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Ying Dou
Science Editor, Editorial Office

Re: Manuscript entitled "Proton Pump Inhibitors and Adverse Effects in Kidney Transplant Recipients: A Meta-Analysis"
Manuscript NO: 46301

Dear Prof. Akbulut, Prof. Papalois and Prof. Salvadori,

Thank you for the thoughtful input and review of our manuscript. We believe as a result of this review, our study will have more value for your readers. We revised the manuscript based on the reviewers' suggestions. We have attached our point by point response.

As an invited manuscript (Number ID: 03475636), we are thankful that it is acknowledged by waiving of the publication.

Thank you for your time and consideration. If you have any additional questions or comments, please let us know.

With many thanks for your attention, I remain.
Sincerely yours,

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Response to Reviewer#1

Recommendation Minor revision

A lot of work has gone into this study and it is an interesting study design and result. My comments:

Response: We thank you for reviewing our manuscript and for your critical evaluation. We really appreciated your input and found your suggestions very helpful. We have now revised the manuscript comprehensively, based on the reviewers' suggestions. We have attached our point by point response.

Comment #1

I have a problem with the adequacy and completeness of the data in the 8 studies used. Some data for the outcomes are absent we are told; inconsistency in the definitions of rejection etc. The authors should explain the extent to which data is complete with respect to each outcome measures.

Response: We thank you for reviewing our manuscript. The reviewer raised very important point. Thus, we have reviewed all included studies and summarized all definition of rejections in the supplementary table 1 as the reviewer suggestion as below. We also added definitions of hypomagnesemia in the manuscript and we also have additionally included data on Mg supplementation to Table 4 as well for completeness.

Study	Definition of biopsy-proven acute rejection	Definition of presumed rejection	Protocol Biopsy
Patel *et al*[32] 2012	NR	NR	NR
Knorr *et al*[20] 2014	All acute cellular or antibody-mediated rejections grade Banff I or higher as well as borderline rejections that were treated.	NR	No
Van Boekel *et al*[22] 2014	Histological examination and classification were done according to the Banff criteria.	Presumed acute rejection diagnosed based on an increase in serum creatinine without another explanation and a biopsy was not performed.	No
Courson *et al*[21] 2014	NR	NR	NR
Patel *et al*[23] 2017	BPAR included rejections diagnosed on per protocol or	Suspected rejections included borderline/subclinical	Yes (3-6 mo and 1 yr)

	clinically indicated biopsies that were Banff criteria grade I or higher.	rejections per Banff criteria or clinically diagnosed rejections without biopsy.	
Rouse *et al*[24] 2017	NR	NR	NR
Uludag *et al*[37] 2017	NR	NR	NR

Comment #2

The study needs to have a statistician review the methodology. Given the multiple outcomes measures is it powered adequately?

> Response: We appreciated the reviewer's input. We respected the reviewer's comment. The statistical methods of this study were reviewed by Charat Thongprayoon from Mayo Clinic, USA and Wisit Cheungpasitporn from University of Mississippi Medical Center, Jackson, Mississippi, USA. Charat Thongprayoon and Wisit Cheungpasitporn completed Postdoctoral Diploma in Clinical and Translational Science (CCaTS) from Mayo Graduate School, Rochester, MN, USA. We have attached the diplomas as the reviewer's comment.

Response to Reviewer#2

Recommendation Minor revision

I have read with great interest the manuscript entitled "Proton Pump Inhibitors and Adverse Effects in Kidney Transplant Recipients: A Meta-Analysis". I would like to congratulate initially the authors on the well written and scientifically sound manuscript. In this meta-analysis the authors investigate the risk of several adverse effects in kidney transplant recipients on PPI compared with those without the exposure. They conclude that PPI use was associated with a high risk of hypomagnesemia. The manuscript's methodology is appropriate, in accordance with the PRISMA guidelines and the subject of clinical interest. Please see major comments below for your attention and clarification

> Response: We thank you for reviewing our manuscript and for your critical evaluation. We really appreciated your input and found your suggestions very helpful. We have now revised the manuscript comprehensively, based on the reviewers' suggestions. We have attached our point by point response.

Comment #1

The introduction discusses extensively the possible issues associated with the interaction between MMF and PPI. I wonder if this is the only class of immunosuppression that interacts

with PPI? In addition, is there any possible mechanistic explanation for all the adverse effects associated with PPI? While those questions do not need extensive discussion in the introduction, they may be touched minimally.

Response: We appreciated the reviewer's input. We agree with the reviewer. We have added the interaction of PPI with other immunosuppressive drugs and mechanism of PPI-induced hypoMg/renal dysfunction as the reviewer's suggestion in the introduction. The following text in bold has been added to the introduction based on the reviewer's suggestion.

"Some studies[25, 26] have shown that concurrent PPI can increase tacrolimus drug concentration, leading to higher risk of toxicity through cytochrome or p-glycoprotein inhibition in patients with certain Cytochrome P450 2C19 (CYP2C19) and/or CYP3A5 genotypes. However, this is not expected to increase the risk of rejection, but calcineurin inhibitor toxicity may lead to renal dysfunction. Other commonly used immunosuppressive drugs are not known to have significant interaction with PPIs.

PPI may also interfere with magnesium absorption in the gastrointestinal tract, causing hypomagnesemia[3]. The mechanism of renal dysfunction related to PPIs is not clear although acute interstitial nephritis (AIN) associated with PPIs has been purposed[1, 2]."

Comment #2

For the hypomagnesemia, the forest plot presented in Figure 4 shows that only three studies were analysed to generate the pooled OR of 1.56. From Table 1, two of them were cross-sectional and one a retrospective study. The number of patients in each experimental group (PPI vs. Non-PPI) and the immunosuppressive regimen do not seem to be available for all the three studies (Table 1). From Table 4, the variation in plasma magnesium levels is apparently minor and not likely to lead to any clinical complication. Those patients may be potentially receiving oral magnesium supplementation, or not, as we cannot say accordingly to the information available in the meta-analysis. Therefore, in face on all these limitations, most of them acknowledged by the authors in the discussion, they should be careful to draw definitive conclusions from the present study. The conclusion of the study should be revised accordingly, the phrase "In the long-term, PPI use may also be associated with kidney dysfunction and increased overall mortality" is not supported from data analyses available in the manuscript and it seems more a personal impression from authors.

Response: We appreciated the reviewer input. We have reviewed all included studies that have available data on magnesium and have added information on Mg supplementation to Table 4 based on the reviewer's suggestion.

We also apologize for including a personal impression in conclusion. We have removed "In the long-term, PPI use may also be associated with kidney dysfunction and increased overall mortality" from the conclusion as the reviewer's suggestion. In

addition, we agree with the reviewer and have emphasized in the limitation of our study that further study is needed to address whether long-term PPI exposure in kidney transplant recipients is associated with worse long-term outcomes including mortality.

Comment #3

The last two phrases of the penultimate paragraph ("Interestingly, Uludag et al… is associated with worse outcomes") are repetitive, and not part of the limitations of the study, which is the topic of the paragraph. This should be removed.

Response: We appreciated the reviewer's thorough review. We agree with the reviewer and we have removed the following sentences from the limitations "Interestingly, Uludag et al.[35] did report significantly higher serum creatinine in the PPI group after a median follow-up duration of 109 months and both Douwes et al.[38] and Gomes-Neto et al.[36] reported significantly higher all-cause mortality in the PPI group after a median follow-up duration of 5.4 years (range, 4.8-6.1 years)."

All authors thank the Editors and reviewers for their valuable suggestions. The manuscript has been improved considerably by the suggested revisions.