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Untersuchung des Effekts der Langzeiteinnahme von Protonenpumpenhemmern auf das Risiko für Herzinfarkt und Schlaganfall

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Contents

Nomenclature

ADMA	asymmetrical dimethylarginine
AOK Bayern	Allgemeine Ortskrankenkasse Bayern (Health insurance provider)
DDAH	dimethylarginine dimethylaminohydrolase
eNOS	endothelial nitric oxide synthase
H2RA	histamine H_2 receptor antagonist
IS	ischaemic stroke
MI	myocardial infarction
NO	nitric oxide
PPI	proton pump inhibitor
SHIP	Study of Health in Pomerania

List of Publications

Publication I - *Pharmacotherapy*, 2021

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Nolde, Bahls, Meisinger and Baumeister contributed equally

Publication II - Alimentary Pharmacology & Therapeutics, 2021

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1. Contribution to the Individual Publications

This dissertation examines the effect of proton pump inhibitor (PPI) therapy on cardiovascular risk using different approaches. In the first publication, we examined a biochemical pathway, by which PPI intake might have a negative effect on the endothelium via inhibition of nitric oxide (NO) synthesis. In the second publication, we estimated the long-term effect of PPI therapy on the risk of myocardial infarction (MI) and ischaemic stroke (IS) using claims data.

1.1 Contribution to Publication I

I developed the idea for the first publication, while I looked for biochemical mechanisms explaining the alleged effect of PPI intake on cardiovascular risk. Based on experiments with ex vivo cells and mice, Ghebremariam and colleagues (Ghebremariam et al., 2013) suggested a biochemical pathway, by which PPIs might increase the risk of cardiovascular events. They proposed that PPI intake inhibits the enzyme dimethylarginine dimethylaminohydrolase (DDAH) and thereby elevates the endothelial level of asymmetrical dimethylarginine (ADMA). This would further reduce the production of NO and lead to endothelial dysfunction. Add-on human studies were unsuccessful to establish a link between PPI exposure and plasma ADMA. Reading a paper by Davids and Teerlink (Davids & Teerlink, 2013), I realized that the plasma concentration of ADMA might not reflect the intracellular endothelial ADMA concentration very well. This could explain why all previous attempts to reproduce the laboratory results in a human population were futile.

Looking at all the chemical reactions involved in endothelial NO synthesis, I identified citrulline as a potential alternative indicator for the effect of PPI intake on the endothelium. Lacking formal education in physiology or biochemistry, I consulted with Dr. Martin Bahls (University Medicine Greifswald) whether citrulline might be a suitable indicator for the effect of PPI intake. Under the guidance of Sebastian Baumeister, I designed the study, planned, and performed the data analysis, drafted, submitted, and revised the manuscript. Martin Bahls and I share first authorship.

1.2 Contribution to Publication II

For the second publication, we gathered claims data from the Allgemeine Ortskrankenkasse (AOK) Bayern, a large health insurance provider. I selected the variables needed for the main and sensitivity analyses and designed a target trial emulation for the estimation of the long-term effect of PPI therapy on the risk of MI and IS. Therefore, I drafted a study protocol, which was registered at ENCePP.eu (EUPAS31559) and described in detail the planned analyses. I set up the IT necessary to process and analyse the big data set in our lab and performed quality controls, data preparation and all statistical analyses. I drafted, submitted, and revised the manuscript.

2. Introduction

2.1 Bias in pharmacoepidemiology

Studies in pharmacoepidemiology are subject to different sources of bias. Any association between the exposure, usually in form of a drug, and the outcome might reflect a true causal relation or bias due to a lack of randomisation. Common sources of bias are confounding, information bias, selection bias, and immortal time bias (Hernán & Robins, 2020; Lash et al., 2021). Confounding is caused by so called open backdoor paths between exposure and outcome (Pearl, 2009). In the statistical analysis of a study, we therefore aim to adjust for a sufficient set of measured variables, that blocks all those open backdoor paths. Another source of bias is information bias. Exposure or outcome are often not measured perfectly, which leads to exposure or outcome misclassification. If the measured outcome variable is directly affected by the exposure, we call this differential misclassification. Selection bias arises whenever the selection into the study is affected by the outcome and the exposure. Finally, studies in pharmacoepidemiology often deal with time to event data, where it is crucial to identify time under risk and attribute it to the treatment or control group correctly. The case where immortal patient time, i.e. time where no event could occur, is wrongly counted for time under risk is seen so often that it gained its own term: immortal time bias (Suissa, 2008).

Failure to address these biases heavily affects effect estimates and is even known to have inverted alleged drug effects. Bias in epidemiological studies is best prevented at the design stage. It has become best practise to design a study along the lines of a hypothetical randomised trial following the so-called target trial design (Hernán & Robins, 2016). Although there are statistical methods to adjust for baseline confounding, if all relevant variables are measured, the researchers should furthermore try to design a study with treatment and control groups, which are not too different regarding the baseline characteristics. This can be achieved by choosing a new user, active comparator design (Lund et al., 2015).

A whole battery of sensitivity analyses should be applied to assess the robustness of effect estimates applying varying study designs, exposure and outcome definitions, and lag times. The analysis of negative control outcomes might reveal residual confounding (Shi et al., 2020).

As each study design and each data source has its own set of advantages and limitations, the researcher should try to triangulate a research question using different designs and different data sources to shed light on various aspects of the problem (Lawlor et al., 2016).

All this reads like the natural thing to do, but only a decade ago it was not so obvious. Studies using observational data often contradicted interventional studies for no obvious reason. I want to highlight two illustrious examples:

In observational studies, hormone replacement therapy was associated with a lower risk of coronary heart disease. This apparent protective effect seemed plausible because oestrogens are known to affect lipid profiles. As a result, hormone replacement therapy was widely prescribed for the prevention of coronary heart disease until large, randomised trials were conducted that could not replicate an effect of hormone replacement therapy on the risk of coronary heart disease in post-menopausal women. This discrepancy could be explained by flaws in the design and analysis of the observational studies, and a more meticulous analysis of observational data from the Nurses' Health Study was able to reach estimates, similar to the ones reported in interventional studies (Hernán et al., 2008). This experience lead later to the development of the target trial approach (Hernán & Robins, 2016).

A second study (Suissa & Azoulay, 2012) examined the observational evidence for a dramatically reduced risk of cancer and cancer mortality in users of metformin that sparked a series of randomised trials of metformin as a potential cancer treatment. Focussing on time-related biases such as immortal time bias, the researchers could explain previous, large effect estimates as the results of bad design choices. Only three studies achieved to avoid these biases, and all reported no effect of metformin therapy on cancer incidence.

Now, pharmacoepidemiology enters an era where more and more real-world data is accessible to researchers, be it in the form of health care claims, electronic health records or genetic studies. We are about to find out if methodological progress (Wyss et al., 2018) prepared us for the challenges ahead (Franklin et al., 2021).

2.2 Proton Pump Inhibitors and the risk of cardiovascular events

Proton pump inhibitors (PPIs) are widely used to treat disorders characterized by excessive gastric acid production (Rückert-Eheberg et al., 2021) and even sold over-the-counter without any clinical indication. Alongside, PPIs are used for gastroprotection in patients on dual antiplatelet therapy consisting of aspirin in combination with a P2Y12 inhibitor such as clopidogrel, prasugrel or ticagrelor to prevent secondary myocardial infarctions and ischaemic strokes.

An effect of PPI intake on cardiovascular events has been discussed for more than a decade. PPIs, especially omeprazole, seem to attenuate clopidogrel's antiplatelet effects by inhibiting CYP2C19, which metabolises clopidogrel to its active metabolites (Pang et al., 2019). In 2009, the European Medicines Agency (EMA) issued a safety warning about co-use of clopidogrel and omeprazole or esomeprazole. Later, several mechanisms have been suggested, by which PPIs might directly affect cardiovascular risk via impaired vascular endothelial function (Ghebremariam et al., 2013) or accelerated endothelial aging (Yepuri et al., 2016).

However, the overall evidence for an effect independent of clopidogrel inhibition was conflicting between randomised trials and observational studies (Batchelor et al., 2018). While randomised trials showed no differences between PPI users and placebo-users (Batchelor et al., 2018; Moayyedi et al., 2019), observational studies indicated a potentially increased cardiovascular risk for PPI users (Batchelor et al., 2018; Li et al., 2019). This seemed concerning, as only observational studies could detect potential long-term effects in the absence of large, long-running randomised trials, which would be hardly feasible, extremely expensive, and deliver results only in the distant future.

2.3 The evidence in 2018

Two different questions arise regarding a potentially increased cardiovascular risk associated with PPI intake. The effect of PPI intake on secondary events as part of dual antiplatelet therapy is a question of short-term effects in a high-risk population and is examined most appropriately by clinical trials (Moayyedi et al., 2019; Pang et al., 2019). The effect of PPI intake as a treatment of gastroesophageal diseases on primary events is a question of long-term effects in a low-risk population, requiring both a large study population and long study period, and thus most efficiently addressed by well-designed observational studies.

Unfortunately, observational studies examining the effect of PPI intake on cardiovascular outcomes are especially prone to confounding, in that patients with worse cardiovascular morbidity are prescribed

PPIs. A common source of bias in published observational studies was the inclusion of prevalent users of PPIs and patients with prevalent cardiovascular disease, which might have resulted in immortal time and other time-related biases. Associations between PPI intake and cardiovascular outcomes could therefore indicate a causal effect of PPI intake or stem from confounding. The most recent meta-analyses on the topic (Batchelor et al., 2018; Farhat et al., 2019; Li et al., 2019; Shiraev & Bullen, 2018) reported a higher risk of cardiovascular events associated with PPI therapy, but pooled effect estimates of studies with varying risk of bias (Sterne et al., 2016).

In addition, the supposed biochemical mechanism that was found to inhibit NO synthase in vitro (Ghebremariam et al., 2013) did not seem to be replicable in human population studies (Ghebremariam et al., 2015; Kruszelnicka et al., 2016; Tommasi et al., 2017).

2.4 Publication I - the biochemical pathway

We started the project trying to contribute to the existing evidence for the proposed biochemical pathway by Ghebremariam and colleagues (Ghebremariam et al., 2013). They suggested that PPI intake might impact on vascular function by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), an enzyme involved in the breakdown of asymmetrical dimethylarginine (ADMA) in endothelial cells. ADMA itself is known to inhibit endothelial nitric oxide synthase (eNOS), an enzyme needed for the production of nictric oxide (NO). NO finally plays a crucial role for endothelial function (see Figure 1 for a schematic representation).

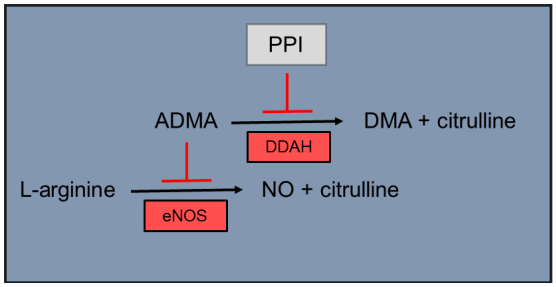

Figure 1: A molecular mediating pathway for an elevated cardiovascular risk: schematic representation of the reactions inhibited by PPI intake.

This chain of reactions was previously only shown with in vitro and murine experiments. Any attempts to measure the effect in human populations had been futile. We realized that ADMA might not be the most suitable biomarker to reflect the mechanism in vivo because there is a weak correlation between ADMA measured in blood and its intracellular concentration (Davids & Teerlink, 2013). We had a closer look at the reactions involved in the biochemical pathway and decided that citrulline might be a more promising choice for assessing the reaction in human populations, as it is involved in both relevant reactions (Figure 2). We therefore conceptualised our study to analyse the effect of PPI intake on plasma citrulline and vascular function, measured by flow-mediated dilation (FMD) of the brachial artery.

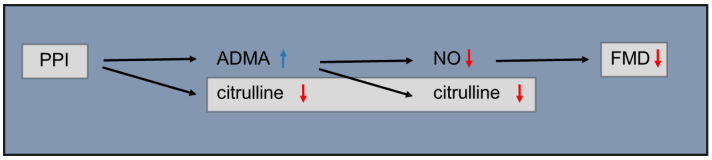

Figure 2: Effect of the reactions in Figure 1 on citrulline and FMD

We found that PPI users had lower plasma citrulline and FMD than non-users (Nolde, Bahls, et al., 2021). It was the first study to use citrulline as a biomarker for DDAH inhibition and the first one to show evidence for PPI induced NO inhibition in humans. Although a plausible biochemical pathway seemed to be established at this point, it remained an open question if the resulting effect on cardiovascular events was clinically relevant.

2.5 Publication II - the long-term effect

The second cornerstone of this dissertation project is the analysis of a large claims database. The study protocol and analysis plan were registered in 2019 at the ENCePP.eu (EUPAS31559), including a detailed description of the emulated target trial and the planned main and sensitivity analyses.

The data was provided by the AOK Bayern (Allgemeine Ortskrankenkasse Bayern), the largest health insurance provider in the Bundesland (state) of Bavaria, Germany, and contained 6.1 million people over 18 with a follow up of up to 12 years between 2007 and 2018.

We set up the study according to the target trial design (Hernán & Robins, 2016). Following an active comparator, new user design (Lund et al., 2015), we compared new users of PPIs to new users of histamine H_2 receptor antagonists (H2RAs) with regard to their risk of first myocardial infarction and first ischaemic stroke. PPI intake was identified via dispensed prescriptions and an observation period of one year was used to ascertain new use prior to inclusion in the study. Cardiovascular events were identified from hospital diagnoses.

We adjusted for baseline confounding factors using inverse probability of treatment weighting. Adjusted Kaplan-Meier curves and confounder-adjusted Cox regression analyses showed no evidence for an increased risk of cardiovascular events of PPI users compared to users of H2RAs.

A major concern in observational studies is the presence of residual confounding. We analysed 97 pre-selected negative control (tracer) outcomes to detect potential unmeasured confounding (Shi et al., 2020). The range of hazard ratio estimates over the set of negative controls did not indicate substantial residual confounding.

Another important concern, that we addressed in our sensitivity analysis, stems from the fact that patients often switch gastrointestinal medication. PPI initiators switch to or add H2RAs, and especially H2RA initiators often switch later to PPIs. This could bias the estimate towards the null. We performed an additional analysis comparing new users of PPIs to non-initiators that, although being generally more prone to confounding, was much less affected by the problem of switching medications. The comparison with non-initiators resulted in estimates similar to the main analysis.

Despite the remarkable size of our dataset, it included just slightly over 36,000 new users of H2RAs, compared to over 1.1 million new users of PPIs. Under these circumstances, we were only able to assess the effect of PPI therapy compared to H2RA therapy. Therefore, although we had planned to examine long-term intake and to estimate a dose-response model, this was not feasible with the data at hand.

Our results are a confirmation of a similar large claims data study published in 2018 regarding myocardial infarction (Landi et al., 2018). Our study on ischaemic stroke includes more events than other published observational studies and provides a substantial addition to the evidence base. Both studies are compatible with evidence from a recent large randomised trial (Moayyedi et al., 2019) that found no effect of PPI intake on the risk of cardiovascular events over three years of continuous intake.

In response to our publication, a letter was published where clinical practitioners from Shanghai asked for additional information about the types of PPIs involved in our study and a potential interaction with clopidogrel. The letter and our response can be found in Appendices C and D.

2.6 The evidence in 2022

Since 2018 two large studies based on claims data have been published that analysed the effect of PPI therapy on the risk of cardiovascular events. Both studies provided no evidence for an adverse effect of PPI therapy (Landi et al., 2018; Nolde, Ahn, et al., 2021). Overall, PPI intake as a treatment of gastroesophageal disease does not seem to increase the risk of first cardiovascular events.

Although our analysis of a proposed biochemical pathway indicated that PPIs inhibit endothelial NO production (Ghebremariam et al., 2013; Nolde, Bahls, et al., 2021), results of a large randomised trial do not suggest that the common dosage of 40 mg pantoprazole taken daily over three years increases cardiovascular risk (Moayyedi et al., 2019).

It seems therefore questionable, whether PPI intake constitutes a cardiovascular risk factor independent of clopidogrel.

3. Abstract

This cumulative dissertation deals with the question, whether proton pump inhibitor (PPI) intake affects the risk of myocardial infarction or ischaemic stroke.

Observational studies had raised concerns that the intake of PPIs might increase the risk of cardiovascular events. Two separate underlying mechanisms were discussed. First, an interaction with clopidogrel, that might reduce its ability to prevent platelets from sticking together and forming dangerous blood clots. Second, an effect independent of clopidogrel, where PPI intake might reduce vascular function by blocking an enzyme that is necessary for producing nitric oxide (NO) in endothelial cells.

Even in 2018, ten years after the first studies had been reported, the question of cardiovascular safety of PPI use was unsettled, and meta-analyses reported increased risks for users of PPIs. In this setting, we started the dissertation project with a study examining a biochemical mechanism, that had been put forward to describe an effect of PPI intake on endothelial function. The theory was based on cellular experiments and investigations in mice and was published in 2013 in *Circulation.* Later attempts to replicate the findings in humans were futile, though. With the novel approach of using citrulline instead of asymmetrical dimethylarginine (ADMA) as an indicator for the impact of PPIs on endothelial NO production we could provide the first evidence in humans for the proposed mechanism.

Thereby, the evidence for a biochemical mechanism was endorsed, but the question of clinical relevance of this cellular process for the overall risk of cardiovascular events was still open. We, therefore, continued our project with a study about the effect of PPI intake on the risk of cardiovascular events in a large claims data set provided by the AOK Bayern (Allgemeine Ortskrankenkasse Bayern), the largest health insurance provider in the Bundesland (state) of Bavaria, Germany. We identified new users without prior cardiovascular events and estimated the effect of PPI therapy on the risk of a first myocardial infarction or a first ischaemic stroke over a period of ten years. Our results did not indicate that PPI intake would increase the risk of myocardial infarction or ischaemic stroke, suggesting that PPI intake has only a small and reversible effect on endothelial function.

Together with our results, two further studies had been published that addressed the question of cardiovascular effects of PPI intake. A large study using claims data (Landi et al., 2018) examined the effect of PPI intake on the risk of myocardial infarction and yielded estimates similar to our study. A randomised trial (Moayyedi et al., 2019) including more than 17,000 participants investigated the effect of continuous intake of pantoprazole on the risk of a broad spectrum of outcomes over a period of three years. In a study population with a significant proportion of prevalent cardiovascular disease there was no indication for an increased risk of cardiovascular events or cardiovascular mortality.

Our studies substantially contributed to the evidence about the effect of PPI intake and helped alleviate concerns regarding the risk of cardiovascular events. Although there is convincing evidence for impaired endothelial function induced by PPI intake, the mechanism does not appear to be strong enough to have a clinically relevant effect on the risk of myocardial infarction or ischaemic stroke.

4. Zusammenfassung (German)

Die vorliegende Arbeit behandelt die Frage, ob die Einnahme von Protonenpumpenhemmern (PPIs) eine Auswirkung auf das Risiko für Herzinfarkt oder Schlaganfall hat.

Beobachtungsstudien hatten nahegelegt, dass die Einnahme von PPIs das Risiko für kardiovaskuläre Erkrankungen erhöhen könnte. Zwei unterschiedliche zugrundeliegende Mechanismen wurden diskutiert. Erstens, eine Wechselwirkung mit Clopidogrel, die zu einer reduzierten gerinnungshemmenden Wirkung von Clopidogrel führt. Zum anderen, ein Effekt unabhängig von Clopidogrel, bei dem die Einnahme von PPIs die vaskuläre Funktion der Blutgefäße beeinträchtigt, indem der PPI in endothelialen Zellen ein Enzym blockiert, und dadurch die Bildung von Stickoxid (NO) verhindert.

Auch 2018, zehn Jahre nach den ersten Berichten, war die Frage nach der kardiovaskulären Sicherheit der Einnahme von PPIs ungelöst und Metaanalysen berichteten insgesamt erhöhte Risiken für PPI-Einnehmer. In diesem Umfeld startete dieses Promotionsprojekt mit einer Studie zu einem biochemischen Mechanismus, der die Wirkung von PPIs auf die Endothelfunktion erklären soll. Dieser war auf Basis von Zellversuchen und Mausexperimenten 2013 in *Circulation* vorgestellt worden. Nachfolgende Versuche, diesen Mechanismus in lebenden menschlichen Organismen nachzuweisen, waren gescheitert. Mit der Idee, Citrullin anstelle von asymmetrischem Dimethylarginin (ADMA) als relevanten Indikator für die Reaktionskette zu betrachten, konnten wir den ersten Hinweis für diesen Mechanismus am Menschen erbringen.

Damit war zwar der biochemische Reaktionsweg bestätigt worden, die Frage nach der klinischen Relevanz der Reaktion für das Risiko für kardiovaskuläre Ereignisse war aber weiterhin ungeklärt. Deshalb untersuchten wir als nächstes den Effekt von PPI-Einnahme auf kardiovaskuläre Endpunkte in einer großen Datenbank von Abrechnungsdaten der AOK Bayern. Wir identifizierten Ersteinnehmer ohne kardiovaskuläre Vorerkrankungen und schätzten den Effekt einer PPI-Therapie auf das Risiko für einen ersten Herzinfarkt oder Schlaganfall über einen Zeitraum von zehn Jahren. Unsere Ergebnisse lieferten keinen Hinweis darauf, dass PPI-Einnahme die Risiken für Herzinfarkt oder Schlaganfall erhöht. Dies legt die Vermutung nahe, dass die Einnahme von PPIs höchstens einen geringen und reversiblen Effekt auf die Endothelfunktion hat.

Parallel zu unseren Studien waren zwei weitere wichtige Studien erschienen, die die Frage der kardiovaskulären Folgen von PPI-Einnahme behandelten. Eine große Studie mit Abrechnungsdaten (Landi et al., 2018) untersuchte den Effekt von PPI-Einnahme auf das Risiko für Herzinfarkt und kam zu ähnlichen Ergebnissen wie unsere Analysen. Eine randomisierte Studie (Moayyedi et al., 2019) mit mehr als 17,000 Teilnehmern untersuchte den Effekt der Dauereinnahme von Pantoprazol auf das Risiko für eine Vielzahl von Endpunkten über drei Jahre. In einer Studienpopulation mit einem erheblichen Anteil an kardiovaskulären Vorerkrankungen zeigte sich kein Hinweis auf ein erhöhtes Risiko für kardiovaskuläre Ereignisse oder kardiovaskuläre Mortalität.

Unsere Studien haben wesentlich dazu beigetragen, die Bedenken bezüglich kardiovaskulärer Ereignisse verbunden mit der Einnahme von PPIs zu relativieren. Zwar gibt es überzeugende Anzeichen für eine Beeinträchtigung der Gefäßfunktion durch die Einnahme von PPI, allerdings scheint der Effekt nicht stark genug zu sein, um einen klinisch relevanten Einfluss auf das Risiko für Herzinfarkt oder Schlaganfall auszuüben.

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