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

We thank Dr. Xueyang Zheng and colleagues for their interest in our study\textsuperscript{1,2} 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\textsubscript{2}-receptor antagonists (H\textsubscript{2}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.\textsuperscript{2} However, analysis after exclusion of individuals with clopidogrel intake did not alter the estimates for PPIs versus H\textsubscript{2}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.\textsuperscript{3-5}

Biochemical studies suggest that PPI intake might steadily reduce vascular function, which in the long run could have an impact on cardiovascular risk.\textsuperscript{6,7} 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.\textsuperscript{2}

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

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
Exposure & HR & CI & P  \\
\hline
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  \\
\hline
\end{tabular}
\caption{Hazard ratios for myocardial infarction from weighted Cox regression models (as-started analysis)}
\end{table}

Abbreviations: CI, 95% confidence interval; HR, hazard ratio; P, P-value; PPI, proton pump inhibitor.
Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany

8 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**