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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

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Background—The concomitant use of proton pump inhibitors (PPIs) with clopidogrel is suspected to be associated with an adverse impact on clinical outcomes in patients with coronary artery disease. We sought to evaluate whether the use of PPIs with clopidogrel was associated with worse clinical outcomes after percutaneous coronary intervention (PCI) compared with the use of clopidogrel alone.

Methods and Results—We studied 2651 consecutive patients discharged alive after coronary stenting for stable or unstable coronary artery disease between 2001 and 2007. All patients received aspirin indefinitely and a thienopyridine for 1 to 12 months. Patients were categorized into 2 groups: those taking a PPI [PPI (+), n=751] and those not taking a PPI [PPI (−), n=1900] at discharge. The primary end points were the 6-month incidence of major adverse cardiovascular events (MACE) (composite of death, myocardial infarction, target vessel revascularization, and stent thrombosis) and net adverse clinical events (NACE) (composite of MACE and thrombolysis in myocardial infarction major or minor bleeding), which were evaluated using propensity-adjusted Cox regression analysis. In addition, propensity-matched analysis was performed in 685 pairs of patients. The PPI (+) group was older and had more comorbid conditions than the PPI (−) group. In propensity-adjusted as well as propensity-matched analyses, the use of PPIs was not associated with an increased risk of MACE or NACE.

Conclusions—The use of PPIs with dual antiplatelet therapy was not associated with any adverse influence on MACE or NACE after PCI. (***Circ Cardiovasc Interv*. 2011;4:162-170.**)

Key Words: angioplasty ■ clopidogrel ■ proton pump inhibitors

The American College of Cardiology/American College of Gastroenterology/American Heart Association expert consensus document recommends prophylactic treatment with a proton pump inhibitor (PPI) for patients on dual antiplatelet therapy who are at high risk for gastrointestinal injury.[1] However, recent concerns have been raised regarding the concomitant use of clopidogrel and PPIs in patients with coronary artery disease. These concerns are based on reports of attenuation of platelet inhibition due to an interaction between clopidogrel and PPIs related to their metabolism by the cytochrome P450 2C19 (CYP2C19) pathway.[2–4] Further, some clinical studies[5–9] have demonstrated worse cardiovascular outcomes in patients taking clopidogrel with PPIs compared with clopidogrel alone. However, other studies, including a large, randomized placebo-controlled trial, did not show worse outcomes with the clopidogrel-PPI combination.[10–12] The merits of the recent US Food and Drug Administration warning against the use of PPI with clopidogrel, based largely on observational data, has been intensely debated.[13]

Clinical Perspective on p 170

Previous studies assessed the impact of concurrent dual antiplatelet agents and PPI use on major adverse cardiac events (MACE) but not on net adverse clinical events (NACE), a composite of MACE and post-percutaneous coronary intervention (PCI) bleeding. We evaluated the impact of concurrent use of dual antiplatelet agents and PPI on MACE and NACE in patients after PCI.

Methods

Guthrie PCI Registry

The Guthrie PCI Registry is a prospective, observational registry initiated in July 2001 that includes all patients who undergo PCI at the Guthrie Health System (Sayre, PA). The details of the design of this registry have been described previously.[14] Demographic, clinical, and procedural data are collected in accordance with the American College of Cardiology National Cardiovascular Data Registry definitions and entered in an Excel spreadsheet. After

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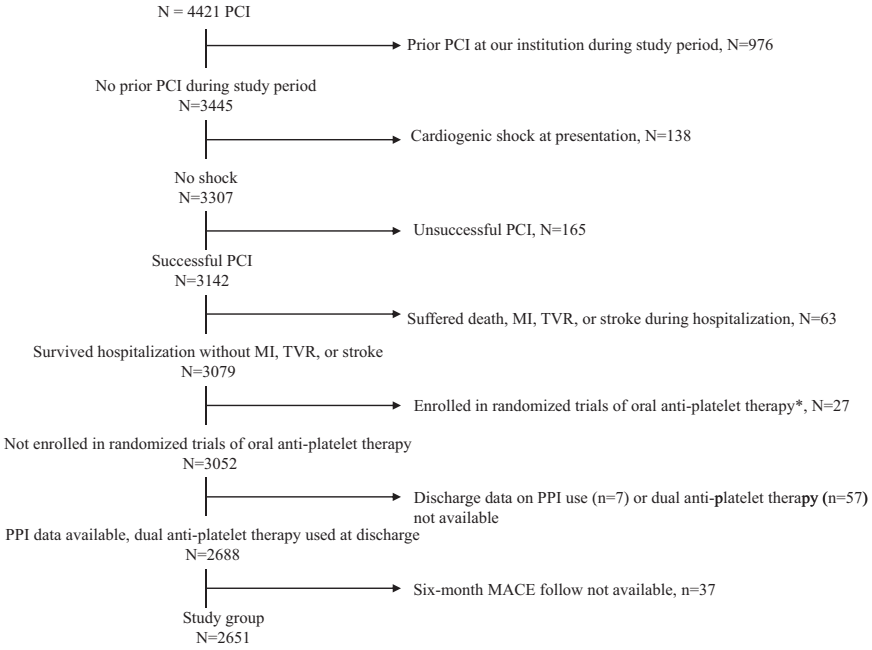

Figure 1. Study patients. Arrows indicate the number of patients excluded and the reasons for exclusion. Randomized, double-blind clinical studies of oral antiplatelet agents active at our site during the period of this registry included PLATO (A Study of Platelet Inhibition and Patient Outcomes), TIMI-38 (Thrombolysis in Myocardial Infarction-38), and TIMI-46. MACE indicates major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

discharge from the hospital, all patients are prescribed aspirin to be continued indefinitely. Clopidogrel 75 mg/d is recommended for up to 1 year but left to the discretion of the treating cardiologist. Similarly, guidelines-recommended strategies for secondary prevention[15] are strongly endorsed. Patients are scheduled for follow-up with a cardiologist at 1 and 12 months and with the primary-care physician at 1 to 2 months; additional visits are scheduled as necessary. The occurrence of death, myocardial infarction (MI), or target vessel revascularization (TVR) is evaluated annually (for up to 5 years) from patients' medical records, discussion with the primary-care provider, or by a telephone interview with the patient or family. Data on readmissions occurring at our hospital up to 365 days and the reason for readmission are collected. We also obtain mortality follow-up using the Social Security Death Index. Inconsistencies between the Social Security Death Index and clinical follow-up are resolved by additional review of medical records and telephone interview with the family. Data collection is supervised by an experienced nurse committed to the database. The registry is funded entirely by the Guthrie Health System and receives no external funding.

Study Population

This analysis is based on 4421 PCI procedures performed between July 2001 and December 2007. Patients were included if they underwent successful PCI of a native coronary artery or bypass graft for stable or unstable coronary artery disease (excluding cardiogenic shock) and were discharged from the hospital alive without MI, TVR, or stroke. In patients who had undergone multiple PCIs during the study period, only the first PCI was included. Patients were excluded if they were enrolled in a randomized trial of antiplatelet therapy, if discharge data on the use of PPI or dual antiplatelet therapy were not available, or if the patients did not complete the 6-month follow-up. Based on these criteria, 2651 patients comprised the study group (Figure 1). The local institutional review board approved the study.

Study Groups and Outcomes

We classified patients into 2 groups: those who were prescribed PPI at the time of discharge from the hospital [PPI (+) group, n=751, 28%] and those who were not [PPI (−) group, n=1900, 72%]. We assessed the self-reported compliance of patients with PPIs at 6 months.

We studied 2 primary end points: 6-month MACE (defined as composite of death, MI, TVR, and stent thrombosis) and 6-month NACE (the composite of MACE or hospitalization for thrombolysis in MI [TIMI] major or minor bleeding). Secondary outcomes of interest included rates of each of the following events up to 6 months: death, MI, death or MI, TVR, stent thrombosis, and TIMI (major or minor) bleeding. We estimated the occurrence of definite or probable stent thrombosis defined per Academic Research Consortium criteria.[16] TIMI major bleeding was defined as intracranial hemorrhage or a ≥5-g/dL decrease in hemoglobin concentration or a ≥15% absolute decrease in hematocrit level. TIMI minor bleeding was defined as an observed blood loss with a ≥3-g/dL decrease in hemoglobin concentration or a ≥10% decrease in hematocrit level or no observed blood loss with a ≥4-g/dL decrease in hemoglobin concentration or a ≥12% decrease in hematocrit level. Evaluation of the occurrence of bleeding was performed by review of patient records and assessment of nadir hemoglobin concentration and use of blood transfusions after PCI. Blood transfusions were accounted for while defining TIMI bleeding so that hemoglobin and hematocrit values were adjusted by 1 g/dL and 3%, respectively, for each unit of blood transfused.[17]

Statistical Analysis

Baseline characteristics are described as mean±1 SD (median) for continuous variables and as percentages for categorical variables. Missing values were not defaulted to negative, and denominators represent cases with complete information. Differences in baseline characteristics between PPI (+) and PPI (−) groups were compared using the χ^2 test or Fisher exact test (where appropriate) for categorical variables. Continuous variables were examined using unpaired *t* tests or nonparametric Wilcoxon rank tests. The crude incidences of study end points between the PPI (+) and PPI (−) groups were compared using the χ^2 test. The time to occurrence of each end point was compared between the PPI (+) and PPI (−) groups using actuarial life table survival analysis. Cumulative hazard curves were constructed and log-rank *P* values estimated. In selected subsets, we assessed the univariable association of PPI use with MACE and NACE using Cox proportional hazards regression.

To estimate the propensity of a patient to receive PPI at discharge, we performed a step-down multiple logistic regression analysis using all the variables that showed a univariable relation ($P<0.10$) with PPI use. The final multivariable model included all variables that showed an independent association with PPI use ($P<0.05$). Using

Table 1. Baseline Differences Between Patients Who Received PPIs After PCI and Those Who Did Not

	PPI (−) Group (n=1902)	PPI (+) Group (n=751)	*P*
Clinical characteristics			
Male sex	1368 (72)	463 (62)	<0.0001
Age, years	64±12 (64)	66±11 (67)	<0.0001
Height, cm	172±10 (173)	170±10 (170)	<0.0001
Weight, kg	89±19 (87)	88±19 (86)	0.08
BSA, m^2	2.02±0.24 (2.02)	1.99±0.24 (1.99)	0.002
Baseline serum creatinine, mg/dL	1.12±0.70 (1.0)	1.22±0.86 (1.1)	<0.0001
Baseline GFR, mL/min	103±75 (93)	102±72 (92)	0.25
Urgency of the procedure			
Urgent	789 (42)	314 (42)	0.88
Emergent	390 (21)	109 (15)	0.0004
NSTEMI or STEMI	790 (42)	238 (32)	<0.0001
Diabetes mellitus	505 (27)	225 (30)	0.077
Cerebrovascular disease	142 (7.5)	81 (11)	0.0055
Peripheral arterial disease	210 (11)	123 (16)	0.0002
Current smoker	494 (26)	160 (21)	0.012
Hypertension	1237 (65)	548 (73)	<0.0001
Dyslipidemia	1335 (70)	591 (79)	<0.0001
Prior PCI	347 (18)	165 (22)	0.028
Prior CABG	294 (16)	163 (22)	0.0001
Prior MI	399 (21)	168 (22)	0.43
Chronic lung disease	279 (15)	167 (22)	<0.0001
Angiographic characteristics			
Multivessel PCI	228 (12)	82 (11)	0.44
Stent used	1827 (96)	700 (93)	0.0019
Final vessel diameter	3.2±0.5 (3.0)	3.1±0.5 (3.0)	0.07
Left ventricular ejection fraction	48±12 (50)	48±12 (50)	0.95
Use of IABP during PCI	72 (3.8)	27 (3.6)	0.82

Continuous variables are expressed as mean±SD (median). Categorical variables are expressed counts (percentages). BSA indicates body surface area; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; IABP, intra-aortic balloon pump; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; STEMI, ST-elevation myocardial infarction.

this model, a propensity score for PPI use was calculated for each patient. To estimate the independent effect of PPI use on the study outcomes, we performed Cox proportional hazards regression analysis. In addition to PPI use and the propensity score (expressed as a continuous score), those variables with a univariable relation with the study outcome ($P<0.10$) were included in the first step of the model. PPI use was kept in the final models irrespective of its statistical significance. Hazards ratios (HRs) and 95% CIs were estimated for each variable in the final models.

Table 2. Medications Used at the Time of Discharge From the Hospital

	PPI (−) Group (n=1902)	PPI (+) Group (n=751)	*P*
Aspirin	1873 (99)	732 (98)	0.08
Aspirin dose, mg/d	298±77	288±88	0.0082
Warfarin	160 (8.4)	63 (8.4)	0.98
Statin	1724 (91)	666 (89)	0.13
β-blocker	1589 (84)	604 (80)	0.056
ACE-I or ARB	1503 (79)	572 (76)	0.11
Calcium channel blocker	216 (11)	120 (16)	0.0013

Data are presented as mean±SD or n (%). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, proton pump inhibitor.

To perform propensity-matched analysis, we created subsets of PPI (+) and PPI (−) patients matched within 3 decimal places of the propensity score. Matching identified 685 pairs of patients. The matched groups had similar baseline characteristics with the exception of higher baseline serum creatinine level and greater prevalence of peripheral arterial disease in the PPI (+) group. All clinical outcomes were compared between the matched groups using χ^2 test (unadjusted analysis) and multiple logistic regression (with adjustment for serum creatinine level and peripheral arterial disease). To further eliminate the possibility of residual bias, we performed sensitivity analyses by classifying patients into quartiles of the propensity score. Within each propensity score quartile, we compared clinical outcomes between the PPI (+) and the PPI (−) patients. On the basis of the suspected stronger antagonism of the antiplatelet effect of clopidogrel by omeprazole and esomeprazole,[18] additional sensitivity analyses were performed comparing primary and secondary outcomes of interest in patients who received either omeprazole or esomeprazole (n=312) with the PPI (−) group. A separate propensity score was calculated to estimate the propensity of patients to receive either omeprazole or esomeprazole and was used as a continuous variable in Cox proportional hazards regression models. All analyses were performed using SAS version 9.2 (SAS Institute Inc; Cary, NC) statistical software.

Results

Baseline Characteristics

Compared with the PPI (−) group, patients in the PPI (+) group were older, more likely to be women, had a lower body surface area, and had higher baseline serum creatinine levels. They were less likely to have emergent PCI, to have experienced an MI before PCI, or to be current smokers but were more likely to have underlying cerebrovascular disease, peripheral arterial disease, hypertension, dyslipidemia, prior PCI, prior coronary artery bypass graft surgery, and chronic lung disease (Table 1). Angiographic characteristics of the 2 groups were similar except for lower use of stents and marginally lower final vessel diameter in the PPI (+) group. At the time of discharge from the hospital, the PPI (+) patients tended to be taking a lower daily dose of aspirin, were less likely to receive β-blockers, and were more likely to receive calcium channel blockers. The use of warfarin at discharge was similar between the groups (Table 2).

Use of PPI at 6 Months

Data on use of PPI at 6 months was available in 2604 (98.2%) patients, including 707 (94.2%) in the PPI (+) group and

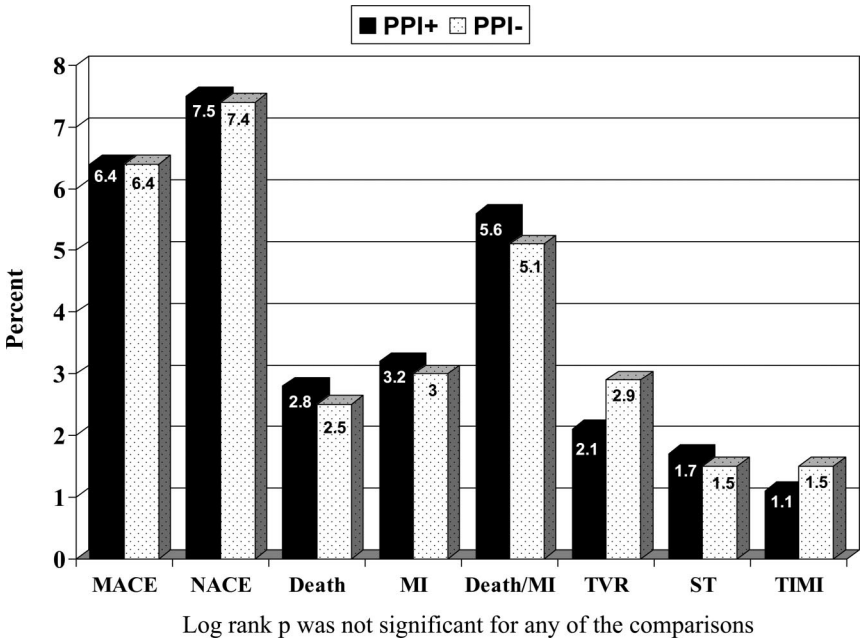

Figure 2. Crude incidence of the primary and secondary study outcomes in the proton pump inhibitor (PPI) (+) and PPI (−) groups. MACE indicates major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularization; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

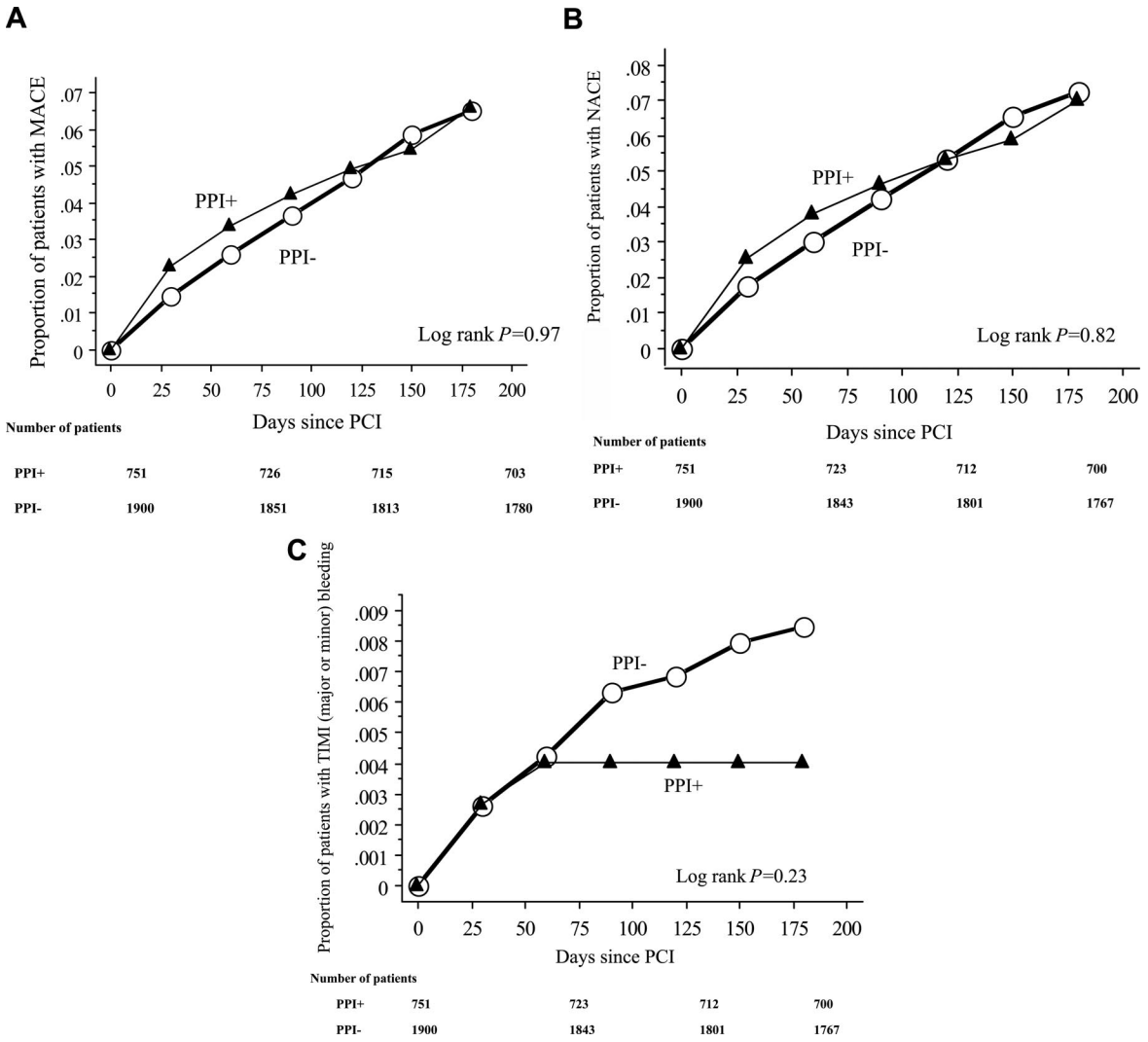

Figure 3. Kaplan–Meier survival curves representing the estimated cumulative incidence of MACE (A), NACE (B), and TIMI bleeding (C) in the PPI (+) and PPI (−) groups. MACE indicates major adverse cardiovascular event; PPI, proton pump inhibitor; PCI, percutaneous coronary intervention; NACE, net adverse clinical events; TIMI, thrombolysis in myocardial infarction.

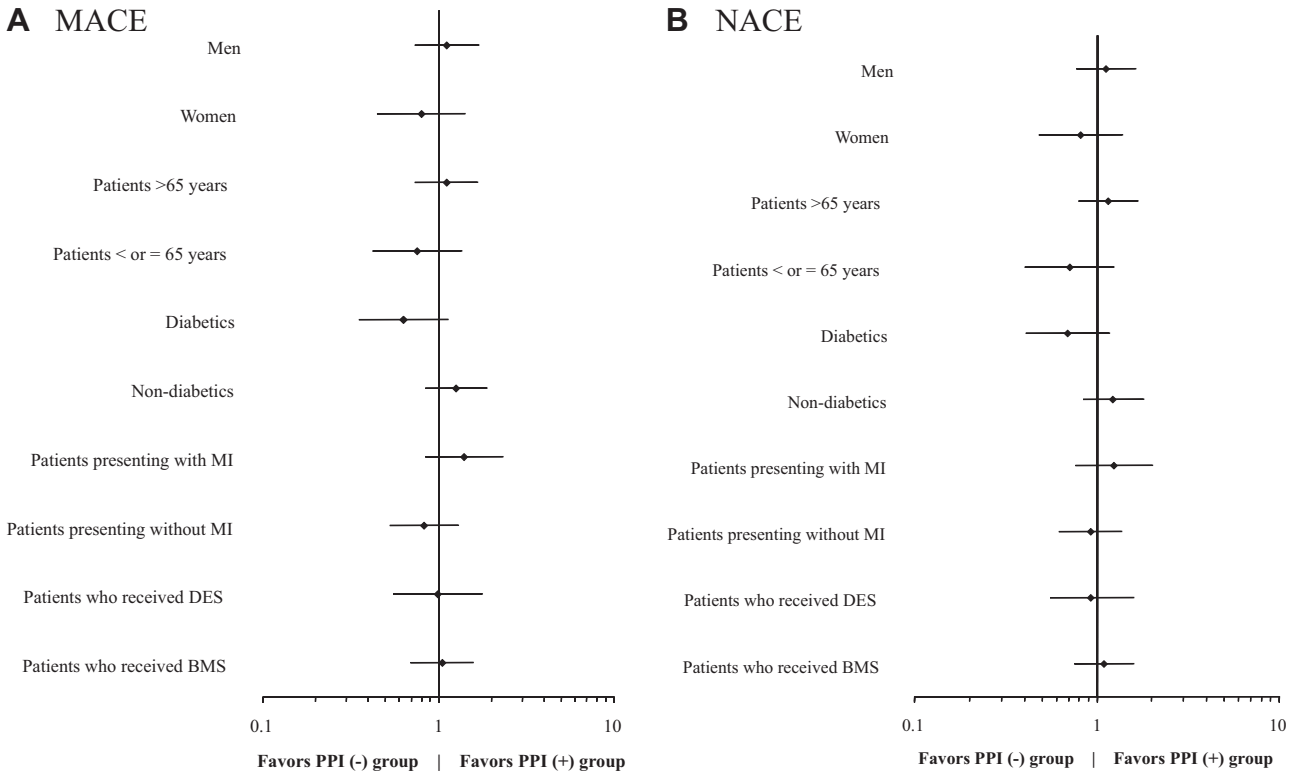

Figure 4. The association of PPI use on MACE (A) and NACE (B) in selected subgroups. PPI indicates proton pump inhibitor; MACE, major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; BMS, bare metal stents; DES, drug-eluting stents.

1897 (99.8%) in the PPI (−) group. In the PPI (+) group, 666 (94%) patients reported taking PPI agents at 6 months. In the PPI (−) group, 1631 (86%) reported not taking PPI agents at 6 months. In the entire study group, concordance between use of PPI agents at hospital discharge and at 6 months was noted in 2297 (88.2%) patients, whereas crossover was noted in 307 (11.8%).

Study Outcomes

The crude incidence of the primary and secondary study outcomes was similar in the PPI (+) and PPI (−) groups (Figure 2). In survival analysis, no differences were seen between the groups with respect to time to first occurrence of MACE, NACE, TIMI (major or minor) bleeding (Figure 3), death, MI, death or MI, TVR, or stent thrombosis. In selected subsets, the incidence of MACE and NACE was similar between PPI (+) and PPI (−) patients (Figure 4).

The propensity to receive a PPI was directly related to female sex (adjusted odds ratio [OR], 1.67; 95% CI, 1.39 to 2.0), renal insufficiency (OR, 2.02; 95% CI, 1.36 to 3.01), chronic lung disease (OR, 1.65; 95% CI, 1.32 to 2.05), dyslipidemia (OR, 1.41; 95% CI, 1.14 to 1.74), and prior coronary artery bypass graft surgery (OR, 1.37; 95% CI, 1.09 to 1.71) and inversely related to presentation with MI (OR, 0.71; 95% CI, 0.59 to 0.86), use of stents (OR, 0.58; 95% CI, 0.40 to 0.85), and aspirin dose at discharge from the hospital (OR, 0.999; 95% CI, 0.998 to 1.000). The C statistic for the final propensity model was 0.63. In multivariable analyses using the propensity score as a continuous variable, the use of PPIs had no impact on any of the study outcomes (Table 3).

Propensity matching yielded 685 pairs of patients. The baseline clinical and angiographic characteristics of matched patients were similar with the exception of higher baseline serum creatinine levels (1.16±0.66 versus 1.10±0.55 mg/dL, $P=0.0012$) and greater prevalence of peripheral arterial disease (16% versus 12%, $P=0.051$) in the PPI (+) subset. Clinical outcomes were similar between the PPI (+) and PPI (−) patients in the propensity-matched cohorts in unadjusted and adjusted analyses (Table 4).

The frequency of use of any PPI agent among the propensity score quartiles was 17%, 25%, 30%, and 41%, respectively. Comparison of the study outcomes between the PPI (+) and the PPI (−) patients within each quartile of propensity score revealed no significant differences except for a lower incidence of MI in the PPI (+) patients in the highest quartile of propensity score (Table 5). After adjustment for baseline difference, PPI use was associated with a lower incidence of MI (adjusted HR, 0.34; 95% CI, 0.13 to 0.91) in the PPI (+) patients in this quartile.

Comparison of Outcomes in Patients Treated With Either Omeprazole or Esomeprazole Versus PPI (−) Group

The crude incidence of study outcomes in the patients taking omeprazole or esomeprazole versus the PPI (−) patients is shown in Figure 5. In survival analysis, the cumulative hazard of TVR ($P=0.048$) was lower among patients who received omeprazole or esomeprazole. No significant differences were seen between groups with respect to time to first occurrence of MACE ($P=0.09$), NACE ($P=0.10$), death ($P=0.35$), MI

Table 3. Propensity-Adjusted Multivariable Impact of PPI Use Versus No PPI Use on Study Outcomes

Study Outcome	Adjusted Hazard Ratio (95% CI)	P
MACE	0.89 (0.63–1.27)	0.40
NACE	0.84 (0.60–1.16)	0.28
Death	0.95 (0.56–1.63)	0.86
MI	1.04 (0.64–1.69)	0.89
Death or MI	0.99 (0.68–1.44)	0.94
TVR	0.74 (0.42–1.29)	0.28
Stent thrombosis	1.32 (0.67–2.58)	0.42
TIMI (major or minor) bleeding	0.67 (0.31–1.47)	0.32

Multivariable correlates of MACE included history of heart failure, peripheral arterial disease, prior coronary artery bypass graft (CABG), multivessel percutaneous coronary intervention (PCI), lower left ventricular ejection fraction, and lack of stent implantation. Multivariable correlates of NACE included lack of stent implantation, lower left ventricular ejection fraction, history of heart failure, prior CABG, peripheral arterial disease, multivessel PCI, and older age. Multivariable correlates of death included older age, history of heart failure, diabetes mellitus, cerebrovascular disease, lack of stent implantation, lower left ventricular ejection fraction, and use of warfarin at the time of discharge from the hospital. Multivariable correlates of MI included prior MI, prior CABG, and lower left ventricular ejection fraction; use of intra-aortic balloon pump during PCI; and use of β-blockers at discharge. Multivariable correlates of the composite of death or MI included older age, history of heart failure, diabetes mellitus, prior MI, prior CABG, lower left ventricular ejection fraction, use of IABP during PCI, and use of β-blockers at the time of discharge from the hospital. Multivariable correlates of TVR included prior MI and multivessel PCI. Multivariable correlates of stent thrombosis included current smoking, dyslipidemia, prior MI, multivessel PCI, and lower left ventricular ejection fraction. Multivariable correlates of TIMI (major or minor) bleeding included age, current or former smoking, use of warfarin at the time of discharge from the hospital, and diabetes mellitus. PPI indicates proton pump inhibitor; MACE, major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction.

(P=0.49), death or MI (P=0.15), stent thrombosis (P=0.48), or TIMI (major or minor) bleeding (P=0.46). In multivariable analysis, use of omeprazole or esomeprazole was associated with significantly lower rates of MACE, a trend toward lower rates of NACE, death or MI, and TVR (Table 6), with no differences between the groups in other events.

Table 4. Comparison of Study Outcomes in Propensity-Matched Patients

Outcome	PPI (−) (n=685)	PPI (+) (n=685)	P (Unadjusted)	P (Adjusted)*
MACE	42 (6.1)	40 (5.8)	0.82	0.60
NACE	51 (7.5)	47 (6.9)	0.68	0.48
Death	20 (2.9)	17 (2.5)	0.62	0.46
MI	20/665 (3.0)	20/667 (3.0)	0.99	0.73
Death or MI	37 (5.4)	35 (5.1)	0.81	0.58
TVR	15 (2.3)	14 (2.1)	0.85	0.66
Stent thrombosis	11 (1.7)	11 (1.7)	0.99	0.56
TIMI (major or minor) bleeding	15 (2.2)	7 (1.0)	0.09	0.12

Data are presented as n (%). PPI indicates proton pump inhibitor; MACE, major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction.

*Adjusted for baseline serum creatinine level and history of peripheral arterial disease.

Discussion

We found that use of PPI agents in conjunction with clopidogrel and aspirin was not associated with worse cardiovascular outcomes after PCI. Specifically, the incidence of MACE and NACE as well as the individual components of these end points did not differ significantly in patients who received PPIs versus those who did not, despite the fact that the PPI (+) group had more comorbid conditions and was expected to have higher adjusted event rates at 6 months. In propensity-adjusted as well as propensity-matched analyses, PPI use did not confer worse 6-month outcomes. Furthermore, contrary to prior experience,[5,6,8] patients who were prescribed either omeprazole or esomeprazole did not have higher adjusted MACE, NACE, death or MI, and TVR rates than PPI (−) patients. Unlike prior observational analyses, our study assessed not only ischemic end points after PCI, but also safety (TIMI bleeding) and the composite NACE end point.

Comparisons With Prior Studies

PPIs have been shown to reduce both aspirin- and clopidogrel-related gastrointestinal bleeding.[3,19] PPIs are metabolized predominantly by the CYPP450 enzymes—primarily CYP2C19—and can inhibit the enzyme by competition for its catalytic site.[20] Clopidogrel is a prodrug metabolized in the liver to its active metabolite by several CYPP450 isoenzymes, including CYP2C19.[21] Because PPIs can be substrates as well as inhibitors of CYP2C19, patients taking PPIs are at risk for decreased clopidogrel efficacy from lower levels of active metabolite. Such drug-drug interactions have been reported to be the highest for omeprazole and esomeprazole.[18]

The first reports of an interaction between clopidogrel and PPIs were platelet aggregation studies by Gilard et al.[3,4] Additional platelet aggregation studies observed consistent findings with omeprazole but not with esomeprazole or pantoprazole.[2,22–24] Subsequently, observational studies[6–9] and a post hoc analysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial[5] demonstrated that use of a PPI in combination with clopidogrel was associated with an increase in the risk of acute MI, death, or rehospitalization for acute coronary syndromes. Interestingly, PPI use alone, without concomitant clopidogrel use, may not be associated with an increase in adverse events.[7,8] In contrast, other observational studies[10,11] and post hoc analyses of 2 large, randomized clinical trials[25–27] showed no impact on cardiovascular outcomes with concomitant use of clopidogrel and PPIs.

The only randomized placebo-controlled trial—COGENT-1 (The Clopidogrel and the Optimization of Gastrointestinal Events)—was terminated prematurely before enrollment of the planned 5000 patients.[12] In 3627 patients with an acute coronary syndrome who received aspirin and clopidogrel, COGENT-1 assessed the safety and efficacy of concomitant omeprazole. The omeprazole group had a significantly lower risk of achieving the primary end point, which was a composite of gastroduodenal bleeding; symp-

Table 5. Comparison of Unadjusted Six-Month Study Outcomes in the Propensity Score Quartiles

	PS Quartile 1 (n=694)		PS Quartile 2 (n=632)		PS Quartile 3 (n=656)		PS Quartile 4 (n=667)	
Outcome	PPI (−) n=578	PPI (+) n=116	PPI (−) n=471	PPI (+) n=161	PPI (−) n=458	PPI (+) n=198	PPI (−) n=391	PPI (+) n=276
MACE	4.0	4.3	6.4	5.6	6.1	8.6	9.5	6.2
NACE	5.0	6.0	6.8	5.6	7.6	9.1	11	8.0
Death	0.9	2.6	2.3	0.6	2.2	3.5	4.6	3.6
MI	1.9	2.7	3.0	4.4	2.9	4.7	4.8*	1.9*
Death or MI	2.8	4.3	4.7	5.0	5.0	8.1	8.4	4.7
TVR	2.3	1.8	3.7	3.1	2.7	1.6	3.5	2.3
Stent thrombosis	1.2	1.8	1.1	2.5	1.3	1.6	2.7	1.5
TIMI (major or minor) bleeding	1.4	1.7	0.9	0	2.0	0.5	1.8	1.8

Within each quartile, no significant differences were seen between the PPI (+) and PPI (−) patients, except for a higher incidence of MI in the PPI (−) patients in quartile 4. PS indicates propensity score; PPI, proton pump inhibitor; MACE, major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction.

*P=0.049.

tomatic gastroduodenal ulcer; and persistent pain with multiple gastric erosions, obstruction, or perforation (HR, 0.55; 95% CI, 0.36 to 0.85; P=0.007). There was no increase in the risk of cardiovascular events from use of omeprazole (HR, 1.02; 95% CI, 0.70 to 1.51).

Furthermore, in contrast to the findings of prior observational studies, the present study suggests that use of either omeprazole or esomeprazole may be associated with lower rates of MACE, NACE, and TVR. These data should be regarded as hypothesis generating, and the exact mechanism by which omeprazole or esomeprazole could potentially confer protection from cardiovascular events only can be speculated. It is possible that potentially fewer gastrointestinal events from PPI use resulted in lower rates of temporary or permanent discontinuation of clopidogrel therapy and, consequently, fewer cardiovascular events. This hypothesis was supported in our data by the fact that the use of clopidogrel at 6 months was higher in the omeprazole or esomeprazole group than in the PPI (−) group (78% versus 70%, P=0.0085). Among patients taking other PPI agents, the use of clopidogrel at 6 months was not significantly different than among patients in the PPI (−) group (72% versus 70%).

Clinical Implications

We did not detect a clinically relevant interaction between clopidogrel and PPIs. Gastrointestinal side effects are a common reason for premature discontinuation of antiplatelet therapy after PCI,[1] which is associated with increased risk of adverse clinical cardiovascular events. Use of PPIs decreases gastrointestinal side effects related to antiplatelet agents. Our findings are reassuring and support the recent endorsement for PPI use in combination with dual antiplatelet therapy in high-risk patients.[1] Future randomized clinical trials remain the best way of resolving the issue of the safety of dual antiplatelet therapy with PPIs.

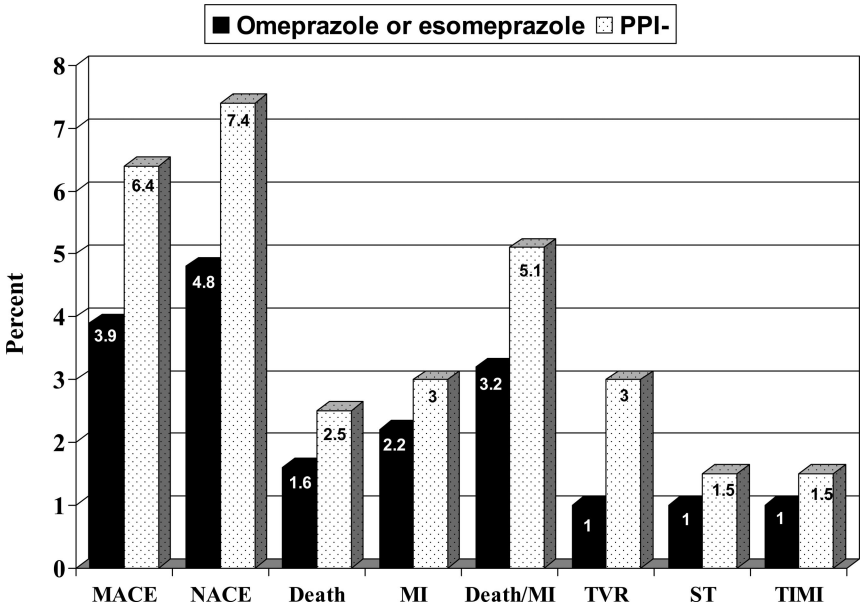

Figure 5. Crude incidence of the primary and secondary study outcomes in the omeprazole or esomeprazole and PPI (−) groups. PPI indicates proton pump inhibitor; MACE, major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularization; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

Table 6. Propensity-Adjusted Multivariable Impact of Omeprazole or Esomeprazole Use Versus No PPI use on Study Outcomes

Study Outcome	Adjusted Hazard Ratio (95% CI)	*P*
MACE	0.51 (0.28–0.92)	0.026
NACE	0.59 (0.35–1.01)	0.052
Death	0.49 (0.17–1.37)	0.17
MI	0.65 (0.29–1.43)	0.28
Death or MI	0.52 (0.26–1.03)	0.062
TVR	0.32 (0.10–1.03)	0.056
Stent thrombosis	0.59 (0.18–1.97)	0.39
TIMI (major or minor) bleeding	0.59 (0.18–1.94)	0.38

Multivariable correlates of MACE included history of heart failure, diabetes mellitus, peripheral arterial disease, and prior coronary artery bypass graft (CABG). Multivariable correlates of NACE included diabetes mellitus, peripheral arterial disease, history of heart failure, body surface area, and use of warfarin at the time of discharge from the hospital. Multivariable correlates of death included history of heart failure, diabetes mellitus, peripheral arterial disease, current smoking, and lower left ventricular ejection fraction. Multivariable correlates of MI included prior MI, prior CABG, ST-elevation myocardial infarction, or non-ST-elevation as the reason for percutaneous coronary intervention (PCI), diabetes mellitus, and peripheral arterial disease. Multivariable correlates of the composite of death or MI included diabetes mellitus, prior CABG, lower left ventricular ejection fraction, peripheral arterial disease, and use of warfarin at the time of discharge from the hospital. Multivariable correlates of TVR included prior MI, multivessel PCI, and peripheral arterial disease. Multivariable correlates of stent thrombosis included dyslipidemia, peripheral arterial disease, and lower left ventricular ejection fraction. Multivariable correlates of TIMI (major or minor) bleeding included emergent PCI, use of warfarin at the time of discharge from the hospital, diabetes mellitus, hypertension, body weight, and prior CABG. PPI indicates proton pump inhibitor; MACE, major adverse cardiovascular event; NACE, net adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction.

Limitations

Because of the observational nature of our study, the possibility of residual confounding remains despite multivariable adjustment and the use of a propensity-matched cohort. Our registry includes predominantly (99%) white patients who are less likely to have CYP2C19 loss-of-function alleles[28] and, therefore, may be less likely to exhibit any adverse impact from PPI use. Thus, our results may not be generalized to other ethnic populations. Our study population is relatively small; hence, our analysis may lack the statistical power to detect smaller differences in outcomes between the PPI (+) and the PPI (−) groups. Concomitant drug therapy was not assessed, which could well confound a possible PPI-clopidogrel interaction. Finally, the duration of PPI use before PCI was not assessed in the present study and could possibly have an impact on the degree of a possible PPI-clopidogrel interaction.

Conclusions

The use of PPIs with dual antiplatelet agents was not associated with any adverse influence on 6-month cardiovascular outcomes after PCI. Our findings do not support the avoidance of concomitant use of clopidogrel and PPIs when clinically indicated.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Some observational studies have demonstrated higher adverse cardiovascular outcomes in patients taking clopidogrel with proton pump inhibitors (PPIs) compared with clopidogrel alone. However, other studies, including a large, randomized placebo-controlled trial, have failed to demonstrate any increase in the risk of adverse clinical events with the combination. In 2651 consecutive patients discharged from the hospital alive after coronary stenting, we found no difference in the 6-month incidence of major adverse cardiovascular events or net adverse clinical events (a composite of major adverse clinical events and thrombolysis in myocardial infarction major or minor bleeding) in patients who received PPI at discharge versus those who did not. Thus, the present study does not suggest a clinically relevant interaction between clopidogrel and PPIs. Gastrointestinal side effects are a common reason for premature discontinuation of antiplatelet therapy after percutaneous coronary intervention, which is associated with an increased risk of adverse clinical cardiovascular events. Use of PPIs decreases gastrointestinal side effects related to antiplatelet agents. Our findings are reassuring and support the recent endorsement for PPI use in combination with dual antiplatelet therapy in high-risk patients.