Author's response to reviews

Title: Symptom profile in partial responders to a proton pump inhibitor compared with treatment-naive patients with gastroesophageal reflux disease: a post hoc analysis of two study populations

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Author's response to reviews: see over
Dr Magdalena Morawska  
Executive editor, *BMC Gastroenterology*  
1 July 2014

Dear Dr Morawska

Thank you for accepting our manuscript entitled ‘Symptom profile in partial responders to a proton pump inhibitor compared with treatment-naïve patients with gastroesophageal reflux disease: a post hoc analysis of two study populations’ for publication in *BMC Gastroenterology*, subject to addressing the reviewers’ comments.

Enclosed is a revised manuscript that addresses all the questions raised by the reviewers, with all revisions indicated using a bold, red font. Please see below our point-by-point responses to the reviewers’ comments.

We hope that the revised manuscript is now acceptable for publication in *BMC Gastroenterology*, but please do not hesitate to contact us if there is anything further that you require.

Sincerely,

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**Response to reviewers’ comments**

**Reviewer 1 (Alexander Dowli)**

**Major compulsory revisions**

Comment #1.1

“The authors are encouraged to expand on how this conclusion is relevant to clinical practice. The title did hint that this would be the focus of the paper. Would these results help in preventing partial response to PPI.”

Response #1.1

We have now added the following text to the Conclusions section: “The relevance to clinical practice of our results is, first, that partial PPI responders have a similar symptom profile as untreated patients with GERD and thus cannot be identified at baseline. And second, that the symptom burden, even with treatment, is as high in partial PPI responders as in untreated patients with GERD.”

Comment #1.2

“The authors are encouraged to repeat the analysis with adjusting for the difference in women. If you have the raw data that should be feasible.”

Response #1.2

Unfortunately, we do not have the statistical support to conduct additional statistical analyses for this manuscript.

Comment #1.3

“Did you have the raw data of the studies? If so it should not be hard to come up with p-values using t-test. This would add strength to the paper. It would be better than using the 0.5 difference to look for significance.”

Response #1.3

As noted above, we unfortunately do not have the statistical support to conduct additional statistical analyses for this manuscript. However, we would prefer not to present such data in the paper, because using p-values to compare symptom patterns in different patient populations is not a correct statistical approach.
Comment #1.4
“Patients in the Diamond study received esomeprazole 40 mg once daily for 2 weeks as a treatment trial.” Did those in the PRO trial receive the same PPI and dosage? This is not clear from the text. The legends of the figure and table hint at this but it’s not clear.”

Response #1.4
Patients in the PRO validation study had PPI therapy that was individually optimized according to the physician’s judgment, within the approved dose range for any GERD indication. This information has now been added to the Methods section.

Minor compulsory revisions
None

Discretionary revisions
Comment #1.5
“Please consider rephrasing this in the background: ‘Persistent reflux of acidic and weakly acidic content has been described in patients with residual reflux symptoms and delayed gastric emptying may predispose to persistent reflux in some patients [3, 4].’ It’s better to put it in two sentences as this sentence is too long.”

Response #1.5
The sentence has now been split, as follows: ‘Persistent reflux of acidic and weakly acidic content has been described in patients with residual reflux symptoms [3, 4]. Delayed gastric emptying may predispose to persistent reflux in some patients with GERD [3].

Comment #1.6
“Were the two studies done in the same time of year? Reflux patterns can vary according to season. In addition, should the study be done during a fasting season (such as Lent) the incidence of reflux will increase. Have a look at this article for more info: 1: Hamdan AL, Nassar J, Dowli A, Al Zaghal Z, Sabri A. Effect of fasting on laryngopharyngeal reflux disease in male subjects. Eur Arch Otorhinolaryngol. 2012 Nov;269(11):2361-6. doi: 10.1007/s00405-012-2038-z. Epub 2012 May 11. PubMed PMID: 22576248.”
Response #1.6
The Diamond study was conducted in the northern hemisphere between September 2005 and October 2006 (first patient enrolled: 19 September 2005; last patient completed: 31 October 2006). It thus covered all four seasons and was not focused around Lent. The PRO validation study was conducted in the northern hemisphere between May 2008 and December 2008 (first patient enrolled: 27 May 2008; last patient completed: 23 December 2008). It thus covered all of summer and autumn, and parts of spring and winter, and excluded Lent. We have now added the study dates to the Methods section.

Comment #1.7
“How many of the patients had diabetes? This can affect your results. Please look at this paper: Hamdan AL, Jabbour J, Barazi R, Korban Z, Azar ST. Prevalence of laryngopharyngeal reflux disease in patients with diabetes mellitus. J Voice. 2013 Jul;27(4):495-9. doi: 10.1016/j.jvoice.2012.07.010. Epub 2013 Apr 16. PubMed PMID: 23602088. Please note that the two articles I sited in the paper above were written by a PI that I worked for. I only wrote them down as I am very knowledgeable of the subject (I worked on those publications) and would think that inclusion of such information would be useful. These articles are only meant for guidance. Please feel free to obtain similar articles from other authors so as not to quote me.”

Response #1.7
The proportion of patients with diabetes was extremely low (2.8% in the PRO validation study) and thus could not have had any major impact on the results.

Reviewer 2 (Edoardo Savarino)

Major compulsory revisions
None

Minor compulsory revisions
Comment #2.1
“Methods. A major limitation of the PRO validation study is that symptoms relief has been evaluated after a short PPI trial (4 weeks). Indeed, 12 weeks represents, to date, the
best time interval before defining patients as responders or non-responders to PPI therapy (Gut 2012, 61(9):1340–322 1354). Moreover, it is not clear if PPI was given at single or double dose. Also in the Diamond study the duration of PPI trial was too short and at low dosing. Please, clarify and discuss.

Response #2.1
There is no consensus definition for partial response. Four weeks is a standard time period used in clinical studies to determine efficacy or partial response (e.g. Shaheen et al. Am J Gastroenterol 2013;108:429–34. Shaheen et al. Gut 2013;62:1248–55. Weijenborg et al. Neurogastroenterol Motil 2012; 24:747–57. Bytzer et al. Aliment Pharmacol Ther 2012;36:635–43). The paper by Sifrim & Zerbib that the reviewer mentions proposes a definition of < 50% response after12 weeks, but this definition is not explained further or referenced. In the Diamond study, the PPI test was used to assess its validity as a diagnostic tool, not to define partial response.

Comment #2.2
“Discussion. Given the final conclusion on the relevance of heartburn and regurgitation in favouring partial PPI response, the role of weakly acidic or bile reflux should be more emphasized in the discussion section.”

Response #2.2
The following text has now been added to the Discussion section: “Results from a systematic literature review indicate that in partial PPI responders more than 80% of reflux-related symptoms are associated with weakly acidic or alkaline reflux therapy (Boeckxstaens & Smout. Aliment Pharmacol Ther 2010;32:334–43). The likely mechanism by which weakly acidic/alkaline reflux generates symptoms is mechanical stimulation, potentially occurring in combination with esophageal hypersensitivity.”

Comment #2.3
“Discussion. I would eliminate the term “well-defined” patients population since the criteria used to define GERD are different in the two studies as well as the criteria used to define patients as partial responders (see above).”
Response #2.3
The term “well-defined patient populations” has now been replaced with “well-characterized patient populations”.

Comment #2.4
“References. There are few important and more recent articles about the overlap between GERD and functional GI disorders that have not been cited (J Gastroenterol. 2014 Apr;49(4):628-37; Gut. 2009 Sep;58(9):1185-91; Nat Rev Gastroenterol Hepatol. 2013 Mar;10(3):175-86; World J Gastroenterol. 2013 Sep 21;19(35):5787-97).

Response #2.4
We have now referenced the following three papers suggested by the reviewer in our Introduction section:


However, we have not referenced the paper by Kinoshita et al., because 100% of included patients had GERD and dyspepsia, and it thus does not provide information on the extent of overlap between GERD and GI disorders.

Discretionary revisions
None

Reviewer 3 (Walter W Chan)

Major compulsory revisions

Comment #3.1
“The authors stated that the duration of symptoms were different between the 2 groups, with the partial responders having a higher mean symptom duration compared to treatment-naïve patients. However, the inclusion criteria of the 2 studies were different
with regards to length of symptoms prior to study entry, with the PRO Validation study requiring patients to be symptomatic for at least 6 months and the Diamond study requiring only 4 weeks. This may explain the difference in mean symptom duration between the 2 groups. Although the means for both groups are higher than 6 months, such bias in patient enrolment may still account for the difference in mean symptom duration observed, especially if the distribution within each group is non-normal. What are the medians for symptom duration between the 2 groups? Are both medians still significantly higher than 6 months and different from each other statistically?

Response #3.1
The median duration of symptoms in the partial PPI responders group was 7 years (95% confidence interval [CI]: 6–8 years). In the treatment-naïve group, the median duration of symptoms was 1.96 years (95% CI: 1.25–2.40 years). Mood’s median test gives a P-value < 0.001 for the null hypothesis that the medians are equal. A Wilcoxon test of the durations gives a P-value < 0.001, as does a t-test.

Comment #3.2
“As indicated by the authors, the definition of the 2 patient populations represents a significant limitation and cannot be understated. The partial responder group included all patients with reflux symptoms who did not achieve complete relief with PPI, regardless of endoscopic or reflux testing findings. Therefore, this group likely represents a mixture of patients ranging from those with severe reflux requiring higher doses of PPI or surgical therapy, non-acidic/weakly acidic reflux, visceral hypersensitivity, or functional heartburn/dyspepsia. On the other hand, the treatment naïve group included only patients with either esophagitis on endoscopy or a positive pH monitoring (increased acid exposure OR positive symptom-association). Patients with functional causes for their symptoms were likely excluded from this study as a result. Therefore, a selection bias was likely introduced, affecting the analysis. While it is true that both clinical diagnoses and objective data are used in clinical practice for GERD as stated by the authors, the fact that the 2 comparison groups employed distinct methods for diagnosis remains problematic.
Response #3.2
We agree that this is a methodological limitation and have stated this in the Discussion section already. We have now expanded the limitations section, as follows: “One possible limitation of the analysis is that the criteria used to define GERD differed in the two studies, thus potentially introducing a selection bias. In the PRO Validation Study, GERD was defined based on clinical diagnosis and the presence of frequent reflux symptoms. The study may thus also have included patients with visceral hypersensitivity, functional heartburn or dyspepsia. In the Diamond study, GERD was defined based on objective investigative findings (reflux esophagitis on endoscopy, pathological esophageal acid exposure and/or a positive symptom-acid association probability), and patients with functional causes for their symptoms were thus likely to have been excluded.” However, as also noted in the Discussion, the patient materials that we have access to are unique and are, to our knowledge, the best currently available for comparing symptom patterns in partial responders and treatment-naïve patients with GERD.

Comment #3.3
“What were the treatment responses of the subjects in the treatment naïve group after 2 weeks of PPI? In other words, what proportion of them achieved complete vs partial vs no response? If the treatment naïve group also included patients who partially responded to PPI, the results may have been biased (but likely towards the null). A more robust analysis may involve comparing the subgroup of partial responders to the subgroup of complete responders or the whole population within the Diamond study.”

Response #3.3
As noted above, we unfortunately do not have the statistical support to conduct additional statistical analyses for this manuscript. However, the data from the Diamond study PPI test are unsuitable for identifying partial response, because patients received only 2 weeks of treatment, which is too short for this assessment. In the Diamond study, the PPI test was used to assess its validity as a diagnostic tool, not to define partial response. Also, as already indicated by the reviewer, the results would be biased towards the null and are thus not weakened by the potential inclusion of partial responders.
Comment #3.4

“In the conclusion, the authors stated that “while visceral sensitivity in the esophagus remains a possible explanation for persistent symptoms while receiving PPI therapy, the absence of meaningful differences in Indigestion or Diarrhea domain scores between PPI partial responders and treatment-naïve patients suggests that a generalized disorder of gastrointestinal visceral hypersensitivity is unlikely.” This statement may be problematic because, as stated in comment #3 above, the lack of significant difference in indigestion and diarrhea observed may have resulted from a selection bias due to the treatment naïve group potentially including patients who were later partial responders.”

Response #3.4

We have now included a comment in the study limitations section about potential selection bias.

Comment #3.5

“In the introduction, the authors stated that “a better understanding of symptom patterns in partial PPI responders with GERD is needed to understand the genesis of symptoms and to improve medical management in this patient group.” How did the results and conclusions from this study contribute to these goals? It is not completely clear that comparing the symptoms of a group of clinically diagnosed GERD patients on PPI with partial response to those from a group of objectively-defined GERD patients pre-PPI therapy would yield much relevant information regarding the pathophysiology or clinical management of partial PPI responders. A more detailed discussion of why the comparison group (treatment naïve group) was selected and the clinical or pathophysiological implications of the results observed would be helpful.”

Response #3.5

The two clinical points of relevance are, first, that partial PPI responders have the same symptom profile as untreated patients with GERD and thus cannot be identified at baseline and, second, that the symptom burden in partial PPI responders even on treatment is as high as in untreated patients with GERD. This information has now been added to the Conclusions section, as follows: “The relevance to clinical practice of our results is, first, that partial PPI responders have a similar symptom profile as untreated
patients with GERD and thus cannot be identified at baseline. And second, that the symptom burden, even with treatment, is as high in partial PPI responders as in untreated patients with GERD.” For background on pathophysiology, we have also added the following text to the Discussion section: “Results from a systematic literature review indicate that in partial PPI responders more than 80% of reflux-related symptoms are associated with weakly acidic or alkaline reflux therapy (Boeckxstaens & Smout. Aliment Pharmacol Ther 2010;32:334–43). The likely mechanism by which weakly acidic/alkaline reflux generates symptoms is mechanical stimulation, potentially occurring in combination with esophageal hypersensitivity.”

Comment #3.6
“In the Discussion, there was a paragraph regarding the prior evidence of reflux inhibitors’ effects on symptoms: “Treatment with reflux inhibitors has been explored as a possible alternative to PPI therapy when remaining symptoms are clearly reflux related [19, 20]. Studies of drugs designed to decrease transient lower esophageal sphincter relaxations have, however, shown disappointing results so far [21-23]. A few insights have emerged from these trials, such as that mild reflux symptoms in patients on PPI therapy do not appear to respond well to reflux inhibitors [23], whereas moderate or severe symptoms might be more responsive [22, 23].” What is the purpose of this paragraph, especially in the context of the results of this study? The relevance of this paragraph to the current study should be better explained and expanded, or it should be removed.”

Response #3.6
This paragraph forms part of the Discussion about disease management in partial PPI responders. We have now added an opening sentence, as follows: “Partial PPI response is an important clinical problem and the proper management of patients with GERD who have only a partial response to PPI therapy is still uncertain”.

Comment #3.7
“As stated in the Discussion, the interpretation of the data should be taken with caution, since the GSRS and the clinically significant difference established were mainly
validated and used for within group comparison, rather than inter-group differences. Therefore, the true clinical significance and implication of the small differences in domain scores observed between the two patient groups in this study are not clear. The authors should be careful to state their results and conclusions in this context.”

Response #3.7
This limitation, which is relevant for only one of the domains tested, is already discussed in the Discussion section. Our primary interpretation of differences, as shown in the Results section (Figure 1), was based on whether or not the 95% CIs overlap.

**Minor compulsory revisions**  
None

**Discretionary revisions**  
None