

# Comparison of oral efficacy between PPIs and H2RAs in subjects for prevention and monitoring of peptic ulcer-associated recurrence rates from 1985 to 2021: A systematic review and meta-analysis

Cao Kim Xoa<sup>1</sup>, Tran Vo Ngoc Minh<sup>1</sup>, Nguyen Diem Kieu<sup>2</sup>

<sup>1</sup>Faculty of Medicine, Nguyen Tat Thanh University

<sup>2</sup>Faculty of Medicine, Pham Ngoc Thach Hospital

ckxoa@ntt.edu.vn

## Abstract

Currently, although there are many randomized controlled trials comparing the effectiveness of proton pump inhibitors and H2-antihistamines in relation to peptic ulcer disease, meta-analytical studies on this topic are still limited and conclusions have not come to consensus. Therefore, a meta-analysis of randomized controlled trials evaluated by the Cochrane Collaboration tool is essential. From January 1<sup>st</sup>, 1985, to May 31<sup>st</sup>, 2022, the study was carried out on three databases: Pubmed, Cochrane, and Embase. Statistics are expressed as odds ratios, with confidence intervals of 95 %, and a random effects model is used. Results: Proton pump inhibitors increase the effectiveness of treatment more than H2-antihistamines. Specifically, on prevention subjects = 0.15 (95 % CI: 0.05-0.44), patients who are monitored for relapse rates without medication = 0.92 (95 % CI: 0.75-1.14), and with medication = 0.50 (95 % CI: 0.31-0.80). In conclusion, proton pump inhibitors are the first-line medicine for ulcer prevention and post-healing monitoring.

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meta-analysis,  
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## 1 Introduction

Peptic ulcer is the name for an ulcer caused by stomach acid. In this instance, damage to the intestinal tract's lining has exposed the underlying tissue (an ulcer in the stomach lining is called a gastric ulcer, an ulcer in the lining of the duodenum is called a duodenal ulcer). Gastric ulcers are four times less frequent than duodenal ulcers. Peptic ulcer patients typically experience epigastric discomfort within (15-30) minutes of eating, whereas duodenal ulcer patients typically experience pain (2-3) h after eating [1]. Peptic ulcer disease (PUD) affects 10 % of people in developing countries, with a 26 % prevalence rate in Viet Nam and a rising rate overall [2].

Proton pump inhibitors (PPIs) have gradually taken over as the primary active component in the treatment of illnesses associated to acidity. Its purpose is to prevent the stomach from secreting acid. After being taken orally, the medication is absorbed in the small intestine, transported to parietal cells, and then absorbed into the bloodstream where it is activated in an acidic environment to produce sulfenic and/or sulfonamides. Proton pumps are permanently bound by this type of activity, rendering them inactive. To obtain the greatest therapeutic impact, PPIs must be taken (30-60) minutes before meals because this inhibition only happens with functioning pumps [3]. The United States Food and Drug Administration approved six PPIs for widespread use in treatment in 2015, including



Omeprazole (1989), Lansoprazole (1995), Rabeprazole (1999), Pantoprazole (2000), Esomeprazole (2001), and Dexlansoprazole (2009) [4].

According to the knowledge of the author group [5], in the early 1990s, H<sub>2</sub>-antihistamines (H<sub>2</sub>RAs) were first developed by SJ Black, who received the Nobel Prize for the creation of a specific receptor antagonist for use in medicine. According to that, H<sub>2</sub>RAs act as a competitive antagonist by blocking the histamine receptor that inhibits the enzyme adenylate cyclase, which reduces cAMP synthesis, thereby reducing gastric volume, reducing H<sup>+</sup> concentration, and inhibiting the activity of pepsin. Cimetidine (1977), ranitidine (1983), famotidine (1986), and nizatidine (1988) were the first H<sub>2</sub>RAs to be licensed for use in the United States. Studies have demonstrated that the anti-acid effect of H<sub>2</sub>RAs is similar whether taken several times a day or taken as a single compound dose after dinner. This is the best way to use anti-acid secretion at night. However, the disadvantage of H<sub>2</sub>RAs is that it is easily tolerated after (3-5) days. This medicine starts working in the stomach in approximately 60 minutes, and its effects last for (4 to 10) h.

Currently, although there are many randomized controlled trials (RCTs) comparing the efficacy of PPIs and H<sub>2</sub>RAs drugs in the treatment of PUD, the results obtained are still controversial. By way of illustration, while using the same design methodology, there are studies that indicate better PPIs than H<sub>2</sub>RAs [6,7], others demonstrates that H<sub>2</sub>RAs were superior [8,9], and even research found that PPIs and H<sub>2</sub>RAs had the same impact [10]. In addition, the number of studies on prevention and monitoring of relapse rates is still limited. Most of the published studies have been tested on people who are being treated for ulcers. Thus, the study comparing the oral efficacy of PPIs and H<sub>2</sub>RAs in PUD-related from 1985 to 2022 will continue to assess and update the most recent drug use situation, simultaneously considering the benefit and risk to determine which is the superior drug in the subjects' pattern for the prevention of gastroduodenal ulcers, patients who are monitored for relapse rates without medication (PWOM), and patients who are monitored for relapse rates with medication (PWM).

## 2 Materials and methods

### 2.1 Search strategy and inclusion criteria

In order to evaluate the effectiveness of PPIs with H<sub>2</sub>RAs in prospective patient prevention, PWOM, and PWM, RCTs from three databases – Embase, Cochrane, and Pubmed – were screened over a 38-year period from 1985 to 2022.

Studies were eligible if the subjects were patients over 18 years of age. The drugs used, including PPIs and H<sub>2</sub>RAs, met the requirements for dosage and frequency of oral administration as indicated in the British National Formulation (BNF) version 83 in 2022. The studies must be designed in parallel to avoid the carry-over effect. Finally, the data included in this meta-analysis included the final outcomes of ulceration and ulcer recurrence.

Reports with any one of the following criteria were excluded: studies in healthy subjects, pregnant women, children, or animals; the study cannot access the full text; studies with insufficient trial period according to the pharmacopeia; do not use oral preparations. In addition, duplicate trials between 3 data sources and too small sample sizes ( $n < 10$ ) were also excluded.

### 2.2 Study selection and quality assessment

Using a complex search engine and a combination of AND, OR, and NOT algorithms, tests are searched for and screened. The two authors independently selected RCTs from three sources based on titles and abstracts. The full-text version was then screened to identify eligible studies. The conflicts have been resolved by discussion and consensus. If the disagreement is not resolved, it will be approved by a third person. Key search terms include "Proton Pump Inhibitor", "Histamine Agonists H<sub>2</sub>", "Peptic ulcer", "Prevention", " Recurrent".

The methodological quality of the RCTs was assessed using the Cochrane Collaboration tool. In which the quality assessment is performed separately for different areas, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and drug-related mortality. Reports were of high quality when the overall risk of bias for each trial was classified as low by 6/7 of the criteria, medium quality when classified unclearly, or high in two areas. In addition, studies with 1 area of unclear rating and 1 area of high risk will also be rated medium. Finally, if the report has 3 or more

non-low criteria, it will be classified as a poor quality study.

The RCTs whose subjects were PWOM will not be included in the quality assessment because most of the reports collected on this subject were part of the original study, so they were only included in the review. Refers to the results obtained without specific research methods.

### 2.3 Data extraction and analysis

Data extraction was performed by two authors according to the designed template. The extracted entries included author, year of publication, region, sample size recorded concurrently per protocol (PP), dose and frequency of the intervention, and event-to-total ratio patient. For PWOM, the intervention drug data that will be provided are the drugs taken during the ulcer treatment.

The meta-analysis was performed by RevMan 5.4 software. The analytical data item is dichotomous. The effect model Random effects (RE) was selected to minimize errors in genetics, races, ecosystems and so on. The data is presented as an odds ratios (OR) with a 95 % confidence intervals (CI). Statistical heterogeneity was assessed by the  $I^2$  test ( $P < 0.05$  was set as the level of statistical significance).

## 3 Results and Discussion

### 3.1 Review results

Between January 1<sup>st</sup>, 1985 and May 3<sup>st</sup>, 2022, a total of 10,540 records were carefully screened (883 records

from Cochrane, 1,264 records from Pubmed, and 8,393 records from Embase). Then, because 9,257 RCTs were removed by the automation tool, the number of remaining reports was 1,283. In the first screening, 586 trials were excluded because of a false mismatch when screening titles and abstracts. 293 further studies were excluded due to inaccessibility. Therefore, only 404 articles can access the full content. In this final check, there were quite a few studies ( $n = 380$ ) that were excluded due to duplicates ( $n = 263$ ), sample sizes too small ( $n = 29$ ), studies in healthy subjects, pregnant women, and children ( $n = 45$ ), unsatisfactory trial duration ( $n = 17$ ), and study design was not parallel ( $n = 26$ ). Finally, 24 RCTs with a total sample size of 5,317 patients were included in this meta-analysis, of which there were 4 studies on prevention subjects, 7 studies on PWM, and 13 studies on PWOM (Figure 1). Nevertheless, the RCTs on the subjects of PWOM by KD Bardhan et al. [11], A Walan et al. [12], W Londong et al. [13], Cooperative Study Group [14] and tested on subjects PWM by KD Bardhan et al. [15], K Lauritsen et al. [16] performed on 2 concentrations or 2 different drugs of the same group PPIs. Therefore, this study will be presented into 17 reports based on the original 13 RCTs for PWOM studies and 9 reports based on the original 7 RCTs for PWM studies and 4 studies on prevention subjects. Reports which are extracted from the same study will be distinguished by numbering 1 and 2 after the author's name (Table 1).

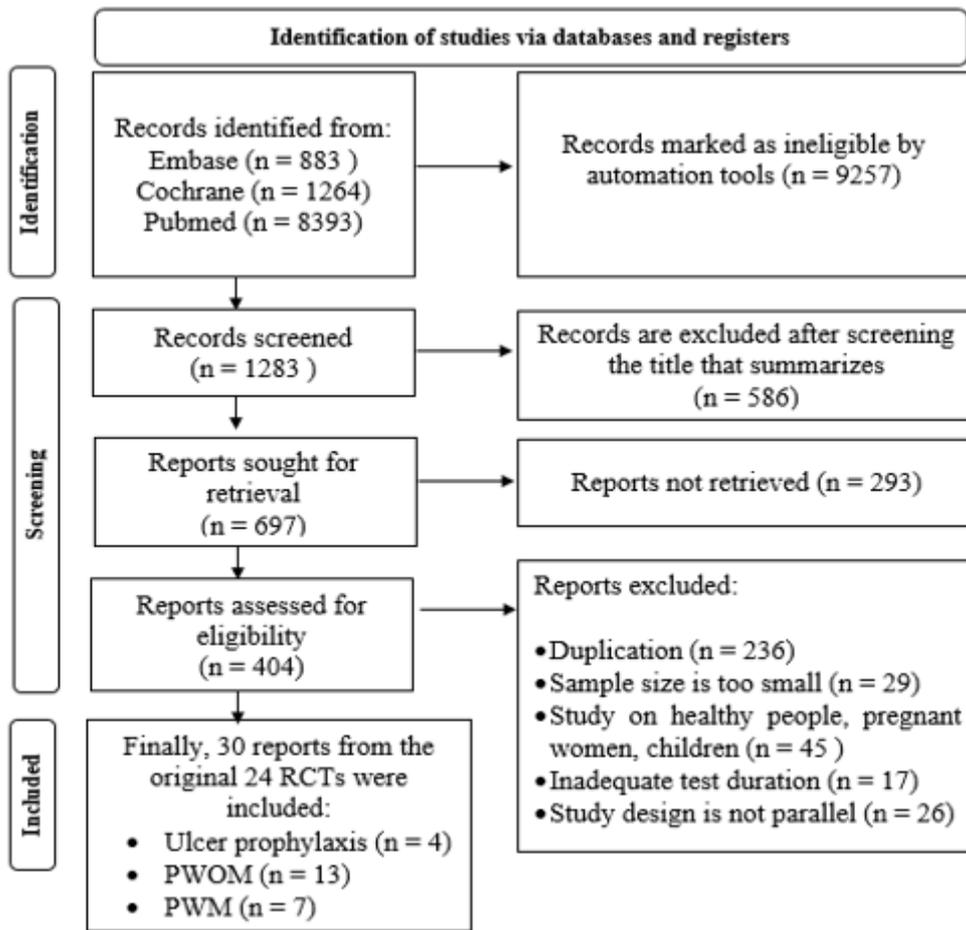


Figure 1 Flow diagram for study selection

Table 1 Information about the reports included in the analysis

Year	Study	Country	Intervention		Event/Total	
			Intervention (n)	Dosage (mg/day)	PPIs	H2RAs
<b>Ulcer prophylaxis</b>						
2005	M Hata [17]	Japan	rabeprazole (70) ranitidine (70)	10 300	5/70	30/70
2009	FH Ng 1 [18]	Hong Kong	pantoprazole (63) famotidine (65)	20 40	0/63	13/65
2012	FH Ng 2 [18]	Hong Kong	esomeprazole (163) famotidine (148)	20 40	1/163	9/148
2021	ZF Tseng [19]	China	omeprazole (78) famotidine (76)	20 40	8/78	16/76
<i>In 2022, no new relevant RCTs on ulcer prophylaxis subjects are conducted (included study, for which it is not possible to get the full text information)</i>						
<b>Patients after the treatment of ulcer healing are monitored without medication</b>						
1985	K Lauritsen [16]	Denmark	omeprazole (47) cimetidine (37)	30 1000	21/47	22/37

1986	KD Bardhan 1 [11]	UK, Italy, Sweden	omeprazole (24) ranitidine (25)	20 300	14/24	15/25
1986	KD Bardhan 2 [11]	UK, Italy, Sweden	omeprazole (23) ranitidine (25)	40 300	19/23	15/25
1989	A Walan 1 [12]	13 countries	omeprazole (118) ranitidine (117)	20 300	63/118	69/117
1989	A Walan 2 [12]	13 countries	omeprazole (112) ranitidine (117)	40 300	59/112	69/117
1989	K. Lauritsen [26]	Denmark	omeprazole (86) cimetidine (89)	30 1000	33/86	39/89
1990	Cooperative Study Group [14]	Multicenter trial	omeprazole (74) ranitidine (70)	40 300	19/74	17/70
1990	Cooperative Study Group [14]	Multicenter trial	omeprazole (12) ranitidine (15)	40 300	7/12	5/15
1991	W Londong 1 [13]	Germany	lansoprazole (62) ranitidine (61)	15 300	18/62	12/61
1991	W Londong 2 [13]	Germany	lansoprazole (64) ranitidine (61)	15 300	14/64	12/61
1992	J Hotz [27]	Germany	lansoprazole (158) famotidine (69)	20 40	47/158	18/69
1993	SC Misra [28]	India	omeprazole (30) famotidine (30)	20 40	12/30	11/30
1994	S Pan [29]	China	omeprazole (32) cimetidine (28)	20 800	4/32	7/28
1994	NY Kim [20]	Korea	omeprazole (12) cimetidine (11)	20 600	10/12	10/11
1995	A Archimand [30]	Greek	omeprazole (70) ranitidine (62)	20 300	2/70	3/62
1996	A Spadaccini [31]	Italy	<u>First week:</u> omeprazole + antibiotic ranitidine + antibiotic  <u>3 weeks later :</u> omeprazole (49) ranitidine (49)	<u>First week:</u> 40 600  <u>3 weeks later :</u> 20 300	4/49	7/49
1996	F Catalano [32]	Italy	omeprazole (20) ranitidine(19)	20 300	0/20	1/19

*From 1997 to 2022, no new relevant RCTs on PWOM are conducted (included study, for which it is not possible to get the full text information)*

#### **Patients after the treatment of ulcer healing are monitored with medication**

1995	N Figura [23]	Italy	omeprazole (14) ranitidine (13)	20 150	2/14	0/13
1998	FDD Rojas [33]	Spain	omeprazole (193) ranitidine (200)	20 150	20/193	36/200
1998	ND Yeomans [21]	15 countries	omeprazole (145) ranitidine (114)	20 300	27/145	59/114
1999	KD Bardhan 1 [15]	UK, Eire, Sweden, Australia	lansoprazole (104) ranitidine (91)	15 150	12/104	19/91

1999	KD Bardhan 2 [15]	UK, Eire, Sweden, Australia	lansoprazole (88) ranitidine (91)	30 150	4/88	19/91
1999	K Lauritsen 1 [22]	16 countries	omeprazole (308) ranitidine (312)	10 150	62/309	59/312
1999	K Lauritsen 2 [22]	16 countries	omeprazole (308) ranitidine (312)	20 150	22/308	59/312
2017	FKL Chan [24]	Hong Kong, Japan	rabeprazole (108) famotidine (100)	20 40	9/108	13/100
2019	GLH Wong [25]	Hong Kong	lansoprazole (88) famotidine (87)	30 40	16/88	18/87
<i>From 2020 to 2022, no new relevant RCTs on PWM are conducted (included study, for which it is not possible to get the full text information)</i>						

### 3.2 Study characteristics

This study involved 5,287 patients across a total of RCTs, of which 733 patients for ulcer prevention, 1,878 for PWOM, and 2,676 for PWM.

Four reports were included in participants receiving ulcer prevention. All of these studies were carried out in industrialized nations in Asia, including Japan, Hong Kong, and China. The number of study participants ranged from 70 to more than 160. The rate of ulcer prevention in the PPIs group was significantly higher than that of H2RAs, even though each trial utilized a different PPIs: M Hata et al. [17] (rabeprazole), FH Ng 1 et al. [18] (pantoprazole), FH Ng 2 et al. [18] (esomeprazole), and ZF Tseng et al. [19] (omeprazole). Moreover, the percentage of people without ulcers in the PPIs group better than the H2RAs group was 2 times [19], 6 times [17] and even no ulcer occurred, as opposed to 13 persons in the H2RAs group [18].

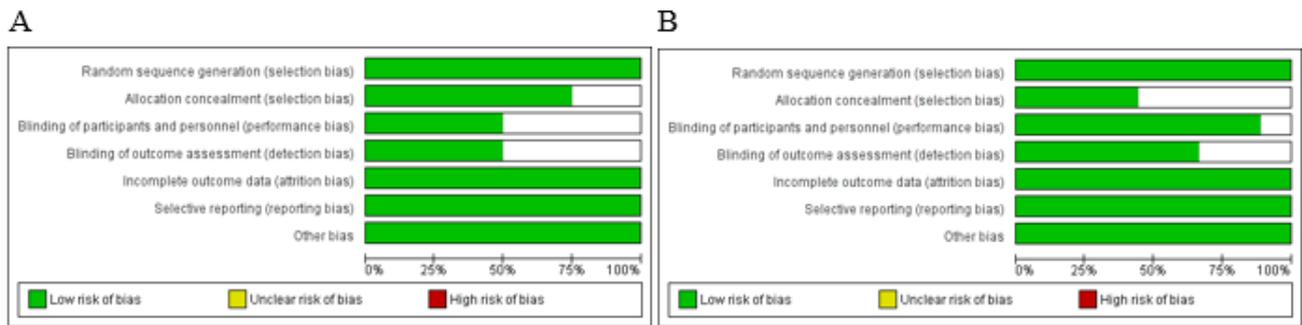
Regarding PWOM, research has increased in various nations around the globe; in fact, several studies have been carried out in other nations, not just one. A study by KD Bardhan 1 et al. [11] conducted in the UK, Italy, and Sweden, a multi-center study by the Cooperative Study Group [14], and a study by A Walan et al. [12] with coverage in up to 13 nations are all good examples of the kind. The research with the fewest participants in the analysis was NY Kim et al. [20], which included 23 patients, while the study with the most participants in the analysis was A Walan et al. [12], which included 347 patients. The majority of trials employed ranitidine and famotidine, whereas omeprazole and lansoprazole were largely used in the PPIs group. When both patient groups were followed up on, the end results did not reveal a significant difference in the recurrence rate.

Similar to the PWOM subject, data for the PWM research were collected from nations all around the world, from Europe to Asia. The two investigations with the widest trial scope in this meta-analysis are those by ND Yeomans et al. [21], completed in 15 countries, and K Lauritsen et al. [22] conducted in 16 countries. N Figura's research [23] with just 27 patients, had the fewest participants in the analysis, whereas K Lauritsen et al. [22], a study with 928 patients, had the most. The majority of the investigations utilized omeprazole and lansoprazole; just one experiment by FKL Chan et al. [24] conducted in Hong Kong and Japan used rabeprazole. Only two RCTs using the H2RAs medication group – those by FKL Chan et al. [24] and GLH Wong et al. [25] – used famotidine; the remaining reports used ranitidine. Omeprazole 10 mg, as reported in the preliminary report of K. Lauritsen's 16-country study [22], produced worse results than omeprazole 20 mg. Therefore, we need to consider more about the dose in addition to the medication choice. In conclusion, only 2 of the 9 included publications demonstrated that H2RAs was superior to PPIs; the others indicated that PPIs was superior to H2RAs in the utilization of relapse prevention measures following therapy.

### 3.3 Evaluation of research quality

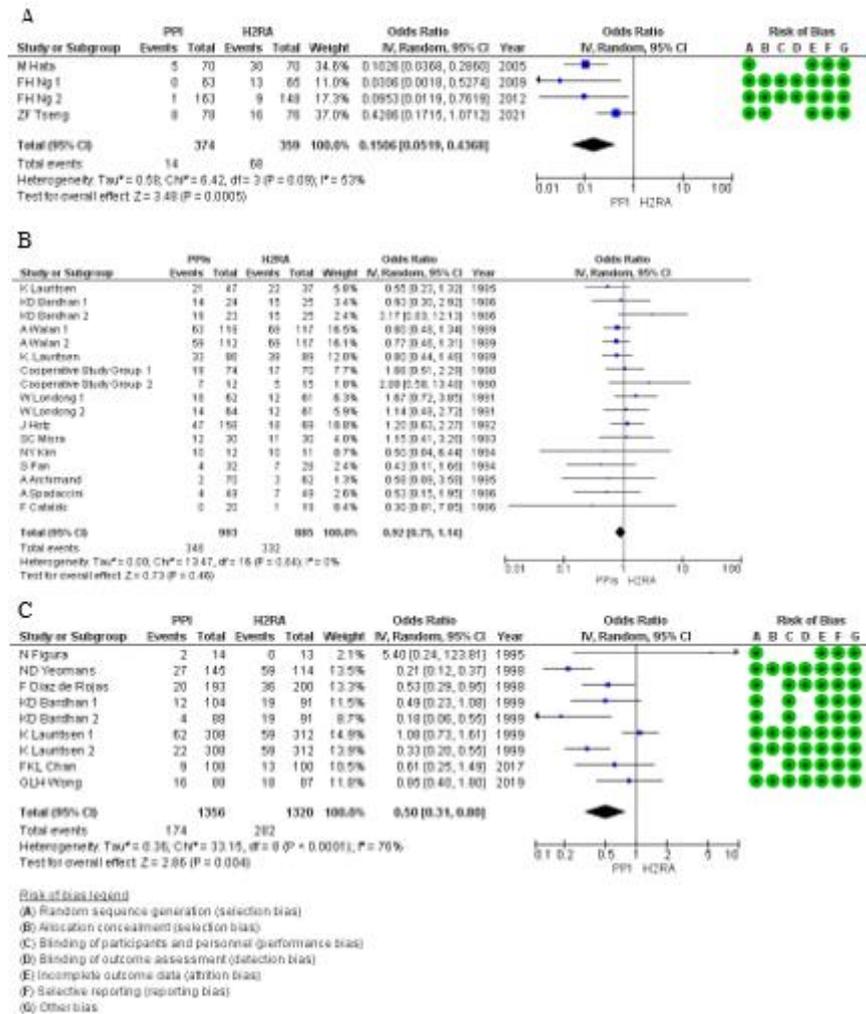
Based on the prior design, 100 % low risk is defined as meeting all four criteria: randomization, trial completion, selective reporting, and drug-related mortality (Figure 2). The report from M Hata et al. [17] and N Figura et al. [23] received the lowest score with a score of 04/07, and the studies by FH Ng et al. [18], ND Yeomans et al. [21] and K Lauritsen et al. [22] that achieved low risk across all 07 categories received the perfect score in this meta-analysis.





**Figure 2** Evaluation of the reliability of the RCTs using the Cochrane Collaboration tool

For patients on medication for ulcer prevention, there was 1 report of low quality, 1 report of medium quality, and 2 reports of high quality – these are all studies by FH Ng et al. [18]. In PWM, 1 reported low quality, 2 reported medium quality, and 6 reported high quality (Figure 3). The method of clustering and blinding was not mentioned in the majority of studies that were classified as low- or medium-quality.



**Figure 3** Results of meta-analysis evaluating the effectiveness and reliability

- A. Effective in preventing ulcers;
- B. The recurrence rate in patients after ulcer healing was monitored without medication;
- C. The recurrence rate in patients after ulcer healing was monitored with medication.

### 3.4 Meta analysis results

A forest plot in figure 3 illustrates the outcome following data processing. Although the proportion of patients on PPIs was consistently higher than that of H2RAs in all three subjects, there were substantially fewer ulcer cases in the PPIs group compared to the H2RAs group.

According to the data in Table 1, when contrasting the effectiveness of PPIs and H2RAs in preventing ulcers, four reports were included. The sample size of people taking PPIs was 374 patients, and the H2RAs were 359 patients. 03/04 reported that PPIs are more effective in preventing ulcers. Among those three reports, the study of M Hata et al. [17] associated accounted for the highest proportion with 34.6 %, followed by the study of F.H. Ng et al. [18] which although not a large weight, at 17.3 %, is of the highest quality when reaching the 07/07 assessment criteria on risk of bias. Finally, the final results concluded that PPIs were better than H2RAs when it came to ulcer prevention for patients, specifically 0.15 (95 % CI: 0.05-0.44) (Figure 3A).

There were 17 reports included in the analysis of the group of PWOM. The high-weighted studies were those of A Walan 1 and 2 [12] with 16.5 % and 16.1 % respectively. In contrast, the low-weighted studies were F Catalano et al. [32] and NY Kim et al. [20] with 0.4 % and 0.7 % respectively. The results of the meta-analysis show that the recurrence rate is similar among people who have used PPIs or H2RAs to treat ulcer healing. The ratio between the two interventions was 0.92 (95 % CI: 0.75-1.14). All of the combined results showed that none of the studies fully supported either PPIs or H2RAs (Figure 3B).

A total of 07 RCTs with PWM subjects were included in the meta-analysis, and 02/07 of those RCTs published research findings on 2 distinct concentrations of the same PPIs medication. In which lansoprazole 15 mg and 30 mg were utilized in KD Bardhan [15]. When compared to lansoprazole 30 mg, which had a statistically significant OR = 0.18 (95 % CI: 0.06-0.55), lansoprazole 15 mg had a statistically insignificant OR = 0.49 (95 % CI: 0.23-1.08). Similar findings were obtained by K. Lauritsen's research [22], which found that omeprazole 20 mg was much more effective than omeprazole 10 mg; the OR = 0.33 (95 % CI: 0.20-0.55) and OR = 1.08 (95 % CI: 0.73-1.61), respectively. N. Figura's report [23], with a weight of 2.1 %, has the

least weight. KD Bardhan's report [15] has the most reliability, at 14.9 %. Furthermore, while coming in second in terms of accountability (13.9 %), the KD Bardhan 2 et al. [15] report is not only statistically significant but also has a substantial impact on the research. In all, there were 9 reports; 4 supported PPIs, 5 were neutral, and none supported H2RAs. This led to a final outcome of OR = 0.50 (95 % CI: 0.31-0.80), which supported the conclusion that PPIs were more effective than H2RAs at preventing ulcer recurrence in PWM therapy. It contains the research done by ND Yeomans et al. [21] and K Lauritsen et al. [16], which satisfied the criteria for assessing the risk of bias for the 07/07 grade with high quality (Figure 3C).

### 3.5 Discussion

Today, meta-analysis is a model that has steadily gained in significance. By merging results and passing judgment, this strategy aids in removing the majority of the uncertainty surrounding research findings. Additionally, as this method does not rely on the findings of a single study, an existing outcome, or several narrative reviews, meta-analysis of RCTs aids us in avoiding a subjective viewpoint. Looking at the big picture, this enables us to recognize the parallels and discrepancies between the techniques and outcomes of numerous studies. In addition, researchers frequently use the term "statistical significance" in the literature of psychology, medicine, and a variety of other disciplines. A study is deemed successful if its findings are statistically significant; otherwise, it is deemed unsuccessful. As a result, people frequently overlook the significance of trials for large groups of people in favor of statistically significant results from vast sample sizes. Meta-analysis assists in avoiding this. This approach aids researchers in realizing that multiple studies' consistent results - even if they are small - are considerably more persuasive evidence than a significant study. Particularly in the fields of medicine and pharmacy, the clinical application of what is learned from the accumulation of knowledge and practice, even if it is very small, can help increase the efficacy of the therapeutic process.

This meta-analysis of data from 30 RCTs of the main gastroprotectant drugs currently in use, which included more than 5,000 participants in total. Generally, different therapeutic dosages of each drug were administered in each trial. In all 3 meta-analyses,

ranitidine and omeprazole were the most preferred in the reports. Considering each group of study subjects, there are specific differences as follows: For ulcer prophylaxis, omeprazole and famotidine accounted for the majority. For PWOM, omeprazole also dominated, but famotidine of the H2RAs group was more dominant than ranitidine, and in PWM, there were similarities with PWOM subjects when omeprazole from the PPIs group and ranitidine of the H2RAs group were used superiorly. Most of the included RCTs were performed all over the world, even studies conducted in more than ten different nations have helped to strengthen the study's accuracy and dependability. During the period from 1985 to 1996, the RCTs mainly monitored PWOM. However, the ulcer recurrence rate may be rather high mainly because of post-treatment follow-up without medication intervention, which is why PWM has been examined by experts since 1996 and has shown far more promising outcomes.

The results of two meta-analyses in patients with ulcer prevention and PWM both showed better PPIs than H2RAs, but the data of PWOM subjects showed that the ulcer recurrence rate was similar after treatment with PPIs or H2RAs. No single study has shown that H2RAs are statistically superior to PPIs. The sample size obtained was quite small, just over 600 people for the study with the largest number of participants. Although there were more PPI users than H2RA users in the studies, there were five times fewer in the ulcer prevention group and 1.6 times more in the PWM group. When comparing the results of this meta-analysis with other studies in the world, such as those published in 2011, two meta-analyses, including six RCTs with 522 patients, were conducted by Z. Yang et al. [7] and 12 RCTs with 3301 patients from ZM Yi et al. [34] demonstrated that PPIs heal duodenal ulcers better than H2RAs. Furthermore, the most recent study by B. Scally et al. [35] on two subjects for the prevention and treatment of gastrointestinal ulcers in 2018, it was also concluded that PPIs were superior to H2RAs in ulcer healing. In contrast, to the report of JP Gisbert et al. [36] produces a completely different outcome when it is claimed that the H2RAs group has superior therapeutic benefits than the PPIs drug group. However, a detailed analysis of this paper reveals that it is a research paper on peptic ulcers that are *H. pylori* positive. When a patient has an *H. pylori* infection, a

combination of antibiotics to kill the bacteria is unavoidable, as is the aforementioned test. For that reason, this conclusion cannot yet prove whether H2RA is better than PPI or whether the combination of H2RA with antibiotics is better than PPI for *H. pylori* removal and ulcer healing.

According to some research, stomach acid serves as a natural barrier against infection, hence using PPIs or H2RAs to reduce gastric acid production over an extended period of time weakens this barrier and promotes the overproduction of gastric juice. Because of this, it's crucial to analyze RCTs that use PPIs and H2RAs in accordance with the dosage and indications of the BNF 83 (2022). In addition, the authors' research indicates that this study is one of the few that implements a meta-analysis model for PUD pathophysiology. Another strong point is that the use of PP data rather than ITT to most precisely determine clinical treatment success is a further benefit that has to be mentioned. This has helped to raise the validity and caliber of the research. Since PUD is a social disease that affects people not only in Viet Nam but also in other nations across the world, this meta-analysis has made a lot of sense when it comes to updating the treatment status for this disease.

#### 4 Conclusion

In general, the meta-analysis results show that PPIs are more effective than H2RAs in PWM and preventive individuals, with OR = 0.50 (95% CI: 0.31-0.80) and OR = 0.15 (95% CI: 0.05-0.44), respectively. The outcomes for patients who underwent drug-free ulcer recurrence rate monitoring were comparable, with a rate of 0.92 (95% CI: 0.75-1.14). The majority of the studies were high-quality, and none of these included high risk. Consequentially, PPIs are still typically the first line of treatment for conditions affecting the stomach and duodenum.

There are still a few things to consider in this meta-analysis, including the following: first of all, the studies that have been gathered have a small sample size, so the conclusions cannot account for the overall state of a region. Even while all RCTs have produced excellent healing results in the process of preventing ulcers, only a small number of studies have examined the recurrence rate after therapy, despite the fact that PUD is a condition that has the potential to become chronic.

Additionally, because just three specific data sources were used in the study, it is possible that crucial RCTs that could have improved the meta-analysis were overlooked. For the aforementioned reasons, the

authors suggest conducting more meta-analysis on more databases and paying closer attention to the patients' health monitoring.

## References

1. Malik, T. F., Gnanapandithan, K., & Singh, K. (2022). Peptic Ulcer Disease. In *StatPearls*. Treasure Island (FL).
2. Nguyễn Thị Huyền Trang, & Ngô Huy Hoàng. (2018). Thay đổi nhận thức về phòng tái phát bệnh của người bệnh loét dạ dày tá tràng sau can thiệp giáo dục tại Bệnh viện đa khoa tỉnh Nam Định 2017. *Tạp chí Khoa học Điều dưỡng*, 1(1), 28-34.
3. Ahmed, A., & Clarke, J. O. (2022). Proton Pump Inhibitors (PPI). In *StatPearls*. Treasure Island (FL): StatPearls Publishing
4. Proton Pump Inhibitors. (2012). In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases.
5. Histamine Type-2 Receptor Antagonists (H2 Blockers). (2012). In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases.
6. Gisbert, J. P., Gonzalez, L., Calvet, X., Roque, M., Gabriel, R., & Pajares, J. M. (2001). Proton pump inhibitors versus H2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. *Aliment Pharmacol Ther*, 15(7), 917-926. DOI:10.1046/j.1365-2036.2001.01012.x
7. Yang, Z., Wu, Q., Liu, Z., Wu, K., & Fan, D. (2011). Proton pump inhibitors versus histamine-2-receptor antagonists for the management of iatrogenic gastric ulcer after endoscopic mucosal resection or endoscopic submucosal dissection: a meta-analysis of randomized trials. *Digestion*, 84(4), 315-320. DOI:10.1159/000331138
8. Azab, M., Doo, L., Doo, D. H., Elmofti, Y., Ahmed, M., Cadavona, J. J., . . . Yoo, J. W. (2017). Comparison of the Hospital-Acquired Clostridium difficile Infection Risk of Using Proton Pump Inhibitors versus Histamine-2 Receptor Antagonists for Prophylaxis and Treatment of Stress Ulcers: A Systematic Review and Meta-Analysis. *Gut Liver*, 11(6), 781-788. DOI:10.5009/gnl16568
9. Zhang, G., Zou, J., Liu, F., Bao, Z., Dong, F., Huang, Y., & Yin, S. (2013). The efficacy of moxifloxacin-based triple therapy in treatment of Helicobacter pylori infection: a systematic review and meta-analysis of randomized clinical trials. *Brazilian Journal of Medical and Biological Research*, 46, 607-613.
10. Graham, D. Y., Hammoud, F., El-Zimaity, H. M., Kim, J. G., Osato, M. S., & El-Serag, H. B. (2003). Meta-analysis: proton pump inhibitor or H2-receptor antagonist for Helicobacter pylori eradication. *Aliment Pharmacol Ther*, 17(10), 1229-1236. DOI:10.1046/j.1365-2036.2003.01583.x
11. Bardhan, K. D., Bianchi Porro, G., Bose, K., Daly, M., Hinchliffe, R. F., Jonsson, E., . . . Walan, A. (1986). A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. *J Clin Gastroenterol*, 8(4), 408-413. DOI:10.1097/00004836-198608000-00005
12. Walan, A., Bader, J. P., Classen, M., Lamers, C. B., Piper, D. W., Rutgersson, K., & Eriksson, S. (1989). Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N Engl J Med*, 320(2), 69-75. DOI:10.1056/NEJM198901123200201
13. Londong, W., Barth, H., Dammann, H. G., Hengels, K. J., Kleinert, R., Muller, P., . . . Simon, B. (1991). Dose-related healing of duodenal ulcer with the proton pump inhibitor lansoprazole. *Aliment Pharmacol Ther*, 5(3), 245-254. DOI:10.1111/j.1365-2036.1991.tb00025.x
14. DALY, M. J. G. (1990). Double blind comparative study of omeprazole and ranitidine in patients with duodenal or gastric ulcer: a multicentre trial. *Gut*, 31(6), 653-656. DOI:10.1136/gut.31.6.653

15. Bardhan, K., Crowe, J., Thompson, R., Trewby, P., Keeling, P., Weir, D., . . . Group, U. E. L. (1999). Lansoprazole is superior to ranitidine as maintenance treatment for the prevention of duodenal ulcer relapse. *Alimentary Pharmacology & Therapeutics*, 13(6), 827-832.
16. Lauritsen, K., Rune, S. J., Bytzer, P., Kelbaek, H., Jensen, K. G., Rask-Madsen, J., . . . et al. (1985). Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. *N Engl J Med*, 312(15), 958-961. DOI:10.1056/NEJM198504113121505
17. Hata, M., Shiono, M., Sekino, H., Furukawa, H., Sezai, A., Iida, M., . . . Sezai, Y. (2005). Prospective randomized trial for optimal prophylactic treatment of the upper gastrointestinal complications after open heart surgery. *Circ J*, 69(3), 331-334. DOI:10.1253/circj.69.331
18. Ng, F. H., Wong, S. Y., Lam, K. F., Chu, W. M., Chan, P., Ling, Y. H., . . . Wong, B. C. (2010). Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. *Gastroenterology*, 138(1), 82-88. DOI:10.1053/j.gastro.2009.09.063
19. Tseng, Z. F., Hsu, P. I., Peng, N. J., Kao, S. S., Tsay, F. W., Cheng, J. S., . . . Shie, C. B. (2021). Omeprazole vs famotidine for the prevention of gastroduodenal injury in high-risk users of low-dose aspirin: A randomized controlled trial. *J Chin Med Assoc*, 84(1), 19-24. DOI:10.1097/JCMA.0000000000000465
20. Kim, N. Y., Oh, H. S., Jung, H. M., Wee, S. H., Choi, J. H., & Lee, K. H. (1994). The Effect of Eradication of *Helicobacter pylori* upon the Duodenal Ulcer Recurrence:—A 24 month follow-up study—. *The Korean Journal of Internal Medicine*, 9(2), 72.
21. Yeomans, N. D., Tulassay, Z., Juhasz, L., Racz, I., Howard, J. M., van Rensburg, C. J., . . . Hawkey, C. J. (1998). A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. *N Engl J Med*, 338(11), 719-726. DOI:10.1056/NEJM199803123381104
22. Lauritsen, K., Rutgersson, K., Bolling, E., Brunner, G., Eriksson, S., Galmiche, J., . . . Bailey, R. (1999). Omeprazole and ranitidine in the prevention of relapse in patients with duodenal ulcer disease. *Canadian Journal of Gastroenterology*, 13(10), 806-813.
23. Figura, N., Minoli, G., Fedeli, G., Cammarota, G., Mazzilli, D., & Bayeli, P. F. (1995). Omeprazole versus ranitidine in the prevention of duodenal ulcer recurrence after eradication therapy. *Current Therapeutic Research*, 56(6), 568-572. DOI:10.1016/0011-393x(95)85048-1
24. Chan, F. K., Kyaw, M., Tanigawa, T., Higuchi, K., Fujimoto, K., Cheong, P. K., . . . Arakawa, T. (2017). Similar Efficacy of Proton-Pump Inhibitors vs H2-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin. *Gastroenterology*, 152(1), 105-110 e101. DOI:10.1053/j.gastro.2016.09.006
25. Wong, G. L. H., Lau, L. H. S., Ching, J. Y. L., Tse, Y. K., Ling, R. H. Y., Wong, V. W. S., . . . Chan, F. K. L. (2020). Prevention of recurrent idiopathic gastroduodenal ulcer bleeding: a double-blind, randomised trial. *Gut*, 69(4), 652-657. DOI:10.1136/gutjnl-2019-318715
26. K. Lauritsen, M. D., Dept. (1989). Relapse of gastric ulcers after healing with omeprazole and cimetidine. A double-blind follow-up study. Danish Omeprazole Study Group. *Scand J Gastroenterol*, 24(5), 557-560. DOI:10.3109/00365528909093088
27. Hotz, J., Kleinert, R., Grymbowski, T., Hennig, U., & Schwarz, J. A. (1992). Lansoprazole versus famotidine: efficacy and tolerance in the acute management of duodenal ulceration. *Aliment Pharmacol Ther*, 6(1), 87-95. DOI:10.1111/j.1365-2036.1992.tb00548.x
28. Misra, S. C., Dasarathy, S., & Sharma, M. P. (1993). Omeprazole versus famotidine in the healing and relapse of duodenal ulcer. *Aliment Pharmacol Ther*, 7(4), 443-449. DOI:10.1111/j.1365-2036.1993.tb00118.x
29. Pan, S., Liao, C., Lien, G., Chen, S.-H. J. J. o. g., & hepatology. (1994). Histological maturity of healed duodenal ulcer and ulcer recurrence after treatment with omeprazole or cimetidine. *J Gastroenterol Hepatol*, 9(S1), S84-S87. DOI:10.1111/j.1440-1746.1994.tb01308.x

30. Archimandritis, A., Balatsos, V., Delis, V., Mentis, A., Kastanas, K., & Scandalis, N. (1995). Triple therapy eradicated *H. pylori* equally in patients pretreated with omeprazole or ranitidine. A 12-month follow-up. *J Clin Gastroenterol*, 20(1), 12-16. DOI:10.1097/00004836-199501000-00005
31. Spadaccini, A., De Fanis, C., Sciampa, G., Masciulli, V., Pantaleone, U., Di Virgilio, M., . . . Pizzicannella, G. (1996). Omeprazole versus ranitidine: short-term triple-therapy in patients with *Helicobacter pylori*-positive duodenal ulcers. *Aliment Pharmacol Ther*, 10(5), 829-831. DOI:10.1046/j.1365-2036.1996.54196000.x
32. Catalano, F., Catanzaro, R., Bentivegna, C., Brogna, A., Condorelli, G., Cipolla, R. J. A. p., & therapeutics. (1998). Ranitidine bismuth citrate versus omeprazole triple therapy for the eradication of *Helicobacter pylori* and healing of duodenal ulcer. *Aliment Pharmacol Ther*, 12(1), 59-62. DOI:10.1046/j.1365-2036.1998.00270.x
33. Diaz de Rojas, F., Berenguer, J., Rodrigo, L., Aran-Suau, R., Da Silveira, J. C., Clerch, L., . . . Caswell, C. (1998). Omeprazole and ranitidine in long-term treatment of duodenal ulcer: a double-blind comparison of length of time in remission. *Dig Dis Sci*, 43(9), 1964-1969. DOI:10.1023/a:1018882425236
34. Yi, Z.-M., Qiu, T.-T., Zhang, Y., Liu, Z.-Y., & Zhai, S.-D. (2017). Comparison of prophylactic effect of UGIB and effects on platelet function between PPIs and H2RAs combined with DAPT: systematic review and meta-analysis. *Therapeutics and Clinical Risk Management*, 13, 367.
35. Scally, B., Emberson, J. R., Spata, E., Reith, C., Davies, K., Halls, H., . . . Hawkey, C. (2018). Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. *The Lancet Gastroenterology & Hepatology*, 3(4), 231-241.
36. Beales, I. L. (2001). Efficacy of *Helicobacter pylori* eradication therapies: a single centre observational study. *BMC Gastroenterology*, 1(1), 1-9.

## So sánh hiệu quả dùng đường uống giữa PPIs và H2RAs trên đối tượng dự phòng và theo dõi tỉ lệ tái phát liên quan đến loét dạ dày-tá tràng từ năm 1985-2022: đánh giá hệ thống và phân tích tổng hợp

Cao Kim Xoa<sup>1</sup>, Trần Võ Ngọc Minh<sup>1</sup>, Nguyễn Diễm Kiều<sup>2</sup>

<sup>1</sup>Khoa Dược, Đại học Nguyễn Tất Thành

<sup>2</sup>Khoa Dược, Bệnh viện Phạm Ngọc Thạch

ckxoa@ntt.edu.vn

**Tóm tắt** Hiện nay, mặc dù có nhiều nghiên cứu ngẫu nhiên đối chứng so sánh hiệu quả của thuốc ức chế bơm proton và thuốc kháng histamin H2 liên quan đến bệnh lí loét dạ dày-tá tràng nhưng các nghiên cứu phân tích gộp về đề tài này còn hạn chế và những kết luận chưa đi đến thống nhất. Vậy nên, một phân tích theo mô hình tổng hợp các RCT được đánh giá chất lượng bằng công cụ Cochrane Collaboration là điều cần thiết. Nghiên cứu được sàng lọc trên 3 nguồn dữ liệu Pubmed, Cochrane, Embase từ 01/01/1985 đến 31/05/2022. Số liệu thống kê được thể hiện dưới dạng tỉ số chênh, khoảng tin cậy (KTC) là 95 % và sử dụng mô hình hiệu ứng ngẫu nhiên. Kết quả: thuốc ức chế bơm proton có hiệu quả điều trị tốt hơn thuốc kháng histamin H2. Cụ thể trên đối tượng dự phòng là 0,15 (KTC 95 %: 0,05-0,44), theo dõi tỉ lệ tái phát sau điều trị không dùng thuốc là 0,92 (KTC 95 %: 0,75-1,14) và có dùng thuốc là 0,50 (KTC 95 %: 0,31-0,80). Kết luận: thuốc ức chế bơm proton là thuốc đầu tay trong dự phòng và theo dõi tỉ lệ tái phát sau khi điều trị lành vết loét.

**Từ khóa** phân tích gộp, dự phòng loét, tái phát vết loét, loét dạ dày-tá tràng