Effect of *Helicobacter pylori* treatment on the long-term mortality in patients with type 2 diabetes

Young-II Kim¹, Young Ae Kim², Hak Jin Kim³, Su-Hyun Kim⁴, Yul Hwangbo⁵, Jae Gyu Kim⁶, Jae J. Kim⁷, and Il Ju Choi¹

¹Center for Gastric Cancer, ²National Cancer Control Institute, ³Branch of Cardiology, Department of Internal Medicine, ⁴Department of Neurology, Research Institute and Hospital, ⁵Division of Endocrinology, Department of Internal Medicine, National Cancer Center, Goyang; ⁶Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul; ⁷Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Background/Aims:** Meta-analyses of randomized trials reported a non-significant increase in overall mortality risk after *Helicobacter pylori* eradication. In this study, we investigated whether *H. pylori* treatment is associated with increased risk of overall mortality in patients with type 2 diabetes.

**Methods:** In this retrospective population-based cohort study, we identified 66,706 patients treated for type 2 diabetes between 2002 and 2010 from the Korean National Health Insurance Service-National Sample Cohort. Patients who received *H. pylori* treatment (Hp-treatment cohort, 1,727 patients) were matched to those who did not (non-treatment cohort, 3,454 patients) at a 1:2 ratio. The primary outcome was overall mortality. The secondary outcomes were mortalities due to cardiovascular disease, cerebrovascular disease, or cancers. To estimate hazard ratio (HR) with confidential interval (CI), we used the Cox proportional-hazard model.

**Results:** During a median follow-up of 4.7 years, the overall mortality was 5.9% (101/1,727 patients) among patients in the Hp-treatment cohort and 7.6% (364/3,454 patients) among patients in the non-treatment cohort. Adjusted HR (aHR) for overall mortality in the Hp-treatment cohort was 0.74 (95% CI, 0.59 to 0.93; *p* = 0.011). The mortality risks due to cardiovascular disease (aHR, 1.34; 95% CI, 0.54 to 3.30; *p* = 0.529), cerebrovascular disease (aHR, 0.97; 95% CI, 0.37 to 2.55; *p* = 0.947), and cancer (aHR, 1.08; 95% CI, 0.68 to 1.72; *p* = 0.742) were not significantly different between the groups.

**Conclusions:** In type 2 diabetes patients, overall mortality did not increase after *H. pylori* treatment.

**Keywords:** Helicobacter pylori; Mortality; Diabetes mellitus, type 2

---

**INTRODUCTION**

A meta-analysis of randomized controlled trials (RCTs) conducted in asymptomatic general population reported 34% reduction in gastric cancer incidence after *Helicobacter pylori* eradication [1]. Gastric cancer mortality risk also decreased by 33%, but a non-significant 9% increase in the overall mortality risk was found after *H. pylori* eradication [1]. A RCT in high-risk patients who underwent endoscopic resection for early gastric cancer reported a non-significant increased overall mortality risk among patients included in the *H. pylori* treatment group (hazard ratio [HR], 1.95; *p* = 0.19) despite a significant reduction of metachronous gastric cancer risk [2]. A more recent meta-analysis also demonstrated a non-significant risk increase in overall mortality with *H. pylori* treatment (risk ratio, 1.12; 95% confidence interval [CI], 0.93 to 1.34) [3]. These data suggest a potential harmful ef-
fect of H. pylori treatment in terms of increased non-gastric cancer mortality. However, the true nature of this observation and the plausible underlying mechanisms remain unclear.

Globally, the leading causes of death include ischemic heart disease and stroke and cancer [4-6]. A significant association between increased cardiovascular disease mortality and clarithromycin, which is a commonly used antibiotic for H. pylori eradication, has been suggested [7-9]. Thus, we hypothesized that H. pylori treatment might be associated with increased risk of mortality due to these major causes of death which might over-compensate the decrease of gastric cancer mortality. Type 2 diabetes is an important risk factor for cardiovascular disease, cerebrovascular disease, and cancers [10,11]. In this retrospective cohort study, we investigated whether H. pylori treatment is associated with overall mortality increase or with mortality increase from the main causes in patients with type 2 diabetes.

METHODS

Data source
This study used the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) database from 2002 to 2013 [12]. Using probability sampling, a representative sample cohort of approximately one million subjects (2.2% of the total eligible population) was extracted from all beneficiaries of the National Health insurance and National Medical Aid in 2002 depending on the entire national cohort information. The cohort follow-up was for 11 years until 2013 [12]. In this cohort, we used disease codes of the International Classification of Diseases, 10th Revision (ICD-10) to identify the disease diagnosis and the cause of death [13]. The database has been validated in several studies performed in Korea [14-16].

Study design and population
Our study design is a population-based retrospective cohort study. The Institutional Review Board of the National Cancer Center approved this study (NCC2016-0043). Requirement for informed consent from each individual was waived.

Detailed patient selection methods have been described in our previous study evaluating the association between overall mortality and H. pylori treatment in hypertension patients [16]. Using the disease codes for type 2 diabetes (ICD-10 code, E11 to E14), type 2 diabetes patients aged 20 years or older were selected between 2002 and 2010. Patients who had been prescribed one or more anti-diabetic drugs were finally included in the analyses.

Patients who received H. pylori eradication treatment after the diagnosis of type 2 diabetes until June 2013 were included in the H. pylori treatment cohort. The prescription of H. pylori eradication medication was examined using drug codes for standard triple therapy (proton-pump inhibitor [PPI], amoxicillin, and clarithromycin for 7 to 14 days) or bismuth quadruple therapy (PPIs, bismuth, tetracycline, and metronidazole for 7 to 14 days), which were approved for the first-line and the second-line treatment in Korea [17]. Each patient in the H. pylori treatment cohort was matched with those in the non-treatment cohort at an 1:2 ratio by using a simple random sampling method without replacement. Variables for matching included age group, sex, date of type 2 diabetes diagnosis, and Charlson comorbidity index (CCI) score [18].

The observation periods for study outcomes started on the prescription date for H. pylori therapy in the treatment cohort and the corresponding date in matched control patients in the non-treatment cohort. The observation periods ended on December 31st, 2013 (Supplementary Fig. 1). Patients who died due to any causes or those who were diagnosed with cancers, cardiovascular diseases, or cerebrovascular diseases before or within the 6 months after the initiation of the observation periods were excluded.

Study outcomes
The primary outcome was overall (all-cause) mortality, and the secondary outcomes included cardiovascular disease mortality, cerebrovascular mortality, and overall cancer mortality occurring at least 6 months after the start of the observation period. The specific ICD-10 code for cancers (C00 to 97), cardiovascular diseases (I20 to I25), and cerebrovascular diseases (I60 to I66) are provided in Supplementary Table 1.

Statistical analysis
Student t test and chi-square test were used for descriptive analyses to compare baseline characteristics between
groups. Overall mortality was compared using the Kaplan-Meier curves with log-rank test. We used univariate and multivariate Cox proportional hazard regression models to estimate HR with 95% CI for mortalities and incidences of cancers, cardiovascular, and cerebrovascular diseases according to the *H. pylori* treatment.

Age, sex, socioeconomic status, CCI scores, and the use of aspirin and metformin were included as the covariates for the multivariate analysis. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), and *p* values less than 0.05 were considered statistically significant.

**RESULTS**

**Baseline characteristics of the study population**

A total of 66,706 type 2 diabetes patients aged ≥ 20 years were prescribed at least one anti-diabetic medication between 2002 and 2010. A total of 3,059 patients received prescription for *H. pylori* treatment from the date of diagnosis for type 2 diabetes to June 30, 2013. Among them, 1,251 patients who died from any causes or were diagnosed with cancer, cardiovascular, or cerebrovascular diseases within 6 months before or after *H. pylori* treatment were excluded. Finally, a total of 1,727 patients in the *H. pylori* treatment cohort and 3,454 matched patients in the non-treatment cohort were selected for the analysis (Fig. 1).

![Study flow](https://doi.org/10.3904/kjim.2019.428)

**Figure 1.** Study flow. A total of 1,727 patients in the *Helicobacter pylori* treatment cohort were matched with 3,454 patients in the non-treatment cohort at a 1:2 ratio by using simple random sampling without replacement.
Patients in the *H. pylori* treatment cohort had a higher proportion of patients with household income level > 50% (62.3% vs. 57.3%, *p* = 0.001) and metformin users (83.6% vs. 80.1%, *p* = 0.011) compared to the non-treatment cohort. Other baseline characteristics were not significantly different between the two cohorts. The standard triple therapy regimen was prescribed in 98.4% of patients in the *H. pylori* treatment cohort (Table 1).

**Risk factors for overall mortality after *H. pylori* treatment**

During the observation periods until December 2013 (median, 4.7 years; interquartile range, 2.5 to 7.3), death occurred in 364 (7.0%) patients; 101 (5.9%) patients in the *H. pylori* treatment cohort and 263 (7.6%) in the non-treatment cohort. The *H. pylori* treatment cohort had a significantly higher overall survival rate compared to the non-treatment cohort (5-year overall survival rates, 95.4% vs. 92.6%, respectively; *p* = 0.015 by the log-rank test) (Fig. 2). In a multivariate Cox-proportional hazard regression analysis, *H. pylori* treatment cohort had a significantly reduced risk for overall mortality with an adjusted HR (aHR) of 0.74 (95% CI, 0.59 to 0.93; *p* = 0.011) (Table 2). Other significant risk factors associated with

![Figure 2. Kaplan-Meier curves for overall survival according to the Helicobacter pylori treatment. During a median follow-up of 4.7 years, death of any cause was reported in 5.9% of patients in the *H. pylori* treatment cohort and 7.6% of patients in the non-treatment cohort. The *H. pylori* treatment cohort had a significantly higher overall survival rate as compared with the non-treatment cohort (*p* = 0.015 by the log-rank test).](https://doi.org/10.3904/kjim.2019.428)

---

**Table 1. Baseline characteristics of the study population**

| Characteristic               | *H. pylori* treatment cohort (n = 1,727) | Non-treatment cohort (n = 3,454) | *p* value |
|-----------------------------|----------------------------------------|---------------------------------|-----------|
| Age, yr                     |                                        |                                 | 1.000     |
| 20–29                       | 15 (0.9)                               | 30 (0.9)                        |           |
| 30–39                       | 180 (10.4)                             | 360 (10.4)                      |           |
| 40–49                       | 528 (33.5)                             | 1,156 (33.5)                    |           |
| 50–59                       | 586 (33.9)                             | 1,172 (33.9)                    |           |
| 60–69                       | 326 (18.9)                             | 652 (18.9)                      |           |
| 70–79                       | 39 (2.3)                               | 78 (2.3)                        |           |
| ≥ 80                        | 3 (0.2)                                | 6 (0.2)                         |           |
| Sex                         |                                        |                                 | 1.000     |
| Male                        | 1,090 (63.1)                           | 2,180 (63.1)                    |           |
| Female                      | 637 (36.9)                             | 1,274 (36.9)                    |           |
| Residential area            |                                        |                                 | 0.090     |
| Metropolitan                | 836 (48.4)                             | 1,586 (45.9)                    |           |
| Small city or rural         | 891 (51.6)                             | 1,868 (54.1)                    |           |
| Household income level      |                                        |                                 | 0.001     |
| 0%–50%                      | 651 (37.7)                             | 1,475 (42.7)                    |           |

https://doi.org/10.3904/kjim.2019.428
increased overall mortality were age ≥ 60 years, male sex, household income level lower than 50%, CCI score ≥ 2 (vs. CCI score 0). Aspirin use (aHR, 0.76; 95% CI, 0.58 to 0.99; \( p = 0.039 \)) and metformin use (aHR, 0.56; 95% CI, 0.44 to 0.71; \( p < 0.001 \)) were associated with decreased overall mortality.

| Characteristic | \( H. pylori \) treatment cohort (n = 1,727) | Non-treatment cohort (n = 3,454) | \( p \) value |
|----------------|------------------------------------------|----------------------------------|--------------|
| Smoking        |                                          |                                  | 0.003        |
| Never smoker   | 679 (39.3)                               | 1,215 (35.2)                    |              |
| Ex-smoker      | 167 (9.7)                                | 258 (7.5)                       |              |
| Current smoker | 403 (23.3)                               | 546 (15.8)                      |              |
| Missing        | 478 (27.6)                               | 1,435 (41.5)                    |              |
| Alcohol drinking |                                      |                                  | 0.425        |
| Never drinking | 707 (40.9)                               | 1,181 (34.2)                    |              |
| 1–2 time/wk    | 378 (21.9)                               | 600 (17.4)                      |              |
| 3–4 time/wk    | 129 (7.5)                                | 212 (6.1)                       |              |
| 5–7 time/wk    | 83 (4.8)                                 | 168 (4.8)                       |              |
| Missing        | 430 (24.9)                               | 1,353 (39.2)                    |              |
| Body mass index, kg/m\(^2\) |                                    |                                  | 0.208        |
| ≤ 18.5         | 11 (0.6)                                 | 31 (0.9)                        |              |
| 18.6–24.9      | 338 (19.6)                               | 522 (15.1)                      |              |
| 23.0–24.9      | 362 (21.0)                               | 565 (16.4)                      |              |
| ≥ 25.0         | 600 (34.7)                               | 1,031 (29.8)                    |              |
| Missing        | 416 (24.1)                               | 1,305 (37.8)                    |              |
| CCI score at the time of type 2 diabetes diagnosis |                                  |                                  | 1.000        |
| 0              | 665 (38.5)                               | 1,330 (38.5)                    |              |
| 1              | 381 (22.1)                               | 762 (22.1)                      |              |
| ≥ 2            | 681 (39.4)                               | 1,362 (39.4)                    |              |
| Aspirin use\(a\) |                                      |                                  | 0.963        |
| No             | 1,338 (77.5)                             | 2,678 (77.5)                    |              |
| Yes            | 389 (22.5)                               | 776 (22.5)                      |              |
| Metformin use\(a\) |                                      |                                  | 0.011        |
| No             | 294 (17.0)                               | 689 (19.9)                      |              |
| Yes            | 1,433 (83.0)                             | 2,765 (80.1)                    |              |
| \( H. pylori \) treatment regimen |                                  |                                  |              |
| PPI-clarithromycin containing triple therapy | 1,658 (96.0) | -                              |              |
| Bismuth-containing quadruple therapy | 27 (1.6) | -                              |              |
| Both           | 42 (2.4)                                 | -                               |              |
| Follow-up period, yr | 4.79 (2.61–7.35) | 4.71 (2.50–7.26) | 0.360 |

Values are presented as number (%) or median (interquartile range).

\( H. pylori \), Helicobacter pylori; CCI, Charlson comorbidity index; PPI, proton-pump inhibitor.

\( a \)Patients who used aspirin and metformin were defined as those who were prescribed the drugs for at least 30 days.
Table 2. Risk factors associated with overall mortality

| Variable                  | No. | Univariate analysis | p value | Multivariate analysis | p value |
|---------------------------|-----|---------------------|---------|-----------------------|---------|
|                           |     | Unadjusted HR (95% CI) |         | Adjusted HR (95% CI) |         |
| Age, yr                   |     |                     |         |                       |         |
| < 60                      | 4,077 | 1.00                 | < 0.001 | 1.00                  | < 0.001 |
| ≥ 60                      | 1,104 | 3.39 (2.75–4.17)     |         | 3.58 (2.90–4.42)      |         |
| Sex                       |     |                     |         |                       |         |
| Female                    | 3,270 | 1.00                 |         | 1.00                  |         |
| Male                      | 1,911 | 1.38 (1.10–1.73)     |         | 1.64 (1.31–2.05)      |         |
| Household income level    |     |                     | < 0.001 | < 0.001               |         |
| 0%–50%                    | 2,126 | 1.00                 |         | 1.00                  |         |
| 51%–100%                  | 3,055 | 0.68 (0.55–0.83)     |         | 0.68 (0.55–0.84)      |         |
| Residential area          |     |                     |         |                       |         |
| Metropolitan              | 2,422 | 1.00                 |         | 1.00                  |         |
| Small city or rural       | 2,759 | 1.08 (0.88–1.33)     |         | 1.00 (0.81–1.23)      |         |
| CCI score                 |     |                     |         |                       |         |
| 0                         | 1,802 | 1.00                 |         | 1.00                  |         |
| 1                         | 1,310 | 1.11 (0.83–1.50)     | 0.486   | 1.18 (0.87–1.58)      | 0.291   |
| ≥ 2                       | 2,069 | 1.68 (1.31–2.14)     | < 0.001 | 1.73 (1.35–2.22)      | < 0.001 |
| H. pylori treatment       |     |                     |         |                       |         |
| No                        | 3,454 | 1.00                 |         | 1.00                  |         |
| Yes                       | 1,727 | 0.75 (0.60–0.95)     |         | 0.74 (0.59–0.93)      |         |
| Aspirin use               |     |                     |         |                       |         |
| No                        | 4,016 | 1.00                 |         | 1.00                  |         |
| Yes                       | 1,165 | 0.89 (0.69–1.15)     |         | 0.76 (0.58–0.99)      |         |
| Metformin use             |     |                     | < 0.001 | < 0.001               |         |
| No                        | 983  | 1.00                 |         | 1.00                  |         |
| Yes                       | 4,198 | 0.53 (0.42–0.67)     | 0.56    | (0.44–0.71)           |         |

HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; H. pylori, Helicobacter pylori.

aAnalyses were performed using the Cox-proportional hazard model.

bCovariates for multivariate analysis included age, sex, economic status level, residential area, Charlson comorbidity index score, H. pylori treatment, and aspirin and metformin use.

Risk of cardiovascular disease, cerebrovascular disease, and overall cancer incidence according to H. pylori treatment

No significant differences were found in cardiovascular and cerebrovascular disease incidences between H. pylori treatment cohort and non-treatment cohort. H. pylori treatment cohort had increased risk for overall cancer incidence (aHR, 1.28; 95% CI, 1.03 to 1.58; p = 0.024) compared with the non-treatment cohort. According to cancer type, the H. pylori treatment cohort showed significant incidence increase in colorectal cancer (aHR, 2.25; 95% CI, 1.25 to 4.04; p = 0.007) and thyroid cancer (aHR, 1.54; 95% CI, 1.02 to 2.31; p = 0.039) (Table 3).

Mortality risk due to cardiovascular disease, cerebrovascular disease, and overall cancers according to H. pylori treatment

Mortality risks due to common cause of death including cardiovascular disease, cerebrovascular disease and cancers are described in Table 4. Mortality risks due to cardiovascular disease (aHR, 1.34; 95% CI, 0.54 to 3.30; p = 0.529), cerebrovascular disease (aHR, 0.97; 95% CI, 0.37
to 2.55; \( p = 0.947 \)), and overall cancers (aHR, 1.08; 95% CI, 0.68 to 1.72; \( p = 0.742 \)) were not significantly different between the \( H. \) pylori treatment and non-treatment cohorts. No significant associations between \( H. \) pylori treatment and mortality risks for gastric cancer (aHR, 1.75; 95% CI, 0.46 to 6.60; \( p = 0.411 \)) as well as other cancer types were found (Table 4).

**DISCUSSION**

In this retrospective cohort study, we investigated overall mortality risk according to \( H. \) pylori treatment as the primary outcome, and evaluated cause-specific mortality risks due to major causes of death in patients with type 2 diabetes. \( H. \) pylori treatment was associated with a significant decrease in the risk of overall mortality. However, \( H. \) pylori treatment was not associated with mortality risks due to cardiovascular disease, cerebrovascular disease, and overall cancers.

In the report of global cancer statistics 2018 (GLOBOCAN 2018), gastric cancer was the fifth most common cancer, and the third leading cause of cancer death worldwide [19]. \( H. \) pylori was classified as a group 1 carcinogen for gastric cancer by the International Agency for Research on Cancer [20]. More than 50% of the world’s population (approximately 4.4 billion individuals) was infected with \( H. \) pylori in 2015 [21]. In Korea, gastric cancer was the most commonly diagnosed cancer in 2015 [22], and the estimated prevalence of \( H. \) pylori infection is about 54% [21]. However, \( H. \) pylori treatment as a primary prevention strategy for gastric cancer has not yet been implemented. Meta-analysis of RCTs showed 9% to 12% non-significant increase of overall mortality [13].

### Table 3. Risk of incidence of cardiovascular diseases, cerebrovascular diseases, and cancer according to \( H. \) pylori treatment

| Variable                  | No. of incidence (%) | Risk of incidence for \( H. \) pylori treatment cohort* |
|---------------------------|----------------------|--------------------------------------------------------|
|                           | \( H. \) pylori       | Non-treatment                                        |
|                           | cohort \( (n = 1,727)\) | cohort \( (n = 3,454)\) | Unadjusted HR (95% CI) | \( p \) value | Adjusted HR (95% CI) | \( p \) value |
| Cardiovascular disease    | 240 (13.90)          | 408 (11.81) | 1.20 (1.02–1.40) | 0.028 | 1.16 (0.98–1.36) | 0.078 |
| Cerebrovascular disease   | 140 (8.11)           | 270 (7.82) | 1.04 (0.85–1.28) | 0.692 | 1.02 (0.83–1.25) | 0.843 |
| Overall cancers           | 143 (8.28)           | 226 (6.54) | 1.29 (1.04–1.59) | 0.019 | 1.28 (1.03–1.58) | 0.024 |
| Stomach cancer            | 21 (1.22)            | 31 (0.90)  | 1.36 (0.78–2.36) | 0.279 | 1.48 (0.85–2.66) | 0.169 |
| Oral cancer               | 8 (0.46)             | 7 (0.20)   | 2.29 (0.83–6.31) | 0.110 | 2.12 (0.77–5.88) | 0.148 |
| Esophageal cancer         | 1 (0.06)             | 1 (0.03)   | NA             | NA    | NA             | NA    |
| Colorectal cancer         | 24 (1.39)            | 22 (0.64)  | 2.20 (1.23–3.92) | 0.008 | 2.25 (1.25–4.04) | 0.007 |
| Liver cancer              | 20 (1.16)            | 39 (1.13)  | 1.03 (0.60–1.76) | 0.922 | 0.91 (0.53–1.57) | 0.739 |
| Biliary tract cancer      | 5 (0.29)             | 4 (0.12)   | 2.50 (0.67–9.32) | 0.172 | 2.50 (0.66–9.44) | 0.177 |
| Pancreatic cancer         | 8 (0.46)             | 11 (0.32)  | 1.46 (0.59–3.62) | 0.419 | 1.30 (0.52–3.25) | 0.575 |
| Lung cancer               | 9 (0.52)             | 25 (0.72)  | 0.72 (0.34–1.54) | 0.397 | 0.75 (0.35–1.62) | 0.470 |
| Breast cancer             | 3 (0.17)             | 7 (0.20)   | 0.86 (0.22–3.31) | 0.823 | 0.70 (0.18–2.75) | 0.614 |
| Prostate cancer           | 12 (0.69)            | 23 (0.67)  | 1.04 (0.52–2.10) | 0.906 | 1.04 (0.24–4.43) | 0.957 |
| Bladder cancer            | 3 (0.17)             | 5 (0.14)   | 1.20 (0.29–5.02) | 0.863 | 1.67 (0.64–4.37) | 0.296 |
| Thyroid cancer            | 8 (0.46)             | 9 (0.26)   | 1.78 (0.69–4.61) | 0.236 | 1.54 (1.02–2.31) | 0.039 |
| Brain, CNS cancer         | 0                    | 2 (0.06)   | NA             | NA    | NA             | NA    |
| Non-Hodgkin lymphoma      | 2 (0.12)             | 1 (0.03)   | 4.00 (0.36–44.12) | 0.258 | 3.57 (0.32–39.93) | 0.302 |
| Leukemia                  | 2 (0.12)             | 2 (0.06)   | 2.00 (0.28–14.21) | 0.488 | 2.34 (0.33–16.75) | 0.397 |

\( H. \) pylori, Helicobacter pylori; HR, hazard ratio; CI, confidence interval; NA, not available; CNS, cerebral nervous system.

*The Cox-proportional hazard model was used for calculation of HR. In the multivariate analyses, covariates included were age, sex, economic status level, residential area, Charlson comorbidity index score, and aspirin and metformin use.*
Of the two largest RCTs included in those meta-analyses, Wong et al. [23] reported no increase in overall mortality risk (relative risk, 0.95; 95% CI, 0.53 to 1.69), whereas Ma et al. [24] showed 10% non-significant increase of overall mortality risk (relative risk, 1.10; 95% CI 0.89 to 1.36). However, overall mortality was evaluated as a secondary outcome in the previous trials and no primary outcome study has been performed [1,23,24]. Therefore, we evaluated the overall mortality after _H. pylori_ treatment as the primary study outcome in type 2 diabetes patients selected from the national cohort database who had increased cardiovascular or cerebrovascular disease risks. This database provides reliable data for mortality including exact date and cause of death. Overall mortality risk did not increase after _H. pylori_ treatment, and this result is similar to that of our previous study evaluating the association between overall mortality and _H. pylori_ treatment in a hypertension patient cohort [16]. These results might be an evidence for supporting the use of _H. pylori_ treatment as a primary prevention strategy for gastric cancer.

In the present study, most of the patients (98.4%) in the _H. pylori_ treatment cohort received clarithromycin-containing standard triple therapy. A clinical trial reported that clarithromycin use for 2 weeks in stable coronary artery disease increased cardiovascular mortality and overall mortality risk during 10-year follow-up period, although the exact underlying mechanism is unknown [7,25,26]. In addition, clarithromycin use was associated with increased risk of cardiovascular mortality during short-term periods, especially because of arrhythmia-related cardiovascular events [9,27]. Meanwhile, retrospective studies evaluating the association between mortality and clarithromycin use for _H. pylori_ Table 4. Risk of cause-specific mortality according to _H. pylori_ treatment

| Variable                      | No. of death (%) | Risk of mortality for _H. pylori_ treatment cohort<sup>a</sup> | Unadjusted HR (95% CI) | Unadjusted p value | Adjusted HR (95% CI) | Adjusted p value |
|-------------------------------|------------------|---------------------------------------------------------------|------------------------|--------------------|----------------------|-----------------|
|                               | _H. pylori_       | Non-treatment                                                | p value                | p value            |                     |                 |
|                               | treatment cohort  | cohort (n = 3,454)                                           |                        |                    |                      |                 |
| Overall                       | 101 (5.85)       | 263 (7.61)                                                   | 0.75 (0.60–0.95)       | 0.016              | 0.74 (0.59–0.93)     | 0.011 |
| Cardiovascular disease        | 8 (0.46)         | 12 (0.35)                                                    | 1.33 (0.55–3.26)       | 0.529              | 1.34 (0.54–3.30)     | 0.529 |
| Cerebrovascular disease       | 6 (0.35)         | 14 (0.41)                                                    | 0.86 (0.33–2.23)       | 0.754              | 0.97 (0.37–2.55)     | 0.947 |
| Overall cancers               | 28 (1.62)        | 53 (1.53)                                                    | 1.06 (0.67–1.67)       | 0.811              | 1.08 (0.68–1.72)     | 0.742 |
| Stomach cancer                | 4 (0.23)         | 5 (0.14)                                                     | 1.60 (0.43–5.96)       | 0.483              | 1.75 (0.46–6.60)     | 0.411 |
| Oral cancer                   | 0                | 0                                                             | NA                     | NA                 | NA                   |     |
| Esophageal cancer             | 1 (0.06)         | 1 (0.03)                                                     | NA                     | NA                 | NA                   |     |
| Colorectal cancer             | 1 (0.06)         | 3 (0.09)                                                     | 0.67 (0.47–7.41)       | 0.726              | 0.76 (0.49–1.19)     | 0.380 |
| Liver cancer                  | 6 (0.35)         | 16 (0.46)                                                    | 0.75 (0.29–2.19)       | 0.545              | 0.65 (0.25–1.69)     | 0.380 |
| Biliary tract cancer          | 4 (0.23)         | 3 (0.09)                                                     | 2.67 (0.60–11.93)      | 0.199              | 2.97 (0.65–13.39)    | 0.162 |
| Pancreatic cancer             | 2 (0.12)         | 6 (0.17)                                                     | 0.67 (0.14–3.30)       | 0.619              | 0.64 (0.13–3.22)     | 0.590 |
| Lung cancer                   | 6 (0.35)         | 10 (0.29)                                                    | 1.20 (0.44–3.31)       | 0.721              | 1.47 (0.53–4.10)     | 0.466 |
| Breast cancer                 | 0                | 0                                                             | NA                     | NA                 | NA                   |     |
| Prostate cancer               | 0                | 0                                                             | NA                     | NA                 | NA                   |     |
| Bladder cancer                | 0                | 0                                                             | NA                     | NA                 | NA                   |     |
| Thyroid cancer                | 0                | 0                                                             | NA                     | NA                 | NA                   |     |
| Brain, CNS cancer             | 0                | 1 (0.03)                                                     | NA                     | NA                 | NA                   |     |
| Non-Hodgkin lymphoma          | 2 (0.12)         | 0                                                             | NA                     | NA                 | NA                   |     |
| Leukemia                      | 0                | 0                                                             | NA                     | NA                 | NA                   |     |

_H. pylori_, _Helicobacter pylori_; HR, hazard ratio; CI, confidence interval; NA, not available; CNS, cerebral nervous system.

<sup>a</sup>The Cox-proportional hazard model was used for calculation of HR. In the multivariate analyses, covariates included were age, sex, economic status level, residential area, Charlson comorbidity index, and aspirin and metformin use.
treatment have reported inconsistent results [28-30]. A retrospective study demonstrated that overall mortality risk after clarithromycin-containing \textit{H. pylori} treatment significantly increased during a median follow-up of 3 years (aHR, 1.09; 95% CI, 1.00 to 1.18) [28], whereas two studies did not show any increased risk in long-term overall mortality [29,30]. Previous studies included high-risk patients diagnosed with cardiovascular diseases (arrhythmia, ischemic heart disease, or heart failure) who might develop short-term adverse events or mortality associated with clarithromycin use [28-30]. We excluded patients with cardiovascular or cerebrovascular diseases before or within 6 months after \textit{H. pylori} treatment to avoid the short-term cardiovascular effects of clarithromycin use. In our study, the long-term cardiovascular mortality was not significantly associated with \textit{H. pylori} treatment, although almost all patients (98.4%) received a clarithromycin-containing standard triple regimen.

Our study showed that \textit{H. pylori} treatment was associated with increased risk in overall cancer incidence but reduced risk in overall cancer mortality. Previous studies reported that antibiotics use was associated with increased overall cancer risks [31], and the risk of various cancers including lung, colon, prostate, and breast cancer [31,32]. One of the suggested mechanisms for increased cancer risks is disrupted gut microbiota (dysbiosis) by antibiotics use. Dysbiosis might have negative effects on the process of carcinogenesis including initiation, progression, and dissemination of cancer or cancer treatment efficacy [33,34]. However, in our study, significant increased risks were found only in colorectal cancer and thyroid cancer. In contrast, the colorectal cancer mortality risk did not increase, and no thyroid cancer mortality was observed. In Korea, colorectal cancer incidence also increased after the introduction of colorectal cancer screening program in 2004 with decreased trends of colorectal cancer mortality [22,35]. In addition, opportunistic thyroid cancer screening was associated with increased thyroid cancer incidence without a concomitant increase in thyroid cancer-related mortality [36]. Thus, increased overall cancer incidence risk in the \textit{H. pylori} treatment cohort seemed to be associated with increased cancer screening. Another explanation for the increased risk of overall cancer incidence in the treatment cohort might be associated with higher economic status. Because the treatment cohort had a higher proportion of patients with household income level of > 50% than the non-treatment cohort, patients in the treatment cohort might have accessed more health-care services, including opportunistic health screening programs. Further prospective studies are needed to investigate whether short duration of antibiotics use for \textit{H. pylori} treatment (7 to 14 days) is associated with increased cancer risks due to dysbiosis.

Despite increased risks of cardiovascular disease and cancers in the \textit{H. pylori} treatment cohort, no increase in overall mortality risk and cause-specific mortality risks due to cardiovascular disease and cancers were observed. In addition to the \textit{H. pylori} treatment, the use of metformin (aHR, 0.56; \(p < 0.001\)) and aspirin (aHR, 0.76; \(p = 0.039\)) were significant factors associated with reduced overall mortality risk. These results might be explained by the healthy user bias, that is, health-seeking patients tend to initiate preventive therapies and try to engage in healthy lifestyle behaviors, and metformin users are more likely to be engaged in healthy behaviors [37]. In the present study, healthy user bias might be present, and the treatment cohort had higher proportions of better household income levels, and metformin users.

Our study findings should be interpreted in light of several limitations. First, our study population was type 2 diabetes patients, and the severity of diabetes might have been different between the \textit{H. pylori} treatment cohort and non-treatment cohort. The severity of diabetes could not be assessed because the NHIS-NSC database did not provide any laboratory data such as glycated hemoglobin or blood glucose level. Second, the severity and treatment results of cardiovascular disease, cerebrovascular disease, or cancers might affect overall or disease-specific mortality. However, we could not assess the information due to the limitation of the NHIS-NSC database. Third, compliance for the \textit{H. pylori} treatment and \textit{H. pylori} eradication status after the treatment were not available from the database. Thus, we could not analyze whether \textit{H. pylori} eradication status after treatment affected overall mortality or not. Third, in the non-treatment cohort, both \textit{H. pylori} infected patients who were not treated and those who were not infected were included. Finally, although we included aspirin and metformin use as the covariate to evaluate risks of incidence and mortality from cardiovascular disease, cerebrovascular disease, and cancers, several factors were not con-
sidered in our analyses such as the type of intervention treatment or other drugs including anti-platelet agents or statins.

In conclusion, *H. pylori* treatment in patients with type 2 diabetes was not significantly associated with increased overall mortality. Among the major causes of death, no significant increase in the risk of mortality due to cardiovascular disease, cerebrovascular diseases, or overall cancers were observed. However, long-term prospective trials are necessary to confirm our findings and to apply *H. pylori* eradication as a primary gastric cancer prevention strategy in the general population without concern of overall mortality increase.

**KEY MESSAGE**

1. In this population-based retrospective cohort study using the Korean National Health Insurance Service-National Sample Cohort database, long-term overall mortality risk was not increased after *Helicobacter pylori* treatment in patients with type 2 diabetes.
2. In addition, *H. pylori* treatment was not associated with mortality risk increase due to cardiovascular disease, cerebrovascular disease, and all cancers.
3. However, further long-term prospective trials are necessary to confirm our findings and to apply *H. pylori* eradication as a primary gastric cancer prevention strategy in the general population without concern of overall mortality increase.

**Conflict of interest**

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

**Acknowledgments**

This study used the Korean National Health Insurance Service-National Sample Cohort database (NHIS-2016-2-191) provided by the National Health Insurance Service. This study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number HC15C1077) and partially supported by the grant from the National Cancer Center, Republic of Korea (grant number 1910370).

**REFERENCES**

1. 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: version 2. BMJ 2014;349:g3174.
2. Choi IJ, Kook MC, Kim YI, et al. Helicobacter pylori therapy for the prevention of metachronous gastric cancer. N Engl J Med 2018;378:1085-1095.
3. Gyawali B, Kesselheim AS, D’Andrea E. Does Helicobacter pylori eradication therapy to prevent gastric cancer increase all-cause mortality? Int J Cancer 2019;144:411-412.
4. World Health Organization. The top 10 causes of death [Internet]. Geneva (CH): World Health Organization, 2018 [cited 2019 Mar 7]. Available from: http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
5. Sherry LM, Jiaguan X, Kenneth DK, Elizabeth A. Mortality in the United States 2017 [Internet]. Atlanta (GA): Centers for Disease Control and Prevention, 2019 [cited 2019 Mar 7]. Available from: http://www.cdc.gov/nchs/products/databriefs/db328.htm.
6. Statistics Korea. Statistics for cause of death [Internet]. Daejeon (KR): Statistics Korea, 2019 [cited 2019 Mar 7]. http://kostat.go.kr/portal/korea/kor_nw/1/index.board?bmode=read&bSeq=&aSeq=370710&pageno=1&rowNum=10&navCount=10&currPg=&sTarget=title&sTtxt=.
7. Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. BMJ 2006;333:222-27.
8. Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study: version 2. BMJ 2014;349:g4930.
9. Wong AY, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ 2016;352:h6926.
10. American Diabetes Association. 9. Cardiovascular disease and risk management. Standards of Medical Care in Dia-
11. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1694-1685.
12. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15.
13. World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems. 10th ed. Geneva (CH): World Health Organization, 1992.
14. Lee SS, Ae Kong K, Kim D, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. Eur Heart J 2017;38:2599-2607.
15. Kim MH, Chang J, Kim WJ, Banerjee S, Park SM. Cumulative dose threshold for the chemopreventive effect of aspirin against gastric cancer. Am J Gastroenterol 2018;113:849-854.
16. Kim YI, Kim YA, Lee JW, et al. Effect of Helicobacter pylori treatment on long-term mortality in patients with hypertension. Gut Liver 2020;14:59-65.
17. Kim SG, Jung HK, Lee HL, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol 2014;29:1371-1386.
18. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676-682.
19. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
20. 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.
21. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology 2017;153:420-429.
22. Jung KW, Won YJ, Hong JH, Lee ES; Community of Population-Based Regional Cancer Registries. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015. Cancer Res Treat 2018;50:301-316.
23. 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;291:187-194.
24. 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;104:488-492.
25. Glud C, Als-Nielsen B, Damgaard M, et al. Clarithromycin for 2 weeks for stable coronary heart disease: 6-year follow-up of the CLARICOR randomized trial and updated meta-analysis of antibiotics for coronary heart disease. Cardiology 2008;111:280-287.
26. Winkel P, Hilden J, Hansen JF, et al. Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10 years in the CLARICOR randomised, blinded clinical trial. Int J Cardiol 2015;182:459-465.
27. Cheng YJ, Nie XY, Chen XM, et al. The role of macrolide antibiotics in increasing cardiovascular risk. J Am Coll Cardiol 2015;66:2173-2184.
28. Mosholder AD, Lee JY, Zhou EH, et al. Long-term risk of acute myocardial infarction, stroke, and death with outpatient use of clarithromycin: a retrospective cohort study. Am J Epidemiol 2018;187:786-792.
29. Andersen SS, Hansen ML, Norgaard ML, et al. Clarithromycin use and risk of death in patients with ischemic heart disease. Cardiology 2010;116:89-97.
30. Root AA, Wong AY, Ghebremichael-Weldeselassie Y, et al. Evaluation of the risk of cardiovascular events with clarithromycin using both propensity score and self-controlled study designs. Br J Clin Pharmacol 2016;82:512-521.
31. Kilkkinen A, Rissanen H, Klaukka T, et al. Antibiotic use predicts an increased risk of cancer. Int J Cancer 2018;142:2152-2155.
32. Boursi B, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation: another step in understanding the role of the human microbiota? Eur J Cancer 2015;51:2659-2664.
33. Bhatt AP, Redinbo MR, Bullman SJ. The role of the microbiome in cancer development and therapy. CA Cancer J Clin 2017;67:326-344.
34. Garrett WS. Cancer and the microbiota. Science 2015;348:80-86.
35. Shin A, Kim KZ, Jung KW, et al. Increasing trend of col-
orectal cancer incidence in Korea, 1999-2009. Cancer Res Treat 2012;44:219-226.
36. Ahn HS, Kim HJ, Kim KH, et al. Thyroid cancer screening in south Korea increases detection of papillary cancers with no impact on other subtypes or thyroid cancer mortality. Thyroid 2016;26:1535-1540.
37. Eskin M, Simpson SH, Eurich DT. Evaluation of healthy user effects with metformin and other oral antihyperglycemia medication users in adult patients with type 2 diabetes. Can J Diabetes 2019;43:322-328.
**Supplementary Table 1. Disease codes used for patient selection and outcome evaluation**

| Terms in article | ICD-10th code | Diagnosis                                      |
|------------------|---------------|-----------------------------------------------|
| Type 2 diabetes mellitus | E11           | Type 2 diabetes mellitus                      |
|                  | E12           | Malnutrition-related diabetes mellitus        |
|                  | E13           | Other specified diabetes mellitus             |
|                  | E14           | Unspecified diabetes mellitus                 |
| Cardiovascular disease | I20           | Angina pectoris                                |
|                  | I21           | Acute myocardial infarction                   |
|                  | I22           | Subsequent myocardial infarction              |
|                  | I23           | Certain current complications following acute myocardial infarction |
|                  | I24           | Other acute ischaemic heart diseases          |
|                  | I25           | Chronic ischaemic heart disease               |
| Cerebrovascular disease | I60           | Subarachnoid haemorrhage                      |
|                  | I61           | Intracerebral haemorrhage                     |
|                  | I62           | Other nontraumatic intracranial haemorrhage   |
|                  | I63           | Cerebral infarction                           |
|                  | I64           | Stroke, not specified as haemorrhage or infarction |
|                  | I65           | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
| Oral cancer | C00-14         | Malignant neoplasms of lip, oral cavity and pharynx |
| Esophagus cancer | C15           | Malignant neoplasm of oesophagus              |
| Stomach cancer | C16           | Malignant neoplasm of stomach                 |
| Colorectal cancer | C18          | Malignant neoplasm of colon                   |
|                  | C19           | Malignant neoplasm of rectosigmoid junction   |
|                  | C20           | Malignant neoplasm of rectum                  |
| Liver cancer | C22           | Malignant neoplasm of liver and intrahepatic bile ducts |
| Biliary tract cancer | C23         | Malignant neoplasm of gallbladder             |
|                  | C24           | Malignant neoplasm of other and unspecified parts of biliary tract |
| Pancreatic cancer | C25         | Malignant neoplasm of pancreas                |
| Larynx cancer | C32           | Malignant neoplasm of larynx                  |
|                  | C33           | Malignant neoplasm of trachea                 |
| Lung cancer | C34           | Malignant neoplasm of bronchus and lung        |
| Breast cancer | C50           | Malignant neoplasm of breast                  |
| Ovary cancer | C56           | Malignant neoplasm of ovary                   |
| Prostate cancer | C61          | Malignant neoplasm of prostate                |
| Kidney cancer | C64           | Malignant neoplasm of kidney, except renal pelvis |
| Bladder cancer | C67           | Malignant neoplasm of bladder                 |
| Brain and CNS cancer | C70        | Malignant neoplasm of meninges                |
|                  | C71           | Malignant neoplasm of brain                   |
|                  | C72           | Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system |
| Thyroid cancer | C73           | Malignant neoplasm of thyroid gland           |
| Hodgkin lymphoma | C81          | Hodgkin lymphoma                              |
### Supplementary Table 1. Continued

| Terms in article                        | ICD-10th code | Diagnosis                                                                 |
|----------------------------------------|---------------|---------------------------------------------------------------------------|
| Non-Hodgkin lymphoma                   | C82           | Follicular lymphoma                                                       |
|                                        | C83           | Non-follicular lymphoma                                                   |
|                                        | C84           | Mature T/NK-cell lymphomas                                                |
|                                        | C85           | Other and unspecified types of non-Hodgkin lymphoma                       |
|                                        | C96           | Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue |
| Leukaemia                              | C91           | Lymphoid leukaemia                                                        |
|                                        | C92           | Myeloid leukaemia                                                         |
|                                        | C93           | Monocytic leukaemia                                                        |
|                                        | C94           | Other leukaemias of specified cell type                                   |
|                                        | C95           | Leukaemia of unspecified cell type                                        |

ICD-10, International Classification of Diseases, 10th Revision; CNS, cerebral nervous system; NK, natural killer.
Supplementary Figure 1. The observation periods for study outcome evaluation. The initiation dates of observation period were *Helicobacter pylori* treatment prescription date in the treatment cohort and the corresponding date of *H. pylori* treatment prescription in matched patients of the non-treatment cohort. Outcome assessments were continued until December 2013.