

# Letter: proton pump inhibitors and risk of myocardial infarction—authors' reply

We thank Dr. Xueyang Zheng and colleagues for their interest in our study<sup>1,2</sup> and gladly take the opportunity to address their concerns.

First, the authors pointed to potential differences between individual proton pump inhibitors (PPIs) with regard to the risk of myocardial infarction (MI), possibly linked to concomitant antiplatelet therapy - and especially to clopidogrel. Our study used claims data from Germany. About 61% of all PPI prescriptions were for pantoprazole and 33% were for omeprazole. Confounder-adjusted estimates for different PPIs versus H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) provided little evidence for substantial differences (Table 1). Although we excluded cases of prevalent cardiovascular disease, 0.2% of the study population obtained clopidogrel within 90 days before initiating a new PPI therapy.<sup>2</sup> However, analysis after exclusion of individuals with clopidogrel intake did not alter the estimates for PPIs versus H<sub>2</sub>RAs (HR 0.96; 95% CI 0.80-1.16).

Second, the authors rightly mention that our study did not address the question of whether PPI use modifies the risk of recurrent cardiovascular events. Our observational study has its merits regarding the analysis of long-term effects in a low-risk population requiring a large study population and a long study period. For this reason, we explicitly chose first MI as the outcome and excluded any patients with a history of MI. We believe that the question of short-term effects in a high-risk population can be—and was—examined more appropriately by clinical trials.<sup>3-5</sup>

Biochemical studies suggest that PPI intake might steadily reduce vascular function, which in the long run could have an impact

on cardiovascular risk.<sup>6,7</sup> Therefore, future studies should address the effects of long-term and high-dose PPI use.

## FUNDING INFORMATION

Gemeinsamer Bundesausschuss, G-BA, Grant/Award Number: 01VSF18013

## ACKNOWLEDGEMENT

The authors' declarations of personal and financial interests are unchanged from those in the original article.<sup>2</sup>

## LINKED CONTENT

This article is linked to Nolde et al papers. To view these articles, visit <https://doi.org/10.1111/apt.16565> and <https://doi.org/10.1111/apt.16644>

**TABLE 1** Hazard ratios for myocardial infarction from weighted Cox regression models (as-started analysis)

Exposure	HR	CI	P
All PPIs	0.96	0.80-1.16	0.68
Pantoprazole	0.92	0.78-1.09	0.33
Omeprazole	1.02	0.87-1.19	0.80

Abbreviations: CI, 95% confidence interval; HR, hazard ratio; P, P-value; PPI, proton pump inhibitor.

AP&T correspondence columns are restricted to invited editorials and letters discussing papers that have been published in the journal. An invited editorial or letter must have a maximum of 500 words, may contain one table or figure, and should have no more than 10 references. It should be submitted electronically to the Editors via <http://mc.manuscriptcentral.com/apt>.

Michael Nolde<sup>1,2</sup>   
 Nayeon Ahn<sup>1,2</sup>   
 Tobias Dreischulte<sup>3</sup>  
 Ina-Maria Rückert-Eheberg<sup>1,2,4</sup>   
 Florian Güntner<sup>5</sup>  
 Alexander Günter<sup>5</sup>  
 Roman Gerlach<sup>6</sup>  
 Martin Tauscher<sup>6</sup>  
 Ute Amann<sup>7</sup>  
 Jakob Linseisen<sup>1,2,7</sup>  
 Christa Meisinger<sup>2</sup>  
 Sebastian-Edgar Baumeister<sup>8</sup>

<sup>1</sup>Institute for Medical Information Processing, Biometry, and Epidemiology - IBE, LMU Munich, Munich, Germany

<sup>2</sup>Department of Epidemiology, University of Augsburg, at University Hospital Augsburg, Augsburg, Germany  
 Email: michael.nolde@med.uni-augsburg.de

<sup>3</sup>Department of General Practice and Family Medicine, LMU Munich, Munich, Germany

<sup>4</sup>Institute of Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany

<sup>5</sup>Bereich Versorgungsmanagement, AOK Bayern, Munich, Germany

<sup>6</sup>Association of Statutory Health Insurance Physicians in Bavaria (Kassenärztliche Vereinigung Bayerns, KVB), Munich, Germany


<sup>7</sup>Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany

<sup>8</sup>Institute of Health Services Research in Dentistry, University of Münster, Münster, Germany

#### ORCID

Michael Nolde  <https://orcid.org/0000-0001-6893-7367>

Nayeon Ahn  <https://orcid.org/0000-0003-4414-114X>

Ina-Maria Rückert-Eheberg  <https://orcid.org/0000-0001-5418-283X>

#### REFERENCES

1. Zheng X, Li N, Zhao J. Letter: proton pump inhibitors and risk of myocardial infarction. *Aliment Pharmacol Ther.* 2022; 55:139-140.
2. Nolde M, Ahn N, Dreischulte T, et al. The long-term risk for myocardial infarction or stroke after proton pump inhibitor therapy (2008-2018). *Aliment Pharmacol Ther.* 2021;54:1033-1040.
3. Pang J, Wu Q, Zhang Z, et al. Efficacy and safety of clopidogrel only vs. clopidogrel added proton pump inhibitors in the treatment of patients with coronary heart disease after percutaneous coronary intervention: a systematic review and meta-analysis. *IJC Heart Vasculat.* 2019;23:100317.
4. Li Y, Ren X, Fang Z. Systematic review and meta-analysis: the effects of prophylactic proton pump inhibitor treatment in patients with coronary heart disease receiving dual antiplatelet therapy. *J Cardiovasc Pharmacol.* 2021;77:835-861.
5. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology.* 2019;157:682-691.e2.
6. Nolde M, Bahls M, Friedrich N, et al. Association of proton pump inhibitor use with endothelial function and metabolites of the nitric oxide pathway: a cross-sectional study. *Pharmacotherapy.* 2021;41:198-204.
7. Ghebremariam YT, LePendou P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. *Circulation.* 2013;128:845-853.