

Cardiovascular Outcomes Associated With Clinical Use of Citalopram and Omeprazole: A Nationwide Population-Based Cohort Study

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Background—Recent studies have raised concerns about the reduced efficacy of citalopram when used concurrently with proton pump inhibitors. The aim of this study was to evaluate the associations between clinical use of citalopram and omeprazole and the risk of sudden cardiac arrest (SCA) in an Asian population.

Methods and Results—A retrospective cohort study was conducted using the National Health Insurance Research Database of Taiwan dated from 2000 to 2013. The study cohorts comprised 3882 patients with citalopram use alone, 31 090 patients with omeprazole use alone, and 405 patients with concomitant use of citalopram and omeprazole (as the exposed cohort), and 141 508 patients received treatment with antidepressants without the risk of SCA and/or proton pump inhibitors other than omeprazole (as the comparison cohort). The primary outcome was the occurrence of SCA. The hazard ratios and 95% CIs derived from the time-dependent Cox regression model were used to assess the association between the proposed drug treatments and risk of SCA. The adjusted hazard ratios of SCA was 1.32 (95% CI, 1.17–1.50) for citalopram use alone, 1.08 (95% CI, 0.98–1.20) for omeprazole use alone, and 2.23 (95% CI, 1.79–2.78) for concomitant use of citalopram and omeprazole. The cumulative incidence of SCA over the Kaplan-Meier curves was more pronounced in patients with concomitant use of citalopram and omeprazole than those treated with citalopram alone and omeprazole alone.

Conclusions—This cohort study demonstrated use of citalopram and omeprazole either in isolation use or in concomitant use to be at increased risk for SCA. (*J Am Heart Assoc.* 2019;8:e011607. DOI: 10.1161/JAHA.118.011607.)

Key Words: citalopram • drug-drug interaction • omeprazole • sudden cardiac arrest

Depression is a widespread disease, especially among patients with coronary heart disease (CHD), and has been identified as an independent risk factor for sudden cardiac arrest (SCA) and CHD-related mortality.^{1,2} Antidepressants are among the most commonly prescribed classes of medication.³ However, tricyclic antidepressants have previously been associated with increased risk of sudden

cardiac death and myocardial infarction owing to possible cardiotoxic properties.^{4,5} By contrast, selective serotonin reuptake inhibitor (SSRI) antidepressants are considered relatively safe, which is why tricyclic antidepressants have been largely replaced by SSRI antidepressants for treatment of depression.⁶ Among SSRIs, citalopram is one of the most frequently used SSRIs, its affinity with the 5-HT receptor has the strongest drug receptor interactions in the same pharmacological class.^{7,8} However, the US Food and Drug Administration issued a warning about citalopram (>40 mg/daily) and risk of prolonged QT interval and torsade de pointes as a consequence of the findings made in a thorough QT study and in postmarketing surveillance.⁹ Notably, the warning issued by the agency about the citalopram has raised concerns about the safety of SSRI antidepressants.

From pharmacokinetic viewpoints, it is known that citalopram is metabolized in the liver mostly by the hepatic cytochrome P450 2C19 (CYP2C19) isoenzyme, but also by CYP3A4 and CYP2D6.¹⁰ Polymorphisms of the CYP2C19 has been classified into 3 genotype groups: the rapid extensive metabolizer group, the intermediate metabolizer group, and the poor metabolizer group. The average percentage of poor metabolizer subjects was 2% to 4.8% worldwide, except for a

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Clinical Perspective

What Is New?

- In this real-world prospective study, patients with concomitant use of citalopram and omeprazole had an increased incidence of sudden cardiac arrest.

What Are the Clinical Implications?

- The risks of these medications should be factored into prospective clinical decision-making when considering the potential for medication-related benefits and harms in each patient.

markedly greater prevalence of up to 22.5% among East Asians.¹⁰ Several studies showed that the plasma concentration of citalopram is affected by CYP2C19 variants. Poor metabolizers of CYP2C19 had a reduced clearance of citalopram.¹¹ Patients with ultrarapid CYP2C19 alleles had a lower serum concentration of S-citalopram.¹² There is evidence that the CYP2D6 poor metabolizer genotype in combination with CYP2C19 poor metabolizer genotype can increase citalopram half-life.¹³ As a result, the pharmacokinetics of citalopram is affected by CYP2C19 and CYP2D6 genotypes.

Omeprazole, one of the most important proton pump inhibitors (PPIs), is a medication used in the treatment of gastroesophageal reflux disease and peptic ulcer disease. Omeprazole has been found to reversibly inhibit both CYP2C19 and CYP3A4 *in vitro*,^{14–16} and recent investigations have shown that omeprazole is also a time-dependent inhibitor of CYP2C19.¹⁷ Furthermore, Shirasaka et al used the inhibition of CYP2C19 and CYP3A4 by omeprazole and its metabolites as a model to evaluate the contribution of metabolites to drug-drug interactions.¹⁸ In clinical settings, omeprazole has been found to significantly increase the risk of acute coronary syndrome because of drug-drug interactions between omeprazole and clopidogrel.¹⁹ Therefore, we investigated the potential risk of SCA in relationship to clinical use of citalopram and omeprazole in an Asian population using Taiwan's National Health Insurance Research Database (NHIRD).

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure by reasons of ethical and data-protective legislation. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application.

Data Source

The present study was a retrospective cohort study using claims data from the NHIRD. The universal National Health Insurance program, which was instituted in Taiwan in 1995, is a single-payer compulsory social insurance plan that covers all types of healthcare institutions and enrolls approximately 99% of the population of Taiwan. The NHIRD contains comprehensive healthcare information, including demographic data of insured individuals, data of clinical visits, diagnostic codes, and prescription details. NHIRD has been used for high quality epidemiological study and had a good validity.^{20,21} The data of this study was obtained from the Longitudinal Health Insurance Database (LHID 2000), a subset of NHIRD. The LHID 2000 data set contains historical ambulatory and inpatient care data for 1 million randomly sampled beneficiaries enrolled in the National Health Insurance system in 2000. The LHID 2000 database allows researcher to approach the medical service use history of these patients. There were no significant differences in the distributions of age, sex, and healthcare costs between the individuals in LHID and NHIRD. Since the data set was released for research purposes and included only scrambled information on patient identification, the study was exempt from informed consent from the subjects. Meanwhile, the study protocol has been approved by the Institutional Review Board of Fu-Jen Catholic University (FJU-IRB No:C104014).

Study Subjects

We identified patients who have ever received citalopram and/or omeprazole between January 1, 2000 and December 31, 2005 as the exposed cohort. In addition, we included patients who have been treated with antidepressants without the risk of SCA (eg, imipramine, amitriptyline, fluoxetine, paroxetine, fluvoxamine, trazodone, bupropion, or duloxetine)²² and/or PPIs other than omeprazole (eg, pantoprazole, lansoprazole, rabeprazole, or dexlansoprazole) between January 1, 2000 and December 31, 2005 as the non-exposed cohort to reduce the possible problem of confounding by indication. We applied propensity score matching at a ratio of 1:4 for exposed cohort to the matched comparator cohort. The date of initial use of citalopram or other antidepressants under study and/or omeprazole or other PPIs under study for each patient was assigned as their enrollment date. Initiation was defined as being free from any prescribed medication under study for 12 months before the first prescription. Patients aged <18 years (n=2231) with a diagnosis of SCA before the enrollment date (n=12 016) were excluded. We finally included 35 377 patients as the exposed cohort and 141 508 patients as the comparison cohort.

Cumulative Exposure of Studied Medications

Drug use information was obtained from the outpatient pharmacy prescription database. It includes prescribed drug dosage, date of prescription, supply days, and total number of pills dispensed. Because patients might discontinue or restart drug therapy, we assumed that patients' exposure to each studied medication contributed both cumulatively and continuously to their risk of SCA. Defined daily dose (DDD) was used to estimate the cumulative exposure to studied medications. DDD is a unit to measure prescribed amount of drug and represent the average maintenance dose per day of a drug used for its main indication in adults. Number of DDDs was calculated as the total amount of days per prescription divided by amount of drug in a DDD. The cumulative DDD (cDDD) of each medication was calculated as the accumulation of DDD during the exposure-risk period (from the enrollment date to the end of follow-up). When an SCA event occurred, the cumulative dosages of studied medications were recorded as a total of DDD from drug initiation to the day that the diagnosis of SCA was made. Dosage categories of study drugs were classified as 1 to 28 cDDD, 29 to 90 cDDD, and >90 cDDD because the duration of the refill card was 3 months.

Clinical Outcomes

The primary clinical outcome was the incidence of SCA. To identify patients with SCA with sufficient accuracy, we determined patients with SCA as having primary diagnosis of SCA based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes of 427.4 (ventricular fibrillation and flutter), 427.5 (cardiac arrest), 498.1 (instantaneous death), 498.2 (death within 24 hours symptom), and *ICD_OP_CODE:47028* (ever received electrical defibrillation). Patients diagnosed with SCA were required to have one outpatient visit or one inpatient hospitalization for SCA. All of the study participants were followed from the enrollment date to the onset of SCA, death (as indicated by disenrollment from the National Health Insurance or the end of the study date (December 31, 2013), whichever occurred first.

Covariate Assessment and Adjustment

Covariates included sex, age, and baseline comorbidities. Inpatient and outpatient files were used to ascertain whether they had comorbidities, including alcoholic liver disease (*ICD-9-CM* codes: 5710, 5711, 5712, and 5713), chronic obstructive pulmonary disease (*ICD-9-CM* codes: 490-496), chronic kidney disease (CKD, *ICD-9-CM* code: 585), liver chronic and cirrhosis hepatitis (*ICD-9-CM* code: 571), coronary artery disease (*ICD-9-CM* codes: 410-414), hyperlipidemia

(*icdcode:272.x*), diabetes mellitus (*ICD-9-CM* code: 250) and hypertension (*ICD-9-CM* codes: 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, and 405.9). Comorbidities were defined in a patient if he or she was diagnosed for any of the aforementioned diseases on at least two outpatient claims or one inpatient claims during the follow-up period. A propensity score, which represents the probability of receiving studied medications, was calculated for each patient by using a logistic regression model with covariates of age, sex, and aforementioned comorbidities.

Statistical Analysis

Chi-square and t-tests were used to evaluate the distributions of categorical and continuous variables between the study cohorts. Because the exposure in the observational cohort is time-dependent and non-proportional hazards of SCA exist between study cohorts, as indicated by the Schoenfeld global test ($P=0.0255$), the Cox regression model with time-dependent covariates were used to determine the association between use of citalopram and/or omeprazole and risk of SCA and the results were presented as a hazard ratio (HR) and a 95% CI. In this model, patients treated with citalopram and/or omeprazole were defined as the exposure group during a specified period of time, and patients would be switched to the non-exposure group when they stopped citalopram and/or omeprazole treatments during another specified period of time. We included the propensity score as a covariate in the time-dependent Cox regression model to adjust for the effects of potential confounders. We also included a composite variable representing the use of drugs potential for induction of QT-prolongation,²³ QT prolonging drugs, in the time-dependent Cox regression model for the adjustment. Furthermore, PPIs have been shown to interact with clopidogrel, the platelet aggregation inhibitor, reducing its platelet inhibiting effect, probably by competitive effects on CYP2C19.²⁴ Thus, the use of clopidogrel (ATC [Anatomical Therapeutic Chemical] code: B01AC04) was also included in the time-dependent Cox regression model for the adjustment. In order to evaluate the drug-drug interaction, the exposed cohort was divided into three subgroups: use of citalopram alone, use of omeprazole alone, and concomitant use of citalopram and omeprazole. Patients in each subgroup were compared with patients who received treatment with antidepressants without the risk of SCA and/or PPIs other than omeprazole. Differences in the cumulative risk of SCA between the cohorts were estimated using the Kaplan-Meier method. Given the presence of non-proportional hazards of SCA in the study cohorts, a variant of the log-rank test, the Tarone-Ware test, was used to examine the difference in the cumulative incidence curves of SCA between study cohorts. All statistical tests were two-sided, and an α level of 0.05 was considered statistically significant.

All data analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

Data for 35 377 patients who were prescribed for citalopram and/or omeprazole between 2000 and 2005 were retrieved from NHIRD. These patients represented the exposed group. Among them, 3882 patients who had used citalopram but no omeprazole during the follow-up period formed the citalopram alone group, and 31 090 patients who had used omeprazole but no citalopram during the follow-up period formed the omeprazole alone group, while 405 patients who had concomitant used citalopram and omeprazole during the follow-up period formed the citalopram plus omeprazole group. The median length of follow-up after the enrollment date was 10.28 years in the original exposed cohort. After propensity score matching, 141 508 patients who were treated with antidepressants without the risk of SCA and/or PPIs other than omeprazole during the follow-up period formed the comparison cohort. The median length of follow-up after the enrollment date was 12.22 years in the comparison cohort.

The demographic and health characteristics of the exposed and the comparison cohorts are provided in Table 1. Among

the exposed cohort, the patients with concomitant use of citalopram and omeprazole were relatively older and had higher proportions of women, baseline comorbidities, and use of clopidogrel than the patients with use of citalopram alone and those with use of omeprazole alone. Globally, there were no significant differences in age, sex, and baseline comorbidities except hyperlipidemia, between the exposed cohort and the comparison cohort. However, the exposed cohort had a significant higher proportion of medication use of QT prolonging drugs and clopidogrel than the comparison cohort.

Results in Table 2 show that there was a trend toward an increased risk of SCA with a higher cumulative dose of citalopram prescription (P for trend <0.0001). Compared with the comparison cohort, citalopram users with cDDD <28 , 28 to 90, and >90 had significantly higher risk of developing SCA (adjusted HRs [95% CI] were 1.74 [1.14–2.65], 3.49 [2.38–5.10], and 2.31 [1.66–3.20], respectively).

Table 3 presents results of multivariable time-dependent Cox regression analysis of the risk of SCA associated with use of citalopram alone, use of omeprazole alone, and concomitant use of citalopram and omeprazole. The patients with single use of citalopram and omeprazole as well as those with concomitant use of citalopram and omeprazole had a significantly higher risk of developing SCA than the comparison cohort. The adjusted HRs (95% CI) of SCA associated

Table 1. Demographic and Clinical Characteristics of Study Subjects

Variable	Exposed Group			Total Exposed Group n=35 377	Comparator Group n=141 508	P Value
	Citalopram Alone n=3882	Omeprazole Alone n=31 090	Citalopram Plus Omeprazole n=405			
Age, y (Mean±SD)	45.94±18.10	52.08±16.77	51.98±16.78	51.41±17.03	50.70±17.16	0.691
Sex, No. (%)						
Men	1528 (39.36)	17 562 (56.49)	179 (44.20)	19 269 (54.47)	76 845 (54.30)	0.581
Women	2354 (60.64)	13 528 (43.51)	226 (55.80)	16 108 (45.53)	64 663 (45.70)	
Comorbidities, No. (%)						
HTN	1287 (33.15)	12 215 (39.29)	197 (48.64)	13 699 (38.72)	55 578 (39.28)	0.057
DM	560 (14.43)	5569 (17.91)	74 (18.27)	6203 (17.53)	24 888 (17.59)	0.812
HL	880 (22.67)	7199 (23.16)	122 (30.12)	8201 (23.18)	33 892 (23.95)	0.002
CAD	713 (18.37)	5811 (18.69)	115 (28.40)	6639 (18.77)	26 672 (18.85)	0.724
CKD	140 (3.61)	1411 (4.54)	26 (6.42)	1577 (4.46)	5998 (4.24)	0.069
ALD	72 (1.85)	469 (1.51)	16 (3.95)	557 (1.57)	2098 (1.48)	0.204
LCCH	851 (21.92)	7144 (22.98)	132 (32.59)	8127 (22.97)	32 546 (23.00)	0.915
COPD	187 (4.82)	1250 (4.02)	32 (7.90)	1469 (4.15)	5705 (4.00)	0.303
Medication use, No. (%)						
QT prolonging drugs	3882 (100)	31 090 (100)	405 (100)	35 377 (100)	104 332 (73.73)	<0.001
Clopidogrel	238 (6.13)	3218 (10.35)	56 (13.83)	3512 (9.93)	8631 (6.10)	<0.001

ALD indicates alcoholic liver disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HL, hyperlipidemia; HTN, hypertension; LCCH, liver chronic hepatitis and cirrhosis.

Table 2. Multivariable Cox Proportional Hazard Regression Analysis of the Association Between Use of Citalopram and Risk of Sudden Cardiac Arrest

Variable	Person-Years	No. of SCA Cases	Incidence Rate (per 10 000)	Adjusted HR (95% CI)
The comparator group (n=141 508)	1 668 780.12	1776	10.51	Reference
Citalopram alone cDDD				
1 to 28 (n=1656)	16 033.55	22	13.72	1.74 (1.14–2.65)
29 to 90 (n=839)	8177.23	27	33.02	3.49 (2.38–5.10)
>90 (n=1972)	17 790.03	37	20.80	2.31 (1.66–3.20)

Hazard ratios were adjusted for age, sex and baseline comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, alcoholic liver disease, liver chronic hepatitis and cirrhosis, and chronic obstructive pulmonary disease, as well as medication use, including QT-prolonging drugs and clopidogrel. cDDD indicates cumulative defined daily dose=(dosage×ingredient)/DDD; HR, hazard ratio; SCA, sudden cardiac arrest.

with use of citalopram alone, use of omeprazole alone, and concomitant use of citalopram and omeprazole were 1.32 (1.17–1.50), 1.08 (0.98–1.20), and 2.23 (1.79–2.78), respectively. According to the Kaplan-Meier analysis, the cumulative incidence of SCA was more pronounced in the patients with concomitant use of citalopram and omeprazole as compared with other study groups (Figure).

Discussion

This study based on claimed data made available by Taiwan's NHIRD demonstrated that patients with use of citalopram and omeprazole had an increased incidence of SCA as compared with those without use of citalopram and omeprazole in an Asian population. Moreover, the risk of SCA was more pronounced in patients with concomitant use of citalopram and omeprazole than that in patients with single use of citalopram and omeprazole. With the greater prevalence rate of CYP2C19 loss-of-function alleles among Asians compared with other populations,¹⁰ potential drug interactions could exist between citalopram and omeprazole.

Depression is a widespread disease, especially among patients with CHD, and has been identified as an independent risk factor for sudden cardiac death and CHD-related mortality.² Currently, antidepressants are among the most commonly prescribed medication.³ Citalopram is a commonly used

antidepressant of the SSRI class. However, the US Food and Drug Administration has issued a warning about citalopram (>40 mg/daily) and the risk of prolonged QT interval and torsade de points as a consequence of the finding made in a thorough QT study and in postmarketing surveillance.⁹ Notably, the warning issued by agency about citalopram and the studies linking the use of SSRIs with sudden cardiac death in patients with and without CHD^{25,26} have raised concerns about the safety of SSRI antidepressants. Indeed, several studies have demonstrated a significant association between antidepressant medication use (including citalopram) and risk of SCA and sudden cardiac death. A nationwide case-control study based on the Danish Cardiac Arrest Registry revealed that antidepressant therapy with SSRIs was associated with SCA.²⁷ Whang et al studied depressive symptoms and antidepressant medications use and their relationship to cardiac events in the Nurses' Health Study. This prospective study of women without baseline CHD found that antidepressant use was associated with sudden cardiac death.²⁵ In agreement with these notions, the present study identified a significant association between the use of citalopram and risk of SCA (adjusted HR, 1.32; 95% CI, 1.17–1.50).

PPIs are widely prescribed and their efficacy in suppressing gastric acid secretion has led them to be preferred over other drugs such as histamine H2 receptor antagonists.²⁸ Several observational studies suggest that PPI use is associated with

Table 3. Multivariable Time-Dependent Cox Regression Analysis of the Risk of Sudden Cardiac Arrest in Relationship to Medication Use of Citalopram Alone, Omeprazole Alone, and Citalopram Plus Omeprazole

Variable	No. of Subjects	No. of Person-Years	No. of SCA Cases	Incidence Rate (per 10 000)	Adjusted HR (95% CI)
The comparison cohort	141 508	1 668 780.12	1776	10.51	Reference
Citalopram alone	3882	37 950.29	74	19.50	1.32 (1.17–1.50)
Omeprazole alone	31 090	319 022.25	520	16.30	1.08 (0.98–1.20)
Citalopram plus Omeprazole	405	4058.83	12	29.57	2.23 (1.79–2.78)

Hazard ratios were adjusted for age, sex, and baseline comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, alcoholic liver disease, liver chronic hepatitis and cirrhosis, and chronic obstructive pulmonary disease, as well as medication use, including QT-prolonging drugs and clopidogrel. HR indicates hazard ratio.

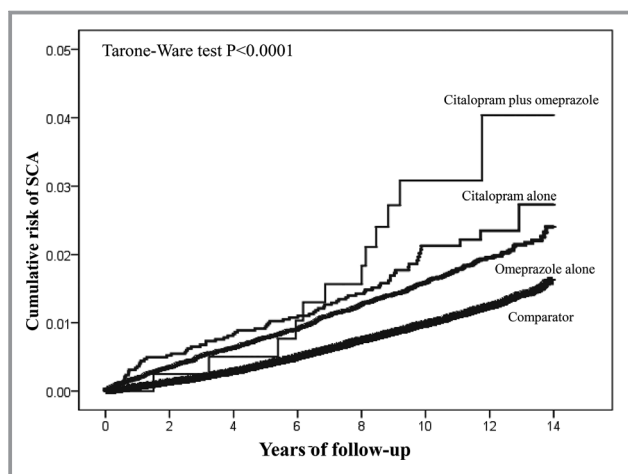


Figure. Kaplan–Meier curves for the cumulative risk of sudden cardiac arrest (SCA) among patients who had used citalopram alone, omeprazole alone, citalopram plus omeprazole, and had not used citalopram and omeprazole.

increased risk of a number of adverse health outcomes.²⁹ It has been suggested that PPIs may increase the incidence of cardiovascular events in patients with coronary artery disease by decreasing the effect of aspirin and, mainly, clopidogrel on platelet aggregation.^{30,31} In addition, a nationwide cohort study in Denmark demonstrated that use of PPIs was associated with an increase in the risk of adverse cardiovascular outcomes regardless of clopidogrel use.³² Furthermore, a clinical data mining study for pharmacovigilance study found that PPI exposure was associated with increased cardiovascular risk in the general population.³³ In the present study, PPI use was associated with a non-significant increase in the incidence of SCA.

It has been noted that the PPIs are all substrates of CYP2C19, and a theoretical rationale exists for a decreased metabolism of citalopram by concomitant treatment with PPIs.^{34,35} The impact of omeprazole on the metabolism of citalopram has been studied in humans in previous studies. In the first of these, a mean 51% increase in the plasma levels of citalopram was seen after the administration of omeprazole to 16 healthy volunteers.³⁶ In the second, about a 2-fold increase in the concentration of S-citalopram and 25% increase of the concentration of R-citalopram were found in 9 subjects.³⁴ In the present population-based study, patients with concomitant use of omeprazole and citalopram had a significantly higher risk of SCA as compared with the comparison cohort (adjusted HR, 2.23; 95% CI, 1.79–2.78). Moreover, the cumulative incidence of SCA was more pronounced in patients with co-administration of omeprazole and citalopram than those with omeprazole use alone and citalopram use alone (Figure). Indeed, observational pharmacosurveillance study involved examining geriatric inpatients health records revealed that treatment with citalopram plus omeprazole led to a statistically significant prolongation in

QT interval.³⁷ It is noted that citalopram and omeprazole are commonly co-prescribed in the elderly and this observational pharmacosurveillance study suggested that citalopram and omeprazole interact significantly in the elderly population to prolong the QT interval. Overall, these study findings suggest a drug-drug interaction between citalopram and omeprazole and there is a potential adverse effect on cardiovascular events.

This study has several limitations. The information with respect to patient adherence or self-paid medications is not available. Non-adherence would most likely result in non-differential misclassification of the exposure, which would lead to underestimation of the actual risk. In addition, a number of potential confounding factors that might affect SCA risk such as cigarette smoking, alcohol intake, and dietary habits were not available in the database. Moreover, all data in the NHIRD are anonymous; therefore, relevant clinical variables such as serum laboratory data and pathology results were also unavailable.

Strengths of this study include a nationwide cohort study based on Taiwan's NHIRD, which contains data from Taiwan's compulsory and universal healthcare system with high coverage rate. This allowed us to perform our analysis in a real-life setting with an unselected patient population. In addition, patient dropout was avoided and selection or recall bias minimized because of the use of routine database records.

Conclusions

This population-based cohort study demonstrated citalopram and omeprazole users either in isolation use or in concomitant use to be at increased risk for SCA. The clinical implications of the present study merit further investigations.

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Disclosures

None.

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