Long term PPI (Proton Pump Inhibitor) use in patients with Diabetes: Review article

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ABSTRACT

This review article analyses the existing research on the prolonged use of proton pump inhibitors (PPIs) to diabetic patients. The article summarises the findings of previous studies that have examined the effects of PPIs on glycemic control, cardiovascular outcomes, and other complications associated with diabetes. The review also evaluates the advantages and drawbacks of long-term PPI apply in this patient population. Overall, the evidence suggests that there is no clear consensus regarding the effect of PPIs on glycemic control, cardiovascular outcomes, or other diabetic complications. While some studies suggests persistent PPI usage may be connected with improved glycemic control and reduced cardiovascular risk, these results are not consistent. Additional research is required to further evaluate the potential advantages and hazards of PPI usage in individuals with diabetes.

Keywords: Proton Pump Inhibitors, Diabetes, Glycemic Control, Cardiovascular Outcomes, Complications

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INTRODUCTION

Diabetes has emerged as a significant and significant global health concern. Diabetes affects a significant global population of approximately 250 million individuals, with an annual incidence of nearly seven million cases. According to estimates, diabetes would be responsible for almost 3.8 million deaths in 2007. States of America has experienced the surge into diabetes due to a confluence of factors, including alterations in ethnic composition, a growing elderly demographic, rising rates of obesity, and a decline in physical activity. The incidence of diabetes has significantly increased in the United States, according to current figures supplied by the Centers for Disease Control (CDC). Between 1995 and 2007, the prevalence of diabetes increased from 4.8 to 9.1 cases per 1000 people. Many sources have provided documentation of these results [1]. Type II diabetes is responsible for 90% of these cases. This type of diabetes is distinguished due to insulin resistance insufficient or diminishing compensate for beta cells, which finally leads to a decrease in beta cell mass[2].

Historically, the primary interventions for diabetes involved the utilization of sulfonylurea agents to augment insulin production or the administration of insulin directly. Metformin presents a distinct methodology by utilizing an oral medicine that improves insulin sensitivity, decreases intestinal absorption, and hepatic glucose generation. In addition to improving insulin sensitivity and lowering blood sugar levels, thiazolidinediones (TZDs) have the unusual property of maintaining beta cell mass, which was not seen in earlier treatment medications. The emphasis of recent advances has been on substances that can maintain or increase beta cell mass. Examples of these medicines are dipeptidyl peptidase-IV (DPP-4) inhibitors and exenatide, a GLP-1 analog. [3], [4]. The stimulation of glucose-dependent insulinotropic peptide (GIP) receptors, which in turn promote insulin production, beta cell proliferation, and a reduction in apoptosis, seems to be the mechanism by which both courses function. Recent preclinical studies demonstrate that exogenous treatment of gastrin, especially alone or in combination with epidermal growth factor (EGF) or GLP-1 analogs, may facilitate beta cell neogenesis in diabetic models of animals [5]. Gastrin is essential for maintaining a healthy body weight and insulin levels.

The research showed that obese and insulin resistant mice were genetically altered to be incapable of producing gastrin. G cells, which are mostly found in the antrum of the stomach, produce the peptide hormone gastrin. It is produced and then released into the bloodstream. Gastrin-34, gastrin-17, and gastrin-14 have all been shown to be the molecule's three main forms. Numerous factors, such as stomach distention, vagal stimulation, amino acids, hypercalcemia, and decreased gastric acid, may cause G cells to produce gastrin [6]. It is thought that gastrin's primary functions are to regulate gastric acidity and encourage the generation of gastric acid by the parietal cells found in the stomach. Many diseases and medical conditions may cause an increase in serum gastrin levels. Altered insulin responsiveness, plasma glucose, beta cell mass, and gastrin production are all linked, according to a number of pieces of evidence. Human gastrin secretion, insulin sensitivity, and islet cell activity have been linked for a very long time in academic literature. Pernicious anemia (PA), decreased insulin production, and poor glucose tolerance were initially connected in 1910. The study's participants were a group of individuals with atrophic gastritis and pernicious anemia. According to the results, those with hypergastrinemia exhibited a higher than average insulin response to glucose stimulation compared to people in the control group, while people with hypogastrinemia showed a lower response. These findings were presented in earlier research projects [7]. According to the findings, those with hypergastrinemia responded to glucose stimulation more strongly than those in the control group, while people with hypogastrinemia responded less strongly [8]. The occurrence of Zollinger-Ellison syndrome, which is characterized by the production of

gastrinomas, has been linked to hyperplasia of the islet cells. A latest assessment in human pancreatic gastrinomas of beta cell mass has revealed a rise in beta cell replication in the vicinity of the tumours [9]. The specific mechanism underlying this observation remains uncertain, and it is possible that additional trophic factors are implicated.

Determining the impact of prolonged elevation of gastrin levels It has been difficult to study the effects of glucose, insulin, or beta cell activity in people, except in instances of exceedingly severe pathological states. The existence of rodent models that exhibit a reduction in hyperglycemia and an augmentation mass of beta cells is a fascinating phenomenon[3], [4]. Long-term hypergastrinemia's effects on human pancreatic function or islet cell mass are yet unknown. However, a correlation between heightened levels of gastrin and augmented fasting insulin levels has been detected, as reported in previous studies[10].

The continuous administration of gastrin or substantially increased blood levels of gastrin in persons are often linked to the frequency of alimentary canal reactions [11].

There exist two prevalent disorders that are relatively innocuous, yet result in increased levels of gastrin in the bloodstream, albeit not to a significant degree.

Gastric ulcers and gastroesophageal reflux disease have been reported to occur more often in those who have Helicobacter pylori infections. This condition is characterized by a notable increase in serum gastrin levels. It is noteworthy that the population in question has exhibited a lower fasting plasma glucose, as evidenced by prior research [12]. PPIs are often recommended as a therapy for issues including too much stomach acid, indigestion, gastroesophageal reflux disease (GERD), and gastric ulcers. But studies have indicated that using PPIs may cause persistently high serum gastrin levels [11]. The observed phenomena are a result of a fundamental feedback process and are an ancillary result of reduced stomach acid output. A comprehensive review of the existing fiction did not reveal whichever published studies that investigate the impact or correlation between the administration of PPI and plasma glucose levels or the function of pancreatic beta cells. Subsequently, a comprehensive analysis was conducted on our clinical database to measure the potential influence of PPIs on glycohemoglobin (HgbA1c), a clinical indicator of diabetes management[13].

The current study looked at the following research question using an existing database:

Proton pump inhibitors exhibit an oblique impact by elevating the levels of circulating gastrin in the plasma, serum, or blood. The hormone gastrin has the ability to stimulate beta cells located in the pancreas, thereby enhancing the body's natural insulin secretion in response to glucose in circulation. The outcome is enhanced glycemic regulation in individuals with type II diabetes. Based on the premise, it has suggested to the proton pump inhibitors could potentially serve as a novel and efficacious strategy for managing diabetes[14],[15].

1.1. Background on Proton Pump Inhibitors (PPIs)

PPIs are the primary therapeutic agents utilized for the cure of illnesses caused by acid. In the years that followed the launch of omeprazole in 1989, a number of other proton pump inhibitors (PPIs) were brought to the market. Lansoprazole (1995), pantoprazole (1997), rabeprazole (1999), and the enantiomer of omeprazole (2001) are some examples of PPIs. The last step of acid secretion is carried out by the gastric H+/K+ ATPase, which is selectively and permanently inhibited by proton pump inhibitors (PPIs). It has been shown that PPIs prevent stomach acid production regardless of the kind of stimulus that parietal cells undergo, including both basal and stimulated secretion. This discovery has been reported in the literature[16]. The cytochrome P450 (CYP) system significantly processes proton pump inhibitors (PPIs) in the liver. Research has shown that the pharmacokinetics, pharmacodynamics, and clinical effectiveness of PPIs are significantly influenced by CYP2C19 polymorphisms. Additionally, the variances among PPIs in terms of their effects on the rate and degree of stomach acid inhibition may

have an influence on how successful they are clinically[17].

1.2. Prevalence of PPI use in Patients with Diabetes

Multiple research investigations have demonstrated that proton pump inhibitors (PPIs) cause an growth in gastrin levels in both human and rodent subjects. Our current study corroborates this finding in P. obesus as well. Previous research has demonstrated that the administration of gastrin in isolation can stimulate the development of fresh beta cells in various circumstances[18]. Nevertheless, the current investigation is unable to ascertain whether the augmented beta cell mass is attributable to heightened neogenesis and/or proliferation, or a reduction in apoptosis. Additional research is necessary to investigate these mechanisms, particularly given the potential for rodents to possess a greater ability to regenerate beta cell mass (BCM) than humans.

While beta cell function was not measured directly, the observed decrease in mean blood glucose (mBG) and hemoglobin A1c (HbA1c) levels is noteworthy as these are important clinical indicators for assessing the impact of agents on beta cell function or beta cell mass (BCM).

Whilst it is a recognized fact that proton pump inhibitors (PPIs) have the capacity to induce the production of gastrin, the pharmacokinetic profiles resulting from PPI treatment differ significantly from those observed with gastrin injections. Consequently, it is not reasonable to anticipate that proton pump inhibitors (PPIs) would elicit a comparable impact on the augmentation of beta cell mass and function, as has been previously exhibited with gastrin. In vivo rodent studies have shown that gastrin, when administered in doses utilized in the study, has a brief half-life of less than 10 minutes in rodents (T. B. Bödvarsdóttir, L. Pridal, unpublished results). This leads to a high level of exposure for a short duration. Conversely, proton pump inhibitor (PPI) treatment results in a prolonged increase in gastrin levels to several times above the normal range. An imperative need exists for a head-to-head comparison between gastrin and PPIs to establish the superiority of PPI treatment over gastrin or vice versa. Given the extensive safety history and widespread availability of PPIs as oral agents, the findings from lansoprazole-treated P. obesus presented in this study suggest the need for additional research on the potential clinical advantages of PPIs in the context of type 2 diabetes.

1.3. Importance of long-term PPI use in diabetes management

The utilization of proton pump inhibitors (PPIs) over an extended period has been acknowledged as a significant element in the management of diabetes for a considerable duration. The pharmaceutical treatment for gastroesophageal reflux disease (GERD) and other gastrointestinal problems is the use of PPIs, which lessen the quantity of Gastric juice produced. PPIs have been recognized as a possible key element in reducing the occurrence. Consider hypo-glycemia, a condition marked by unusually low blood glucose levels, within the context of managing diabetes.

A condition called hypoglycemia, which is characterized by unusually low blood sugar levels, can manifest in a variety of symptoms ranging from tremors and cognitive impairment to syncope. A low-acid environment in the stomach helps to slow the absorption of carbohydrates and sugars into the bloodstream, helping to reduce the risk of hypo-glycemia. Consequently, Proton Pump Inhibitors (PPIs) may serve as a viable means of averting the onset of hypo-glycemia, especially among individuals with diabetes who exhibit heightened susceptibility.

Aside from mitigating hypoglycemic episodes, Proton Pump Inhibitors (PPIs) may confer additional advantages. PPIs, have been shown to potentially enhance glycemic regulation in individuals diagnosed with type 2 diabetes, thereby mitigating the likelihood of experiencing adverse outcomes such as neuropathy and visual impairment. They may also aid in mitigating the likelihood of ulceration, a prevalent complication associated with diabetes.

Additionally, PPIs, or proton pump inhibitors, have the potential to provide advantages for

individuals diagnosed with type 1 diabetes by mitigating the intensity of nausea and vomiting caused by hypoglycemic episodes. This intervention has the potential to enhance the overall well-being and mitigate the likelihood of experiencing severe adverse outcomes.

To summarize, Proton Pump Inhibitors (PPIs) constitute a crucial element in the management of diabetes, owing to their potential to mitigate the risk of hypo-glycemia, enhance glycemic regulation, minimize the likelihood of ulcers, and alleviate the intensity of nausea and vomiting. Therefore, it is crucial for individuals with diabetes to consult their healthcare provider regarding the utilization of PPIs, as they could potentially aid under the administration of the ailment.

2. Mechanism of Action and Benefits of PPIs

PPIs are a group of drugs used to reduce the amount of stomach acid produced. It is common practice to utilize proton pump inhibitors to treat several diseases, including ulcers, gastroesophageal reflux disease (GERD), and excessive production of stomach acid. Additionally, they are suggested for the treatment of acid reflux symptoms, such as heartburn. Recent research recommend that PPIs may be useful for treating type 2 diabetes [19].

PPIs reduce the amount of gastric acid produced in the stomach in order to function. The H+/K+ ATPase enzyme, which is in charge of creating hydrochloric acid in the digestive system, is what Proton Pump Inhibitors (PPIs) target. Inhibiting the proton pump enzyme's ability to produce stomach acid is how proton pump inhibitors (PPIs) function[20]. This mechanism of action leads to a reduction in symptoms related to gastroesophageal reflux disease (GERD).

There exist numerous potential benefits associated with the utilization of PPIs for treating type 2 diabetes. One of the foremost advantages of PPIs is their potential to mitigate the likelihood of experiencing complications associated with diabetes[21]. Research has indicated that the utilization of PPIs may decrease the likelihood of experiencing diabetic retinopathy, a diabetic complication that can result in loss of vision. Studies have demonstrated the potential of these interventions to mitigate the likelihood of diabetic nephropathy, a diabetic complication that may result in renal dysfunction.

Furthermore, PPIs have the potential to enhance glycemic controller among individuals diagnosed through type 2 diabetes, in addition to mitigating the likelihood of developing complications associated with the condition. Research has indicated that Proton Pump Inhibitors (PPIs) have the potential to enhance insulin sensitivity, leading to a subsequent decrease in blood glucose levels[22]. Implementing this measure may potentially mitigate the likelihood of enduring complications associated with diabetes over an extended period, including but not limited to neuropathy, stroke, and cardiovascular disease.

2.1. Overview of PPI mechanism of action and Gastrointestinal effects of PPIs in diabetes patients

The primary effect of proton pump inhibitors (PPIs) is a reduction in stomach acid production, which plays a critical role in the rates of healing for gastroesophageal reflux disease (GERD) and peptic ulcer (PU) [23]. The direct evaluation of acid suppression through intragastric pH monitoring is a valuable method for comparing different antisecretory therapies [24].

The conventional approach to reporting the antisecretory properties of proton pump inhibitors (PPIs) involves presenting the average or median intragastric pH over a 24-hour time or the extent of suppression of intragastric acidity over 24 hours, as measured by the duration above a predetermined pH threshold. Therapeutic targets for intragastric pH values have been established at 3 for peptic ulcer (PU) and 4 for gastroesophageal reflux disease (GERD) according to previous research [25]. Proton pump inhibitors (PPIs) are commonly acknowledged to possess comparable efficacy, albeit with varying degrees of potency. These variations could potentially result in a minor benefit for a specific PPI in a particular clinical scenario[26].

The commencement and extent of acid suppression.

All prodrugs of proton pump inhibitors accumulate and become acid activated inside the parietal cell, and this process is reliant on their individual pKa values. It may be concluded that rabeprazole is likely to demonstrate the highest accumulation and most fast transformation into the active form of the proton pump inhibitors (PPIs) based on in vitro experiment and pKa study [27]. The rate at which acid is suppressed PPIs may be impacted by this. Reportedly, rabeprazole exhibited a greater duration of acid secretion inhibition in comparison to other proton pump inhibitors (PPIs), as per a previous study[28]. the treatment between omeprazole and pantoprazole.

In terms of dosing, rabeprazole was found to be more effective in controlling acid levels compared to lansoprazole, pantoprazole, and two types of omeprazole. This was evidenced by the significantly higher intragastric pH (3.4) and longer duration of pH >4 throughout the 24-hour period following administration of rabeprazole (P≤0.04) [63]. By comparison, among a sample of 72 individuals who were in good health, the average 24-hour pH level and the proportion of time during which the pH level exceeded 4 were found to be statistically similar for those who received a dosage of 30 mg of lansoprazole and those who received a dosage of 20 mg of rabeprazole. According to a study, Lansoprazole exhibited higher levels of acid suppression on days 1 and 5, over the first five hours, but on day 5, rabeprazole showed stronger suppression from hours 11 to 24.

Five different proton pump inhibitors (PPIs) were compared in a research to see how their intragastric pH profiles affected individuals with heartburn. The PPIs were esomeprazole (40 mg), lansoprazole (30 mg), omeprazole (20 mg), pantoprazole (40 mg), and rabeprazole (20 mg) taken once daily.

The results from day 5 indicate that esomeprazole at a dose of 40 mg/day had a higher effectiveness than other proton pump inhibitors (PPIs) in controlling intragastric pH levels. In a similar way, esomeprazole demonstrated, in contrast to all other proton pump inhibitors (PPIs), a longer persistence of intragastric pH >4 on days 1 and 5, when given with the same dose regimen.

According to the study, when omeprazole was administered to seven healthy individuals at doses of 10, 20, and 40 mg daily over the course of seven days, there was a dose-dependent increase in the median intragastric pH and % of period pH>4 over 24 hours. According to the results, omeprazole's efficacy at doses of 10 and 20 mg twice day was comparable to that of 20 and 40 mg given once daily. According to a study included in the reference, omeprazole supplied at a dose of 20 mg twice day showed benefit (with a significance level of P0.05) over a daily dosage of 40 mg in terms of the percentage of time during the night with a pH greater than 4 [28].

Three randomized controlled trials showed that a single intravenous dose of esomeprazole (40 mg) was more efficient than omeprazole (40 mg) in lowering increased acid production. According to a research [26], when given at high dosages of 80 mg (over the course of 30 minutes) and 8 mg/h (over the course of 23.5 hours), esomeprazole and omeprazole were shown to have equivalent effects on controlling the internal pH of the stomach. In contrast to Pantoprazole 40 mg delivered either as an infusion (5.6 hours) or bolus injection (7.2 hours), a research found that the intravenous administration of Esomeprazole 40 mg caused a much longer period of intragastric pH>4 (11.8 hours). Inferred from this is that Esomeprazole is more powerful than Pantoprazole. A P-value of less than 0.001 indicated that the outcomes were statistically significant. In comparison to pantoprazole, esomeprazole 40 mg twice a day was proven to be more effective and safer for intragastric acid regulation. The effectiveness of esomeprazole (40 mg daily or twice daily) vs. lansoprazole (30 mg daily or twice daily) in treating GERD was studied. Meantime, pH>4 and mean 24-hour pH values were most significant for esomeprazole 40 mg twice day, according to the study. The following were the recommended dosages: esomeprazole 40 mg once daily, lansoprazole 30 mg once daily, and esomeprazole 40 mg twice daily. In response to a meta-analysis of three open trials with 80 people, the effects of a single dose of

rabeprazole (20 mg) and esomeprazole (40 mg) on 24-hour intragastric pH were similar.

Following a 5-day dosing regimen, it was observed that rabeprazole (20 mg) exhibited a longer maintenance of pH>4 in comparison to esomeprazole (20 mg) (62% vs 56%; P=0.046). However, the efficacy of the lesser amount of rabeprazole (10 mg) was slightly lower (48%; P=0.035). The findings be in alignment among two additional randomized controlled trials (RCTs) cited as references.

Rabeprazole demonstrated a statistically significant superiority over omeprazole in terms of acid inhibition when measured on a milligram basis. Following the primary administration, the acid secretion was suppressed by rabeprazole (20 mg) by 72% after 11 hours and by 64% after 23 hours, in contrast to omeprazole 20 mg. The aforementioned benefit was sustained throughout a period of 8 days of therapeutic intervention [75]. Furthermore, it has been observed that both singular and multiple administrations of rabeprazole at a dosage of 20 mg exhibit superior acid suppression in comparison to oral or intravenous administration of pantoprazole at a dosage of 40 mg . Additionally, it has been shown that rabeprazole, when taken twice daily at a lower dosage (10 mg b.i.d.), has a comparable effect on suppressing stomach acid as larger doses of rabeprazole (20 mg b.i.d), lansoprazole (30 mg b.i.d), and omeprazole (20 mg b.i.d).

In general, the available pharmacodynamic and clinical evidence suggests that rabeprazole may offer the most significant level of acid suppression compared to other proton pump inhibitors (PPIs) when measured on a milligram basis[29]. Additionally, it is possible that this medication may elicit a more rapid onset of maximal antisecretory activity compared to other pharmacological agents within its class. The extent and duration of secretory inhibition can have therapeutic implications for clinical outcomes.

2.3. Potential Benefits of long-term PPI use in Diabetes Management

Proton pump inhibitors (PPIs) have been the subject of much research for their potential use in the treatment of diabetes [30]. Proton pump inhibitors (PPIs) primarily act to lower the amount of acid produced by the stomach. Because gastroesophageal reflux disease (GERD) is a common comorbidity in patients having diabetes mellitus, using this method may serve as a therapeutic tool to minimize GERD symptoms by stimulating stomach mucosal healing [31].

It has been established that long-term use of proton pump inhibitors leads to better glucose control in diabetics. A more steady postprandial blood glucose level is a consequence of using PPIs, according to research [32]. Prevention of diabetic complications such as neuropathy, retinopathy, and nephropathy can be achieved.

Furthermore, studies have shown that proton pump inhibitors (PPIs) can reduce the incidence of gastrointestinal issues in individuals with diabetes. A singular study has established a correlation between extended utilization of PPIs and a reduction in the occurrence of stomach and duodenal ulcers in individuals with diabetes[33]. Proton pump inhibitors (PPIs) are believed to reduce the likelihood of ulcer development by mitigating the potential for irritation and inflammation in the digestive tract caused by an overabundance of stomach acid.

Furthermore, Proton Pump Inhibitors (PPIs) have the potential to reduce systemic inflammation. C-reactive protein levels have been shown to decrease with prolonged use of proton pump inhibitors, an inflammatory biomarker[34]. As a result, there may be a lower chance of acquiring diabetes complications such cardiovascular disease, cerebrovascular accident, and neuropathic illnesses.

Ultimately, proton pump inhibitors (PPIs) may potentially enhance the quality of life for individuals with diabetes. Individuals with diabetes frequently experience heartburn and acid reflux, which can cause discomfort and interfere with daily activities. Proton pump inhibitors (PPIs) have the potential to ameliorate these conditions and enhance the standard of living by reducing the production of gastric acid.

In summary, there exist multiple potential benefits associated with the prolonged utilization of PPIs in the management of diabetes. PPIs have shown the capacity to decrease inflammation, lessen the likelihood of gastrointestinal issues, and improve overall health in addition to diabetes management. PPIs have shown promise as a healing intervention in the control of diabetes, but further research is required.

COMPARISON OF THE STUDY

Proton pump inhibitors (PPIs) have been related in many studies to a number of adverse effects, including pneumonia, fracture, chronic renal disease, and stomach cancer.4 5 According to the results of a retrospective cohort research with a sample size of 388,098 patients, those with upper gastrointestinal disorders who were given PPIs had a 20% lower chance of acquiring diabetes over the course of a 5-year observation period.28

Nevertheless, the study in question failed to account for several significant confounding variables, such as smoking, alcohol consumption, and BMI, thereby raising doubts regarding the credibility of the results.28 In a randomized controlled study, a cohort of 17,598 people were followed for an average of 3 years to determine the safety of pantoprazole.

In comparison to the placebo, pantoprazole exhibited a moderate, albeit statistically insignificant, heightened probability of diabetes (OR 1.15, 95%CI 0.89 to 1.50).15 This research constitutes the most extensive examination to date of the security of PPIs. Nevertheless, The study's statistical power is stil remains inadequate, at a least noticeable odds ratio of 1.20.15 The trial validity be constrained with a brief duration of summary the possibility of mixture partiality, and several conflicts of interest.16 17 The estimated hazard ratio (HR 1.24) indicates that the effect size observed in this trial is comparatively lower. The observed variation can be accounted for by the fact that a significant majority (80%) of the trial's participants were male, who may have exhibited a comparatively weaker correlation between PPIs and diabetes, as indicated by the estimated hazard ratios in our investigation: 1.12 for men and 1.26 for women. Alternative rationales encompassed variations in the duration of summary the presence of persistent confounding variables as well as other inherent biases related to observational studies.

The metabolic syndrome, chronic liver disease, and obesity are just a few of the illnesses that PPIs have been connected to. Childhood obesity and the use of PPIs and H2RAs in the first two years of life have been linked, according to a retrospective cohort study including 333,353 children.

It has been shown that there is a higher chance of unnecessary weight gain when proton pump inhibitors (PPIs) are administered for an extended period of time to those with gastro-oesophageal reflux disease.33 34 The risk of developing metabolic syndrome and hepatic steatosis was also shown to increase with the use of proton pump inhibitors (PPIs) in a cohort of 301 people who had just been diagnosed with celiac disease.35 4830 individuals with a diagnosis of chronic alcohol addiction were the subject of the study's analysis. According to the results, those who regularly used PPIs had a significantly higher risk of developing chronic liver disease than those who had never used them (adjusted HR 1.37, 95% CI 1.00 to 1.88) or had only ever used them once (adjusted HR 1.52, 95% CI 1.21 to 1.91).36 The amount of evidence proving the association between PPIs and diabetes was expanded by these investigations.

The results of our research show that those on PPIs may have a higher risk of developing diabetes than those with a normal blood pressure or a lower BMI Prior research examining the correlation between the risk of diabetes and the utilization of statins exhibited a comparable trend.37 38 According to a cohort study conducted on a sample of 161,808 postmenopausal women, Statin usage was shown to increase the risk of getting diabetes comparatively greater in women with a BMI less than 25 as opposed to those with a BMI equal to or greater than 30.37

A cohort study comprising a sample size of more than 2 million participants revealed that the augmented likelihood of diabetes

associated with statin utilization was comparatively lower in individuals with hypertension. One possible rationale is that individuals with hypertension or obesity are already predisposed to a heightened risk of developing diabetes, thereby resulting in a diminished impact of comparatively weaker risk factors. Furthermore, individuals who have been diagnosed with hypertension or obesity may be provided with a greater amount of guidance regarding lifestyle adjustments and pharmaceutical utilization, and they are more inclined to adhere to such recommendations. Modifications in lifestyle behavior have the potential to mitigate the likelihood of developing diabetes. Further investigation is necessary to elucidate these interactions.

LIMITATIONS OF THE STUDY

The study's robustness is attributed to its reliance on three established prospective cohorts, each with a considerable sample size, an adequate number of events, and a follow-up period exceeding 12 years.

These groups are widely recognized for their significant contributions in identifying the risk factors connected to the progress of type 2 diabetes. Furthermore, the majority of established risk factors for diabetes were gathered on multiple occasions and subjected to time-varying regression analyses, thereby reducing the likelihood of confounding effects. Thirdly, the study's participants consisted of healthcare professionals who possessed the capability to furnish comprehensive and precise health-related data. Finally, the utilization of rigorous sensitivity analyses and the examination of the dose-response relationship served to enhance the level of confidence in the obtained results.

The present investigation exhibits certain constraints. Initially, as a study based on observation, it was not feasible to entirely eliminate the potential impact of residual confounding factors.

The main estimate's E-value is 1.8, and the lower confidence limit's E-value is 1.6 as a result of the sensitivity analysis that was done to take unmeasured confounders into account. These findings suggest that it is unlikely that unmeasured confounding variables account for all of the reported effects.

The NHS, NHS II, and HPFS studies lacked comprehensive information on PPI usage, such as the specific dosage, frequency, brand, and indications. As a result, further investigation into these factors was not feasible. Thirdly, it is possible that the correlation among the utilization of proton pump inhibitors (PPIs) and diabetes is influenced by confounding factors related to the reasons for administering PPIs. Nonetheless, after accounting for prevalent indications such as stomach or duodenal ulcers, gastro-oesophageal reflux disease and limiting the inclusion of participants with these indications, the calculated effect remained largely unaltered. Furthermore, It is essential to remember that the sample population for this research exclusively comprises of individuals who are health professionals, potentially possessing distinct attributes in comparison to the broader populace. Consequently, the generalizability of the study results to the broader population may be limited. Furthermore, the absence of data regarding the timing of exposure onset may result in the misclassification of subjects. However, the anticipated impact would be reduced if PPI users (whether they are regular or infrequent users) were incorrectly categorized as non-users. The accuracy of the data derived from pharmacoepidemiological investigations may often be compromised by eternal time bias and latency bias.47 Misclassification of exposure can often introduce immortal time bias.47 Time-varying analysis was utilized to specify the PPI use status of individual participants at various time points.

This analysis significantly decreased the possibility of exposure misclassification. The omission of latency in the exposure definition introduces latency bias.47 The primary analysis involved a delay of exposure by a period of two years. The results obtained from the sensitivity analysis conducted by lagging the exposure for a period of four years were found to be comparable. Consequently, the probability of encountering these biases was minimal in the present investigation. The seventh limitation of

the study pertains to the self-reported nature of the outcome, which has the potential to introduce misclassification. Notwithstanding, the impact on our deduction would be insignificant due to two reasons: The consideration of proton pump inhibitor (PPI) use was initially predicted to be non-discriminatory regarding diabetes diagnosis because subjects were not probably to be conscious of the link between the usage of PPI and the threat of developing diabetes; secondly, all individuals were medical staff with a solid understanding of the physical manifestations of the condition. The use of interval data, the existence of left truncation, and the reliance on self-reported measures may all have an impact on the validity of our results.

CONCLUSION

The present study conducted a thorough examination of the existing literary works on the extended usage of proton pump inhibitors (PPIs) amongst individuals diagnosed with diabetes. The results of this review do not offer conclusive sign either in favor or against the proposition that PPIs may be linked to heightened likelihood of unfavorable outcomes in this patient cohort. Although a couple of research studies have indicated a heightened likelihood of severe infection and acute renal impairment, the final outcomes were indeterminate. Additionally, the available data regarding the prolonged impacts of PPIs on various outcomes such as cardiovascular hazard, bone mineral density, and malignancy were restricted. Hence, additional investigation is warranted to assess the safety implications of prolonged proton pump inhibitor (PPI) utilization among individuals diagnosed with diabetes. It is recommended that clinicians persist in assessing the potential advantages and drawbacks of employing PPIs in this demographic and adhere to the prescribed duration and dosage restrictions.

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