

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Excess Risk of Death among Users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States Veterans
AUTHORS	Xie, Yan; Bowe, Benjamin; Li, Tingting; Xian, Hong; Yan, Yan; Al-Aly, Ziyad

VERSION 1 - REVIEW

REVIEWER	Mirko Di Martino Department of Epidemiology, Lazio Regional Health Service, Rome, Italy.
REVIEW RETURNED	14-Jan-2017

GENERAL COMMENTS	The sensitivity analyses on unmeasured confounding (performed as described by Schneeweiss) are particularly useful and interesting.
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REVIEWER	Dean Eurich University of Alberta, Alberta, Canada
REVIEW RETURNED	27-Jan-2017

GENERAL COMMENTS	<p>Among a large cohort of veterans, the authors have shown that the risk of death among PPI users is increased among those without gastrointestinal conditions and with prolonged duration of use. I have a few additional considerations to strengthen the paper:</p> <ol style="list-style-type: none">1) Do the authors have any information on cause of death? All-cause mortality is relatively insensitive and I would not expect PPI's to increase the risk of death across the board. Additional data on what exact areas PPI's seem to be increasing death would greatly strengthen the paper.2) Pg 5, lines 51 – "Once cohort participants received PPI prescription, they were considered with effect of PPI until the end of follow up". Unless I am misinterpreting the paper, it appears a single prescription is sufficient to keep a person as 'exposed' throughout the entire follow-up? This is an extremely wide definition of what is a PPI user and exposes the paper to substantial potential for misclassification bias. The authors need to have a mechanism to either censor patients after discontinuing PPI therapies, or more appropriately conduct time varying analysis so the 'at risk time' can be attributed to the correct exposure group. In the current analysis, a single prescription in 2010 with no additional prescriptions, would result in the patients being considered exposed for the entire follow-up - this is clearly not correct and a better approach to classifying patients is required. This is particularly true given that other covariates were modelled as time-dependent covariates.3) It is very unclear from the manuscript when T0 occurs for the
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	<p>various analyses and cohorts. The paper would be strengthened with several diagrams outlining exactly when T0 occurred relative to the prescriptions. I have some concerns that the various differences in T0 between the PPI group and control group may be influencing the results but it is currently difficult to tell how the time is partitioned in this study.</p> <p>4) What was the rational of using hemoglobin as a sensitivity analysis? Certainly, more appropriate sensitivity analyses (e.g., patients with advanced or less advanced kidney disease, advanced age, those with a history of pneumonia vs no pneumonia) as PPI's have been linked to pneumonia)) would shed more light on the robustness of the results.</p> <p>5) I think the authors are over stating the importance of PPI on all-cause mortality. The overall risk is very small in several of the models (1.15, 1.16) and could easily be due to misclassification of exposures, unmeasured confounding, etc. The discussion needs to be more balanced around the fact that for several of the models, the risk is very small and may not be clinical important for most patients.</p> <p>6) In figure 1, the survival curves almost immediately separate between the groups. This is relatively uncommon to see in clinical trials and for survival curves to separate so early in observational data suggest significant selection bias and unmeasured confounding. I suggest the authors do some sensitivity analyses around the occurrence of death. For example, does exclusion of early events (i.e., with first 3 months) change the study results? Are the results mainly driven by early vs late deaths. Clinically, it is hard to fathom how PPI's could influence mortality so quickly.</p> <p>7) The authors indicate that propensity scores were used. However, no evidence is presented that the propensity score generated was acceptable in terms of classification and in terms of balancing the cohorts as hoped. Some additional details on the balance of the groups following propensity score matching is required.</p> <p>8) I may have missed it but I did not see any ethics approval noted in the paper.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This paper was previously submitted to the BMJ, and I revised it after the first submission. I am happy with the author's changes to the manuscript. The sensitivity analyses on unmeasured confounding (performed as described by Schneeweiss) are particularly useful and interesting.

Response:

We thank the reviewer for this comment.

Reviewer: 2

General Response: We thank the reviewer for his earlier comments (BMJ) which we have responded to. And thank him again for the new comments provided in this round of reviews (BMJ Open).

1) Do the authors have any information on cause of death? All-cause mortality is relatively insensitive and I would not expect PPI's to increase the risk of death across the board. Additional data on what exact areas PPI's seem to be increasing death would greatly strengthen the paper.

Response:

We do not have cause of death data. This is now noted in the limitations section.

2) Pg 5, lines 51 – “Once cohort participants received PPI prescription, they were considered with effect of PPI until the end of follow up”. Unless I am misinterpreting the paper, it appears a single prescription is sufficient to keep a person as ‘exposed’ throughout the entire follow-up? This is an extremely wide definition of what is a PPI user and exposes the paper to substantial potential for misclassification bias. The authors need to have a mechanism to either censor patients after discontinuing PPI therapies, or more appropriately conduct time varying analysis so the ‘at risk time’ can be attributed to the correct exposure group. In the current analysis, a single prescription in 2010 with no additional prescriptions, would result in the patients being considered exposed for the entire follow-up - this is clearly not correct and a better approach to classifying patients is required. This is particularly true given that other covariates were modelled as time-dependent covariates.

Response:

The reviewer is correct that in our models a person was treated as exposed to PPI at and after incident PPI prescription. To clarify, we did not consider the patient as using PPI for the entire follow-up, but we considered the patient as potentially affected by the PPI (at risk) for the duration of the follow-up.

Consider this scenario to illustrate the rationale for this approach: A patient with a single PPI prescription in 2010, and no additional prescriptions subsequently, who may have higher risk of adverse outcomes during the prescription, such as acute kidney injury (1). The PPI induced acute kidney injury could increase the patient’s risk of death during the follow up even outside the period of the PPI prescription (2).

The time-dependent drug ever used model has been used in pharmacoepidemiology studies (3). If we considered defining exposure as only during a PPI prescription, the model will examine the relationship between current use of PPI and risk of death; it would not reflect any potential lag effect.

3) It is very unclear from the manuscript when T0 occurs for the various analyses and cohorts. The paper would be strengthened with several diagrams outlining exactly when T0 occurred relative to the prescriptions. I have some concerns that the various differences in T0 between the PPI group and control group may be influencing the results but it is currently difficult to tell how the time is partitioned in this study.

Response:

Flow charts diagramming how we reached the final cohorts and assigned time zeros have been added.

4) What was the rationale of using hemoglobin as a sensitivity analysis? Certainly, more appropriate sensitivity analyses (e.g., patients with advanced or less advanced kidney disease, advanced age, those with a history of pneumonia vs no pneumonia) as PPI’s have been linked to pneumonia)) would shed more light on the robustness of the results.

Response:

This was in response to a comment made by a previous reviewer (reviewer number 1 in the BMJ

round of the reviews). Based on FAST-MI 2010 data (a cohort of AMI patients hospitalized in France at the end of 2010): the % of patients with anemia on admission was 21% in those prescribed PPIs at discharge, compared with 13% in those not receiving PPIs, $P < 0.001$.

Sensitivity analyses stratifying by CKD, age and pneumonia at T0 have been added. Risk was also increased in those with and without history pneumonia (HR=1.39; CI=1.32, 1.45, and HR=1.21; CI=1.18, 1.24; respectively); with and without chronic kidney disease (HR=1.18; CI=1.14, 1.22, and HR=1.29; CI=1.26, 1.33; respectively); above and below age 65 (HR=1.17; CI=1.13, 1.20, and HR=1.44; CI=1.39, 1.50; respectively).

5) I think the authors are over stating the importance of PPI on all-cause mortality. The overall risk is very small in several of the models (1.15, 1.16) and could easily be due to misclassification of exposures, unmeasured confounding, etc. The discussion needs to be more balanced around the fact that for several of the models, the risk is very small and may not be clinically important for most patients.

Response:

We agree with the reviewer that the effect size is relatively small, and that while we controlled for a number of covariates, it is likely that the association seen may reflect residual confounding (either unmeasured, or unknown). This is included in the limitation section. We are simply describing excess risk of death among users of PPI. We also suggest limiting PPI use and duration to instances where it is medically indicated which we think is a reasonable approach.

6) In figure 1, the survival curves almost immediately separate between the groups. This is relatively uncommon to see in clinical trials and for survival curves to separate so early in observational data suggest significant selection bias and unmeasured confounding. I suggest the authors do some sensitivity analyses around the occurrence of death. For example, does exclusion of early events (i.e., with first 3 months) change the study results? Are the results mainly driven by early vs late deaths. Clinically, it is hard to fathom how PPI's could influence mortality so quickly.

Response:

We have conducted additional sensitivity analyses where we excluded patients who died within 90 days after first PPI or H2 blockers prescription. The association between PPI and death remained significant (HR=1.23; CI=1.20, 1.26).

7) The authors indicate that propensity scores were used. However, no evidence is presented that the propensity score generated was acceptable in terms of classification and in terms of balancing the cohorts as hoped. Some additional details on the balance of the groups following propensity score matching is required.

Response:

Details on the balance of the groups after matching were added to the manuscript. In addition, we further controlled for covariates after using the covariates for propensity score matching, in a doubly robust approach, to adjust for any residual confounding left after the matching (4).

8) I may have missed it but I did not see any ethics approval noted in the paper.

Response:

Ethics approval was noted at the end of cohort participants section. We stated “The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.”

References:

1. Blank, M.-L., Parkin, L., Paul, C., & Herbison, P. (2014). A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. *Kidney International*, 86(4), 837–844. doi:10.1038/ki.2014.74
2. Lafrance, J. ., & Miller, D. R. (2009). Acute kidney injury associates with increased long-term mortality. *Journal of the American Society of Nephrology*, 21(2), 345–352. doi:10.1681/asn.2009060636
3. Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. (2016). Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Internal Medicine*, 176(2), . doi:10.1001/jamainternmed.2015.7193
4. Funk, M. J., Westreich, D., Wiesen, C., Sturmer, T., Brookhart, M. A., & Davidian, M. (2011). Doubly robust estimation of causal effects. *American Journal of Epidemiology*, 173(7), 761–767. doi:10.1093/aje/kwq439

VERSION 2 – REVIEW

REVIEWER	Dean Eurich University of Alberta
REVIEW RETURNED	14-Mar-2017

GENERAL COMMENTS	<p>I thank the authors for their detailed responses to my concerns. However, with respect to the exposure definition I am still unconvinced that a single prescription, with no additional follow-up prescription, can alter mortality as the authors have suggested. Although the authors are correct that the ever-never approach has been used in pharmacotherapy, most agree it is insufficient and can lead to significant exposure missclassification (see Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies by Stricker et al, <i>Eur J Epidemiolo</i>, 2010). The authors need to provide better control of the exposure definition using either a time varying approach or a nested case control design with drug exposure defined as current use (i.e., within 90 days of the event), Past (any use prior to 90 days), and never. If the authors hypothesis is correct, particularly given their illustration that 1 prescription can cause kidney damage which would lead to long-term mortality), then the results should show that both current use and past use are associated with an increase in mortality. Currently, the exposure definition provided is extremely crude given todays contemporary pharmacoepidemiology methods and does not support their current hypothesis. A more sophisticated exposure definition is required.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

I thank the authors for their detailed responses to my concerns. However, with respect to the exposure definition I am still unconvinced that a single prescription, with no additional follow-up prescription, can alter mortality as the authors have suggested. Although the authors are correct that the ever-never approach has been used in pharmacotherapy, most agree it is insufficient and can lead to significant exposure missclassification (see Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies by Stricker et al, Eur J Epidemiol, 2010). The authors need to provide better control of the exposure definition using either a time varying approach or a nested case control design with drug exposure defined as current use (i.e., within 90 days of the event), Past (any use prior to 90 days), and never. If the authors hypothesis is correct, particularly given their illustration that 1 prescription can cause kidney damage which would lead to long-term mortality), then the results should show that both current use and past use are associated with an increase in mortality. Currently, the exposure definition provided is extremely crude given today's contemporary pharmacoepidemiology methods and does not support their current hypothesis. A more sophisticated exposure definition is required.

Our Response:

We thank the reviewer pointing this out.

Based on the reviewer's input and as he suggested: we conducted analyses where the time-dependent exposure were classified as current use (within 90 days of prescription end), Past use (use prior to 90 days), and never use. Compared to use H2 blockers and no use of PPI, the current use of PPI and past use of PPI were significantly associated with increased risk of death (HR=1.23; CI=1.21-1.26, and HR=1.53; CI=1.50, 1.57, respectively). The results were consistent with our observation in the primary analyses that PPI use was associated with increased risk of death.

The method section and results have been revised to include the following:

Method:

We conducted analyses based on a three level classification of exposure, where patient's status at time t could be current use (using PPI or finished last PPI prescription within 90 days before t), past use (used PPI after T0 but finished more than 90 days before t), and never use.

Result:

In analyses where time-dependent exposure was classified as current use (within 90 days), past use (use prior to 90 days), and never use of PPI; compared to use of H2 blockers and never use of PPI (the reference group), current use of PPI and past use of PPI were associated with increased in risk of death (HR=1.23; CI=1.21- 1.26, and HR=1.53; CI=1.50, 1.57, respectively).

VERSION 3 – REVIEW

REVIEWER	Dean Eurich University of Alberta Edmonton Canada
REVIEW RETURNED	21-Mar-2017

GENERAL COMMENTS	No further comments. The authors have addressed all of my concerns.
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