The long-term risk for myocardial infarction or stroke after proton pump inhibitor therapy (2008-2018)

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Summary
Background: Proton pump inhibitors (PPIs) are well tolerated in the short term but have recently been associated with increased long-term cardiovascular risk in observational studies.
Aims: To evaluate long-term risks of myocardial infarction (MI) and ischaemic stroke (IS) associated with PPI vs H$_2$-receptor antagonist (H$_2$RA) therapy in adults without pre-existing cardiovascular or cerebrovascular disease
Methods: Using administrative claims data (2008–2018), we emulated a target trial comparing MI and IS risks in new users of PPIs vs H$_2$RAs. Treatment was identified using dispensed prescriptions. MI and IS were defined using hospital discharge codes. Inverse probability weighting was used to adjust for confounding, and Cox models to estimate hazard ratios (HRs). Survival curves were estimated using weighted Kaplan-Meier estimators.
Results: We identified 1 143 948 new users of PPIs and 36 229 new users of H$_2$RAs who were free of prevalent cardiovascular or cerebrovascular disease. The mean follow-up time was 6.2 years for PPI initiators and 5.3 years for H$_2$RA initiators. After 10 years, the HRs for MI and IS were 0.96 (95% confidence interval (CI): 0.80-1.16) and 0.98 (95% CI: 0.89-1.08), respectively.
1 | INTRODUCTION

Proton pump inhibitors (PPIs) are widely used to treat disorders characterized by excessive gastric acid production. For more than a decade, PPIs have also been sold over-the-counter and are often consumed without medical supervision. The long-term risk of PPI intake has received considerable attention in recent years, with large and well-controlled cohort studies linking PPI use to an increased risk of myocardial infarction (MI), ischaemic stroke (IS) and cardiovascular death. The elevated risk was associated with PPI use but not with the use of H2-receptor antagonists (H2RAs), the most commonly used alternative class of medications to treat acid-related gastrointestinal conditions. A potential mechanism to explain an increased long-term cardiovascular risk is that intake of PPIs inhibits the enzyme dimethylarginine dimethylaminohydrolase and might thereby impair endothelial nitric oxide production and vascular endothelial function. This pathway has been established ex vivo, in mice and was recently observed in humans.

In contrast, a large randomized controlled trial with 3 years of follow-up found no increased risk for MI or IS in patients with stable cardiovascular disease and peripheral artery disease. Similarly, a large analysis of administrative claims data found no increased risk for a first MI during PPI intake of up to 3 years and an analysis of 68,514 women enrolled in the Nurses’ Health Study found no increased risk for primary IS in prevalent users of PPIs.

However, if PPI intake was to cause vascular damage and therefore increase the risk for cardiovascular disease, an observational window of more than 3 years might be necessary, especially for patients without pre-existing cardiovascular conditions. We conceptualized an emulation of a target trial to examine the long-term effect of PPI vs H2RA therapy on the risk of MI and IS in a general population without prior cardiovascular events.

2 | METHODS

2.1 | Data source

For this study, we analysed claims data from the Allgemeine Ortskrankenkasse (AOK) Bayern, a large regional German Statutory Health Insurance Provider. The dataset included about 6.1 million adult persons, who received health insurance cover from the AOK Bayern for at least 2 years since January 2007. Outpatient and hospital diagnoses were coded according to the German Modification of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM), released by the German Institute of Medical Documentation and Information (DIMDI). Drugs purchased over-the-counter, or administered in hospital, are not contained in the database. For data protection reasons, the data were pseudonymized. The study received approval from the Ethics Committee of the LMU Munich and the institutional review board of the AOK Bayern. It was registered at ENCePP.eu (EUPAS31559), where the study protocol, including a detailed description of the emulated target trial, was deposited. The investigators had full control over protocol development, analyses and publication. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. This study adhered to the RECORD-PE guidelines.

2.2 | Study population

The study cohort included new users of PPIs and new users of H2RAs, who started therapy between 2009 and 2018. We demanded no prior treatment with PPIs or H2RAs with at least 1 year of medical history before treatment initiation recorded in the data. Cohort entry was the day of the first dispensed prescription of any of those drugs. All patients were required to be at least 18 years old and free of prevalent cardiovascular (ICD-Codes I21, I22, I23, I24.1, I25.2) or cerebrovascular disease (ICD-Codes 160, 161, 163, 164, G46) at cohort entry. A graphical depiction of our study design is shown in Figure 1.

2.3 | Medication exposure, follow-up and outcomes

New users of PPIs (ATC Code A02BC) were compared to new users of H2RAs (ATC Code A02BA), as the use of an active comparator might reduce the potential for confounding by indication, compared to a non-user control. We defined exposure by identifying drug dispensing in prescription claims. Follow-up for study outcomes started the day after initiation of treatment and continued in an ‘as-started’ approach until the occurrence of an outcome of interest, death, disenrollment or the end of the study period on 31 December 2018 (Figure 1). The two study endpoints were primary MI and primary IS. Patients were considered a case of MI or IS after a hospital admission with the corresponding main discharge diagnosis (MI: I21; IS: I63, G46.5, G46.6). The validity of these claims-based diagnoses has been established.

2.4 | Covariates

We controlled for several confounders, assuming that direct causes of the exposure or outcome, excluding possible instrumental variables, would identify a sufficient set of confounding variables. Accordingly, we adjusted for demographics (age, sex and nationality),...
calendar time of inclusion (in quarters and years), relevant comorbidities and medications. It remains unclear, whether treatment indication (e.g. gastroesophageal reflux disease [GERD]) has any direct or indirect effect on our outcomes. Therefore, adjusting for treatment indication could mean adjusting for an instrumental variable, and introduce bias instead of reducing it. Despite that, we included treatment indications in the model for the propensity scores to minimize unmeasured confounding and indication bias.

Patient baseline characteristics were measured during the 90 days before and including the date of cohort entry. We also adjusted for the number of concurrently used drugs and the Elixhauser comorbidity score, adapted to administrative data, taking both inpatient and outpatient diagnoses into account. Due to intrinsic properties of the data, both were measured in the quarter preceding treatment initiation. A complete list of baseline patient characteristics and a definition of covariates are provided in Tables S1 and S2.

2.5 | Statistical analysis

We used inverse probability of treatment (IPT) weighting to adjust for confounding. Propensity scores were estimated from a confounder-adjusted logistic regression model and used to calculate stabilized weights. Standardized mean differences were used to assess balance in patient characteristics between treatment groups before and after weighting. Raw incidence rates per 1000 person-years were computed. Overall exposure-specific survival was plotted as adjusted Kaplan-Meier estimates. We estimated hazard ratios (HRs) with the corresponding 95% confidence intervals (CI) using weighted Cox proportional hazards models with robust standard errors. Sensitivity analyses included a comparison of PPI initiators with non-initiators, and the consideration of 97 pre-selected negative control (tracer) outcomes (NCOs) to detect potential unmeasured confounding. We imposed various lag times by excluding

| FIGURE 1 Study design |

a. Baseline conditions included: comorbidities (Elixhauser score), number of medications, antidiabetic drugs, antplatelets, anticoagulents, non-steroidal anti-inflammatory drugs, statins, aspirin, clopidogrel, selective serotonin reuptake inhibitors, obesity, diabetes, chronic pulmonary disease, hypertension, renal failure, liver disease and indications for PPI/H2RA therapy (gastroesophageal reflux disease, esophagitis, gastritis, duodenal ulcer, peptic ulcer, Zollinger-Ellison syndrome, helicobacter pylori, heartburn)

b. Earliest of: outcome of interest, death, disenrollment, end of the study period

PPI = proton pump inhibitor
H2RA = histamine-2 receptor antagonist
events that occurred during the first 10, 30, 90 and 180 days after baseline. The statistical software R (version 3.6.3, Foundation for Statistical Computing) was used.

3 | RESULTS

We identified 1,143,948 initiators of PPI therapy and 36,229 initiators of H2RA therapy meeting the eligibility criteria in our data set of 6,097,740 individuals. 22,020 PPI initiators and 16,201 H2RA initiators received both medications during follow-up. Rates per 1000 person-years of MI and IS by exposure group are presented in Table 1. Covariate summaries of PPI and H2RA initiators, before and after weighting, are provided in Table 2 and Table S1. In the unweighted data, patients who started PPI therapy were older, more likely to take non-steroidal anti-inflammatory drugs or anticoagulants. After weighting, both groups were well balanced on the confounders.

We found no evidence for an association of PPI vs H2RA initiation with MI or IS. The HR comparing PPI and H2RA initiation over 10 years was 0.96 (95% CI: 0.80-1.16) for MI and 0.98 (95% CI: 0.89-1.08) for IS. HRs for several follow-up periods are given in Table 3. Survival curves comparing the outcome-free survival among initiators of PPI therapy vs H2RA therapy were consistent with these findings (Figures 2 and 3). The HRs for comparing PPI initiators and non-initiators were 1.02 (95% CI: 0.94-1.10) for MI and 0.98 (95% CI: 0.94-1.02) for IS (Table 3). The lag time approach did not substantially change point estimates or precision (Table 3). The negative control analysis pointed to a small potential of unmeasured confounding influencing our observed HRs (Figure S1).

4 | DISCUSSION

We estimated the long-term effect of PPI compared to H2RA therapy on MI and IS risk in adults without pre-existing cardiovascular disease. Our analyses do not indicate an increased risk of MI or IS in the first decade after PPI therapy. PPIs are among the most frequently used medications. This makes their safety an important clinical concern.

Our study adds information to the safety evaluation of PPIs. Large and well-controlled cohort studies had linked PPI use to an increased risk of MI and IS, but more recently these concerns have been attenuated. In a large study using administrative claims data from commercial and Medicare Supplemental plans, researchers found no increase in risk of primary MI during PPI intake of up to 3 years. In addition, a large randomized trial with 17,598 participants comparing pantoprazole intake vs placebo over 3 years showed no increase in the overall cardiovascular risk. This study included patients with stable cardiovascular disease and peripheral artery disease, while our study included subjects without the history of cardiovascular conditions. Also, an analysis of 68,514 women enrolled in the Nurses’ Health Study found no increased risk for primary IS in prevalent users of PPIs.

Given that some patients use PPIs for many years, an observational window of more than 3 years might be necessary, especially for patients without prevalent cardiovascular disease at baseline, if PPI intake was to cause vascular damage and thereby increase cardiovascular risk.

The study has several limitations. First, exposure was identified using dispensed prescriptions. Use of over-the-counter (OTC) medications and combination products (ATC Code A02BD) was not included in our exposure definition. This means that prevalent OTC users might have been included in our cohort, regardless of the 1-year exclusion period before study entry. We assumed that therapy is usually initiated by a physician, and therefore new users were well captured by our approach.

Another limitation is that our estimates relied on the assumption that the measured baseline covariates were sufficient to adjust for confounding. Large-scale randomized trials provide the most reliable evidence to detect small to moderate effects, while observational studies always remain under the risk of unadjusted confounding.

Only a minority of PPI and H2RA initiators had any condition that would indicate therapy at the start of treatment. This made control for confounding by indication more difficult. At the same time, it made it suitable to create a second control group of non-initiators that did not start any treatment at all. Indication bias might have played different roles at different times of our study. During the initial phase of our observation period PPIs were regarded as the more modern and effective drug, but later on concerns about the safety of PPIs were raised following a FDA warning regarding a clopidogrel-omeprazole interaction in 2009.

We addressed these issues by analysing 97 pre-selected negative

| Myocardial infarction | Ischaemic stroke |
|-----------------------|------------------|
| **H2RA** | **PPI** | **H2RA** | **PPI** |
| Number of individuals | 36,229 | 1,143,948 | 36,229 | 1,143,948 |
| Person-years | 226,051 | 6,091,226 | 224,733 | 6,054,149 |
| Average days under risk | 2,277 | 1,944 | 2,264 | 1,932 |
| Number of events | 156 | 4,450 | 595 | 17,798 |
| Crude rate per 1000 person-years | 0.69 | 0.73 | 2.65 | 2.94 |

**TABLE 1** Characteristics regarding the ‘as-started’ analysis in the raw/unweighted datasets of new users

Abbreviations: H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.
control (tracer) outcomes and found it unlikely that unmeasured or residual confounding would bias the estimates away from the null. We performed an ‘as-started’ analysis capturing the long-term effect of PPI therapy understood as a point treatment and thereby neglecting any effects of dose or duration of PPI intake. This approach is ideal to address the long-term effect of PPI therapy, if intake causes irreversible vascular damage, but has limited power to detect effects, if only high-dose or long-term intake were to raise the cardiovascular risk.

Finally, many H₂RA initiators switched to PPIs later on and H₂RA initiators were much more likely to switch to a PPI than vice versa. Switching medication does bias the estimate towards the

| TABLE 2 Baseline characteristics for initiators of PPI or H₂RA before/after inverse probability of treatment weighting |
|-------------------------------------------------------------|
| | Unweighted population | Weighted population |
| | H₂RA | PPI | SMD | H₂RA | PPI | SMD |
| N | 36 229 | 1 143 948 | | 36 282 | 1 143 952 | |
| Age (years)a | 49.3 (16.6) | 51.1 (16.5) | 0.113 | 51.4 (16.5) | 51.1 (16.5) | 0.017 |
| Female (%) | 60.1 | 55.9 | 0.085 | 56.4 | 56.0 | 0.007 |
| German (%) | 80.1 | 80.8 | 0.018 | 80.6 | 80.8 | 0.006 |
| Quarter of inclusionb | | 0.402 | | | | 0.106 |
| Baseline-Yearb | | 0.393 | | | | 0.084 |
| Elixhauser Scorea | 1.22 (4.36) | 1.19 (4.34) | 0.007 | 1.26 (4.46) | 1.19 (4.34) | 0.015 |
| Number of Comedicationsa | 1.48 (2.09) | 1.44 (2.02) | 0.015 | 1.47 (2.06) | 1.45 (2.02) | 0.014 |
| Medications (%) | | | | | | |
| Antidiabetic drugs | 4.6 | 5.2 | 0.026 | 5.3 | 5.2 | 0.005 |
| Antiplatelets | 1.1 | 0.9 | 0.018 | 0.9 | 0.9 | 0.001 |
| Anticoagulants | 3.0 | 5.7 | 0.134 | 6.0 | 5.6 | 0.016 |
| Non-steroidal anti-inflammatory drugs | 29.3 | 34.6 | 0.114 | 33.5 | 34.4 | 0.019 |
| Statins | 3.9 | 4.2 | 0.013 | 4.2 | 4.1 | 0.002 |
| Aspirin | 0.8 | 0.7 | 0.010 | 0.8 | 0.7 | 0.004 |
| Clopidogrel | 0.4 | 0.2 | 0.040 | 0.2 | 0.2 | 0.003 |
| Selective serotonin reuptake inhibitors | 2.2 | 2.5 | 0.021 | 2.6 | 2.5 | 0.005 |
| Comorbidities (%) | | | | | | |
| Obesity | 8.5 | 9.1 | 0.022 | 9.2 | 9.1 | 0.003 |
| Diabetes | 8.7 | 10.1 | 0.048 | 10.4 | 10.0 | 0.013 |
| Chronic pulmonary disease | 12.3 | 12.5 | 0.006 | 12.8 | 12.5 | 0.007 |
| Hypertension | 23.2 | 26.4 | 0.075 | 26.8 | 26.3 | 0.010 |
| Renal failure | 2.0 | 2.7 | 0.047 | 2.9 | 2.7 | 0.012 |
| Liver disease | 6.7 | 8.3 | 0.059 | 8.6 | 8.2 | 0.014 |
| Indications (%) | | | | | | |
| Gastro-oesophageal reflux disease | 8.4 | 14.7 | 0.200 | 15.4 | 14.5 | 0.024 |
| Oesophagitis | 0.2 | 0.4 | 0.036 | 0.5 | 0.4 | 0.007 |
| Gastritis | 18.0 | 21.5 | 0.089 | 21.9 | 21.4 | 0.012 |
| Duodenal ulcer | 0.4 | 1.2 | 0.080 | 1.2 | 1.1 | 0.009 |
| Peptic ulcer | 0.1 | 0.1 | 0.004 | 0.1 | 0.1 | 0.001 |
| Zollinger-Ellison syndrome | 0.0 | 0.0 | 0.008 | 0.0 | 0.0 | 0.002 |
| Helicobacter pylori | 0.3 | 1.5 | 0.123 | 1.6 | 1.5 | 0.012 |
| Heartburn | 2.9 | 2.5 | 0.027 | 2.5 | 2.5 | 0.002 |

aContinuous variables with (mean (standard deviation)). PPI, proton pump inhibitor; H₂RA, H₂-receptor antagonist; SMD, standardized mean difference

bFor details on the balance of the factor variables ‘Quarter of inclusion’ and ‘Baseline-Year’ see Table S1.
null. However, this problem did not affect the comparison with non-initiators, which resulted in similar estimates.

Despite these limitations, this study represents a significant contribution to the literature on the safety of PPIs. The large cohort size, the very good capture of acute cardiovascular outcomes in hospital records, the use of an active comparator in combination with high-dimensional IPT-weighting for confounding control and an extensive analysis of negative control outcomes make this study a highly reliable source of information with a moderate risk of bias.\textsuperscript{36}

In summary, for patients with no history of MI or IS PPI therapy does not appear to increase the risk of MI or IS in the first decade after treatment initiation; any presumed effect is moderate, at most. Thus, physicians and patients should not avoid starting an indicated PPI therapy because of concerns related to increased cardiovascular

\begin{table*}[h]
\centering
\caption{Hazard ratios of weighted Cox regression models (As-started analysis)}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Comparator & Follow-up time & Myocardial infarction & & Ischaemic stroke & \\
 & & HR & CI & P & HR & CI & P \\
\hline
PPI vs H\textsubscript{2}RA & Full Study (FS) [10 years] & 0.96 & 0.80-1.16 & 0.68 & 0.98 & 0.89-1.08 & 0.65 \\
 & 1 year & 1.17 & 0.70-1.96 & 0.55 & 1.12 & 0.86-1.46 & 0.41 \\
 & 2 years & 1.11 & 0.77-1.62 & 0.57 & 1.14 & 0.94-1.38 & 0.17 \\
 & 3 years & 1.01 & 0.76-1.35 & 0.94 & 1.05 & 0.89-1.25 & 0.54 \\
 & 4 years & 0.97 & 0.76-1.25 & 0.82 & 1.04 & 0.90-1.21 & 0.57 \\
 & 6 years & 0.90 & 0.74-1.10 & 0.31 & 0.98 & 0.87-1.10 & 0.73 \\
 & 8 years & 0.94 & 0.78-1.13 & 0.51 & 0.98 & 0.88-1.08 & 0.67 \\
\hline
PPI vs No intake & FS & 1.02 & 0.94-1.10 & 0.70 & 0.98 & 0.94-1.02 & 0.32 \\
\hline
PPI vs H\textsubscript{2}RA & FS, Lag Time (LT): 10 days & 0.95 & 0.79-1.15 & 0.61 & 0.97 & 0.88-1.08 & 0.61 \\
 & FS, LT: 30 days & 0.96 & 0.80-1.16 & 0.69 & 0.97 & 0.88-1.07 & 0.58 \\
 & FS, LT: 90 days & 0.95 & 0.78-1.15 & 0.59 & 0.98 & 0.88-1.08 & 0.65 \\
 & FS, LT: 180 days & 0.99 & 0.81-1.20 & 0.90 & 0.98 & 0.88-1.08 & 0.65 \\
\hline
\end{tabular}
\end{table*}

Abbreviations: CI, 95% confidence interval; H\textsubscript{2}RA, H\textsubscript{2}-receptor antagonist; HR, hazard ratio; PPI, proton pump inhibitor; P, P-value.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{As-started: PPI vs H\textsubscript{2}RA—baseline adjusted survival (Kaplan-Meier) curve for myocardial infarction}
\end{figure}
risk. Further studies should examine the effects of long-term and high-dose intake of PPIs.

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AUTHORSHIP
Guarantor of the article: Michael Nolde takes responsibility for the integrity of the work as a whole, from inception to published article.

Author contributions: MN, NA, TD, IR, UA, JL, CM and SB were involved in conceptualization and data interpretation of the study. FG, AG, RG and MT carried out data collection. MN analysed the data and wrote the manuscript. All authors revised and approved the final draft submitted.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from AOK Bayern by contractual agreement.

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SUPPORTING INFORMATION
Additional supporting information will be found online in the Supporting Information section.

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