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Research Article

Association of the Use of Gastric Acid Suppressants and Risk of Inflammatory Bowel Disease Exacerbation in Adult Patients: A Systematic Review and Meta-Analysis

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Received: May 11, 2021; **Published:** June 11, 2021

Abstract

Background: Gastric acid suppressants such as proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RAs) are common gastrointestinal medications used to manage symptoms of acid related diseases. Studies have shown that these medications are associated with increased risk of pneumonia, vitamin deficiency, osteoporosis and fractures. Few studies have described the potential risk of inflammatory bowel disease (IBD) exacerbation among patients on gastric acid suppressants but little is known on its association. This study aims to investigate the effect of the use of gastric acid suppressants (PPI and H2RA) in the risk of IBD (Crohn's disease and ulcerative colitis) exacerbation.

Methods: A comprehensive, computerized literature search from the electronic database of MEDLINE, Google scholar, Cochrane Library, and OVID was performed with the following search terms: gastric acid suppressants, proton pump inhibitors, histamine-2-receptor antagonists, inflammatory bowel disease, Crohn's disease, ulcerative colitis, outcomes, and disease activity exacerbation. Two cohort studies were selected and validated using the GRADE and Newcastle-Ottawa criteria. Trial results were combined under a random effects model using pooled adjusted relative risks (RRs). The Cochrane Review Manager Software version 5.4 was used for all analyses.

Results: Two cohort studies comprising of 36,293 patients were analyzed by pooling reported adjusted RRs using the random effects model. Disease activity exacerbation was associated with the use of gastric acid suppressants with pooled adjusted RR 1.14 [95% CI, 1.08 - 1.20, I^2 = 0%] with no heterogeneity. The effects of PPIs and H2RAs were also separately analyzed. The pooled adjusted RR of IBD activity exacerbation with the use of PPIs was 1.12 [95% CI, 1.05 - 1.19, I^2 = 0%] for any IBD, while the pooled adjusted RR of disease activity exacerbation with the use of H2RAs was 1.21 [1.04 - 1.40, I^2 = 42%] for any IBD, with moderate heterogeneity. The effect of acid suppression was more marked in patients with Crohn's disease, RR 1.44 [0.89 - 2.33, I^2 = 77%], but this was statistically insignificant with marked heterogeneity; than in ulcerative colitis RR 1.12 [1.05 - 1.20, I^2 = 0%].

Conclusion: Use of gastric acid suppressants such as PPIs and H2Ras may be associated with increased risk of disease exacerbation in patients with IBD. This meta-analysis confirms the need for further prospective studies in examining this relationship.

Keywords: *Proton Pump Inhibitor; Histamine 2 Receptor Antagonist; Inflammatory Bowel Disease*

Background

Inflammatory bowel disease (IBD) is a chronic idiopathic disorder affecting the gastrointestinal tract but also involves other extraintestinal organs [1-3]. This disease causes remitting and relapsing intestinal inflammation that may cause abdominal pain and gastrointestinal bleeding. Crohn's disease (CD) and ulcerative colitis (UC) are the two different types of this inflammatory disorder. Ulcerative colitis is a diffuse inflammatory disorder that affects the colonic mucosa and forms ulcerations and erosions. On the other hand, Crohn's disease is characterized by transmural granulomatous inflammation and involves the small and large intestine and the perianal region [1]. The etiology of IBD is unknown but an abnormal intestinal immunity and gut dysbiosis caused by environmental factors such as infection, lifestyle and diet in a genetically susceptible individual can develop into CD or UC [1,3].

The onset of IBD occurs in the second and third decade of life [4]. Patients affected by this disease experience abdominal symptoms such as diarrhoea, abdominal pain, vomiting and bloody stools [5]. Abnormalities in the intestinal integrity and mucosal barrier also occurs with patients with IBD. Extraintestinal manifestations are also prevalent in both CD and UC. These manifestations affect multiple organ systems such as the musculoskeletal, dermatologic, hepato-pancreato-biliary, ocular, renal and pulmonary systems [6]. These symptoms create a disease burden and can affect the quality of life of patients.

There is no cure for IBD; however, the goal of therapy is to control active disease symptoms and maintain remission [5]. Treatment involving a step-up approach involves the use of steroids, non-steroidal anti-inflammatory drugs, immunomodulators, biologics and surgery [7].

In spite of therapy, some patients would develop recurrence of symptoms of IBD. A survey by Rubin., *et al*. showed that in 451 patients with UC, an average of 8 self-defined flares were reported per year [8]. One of the common causes of flares of IBD can be attributed to enteric infections. A cross-sectional study by Axelrad., *et al*. showed that non-*Clostridium difficile* enteric infections were identified in 17% of symptomatic patients with IBD. Other enteric pathogens that may play in important role in flare of IBD are norovirus and *Escherichia coli* [9].

Some retrospective studies have also shown that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics has been associated with disease activity exacerbations or flares of IBD. NSAIDs can disrupt prostaglandin production by increasing leukotrienes causing flares; whereas antibiotics alter bowel flora thereby decreasing the protective bacteria in the gut [10]. An article by Reinink posed a question on whether acid suppressing medications such as proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA) increase the risk for flares of IBD [11].

PPIs and H2RA medications are used to gastrointestinal bleeding and acid related disorders in the stomach such as gastroesophageal reflux disease, gastric and duodenal ulcers, gastritis and *Helicobacter pylori* infection. A nationwide population-based drug utilization study was done by Hálfdánasrson., *et al*. in 2018, showed that from a total of 1,372,790 prescriptions, 95% were for high-dose PPIs. Prevalence was observed to be higher in women compared to men [12]. The Japanese Society of Gastroenterology has recommended the use of PPIs as treatment for active upper gastrointestinal tract lesions in IBD [1].

The use of PPIs are associated with increased risk of pneumonia, Vitamin B12 and magnesium deficiency, osteoporosis, fractures, chronic renal insufficiency and dementia [11]. Long term use of acid-suppressing medications, most especially PPIs causes gastric hypochlorhydria which triggers changes in gut microbiota composition [13]. The early use of PPIs in children also appears to be associated with increased risk of IBD [14].

Whether acid suppression poses a risk for disease exacerbation among patients with IBD has not been thoroughly studied. As IBD symptoms may be interpreted non-specifically and can be interpreted as an acid-related disorder, it is important to discern whether the use of acid suppression may trigger an exacerbation, with knowledge that its use may be more deleterious than beneficial.

Objective of the Study

This meta-analysis aimed to determine whether the use of gastric acid suppressants such as PPIs and H2RAs is associated with the development of symptom flares of inflammatory bowel disease. Specifically, we planned to document the association of PPIs or H2RAs in disease activity flares in both CD and UC and independently. We also planned to document if there is a difference in the degree of association of either PPI or H2RA on disease flares in IBD.

Methods

Study selection

We conducted a comprehensive computerized search for publications listed in the electronic database of MEDLINE. A free-search of articles was also done in Google scholar for any cohort, case control, case series or case studies regarding this topic. The following terms were used for the search: "gastric acid suppressants, proton pump inhibitors, histamine 2 receptor antagonists, inflammatory bowel disease, Crohn's disease, ulcerative colitis, outcomes, association, response, impact of drug, flare, disease activity exacerbation, hospitalization, surgery".

Studies were selected based on the title and abstract by the researchers. The researchers verified whether the inclusion and exclusion criteria were met. In an event where there is uncertainty, the full text article was retrieved and reviewed. To be included in this review, the focus of the study had to be the association of gastric acid suppressants with the occurrence of symptoms of adult patients with inflammatory bowel disease.

Included studies were cohort, case series or case studies on the use of PPIs or H2RAs on adult patients with inflammatory bowel disease. Outcomes of the studies included occurrence of symptom flares, hospitalization, need for surgery and/or death. The studies were excluded if they were review articles, the patients presented were not adults who have inflammatory bowel disease, studies not using PPIs or H2RAs, and outcomes did not assess for flare occurrence, hospitalization, need for surgery and/or death.

Outcome assessment

The outcome measures were defined a priori. The end points of each study were occurrence of disease activity exacerbations, hospitalization, surgery or death. Characteristics of the studies included can be seen in table 1.

Data collection

Data extraction was carried out independently by the researchers. The following data were retrieved: journal, year, author, number of patients in the study, method of selection of cohorts, type of gastric acid suppressant used (PPI or H2RAs), clinical outcome (severity of symptoms, step-up of medications, hospitalization, surgery, death).

Extracted data included the adjusted risk ratios (RR) with their respective 95% confidence intervals (CI). Assessment of quality was performed using the NewcastleOttawa (NOS) criteria for observational studies. For cohorts, the NOS includes validity criteria for selection of the exposed and non-exposed cohort, comparability of the exposed and the non-exposed cohort and adequacy of outcome by definition, completeness and length of follow-up. For case-control studies, the NOS assesses appropriateness of selection of cases and controls, comparability of cases and controls and criteria on the ascertainment of exposure as well as non-response. We set a score of 7 in the NOS as having low risk of bias.

Data synthesis and analysis

The primary objective of the meta-analysis was to assess the association between the use of gastric acid suppressants and clinical flares of inflammatory bowel disease (hospitalization, IBD-related surgery, medication escalation and death). Secondary objectives are to compare the difference in the risk of developing disease flare between the use of PPIs and H2RAs and the difference in risk between UC and CD.

Meta-analysis summary estimates (RR) and 95% CI were obtained by pooling effect estimates (adjusted RRs) from all the eligible studies using random effects model. Statistical heterogeneity was ascertained using a Chi-square (X^2) of p50% was defined as significant heterogeneity. Assessment of publication bias was used using the funnel plot for analysis. All analysis was performed using Review Manager (Revman) version 5.4 software.

Results

Literature search

The search strategy resulted in 289 citations from the different databases (Figure 1). Of these, a total of two studies were included in the final systematic review. The rest of the articles did not include any gastric acid suppressant drugs or patients with inflammatory bowel disease. Both articles studied the use of acid suppressant drugs and its association on the disease activity exacerbation of adult patients with inflammatory bowel disease.

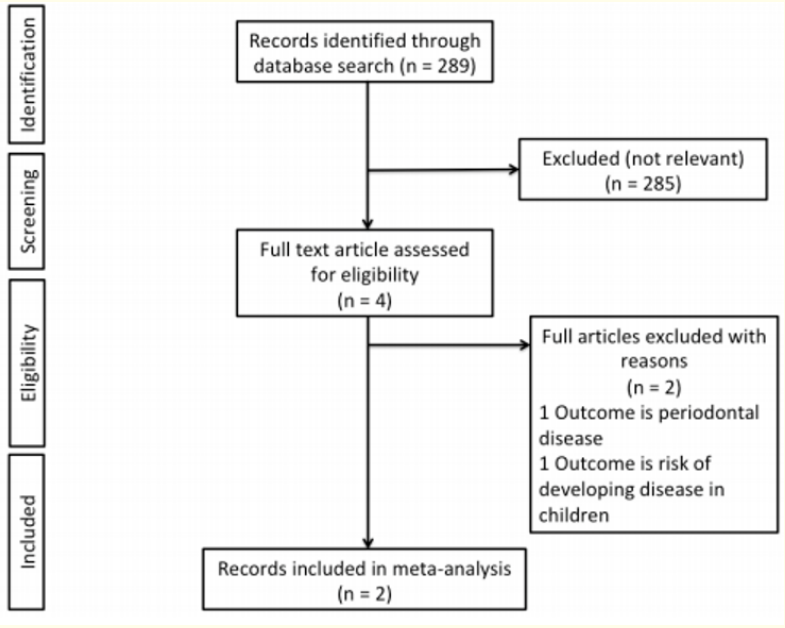

Figure 1: *PRISMA flow diagram of eligible studies.*

Study characteristics

Studies undertaken to expound on the relationship of the PPIs and H2RAs use and disease activity of inflammatory bowel disease are outlined in table 1. The two included articles are cohort studies published in 2012 and 2017. Both studies examined occurrence of flares, disease activity exacerbation characterized by step-up of medications, hospitalizations and need for surgery [15,16]. A quality assessment using Newcastle-Ottawa scale was conducted due to inherent qualitative differences among both studies (Table 2 and 3). Studies with a score of seven or greater in the Newcastle-Ottawa scale were considered to have low risk of bias.

Author	Year	Study Design	Sample Size	Exposure Definition	Outcome Definition	Statistical Analysis	Newcastle -Ottawa Score
Juillerat., *et al*.	201 2	Retrospective cohort	7,024	PPIs and H2RAs	Prescription changes; Hospitalization; Surgery		7
Shah., *et al*.	2017	Nested case control (retrospective cohort)	29,269	PPIs and H2RAs	Hospitalization; Surgery		7

Table 1: *Characteristics of studies included in the meta-analysis of gastric acid suppressants use and risk of inflammatory bowel disease exacerbation.*

Juillerat., *et al*. (2012)		
Selection	Selection Representative of the exposed cohort	*
	Selection of non-exposed cohort	*
	Ascertainment of exposure	*
	Demonstration that outcome of interest was not present at start of study	*
Comparability	Comparability of cohorts on the basis of the design or analysis	*
Outcome	Assessment of outcome	*
	Was follow-up long enough for outcomes to occur	*
	Adequacy of follow-up of cohorts	*
	Total	7

Table 2: *Newcastle-Ottawa criteria for cohort studies.*

** * * *: Comparability; *: Outcome; * * *: Total 7.*

Shah., *et al*. (2012)		
Selection	Is the case definition adequate?	*
	Representativeness of the cases	*
	Selection of controls	*
	Definition of controls	*
Comparability	Comparability of cases and controls on the basis of the design or analysis	*
Outcome	Assessment of exposure	*
	Same method of ascertainment for cases and controls	*
	Non-response rate	*
	Total	7

Table 3: *Newcastle-Ottawa criteria for case-control studies.*

Analysis of gastric acid suppressants with inflammatory bowel disease exacerbation

Juillerat., *et al*. conducted a retrospective cohort study examining the risk of inflammatory bowel disease exacerbation with the use of PPIs and H2RAs. The use of H2RAs doubled the risk of hospitalization and/or surgery in patients with Crohn's disease with an adjusted RR (aRR) 1.94 [1.24 - 3.10], adjusted for age, immunosuppression, baseline medications, medical encounters and comorbidity index using propensity score matching. The association of H2Ras in exacerbations of UC is less in magnitude with aRR 1.11 [0.61 - 2.03]. The use of PPIs was associated with medication change in ulcerative colitis patients but without increased risk of hospitalization and/or surgery among Crohn's disease or ulcerative colitis patients [15].

The study done by Shah., *et al*. showed an increased risk of inflammatory bowel disease-associated hospitalization and surgery with the use of PPIs with aRR 1.11 [1.02 - 1.21] for UC and aRR 1.12 [1.02 - 1.22] for CD. This was also observed with the use of H2RAs in UC aRR 1.13 [0.99 - 1.28] and CD aRR 1.18 [1.03 - 1.34]. This study adjusted for sex, race, ethnicity, morbidity index and use of other IBD medications [16].

Meta-analysis of these two studies comprising of 36,293 patients showed a pooled adjusted RR 1.14 [1.08, 1.20] showing an increased risk for exacerbation of IBD on the use of either PPI or H2RA with no heterogeneity (I^2 = 0%) (Figure 2). When analyzed by type of acid suppression, H2RAs were shown to have a greater magnitude of association with disease exacerbation of any IBD (aRR 1.21, 1.04 - 1.40, I^2 = 42%) than PPIs (aRR 1.12, 1.05 - 1.19, I^2 = 0%), but the presence of mild heterogeneity precludes generalizability (Figure 3 and 4). PPI use in CD has a comparable aRR 1.12 [1.03, 1.23, I^2 = 0%], compared with use in UC aRR 1.11 [1.03, 1.21, I^2 = 0%], while use of H2RA in CD was associated with a greater magnitude of exacerbation, aRR 1.44 [0.89, 2.33, I^2 = 77%], than when used in UC, aRR 1.13 [0.99, 1.28, I^2 = 0%] (Figure 3 and 4). Lastly, comparing medication class by disease, H2RAs are more associated with exacerbations in CD (aRR 1.44 [0.89, 2.33, I^2 = 77%]) when compared to PPIs (aRR1.12 [1.03, 1.23, I^2 = 0%]) but both have similar degrees of association when used in UC (Figure 5 and 6). These results are also summarized in the summary of findings table (Table 4).

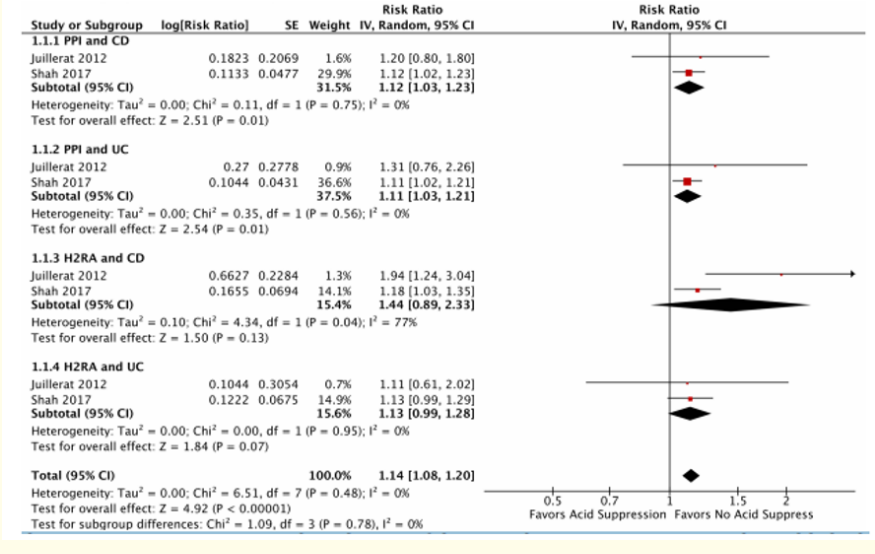

Figure 2: *Summary forest plot on the use of acid suppression and IBD exacerbation.*

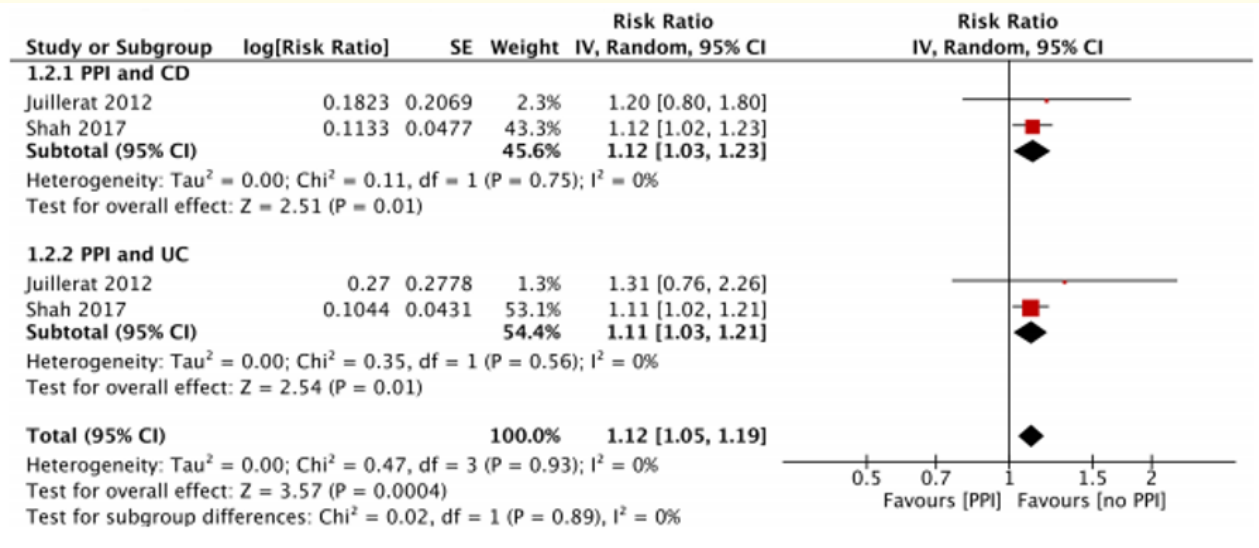

Figure 3: *PPI use and IBD exacerbation in UC and CD.*

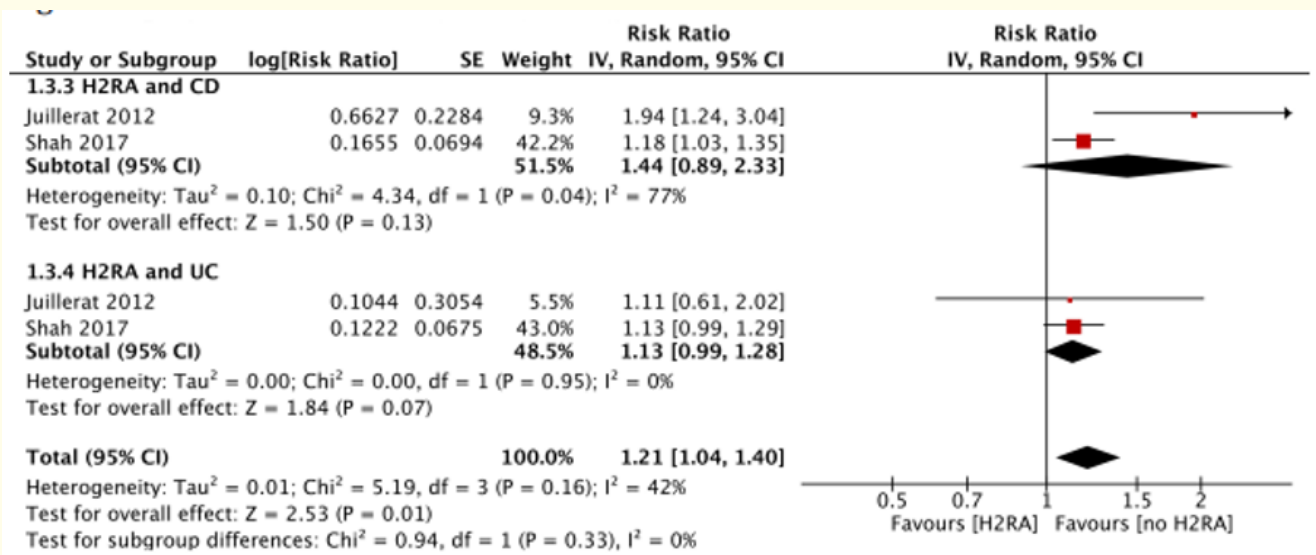

Figure 4: *H2RA use and IBD exacerbation in UC and CD.*

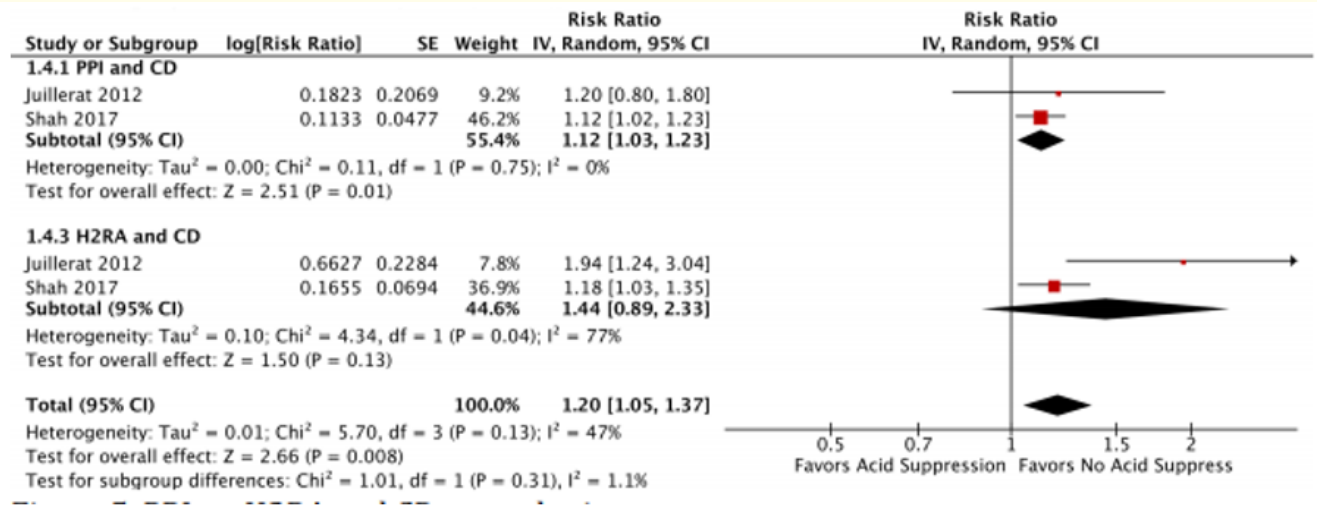

Figure 5: *PPI vs. H2RA and CD exacerbation.*

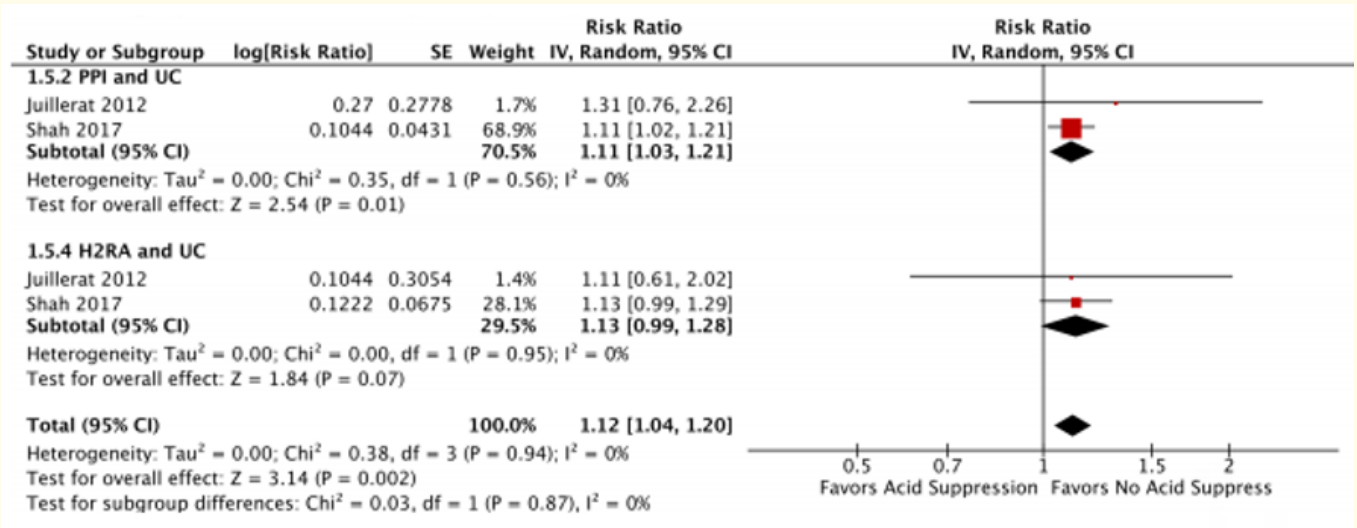

Figure 6: *PPI vs H2RA and UC exacerbation.*

Patient or population: Adult patients with inflammatory bowel disease Settings: Observational studies Intervention: PPI or H2RAs Comparison: no PPI or no H2RAs				
Outcomes	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
PPI and CD	RR 1.12 [1.03, 1.23]	16,695 (2)	⊕⊕⊕⊖ moderate	Good quality observational studies, no heterogeneity
PPI and UC	RR 1.11 [1.03, 1.21]	16,640 (2)	⊕⊕⊕⊖ moderate	Good quality observational studies, no heterogeneity
PPI in IBD	RR 1.12 [1.05, 1.19]	33,335 (2)	⊕⊕⊕⊖ moderate	Good quality observational studies, no heterogeneity
H2RA and CD	RR 1.44 [0.89, 2.33]	16,103 (2)	⊕⊕⊖⊖ low	Good quality observational studies, significant heterogeneity
H2RA and UC	RR 1.13 [0.99, 1.28]	16,124 (2)	⊕⊕⊕⊖ moderate	Good quality observational studies, no heterogeneity
H2RA in IBD	RR 1.21 [1.04, 1.40]	32,227 (2)	⊕⊕⊖⊖ low	Good quality observational studies, moderate heterogeneity
Acid Suppression in CD	RR 1.20 [1.05-1.37]	32,798 (2)	⊕⊕⊖⊖ low	Good quality observational studies, moderate heterogeneity
Acid Suppression in UC	RR 1.12 [1.04-1.20]	32,724 (2)	⊕⊕⊕⊖ moderate	Good quality observational studies, no heterogeneity
Acid Suppression and IBD exacerbation	RR 1.14 [1.08, 1.20]	36,293 (2)	⊕⊕⊕⊖ moderate	Good quality observational studies, no heterogeneity

Table 4: *Summary of findings the association of gastric acid suppression and disease exacerbation among adult inflammatory bowel disease patients.*

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Discussion

In this systematic review and meta-analysis of prior studies, association between PPI and H2Ras use and the risk of inflammatory bowel disease exacerbation was noted. Individual data of each study and pooled data showed risk of disease activity exacerbation was increased with the use of gastric acid suppressants.

PPIs and H2RAs are used to reduce the clinical manifestations of gastroesophageal reflux disease and other gastric acid related disorders. The American College of Gastroenterology guidelines for the management of inflammatory bowel disease has stated potential drugs

such as NSAIDs promote disease exacerbations in inflammatory bowel disease raising concern regarding the use of these medications in patients with established disease [17]. However, no guidelines have recognized the negative effects of PPIs and H2RAs on inflammatory bowel disease.

Gastric acid suppressants, such as PPIs and H2RAs, alters the gut microbiome similar to the pathophysiology of inflammatory bowel disease [13,14]. The link of PPI use and intestinal dysbiosis was evaluated in previous studies. Takagi., *et al*. analyzed 36 PPI users and 36 non-PPI users. Results of this study showed there was alteration in the gut microbiome in PPI users [19]. On the other hand, H2RAs affect suppression of proinflammatory responses and thus promote further inflammation. H2RAs compete with histamine, which is a key immunoregulator in hypersensitivity reactions and chronic inflammatory responses. Smolisnka., *et al*. showed that manipulation of histamine 2 receptors, such as the use of H2RAs, diminish anti-inflammatory signaling effects associated with histamine 2 receptor signaling [20]. This inhibition suppresses toll like receptors in response to bacterial inflammatory responses, especially in patients with inflammatory bowel disease. Although it is well established on the effects of gastric acid suppressants on intestinal microbiome, the precise mechanism which PPIs and H2RAs promote inflammatory bowel disease exacerbation remains unknown.

This study has several limitations. Statistical heterogeneity, albeit moderate in magnitude was evident but may be due to the differences in the study designs. Both studies have potential for residual confounders, which were inherent in their study designs. Other factors that may cause disease activity exacerbation such as smoking, use of oral contraceptive medications, use of antibiotics and use of NSAIDs were not controlled for in the studies. The duration of the disease was not also characterized, which also can be a factor in occurrence of disease flares. Inflammatory bowel disease is a complex disease with multiple factors that may cause disease exacerbation. Therefore, further studies focused on controlling confounders and isolating the effects of PPIs and H2RAs are needed. Prospective studies which track the indications and timing of the use of gastric acid suppressants, measure baseline disease severity and accounting other clinical covariates are needed [11].

Conclusion

Moderate quality evidence from two, good quality observational studies show that the use of gastric acid suppressants such as PPIs and H2RAs is associated with inflammatory bowel disease exacerbation, and caution must be observed in the use of these medications in patients with IBD. The studies included however, have several limitations, which can limit the strength of this conclusion. This meta-analysis confirms the need for further prospective studies in examining the relationship between PPIs and H2RAs, and disease activity among patients with established inflammatory bowel disease.

Declaration of Conflict of Interest

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

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Volume 8 Issue 7 July 2021