ORIGINAL ARTICLE

Clopidogrel with or without Omeprazole in Coronary Artery Disease

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ABSTRACT

BACKGROUND

Gastrointestinal complications are an important problem of antithrombotic therapy. Proton-pump inhibitors (PPIs) are believed to decrease the risk of such complications, though no randomized trial has proved this in patients receiving dual antiplatelet therapy. Recently, concerns have been raised about the potential for PPIs to blunt the efficacy of clopidogrel.

METHODS

We randomly assigned patients with an indication for dual antiplatelet therapy to receive clopidogrel in combination with either omeprazole or placebo, in addition to aspirin. The primary gastrointestinal end point was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke. The trial was terminated prematurely when the sponsor lost financing.

RESULTS

We planned to enroll about 5000 patients; a total of 3873 were randomly assigned and 3761 were included in analyses. In all, 51 patients had a gastrointestinal event; the event rate was 1.1% with omeprazole and 2.9% with placebo at 180 days (hazard ratio with omeprazole, 0.34, 95% confidence interval [CI], 0.18 to 0.63; P<0.001). The rate of overt upper gastrointestinal bleeding was also reduced with omeprazole as compared with placebo (hazard ratio, 0.13; 95% CI, 0.03 to 0.56; P=0.001). A total of 109 patients had a cardiovascular event, with event rates of 4.9% with omeprazole and 5.7% with placebo (hazard ratio with omeprazole, 0.99; 95% CI, 0.68 to 1.44; P=0.96); high-risk subgroups did not show significant heterogeneity. The two groups did not differ significantly in the rate of serious adverse events, though the risk of diarrhea was increased with omeprazole.

CONCLUSIONS

Among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper gastrointestinal bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but our results do not rule out a clinically meaningful difference in cardiovascular events due to use of a PPI. (Funded by Cogentus Pharmaceuticals; ClinicalTrials.gov number, NCT00557921.)

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On the basis of data from several studies, clopidogrel has become the second most commonly used prescription drug worldwide.[1-9] Gastrointestinal hemorrhage is the most common serious bleeding complication from the use of long-term antiplatelet therapy.[10,11] Data from randomized studies support the concept that therapies reducing acidity decrease gastrointestinal complications of antiplatelet therapy involving aspirin, though the data are largely based on endoscopic end points; observational data also support this effect.[12-16] Randomized, controlled trials have shown that proton-pump inhibitors (PPIs) reduce the rate of recurrent gastrointestinal bleeding in high-risk patients receiving aspirin.[17] Observational studies, however, have suggested that there may be an interaction between clopidogrel and PPIs that, if real, could have significant clinical effects.[18,19] These studies have been bolstered by results of ex vivo analyses, many of which have shown inhibition of the antiplatelet effect of clopidogrel by PPIs, omeprazole most consistently.[20-22] In addition, genetic polymorphisms have been identified that could affect the response to clopidogrel and, at least theoretically, could increase the likelihood of drug interactions mediated by cytochrome P-450.[23-27] A number of other observational studies, however, did not show an interaction between clopidogrel and PPIs.[28,29] Given the conflicting data regarding a possible interaction, the optimal care of patients who require concomitant therapy with clopidogrel and PPIs remains uncertain.[30-34]

We initiated the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) to assess the efficacy and safety of concomitant administration of clopidogrel and PPIs in patients with coronary artery disease who are receiving clopidogrel plus aspirin.

METHODS

STUDY CONDUCT

The trial was designed by an academic steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) and the sponsor, Cogentus Pharmaceuticals. The steering committee was responsible for the overall leadership of the trial. A clinical research organization, Parexel, performed the data management and site monitoring. Randomization was performed centrally with the use of an interactive voice-response system before the initiation of study treatment. Parexel generated the randomization sequence. All sites operated under approval from institutional review boards or ethics committees, and all patients gave written informed consent to participate in the trial. The study was conducted according to the study protocol (available at NEJM.org). At the conclusion of the trial, the full database was transferred to an academic principal investigator. The analyses were performed independently of the sponsor, by two academic authors. An academic principal investigator prepared the first draft of the manuscript, which was then reviewed and edited by the academic steering committee and other authors; all the academic authors made the decision to submit the paper for publication. There was no agreement made regarding confidentiality of the data between the sponsor and the academic authors or their institutions. The sponsor did not have the right to approve the final manuscript. The academic principal investigators vouch for the accuracy and integrity of the analyses and interpretation of the data.

The initial planned sample size was 3200 patients, with an accrual period of 1 year and a maximum follow-up period of 2 years. The target sample size was increased to 4200 and then to 5000 to ensure an adequate number of gastrointestinal events. The study was designed to end once 143 gastrointestinal events had occurred; however, the study ended prematurely, when the sponsor suddenly and unexpectedly lost its financial backing; the sponsor is now defunct.

PATIENTS

COGENT was an international, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, phase 3 study of the efficacy and safety of CGT-2168, a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg), as compared with clopidogrel alone. Randomization was performed with the use of stratified permuted blocks. Stratification was based on two baseline factors: serologic findings for *Helicobacter pylori* (positive or negative) and concomitant use (vs. nonuse) of any nonaspirin nonsteroidal antiinflammatory drug (NSAID), including agents selective or nonselective for cyclooxygenase-2. All patients were to receive enteric-coated aspirin at a dose of 75 to 325 mg daily. Blinded

study kits and open-label enteric-coated aspirin were supplied by Parexel to the investigators.

Patients were eligible if they were 21 years of age or older and if the use of clopidogrel therapy with concomitant aspirin was anticipated for at least the next 12 months, including patients presenting with an acute coronary syndrome or undergoing placement of a coronary stent. Patients were enrolled at 393 sites in 15 countries from January 2008 through December 2008.

Hospitalized patients for whom discharge within 48 hours after randomization was not anticipated were excluded from the study. Additional exclusion criteria were the need for short-term or long-term use of a PPI, an H_2-receptor antagonist, sucralfate, or misoprostol; preexisting erosive esophagitis or esophageal or gastric variceal disease or previous nonendoscopic gastric surgery; receipt of clopidogrel or another thienopyridine for more than 21 days before randomization; receipt of oral anticoagulation therapy that could not be safely discontinued for the duration of the study; or recent fibrinolytic therapy.

END POINTS

The prespecified primary gastrointestinal efficacy end point was the time from randomization to the first occurrence of a composite of upper gastrointestinal clinical events: overt bleeding of gastroduodenal origin (confirmed by means of upper endoscopy or radiography), overt upper gastrointestinal bleeding of unknown origin, bleeding of presumed occult gastrointestinal origin with a documented decrease in hemoglobin of 2 g per deciliter or more or in the hematocrit by 10% or more from the baseline value, symptomatic uncomplicated gastroduodenal ulcer (confirmed by means of endoscopy or radiography), persistent pain of presumed gastrointestinal origin with a duration of 3 days or more and with five or more gastroduodenal erosions (confirmed by means of endoscopy), obstruction, or perforation. The time from randomization to the first occurrence of gastroesophageal reflux disease, as evidenced by symptomatic, endoscopically confirmed erosive esophagitis, was a predefined secondary end point. Adjudication of gastrointestinal events was performed by an independent committee of gastroenterologists who were unaware of the study-drug assignments.

The prespecified primary cardiovascular safety end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or ischemic stroke. There was no a priori sample-size calculation or explicit noninferiority hypothesis for the cardiovascular end point. Adjudication of cardiovascular events was performed by an independent committee of cardiologists who were unaware of the study-drug assignments. Nongastrointestinal bleeding events were also recorded and adjudicated.

STATISTICAL ANALYSIS

Medians and interquartile ranges are reported for continuous variables, and counts and percentages for categorical variables. Analyses of time-to-event variables were performed with the use of log-rank statistics, Kaplan–Meier survival curves, and Cox proportional-hazards models. The two major stratification variables were included in the models. These analyses were performed on data for the adjudicated events and secondarily on data for the events ascertained by the site investigators: the gastrointestinal composite event, the cardiovascular composite event, myocardial infarction, and revascularization. Other end points were analyzed descriptively. Kaplan–Meier event rates were calculated at 180 days, covering approximately 85% of the total follow-up period. Hazard ratios with 95% confidence intervals are reported. Given the premature termination of the trial, two academic authors separately analyzed the database and reconciled any discrepancies. All tests were two-sided. P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with the use of Stata software, version 9.2, and R software, version 2.92 (R Development Core Team, 2009).

RESULTS

STUDY PARTICIPANTS

A total of 4444 patients were screened for inclusion in the study (Fig. 1 in the Supplementary Appendix). Of these patients, 3873 underwent randomization and 571 did not. A total of 3761 patients were included in analyses: 1876 in the omeprazole group and 1885 in the placebo group. The median duration of follow-up was 106 days, with a maximum of 341 days (interquartile range, 55 to 166). The two study groups were well matched with respect to baseline characteristics

(Table 1). The study population represented patients at elevated risk for death from cardiovascular causes, with over a quarter having a history of myocardial infarction. The rate of study-drug compliance ([number of pills given − number of pills taken] ÷ number of pills given) was 84.5% in the omeprazole group and 83.3% in the placebo group (P=0.25).

GASTROINTESTINAL OUTCOMES

There were 55 adjudicated gastrointestinal events, with 47 patients having a single event and 4 patients having two events. A total of 51 first gastrointestinal events were included in the time-to-event analyses. The event rate, based on Kaplan–Meier analysis, for the primary gastrointestinal end point was reduced from 2.9% with placebo to 1.1%

Table 1. Baseline Characteristics of the Patients, According to Study Treatment.*

Characteristic	Omeprazole	Placebo
Age — yr†		
Median	68.5	68.7
Interquartile range	60.7–74.4	60.6–74.7
Male sex — no./total no. (%)	1255/1876 (66.9)	1308/1883 (69.5)
White race — no./total no. (%)‡	1754/1875 (93.5)	1769/1883 (93.9)
Body-mass index§		
Median	28.4	28.3
Interquartile range	25.5–31.9	25.5–32.0
Negative for *Helicobacter pylori* — no./total no. (%)	980/1876 (52.2)	974/1885 (51.7)
NSAID use — no./total no. (%)	160/1876 (8.5)	164/1885 (8.7)
Cardiovascular history — no./total no. (%)		
PCI	1334/1861 (71.7)	1331/1863 (71.4)
ACS	782/1855 (42.2)	792/1861 (42.6)
MI	566/1855 (30.5)	531/1861 (28.5)
PAD	223/1855 (12.0)	223/1861 (12.0)
Stroke	136/1855 (7.3)	151/1861 (8.1)
Other vascular disease	916/1855 (49.4)	948/1861 (50.9)
Cardiovascular risk factors — no./total no. (%)		
Hypertension	1497/1869 (80.1)	1526/1874 (81.4)
Diabetes	593/1869 (31.7)	536/1875 (28.6)
Hypercholesterolemia	1478/1869 (79.1)	1446/1875 (77.1)
Other	772/1868 (41.3)	756/1872 (40.4)
Current smoking — no./total no. (%)	234/1868 (12.5)	265/1877 (14.1)
Current alcohol use — no./total no. (%)	992/1876 (52.9)	961/1885 (51.0)
History of GI bleeding or ulcer — no./total no. (%)	78/1876 (4.2)	77/1885 (4.1)
Medications at study entry — no./total no. (%)		
Aspirin	1111/1876 (59.2)	1119/1885 (59.4)
Statin	1274/1876 (67.9)	1254/1885 (66.5)
Clopidogrel	1300/1876 (69.3)	1300/1885 (69.0)

* ACS denotes acute coronary syndrome, GI gastrointestinal, MI myocardial infarction, NSAID nonsteroidal antiinflammatory drug, PAD peripheral artery disease, and PCI percutaneous coronary intervention.
† Data for age were missing for two patients in the omeprazole group and for one patient in the placebo group.
‡ Race was reported by the investigator.
§ Data for the body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 35 patients in the omeprazole group and for 34 patients in the placebo group.

with omeprazole at 180 days after randomization (P<0.001 by the log-rank test) (Fig. 1). The hazard ratio derived from the Cox model was 0.34 (95% confidence interval [CI], 0.18 to 0.63; P<0.001). There were no significant interactions among subgroups or according to the stratification variables: presence versus absence of *H. pylori* (P=0.47 for interaction) and use versus nonuse of an NSAID (P=0.97 for interaction) (Fig. 2 in the Supplementary Appendix). There was a borderline significant interaction on the basis of sex (P=0.05 for interaction).

Event rates for individual components of the composite gastrointestinal end point are listed in Table 2. Significant differences were seen between the omeprazole group and the placebo group with regard to overt gastroduodenal bleeding (hazard ratio with omeprazole, 0.12) and overt upper gastrointestinal bleeding of unknown origin (hazard ratio, 0.13). The rate of the composite end point of overall (overt and occult) clinical gastrointestinal bleeding was also reduced with omeprazole as compared with placebo (hazard ratio, 0.30; 95% CI, 0.13 to 0.66; P=0.001), as was the rate of the composite end point of overt gastroduodenal bleeding or overt upper gastrointestinal bleeding of unknown origin: from 1.2% in the placebo group (occurring in 15 of 1885 patients) to 0.2% (occurring in 2 of 1876 patients) (hazard ratio with omeprazole, 0.13; 95% CI, 0.03 to 0.56; P=0.001). The number of patients who would need to be treated for 6 months to prevent one occurrence of an event that was part of the primary gastrointestinal end point was 55, and the number needed to treat to prevent one occurrence of overt gastrointestinal bleeding was 98. There was also a significant reduction in the number of patients with investigator-defined gastrointestinal events with omeprazole (39 patients) as compared with placebo (68 patients) (hazard ratio with omeprazole, 0.57; 95% CI, 0.38 to 0.84; P=0.005). The rate of symptoms of gastroesophageal reflux disease at 180 days was 0.2% in the omeprazole group and 1.2% in the placebo group (hazard ratio, 0.22; 95% CI, 0.06 to 0.79; P=0.01). There was one case of gastrointestinal obstruction in each of the two groups, with no perforations in either group.

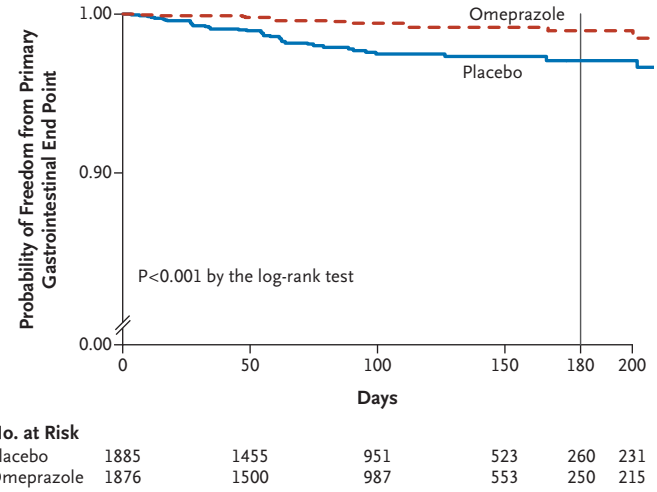

Figure 1. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Gastrointestinal Events, According to Study Group.

The event rate for the primary gastrointestinal end point at day 180 was 1.1% in the omeprazole group and 2.9% in the placebo group.

CARDIOVASCULAR AND OTHER OUTCOMES

There were 109 adjudicated cardiovascular events (54 in the placebo group and 55 in the omeprazole group), with no significant difference in the rate of the primary cardiovascular end point between the two groups (P=0.98 by the log-rank test) (Fig. 2). The event rate at 180 days after randomization was 5.7% in the placebo group and 4.9% in the omeprazole group (hazard ratio with omeprazole, 0.99; 95% CI, 0.68 to 1.44; P=0.96).

Analysis of subgroups of patients with various forms of vascular disease, including previous myocardial infarction, did not show significant heterogeneity (Fig. 3 in the Supplementary Appendix). Nor did the overall results differ significantly on the basis of serologic data regarding *H. pylori* or concomitant NSAID use (P=0.42 and P=0.68, respectively, for interaction). The rates of individual components of the cardiovascular end point did not differ significantly between the two groups (Tables 2 and 3). There were two cases of definite or probable stent thrombosis in the placebo group and none in the omeprazole group. No significant difference was found between the two groups in the number of patients with investigator-defined cardiovascular events with omeprazole (61 patients) as compared with placebo (58 patients) (hazard ratio with omeprazole, 1.03; 95% CI, 0.72 to 1.47; P=0.89).

The rate of adjudicated nongastrointestinal bleeding events did not differ significantly be-

Table 2. Event Rates for Primary Composite End Points and Their Individual Components at 180 Days after Randomization, According to Study Treatment.*

Event	Omeprazole (N=1876)	Placebo (N=1885)	Event Rate (95% CI)		Log-Rank P Value
			Omeprazole	Placebo	
	no. of patients with event				
Composite of GI events	13	38	1.1 (0.4–1.8)	2.9 (1.9–3.9)	<0.001
Overt gastroduodenal bleeding	1	8	0.1 (0.0–0.3)	0.6 (0.1–1.0)	0.03
Overt upper GI bleeding of unknown origin	1	7	0.1 (0.0–0.3)	0.6 (0.1–1.1)	0.03
Occult bleeding	6	11	0.6 (0.0–1.2)	0.8 (0.3–1.3)	0.21
GI pain with underlying multiple erosive diseases	3	8	0.2 (0.0–0.4)	0.7 (0.1–1.3)	0.05
Symptomatic gastroduodenal ulcer	2	6	0.1 (0.0–0.2)	0.2 (0.0–0.5)	0.27
Cardiovascular event	55	54	4.9 (3.4–6.4)	5.7 (4.0–7.3)	0.98
Myocardial infarction	14	15	1.2 (0.5–2.0)	1.5 (0.6–2.4)	0.83
Revascularization	42	45	4.0 (2.6–5.4)	4.6 (3.1–6.1)	0.70
Stroke	4	2	0.2 (0.0–0.5)	0.3 (0.0–0.7)	0.43
Death from cardiovascular causes	5	3	0.4 (0.0–0.7)	0.3 (0.0–0.8)	0.49
Death from any cause	5	5	0.4 (0.0–0.7)	0.5 (0.0–1.1)	1.00

* GI denotes gastrointestinal.

tween the omeprazole group (0.5%) and the placebo group (0.1%) (hazard ratio with omeprazole, 2.32; 95% CI, 0.60 to 8.98; P=0.21).

ADVERSE EVENTS

The rate of serious adverse events did not differ significantly between the two groups (10.1% with omeprazole and 9.4% with placebo, P=0.48), nor did the rate of overall adverse events (41.3% and 42.8%, respectively; P=0.33). Diarrhea was reported in 3.0% of patients receiving omeprazole, as compared with 1.8% of those receiving placebo (P=0.01). No patient had diarrhea caused by infection with *Clostridium difficile*. There were no newly diagnosed cases of osteoporosis. One case of peripheral neuropathy was reported in the placebo group. There were no significant differences between the two groups in the rates of pneumonia, headache, nausea, anemia, or fracture.

DISCUSSION

We found a significant reduction in the risk of gastrointestinal clinical events, including overt upper gastrointestinal bleeding, in patients receiving dual antiplatelet therapy who were randomly assigned to also receive a PPI. Furthermore, our prospective, double-blind, randomized trial did not show any significant increases in the risk of cardiovascular events with concomitant use of clopidogrel and omeprazole, a finding that was consistent even in high-risk subgroups and for individual end points. Although previous observational studies have yielded conflicting results in this regard, the current study reveals no signal of harm from concomitant clopidogrel and PPI use.

Gastrointestinal bleeding is an important potential complication of antithrombotic therapy. Previous randomized studies have shown that prophylactic use of PPIs and H_2-receptor antagonists reduces the risk of endoscopically ascertained ulcers in patients receiving aspirin.[13,14] These trials, however, have not been powered to evaluate clinical gastrointestinal events, nor have they assessed the potential benefit for patients receiving combination antiplatelet therapy. Trials showing the value of PPIs in preventing recur-

rent gastrointestinal bleeding have been conducted in populations at high risk for gastrointestinal bleeding.[17] Our trial, in which the study population was at least 10 times as large as those in previous randomized studies and was not selected to represent high-risk patients, showed a significant reduction in clinically manifested gastrointestinal bleeding events, including overt bleeding, with a PPI as compared with placebo. The number needed to treat would most likely be lower for a patient population at higher gastrointestinal risk than our study population.

Newer, more potent antiplatelet agents are entering the clinical arena.[35-40] Nevertheless, research into clopidogrel remains important, given that it has a wide range of uses and that the generic form is already available in certain parts of the world and may be more widely available relatively soon. In addition, studies with higher doses of clopidogrel are ongoing. Therefore, evaluation of possible drug interactions with clopidogrel remains important.

The fact that several (though not all) studies have shown that PPIs blunt the antiplatelet effect of clopidogrel, even though there does not appear to be any significant clinical interaction between the drugs, also calls into question the use of ex vivo antiplatelet testing to alter clinical therapy.[28] Ex vivo platelet assays have already been shown to be potentially misleading, particularly for assessing drug interactions. For example, initial concerns about ex vivo manifestations of clopidogrel–statin interactions were not borne out in clinical studies.[41,42] Further work in the evolving area of platelet-function assays is clearly necessary. The potential for observational studies to be misleading is also worth noting.

There are limitations to our analysis. First, since the trial was terminated prematurely, its power is limited, owing to a smaller number of events than had been anticipated. Second, because the confidence interval around the hazard ratio for cardiovascular events is wide, the absence of interaction between clopidogrel and omeprazole cannot be viewed as a definitive finding. Given that 94% of the population was white, the expected prevalence of homozygosity for the loss-of-function cytochrome P-450 gene *CYP2C19* was 2 to 3%, and in homozygous patients, PPIs may further reduce the level of the active metabolite of clopidogrel to a degree that does indeed blunt the effectiveness of clopidogrel. A much larger study involving genotyping would be necessary to determine whether this is the case. Nevertheless, with respect to the cardiovascular safety end point, a greater number of patients than initially planned were enrolled, and though the follow-up period was truncated, the risk of cardiovascular events would be expected to be greatest soon after the onset of an acute coronary syndrome or percutaneous coronary intervention. The absence of an effect on nongastrointestinal bleeding also supports the absence of an interaction between clopidogrel and omeprazole, since if PPIs diminish the antiplatelet effect of clopidogrel, they should also decrease the rate of nongastrointestinal bleeding.

An additional limitation of the study is that the single-pill formulation we used differs from generic omeprazole with respect to its release kinetics. Finally, this study was not designed to detect any differences among PPIs with respect to a possible interaction, though the PPI most commonly and consistently implicated in ex vivo studies has been omeprazole.[21,43]

In conclusion, our randomized assessment of PPIs versus placebo in patients with coronary artery disease who were receiving dual antiplate-

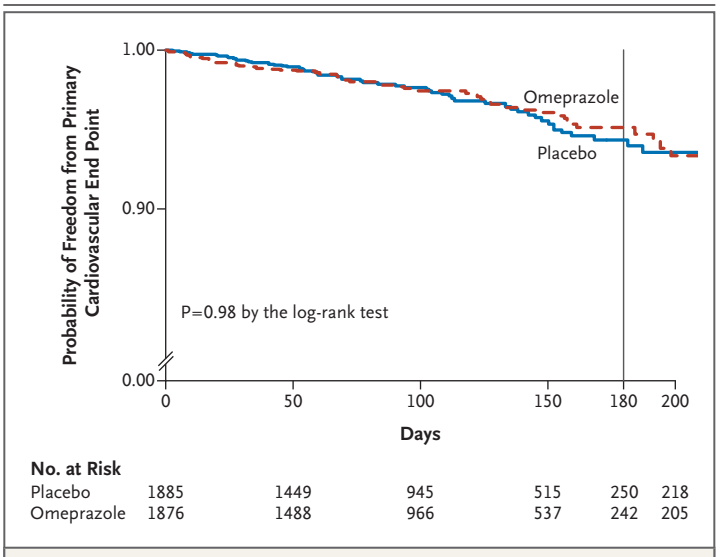

Figure 2. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Cardiovascular Events, According to Study Group.

The event rate for the primary cardiovascular end point at day 180 was 4.9% in the omeprazole group and 5.7% in the placebo group.

Table 3. Hazard Ratios for Treatment with Omeprazole, versus Placebo, from Cox Proportional-Hazards Modeling.

Event	Hazard Ratio (95% CI)	P Value
Composite of gastrointestinal events	0.34 (0.18–0.63)	<0.001
Composite of cardiovascular events	0.99 (0.68–1.44)	0.96
Myocardial infarction	0.92 (0.44–1.90)	0.81
Revascularization	0.91 (0.59–1.38)	0.64

let therapy provides reassurance that there is no clinically significant cardiovascular interaction between PPIs and clopidogrel, whereas there is a significant reduction in gastrointestinal bleeding with PPI use as compared with placebo. Further research will be necessary to determine the optimal approach to reducing the risk of gastrointestinal adverse events among patients receiving potent antithrombotic therapy, but prophylactic proton-pump inhibition appears to be promising.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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