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ORIGINAL ARTICLE

Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function: A population-based cohort study

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AIM

To estimate the risk of gastrointestinal (GI) bleeding associated with serotonin reuptake inhibitors (SSRIs) by level of kidney function.

METHODS

We conducted a cohort study using the Clinical Practice Research Datalink linked to Hospital Episode Statistics. We identified patients with chronic kidney disease (CKD; estimated glomerular filtration rate $<$60 ml min^{-1} 1.73 m^{-2} for $\geq$3 months), and a comparison group of patients without it. Patients with CKD were further classified as stage 3a (eGFR 45–59 ml min^{-1} 1.73 m^{-2}), 3b (30–44 ml min^{-1} 1.73 m^{-2}) and 4/5 ($<$30 ml min^{-1} 1.73 m^{-2}). We excluded prevalent SSRI users at cohort entry. Exposure was time-dependent SSRI prescription and outcome was first hospitalization for GI bleeding. We estimated adjusted rate ratio (aRR) and rate difference (aRD) of GI bleeding comparing periods with and without SSRI prescription at each level of kidney function.

RESULTS

The aRRs and aRDs were: (i) no CKD (n = 202 121) aRR: 1.66 (95%CI 1.37–2.01), aRD: 2.0/1000 person–years (5.5 *vs.* 3.5/1000 person–years in period with and without SSRIs); (ii) CKD stage 3a (n = 153 316) aRR: 1.86 (1.62–2.15), aRD: 4.2/1000 person–years (8.3 *vs.* 4.1/1000 person–years); (iii) CKD stage 3b (n = 46 482) aRR: 1.61 (1.27–2.04), aRD: 4.8/1000 person–years (9.9 *vs.* 5.1/1000 person–years); and (iv) CKD stage 4/5 (n = 11 197) aRR: 1.84 (1.14–2.96), aRD: 7.9/1000 person–years (15.3 *vs.* 7.4/1000 person–years). While there was no evidence of increase in the aRR (P = 0.922), there was strong evidence that the aRD increased as kidney function deteriorated (P = 0.001).

CONCLUSIONS

While the relative risk was constant, the excess risk of GI bleeding associated with SSRIs markedly increased among patients with decreased kidney function.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Previous studies have suggested that use of selective serotonin reuptake inhibitors (SSRIs) is associated with increased risk of gastrointestinal (GI) bleeding.
- Patients with decreased kidney function are known to have an increased risk of bleeding.
- However, no study has investigated the risk of GI bleeding associated with SSRIs at different levels of kidney function.

WHAT THIS STUDY ADDS

- We estimated the relative and absolute risks of GI bleeding associated with SSRI prescription at different levels of kidney function.
- While the relative risk of GI bleeding associated with SSRIs was similar at different levels of kidney function, the excess risk of GI bleeding associated with SSRIs increased as kidney function deteriorated.
- Therefore, we recommend careful use of SSRIs in patients with decreased kidney function.

Introduction

Chronic kidney disease (CKD) is a common condition in the community [1], and is independently associated with increased risk of bleeding in operative and nonoperative settings [2–4]. Gastrointestinal (GI) bleeding is the most common manifestation of bleeding [5].

Patients with CKD are known to have increased prevalence of mental-health problems such as depression and anxiety [6, 7]. Accordingly, our recent study suggested that patients with CKD (not on dialysis) have antidepressants prescribed more frequently than patients without it [8]. Selective serotonin reuptake inhibitors (SSRIs) are currently recommended as the first choice of drug therapy for depressed patients [9]. The number of SSRI prescriptions has been steadily increasing in the UK and US [10, 11].

There is concern regarding the bleeding risk associated with SSRIs, because SSRIs block serotonin reuptake in platelets and inhibit platelet aggregation [12, 13]. A number of studies have shown an association between the use of SSRIs and GI bleeding [14–24]. However, none of these studies focused on the risk of GI bleeding associated with SSRIs among patients with CKD. SSRI-associated GI bleeding is of particular concern among patients with CKD [25, 26], because: (i) CKD is itself a risk factor for GI bleeding [3]; and (ii) SSRIs may accumulate in patients with CKD due to reduced renal clearance and altered pharmacokinetics [27].

Despite these concerns, the absolute and relative risks of GI bleeding associated with SSRI use amongst patients with reduced kidney function have not been quantified. We therefore undertook a population-based study addressing this question in a large UK primary care database.

Methods

Data sources

The Clinical Practice Research Datalink (CPRD) is a database of routinely recorded primary care electronic health record data from 7% of the UK population [28]. The CPRD includes the following information: patient demographics, coded diagnoses (Read codes), prescriptions, laboratory test results, and referrals recorded by general practitioners (GPs). The CPRD is linked with other resources, including Hospital Episode Statistics (HES), Office for National Statistics mortality data and Index of Multiple Deprivation data. HES contains details of all hospital admissions to the National Health Service hospitals in England, and consists of primary and subsidiary diagnoses recorded during admission using the 10th revision of International Classification of Disease (ICD-10) codes [29]. Currently, around 400 general practices in CPRD (accounting for 75% of general practices in CPRD in England) have agreed to linkage with HES data for research purposes. Study approval was obtained from the ethics committee of the London School of Hygiene and Tropical Medicine (reference: 9196) and the Independent Scientific Advisory Committee, which oversees research involving CPRD data (Protocol 15_219R).

Study cohort

We used a matched cohort including 242 349 patients with CKD and 242 349 patients without it, which was established in our previous study for the prevalence and incidence of antidepressant prescribing by CKD status [8]. Using HES-linked CPRD between 1 April 2004 and 31 March 2014, we first identified adult patients with CKD (not on renal replacement therapy) based on two consecutive measurements of eGFR <60 ml min^{-1} 1.73 m^{-2} for $\geq$3 months [30] (Figure 1). Estimated GFR was calculated from serum creatinine values recorded in CPRD, using the Chronic Kidney Disease Epidemiology Collaboration equation [31]. Patients were eligible for cohort entry from the latest of: 1 April 2004, 1 year after practice registration (to allow GPs to record the past medical history of newly registered patients) or the date the patient's general practice reached CPRD's data quality standards [28]. Patients entered the cohort on the date when they first satisfied the CKD definition (i.e. second eGFR <60 ml min^{-1} 1.73 m^{-2}) after meeting the eligibility criteria. We then identified a comparison group of patients without known CKD from the remaining HES-linked CPRD population. To establish a balanced comparison group in terms of basic patient characteristics, we randomly selected a patient without known CKD with the same age, sex, general practice and calendar time (i.e. same date of cohort entry) as a patient with CKD.

Patients with CKD were further classified according to eGFR on the date of cohort entry: CKD stage 3a (eGFR 45–59 ml min^{-1} 1.73 m^{-2}), stage 3b (30–44 ml min^{-1} 1.73 m^{-2}), and stage 4 or 5 (<30 ml min^{-1} 1.73 m^{-2}) [30]. CKD stage

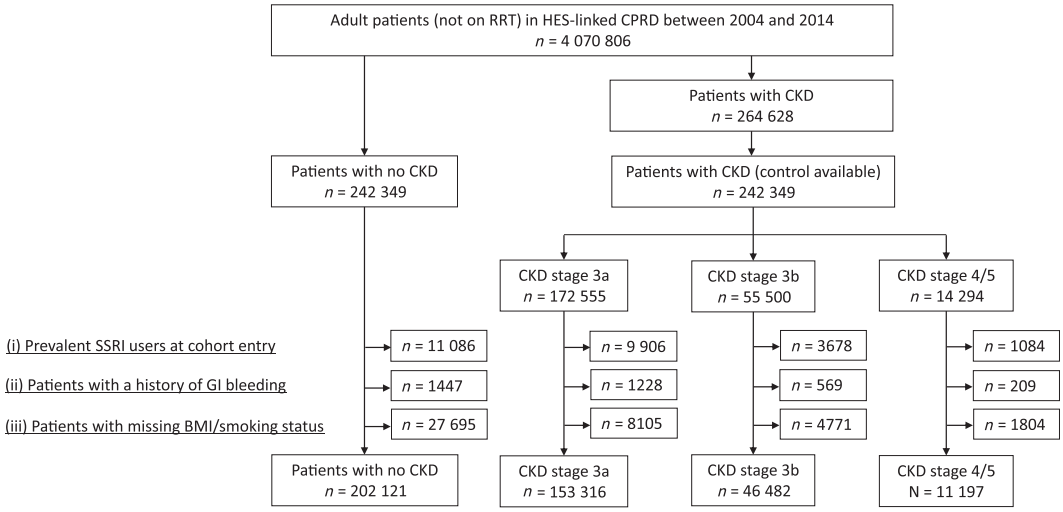

Figure 1

Flow chart for selecting the study participants. BMI = body mass index, CKD = chronic kidney disease, CPRD = Clinical Practice Research Datalink, GI = gastrointestinal, HES = Hospital Episode Statistics, RRT = renal replacement therapy, SSRI = selective serotonin reuptake inhibitor

was regarded as constant (i.e. non-time updated) during follow-up. We then excluded the following patients: (i) prevalent SSRI users (GI bleeding could occur shortly after SSRI initiation [17], therefore inclusion of prevalent SSRI users with drug tolerance may cause bias [32]); (ii) those with a history of GI bleeding (to capture new-onset GI bleeding more likely to be related to drug exposure); and (iii) those with missing values of smoking status and body mass index (BMI).

Exposure and outcome

SSRIs are frequently started and stopped in clinical care [33]. Our exposure of interest was therefore *time-dependent* prescription of SSRIs. The duration of each prescription was estimated by dividing the total number of tablets prescribed by the number of tablets to be taken each day (daily dose). When the daily dose or total number of tablets was missing (9.6% of the records), we imputed the median prescription duration (28 days). We assumed that patients were continuously exposed to SSRIs if there were no gaps of more than 30 days between the end of one prescription and the start of the next (to allow potential medication stockpiling or prescribing in secondary care) [14]. If there was no subsequent prescription of SSRIs, we considered patients could be influenced by the effect of SSRIs until 30 days after the end of the prescription. Thus, each episode of SSRI treatment started at the first SSRI prescription (as a new treatment episode) and continued until 30 days after a break in continuous prescribing of 30 days (or more). A patient could contribute multiple episodes of SSRI treatment during follow-up. In sensitivity analyses, we changed our assumption of a 30-day duration of periods between prescriptions and washout periods to 60 days and 90 days.

The outcome was the first hospitalization with a primary diagnosis of GI bleeding, based on a list of ICD-10 codes (Appendix S1). Patients were followed up until the earliest of: the outcome of interest, initiation of renal replacement therapy, death, change of general practice, last data collection from the practice or 31 March 2014.

Covariates

We considered the following potential confounders in the association between SSRI prescription and GI bleeding [14–24]: age and sex; ethnicity; socio-economic status; BMI; smoking status; comorbidities (diabetes mellitus, chronic liver disease, congestive heart failure, cancer, and rheumatoid arthritis); and prescribed drugs including anticoagulants, antiplatelet drugs (including aspirin), nonsteroidal anti-inflammatory drugs (excluding aspirin), oral corticosteroids, and acid-suppressing agents. We classified patients with no record of ethnicity as white, consistent with previous UK studies [34]. Socioeconomic status was assigned at an individual level, using quintiles of 2010 Office for National Statistics estimates of the Index of Multiple Deprivation (a composite area-level marker of deprivation) [35]. Smoking status and BMI were assigned using the data recorded closest to cohort entry and assumed to be constant during follow-up. We defined each comorbidity as present or absent based on recording of a relevant diagnostic code in CPRD on the day of, or prior to, cohort entry. For prescribed drugs, we used the same strategy as SSRIs by regarding them as *time-dependent* confounding factors.

Statistical analysis

We described baseline patient characteristics by level of kidney function. We showed the length of time people received an SSRI prescription and the time without, at each level of kidney function (i.e. no CKD, CKD stage 3a, stage 3b, and stage 4 or 5). We also showed the number of first hospitalizations due to GI bleeding, providing the crude incidence rate of the outcome by SSRI prescription status at each level of kidney function.

We conducted prespecified analyses using two common measures of effect to understand the GI bleeding risk

associated with SSRIs: risk ratio and risk difference [36]. First, we estimated an adjusted rate ratio for GI bleeding when prescribed an SSRI, compared to time not prescribed an SSRI, using *multiplicative* Poisson regression analyses. Multiplicative models assume that the risk of the outcome is multiplied by different risk factors. We established multiplicative Poisson models for hospitalization due to GI bleeding comparing periods with and without SSRI prescription at each level of kidney function, first adjusting for age and sex; and then further adjusting for ethnicity, socioeconomic status, BMI, smoking status, comorbidities, and prescribed drugs. We then conducted a test for multiplicative interaction (effect modification) between SSRI prescription and kidney function in the fully-adjusted model. A significant multiplicative interaction would suggest that the risk ratio (period with *vs*. without SSRI prescription) is different at different levels of kidney function. We estimated a multiplicative interaction *P*-value for trend, using the log-likelihood ratio test comparing the Poisson models with and without an interaction term between SSRI prescription status and kidney function.

Next, we estimated an adjusted rate difference (between period with and without SSRI prescription) for GI bleeding at each level of kidney function and tested whether the adjusted rate difference increased as kidney function deteriorated, using *additive* Poisson regression analyses. Additive models assume that risk differences from different risk factors are added together to estimate the risk of outcome [37] and, therefore, can directly test an additive interaction [38]. We established a fully-adjusted additive Poisson model for GI bleeding (Appendix S2 for more detail). We then calculated an adjusted incidence rate with or without SSRI prescription at each level of kidney function, by applying the average effect of each covariate on the risk of GI bleeding in the study population in the fully-adjusted additive Poisson model (Appendix S3 for more detail). Thus, the adjusted incidence rate in each group stratified by SSRI prescription status and level of kidney function represents a hypothetical incidence rate if the confounders (e.g. diabetes) are equally distributed between the groups. We then estimated an adjusted rate difference between the period with and without SSRI prescription at each level of kidney function. Finally, we conducted a test for additive interaction between SSRI prescription status and kidney function. A significant additive interaction would suggest that the risk difference (between period with and without SSRI prescription) is different at different levels of kidney function. We calculated an additive interaction *P*-value for trend, using the log-likelihood ratio test comparing the models with and without an interaction term between SSRI prescription and kidney function.

All the data management and statistical analyses were conducted using STATA version 14 (Stata Corp, Texas). A *P*-value of < 0.05 was inferred as statistically significant.

Subgroup analysis

We conducted *posthoc* subgroup analyses (separately) by SSRI dose and receptor affinity in the fully-adjusted multiplicative Poisson regression models. Based on the defined daily dose (DDD) of each SSRI (20 mg day^{-1} for citalopram, 10 mg day^{-1} for escitalopram, 20 mg day^{-1} for fluoxetine, 100 mg day^{-1} for fluvoxamine, 20 mg day^{-1} for paroxetine and 50 mg day^{-1} for sertraline) [39], we dichotomized the periods of SSRI prescription into two categories: periods of low dose (i.e. smaller daily dose than DDD), and periods of normal or high dose (i.e. same as or higher dose than DDD). Low and normal/high dose periods were compared to periods without SSRI prescription. For the serotonin receptor affinity subgroup analysis, we divided the periods of SSRI prescription into two categories [17]: SSRIs with intermediate affinity to the serotonin receptor (including citalopram, fluvoxamine and escitalopram), and those with high affinity (including fluoxetine, paroxetine and sertraline).

Results

Among 4 070 806 adult patients without renal replacement therapy [median age 39 years (interquartile range, IQR 27–56), male 48.8%] registered in HES-linked CPRD between 2004 and 2014, we identified 264 628 patients with CKD [median age 77 years (IQR 71–83), male 38.7%]. Of those with CKD, 242349 [92%; median age 76 years (IQR 70–82), male 39.3%] were matched with a patient without known CKD who had the same age, sex, general practice, and same date of cohort entry (Figure 1). After excluding (i) prevalent SSRI users at cohort entry, (ii) those with a history of GI bleeding and (iii) those with missing values of BMI and smoking status, there were 413 116 study participants including 202 121 patients without known CKD, 153316 patients with CKD stage 3a, 46 482 patients with CKD stage 3b, and 11 197 patients with CKD stage 4 or 5. The number of patients exposed to SSRIs during the study period was 16 911 (4.1% of patients without known CKD), 18 545 (12.1% of patients with CKD stage 3a), 5803 (12.5% of patients with CKD stage 3b) and 1063 (9.5% of patients with CKD stage 4 or 5), respectively. The patterns of prescribed SSRI and dose were similar at different levels of kidney function (Appendix S4). Patients with CKD were more likely to have a lower socioeconomic status, had a higher prevalence of many comorbidities and were more likely to be prescribed medications at baseline (Table 1).

In the total cohort, there were 7249 first hospitalizations due to GI bleeding during total follow up of 1 801 316 person–years [median follow-up length 4.0 years (IQR 1.7–6.8 years)]. Crude incidence rate for GI bleeding was generally higher among patients with more advanced CKD stages, and was higher during the period with SSRI prescription than the period without SSRI prescription at each level of kidney function (Table 2).

In the fully-adjusted multiplicative Poisson regression model, the adjusted rate ratio (period with *vs*. without SSRI prescription) was 1.66 [95% confidence interval (CI), 1.37–2.01] among patients with no CKD, 1.86 (1.62–2.15) among patients with CKD stage 3a, 1.61 (1.27–2.04) among patients with CKD stage 3b, and 1.84 (1.14–2.96) among patients with CKD stage 4 or 5 (Table 2). A test for multiplicative interaction in the fully-adjusted multiplicative Poisson model gave a *P*-value for trend of 0.922, suggesting that there is no evidence of increased relative risk of GI bleeding related to SSRI prescription among patients with more advanced CKD stages.

Table 1

Baseline characteristics of patients by level of kidney function

	Patients with no CKD (*N* = 202 121) *n* (%)	Patients with CKD stage 3a (*N* = 153 316) *n* (%)	Patients with CKD stage 3b (*N* = 46 482) *n* (%)	Patients with CKD s tage 4/5 (*N* = 11 197) *n* (%)
Age (years):				
<65	26 464 (13.1)	21 437 (14.0)	3835 (8.3)	1565 (14.0)
65–74	63 882 (31.6)	52 388 (34.2)	10 676 (23.0)	2292 (20.5)
75–84	86 433 (42.8)	63 509 (41.4)	22 241 (47.9)	4653 (41.6)
≥85	25 342 (12.5)	15 982 (10.4)	9730 (20.9)	2687 (24.0)
Sex (male)	81 861 (40.5)	62 828 (41.0)	17 928 (38.6)	5044 (45.1)
Ethnicity:				
White/not recorded	198 618 (98.3)	150 538 (98.2)	45 673 (98.3)	10 855 (97.0)
South Asian	1657 (0.8)	1552 (1.0)	444 (1.0)	164 (1.5)
Black	1089 (0.5)	687 (0.5)	194 (0.4)	121 (1.1)
Other ethnicity	757 (0.4)	539 (0.4)	171 (0.4)	57 (0.5)
Socioeconomic status:				
1 (least deprived)	47 706 (23.6)	34 538 (22.5)	9552 (20.6)	2083 (18.6)
2	51 542 (25.5)	38 806 (25.3)	11 362 (24.4)	2567 (22.9)
3	41 977 (20.8)	31 792 (20.7)	9749 (21.0)	2394 (21.4)
4	35 234 (17.4)	27 911 (18.2)	8860 (19.1)	2318 (20.7)
5 (most deprived)	25 662 (12.7)	20 269 (13.2)	6959 (15.0)	1835 (16.4)
Body mass index (kg m^{-2}):				
<18.5	6105 (3.0)	2590 (1.7)	1193 (2.6)	338 (3.0)
18.5–25	81 294 (40.2)	46 340 (30.2)	15 342 (33.0)	3898 (34.8)
≥25	76 780 (38.0)	61 231 (39.9)	17 618 (37.9)	3997 (35.7)
≥30	37 942 (18.8)	43 155 (28.2)	12 329 (26.5)	2964 (26.5)
Smoking status:				
Non-smoker	74 991 (37.1)	48 878 (31.9)	15 173 (32.6)	3636 (32.5)
Ex-smoker	96 231 (47.6)	86 433 (56.4)	25 597 (55.1)	6056 (54.1)
Current-smoker	30 899 (15.3)	18 005 (11.7)	5712 (12.3)	1505 (13.4)
Comorbidities:				
Diabetes mellitus	21 908 (10.8)	33 463 (21.8)	11 082 (23.8)	3205 (28.6)
Chronic liver disease	963 (0.5)	1068 (0.7)	348 (0.8)	95 (0.9)
Congestive heart failure	5873 (2.9)	10 700 (7.0)	6607 (14.2)	2344 (20.9)
Cancer	40 291 (19.9)	32 872 (21.4)	11 240 (24.2)	2864 (25.6)
Rheumatoid arthritis	3571 (1.8)	3667 (2.4)	1156 (2.5)	276 (2.5)
Prescribed drugs (at cohort entry)[a]:				
Antiplatelet drugs	46 531 (23.0)	55 929 (36.5)	19 082 (41.1)	4655 (41.6)
Anticoagulants	6672 (3.3)	10 120 (6.6)	3882 (8.4)	904 (8.1)
Non-steroidal anti-inflammatory drugs	14 084 (7.0)	14 245 (9.3)	4810 (10.4)	933 (8.3)
Oral corticosteroids	5343 (2.6)	6319 (4.1)	2432 (5.2)	673 (6.0)
Acid-suppressing agents	32 476 (16.1)	37 370 (24.4)	12 803 (27.5)	3472 (31.0)

CKD, chronic kidney disease.

[a]prescribed drugs were time-updated during the follow-up.

Table 2

Crude incidence rate by selective serotonin reuptake inhibitor prescription status and adjusted rate ratio for the first hospitalization due to gastrointestinal bleeding among patients with different levels of kidney function

	Length of follow-up (person–years)	Number of outcomes	Crude incidence rate (95%CI) (/1000 person–years)	Age- and sex-adjusted rate ratio (95% CI)	Fully-adjusted[a] rate ratio (95% CI)
Total in the cohort (*N* = 413 116)	1 801 316	7249	4.0 (3.9–4.1)	-	-
Among patients with no CKD (*N* = 202 121):					
Period without SSRI prescription	808 125	2413	3.0 (2.9–3.1)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	19 152	110	5.7 (4.8–6.9)	1.98 (1.64–2.40)	1.66 (1.37–2.01)
Among patients with CKD stage 3a (*N* = 153 316):					
Period without SSRI prescription	709 140	2962	4.2 (4.0–4.3)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	23 311	204	8.8 (7.6–10.0)	2.16 (1.88–2.49)	1.86 (1.62–2.15)
Among patients with CKD stage 3b (*N* = 46 482):					
Period without SSRI prescription	198 735	1174	5.9 (5.6–6.3)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	6904	73	10.6 (8.4–13.3)	1.85 (1.46–2.34)	1.61 (1.27–2.04)
Among patients with CKD stage 4/5 (*N* = 11 197):					
Period without SSRI prescription	34 894	295	8.5 (7.5–9.5)	1 (Ref.)	1 (Ref.)
Period with SSRI prescription	1055	18	17.1 (10.8–27.1)	2.10 (1.30–3.38)	1.84 (1.14–2.96)

CI = confidence interval, CKD = chronic kidney disease, SSRI = selective serotonin reuptake inhibitor.
[a]adjusted for age, sex, ethnicity, socio-economic status, body mass index, smoking status, comorbidities (diabetes mellitus, chronic liver disease, congestive heart failure, cancer, and rheumatoid arthritis), and prescribed drugs (antiplatelet drugs, anticoagulants, non-steroidal anti-inflammatory drugs, oral corticosteroids, and acid-suppressing agents).

In the fully-adjusted additive Poisson model (Appendix S2), we applied the average effect of each covariate on the risk of GI bleeding in the study population (Appendix S3) to estimate adjusted rates for GI bleeding by SSRI prescription status at each level of kidney function (Figure 2). The adjusted rate difference increased from 2.0/1000 person–years among patients with no CKD (due to the adjusted rate of 5.5 *vs*. 3.5/1000 person–years in period with and without SSRI prescription, respectively), to 4.2/1000 person–years among patients with CKD stage 3a (8.3 *vs*. 4.1/1000 person–years), to 4.8/1000 person–years among patients with CKD stage 3b (9.9 *vs*. 5.1/1000 person–years), and to 7.9/1000 person–years among patients with CKD stage 4/5 (15.3 *vs*. 7.4/1000 person–years). A test for additive interaction gave a *P*-value for trend of 0.001, suggesting that there is strong evidence of increased risk difference of GI bleeding related to SSRI prescription as kidney function deteriorates.

In sensitivity analyses, the results were similar after changing our assumption about the length of periods between prescriptions and washout periods of SSRI prescription from 30 days to 60 and 90 days (Appendix S5).

In subgroup analyses, at each level of kidney function, the 95% CIs of adjusted rate ratios for periods with low and normal/higher dose of SSRIs largely overlapped, as did the CIs for periods exposed to SSRIs with intermediate affinity and those for SSRIs with high affinity (Appendices S6 and S7).

Discussion

In this large population-based study, we demonstrated that the relative risk of GI bleeding associated with SSRI exposure (i.e. the fully-adjusted rate ratio between periods with and without SSRI prescription) was around 1.7 regardless of kidney function. However, we showed strong evidence that the excess risk of GI bleeding (i.e. the fully-adjusted rate difference between periods with and without SSRI exposure) increased substantially as renal function declined; ranging from 2.0/1000 person–years among patients with no CKD to 7.9/1000 person–years among patients with CKD stage 4/5.

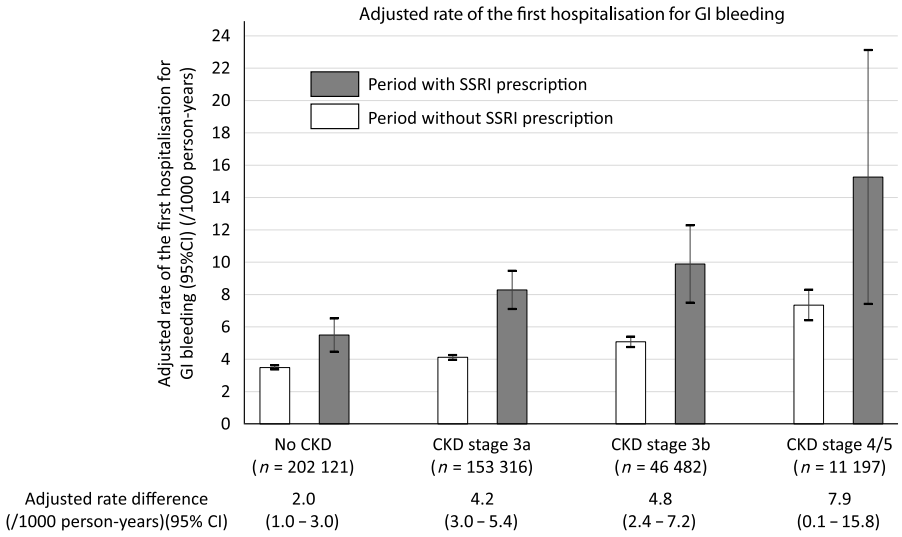

Figure 2

Adjusted rates and rate difference (between period with and without selective serotonin reuptake inhibitor prescription) for the first hospitalization due to gastrointestinal bleeding among patients with different levels of kidney function. CKD = chronic kidney disease, CI = confidence interval, GI = gastrointestinal, SSRI = selective serotonin reuptake inhibitor

To our knowledge, this is the first study examining the risk of GI bleeding associated with SSRIs at different levels of kidney function, and testing multiplicative and additive interactions between SSRI prescription and kidney function. The relative risk of GI bleeding due to SSRI prescription found in our study (around 1.7 regardless of kidney function) was consistent with that of a recent meta-analysis [13], which found a pooled relative risk of GI bleeding associated with SSRI use of 1.55 (95% CI, 1.35–1.78) across 22 studies. However, none of the studies included in the meta-analysis estimated an adjusted rate difference between patients (or periods of time) with and without SSRI prescription. This additional information is extremely useful. Because there are likely to be many confounders between patients (or periods of time) with and without SSRI prescriptions, a crude rate difference of the outcome between the groups may be substantially different from that attributable to the medication.

There are several reasons for being concerned about a potential amplification of the relative risk of GI bleeding associated with SSRIs among patients with decreased kidney function. Firstly, there is some evidence that renal clearance of SSRIs is decreased and their elimination half-life is prolonged in patients with decreased kidney function [27]. Other aspects of pharmacokinetics, such as liver metabolism and plasma protein binding, may also be altered among patients with CKD [40]. Furthermore, polypharmacy is common among patients with CKD [41], and, therefore, a potential drug–drug interaction between SSRIs and other drugs could increase the bleeding risk of SSRIs in the CKD population. However, in our real-world data, the relative risk of SSRIs was found to be similar irrespective of baseline kidney function, with no evidence of multiplicative interaction.

However, there was strong evidence that the excess risk of GI bleeding associated with SSRI exposure increased substantially as kidney function declined. This represents a *public-health interaction* [42]; a larger absolute risk increase means a larger number of patients experiencing the outcome, suggesting a larger public-health burden in the population. Even when the relative risk of a drug is constant across subgroups, the absolute number of patients who experience an adverse effect of the drug will be larger in a group with a high risk of the outcome. We formally tested if this was the case in our study by adjusting for comorbidities and medications, the distribution of which was different between the groups at each level of kidney function. Therefore, the observed graded increase in the excess risk of GI bleeding (i.e. adjusted rate difference between periods with and without SSRIs) can be ascribed to CKD itself, rather than conditions associated with CKD (e.g. diabetes, antiplatelet use). The pathophysiology of bleeding tendency in patients with CKD is multifactorial, including platelet dysfunction and vessel wall damage [43]. In addition, patients with CKD are more likely to have antecedents of GI bleeding, such as peptic ulcer disease [44].

We need to acknowledge several limitations of the study. Firstly, we defined CKD using strict criteria based on two serum creatinine results in CPRD, and identified a comparison group sampled from the rest of the general population. However, creatinine testing in primary care is not universal (currently, this is recommended and incentivized for people at risk of CKD [45, 46]), and therefore we may have misclassified some patients with unmeasured CKD into the comparison group. Nevertheless, because the prevalence of CKD (eGFR <60 ml min^{-1} 1.73 m^{-2}) identified in CPRD is known to be similar to that in a nationally-representative survey (Health Survey for England) [47], we expect that the proportion of unmeasured CKD is small in CPRD and people

without creatinine tests are unlikely to have CKD. It would have been inappropriate for us to use a comparison group sampled from people with creatinine testing in CPRD, because those with creatinine testing are a less healthy group of individuals who were not representative of the general population [48]. Secondly, consistent with a recent US study [3], our outcome definition was based on hospitalization recorded in linked hospital inpatient data, because the timing of GI bleeding recorded in HES is likely to be more accurate than that recorded in CPRD [49]. Moreover, we expect that hospitalization recorded with a primary diagnosis of GI bleeding will capture most severe cases. However, we lack greater detail such as endoscopy findings and requirement for blood transfusion. Nevertheless, we would not anticipate that these characteristics are substantially different between patients (or periods of time) with and without SSRI prescription. Thirdly, we adjusted for a variety of potential confounders of the relationship between SSRI prescription and GI bleeding, including demographics, socioeconomic and smoking status, BMI, comorbidities, and prescribed drugs [14–24]. However, confounding cannot be fully removed in observational studies. Unmeasured confounders could include over-the-counter aspirin and nonsteroidal anti-inflammatory drugs, as well as severity of depression or anxiety; although to our knowledge there is no clear evidence that mental-health conditions directly increase the risk of GI bleeding. Fourth, we excluded patients with missing records for BMI and smoking status, prioritizing the statistical adjustment for these important confounding factors over maximizing the sample size. Although the proportion of patients with missing data was not large [with 8.7% of study participants (42 375/484698)], the exclusion of these patients could affect the generalizability of our study results. This would imply that our study findings may be limited to people who are well monitored in primary care and thus have had these characteristics recorded. Finally, although the current study is one of the largest studies of the association between SSRIs and GI bleeding to date [13], the statistical power may still be insufficient in the group with the most severely reduced kidney function (as indicated by the wide confidence intervals). Study power also made it difficult to draw robust conclusions from our *posthoc* subgroup analyses by SSRI dose and receptor affinity.

It is recommended that any increase in the absolute risk of adverse outcomes should be taken into account in clinical decision-making [42]. In our study, we found that at more advanced stages of CKD, a larger number of patients suffered from GI bleeding potentially related to SSRIs. Therefore, the balance between risks and benefits of SSRI prescription may need to be considered differently in patients with decreased kidney function. Careful consideration of the potential risks of GI bleeding after SSRI prescription for patients with CKD is recommended.

Contributors

M.I. planned the study, carried out the data extraction, processing and analysis, and drafted the manuscript. D.N. and L.A.T. contributed substantially to the study design, interpretation of the results, and writing of the manuscript. K.M. supported the data processing and writing of the manuscript. I.J.D. and L.S. was involved in discussions of the analytical approach to this study and made comments on the results. All authors read and approved the final manuscript.

Competing Interests

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix S1 List of International Classification of Diseases 10th Revision codes used to identify hospitalization due to gastrointestinal bleeding
Appendix S2 Equation to estimate the adjusted incidence rate for the first hospitalization due to gastrointestinal bleeding based on a fully-adjusted additive Poisson model
Appendix S3 Average effect of each covariate on the risk of gastrointestinal bleeding in the study population applied in the fully-adjusted additive Poisson model
Appendix S4 Patterns in the choice of selective serotonin reuptake inhibitors and daily dose among patients with different levels of kidney function
Appendix S5 Sensitivity analysis changing our assumption on the length of grace and washout periods of selective serotonin reuptake inhibitor prescription
Appendix S6 Subgroup analysis by dose of selective serotonin reuptake inhibitors
Appendix S7 Subgroup analysis by affinity of selective serotonin reuptake inhibitors to the serotonin receptor