Evaluation of the frequency and necessity of proton-pump-inhibitor therapy in geriatric patients

Müller, Anna Laura Emma

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Anna Müller

EVALUATION OF THE FREQUENCY AND NECESSITY OF PROTON-PUMP-INHIBITOR THERAPY IN GERIATRIC PATIENTS

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Prof. Johannes Brachmann, MD, PhD

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LIST OF ABBREVIATIONS

PPI – Proton pump inhibitors

GI – Gastrointestinal

HCl – Hydrochloric acid

IF – Intrinsic Factor

LES – Lower esophageal sphincter

NSAID – Non-steroidal anti-inflammatory drug

GERD – Gastroesophageal reflux disease

ATP – Adenosine triphosphate

P.o. – Per os

I.v. – Intravenous

C_{max} – Maximal plasma drug concentration

AUC – Area under the curve

PM – Poor metabolizers

EM – Extensive metabolizers

NERD – Non-erosive reflux disease

ERD – Erosive reflux disease

H. pylori – Helicobacter pylori

ZES – Zollinger-Ellison syndrome

COX – Cyclooxygenase

CAP – Community-acquired pneumonia

CDI – Clostridium difficile infection

CKD – Chronic kidney disease

RAHS – Rebound acid hypersecretion

IQR – Interquartile range

PIM – Potentially inadequate medication

1. INTRODUCTION

1.1 Growing challenges of the aging population: Proton Pump Inhibitor usage

The rapid aging of the European population is a well-documented phenomenon. Demographic change presents a significant challenge, especially in the healthcare sector. The senior population is expanding, with estimates indicating that by 2050, approximately 30% of the total population will be over the age of 65 (1). This shift will alter the needs of society, increasing the demand for health care services and medications. The aging correlates with an increase in multimorbidity, defined as the concurrent existence of at least two conditions in one individual, leading to an increased need for health care services and medications (2). Consequently, this trend also exacerbates the issue of polypharmacy.

Polypharmacy is the prescription of multiple medications in a single patient, usually defined as taking five or more drugs (3). While taking numerous medications can be necessary, especially in multimorbid patients, it requires careful consideration of the benefits and risks. It has been shown that this is often not done thoroughly enough in a clinical setting, resulting in high numbers of medications being prescribed inappropriately. Up to 50% of the elderly population may be taking medications that are not medically necessary (4). Moreover, patients over 65 are underrepresented in clinical trials, causing a lack of sufficient data on drug safety, drug interactions, and side effects in this age group (5). In the context of an aging population and the associated issue of polypharmacy, studies analyzing global prescription patterns reveal significant similarities in the most frequently prescribed medications. Proton pump inhibitors (PPIs) are one such class of medications (5).

PPIs are among the most common drugs worldwide. Omeprazole, a type of PPI, is ranked 8th and pantoprazole 20th among the pharmaceuticals used across all age groups in the United States (6). In Germany, 3.8 billion daily doses of PPIs were prescribed in 2016 (7). PPIs are a group of gastroprotective drugs, used to treat various gastrointestinal (GI) diseases. They have gained popularity over the last 35 years, proving to be an efficient agent for inhibiting acid secretion from parietal cells. Their safety profile and low cost have led to a rise in their usage since they were introduced into the market. Whilst the number of their prescriptions has increased, the amount of diseases which indicate them, has not changed, suggesting an inappropriate use (7).

With polypharmacy getting attention, deprescribing medication should be something to aim for in every medical discipline. Deprescribing is the process of reducing or stopping a medication when there is no more medical indication or when the risks exceed the benefits. Even though PPIs are very convenient, their concurrent use alongside other drugs and long-term effects, especially in the geriatric population, must be carefully considered and evaluated.

1.2 Anatomy and physiology of the stomach

The main site of the action of PPIs is the stomach. As part of the GI system, the stomach serves as a storage reservoir and breaks down the food we eat into nutrients needed by the body to use for energy, growth, and cell repair.

The process of digestion starts in the mouth, where the food is chewed and mixed with saliva, working to moisten the food particles and containing enzymes to initiate the breakdown (8, 9). Through a muscular action known as peristalsis, the bolus of ingested food is propelled down the esophagus and through the thoracic cavity. When the lower esophageal sphincter (LES) muscle relaxes, the partially digested foodstuff can pass through the *ostium cardiacum* into the stomach. This hollow organ, a muscular tube situated between the esophagus and the duodenum, allows chyme to pass through and to continue into the small intestine(10).

The stomach has a unique structure and function in the body, performing further mechanical and chemical digestion. It is located mostly in the left upper quadrant of the abdominal cavity. The top of the stomach is directly under the diaphragm and it is connected to other peritoneal organs by the greater and lesser omentum, ventral the liver can be found, and dorsal the pancreas.

The stomach consists of four regions, according to its anatomy (Figure 1). The cardia (*pars cardiaca*) comprises the esophageal opening, where food bolus passes into the stomach. It contains a region called “z-line”, where the epithelium changes from the stratified squamous epithelium of the esophagus, to the columnar epithelium of the stomach. The esophagogastric angle, or “angle of his”, is the angle created between the cardia and esophagus. It normally acts as an antireflux barrier by functioning like a valve and physiologically ranges between 50-60°. The dome-shaped protrusion, marking the highest point of the stomach, touching the diaphragm, is the fundus (*fundus gastricum*). The central body of the stomach is the corpus (*corpus gastricum*), lying between the fundus and antrum. The last section is the pylorus (*pars pylorica*), which contains the *antrum pyloricum*, leading into the *canalis pyloricus* and ending at the pylorus, where the *M. sphincter pylori* acts as a barrier between the stomach and duodenum (10, 11).

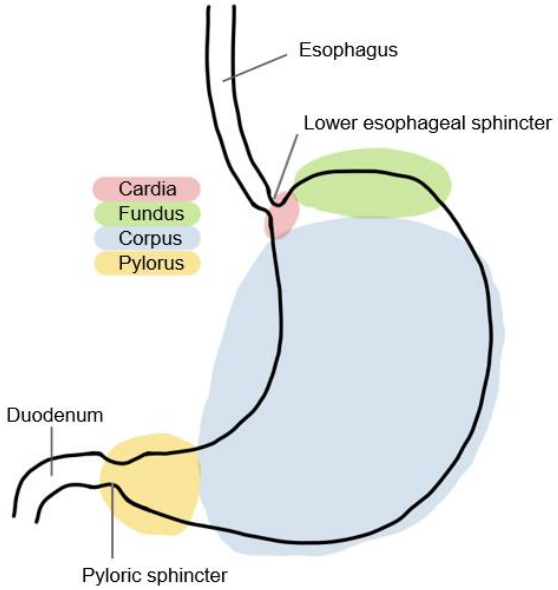

Figure 1. Parts of the stomach
Source: Gray H, Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Third edition. Philadelphia, PA: Churchill Livingstone Elsevier; 2015.

Microscopically, the stomach wall can be distinguished into different layers: *mucosa*, *submucosa*, *muscularis*, and *serosa*. Their combined action is of utmost importance for the digestion of the food bolus (8). The muscular layer is responsible for the smooth muscle action, which is called propulsion and retro propulsion. By contracting periodically, it causes the food particles to move around in the stomach thereby grinding it to smaller pieces. This mechanical process is accompanied by chemical processes. The gastric glands located in the mucosal layer produce gastric juice, helping in nutrient breakdown. These processes turn the partially digested foodstuff from the esophagus into chyme, which will leave the stomach and pass through the pylorus into the duodenum (11).

1.3 Gastric mucosa and gastric acid

The gastric mucosa constitutes a complex structure that requires a balance between protective factors, aiming at maintaining the integrity of the mucosal barrier and the acidic environment of gastric juices.

Gastric glands vary depending on their location within the stomach. Oxyntic and pyloric glands are primarily responsible for digestion and are important for understanding the mechanism of PPIs (8). There are also cardiac glands, smaller in number and found in the cardia of the stomach, primarily secreting mucus.

Oxyntic glands are present in almost 80% of the hollow organ and are comprised of parietal and chief cell types. Parietal cells are situated in the walls of the glands. They secrete

hydrochloric acid (HCl) and intrinsic factor (IF), both important for the function of the digestive tract. By creating an acidic pH in the stomach, HCl aids in creating a hostile environment for pathogenic microorganisms, denaturing proteins, and activating zymogen pepsinogen to its active form. IF is a glycoprotein needed for the uptake of Vitamin B12 in the small intestine. The secretions are stimulated by several factors, including acetylcholine, gastrin, and histamine. Situated at the basal regions of the oxyntic glands are the chief cells, releasing zymogen pepsinogen, the precursor to the enzyme pepsin. This enzyme is active in the acidic pH and can break down protein into smaller peptides and amino acids.

Approximately 20% of the stomach is composed of pyloric glands, which are predominantly located in the pylorus. The glandular composition includes mucous cells and G-cells. Because the stomach's acidic contents can be harmful to the mucosa, the mucous cells secrete a bicarbonate film to protect it. G-cells will secrete the endocrine hormone gastrin, which works by stimulating the secretion of HCl by parietal cells. An overview of the cells mentioned in this chapter is seen in Table 1.

Table 1. Selected cells of the gastric glands,

Cells	**Parietal cell**	**Chief cell**	**Mucous cell**	**G-cell**
Location	Fundus, corpus	Fundus, corpus	Fundus, corpus, antrum, pylorus	Pylorus, antrum
Secretions	HCl[a], IF[b]	Pepsinogen	Mucin	Gastrin

[a] Hydrochloric acid
[b] Intrinsic factor
Source: Stomach - AMBOSS [Internet]. [cited 2024 Jun 20]. Available from: https://next.amboss.com /us/article/U60b4S?q=stomach.

To elucidate the mechanism of action for PPIs, Figure 2 illustrates the process of gastric acid secretion by parietal cells. The acidic pH of the stomach is dependent on the production of HCl. On a cellular level, HCl is secreted by a series of transports, leading to its release by parietal cells into the gastric lumen. Protons and bicarbonate are produced by carbonic anhydrase in the cytoplasm of the cells. These protons are then pumped out of the cell in exchange for potassium by the H+/K+-ATPase. Potassium will be transported back into the lumen by an apical K+ channel. Bicarbonate will be exchanged for chloride on the basolateral membrane of the cells. Chloride-ion will be able to move out of the cell into the gastric lumen by apical chloride channels. Additionally, Na+/K+-ATPase transports two K+ into the cell in exchange for 3 Na+. Ultimately there are protons and chloride in the gastric lumen forming HCl (11).

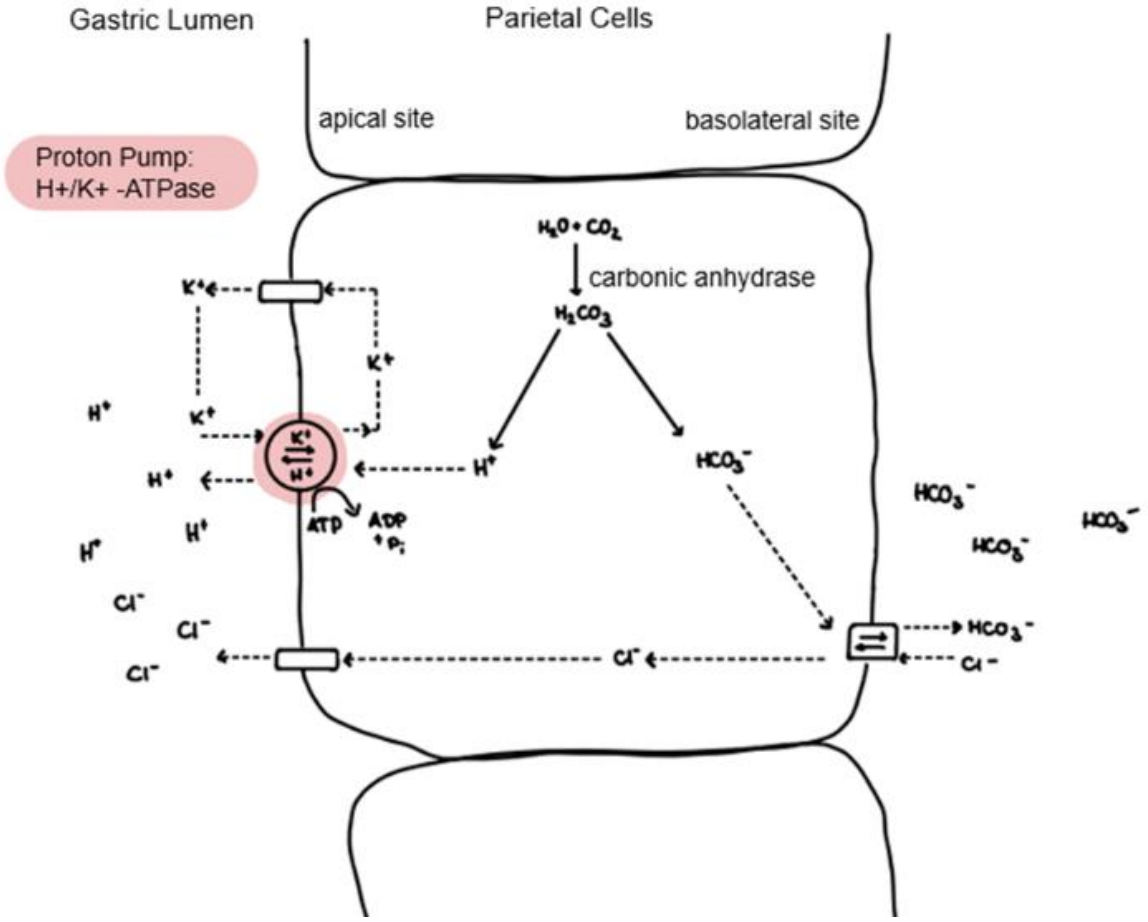

Figure 2. Schematic of parietal cell
Source: Magen - AMBOSS [Internet]. [cited 2024 Mar 31]. Available from: https://next.amboss.com/de/article/XK09US?q=Magen.

Gastric juices are a combination of water, HCl, pepsin, mucin, bicarbonate, and IF, approximately 2L are produced daily. They are secreted in three different phases:

The process begins with the cephalic phase, during which the stomach responds to stimuli like sight, smell, taste or thought of food. By the stimulation via acetylcholine from the vagal nerve, the parietal cells secrete H+ and IF, enteroendocrine cells secrete gastrin, and the chief cells pepsinogen. Thereby they prepare the GI system for nutrition intake.

Following this, the gastric phase ensues. Ingested food stretches the walls of the GI tract, causing acetylcholine release to stimulate enteroendocrine cells to release gastrin and histamine. All three substances, acetylcholine, gastrin, and histamine act on parietal cells to secrete HCl and IF, as well as on the chief cells for pepsinogen.

The final phase, the intestinal phase, occurs when the chymus from the stomach enters the duodenum, leading to an inhibition of gastric secretions (11).

1.4 Gastric pathologies

To recapitulate, the stomach is a sophisticated structure, serving as a temporary storage reservoir for ingested foods and liquids. It's a place of mechanical and chemical digestion. Gastric acid is necessary, though can still be harmful. The functions are needed to activate enzymes and break down proteins. The acidic environment helps kill ingested microorganisms, thereby it is crucial in the defense of the gut against bacteria (13). On the other side, there are protective factors, that aim to keep the gastric mucosa intact, like bicarbonate, mucus-barrier layer, and cell turnover.

An imbalance leading to excessive acidity in the stomach pH can precipitate various diseases. Any disturbance in the barrier function of the gastric mucosa can potentially damage the GI tract (Table 2) (14).

Table 2. Potential etiologies for gastric mucosal damage

Mechanical damage	Chemical damage	Microbiological damage
Iatrogenic manipulation	Medication (e.g., ASS, NSAR)	Bacteria (e.g., Helicobacter Pylori)
Trauma	Nicotine	Virus
Stress	Alcohol	Fungi (e.g., Candida)
Radiation Therapy	Acids	
	Cytostatic	

Source: Rezar TR. Protonenpumpenhemmer Kritische Betrachtung der Therapie mit Fokus auf Neben- und Wechselwirkungen. [dissertation]. MEDonline: Medizinischen Universität Graz; 2022.

1.5 Proton Pump Inhibitors

Omeprazole was first established in 1989 and after 35 years of usage, PPIs became a group of the most prescribed medications in Europe and even worldwide (15). They mostly replaced the former drugs like histamine-receptor antagonists, prostaglandin analogs, and anticholinergics by having a better safety- and efficiency profile and being superior to the previous drugs in treating acid-related disorders.

As of today, the most common, approved PPIs in Germany are Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole (15). These agents are in a group called benzimidazole derivatives, they are all similar in their pharmacological profile and seem to be comparable in clinical parameters. Whereas tenatoprazole, a novel PPI, is an imidazopyridine still undergoing preclinical testing and yet to be approved in Germany (16).

1.5.1 Pharmacological properties of PPIs

The approved PPIs are derived from benzimidazole, a type of heterocyclic organic molecule. They consist of a pyridine unit and a benzimidazole unit, linked by a methyl sulfinyl bridge (17).

All PPIs can be administered orally and parenterally. For rapid acid suppression, intravenous (i.v.) administration is available for omeprazole, pantoprazole, and esomeprazole (16).

Generally, PPIs are prodrugs meaning they are given as inactive compounds, which can be metabolized in the body to become an active drug. To ensure the prodrug is not prematurely activated or degraded, it is encased in an acid-resistant coating. These delivery systems may include enteric-coated tablets, gelatin capsules, suspensions containing coated granules or formulations combined with bicarbonate. These methods lead to the passing of PPI prodrugs through the stomach and absorption in the upper small intestines (8). The chemistry of how PPIs act on H+/K+ ATPase involves several steps:

Protonation: After uptake, the drugs circulate to the gastric cells. PPIs are weak bases, which allows them a selective accumulation in the secretory canaliculi of parietal cells. Here PPIs are protonated and therefore transformed into their active form by the acidic environment.

Diffusion: The protonated PPIs diffuse across the parietal cell membrane and enter the acidic canaliculi where the H+/K+ ATPase is located.

Activation: Within the canaliculi, the protonated PPIs undergo a chemical transformation to form reactive sulfenamide or sulfenic acid intermediates.

Covalent Binding: The reactive intermediates, sulfenamide or sulfenic acid, form covalent bonds with specific cysteine residues on the H+/K+ ATPase enzyme. This covalent binding occurs at the active site of the enzyme, which is responsible for the transport of protons. However, for the PPI to bind, there has to be an active expression of the proton pump in the canaliculi, a process triggered by food intake.

Inhibition: Once bound to the H+/K+ ATPase enzyme, the PPIs irreversibly inhibit its activity. This inhibition prevents the enzyme from pumping protons into the stomach lumen, thereby reducing the secretion of gastric acid. The bond made between s PPI and ATPase is irreversible, hence the strength of this covalent bond results in a longer-than-anticipated duration of effect compared to what would be expected based on blood levels of the drug (16).

During a meal, neither all parietal cells are active, nor are all of their H+/K+ pumps in the active ones. A single dose of PPIs can therefore only inhibit around two-thirds of proton pumps, leaving the rest unaffected. As a result, there will never be a complete achlorhydria.

In this context, it can be explained why PPIs are advised to be taken 60 minutes before a meal, this is called pre-prandial dosing. When taken before a meal, PPIs have sufficient time to be absorbed and to reach the bloodstream. As the meal stimulates gastric acid secretion, more proton pumps become active, making them susceptible to inhibition by PPIs. Consequently, taking PPIs before a meal maximizes the inhibition of active proton pumps, enhancing their effectiveness. The blockage of the proton pump will last up to 36 hours until new pumps are synthesized to replace the inhibited ones (16). Typically it requires 2-3 days to achieve a steady-state inhibition of acid secretion (17).

The plasma half-life of PPIs is short: on average one hour, depending on the type of PPI ranging between 0.6 – 1.9 hours. To enhance the inhibiting effect of PPIs, the plasma half-life would have to be increased. This is currently studied by replacing the benzimidazole with imidazolepyridine in tenatoprazole, as mentioned above. Since the maximal plasma drug concentration (C_{max}) is a poor indicator of the effect of PPIs, acid suppression can be correlated with the plasma concentration-time curve. The area under the curve (AUC) is a measurement of systemic exposure to the drug. However overall studies have not shown a significant difference in acid suppression between the approved PPIs, with only esomeprazole having a longer period of acid inhibition (17).

When administered orally PPIs will undergo the first-pass-effect, meaning they undergo initial metabolism as they pass through the liver. Bioavailability is still very good, ranging between 50-90%. They are metabolized in the liver by enzymes of the cytochrome-isoenzymes CYP2C19 and CYP3A4. This metabolization is strongly dependent on the phenotypes of the patient. Examples of phenotypes are poor metabolizers (PM) and extensive metabolizers (EM) which can cause a difference of up to 7.5-fold for omeprazole metabolization between PM and EM. Hepatic impairment and old age can also reduce the clearance of PPIs (17).

Further, the metabolization by the Cytochrome P450 system can also lead to drug interactions. These interactions are manifested by induction or inhibition of these enzymes when they process drugs. For example, when omeprazole is metabolized by CYP2C19, this can affect the efficacy of the platelet inhibitor clopidogrel, ultimately reducing its effect (18).
Following hepatic metabolism, most benzimidazoles are mainly excreted through the kidneys. However, lansoprazole is also eliminated via the biliary system (16). The dosing of PPIs depends on the different preparations and indications. Pharmacological features of PPIs are summarized in Table 3.

Table 3. Overview pharmacology of PPIs

	Esomeprazol	**Lansoprazol**	**Omeprazol**	**Pantoprazol**	**Rabeprazol**
Dosage (mg)	20, 40	15, 30	20, 40	20, 40	20
Application	p.o.[a], i.v.[b]	p.o.[a], i.v.[b]	p.o.[a], i.v.[b]	p.o.[a], i.v.[b]	p.o.[a],
Bioavailability (%)	64-90	80-85	30-40	77	52
Half-life (h)	1-1.5	1.6	0.5-1	1-1.9	1-2
AUC (µg×h/mL)	7.3-12.6	1.7-5.2	0.2-2	2-15.9	0.8-2.2
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19, CYP4A4	CYP2C19

[a] per os
[b] intravenous
Sources: Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut and Liver. Editorial Office of Gut and Liver; 2017; 11(1):27, Shin JM, Sachs G. Pharmacology of Proton Pump Inhibitors. Curr Gastroenterol Rep. 2008; 10(6):528–34.

1.5.2 Clinical applications of PPIs

Gastric acid secretion is a complex process driven by multiple factors and stimuli, including acetylcholine, gastrin, and histamine. PPIs target the final common pathway of acid secretion by acting on the H+/K+ ATPase. This is the reason why PPIs are superior to other drugs for acid-related disorders. Unlike anticholinergics and histamine-receptor blockers, PPIs block the proton pump regardless of the stimuli. They maintain intragastric pH >4 for a longer duration compared to the others and therefore lead to superior postprandial and nocturnal intragastric pH control. Moreover, with PPIs, the effect remains consistent even over longer therapy and without the need for dose escalation, whereas histamine-receptor blockers may have tachyphylaxis with prolonged use (16).

In Germany, PPIs are approved for short-term use in the following acid-related disorders: gastroesophageal reflux disease (GERD), gastroduodenal ulcers (*ulcus duodeni / ventriculi*), prophylaxis of gastroduodenal ulcers during non-steroidal anti-inflammatory drug (NSAID) therapy, *Helicobacter pylori* (*H. pylori*) eradication therapy and Zollinger-Ellison-syndrome (ZES) (14). These short-term therapies should always be considered carefully with the patient and suitable for their specific situation. A timeline and therapy goal should be established before starting. Short-term is defined as a period no longer than eight weeks.

For long-term therapy (> eight weeks) the only justification is a history of gastroduodenal ulcer bleeding and a risk constellation for new bleeding, like long-term aspirin therapy and ulcerogenic medication (e.g. nonsteroidal anti-inflammatory drugs) (7).

There are no indications for life-long therapy, hence PPIs should be reevaluated regularly to reduce or stop their usage. Mere prophylactic therapy, without any of the aforementioned indications, for example in patients with polypharmacy is not advisable.

1.5.2.1 Gastroesophageal reflux disease

According to the Montreal definition and classification of GERD, it is described as troublesome symptoms and complications caused by the reflux of stomach contents (19). It is a very common disease, affecting up to 20% of the population in industrialized countries. There are several subcategories: GERD with erosive lesions (reflux esophagitis and strictures), GERD with complications (Barrett's esophagus, esophageal adenocarcinoma) and GERD without esophageal lesions, called NERD (NERD with increased reflux, hypersensitive esophagus).

Many factors may play a role in the development of GERD, the most common etiology is the insufficiency of the LES, which can be caused mainly by two factors. Firstly, anatomical factors such as pylorus or duodenal stenosis, an increased angle of His or the presence of a hiatal hernia can contribute to LES dysfunction. Secondly, the increase in intraabdominal pressure is observed during pregnancy or in individuals with obesity. Additionally, GERD can also result from medications, scleroderma or after gastrectomy.

Clinically, GERD has two typical symptoms: heartburn and regurgitation. While heartburn is a painful sensation located behind the sternum, regurgitation is a painless feeling of stomach contest flowing back to the mouth. Other unspecific symptoms can be atypical thoracic pain, coughing, dental erosions, halitosis, laryngitis or asthma. The symptoms can be triggered by swallowing, alcohol consumption, coughing, physical exertion, bending down or lying down, especially if this is done shortly after eating.

The diagnosis of GERD can be challenging since there is no gold standard test available. It can be made solely clinically or in combination with other factors, like responsiveness to therapy and diagnostic tests. The first step is a thorough anamnesis and examination, looking for typical symptoms and clinical signs. An esophagogastroduodenoscopy can be performed to check for erosion and complications like Barrett’s esophagus. Another diagnostic tool is the long-term pH monitoring and multichannel intraluminal impedance, where reflux can be found and therefore this can verify a diagnosis of NERD.

The goals of therapy for GERD are symptom relief and prevention of complications. This can be achieved by three main options: lifestyle modifications, medical therapy and surgical treatment. Lifestyle modifications include adequate diet, physical activity and restriction of risk factors. The drug of choice for the therapy of GERD is PPIs. They are used for empiric as well as for definitive therapy. Important for both is, that after the acute therapy which should always be limited, usually to four weeks, the treatment with PPIs should be reevaluated. Either these four weeks showed an effect, in which case the therapy can be reduced or ended, or another four-week period can follow. After these 8 weeks of PPIs, another evaluation should be done, leading to a definitive treatment decision of either dose reduction, switching to on-demand therapy, or stopping. Surgical options are laparoscopic Nissen fundoplication, hiatal plastics fundopexy or bariatric surgery in obese patients. (20, 21).

1.5.2.2 Gastroduodenal ulcers

Stomach or duodenal ulcers, known as peptic ulcers or peptic ulcer disease (PUD), describe a defect of the organ wall which extends to the *muscularis mucosae* or even deeper. PUD results from increased destructive factors of gastric acid on the wall of the GI tract. They can be classified according to their location, *ulcus ventriculi*, located in the stomach, and *ulcus duodeni*, in the duodenum. The lifetime risk of PUD is between 5-10%, with duodenal ulcers being more frequent than gastric ones (22).

The common causes include *H. pylori* infections and NSAID use. Less frequent causes are ZES, malignancies, viral infections, severe stress such as from illness, burn or injuries, vascular insufficiency, radiation therapy, Crohn's disease or chemotherapy (22). Clinically epigastric pain is common, but there are also asymptomatic courses of PUD.

When there is a suspicion of gastroduodenal ulcer, the gold standard diagnostic test is the esophagogastroduodenoscopy with biopsies, followed by *H. pylori* diagnostic tests. When *H. pylori* is negative and there is no other cause found, further testing for gastrin, serum calcium, and parathormone is ordered. The therapy of PUD depends on the etiology. In *H. pylori*-negative PUD, lifestyle modifications are indicated as well as PPIs for 4-8 weeks with consecutive reevaluation. The treatment for *H. pylori*-positive ulcers will be discussed in the next section. Aside from the medical therapy, endoscopic interventions and operations, especially when there are severe ulcer bleedings, can take place.

Complications of PUD include GI bleeding, perforations, stenosis as well as carcinogenic mutations of *ulcus ventriculi* (22, 23).

1.5.2.3 Helicobacter pylori

H. pylori is a gram-negative bacterium which causes gastric inflammation. The clinical picture is variable, but commonly infection leads to chronic gastritis, associated with the risk of ulcers, mucosal atrophy and carcinomas (9).

There is a prevalence of about 20-50% in industrialized countries. Transmission in Western countries happens from person to person via bodily fluids like vomit, saliva, or feces (24). Diagnostics can be done by noninvasive or endoscopic interventions. Noninvasive testing involves the urea breath test, serologic tests, and stool antigens. Endoscopic biopsies are taken and also checked according to histology, urease rapid testing, microbiologic cultures, and antibiotic-susceptibility tests. The infection is usually chronic and will not heal without therapy. The first line of *H. pylori* eradication therapy in Germany is the Bismut-Quadruple therapy. This regime includes PPI, bismuth, tetracycline, and metronidazole. It is indicated for every *H. pylori*-positive patient and aims to eliminate the organism completely. The Bismut-quadruple therapy lasts at least 10 days. The concurrent treatment of PPIs with two antibiotics provides a synergistic effect, making it very efficient. Two antibiotics are used simultaneously to prevent bacterial resistance development (16).

1.5.2.4 Zollinger-Ellison syndrome

ZES is the umbrella term for a rare group of symptoms, namely severe peptic ulcer disease, GERD, and chronic diarrhea (25). The syndrome is caused by a gastrin-secreting tumor, also called gastrinoma, mostly located in the pancreas or less common in the stomach or duodenum. These gastrinomas are mostly sporadic, with only 25% being associated with MEN1-syndromes. The gastrin secretion of the tumor cells leads to chronic hypergastrinemia, causing the abovementioned symptoms.

The diagnosis is established by taking fasting gastrin levels. Other tests include measurement of gastric juice pH, secretin test as well as gene diagnostics and pathology. The treatment can be divided into symptomatic and curative. Complete surgical resection is the only definitive therapy. PPIs, H2 blockers and somatostatin analogs may be used for symptom control (26). Due to the widespread use of PPIs which partly alleviate the symptoms of ZES, there is a delay in diagnosis of the disease, on average taking eight years to diagnose (25).

1.5.2.5 Prevention of NSAID-induced gastroduodenal ulcers

NSAIDs, including aspirin, are used for their analgesic, anti-inflammatory and antipyretic effects. They work by inhibition of cyclooxygenase (COX) enzymes, COX-1 and COX-2. Both of these enzyme isoforms act on the membrane phospholipid arachidonic acid, to produce prostaglandins which then act on the body. In the gastric mucosa prostaglandins have a cytoprotective effect by enhancing the mucus, amplifying intracellular bicarbonate and increasing blood flow. Inhibiting the abovementioned functions of the COX enzyme (especially COX-1), NSAIDs can have significant GI side effects (27). In the United States, there are 2600 estimated deaths each year from this GI toxicity (16). While short NSAID therapy doesn't seem to be related to severe side effects, long-term therapy increases the risk for GI toxicity. The co-prescribing of NSAIDs with PPIs can be indicated in patients with predisposing factors, making them more vulnerable to further complications. At risk may be those with a history of ulcers or concurrent use of anticoagulants or corticosteroids

1.5.3 Disadvantages of PPIs

Following the last chapter on the clinical uses and advantages of PPIs in the therapy of acid-related disorders, this chapter considers the downside of their usage. While PPIs are an integral part of modern gastroenterological practice, their long-term application raises several concerns that call for careful consideration.

Prolonged PPI usage can alter the mucosa. Histologically, changes may include polyps, lesions, cobblestone-like mucosa and black spots (28).

From a clinical perspective, chronic use of PPIs, defined as longer than eight weeks, has many potential side effects, including nutritional deficiencies (such as B12, magnesium, and iron), increased susceptibility to infections (like pneumonia and enteric infections) and more severe complications such as fractures, kidney damage and dementia.

Vitamin B12 (cobalamin) is a water-soluble vitamin, it is protein-bound and the primary nutritional sources are meat and eggs. B12 is essential for DNA synthesis, red blood cell formation and neurologic functioning. For the uptake of B12, the pH is essential, leading to breakage of the protein-vitamin bond. Some studies have shown a possible connection between PPIs and a decreased absorption of cobalamin, leading to hematologic, neurologic, and psychiatric abnormalities, which are of particular concern in older adults (29).

The inhibition of the proton pump and therefore a higher pH in the stomach may also influence iron absorption in a similar fashion as Vitamin B12.

Hypomagnesemia is a rare occurrence in patients with PPI therapy, which has been suggested in some studies. Although a clear connection or mechanism has not been established yet, the German Federal Institute for Drugs and Medical Devices has issued a warning for hypomagnesemia and possible associated symptoms like fatigue, muscle contraction, neurological symptoms and tachycardia under the treatment with PPIs (30).

Community-acquired pneumonia (CAP) and *Clostridium difficile* infection (CDI) have also been connected to PPIs. Since stomach acid acts as a barrier for ingested pathogens, its suppression can lead to increased susceptibility to infections. CAP is a serious complication, ranking eighth in the leading cause of death among older adults (29). Evidence of links between PPI and CAP is inconclusive still, but consideration in the therapy of geriatric patients with PPIs should include the possibility. For CDI on the other hand, there is an association between PPI and CDI. The bacterium is a gram-positive anaerobe and the major cause of antibiotic-associated diarrhea, leading as far as sepsis and death. By increasing the pH in the stomach, *Clostridium difficile* can survive, ultimately leading to an increased risk of CDI in PPI users, especially if other risk factors like antibiotic therapy or increased age are involved.

Osteoporosis and increased bone fractures are a big healthcare concern in the elderly. For example, 75% of the hip, spine and distal forearm fractures occur in patients over 65 (29). PPIs are thought to interfere with the calcium metabolism and osteoclast activity. Although controversial, studies have led the FDA to enforce a warning on PPI product labels about the possible risk of fractures when taking high doses or long-term therapy, which may lead up to a 25-50 % higher risk of a hip fracture when taking PPIs (16, 29).

Studies suggest there may be a connection between PPI use and chronic kidney disease (CKD) which may be caused by an increased risk of acute injury of the kidney by PPI use. Since an acute injury is often unrecognized, it is difficult to establish a link and more studies are needed to confirm (29).

Animal trials have shown that PPI use can alter the metabolism of amyloid peptides which play a role in dementia by increasing the production and accumulation of ß-amyloid in the brain of mice. There have not been enough big studies on the topic to determine a clear risk in humans, but it is worth observing the association in patients with long-term acid-lowering therapy (14).

As described in Chapter 1.5.1, PPIs are metabolized by the CYP450 system, leading to drug interaction. Their impact primarily affects other drugs that also go through the cytochrome, especially clopidogrel as well as others like warfarin, phenytoin, diazepam, voriconazole and so on (14, 16).

The awareness of potential adverse effects and drug interactions has increased since PPIs were introduced 25 years ago. Research regarding the risk of PPIs has to be conducted further, but for now, given the potential harm in elderly patients, it should warrant periodical evaluation of the need for PPI therapy, and in some cases a consequent discontinuation or step-down treatment (29).

Although these consequences are infrequent and connections are primarily from observational research without distinct causation, elevated long-term utilization of PPIs exposes a greater number of individuals to potential harm. If PPIs are wrongly administered or extended past the suggested treatment duration, the likelihood of them yielding advantages is extremely low (31).

1.5.4 Deprescribing PPIs

Seen in Figure 3 is a diagram for possible prescription and deprescription PPIs in clinical practice adapted from Helgadottir and Bjornsson (31).

Appropriate management of PPI therapy requires a careful approach that begins with reviewing the indications and benefits for each patient. Clearly defining goals for PPI treatment and establishing a timeline is crucial. Assessment must consider the balance between benefits and harms, taking into account the patient's quality of life and adherence to drug taking which should be done one hour before a meal. Based on the evaluation a decision for prescribing, continuation, dose escalation/de-escalation or discontinuation of PPI therapy is made, followed by continuous monitoring. This may be repeated until either a patient with an indication continues PPIs with the lowest effective dose or PPI is deprescribed.

Deprescribing lacks a unitary definition, but Helgadottir *et al*. describes it as "the process of reducing and/or stopping PPI therapy after consideration of therapeutic indication, benefits, and risk" (31). There is no evidence-based method for stopping the acid-lowering treatment, but three options exist. One would be an abrupt discontinuation. This method has the highest relapse rate, due to rebound acid hypersecretion (RAHS). When stopping PPI therapy, there is a compensatory elevation of gastrin, leading to increased acid production and acid-related complaints, shortly after the discontinuation of PPIs. Patients should be informed that rebound symptoms usually cease after one week. The second option would be temporary replacement of PPI with H2-blockers. This decreases the effects of RAHS and the medication can be stopped after a short period. Third is the dose reduction of PPI and interval increase. Gradually lowering PPI intake until it can be stopped completely. Additionally, lifestyle changes may be indicated to manage occasional mild symptoms (31).

Although PPI treatment is primarily initiated in primary care, there are opportunities to optimize PPI usage among both primary care and hospital patients. Previous chapters have highlighted the therapeutic benefits but also potential disadvantages. Clinicians must prescribe PPIs judiciously and manage therapy carefully to optimize outcomes and minimize adverse effects, supported by ongoing research to address long-term risks. Chronic use of PPIs is associated with health risks such as nutritional deficiencies, renal issues, increased risk of dementia and compromised bone health. In an elderly population, where multimorbidity and polypharmacy are heightened, this may be even more important.

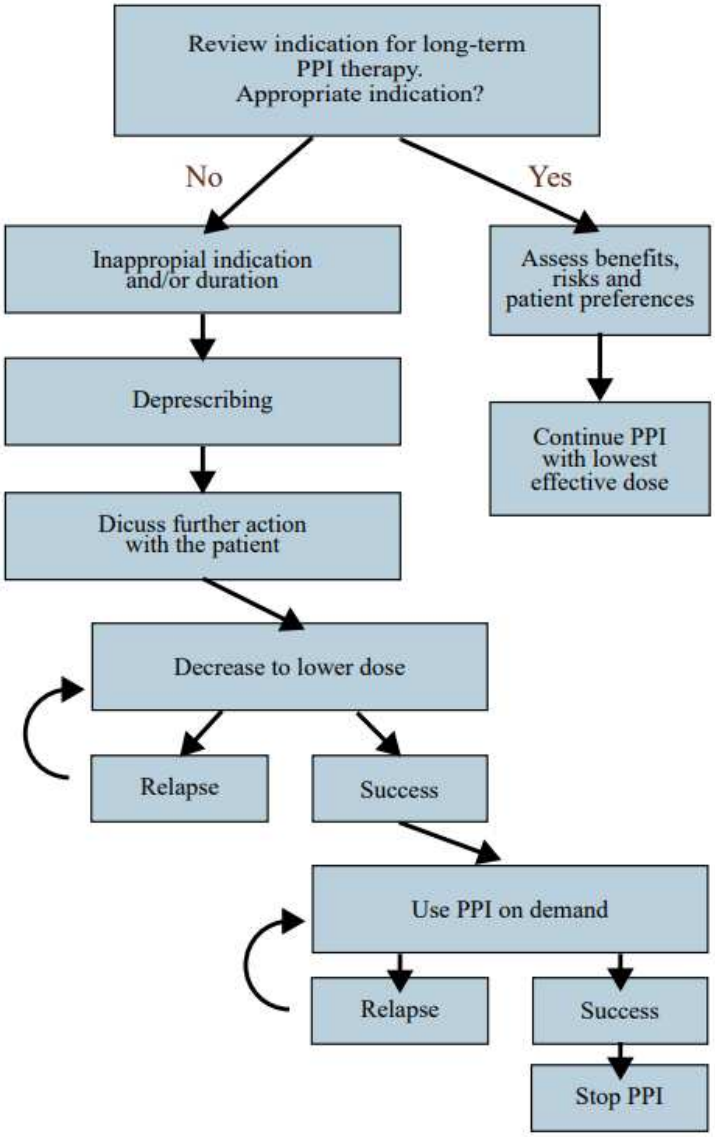

Figure 3. Algorithm for PPI therapy
Source: Helgadottir H, Bjornsson ES. Problems Associated with Deprescribing of Proton Pump Inhibitors. Int J Mol Sci. 2019; 20(21):5469

2. OBJECTIVES

2.1 Aim of the study

The aim of this cross-sectional study was to analyze the patient's data of geriatric patients in the general medicine ward in order to determine their use of PPI therapy. Additionally, the study investigates the polypharmacy of those patients.

2.2 Hypothesis

Geriatric Patients have proton pump therapy without indication in their medical history.

3. SUBJECTS AND METHODS

3.1 Design and description of the study

This retrospective study has reviewed medical history and medication lists of patients who were admitted to the general medicine ward of the Regiomed Klinikum Coburg in June 2019 and June 2023. In order to evaluate the usage of PPIs, anonymized medical data was collected. This information included the type of PPI, dosage, indications, changes in medication regimens and possible side effects. Furthermore, it was checked for polypharmacy. An observational, cross-sectional design was used for this study. This enabled a snapshot assessment of the patient's medical records within the specific timeframe, allowing for an analysis of PPI prescription patterns and associated indications. The data was drawn exclusively from patient admission and discharge forms which document medical histories and medication regimens. All the data are analyzed anonymously, ensuring that backtracing to the individual patients is not possible.

3.2 Subjects and methods

The sample under investigation comprises patients that were admitted to the family medicine floor of Coburg Hospital in Germany. Using a convenience sampling approach, the study focused on geriatric patients in the selected months. Patients were considered for this study, if they met the inclusion criteria of hospital admission to the family medicine floor within June 2019 and June 2023 to Regiomed Klinikum Coburg. Patients who were under 65 years or died during the inpatient stay and those with incomplete data were excluded. Figure 4 shows the process of choosing patients in this study. For the collection of the data, medical records, specifically the admission form and hospital discharge letter were used. This study encompasses fundamental demographic and medical information about each geriatric patient, the age (in years), gender, ‘male' or 'female' to analyze any gender-based differences in PPI prescription patterns, admission in a chosen month, medical history, specifically prior medical conditions that might warrant PPI prescription, taking of PPI and number of medications taken. The data evaluation is conducted in an anonymized manner, making it impossible to trace back to specific patients.

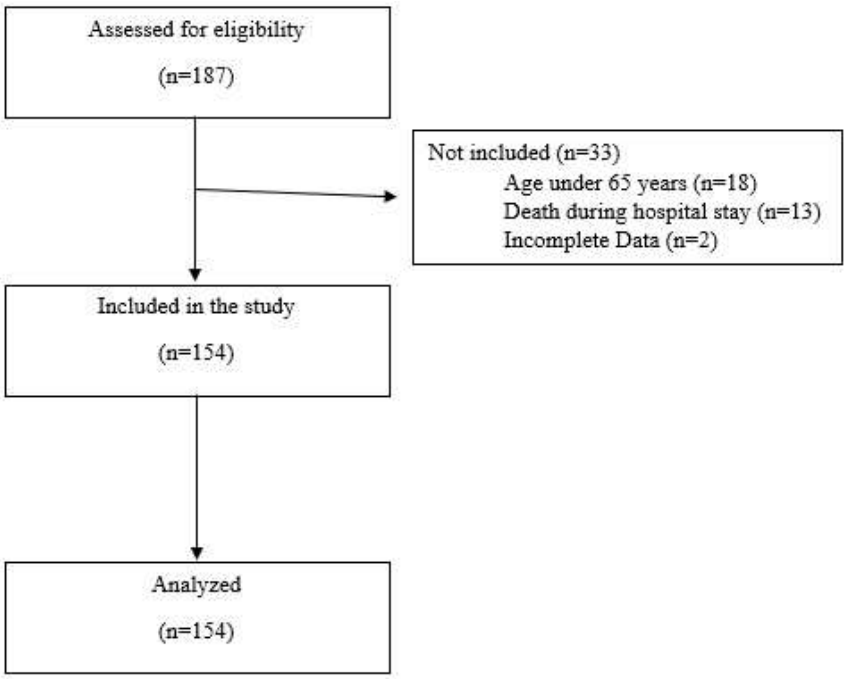

Figure 4. STROBE Flow Chart

3.3 Statistical analysis

The data was entered and processed using Excel tables (Microsoft Corporation, Redmond, United States). Python (Python Software Foundation, Wilmington, United States) and JMP Clinical 17 (SAS Institute Inc., Cary, United States) were used for statistical tests. In this cross-sectional observational study, a measure of effects was done by presenting proportions and comparing them. Furthermore, the age distribution of the sample is checked for normal distribution, using a histogram and Shapiro-Wilk test. The relationships between age and PPI usage as well as gender and PPI usage were checked using the point-biserial correlation coefficient, chi-square-test and logistic regression. The association between taking PPI (yes/no) and indication for PPI (yes/no) is examined using the chi-square test. A significance level of $p < 0.05$ was used.

3.4 Possible biases and confounding variables

Potential biases and confounding variables may be sampling, recall and information bias. Convenience sampling is prone to biases since the patient group is not randomly selected from the entire population, therefore certain groups may be over- or underrepresented and the sample may be homogenous. Recall bias may be present due to retrospective data collection. Bias could also arise from incorrect data given, but this is minimized by standardized medical records. Incompleteness of the medical records could lead to misinterpretation, possibly leading to information biases.

3.5 Ethical approval

Ethical approval was obtained from the IRB of the Medical School Regiomed Coburg on February 19, 2024.

4. RESULTS

4.1 Patient Characteristics

The patient-related data was extracted from the patient's files and analyzed. Initially, the dataset included 187 patients admitted to the general medicine ward in June 2019 and 2023. 33 patients were excluded due to their age being lower than 65, death during the hospital stay, or insufficient data. Ultimately, the data of 154 patients was used. A summary is presented in Table 4. The patient of this retrospective study can be classified based on several variables, presented as absolute number n (percentage %).

Table 4. Patient characteristics

Characteristics	**Absolute number (n)**	**Percentage (%)**
Total patients	154	100
Gender		
- Male	46	29.9
- Female	108	70.1
Age		
- Mean age	85,0	
- Age range	68-98	
Patients with polypharmacy (>5)		
- Upon admission	123	79.9
- Upon discharge	139	90.3
Patients on PPI[a]	94	61.0
- Upon admission	75	48.7
- Upon discharge	83	53.9
Patients not on PPI[a]	60	39.0
- Upon admission	79	51.3
- Upon discharge	71	46.1
Patients with indication for PPI[a]	24	15.6
Patients without indication for PPI[a]	59	38.3

Data are presented as numbers
[a] PPI

Of the total of 154 patients, 108 (70.1%) were female and 46 (29.9%) were male. The distribution can be seen in Figure 5. The mean age at the time of selection was 85 years with an overall age distribution ranging from 68-98 years. The age distribution was checked using a histogram, seen in Figure 6 and the Shapiro-Wilk-test (p=0.057), both concluding that the data is normally distributed with a standard deviation of 6.6 years. Upon admission, the number of patients with polypharmacy was 123 (79.9%) and 139 (90.3%) at the time of discharge. The mean number of drugs taken upon hospital admission was 8.7 and the mean at hospital release was 9.2. The number of medications taken ranged between 0 to 20 drugs with interquartile ranges (IQRs) of 6-11 for admission and 8-12 for release.

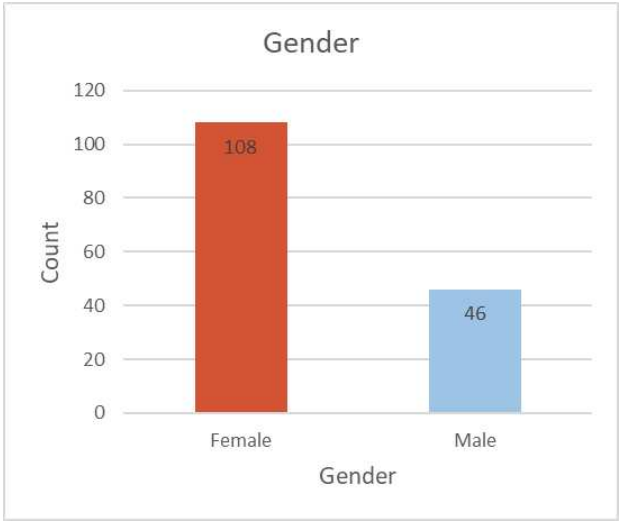

Figure 5. Gender distribution

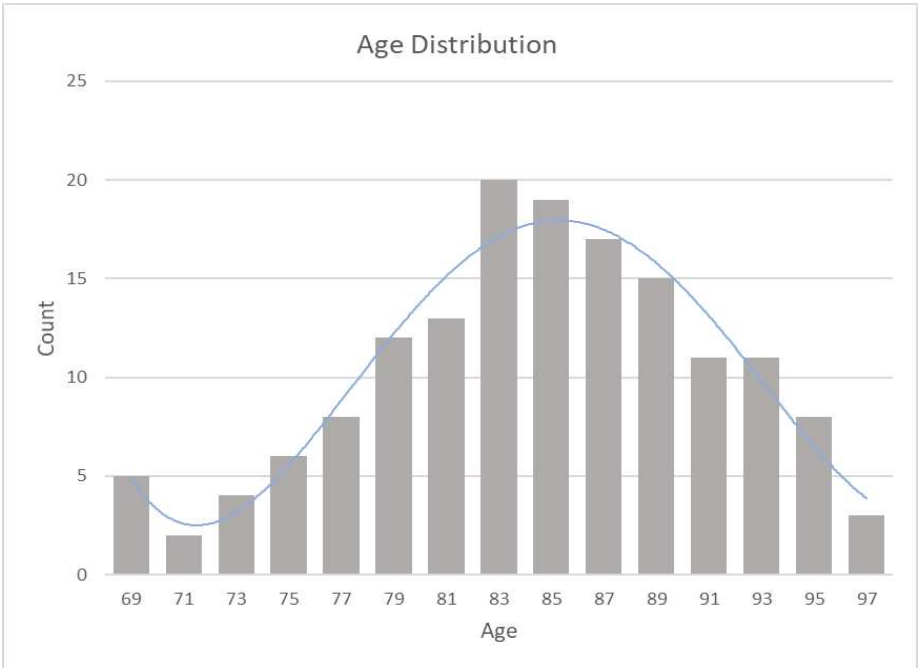

Figure 6. Histogram of age distribution

4.2 Proton Pump Inhibitor usage

Regarding the use of PPIs data was obtained on the number of PPIs upon admission and at discharge, type and dosage of PPI, duration of therapy and indication which warrants PPI usage, as well as possible adverse effects.

Out of all 154 patients, 94 (61%) were taking PPI at some point during their hospital stay, consisting of 60 (68.2%) in June 2019 and 34 (51.5%) in June 2023. A total of 13 (8.4%) patients started PPIs during their hospital stay and in 11(7.1%) patients the therapy was stopped during the hospital stay. The PPI types and dosages can be seen in Figure 7, with Pantoprazole 40mg being the most frequently used PPI. 42 (27.3%) patients took it at admission and 60 (39.0%) patients upon release.

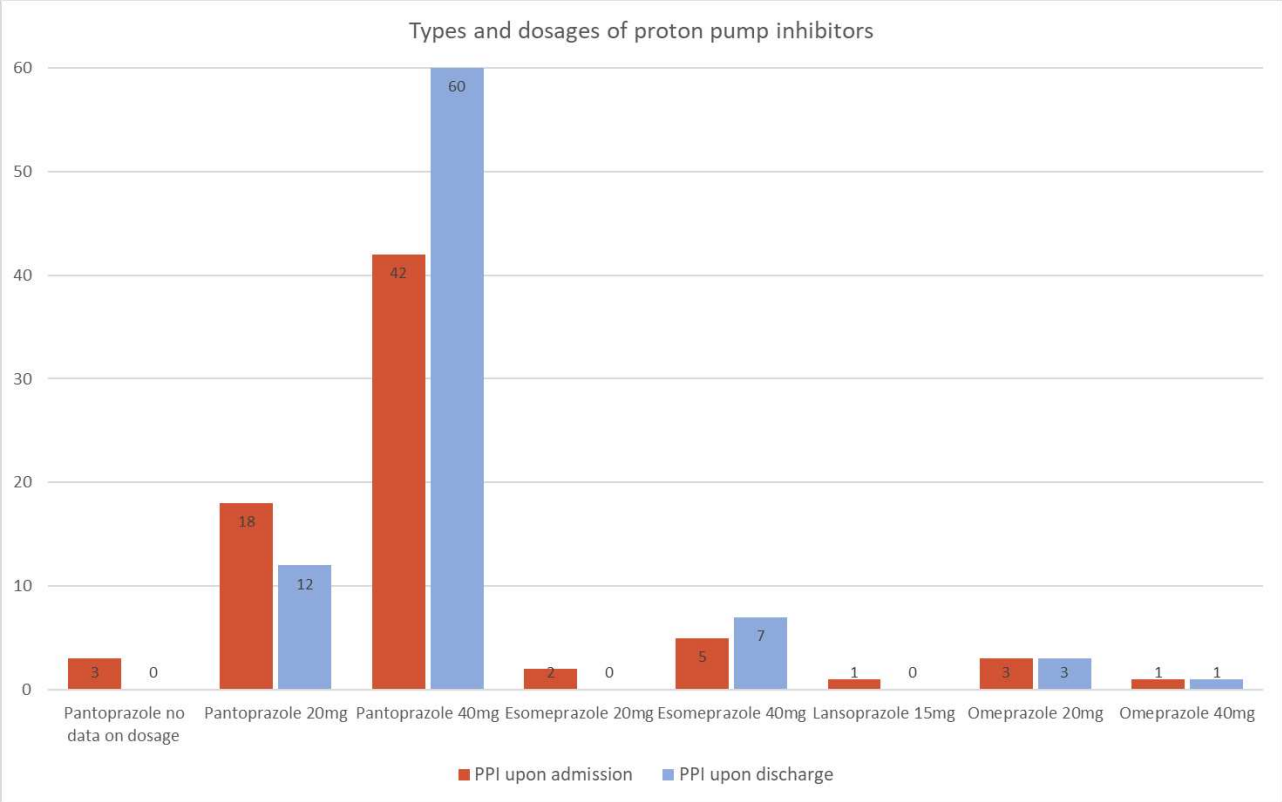

Figure 7. Types and dosages of proton pump inhibitors upon admission and discharge

In 13 (8.4%) cases the medications were changed, with 1 (0.6%) patient receiving a different PPI and 12 (7.8%) patients getting a change in dosage.

Overall, in 68 (44.2%) cases, the PPI therapy was counted as a long-term therapy since no end of therapy was defined, that makes up 72.3% of the 94 patients taking PPI. By contrast, 15 (9.7%) patients had a short-term therapy with a clearly stated goal or end, warranting a usage of PPIs that is shorter than eight weeks (Figure 8).

In 2019, among 60 (39.0%) patients who took PPI, in 7 (4.5%) the therapy was ended, in 18 (11.7%) a clear indication was found and in 35 (22.7%) there was no indication for the treatment. In 2023 out of 34 (22.1%) patients taking PPI, the therapy ended in 4 (2.6%), 6 (3.9%) had an indication for the usage of PPI and 24 (16.6%) had no indication. These data show that out of the 83 (53.9%) who continued taking PPI after their hospital stay, only 23 (14.9%) patients have an indication for therapy that is stated in their hospital discharge letter. Consequently, 60 (39.0%) patients had no stated indication to justify therapy, constituting 62.8% of patients taking PPI. In 7 (4.5%) cases the hospital discharge letter included a notice to check the indication of the PPI for the general practitioner.

Figure 9 presents the indications among the patients, including 12 (7.8%) cases of reflux esophagitis, 5 (3.2%) cases of gastric ulcer, 3 (1.9%) cases of hemorrhagic-erosive gastritis, and 3 (1.9%) cases of various other indications, with the "other" category comprising short-term therapies for miscellaneous reasons.

The association between age and PPI usage was tested using the point-biserial test. The conclusion was, that there could be a positive association between age and PPI usage however, this was not statistically significant ($p=0.328$). The relation between taking a PPI and not taking a PPI is illustrated in Figure 10, showing similar age distribution for both groups with no significant difference ($p=0.319$). The chi-square test for gender and PPI usage with $p=0.697$, indicated no statistically relevant association between gender and PPI usage. Logistic regression, used on patients with and without PPI therapy, concluded that there is no significant influence on the likelihood of being on PPI therapy and the age and gender of patients with $p>0.05$ for both variables. The chi-square test showed a significant association between the two categorical variables of having an indication for PPI therapy (yes/no) and being treated with PPI (yes/no) with $p<0.001$.

In 19 (12.3%) patients, a diagnosis in their discharge letter was found, which could be regarded as adverse effects of PPIs with long-term usage. These included nutritional deficiencies 5 (3.2%), fractures 5 (3.2%), increased susceptibility to infection 3 (1.9%) and kidney damage 9 (5.8%), demonstrated in Figure 11.

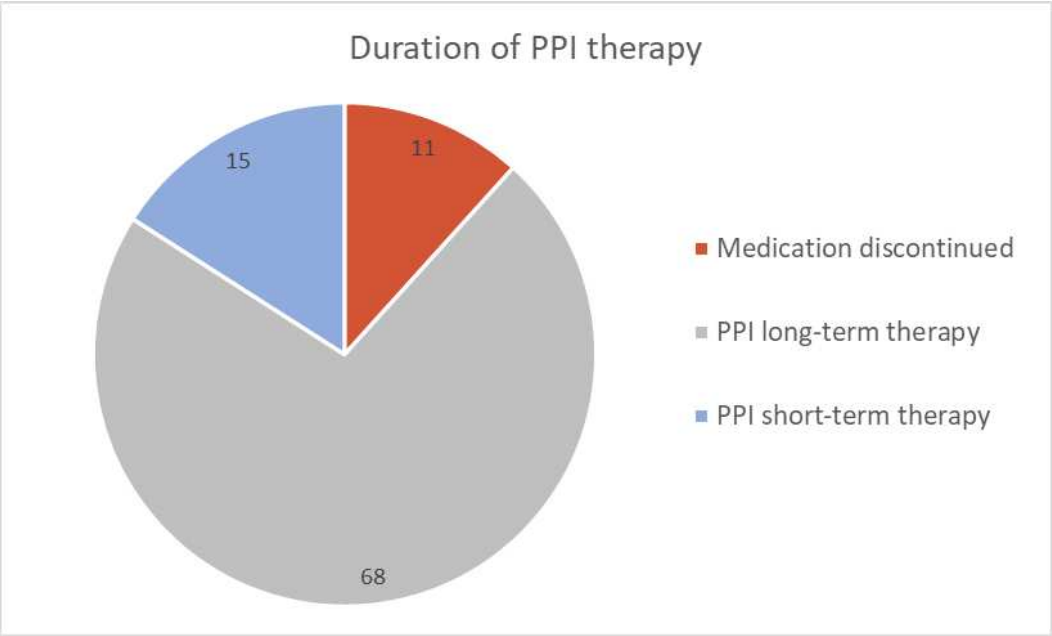

Figure 8. Duration of PPI therapy

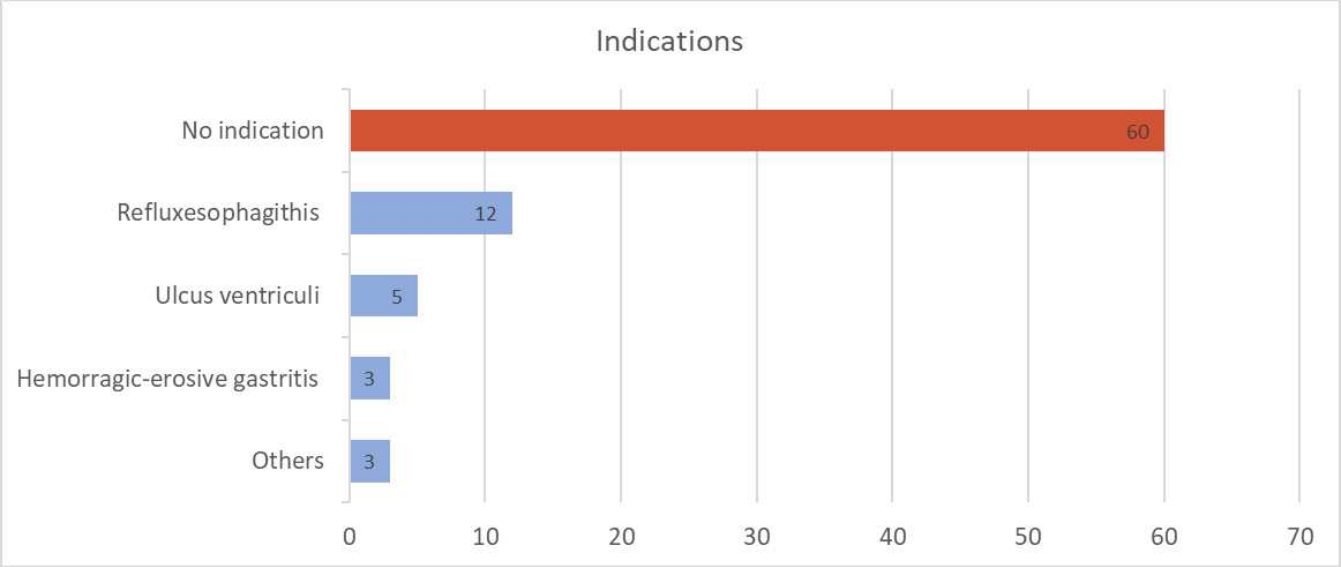

Figure 9. Indications for PPI use

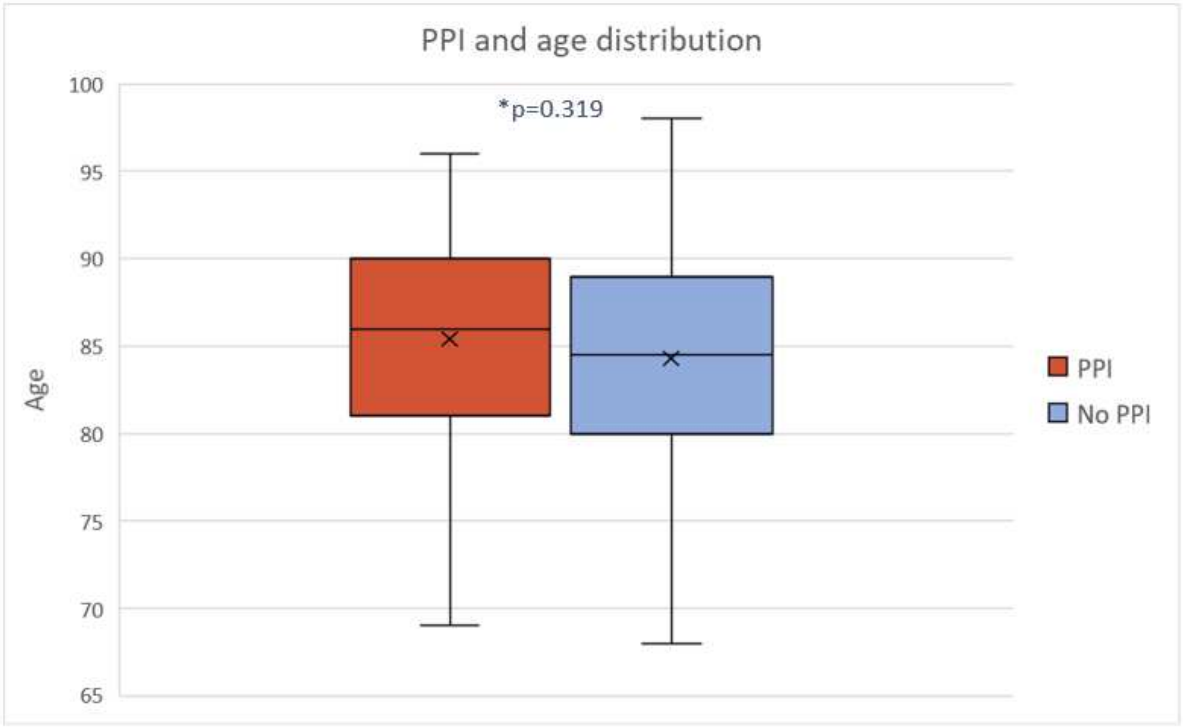

Figure 10. Comparison between PPI use and age,
*t-test for unpaired samples

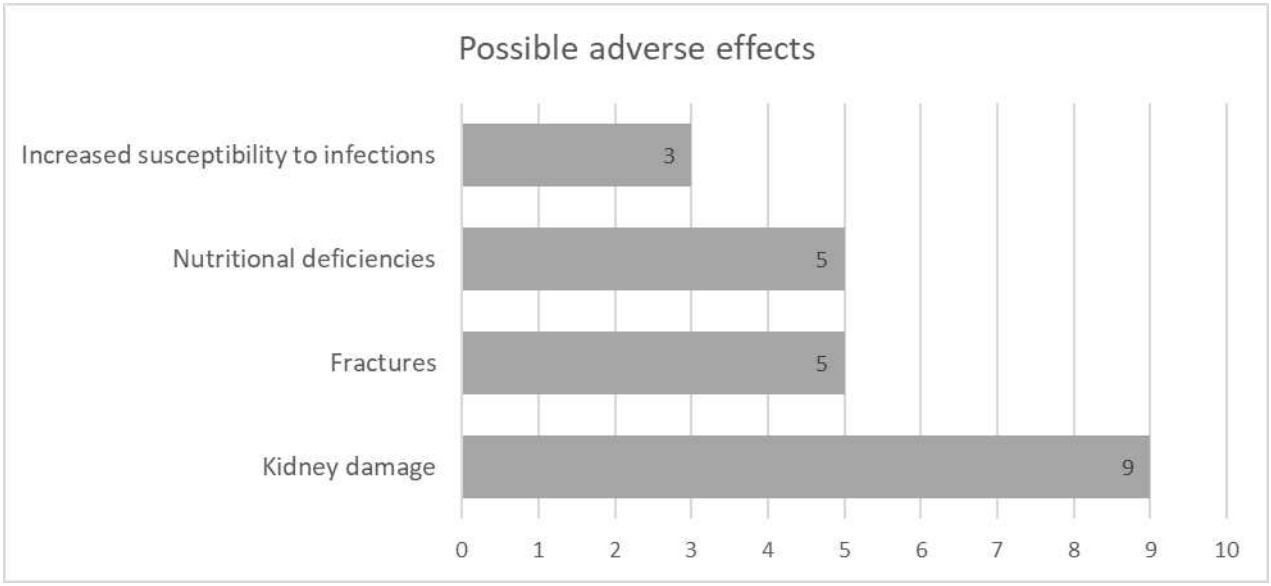

Figure 11. Possible adverse effects of PPI therapy

5. DISCUSSION

This study investigated the frequency and necessity of PPI therapy in 154 geriatric patients. The results showed that a significant percentage (61%) were on PPI therapy and that 63.8% of those received it without a documented clinical indication.

The age distribution of the sample population, with a mean age of 85 years, indicated that most patients were around this age with few patients being younger or older than that. Since the inclusion criteria were age above 65 but the mean was 85 years, it could be concluded that results may rather be applicable to this older patient group. The high use of PPIs in this demographic is in adherence with existing studies which attribute it to higher rates of comorbidities, polypharmacy, increased risk for acid-related disorders and lack of deprescribing efforts (32).

The gender distribution in this sample shows a high percentage of female patients (70.1%). This could be explained by several factors, such as higher life expectancy in women, social and cultural factors. It could also be caused by the selection process of this study.

The lack of a significant association between age, gender and PPI use in the patient collective suggests that other factors may influence the decision of clinicians when prescribing PPIs. Age and gender were therefore no distorting factor for the patient data. The relationship between documented indications and PPI therapy suggests an appropriate decision to prescribe PPIs when a clear indication is present and therefore adherence to the guidelines. However, this disregards the necessity for the adaption of clinical guidelines when prescribing PPIs to vulnerable populations like geriatric patients.

The most prevalent PPI preparation in these patients was Pantoprazole 40mg, being a high-dose PPI. Globally the most frequently prescribed PPI is Omeprazole, followed by Esomeprazole. The discrepancy in types could be explained by local guidelines and protocols, physician preferences and marketing in the region of the hospital compared to the world.

Regarding the duration of therapy, the results showed, that with 44.2% of all patients being affected, most PPI therapies were long-term. The existing literature suggests that the effects of long-term therapy are associated with unforeseeable disadvantages, especially in the elderly population. These may outweigh the positive effects of the medication (30, 33).

While 39% had no documented indication at all that warrants PPI therapy, in 14.9% a reason for treatment was found, the most prevalent being reflux esophagitis. This finding is plausible since 20% of the whole population is estimated to have GERD, with prevalence increasing with age (20).

The key result of more patients not having a clear indication than those having one demands a critical reflection on the current habit of prescribing PPI therapy in the elderly population. The high prevalence of PPI therapy among geriatric patients aligns with existing studies (32). This overuse is concerning due to the risks associated with long-term PPI use, like malabsorption, infections, fractures and renal complications. The possible adverse effects and a high number of long-term usage found in this study support the importance of deprescribing efforts in the elderly, one of which is the PRISCUS list which is made to decrease potentially inadequate medications (PIM) in this demographic (33). However, due to the retrospective design of this study and possible information biases the causality between adverse effect found and PPI usage in this study cannot be clearly established.

Overall, the results highlight the necessity for strict adherence to clinical guidelines when prescribing PPI therapy to geriatric patients. This includes prescribing when clinically necessary, but on the other hand, also deprescribing when no plausible indication can be found. Healthcare professionals should ensure that the initiation of PPI treatment is backed by a well-documented indication to avoid unnecessary use. Regular re-evaluation of ongoing PPI therapy is crucial to reduce the prevalence of inappropriate use. Additionally, the findings emphasize the need for better education and awareness regarding risks associated with prolonged PPI use in vulnerable populations. Implementations of re-evaluation and deprescribing protocols should be a beneficial strategy.

Another main finding is a high rate of polypharmacy. With 79.9% of patients having more than five medications upon admission and even 90.3% upon release, the data affirm the consensus of other studies (34, 35). Polypharmacy is a global health risk for elderly people and the potential harms and risks should always be considered and remembered, aiming for a decrease in unnecessary and inappropriate medication prescription. In this study the average of 9 drugs taken was at the upper level of the global average per day for elderly people, putting focus on the presence of this problem in geriatric patients in Regiomed Klinikum Coburg (34).

By examining the geriatric demographic, this study focuses on a vulnerable population that is often subjected to polypharmacy and potentially inappropriate medication use as exemplified by PPIs. This study gave insight and understanding into this clinically relevant topic. However, the retrospective design limits the ability to establish causality and is prone to biases. The data on indication may not fully show the reasons for clinical decision-making and some indications might be underreported or simply inaccurately documented. The findings are also not generalizable to a broader population due to the small sample size and convenience sampling.

Future research should aim to explore over-prescription and the necessity of PPI in the elderly further. Studies and systemic reviews could provide more robust data on the appropriateness of PPI prescriptions and work to enhance suitable practices when dealing with the geriatric population. Investigating prescribing practices of PPIs or even outcomes of deprescribing initiatives in geriatric patients could offer further valuable input on the benefits and risks of discontinuation of unnecessary PPI therapy and polypharmacy.

6. CONCLUSION

The results of this study highlight the prevalence of PPI therapy and polypharmacy among geriatric patients, with 61% of the sample receiving PPIs. A significant portion of the sample received acid-lowering therapy without any documented indication. The prevalence of long-term therapy was particularly elevated, implying overuse of PPIs in the elderly and therefore raising the risk of adverse effects. In summary, this study emphasizes a critical area for improvement in the management of geriatric patients and calls for enhanced strategies to ensure the safe and appropriate use of PPIs in this vulnerable population.

7. REFERENCES

1. The impact of demographic change in Europe - European Commission [Internet]. 2023 [cited 2024 Mar 2]. Available from: https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/new-push-european-democracy/impact-demographic-change-europe_en.
2. Skou ST, Mair FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ et al. Multimorbidity. Nat Rev Dis Primers. 2022; 8(1):48.
3. Varghese D, Ishida C, Haseer Koya H. Polypharmacy. Treasure Island (FL): StatPearls Publishing; 2024.
4. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014; 13(1):57–65.
5. Strampelli A, Cerreta F, Vučić K. Medication use among older people in Europe: Implications for regulatory assessment and co-prescription of new medicines Strampelli - 2020. British Journal of Clinical Pharmacology - Wiley Online Library. 2020;10:1912-1920.
6. ClinCalc DrugStats Database. The Top 300 of 2021 [Internet]. [cited 2024 Jan 25]. Available from: https://clincalc.com/DrugStats/Top300Drugs.aspx.
7. Dr. med. Rosien U. Deprescribing PPI: Weniger Protonenpumpeninhibitoren-Verordnung ist möglich! Arzneimittelkommission der deutschen Ärzteschaft [Internet]. 2022 [cited 2024 Jan 25]. Available from: https://www.akdae.de/arzneimitteltherapie/arzneiverordnung-in-der-praxis/ausgaben-archiv/ausgaben-ab-2015/ausgabe/artikel?tx_lnsissuearchive_articleshow%5Baction%5D=show&tx_lnsissuearchive_articleshow%5Barticle%5D=4698&tx_lnsissuearchive_articleshow%5Bcontroller%5D=Article&tx_lnsissuearchive_articleshow%5Bissue%5D=22&tx_lnsissuearchive_articleshow%5Byear%5D=2019&cHash=3b0ea6ebc7ea4699221df4a12f0423f5.
8. Patricia JJ, Dhamoon AS. Physiology, Digestion. Treasure Island (FL): StatPearls Publishing; 2022.
9. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 12th ed. Philadelphia, Pa: Saunders/Elsevier; 2011.
10. Gray H, Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Third edition. Philadelphia, PA: Churchill Livingstone Elsevier; 2015.p.303-366.
11. Magen. AMBOSS [Internet]. [cited 2024 Mar 31]. Available from: https://next.amboss.com/de/article/XK09US?q=Magen.

13. Martinsen TC, Fossmark R, Waldum HL. The Phylogeny and Biological Function of Gastric Juice—Microbiological Consequences of Removing Gastric Acid. Int J Mol Sci. 2019; 20(23):6031.
14. Rezar TR. Protonenpumpenhemmer Kritische Betrachtung der Therapie mit Fokus auf Neben- und Wechselwirkungen. [dissertation]. MEDonline: Medizinischen Universität Graz; 2022.
15. Mössner J. The Indications, Applications, and Risks of Proton Pump Inhibitors. Deutsches Ärzteblatt international [Internet]. 2016 [cited 2024 Jan 25]. Available from: https://www.aerzteblatt.de/10.3238/arztebl.2016.0477.
16. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut and Liver. Editorial Office of Gut and Liver; 2017; 11(1):27.
17. Shin JM, Sachs G. Pharmacology of Proton Pump Inhibitors. Curr Gastroenterol Rep. 2008; 10(6):528–34.
18. Wedemeyer R-S, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. Drug Saf. 2014; 37(4):201–11.
19. Vakil N, Zanten SV van, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006; 101(8):1900–20; quiz 1943.
20. Gastroösophageale Refluxkrankheit. AMBOSS [Internet]. [cited 2024 Apr 16]. Available from: https://next.amboss.com/de/article/vg0AC2?q=ppi#Z89068c46b5e7a2b542fbb1d5467c7307.
21. Antunes C, Aleem A, Curtis SA. Gastroesophageal Reflux Disease. Treasure Island (FL): StatPearls Publishing; 2024.
22. Malik TF, Gnanapandithan K, Singh K. Peptic Ulcer Disease. Treasure Island (FL): StatPearls Publishing; 2023.
23. Gastroduodenale Ulkuskrankheit. AMBOSS [Internet]. [cited 2024 Apr 21]. Available from: https://next.amboss.com/de/article/zg0rB2?q=ulcus%20ventriculi#Zd28f88477c79919bf80d984d5995d640.
24. Suerbaum Sebastian, Michetti Pierre. Helicobacter pylori Infection. New England Journal of Medicine. Massachusetts Medical Society; 2002; 347(15):1175–86.
25. Cho MS, Kasi A. Zollinger-Ellison Syndrome. Treasure Island (FL): StatPearls Publishing; 2022.

26. Rossi RE, Elvevi A, Citterio D, Coppa J, Invernizzi P, Mazzaferro V et al. Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies. World J Gastroenterol. 2021; 27(35):5890–907.
27. Sohail R, Mathew M, Patel KK, Reddy SA, Haider Z, Naria M et al. Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review. Cureus. 2023; 15(4):e37080.
28. Kim GH. Proton Pump Inhibitor-Related Gastric Mucosal Changes. Gut and Liver. 2021; 15(5):646–52.
29. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Therapeutic Advances in Drug Safety. 2017; 8(9):273–97.
30. Scheurlen M. Langzeitbehandlung mit Protonenpumpenhemmern: Wer braucht die Prophylaxe tatsächlich? Internist. 2013; 54(3):366–72.
31. Helgadottir H, Bjornsson ES. Problems Associated with Deprescribing of Proton Pump Inhibitors. Int J Mol Sci. 2019; 20(21):5469.
32. Shanika LGT, Reynolds A, Pattison S, Braund R. Proton pump inhibitor use: systematic review of global trends and practices. Eur J Clin Pharmacol. 2023; 79(9):1159–72.
33. Mann N-K, Mathes T, Sönnichsen A, Pieper D, Klager E, Moussa M et al. Potentially inadequate medications in the elderly: PRISCUS 2.0—first update of the PRISCUS list. Deutsches Ärzteblatt international [Internet]. 2023 [cited 2024 Jun 10]. Available from: https://www.aerzteblatt.de/10.3238/arztebl.m2022.0377.
34. Dagli RJ, Sharma A. Polypharmacy: A Global Risk Factor for Elderly People. J Int Oral Health. 2014; 6(6):i–ii.
35. Payne RA. The epidemiology of polypharmacy. Clin Med (Lond). 2016; 16(5):465–9.

8. SUMMARY

Objectives: The aim of this study was to investigate the usage of proton pump inhibitors in geriatric patients in the general medicine ward. Additionally, the study also looked into polypharmacy among those patients.

Materials and Methods: This retrospective study analyzed medical histories and medication lists of patients in the general medicine ward at Regiomed Klinikum Coburg during June 2019 and June 2023. A convenience sample of 154 geriatric patients was used during the selection process. Admission within the defined time period was required for inclusion. Excluded were patients below the age of 65, patients who died during the hospital stay and those with incomplete data. Data collection focused on demographic and medical information from the admission and discharge forms, like age, gender, medical conditions, PPI use, and number of medications taken. The data was analyzed anonymously to provide a snapshot of prescription patterns and indications. Potential biases included sampling, recall, and information bias.

Results: In 154 geriatric patients, 61% were on PPI therapy during their hospital stay with Pantoprazole 40mg being the most frequently used PPI. Of the patients on PPIs, 63.8% had no documented clinical indication for PPI therapy, constituting 39% of the total sample. In addition, the study found that 44.2% of PPI therapies were long-term without a defined end date. Adverse effects could be suspected in 12.3% of patients. The sample demographics included an average patient age of 85 years, with 70.1% being female and 29.9% being male patients. Polypharmacy was prevalent with 79.9% of patients upon admission, meaning taking more than five medications, and with 90.3% at discharge. The mean number of medications taken was 9. Statistical tests showed no significant association between age, gender, and PPI usage. However, it was found that there may be connections between polymedication and PPI treatment, as well as between indication and PPI.

Conclusion: This study investigated the frequency and necessity of PPI therapy in geriatric patients, revealing that 61% were on PPI therapy. The majority of those who used PPIs did not have a documented clinical indication. Long-term therapy was particularly prevalent, raising concerns about potential adverse effects. Furthermore, significant polypharmacy was found. In order to guarantee the safe and proper use of PPIs in the older population, this study emphasized the necessity of improved prescribing practices and regular medication reviews.

9. CROATIAN SUMMARY

Naslov: Procjena učestalosti i potrebe terapije inhibitorima protonske pumpe u gerijatrijskih bolesnika

Ciljevi: Cilj ovog istraživanja bio je pregledati podatke gerijatrijskih bolesnika na odjelu opće medicine kako bi se analizirala njihova upotreba inhibitora protonske pumpe. Osim toga, istraživanje ispituje polifarmaciju među tim pacijentima.

Materijali i metode: Ovo retrospektivno istraživanje pregledalo je medicinske povijesti i popise lijekova bolesnikana odjelu opće medicine u bolnici Coburg unutar određenog vremenskog okvira od lipnja 2019. do lipnja 2023. Ukupno je 154 gerijatrijskih pacijenata odabrano prigodnim uzorkovanjem. Kriterij za uključivanje bio je prijem unutar definiranog vremenskog razdoblja. Isključeni su bolesnici mlađi od 65 godina, bolesnici koji su umrli tijekom boravka u bolnici i oni s nepotpunim podacima. Prikupljanje podataka fokusiralo se na demografske i medicinske informacije iz prijemnih i otpustnih obrazaca, poput dobi, spola, medicinskih stanja, upotrebe PPI-a i broja uzetih lijekova. Podaci su analizirani anonimno kako bi se dobio pregled obrazaca propisivanja i indikacija. Potencijalne pristranosti uključuju pristranost uzorkovanja, prisjećanja i informacija.

Rezultati: Od 154 gerijatrijskih pacijenata, 61% je bilo na PPI terapiji tijekom boravka u bolnici, pri čemu je Pantoprazol 40 mg bio najčešće korišteni PPI. 63.8% pacijenata koji su uzimali PPI nisu imali dokumentiranu kliničku indikaciju za PPI terapiju, što je 39% ukupnog uzorka. Studija je također otkrila da je 44,2% PPI terapija bilo dugotrajno, bez definiranog krajnjeg datuma. Nuspojave su se mogle sumnjati kod 12,3% pacijenata. Demografski podaci uzorka uključivali su prosječnu dob pacijenta od 85 godina, s 70,1% ženskih i 29,9% muških pacijenata. Polifarmacija je bila prisutna u 79,9% pacijenata pri prijemu, što znači da su uzimali više od pet lijekova, te kod 90,3% pri otpustu. Prosječan broj uzetih lijekova bio je 9. Statistički testovi nisu pokazali značajnu korelaciju između dobi, spola i upotrebe PPI-a. Međutim, moguće veze pronađene su između polimedikacije i PPI terapije, kao i između indikacije i PPI.

Zaključak: Ovo istraživanje ispitivalo je učestalost i potrebu za PPI terapijom kod gerijatrijskih pacijenata, otkrivajući da je 61% bilo na PPI terapiji. Većina tih pacijenata nije imala dokumentiranu kliničku indikaciju za upotrebu PPI-a. Dugotrajna terapija bila je posebno česta, što je izazvalo zabrinutost zbog mogućih nuspojava. Osim toga, otkrivena je značajna polifarmacija. Rezultati istraživanja istaknuli su potrebu za poboljšanim praksama propisivanja

i redovitim pregledom lijekova kako bi se osigurala sigurna i odgovarajuća upotreba PPI-a u starijoj populaciji.