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Comparative efficacy of various anti-ulcer medications after gastric endoscopic submucosal dissection: a systematic review and network meta-analysis

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Abstract

Background The comparative efficacy of various anti-ulcer medications after gastric endoscopic submucosal dissection (ESD) has not been fully evaluated. Recently, vonoprazan, a novel potassium-competitive acid blocker, has also been used in ulcer treatment after ESD.

Methods We searched for all relevant randomized controlled trials examining the efficacy of anti-ulcer medications after gastric ESD, published through October 2017. Healing of iatrogenic ulcers was investigated at 4–8 weeks after ESD. A network meta-analysis was performed to calculate the network estimates.

Results Twenty-one studies with 2005 patients were included. Concerning the comparative efficacy for ulcer healing at 4 weeks after ESD, no network inconsistency was identified (Cochran's Q-test, df = 10, $P = 0.13$; $I^2 = 34\%$). A combination therapy of proton-pump inhibitor (PPI) and muco-protective agent was superior to PPI alone [risk ratio (RR) (95% confidence interval, CI) 1.69 (1.20–2.39)]. The combination therapy of PPI and muco-protective agents tended to be superior to vonoprazan [RR (95% CI) 1.98 (0.99–3.94)]. There was no difference of ulcer healing effect between PPI and vonoprazan [RR (95% CI) PPI vs. vonoprazan, 1.17 (0.64–2.12)]. Concerning the ulcer healing rate at 8 weeks after ESD, however, vonoprazan was superior to PPI [RR (95% CI) 1.27 (1.03–1.56)]. Additionally, vonoprazan tended to be superior to the combination therapy of PPI and muco-protective agent [RR (95% CI) 1.20 (0.96–1.51)].

Conclusions A combination therapy of PPI and muco-protective agent was superior to PPI alone for ulcer healing at 4 weeks after ESD. In the ulcer healing effect at 8 weeks after ESD, vonoprazan was superior to PPI.

Keywords Endoscopic submucosal dissection · Anti-ulcer medication · Proton-pump inhibitor · Vonoprazan

Gastric endoscopic submucosal dissection (ESD) has been widely used for the treatment of early gastric cancer and gastric adenoma [1]. Despite the minimal invasiveness of ESD, iatrogenic ulcer bleeding is a concern because it is the most common adverse event after the procedure and can be life threatening [2, 3]. To prevent iatrogenic ulcer bleeding, endoscopists may perform second-look endoscopy after ESD [4]. Unfortunately, however, many studies reported that second-look endoscopy cannot reduce the risk of post-ESD bleeding [5].

Currently, the best way to reduce iatrogenic ulcer bleeding is to administer anti-ulcer drugs, including proton-pump

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inhibitors (PPIs) [3]. Several studies reported that PPIs were superior to histamine-2-receptor antagonists (H2RAs) in terms of avoiding bleeding [3, 6]. In addition, it has been suggested that a combination therapy of PPI and muco-protective agents including rebamipide may be effective for iatrogenic ulcer healing [6].

Recently, vonoprazan (VPZ), a novel potassium-competitive acid blocker, has been used for gastric acid inhibition [7]. Similar to PPIs, VPZ inhibits gastric H^+/K^+-adenosine triphosphatase [8]. However, it has a more rapid and potent acid-inhibitory effect than PPIs [7]. The efficacy of VPZ has been proven in various gastrointestinal diseases, including erosive esophagitis, peptic ulcers, and *Helicobacter pylori* infection [9–11]. In addition, one prospective study with a historical comparison showed that the risk of post-ESD bleeding can be reduced through the administration of VPZ after ESD [12]. VPZ may be a promising drug that facilitates iatrogenic ulcer healing.

To date, two pairwise meta-analyses have compared iatrogenic ulcer healing between PPI and H2RA, or between PPI alone and PPI with a muco-protective agent [6, 13]. However, comprehensive comparisons among the various drug regimens for iatrogenic ulcers have yet to be conducted. In addition, there are other studies comparing iatrogenic ulcer healing between PPI and muco-protective agents, H2RA and muco-protective agents, or PPI and VPZ [14–18]. In this situation, all relevant evidence, both direct and indirect, should be considered in order to fully analyze each pairwise comparison [19]. Unlike the traditional pairwise meta-analysis, a network meta-analysis can synthesize direct and indirect estimates of multiple drug regimens [20]. In this study, therefore, we conducted a network meta-analysis of randomized controlled trials (RCTs) in order to identify the efficacy of various drug regimens for iatrogenic ulcer healing after ESD.

Methods

This systematic review and network meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [21] and the report of the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons Good Research Practices [22]. Approval of Institutional Review Board was not needed in this study because the meta-analysis only analyzed data derived from published articles or abstract proceedings.

Search strategy

We searched for all relevant studies published between January 1970 and October 2017 that examined the efficacy of anti-ulcer medications after gastric endoscopic resection, by using the MEDLINE, Embase, and Cochrane Library databases. The following search string was used: ((ESD) OR (endoscopic submucosal dissection) OR (EMR) OR (endoscopic mucosal resection) OR (iatrogenic) OR (artificial)) AND (ulcer*) AND ((vonoprazan) OR (TAK-438) OR (revaprazan) OR (YH1885) OR ((potassium) AND (competitive)) OR (potassium-competitive) OR (PPI) OR (proton pump inhibitor*) OR (dexlansoprazole) OR (esomeprazole) OR (ilaprazole) OR (lansoprazole) OR (omeprazole) OR (pantoprazole) OR (rabeprazole) OR (((histamine) OR (histamine2) OR (histamine-2) OR (h2) OR (h-2)) AND ((antagonist*) OR (blocker*))) OR (h2ra) OR (famotidine) OR (cimetidine) OR (ranitidine) OR (nizatidine) OR (lafutidine) OR (misoprostol) OR (rebamipide) OR (ecabet) OR (irsogladine) OR (polaprezinc) OR (muco-protective) OR (mucoprotective)). The detailed search strategies for each database are shown in "Appendix". In order to identify additional studies, we also examined the references of the screened articles. The latest date for updating our search was October 31, 2017.

Study selection

In the first stage of the study selection, the titles and abstracts of papers identified by our search were examined to exclude irrelevant articles. Next, the full texts of all selected studies were screened according to inclusion and exclusion criteria. The inclusion criteria were as follows: (a) patients: patients who underwent gastric ESD; (b) intervention: anti-ulcer medication after the procedure; (c) comparator: another regimen of anti-ulcer medication; and (d) outcome: ulcer healing rate. The exclusion criteria were (a) non-RCTs, (b) non-human studies, and (c) publications in a language other than English.

Two investigators (E.H.K. and C.H.P.) independently evaluated the studies for eligibility and resolved any disagreements through discussion and consensus. If no agreement could be reached, a third investigator (S.W.P.) determined eligibility. The Cochrane Risk of Bias assessment tool was used for assessing the risk of bias in individual studies [23].

Data extraction

Using a data extraction form developed in advance, two reviewers (E.H.K. and C.H.P.) independently extracted the following information from each chosen study: first author, year of publication, study design, country, enrollment period, drug name and dosage of anti-ulcer medications, assessment timing of ulcer healing, and ulcer healing rate according to the drug regimens. The assessment timing of ulcer healing was categorized into two groups (4 weeks

after ESD vs. 8 weeks after ESD), by using a cutoff value of 6 weeks because most studies reported the ulcer healing rate at 4 or 8 weeks after endoscopic resection whereas a few studies assessed iatrogenic ulcer at 4–6 weeks after ESD.

The primary end point of this meta-analysis was the comparative efficacy of anti-ulcer drug regimens for iatrogenic ulcer healing at 4 weeks after ESD. The secondary end point was the comparative efficacy of anti-ulcer drug regimens for iatrogenic ulcer healing at 8 weeks after ESD.

Quality of evidence

Quality of evidence was rated for results from the network meta-analysis according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) working group approach [24]. In this approach, the rating of estimates from the direct evidence of RCTs begins with a high quality rating. The rating can then be lowered to moderate, low, and very low quality, based on the risk of bias, indirectness, imprecision, heterogeneity, and/or publication bias. The rating of estimates from indirect evidence begins with a lowest rating of the two pairwise estimates that make the first-order loops for indirect estimate. The rating is lowered when imprecision or intransitivity is identified. If there was no network inconsistency for each comparison, the higher of the ratings between direct and indirect estimates was considered as the rating of network meta-analysis estimates. If the first-order loops were not made between any two comparators, the rating of direct estimates was regarded as that of network estimates.

Statistical analysis

We calculated the pooled estimates of ulcer healing rates with 95% confidence intervals (CIs) in each regimen. Then, to compare the ulcer healing effect for each pairwise comparison, pooled risk ratios (RRs) with 95% CIs were calculated through direct meta-analysis using a random-effects model with Mantel–Haenszel methods. Statistical heterogeneity was assessed using two methods: Cochrane's Q-test, in which values were considered statistically significant for heterogeneity if P was <0.1, and I^2 statistics, wherein values $>50\%$ suggested significant heterogeneity [25]. The test for funnel plot asymmetry was not conducted when the number of included studies for each pairwise comparison was <10 [26]. The pooled estimate of ulcer healing rate was calculated using Comprehensive Meta-Analysis (version 2.2.064; Biostat Inc., Englewood, NJ, USA). Direct pairwise meta-analysis was performed using Review Manager 5.3 statistical software (version 5.3.5; Cochrane Collaboration, Copenhagen, Denmark).

A frequentist network meta-analysis was performed to calculate the direct and indirect estimates, and to combine the mixed estimates [27]. In addition, we calculated P-scores, which measured the extent of certainty that one treatment was better than another treatment, averaged over all competing treatments [28]. To assess the robustness of results from the network meta-analysis, we performed a sensitivity analysis after excluding abstract-only publications. Network meta-analysis was conducted using the statistical software R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria) with the netmeta package (version 0.9-1; Rücker et al. [28]).

Results

Study selection

A flow diagram for our systematic review is shown in Fig. 1. A total of 539 studies were identified by our literature search. After scanning titles and abstracts, we discarded 171 duplicate articles retrieved through multiple search engines. Another 343 irrelevant articles were excluded based on the titles and abstracts. After the full texts of the 25 remaining articles were reviewed, three studies that did not provide ulcer healing rates and one study published in a language other than English [29] were excluded. Finally, 21 RCTs were included in our meta-analysis [14–16, 18, 30–46]. Among them, three were abstract-only publications [40, 43, 46], whereas the others were original articles.

Study characteristics and risk of bias assessment

The studies were published between 2005 and 2017 with an enrollment period that ranged from 2003 to 2016 (Table 1). They included a total of 2,005 patients who underwent ESD for gastric neoplasms. Among 18 original articles, one included patients who had undergone either gastric EMR or ESD [30]. The remaining 17 original articles included only patients who had undergone gastric ESD [14–16, 18, 31–39, 41, 42, 44, 45]. In addition, three abstract-only publications included only patients who had been treated with ESD [40, 43, 46]. Healing of iatrogenic ulcer at 4 weeks (or 6 weeks) after the procedure was assessed in 14 studies, and ulcer healing at 8 weeks after the procedure was assessed in 11 studies. Figure S1 shows the network of included studies according to the assessment timing of iatrogenic ulcer healing.

Quality assessments for individual studies are presented in Fig. S2. Seven studies (33.3%) showed a low risk of selection bias. However, high risk of selection bias was identified in one study (4.8%). The study allocated patients to one of the groups alternatively. In addition, all studies did not clarify how allocation concealment was performed. Performance bias was assessed as low risk in all studies, as ulcer healing

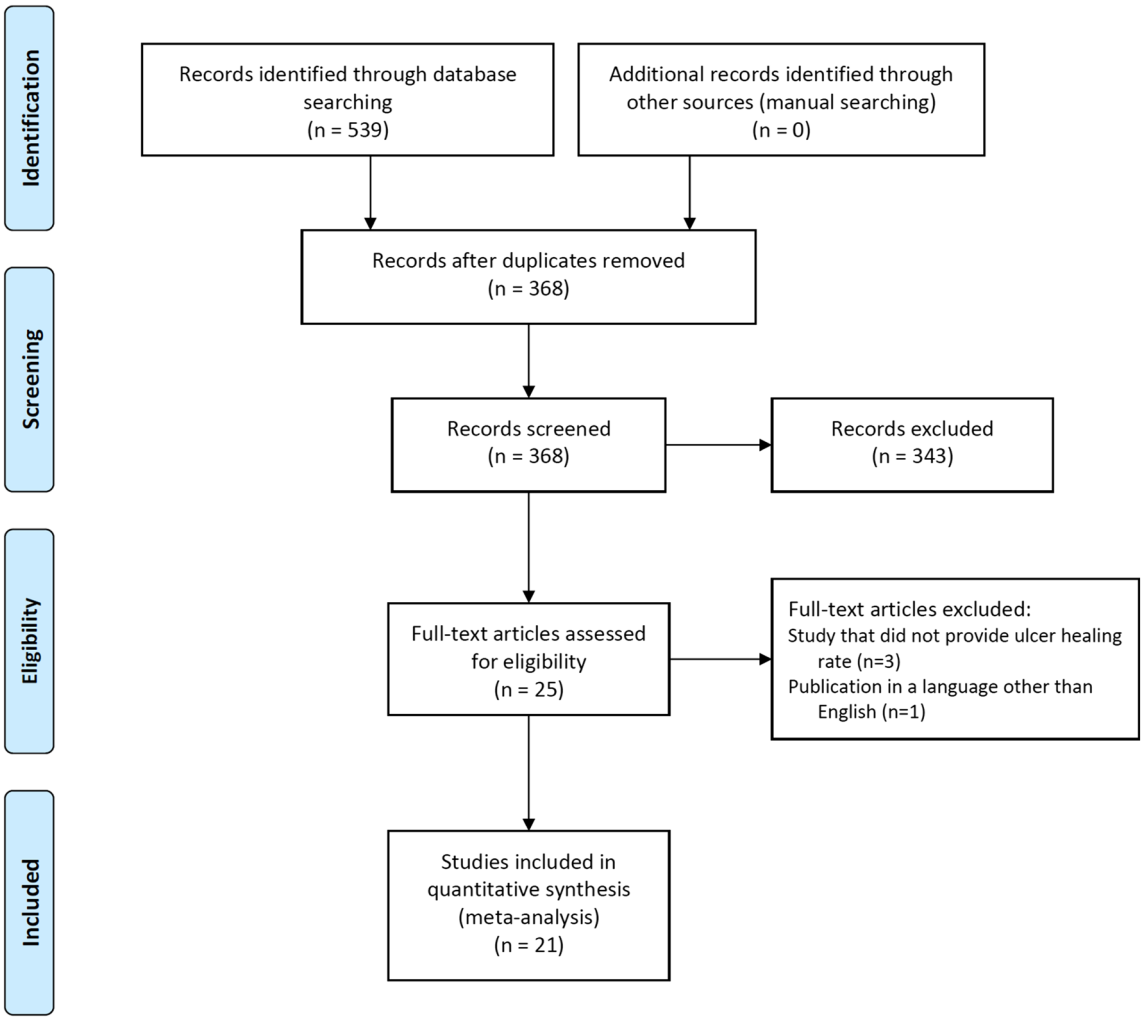

Fig. 1 Flow diagram of the studies included in the meta-analysis

is unlikely to be affected by blinding of the participants. Detection bias was assessed as high risk in one study (4.8%), because the study clarified that blinding was not performed during the endoscopic examination for the assessment of ulcer healing. Eleven studies (52.4%) did not provide any information about blinding of outcome assessors. In the remaining nine studies (42.9%), ulcer healing was assessed by blinded investigators. Three abstract-only publications (14.3%) were regarded as having a high risk of other biases. In addition, one study by Takahashi et al. [14] was regarded as having a high risk of other biases because the study used a different definition of ulcer healing (> 90% healing of ulcer base rather than complete healing) from other studies.

Pooled estimate of ulcer healing rate

The pooled estimate of ulcer healing rate of PPI therapy was 25.0% (95% CI 15.7–37.5%) at 4 weeks and 80.5% (95% CI 76.0–84.4%) at 8 weeks after the procedure. In cases of a combination therapy of PPI and a muco-protective agent, the pooled estimate of ulcer healing rate was 26.1% (95% CI 15.8–39.9%) at 4 weeks and 84.3% (95% CI 77.8–89.2%) at 8 weeks after the procedure. Although VPZ showed a high ulcer healing rate at 4 weeks after the procedure [78.6% (95% CI 50.6–92.9%)], the data should be cautiously interpreted because only one study was included in the analysis and the study used a different definition of ulcer healing from that of other studies [14]. Detailed data about the pooled estimate of ulcer healing rate in each regimen are shown in Table S1.

Pairwise meta-analysis of anti-ulcer medications

Figure 2 shows direct comparisons of iatrogenic ulcer healing at 4 weeks after the procedure by using a traditional pairwise meta-analysis. There was no difference in ulcer healing at 4 weeks after the procedure for VPZ versus PPI, H2RA versus PPI, and muco-protective agent alone versus PPI;

Table 1 Baseline characteristics of included studies

First author	Year of publication	Type of publication	Country	Study period	Comparison	Number of patients	Age, mean ± SD, year	Male (%)	Drug regimen		Assessment of ulcer healing
									Group A	Group B	
Yamaguchi	2005	Original article	Japan	2003–2004	A: PPI B: H2RA	57	A: 71.8 ± 9.2 B: 72.5 ± 8.6	A: 69.0 B: 82.1	OPZ 20 mg	Famotidine 40 mg	8 weeks
Uedo	2007	Original article	Japan	2005–2006	A: PPI B: H2RA	106	A: 68.1 ± 8.5 B: 65.7 ± 7.6	A: 78.1 B: 78.6	RPZ 20 mg	Cimetidine 800 mg	8 weeks
Asakuma	2009	Original article	Japan	2006–2007	A: PPI B: PPI + mucoprotective agent	55	A: 71.4 ± 9.3 B: 70.1 ± 9.0	A: 64.3 B: 60.7	RPZ 40 mg	RPZ 20 mg + ecabet sodium 3 g	4 or 8 weeks
Inaba	2010	Original article	Japan	2005–2008	A: PPI B: PPI + mucoprotective agent	159	A: 69.8 ± 8.8 B: 71.3 ± 8.7	A: 74.0 B: 74.0	LPZ 30 mg	LPZ 30 mg + polaprezinc 150 mg	8 weeks
Kato	2010	Original article	Japan	2006–2007	A: PPI B: PPI + mucoprotective agent	62	A: median (range), 73 (57–82) B: median (range), 73(50–87)	A: 77.4 B: 64.5	RPZ 10 mg	RPZ 10 mg + rebamipide 300 mg	4 weeks
Ohya	2010	Original article	Japan	2005–2006	A: PPI B: H2RA	64	A: 65.4 ± 9.0 B: 65.3 ± 8.0	A: 74.2 B: 72.4	RPZ 10 mg	Lafutidine 20 mg	4 weeks
Fujiwara	2011	Original article	Japan	2007–2009	A: PPI B: PPI + mucoprotective agent	61	A: 69 ± 7 B: 68 ± 7	A: 77.4 B: 70.0	RPZ 20 mg	RPZ 20 mg + rebamipide 300 mg	8 weeks
Imaeda	2011	Original article	Japan	2008–2010	A: PPI B: H2RA	123	A: 68.4 ± 8.0 B: 67.6 ± 8.5	A: 75.8 B: 85.2	LPZ 30 mg	Roxatidine 150 mg	8 weeks
Araki	2012	Original article	Japan	2007–2010	A: PPI B: PPI + mucoprotective agent	87	A: median (range), 69.5 (52–85) B: median (range), 71 (45–87)	A: 71.4 B: 66.7	PPI (OPZ 20 mg, LPZ 30 mg, or RPZ 10 mg)	PPI (OPZ 20 mg, LPZ 30 mg, or RPZ 10 mg) + rebamipide	4 weeks
Kobayashi	2012	Original article	Japan	2009–2010	A: PPI B: PPI + mucoprotective agent	170	A: 70.8 ± 9.0 B: 70.0 ± 9.0	A: 80.0 B: 77.6	RPZ 20 mg (or LPZ 30 mg)	RPZ 20 mg (or LPZ 30 mg) + rebamipide 300 mg	4–6 weeks
Shin	2012	Original article	Korea	2008–2010	A: PPI B: PPI + mucoprotective agent	278	A: 64.9 ± 10.2 B: 63.4 ± 10.0	A: 69.0 B: 68.2	PPZ 40 mg	PPZ 40 mg + rebamipide 300 mg	4 weeks

Table 1 (continued)

First author	Year of publication	Type of publication	Country	Study period	Comparison	Number of patients	Age, mean ± SD, year	Male (%)	Drug regimen		Assessment of ulcer healing
									Group A	Group B	
Tomita	2012	Original article	Japan	2008–2010	A: PPI B: H2RA	140	A: 70.4 ± 8.7 B: 70.6 ± 9.5	A: 76.6 B: 74.7	OPZ 20 mg	Famotidine 40 mg	6 weeks
Takayama	2013	Original article	Japan	2011–2013	A: PPI B: mucoprotective agent	89	A: 70 ± 7.8 B: 67 ± 8.0	A: 80.0 B: 68.9	LPZ 30 mg	Rebamipide 300 mg	4 or 8 weeks
Ahn	2015	Original article	Korea	2008–2009	A: PPI B: mucoprotective agent	79	A: 62.9 ± 7.8 B: 61.5 ± 7.4	A: 57.5 B: 69.2	LPZ 30 mg	Ecabet sodium 3 g	4 weeks
Nakamura	2015	Original article	Japan	N/A	A: PPI B: PPI + mucoprotective agent	67	A: 67 ± 6 B: 68 ± 8	A: 77.8 B: 79.4	RPZ 20 mg	RPZ 20 mg + rebamipide 300 mg	4 or 8 weeks
Nakamura	2016	Original article	Japan	2010–2012	A: PPI B: PPI + mucoprotective agent	121	A: 70.3 ± 8.6 B: 68.7 ± 8.5	A: 64.1 B: 65.2	RPZ 10 mg	RPZ 10 mg + rebamipide 300 mg	4 or 8 weeks
Takahashi	2016	Original article	Japan	2015–2016	A: VPZ B: PPI	26	A: 71.9 ± 7.9 B: 74.8 ± 8.3	A: 85.7 B: 83.3	VPZ 20 mg	LPZ 30 mg	4 weeks
Tsuchiya	2016	Original article	Japan	2015–2016	A: VPZ B: PPI	80	A: median (IQR), 73 (67.5–80) B: median (IQR), 74 (71–80)	A: 69.2 B: 73.2	VPZ 20 mg	EPZ 20 mg	8 weeks
Matsui	2012	Abstract	Japan	N/A	A: PPI B: mucoprotective agent	54	N/A	N/A	LPZ 30 mg	Rebamipide 300 mg	4 weeks
Miyahara	2013	Abstract	Japan	N/A	A: PPI B: PPI + mucoprotective agent	96	N/A	N/A	RPZ 10 mg	RPZ 10 mg + irsogladine 4 mg	4 weeks
Ban	2017	Abstract	Japan	N/A	A: VPZ B: PPI	31	N/A	N/A	VPZ 20 mg	LPZ 30 mg	8 weeks

H2RA histamine-2 receptor antagonist, *OPZ* omeprazole, *RPZ* rabeprazole, *LPZ* lansoprazole, *EPZ* esomeprazole, *SD* standard deviation, *IQR* interquartile range, *N/A* not available

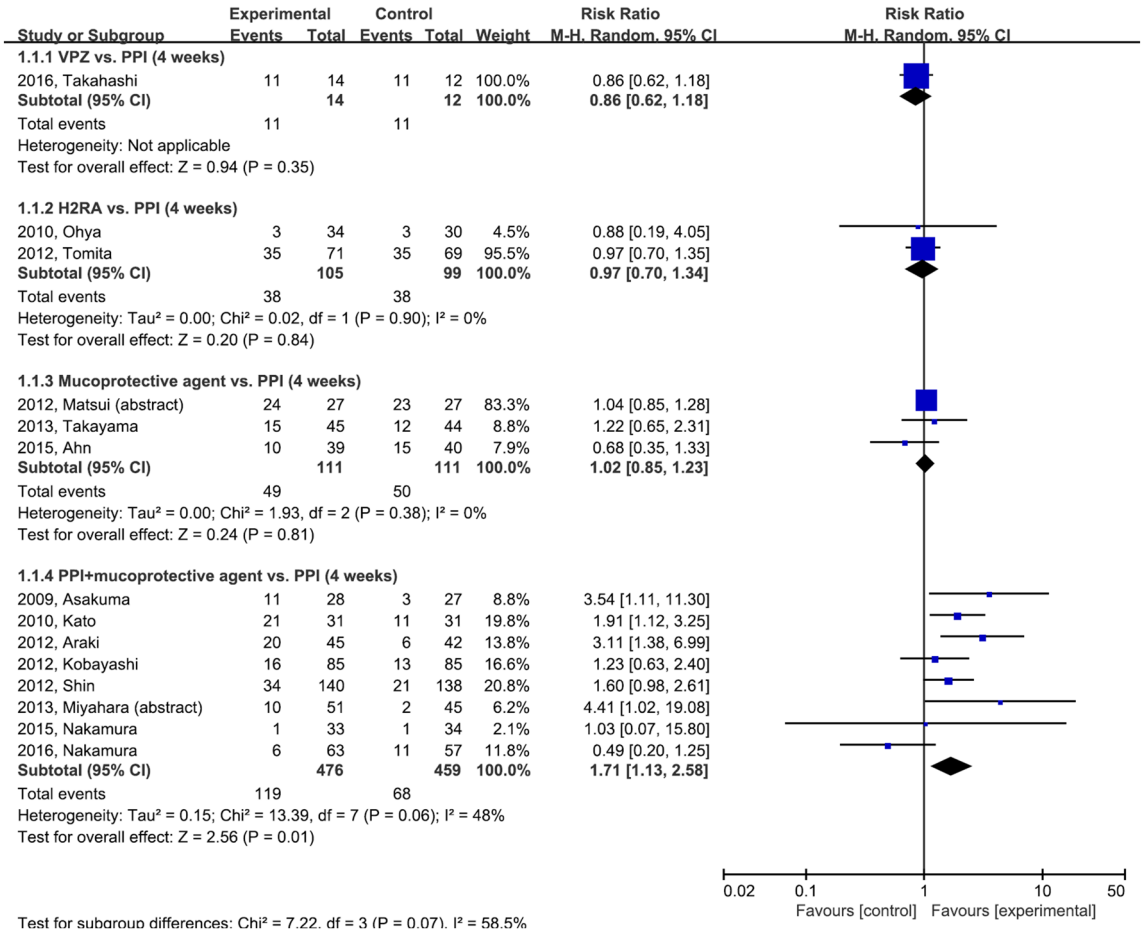

Fig. 2 Direct meta-analysis of different anti-ulcer medications for iatrogenic ulcer healing at 4 weeks after the procedure. *VPZ* vonoprazan, *PPI* proton-pump inhibitor, *H2RA* histamine-2 receptor antagonist, *CI* confidence interval

however, the combination therapy of PPI and a muco-protective agent was superior to PPI alone [RR (95% CI) 1.71 (1.13–2.58); Cochran's Q-test, df = 7, $P = 0.06$; $I^2 = 48\%$].

Direct comparisons of iatrogenic ulcer healing at 8 weeks after the procedure are shown in Fig. 3. Although the combination therapy of PPI and a muco-protective agent tended to be superior to PPI alone [RR (95% CI) 1.09 (0.94–1.25)], there was no significant difference. In comparisons between VPZ and PPI, VPZ tended to be superior to PPI in terms of ulcer healing at 8 weeks after the procedure, although statistical significance was not identified [RR (95% CI) 1.44 (0.83–2.48)].

Network meta-analysis of anti-ulcer medications

The pooled summary estimates derived from network meta-analysis for iatrogenic ulcer healing at 4 weeks after the procedure are demonstrated in Fig. 4. Concerning ulcer healing at 4 weeks after the procedure, network inconsistency was not identified (Cochran's Q-test, df = 10, $P = 0.13$; $I^2 = 34\%$). The combination therapy of PPI and a muco-protective agent was superior to PPI alone [RR (95% CI) 1.69 (1.23–2.31), high quality of evidence]. The combination therapy of PPI and a muco-protective agent tended to be superior to VPZ [RR (95% CI) 1.98 (0.99–3.94), very low quality of evidence]. There was no difference of ulcer healing effect between PPI and VPZ [RR (95% CI): PPI vs. VPZ, 1.17 (0.64–2.12), very low quality of evidence]. The detailed values of comparative efficacy at 4 weeks after the procedure among groups are shown in Table S2. The P-score of the combination therapy of PPI and a muco-protective agent for ulcer healing at 4 weeks after the procedure was 97.6%. The P-scores of PPI and VPZ were 44.5% and 27.0%, respectively.

Figure 5 shows the pooled summary estimates derived from the network meta-analysis for ulcer healing at 8 weeks after the procedure. Concerning ulcer healing at 8 weeks after the procedure, a modest network inconsistency was identified by Chi square test (Cochran's Q-test, df = 7, $P = 0.09$; $I^2 = 44\%$). Unlike the comparison at 4 weeks,

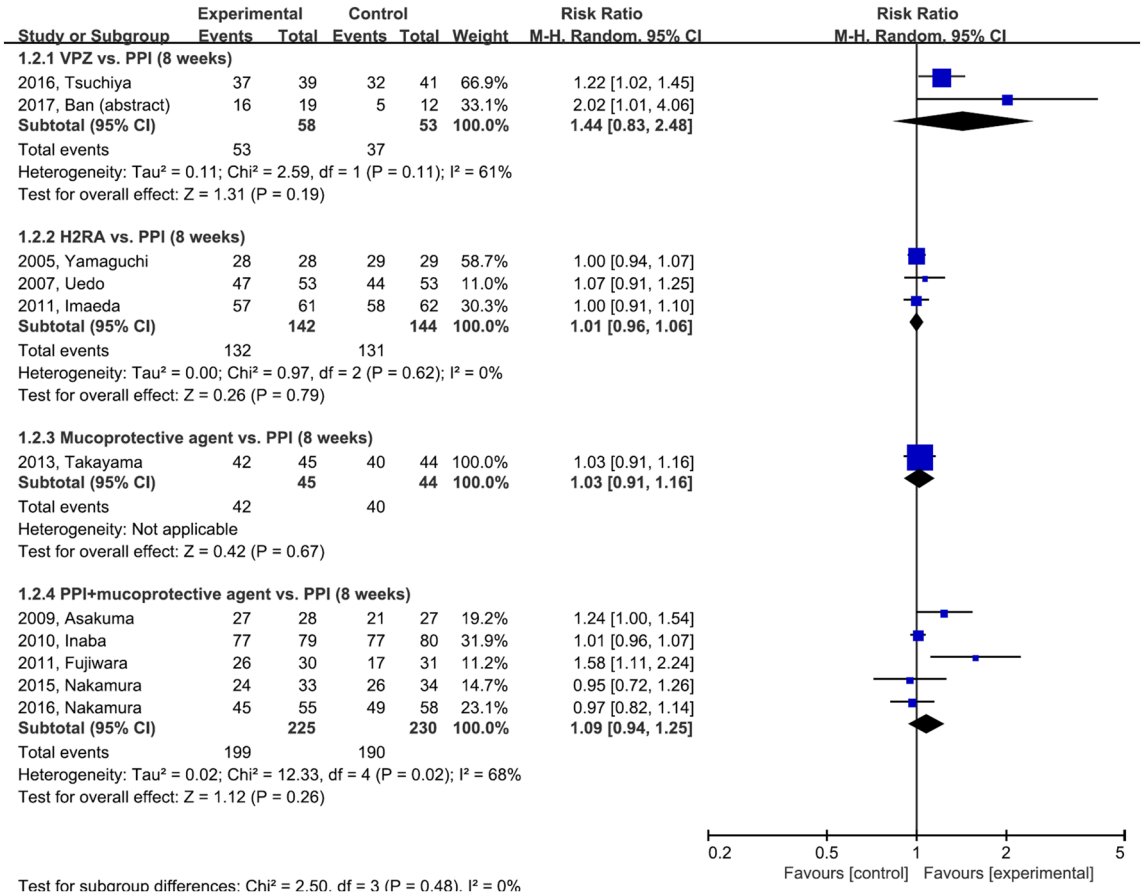

Fig. 3 Direct meta-analysis of different anti-ulcer medications for iatrogenic ulcer healing at 8 weeks after the procedure. *VPZ* vonoprazan, *PPI* proton-pump inhibitor, *H2RA* histamine-2 receptor antagonist, *CI* confidence interval

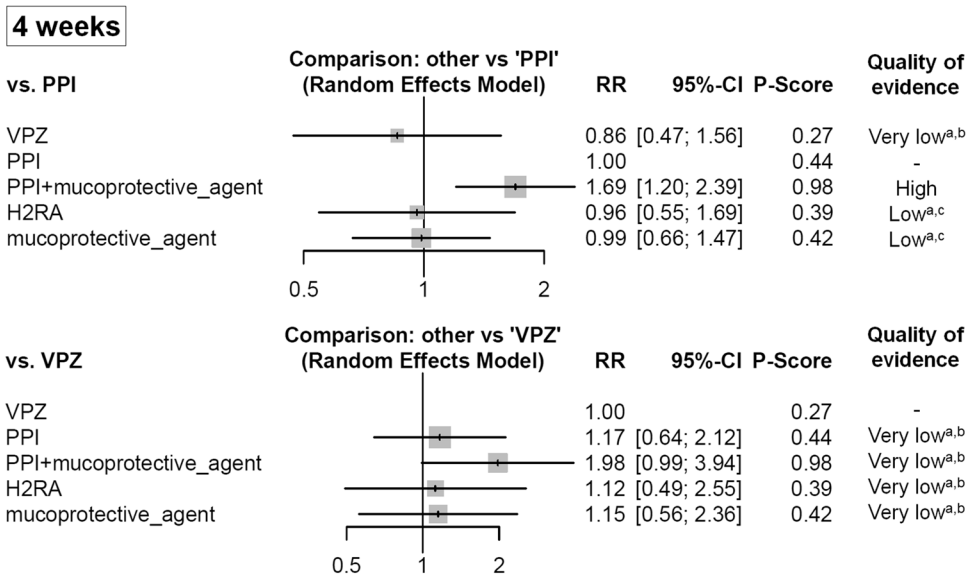

Fig. 4 Comparative efficacy of anti-ulcer medications for iatrogenic ulcer healing at 4 weeks after the procedure from the network meta-analysis. *VPZ* vonoprazan, *PPI* proton-pump inhibitor, *H2RA* histamine-2 receptor antagonist, *RR* risk ratio, *CI* confidence interval. Small letter 'a' represents rated down for imprecision. Small letter 'b' represents rated down twice because estimate was derived from a single study. Small letter 'c' represents rated down due to small number of included studies

VPZ showed the highest P-score among the regimens (96.0%), whereas the combination therapy of PPI and a muco-protective agent showed a P-score of 57.1%. VPZ was superior to PPI in terms of ulcer healing at 8 weeks after the procedure [RR (95% CI) 1.27 (1.03–1.56), low quality of evidence]. In addition, VPZ tended to be superior to

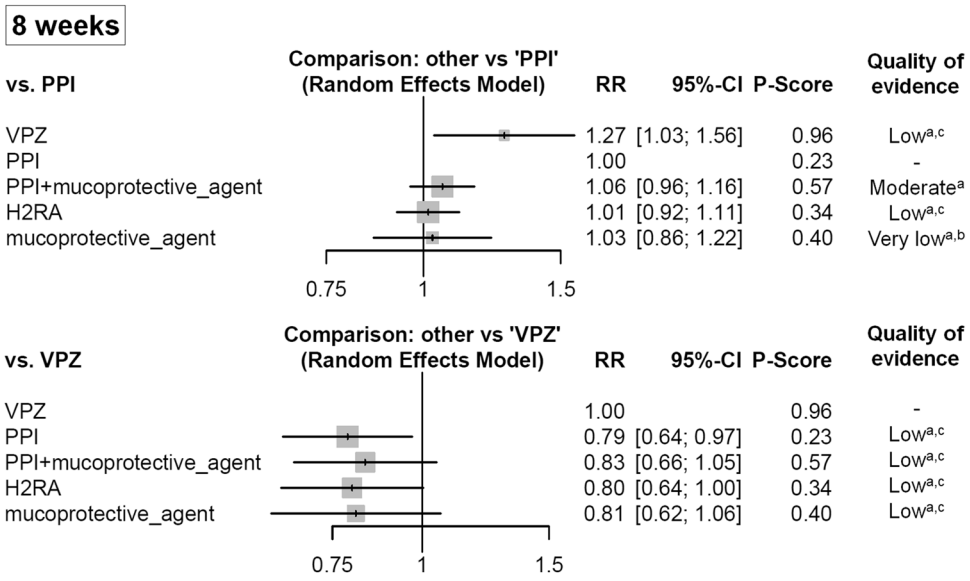

Fig. 5 Comparative efficacy of anti-ulcer medications for iatrogenic ulcer healing at 8 weeks after the procedure from the network meta-analysis. *VPZ* vonoprazan, *PPI* proton-pump inhibitor, *H2RA* histamine-2 receptor antagonist, *RR* risk ratio, *CI* confidence interval

PPI + muco-protective agent [RR (95% CI) 1.20 (0.96–1.51), low quality of evidence]. The detailed values of comparative efficacy at 8 weeks after the procedure among groups are shown in Table S3.

Sensitivity analysis

Network meta-analysis estimates, which were calculated using sensitivity analyses, are shown in Fig. S3. Overall, the results from the sensitivity analysis were similar to the main outcomes. Even after excluding abstract-only publications, the combination therapy of PPI and a muco-protective agent showed superior results of ulcer healing at 4 weeks after the procedure compared with PPI alone [RR (95% CI) 1.69 (1.23–2.31)]. In addition, the combination therapy of PPI and a muco-protective agent was superior to VPZ [RR (95% CI) 1.97 (1.09–3.56)]. Concerning the comparative efficacy for ulcer healing at 8 weeks after the procedure, VPZ tended to be superior to other regimens [RR (95% CI) vs. PPI alone, 1.22 (0.98–1.50); vs. PPI + muco-protective agent, 1.15 (0.92–1.45); vs. H2RA, 1.20 (0.95–1.51); vs. muco-protective agent, 1.18 (0.90–1.55)].

Discussion

With the improvements in endoscopic devices, ESD has become safer than ever [3]. Nevertheless, the incidence of post-ESD ulcer bleeding has been reported to be approximately 5% [5]. It has been well known that second-look endoscopy after gastric ESD cannot reduce the risk of delayed bleeding [5]. Moreover, post-ESD ulcers treated with prophylactic hemostasis during second-look endoscopy are more likely to have bleeding than those that do not [5]. Therefore, attention has been focused on pharmacologic therapy rather than endoscopic intervention for preventing iatrogenic ulcer bleeding.

As is well known, the most commonly used anti-ulcer medication is PPI [3]. However, currently, two treatment options to further promote iatrogenic ulcer healing can be considered. The first option is a combination therapy of PPI and a muco-protective agent, and the second one is VPZ therapy. At 4 weeks after the procedure, in our meta-analysis, the ulcer healing rate was higher in the combination therapy of PPI and a muco-protective agent than in PPI alone. The combination therapy of PPI and a muco-protective agent showed a 69% higher ulcer healing rate than the PPI alone therapy. In addition, the ulcer healing rate of the combination therapy of PPI and a muco-protective agent tended to be higher than that of VPZ at 4 weeks after the procedure. In contrast to the results at 4 weeks after the procedure, the ulcer healing effect at 8 weeks after the procedure was the highest in VPZ therapy, among the regimens. VPZ therapy showed an about 20–27% higher ulcer healing rate than the other regimens. In summary, the combination therapy of PPI and a muco-protective agent is effective for ulcer healing in the early phase, whereas VPZ therapy is effective for final ulcer healing at 8 weeks after the procedure.

The superiority of VPZ in terms of the final healing rate may be due to its potent and long-lasting acid-inhibitory effect without the need for acidity [8]. The prodrug form of PPI requires acid to be converted to a sulfenamide intermediate capable of binding to proton pumps [47]. Therefore, additionally administered PPI may be less activated owing to the relatively higher intragastric pH under long-term administration of PPI (e.g., 8 weeks). On the contrary, VPZ may show long-lasting and potent acid inhibition in both the early and late phases of anti-ulcer treatment. In our

meta-analysis, there was no significant difference in ulcer healing at 4 weeks after the procedure between PPI and VPZ, whereas VPZ was superior to PPI in terms of ulcer healing at 8 weeks after the procedure.

However, we believe that rapid healing of iatrogenic ulcers in the early phase (such as within 4 weeks after the procedure) is more important than the healing rate in the late phase, because post-ESD bleeding mostly occurs in the early phase of ulcer healing [4]. In our meta-analysis, additionally, the pooled ulcer healing rate at 8 weeks after the procedure ranged from 81 to 93% across all included regimens. Therefore, the 20–27% higher comparative efficacy of VPZ may have a clinically less significant meaning. From these points of view, the combination therapy of PPI and a muco-protective agent should be considered as the first treatment option for healing of iatrogenic ulcers.

Although our meta-analysis showed that the combination therapy of PPI and a muco-protective agent was the most effective regimen for ulcer healing at 4 weeks after the procedure among the included regimens, a combination therapy of VPZ and a muco-protective agent has not been compared. To determine the optimal regimen for iatrogenic ulcer healing, the efficacy of the combination therapy of VPZ and a muco-protective agent should be evaluated in future studies. To date, the efficacy of VPZ has been demonstrated in various acid-related diseases including erosive esophagitis and peptic ulcers [9–11]. Additionally, the VPZ-based triple therapy was shown to be superior to the PPI-based conventional triple therapy in terms of *H. pylori* eradication, even in patients with clarithromycin-resistant *H. pylori* infection [48].

Although our meta-analysis identified the best regimens for iatrogenic ulcer healing in the early and late phases, it has several limitations. First, the efficacy of VPZ was evaluated in only three studies with small sample sizes, as the drug was developed only recently. Therefore, quality of evidence for comparisons between VPZ and other regimen was rated as low or very low quality. A larger RCT on VPZ is required in order to reach a definitive conclusion on the efficacy of VPZ for iatrogenic ulcer healing. Second, 3 of 23 included studies were abstract-only publications. Although we included abstract-only publications to minimize publication bias, there is a possibility of other potential biases because the baseline characteristics of the included patients and the detailed study methods were not provided in the abstracts. However, the sensitivity analysis showed that the overall results did not differ significantly between the main analysis and the sensitivity analysis after excluding abstract-only publications. Third, a modest network inconsistency was identified in the analysis of the late phase of ulcer healing. Therefore, the superiority of VPZ in terms of ulcer healing at 8 weeks after the procedure should be interpreted with caution. More studies among regimens are needed to clarify the efficacy of anti-ulcer medication at 8 weeks after the procedure. Fourth, although each individual study usually used same type of PPIs in both groups, different PPIs were used across individual studies. Because drug metabolism differs depending on the type of PPIs, ulcer healing effect might be influenced by the different type of PPIs across studies. Unfortunately, however, we could not assess the efficacy of PPIs individually due to the limited number of individual studies. Fifth, exclusion of a publication in a language other than English was another limitation. The excluded study which was conducted in China compared the ulcer healing effect between rabeprazole alone and a combination of rabeprazole and teprenone, which is one of the mucosal protective agents [29]. English abstract of the study showed that the combination therapy of rabeprazole and teprenone was superior in terms of ulcer healing to rabeprazole alone. This result is consistent with our meta-analysis; therefore, the exclusion of non-English publications would not have caused a serious bias. Finally, all of the included studies were performed in Korea or Japan. To generalize our results, worldwide trials are needed.

Despite these limitations, our meta-analysis provides a better understanding of the efficacy of anti-ulcer medications after ESD. The combination therapy of PPI and a muco-protective agent was shown to be superior to PPI alone in terms of ulcer healing at 4 weeks after ESD. In the ulcer healing effect at 8 weeks after ESD, vonoprazan was superior to PPI.

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Compliance with ethical standards

Disclosures Eun Hye Kim, Se Woo Park, Eunwoo Nam, Jae Gon Lee, and Chan Hyuk Park have no conflicts of interest or financial ties to disclose.

Appendix: Detailed search strategy

MEDLINE

(ESD[Title/Abstract] OR endoscopic submucosal dissection[Title/Abstract] OR EMR[Title/Abstract] OR endoscopic mucosal resection[Title/Abstract] OR endoscopic resection[Title/Abstract] OR iatrogenic[Title/Abstract] OR artificial[Title/Abstract]) AND (ulcer*[Title/Abstract]) AND (vonoprazan[Title/Abstract] OR TAK-438[Title/Abstract] OR revaprazan[Title/Abstract] OR YH1885[Title/Abstract] OR (potassium[Title/Abstract] AND competitive[Title/Abstract]) OR potassium-competitive[Title/Abstract] OR ppi[Title/Abstract] OR proton pump inhibitor*[Title/Abstract] OR

dexlansoprazole[Title/Abstract] or esomeprazole[Title/Abstract] OR ilaprazole[Title/Abstract] OR lansoprazole[Title/Abstract] OR omeprazole[Title/Abstract] OR pantoprazole[Title/Abstract] OR rabeprazole[Title/Abstract] OR ((histamine[Title/Abstract] OR histamine2[Title/Abstract] OR histamine-2[Title/Abstract] OR h2[Title/Abstract] OR h-2[Title/Abstract]) AND (antagonist*[Title/Abstract] OR blocker*[Title/Abstract])) OR h2ra[Title/Abstract] OR famotidine[Title/Abstract] OR cimetidine[Title/Abstract] OR ranitidine[Title/Abstract] OR nizatidine[Title/Abstract] OR lafutidine[Title/Abstract] OR misoprostol[Title/Abstract] OR rebamipide[Title/Abstract] OR ecabet[Title/Abstract] OR irsogladine[Title/Abstract] OR polaprezinc[Title/Abstract] OR mucoprotective[Title/Abstract] OR mucoprotective[Title/Abstract]) AND ("1990/01/01"[Date—Publication] : "2017/10/31"[Date—Publication]).

EMBASE

(ESD:ab,ti OR 'endoscopic submucosal dissection':ab,ti OR EMR:ab,ti OR 'endoscopic mucosal resection':ab,ti OR 'endoscopic resection':ab,ti OR iatrogenic:ab,ti OR artificial:ab,ti) AND (ulcer*:ab,ti) AND (vonoprazan:ab,ti OR TAK-438:ab,ti OR revaprazan:ab,ti OR YH1885:ab,ti OR (potassium:ab,ti AND competitive:ab,ti) OR potassium-competitive:ab,ti OR ppi:ab,ti OR proton pump inhibitor*:ab,ti OR dexlansoprazole:ab,ti or esomeprazole:ab,ti OR ilaprazole:ab,ti OR lansoprazole:ab,ti OR omeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR ((histamine:ab,ti OR histamine2:ab,ti OR histamine-2:ab,ti OR h2:ab,ti OR h-2:ab,ti) AND (antagonist*:ab,ti OR blocker*:ab,ti)) OR h2ra:ab,ti OR famotidine:ab,ti OR cimetidine:ab,ti OR ranitidine:ab,ti OR nizatidine:ab,ti OR lafutidine:ab,ti OR misoprostol:ab,ti OR rebamipide:ab,ti OR ecabet:ab,ti OR irsogladine:ab,ti OR polaprezinc:ab,ti OR muco-protective:ab,ti OR mucoprotective:ab,ti) AND [1990–2017]/py AND [embase]/lim.

Cochrane

1. ESD or "endoscopic submucosal dissection" or EMR or "endoscopic mucosal resection" or "endoscopic resection" or iatrogenic or artificial
2. ulcer*
3. vonoprazan or TAK-438 or revaprazan or YH1885
4. potassium and competitive
5. ppi or 'proton pump inhibitor*' or dexlansoprazole or esomeprazole or ilaprazole or lansoprazole or omeprazole or pantoprazole or rabeprazole
6. histamine or histamine2 or histamine-2 or h2 or h-2
7. antagonist* or blocker*
8. h2ra or famotidine or cimetidine or ranitidine or nazatidine or lafutidine
9. misoprostol or rebamipide or ecabet or irsogladine or polaprezinc or muco-protective or mucoprotective
10. #3 or #4
11. #6 and #7
12. #11 or #8
13. #10 or #5 or #12 or #9
14. #1 and #2 and #13 (Publication year from 1990 to 2017)

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