REVIEW ARTICLE

The Indications, Applications, and Risks of Proton Pump Inhibitors

A Review After 25 Years

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SUMMARY

Background: Proton pump inhibitors (PPI) are the most effective drugs for inhibiting gastric acid secretion. They have been in clinical use for more than 25 years. In 2014, 3.475 billion daily defined doses (DDD) of PPI were prescribed in Germany. This high number alone calls for a critical analysis of the spectrum of indications for PPI and their potential adverse effects.

Methods: This review is based on pertinent publications retrieved by a selective search in the PubMed and Cochrane Library databases, with particular emphasis on randomized, prospective multicenter trials, cohort studies, case-control studies, and meta-analyses.

Results: The inhibition of gastric acid secretion with PPI is successfully used for the treatment of gastroesophageal reflux disease and of gastric and duodenal ulcers, for the secondary prevention of gastroduodenal lesions that have arisen under treatment with nonsteroidal anti-inflammatory drugs and acetylsalicylic acid, and for the prevention of recurrent hemorrhage from ulcers after successful endoscopic hemostasis. PPI are given along with practically all antibiotic regimens for the eradication of *Helicobacter pylori* infection. The number of prescriptions for PPI has risen linearly over the past 25 years. As there has been no broadening of indications, one may well ask whether the current, extensive use of PPI is justified. There is evidence that patients taking PPI are at greater risk for fractures. Moreover, the vitamin B12 level should be checked occasionally in all patients taking PPI.

Conclusion: PPI are among the more effective drugs for the treatment of diseases associated with gastric acid. In view of their cost and potential adverse effects, they should only be prescribed for scientifically validated indications.

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Parmacological inhibition of gastric acid secretion is achieved most effectively with proton pump inhibitors (PPIs), more correctly referred to as hydrogen-potassium ATPase inhibitors (e1, e2). Since the launch of the first representative of this group in 1989, omeprazole, the number of PPI prescriptions has shown a linear increase. In 2014, 3.475 billion daily defined doses (DDD) of PPIs were used in Germany (1). With no additional indications approved over the last years, this level of prescriptions needs to be challenged, despite the global increase in the incidence of gastroesophageal reflux disease (e3, e4) and one of its most important complications, Barrett's esophagus/intestinal metaplasia, which is associated with the risk of developing esophageal adenocarcinoma (e5). Presumably, PPIs are also used to treat functional dyspepsia, which is very common; however, there is virtually no evidence to support its use for this indication (e6–e8). Another reason to prescribe PPIs which is not supported by studies could be the concern over gastroduodenal side effects of polypharmacy, with the exemption of nonsteroidal anti-inflammatory drugs (NSAIDs). With 3.475 billion DDDs annually, 11.9% of all Germans take, in statistical terms, one DDD of a PPI daily. In the light of these figures, there can be little doubt that PPIs should be classed as safe medicines.

Since more recently, side effects of long-term and also short-term use of PPIs have been reported, not only the proven indications but also the profile and risk of side effects will be discussed in this review, based on the evaluable evidence.

Methods

This review is based on a selective search of the PubMed database for articles evaluating the use of PPIs, with special consideration of randomized, prospective multicenter studies, meta-analyses, cohort studies, and case-control studies. In addition, 28 reviews of the Cochrane Library were taken into consideration (*Table 1*). The publications were analyzed to identify the indications where the efficacy of PPIs was undisputed and to define the risk of side effects associated with PPIs. A further aim of the analysis was to reveal any clinically relevant differences that may exist between the various prescribed PPIs (esomeprazole,

lansoprazole, omeprazole, pantoprazole, and rabeprazole). The following search terms were used: “randomized controlled trial and proton pump inhibitor”, “meta-analysis and proton pump inhibitor”, “- and gastro(o)esophageal reflux disease“, “- and esomeprazole“, “- and pantoprazole“, “- and omeprazole“, “- and lansoprazole“, “- and rabeprazole“, “- and NSAID and proton pump inhibitor”, “*Helicobacter pylori* eradication and proton pump inhibitor”, “proton pump inhibitor and side effects”. Furthermore, the guideline of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS, Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten) on gastroesophageal reflux disease was taken into consideration (www.awmf.org/leitlinien/de tail/II/021-013.html; valid until 31 May 2019).

Pharmacodynamics and pharmacokinetics

PPIs are racemates. In the racemic mixture, the covalent bonding strength to the enzyme is the same for the R-enantiomer and S-enantiomer. Administered orally as prodrugs, the PPIs would be broken down by the gastric hydrochloric acid. Consequently, to protect the PPI against gastric acid exposure, a galenic formulation is required that only allows the release of the ingredients once the pH value has increased in the upper small intestine. To this end, the multiple-unit pellet system (MUPS) uses small pellets containing the PPI. This production method is most suitable when the PPI preparation is to be administered via a tube. No evidence from studies is available as to whether this galenic formulation accelerates the increase in pH value as the result of faster gastric emptying and thereby offers clinical benefits.

During the first passage through the liver, PPIs are partly metabolized, and consequently inactivated, by the cytochrome P450 enzyme system. For omeprazole, it was shown that the right-handed enantiomer, (R)-omeprazole, is metabolized comparatively fast, primarily by cytochrome P450 2C19 (CYP2C19). In contrast, (S)-omeprazole (left-handed; S, sinister) is mainly metabolized by P450 3A4 at a slower rate (e9). Thus, acid inhibition per weight unit is somewhat stronger with esomeprazole compared with omeprazole (e10). The inhibition of the H⁺/K⁺-ATPase, and consequently the ability to increase the pH in the stomach, is likely to be the same for all PPIs (e10).

The clinical relevance of differences in the rates of metabolism between the approved PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) is questionable (e10). The standard doses set in the DDDs for the various PPIs are not identical with the equivalent doses with regard to acid inhibition. Omeprazole was approved with a daily standard dose of 20 mg. Subsequent PPIs, except for rabeprazole, were given in higher doses than omeprazole: lansoprazole 30 mg, pantoprazole 40 mg, esomeprazole 40 mg. Pivotal studies comparing esomeprazole 40 mg with the approved dose of 20 mg omeprazole cannot demonstrate that, for example, faster healing of reflux esophagitis in

patients treated with esomeprazole is due the difference in drug metabolism. In the EXPO study, healing of erosive oesophagitis was faster with esomeprazole 40 mg compared with pantoprazole 40 mg (e11).

Likewise, esomeprazole 20 mg was superior to pantoprazole with regard to prevention of recurrence (e12, e13). However, an earlier study had found no difference (e14). A meta-analysis arrived at the conclusion that esomeprazole appeared to have a negligible clinical benefit in more severe reflux esophagitis (e15).

Since omeprazole is an inhibitor of CYP2C19, the breakdown of other substances metabolized via the same metabolic pathway can be inhibited as well. The drug interaction potential of other PPIs, such as pantoprazole, is lower (e16). Furthermore, the pH increase can by itself lead to drug interactions, e.g. lower plasma levels of mycophenolate mofetil (e16). It is undisputed that PPIs, especially omeprazole, can cause drug interactions. Since many multimorbid patients are treated with multiple medicines, it should be recommended to always replace omeprazole by other PPIs. However, due to the lack of clinical evidence, such a recommendation could be challenged.

Indications and usage

Inhibiting gastric acid secretion, PPIs are successfully used for the short-term treatment of gastroesophageal reflux disease (GERD) (2, 3, e3, e10, e14, e17–e29) and the long-term prevention of recurrence (e12, e13, e30–e33). On-demand PPI treatment may be used to prevent recurrence in patients with non-erosive gastroesophageal reflux disease (NERD) (e31, e32). In patients with erosive reflux esophagitis, daily PPI intake is more effective in preventing recurrence after healing (e31, e33). However, half of the dose initially used for acute treatment may be sufficient for long-term prevention. Whether PPIs can delay the progression of intestinal metaplasia of the esophagus (Barrett’s esophagus) has not been conclusively proven.

PPIs are effective—and superior to histamine-2 receptor antagonists (H₂ blockers, H₂RAs)—in the healing of gastric ulcer and duodenal ulcer, regardless whether the ulcer is caused by NSAID use or *Helicobacter pylori* (e34–e39). PPIs are the first-line treatment for secondary prevention of gastroduodenal lesions associated with the use of NSAIDs, including aspirin (acetylsalicylic acid, ASA), and for the acute treatment of ulcer bleeding and the prevention of recurrent ulcer bleeding after successful primary endoscopic hemostasis (4–6, e40–e43).

Due to the lack of large-scale studies, it is not possible to draw conclusions about the role of PPIs for primary prevention in patients treated with NSAIDs, with regard to the number needed to treat (NNT) and the number needed to harm (NNH). Consequently, PPIs are not approved for this indication. However, some evidence supporting the use of PPIs for primary prevention is available: PPIs reduce the risk of developing NSAID-related ulcers (e44–e46). Furthermore, they lower the bleeding risk associated with dual antiplatelet

TABLE 1

Proton pump inhibitors (PPIs): Selection of indications reviewed in Cochrane meta-analyses

Indication	Results	Reference
Short-term management of reflux oesophagitis	PPIs: most effective medical treatment of reflux esophagitis. H2RAs more effective than placebo.	e29
Short-term treatment of non-erosive reflux disease (NERD)	PPIs: more effective improvement of heartburn than H2RAs, both with empiric treatment and in endoscopically confirmed NERD	e28
Long-term treatment of reflux disease	PPIs: most effective long-term medical treatment to prevent recurrences, with regard to both symptoms and endoscopically confirmed lesions. With PPIs more side effects compared with H2RAs, especially headache	e53
Long-term treatment of reflux disease: PPIs versus laparoscopic fundoplication surgery	Results of the available studies are still inconclusive. Among others, the benefits and risks of surgery must be compared with the risk of long-term PPI treatment.	e54
Interventions for heartburn in pregnancy	Available studies evaluated the use of antacids, sucralfate and acupuncture, but not PPIs. Lack of studies leaves questions unanswered, such as the risk of miscarriage or preterm birth, patient satisfaction, malformation rate, intrauterine growth retardation, low birth weight.	e55
Treatment of heartburn in children	PPIs effectively treat erosive esophagitis; level of evidence low because of low number of insufficient studies	e56
PPIs for asthma	No improvement of pulmonary function or asthma symptoms	e57
PPIs for non-specific cough	PPIs likely to have no effect	e58
PPI treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding	Endoscopy may find signs of previous bleeding less frequently if treatment has already been started. Need for endoscopic treatment is reduced. No effect on key clinical parameters, such as rebleeding rates, lethality and indication for surgery.	e59
PPIs for peptic ulcer bleeding	PPIs reduce the rebleeding rate after endoscopic hemostasis and the need for surgery compared with H2RAs and placebo, but not lethality.	e60
Dose and route of administration of PPIs for peptic ulcer bleeding	The currently available studies do not answer questions about the equivalence, superiority or inferiority of high-dose PPI treatment versus low-dose PPI treatment for the endpoints rebleeding rate, need for surgery and lethality.	e61
Helicobacter pylori eradication	Triple therapy (PPI + amoxicillin + clarithromycin, or PPI + clarithromycin + metronidazole): 2-week treatment regimen achieves higher eradication rates compared with one-week regimen.	17
Prevention of NSAID-induced gastroduodenal ulcers	PPI, misoprostol and double dose H2RA reduce risk of developing gastric or duodenal ulcers. Misoprostol has more side effects (diarrhea).	e44

NERD, non-erosive reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs; H2RA, histamine-2 receptor antagonists

therapy with low-dose aspirin and clopidogrel (7). PPIs are a component of almost all of today's antibiotic combination regimens for the eradication of *H. pylori* infection (8–17). In addition, PPIs are also used temporarily after esophageal variceal ligation for the prevention of bleeding from ligation-related ulcers (18, 19). However, the evidence level for this treatment approach is not high.

The evidence supporting PPI treatment of functional dyspepsia is not convincing either (e6, e7, e47, e48). Classical indication for strong acid secretion inhibition with PPIs is the rare Zollinger-Ellison syndrome caused by gastrin-secreting tumors (20, e49–e52). The above-named and other pertinent reviews are available in the Cochrane Library (Table 1).

Adverse reactions

Gastrin is produced in G cells in the antrum of the stomach. Regardless of its cause, any increase in gastric pH stimulates gastrin secretion. High gastrin levels stimulate the production of enterochromaffine-like cells (ECL cells). Treatment with approved daily doses of PPIs leads to mild hypergastrinemia. In humans, no association between long-term PPI use and the development of neuroendocrine tumors (NETs) has been reported. An analysis of the studies published to date found no evidence to suggest that long-term PPI use leads to atrophic gastritis or intestinal metaplasia. However, long-term use of PPIs augments the risk of developing diffuse or focal micronodular ECL cell hyperplasia (e62), most likely due to increased gastrin levels.

TABLE 2

Manufacturers' information about drug interactions of proton pump inhibitors

Indication	Type of interaction	Omeprazole Esomeprazole	Lansoprazole	Rabeprazole	Pantoprazole
Treating anxiety	increased plasma levels	Benzodiazepines, e.g. diazepam			
Anticoagulation Vitamin K antagonists	increased plasma levels	Phenprocoumon Warfarin			Phenprocoumon Warfarin
Antiplatelet therapy	reduced activation of prodrug	Clopidogrel	Clopidogrel	Clopidogrel	Clopidogrel
Depression	reduced PPI levels increased plasma levels	St. John's wort Citalopram Clomipramine Imipramine	St. John's wort Fluvoxamine		
Diabetes			Glibenclamide Tolbutamide		
Epilepsy	increased plasma levels	Phenytoin			
Infectious diseases HIV	severely reduced plasma levels; thus, PPIs contraindicated	Atazanavir Nelfinavir Saquinavir	Atazanavir	Atazanavir	Atazanavir
Bacteria	absorption reduced with acid deficiency	Rifampicin	Erythromycin Rifampicin		
Mycoses	azole antifungals inhibit the metabolism of PPIs	Itraconazole Ketoconazole Posaconazole Voriconazole	Itraconazole Ketoconazole	Itraconazole Ketoconazole	Itraconazole Ketoconazole Posaconazole
Immunosuppressants	Conflicting data: increased plasma levels possible	Cyclosporine Tacrolimus	Tacrolimus		
Cardiology	10% higher digoxin levels along with increased pH	Digoxin	Digoxin		
Oncology	decreased plasma levels question- able increased plasma levels, delayed elimination	Erlotinib Methotrexate in high doses			Erlotinib
Reflux disease	reduced absorption of PPIs		Antacids Sucralfate	Antacids	

The information presented in this table is derived from the patient information leaflets of the manufacturers of proton pump inhibitors (PPIs) producing PPIs as follow-on and generic products. A different listing of medications in this table does not mean that this interaction has been excluded for the respective PPI. Not all listed drugs are included in the package leaflets of each manufacturer. Less drug interactions are reported for pantoprazole (e15) because of its lower level of interaction with CYP2C19. However, with regard to interactions basically the same drugs are listed.

Gastric hydrochloric acid kills germs that have been swallowed with contaminated food. The lack of hydrochloric acid could be responsible for an increased risk of infection. Furthermore, hydrochloric acid plays a role in digestion, e.g. in the denaturation of proteins which represents the start of proteolysis in the stomach where it acts together with the protease pepsin. However, to ensure proper digestion, gastric hydrochloric acid has to be neutralized in the duodenum by bicarbonate from the pancreas to prevent the degradation of lipase, an enzyme essential for lipid digestion. Thus, it is unlikely that the PPI-

induced inhibition of gastric acid secretion leads to maldigestion and malabsorption.

Complex mechanisms govern calcium homeostasis. Calcium is primarily absorbed in the upper small intestine by active transcellular transport, but also by passive paracellular absorption. Impaired calcium release from food and decreased vitamin D absorption due to a lack of gastric acid can increase the risk of osteoporosis. Upon discontinuation of PPI treatment, a temporary excessive increase in gastric acid secretion may occur. Healthy persons may experience heartburn for a short time (21).

Side effects listed in patient information leaflets

Common side effects (less than 1 in 10, more than 1 in 100 people) include abdominal pain, diarrhea, vomiting, flatulence, headache, constipation, and nausea. Since studies reported similar side effects in patients receiving placebo treatment, it can be assumed that these adverse reactions are not substance-specific. The spectrum of drug interactions listed in the patient information leaflets is summarized in *Table 2*. However, since the incidence of headache was higher among patients treated with PPIs compared with those receiving H2-receptor antagonists (H2RA), a substance-specific effect must be assumed. The underlying pathomechanisms remain unclear.

Anterior ischemic optic neuropathy

Following the introduction of the intravenous form of omeprazole, individual cases of serious adverse events, such as blindness, were reported (e63–e67). Until today, no further cases of this complication have been described (22, e52).

Vitamin B12 deficiency

Gastric acid is needed for the release of vitamin B12 from ingested proteins. Thus, it is conceivable that the use of inhibitors of gastric acid secretion, such as PPIs and H2RAs, can lead to vitamin B12 deficiency. In a case control study, 12% of participants with vitamin B12 deficiency had received a PPI and 4.2% an H2RA compared with 7.2% and 3.2%, respectively, in the control group (23). This study also demonstrated a temporal relationship: Patients receiving or having recently received prescriptions for PPIs experienced vitamin B12 deficiency more frequently compared with patients who received PPI prescriptions longer ago. Based on these data, it could be argued that a blood count (query: megaloblastic anemia) and serum vitamin B12 test should be performed in patients with long-term PPI treatment, e.g. after 2 years of PPI use.

Osteoporosis, risk of fracture

Whether gastric acid suppression is associated with an increased risk of osteoporosis and, consequently, an increased risk of fracture due to reduced calcium and/or vitamin D absorption, is still discussed controversially. Some studies found no impact of PPI use on calcium absorption (e68, e69). Case-control studies and meta-analyses reported a small increase in risk of fracture, especially femoral neck fractures and vertebral body fractures, in patients with long-term use of PPIs (24–27, e70, e71). Why, according to another meta-analysis, the risk of fracture should be increased after short-term treatment with PPIs, even at low doses, compared with long-term PPI treatment remains elusive (28). This analysis also reported a lack of risk for forearm fractures. In a prospective cohort study with post-menopausal women, the risk of femoral neck fractures was only increased in smokers (e72).

In the light of potential confounding factors and the lack of prospective, randomized trials, the results avail-

able to date should be interpreted with caution (24, 28). It seems that gastric acid suppression alone, in the absence of other risk factors, does not increase the risk of fracture.

Infectious complications

The risk to acquire an infection due to a lack of gastric acid is very low, regardless of what caused the gastric acid deficiency, even under long-term treatment with PPIs. An increased number of cases of both community-acquired and hospital-acquired pneumonia has been reported (29–31). However, these analyses should be viewed critically because of the presence of confounding factors. For example, elderly patients with comorbidities have an increased risk of pneumonia, but also receive PPIs more frequently because of polypharmacy.

An analysis of cohorts from Canada and the United Kingdom, which were selected using very stringent criteria, showed remarkable results. Of the 4 238 504 patients taking NSAIDs, only 2.3% concomitantly received a PPI. Of these patients, 0.17% were hospitalized for pneumonia within a period of 6 months, while this was the case in 0.12% of the patients without PPI treatment; this difference is not statistically significant (32).

The available data on the risk of spontaneous bacterial peritonitis are inconsistent; while some studies reported an increased risk with PPIs (33, 34), others found no risk increase (18). It is likely that PPIs increase the incidence of *Clostridium difficile* colitis (35–37). However, one study demonstrated no increased risk of recurrence of *Clostridium difficile* infection with continued PPI treatment (e73). The same working group highlighted a pathophysiological mechanism which may explain the increased risk of *C. difficile* infection. In patients treated with PPIs, microbiome composition changes, showing an increase in genes involved in bacterial invasion (e74). The level of the associated risk of traveler's diarrhea remains unclear.

Chronic kidney disease, dementia, myocardial infarction

Further risks of diseases potentially associated with the long-term use of PPIs have been discussed, for example chronic kidney disease (e75). A prospective cohort study found an increased incidence of dementia (e76). Another study reported an increased risk of myocardial infarction along with long-term PPI treatment, regardless of clopidogrel co-medication (e77). Against the background of confounding factors, interpretations of these data should be critically discussed (e78).

Drug interactions

Various pathomechanisms can lead to interactions of PPIs with other drugs (*Table 2*). The absorption of oral thyroxine is reduced in the presence of higher pH values, requiring a compensatory dose increase (e79). Competitive effects with other drugs metabolized by the cytochrome P450 enzyme system can lead to decreased or increased plasma levels of such agents.

Omeprazole is an inhibitor of CYP2C19. Therefore, it can interfere with the metabolism of other drugs metabolized via the same pathway. The interaction potential of other PPIs is lower (e10). This difference should be clinically relevant, i.e. there should be noticeably less side effects, despite the fact that data from available studies have not confirmed this so far.

Whether drug-drug interactions between PPIs and clopidogrel can lead to stent thrombosis is discussed controversially. CYP2C19, playing a key role in the formation of the active metabolite of clopidogrel, is inhibited by the various PPIs to different degrees. In one study, patients receiving clopidogrel and PPIs concomitantly following acute coronary syndrome (ACS) had a higher risk of rehospitalization for ACS compared with patients with clopidogrel alone (38). However, several other studies on this question did not demonstrate a clinically relevant risk; it appears that the benefits of PPIs administered to prevent gastrointestinal bleeding outweigh the risks (39, 40). Thus, the American Heart Association recommends to prescribe PPIs to patients with dual antiplatelet therapy—it remains to be clearly defined which patients actually fall under this category—to prevent bleeding in the upper intestinal tract. It is also advisable, despite the lack of unequivocal clinical evidence, not to use omeprazole and esomeprazole as PPIs because of their above mentioned interaction with CYP2C19 (e80). This recommendation would, in turn, conflict with the increased risk of myocardial infarction associated with PPIs, as discussed above.

Conflict of interest statement

Prof. Mössner participated in and was the principle investigator of clinical studies evaluating the efficacy of lansoprazole, esomeprazole, pantoprazole, and omeprazole. Until 2009, he received study support and fees for presentations during satellite symposia and CME events sponsored by the pharmaceutical industry, namely by Altana Nycomed, AstraZeneca, Eisai, and Takeda. He received reimbursement of conference fees and travel expenses from AstraZeneca.

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KEY MESSAGES

- Proton pump inhibitors (PPIs) are the most effective drugs to treat acid-related diseases with potentially life-threatening complications, such as bleeding and perforation of gastric and duodenal ulcers.
- PPIs are effective in the treatment and secondary prevention of gastric and duodenal lesions caused by nonsteroidal anti-inflammatory drugs (NSAIDs).
- The uncritical use of PPIs to treat symptoms not caused by an underlying acid-related disease is a widespread problem.
- Potential side effects of long-term PPI use, such as increased risk of fracture, chronic renal disease or dementia, must not be overlooked.
- There are only few clear indications for the long-term use of PPIs, including refractory gastroesophageal reflux disease, Barrett's esophagus, Zollinger-Ellison syndrome, idiopathic chronic ulcer, and bleeding prevention in selected patients.

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Supplementary material
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A Review After 25 Years

by Joachim Mössner

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