Article details: 2021-0240
Title: Prescribing, deprescribing and potential adverse effects of proton pump inhibitors in older multimorbid patients: an observational study
Authors: Carole E. Aubert MD, Manuel R. Blum MD MSc, Viktoria Gastens, Olivia Dalleur PhD, Fanny Vaillant, Emma Jennings, Drahomir Aujesky MD MSc, Wade Thompson PharmD PhD, Tijn Kool MD PhD, Kees Kramers MD PhD, Wilma Knol MD, Denis O'Mahony MD, Nicolas Rodondi MD MAS

Reviewer 1: Dr. Emily McDonald
Institution: McGill University
General comments (author response in bold)

Comment 32
A larger cohort would be needed to demonstrate a reduction in ADEs due to PPI deprescribing. Readmission has been shown with PPIs (along with many other adverse outcomes) and so the analysis, unfortunately, doesn't add any major new findings to the literature, I'm afraid. I am a proponent of PPI deprescribing, but I don't think this analysis adds to the case for deprescribing. Apologies, as I am sure this is a disappointing review to receive.
We appreciate the honesty of the reviewer. While we agree that our cohort might have been underpowered for some of the analyses, we still think that our study adds to the previous knowledge. Our aim was not to demonstrate a reduction in ADEs due to PPI deprescribing, which we did also not analyze in the study. While there is literature on PPI prescribing and deprescribing, as well as on PPI ADEs, we lack data for the specific vulnerable population of older multimorbid patients. Our study contributes to filling out this lack. We highlighted this in the introduction and discussion:
Page 3, paragraph 1:
"Before, it is important to increase knowledge on current state of PPI prescribing, adverse effect risks, and discontinuation safety in older multimorbid patients, an understudied population particularly vulnerable to adverse effects of medications."
Page 11, paragraph 2:
"Third, we focused on an older multimorbid population with polypharmacy, which is understudied."

Reviewer 2: Dr. Cheryl Sadowski
Institution: University of Alberta
General comments (author response in bold)

This international study does answer some questions about PPI's and safety and the effect of hospitalization. This does add value to the literature on PPIs and deRx.

A few suggestions to consider:

Comment 33
Abstract - specify here if this is a community-dwelling population. If it is a nursing home sample then the findings would be interpreted differently.
The OPERAM trial included both community-dwelling and nursing home patients. 146 (8%) of the patients included in the present analysis were discharged to a nursing home or palliative setting. Because of the word count limit, we could not

add this information in the abstract, but in the methods of the manuscript (page 4, paragraph 1):
"The OPERAM trial9,10 included community-dwelling and nursing home (9%) patients aged ≥70 years, with multimorbidity (≥3 chronic conditions, i.e., international classification of diseases, 10th revision, codes with an estimated duration of ≥6 months or based on a clinical decision) polypharmacy (≥5 chronic medications), and admission to an acute hospital between 12/2016 and 12/2019."

Comment 34
Abstract - I would suggest giving a one sentence explanation of what OPERAM is because the abstract should be a summary in itself, not require the reader to look up other articles. It is good to describe the intervention point in the abstract.
We added this information about OPERAM intervention in the abstract (page 2, paragraph 2):
"Prospective longitudinal cohort study using data from the OPERAM trial (2016-2018, 1-year follow-up, four European countries, intervention to reduce inappropriate prescribing; adults ≥70 years, ≥3 chronic conditions, ≥5 chronic medications)."

Comment 35
Introduction - extremely well written.
Suggest on 4th line of Introduction to explain if total costs are worldwide vs just in the US, or just the countries in this study?
The costs applied only to a single US managed-care organization. Given that clarifying what this amount was exactly referring to would have been out of the scope of our introduction (given the word-count limit also), and that this amount is hard to extrapolate, we simplified this sentence (please see response to Comment 25).

Comment 36
Methods - also well written. Good structure, complete. For the ACCF/ACG/AHA potentially appropriate indications - antiplatelet therapy is listed which should include anticoagulants, or if this is not correct please explain why something that increases risk is not included.
The ACCF/ACG/AHA list antiplatelet medication as an indication when associated with another risk factor, such as age >60 years old or anticoagulant medication. However, anticoagulant without antiplatelet medication is not listed as an indication for PPI. Anticoagulants do indeed not act on acid secretion. All participants of the OPERAM trial had the additional risk factor "age >60 years" so that antiplatelet medication was considered a potentially appropriate indication for all the patients (whether they did or not have a co-medication with an anticoagulant). Anticoagulant alone however was not considered an appropriate indication, based on guidelines and ACCF/ACG/AHA consensus (see references 6, 13, 15), so we did not add it as an indication. We clarified the reason for including antiplatelet medication in the methods (page 4, paragraph 2):
"According to guidelines and expert consensus of the ACCF/ACG/AHA, potentially appropriate indications for PPIs in adults aged ≥65 years include: 1) gastro-esophageal reflux disease with acid-related complications (i.e., erosive esophagitis or peptic stricture) or symptomatic gastro-esophageal reflux disease; 2) Barrett's esophagus; 3) current treatment of gastro-duodenal ulcer; 4) current

treatment of Helicobacter pylori; 5) acute gastritis; 6) peptic gastro-intestinal bleeding; 7) persistent use of non-steroidal anti-inflammatory drug and/or co-therapy with antiplatelet medication (given all patients in OPERAM were aged over 60 years as an additional risk factor). PPI administration without any of those indications was considered potentially inappropriate."

Comment 37
Outcomes - final sentence here notes that readmissions were assessed as both combined and distinct outcomes. Was that pre-specified? What was the rationale? When both methods are used it appears as if you were hoping for something to be statistically significant.
This was pre-specified. The reason is that we wanted to study both the overall potential adverse impact of PPIs (PPI-related readmissions) and the specificities of those potential adverse effects (i.e., which cause, such as pneumonia or fracture). Readmissions related to bacterial intestinal infection (N=3) and acute interstitial nephritis (N=1), as well as GI bleeding (N=0), were however not analyzed because of the low event rates for these outcomes.

Comment 38
Results – Well written. Table 1 - It's unclear for the study site being statistically significant - what is being compared?
This p-value was for the overall comparison across all study sites. We can see that the percentages highly vary across sites. For example, in Ireland, more participants were without than with PPI, while the opposite was true in Belgium. We added a note below the table:
"*p-value for comparison across all study sites."

Comment 39
Table 2 - a simple table but it's unusual that the Legend is longer than the table. I'm wondering if some of this content can be moved into the Results text. This also applies to Fig2.
Thank you for the comment. We had put all details so that the results described in Table 2 and Figure 2 are clearly understandable by themselves without any reference to the manuscript text. We now simplified the legends keeping only the main information on the analyses.

Comment 40
Fig 1C - suggest adding in the actual n for each textbox as it's unclear if it's a fraction of a fraction vs the percentage of the original value. (For example is the 18% of the original 41% or new patients in this group?)
We appreciate this suggestion. We have added the numbers (numerators and denominators) in addition to the percentages, to clarify. There are now two figures, separating intervention and control patients (see response to Comment 10).

Comment 41
Discussion: Excellent opening paragraph, but I do not support including trends. The last sentence in the first paragraph highlights that the AE of PPIs showed a pattern but statistically it did not. However, you do later in Discussion point out that there probably wasn't enough power to answer all of these questions about uncommon AE. I think that type of note about a trend is better placed within the discussion of statistical power.

Thank you for the comment. We removed the second part of the last sentence, and let the discussion about that later in the limitation section (page 10, paragraph 4):
"Second, we used only the first readmission diagnosis to define readmissions potentially related to PPI adverse effects. This yielded a low event rate with broad confidence intervals suggesting we may have lacked power."

Comment 42
There is not a lot of emphasis on medication reviews but it is noted midway through the Discussion that OPERAM triggered physician medication reviews. What about pharmacist reviews? There is literature about pharmacist medication review and in some countries (although I do not know the scope of practice for pharmacists in all the countries in this study) pharmacists can be prescribe and would certainly influence medication use. Other healthcare professionals can be considered as well, such as nurse practitioners who prescribe.
In Switzerland, physicians only have access to data needed for a medication review in ambulatory care. However, in other countries (e.g., Belgium), this can be done by pharmacists. We modified this sentence in the discussion (page 9, paragraph 3, and page 10, paragraph 1).
"It is also possible that primary care provider information about the fact that their patient had been included in the OPERAM trial has stimulated healthcare professionals to conduct medication reviews."