Proton Pump Inhibitors Increase the Risk of Nonsteroidal Anti-inflammatory Drug-Related Small-Bowel Injury: A Systematic Review With Meta-analysis

Xian Zhang, MD[1,2,*], Xue Xiao, MD[1,3,*], Ping-Run Chen, MD[3,*], Yi-Na Li, MD[4], Xiu-He Lv, MD[1,3] and Jin-Lin Yang, MD[1,3]

INTRODUCTION: **Conflicting results exist on the association between proton-pump inhibitor (PPI) and nonsteroidal anti-inflammatory drug (NSAID)-related small-bowel damage. The aim of this study was to determine whether PPIs increased the risk of NSAID-related small-bowel damage by meta-analysis.**

METHODS: **A systematic electronic search in PubMed, Embase, and Web of Science was conducted from the time the database was created until March 31, 2022, for studies reporting associations between PPI use and outcomes, including the endoscopy-verified prevalence of small-bowel injury, mean number of small-bowel injuries per patient, change in hemoglobin level, and risk of small-bowel bleeding in subjects taking NSAIDs. Meta-analytical calculations for odds ratio (OR) and mean difference (MD) were performed with the random-effects model and interpreted with 95% confidence intervals (CIs).**

RESULTS: **Fourteen studies comprising 1996 subjects were included. Pooled analysis demonstrated that concomitant use of PPIs significantly increased the prevalence and number of endoscopy-verified small-bowel injuries (prevalence: OR = 3.00; 95% CI: 1.74–5.16; number: MD = 2.30; 95% CI: 0.61–3.99) and decreased hemoglobin levels (MD = −0.50 g/dL; 95% CI: 0.88 to −0.12) in NSAID users but did not change the risk of small-bowel bleeding (OR = 1.24; 95% CI: 0.80–1.92). Subgroup analysis demonstrated that PPIs significantly increased the prevalence of small-bowel injury in subjects taking nonselective NSAIDs (OR = 7.05; 95% CI: 4.70–10.59, 4 studies, $I^2 = 0$) and COX-2 inhibitors (OR = 4.00; 95% CI: 1.18–13.60, 1 study, no calculated I^2) when compared with COX-2 inhibitors alone.**

DISCUSSION: **PPIs increased the risk of NSAID-related small-bowel damage, and the clinical significance of higher prevalence of small-bowel injuries should be studied in the future.**

KEYWORDS: Proton pump inhibitor; Nonsteroidal anti-inflammatory drug; Small bowel; Meta-analysis

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A932

Clinical and Translational Gastroenterology 2023;14:e00588. https://doi.org/10.14309/ctg.0000000000000588

INTRODUCTION

The commonly prescribed analgesic and anti-inflammatory medications termed nonsteroidal anti-inflammatory drugs (NSAIDs) induce gastroduodenal ulcerations that in turn are well recognized as the basis for upper gastrointestinal bleeding and perforation; less well appreciated are the ulcerating effects of NSAIDs on the small intestine distal to the second part of the duodenum. The application of capsule endoscopy and balloon-assisted enteroscopy revealed that NSAID-related small-bowel damage was more frequent than previously believed, including the development of increased mucosal permeability, inflammation, erosions, ulcers, malabsorption, stricture, perforation, and blood loss that can be either acute or chronic in course (1). Risk factors for and protective strategies against small-bowel damage in NSAID users are poorly understood.

Proton-pump inhibitors (PPIs) have been proven efficacious in healing NSAID-associated upper gastrointestinal complications through potent and long-lasting inhibition of gastric acid secretion (2). As such, they are often coprescribed with NSAIDs (2,3).

[1]Sichuan University-Oxford University Huaxi Gastrointestinal Cancer Centre, Department of Gastroenterology & Hepatology, West China Hospital, Sichuan, University, Chengdu, China; [2]Department of Pathology, West China Hospital, Sichuan University, Chengdu, China; [3]Department of Gastroenterology & Hepatology, West China Hospital, Sichuan University, Chengdu, China; [4]Department of Respiratory Diseases, West China Hospital, Sichuan University, Chengdu, China.
Correspondence: Jin-Lin Yang, MD. E-mail: yangjinlin@wchscu.cn.
*These authors contributed equally to this work.
Received September 5, 2022; accepted March 28, 2023; published online April 5, 2023

Wallace et al (4) demonstrated that PPIs exacerbate the risk of small-bowel injury through gut microbiota dysbiosis in an experimental model. It has been reported that capsule endoscopy showed a high incidence of small-bowel injury in subjects who took NSAIDs and PPIs simultaneously (5). However, in population-based studies, no consistent conclusions have been reached about the association between PPI and NSAID-related small bowel damage, which has been explored from the development of small bowel injury to clinically significant small bowel bleeding. (6,7). Owing to the combination of PPIs and NSAIDs leading to excessive costs for both patients and governments, this potential risk for iatrogenic harm has an essential impact on clinical practice (8). Thus, we conducted this meta-analysis to systematically define the associations between PPIs and NSAID-related small-bowel damage and provide evidence for the reasonable clinical use of PPIs and NSAIDs.

METHODS

Search strategy

We conducted a comprehensive search in electronic databases, including PubMed, Embase, and Web of Science, for studies reporting associations between PPI use and NSAID-related small-bowel damage published from inception to March 31, 2022. A combination of subject terms and free words was applied. Meanwhile, the references cited in the included studies and relevant review papers were also searched. The detailed search strategy of the PubMed database is presented in Supplementary Table 1 (see Supplementary Digital Content, http://links.lww.com/CTG/A932). This meta-analysis was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (9).

Inclusion and exclusion criteria

Two investigators (X.Z. and P.-R.C.) independently screened the study titles and abstracts and assessed the full texts of studies that met the inclusion criteria. Disagreements concerning article inclusion were resolved through discussion; otherwise, a third reviewer (X.X.) was available to make the final decision. The inclusion criteria were as follows: (i) studies performed on human subjects; (ii) cohort studies, case-control studies, cross-sectional studies, and randomized trials were included; (iii) all study subjects had a history or current usage of taking NSAIDs; (iv) studies reporting or containing the association between PPIs and risk of small-bowel damage in subjects taking NSAIDs; (v) eligible control group included subjects taking placebo or no treatment including PPIs or other acid-suppressive drugs; and (vi) all study subjects underwent capsule endoscopy, video capsule endoscopy, and/or double-balloon enteroscopy for small-bowel damage. The exclusion criteria were as follows: (i) nonhuman studies; (ii) studies published as conference abstracts only, case reports, review papers, and letters; (iii) studies not reporting available data for the calculation of effect estimates of PPI and risk of NSAID-related small-bowel damage among subjects receiving NSAID therapy; and (iv) duplicate publications, and we included the study providing the most comprehensive details.

Data extraction

Data were extracted by 2 independent authors (X.Z. and Y.-N.L.) into a Microsoft Excel spreadsheet (Microsoft Corporation). The following data were extracted: first author, publication year, country, study design, total number of participants, age, number of men and women recruited, types of NSAIDs, duration and dosage of PPI as well as the types of PPI(s) used if available, definition and measurement evaluating small-bowel damage, adjusted confounding variables, outcomes of interest, and study duration. For studies not providing adjusted effect estimates, we calculated the unadjusted odds ratio (OR) according to the reported number of patients with or without PPI therapy and the respective number of patients with small-bowel damage.

Outcome assessment

The primary outcome was the endoscopy-verified prevalence of small-bowel injury. Secondary outcomes included the number of small-bowel injuries per patient, changes in hemoglobin levels, and/or risk of small-bowel bleeding. The definition and measurement evaluating small-bowel injury and small-bowel bleeding are listed in Table 1 for an overview.

Risk of bias assessment

The quality assessment of the included randomized trials was performed in accordance with guidance published in the Cochrane handbook (10), which includes the following domains: random sequence generation, allocation concealment, participant blinding, outcome assessor blinding, incomplete outcome data, and selective reporting. Each domain was judged by low risk of bias, high risk of bias, or unclear risk of bias.

We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of observational studies (11,12). This assessment scale measures quality in 3 parameters of selection, comparability, and exposure/outcome and allocates a maximum of 4, 2, and 3 points, respectively. For comparability of cases and controls and of cohorts, a point was given if the study controlled for age, and a second point was given if the study controlled for 2 or more common important factors for small-bowel damage. We used the modified NOS adapted from the study of Herzog et al (13) for a cross-sectional study. High-quality studies have scores of 7 or higher, moderate-quality studies have scores between 4 and 6, and low-quality studies have scores less than 4. Two investigators (P.-R.C. and Y.-N.L.) assessed quality independently, with any disagreement to be resolved by consensus.

Statistical analysis

For categorical variables, the pooled effect estimate was calculated as the odds ratio (OR) with 95% confidence intervals CIs). For continuous variables, we calculated pooled mean differences (MD) with 95% CIs. A random-effects model was used to pool data to give more conservative estimates. To estimate statistical heterogeneity, we used the Cochran Q test and I^2 statistics. A P value of less than 0.1 for the Cochran Q test was defined as the presence of statistical heterogeneity. I^2 values of 30%–50%, 50%–75%, and ≥75% corresponded to moderate, substantial, and considerable heterogeneity, respectively (14). The leave-one-out method used as sensitivity analysis was conducted to assess the robustness of conclusions concerning the effect sizes. Publication bias was evaluated using the Begg funnel plot and Egger test, where there were sufficient studies identified (≥10), in line with previous recommendations (15). Moreover, we explored the impacts of study design, country of study, and types of NSAIDs on risk estimates by subgroup analyses. All analyses were conducted using Review Manager (Version 5.3, The Cochrane

Table 1. Overview of definitions and methods evaluating NSAID-related small-bowel damage

Studies	Definition and methods
Small-bowel injury	
Goldstein 2005	Small-bowel injury was defined as any break in the mucosa with or without hemorrhage/web/stricture bowel in the small bowel detected by video capsule endoscopy. There was no attempt to differentiate between ulcers and erosions because video capsule technology cannot accurately assess either lesion size or depth.
Goldstein 2007	Small-bowel injury was defined as any break in the mucosa with or without hemorrhage/web/stricture bowel in the small bowel detected by video capsule endoscopy.
Hawkey 2008	Small-bowel injury was defined as mucosal break with or without hemorrhage/web/stricture based on video capsule endoscopy findings.
Watanabe 2012	Small-bowel injury was defined as no less than 2 points when video capsule endoscopy findings was scored according to the following method: (0) normal; (1) red spots; (2) 1-4 erosions; (3) >4 erosions; (4) large erosions/ulcers. A small erosion was defined as a circumscribed area of mucosal disruption that was denuded of villi with or without exudates or red color and that involved, at most, a diameter that was equivalent to those of valvulae conniventes. Large erosions were defined as circumscribed breaks in the mucosa that were larger than the equivalent diameter of a valvulae conniventes. Ulcers were defined as large erosions with a central area with exudates, typically with a surrounding border of elevated mucosa.
Endo 2014	Small-bowel injury included small erosions, large erosions, or ulcers according to the capsule endoscopy findings. A small-bowel erosion was defined as a circumscribed area of mucosal disruption denuded of villi that was no greater in diameter than that of the valvulae conniventes, with or without exudate, and red or not in color. Large erosions were defined as circumscribed breaks in the mucosa that were larger in diameter than that of the valvulae conniventes. Ulcers were defined as large erosions with a central area covered with exudate, typically with a surrounding border of elevated mucosa. Large erosions were combined with small erosions into the category of erosions (small erosions and/or large erosions).
Ishihara 2014	The definition of NSAID-induced small-bowel injury was (i) having a history of NSAIDs use; (ii) having endoscopic findings of erosion, ulcer, or typical diaphragm-like strictures; (iii) having symptoms, such as obscure gastrointestinal bleeding or small-bowel obstruction; (iv) showing improved clinical findings and/or endoscopic findings after the cessation of NSAIDs, except for diaphragm-like strictures; and (v) having no other causes, such as malignant tumor, inflammatory bowel disease or infectious disease.
Fujimori 2016	Defined as mucosal breaks in the small intestine with a slough surrounded by erythema through video capsule endoscopy examination. Depth of ulcers or the sizes of lesions were not considered.
Washio 2016	Defined as positive capsule endoscopy findings that classified as either ulcer or erosion. A circumscribed mucosal defect with obvious whitish mucous that was estimated to be 3 mm or larger in diameter was defined as an ulcer. Although it is sometimes difficult to distinguish a small ulcer from an area of erosion, a small mucosal break surrounded by redness was regarded as an erosion.
Yamada 2017	Including erosion or ulcer, defined as a central pallor and surrounding erythema and loss of villi based on capsule endoscopy findings.
Hara 2018	Small-bowel injury was evaluated through the capsule endoscopy findings to identify mucosal breaks (erosion and ulcer). In addition, if bleeding or stenosis were detected, they were appended to findings concerning the mucosal injuries. A mucosal break was defined as a defect in the normal villus mucosa, based on previous classifications, with slight modifications.
Contaldo 2019	Small-bowel injury were defined as the following video capsule endoscopy findings: (i) "petechia": circular area of crimson mucosa with preservation of villi; (ii) "denuded area": loss of villous architecture without clear breach of the epithelium; (iii) "angiodysplasia": enlarged blood vessels, usually a consequence of arterovenous malformations. Other recorded alterations were mucosal breaks (i.e., ulcers and erosion), hemorrhagic areas, strictures, and neoplasms.
Small-bowel bleeding	
Cho 2015	Small-bowel bleeding was defined as visible small-bowel bleeding that persisted or recurred after negative results were obtained from the initial evaluation including esophagogastroduodenoscopy and colonoscopy.
Park 2018	Small-bowel rebleeding due to NSAID-induced enteropathy was defined as when the patient showed recurrent bleeding and was evaluated endoscopically after conventional upper and lower endoscopy to exclude rebleeding from the common locations.
Handa 2021	Small-bowel bleeding was defined as patients with suspected small-bowel bleeding who underwent video capsule endoscopy within 1 month and have positive video capsule endoscopy findings such as multiple erosions and/or ulcers. Patients who had complaints of fresh gastrointestinal bleeding or exacerbated anemia with a positive fecal occult blood test had undergone abdominal ultrasonography, upper gastrointestinal endoscopy, and total colonoscopy. If the patient had no identified source in the upper gastrointestinal tract and colon, bleeding from the small intestine was suspected.

Collaboration, Denmark) and STATA software (Version 16.0, Stata Corp LLC, College Station, TX).

RESULTS

Study selection and characteristics

Our search strategy identified 2,382 articles, of which 364 were excluded as duplicate publications and an additional 1,908 articles were excluded as irrelevant articles after screening the titles and abstracts. The remaining 110 articles underwent full-text review, after which 96 were excluded for the reasons stated in Figure 1. Ultimately, 14 studies were included (5–7,16–26). Of these, 11 studies were included in the endoscopy-verified small-bowel injury prevalence analysis, 5 studies assessed the association between the number of small-bowel mucosal injuries and coadministration of PPIs, 2 studies investigated the association between changes in hemoglobin levels and PPIs, and 3 studies were included in the endoscopy-verified small-bowel bleeding risk analysis. Nine studies were observational studies, including 1 population cohort study, 4 case-control studies, and 4 cross-sectional studies, and the remaining 5 studies were randomized trials.

A total of 1,996 subjects were included in our analysis. There were 847 PPI users and 1,149 nonusers. Detailed study characteristics are outlined in Table 2. As per NOS assessment, the median quality score of the included studies was 6 (range 5–8), indicating moderate quality (see Supplementary Table 2, Supplementary Digital Content, http://links.lww.com/CTG/A932). Five randomized trials underwent an evaluation of the risk of bias. The summary of the risk of bias is presented in Figure 2.

Meta-analysis

Endoscopy-verified small-bowel injury. In the pooled analysis of 11 studies using the random-effects model, subjects taking a combination of PPIs and NSAIDs experienced a significantly higher prevalence of small-bowel injury than subjects taking NSAIDs without PPIs (OR = 3.00, 95% CI: 1.74–5.16), but there was significant heterogeneity between studies (I^2 = 73%, P < 0.0001) (Figure 3a). Subgroup analysis according to the study design demonstrated that PPI significantly increased the prevalence of NSAID-related small-bowel injury in randomized studies (OR = 6.66, 95% CI: 4.53–9.80, 5 studies, I^2 = 0%) but not in observational studies (OR = 1.49, 95% CI: 0.94–2.36, 6 studies, I^2 = 25%) (Figure 3a and Table 3). The difference between the 2 subgroups was significant (test of subgroup difference: P < 0.001, I^2 = 95.8%).

Subgroup analyses were further performed according to the country of study and types of NSAIDs, as listed in Table 3. Among studies evaluating the association between PPI use and the prevalence of NSAID-related small-bowel injury, there was a significantly elevated association in Asian countries (OR = 2.03, 95% CI: 1.08–3.82, 7 studies, I^2 = 69%) and in non-Asian countries (OR = 6.56, 95% CI: 4.21–10.22, 4 studies, I^2 = 0%) (test of subgroup difference: P = 0.003, I^2 = 88.7%) (see Supplementary Figure 1A, Supplementary Digital Content, http://links.lww.com/CTG/A932). According to the type of NSAID,

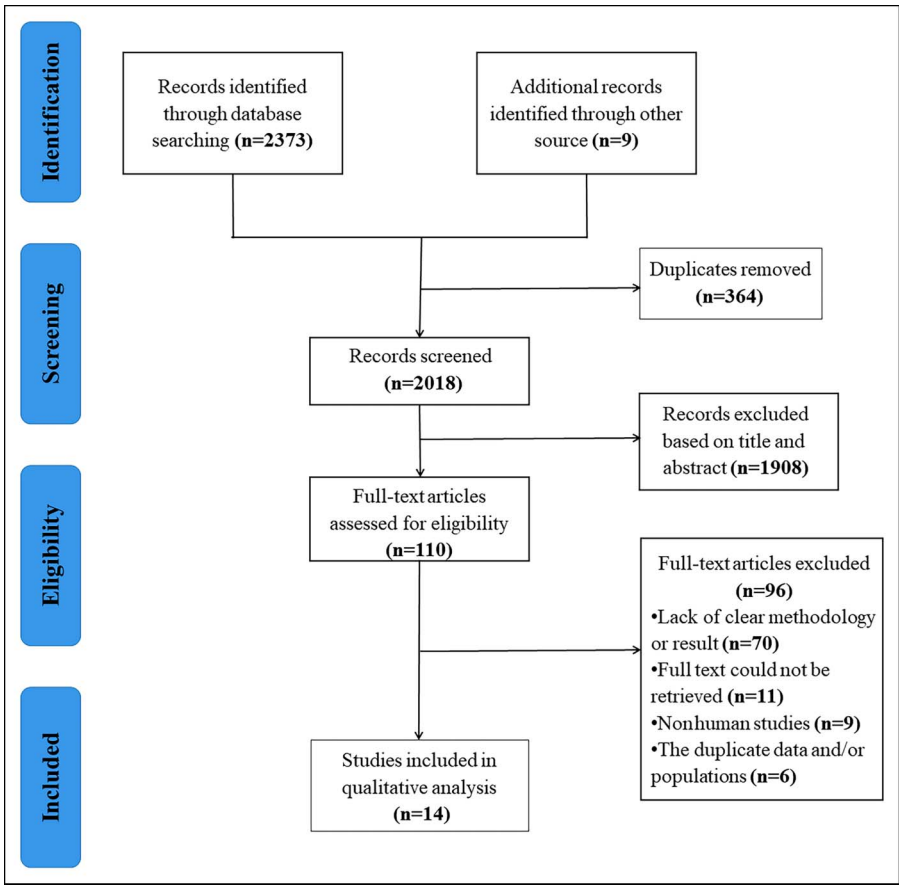

Figure 1. Flow diagram of the literature search and selection of studies for the meta-analysis.

Table 2. Characteristics of the included studies

Study	Country	Design	Groups	Types of PPIs	Types of NSAIDs	N	Age	Men	Outcomes of interest	Method of assessment	Variables adjusted in analysis
Goldstein 2005	United States of America	Randomized	PPI users Nonusers	Omeprazole No drug	Naproxen Celecoxib	111 115	33.1 ± 10.3 33.9 ± 10.8	46 50	Incidence and numbers of small intestinal injuries	VCE	NA
Goldstein 2007	United States of America	Randomized	PPI users Nonusers	Omeprazole No drug	Ibuprofen Celecoxib	112 109	34.4 ± 11.1 33.5 ± 10.3	35 44	Incidence and numbers of small intestinal injuries	VCE	NA
Hawkey 2008	Germany	Randomized	PPI users Nonusers	Omeprazole No drug	Naproxen Lumiracoxib	45 47	30.9 ± 8.67 29.9 ± 8.41	22 26	Incidence of small-bowel injuries	VCE	NA
Watanabe 2013	Japan	Cross-sectional	PPI users Nonusers	Rabeprazole, lansoprazole, and omeprazole —	Nonaspirin NSAIDs	20 88	60.2 ± 9.8	21	Risk factors for small-bowel injuries	VCE	NA
Endo 2014	Japan	Cross-sectional	PPI users Nonusers	Lansoprazole, omeprazole, and rabeprazole —	LDA	72 126	71.9 ± 9.6	143	Risk factors for small-bowel injuries in chronic low-dose aspirin users	CE	Ischemic heart disease, type of aspirin formulation, thienopyridine use, and H2RA use
Ishihara 2014	Japan	Case-control	PPI users Nonusers	Not list —	NSAIDs	59 97	68.2 ± 11.9	80	Risk factors for symptomatic NSAID-related small intestinal injuries	VCE and/or DBE	Age, sex, comorbidities, and type and duration of NSAIDs
Cho 2015	Korea	Case-control	PPI users Nonusers	Not list —	Nonselective NSAIDs	63 84	58.6 ± 11.7	72	Risk factors for small-bowel bleeding in chronic NSAIDs users	VCE	NA
Fujimori 2016	Japan	Randomized	PPI users Nonusers	Lansoprazole Placebo	Loxoprofen Celecoxib	72 69	48.8 ± 6.0 48.8 ± 7.0	38 37	Incidence and numbers of small intestinal injuries; change in hemoglobin level	VCE	NA
Washio 2016	Japan	Randomized	PPI users Nonusers	Rabeprazole Placebo	Celecoxib	27 30	34.0 ± 8.3 32.0 ± 8.5	17 17	Incidence and numbers of small-bowel injuries (ulcers and erosions); change in hemoglobin level	CE	NA
Yamada 2017	Japan	Cohort study	PPI users Nonusers	Lansoprazole, omeprazole, and rabeprazole —	Nonaspirin NSAIDs	29 30	NA	NA	Prevalence of small-bowel injuries (ulcers and/or erosions)	CE	NA
Hara 2018	Japan	Cross-sectional	PPI users Nonusers	Not list —	LDA	22 23	71.1 ± 8.6	21	Effects of PPI on incidence and number of LDA-induced small intestinal mucosal injuries	CE	NA

Table 2. ***(continued)***

Study	Country	Design	Groups	Types of PPIs	Types of NSAIDs	N	Age	Men	Outcomes of interest	Method of assessment	Variables adjusted in analysis
Park 2018	South Korea	Case-control	PPI users Nonusers	Not list —	NSAIDs	29 20	61.6 ± 17.0	33	Bleeding rate of NSAID-induced enteropathy and associated clinical factors	VCE	NA
Contaldo 2019	Italy	Cross-sectional	PPI users Nonusers	Not list —	NSAIDs	6 25	NA	NA	Predictive factors related to the presence of small-bowel injuries	VCE	NA
Handa 2021	Japan	Case-control	PPI users Nonusers	Not list —	LDA	180 286	Mean age: 71.0	315	Risk factors for LDA-induced small-bowel bleeding.	VCE	NA

CE, capsule endoscopy; DBE, double-balloon enteroscopy; H2RA, histamine 2 receptor antagonist; LDA, low-dose aspirin; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; VCE, video capsule endoscopy.

the prevalence of NSAID-related small-bowel injury was higher in subjects taking PPIs plus nonselective NSAIDs (OR = 7.05; 95% CI: 4.70–10.59, 4 studies, $I^2 = 0$) and in subjects taking PPIs plus COX-2 inhibitors (OR = 4.00; 95% CI: 1.18–13.60, 1 study, no calculated I^2) when compared with that in subjects taking COX-2 inhibitors alone. Four studies did not differentiate the types of NSAIDs in subjects taking PPIs or not, the pooled result of which indicated a similar prevalence of small-bowel injury between the 2 groups (OR = 1.33; 95% CI: 0.68–2.61, 4 studies, $I^2 = 40\%$). The prevalence of small-bowel injury was similar in aspirin users with and without PPI (OR = 1.65; 95% CI: 0.74–3.69, 2 studies, $I^2 = 41\%$). The difference between this subgroup by type of NSAID was significant (test of subgroup difference: $P < 0.001$, $I^2 = 86.6\%$) (see Supplementary Figure 1B, Supplementary Digital Content, http://links.lww.com/CTG/A932).

Number of endoscopy-verified small-bowel injuries. Five studies evaluated the impact of PPIs on the number of small-bowel injuries identified through endoscopy in subjects taking NSAIDs. The mean number of detected small-bowel injuries was 3.24 in the subjects taking NSAIDs with PPIs compared with 0.39 in subjects taking NSAIDs without PPIs (MD = 2.30, 95% CI 0.61–3.99), with significant heterogeneity ($I^2 = 96\%$, $P < 0.0001$) (Figure 3B). Subgroup analysis was also performed according to the study design, country of study, and types of NSAIDs (see Supplementary Figure 2, Supplementary Digital Content, http://links.lww.com/CTG/A932). Despite heterogeneity among studies, the exclusion of any 1 study from the sensitivity analysis did not affect the overall conclusion in this result (see Supplementary Figure 3, Supplementary Digital Content, http://links.lww.com/CTG/A932). The exclusion of the Goldstein study (17) from the pooled analysis significantly reduced the heterogeneity ($I^2 = 0\%$, $P = 0.41\%$) but did not affect the overall conclusion (MD = 2.67, 95% CI 2.57–2.77).

Hemoglobin level change. Only 2 studies evaluated changes in hemoglobin levels before and after PPI use in subjects taking NSAIDs. The pooled results revealed that hemoglobin levels in the PPI use group dropped more significantly than those in the group without PPI use, with a pooled mean difference of −0.50 g/dL (95% CI: 0.88 to −0.12) (Figure 3C).

Risk of small-bowel bleeding. Three studies reported the relationship between PPI use and the risk of endoscopically verified small-bowel bleeding in NSAID users. The results indicated that PPI did not change the risk of NSAID-related small-bowel bleeding (OR = 1.24, 95% CI: 0.80–1.92) (Figure 3D).

Sensitivity analysis. The sensitivity analyses that focused on the prevalence of small-bowel injury were conducted by excluding each study one by one. According to the pooled OR of each analysis, PPI use was associated with a significantly increased risk of NSAID-related small-bowel injury, revealing that the results of this study were stable and reliable (Figure 4).

Publication bias. Publication bias detection for studies related to the prevalence of small-bowel injury in subjects taking NSAIDs was conducted with an asymmetric Begg funnel plot (Figure 5), and a P value of 0.34 was observed using the Egger test, which indicated no obvious publication bias.

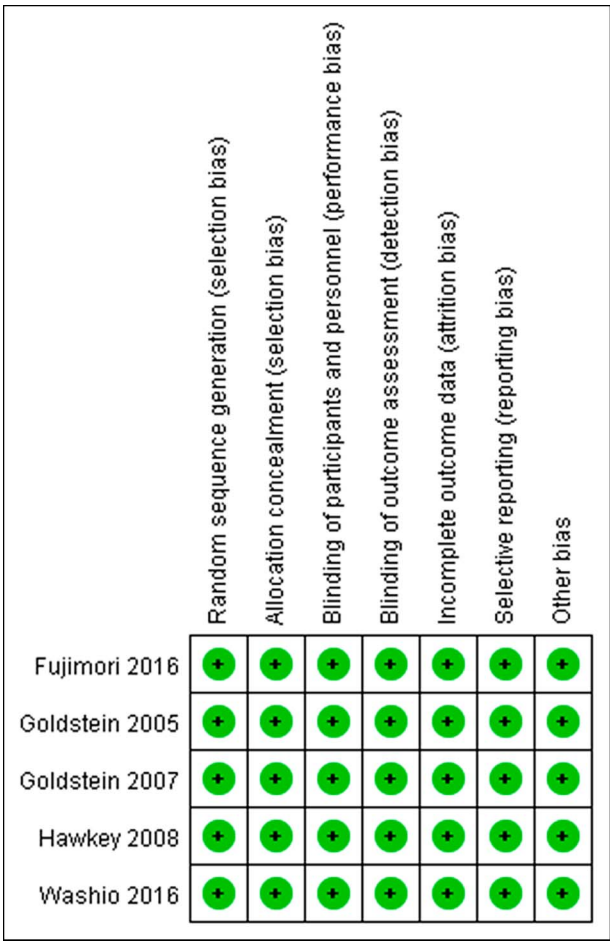

Figure 2. Risk bias graph of included randomized trials.

DISCUSSION

Cotherapy with PPIs is widely recognized and commonly prescribed to reduce the risk of peptic ulcers and upper gastrointestinal complications in at-risk patients taking long-term NSAIDs (2,3). Currently, this cotherapy is questioned because of the risk of small-bowel damage (27). To our knowledge, this is the first systematic review and meta-analysis focused on comprehensively examining the potential association between PPI and NSAID-related small-bowel damage, evaluating clinical outcomes including endoscopy-verified small-bowel injury, changes in hemoglobin levels, and bleeding complications. The pooled analysis showed that PPI use was associated with increased odds of the prevalence and number of endoscopic small-bowel mucosal injuries in NSAID users. Furthermore, analysis of 2 randomized studies indicated that among subjects taking NSAIDs, the decrease in hemoglobin level was more significant in PPI users than in nonusers. However, we did not find a significant association between PPI use and the risk of clinically significant small-bowel hemorrhage among subjects taking NSAIDs. These findings suggest the possible contribution of PPIs to NSAID-related small-bowel damage, and their clinical significance is worthy of further study.

Our study found that subjects with PPI-NSAID cotherapy have a higher prevalence of endoscopy-verified mucosal small-bowel injury by synthesizing the results of randomized trials. Conversely, the pooled result from observational studies was not statistically significant. There may be several reasons to explain the different conclusions. First, there is a lack of a temporal relationship between PPI use and NSAID-related small-bowel injury regarding the diagnosis or onset time in observational studies. In addition, we relied mainly on raw data from studies because of a lack of reporting of adjusted estimates of association in the observational studies included. Only 2 observational studies from Japan have reported adjusted ORs (7,19). Endo et al reported an observational cross-sectional study in which PPI use was identified as a risk factor for small-bowel injury in chronic low-dose aspirin users after adjusting for ischemic heart disease, type of aspirin formulation, and thienopyridine use (7). The study of Ishihara et al (19) was a cross-sectional study that indicated that the use of PPIs was unrelated to an increased risk of NSAID-related small-bowel injury after adjusting for age, sex, comorbidities, and type and duration of NSAID use. Considering

Table 3. Subgroup analysis for prevalence of small-bowel injury

Subgroup	No. of studies	OR (95% CI)	Heterogeneity I^2, %	Heterogeneity *P*	Test for subgroup difference
Study design					
Randomized studies	5	6.66 (4.53, 9.80)	0	0.74	$P < 0.001$, $I^2 = 95.8\%$
Observational studies	6	1.49 (0.94, 2.36)	25	0.25	
Country of study					
Asia	7	2.03 (1.08, 3.82)	69	0.004	$P = 0.003$, $I^2 = 88.7\%$
Non-Asia	4	6.56 (4.21, 10.22)	0	0.83	
Types of NSAIDs					
[a]NSAIDs plus PPI vs [a]NSAIDs	4	1.33 (0.68, 2.61)	30	0.23	$P < 0.001$, $I^2 = 86.6\%$
Nonselective NSAIDs plus PPI vs selective COX-2 inhibitor	4	7.05 (4.70, 10.59)	0	0.75	
Celecoxib plus rabeprazole vs celecoxib	1	4.00 (1.18, 13.60)	NA	NA	
Aspirin plus PPI vs Aspirin	2	1.65 (0.74, 3.69)	41	0.19	

NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.
[a]NSAIDs, included traditional NSAIDs, selective COX-2, inhibitors and aspirin.

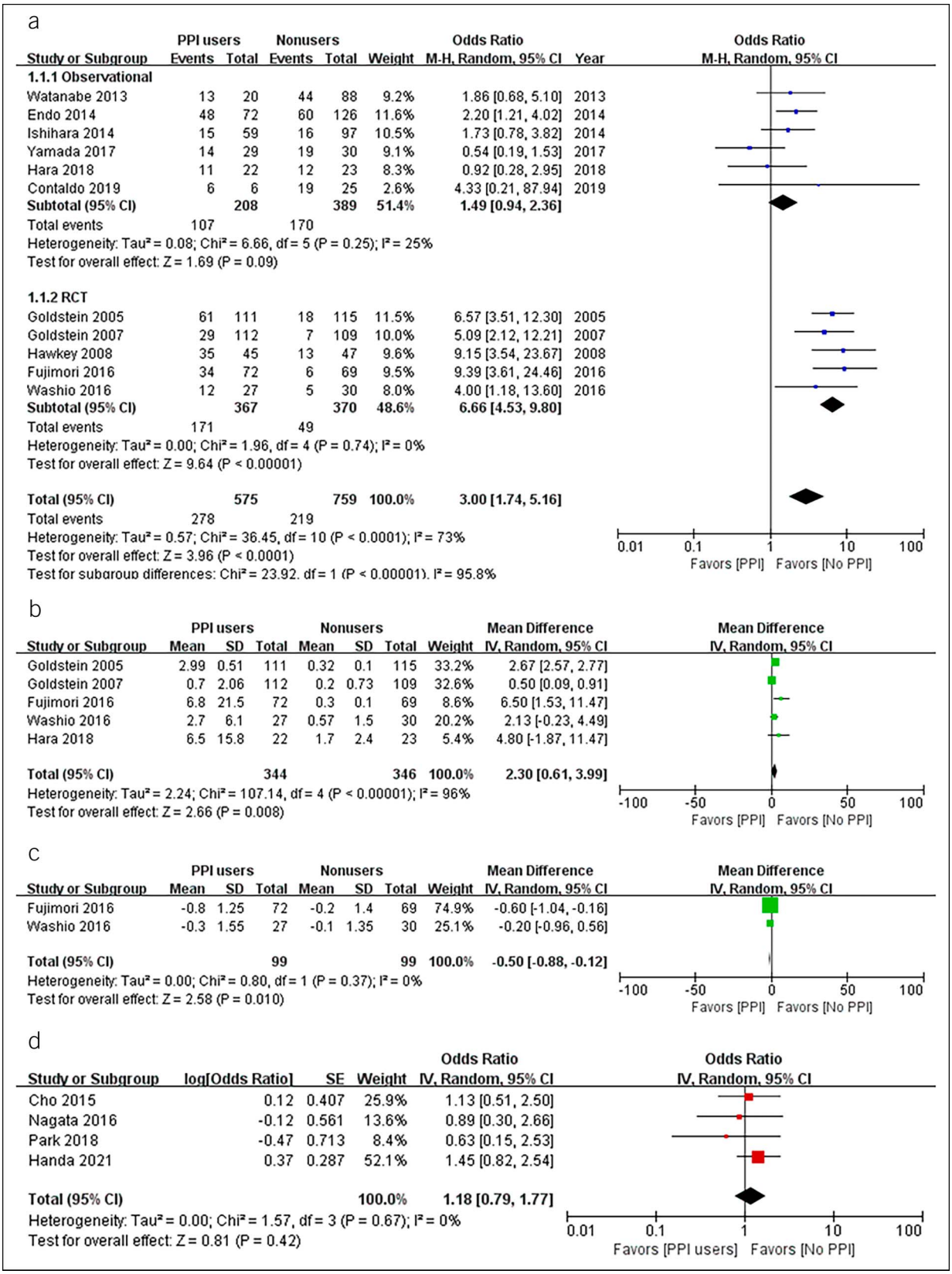

Figure 3. Forest plot of the association of PPIs and risk of nonsteroidal anti-inflammatory drugs-related small-bowel damage: (**a**) prevalence of small-bowel injury, (**b**) number of small-bowel injuries, (**c**) hemoglobin level change, and (**d**) risk of small-bowel bleeding. CI, confidence interval; PPI, proton pump inhibitors; RCT, randomized controlled trial.

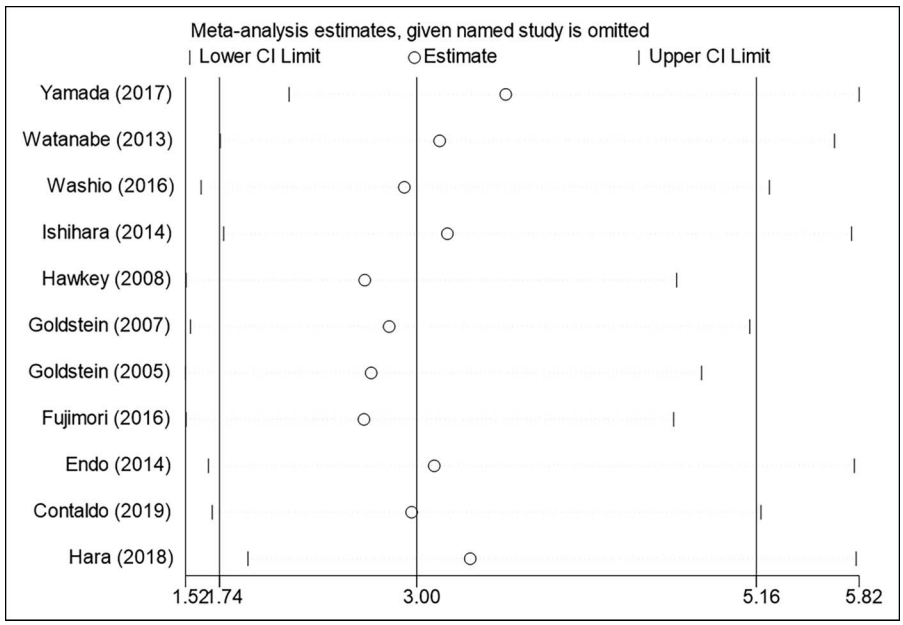

Figure 4. Sensitivity analysis for prevalence of small-bowel injury. CI, confidence interval.

that the risk factors for NSAID-induced injuries in the small intestine have not been well identified, analyses controlled for confounding were not comparable, contributing to the estimates being different. By contrast, the randomized studies included in our analysis that reported an increased risk of small-bowel injury and PPI use more rigorously recruited subjects and had more comparable baseline data. Sensitivity analysis was performed, and no obvious changes in our estimates were found, which indicated the robustness of our results. Publication bias was not found in increased risk of small-bowel injury and PPI use.

This meta-analysis stratified by the types of NSAIDs based on limited data found that PPIs significantly increased the prevalence of small-bowel injury in subjects taking both nonselective NSAIDs and COX-2 inhibitors. Of note, this add-on effect may be attributed to the fact that the above studies considered subjects taking COX-2 inhibitors with placebo or no treatment as the control group. Seriously speaking, the former comparison between nonselective NSAIDs plus PPIs and COX-2 inhibitors was more likely to conclude that celecoxib is superior to NSAID-PPI cotherapy in reducing small-bowel injury. However, nonselective NSAIDs alone cannot be studied as a control group in randomized trials for comparison of the effect of PPIs on the small bowel associated with NSAIDs because the well-established upper gastrointestinal toxicity of nonselective NSAIDs without prevention strategies is in breach of ethical principles and compromises human subjects' interests. The

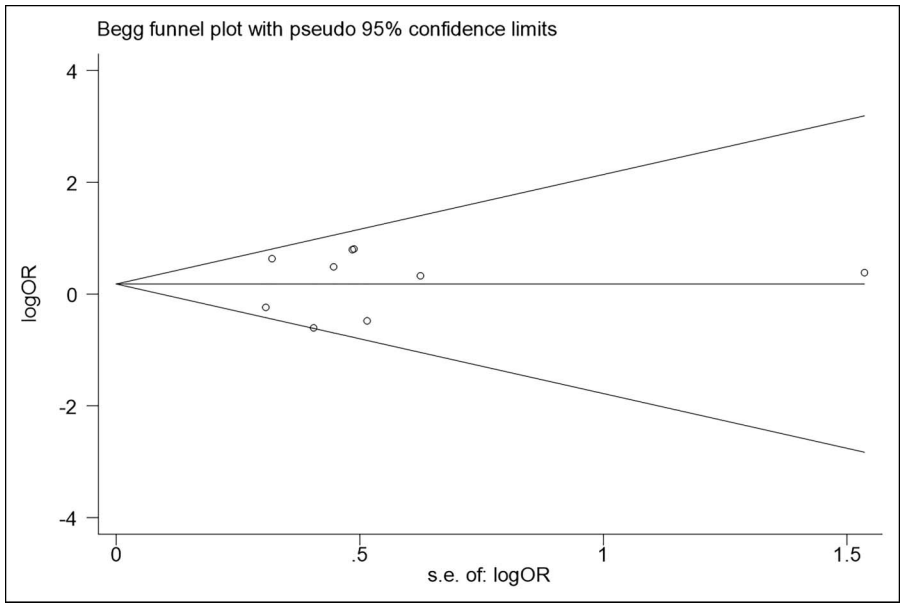

Figure 5. The Begg funnel plot for the risk of nonsteroidal anti-inflammatory drugs-related small-bowel injury.

comparison between COX-2 inhibitors plus PPI and COX-2 inhibitors alone was based on one study (21). Hence, to some extent, our results suggested that a difference in the extent of small-bowel injury exists between COX-2 inhibitors plus PPI and COX-2 inhibitors alone. The conclusions of this comparison should be interpreted with more caution. Interestingly, data from the literature do demonstrate that patients receiving treatment with conventional NSAIDs or COX-2-selective agents had a comparable prevalence of macroscopic small-bowel damage on capsule enteroscopy (28). These data are in line with experimental reports that the pathogenesis of NSAID enteropathy in rats seems to be less dependent on COX inhibition (29). Based on this, we recommend the physicians to be cautious about the possibility of small-bowel damage from empirical PPI prescription in NSAID users, regardless of whether they are using selective or nonselective NSAIDs.

Significant heterogeneity was observed when comparing the number of endoscopic small-bowel injuries. The sensitivity analysis based on the leave-one-out method suggested that the study of Goldstein et al (17) might be the source of heterogeneity; the pooled result of the remaining studies was consistent with the overall conclusion without significant heterogeneity. It is unlikely that the heterogeneity of this study is related to the technique because comparable protocols and subject populations were used in another study by Goldstein et al (16) which was also included. Goldstein et al (17) speculated that fewer small-bowel injuries in this study compared with previous investigations could be due to pharmacokinetic and pharmacodynamic differences between the different nonselective NSAID agents. These data further highlight the need for more direct comparisons.

The interpretation of the increased risk of PPI on small-bowel injury in patients taking NSAIDs is unclear. Yamada et al (22) indicated that PPI therapy did not increase the prevalence of small-bowel injury, regardless of the type of PPI used. It partially excludes the additional damage simply induced by PPI in the small bowel, thus requiring evaluation of the association between PPI-NSAID cotherapy in small-bowel injuries as mechanistic questions. Gastric acid prevents bacterial colonization of the upper gastrointestinal tract and can influence the proper composition of the intestinal flora (30). The suppression of acid secretion with PPIs may lead to bacterial overgrowth in the stomach and small intestine. Yoshihara et al reported that lansoprazole increased the relative abundance of Bacteroidetes and reduced the thickness of the jejunum mucus layer and goblet cells, thereby promoting damage to the small intestine (31). The administration of *Bifidobacterium bifidum* could improve NSAID-related small-bowel injury (31). Blackler et al further indicated that PPI-induced changes in the microbiota contributed significantly to the cytotoxicity of bile and exacerbated mucosal injury (32). The study of Muraki et al (33) was an observational cross-sectional study in which the identification of small intestinal bacterial overgrowth was significantly associated with the development of severe small intestinal damage in chronic NSAID users. The other interpretation that PPI was associated with a significantly increased small-bowel injury risk assumed that PPI use is a well-known marker of comorbidity that might not have been properly controlled for in the analysis. Data from previous literature have shown that patients who have significant comorbid illnesses are more likely to receive PPIs (34), and the risk of small-bowel bleeding was reported to be dependent on comorbidities (35).

Perhaps more important for patients and clinicians than the higher prevalence and number of NSAID-related injuries is the clinical significance of these endoscopic findings. The pooled result of 2 randomized studies indicated that hemoglobin levels of the group took PPIs dropped more significantly than those of the group did not. There were no details about endoscopy examination, so we considered that the hemoglobin drops reflected the severity of the whole gastrointestinal injury. In addition, the pooled result that PPIs did not change the risk of clinically significant bleeding in NSAID users, making the decline in hemoglobin a less clinically significant result. Do the small intestinal erosions and ulcers lead to clinically appreciable bleeding? According to our analysis, PPI-NSAID cotherapy was associated with a significant hemoglobin drop that was still within the normal range but was not associated with significant risk of clinical bleeding. Two large clinical trials demonstrated that occult gastrointestinal bleeding from NSAIDs was uncommon (0.4%–2.3%) (36,37). The significance of the majority of erosive and ulcerative small intestinal lesions commonly observed with capsule endoscopy (CE) remains to be determined. According to current evidence, we would not aim to overemphasize that PPIs could increase the risk of small bowel in subjects taking NSAIDs until more conclusive research evidence emerges. Instead, we suggest that physicians be aware of the possibility of small-bowel occult bleeding in NSAID users with unexplained anemia. These patients could consider small-bowel investigations rather than mechanically receiving empirical PPI.

Our study has some limitations. First, the pre-established primary outcome occurs uncommonly, and accordingly, this meta-analysis pooled data from both randomized and observational study designs, leading to high heterogeneity. However, the confidence in the pooled result is strengthened by large effects, stable sensitivity analysis, and the lack of significant public bias. Second, over half of the included studies were from Japan. The results may not be readily generalizable to other parts of the world. Third, studies with subjects who underwent capsule endoscopy, video capsule endoscopy, and/or double balloon enteroscopy for small intestinal damage evaluation were included in this meta-analysis, and most studies used capsule endoscopy or video capsule endoscopy for evaluation with better comparability. Fourth, there were not enough data to conduct an analysis of dose-response or duration-response effects, and the causal relationship was poorly inferred. Finally, PPI use has been demonstrated to increase the prevalence and number of small-bowel injuries identified through endoscopy in NSAID users, and the definition of small-bowel injury was mostly erosion or ulcers. However, there is limited evidence to support that PPI increases the risk of clinical significance of these findings. Balancing the potential risks and benefits of NSAIDs and PPI use should be studied in the future.

This meta-analysis demonstrates that PPI use increases the prevalence and number of endoscopy-verified small-bowel injuries related to NSAID use. However, no association between PPI use and NSAID-related small-bowel bleeding has been proven. Whether erosions or ulcers detected in patients taking NSAIDs are of clinical significance needs further research to help gain consensus on whether we need to accept a change in the current strategy of preventing NSAID-associated gastrointestinal damage.

CONFLICTS OF INTEREST

Guarantor of the article: Jin-Lin Yang, MD.

Specific author contributions: X.Z., X.X., and J.-L.Y.: conception and design. X.Z., P.-R.C., and Y.-N.L: collecting data. X.Z., X.X., and P.-R.C.: drafting of the article. X.X., X.-H.L., and J.-L.Y.: critical revision of the article: all authors: final approval of the article.

Financial support: This work was supported by the National Natural Science Foundation of China (No. 82173253), 1.3.5 project for disciplines of excellence-clinical research incubation project (2020HXFH054 and 2020HXFH039), and the Sichuan Science and Technology Program(2022YFH0003).

Potential competing interests: None to report.

REFERENCES

1. Laine L, Smith R, Min K, et al. Systematic review: The lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2006;24(5):751–67.
2. Chan FK, Abraham NS, Scheiman JM, et al. Management of patients on nonsteroidal anti-inflammatory drugs: A clinical practice recommendation from the first international working party on gastrointestinal and cardiovascular effects of nonsteroidal anti-inflammatory drugs and anti-platelet agents. Am J Gastroenterol 2008; 103(11):2908–18.
3. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: Expert review and best practice advice from the American Gastroenterological Association. Gastroenterology 2017; 152(4):706–15.
4. Wallace JL, Syer S, Denou E, et al. Proton pump inhibitors exacerbate NSAID-induced small intestinal injury by inducing dysbiosis. Gastroenterology 2011;141(4):1314–22.e5.
5. Hawkey CJ, Ell C, Simon B, et al. Less small-bowel injury with lumiracoxib compared with naproxen plus omeprazole. Clin Gastroenterol Hepatol 2008;6(5):536–44.
6. Cho KM, Park SY, Chung JO, et al. Risk factors for small bowel bleeding in chronic nonsteroidal anti-inflammatory drug users. J Dig Dis 2015;16(9): 499–504.
7. Endo H, Sakai E, Taniguchi L, et al. Risk factors for small-bowel mucosal breaks in chronic low-dose aspirin users: Data from a prospective multicenter capsule endoscopy registry. Gastrointest Endosc 2014;80(5):826–34.
8. Chau SH, Sluiter RL, Hugtenburg JG, et al. Cost-utility and budget impact analysis for stopping the inappropriate use of proton pump inhibitors after cessation of NSAID or low-dose acetylsalicylic acid treatment. Drugs Aging 2020;37(1):67–74.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Rev Espanola Cardiol 2021;74(9):790–9.
10. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester, UK: Wiley-Blackwell, 2019. p. 703.
11. Wells GA, Shea B, O'Connell J. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses, 2014.
12. Yuan T, Fitzpatrick T, Ko NY, et al. Circumcision to prevent HIV and other sexually transmitted infections in men who have sex with men: A systematic review and meta-analysis of global data. Lancet Glob Health 2019;7(4):e436–e447.
13. Herzog R, Álvarez-Pasquin MJ, Díaz C, et al. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health 2013;13(1):154.
14. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: A new edition of the Cochrane handbook for systematic reviews of interventions. Cochrane database Syst Rev 2019;10:Ed000142.
15. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj 2011;343(jul22 1):d4002.
16. Goldstein JL, Eisen GM, Lewis B, et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol 2005;3(2):133–41.
17. Goldstein JL, Eisen GM, Lewis B, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. Aliment Pharmacol Ther 2007;25(10):1211–22.
18. Watanabe T, Tanigawa T, Nadatani Y, et al. Risk factors for severe nonsteroidal anti-inflammatory drug-induced small intestinal damage. Dig Liver Dis 2013;45:390–5.
19. Ishihara M, Ohmiya N, Nakamura M, et al. Risk factors of symptomatic NSAID-induced small intestinal injury and diaphragm disease. Aliment Pharmacol Ther 2014;40(5):538–47.
20. Fujimori S, Hanada R, Hayashida M, et al. Celecoxib monotherapy maintained small intestinal mucosa better compared with loxoprofen plus lansoprazole treatment a double-blind, randomized, controlled trial. J Clin Gastroenterol 2016;50(3):218–26.
21. Washio E, Esaki M, Maehata Y, et al. Proton pump inhibitors increase incidence of nonsteroidal anti-inflammatory drug-induced small bowel injury: A randomized, placebo-controlled trial. Clin Gastroenterol Hepatol 2016;14(6):809–15.e1.
22. Yamada A, Niikura R, Maki K, et al. Proton pump inhibitor therapy did not increase the prevalence of small-bowel injury: A propensity-matched analysis. PLoS One 2017;12(8):e0182586.
23. Hara A, Ota K, Takeuchi T, et al. Dual antiplatelet therapy does not affect the incidence of low-dose aspirin-induced small intestinal mucosal injury in patients after percutaneous coronary intervention for coronary stenosis: A multicenter cross-sectional study. J Clin Biochem Nutr 2018;63(3):224–9.
24. Park J, Jeon SR, Kim JO, et al. Rebleeding rate and risk factors in nonsteroidal anti-inflammatory drug-induced enteropathy. J Dig Dis 2018;19(5):279–87.
25. Contaldo A, Losurdo G, Albano F, et al. The spectrum of small intestinal lesions in patients with unexplained iron deficiency anemia detected by video capsule endoscopy. Medicina. 2019;55:59.
26. Handa Y, Fukushima S, Yo S, et al. A novel gene associated with small bowel bleeding in patients taking low-dose aspirin. Dig Liver Dis 2021; 53(7):841–5.
27. Lanas A, Sostres C. PPI therapy. The small bowel, low-dose aspirin and PPIs—should we be concerned? Nat Rev Gastroenterol Hepatol 2014; 11(8):458–60.
28. Maiden L, Thjodleifsson B, Seigal A, et al. Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: A cross-sectional capsule enteroscopy study. Clin Gastroenterol Hepatol 2007;5(9):1040–5.
29. Zhang MY, Xia F, Xia SH, et al. NSAID-associated small intestinal injury: An overview from animal model development to pathogenesis, treatment, and prevention. Front Pharmacol 2022;13:818877.
30. Macke L, Schulz C, Koletzko L, et al. Systematic review: The effects of proton pump inhibitors on the microbiome of the digestive tract-evidence from next-generation sequencing studies. Aliment Pharmacol Ther 2020;51(5):505–26.
31. Yoshihara T, Oikawa Y, Kato T, et al. The protective effect of Bifidobacterium bifidum G9-1 against mucus degradation by Akkermansia muciniphila following small intestine injury caused by a proton pump inhibitor and aspirin. Gut Microbes 2020;11(5):1385–404.
32. Blackler RW, De Palma G, Manko A, et al. Deciphering the pathogenesis of NSAID enteropathy using proton pump inhibitors and a hydrogen sulfide-releasing NSAID. Am J Physiol 2015;308(12):G994–1003.
33. Muraki M, Fujiwara Y, Machida H, et al. Role of small intestinal bacterial overgrowth in severe small intestinal damage in chronic non-steroidal anti-inflammatory drug users. Scand J Gastroenterol 2014;49(3):267–73.
34. Chan FKL. Do proton pump inhibitors exacerbate nonsteroidal anti-inflammatory drug-induced small-bowel enteropathy? Clin Gastroenterol Hepatol 2016;14(6):816–7.
35. Ohmiya N, Nakamura M, Osaki H, et al. Development of a comorbidity index to identify patients with small bowel bleeding at risk for rebleeding and small bowel vascular diseases. Clin Gastroenterol Hepatol 2019;17(5):896–904.e4.
36. Cryer B, Li C, Simon LS, et al. GI-REASONS: A novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial. Am J Gastroenterol 2013;108(3):392–400.
37. Chan FK, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): A randomised trial. Lancet 2010;376(9736):173–9.