 (16.2)	21,440 (17.3)
Northeast	1159 (16.3)	260 (13.7)	21,017 (17.0)
South	4171 (58.7)	1013 (53.2)	64,823 (52.4)
West	725 (10.2)	323 (17.0)	16,389 (13.3)
Annualized CABG volume			
Low	576 (8.1)	158 (8.3)	11,380 (9.2)
Medium	1695 (23.8)	493 (25.9)	31,575 (25.5)
High	4841 (68.1)	1254 (65.8)	80,714 (65.3)
Pre-operative clinical characteristics			
Drug administration			
Aldosterone agonists	260 (3.7)	75 (3.9)	3322 (2.7)
ACEIs	3429 (48.2)	821 (43.1)	49,327 (39.9)

Table 1 continued

Characteristic	SSRI ($n = 7112$)	Other AD ($n = 1905$)	No AD ($n = 123,669$)
Angiotensin receptor blockers	1119 (15.7)	274 (14.4)	12,358 (10.0)
Anti-arrhythmics	972 (13.7)	232 (12.2)	13,801 (11.2)
Aspirin	5126 (72.1)	1252 (65.7)	77,062 (62.3)
Beta-blockers	5976 (84.0)	1556 (81.7)	94,133 (76.1)
Calcium channel blockers	2101 (29.5)	490 (25.7)	25,271 (20.4)
Clopidogrel	1602 (22.5)	387 (20.3)	21,114 (17.1)
Digoxin	435 (6.1)	111 (5.8)	6407 (5.2)
Dipyridamole	147 (2.1)	33 (1.7)	1636 (1.3)
Direct renin agonists	7 (0.1)	1 (0.1)	45 (0.0)
Fibrates	481 (6.8)	117 (6.1)	4539 (3.7)
Oral corticosteroids	538 (7.6)	126 (6.6)	4752 (3.8)
IV corticosteroids	813 (11.4)	199 (10.5)	10,088 (8.2)
H2-blockers	1517 (21.3)	430 (22.6)	22,376 (18.1)
Heparin	4459 (62.7)	1139 (59.8)	70,967 (57.4)
Loop diuretics	2225 (31.3)	544 (28.6)	26,901 (21.8)
Medication to treat COPD	1602 (22.5)	401 (21.1)	17,091 (13.8)
Medication to treat diabetes (including insulin)	3064 (43.1)	797 (41.8)	38,348 (31.0)
NRT	296 (4.2)	66 (3.5)	3062 (2.5)
PPI	3877 (54.5)	955 (50.1)	46,003 (37.2)
Statin	5345 (75.2)	1366 (71.7)	77,754 (62.9)
Thiazide diuretic	1031 (14.5)	255 (13.4)	11,750 (9.5)
Vitamin K	176 (2.5)	45 (2.4)	2172 (1.8)
Warfarin	135 (1.9)	27 (1.4)	1364 (1.1)
Echocardiogram	2883 (40.5)	701 (36.8)	43,778 (35.4)
ESRD	420 (5.9)	93 (4.9)	4450 (3.6)
ICU stay	4173 (58.7)	1072 (56.3)	71,336 (57.7)
Oxygen use	3336 (46.9)	865 (45.4)	49,998 (40.4)
Prior CABG	162 (2.3)	45 (2.4)	2153 (1.7)
Prior PCI	300 (4.2)	68 (3.6)	5963 (4.8)
Telemetry	2547 (35.8)	712 (37.4)	41,312 (33.4)

Data are presented as *n* (%) unless otherwise indicated

ACEI angiotensin-converting enzyme inhibitor, *AD* antidepressant, *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *ESRD* end-stage renal disease, *ICU* intensive care unit, *IV* intravenous, *NRT* nicotine-replacement therapy, *PCI* percutaneous coronary intervention, *PPI* proton pump inhibitor, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor

4 Discussion

4.1 Interpretation of Results

In this study of >125,000 CABG patients, we evaluated the association between SSRI exposure and bleeding events in a large US-representative cohort of patients undergoing CABG. Those exposed to either SSRIs or other antidepressants prior to surgery were not substantially more likely to experience the primary composite bleeding endpoint, any of the components of the composite outcome, or mortality. However, antidepressant-treated patients were more likely to receive post-operative pRBC transfusions of one or more units. Strengths of the study include the automated capture of both exposure and outcome identification that reduces the risk of differential ascertainment of this information, the large size of the study that provides considerable precision to study estimates, and what appears to be relatively complete mortality ascertainment (our finding of a 2.8 % mortality risk among CABG patients is consistent with other findings [27]).

SSRIs are hypothesized to increase bleeding risk by depleting platelet serotonin, which can reduce platelet

Table 2 Bleeding events and in-hospital mortality according to preoperative antidepressant exposure category

	Total (n = 132,686)	SSRIs (n = 7112)	Other AD (n = 1905)	No AD (n = 123,669)
Composite bleed[a]	7580 (5.7)	390 (5.5)	117 (6.1)	7073 (5.7)
RBC transfusion (≥3 units)	7283 (5.5)	444 (6.2)	120 (6.3)	6719 (5.4)
Platelet transfusion	2461 (1.9)	123 (1.7)	33 (1.7)	2305 (1.9)
Fresh frozen plasma transfusion	6524 (4.9)	324 (4.6)	102 (5.4)	6098 (4.9)
Receipt of cryoprecipitate	1478 (1.1)	83 (1.2)	24 (1.3)	1371 (1.1)
Gastrointestinal bleed	322 (0.2)	18 (0.3)	4 (0.2)	300 (0.2)
Death	3644 (2.8)	202 (2.8)	43 (2.3)	3399 (2.8)

Data are presented as n (%)

AD antidepressant, *RBC* red blood cell, *SSRI* selective serotonin reuptake inhibitor

[a] Components of the composite bleed outcome sum to more than the total number of composite bleed events because some patients experienced multiple component outcomes

Table 3 Hazard ratios for post-coronary artery bypass grafting bleed and death among patients exposed to preoperative antidepressants

	Hazard ratio (95 % confidence interval)		
	Crude	Model 1[a]	Model 2[b]
Composite bleed[c]			
No antidepressant	Reference	Reference	Reference
SSRI	0.99 (0.92–1.08)	0.98 (0.90–1.07)	0.98 (0.90–1.06)
Other antidepressants	1.10 (0.95–1.27)	1.11 (0.96–1.28)	1.11 (0.96–1.28)
Packed red blood cell transfusion (≥3 units)			
No antidepressant	Reference	Reference	Reference
SSRI	1.11 (1.06–1.22)	1.06 (0.96–1.17)	1.05 (0.95–1.16)
Other antidepressants	1.12 (0.94–1.34)	1.09 (0.91–1.31)	1.09 (0.91–1.30)
Platelet transfusion			
No antidepressant	Reference	Reference	Reference
SSRI	0.89 (0.74–1.07)	1.01 (0.84–1.22)	0.99 (0.82–1.19)
Other antidepressants	0.91 (0.64–1.27)	1.08 (0.76–1.52)	1.06 (0.75–1.49)
Fresh frozen plasma transfusion			
No antidepressant	Reference	Reference	Reference
SSRI	0.86 (0.77–0.97)	0.89 (0.79–0.99)	0.88 (0.80–0.99)
Other antidepressants	1.03 (0.85–1.26)	1.10 (0.91–1.34)	1.09 (0.89–1.32)
Receipt of cryoprecipitate			
No antidepressant	Reference	Reference	Reference
SSRI	1.02 (0.82–1.27)	1.01 (0.81–1.27)	1.02 (0.81–1.28)
Other antidepressants	1.11 (0.74–1.67)	1.13 (0.75–1.69)	1.13 (0.75–1.69)
Gastrointestinal bleed			
No antidepressant	Reference	Reference	Reference
SSRI	0.89 (0.55–1.44)	0.87 (0.53–1.41)	0.91 (0.56–1.48)
Other antidepressants	0.79 (0.29–2.11)	0.81 (0.30–2.17)	0.81 (0.30–2.19)
Death			
No antidepressant	Reference	Reference	Reference
SSRI	0.91 (0.79–1.05)	0.93 (0.80–1.07)	0.93 (0.80–1.07)
Other antidepressants	0.76 (0.56–1.03)	0.84 (0.62–1.14)	0.84 (0.62–1.14)

CABG coronary artery bypass grafting, *SSRI* selective serotonin reuptake inhibitor

[a] Model 1 adjusted for all variables in Table 1 measured on the day before surgery for patients who underwent CABG on day 2, and measured on the 2 days prior to CABG for patients who underwent CABG on day 3 or later

[b] Model 2 adjusted for all variables in Table 1 measured over all days before surgery

[c] The composite bleed outcome comprised red blood cell transfusion of three or more units, any platelet transfusion, any fresh frozen plasma transfusion, any receipt of cryoprecipitate, and gastrointestinal bleed

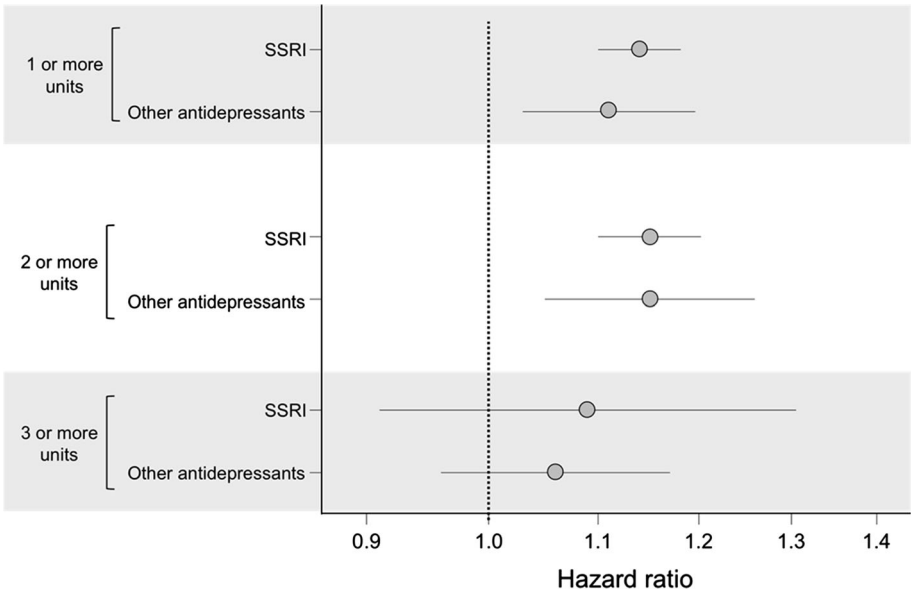

Fig. 1 Association between antidepressant exposure (vs. no exposure) and transfusion of different numbers of packed red blood cells

activation [6, 7]. Our findings that both SSRIs and other antidepressants were associated with the need for one or more units of pRBCs suggest that either underlying depression, or comorbid conditions, rather than the antidepressants themselves may be responsible for this association or that a different mechanism linking these drugs to bleeding risk may be implicated. Nevertheless, our results suggest that, while antidepressant exposure might be associated with a small increase in pRBC transfusion requirements, it does not enhance patients' propensity to bleed to the point of increasing GI bleed risk, mortality, or need for large amounts of blood cells.

4.2 Comparison to Prior Studies

Prior studies have found mixed results with respect to post-CABG outcomes among patients exposed to SSRIs. In a cohort of 5364 patients who underwent CABG surgery at Duke University Medical Center between 1999 and 2003, Xiong et al. [13] found that exposure to SSRIs was associated with a 61 % increased hazard of long-term mortality (up to 6 years) as compared with no antidepressant exposure. Andreasen et al. [14] also observed a 40 % elevated rate of 30-day mortality associated with SSRIs among 3454 patients who underwent CABG at two Danish hospitals between 1998 and 2003, but CIs were wide (rate ratio 1.4; 95 % CI. 0.7–3.1). In contrast, and in line with our results, Xiong et al. [16] did not find an association between SSRI exposure and 30-day mortality and Kim et al. [15] did not find any elevation in in-hospital mortality associated with SSRIs vs. other antidepressants. In addition, our finding that SSRIs are not associated with an increased risk of major bleeding events is largely consistent with results from other studies [13–15].

4.3 Study Limitations

Our study has several limitations. In order to ensure exposure ascertainment prior to CABG, we excluded patients who underwent surgery on the day of hospital admission. This reduced our sample size and may affect the generalizability of our results. Additionally, because we used an inpatient database, we were not able to ascertain outpatient antidepressant use prior to the index hospitalization. Some patients classified as unexposed may have been misclassified if they used antidepressants and discontinued them prior to hospitalization. Furthermore, we were not able to link index CABG hospitalizations to prior hospitalizations to assess whether patients may have been previously exposed to antidepressants. We also were not able to identify outcomes following discharge from the index hospitalization. While we adjusted for a large number of variables, residual confounding cannot be ruled out and may explain the association between antidepressant exposure and increased rate of transfusion of one or more pRBC units. Finally, data available for use in this study were through only 2008. However, we do not believe that using more recent data would change the study findings, since SSRIs remain the most widely used antidepressants, as they were during the study period, and the biology of the underlying association between SSRIs and bleeding has not changed over time.

5 Conclusion

Our findings suggest that current exposure to SSRIs may increase the need for pRBC transfusion of one or more units during CABG surgery but neither SSRIs nor other

antidepressants increase patients' propensity for GI bleeding or death. Future large studies should focus on whether SSRIs are associated with long-term mortality and whether SSRIs increase risk of bleeding in other types of surgery.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this study.

Conflicts of interest Joshua J. Gagne was previously Principal Investigator of investigator-initiated grants to the Brigham and Women's Hospital from Novartis Pharmaceuticals Corporation for methods research unrelated to the topic of the study. He is a consultant to Aetion, Inc. Jennifer M. Polinski and Jeremy A. Rassen were employees of the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School at the time that this study was conducted. Jeremy A. Rassen is an employee and co-owner of Aetion, Inc. Michael A. Fischer reports research grants to his institution from Otsuka Pharmaceutical and CVS-Caremark for research evaluating medication adherence. John D. Seeger is a paid consultant to Optum and WHISCON for unrelated projects. Jessica M. Franklin has received grant funding for unrelated work from Merck and has consulted with Aetion, Inc. Sebastian Schneeweiss is a consultant to WHISCON, LLC and to Aetion, Inc., a software manufacturer of which he also owns shares. He is Principal Investigator of investigator-initiated grants to the Brigham and Women's Hospital from Novartis and Boehringer Ingelheim, unrelated to the topic of the study. Jun Liu and Niteesh K. Choudhry have no conflicts of interest that are directly relevant to the content of this study.

Ethics approval This study was approved by the Brigham and Women's Hospital Institutional Review Board.

References

1. Mallik S, Krumholz HM, Lin ZQ, et al. Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. Circulation. 2005;111:271–7.
2. Hata M, Yagi Y, Sezai A, et al. Efficacy of prophylactic treatment with selective serotonin reuptake inhibitors for depression after open-heart surgery. Surg Today. 2011;41:791–4.
3. Czarny MJ, Arthurs E, Coffie DF, et al. Prevalence of antidepressant prescription use in patients with acute coronary syndrome: a systematic review. PLoS One 2011;6:e27671.
4. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. BMJ. 2005;331:529–30.
5. de Abajo FJ, Montero D, Rodriguez LA, Madurga M. Antidepressants and risk of upper gastrointestinal bleeding. Basic Clin Pharmacol Toxicol. 2006;98:304–10.
6. Li N, Wallen NH, Ladjevardi M, Hjemdahl P. Effects of serotonin on platelet activation in whole blood. Blood Coagul Fibrinolysis. 1997;8:517–23.
7. Maurer-Spurej E, Pittendreigh C, Solomons K. The influence of selective serotonin reuptake inhibitors on human platelet serotonin. Thromb Haemost. 2004;91:119–28.
8. Hackam DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. Neurology. 2012;79:1862–5.
9. Yuan Y, Tsoi K, Hunt RH. Selective serotonin reuptake inhibitors and risk of upper GI bleeding: confusion or confounding? Am J Med. 2006;119:719–27.
10. Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med. 2003;163:59–64.
11. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ. 2001;323:655–8.
12. Tully PJ, Cardinal T, Bennetts JS, Baker RA. Selective serotonin reuptake inhibitors, venlafaxine and duloxetine are associated with in hospital morbidity but not bleeding or late mortality after coronary artery bypass graft surgery. Heart Lung Circ. 2012;21:206–14.
13. Xiong GL, Jiang W, Clare R, et al. Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. Am J Cardiol. 2006;98:42–7.
14. Andreasen JJ, Riis A, Hjortdal VE, Jorgensen J, Sorensen HT, Johnsen SP. Effect of selective serotonin reuptake inhibitors on requirement for allogeneic red blood cell transfusion following coronary artery bypass surgery. Am J Cardiovasc Drugs. 2006;6:243–50.
15. Kim DH, Daskalakis C, Whellan DJ, et al. Safety of selective serotonin reuptake inhibitor in adults undergoing coronary artery bypass grafting. Am J Cardiol. 2009;103:1391–5.
16. Xiong GL, Jiang W, Clare RM, et al. Safety of selective serotonin reuptake inhibitor use prior to coronary artery bypass grafting. Clin Cardiol. 2010;33:E94–8.
17. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg. 2002;74:1180–6.
18. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. JAMA. 2004;291:2092–9.
19. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med. 2005;353:349–61.
20. Rassen JA, Mittleman MA, Glynn RJ, Brookhart AM, Schneeweiss S. Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention. Eur Heart J. 2010;31:561–72.
21. Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. N Engl J Med. 2008;358:771–83.
22. Kulik A, Rassen JA, Myers J, et al. Comparative effectiveness of preventative therapy for venous thromboembolism after coronary artery bypass graft surgery. Circ Cardiovasc Interv. 2012;5:590–6.
23. Bateman BT, Rassen JA, Schneeweiss S, et al. Adjuvant vancomycin for antibiotic prophylaxis and risk of *Clostridium difficile* infection after coronary artery bypass graft surgery. J Thorac Cardiovasc Surg. 2013;147(2):472–8.
24. Bateman BT, Bykov K, Choudhry NK, et al. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. BMJ. 2013;347:f5416.
25. Davis LA, Mann A, Cannon GW, Mikuls TR, Reimold AM, Caplan L. Validation of diagnostic and procedural codes for identification of acute cardiovascular events in US veterans with rheumatoid arthritis. EGEMS (Wash DC). 2014;1:1023.
26. Brunton LL, Chabner BA, Knollman BC. Goodman & Gillman's the pharmacological basis of therapeutics, 12th edn. New York: The McGraw-Hill Companies, Inc.; 2011.
27. Ferguson TB Jr. Mortality in CABG: what's next? Circulation. 2012;125(20):2409–11.