Supplementary Method 1. Statistical Analysis and Sensitivity/Subgroup Analyses

**Statistical Analyses**

Continuous variables are expressed as the median and interquartile range (IQR). Statistical significance for 2-tailed *P* values was set at .05. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute). The primary analysis compared the subdistribution hazard of gastric cancer obtained from the Fine and Gray model between medication groups in propensity-score (PS) weighted cohorts (Supplementary Table 2).(1) Weights were derived to obtain estimates representing population-average treatment effects with an optimal balance between groups. Standardized mean differences (SMDs) are the absolute value of the difference in the mean or proportions divided by a pooled standard deviation. We calculated SMDs as the difference between groups in the number of the standard deviation, which is a more meaningful measure than *P* values from *t* tests on large samples. The proportional hazards assumptions were verified by examining the Schoenfeld residuals over time.(2) Cumulative incidence curves were generated using the Gray method.(1)

To account for potential differences in health status relevant to the likelihood of receiving a prescription for a PPI or H2RA, we estimated a PS for needing a PPI or H2RA using a logistic regression model, including all *priori* covariates that were identified up to the index dates. The predicted probability from this model represents PPI/H2RA long-term use.

The weighted cohort was formed by estimating weights from the PSs and up- or down-weighting patients to more closely resemble each other.(3, 4) As listed in Table 1, the baseline covariates were age, sex, calendar period of prescription, time from medication start to 180 cDDD-days (months), socioeconomic characteristics (income, smoking and alcohol use), indication for drug use (gastroesophageal reflux disease or peptic ulcer), Charlson Comorbidity Index, *H. pylori* eradication, and the use of other medications (aspirin, metformin, and statin).

We assessed the balance and distribution of the PSs using the following diagnostic tests. First, we compared the SMD between individual covariates in the PPI and H2RA groups before and after calculating the PS weights. After adjusting the weighting, we found evidence of a good covariate balance (all SMD < 0.1) (Table 1). Second, we examined the overlap in the PS distribution between PPI users and H2RA users, in whom the range of PSs was 0.137–0.999 and 0.114–0.999, respectively. Third, we examined the balance and distribution of PSs within the PS deciles, and we found the scores to be appropriately balanced (Supplementary Table 3 and Supplementary Figure 3).

In the main study, we excluded 2,751 (2%) patients with missing data in the health examination database and conducted the study using only complete cases.(5)

**Sensitivity and Subgroup Analyses**

We performed sensitivity analyses to assess the robustness of our study findings. As the first sensitivity analysis, we evaluated the association between long-term use of PPIs or H2RAs and gastric cancer in unadjusted and adjusted subdistribution proportional hazards regressions to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for gastric cancer between PPI users and H2RA users in the full unweighted cohort. We conducted additional analyses with a PS–matched cohort to evaluate variability caused by the study design. In the PS-matching design, respective pairs were created for each PS model using sociodemographic characteristics (age, sex, income), behavioral factors (cigarette smoking, alcohol consumption), medical conditions (body mass index, disability registry, Charlson Comorbidity Index, history of gastric ulcer, history of gastrointestinal bleeding), and gastrointestinal medication use (aspirin, metformin, statin). On the basis of the PS (specified above), an exact matching variable, and the index date, each PPI user was matched in a 1:1 fixed ratio to an H2RA user by means of an established 5 🡪1 digit within-caliper greedy nearest neighbor matching method without replacement.(6) Using this approach, we successfully matched 38,512 new PPI users to 38,512 new H2RA users, thereby creating a PS-matched cohort of 77,024 adults.

The second sensitivity analysis evaluated a cohort in which the definition of long-term use of PPIs or H2RAs was 365 cDDD-days to check for possible confounding caused by medication consumption after the baseline date, as well as by the length of the exposure duration, in the PS-weighted, full unweighted, and PS–matched cohorts. To better gauge the relative risk of cancer development by the two study drugs, we performed a longer duration sensitivity analysis (545, 730, 910 and 1,090 cDDD-days) in PS-weighted and full unweighted cohorts. Third, we considered unadjusted and adjusted full unweighted cohorts to evaluate the subdistribution hazard for gastric cancer incidence between two groups according to their medication possession ratio (MPR). Medication adherence, which in turn correlates with long-term consistent use, was measured using the MPR,(7) which was calculated as days of drug supply/days between first and last refills + days of supply in last refill. An MPR ≥ 0.8 was defined as an adherent long-term user, and patients with an MPR < 0.8 were defined as non-adherent long-term users; this cutoff value is used widely.(8, 9) To account for potential stockpiling from multiple prescriptions, MPR was capped at 100%. The MPR values were further categorized as 50–80%, 20–50%, and 0–20%. Finally, subgroup analyses tested for effect modification by including interaction terms in pre-specified covariates.