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
markedly greater prevalence of up to 22.5% among East Asians.\textsuperscript{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.\textsuperscript{11} Patients with ultrarapid CYP2C19 alleles had a lower serum concentration of S-citalopram.\textsuperscript{12} There is evidence that the CYP2D6 poor metabolizer genotype in combination with CYP2C19 poor metabolizer genotype can increase citalopram half-life.\textsuperscript{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,\textsuperscript{14-16} and recent investigations have shown that omeprazole is also a time-dependent inhibitor of CYP2C19.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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)\textsuperscript{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 (icode: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, 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. 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, 3,882 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 use of 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

| Variable | Exposed Group | Proj Exposed Comparator Group | Total Exposed Comparator Group | P Value |
|----------|---------------|-------------------------------|-------------------------------|---------|
|            | Citalopram Alone | Omeprazole Alone | Citalopram Plus Omeprazole | n=35 377 | n=141 508 | |
| 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.
Use of Citalopram and Omeprazole and Risk of SCA  
Wu et al

DOI: 10.1161/JAHA.118.011607

Journal of the American Heart Association

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 x ingredient)/DDD; HR, hazard ratio; SCA, sudden cardiac arrest.

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.

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, 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. Currently, antidepressants are among the most commonly prescribed medication. 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. 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 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. 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. 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. Several observational studies suggest that PPI use is associate with...
increased risk of a number of adverse health outcomes. 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. 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. Furthermore, a clinical data mining study for pharmacovigilance study found that PPI exposure was associated with increased cardiovascular risk in the general population. 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. 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. 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. 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 pharmacovigilance study involved examining geriatric patients health records revealed that treatment with citalopram plus omeprazole led to a statistically significant prolongation in QT interval. It is noted that citalopram and omeprazole are commonly co-prescribed in the elderly and this observational pharmacovigilance 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 no 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.

Acknowledgments
The authors thank the enrollees of the National Health Insurance Research Database for important contributions.

Sources of Funding
This study was supported by a grant from the Chi-Mei Hospital (107-CM-FIU-06).

Disclosures
None.

References
1. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res. 2015;116:1887–1906.
2. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men: the Precursors Study. Arch Intern Med. 1998;158:1422–1426.
3. Olsson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry. 2009;66:848–856.
4. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. Clin Pharmacol Ther. 2004;75:234–241.

5. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med. 2000;108:2–8.

6. Glassman AH. Cardiovascular effects of antidepressant drugs: updated. J Clin Psychiatry. 1998;59:13–18.

7. Tan JY, Levin GM. Citalopram in the treatment of depression and other psychiatric patients. Clin Pharmacol Ther. 2008;83:322–327.

8. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord. 1998;51:1:215–235.

9. US Food and Drug Administration. FDA drug safety communication: Abnormal heart rhythms associated with high doses of Celalexa (Citalopram Hydrobromide). 2011.

10. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet. 2005;20:153–167.

11. Yu BN, Chen GL, He N, Ouyang DS, Chen XP, Liu ZQ, Zhou HH. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos. 2003;3:1:1255–1259.

12. Rudberg I, Mohebi B, Hermann M, Refsum H, Molemd E. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther. 2008;83:322–327.

13. Bondolfs G, Chaeutems C, Rochat B, Bertschy G, Baumann P. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacology. 1996;128:421–425.

14. Andersson T, Miners J, Veronese M, Birkett D. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacology. 1996;128:421–425.

15. Yu KS, Yim DS, Cho JY, Park SS, Park JY, Lee KH, Jang IJ, Yi SY, Bae KS, Shin SG. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. Clin Pharmacol Ther. 2001;69:266–273.

16. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos. 2004;32:821–827.

17. Boucén X, Djebi N, Shi J, Perrin L, Brian W, Van Horn R, Birkett D. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. Clin Pharmacol Ther. 2001;69:266–273.

18. Shirasaka Y, Sager JE, Lutz JD, Davis C, Isoheranen N. Inhibition of CYP2C19 and CYP3A4 by omeprazole metabolites and their contribution to drug-drug interactions. Drug Metab Dispos. 2013;41:1414–1424.

19. Juurlink DN, Gomes T, Ko DT, Szrimko PE, Austin PC, Tu JV, Henry DA, Kopp A, Mamdani MM. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. Can Med Assoc J. 2009;180:713–718.

20. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, Lin JT. Association between nesolid analogues and risk of hepatitis B virus-related hepatic cellular carcinoma recurrence following liver resection. J Am Med Assoc. 2012;308:1906–1913.

21. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoeconomiol Drug Saf. 2011;20:236–242.

22. Wu CS, Tsai YT, Hsiung CA, Tsai HJ. Comparative risk of ventricular arrhythmia and sudden cardiac death across antidepressants in patients with depressive disorders. J Clin Psychopharmacol. 2017;37:32–39.

23. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350:1013–1022.

24. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. J Am Med Assoc. 2009;301:937–944.

25. Whang W, Kubzansky LD, Kawachi I, Rexrode KM, Kroenke CH, Gunnell R, Garan H, Albert CM. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses’ Health Study. J Am Coll Cardiol. 2009;53:950–958.

26. Smoller JW, Allison M, Cochrane BB, Curb JD, Perlis RH, Robinson JG, Rosal MC, Wenger NK, Wassertheil-Smoller S. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women’s Health Initiative Study. Arch Intern Med. 2009;169:2128–2139.

27. Weeke P, Jensen A, Folke F, Gislason G, Olesen J, Andersson C, Fosbol E, Larsen J, Lippert F, Nielsen SL. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case–time–control study. Clin Pharmacol Ther. 2012;92:72–79.

28. Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH, King Carolyn YN, Yuen WC, Lau YK, Kwan A, Wong BC. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterology. 2010;138:82–88.

29. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. J Am Med Assoc Int Med. 2016;176:172–174.

30. Gilard M, Arnaud B, Cornily J-C, Le Gal G, Lacut K, Le Calvez G, Mansourat J, Motter D, Abgrall J-F, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) Study. J Am Coll Cardiol. 2008;51:256–260.

31. Ray WA, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K, Daugherty JR, Kaltenbach LA, Stein CM. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med. 2010;152:337–345.

32. Charlot M, Ahlehoff O, Norgaard ML, Jørgensen CH, Sørensen R, Abildstrøm SZ, Hansen PR, Madsen JK, Kabeer L, Torp-Pedersen C. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. Ann Intern Med. 2010;153:378–386.

33. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, Mollé D, Abgrall J-F, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) Study. J Am Coll Cardiol. 2008;51:256–260.

34. Rocha A, Coelho EB, Sampaio SA, Lanchote VL. Omeprazole preferentially inhibits themetabolism of (S)-citalopram in healthy volunteers. Br J Clin Pharmacol. 2010;70:43.

35. Ogilvie BW, Verino P, Kazmi F, Buckley DB, Rostami-Hodjegan A, Paris BL, Toren P, Parkinson A. The proton pump inhibitor, omeprazole, but not lansoprazole or pantoprazole, is a metabolism-dependent inhibitor of CYP2C19: implications for coadministration with clopidogrel. Drug Metab Dispos. 2011;39:2020–2033.

36. Malling D, Poulsen M, Søgaard B. The effect of omeprazole on the pharmacokinetics of escitalopram in healthy subjects. Br J Clin Pharmacol. 2005;60:287–290.

37. Lozano R, Bibian C, Quilez RM, Gil J, Constante Y, Garcia-Arilla E. Clinical relevance of the (S)-citalopram-omeprazole interaction in geriatric patients. Br J Clin Pharmacol. 2013;77:1086–1087.