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## The consequences of long-term therapy with proton pump inhibitors

Zuzanna Drygała

4th Military Hospital, Weigla Street 5 Street, 53-114 Wrocław

[zuzadrygala@gmail.com](mailto:zuzadrygala@gmail.com)

ORCID ID: 0009-0000-1484-2696

Julia Wyrwał

4th Military Hospital, Weigla Street 5 Street, 53-114 Wrocław

[julia.wyrwal@wp.pl](mailto:julia.wyrwal@wp.pl)

ORCID ID: 0009-0003-2566-3353

Martyna Krasuska

Mikulicz-Radecki University Clinical Hospital in Wrocław, Borowska 213 Street, 50-556

Wrocław

[martynakrasuska102@gmail.com](mailto:martynakrasuska102@gmail.com)

ORCID ID: 0009-0005-1210-3511

Karolina Nowak

Rear Admiral Professor Wiesław Łasiński 7th Military Navy Hospital with Outpatient Clinic  
in Gdańsk, Polanki 117 Street, 80-305 Gdańsk

[karolinanowakmd@gmail.com](mailto:karolinanowakmd@gmail.com)

ORCID ID: 0009-0000-2719-8326

Zuzanna Olejarz

Rear Admiral Professor Wiesław Łasiński 7th Military Navy Hospital with Outpatient Clinic  
in Gdańsk, Polanki 117 Street, 80-305 Gdańsk

[olejarz.zuzanna@gmail.com](mailto:olejarz.zuzanna@gmail.com)

ORCID ID: 0009-0009-3750-7124

Zuzanna Zielińska

St. Alexander Hospital, Kościuszki 25 Street, 25-316 Kielce

[z.zielinska@icloud.com](mailto:z.zielinska@icloud.com)

ORCID ID: 0009-0007-1417-0106

Magdalena Słowik

St. Barbara Specialist Hospital No. 5 in Sosnowiec, Medyków Square 1, 41-200 Sosnowiec

[97magda@gmail.com](mailto:97magda@gmail.com)

ORCID ID: 0009-0006-4337-5277

Karolina Nowak

Rear Admiral Professor Wiesław Łasiński 7th Military Navy Hospital with Outpatient Clinic  
named after in Gdańsk, Polanki 117 Street, 80-305 Gdańsk

[knowak19988@gmail.com](mailto:knowak19988@gmail.com)

ORCID ID: 0009-0007-4885-9622

Maria Nieć

Szpital Specjalistyczny im. Ludwika Rydygiera w Krakowie, os. Złotej Jesieni 1,  
31-826 Kraków

[mniec97@gmail.com](mailto:mniec97@gmail.com)

ORCID ID: 0009-0006-7569-9137

Ludwik Rydygier Specialist Hospital, Złota Jesień 1 Street, 31-826 Kraków

Katarzyna Olga Gierlach

District Railway Hospital in Katowice, Panewnicka 65 Street, 40-760 Katowice

[kaasia.gierlach@gmail.com](mailto:kaasia.gierlach@gmail.com)

ORCID ID: 0009-0004-6767-4875

## **ABSTRACT**

### *Introduction and purpose:*

Proton pump inhibitors (PPIs) were first developed in the late 1970s and introduced to the market in 1989. They are one of the most commonly prescribed medications worldwide.

PPIs reduce gastric acid secretion in the stomach by inhibiting the hydrogen-potassium ATPase enzyme. They have revolutionized the treatment of diseases related to excessive stomach acid secretion. Among the drugs belonging to this class, we should mention omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprasole and rabeprazole.

### *A brief description of the state of knowledge:*

Since the 1990s, the use of proton pump inhibitors has been consistently increasing. Doctors prescribe these drugs more frequently, in higher doses, and for longer durations, although such practices are only sometimes fully justified.

Although using them for a short period (less than eight weeks) is relatively safe, there is growing evidence of possible risks linked to their extended use. Many studies highlight the impact of long-term therapy on the development of tumors, deficiencies in micronutrients, the functioning of the skeletal, urinary, nervous, and cardiovascular systems, and the development of infections and diabetes.

### *Summary (conclusions):*

Indeed, long-term therapy with proton pump inhibitors has an impact on the functioning of the body. Considering the increasing popularity of proton pump inhibitors and their expanding use, it is worth contemplating a more prudent prescription of these drugs by doctors.

It should also be noted that the majority of studies are based on prescription PPIs. Future researchers must also take over-the-counter (OTC) medications into account.

**Keywords:** proton pump inhibitors, gastric acid, omeprazole, lansoprazole, cardiovascular system, micronutrients, diabetes mellitus

## **Introduction**

Proton pump inhibitors (PPIs) are a type of medicine that helps with different stomach issues by regulating the production of stomach acid. They inhibit the potassium and hydrogen ion-dependent ATPase in the gastric parietal cells, reducing stomach acid secretion and raising the stomach's pH.

They are used in the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), dyspepsia, Zollinger-Ellison syndrome, as well as for *H. pylori* eradication, and the treatment and prevention of upper gastrointestinal mucosal damage during long-term therapy with nonsteroidal anti-inflammatory drugs [13].

Proton pump inhibitors (PPIs) rank among the most frequently prescribed types of medications.

According to research, nearly 24% of the adult population worldwide uses PPIs. They were most popular among the population above 65 (37.1%) and below 49 (34.7%). More than half of the patients taking these medications are women. Over 75% of the surveyed population are White, 15.6% are Black or African American, and only 1.3% are Asians. Despite recommending the prescription of proton pump inhibitors for a short duration (below eight weeks) and in low doses, the number of patients using them in high doses (63.7%) and for more than a year (25.1%) continues to rise [1].

## **Mucosal changes**

The research has shown that the changes caused by the use of PPIs include:

- hyperplastic and fundic gland polyps
- cobblestone-like mucosa
- multiple white and flat elevated lesions
- black spots

As a result of reduced gastric acid production, there is an increase in the secretion of gastrin. It has a trophic effect on parietal cells and enterochromaffin cells.

PPIs inhibit gastric acid secretion, causing it to remain in the parietal cells, leading to their enlargement. This takes the form of so-called parietal cell protrusion (PCP). The gastric glands enlarge in a cystic manner, forming polyps (fundic gland type, hyperplastic type, and inflammatory type). According to studies, these changes occur between 8 and 60 months after

the initiation of PPI use [6]. It is worth noting that the polyps decreased after discontinuing the medications [6].

Hyperplastic polyps arise against the background of hyperplasia of the foveolar epithelium of the stomach, which contains gastrin receptors. Gastrin enhances epithelial proliferation through epidermal growth factor and tumor necrosis factor-alpha [6].

Cobblestone-like mucosa refers to raised, uneven changes within the mucous membrane with unchanged color, typically measuring around 3-5 mm. They are usually located between the folds of the stomach [6].

Multiple white and flat elevated lesions are nothing more than sharply defined, white, round, slightly raised fragments of the mucous membrane with a smooth surface. They may be mistakenly identified as intestinal metaplasia. Typically, they are found in the upper part of the corpus and the fundus of the stomach. They differ from polyps without dilated blood vessels [6].

Black spots are pigmented areas of the mucous membrane, mainly located in the corpus and fundus of the stomach. They may resemble blood clots. Their composition has not been fully understood, but they likely contain secretions from the glands of the gastric fundus, such as brown substances and eosinophilic exudates [6].

### **Gastric cancer**

Stomach cancer is among the leading cancers in terms of global occurrence. Proton pump inhibitor therapy may also impact the development of this cancer. The risk may reach up to 80% [19].

PPIs induce changes in the stomach, such as hypergastrinemia, hyperplasia of enterochromaffin-like cells, bacterial overgrowth, and mucosal atrophy. Interestingly, the connection between these phenomena and carcinogenesis was observed even before the described drug group was invented [7]. Studies conducted on animals confirm the hypotheses above; however, observations in humans can be controversial.

Proton pump inhibitors block stomach acid secretion, increasing gastrin production (through a negative feedback mechanism). Gastrin, in turn, acts on enterochromaffin cells, causing their excessive stimulation. There is an extreme expression of cholecystokinin 2, which can result in the development of neuroendocrine tumors [2,18,19].

A low level of stomach acid can lead to bacterial overgrowth and chronic atrophic gastritis. It has been observed that microorganisms from the oral cavity flora develop in the stomach, producing nitrogen compounds that are known carcinogens [18].

In summary, from the available sources, it appears that stomach cancers develop more frequently in individuals who chronically use proton pump inhibitors compared to those who do not use these drugs.

### **Deficiency of vitamin B12**

Vitamin B12 is absorbed in the final part of the small intestine, but first, it must be adequately prepared in the stomach. The vitamin contained in food is non-absorbable because it is bound to proteins. Under the influence of gastric acid and pepsin in the stomach, it can be released from proteins and bind to intrinsic factors essential in absorption. Reducing the production of stomach acid by proton pump inhibitors (PPIs) makes the whole process inefficient. As a consequence, there is a decrease in the absorption of vitamin B12[2,3,7,12].

In other studies, it has been observed that a lower level of vitamin B12 may correlate with bacterial overgrowth occurring in individuals chronically using proton pump inhibitors (PPIs)[2,3].

Indeed, the National Health and Nutrition has published data on vitamin B12 deficiencies - only 3.2% of adults chronically using PPIs experience deficiencies. However, other sources mention that the longer these drugs are used, the higher the risk of deficiency - after two years, it can reach up to 65%[2]. This risk also increases with patients' age. Therefore, the level of vitamin B12 should be monitored in elderly individuals chronically treated with proton pump inhibitors. It has been observed that treatment with cyanocobalamin may benefit and reduce B12 deficiency in these patients [3].

### **Deficiency of magnesium and iron**

During the treatment with proton pump inhibitors, decreased magnesium and iron levels were also observed[2,3,7]. Most likely, this is associated with impaired absorption. More stomach acid levels can result in microelements needing to be adequately prepared, making them unabsorbable. There is a reference to the influence of irregular gut microbiota on absorption.

The FDA warned in 2011 and 2017 about low magnesium levels when using PPIs[7]. Unfortunately, the mechanism is still not fully understood. Proton pump inhibitors (PPIs) are believed to affect specific tiny intestine receptors involved in magnesium absorption, such as TRPM6 and TRPM7.

The iron that we consume through our food is in its trivalent form. To be absorbed in the intestine, ferric iron ( $\text{Fe}^{3+}$ ) needs to be oxidized in the stomach to ferrous iron ( $\text{Fe}^{2+}$ ). This process is possible due to the acidic pH in the stomach and with the help of vitamin C, which is secreted along with stomach acid. The iron levels should be monitored in patients taking PPIs, as they may develop iron-deficiency anemia[2,3].

### **Deficiency of calcium and risk of fractures**

It has been observed that prolonged use of PPIs may affect bone density and increase the risk of fractures[2,4,7].

Proton pump inhibitors (PPIs) lower calcium absorption in the intestines. The acidic pH of the stomach causes insoluble calcium salts to become soluble, making them more readily absorbable in the small intestine. Proton pump inhibitors (PPIs), by increasing the pH in the stomach, inhibit the absorption of calcium [2,4,7,14].

Interestingly, a similar effect was not observed when using H<sub>2</sub>-blockers, which also raise the pH in the stomach[16], so the mechanism described above becomes less likely.

Another mechanism leading to osteoporotic fractures may be an imbalance in the activities of osteoblasts and osteoclasts, along with increased bone resorption[14,15,16].

During in vitro studies, it was inferred that prolonged PPI therapy disrupts the functioning of osteoclasts. Unfortunately, no confirmation has been found in human observations (possibly due to other interfering factors)[17].

The action of parathyroid hormone can also cause bone resorption. Parathyroid hormone induces bone resorption and elevates blood calcium levels by fostering calcium reabsorption in the kidneys and augmenting calcium absorption in the intestine. PPIs, in addition to inhibiting the secretion of HCl in the stomach, also inhibit the secretion of somatostatin by gastric cells. Somatostatin acts in balance with gastrin - a decrease in somatostatin levels is associated with increased gastrin levels. Hypergastrinemia causes hyperplasia of enterochromaffin-like cells (ECL), resulting in increased histamine secretion. Histamine attaches to receptors on osteoclasts, triggering osteoclastogenesis and the process of bone resorption.[14].

Other research has indicated that the utilization of PPIs was linked to heightened calcium and deoxyypyridinoline release. Deoxyypyridinoline, a crosslink contributing to the structural rigidity of type I collagen in bones, suggests that using PPIs may influence crucial elements of bone structure [17].

The statement regarding the relationship between the use of PPIs and changes in bones needs to be well-established, probably due to the presence of many confounding factors.

It's worth noting that in 2010, the FDA issued a warning about an increased risk of spine, wrist, and hip fractures associated with long-term use of proton pump inhibitors (PPIs)[2,7].

### **Renal damage**

The damage to the kidneys has become an important aspect to consider when managing patients taking ACE inhibitors. The initial stage of damage may be acute interstitial nephritis (AIN). The subsequent step could be acute kidney injury (AKI), which, if left untreated, can progress to chronic kidney disease (CKD) and further into end-stage renal disease (ESRD) [2,3,7,20].

During an almost 14-year observation period, it was observed that individuals taking ACE inhibitors have between 20% and 50% higher risk of developing chronic kidney disease compared to those not taking these medications [2,20]. In other cohort studies, where patients were observed for over six years, it was found that the risk increased to 17% and was proportional to the dose taken [2].

The most common adverse effect of ACE inhibitors related to the kidneys is acute kidney injury (AKI). It may account for up to 20% of all AKI cases [3]. ACE inhibitor-induced AKI can develop due to cross-reaction with antigens present on the basement membrane of renal tubules. The drugs act as haptens, stimulating antibody production and forming immune complexes that accumulate in the renal tubules. This damages the kidney parenchyma and endothelial dysfunction [3]. This process leads to acute interstitial nephritis (AIN) and acute kidney injury (AKI) [3,7].

Chronic use of ACE inhibitors can also lead to hypomagnesemia, which can consequently result in endothelial dysfunction and increased oxidative stress. In the long term, this may lead to kidney fibrosis and the development of chronic kidney damage [3,7].

In summary, studies suggest that the use of ACE inhibitors may be associated with kidney damage. Particular caution should be exercised in elderly patients, those taking ACE inhibitors for a prolonged period, and those with pre-existing kidney diseases. Monitoring kidney function is essential, and in case of initial signs of damage, discontinuation of the medication and consideration of steroid therapy may be warranted. H2 receptor antagonists may be a better choice for patients needing to reduce gastric acid secretion [3].



## **Cardiovascular risk**

People suffering from cardiovascular diseases typically use many medications, including anticoagulants, which may predispose them to gastrointestinal bleeding. For this reason, they take proton pump inhibitors (PPIs) to prevent bleeding.

The observation indicates that prolonged use of proton pump inhibitors (PPIs) alone may predispose to the development of cardiovascular diseases, but unfortunately, the collected data are not conclusive. Various acute conditions are mentioned, such as acute coronary syndromes, ischemic stroke, arrhythmias, or stent thrombosis [2,3,22].

Among the studied individuals above 65 years old, increased mortality has been demonstrated compared to those not taking proton pump inhibitors (PPIs). However, it's important to note that the study only included white male participants, which makes its reliability questionable [2].

The impact of proton pump inhibitors (PPIs) on the cardiovascular system is multifaceted. These medications inhibit dimethylarginine dimethylaminohydrolase (ADHD), which is responsible for the breakdown of dimethylarginine (ADMA). This, in turn, reduces the synthesis of nitric oxide, resulting in decreased vascular dilation [2,7,22]. Opponents of this theory argue that the concentrations of drugs used in practice are so low that they would not be able to produce such an effect [2].

Proton pump inhibitors (PPIs) may also reduce the levels of anti-atherogenic chemokines in the endothelium of coronary vessels. Additionally, this could lead to an acceleration of vascular aging and an intensification of oxidative stress [2,22].

Proton pump inhibitors (PPIs) may also induce a negative inotropic effect, which is unfavorable for patients with heart failure [2].

It's worth noting that in 2009, the FDA issued a warning regarding the potential interaction between PPIs and clopidogrel. Both drugs were thought to compete for cytochrome CYP2C19, which could diminish the antiplatelet effect [2,3,22]. However, subsequent studies indicated that the increased risk of cardiovascular events is more likely associated with the use of PPIs themselves rather than their interaction with clopidogrel [21].

At this moment, there is still no conclusive evidence of the adverse effects of proton pump inhibitors (PPIs) on patients with cardiovascular diseases. More randomized studies are needed to delve into potential interactions and negative effects.

The benefits of using proton pump inhibitors (PPIs) outweigh the risks, so discontinuing the prescription of PPIs for patients taking anticoagulant medications is not recommended. This conclusion is supported by the COGENT study, which found that individuals taking only

clopidogrel and those taking clopidogrel in combination with PPIs had a similar mortality rate [21]. However, another study in 2012 indicated that patients taking PPIs had a higher risk of cardiovascular events. Some reports suggest switching from PPIs to H2 receptor antagonists [2,3]. Follow-up studies have shown that using H2 receptor antagonists does not increase the risk of cardiovascular events [21].

## **Dementia**

Recent research indicates that the usage of proton pump inhibitors may influence the onset of cognitive disorders. [7,8]. However, most of them had an observational nature, thus requiring confirmation in controlled randomized trials.

The etiopathogenesis of Alzheimer's disease is varied and not fully understood. However, one of the theories is beta-amyloid accumulation in the brain.

Beta-amyloid is removed by lysosomes, which require an acidic environment provided by proton pumps for proper functioning. PPIs block the acidification of lysosomes, causing them to be less efficient in removing  $\beta$ -amyloid and other harmful substances [7,8,9,10,11].

Another theory regarding Alzheimer's disease is associated with a reduced concentration of vitamin B12. A deficiency in vitamin B12 leads to a decrease in the synthesis of deoxyribonucleic acid (DNA) and an increased level of homocysteine (which is neurotoxic), resulting in cognitive function disorders [7].

## **Infections**

There are many reports about an increased risk of intestinal and extraintestinal infections among individuals using proton pump inhibitors [2,3]. Among the probable causes of infections, factors such as an increase in gastric pH, changes in intercellular connections, and an anti-neutrophil effect are mentioned. As known, PPIs raise the pH of the gastric environment, negatively affecting the body's natural defense mechanisms. Under hypochlorhydria conditions, bacteria can more easily enter the gastrointestinal tract, developing various infections [23]. H<sup>+</sup>-ATPase is also present in neutrophils and endothelial cells, potentially influencing PPIs. These drugs may be responsible for a decrease in mRNA expression, inhibiting the production of IL-1 $\beta$  and TNF- $\alpha$ . They might also decrease the function of natural killer (NK) cells [23,27].

Among individuals using PPIs, a higher tendency for *Clostridium difficile* infections has also been observed - up to 65% of patients were infected [2,23]. One hypothesis is based on the earlier mechanism involving a reduced amount of stomach acid. Although the spores are

resistant to acid, the vegetative forms are not. Therefore, an increase in pH is responsible for the survival of vegetative forms and colonization of the intestine [3,7,24,25]. However, recent studies have challenged this hypothesis. The increase in pH is likely associated with the cessation of the body's natural defense mechanism and excessive bacterial overgrowth in the intestine [23,25]. Changes in the microbiota, in turn, predispose to infections with *Clostridium difficile*, as well as *Campylobacter* and *Salmonella* [3,12,23].

In 2012, the FDA warned about the increased risk of infection associated with the use of PPIs [7].

As mentioned earlier, the elevated pH allows more bacteria to survive, leading to excessive bacterial overgrowth and the development of Small Intestinal Bacterial Overgrowth (SIBO). Research results are inconclusive. Some meta-analyses have shown a higher occurrence of SIBO in individuals using PPIs, while others have not observed a significant association between drug use and SIBO [2,3,23]. However, it is essential to keep this in mind and consider it in patients with recurrent diarrhea.

In a study of patients suffering from liver cirrhosis and ascites, the use of PPIs was identified as a risk factor for peritonitis, with the risk doubling compared to patients who did not use these drugs. However, these results are controversial, as other studies have not confirmed this hypothesis [2,3].

There is also an observed higher susceptibility to pneumonia in patients using PPIs. The overall risk was higher by 73% [3,12,26]. Interestingly, the risk was greater during the first 30 days of therapy, contrary to other adverse effects associated with PPI therapy [3]. Bacteria that more easily enter the upper gastrointestinal tract may also migrate to the respiratory tract [3,7,26].

Intestinal dysbiosis and SIBO are associated with increased intestinal permeability, which, in turn, can lead to the passage of pathogens into the bloodstream and immune system dysfunction. However, the gathered data provide diverse evidence, so further research is necessary [3].

Several scientific investigations have suggested that the utilization of proton pump inhibitors (PPIs) raises the likelihood of contracting COVID-19 and also amplifies the mortality associated with illness caused by the coronavirus [7,27]. The virus binds to ACE-2 receptors on type 2 lung alveolar cells using specific proteins on its surface. The gastrointestinal tract is also rich in these receptors, so individuals using PPIs may be more susceptible to infection [27].

Researchers continue to explore ways to alleviate the adverse effects caused by proton pump inhibitors (PPIs). Probiotics containing strains such as *Lactobacillus reuteri*, *L. rhamnosus*, or *L. pentosus* may help mitigate changes in gut microbiota [23].

## **Diabetes**

Among the undesirable effects, the development of diabetes is also considered. Nevertheless, conflicting outcomes have emerged from observational studies, and no randomized clinical trials have been conducted.

During a study conducted in Italy, prolonged usage of proton pump inhibitors (PPIs) was associated with an elevated risk of developing diabetes. The estimated increase in risk was approximately 24% [5].

The pathomechanism of diabetes development may be associated with changes in the gut microbiota. Bacteria in the small intestine break down undigested carbohydrates into fatty acids. They act anti-inflammatory by producing immunoglobulin A and immunosuppressive cytokines. They also influence the secretion of glucagon-like peptide-1 (GLP-1), which is an incretin hormone. GLP-1 is responsible for delayed gastric emptying, decreased appetite, and insulin and glucagon secretion. Changes in the microbiota can, therefore, affect glucose homeostasis [5,28,29].

Furthermore, damage to the epithelium may also promote the increased entry of bacterial components into the portal circulation. These phenomena may result in insulin resistance and the development of non-alcoholic liver inflammation [5,28].

PPIs may also influence the regulation of glucose levels by the liver by reducing the production of IGF-1 [5,29]. IGF-1 positively impacts carbohydrate metabolism, improving insulin sensitivity and reducing glucose production in the liver. Low levels of IGF-1 have been observed in obesity, diabetes, and metabolic syndrome [29].

Another mechanism may result from the activation of the nuclear receptor pregnane X (PXR), which also influences glucose metabolism in the liver. While the activation of PXR (pregnane X receptor) suppresses gluconeogenesis, it also hinders the glucose transporter in the liver, thereby playing a role in the onset of diabetes [29].

The decrease in gastric acid secretion leads to hypergastrinemia, which induces the formation of pancreatic beta cells that secrete insulin. Continued stimulation results in the exhaustion of reserves, ultimately leading to the onset of diabetes [28,29].

Hypomagnesemia caused by PPIs may lead to insulin resistance [29]. Studies also suggest a beneficial impact of PPIs on glucose levels, indicating a 20% reduction in the risk of

developing diabetes [28,29]. However, more credible sources tend to highlight articles regarding the unfavorable effects of PPIs on diabetic metabolism.

Based on the above conclusions, it is essential to exercise increased vigilance towards patients who use PPIs for an extended period and in higher doses. Special consideration should be directed towards individuals with risk factors predisposing them to the onset of diabetes.

### **Summary**

Proton pump inhibitors (PPIs) are among the leading prescribed medications globally. In recent years, numerous studies and articles have emerged regarding the adverse effects associated with the use of these drugs. Factors such as the dosage and duration of therapy have been considered. Unfortunately, most of these studies were observational, lacking standardized, randomized trials to confirm the drawn conclusions. It is advisable to recommend PPIs to patients more judiciously, as it is estimated that 25% to even 70% of prescribed drugs in this category lack appropriate indications. As a result, patients take medications without benefit and are exposed to unnecessary adverse effects. It should also be considered whether PPIs should belong to the group of over-the-counter drugs, as this would result in a lack of control over dosage and therapy duration.

### **KEYWORDS:**

proton pump inhibitors; gastric acid; omeprazole; lansoprazole; cardiovascular system; micronutrients; diabetes mellitus

Conceptualization, supervision and project administration: Zuzanna Drygała, Julia Wyrwał, Martyna Krasuska

Methodology: Karolina Nowak, Zuzanna Zielińska, Zuzanna Olejarz, Maria Nieć, Julia Wyrwał

Software, validation, formal analysis, investigation, resources, writing original draft preparation: Martyna Krasuska, Zuzanna Drygała, Magdalena Słowik

Writing review editing and visualization: Katarzyna Gierlach, Karolina Nowak, Magdalena Słowik

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