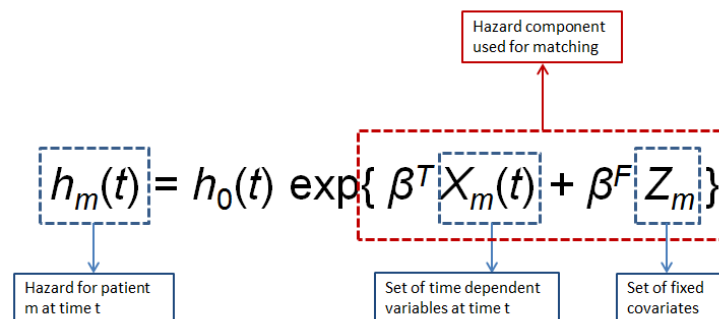## Supplemental Methods:

Time Dependent Propensity Score Matching

1. Using the primary cohort (N=349, 312), all covariates except for age, race and gender were treated as time-dependent variables from T0 till date of PPI use or end of follow up, whichever occurred first. Specifically, time-dependent eGFR indicated the eGFR at day t (where the value was equal to the outpatient eGFR measurement most close and prior to time t); time-dependent number of outpatient serum creatinine measurements and number of hospitalizations indicated the cumulative value from October 01, 1998 till day t; time-dependent disease status including diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma indicated if participants were diagnosed with the disease between October 01, 1998 and day t.

2. Time-dependent Cox regression was applied, where time until receipt of first PPI prescription was the outcome (participants receiving PPI prescription at T0 were considered to have the event with survival time equal to 0 days). Time-dependent variables from step 1 and age, race and gender were used as predictors in the model in order to obtain parameter estimates for the predictors.

3. Every participant's hazard component at day t was computed based on the parameter estimates from step 2 and their covariate values at day t.

$$ h_m(t) = h_0(t) \exp\{ \beta^T X_m(t) + \beta^F Z_m \} $$

Hazard component used for matching

Hazard for patient m at time t

Set of time dependent variables at time t

Set of fixed covariates

The hazard component was used as the time-dependent propensity score.

4. Beginning from T0 (day 0), a 1:1 sequential greedy matching without replacement was conducted. People who received PPI prescription at day t (case group at day t) were matched with people who had not yet received PPI prescription at day t (control group at day t) based on their propensity score at day

t. The order of both case and control groups was randomized before matching. A matched pair was considered successfully matched only if the propensity score difference was less than 0.2 times the standard deviation of the hazard component at time t. If no successful match was made the case in the pair was withdrawn from the further matching while the control was left in the data pool. Matching was ended when 1/ all participants in control or case group were matched or 2/ day t equaled day 1827.

5. After the matching, conditional Cox regressions stratified by matched pairs were conducted to examine the association between PPI and death.

High-dimensional propensity score:

1. Using the primary cohort (N=349,312), participants data from 1 year before T0 till T0 were collected in 5 dimensions consisting off: the first 3 digits of outpatient diagnoses ICD9 codes, the outpatient procedures CPT codes, the first 3 digits of inpatient diagnoses ICD9 codes, the first 3 digits of inpatient procedures ICD9 codes, and the outpatient drug names without dose.

2. Within each of the 5 dimensions, the top 300 most frequent items were selected, which yielded 300*5=1500 potential items.

3. For each participant, we determined if each of the 1500 potential items 1\ ever occurred, 2\ if the number of occurrences for the participant was higher than the number of occurrences in 50% of the participants and 3\ if the number of occurrences for the participant was higher than the number of occurrences in 75% of the participants. This step results in 1500*3=4500 binary potential variables. If the 50% or 75% percentile of the number of item occurrences was less than 1, then the variable were coded as 0 for all participants. If the 50% and 75% percentile of the number of item occurrences had the same value, then the 75% variable was coded as 0 for all participants.

4. Bias was calculated using formula based on apparent relative risk for each of the 4500 variables:

$$\text{Bias}=(P\_C1 (RR\_CD -1)+1)/(P\_C0 (RR\_CD -1)+1) \text{ ,if } RR\_CD \geq 1$$

$$\text{Bias}=(P\_C1 (1/RR\_CD -1)+1)/(P\_C0 (1/RR\_CD -1)+1) \text{ ,if } RR\_CD <1$$

Where P_C1 indicates the prevalence of the variable in the PPI group, P_C0 indicates the prevalece of the variable in the control group, and RR_CD indicate relative risk of death associated with the variable.

5. The top 500 variables with the largest | log(bias)| value were selected as binary empirical covariates for inclusion in the propensity score modeling.

6. The 500 variables and age, gender, race, and eGFR were used to obtain propensity scores from logistic regression where the outcome was receipt of PPI or not at T0. Propensity scores were then categorized into deciles.

7. Multivariate Cox regression with an indicator for propensity score decile was used to evaluate the association between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

Two-stage residual inclusion estimation (Instrumental Variable):

1. Based on the primary cohort (N=349,312), for each participant, data on prescriptions by the physician who prescribed the participant the acid suppression therapy at T0 was collected from 6 months before the participant's T0 till T0.

2. For each participant, the percentage of PPIs prescribed to new acid suppression therapy users by their prescribing physician, excluding the prescription of the participant, in the 6 months prior to and including T0 was computed and used as an instrumental variable. Participants whose prescribing physician did not prescribe any other acid suppression therapy to new users in the 6 months prior to and including T0 were excluded from the analysis.

3. In order to predict the participants' possibility of receiving PPI, instrumental variable and co-variables were used in a logistic regression model where the outcome was acid suppression therapy prescription at T0.

4. Residual terms were computed as the difference between participants' real probability (1 if PPI, 0 if H2 blocker) and predicted probability.

5. Multivariate Cox regression, which included the residual term and co-variables, were conducted to evaluate the relationship between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.