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The effects of proton pump inhibition on patient-reported severity of dyspepsia when receiving dual anti-platelet therapy with clopidogrel and low-dose aspirin: Analysis from the

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Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT)

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Summary

Background—Dual antiplatelet therapy with clopidogrel and low-dose aspirin increases the risk for gastrointestinal clinical events. Omeprazole has been shown to significantly reduce these events without compromising cardiovascular safety in patients treated with dual antiplatelet therapy. Whether or not omeprazole improves patient-reported outcomes is undetermined.

Aim—To assess the impact of prophylactic omeprazole with background dual antiplatelet therapy on patient-reported symptoms of dyspepsia compared to placebo.

Methods—We analyzed results of the Severity of Dyspepsia Assessment questionnaires collected in the Clopidogrel and the Optimization of Gastrointestinal Events Trial.

Results—Patient reported outcome data from 3759 subjects were available for analysis. At 4 weeks, the mean scores of pain intensity and non-pain symptoms were lower in the omeprazole group (5.61 ± 0.17 vs. 6.40 ± 0.17 , $p < 0.001$, and 10.61 ± 0.07 vs. 11.00 ± 0.07 , $p < 0.001$, respectively). These differences were maintained at 24 weeks (5.91 ± 0.35 vs. 7.10 ± 0.37 , $p = 0.020$ for pain intensity; 10.36 ± 0.12 vs. 10.93 ± 0.13 , $p = 0.001$ for non-pain symptoms). After adjusting for

covariates there were no statistically significant differences between the groups in the percent of patients with dyspepsia during follow-up.

Conclusions—In addition to reducing the risk of gastrointestinal bleeding, statistically significant benefits with prophylactic omeprazole use on both pain and non-pain symptoms were evident at 4 weeks and sustained through 24 weeks. The clinical significance of these results is doubtful.

Keywords

dual antiplatelet therapy; omeprazole; patient reported outcomes; Severity of Dyspepsia Assessment questionnaire

Introduction

Dyspepsia is a common condition, affecting approximately 25% of the population(1, 2), and causing significant impairment of quality of life(3, 4). Dyspepsia can represent conditions such as peptic ulcer, gastroesophageal reflux disease (GERD), or stomach tumors, but the most common etiology is functional dyspepsia in which no evidence of structural disease is present(4-6). The Severity of Dyspepsia Assessment (SODA) questionnaire is a patient reported outcome tool which assesses dyspepsia symptoms. The tool has been reported to have good internal consistency, including in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs)(7, 8).

Low-dose aspirin may cause dyspepsia, ulcers, and gastrointestinal (GI) complications such as bleeding(9). An estimated 50 million Americans are taking low dose aspirin (325mg) daily. Pooled data estimate the absolute increase in risk per year of symptomatic or complicated ulcers with aspirin to be 0.12% when compared with placebo (number needed to harm833), and the use of enteric-coated or buffered formulations does not appear to reduce this risk(10, 11). The use of dual anti-platelet therapy (DAPT)with clopidogrel and low dose aspirin further increases the risk for serious clinical gastrointestinal events, and use of more potent antiplatelet agents results in even greater bleeding risk(12, 13). Aspirin therapy may lead to dyspepsia in 20%-40% of chronic users(14, 15), and dyspepsia is associated with reduced compliance(16, 17), increased healthcare costs(18) and reduced health-related quality of life(19). The magnitude of dyspepsia and the effect of proton-pump inhibitors in reducing it have not been thoroughly evaluated to date.

Despite its early termination, the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT, NCT00557921) is the only large scale randomized controlled study in which omeprazole was compared with placebo inpatients receiving DAPT. No significant difference in CV events was shown between the study groups (Hazard Ratio [HR] 0.99; 95% confidence interval [CI] 0.68-1.44), while a significant reduction in GI events occurred (HR 0.34; 95% CI 0.18-0.63)(20). The purpose of the current analysis of the COGENT data is to evaluate further the impact of omeprazoleon dyspepsia in patients treated with DAPT, as assessed by the SODA questionnaire. We also evaluated predictors of dyspepsia and for GI events in this population.

Methods

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, administered on background aspirin therapy. Randomization was stratified according to baseline *H. pylori* serology status and the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs). The study methodology has been previously described in detail(20).

Patients

Patients aged 21 years or older on clopidogrel therapy with concomitant aspirin anticipated for at least the next 12 months were eligible for inclusion. Major exclusion criteria included delayed hospital discharge, clinical indication for use of antacids; preexisting erosive esophagitis or esophageal or gastric variceal disease; previous non-endoscopic gastric surgery; receipt of clopidogrel or another thienopyridine for more than 21 days before randomization; receipt of oral anticoagulation, or recent fibrinolysis.

Endpoints

The primary gastrointestinal efficacy end point in the COGENT study 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 prespecified primary cardiovascular safety end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or ischemic stroke.

We assessed the SODA scores at 4 and 24 weeks and the change in SODA scores from baseline to 4 weeks (early response) and from baseline to 24 weeks (late response). The SODA assesses symptoms in three dimensions: pain intensity (6 items that ask patients to rate their abdominal discomfort over the past 7 days; range 2–47), non-pain related symptoms (7 items that ask patients on common symptoms of dyspepsia in the last 7 days; range 7–35), and satisfaction with dyspepsia-related health (4 items that assess the degree to which patients are satisfied with their levels of abdominal discomfort; range 2–23).

To assess the impact on clinical dyspepsia we primarily used a definition of an increase greater or equal to 10 points on the pain intensity component of the SODA instrument from baseline to 4 or 24 weeks. To test the robustness of this clinical assumption we assessed the impact of using different thresholds for the definition of dyspepsia on the outcome.

Statistical analysis

All randomized subjects were included in this analysis. Baseline characteristics and baseline SODA scores were compared between the two treatment groups using chi-square tests for discrete variables and t-tests for continuous variables.

SODA scores and change from baseline in SODA scores at the two follow-up time-points were compared between the two treatment groups using a mixed effects linear model. In view of observed trend towards lower pain intensity SODA scores in the omeprazole group at baseline, adjustment of follow-up SODA scores to baseline SODA scores was performed to account for the impact of differences in baseline SODA scores on follow-up scores. Baseline scores, treatment, time (operationalized as week 4 and week 24), and their interaction were included in the model as fixed effects. A random effect was included for the intercept. Treatment effect at week 4 and week 24 was estimated using estimate statements.

The potential modifying effect of baseline H. Pylori status was assessed at 4 and 24 weeks visits by estimating the treatment for each baseline H. Pylori status using a random intercept mixed effects model with time, treatment, baseline H. Pylori status and all interactions among these predictors as fixed effects.

Sensitivity analyses were conducted to assess the robustness of our results to missingness. The vast majority of missing data was due to early termination of the trial with only a very small proportion due to other reasons. The sensitivity analyses were carried out by utilizing the last observation carried forward (LOCF) approach and multiple imputation. With multiple imputation, each missing value in the response was replaced with a set of 10 imputed values. Multiple imputations were carried out separately for each time point (4 and 24 weeks), with baseline characteristics (listed in Table 1) included in each model.

We evaluated predictors for dyspepsia by using a logistic regression model and for the composite GI endpoint by using a Cox proportional regression model. SODA scores at baseline and other patient baseline characteristics (listed in Table 1) were selected in a step-wise approach using entry and stay levels of 0.2.

All statistical analyses were performed with SAS version 9.1.3 (SAS Institute Inc., Cary, NC).

Results

The COGENT study ended prematurely due to loss of sponsorship. The current analysis includes 3759 patients for whom data were available for analysis. The mean duration of follow-up was 110 and 107 days ($p=0.23$), with a maximum of 1090 and 840 days in the omeprazole and placebo groups, respectively. Baseline characteristics were largely similar between the groups, with the exception of diabetes mellitus status (31.7% in the omeprazole vs. 28.6% in the placebo groups, $p=0.038$). There were no statistically significant differences in SODA scores components between the omeprazole and placebo groups, but there was a trend toward higher pain intensity scores in the placebo group (5.76 ± 0.18 vs. 6.25 ± 0.18 , $p=0.053$; Table 1).

There were 55 adjudicated gastrointestinal events, with 47 patients having a single event and 4 patients having two events. Thirteen subjects were in omeprazole group and 38 were in placebo group, of whom 11 and 36 subjects experienced an event before 180 days. The cumulative KM estimates ($\pm$ SE) for the GI efficacy composite endpoint through 180 days were 1.01% ($\pm$ 0.36%) vs. 2.85% ($\pm$ 0.51%) in the omeprazole and placebo groups, respectively (log-rank p-value <0.001).

Compliance with the SODA score evaluation (evaluated per the number of SODA assessments divided by the number of patients with sufficient follow-up) was 97.66% (3671/3759), 97.08% (3353/3454) and 96.95% (954/984) at baseline, 4 weeks, and 24 weeks, respectively.

At 4 weeks both the mean ($\pm$ SE) pain intensity and mean ($\pm$ SE) non-pain symptoms were lower in the omeprazole group (5.61 ± 0.17 vs. 6.40 ± 0.17 , $p<0.001$, and 10.61 ± 0.07 vs. 11.00 ± 0.07 , $p<0.001$, respectively). These differences were maintained at 24 weeks (5.91 ± 0.35 vs. 7.10 ± 0.37 , $p=0.020$ for pain intensity; 10.36 ± 0.12 vs. 10.93 ± 0.13 , $p=0.001$ for non-pain symptoms). Changes in SODA scores from baseline to 4 and 24 weeks were significant for pain intensity and non-pain symptoms (Table 2a and Table 2b). There was no significant interaction between treatment and *H. pylori* status at enrollment in any of the SODA domains (Table 3). Only a minority of patients received non-aspirin NSAIDs at baseline, and thus further exploratory analyses of this subgroup were not pursued.

We evaluated the rate of clinical dyspepsia, defined as an increase of at least 10 points on the pain intensity component of the SODA instrument from baseline to 4 or 24 weeks. There was no significant difference between the omeprazole and placebo treated groups (10.8% [157/1454] vs. 12.0% [171/1426], respectively; $p=0.31$). We also assessed other thresholds for change in the pain-intensity score. We found no statistically significant difference between the groups for any of the thresholds (Figure 1).

In sensitivity analyses, differences between the groups at 24 weeks remained statistically significant after imputing for missing data using the LOCF approach, with favorable mean scores of pain and non-pain symptoms in the omeprazole group. With multiple imputations there were significantly favorable scores for omeprazole treatment in all SODA domains at 4 weeks and in the pain intensity and non-pain symptoms at 24 weeks (Appendix Table 1).

The only significant predictor for dyspepsia was age. Significant predictors for GI events were treatment, pain intensity at baseline and current smoking (Table 4).

Discussion

This analysis from the COGENT trial found statistically significant improvements in the pain and non-pain related dimensions of the SODA tool at 4 and 24 weeks with prophylactic omeprazole versus placebo in patients receiving DAPT who were not otherwise at high gastrointestinal risk. The impact of omeprazole on the percent of patients with dyspepsia did not reach statistical significance.

The answers in the SODA questionnaire undergo a series of numeric conversions before they are added up into a single value representing each of the 3 SODA categories. The increment in SODA scores is non-linear, and thus it is difficult to ascribe a quantitative clinical interpretation to it. Specifically, for the definition of clinical dyspepsia no clear and agreed upon threshold for change in SODA score has been set. However, the SODA questionnaire has been repeatedly shown to be able to measure a meaningful or clinically important change in a clinical state (“responsiveness”)(7, 8). Based on these reports, the clinical significance of the differences found between the omeprazole and control groups are doubtful.

With the caveats of data missingness, it seems that the addition of omeprazole to DAPT is perceived by patients to add significant value across pain intensity and non-pain symptoms domains. These findings are strengthened by the analyses of missing data, and depict added value to omeprazole treatment beyond the objective clinical findings from the primary COGENT publication.

Some modelling data already exist suggesting that proton pump inhibitor use and its related decrease in dyspepsia are associated with improvement in aspirin adherence(21). It is unclear from the results of our analysis whether or not the use of omeprazole indeed leads to decreased GI symptoms in a way that will potentially lead to better long term compliance with antiplatelet therapy. It is, however, suggested in our analysis that dyspepsia is associated with higher risk for GI events, a finding that strengthens the notion that dyspepsia should be regarded as a target for treatment.

Limitations

The current analysis is limited by the fact that the COGENT trial was terminated early and thus longer term data are unavailable. As reported, the compliance of patients with filling the SODA questionnaire was extremely high (in those patients seen at long term visits). Both this and the fact that missingness is related to study termination and can be regarded to as ‘at random’ largely alleviate the concerns of reporting bias. Our results were also validated with LOCF and multiple imputation techniques, and indeed were shown to be robust. A trend towards differences in SODA scores between groups at baseline is a potential concern but was addressed with proper statistical modelling.

Conclusions

The data presented suggest improvement in patients' perspective of the severity of their gastrointestinal symptoms, but the clinical implications of these changes are of unknown magnitude. These data combined with the primary outcome data from the COGENT trial provide additional insight into the decision on proton pump inhibition in patients who are treated with DAPT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Changes in Pain Intensity SODA Component

Percentage of patients with different changes in Pain Intensity scores. Negative changes denote a decrease in Pain Intensity scores at 4 or 24 weeks of follow-up compared to baseline (improvement), and positive changes denote an increase in Pain Intensity scores at 4 or 24 weeks (worse change of the two) of follow-up compared to baseline (decline).

Table 1
Baseline Characteristics

	Omeprazole (N=1875)	Placebo (N=1884)	p-value
Clinical Characteristics			
Age			
Mean±SD (N)	66.6±10.8 (1874)	66.6±10.9 (1880)	0.963
Median (IQ Range)	68.0 (60.0,74.0)	68.0 (60.0,74.0)	
Range (min,max)	(23.0,94.0)	(28.0,93.0)	
Male sex	66.9% (1254/1875)	69.5% (1308/1882)	0.085
White race	93.6% (1754/1873)	94.0% (1768/1881)	0.862
Body-mass			
Mean±SD (N)	29.2±5.5 (1857)	29.3±6.6 (1867)	0.657
Median (IQ Range)	28.3 (25.4,31.9)	28.3 (25.6,32.1)	
Range (min,max)	(14.4,71.1)	(16.8,202.9)	
Negative for H. Pylori	52.2% (979/1875)	51.7% (974/1884)	0.752
NSAID use	8.5% (160/1875)	8.7% (164/1884)	0.851
Cardiovascular history			
PCI	72.1% (1341/1860)	71.7% (1335/1863)	0.766
ACS	42.0% (781/1861)	42.6% (792/1860)	0.705
MI	30.4% (566/1862)	28.5% (531/1861)	0.212
PAD	12.0% (223/1863)	12.0% (223/1863)	1.000
Stroke	7.3% (136/1863)	8.1% (151/1863)	0.357
Other	49.1% (915/1862)	50.9% (948/1862)	0.279
Cardiovascular risk factors			
Hypertension	80.1% (1496/1868)	81.4% (1526/1874)	0.297
Diabetes	31.7% (592/1868)	28.6% (536/1875)	0.038
Hypercholesterolemia	79.1% (1477/1868)	77.1% (1446/1875)	0.150
Other	41.3% (772/1867)	40.4% (756/1872)	0.548
Current smoking *	13.8% (256/1861)	15.3% (284/1857)	0.183
Current alcohol use [†]	46.9% (875/1867)	48.8% (916/1877)	0.236
Follow-up days			
Mean±SD (N)	110.3±80.0 (1875)	107.3±76.3 (1884)	0.234
Median (IQ Range)	110.0 (56.0,168.0)	109.0 (55.0,167.0)	
Range (min,max)	(0.0,1090.0)	(0.0,840.0)	
Baseline SODA scores			
Pain Intensity			
Mean±SE (N)	5.76±0.18(1611)	6.25±0.18(1621)	0.053
Median (IQ Range)	2.00 (2.00,6.00)	2.00 (2.00,9.00)	
Range (min,max)	(2.00,37.00)	(2.00,37.00)	
Non-Pain Symptom			
Mean±SE (N)	10.94±0.08(1822)	10.85±0.08(1847)	0.452
Median (IQ Range)	10.00 (7.00,13.00)	10.00 (7.00,13.00)	

	Omeprazole (N=1875)	Placebo (N=1884)	p-value
Range (min,max)	(7.00,24.00)	(7.00,26.00)	
Satisfaction			
Mean±SE (N)	17.83±0.12(1824)	17.73±0.12(1847)	0.575
Median (IQ Range)	20.00 (12.00,23.00)	20.00 (11.00,23.00)	
Range (min,max)	(2.00,23.00)	(2.00,23.00)	

*The numerator includes patients who are currently using cigarettes, cigars, pipe or chewing tobacco.

†The numerator includes patients who are currently having < 1 drink weekly, 1-2 drinks weekly, 1 drink on most days, 2 drinks on most days, three or more drinks on most days, or having drinks occasionally.

Table 2a
Follow-up SODA Scores*

SODA scores	Omeprazole (N=1875)	Placebo (N=1884)	Difference 95% CI	p-value
At Week 4				
Pain Intensity				
Mean±SE (N)	5.61±0.17(1547)	6.40±0.17(1523)	-0.79[-1.26,-0.31]	0.001
Median (IQ Range)	2.00 (2.00,6.00)	2.00 (2.00,9.00)		
Range (min,max)	(2.00,44.00)	(2.00,47.00)		
Non-Pain Symptom				
Mean±SE (N)	10.61±0.07(1691)	11.00±0.07(1659)	-0.39[-0.58,-0.19]	<.001
Median (IQ Range)	10.00 (7.00,13.00)	10.00 (7.00,13.00)		
Range (min,max)	(7.00,26.00)	(7.00,29.00)		
Satisfaction				
Mean±SE (N)	18.61±0.11(1692)	18.31±0.11(1660)	0.29[-0.01,0.60]	0.062
Median (IQ Range)	23.00 (14.00,23.00)	20.00 (13.00,23.00)		
Range (min,max)	(2.00,23.00)	(2.00,23.00)		
At Week 24				
Pain Intensity				
Mean±SE (N)	5.91±0.35(482)	7.10±0.37(472)	-1.19[-2.19,-0.19]	0.020
Median (IQ Range)	2.00 (2.00,6.00)	2.00 (2.00,9.00)		
Range (min,max)	(2.00,37.00)	(2.00,37.00)		
Non-Pain Symptom				
Mean±SE (N)	10.36±0.12(480)	10.93±0.13(471)	-0.57[-0.92,-0.23]	0.001
Median (IQ Range)	10.00 (7.00,13.00)	10.00 (7.00,13.00)		
Range (min,max)	(7.00,26.00)	(7.00,24.00)		
Satisfaction				
Mean±SE (N)	20.89±0.21(482)	20.67±0.21(472)	0.22[-0.35,0.80]	0.447
Median (IQ Range)	23.00 (17.00,23.00)	23.00 (17.00,23.00)		
Range (min,max)	(2.00,23.00)	(2.00,23.00)		

* Least Squares Means estimates (Mean±SE) are presented in this table based on a model using SODA scores as outcome

Table 2b
Baseline Difference Follow-up SODA Scores*

Baseline Difference in SODA scores	Omeprazole (N=1875)	Placebo (N=1884)	Difference 95% CI	p-value
To Week 4				
Pain Intensity				
Mean±SE (N)	-0.45±0.17(1434)	0.34±0.17(1417)	-0.79[-1.26,-0.31]	0.001
Median (IQ Range)	0.00 (0.00,0.00)	0.00 (0.00,0.00)		
Range (min,max)	(-32.00,42.00)	(-29.00,39.00)		
Non-Pain Symptom				
Mean±SE (N)	-0.28±0.07(1653)	0.11±0.07(1637)	-0.39[-0.58,-0.19]	<.001
Median (IQ Range)	0.00 (-2.00,1.00)	0.00 (-1.00,2.00)		
Range (min,max)	(-12.00,15.00)	(-13.00,14.00)		
Satisfaction				
Mean±SE (N)	0.82±0.11(1656)	0.53±0.11(1638)	0.29[-0.01,0.60]	0.062
Median (IQ Range)	0.00 (0.00,3.00)	0.00 (0.00,2.00)		
Range (min,max)	(-21.00,16.00)	(-21.00,21.00)		
To Week 24				
Pain Intensity				
Mean±SE (N)	-0.15±0.35(295)	1.04±0.37(270)	-1.19[-2.19,-0.19]	0.020
Median (IQ Range)	0.00 (0.00,0.00)	0.00 (0.00,0.00)		
Range (min,max)	(-32.00,26.00)	(-29.00,35.00)		
Non-Pain Symptom				
Mean±SE (N)	-0.53±0.12(473)	0.04±0.13(468)	-0.57[-0.92,-0.23]	0.001
Median (IQ Range)	0.00 (-3.00,1.00)	0.00 (-2.00,2.00)		
Range (min,max)	(-15.00,10.00)	(-13.00,15.00)		
Satisfaction				
Mean±SE (N)	3.11±0.21(475)	2.89±0.21(469)	0.22[-0.35,0.80]	0.447
Median (IQ Range)	3.00 (0.00,12.00)	3.00 (0.00,12.00)		
Range (min,max)	(-18.00,21.00)	(-15.00,18.00)		

* Least Squares Means estimates (Mean±SE) are presented in this table based on a model using difference in SODA scores from baseline as outcome. In these models we adjusted for the baseline values of the SODA scores.

Table 3
SODA Scores According to Baseline H. Pylori Status*

SODA scores	Omeprazole (N=1875)	Placebo (N=1884)	Difference 95% CI	p-value
At Week 4				
Pain Intensity				
Positive/intermediate H.Pylori	5.86±0.24(749)	6.39±0.25(769)	-0.53[-1.20,0.15]	0.127
Negative H.Pylori	5.36±0.24(798)	6.41±0.24(754)	-1.05[-1.71,-0.38]	0.002
Difference between H. Pylori groups and p-value for interaction			0.52[-0.43,1.47]	0.281
Non Pain Symptom				
Positive/intermediate H.Pylori	10.55±0.10(791)	10.88±0.10(807)	-0.33[-0.61,-0.05]	0.023
Negative H.Pylori	10.66±0.10(900)	11.10±0.10(852)	-0.45[-0.72,-0.18]	0.001
Difference between H. Pylori groups and p-value for interaction			0.12[-0.27,0.51]	0.541
Satisfaction				
Positive/intermediate H.Pylori	18.78±0.16(791)	18.42±0.16(807)	0.36[-0.09,0.80]	0.117
Negative H.Pylori	18.45±0.15(901)	18.21±0.16(853)	0.25[-0.18,0.67]	0.259
Difference between H. Pylori groups and p-value for interaction			0.11[-0.51,0.73]	0.726
At Week 24				
Pain Intensity				
Positive/intermediate H.Pylori	6.00±0.45(159)	7.05±0.48(172)	-1.04[-2.33,0.24]	0.111
Negative H.Pylori	5.82±0.57(323)	7.18±0.58(300)	-1.36[-2.96,0.23]	0.094
Difference between H. Pylori groups and p-value for interaction			0.32[-1.73,2.37]	0.760
Non Pain Symptom				
Positive/intermediate H.Pylori	10.31±0.21(159)	11.06±0.21(172)	-0.76[-1.34,-0.17]	0.011
Negative H.Pylori	10.39±0.15(321)	10.87±0.16(299)	-0.48[-0.91,-0.05]	0.029
Difference between H. Pylori groups and p-value for interaction			-0.28[-1.00,0.45]	0.456
Satisfaction				
Positive/intermediate H.Pylori	20.79±0.36(159)	20.30±0.34(172)	0.49[-0.49,1.47]	0.324
Negative H.Pylori	20.94±0.25(323)	20.88±0.26(300)	0.06[-0.65,0.77]	0.868
Difference between H. Pylori groups and p-value for interaction			0.43[-0.78,1.64]	0.485

* Least squares means based on a random intercept mixed effects model are presented in this table in Mean±SE

Table 4
Selected Predictors for the Dyspepsia and for Composite of GI events

Predictors for dyspepsia	OR	95% CI for OR	P value
Age	0.984	[0.974,0.995]	0.0028
NSAID use	1.337	[0.921,1.941]	0.1265
Predictor for GI endpoint	HR	95% CI for HR	P value
Pain Intensity at Baseline	1.042	1.0071.077	0.0173
Treatment (Omeprazole vs Placebo)	0.240	0.1160.500	0.0001
Age	1.025	0.9941.056	0.1131
BMI	0.953	0.8951.015	0.1348
Current Smoking	2.175	1.0674.436	0.0325

Predictors for dyspepsia were evaluated by using a logistic regression model and predictors for the composite GI endpoint were evaluated by using a Cox proportional regression model.

BMI: body mass index; CI: confidence interval; HR: hazard ratio; NSAID: non-steroidal anti-inflammatory drugs; OR: odds ratio.