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Cardiac Pharmacology

Effects of Clopidogrel and Proton Pump Inhibitors on Cardiovascular Events in Patients with Type 2 Diabetes Mellitus after Bare Metal Stent Implantation: A Nationwide Cohort Study

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Background: To investigate whether there is an increased risk of cardiovascular (CV) events in patients with diabetes associated with adding proton pump inhibitors (PPIs) to clopidogrel (CLO) therapy after bare-metal stent (BMS) deployment.

Methods: We used the National Health Insurance Research Database to conduct this retrospective cohort study. We enrolled 6,757 patients with diabetes who underwent BMS deployment and received CLO with/without PPIs for 90 days (6,243 in the CLO subgroup and 514 in the CLO plus PPI subgroup). The endpoints were acute coronary syndrome and re-admission for revascularization (PCI or coronary artery bypass graft surgery) after 3, 6, and 12 months.

Results: The patients who received CLO with PPIs had no significant increase in adverse CV events compared to those without PPIs within 1 year after BMS deployment [3-month hazard ratio (HR) = 0.87, 95% confidence interval (CI), 0.65-1.15; 6 months, HR = 0.95, 95% CI, 0.78-1.15; 1 year, HR = 0.60, 95% CI, 0.81-1.12].

Conclusions: In patients with diabetes undergoing BMS deployment, there was no evidence of an increased risk of CV events among concomitant users of CLO and PPIs. Our results indicate that the use of PPIs may not modify the protective effect of CLO after BMS implantation.

Key Words: Bare metal stent • Clopidogrel • Diabetes • Proton pump inhibitor

INTRODUCTION

Patients with diabetes have a higher incidence of coronary artery disease compared to the general population, many of whom are treated with revascularization procedures.[1,2] The use of coronary stents has increased because of the increased efficacy of stents compared to balloon angioplasty.[3] Stents are now used in 80 to 90% of percutaneous coronary intervention (PCI) procedures.[4,5] According to current guidelines, diabetes is a condition in which the use of drug-eluting stents (DES) is preferable to the use of bare-metal stents (BMS). In patients receiving BMS, dual antiplatelet therapy (DAPT) is ideally given for a minimum of 1 to 12 months. However, BMS can be considered in those known to have difficulty with

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DAPT compliance, those who might undergo surgery that requires cessation of DAPT within 1 year, and those known to be at higher risk of bleeding,[6,7] as DAPT has been shown to increase the risk of gastrointestinal (GI) bleeding by 2 to 3 times compared with aspirin alone. Proton pump inhibitors (PPIs) are particularly recommended as treatment for patients with a history of GI bleeding and patients at high risk of bleeding complications, such as those receiving DAPT.[8,9] PPIs are metabolized by cytochrome P450 enzymes (2C19) and may, therefore, interact with clopidogrel (CLO) metabolism.[8,10] Reports of the clinical effects of drug interactions among patients who use CLO concomitantly with PPIs are conflicting.[11-14] Several studies have reported no improvements in clinical cardiovascular (CV) outcomes in patients concomitantly treated with PPIs and CLO undergoing BMS or DES implantation.[15,16] In addition, we previously found that the combination of PPIs and CLO was associated with higher rates of acute coronary syndrome (ACS) in patients with diabetes undergoing DES implantation.[17]

However, clinical data focusing on patients with diabetes undergoing BMS implantation and the concomitant use of CLO and PPIs are still lacking. In patients with diabetes who are at high risk of bleeding and cannot tolerate extended DAPT, BMS implantation remains a common alternative treatment in clinical practice. We developed this study, based on our previous study[17] in a different setting, to investigate whether there was an increased risk of CV events in patients with diabetes associated with adding PPIs to CLO after BMS deployment using the National Health Insurance Research Database (NHIRD) in Taiwan.

MATERIALS AND METHODS

Data source

The National Health Insurance (NHI) program in Taiwan provides comprehensive medical and pharmaceutical coverage among healthcare providers contracted with this program. It covers 99.7% (23 million people) of the population in Taiwan,[17-19] and includes services such as inpatient care, ambulatory care, dental care, and prescription drugs. The NHIRD is comprised of data on physician visits, hospital care, and prescribed medications, and we used data from the NHIRD in this study. This dataset was provided by the National Health Research Institutes. Identifiers of individuals and providers were encrypted prior to release of the data in order to protect privacy and confidentiality. This study protocol was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (No. 201006015IC), and the study was conducted in compliance with the provisions of the Declaration of Helsinki. One of authors, CF Hsieh, worked at National Yang Ming University and the study protocol was sent to IRB of Taipei Veterans General Hospital. Now he transfers to I Shou univeristy.

Study design and patient population

We conducted this retrospective cohort study from 2000 to 2006 using the NHIRD. We identified 8,772 patients who: (1) underwent BMS placement between March 1, 2001, and December 31, 2005; (2) had a diagnosis of type 2 diabetes mellitus (ICD-9-CM codes 250.x0 and 250.x2) before the first BMS deployment; and (3) had received at least one prescription for a hypoglycemic agent in the 1-year period prior to the first placement. Prior to December 2006, only BMS implantation was covered by the NHI program. Patients were excluded if they: (1) did not have an ambulatory visit or received CLO within 90 days after the entry date (n = 1,977), or (2) had revascularization, ACS, or were lost to follow-up within 7 days after the entry date (n = 42). We used the same dataset of patients in our previous study.[17] The indications for BMS deployment covered by NHI case payment include: 1) a length of intima dissection > than 15 mm; 2) severity of dissection above type B; 3) coronary lesion with thrombolysis in myocardial infarction (TIMI) flow $\leq$ 2; 4) residual stenosis > 40% after an approximation of 1:1 balloon-to-coronary artery ratio in balloon angioplasty; 5) ostium lesion; or 6) chronic total occlusion (> 2 months) and acute myocardial infarction (MI) (within 12 hours). A total of 6,757 subjects were included in this analysis. We defined the entry date as the date of discharge after the first BMS implantation, and each patient was followed up for 1 year after the entry date. Patients receiving CLO and PPIs within 90 days after the index date were identified using computer-based prescription claims. Patients were classified into CLO (n = 6,243) or CLO plus PPI (n = 514) groups (Figure 1).

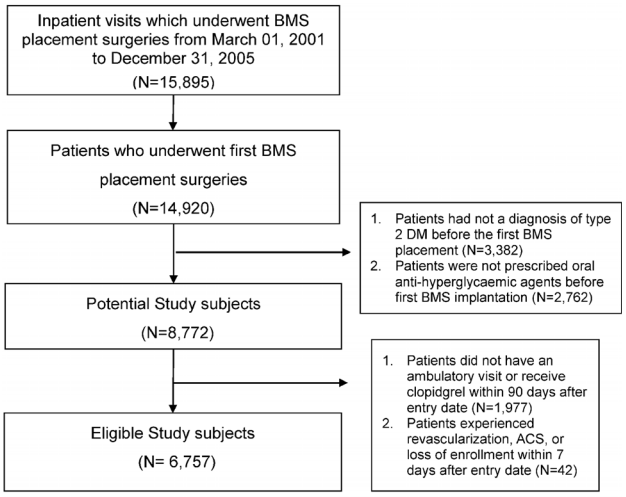

Figure 1. *Flowchart of study design.*

Outcomes and covariates

The outcomes of this study were the time to an event and censoring indicator. The time to an event represented the number of days from the entry date to the date of the earliest occurrence of one of the following events: (1) end of the observation period; (2) occurrence of target events, including revascularization [i.e., PCI or coronary artery bypass graft (CABG) surgery] and ACS (ICD-9-CM codes 410.xx, 411.xx, and 414.9); and (3) date at when they were lost to follow-up. Repeat revascularization was defined as PCI (ICD-9-CM codes 36.0-36.09) or CABG surgery (ICD-9-CM codes 36.1-36.19). The observation period started at the cohort entry date and continued until the first occurrence of any major adverse CV event or up to 1 year of follow-up. Landmark analyses were performed among the patients who were event-free (ACS readmission or revascularization) at 3, 6, and 12 months follow-up. Similar methods were used as those described in the study by Malenka et al.[20] Each patient had nine sets of outcomes with three endpoints (3, 6, and 12 months) and three target events. If the earliest event was the occurrence of a target event, this record was not censored.

We considered the following covariates: age, sex, comorbidities within 1 year before entry date [congestive heart failure (CHF), MI, renal disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, cancer, and history of PCI or CABG], drug use after discharge (thiazolidinedione, metformin, sulfonylurea, insulin, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, lipid-lowering agents, aspirin, and ticlopidine),[20] and the intensity of the use of medical services during the index hospitalization, including the number of days spent in the hospital and number of stents received.

Statistical analysis

The chi-square test was used to examine the association between the two study groups (CLO and CLO plus PPI groups) and categorical variables. The T-test was used to examine associations between drug types and continuous variables. A Cox proportional hazards model was used to estimate the association between exposure to PPIs and risk of CV events. We also adjusted for potential confounders in the multivariate Cox models based on reported risk factors for CV events. Propensity score regression adjustment was used to balance the distribution of confounders between the two groups (CLO group and CLO plus PPI group) by summarizing all covariate information into a single probability and simulating randomization.[21] We further conducted stratified analysis according to the history of ACS. Associations were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The curves for ACS, revascularization and a combination of ACS and revascularization between the CLO and CLO plus PPI groups were drawn using the Kaplan-Meier method and compared using the log-rank test. Two-sided p-values < 0.05 were considered to be statistically significant. All statistical analyses were performed using SAS version 9.3 and IBM SPSS software version 19 (IBM Corp., Armonk, New York).

RESULTS

In total, we identified 6,757 patients with diabetes who underwent BMS implantation between March 1, 2001, and December 31, 2005. Of these patients, 7.61% (n = 514) were prescribed with CLO plus PPIs and 92.39% (n = 6,243) were prescribed with CLO alone. The mean age was 65.50 ± 10.29 years. The percentage of men in the study was 61.34%; 1,588 (23.50%) underwent a stent procedure more than once; 2,465 (36.48%) had a history of MI; and 6,614 (97.88%) had a history of hospi-

talization for PCI. The mean duration of CLO use within 90 days after the entry date was 32.96 ± 16.52 days in the CLO subgroup and 32.66 ± 16.19 days in the CLO plus PPI subgroup. The mean duration of PPI use within 90 days was 27.82 ± 16.21 days. Overall, the patients receiving CLO plus PPIs were older. More patients had a history of CHF, renal disease, cerebrovascular disease, and cancer, and fewer patients received thiazolidinedione, metformin, sulfonylurea, β-blockers, lipid-lowering agents, and aspirin during the study period. In addition, more patients used insulin and ticlopidine during the study period, more patients had a hospital stay of less than 7 days, and more patients had a high Carlson comorbidity index (Table 1).

Table 1. Characteristics of diabetes mellitus patients who had received BMS implantation, stratified by medication taken within 3 months after BMS implantation and comparison between CLO and CLO+PPI subgroup

	Total (n = 6757)	CLO (n = 6243)	CLO+PPI (n = 514)	p-value
Age (year)	65.5 ± 10.29	65.4 ± 10.30	67.3 ± 10.0	< 0.001
Age group				
< 55 y	1210 (17.91%)	1137 (18.21%)	73 (14.20%)	< 0.001
55~64 y	1880 (27.82%)	1755 (28.11%)	125 (24.32%)	
65~74 y	2324 (34.39%)	2145 (34.36%)	179 (34.82%)	
≥ 75 y	1343 (19.88%)	1206 (19.32%)	137 (26.65%)	
Sex				
Female	2612 (38.66%)	2376 (38.06%)	236 (45.91%)	< 0.001
Male	4145 (61.34%)	3867 (61.94%)	278 (54.09%)	
Medical history in prior 1 year				
Congestive heart failure	1684 (24.92%)	1513 (24.24%)	171 (33.27%)	< 0.001
Myocardial infarction	2465 (36.48%)	2294 (36.75%)	171 (33.27%)	0.12
Renal disease	802 (11.87%)	682 (10.92%)	120 (23.35%)	< 0.001
Cerebrovascular disease	1345 (19.91%)	1205 (19.30%)	140 (27.24%)	< 0.001
Peripheral vascular disease	384 (5.68%)	349 (5.59%)	35 (6.81%)	0.25
Chronic pulmonary disease	1296 (19.18%)	1185 (18.98%)	111 (21.60%)	0.15
Liver disease	173 (2.56%)	157 (2.51%)	16 (3.11%)	0.41
Cancer	361 (5.34%)	321 (5.14%)	40 (7.78%)	0.01
PCI	6614 (97.88%)	6121 (98.05%)	493 (95.91%)	< 0.01
CABG surgery	68 (1.01%)	61 (0.98%)	7 (1.36%)	0.40
Characteristics of index hospitalization				
Inpatient for ≤ 7 days	1928 (28.53%)	1700 (27.23%)	228 (44.36%)	< 0.001
Stent no. > 1	1588 (23.50%)	1455 (23.31%)	133 (25.88%)	0.19
Drug use during the follow-up period				
Thiazolidinedione	1341 (19.85%)	1257 (20.13%)	84 (16.34%)	0.04
Metformin	3975 (58.83%)	3753 (60.12%)	222 (43.19%)	< 0.001
Sulfonylurea	4947 (73.21%)	4615 (73.92%)	332 ()64.59%	< 0.001
Insulin	1424 (21.07%)	1278 (20.47%)	146 (28.40%)	< 0.001
β-blocker	4677 (69.22%)	4343 (69.57%)	334 (64.98%)	0.03
Calcium channel blocker	3678 (54.43%)	3386 (54.24%)	292 (56.81%)	0.26
ACEI/ARB	5004 (74.06%)	4637 (74.28%)	367 (71.40%)	0.15
Lipid lowering agents	4108 (60.80%)	3843 (61.56%)	265 (51.56%)	< 0.001
Antiplatelet agents				
Aspirin	5752 (85.13%)	5432 (87.01%)	320 (62.26%)	< 0.001
Ticlopidine	358 (5.30%)	305 (4.89%)	53 (10.31%)	< 0.001
Charlson comorbidity index, mean (SD)	1.35 ± 1.46	1.29 ± 1.42	2.10 ± 1.75	< 0.001

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMS, bare-metal stent; CABG, coronary artery bypass graft; CLO, clopidogrel; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

The crude incidence rates (IR) of readmission for revascularization, ACS, or CV events were higher in the CLO group than in the CLO plus PPI group (revascularization, 0.41 vs. 0.40 per person-year; ACS, 0.12 vs. 0.10 per person-year). Across all events (readmission for revascularization or ACS), the CLO group had a lower crude IR of major adverse CV events than the CLO plus PPI group (Table 2). There were no significant differences among the groups.

Cox proportional hazards analysis showed an association between CLO plus PPIs and the risk of readmission for revascularization, ACS, or CV events. In addition, the CLO plus PPI group had a higher risk of ACS within 6 months after BMS implantation (crude HR = 1.45; 95% CI, 1.04-2.03) than the CLO group. However, after propensity score adjustments for potential self-selection, there were no significant differences between the CLO and CLO plus PPI groups (revascularization, HR = 0.96, 95% CI, 0.81-1.13; ACS, HR = 0.94, 95% CI, 0.69-1.28) (Table 3).

Table 4 shows the stratification analysis according to a history of ACS. The patients without a history of ACS who received CLO plus PPIs had a higher risk of ACS after BMS implantation (crude HR = 1.47; 95% CI, 1.01-2.13) than those who received CLO alone. After propensity score adjustments for potential self-selection, there were no significant differences among the subgroups. Kaplan-Meier curves for ACS, revascularization and a combination of ACS and revascularization are shown in Figure 2A, B and C. There was no significant difference in CV events between the CLO and CLO plus PPI groups.

DISCUSSION

To the best of our knowledge, this is the first study to report no increased risk of ACS and rehospitalization for revascularization with the concomitant use of CLO and PPIs in patients with diabetes treated with BMS after adjustment for propensity score. Two previous studies (PRINCIPLE-TIMI 44 and TRITON-TIMI 38 trials) indicated that the concomitant use of CLO and PPI did not significantly increase the risk of adverse clinical outcomes among patients with ACS undergoing PCI.[22] In addition, analysis of a Denmark nationwide cohort study showed that concomitant PPI therapy did not increase the risk of adverse CV events in patients who were receiving CLO.[23] Moreover, in the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), there was no apparent increase in CV risk when using CLO and omeprazole concomitantly compared with using CLO alone.[24] Furthermore, the concurrent use of PPIs has not been associated with a statistically significant increase in the risk of serious CV events among patients undergoing PCI with BMS or DES.[15,16,25,26] The

Table 2. Crude rates of revascularization and ACS events during the follow-up

	Total (N = 6,757)	CLO (N = 6,243)	CLO + PPI (N = 514)
Readmission within 1 year			
Mean follow-up time (SD), day	279.6 ± 119.8	280.8 ± 119.3	264.7 ± 125.2
Total follow-up of time, person-year	5175.2	4802.5	372.7
Revascularization or ACS Readmission			
3 months	698 (10.3%)	643 (10.3%)	55 (10.7%)
6 months	1519 (22.5%)	1399 (22.4%)	120 (23.4%)
12 months	2206 (32.7%)	2040 (32.7%)	166 (32.3%)
Revascularization			
Events (%), n	2059 (30.5%)	1906 (30.5%)	153 (29.8%)
Incidence rate per person-year	0.40	0.40	0.41
ACS			
Events (%), n	523 (7.7%)	477 (7.6%)	46 (9.0%)
Incidence rate per person-year	0.10	0.10	0.12
Revascularization or ACS			
Events (%), n	2206 (32.7%)	2040(32.7%)	166 (32.3%)
Incidence rate per person-year	0.43	0.42	0.45

Abbreviations as Table 1.

Table 3. Effect of exposure to clopidogrel versus clopidogrel plus proton pump inhibitors after BMS implantation

	Crude HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
Revascularization				
3 months	1.00 (0.74-1.35)	0.98	0.88 (0.64-1.20)	0.40
6 months	1.01 (0.83-1.23)	0.90	0.95 (0.78-1.17)	0.65
12 months	0.98 (0.83-1.15)	0.78	0.96 (0.81-1.13)	0.60
ACS				
3 months	1.44 (0.92-2.26)	0.12	0.95 (0.59-1.52)	0.82
6 months	1.45 (1.04-2.03)	0.03	1.07 (0.76-1.52)	0.70
12 months	1.19 (0.88-1.61)	0.26	0.94 (0.69-1.28)	0.69
Revascularization or ACS				
3 months	1.06 (0.80-1.39)	0.70	0.87 (0.65-1.15)	0.32
6 months	1.05 (0.87-1.27)	0.59	0.95 (0.78-1.15)	0.61
12 months	1.04 (0.89-1.22)	0.60	0.95 (0.81-1.12)	0.53

Abbreviations as Table 1; HR, hazard ratio.

* Adjusted for age, sex, comorbidities in 1 year before entry date (congestive heart failure, myocardial infarction, renal disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, cancer, percutaneous coronary intervention, and history of coronary artery bypass graft), drug use after discharge (thiazolidinedione, metformin, sulfonylurea, insulin, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, lipid-lowering agents, aspirin, and ticlopidine), and the characteristics of index hospitalization (number of days spent in hospital, number of stents), and propensity score.

Table 4. Stratified analysis of outcomes by history of ACS for clopidogrel versus clopidogrel plus proton pump inhibitors after BMS implantation

	Revascularization		ACS		Revascularization or ACS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
History of ACS (n = 2,465)						
Crude	0.89 (0.68-1.18)	0.43	0.88 (0.52-1.48)	0.63	0.94 (0.72-1.22)	0.63
Adjusted*	0.83 (0.62-1.11)	0.20	0.65 (0.38-1.12)	0.12	0.77 (0.59-1.02)	0.07
No history of ACS (n = 4,292)						
Crude	1.04 (0.85-1.28)	0.71	1.47 (1.01-2.13)	0.04	1.12 (0.92-1.37)	0.25
Adjusted*	1.02 (0.83-1.27)	0.84	1.18 (0.80-1.75)	0.40	1.07 (0.87-1.31)	0.54

Abbreviations as Table 1; HR, hazard ratio.

* Adjusted for age, sex, comorbidities in 1 year before entry date (congestive heart failure, myocardial infarction, renal disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, cancer, percutaneous coronary intervention, and history of coronary artery bypass graft), drug use after discharge (thiazolidinedione, metformin, sulfonylurea, insulin, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, lipid-lowering agents, aspirin, and ticlopidine), and the characteristics of index hospitalization (number of days spent in hospital, number of stents), and propensity score.

results of these studies were similar to those of the current study. In the Western Denmark Heart Registry (WDHR) study, CLO was not associated with an increased risk of CV events with the concomitant use of PPIs in 68% of 13,001 patients undergoing BMS implantation.[13] In addition, data from the Tennessee Medicaid program suggested no increased risk of serious CV events with the concurrent use of PPIs and CLO.[15] Moreover, in the study conducted by Tentzeris et al., the use of PPIs with CLO did not increase the risk of adverse clinical CV outcomes in 71% of 1,210 patients undergoing BMS implantation.[16] Furthermore, analysis of the US Veterans Affairs Pharmacy Benefits Management database and the National Patient Care Database showed that the use of PPIs in CLO-treated patients was not associated with an increased risk of adverse CV events in 36.5% of patients undergoing BMS implantation.[25] The sub-analysis of a meta-analysis which included randomized control

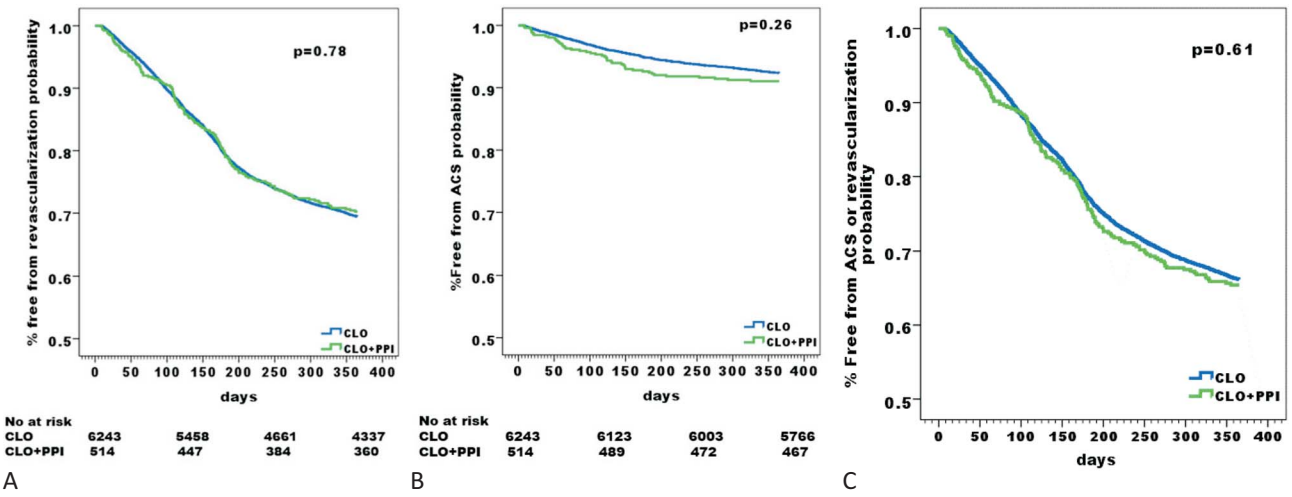

Figure 2. *(A) Kaplan-Meier estimates of revascularization between exposure to clopidogrel (CLO) and clopidogrel plus proton pump inhibitors (CLO + PPI) after bare mental stent (BMS) implantation. (B) Kaplan-Meier estimates of acute coronary syndrome (ACS) between exposure to clopidogrel (CLO) and clopidogrel plus proton pump inhibitors (CLO + PPI) after BMS implantation. (C) Kaplan-Meier estimates of revascularization or ACS between exposure to clopidogrel (CLO) and clopidogrel plus proton pump inhibitors (CLO + PPI) after BMS implantation.*

trials (RCTs) and propensity score matched (PSM) studies showed that adverse CV events were not significantly different between patients with and without PPI therapy.[27] In another meta-analysis, there was no strong evidence of an increased risk of rehospitalization and non-fatal MI among patients who were receiving PPIs and CLO.[28] The results of these studies were similar to those of the current study. We used propensity score regression adjustments to balance the distribution of confounders. However, in contrast to the previous studies, we included patients with diabetes implanted with BMS.[13,15,16,25] The influence of the concomitant use of CLO and PPIs in patients with diabetes implanted with BMS has not been elucidated in previous studies. Our results seemed to indicate that the concomitant use of PPIs and CLO could be considered in patients with diabetes after BMS implantation, particularly in those at increased risk of GI bleeding.

Possible reasons for the conflicting results of previous studies regarding patients who were receiving PPIs and adverse clinical outcomes include selection bias and differences in baseline characteristics between users and non-users of PPIs. In our study as well as in two other studies, a higher prevalence of CHF, chronic kidney injury, and cerebrovascular disease and a higher Charlson comorbidity index at baseline were found in the patients who were receiving PPIs.[23,29] Results from RCTs and PSM studies have shown that the concomitant use of CLO and PPIs did not increase the risk of CV events after decreasing the effect of selection bias. In the current study, the HRs of outcomes were adjusted for propensity score to decrease the unbalanced distribution of baseline characteristics. Another possible reason that may have affected the results was the definition and number of outcomes, as mentioned in the study by Tentzeris et al.[16] In previous studies,[24,30,31] composites of more than two outcomes were analyzed. To decrease the effect of composite outcomes, we investigated the effects of PPIs only on two outcomes — rehospitalization for ACS and revascularization. In the study by Gupta et al.,[30] the risk of target lesion revascularization or failure did not increase in the group receiving PPIs. In patients with diabetes, the use of DES was highly preferred to reduce the risk of target vessel revascularization compared with the use of BMS. However, patients with diabetes implanted with a limus-eluting stent were reported to have a higher risk of ACS when receiving both CLO and PPIs.[17] In contrast, we did not find similar results. We hypothesize that uncoated drug stents may permit earlier arterial wall healing than drug-coated stents, which are potentially associated with a reduced risk of thrombus formation in long-term follow-up.[32]

Limitations and strength

Our nonrandomized design could be confounded by unmeasured variables, particularly because the NHIRD

lacks detailed information on risk factors such as smoking, lipid levels, and stent size and length. Although we attempted to adjust for this by adding a propensity score variable, this may not be the best method to adjust for confounding. Because the NHIRD does not contain data on mortality, we could not analyze the causes of death. However, we tried to use the enrollment data to identify the date of being lost to follow-up. Of the patients, 59% (n = 4,006, mean follow-up days = 365.0) were not observed until the end of the observation period, 33% (n = 2,206, mean follow-up days = 146.6 ± 88.5) had adverse events, and 8% (n = 545, mean follow-up days = 189.5 ± 113.9) were lost to follow-up. Our study has additional limitations. We had no data on CLO resistance, such as platelet function data and functional variability in 2C19 isoenzyme activity. The strengths of this study include the large number of patients since it was based on a nationwide, unselected population that represented average patients with diabetes and BMS implantation in a contemporary clinical setting. In Taiwan, PPIs are mainly prescribed when there is a clear indication, such as peptic ulcer disease or gastroesophageal reflux disease confirmed by esophagogastroduodenoscopy. Moreover, PPIs are not routinely prescribed in combination with DAPT. Although we could not analyze patients who self-paid for PPIs, the dataset we used included all patients enrolled in the NHI and represented the real situation of medical utilization in Taiwan. We performed multiple comparisons that may have increased the possibility of type I errors, however more meaningful clinical findings could be observed. Information on drug use and rehospitalization for ACS or revascularization was collected independently from the NHIRD, avoiding reliance on self-reports, thus reducing the potential for misclassification.

Clinical implication

Our results indicated that the concurrent use of PPIs and CLO did not significantly increase the risk of serious CV events. Although the upper limit of the CI of the HR for CV events did not rule out the possibility of such harm, data from additional studies, including trials, will be important to clarify precise estimates of the effects of concurrent PPI use on CV outcomes. In addition, our results did not support the need to avoid the concomitant use of PPIs for gastric protection in patients receiving CLO who are at an increased risk of GI bleeding.

CONCLUSIONS

BMS implantation remains a common alternative treatment in real-world practice in patients with diabetes who are at a high risk of bleeding and cannot tolerate extended DAPT. In addition, our results showed no evidence of an increased risk of CV events among concomitant users of CLO and PPIs with diabetes treated with BMS implantation. This indicates that the use of PPIs might not modify the protective effect of CLO after BMS implantation. Prospective randomized studies are warranted to provide more definitive evidence regarding interactions between PPIs and CLO in patients with diabetes with BMS deployment.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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None.

REFERENCES

1. Abbott JD, Voss MR, Nakamura M, et al. Unrestricted use of drug-eluting stents compared with bare-metal stents in routine clinical practice: findings from the National Heart, Lung, and Blood Institute Dynamic Registry. *J Am Coll Cardiol* 2007;50: 2029-36.
2. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;28:88-136.

3. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;331:489-95.
4. King SB 3rd. Why have stents replaced balloons? Underwhelming evidence. *Ann Intern Med* 2003;138:842-3.
5. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol* 2002;40:2082-9.
6. Li YH, Fang CY, Hsieh IC, et al. 2018 expert consensus on the management of adverse effects of antiplatelet therapy for acute coronary syndrome in Taiwan. *Acta Cardiol Sin* 2018;34:201.
7. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44-122.
8. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2010; 56:2051-66.
9. Agewall S, Cattaneo M, Collet JP, et al. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013;34:1708-13, 13a-13b.
10. Li XQ, Andersson TB, Ahlstrom M, et al. 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: 821-7.
11. van Boxel OS, van Oijen MG, Hagenaars MP, et al. Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study. *Am J Gastroenterol* 2010;105:2430-6; quiz 37.
12. Harjai KJ, Shenoy C, Orshaw P, et al. Clinical outcomes in patients with the concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention: an analysis from the Guthrie Health Off-Label Stent (GHOST) investigators. *Circ Cardiovasc Interv* 2011;4:162-70.
13. Schmidt M, Johansen MB, Robertson DJ, et al. Concomitant use of clopidogrel and proton pump inhibitors is not associated with major adverse cardiovascular events following coronary stent implantation. *Aliment Pharmacol Ther* 2012;35:165-74.
14. Nicolau JC, Bhatt DL, Roe MT, et al. Concomitant proton-pump inhibitor use, platelet activity, and clinical outcomes in patients with acute coronary syndromes treated with prasugrel versus clopidogrel and managed without revascularization: Insights from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial. *Am Heart J* 2015;170:683-94.e3.
15. Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010;152:337-45.
16. Tentzeris I, Jarai R, Farhan S, et al. Impact of concomitant treatment with proton pump inhibitors and clopidogrel on clinical outcome in patients after coronary stent implantation. *Thromb Haemost* 2010;104:1211-8.
17. Hsieh CF, Huang WF, Chiang YT, et al. effects of clopidogrel and proton pump inhibitors on cardiovascular events in patients with type 2 diabetes mellitus after drug-eluting stent implantation: a nationwide cohort study. *PLoS One* 2015;10:e0135915.
18. Lu PY, Hsieh CF, Tsai YW, et al. Alendronate and raloxifene use related to cardiovascular diseases: differentiation by different dosing regimens of alendronate. *Clin Ther* 2011;33:1173-9.
19. Yeh HT, Hsieh CF, Tsai YW, et al. Effects of thiazolidinediones on cardiovascular events in patients with type 2 diabetes mellitus after drug-eluting stent implantation: a retrospective cohort study using the national health insurance database in Taiwan. *Clin Ther* 2012;34:885-93.
20. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol* 1993;46:1075-9; discussion 81-90.
21. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health* 2000;21:121-45.
22. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;374:989-97.
23. Charlot M, Ahlehoff O, Norgaard ML, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med* 2010;153:378-86.
24. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010;363: 1909-17.
25. Banerjee S, Weideman RA, Weideman MW, et al. Effect of concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention. *Am J Cardiol* 2011; 107:871-8.
26. Aihara H, Sato A, Takeyasu N, et al. Effect of individual proton pump inhibitors on cardiovascular events in patients treated with clopidogrel following coronary stenting: results from the Ibaraki Cardiac Assessment Study Registry. *Catheter Cardiovasc Interv* 2012;80:556-63.
27. Cardoso RN, Benjo AM, DiNicolantonio JJ, et al. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis. *Open Heart* 2015;2:e000248.
28. Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the im-

pact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy: systematic review. *Circ Cardiovasc Qual Outcomes* 2015;8:47-55.
29. Bhurke SM, Martin BC, Li C, et al. Effect of the clopidogrel-proton pump inhibitor drug interaction on adverse cardiovascular events in patients with acute coronary syndrome. *Pharmacotherapy* 2012;32:809-18.
30. Gupta E, Bansal D, Sotos J, et al. Risk of adverse clinical outcomes with concomitant use of clopidogrel and proton pump inhibitors following percutaneous coronary intervention. *Dig Dis Sci* 2010; 55:1964-8.
31. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301: 937-44.
32. Chaabane C, Otsuka F, Virmani R, et al. Biological responses in stented arteries. *Cardiovasc Res* 2013;99:353-63.
33. Chen CY, Hsieh CF, Yeh HI. Effects of clopidogrel and proton pump inhibitors on cardiovascular events in patients with type 2 diabetes mellitus after bare metal stent implantation: a nationwide cohort study. *Eure Heart J* 2017;38 suppl 1:4294.