ORIGINAL ARTICLE

# Family History of Gastric Cancer and *Helicobacter pylori* Treatment

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## ABSTRACT

### BACKGROUND

*Helicobacter pylori* infection and a family history of gastric cancer are the main risk factors for gastric cancer. Whether treatment to eradicate *H. pylori* can reduce the risk of gastric cancer in persons with a family history of gastric cancer in first-degree relatives is unknown.

### METHODS

In this single-center, double-blind, placebo-controlled trial, we screened 3100 first-degree relatives of patients with gastric cancer. We randomly assigned 1838 participants with *H. pylori* infection to receive either eradication therapy (lansoprazole [30 mg], amoxicillin [1000 mg], and clarithromycin [500 mg], each taken twice daily for 7 days) or placebo. The primary outcome was development of gastric cancer. A prespecified secondary outcome was development of gastric cancer according to *H. pylori* eradication status, assessed during the follow-up period.

### RESULTS

A total of 1676 participants were included in the modified intention-to-treat population for the analysis of the primary outcome (832 in the treatment group and 844 in the placebo group). During a median follow-up of 9.2 years, gastric cancer developed in 10 participants (1.2%) in the treatment group and in 23 (2.7%) in the placebo group (hazard ratio, 0.45; 95% confidence interval [CI], 0.21 to 0.94; P=0.03 by log-rank test). Among the 10 participants in the treatment group in whom gastric cancer developed, 5 (50.0%) had persistent *H. pylori* infection. Gastric cancer developed in 0.8% of participants (5 of 608) in whom *H. pylori* infection was eradicated and in 2.9% of participants (28 of 979) who had persistent infection (hazard ratio, 0.27; 95% CI, 0.10 to 0.70). Adverse events were mild and were more common in the treatment group than in the placebo group (53.0% vs. 19.1%; P<0.001).

### CONCLUSIONS

Among persons with *H. pylori* infection who had a family history of gastric cancer in first-degree relatives, *H. pylori* eradication treatment reduced the risk of gastric cancer. (Funded by the National Cancer Center, South Korea; ClinicalTrials.gov number, NCT01678027.)

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*Helicobacter pylori* infection is a common bacterial infection of the human stomach that affects more than half the world population.[1] Two nested case–control studies conducted in the United States showed an association between *H. pylori* infection and gastric cancer.[2,3] A long-term observational study from Japan subsequently showed that gastric cancer developed only in patients with *H. pylori* infection who had various gastric diseases.[4] Our recent randomized trial involving patients with early gastric cancer (a population that usually has severe atrophic changes in the gastric mucosa) showed that treatment of *H. pylori* infection reduced the risk of metachronous gastric cancer by 50%.[5] Treatment of *H. pylori* infection in the general population to prevent gastric cancer is supported by moderate-quality evidence from a meta-analysis of six randomized trials that showed a relative risk of cancer of 0.66.[6] The working group report from the International Agency for Research on Cancer suggested that population-based screening and treatment for *H. pylori* infection should be tailored to local conditions, and further studies are required to investigate the feasibility, efficacy, and adverse consequences of this strategy.[7]

A family history of gastric cancer in a first-degree relative is associated with double to triple the risk of gastric cancer.[8] Patients with gastric cancer and their relatives share risk factors, including exposure to *H. pylori* in the environment and genetic features that may affect immune responses to *H. pylori* infection.[8-10] Family members of patients with gastric cancer have higher rates of *H. pylori* infection than persons in the general population, and the precancerous histologic changes in the gastric mucosa are more severe in these persons.[11-15] However, whether treatment of *H. pylori* infection can reduce the risk of gastric cancer is still unclear because of a lack of evidence from trials in primary prevention. Despite the uncertainty, regional and global consensus reports recommend treatment of *H. pylori* infection in the relatives of patients with gastric cancer.[16-18] In contrast, the American College of Gastroenterology clinical guideline published in 2017 made no recommendation regarding routine testing for and treatment of *H. pylori* infection in this high-risk group because of insufficient evidence.[19] We conducted a randomized trial to evaluate whether treatment of *H. pylori* infection reduces the risk of gastric cancer in first-degree relatives of patients with gastric cancer.

## Methods

### Trial Design and Oversight

This single-center, double-blind, placebo-controlled, randomized trial was conducted at the National Cancer Center in South Korea. The institutional review board at the National Cancer Center approved the trial protocol (available with the full text of this article at NEJM.org), and all participants provided written informed consent before enrollment. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. An independent data and safety monitoring board oversaw the progress and safety of the trial. The trial was not registered until all participants had been enrolled because at the time the trial was initiated, registration was not mandatory. The registration of the trial was delayed further because of an administrative error. The authors verify that no change was made to the trial design, the sample size, or the definition of the primary outcome from the initiation of the protocol to the time the trial was registered. Further details are available in the Supplementary Appendix, available at NEJM.org.

### Participants

Participants were eligible if they were 40 to 65 years of age and if they had confirmed *H. pylori* infection and at least one first-degree relative with gastric cancer whose diagnosis had been histologically confirmed at the National Cancer Center or one of the other referral hospitals in South Korea. Key exclusion criteria were a history of gastric cancer, peptic ulcer, or other organ cancer; previous *H. pylori* eradication therapy; and a history of serious side effects associated with antibiotic therapy. Patients were also excluded if they had severe nonmalignant disease, were pregnant, or had a gastric disease (such as peptic ulcer disease, gastric dysplasia, or cancer) diagnosed on the endoscopy performed at screening.

### Randomization, Treatment, and Follow-up

After consent was obtained, endoscopy was performed to confirm the absence of coexisting

disease and to confirm that participants had *H. pylori* infection. Eligible participants were randomly assigned in a 1:1 ratio, stratified according to sex, to receive either *H. pylori* treatment or placebo. When the trial was designed and executed, treatment of asymptomatic *H. pylori* infection was not standard practice. The computer-generated randomization sequence was kept at the trial pharmacy and was not accessible to the investigators who enrolled participants. Throughout the trial, participants and investigators, including the endoscopist, pathologist, physician, research nurse, and statistician, were unaware of trial-group assignments.

The treatment group received amoxicillin (1000 mg), clarithromycin (500 mg), and the proton-pump inhibitor lansoprazole (30 mg) twice daily for 7 days. The placebo group received the same number of pills, identical in appearance and taste, as the treatment group. Data on adherence to the trial regimen and adverse events were collected by means of telephone contact.

Surveillance endoscopies were performed every 2 years. A closeout endoscopy, with *H. pylori* evaluation, was performed at the end of the trial period (during the period from January 2016 through December 2018). For ethical reasons, participants who still had *H. pylori* infection received bismuth-based quadruple therapy (a proton-pump inhibitor, bismuth, metronidazole, and tetracycline) for 10 days.

### ASSESSMENTS

At each surveillance endoscopy, biopsy specimens were obtained from suspicious lesions to test for gastric cancer. The World Health Organization classification system was used for histologic classification of gastric cancer (Table S1 in the Supplementary Appendix).[20] Gastric epithelial lesions were classified as adenoma or carcinoma according to the criteria of the Vienna classification of gastrointestinal epithelial neoplasia (Table S2).[21]

At the endoscopy performed at screening, biopsy specimens were obtained from the gastric antrum lesser, corpus lesser, and corpus greater curvatures and were evaluated with the use of the updated Sydney System for the classification and grading of gastritis (Fig. S1).[22] *H. pylori* infection status was determined with the use of a rapid urease test on a biopsy specimen obtained from the corpus greater curvature and with Wright–Giemsa staining of biopsy specimens from the three prespecified sites. Positive results on at least two of the four tests were considered to confirm the presence of *H. pylori* infection, as required for eligibility in the trial.

At the first follow-up endoscopy, *H. pylori* infection status was evaluated with the use of a rapid urease test on two biopsy specimens obtained from the corpus and antrum. Status with respect to *H. pylori* infection was concealed from all participants and investigators throughout the trial. At the closeout endoscopy, *H. pylori* infection status was reevaluated with the use of a rapid urease test to determine whether the participant should receive salvage treatment.

### OUTCOMES

The primary outcome was development of gastric cancer. Data for participants were censored at the date of the last endoscopy, death, or withdrawal from the trial. In January 2019, we obtained access to the Korea National Cancer Incidence Database to confirm the cases of gastric cancer that had been diagnosed in our trial by means of surveillance. The database included data on cancer diagnoses for almost the entire South Korean population through December 31, 2016 (e.g., data on the incidence of cancer in 2015 were 98.2% complete).[23]

Prespecified secondary outcomes were the development of gastric cancer according to *H. pylori* eradication status during the follow-up period (after receipt of *H. pylori* treatment or placebo), overall survival, and the development of adenoma. Overall survival was defined as the time from randomization to the date of death from any cause. The Statistics Korea database was accessed to obtain the date and cause of death for participants who had died by December 31, 2017. Survival data were censored at the date of the closeout endoscopy performed in 2018 or on December 31, 2017 (for participants who did not undergo endoscopy in 2018 and were still alive on that date, as confirmed in the database).

### STATISTICAL ANALYSIS

On the basis of age-specific incidence data in South Korea, we estimated that the annual incidence of gastric cancer in the *H. pylori*–infected average-risk population would be about 165 cases per 100,000 persons 40 to 65 years of age (250 cases per 100,000 men and 80 cases per 100,000 women, with a male-to-female ratio of

1:1). The cumulative incidence of gastric cancer would be about 1% (1000 cases per 100,000 persons) at 6 years. Persons with a family history of gastric cancer might have triple the risk of gastric cancer, which would result in a cumulative incidence of 3% at 6 years. We assumed that treatment of *H. pylori* infection would reduce the risk of gastric cancer to one third of that 3% incidence, which would result in a cumulative incidence of 1% at 6 years. Assuming a 15% loss to follow-up, we calculated that 1810 participants (905 in each group) would be required to give the trial 80% power to detect a difference between the treated group and the placebo group, at a two-sided significance level of 0.05. An interim analysis was not planned.

The primary outcome of development of gastric cancer was assessed in the modified intention-to-treat population, which included all participants who underwent randomization, with the exception of those who did not start *H. pylori* treatment or placebo, those who did not have any follow-up data, and those who met major exclusion criteria. Overall survival was assessed in all participants who underwent randomization. The safety analysis included all participants who underwent randomization and received at least one dose of *H. pylori* treatment or placebo. To assess the robustness of the primary analysis, sensitivity analyses that included all participants who underwent randomization were performed with the use of several imputation methods to account for missing primary-outcome data.

We used the Kaplan–Meier method to evaluate the primary and secondary outcomes. The primary outcome was analyzed with the use of a log-rank test with a two-sided significance level of 0.05. A Cox proportional-hazards regression model was used to estimate hazard ratios with 95% confidence intervals. We used a z-test statistic for the between-group comparison of the number of cases of gastric cancer divided by the total person-time accumulated. Statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), and R software, version 3.5.0 (R Foundation for Statistical Computing).

## RESULTS

### PARTICIPANTS

From November 2004 through December 2011, a total of 3100 persons were screened; 1239 did not meet inclusion criteria, including 963 (31.1%) who were excluded because they did not have *H. pylori* infection. An additional 23 declined to participate. Therefore, 1838 participants underwent randomization; 917 were assigned to receive treatment for *H. pylori* infection, and 921 were assigned to receive placebo (Fig. 1). The baseline characteristics of these participants were well-balanced between the groups (Table 1 and Table S3). After the exclusion of 162 participants (3 in whom gastric cancer was detected at the baseline endoscopy, 1 who did not have *H. pylori* infection, 8 who did not start the trial regimen, and 150 who had no follow-up data), a total of 1676 participants — 832 in the treatment group and 844 in the placebo group — were included in the modified intention-to-treat population for the analysis of the primary outcome (Table S4). The baseline characteristics of the 162 excluded participants were similar to those of the participants in the modified intention-to-treat population (Tables S5 and S6). The median duration of follow-up for the assessment of the primary outcome was 9.2 years (interquartile range, 6.2 to 10.6; maximum, 14.1), and the median duration of follow-up for the assessment of overall survival was 10.2 years (interquartile range, 8.9 to 11.6).

### PRIMARY OUTCOME

Gastric cancer developed in 10 of 832 participants (1.2%) in the treatment group and in 23 of 844 (2.7%) in the placebo group (P=0.03 by log-rank test) (Fig. 2). All cases of gastric cancer were detected by means of the surveillance endoscopies, and no cases of gastric cancer were found to have been missed when data were compared with the national database. The hazard ratio for the development of gastric cancer in the treatment group as compared with the placebo group was 0.45 (95% confidence interval [CI], 0.21 to 0.94). The number needed to treat to prevent one case of gastric cancer was 65.7 (95% CI, 35.1 to 503.8) over the duration of the trial. (The characteristics of the diagnosed cases of gastric cancer are provided in Table S7.) Among the 33 participants in whom gastric cancer developed, 30 had stage I disease (90.9%), and 3 had stage II disease (9.1%).

Several sensitivity analyses that included all 1838 participants who underwent randomiza-

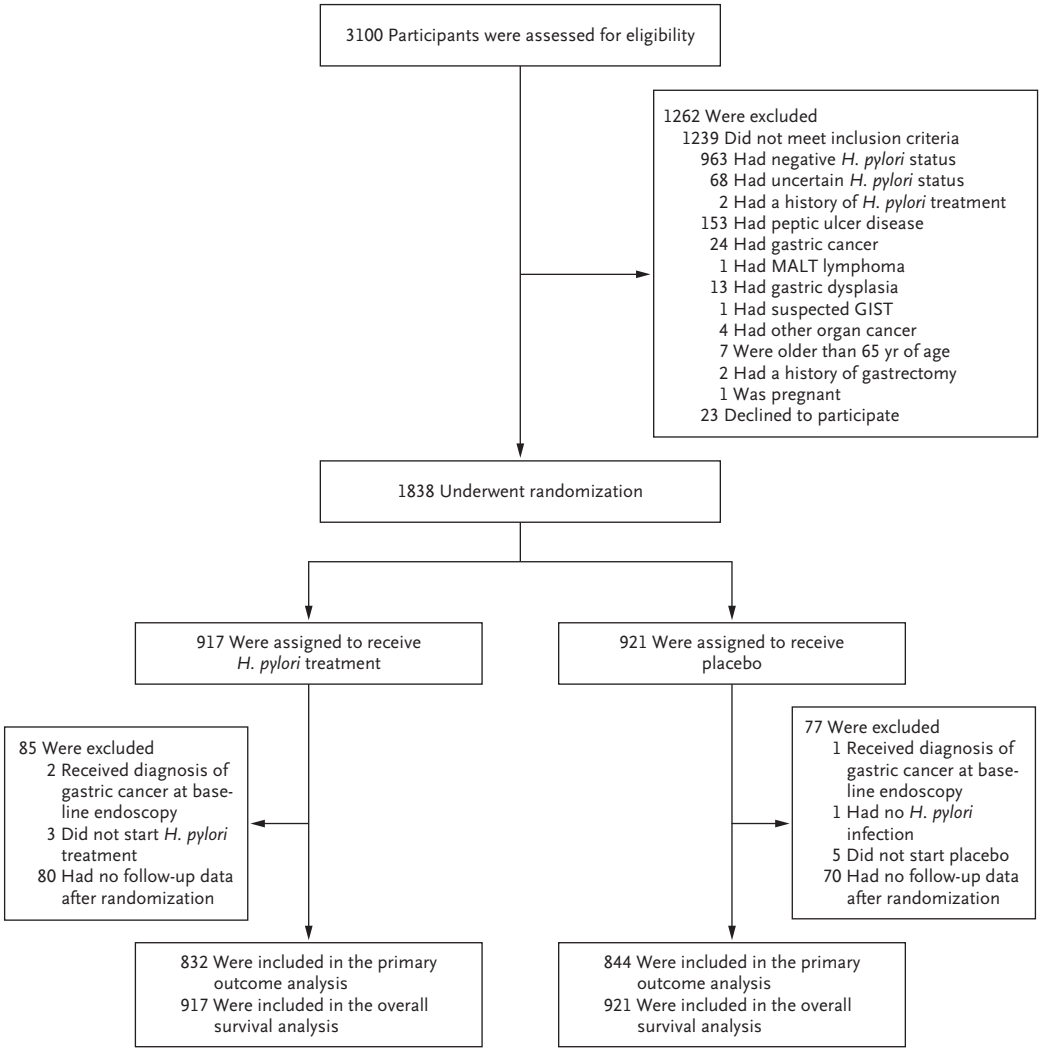



**Figure 1. Enrollment, Randomization, Follow-up, and Analysis.**

The primary outcome was development of gastric cancer during the follow-up period and was assessed in the modified intention-to-treat population, which included all participants who underwent randomization, with the exception of those who did not start *Helicobacter pylori* treatment or placebo, who did not have any follow-up data, or who met major exclusion criteria. The analysis of overall survival (a secondary outcome) was assessed in all participants who underwent randomization. MALT denotes mucosa-associated lymphoid tissue, and GIST gastrointestinal stromal tumor.

tion resulted in findings that were similar to those of the primary analysis and showed the effectiveness of *H. pylori* treatment in preventing gastric cancer (Table S8). In an intention-to-treat analysis that used imputed data from the National Cancer Incidence Database, the hazard ratio for development of gastric cancer with treatment as compared with placebo was 0.42 (95% CI, 0.20 to 0.89) (Fig. S2).

### ANALYSIS ACCORDING TO *H. PYLORI* ERADICATION STATUS

*H. pylori* eradication status was evaluated in 1587 participants during the follow-up period. Eradication was confirmed in 551 of 786 participants (70.1%) in the treatment group and in 57 of 801 participants (7.1%) in the placebo group. *H. pylori* infection persisted in the remaining 979 participants (Table S9).

**Table 1. Baseline Characteristics of All Participants in the Intention-to-Treat Population.***

| Characteristic | *H. pylori* Treatment (N=917) | Placebo (N=921) |
|---|---|---|
| Age — yr | 48.8±6.0 | 48.8±6.3 |
| Male sex — no. (%) | 458 (49.9) | 452 (49.1) |
| Current or former smoker — no. (%) | 403 (43.9) | 378 (41.0) |
| Current or former alcohol drinker — no./total no. (%) | 619/916 (67.6) | 618/921 (67.1) |
| First-degree relative with gastric cancer — no. (%)† | | |
| Father | 352 (38.4) | 336 (36.5) |
| Mother | 248 (27.0) | 251 (27.3) |
| One or more siblings | 425 (46.3) | 429 (46.6) |
| No. of first-degree relatives with gastric cancer — no. (%) | | |
| One | 783 (85.4) | 796 (86.4) |
| Two or more | 134 (14.6) | 125 (13.6) |
| Coexisting illness — no. (%) | | |
| Hypertension | 103 (11.2) | 115 (12.5) |
| Diabetes mellitus | 49 (5.3) | 53 (5.8) |
| Previous screening for gastric cancer — no. (%) | | |
| None | 259 (28.2) | 248 (26.9) |
| Esophagogastroduodenoscopy | 407 (44.4) | 402 (43.6) |
| Upper gastrointestinal series | 72 (7.9) | 81 (8.8) |
| Both esophagogastroduodenoscopy and upper gastrointestinal series | 176 (19.2) | 187 (20.3) |
| Not available | 3 (0.3) | 3 (0.3) |
| Gastrointestinal symptoms at presentation — no. (%)‡ | 293 (32.0) | 275 (29.9) |

* Plus–minus values are means ±SD. Data are shown for the intention-to-treat population, which included all participants who underwent randomization. Percentages may not total 100 because of rounding.
† In the placebo group, 1 participant had a mother and also offspring with gastric cancer, and 1 had a sibling and also offspring with gastric cancer; 39 participants in the treatment group and 36 in the placebo group had 2 or more siblings with gastric cancer.
‡ Symptoms included those associated with gastroesophageal reflux disease or mild nonulcer dyspepsia.

Of the 33 cases of gastric cancer, 28 developed in the 979 participants (2.9%) with persistent infection, and 5 developed in the 608 participants (0.8%) in whom the infection was eradicated (hazard ratio for gastric cancer with eradicated infection as compared with persistent infection, 0.27; 95% CI, 0.10 to 0.70) (Fig. 3). (Characteristics of the gastric cancers according to follow-up *H. pylori* eradication status are provided in Table S10.) The incidence of gastric cancer was lower among participants in whom *H. pylori* infection was eradicated than among participants with persistent infection (0.94 cases vs. 3.41 cases per 1000 person-years).

Of the 10 cases of gastric cancer that developed among participants in the treatment group, 5 cases (50.0%) developed in participants with persistent infection, and 5 (50.0%) developed in participants with confirmed eradication (Fig. S3). The results of a combined analysis of the risk of gastric cancer according to trial-group assignment and follow-up *H. pylori* eradication status are provided in Figure S4. The incidence of gastric cancer among participants in the treatment group who had persistent infection was similar to the incidence among participants in the placebo group with persistent infection.

### OVERALL SURVIVAL

Death occurred in 16 of 917 participants (1.7%) in the treatment group and in 18 of 921 (2.0%) in the placebo group. No significant difference

in overall survival rates was found between the trial groups (Fig. S5). The causes of death did not differ between the groups (Table S11). In the treatment group, 6 participants died from other organ cancers, 1 died from cardiovascular disease, and 9 died from other causes. In the placebo group, 7 participants died from other organ cancers, 4 died from cardiovascular disease, and 7 died from other causes. Death from gastric cancer was not observed in either group.

### INCIDENCE OF ADENOMA

The incidence of gastric adenoma was similar in the two groups. Gastric adenomas developed in 14 participants (1.7%) in the treatment group and in 13 (1.5%) in the placebo group (Fig. S6 and Table S12).

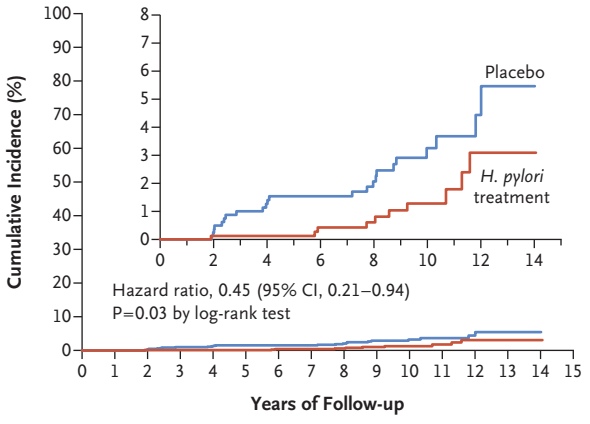
### ADVERSE EVENTS

The safety analysis included 1746 participants; 98.5% of the participants took more than 75% of the assigned trial pills (Table S13). Drug-related adverse events were more common in the treatment group than in the placebo group (53.0% of participants in the treatment group and 19.1% in the placebo group had at least one adverse event; P<0.001), but the severity was usually mild. Taste alteration, nausea, diarrhea, and abdominal pain were common in the treatment group (Table 2).

## DISCUSSION

In this prospective, randomized trial involving first-degree relatives of patients with gastric cancer, the risk of gastric cancer was 55% lower among those who received *H. pylori* eradication treatment than among those who received placebo, during a median follow-up of 9.2 years. Of note, the risk of gastric cancer was 73% lower among persons in whom *H. pylori* eradication was achieved than among those in whom infection was persistent. Adverse events were common in the treatment group, but the severity was usually mild.

A meta-analysis of six randomized trials involving healthy, asymptomatic participants with *H. pylori* infection showed that the risk of gastric cancer was approximately 34% lower among those who received treatment than among those in the control groups.[6] One large study that evaluated gastric cancer as the primary outcome

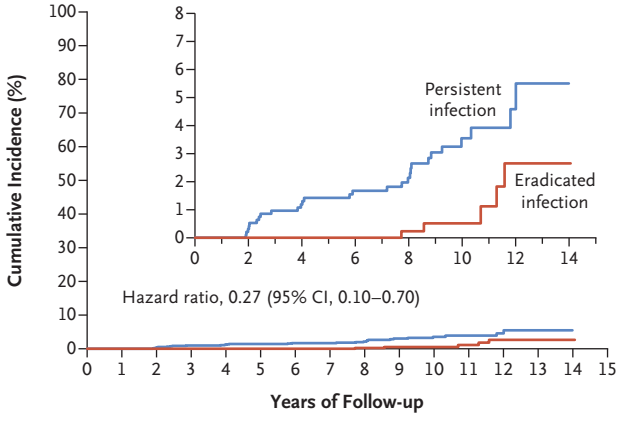



**No. at Risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 844 | 842 | 804 | 769 | 731 | 701 | 640 | 600 | 515 | 423 | 271 | 194 | 94 | 33 | 1 | 0 |
| *H. pylori* treatment | 832 | 832 | 793 | 766 | 727 | 697 | 634 | 593 | 496 | 419 | 275 | 180 | 89 | 31 | 1 | 0 |

**Figure 2. Cumulative Incidence of Gastric Cancer.**

Shown are the Kaplan–Meier curves for the primary outcome of development of gastric cancer. During a median follow-up of 9.2 years, gastric cancer developed in 10 of 832 participants (1.2%) in the treatment group and in 23 of 844 (2.7%) in the placebo group. The inset shows the same data on an enlarged y axis.




**No. at Risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Persistent infection | 979 | 979 | 937 | 899 | 858 | 819 | 743 | 695 | 588 | 482 | 313 | 214 | 105 | 35 | 0 | 0 |
| Eradicated infection | 608 | 608 | 583 | 565 | 547 | 531 | 494 | 465 | 395 | 340 | 221 | 153 | 76 | 27 | 2 | 0 |

**Figure 3. Cumulative Incidence of Gastric Cancer According to *H. pylori* Eradication Status.**

Shown are the Kaplan–Meier curves for gastric cancer according to *H. pylori* eradication status after receipt of *H. pylori* treatment or placebo (a secondary outcome). A total of 1587 participants were included in the analysis after the exclusion of 89 participants who did not have data from a follow-up *H. pylori* test. Gastric cancer developed in 5 of 608 participants (0.8%) in whom infection was eradicated and in 28 of 979 participants (2.9%) with persistent infection. The inset shows the same data on an enlarged y axis.

**Table 2. Adverse Events.***

| Event | *H. pylori* Treatment (N=866) | Placebo (N=880) | P Value† |
|---|---|---|---|
| | *no. of participants (%)* | | |
| Adverse event | | | |
| Taste alteration | 280 (32.3) | 31 (3.5) | <0.001 |
| Dry mouth | 3 (0.3) | 4 (0.5) | 0.99 |
| Dyspepsia | 68 (7.9) | 54 (6.1) | 0.16 |
| Nausea | 57 (6.6) | 28 (3.2) | 0.001 |
| Vomiting | 6 (0.7) | 2 (0.2) | 0.18 |
| Reflux symptoms | 1 (0.1) | 4 (0.5) | 0.37 |
| Diarrhea | 193 (22.3) | 54 (6.1) | <0.001 |
| Constipation | 6 (0.7) | 3 (0.3) | 0.34 |
| Abdominal pain | 40 (4.6) | 8 (0.9) | <0.001 |
| Hypersensitivity | 2 (0.2) | 7 (0.8) | 0.18 |
| Itching | 1 (0.1) | 3 (0.3) | 0.62 |
| General weakness | 5 (0.6) | 5 (0.6) | 0.99 |
| Dizziness | 8 (0.9) | 4 (0.5) | 0.24 |
| Headache | 9 (1.0) | 11 (1.3) | 0.68 |
| Insomnia | 1 (0.1) | 0 | 0.50 |
| Any adverse event | 459 (53.0) | 168 (19.1) | <0.001 |
| Any grade ≥3 adverse event‡ | 7 (0.8) | 1 (0.1) | 0.04 |

* Data are shown for the safety population, which included all participants who underwent randomization and received at least one dose of *H. pylori* treatment or placebo. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

† P values were calculated with the use of Pearson's chi-square test or Fisher's exact test.

‡ In the group that received treatment for *H. pylori* infection, grade 3 adverse events included nausea (in 2 participants), diarrhea (in 3 participants), and abdominal pain (in 2 participants); 5 of the 7 participants took all prescribed treatment tablets. Grade 3 diarrhea developed in 1 participant in the placebo group who took all the placebo tablets.

concluded that the incidence of gastric cancer was similar in the treatment group and the placebo group (7 cases in the treatment group and 11 in the placebo group; P=0.33), which may have been the result of the underpowered design, despite the 7.5-year follow-up of 1630 participants.[24] Another large study (the Shandong Intervention Trial) involving 2258 participants showed that the risk was 39% lower with *H. pylori* treatment than with placebo over an extended follow-up of 15 years; the between-group difference in risk was not significant during the initial 7.3-year follow-up.[25,26] Results of long-term follow-up (22 years) in the same study showed a higher difference in risk (52% lower in the treatment group).[27] The results of these studies emphasize that trials of prevention of gastric cancer by treatment of *H. pylori* infection require many participants who are followed for a long period of time, as is the case in an ongoing randomized trial involving more than 90,000 participants.[28] We were able to conduct this trial with a somewhat smaller sample size because the incidence of gastric cancer among first-degree relatives of patients with gastric cancer was high, and the participants had high adherence to the trial regimen. Sensitivity analyses that used imputation methods for missing data from participants who were lost to follow-up robustly supported our conclusion.

In this trial, the risk of gastric cancer was 55% lower among participants assigned to the group that received treatment for *H. pylori* infection than among those assigned to the placebo group and 73% lower among participants in whom *H. pylori* eradication was confirmed than among those who had persistent infection. These results are similar to those of our previous trial in patients with early gastric cancer (the risk of gastric cancer was 50% lower in the treatment group and 68% lower among participants in whom *H. pylori* was eradicated).[5] In the current trial and in our previous trial, the risk of gastric cancer was lower by 18 percentage points in the analysis according to eradication status than in the analysis according to the assigned group; this finding is most likely the result of the persistent risk in the cases of eradication failure. The 30% *H. pylori* eradication failure rate of clarithromycin-containing triple therapy in our trial was similar to data from a Korean meta-analysis.[29] In contrast to previous trials in China,[24,25] our trial did not test the success of eradication therapy in the treatment group because we wanted to maintain strict blinding. Subgroup analyses of the Shandong Intervention Trial suggested a risk reduction even in cases of eradication failure.[30] However, the results of the current trial, along with those of our previous trial,[5] showed that the risk of gastric cancer among participants in whom infection was not eradi-

cated was similar in the treatment group and in the placebo group. Our data emphasize that eradication success should be confirmed, as the "test–treat–test" approach recommends.[31]

In a meta-analysis, mortality from gastric cancer was about 33% lower among participants who received treatment for *H. pylori* infection than among those who did not — a finding similar to the 34% lower incidence of gastric cancer among treated participants.[6] An unexpected finding from a more recent meta-analysis was a 12% increase in all-cause mortality after *H. pylori* treatment.[32] This potential risk should be clearly addressed before treatment of *H. pylori* infection is applied generally as the primary prevention strategy. In our trial, the clarithromycin-containing triple therapy was not associated with an increase in death from any cause or death from any specific causes. Of note, no death from gastric cancer was reported in either group, presumably because of the detection of disease in its early stages. In previous trials, which adopted 4-year to 5-year intervals for surveillance endoscopy, death from gastric cancer was reported even in the *H. pylori* treatment groups.[24,25] In contrast, in our trial, which used a 2-year surveillance interval, we detected all gastric cancers at a curable stage (all within stage II).[33] The National Cancer Screening Program in Korea recommends a 2-year interval for endoscopies in persons 40 years of age or older, which could reduce mortality from gastric cancer by about 81% if the procedure is performed three or more times.[34] Screening intervals shorter than every 2 years seem unnecessary because stage-specific prognosis of gastric cancer in patients with a family history of gastric cancer has been shown to be similar or better than the prognosis in patients with no family history of gastric cancer.[35]

The results of this trial showed that treatment of *H. pylori* infection did not result in a lower incidence of gastric adenoma than placebo. This finding is similar to that of our previous trial involving patients with early gastric cancer; in that trial, the incidence of adenoma was almost equal in the two groups (8.2% in the treatment group and 8.4% in placebo group).[5] Together, our trials suggest that the preventative effect of *H. pylori* treatment is not preceded by a decrease in the incidence of adenoma, and the adenoma–carcinoma sequence is not the pathway activated by *H. pylori* in the development of gastric cancer.

The main advantage of our trial is that the incidence of gastric cancer was evaluated as the primary outcome in a large-scale, long-term trial. We confirmed outcome data obtained from active surveillance with data from the national databases. The trial has several limitations. First, it was performed at a single center in South Korea. However, the fact that the Korean population is of the same ethnic group and that there is little geographic variation in the incidence of gastric cancer may support the generalizability of the findings to the rest of South Korea.[36] Because family history is a consistent risk factor worldwide, our results may be globally applicable.[9,37] Second, an ethical issue can be raised about conducting a trial with the use of placebo. However, the national health insurance system of South Korea does not currently cover *H. pylori* therapy in our trial population. We provided eradication therapy to all participants who still had *H. pylori* infection at the end of the trial. Third, we did not evaluate the genetic susceptibility of the participants to gastric cancer or the bacterial virulence factors of *H. pylori*, which may be risk factors for gastric cancer.

In conclusion, treatment of *H. pylori* infection reduced the risk of gastric cancer in first-degree relatives of patients with gastric cancer.

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