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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_2RA) 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_2RAs. 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_2RAs 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_2RA 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.

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Conclusions: This analysis of claims data of a large German health insurer did not provide evidence that PPI therapy increased the risk of MI or IS in the first decade after treatment initiation.

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are widely used to treat disorders characterized by excessive gastric acid production.[1] 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)[2-6] and cardiovascular death.[7] The elevated risk was associated with PPI use but not with the use of H_2-receptor antagonists (H_2RAs), the most commonly used alternative class of medications to treat acid-related gastrointestinal conditions.[8] 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[9] and was recently observed in humans.[10]

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.[11] Similarly, a large analysis of administrative claims data found no increased risk for a first MI during PPI intake of up to 3 years,[12] 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.[13]

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[14] to examine the long-term effect of PPI vs H_2RA 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).[15] 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.[16]

2.2 | Study population

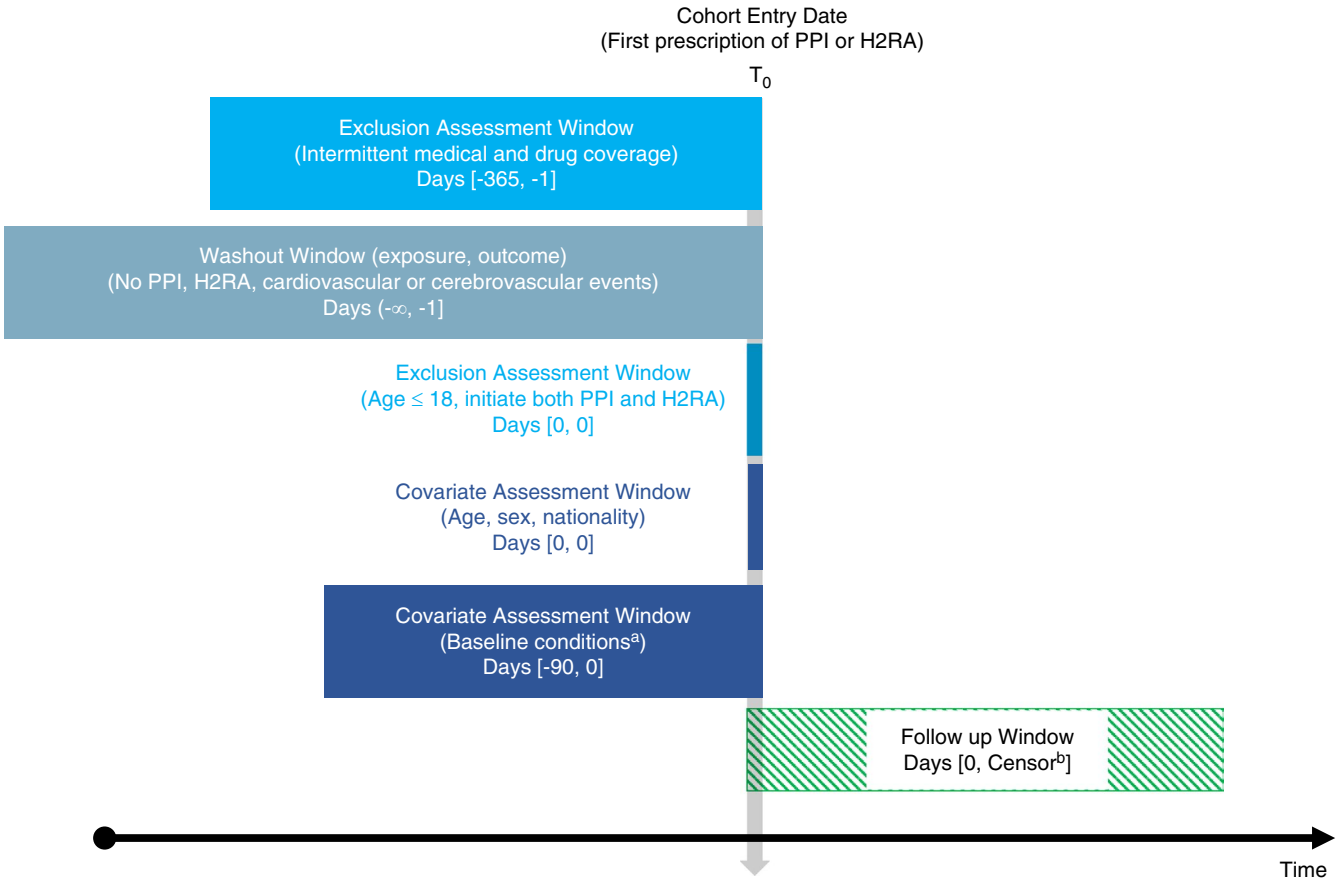
The study cohort included new users of PPIs and new users of H_2RAs, who started therapy between 2009 and 2018. We demanded no prior treatment with PPIs or H_2RAs with at least 1year of medical history before treatment initiation recorded in the data. Cohort entry was the day of the first dispensed prescription 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 I60, I61, I63, I64, G46) at cohort entry. A graphical depiction of our study design is shown in Figure 1.[17]

2.3 | Medication exposure, follow-up and outcomes

New users of PPIs (ATC Code A02BC) were compared to new users of H_2RAs (ATC Code A02BA), as the use of an active comparator might reduce the potential for confounding by indication, compared to a non-user control.[18] 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[19] until the occurrence of an outcome of interest, death, disenrollment or the end of the study period on 31 December 2018 (Figure 1).[17] 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.[20,21]

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.[22] Accordingly, we adjusted for demographics (age, sex and nationality),



a. Baseline conditions included: comorbidities (Elixhauser score), number of medications, antidiabetic drugs, antiplatelets, 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

FIGURE 1 Study design

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.[23] 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.[24] 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,[25] adapted to administrative data, taking both inpatient and outpatient diagnoses into account.[26] 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.[27] Propensity scores were estimated from a confounder-adjusted logistic regression model and used to calculate stabilized weights.[28] Standardized mean differences were used to assess balance in patient characteristics between treatment groups before and after weighting.[29] Raw incidence rates per 1000 person-years were computed. Overall exposure-specific survival was plotted as adjusted Kaplan-Meier estimates.[30,31] 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)[32] to detect potential unmeasured confounding. We imposed various lag times by excluding

events that occurred during the first 10, 30, 90 and 180 days after baseline.[33] 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 H_2RA therapy meeting the eligibility criteria in our data set of 6 097 740 individuals. 22 020 PPI initiators and 16 201 H_2RA 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 H_2RA 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 suffer from GERD or Helicobacter pylori infection, and 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 H_2RA initiation with MI or IS. The HR comparing PPI and H_2RA 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 H_2RA 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 H_2RA 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.[1] 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,[2–6] 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.[12] 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.[11] 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.[13]

Given that some patients use PPIs for many years,[34] 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 H_2RA 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.[35] We addressed these issues by analysing 97 pre-selected negative

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

	Myocardial infarction		Ischaemic stroke	
	H_2RA	PPI	H_2RA	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	2277	1944	2264	1932
Number of events	156	4450	595	17 798
Crude rate per 1000 person-years	0.69	0.73	2.65	2.94

Abbreviations: H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

TABLE 2 Baseline characteristics for initiators of PPI or H_2RA before/after inverse probability of treatment weighting

	Unweighted population			Weighted population		
	H_2RA	PPI	SMD	H_2RA	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 inclusion[b]			0.402			0.106
Baseline-Year[b]			0.393			0.084
Elixhauser Score[a]	1.22 (4.36)	1.19 (4.34)	0.007	1.26 (4.46)	1.19 (4.34)	0.015
Number of Comedications[a]	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

[a]Continuous variables with (mean (standard deviation)). PPI, proton pump inhibitor; H_2RA, H_2-receptor antagonist; SMD, standardized mean difference

[b]For details on the balance of the factor variables 'Quarter of inclusion' and 'Baseline-Year' see Table S1.

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'[19] 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 H_2RA initiators switched to PPIs later on and H_2RA initiators were much more likely to switch to a PPI than vice versa. Switching medication does bias the estimate towards the

TABLE 3 Hazard ratios of weighted Cox regression models (As-started analysis)

		Myocardial infarction			Ischaemic stroke		
Comparator	**Follow-up time**	**HR**	**CI**	***P***	**HR**	**CI**	***P***
PPI vs H_2RA	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
PPI vs No intake	FS	1.02	0.94-1.10	0.70	0.98	0.94-1.02	0.32
PPI vs H_2RA	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

Abbreviations: CI, 95% confidence interval; H_2RA, H_2-receptor antagonist; HR, hazard ratio; PPI, proton pump inhibitor; *P*, *P*-value.

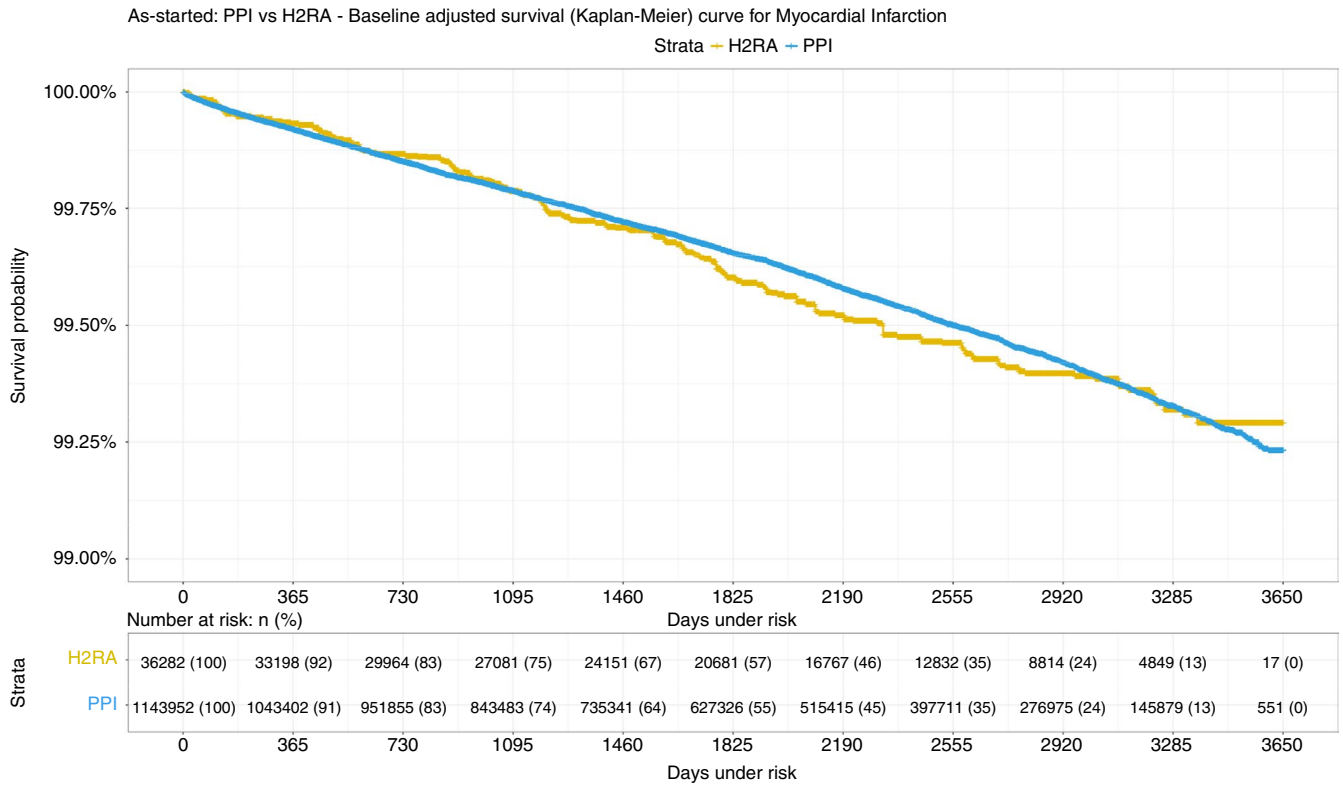


FIGURE 2 As-started: PPI vs H_2RA—baseline adjusted survival (Kaplan-Meier) curve for myocardial infarction

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.[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

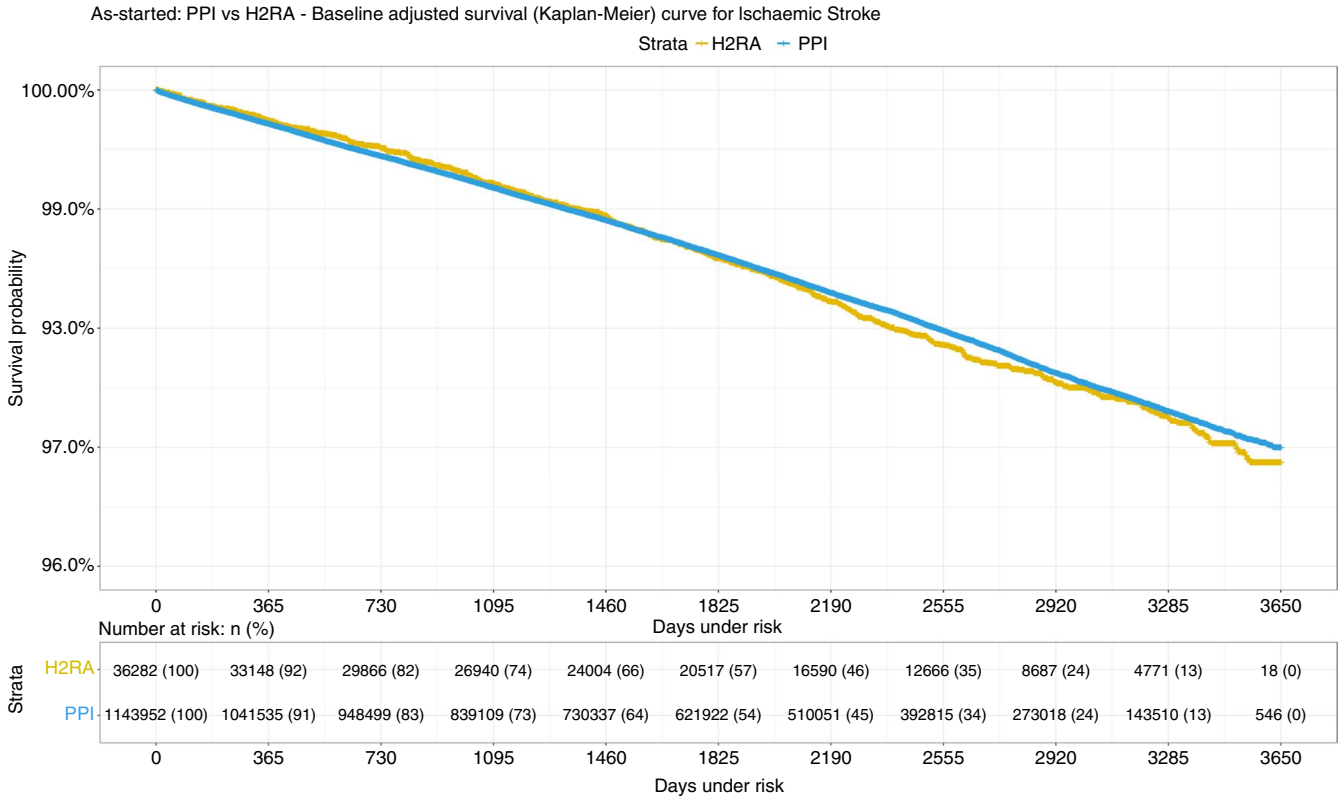


FIGURE 3 As-started: PPI vs H_2RA—baseline adjusted survival (Kaplan-Meier) curve for ischaemic stroke

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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