Dear Ma:

We deeply appreciate the time and effort you've spent in reviewing our manuscript (47641). We have substantially revised our manuscript after reading the comments provided by the reviewer. Thank you very much for your consideration and we wish it to be reconsidered for further review. If there is anything else we need to do, please let us know.

Thank you and best regards.

Yours sincerely,

(Research team)

To L. Lombardo (02462321)

Thank you very much for pointing out the problems in our manuscript. We have revised it according to your recommendations. We would like to know if there are still somewhere need to be amended and elaborated.

Question 1

Major Comments As it is universally accepted, duration and dose of PPI treatment are, generally, essential to inducing unwanted side-effects. Hepatic encephalopathy can be rated in different stages. The AA must do an effort to specify, as long as it is possible from the published studies (or at least address the problem): 1)Number of episodes and level of HE (subclinical, moderate, pre-coma, coma?) 2)Mean Minimal Duration of PPI treatment necessary to induce HE (and which level of HE)

Reply: In the Table 1 of the revised manuscript, we add number of episodes, level of HE, and mean minimal duration of PPI treatment necessary to induce HE. (1). In the included study, HE was graded according to the West Haven criteria in the included study. Thus, level of HE was graded according to the West Haven criteria in the revised manuscript. Is this appropriate? (2). In most included study, follow-up ended at the onset of the first HE episode and number of episodes during follow-up was not described. The columns of "number of episodes" in the revised Table 1 be described as "follow-up ended at the onset of the first HE episode", Is this appropriate?

Question 2

Minor Comments -AM > AIM (title) -In Results section, Studies characteristics: Studies was published > were published L.L.

Reply: In the "ABSTRACT" section of revised manuscript, we change "AM" to "AIM". In the "Studies characteristics" section of revised manuscript, we change "was" to "were".

In addition, the study by Nardelli et al, one of our included studies, demonstrated that PPIs increase minimal HE risk (OR = 3.96; 95% CI: 2.27–6.92) and overt HE risk (OR = 1.83; 95% CI: 1.22–2.74), respectively. According to two above-mentioned different risk, The recalculated result was OR = 1.50 (95% CI: 1.25 - 1.75) using overt HE risk (OR = 1.83; 95% CI: 1.22–2.74) , and OR = 1.49 (95% CI: 1.22–1.76) using minimal HE risk (OR = 3.96; 95% CI:

2.27–6.92). Of remaining 6 studies, 5 studies explored the association between PPI Use and over HE risk, and 1 studies explored the association between PPI Use and total HE risk (minimal + overt HE risk). ultimately, the result of our meta-analysis was changed to OR = 1.50 (95% CI: 1.25 – 1.75) using overt HE risk (OR = 1.83; 95% CI: 1.22–2.74). The purpose of above-mentioned passage aim to tell you the variation of our result.

Once again, on behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate your positive and constructive comments and suggestions. If there is anything else we need to do, please let us know.

Thank you and best regards.

Yours sincerely,

(Research team)

To Anonymous (00036194)

Thank you very much for pointing out the problems in our manuscript. We have revised it according to your recommendations. We would like to know if there are still somewhere need to be amended and elaborated.

Question 1

Introduction Para 1: PPIs are used to prevent NSAID ulcers not what you have stated PPIs are not useful for functional dyspepsia

Reply: In "Introduction Para 1" of the revised manuscript, we revised the sentence as follow: "Proton pump inhibitors (PPIs) are the first choice of treatment for esophagitis and peptic ulcer disease, as well as the prevention of nonsteroidal anti-inflammatory drugs associated with ulcers, Zollinger – Ellison syndrome, and **functional dyspepsia**."

Question 2

Introduction Para 2: HE is secondary to hepatic failure, not cirrhosis perse. Results may be skewed, not restricted as you stated

Reply: In “Introduction Para 2” of the revised manuscript, we revise the sentence as follow: “ Regarding concerns over liver adverse effects, a previous meta-analysis showed that PPIs increase the risk of hepatic encephalopathy (HE) in patients with **hepatic failure**.”

Question 3

Introduction Para 3: You are not lookng at cirrhosis, just HE

Reply: In “Introduction Para 3” of the revised manuscript, the words **“PPI use on HE along with liver cirrhosis”** was changed“PPI use on HE **in patients with liver cirrhosis”**. We revise the sentence as follow: “ Therefore, in this meta-analysis, we aimed to update, compile, and critically review the existing evidence on the risk of PPI use on HE **in patients with liver cirrhosis** and provide a quantitative estimate of the relationship between PPI use and HE risk.”

Question 4

Methods: Most studies have been excluded and only 7 included. You give the exclusion characteristics but it would be helpful, seeing nearly all studies were excluded, to know how many were excluded for each exclusion criterion.

Reply: In “**Study selection**” part of the revised manuscript, we described how many were excluded for each exclusion criterion. The revise sentences was as follow:“The initial database search yielded 888 records, of which 107 duplicates were excluded. **Then, 771 records, including 768 irrelevant studies and 3 reviews, were removed through the primary screening of titles and abstracts**. After assessing 10 full-text studies, **2 conference abstractions and 1 editor comment** were excluded. Finally, 7 articles involving 4574 patients were included in this meta-analysis.”

Question 5

Methods: Is visualisation the appropriate method to determine publication bias?

Reply: In our revised manuscript, we add Table 2 for NOS score.

Once again, on behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate your positive and constructive comments and suggestions. If there is anything else we need to do, please let us know.

Thank you and best regards.

Yours sincerely,

(Research team)

To Vincenzo Savarino (00004403)

Thank you very much for pointing out the problems in our manuscript. We have revised it according to your recommendations. We would like to know if there are still somewhere need to be amended and elaborated.

Question 1

They should add to the study characteristics how many studies were observational and retrospective or prospective and controlled, because the former have a significantly lower clinical meaning.

Reply: In " Study characteristics" part of the revised manuscript, we described the study design as follow: "**Out of the seven included studies, six were retrospective, and one study was prospective**. "

Question 2

In the discussion the authors should report that the use of PPIs must be banned in patients with cirrhosis or portal hypertension, because there is no reason for administering these drugs in hepatic diseases, as clearly stated in many recent papers (for instance Savarino V et al, Dig Liver Dis 2018; 50:894-902). This is the only way to prevent hepatic encephalopathy in cirrhotic patients taking PPIs.

Reply: In "Discussion Para 4", we add some sentence as follow: "Considering that PPI use is associated with an increased risk of HE occurrence in patients with liver cirrhosis, physicians should ban PPI use in these patients and those with portal hypertension when PPIs are used without specific indications. Adhering to evidence-based guidelines is the only way to ensure effective and safe PPI use. Regulatory authorities should also assume supervision and management responsibilities to avoid inappropriate PPI use."

Once again, on behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate your positive and constructive comments and suggestions. If there is anything else we need to do, please let us know.

Thank you and best regards.

Yours sincerely,

(Research team)

To Alain Braillon (00061695)

Thank you very much for pointing out the problems in our manuscript. We have revised it according to your recommendations. We would like to know if there are still somewhere need to be amended and elaborated.

Qusetion 1

introduction a) I’ m not happy with the first paragraph.(this is my only major request for changes) The main issue is not about the indications Proton pump inhibitors (PPIs) and their benefits but their growing prescription, one of the world's most frequently prescribed medications, due to growing incorrect use (indication as well as duration). Moreover reporting bias in published trials and marketing cannot be overlooked: emphasis on positive results while negative results are understated.

Reply: In “Introduction Para 1” of the revised manuscript, we revised the sentence as follow: “Proton pump inhibitors (PPIs) are the first choice of treatment for esophagitis and peptic ulcer disease, as well as the prevention of nonsteroidal anti-inflammatory drugs associated with ulcers, Zollinger–Ellison syndrome, and functional dyspepsia. In acid-related diseases, the benefits of PPI use outweigh their potential harm. Unfortunately, the negative effects of PPI use are generally underestimated due to marketing strategy and neglected reporting bias in published trials. Thus,

not all PPIs are used following evidence-based guidelines in the clinical setting, and PPIs are overprescribed in both inpatient and outpatient settings."

Qusetion 2

b) for the second paragraph b1) please change the beginning "Emerging » by Accumulationg.

Reply: At the beginning of "Introduction Para 2", Emerging is changed by Accumulationg.

Qusetion 3

b2) add to the list of harms 'Chronic Kidney Disease"

Reply: At the beginning of "Introduction Para 2", we add "Chronic Kidney Disease" as follow: Accumulating data illustrate the potential risks associated with long-term PPI therapy, including pneumonia, spontaneous bacterial peritonitis, gastric cancer, vitamin B12 deficiency, *Clostridium difficile*-associated diarrhea, myocardial infarction, hypomagnesemia, **chronic kidney disease**, and hip fracture.

Qusetion 4

Discussion Add a short paragraph about -need for measures to promote the rational use by regulation authorities -need for improving clinicians' concern for benefit/harm ratio -need for pharmaco epidemiological studies Reference Cite doi: 10.1053/j.gastro.2017.04.047

Reply: At the end of "Discussion Para 4", we add the sentence as follow "Adhering to evidence-based guidelines is the only way to ensure effective and safe PPI use. Regulatory authorities should also assume supervision and management responsibilities to avoid inappropriate PPI use."

Once again, on behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate your positive and constructive comments and suggestions. If there is anything else we need to do, please let us know.

Thank you and best regards.

Yours sincerely,

1 (Research team)