Post Authorization Safety Study (PASS) Information

Title	Observational study on the risk of myocardial infarction and stroke associated with proton pump inhibitor use
Protocol version identifier	1.0
Date of last version of protocol	26.09.2019
EU PAS register number	Study not yet registered
Active substance	***Proton pump inhibitors*** (***A02BC***), specifically: omeprazole (A02BC01), pantoprazole (A02BC02), lansoprazole (A02BC03), rabeprazole (A02BC04), esomeprazole (A02BC05), dexlansoprazole (A02BC06)
Medicinal product	Not applicable
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorisation holder(s)	Not applicable
Joint PASS	No
MAH(s) contact	Not applicable
Research question and objectives	(1) Does the ***intake*** of proton pump inhibitors affect the risk of myocardial infarction or stroke (2) Does ***long-term intake*** of proton pump inhibitors affect the risk of myocardial infarction or stroke
Country of study	Germany
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1. Table of contents

2. List of abbreviations

MI	Acute Myocardial Infarction
AOK Bayern	Allgemeine Ortskrankenkasse Bayern (Health insurance company)
ATC	Anatomical Therapeutic Chemical Classification System
CVD	Cardiovascular Disease
DDD	Defined Daily Doses
H2RA	Histamine H_2 Receptor Antagonist
KVB	Kassenärztliche Vereinigung Bayerns (Association of Statutory Health Insurance Physicians in Bavaria)
OTC	Over The Counter
PPI	Proton Pump Inhibitor
RiDe-PPI (Gesundheitliche Risiken und Determinanten der Dauereinnahme von Protonenpumpeninhibitoren)	health risks and determinants of the long-term use of proton pump inhibitors
SHI	Statutory Health Insurance Provider

3. Responsible Parties

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4. Abstract

Title
Observational study on the risk of myocardial infarction and stroke associated with proton pump inhibitor use

Rationale and background
Proton pump inhibitors (PPIs) are used to suppress the production of gastric acid in gastroesophageal reflux and other acid-related diseases. They usually show few side effects and thus have been applied widely, with and without medical indication, on prescription and over the counter (OTC). However, during the last years, accumulating evidence suggests that the long-term use of PPIs may be associated with numerous adverse outcomes, including myocardial infarction and stroke.

Research question and objectives
To investigate whether long-term intake of PPIs is associated with the risk of myocardial infarction and stroke.

Study design
Prospective observational cohort study

Population
All patients aged 18 years or older who have been insured by the statutory health insurance provider Allgemeine Ortskrankenkasse (AOK) Bayern, for at least 2 years since January 2008.

Variables
Exposure/Treatment: initiation of PPI therapy
Outcomes: primary acute myocardial infarction and primary ischaemic stroke
Covariates: risk factors of the outcomes, including comorbidities, comedications and demographics

Data sources
Claims database including data for dispensed and reimbursed drugs from the AOK Bayern.

Study size
All initiators of PPIs and Histamine H_2 receptor antagonists (H2RAs) (>500,000 incident users of PPIs and 50,000 initiators of H2RA therapy are expected in our population of 6.1 million persons).

Data analysis
Estimation of the observational analog of

- the intention-to-treat effect.
  We will fit pooled logistic regression models to estimate hazard ratios and survival curves using time-varying stabilized inverse-probability weights.
- the per-protocol effect.
  We will apply different prespecified dose-response models, and derive a dose-response model from the data estimating a weighted cumulative exposure model. For each of these models we fit marginal structural Cox models using stabilized inverse probability of treatment weights.

Milestones
Data transfer is planned to be finished in October 2019. We want to publish results until March 2021.

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5. Amendments and updates

None

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6. Milestones

Milestone	***Planned Date***
test data transfer	***31 August 2019***
registration in the EU PAS register	***30 September 2019***
start of data collection (start of data transfer)	***01 October 2019***
end of data collection (dataset completely available)	***31 October 2019***
final report of study results	***31 March 2021***

7. Rationale and background

Proton pump inhibitors (PPIs) are valued as the most effective therapeutic agents for all conditions related to gastric acid. The name refers to their mechanism of action as they irreversibly block the proton pump-transport system H+/K+-ATPase of the gastric parietal cells, thus inhibiting the secretion of hydrochloric stomach acid.

The approved main indications are gastroesophageal reflux disease (GERD), Barrett's esophagus, treatment and prophylaxis of gastrointestinal bleeding, treatment of gastric and duodenal ulcers, Helicobacter pylori eradication therapy (in combination with antibiotics), and hypersecretion syndromes (e.g. Zollinger-Ellison syndrome) (1–4).

After their market launch in 1989, PPIs have superseded previous treatment options such as histamine H2 receptor antagonists (H2RAs) and antacids by far, steadily increasing to about three billion defined daily doses (DDD) in 2017 in Germany - a development that cannot be sufficiently explained by extensions of indications or increase in prevalences in the approved indication areas (5). Additionally, in recent years, a number of PPIs have been made available without the need of a prescription (over the counter (OTC)), making them widely available and used without a physician's explicit recommendation.

The safety of long-term intake of PPIs has received considerable attention in recent years (6,7). PPIs had been assumed to be safe, but recent studies linked PPI use to an increased risk of myocardial infarction (MI) and ischemic stroke (8,9). A systematic review and meta-analysis of six prospective observational studies suggested that PPI use increases the risk of cardiovascular events and mortality (9). In addition, a pharmacovigilance data-mining approach including 2.9 million individuals yielded significant associations of PPIs and MI as well as cardiovascular mortality, which were not present in patients using histamine H2RAs (10). This result was confirmed in another systematic review and meta-analysis of 17 observational and randomized studies that examined increased cardiovascular risks independent of clopidogrel (11).

Studies suggest that clopidogrel is less efficacious when used together with a PPI and that receiving PPIs concomitantly with antiplatelet agents increases cardiovascular risk (12,13). Similarly, several cohort studies have identified a potential association between PPI use and stroke (14), but contrast with other prospective studies that did not find an increased risk associated with PPI use (15).

Overall, a large number of observational studies have reported associations between use of PPIs and over a dozen unique complications, including increased risk of cardiovascular events. Despite that, the overall evidence for adverse PPI effects is limited. Most existing studies may be subject to bias (6), including confounding by indication and immortal time bias (16).

Randomized controlled trials instead use randomization to distribute measured and unmeasured confounding variables evenly between treatment groups. A recently published trial examined the safety of pantoprazole among 17,598 participants with stable cardiovascular disease and peripheral artery disease (17) and found no increased risk for cardiovascular events when used for 3 years. This is by far the biggest attempt to examine the impact of long-term intake of PPIs in a randomized trial. However, PPIs were introduced into the market three decades ago and are often

taken for even longer periods. Besides that, there was no variation in dosage or in the type of active agent. The intervention group received a fixed daily dose of 40 mg pantoprazole. Most notably, the study included only patients with prior cardiovascular conditions that took specific cardioprotective drugs (rivaroxaban and/or aspirin). More than 60% of all participants already had suffered previous MIs.

In order to provide additional evidence on the relationship between PPI use and the risk of MI and stroke, we will conduct an observational study using routinely collected health care data. To avoid bias that typically occurs in observational studies, we will emulate a clinical trial with clear inclusion criteria, a defined period of enrolment, active treatment phases, and long-term follow up (18,19).

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8. Research question and objectives

The objective is to assess the risk of MI and ischaemic stroke associated with initiation and long-term intake of PPIs.

8.1. Primary research question

Does the ***initiation*** of PPI therapy affect the risk of myocardial infarction or stroke?

8.2. Secondary research question

Does ***long-term intake*** of PPIs affect the risk of myocardial infarction or stroke?

9. Research methods

9.1. Study design

We will conduct a prospective observational cohort study. Recent discussions have emphasized the benefits of designing observational data analyses as the emulation of a target trial (20). This approach avoids a number of potential biases and makes sure that the calculated estimates have a meaningful clinical interpretation. In the target trial design we try to emulate a target trial, i.e. a hypothetical interventional study designed to answer the research question, which at least in principle could have been performed (19,21,22).

For each of the outcomes of interest (MI/stroke), we imagine two target trials (i) and (ii) with a common set of baseline eligibility criteria (Table 1).

Patients are randomly assigned to

- Target trial (i): PPI therapy vs. no therapy
- Target trial (ii): PPI therapy vs. H2RA therapy (the active comparator medication).

9.1.1. Eligibility / exclusion criteria

Eligibility/exclusion criteria are: age of at least 18 years; no prevalent cardiovascular disease; no prior use of any PPIs. Additionally we demand no prior use of the comparator medication in target trial (ii).

In both trials, patients are followed from baseline (between January 2009 and December 2017) until event (MI or stroke), death, loss to follow-up, or administrative end of the study in December 2018, whichever occurs first.

Table 1: Hypothetical target trials

	Target Trial (i)	Target Trial (ii)
Design:	'Single treatment'	'Head-to-head'
Population: (eligibility/exclusion criteria)	Adults without prior cardiovascular disease or PPI intake.	Adults without prior cardiovascular disease, PPI intake or H2RA intake.
Intervention:	PPI therapy	PPI therapy
Comparator:	No PPI therapy	H2RA therapy
Outcome:	MI/stroke	MI/stroke
Timeframe:	Maximum of 10 years of follow-up between January 2009 and December 2018.	Maximum of 10 years of follow-up between January 2009 and December 2018.

9.2. Setting – emulation of target trials in the data

We apply the same baseline eligibility criteria described above and in addition demand at least 2 years of continuous recording in the database. To ensure no prior history of outcome or treatment, we require that at least one year of a patient's history is available at the time of enrolment.

Individuals in our data can meet the eligibility criteria at several times. We emulate each target trial as a sequence of trials that started at each of the 108 months between January 2009 and December 2017 (22). Eligible individuals at each of the 108 baselines are assigned to a treatment group and followed until the first occurrence of the outcome, death, loss to follow-up (due to change of Statutory Health Insurance Provider (SHI)), or administrative end of the study on 31/12/2018. Individuals might be included in several monthly trials for the no-treatment group in target trial (i), but can enter trial (ii) only once.

In each monthly trial for the ''single treatment'' trial (i), eligible individuals who initiated PPI therapy during the baseline month are assigned to the treatment arm and non-initiators to the no-treatment arm.

In each monthly trial for the ''head-to-head'' trial (ii), eligible individuals who initiated PPI therapy during the baseline month are assigned to one arm, and those initiating H2RA therapy to the other arm; all others, including participants initiating both PPI and H2RA therapy, are excluded.

We define treatment initiation as the time of the first time ever prescription of a PPI or H2RA.

9.3. Variables

9.3.1. Exposure definition

9.3.1.1. Estimation of treatment episodes

The medication class of interest are proton pump inhibitors (A02BC), specifically:

ATC	**Description**
A02BC01	omeprazole
A02BC02	pantoprazole
A02BC03	lansoprazole
A02BC04	rabeprazole
A02BC05	esomeprazole
A02BC06	dexlansoprazole

We will use the prescription data to construct PPI treatment episodes (dose and duration). In a first analysis, we will look at overall PPI intake. Treatment episodes

start at the date of the first prescription. We use consecutive dispensations for dosage estimation. Given a dispensation of x pills with y DDD each, we

- usually assume a daily intake of 1 pill (this is a daily dosage of y DDD).
- assume a daily intake of 2 pills (this is a daily dosage of 2y DDD), if there is a new dispensation within x/2 days after the previous dispensation.
- assume, that the dosage stays constant, if there is no following dispensation in the data.

We then construct periods of episodic intake according to the package sizes (number and dosage of pills) and the estimated daily dosage. If there is a new dispensation, we add unused pills to the stock and extend the intake. Gaps of 14 days or less between two episodes are bridged by extending the first episode, as PPIs are easily available even without prescription. Finally, we assume that the last dispensed package of each of these ultimate episodes is only halfway depleted.

In a second step, we will distinguish between the different types of PPI and perform separate analyses for each agent.

9.3.1.2. Exposure Status

We measure exposure status at treatment initiation and on the first day of each following quarter of the trial. All exposure variables are direct functions of the estimated PPI treatment episodes.

9.3.1.2.1. Observational analog of the intention-to-treat effect

For estimating the observational analog of the intention-to-treat effect, we define exposure as a simple indicator for treatment, coded as 1 for PPI therapy and 0 for the corresponding reference group, i.e. no treatment in target trial (i) and H2RA in target trial (ii).

9.3.1.2.2. Observational analog of the per-protocol effect for continuous intake

For estimating the analog of the per-protocol effect, we have to further specify the concept of long-term intake. In a first analysis, we look at the effect of continuous intake.

9.3.1.2.3. Dose-response-model based analysis

Finally, we will allow periods of no intake and apply a dose-response model using two time-varying exposure definitions:

- the total usage time and
- the current dose.

In a third step, we will perform the analysis using an estimated weighted cumulative exposure (WCE) model as described in (23). With this approach the exposure metric is defined as the weighted sum of flexible splines of past doses.

9.3.2. Outcome definition

The study endpoints are

- Primary acute myocardial infarction (ICD-10-GM code I21)

ICD-10-GM code	Description
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified

- Primary ischaemic stroke (I63, G46.5, G46.6)

ICD-10-GM code	Description
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
G46.5	Pure motor lacunar syndrome
G46.6	Pure sensory lacunar syndrome

A patient will be considered a case of MI or ischaemic stroke after a hospital admission with the corresponding main discharge diagnosis. The validity of these claims-based diagnoses has been established (24,25).

9.3.3. Covariate definition

We adjust for pre-treatment covariates that affect the outcome (26).

9.3.3.1. Confounding at baseline

Demographic information (age and sex) is assessed at baseline.

Baseline comorbidity is measured from data of the quarter preceding treatment initiation, using both in- and outpatient diagnoses, except outpatient diagnoses marked as “diagnosis ruled out”, “status post” or “suspected diagnosis”. An adaptation of the Elixhauser score is used (27), taking both inpatient and outpatient diagnoses into account (28).

Baseline comedication, i.e. use of antidiabetic, antithrombotic or thrombogenic drugs and a polypharmacy score (counting the number of differerent medications) is measured in the quarter preceding treatment intitiation. To address potential changes in medication, antithrombotic or thrombogenic drugs are also assessed in the last 30 days before time zero. For those medications, we do not estimate episodes of intake for every patient, but only look at prescriptions in the specified time intervals.

9.3.3.2. Time-varying confounding

Comorbidity, comedication, polypharmacy score, exposure status and outcome specific risk factors are updated quarterly, using the data of the preceding quarter for all covariates and determining the exposure status on the first day of the quarter. The corresponding outcome status is set at the end of the quarter. This temporal ordering of data reflects the intrinsic structure of our dataset, cf. 9.4, and the relationships between covariates, exposure and outcome used in the statistical analysis, cf. 9.7.

Acute myocardial infarction and ischemic stroke have similar but slightly different known risk factors, listed below.

9.3.3.3. Risk factors for acute myocardial infarction

History of MI, prevalent ischaemic stroke, prevalent coronary artery disease and prevalent peripheral artery disease are risk factors for MI, but we exclude those patients. The following risk factors, as recently published (29), will be assessed:

- arterial hypertension
- diabetes mellitus
- dyslipidaemia
- obesity

We will assess prescriptions of antithrombotic agents, which might be used for thrombosis prevention in patients with known risk factors. We will assess the use of clopidogrel separately, due to reported interactions with omeprazole.

9.3.3.4. Risk factors for cerebrovascular events

History of cerebrovascular events and prevalent MI are risk factors for ischemic stroke, but we exclude those patients. The following risk factors (30) will be assessed:

- aortic atherosclerosis
- arterial hypertension
- atrial fibrillation
- cardiac tumours
- cardiomyopathy
- diabetes mellitus
- dyslipidaemia
- obesity
- patent foramen ovale/atrial septal aneurysm
- sickle cell disease
- valvular heart disease

We will assess prescriptions of antithrombotic agents, which might be used for thrombosis prevention in patients with known risk factors and consider them as a protective factor. We will assess the use of clopidogrel separately, due to reported interactions with omeprazole.

9.4. Data sources

For this study, we analyze claims data from the Allgemeine Ortskrankenkasse (AOK) Bayern, a large regional German SHI covering about 4.5 million people in Bavaria (in 2019) or about one in three of the total population of Bavaria. The dataset includes all adult persons, who have been covered by the AOK Bayern for a period of at least 2 years since 2008; this group consists of about 6.1 million individuals.

The database contains core data, hospitalization data, outpatient prescription data, and outpatient care data/diagnoses. Any drugs purchased OTC, or administered in hospital, are not contained in the database. For data protection reasons, the data is pseudonymized.

Membership in an SHI is compulsory in Germany for employees below an annual income threshold (48,150€ in 2008 and increasing to 59,400€ in 2018). Subjects with incomes that exceed this limit can choose private health insurance providers instead of an SHI and are slightly underrepresented in SHIs. However, around 75% of these higher-income patients remain voluntary members of SHIs, most often because SHIs provide free health insurance for unemployed family members (children and spouse). In private health insurance plans a separate fee must be paid for each family member. About 70 million people (85% of the German population) are SHI members, including about five million voluntary members, children and patients who are retired or unemployed.

Table 2: Structure and Content of Data Files from the SHI AOK Bayern

Core data	Hospital data	Outpatient data	Prescription data
• pseudonymized subject ID No. • sex • birth year • martial status • nationality (German/other) • region of residence • coverage times (entry and exit) • reasons for exit (e.g. death) • insurance status (self/relative-spouse/child) • occupational status	• pseudonymized subject ID No. • day of admission/ discharge • OPS key[1] • day of delivery • DRG (diagnosis-related group) • diagnosis (ICD-10-GM) • type of diagnosis • reason for admission • reason for discharge • type of treatment • artificial ventilation time • receiving unit • releasing unit	• pseudonymized subject ID No. • physician specialty • diagnoses (ICD-10-GM[2], quarterly[3]) • types and dates of treatments and diagnostic procedures (EBM code[4])	• pseudonymized subject ID No. • physician specialty • ATC (GM) code[5] • central pharmaceutical No. (PZN) • DDD • date of prescription • date of dispensation • quantity prescribed • quarterly number of prescribed medications (polypharmacy score)

We consider the core data and hospital data to be the most valid information in our dataset. Diagnoses in outpatient care lack exact dates and might include presumptive or preliminary diagnoses (31). Due to privacy protection, we receive pseudonymized data and can only perform checks for plausibility. The prescription data is a reliable source for the dispensation of prescribed medication. It still remains a challenge to derive information on actual intake, as PPIs in low dosage are also available without prescription (OTC) (32). In the German health system, no information on the intended usage of the medication or the days of supply is recorded. Therefor we pay much attention to transforming prescription data in episodes of actual intake.

[1] Key for diagnostic and surgical/medical procedures, German modification of ICPM (International Classification of Procedures in Medicine)
[2] The International Statistical Classification Of Diseases And Related Health Problems, 10th revision, German Modification
[3] Diagnoses refer to a period of three months, as physicians' services are settled quarterly.
[4] Einheitlicher Bewertungsmaßstab (Uniform Evaluation Scale)
[5] Anatomical Therapeutic Chemical Classification System, German modification

9.5. Study size

The ratio of prescribed PPI to prescribed H2RA has shifted in Germany from 1674 (million DDD) : 114 (million DDD) (~15:1) in 2008 to 3654 : 48 (~76:1) in 2017 (5,33). Our data covers 6.1 million individuals and their medical claims data over a maximum of 11 years. Comparing this to a recent study using a comparable dataset in the US (34) and taking into consideration the slightly different timeframes as well as recent changes in usage of the medications, we estimate well over 500,000 incident users of PPIs and about 50,000 new users of H2RA.

We set the incidence of primary ischaemic stroke in the German population to its 2010 value (35) of 203 events / 100,000, assuming 85% of strokes being ischaemic. We set the incidence for myocardial infarction to its 2010 value of 350 events / 100,000 (36). Assuming a median follow-up time of 4 years, this leads to approximately (406 | 4060 | 49,532) ischaemic strokes and (700 | 7000 | 85,400) myocardial infarctions in the (H2RA-group | PPI-group | total population).

We should, therefore, be able to detect hazard ratios of 1.06 for ischaemic stroke and hazard ratios of 1.05 for myocardial infarction with a statistical power greater than 80%, and a significance level of 5%.

9.6. Data management

We will use R and SAS for data preparation.

The pseudonymized electronic claims data will be stored on an isolated workstation and is only accessible for authorized employees in accordance with our institutional data protection concept.

The study will be conducted according to the Guidelines for Good Pharmacoepidemiology Practice, Good Practice of Secondary Data Analysis, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology as well as Good Epidemiological Practice.

9.7. Data analysis

We will perform statistical analyses in R and publish the respective code on GitHub (https://github.com/RiDe-PPI/RiDe-PPI).

9.7.1. Observational analog of the intention-to-treat effect

First, we estimate the effect of PPI treatment as the effect of being prescribed treatment, in perfect analogy to the intention-to-treat analysis in a randomized trial. We will pool the data of all monthly trials, fit a pooled logistic regression model and estimate hazard ratios (22). Due to well-known limitations of hazard ratios as effect measures (37), we will estimate survival curves by including product terms between treatment variables and follow-up time using subject-specific time-varying stabilized inverse-probability weights.

9.7.2. Observational analog of the per-protocol effect for continuous intake

Our second approach is an observational analog of the per-protocol effect, i.e. the effect observed had all individuals adhered to their assigned treatment strategy. Different to a randomized trial, we do not know the exact treatment strategy, the patient was told to follow, and the strategy is most likely to change over time. In this case participants are often regarded adherent to their assigned treatment, as long as they continue treatment, and censored when they discontinue intake (or in the case of assignment to no-treatment start treatment) (22). Using this censored data, we perform the same analysis as in 9.7.1 and estimate hazard ratios and survival curves. This approach implicitly uses a simple dose-response model. It treats current intake, regardless of the dosage, as the only relevant exposure variable.

9.7.3. Dose-response-model based analysis

9.7.3.1. Dose-response models

Although the dose-response model implicitly used in 9.7.2 is often applied, it might be too simple, to adequately describe cumulative and long-term effects of PPI intake. One major disadvantage is that the model does not allow for cumulative effects that do not simply disappear over periods of treatment discontinuation. We will therefore also consider more realistic dose-response models and replace the simple indicator for treatment arm by a time-varying function of PPI intake since baseline (38). Our first model uses the current dosage and the duration of intake since baseline as variables for exposure. We will derive a second dose-response model from the data estimating a weighted cumulative exposure model (23).

9.7.3.2. Conventional modelling

First, we fit conventional Cox models for each dose-response model described above adjusting only for baseline covariates. Time-varying covariates are not included in these conventional models.

9.7.3.3. Marginal structural modelling

Then, for each dose-response model described above, we fit marginal structural Cox models using stabilized inverse probability of treatment weights. Here, time-varying covariates that are potentially on a causal pathway between exposure and outcome are included and updated for each quarter.

9.7.4. Empirical calibration using negative control outcomes

Negative controls, or falsification endpoints, need to be considered in studies of adverse effects of treatments to uncover the effect of confounding variables that were not captured within the dataset (39). For all models we will derive an empirical null distribution from a sample of negative controls and calibrate p-values, accounting for both random and systematic error (40). In addition, we will use positive controls, which we synthesize by modifying negative controls, for the calibration of confidence intervals (41).

9.7.5. Sensitivity analyses

We perform a series of sensitivity analyses to test the robustness of our primary analysis. Quantitative bias analysis assesses how sensitive an observational treatment effect estimate is with regard to the chosen study design and how conclusions could change due to unaccounted confounding. Among them are:

- Calculation of E-values to quantify the sensitivity of our estimates regarding potential unmeasured confounding (42)
- Variation of arbitrarily set time intervals in our study design, i.e. required look-back time for the exclusion of prior events or medication
- Analyses using alternative models for the construction of intake episodes from prescription data
- Analyses excluding users of clopidogrel
- Analyses excluding all users of NSAIDs due to their potential for co-administration in patients with high cardiovascular risk
- Analyses adjusting for alternative comorbidity scores: Charlson index (43), combined comorbidity score (44) and M3 index (45).
- Analyses using the extreme restriction design approach to reduce confounding by indication (46)
- Analyses using inactive comparators (negative control exposures) (47,48) instead of new users of H2RA or non-users
- Estimation of the vibration of effects (49)
- Bias analysis for differential exposure misclassification (50)

9.8. Quality control

As all data is pseudonymized, we cannot check for validity on an individual level. Instead, we will make an effort to evaluate the validity and plausibility of our data at large.

- We will examine the correlations between certain diagnoses and medications included in standard treatment guidelines.
- We will calculate age- and sex-specific incidence rates of the outcomes and compare them to literature. (35,36)
- We will check demographics and comorbidities for the respective outcome for plausibility.
- We will review a random sample of 100 patient profiles in detail and check their complete medical histories for plausibility. This will include in- and outpatient diagnoses (ICD-10-GM), therapies and medication.

9.9. Limitations of the research methods

This study is primarily limited by the intrinsic limitations of our secondary data. Information on lifestyle (smoking habits, alcohol consumption, body mass index, physical activity) or on socio-economic status is not available. Information on diagnoses in the outpatient system is only available on a quarterly basis. On the exposure side, we lack information about the use of OTC medications and dispensations in hospitals. Even for documented prescriptions of PPIs, the intended treatment duration and prescribed dose are unknown.

Therefore, sensitivity analyses as described in 9.7.5 have to show, how robust our methods are with regard to unmeasured confounding and potentially differential misclassification of PPI intake. Despite these problems, determination of drug therapy based on pharmacy dispensing data is considered the gold standard in secondary data analysis, as recall bias can be ruled out and information is precise in time and dispensed dose (51). Our outcomes will mostly consist of hospital discharge diagnoses, which in general are considered very reliable.

9.10. Other aspects

None

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10. Protection of human subjects

This study protocol will be conducted in accordance with Good Pharmacoepidemiology Practices (52).

The ethics committee of the Ludwig-Maximilians-Universität München ruled, that due to the nature of the data source no further approval was necessary.

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11. Management and reporting of adverse events / adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI– Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required.

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12. Plans for disseminating and communicating study results

The study will be registered on the ENCePP/EU PAS Register website. We intend to publish results from this study in peer review journals.

13. References

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols (Revision 3)

Doc.Ref. EMA/540136/2009

European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

ENCePP Checklist for Study Protocols

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Observational study on the risk of myocardial infarction and stroke associated with proton pump inhibitor use

Study reference number:

not available

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[6]	☒	☐	☐	6
1.1.2 End of data collection[7]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	-
1.1.4 Interim progress report(s)	☐	☐	☒	-
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

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Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7

Comments:

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Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☒	11

[6] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[7] Date from which the analytical dataset is completely available.

Comments:

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Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4, 9.5
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9.4
4.2.1 Study time period?	☒	☐	☐	9.4
4.2.2 Age and sex?	☒	☐	☐	9.4
4.2.3 Country of origin?	☒	☐	☐	9.4
4.2.4 Disease/indication?	☒	☐	☐	9.4
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1, 9.2

Comments:

-

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1

Comments:

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Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8, 9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	-

Comments:

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Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.1, 9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.1, 9.7
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.1, 9.7
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.1, 9.7
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.4

Comments:

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Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

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Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	94.
9.3.3 Covariates?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

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Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	-
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

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Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

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Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.7.5, 9.9
12.1.2 Information bias?	☒	☐	☐	9.7.5, 9.9
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	9.7.5, 9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.4, 9.5

Comments:

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Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

Comments:

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Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

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Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☒	-
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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Name of the main author of the protocol: Nolde Michael

Date: 26/09/2019

Signature: xx

Annex 3. Additional information

None