Estimates of burden of death and cause specific mortality associated with proton pump inhibitors among US veterans: a cohort study

Yan Xie MPH, Benjamin Bowe MPH, Yan Yan MD, PhD, Hong Xian PhD, Tingting Li MD, and Ziyad Al-Aly MD

Supplemental methods

Table of contents:

1) High dimensional propensity score

A high dimensional propensity score [1 2]method was applied as a means of adjusting for differences in the measured baseline covariates between the PPI and H2 blocker group. The incorporation of high dimensional electronic health record data available on diagnoses, procedures, surgeries, prescriptions and laboratory results, may result in a higher probability of adjusting for difference between exposed and control group. The algorithm used is as follows:

1. For each participant, we selected all available data from various sources in year prior to first record of acid suppressant prescription. The sources included outpatient records, inpatient records, pharmacy data and laboratory data. Data was then organized into 7 dimensions: outpatient International Classification of Disease Ninth Revision (ICD9) diagnosis, outpatient Current Procedural Terminology code (CPT), inpatient ICD9 diagnosis, inpatient procedure code, inpatient surgery code, outpatient pharmacy record and laboratory result (outpatient lab value higher than reference range, outpatient lab value lower than reference range, inpatient lab value higher than reference range and inpatient lab value lower than reference range).

2. For each dimension, top 300 items that occurred most frequently within cohort participants were selected, where medication frequency was defined by days of supply of the medication. For each participant, we evaluated the number of occurrence for each of the top 300 * 7 dimension=2100 items and then categorized each items occurrence into a set of three binary value: ever occurred, sometimes occurred (occurred more than 50% of the cohort participants) and frequently occurred (occurred more than 75% of the cohort participants). For the items that frequently occurred for a participant, it would also be considered as ever and sometimes occur. Similarly, if an item sometimes occurred (and thus the binary indicator variable was set to equal 1), then the ever-occurred binary variable would also be set to equal 1.

3. After obtaining the 2100*3=6300 variables, we ranked them based on the degree of imbalance in PPI and H2 blockers group. We ranked the variables based on the univariate relative risk between the variable and PPI[3].Only pre-exposure covariate information was used.

4. The top 500 ranked variables were selected for use in calculating propensity scores.

5. In order to ensure adjustment of basic demographic information and overall health condition, an additional set of fixed variables were constructed to be used in conjunction with the previously ranked variable groups in step 4. The fixed variables included: basic demographic and health services utilization characteristics including age, sex, race, number of outpatient visits, total length of stay in hospital, year of the prescription assigned, and GI disease condition including GERD, Upper GI tract bleeding, Ulcer disease, H. Pylori infection, Barrett's esophagus, Achalasia, Stricture and Esophageal adenocarcinoma[4], level of hospital complexity (defined as outpatient clinic, medical center, and health care system), clinic type (defined as gastroenterology, primary care, and other) and location of hospital (defined by VISN). Age, number of outpatient visits and total length of stay in hospital were treated as cubic spline functions in the model generating the propensity score.

6. The propensity score was then calculated using a logistic regression, which estimates the probability of being a new user of PPI given the 500 ranked variables and fixed covariates.

7. The propensity scores were then used to weight the cohort using the inverse probability of treatment weighting method. This method results in a pseudo cohort where the probability of new use of PPI or H2 blockers is independent of the measured covariates included in the generation of propensity score.

2) Instrumental variable two stage residual inclusion method

In order to reduce the probability of bias from unmeasured confounding, instrumental variable analyses were applied. We use physician-specific prescribing preference as the instrumental variable to potentially reduce bias from difference between PPI and H2 blockers groups in disease severity or other unmeasured confounders[5], where the instrumental variable was defined as the percentage of PPI within PPI and H2 blockers prescribe to participants never use PPI or H2 blockers before.

Use of an instrumental variable is valid if three primary assumptions are met: 1) The IV is strongly associated with the exposure; 2) The IV is not associated with the outcome other than through its association with the exposure (exclusion restriction); and 3) the IV does not share any causes with the outcome[6-9]. To assess the strength of our IV (assumption 1), we conducted a logistic regression of the odds of new use of PPI vs. H2 blockers. Results suggested that a 10% increase in a physician prescribing preference towards prescribing PPI in past patients was associated with a 35% (95% CI: 35%, 35%) increase in odds of the current patient being a new user of PPI compared to H2 blockers after adjustment for patient characteristics at time of prescription. These results suggest that we do not have a weak IV. Because we are using the physicians prescribing preferences for past patients, it is unlikely that there is any direct mediating mechanism though which such prescriptions directly influence the current patient's outcome (assumption 2)[10]. Indirectly, preferences for PPI prescription may be related to preferences for prescription of other drugs, which could alter risk of death in patients[11]; however, the HDPS would incorporate the prescription of any drugs associated with the prescription of PPI into the analysis if relevant. Here we employ a HDPS to include a broad swath of measured covariates to reduce the chance of omitting any relevant confounders (assumption 3). It is possible that certain factors, such as level of complexity of the hospital, specialty of the physician, and geography may lead to instances of clustering of patients with a higher (or lower) severity of disease, which could violate this assumption. However, we included in the HDPS measures of the level of complexity, type of clinic, and the location of the hospital where the prescription was provided to reduce such probability.

We utilized the two-stage residual inclusion method for application of the IV[12]; the steps are presented here:

1. For each cohort participant, data on prescriptions by the physician who prescribed the participant the acid suppression therapy at T0 was collected within the one year before the participant's first record of acid suppressant prescription. We then computed the IV by counting the total number of new PPI or H2 blockers prescriptions and the proportion of these which are PPI. The IV was then included as an independent variable in an inverse probability of treatment weighted logistic regression to predict the probability of new use of PPI.

2. The residual, which is the difference between the observed acid suppressant new use and the predicted probability of acid suppressant new use, is obtained from the logistic regression in step 1.

3. This residual was then adjusted for in the survival analyses in the weighted cohort (pseudo cohort) as a means of accounting for unmeasured confounding

It is worth mentioning that the IV method measures the local average treatment effect[13], which is the average causal effect for "adherers". In other words, this method does not estimate the effect within those participants who will never receive PPI prescription or always receive PPI prescription, no matter what the physician prescribing preferences are, or those who always receive opposite of what was preferred by their physician. We consider these situations unlikely to happen in our cohort, hence the local average treatment effect should be close to the average treatment effect in the cohort.

3) Sensitivity analysis

We conducted a dose response analysis in a cohort of new PPI users only. A time-updated cumulative exposure was defined based on number of days' supply contained in prescription records. Time zero was defined as the end of last prescription to avoid immortal bias. Linear trend between duration increase and risk of outcome was also examined.

In addition, as a significant proportion of new users of H2 blockers used PPI later during follow-up, we conducted other sensitivity analyses that examined PPI ever-use as a time varying exposure. If new users of H2 blockers were subsequently prescribed PPI during follow up, they were then considered in the PPI group from the date of the PPI prescription until the end of follow up. For both analyses, Fine and Gray model was conducted and HDPS was applied to adjusted for baseline confounders. Hazard ratios and their 95% CI are reported.

4) Reporting of results

Absolute results were reported based on estimated survival possibility at ten years:

1. **PPI and H2 blockers event rates are reported as percentages**. The event rate for the H2 blockers group was equal to the average cumulative incidence rate base on Fine and Gray model when we set all cohort participants as being in the H2 blockers group. Similarly, the event rate for PPI was equal to the average cumulative incidence rate base on Fine and Gray model when setting all cohort participants as being in the PPI group.

2. **Excess burden per 1000 people**: The excess burden of an event associated with PPI was calculated from the difference between the PPI event rate and H2 blocker event rate. This number was reported per 1000 persons. The excess burden represents the number of events difference that might occur in every 1000 people when compared between the whole cohort being new users of PPI and being new users of H2 blockers. Estimation of the modeled effect of PPI was done in the setting based on the same covariates distribution as the whole cohort.

5) References:

1. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;**70**(1):41-55
2. Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology (Cambridge, Mass) 2009;**20**(4):512
3. Rassen JA, Glynn RJ, Brookhart MA, et al. Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. American journal of epidemiology 2011;**173**(12):1404-13
4. Xie Y, Bowe B, Li T, et al. Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. BMJ open 2017;**7**(6):e015735
5. Brookhart MA, Wang P, Solomon DH, et al. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. Epidemiology (Cambridge, Mass) 2006;**17**(3):268
6. Swanson SA, Hernan MA. Commentary: how to report instrumental variable analyses (suggestions welcome). Epidemiology 2013;**24**(3):370-4 doi: 10.1097/EDE.0b013e31828d0590[published Online First: Epub Date]|.
7. Lousdal ML. An introduction to instrumental variable assumptions, validation and estimation. Emerging themes in epidemiology 2018;**15**:1 doi: 10.1186/s12982-018-0069-7[published Online First: Epub Date]|.
8. Boef AG, Dekkers OM, le Cessie S, et al. Reporting instrumental variable analyses. Epidemiology 2013;**24**(6):937-8 doi: 10.1097/01.ede.0000434433.14388.a1[published Online First: Epub Date]|.
9. Swanson SA. Instrumental Variable Analyses in Pharmacoepidemiology: What Target Trials Do We Emulate? Current epidemiology reports 2017;**4**(4):281-87 doi: 10.1007/s40471-017-0120-1[published Online First: Epub Date]|.
10. Brookhart MA, Wang PS, Solomon DH, et al. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. Epidemiology 2006;**17**(3):268-75 doi: 10.1097/01.ede.0000193606.58671.c5[published Online First: Epub Date]|.
11. Rassen JA, Brookhart MA, Glynn RJ, et al. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. Journal of clinical epidemiology 2009;**62**(12):1226-32 doi: 10.1016/j.jclinepi.2008.12.005[published Online First: Epub Date]|.
12. Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. J Health Econ 2008;**27**(3):531-43 doi: 10.1016/j.jhealeco.2007.09.009[published Online First: Epub Date]|.
13. Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. Journal of the American statistical Association 1996;**91**(434):444-55