The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 22, 2018 VOL. 378 NO. 12

Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer

Il Ju Choi, M.D., Ph.D., Myeong-Cherl Kook, M.D., Ph.D., Young-Il Kim, M.D., Soo-Jeong Cho, M.D., Ph.D., Jong Yeul Lee, M.D., Chan Gyoo Kim, M.D., Ph.D., Boram Park, M.S., and Byung-Ho Nam, Ph.D.

ABSTRACT

BACKGROUND

Patients with early gastric cancers that are limited to gastric mucosa or submucosa usually have an advanced loss of mucosal glandular tissue (glandular atrophy) and are at high risk for subsequent (metachronous) development of new gastric cancer. The long-term effects of treatment to eradicate *Helicobacter pylori* on histologic improvement and the prevention of metachronous gastric cancer remain unclear.

METHODS

In this prospective, double-blind, placebo-controlled, randomized trial, we assigned 470 patients who had undergone endoscopic resection of early gastric cancer or high-grade adenoma to receive either *H. pylori* eradication therapy with antibiotics or placebo. Two primary outcomes were the incidence of metachronous gastric cancer detected on endoscopy performed at the 1-year follow-up or later and improvement from baseline in the grade of glandular atrophy in the gastric corpus lesser curvature at the 3-year follow-up.

RESULTS

A total of 396 patients were included in the modified intention-to-treat analysis population (194 in the treatment group and 202 in placebo group). During a median follow-up of 5.9 years, metachronous gastric cancer developed in 14 patients (7.2%) in the treatment group and in 27 patients (13.4%) in the placebo group (hazard ratio in the treatment group, 0.50; 95% confidence interval, 0.26 to 0.94; P=0.03). Among the 327 patients in the subgroup that underwent histologic analysis, improvement from baseline in the atrophy grade at the gastric corpus lesser curvature was observed in 48.4% of the patients in the treatment group and in 15.0% of those in the placebo group (P<0.001). There were no serious adverse events; mild adverse events were more common in the treatment group (42.0% vs. 10.2%, P<0.001).

CONCLUSIONS

Patients with early gastric cancer who received *H. pylori* treatment had lower rates of metachronous gastric cancer and more improvement from baseline in the grade of gastric corpus atrophy than patients who received placebo. (Funded by the National Cancer Center, South Korea; ClinicalTrials.gov number, NCT02407119.)

From the Center for Gastric Cancer (I.J.C., M.-C.K., Y.-I.K., S.-J.C., J.Y.L., C.G.K.) and the Biometrics Research Branch, Research Institute (B.P., B.-H.N.), National Cancer Center, Goyang, South Korea. Address reprint requests to Dr. Choi at the Center for Gastric Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, South Korea, or at cij1224@ncc.re.kr.

N Engl J Med 2018;378:1085-95.
DOI: 10.1056/NEJMoa1708423

A Quick Take is available at NEJM.org

The World Health Organization (WHO) categorized *Helicobacter pylori* as a group I carcinogen for gastric cancer in 1994 on the basis of observational studies.[1-3] In 2000, a study showed a preventive effect of *H. pylori* treatment on gastric cancer in Mongolian gerbils.[4] However, the level of evidence that *H. pylori* eradication reduces the risk of gastric cancer is considered to be low, and screening and treatment of asymptomatic persons who test positive for *H. pylori* is not yet recommended,[5,6] possibly owing to a lack of evidence from large studies and to limited long-term follow-up.[7-9]

In South Korea, a screening program for gastric cancer (which has been the most prevalent malignant neoplasm in the country) has allowed for early detection and has reduced mortality from this disease.[10] Endoscopic resection is indicated for early gastric cancers that are not at risk for lymph-node metastasis.[11-13] Because endoscopic resection preserves the stomach, metachronous gastric cancers can develop, with an incidence of approximately 3% per year.[14] In a nonrandomized study, Uemura et al.[15] suggested that *H. pylori* eradication inhibits new cancer development after endoscopic treatment of early gastric cancer. However, two subsequent open-label trials reported inconsistent conclusions in this population.[16,17] Although meta-analyses, including retrospective studies, have suggested preventive effects of *H. pylori* treatment,[18] long-term observational studies have shown a high incidence of metachronous cancer even after *H. pylori* eradication.[14,19]

Patients with gastric cancer usually have advanced precancerous changes in gastric mucosa, including glandular atrophy and intestinal metaplasia, on histologic analysis.[20] The "point of no return" concept suggests that new gastric cancers can occur after eradication of *H. pylori* if histologic changes are already advanced.[21,22] However, there are conflicting results from randomized trials regarding the effectiveness of *H. pylori* treatment in healthy persons without precancerous changes[9] and in older persons with advanced histologic changes.[23]

Our trial was designed to evaluate whether *H. pylori* treatment prevents metachronous cancer and decreases histologic changes in patients with early gastric cancer.

Methods

Trial Oversight

We conducted a single-center, double-blind, randomized, placebo-controlled trial at the National Cancer Center in South Korea. All the patients provided written informed consent before enrollment. The trial was approved by the institutional review board at the National Cancer Center and was conducted in accordance with the provisions of the Declaration of Helsinki.[24] An independent data and safety monitoring board reviewed the progress of the trial.

The trial was designed by the lead author and supported by grants provided by the National Cancer Center. The trial investigators collected and analyzed the data. All the authors vouch for the accuracy and completeness of the data and analyses and for the adherence of the trial to the protocol (available with the full text of this article at NEJM.org). The first draft of the manuscript was written by the first author with assistance from the coauthors; all the authors made the decision to submit the manuscript for publication. The trial was not registered until all the patients had been enrolled because registration was not mandated until after the trial had started.

Patients

Patients between the ages of 18 and 75 years were eligible if they had histologically differentiated early gastric cancer or high-grade adenoma, as confirmed on endoscopic biopsy, and were scheduled for endoscopic resection. Major inclusion criteria included current *H. pylori* infection, endoscopic localization of a mucosal tumor without ulceration, and no lymph-node or distant-organ metastasis on computed tomography. Exclusion criteria included recurrent gastric cancer, previous *H. pylori* eradication treatment, histologic types of poorly differentiated tubular adenocarcinoma or signet-ring-cell carcinoma, a history of serious side effects associated with antibiotic therapy, the need for additional surgical resection after endoscopic resection,[11] and cancer of another organ within 5 years before enrollment.

Trial Design and Treatment

Before endoscopic resection, patients were randomly assigned in a 1:1 ratio to receive either *H. pylori* eradication therapy or placebo. The strati-

fication factor was the severity of the baseline grade of histologic atrophy at the antrum. Computer-generated randomization was performed in a blinded manner, with status concealed from all the patients and the primary physician, endoscopist, pathologist, and statistician. After randomization, endoscopic resection was performed as described previously.[25] The patients started the assigned trial medication within 1 week after endoscopic resection.

In the treatment group, amoxicillin (1000 mg), clarithromycin (500 mg), and the proton-pump inhibitor rabeprazole (10 mg) were given twice daily for 7 days. In the placebo group, rabeprazole (10 mg) and placebo pills were administered. The proton-pump inhibitor was maintained in both groups for an additional 4 weeks to promote ulcer healing.

Participants underwent endoscopic evaluation at 3 months, 6 months, 1 year, and then every 6 months or 12 months until the last enrolled patient reached the 3-year follow-up. Data were censored at the last endoscopic examination for patients who were lost to follow-up or withdrew from the trial. For ethical reasons, quadruple therapy with a proton-pump inhibitor, bismuth, metronidazole, and tetracycline was provided for 10 days if *H. pylori* infection was detected at the closeout endoscopic examination, starting in September 2015.

ASSESSMENTS

Endoscopic biopsy specimens for histologic evaluation of glandular atrophy and intestinal metaplasia were obtained from the gastric antrum lesser, corpus lesser, and corpus greater curvature at baseline, at 3 months, and at 36 months after randomization. According to criteria of the updated Sydney System for the classification of gastritis,[26] glandular atrophy and intestinal metaplasia were scored as absent, mild, moderate, or marked (0, 1, 2, or 3, respectively).

H. pylori infection status was determined by a rapid urease test on samples obtained from the corpus greater curvature and by Wright–Giemsa staining of biopsy specimens from the three predefined sites. Any positive result defined *H. pylori* infection, except in the initial eligibility evaluation, which required at least two positive results.

The WHO classification system was used for histologic classification of gastric cancer.[27] Diagnostic criteria for adenoma and cancer were adopted from the Vienna classification,[28] which divides gastrointestinal epithelial lesions into five categories (with additional subcategories) as follows: category 1, no neoplasia or dysplasia; category 2, indefinite for neoplasia or dysplasia; category 3, noninvasive low-grade neoplasm; category 4, high-grade neoplasm; and category 5, invasive neoplasm (Table S1 in the Supplementary Appendix, available at NEJM.org). In our trial, category 4.3 (suspicion of invasive carcinoma) or higher was considered to be indicative of definite gastric cancer and categories 3 to 4.2 (carcinoma in situ) were considered to be adenomas.

OUTCOMES

The trial had two primary outcomes: the incidence of metachronous gastric cancer, which was defined as a gastric cancer detected on endoscopy at the 1-year follow-up or later, and the improvement from baseline of at least one grade of glandular atrophy at the corpus lesser curvature at the 3-year follow-up. Biopsy samples were evaluated by the study pathologist in a blinded manner.

Secondary outcomes included the incidence of metachronous adenoma and the overall survival rate. Overall survival was defined as the interval between the initiation of a trial medication and the date of death from any cause or June 30, 2016.

STATISTICAL ANALYSIS

We calculated the sample size using two primary outcome variables. For the first primary outcome of metachronous gastric cancer, we assumed that the annual incidence of this condition was 3%. We calculated that 180 patients in each trial group would provide a power of 80% to detect a hazard ratio of 0.50 in the treatment group, as compared with the placebo group, allowing for a 9-year accrual period and 3-year follow-up after the completion of enrollment. For the second primary outcome of histologic assessment, we calculated that 157 patients in each trial group would provide a power of 80% to determine a higher proportion of patients showing improvement of at least one grade of atrophy at the gastric corpus lesser curvature in the treatment group than in the placebo group (20% vs. 10%). We tested the two primary outcomes sequentially, as follows: the first primary outcome

was tested at a two-sided significance level of 0.05; if the between-group difference was significant, then the second primary outcome was tested at a two-sided significance level of 0.05. From the calculations for both primary outcomes, we chose the larger sample size of 180 patients in each group for the trial population. We allowed for a 15% initial dropout rate, owing to the requirement of an additional surgery for noncurative endoscopic resection, and a further 10% loss to follow-up, resulting in the enrollment of 235 patients in each group. An interim analysis was not planned.

All the analyses were performed on a modified intention-to-treat principle. To evaluate the first primary outcome, we used the Kaplan–Meier method to estimate the incidence curve for metachronous cancer and Cox proportional-hazard models to estimate hazard ratios and 95% confidence intervals. To investigate the second primary outcome, we used a binary logistic-regression model to calculate the odds ratio for histologic improvement from baseline. In addition, we used a z-test statistic to compare the number of cases of metachronous cancer divided by the total person-time accumulated. All statistical analyses were performed with the use of SAS software (version 9.4) and R software (version 3.3.0).

RESULTS

PATIENTS

Of the 1350 patients who were screened from August 2003 through March 2013, a total of 470 patients underwent randomization (Fig. 1). Of these patients, 396 were included in the modified intention-to-treat population (194 in the treatment group and 202 in the placebo group) after the exclusion of 74 patients, including 60 who underwent additional surgery after endoscopic resection, 9 who did not receive a trial medication, and 5 who did not meet other eligibility requirements. Demographic and tumor characteristics were similar in the two groups (Table 1, and Table S2 in the Supplementary Appendix). We included 327 patients who had undergone endoscopic biopsy at the 3-year follow-up in the histologic analysis.

The closeout time for primary outcome follow-up was from September 2015 through June 2016. The median duration of follow-up was 5.9 years (interquartile range, 4.0 to 8.2 years; maximum, 12.9 years).

PRIMARY OUTCOMES

The two primary outcomes were sequentially analyzed. In the first primary outcome analysis, during a median follow-up of 5.9 years, metachronous gastric cancer developed in 14 of 194 patients (7.2%) in the treatment group and in 27 of 202 patients (13.4%) in the placebo group (hazard ratio in the treatment group, 0.50; 95% confidence interval [CI], 0.26 to 0.94; P=0.03) (Fig. 2). A comparison of the characteristics of the patients with metachronous gastric cancer showed that the mean age of the patient at diagnosis was younger and surgical treatment was more commonly performed in the placebo group than in the treatment group (Table S3 in the Supplementary Appendix).

Because the between-group difference for the first primary outcome was significant, the second primary outcome was analyzed in the 327 patients who had biopsy specimens at the 3-year follow-up (Fig. 1). The proportion of patients who had an improved grade of atrophy in the corpus lesser curvature was higher in the treatment group than in the placebo group (48.4% vs. 15.0%, P<0.001) (Table 2). The odds ratio for such improvement was 5.30 (95% CI, 3.08 to 9.13) in the treatment group as compared with the placebo group.

In addition, the proportion of patients who had an improved grade of intestinal metaplasia at the same site was also higher in the treatment group than in the placebo group (36.6% vs. 18.3%, P<0.001). However, no significant difference in grade was found for either glandular atrophy or intestinal metaplasia at the antrum. These results were similar in the analysis of the worst-case scenario performed in the 396 patients in the modified intention-to-treat population in which those with missing values were considered to have no improvement (Table S4 in the Supplementary Appendix).

SECONDARY OUTCOMES

During follow-up, metachronous gastric adenomas developed in 16 patients in the treatment group and in 17 in the placebo group, so *H. pylori* treatment did not reduce the incidence of metachronous adenoma (Fig. S1 in the Supplementary

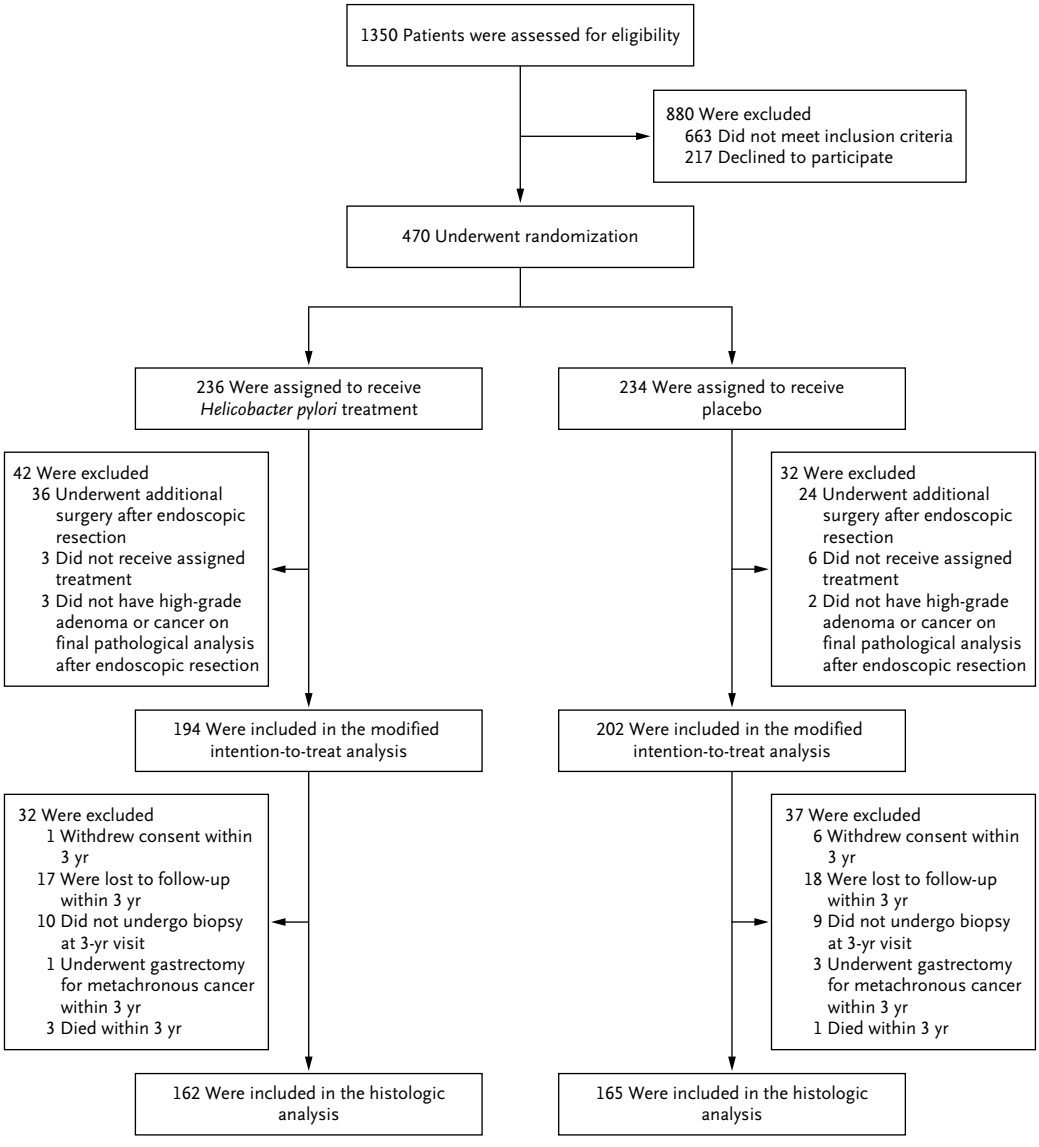

Figure 1. Enrollment, Randomization, and Follow-up.

The incidence of metachronous gastric cancer at the 1-year follow-up or later (the first primary outcome) was evaluated in the modified intention-to-treat population. For the second primary outcome of improvement from baseline in the grade of glandular atrophy in the gastric corpus lesser curvature at the 3-year follow-up, only patients with biopsy specimens obtained at the 3-year follow-up were included in the histologic analysis.

Appendix). Characteristics of the metachronous adenomas are provided in Table S5 in the Supplementary Appendix.

Death from any cause was reported in 11 patients in the treatment group and in 6 in the placebo group (hazard ratio, 1.95; 95% CI, 0.72 to 5.27; P=0.19) (Fig. S2 in the Supplementary Appendix). In the treatment group, 1 patient died from gastric cancer, 6 from other organ cancers, and 4 from causes other than cancer. In the placebo group, 1 patient died from gastric cancer, 1 from colon cancer, and 4 from causes other than cancer (Table S6 in the Supplementary Appendix).

Table 1. Characteristics of the Patients and Tumors at Baseline.*

Characteristic	Modified Intention-to-Treat Population		Histologic-Analysis Population	
	H. pylori Treatment (N=194)	Placebo (N=202)	*H. pylori* Treatment (N=162)	Placebo (N=165)
Age — yr	59.7±8.9	59.9±8.6	59.7±8.6	59.3±8.6
Male sex — no. (%)	141 (72.7)	157 (77.7)	118 (72.8)	128 (77.6)
Family history of gastric cancer — no. (%)†	38 (19.6)	39 (19.3)	34 (21.0)	35 (21.2)
Alcohol drinker — no. (%)	107 (55.2)	128 (63.4)	89 (54.9)	106 (64.2)
Smoker — no. (%)	80 (41.2)	76 (37.6)	65 (40.1)	67 (40.6)
Symptoms at presentation — no. (%)‡	35 (18.0)	45 (22.3)	33 (20.4)	37 (22.4)
Tumor size — cm	1.7±1.0	1.6±0.8	1.7±1.0	1.6±0.8
Tumor location — no. (%)§				
Upper	9 (4.6)	9 (4.5)	8 (4.9)	7 (4.2)
Middle	25 (12.9)	27 (13.4)	21 (13.0)	22 (13.3)
Lower	160 (82.5)	166 (82.2)	133 (82.1)	136 (82.4)
Tumor histologic classification — no. (%)¶				
High-grade adenoma	14 (7.2)	14 (6.9)	5 (3.1)	5 (3.0)
Papillary adenocarcinoma	1 (0.5)	1 (0.5)	1 (0.6)	1 (0.6)
Well-differentiated tubular adenocarcinoma	128 (66.0)	139 (68.8)	111 (68.5)	120 (72.7)
Moderately differentiated tubular adenocarcinoma	51 (26.3)	48 (23.8)	45 (27.8)	39 (23.6)
Tumor depth — no. (%)				
Mucosa	174 (89.7)	189 (93.6)	145 (89.5)	153 (92.7)
Submucosa	20 (10.3)	13 (6.4)	17 (10.5)	12 (7.3)
Initial synchronous tumor — no. (%)‖	14 (7.2)	13 (6.4)	11 (6.8)	12 (7.3)
Atrophy at corpus lesser curvature — no./total no. (%)**				
Absent	22/187 (11.8)	30/194 (15.5)	19/158 (12.0)	26/158 (16.5)
Mild	15/187 (8.0)	14/194 (7.2)	13/158 (8.2)	10/158 (6.3)
Moderate	20/187 (10.7)	14/194 (7.2)	18/158 (11.4)	12/158 (7.6)
Marked	130/187 (69.5)	136/194 (70.1)	108/158 (68.4)	110/158 (69.6)
Intestinal metaplasia at corpus lesser curvature — no./total no. (%)**				
Absent	47/192 (24.5)	51/201 (25.4)	41/161 (25.5)	40/164 (24.4)
Mild	40/192 (20.8)	41/201 (20.4)	34/161 (21.1)	35/164 (21.3)
Moderate	26/192 (13.5)	31/201 (15.4)	21/161 (13.0)	26/164 (15.9)
Marked	79/192 (41.1)	78/201 (38.8)	65/161 (40.4)	63/164 (38.4)

* Plus–minus values are means ±SD.
† A family history of gastric cancer was positive if the disease had been diagnosed in a first-degree relative.
‡ Symptoms included those associated with gastroesophageal reflux disease or mild dyspepsia not caused by an ulcer.
§ The tumor location was classified according to the Japanese classification of gastric carcinoma.
¶ The tumor histologic classification was determined according to the criteria of the World Health Organization.
‖ For the patients who had initial synchronous tumors, only the main tumor characteristics are listed. Priorities for the selection of the main tumor were tumor depth (submucosa invasion), tumor histologic classification (adenocarcinoma), and tumor size.
** Atrophy and intestinal metaplasia were evaluated with the use of the updated Sydney System. In some patients, the grade of atrophy or intestinal metaplasia could not be evaluated.

ANALYSIS ACCORDING TO *H. PYLORI* ERADICATION STATUS

Three months after the receipt of a trial medication, *H. pylori* had been successfully eradicated in 167 patients: 156 of 194 patients (80.4%) in the treatment group and in 11 of 202 patients (5.4%) in the placebo group. *H. pylori* infection was persistent in the remaining 228 patients (Table S7 in the Supplementary Appendix).

Of 41 cases of metachronous gastric cancer, 32 cases developed in 228 patients with persistent infection (14.0%) and 9 cases in 167 patients with eradicated infection (5.4%) at a median of 5.9 years of follow-up. The hazard ratio for the development of metachronous cancer in patients with eradicated infection was 0.32 (95% CI, 0.15 to 0.66; P=0.002) (Fig. 3). In addition, the incidence of metachronous gastric cancer was significantly lower in the group with eradicated infection than in the group with persistent infection (9.1 cases vs. 27.9 cases per 1000 person-years, P=0.003). A combined analysis of the development of metachronous gastric cancer according to the assigned trial group and *H. pylori* eradication status is shown in Figure S3 in the Supplementary Appendix.

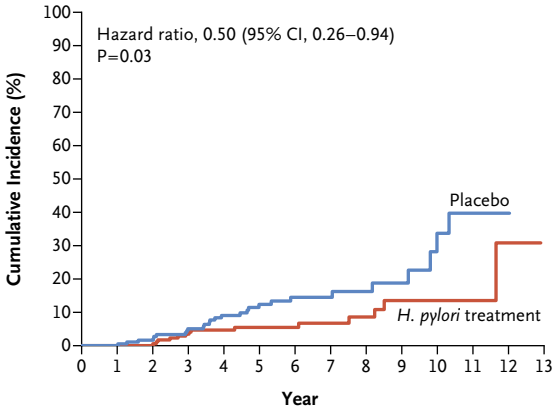

Figure 2. Kaplan–Meier Analysis of the Incidence of Metachronous Gastric Cancer.

Shown is the cumulative incidence of metachronous gastric cancer starting 1 year after endoscopic resection in the two trial groups. During a median follow-up of 5.9 years, metachronous gastric cancer developed in 14 of 194 patients (7.2%) in the treatment group and in 27 of 202 patients (13.4%) in the placebo group.

ADVERSE EVENTS

The safety analysis included the 427 patients who had undergone randomization and received at least one dose of a trial medication. Mild drug-related adverse events, including taste alteration, diarrhea, and dizziness, were more common in the treatment group than in the placebo group (42.0% vs. 10.2%, P<0.001) (Table S8 in the Supplementary Appendix). No serious adverse events were reported. There were no significant between-group differences in the number of patients for whom medications were prescribed to treat gastrointestinal symptoms during the follow-up period (Table S9 in the Supplementary Appendix).

DISCUSSION

In this prospective trial, the incidence of metachronous gastric cancer was approximately 50% lower among patients who had received treatment for *H. pylori* infection than among those who had received placebo. In addition, the proportion of patients with improvement in the grade of gastric corpus atrophy from baseline was significantly higher in the treatment group than in the placebo group at the 3-year follow-up. However, *H. pylori* treatment did not affect the incidence of adenoma or overall survival rates.

In a systematic review of articles involving high-risk groups of patients with gastric cancer, including those who had undergone endoscopic treatment, investigators based their findings mainly on retrospective cohort studies, with data showing a risk reduction of approximately 54% with *H. pylori* treatment.[29] In an open-label, randomized trial, Fukase et al.[16] reported significant risk reduction, with an odds ratio of 0.353 after *H. pylori* treatment. Choi et al.[17] (who are not part of our research group) also suggested the possibility of risk reduction with eradication therapy (17 metachronous cancers in the observation group vs. 10 in the eradication group), despite a negative conclusion due to lack of statistical significance (P=0.15). In our trial, the incidence of metachronous cancer was approximately 50% lower in the treatment group than in the placebo group, a finding that was consis-

Table 2. Improvement from Baseline in Grade of Atrophy and Intestinal Metaplasia at 3-Year Follow-up, According to Trial Group and *H. pylori* Status.*

Variable	Trial Group		Odds Ratio (95% CI)†	P Value	*H. pylori* Infection Status		Odds Ratio (95% CI)‡	P Value
	H. pylori Treatment (N=162)	Placebo (N=165)			Eradicated (N=140)	Persistent (N=187)		
	no./total no. (%)				*no./total no. (%)*			
Improvement in grade of glandular atrophy								
Antrum	39/151 (25.8)	30/160 (18.8)	1.51 (0.88–2.59)	0.13	36/132 (27.3)	33/179 (18.4)	1.66 (0.97–2.84)	0.06
Corpus lesser curvature§	76/157 (48.4)	23/153 (15.0)	5.30 (3.08–9.13)	<0.001	69/135 (51.1)	30/175 (17.1)	5.05 (3.01–8.48)	<0.001
Corpus greater curvature	38/155 (24.5)	25/158 (15.8)	1.73 (0.98–3.03)	0.06	36/133 (27.1)	27/180 (15.0)	2.10 (1.20–3.68)	0.009
Improvement in grade of intestinal metaplasia								
Antrum	42/160 (26.3)	38/164 (23.2)	1.18 (0.71–1.96)	0.52	39/139 (28.1)	41/185 (22.2)	1.37 (0.83–2.28)	0.22
Corpus lesser curvature	59/161 (36.6)	30/164 (18.3)	2.58 (1.55–4.30)	<0.001	55/139 (39.6)	34/186 (18.3)	2.93 (1.77–4.85)	<0.001
Corpus greater curvature	14/158 (8.9)	18/161 (11.2)	0.77 (0.37–1.61)	0.49	13/136 (9.6)	19/183 (10.4)	0.91 (0.43–1.92)	0.81

* Data for the histologic analyses were collected from 327 of the 396 trial patients. (Depending on the biopsy sites, some patients could not be evaluated for glandular atrophy or intestinal metaplasia.) An improvement in the grade of glandular atrophy or intestinal metaplasia was defined as a decrease from baseline in the grade at the 3-year follow-up.

† The odds ratio in this category was calculated by means of a binary logistic-regression model of data for patients who had received *H. pylori* treatment as compared with those who had received placebo.

‡ The odds ratio in this category was calculated by means of a binary logistic-regression model of data for patients in whom *H. pylori* infection had been eradicated as compared with those in whom *H. pylori* infection was persistent after receipt of the trial medication.

§ The second primary outcome was the improvement from baseline in the grade of glandular atrophy at the corpus lesser curvature.

tent with the results of previous systemic reviews and open-label trials.[16,17,29] An important advantage in our trial was a longer median follow-up duration than in the previous trials (5.9 years vs. ≤3 years). A retrospective cohort study showed that the preventive effect of *H. pylori* treatment on metachronous cancer disappeared after a follow-up duration of more than 5 years.[19] Our Kaplan–Meier plots for the incidence of metachronous cancer emphasize the importance of long-term follow-up, because incidence plots began to diverge 3 years after randomization.

Unlike previous trials,[16,17] we excluded patients with synchronous gastric cancers that were initially missed but detected within 1 year after treatment.[14] Kaplan–Meier plots in previous trials suggested that the overall differences in incidence may have been due to differences in the detection of synchronous cancers.[16,17] Although there is a possibility that small synchronous cancers grow slowly or regress after *H. pylori* treatment,[30] the hypotheses need to be tested. By comparing the characteristics of the metachronous cancers in our trial, we found that the cancers developed at a younger age and surgery was more frequently needed in the placebo group than in the treatment group. We speculate that persistent inflammation of gastric mucosa with *H. pylori* infection promotes carcinogenesis and also increases tumor growth or invasiveness.[31] *H. pylori* eradication reduces, but cannot completely abolish, the risk of metachronous gastric cancer. Thus, molecular markers, including aberrant methylation at specific genes, might help to identify high-risk patients even after successful eradication.[32]

Meta-analyses of histologic changes have shown that *H. pylori* eradication is correlated with improvements in the grade of glandular atrophy at the corpus, findings that are consistent with our results.[33,34] Our data also suggest possible improvement in the grade of intestinal metaplasia at the corpus. However, such improvement was not consistent with the findings of previous studies, possibly because of different observation periods or different levels of baseline histologic severity.[33-35]

H. pylori treatment did not affect the subsequent incidence of gastric adenoma or overall survival. In a small retrospective study, patients who received *H. pylori* eradication had a significantly lower risk of metachronous adenoma than those who did not receive such therapy (4.7% vs. 11.4%).[36] A meta-analysis of studies involving asymptomatic persons showed a risk of death that was 9% higher among the patients who had received *H. pylori* treatment than among those who had not.[37] The data suggest that an increased rate of death from causes not related to gastric cancer might overshadow reduced mortality from gastric cancer among patients receiving *H. pylori* treatment. However, in our trial, we did not find a significant between-group difference in the risk of death. In a previous trial, we found that *H. pylori* eradication in patients who had undergone subtotal gastrectomy for gastric cancer did not affect overall mortality.[38]

The hazard ratio for the incidence of metachronous gastric cancer in our trial (0.50) was higher than that in a previous trial (0.339).[16] One possible explanation is that our trial did not confirm *H. pylori* eradication and did not provide salvage treatment to patients in whom eradication had failed, for reasons of trial feasibility and maintenance of blinding. The treatment regimen in our trial was suboptimal because of prevalent resistance to clarithromycin in South Korea (20% or higher).[39] Our trial design, which anticipated

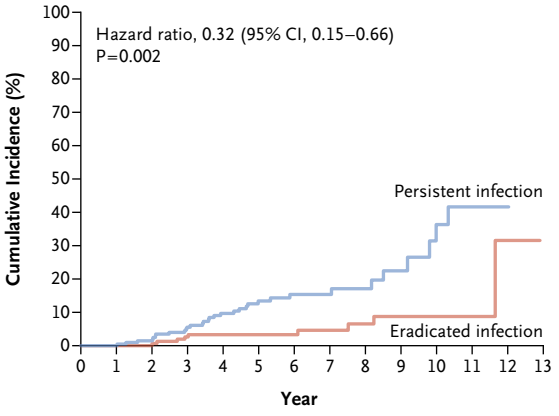

Figure 3. Kaplan–Meier Analysis of the Incidence of Metachronous Gastric Cancer, According to *H. pylori* Status after the Receipt of Trial Medication.

Shown is the cumulative incidence of metachronous gastric cancer starting 1 year after endoscopic resection, according to *H. pylori* status after the receipt of trial medication. At a median follow-up of 5.9 years, metachronous gastric cancer had developed in 32 of 228 patients (14.0%) with persistent *H. pylori* infection and in 9 of 167 patents (5.4%) with eradicated infection.

that *H. pylori* eradication would fail in 20% of the patients in the treatment group, might not have affected our conclusions, because the hazard ratio shifted to the null hypothesis that *H. pylori* therapy would not reduce the incidence of gastric cancer. Additional analysis regarding *H. pylori* status after treatment yielded a much lower hazard ratio (0.32). This hazard ratio may better reflect real-world situations, because salvage treatments are recommended in cases of eradication failure.[5,6]

Our trial has several limitations. First, it was conducted in a single center because endoscopic resection is a technically demanding procedure. However, our conclusions are related to the prevention of gastric cancer and may have implications for East Asian countries and other high-incidence regions. Second, patients with high-grade adenoma were included in our trial, because discrimination from well-differentiated tubular adenocarcinoma on endoscopic biopsy is difficult.[28] However, our primary outcome variable was limited to gastric adenocarcinomas. Finally, an ethical issue can be raised because our trial design included a placebo group. In South Korea, the National Health Insurance System was not providing coverage for *H. pylori* eradication after endoscopic treatment for early gastric cancer at the time that our trial was completed. In our trial, we evaluated *H. pylori* infection status at the last follow-up and provided salvage eradication therapy to patients who were still infected.

In conclusion, patients with early gastric cancer who received *H. pylori* treatment had a lower incidence of metachronous gastric cancer and more improvement from baseline in the grade of gastric glandular atrophy at the corpus than did patients who received placebo.

Supported by grants (0310050, 0410450, 0610080, 0910100, 1210230, 1310280, and 1610180) from the National Cancer Center, South Korea.

No potential conflict of interest relevant to this article was reported.

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

We thank the patients and their families for participating in the trial; members of the data and safety monitoring committee (Dong Ho Lee, Seoul National University Bundang Hospital; Jae Won Lee, Korea University; and Hye Seung Han, Konkuk University School of Medicine) for their advice; external pathologists (Joon Mee Kim, Inha University School of Medicine; Hee Sung Kim, Chung-Ang University School of Medicine; and Baek-Hui Kim, Korea University Guro Hospital, Korea University College of Medicine) for their consultation regarding pathological criteria; and Sang Gyun Kim of Seoul National University College of Medicine, Ho June Song of Asan Medical Center, University of Ulsan College of Medicine, and Eun Kyung Hong and Weon Seo Park of the National Cancer Center for their contributions to the conduct of the trial.

REFERENCES

1. Nomura A, Stemmermann GN, Chyou P-H, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991;325:1132-6.
2. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127-31.
3. Schistosomes, liver flukes and Helicobacter pylori: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum 1994; 61:1-241.
4. Shimizu N, Ikehara Y, Inada K, et al. Eradication diminishes enhancing effects of Helicobacter pylori infection on glandular stomach carcinogenesis in Mongolian gerbils. Cancer Res 2000;60:1512-4.
5. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol 2017;112:212-39.
6. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection — the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
7. Pan KF, Zhang L, Gerhard M, et al. A large randomised controlled intervention trial to prevent gastric cancer by eradication of Helicobacter pylori in Linqu County, China: baseline results and factors affecting the eradication. Gut 2016; 65:9-18.
8. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst 2012;104:488-92.
9. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187-94.
10. Jun JK, Choi KS, Lee HY, et al. Effectiveness of the Korean National Cancer Screening Program in reducing gastric cancer mortality. Gastroenterology 2017; 152(6:)1319-1328.e7.
11. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017; 20:1-19.
12. Lee JH, Kim JG, Jung HK, et al. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. J Gastric Cancer 2014;14:87-104.
13. Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016; 14:1286-312.
14. Mori G, Nakajima T, Asada K, et al. Incidence of and risk factors for metachronous gastric cancer after endoscopic resection and successful Helicobacter pylori eradication: results of a large-scale, multicenter cohort study in Japan. Gastric Cancer 2016;19:911-8.
15. Uemura N, Mukai T, Okamoto S, et al. Effect of Helicobacter pylori eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev 1997;6:639-42.
16. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008; 372:392-7.
17. Choi J, Kim SG, Yoon H, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gas-

tric carcinoma. Clin Gastroenterol Hepatol 2014;12(5):793-800.e1.
18. Yoon SB, Park JM, Lim CH, Cho YK, Choi MG. Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter 2014;19:243-8.
19. Maehata Y, Nakamura S, Fujisawa K, et al. Long-term effect of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. Gastrointest Endosc 2012;75:39-46.
20. Cho SJ, Choi IJ, Kook MC, et al. Staging of intestinal- and diffuse-type gastric cancers with the OLGA and OLGIM staging systems. Aliment Pharmacol Ther 2013;38:1292-302.
21. Correa P. Helicobacter pylori and gastric carcinogenesis. Am J Surg Pathol 1995; 19:Suppl 1:S37-S43.
22. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med 2002;347: 1175-86.
23. Li WQ, Ma JL, Zhang L, et al. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. J Natl Cancer Inst 2014;106: 106.
24. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
25. Lee JY, Choi IJ, Cho SJ, et al. Routine follow-up biopsies after complete endoscopic resection for early gastric cancer may be unnecessary. J Gastric Cancer 2012;12:88-98.
26. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis — the updated Sydney System: International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20:1161-81.
27. Hamilton SR, Aaltonen LA, eds. World Health Organization classification of tumours: pathology and genetics of tumours of the digestive system. Lyon, France: IARC Press, 2000.
28. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47:251-5.
29. Lee YC, Chiang TH, Chou CK, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016;150(5):1113-1124.e5.
30. Asaka M, Kato M, Graham DY. Prevention of gastric cancer by Helicobacter pylori eradication. Intern Med 2010;49: 633-6.
31. Chiba T, Marusawa H, Ushijima T. Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation. Gastroenterology 2012;143:550-63.
32. Asada K, Nakajima T, Shimazu T, et al. Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut 2015; 64:388-96.
33. Kong YJ, Yi HG, Dai JC, Wei MX. Histological changes of gastric mucosa after Helicobacter pylori eradication: a systematic review and meta-analysis. World J Gastroenterol 2014;20:5903-11.
34. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. The long-term impact of Helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. Helicobacter 2007;12: Suppl 2:32-8.
35. Murakami K, Kodama M, Nakagawa Y, Mizukami K, Okimoto T, Fujioka T. Long-term monitoring of gastric atrophy and intestinal metaplasia after Helicobacter pylori eradication. Clin J Gastroenterol 2012;5:247-50.
36. Chon I, Choi C, Shin CM, Park YS, Kim N, Lee DH. Effect of Helicobacter pylori eradication on subsequent dysplasia development after endoscopic resection of gastric dysplasia. Korean J Gastroenterol 2013;61:307-12.
37. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ 2014; 348:g3174.
38. Kim YI, Cho SJ, Lee JY, et al. Effect of Helicobacter pylori eradication on long-term survival after distal gastrectomy for gastric cancer. Cancer Res Treat 2016;48: 1020-9.
39. Lee SW, Kim HJ, Kim JG. Treatment of Helicobacter pylori infection in Korea: a systematic review and meta-analysis. J Korean Med Sci 2015;30:1001-9.