PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Suboptimal prescribing of proton pump inhibitors in low-dose aspirin users; a cohort study in primary care.
AUTHORS	Korevaar, J; de Jong, Hilda; van Dijk, Liset; Voogd, Eef; Dijk, Christel; van Oijen, Martijn

VERSION 1 - REVIEW

REVIEWER	Katia Verhamme Department of Medical Informatics ErasmusMC Rotterdam The Netherlands Conflict of interest: None related to this research topic
REVIEW RETURNED	06-May-2013

GENERAL COMMENTS	This is an interesting topic and provides further information on use of PPI in LDASA users and adherence to guidelines/recommendations In general this is an interesting topic and provides further information on the suboptimal prescribing of PPI in NSAID/aspirin users. I have some questions for the authors: 1/ As the authors mention; the Dutch recommendations for on prescribing of PPI in regular LDASA users was finalised in 2009. However, the study period was from 2008-2010. In the discussion; the authors refer to the fact that the study setting might be too early to measure the influence of the Dutch recommendations. Could the authors stratify the analysis for the different calendar years. It would be interesting to notice whether concomitant use of PPI is higher in 2010 than in 2008? 2/ The authors exclude patients on irregular use of LDASA from the analysis. This only became clear to me when I looked at figure 1. I would clarify this in the method. I suppose the authors excluded also patients with only 1 prescription of LDASA?

	3/ Regular use of LDASA is defined as receiving each consecutive prescription within 6 months of the previous. Personally, I do believe that allowing a gap of 6 months to define a regular user is very generous. Can the authors conduct a sensitivity analysis shortening the gap eg to 3 months to check whether concomitant use of PPI increases? 4/ Concomitant use of PPI is described as either use prior to LDASA, starting PPIs within one week of LDASA or more than one week after LDASA. Especially for prior use and subsequent use, actual concomitant use might be very low. I would be more interested to know how many days of LDASA use are covered by concomitant use of PPI as well. This implies re-programming and thus might be labour intensive however, provides more correct data on concomitant use of PPI and LDASA. 5/ LDASA use is based on ATC codes – The authors included some drugs eg N02BA01 of which some (eg aspirin 500 mg) can not be considered as low dose use. I would exclude those aspirin formulations which are given for treatment of pain. 6/ In the method section, I would combine the 2 paragraphs (on page 8 and 9) on low or increased risk of GI complications into 1. 7/ Table 1 and 2 describes patient characteristics and provides p values for differences amongst the different groups. These differences were probably tested by means of a Chi-Square test? If this is the case, this should be added to the analysis part. 8/ Table 3 provides the probability of receiving PPI prescriptions in LDASA users. I suppose this analysis is only conducted for those LDASA patients who initiated use of PPI on the same day of the LDASA prescription or subsequently? I don't think this analysis would make sense in patients already on PPI when initiating LDASA. Could the authors explain where the number 9887 comes from? 9/ authors take comorbidity and concomitant medication into account. Do the authors have info on smoking? Alcohol use? These factors could be confounders too.

REVIEWER	Professor Marion Bennie Professor of Pharmacy Practice University of Strathclyde Scotland I have no competing interests
REVIEW RETURNED	13-May-2013

THE STUDY	Small point - population of 120 practices - it would be helpful to know how representative this is if the netherland population i.e. % coverage of total population
RESULTS & CONCLUSIONS	minor edits - there is minimal highlighting of thr univariate versus multivariate analysis within the results section - table 1 - line 24 - Tactus digestivus ?? line 54 - cardiac therapy - ill defined
GENERAL COMMENTS	Well desribed pharmacoepidemiology study in a reasonale population sample in general practice

VERSION 1 – AUTHOR RESPONSE

Reviewer: Katia Verhamme
Department of Medical Informatics
ErasmusMC Rotterdam
The Netherlands

Conflict of interest: None related to this research topic

This is an interesting topic and provides further information on use of PPI in LDASA users and adherence to guidelines/recommendations

I have some questions for the authors:

1/ As the authors mention; the Dutch recommendations for on prescribing of PPI in regular LDASA users was finalized in 2009. However, the study period was from 2008-2010. In the discussion; the authors refer to the fact that the study setting might be too early to measure the influence of the Dutch recommendations. Could the authors stratify the analysis for the different calendar years. It would be interesting to notice whether concomitant use of PPI is higher in 2010 than in 2008?

Indeed the recommendations were finalized in 2009, before the start of our study. Taking the complete study period, 46.1% of the patients with a high GI risk were regular PPI users. If we stratify the study per calendar year, thus taking just the incident patients per year, we find a small increase over time in the % of patients with a high GI risk taking regular PPIs. We feel that a longer follow-up period is warranted to determine whether a true increase in regular use of PPI in patients with high GI risk can be noticed. Therefore, we decided to keep the discussion about the influence of the recommendation as it is.

Year % pts with high GI risk and regular PPI usage
2008 42.1%

2009 46.5%
2010 49.3%

2/ The authors exclude patients on irregular use of LDASA from the analysis. This only became clear to me when I looked at figure 1. I would clarify this in the method.
I suppose the authors excluded also patients with only 1 prescription of LDASA?

We have added a sentence to the method section to clarify that we indeed excluded irregular LDASA users and users with just one LDASA prescription.

3/ Regular use of LDASA is defined as receiving each consecutive prescription within 6 months of the previous. Personally, I do believe that allowing a gap of 6 months to define a regular user is very generous. Can the authors conduct a sensitivity analysis shortening the gap e.g. to 3 months to check whether concomitant use of PPI increases?

We agree that a gap of 6 months is generous, yet we have chosen to be generous in order to limit the number of incorrect labeling patients as irregular user, where they are in fact regular users, but irregular collect their LDASA due to storing. With a much stricter gap (3 months instead of 6 months), less patients will be classified as regular LDASA users, and thus will be included in or analyses.
If we apply a gap of 3.5 months (to leaf some space for collecting 2 weeks before or after the 90 days to overcome holidays), we would have included 7350 LDASA patients (out of the 12343 patients). The distribution of regular PPI user, irregular PPI user and no use of PPI is similar within this selected group with a gap of 3.5 months.

6 months gap (N=12343) (as is in the manuscript)
No use of PPI: 5683 (46.0%)
Regular PPI use: 4204 (34.1%)
Irregular PPI use: 2456 (19.9%)

3.5 months gap (N=7350) (new definition of LDASA gap)
No use of PPI: 3492 (47.5%)
Regular PPI use: 2550 (34.7%)
Irregular PPI use: 1308 (17.8%)

Baseline characteristics like age was also similar for the total group (67.4) versus the group with a more stricter gap (68.5 yrs). So, a shortening of the gap from 6 months to 3.5 months did not alter the number (%) of patients who use PPI regular.

4/ Concomitant use of PPI is described as either use prior to LDASA, starting PPIs within one week of LDASA or more than one week after LDASA. Especially for prior use and subsequent use, actual concomitant use might be very low. I would be more interested to know how many days of LDASA use are covered by concomitant use of PPI as well. This implies re-programming and thus might be labor intensive however, provides more correct data on concomitant use of PPI and LDASA.

Patients who obtained their first PPI prescriptions before the start of LDASA (previous starters), were counted as irregular users if they stopped their PPI use somewhere during the follow-up period. So if a previous starter is counted as regular user, they used PPI during the complete follow-up period of LDASA. The same holds for simultaneous starters, if they stopped PPI use somewhere during follow-up, they were counted as irregular users. Irregular users are presented separately in Table 2 and not included in the analyses of Table 3. So, regular users who started previously or simultaneously with

PPI, used PPI during the complete follow-up of LDASA use.
Indeed, concomitant PPI use of the subsequent starter could start any moment after the initiation of LDASA, and if they did not stop PPI use, they are counted as regular users. We feel that this difference in usage period for this subgroup does not bias our results, our main question was which factors influence the probability of obtaining a PPI regularly. All patients in the regular group did take PPI regularly, and even for the simultaneous starters this period of concomitant use could be relative short. For questions regarding the effect of PPI in preventing GI complications this would of course be essential to take into account.

5/ LDASA use is based on ATC codes – The authors included some drugs e.g. N02BA01 of which some (e.g. aspirin 500 mg) cannot be considered as low dose use. I would exclude those aspirin formulations which are given for treatment of pain.

Indeed N02BA01 could be supplied in a high dosage; in our study 4 patients received N02BA01. Two patients received it with a dosage of 100 mg, and the other 2 received a dosage of 180 mg. We decided to leave them into the study due to the low dosage they received.

6/ In the method section, I would combine the 2 paragraphs (on page 8 and 9) on low or increased risk of GI complications into 1.

We have combined both paragraphs.

7/ Table 1 and 2 describe patient characteristics and provides p values for differences amongst the different groups. These differences were probably tested by means of a Chi-Square test? If this is the case, this should be added to the analysis part.

We have added this to the method section.

8/ Table 3 provides the probability of receiving PPI prescriptions in LDASA users. I suppose this analysis is only conducted for those LDASA patients who initiated use of PPI on the same day of the LDASA prescription or subsequently? I don't think this analysis would make sense in patients already on PPI when initiating LDASA.
Could the authors explain where the number 9887 comes from?

In Table 3 just no PPI users (n=5683) and regular PPI users (n=4204) are included, resulting in a total of 9887 patients. Next to the title of the Table, we have added this extra in a footnote.

9/ authors take comorbidity and concomitant medication into account. Do the authors have info on smoking? Alcohol use? These factors could be confounders too.

We are aware that these factors could be confounders as well, but unfortunately, we don't have this information as it is not systematically recorded in the EMR.

Reviewer: Professor Marion Bennie
Professor of Pharmacy Practice
University of Strathclyde
Scotland

I have no competing interests

Small point - population of 120 practices - it would be helpful to know how representative this is if the Netherlands population i.e. % coverage of total population

120 practices is almost 3% of all Dutch practices. Our database is representative for the Netherlands on the level of the patient (age, gender) on the level of practice (type of practice, years of experience), and on the level of geographical distribution and urbanization.

minor edits
- there is minimal highlighting of thr univariate versus multivariate analysis within the results section

There is no highlighting in Table 3 for the univariate vs. multivariate analyses. We leave it up to the editor if this is warranted.

- table 1 - line 24 - Tactus digestivus ??

We changed in into Gastrointestinal tract

line 54 - cardiac therapy - ill defined

Cardiac therapy is defined as a prescription of an ATC-code C01 in the year before or after the first LDASA prescription. We have added this to the method section.

Well desribed pharmacoepidemiology study in a reasonale population sample in general practice

VERSION 2 – REVIEW

REVIEWER	Verhamme, Katia Erasmus Medical Center No conflict of interests
REVIEW RETURNED	25-Jun-2013

- The reviewer completed the checklist but made no further comments.