Authors' reply

Wasit Wongtrakul[a], Nipith Charoenngnam[b], Patompong Ungprasert[c]

Mahidol University, Bangkok, Thailand

We thank Tziatzios *et al* for their interest in our study. While it would be ideal to include only studies that investigate the risk of pneumonia among proton pump inhibitor (PPI) users vs. non-users as the primary outcome with comprehensive adjustment into our meta-analysis, such data do not exist. As Voltaire once said, "the perfect is the enemy of the good"; we would rather have some data, albeit imperfect, to help guide clinical care than none.

We agree that between-study heterogeneity could theoretically be a concern in a meta-analysis of observational studies. However, for the current meta-analysis, all the included studies but one demonstrated a positive association between PPI use and risk of pneumonia, although most of them did not reach statistical significance, probably because of the small sample sizes. The results indicate that there is no major disagreement between studies, allowing for some differences in their methodology.

We believe that our systematic review was sufficiently comprehensive, as we followed the guidance from the Cochrane Collaboration that Medline and EMBASE databases should be searched [1]. It should be noted that several major conference proceedings are indexed in EMBASE. Therefore, a high number of conference abstracts, a major kind of "gray" literature, are searchable from this database. In fact, 2 included studies were published as conference abstracts.

The P-value of less than or "equal" to 0.05 is conventionally considered significant [2] and we stand by our interpretation. Nonetheless, we believe that clinical importance (i.e., effect size) should be the focus of the interpretation, not just statistical significance. The fact that PPI use is associated with a 36% increase in the risk of pneumonia among patients with cirrhosis should be worrisome enough for clinicians only to prescribe them when it is clinically indicated.

References

1. Lefebvre C, Glanville J, Briscoe S, et al. Searching for and selecting studies. Cochrane Handbook for Systematic Reviews of Interventions 2019, pp. 67-107.
2. Grabowski B. "P<0.05" might not mean what you think: American Statistical Association clarifies P values. *J Natl Cancer Inst* 2016;**108**.

[a]Faculty of Medicine Siriraj Hospital (Wasit Wongtrakul); [b]Department of Internal Medicine, Faculty of Medicine Siriraj Hospital (Nipith Charoenngnam); [c]Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital (Patompong Ungprasert), Mahidol University, Bangkok, Thailand

Conflict of Interest: None

Received 27 April 2020; accepted 29 April 2020;
published online 30 May 2020

Correspondence to: Patompong Ungprasert, Clinical Epidemiology Unit, 3rd floor, SIMR building, Siriraj hospital, Bangkok, 10700 Thailand, e-mail: P.Ungprasert@gmail.com

DOI: https://doi.org/10.20524/aog.2020.0502