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Are Proton Pump Inhibitors Suitable Medicines to Prevent Gastrointestinal Events Due to Non-steroidal Anti-inflammatory Drugs?

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Abstract

Background: Proton pump inhibitors (PPIs) are often prescribed to prevent gastrointestinal (GI) events due to non-steroidal anti-inflammatory drugs (NSAIDs) in patients requiring long-term NSAIDs therapy. Are PPIs suitable to prevent GI events due to NSAIDs?

Methods and findings: A narrative review of PPIs, histamine-2 receptor antagonists (H2RAs), misoprostol, and rebamipide was conducted. PPIs prevent upper GI events due to NSAIDs and its evidence is the strongest. However, many articles showed that PPIs were independent risk factor for small intestinal injury or exacerbated NSAIDs-induced small intestinal injury. Moreover, based on meta-analysis, PPIs cause *Clostridium difficile* infection, fracture, fall, pneumonia (either community or hospital acquired), cardiovascular events and deaths, chronic kidney disease, acute kidney injury, etc. Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal ulcers but not gastric ulcers. H2RAs usage was independent risk factors for severe small intestinal damage. Misoprostol significantly reduced the risk of endoscopic ulcers. Small studies showed that misoprostol prevented small intestinal injuries due to NSAIDs. A systematic review and meta-analysis showed that rebamipide acted better than placebo against short-term NSAIDs-induced gastroduodenal injury. Rebamipide was equal to or not superior to traditional strategies. Rebamipide showed beneficial effects against the small bowel damage when compared with placebo group.

Conclusions: In the countries where rebamipide is available, rebamipide is recommended as a first-line therapy. In the countries where rebamipide is not available, PPIs or misoprostol is recommended as a first-line therapy. If efficacy is given priority over adverse effects, PPIs are recommended as a first-line therapy. If fewer adverse effects are given priority over efficacy, misoprostol is recommended as a first-line therapy and PPIs as a second-line therapy.

Keywords: Proton pump inhibitors; Histamine-2 receptor antagonists; Misoprostol; Rebamipide; Anti-ulcerative drug; Non-steroidal anti-inflammatory drugs

Introduction

It has been estimated that at least 16,500 non-steroidal anti-inflammatory drugs (NSAIDs)-related deaths due to gastrointestinal (GI) events occur each year among arthritis patients alone in the U.S [1]. Another large study in Spain reported 15.3 deaths/year out of 100,000 NSAIDs users including aspirin [2]. Proton pump inhibitors (PPIs) are often prescribed to prevent GI events due to NSAIDs in patients requiring long-term NSAIDs therapy. Are PPIs suitable to prevent GI events due to NSAIDs? A narrative review was conducted to examine whether PPIs are suitable medicine to prevent GI events due to NSAIDs.

Results

Proton pump inhibitors (PPIs)

Gastrointestinal complications: Based on the Cochrane Database Systematic Review published in 2002, PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR [relative risk] 0.40, 95% confidence interval [CI] 0.32-0.51 for gastric ulcer), and were better tolerated than misoprostol [3].

A network meta-analysis of randomized clinical trials showed that PPIs were probably more effective for preventing clinically important GI bleeding (GIB) than histamine-2 receptor antagonists (H2RAs) [odds ratio (OR) 0.38, 95% CI: 0.20-0.73], sucralfate (OR 0.30, 95% CI: 0.13-0.69), and placebo (OR 0.24, 95% CI: 0.10-0.60) (all moderate quality evidence) [4].

A systematic review and meta-analysis reported that the H2RAs prevented less effectively low-dose aspirin-related GIB (OR 2.102, 95% CI: 1.008-4.385; p<0.048) and ulcer formation (OR 2.257, 95% CI: 1.277-3.989; p<0.005) than PPIs [5].

A network meta-analysis reported that the pooled estimates were in favor of PPIs and sucralfate for the overt upper GIB in critically ill patients [6].

Scally et al. conducted a systematic review and meta-analysis of unconfounded, randomised trials of a gastroprotectant drug (defined as PPIs, prostaglandin analogue, or H2RAs) versus control, or versus another gastroprotectant [7]. In prevention trials, gastroprotectant drugs reduced development of endoscopic ulcers (OR 0.27, 95% CI: 0.25-0.29; p<0.0001), symptomatic ulcers (0.25, 0.22-0.29; p<0.0001), and upper GIB (0.40, 0.32-0.50; p<0.0001), but did not significantly reduce mortality (0.85, 0.69-1.04; p=0.11). Larger proportional reductions in upper GIB were observed for PPIs than for other gastroprotectant drugs (PPIs 0.21, 99% CI: 0.12-0.36; prostaglandin analogues 0.63, 0.35-1.12; H2RAs 0.49, 0.30-0.80; phet=0.0005). Gastroprotectant drugs were effective in preventing bleeding irrespective of the use of NSAIDs (phet=0.56). In healing trials, gastroprotectants increased endoscopic ulcer healing (3.49, 95% CI: 3.28-3.72; p<0.0001), with PPIs more effective (5.22, 99% CI: 4.00-6.80) than prostaglandin analogues (2.27, 1.91-2.70) and H2RAs (3.80, 3.44-4.20; phet<0·0001). In trials among patients with acute bleeding, gastroprotectants reduced further bleeding (OR 0.68, 95% CI: 0.60-0.78; p<0.0001), blood transfusion (0.75, 0.65-0.88; p=0.0003), further endoscopic intervention (0.56, 0.45-0.70; p<0.0001), and surgery (0.72, 0.61-0.84; p<0.0001), but did not significantly reduce mortality (OR 0.90, 0.72-1.11; p=0.31). PPIs had larger protective effects than did H2RAs for further bleeding (phet=0.0107) and blood transfusion (phet=0.0130).

A systematic review and meta-analysis compared PPIs with H2RAs in adults receiving dual antiplatelet therapy [8]. Compared to H2RAs, PPIs lessened upper GIB (RR 0.16, 95% CI: 0.03-0.70), and there was no significant difference in the incidence of P2Y12 reaction units (PRUs) (mean differences 18.21 PRUs, 95% CI: -4.11 to 40.54), poor responders to clopidogrel (RR 1.21, 95% CI: 0.92-1.61), incidence of major adverse cardiovascular events (RR 0.89, 95% CI: 0.45-1.75) or rehospitalization (RR 1.76, 95% CI: 0.79-3.92). Subgroup analysis confirmed fewer PRUs in the H2RAs group compared to the omeprazole group (2 studies, n=189, mean differences 31.80 PRUs, 95% CI: 11.65-51.96).

A systematic review and net-work meta-analysis reported that PPIs were effective medication for upper GI hemorrhage patients and intravenous PPIs exhibited equivalent effectiveness and safety in comparison to oral PPIs [9].

Lower gastrointestinal complications: A large case-control study demonstrated that PPIs use did not lead to an increased risk of lower GIB, regardless of the type of PPIs used and lower GIB risk was not affected by PPIs use, irrespective of concomitant therapy with NSAIDs [10]. However, many articles showed that PPIs were independent risk factor for small intestinal injury or exacerbated NSAIDs-induced small intestinal injury [11-16]. The results of these articles were summed up that PPIs exacerbated lower GI tract disturbance. Current use of NSAIDs (adjusted odds ratios [AOR] 1.86, 95% CI: 1.39-2.49) and PPIs (AOR 3.37, 95% CI: 2.77-4.09) was associated with microscopic colitis compared to never or past use and strongest associations (fivefold increased risk) were observed for concomitant use of PPIs and NSAIDs [17]. Tai et al. reported that PPIs use worsened NSAIDs enteropathy with more occult bleeding and ulceration and had been linked to gram-negative intestinal dysbiosis [18].

Gastric atrophy: A meta-analysis showed that there was a higher presence of gastric atrophy (15.84%; statistically significant) in PPIs group compared to the control group (13.29%) (OR 1.55, 95% CI: 1.00-2.41) [19].

Efficacy and safety in the long-term aspirin users: A systematic review and meta-analysis reported that PPIs were superior to H2RAs for prevention of low-dose aspirin-associated GI erosion/ulcer (OR 0.28, 95% CI: 0.16-0.50) and bleeding (OR 0.28, 95% CI: 0.14-0.59) [20].

Dahal et al. conducted a meta-analysis of randomized controlled trials to examine safety and efficacy of PPIs in patients using aspirin in long term for prevention of cardiovascular diseases and stroke [21]. Compared with control, PPIs reduced the risks of peptic ulcers (RR 0.19, 95% CI: 0.13-0.26; P<0.00001), gastric ulcers (0.24, 0.16-0.35; P<0.00001), duodenal ulcers (0.12, 0.05-0.29; P 0.00001), bleeding ulcers (0.22, 0.10-0.51; P=0.0004), and erosive esophagitis (0.14, 0.07-0.28; P<0.00001). PPIs increased the resolution of epigastric pain (1.13, 1.03-1.25; P=0.01), heartburn (1.24, 1.18-1.31; P<0.00001), and regurgitation (1.26, 1.13-1.40; P<0.0001), but did not increase the risks of all-cause mortality (1.72, 0.61-4.87; P=0.31), cardiovascular mortality (1.80, 0.59-5.44; P=0.30), nonfatal MI/ischemia (0.56, 0.22-1.41; P=0.22), ischemic stroke/transient ischemic attack (1.09, 0.34-3.53; P=0.89) and other adverse events.

Infection: A systematic review described the available evidence for enhanced susceptibility to enteric infection caused by *Salmonella*, *Campylobacter* and *C. difficile* by PPIs use, with adjusted RR ranges of 4.2-8.3 (two studies); 3.5-11.7 (four studies); and 1.2-5.0 (17 of 27 studies) for the three respective organisms [22]. A systematic review and meta-analysis showed that PPIs use in patients with cirrhosis and ascites was significantly associated with an increased risk of spontaneous bacterial peritonitis (OR 2.17, 95% CI: 1.46-3.23) and overall risk of bacterial infection (OR 1.98, 95% CI: 1.36-2.87) [23]. A multicenter, randomized controlled trial showed that exposure to inhibitors of gastric acidity (H2RAs or PPIs) was significantly associated with the occurrence of late-onset sepsis in preterm very low birth weight preterm infants [24]. A cohort study reported that the rate of spontaneous bacterial peritonitis was not significantly different in users or non-users of PPIs in cirrhotic outpatients with ascites [25]. A meta-analyses showed that PPIs use is a potential risk for the development of enteric infections caused by *Clostridium difficile*, as well as small intestinal bacterial overgrowth, spontaneous bacterial peritonitis, community-acquired pneumonia, hepatic encephalopathy, and adverse outcomes in inflammatory bowel disease [26]. Haas et al. reported that a higher rate of infections in patients receiving permanent PPIs medication in retrospective analysis was uncovered [27]. Patients undergoing cardiac surgery with cardiopulmonary bypass and regular PPIs medication developed significant more infections

retrospectively indicating a clinical impact of the immunosuppressive influence of PPIs [27]. A systematic review and meta-analysis reported that PPIs users had an increased risk of developing community-acquired enteric infection (pooled OR 4.28, 95% CI: 3.01-6.08) [28].

Clostridium difficile **infection**: Many systematic reviews and meta-analyses showed that PPIs therapy increased the risk for *Clostridium difficile* infection (CDI) [29-38]. A systematic review and meta-analysis showed that the use of PPIs for both the prevention and treatment of stress ulcers was associated with a 38.6% increased risk of hospital-acquired CDI occurrence compared to H2RAs use (pooled OR 1.386, 95% CI: 1.152-1.668; p=0.001; I^2=42.81%) [39]. A study on 136 patients with CDI showed that one of the major risk factors of infection was long-term PPIs treatment [40]. A case-control study using a national claims dataset reported that PPIs use was one of risk factors of CDI [41]. A systematic review and meta-analysis showed that patients who receive gastric acid suppressants (PPIs and H2RAs) might be at increased risk for recurrent CDI (OR 1.38, 95% CI: 1.08-1.76; P=.02), because there was significant heterogeneity among the studies, with an I^2 value of 64% [42]. A multicenter retrospective cohort study of over 1 million patients reported that PPIs increased the odds of a patient having hospital-onset CDI [43]. A descriptive case series study of patients with CDI hospitalized showed that the risk factors associated with the infection were: previous use of antibiotics (94.4%), prior hospitalization in the last three months (66.7%) and use of PPIs (50%) [44]. A systematic review and meta-analysis reported that frequently use PPIs were at higher risk for community-acquired CDI [45]. A systematic review and meta-analysis showed that two studies assessed risk factors for CDI recurrence, identifying use of PPIs as factors increasing the risk of initial and/or recurrent CDI [46]. A secondary database analysis in a five-hospital health system (consisting of 97,130 hospitalized patients admitted for greater than 48 h) showed that thirty-day predictors of CDI were increased number of high-risk antibiotics, Charlson Comorbidity Index score, age, and receipt of PPIs [47].

However, Villafuerte-Gálvez et al. reported that the PPIs and CDI association was not proven due to extensive and difficult to control confounding in observational studies of CDI patient populations with complex comorbidities [48]. A case-control study involving 112 patients reported that no significant association between established CDI risk factors (eg, prior exposure to antibiotics and the use of PPIs or H2RAs) and the risk for the *C. difficile* enteropathy was found in multivariate analysis [49].

Pneumonia: A meta-analysis of eight databases indicated that PPIs were not associated with an increased risk of hospitalization for community-acquired pneumonia (CAP) (AOR 1.05, 95% CI: 0.89-1.25) [50]. PPIs therapy was associated with 2.23 times (95% CI, 1.28-3.75) increased risk to develop CAP possibly as a result of *S. pneumoniae* infection [51]. A systematic review and meta-analysis showed that a pooled risk of CAP with ambulatory PPIs therapy was 1.49 (95% CI: 1.16-1.92) and this risk was increased during the first month of therapy (OR 2.10, 95% CI: 1.39-3.16), regardless of PPIs dose or patient age [52]. Another systematic review and meta-analysis showed that the overall risk of pneumonia (either community or hospital acquired) was higher among people using PPIs (AOR 1.27, 95% CI: 1.11-1.46) [53]. A case-control study showed that the adjusted RR for CAP among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (95% CI: 1.36-2.62) and a significant positive dose-response relationship was observed for current PPIs users [54]. A nested case-control study showed that there was a strong increase in risk for CAP associated with current use of PPIs therapy that was started within the previous 2 days (AOR 6.53, 95% CI: 3.95-10.80), 7 days (3.79, 2.66-5.42), and 14 days (3.21, 2.46-4.18), but there was no significant association for longer-term current PPIs therapy [55]. A meta-analysis of six nested case-control studies showed an increased risk of CAP associated with PPIs use (OR 1.36, 95% CI: 1.12-1.65) [56]. A multinational, randomized, blinded, parallel-group, placebo-controlled trial randomized 2426 ambulatory adults to 40 mg esomeprazole, 20 mg esomeprazole, and placebo for 26-week for the purpose of ulcer prevention and found similar rates of upper respiratory tract infection (0.9%, 1.0%, and 1.9%, respectively) [57]. In a manufacturer-sponsored analysis of 24 short-term randomized, incidences of community-acquired respiratory tract infections including pneumonia were similar in patients receiving esomeprazole and in those receiving placebo [58]. A population-based cohort study showed that patients with gastroesophageal reflux disease using PPIs longer than 4 months were at a significantly increased risk of pneumonia than those who did not use PPIs (adjusted HR 1.93, 95% CI: 1.64 ± 2.28) or took PPIs less than 4 months (adjusted HR 1.33, 95% CI: 1.17 ± 1.52) [59]. A network meta-analysis of randomized clinical trials showed that PPIs probably increase the risk of developing pneumonia compared with H2RAs (OR 1.27, 95% CI: 0.96-1.68), sucralfate (OR 1.65, 95% CI 1.20-2.27), and placebo (OR 1.52, 95% CI: 0.95-2.42) (all moderate quality) [4]. A network meta-analysis reported that PPIs bolus was associated with increased risk of gastric colonization and pneumonia [6].

Small bowel bacterial overgrowth: A prospective cohort study showed that long-term PPIs use was found to be significantly associated with small bowel bacterial overgrowth development [60]. A systematic review and meta-analysis showed that the pooled OR of small intestinal bacterial overgrowth in PPIs users' *vs.* nonusers was 2.282 (95% CI: 1.238-4.205) [61]. A systematic review and meta-analysis reported that the pooled OR showed a statistically significant association between increased risk of small intestinal bacterial overgrowth and PPIs use (OR 1.71, 95% CI: 1.20-2.43) [62].

Gut micro biota: Takagi et al. reported that there were significant differences in the microbial structure between PPIs non-users and PPIs users and the genera *Streptococcus* was significantly abundant and the genera *Faecalibacterium* was significantly decreased in PPIs users when comparing in genus level between these two groups [63]. These alterations might provide a mechanism by which PPIs predispose enteric infection such as CDI [63]. Tranberg et al. reported that PPIs medication was the strongest independent factor associated with the presence of gut flora in the oropharynx in both ward and critically ill patients (P=0.030 and P=0.044, respectively) [64]. A network meta-analysis reported that PPIs bolus was associated

with increased risk of gastric colonization [6]. PPIs use significantly increased the presence of *Streptococcaceae* and *Enterococcaceae*, which are risk factors for CDI, and decreased that of *Faecalibacterium*, a commensal anti-inflammatory microorganism [26]. Tai et al. reported that PPIs use worsened NSAIDs enteropathy with more occult bleeding and ulceration and had been linked to gram-negative intestinal dysbiosis [18].

Asthma: A systematic review and meta-analysis showed that acid-suppressive drug use in pregnancy was associated with an increased risk of asthma in childhood (RR 1.45, 95% CI: 1.35-1.56; I2=0%; P<.00001) and the overall risk of asthma in childhood increased among PPIs users (RR 1.34, 95% CI: 1.18-1.52; I2=46%; P<.00001) [65].

Severe acute pancreatitis: Ma et al. reported that PPIs therapy did not show benefit on alleviating systemic inflammatory response and clinical scores in severe acute pancreatitis patients, and didn't improve the prevention of peptic ulcer and GI hemorrhage [66].

Bone mineral density (BMD): PPIs might have a direct deleterious effect on bone cells, with the possibility of decreased bone turnover [67]. Targownik et al. reported that long-term PPIs use was not associated with any changes in BMD or bone strength (52 PPIs users and 52 PPIs non-users) [68]. A population-based study showed that PPIs users had lower BMD at baseline than PPIs non-users, but PPIs use over 10 years did not appear to be associated with accelerated BMD loss [69]. A prospective randomized study showed that administering PPIs for 8-week altered bone parameters in elderly patients [70]. However, using peripheral quantitative computer tomography, a small crosssectional study reported that PPIs were associated with lower trabecular BMD but not cortical BMD in community dwelling older persons [71].

Fracture: PPIs are reported to be associated with fracture [72-79]. A systematic review and meta-analysis showed that the pooled OR for fracture was 1.29 (95% CI: 1.18-1.41) with use of PPIs and long-term use of PPIs increased the risk of any fracture (AOR 1.30, 95% CI: 1.15-1.48) and hip fracture risk (AOR 1.34, 95% CI: 1.09-1.66) [78]. A population-based propensity-matched retrospective cohort study showed that PPIs use after stroke was associated with an increased risk of osteoporosis, hip fracture, and vertebral fracture in stroke patients [80]. A retrospective cohort study including data on 4438 participants aged 65 and older who had no fracture in the year prior to baseline reported that no association was observed between PPIs use and fracture risk among older adults [81]. A nested case-control study showed that long-term or cumulative PPIs use was not associated with an increased risk of hip fracture [82]. Current PPIs use was associated with an increased risk of hip fracture (adjusted OR 1.12, 95% CI: 1.03-1.22) [82]. The risk was increased in short-term current use (<1 year) (adjusted OR 1.23, 95% CI: 1.10-1.37) [82].

Fall: A systematic review and meta-analysis showed that consistent associations with falls were observed for long-term PPIs use in a descriptive synthesis [83].

Kidney disease: PPIs exposure may increase the odds of acute interstitial nephritis (AIN) [84]. Current use of PPIs was associated with a significantly increased risk of AIN, relative to past use [85]. PPIs are reported to be associated with AIN [86,87]. A population-based cohort study showed that the rates of acute kidney injury (AKI) (HR 2.52, 95% CI: 2.27-2.79) and AIN (HR 3.00, 95% CI: 1.47-6.14) were higher among patients given PPIs than among controls [88].

A large cohort study showed that the PPIs group, compared with the H2RAs group, had an increased risk of incident chronic kidney disease (CKD) (hazard ratio [HR] 1.28, 95% CI: 1.23-1.34) and progression to end-stage renal disease (ESRD) (HR 1.96, 95% CI: 1.21-3.18) [89]. They detected a graded association between duration of PPIs exposure and risk of renal outcomes among those exposed to PPIs for 31-90, 91-180, 181-360, and 361-720 days compared with those exposed for ≤ 30 days [89].

A population-based cohort study showed that PPIs use was associated with a higher risk of incident CKD [90].

A systematic review and meta-analysis showed that pooled RR of 1.22 (95% CI: 1.14-1.30) for association between PPIs use and CKD and 1.88 (95% CI: 1.71-2.06) for association between PPIs use and ESRD, respectively, and pooled RR of CKD in patients with PPIs use was 1.29 (95% CI: 1.22-1.36) compared with the use of H2RAs [91].

A review reported that the majority of studies showed higher risk of kidney outcomes among persons prescribed PPIs, with effect sizes that were slightly higher for AKI (2-3-fold) compared with CKD and ESRD (1.2- to 1.8-fold) [92].

A nationwide database-derived case-controlled study showed that the OR for CKD was 1.41 for subjects using PPIs (95% CI: 1.34-1.48) compared with subjects who had never used PPIs and the OR in relation to cumulative duration (per month) of PPIs use was 1.02 (95% CI: 1.01-1.02) and the OR in relation to cumulative dosage (per microgram) of PPIs use was 1.23 (95% CI 1.18-1.28) [93].

Longitudinal data of patients with diabetes obtained from a large Japanese diabetes registry showed that PPIs use was not associated with the subsequent risk of development or progression of albuminuria, or eGFR decline in patients with diabetes [94].

Li et al. reported that the constellation of evidence from all available studies suggested that PPIs use was associated with increased risk of adverse kidney outcomes [95].

A meta-analysis of observational studies showed that the pooled adjusted RR of AKI in patients with PPIs use was 1.61 (95% CI: 1.16-2.22; I2=98.1%) [96].

A systematic review and meta-analysis showed that compared with non-PPIs users, PPIs users experienced a significantly higher risk of AKI (RR 1.44, 95% CI: 1.08-1.91; P=0.013; strength of evidence [SOE], low) and CKD (RR 1.36, 95% CI: 1.07-1.72; P=0.012; SOE, low) [97]. Moreover, PPIs increased the risk of AIN (RR 3.61, 95% CI: 2.37-5.51; P<0.001; SOE, insufficient) and ESRD (RR 1.42, 95% CI: 1.28-1.58; P<0.001; SOE, insufficient) [97].

A large retrospective analysis reported that users of PPIs, compared with users of H2RAs, had an increased risk for doubled levels of creatinine (1985 events; adjusted HR 1.26, 95%

CI: 1.05-1.51) and decrease in eGFR of 30% or more (11,045 events; 1.26, 95% CI: 1.16-1.36) [98]. PPIs use also associated with development of ESRD (HR, 2.40; 95% CI: 0.76-7.58) and AKI (HR, 1.30; 95% CI: 1.00-1.69) [98]. There was a graded association between cumulative exposure to PPIs and risk of CKD progression [98]. This was not the case for cumulative H2RAs use [98].

Hepatic encephalopathy in patients with liver dysfunction: A meta-analysis reported that compared with nonusers, chronic and acute hepatic insufficiency patients receiving PPIs therapy had a significantly increased risk of developing hepatic encephalopathy (OR 1.76, 95% CI: 1.15-2.69), with notable heterogeneity (I = 61.4%, P=.075) and publication bias [99].

Depression: A population-based study reported that use of PPIs was associated with increased adjusted probability of depression in logistic regression (OR 2.38, 95% CI 1.02-5.58; p=0.045) and higher PPIs dosages were associated with increased probability of depression (p for trend=0.014) [100]. Calculation of the population attributable risk indicated that 14% of depression cases could be avoided by withdrawal of PPIs [100].

Dementia: A large prospective cohort study showed that the patients receiving regular PPIs had a significantly increased risk of incident dementia compared with the patients not receiving PPIs (HR 1.44, 95% CI: 1.36-1.52) [101]. A longitudinal, multicenter cohort study showed that older patients receiving PPIs medication had a significantly increased risk of any dementia (HR 1.38, 95% CI: 1.04-1.83) and Alzheimer's disease (HR 1.44, 95% CI: 1.01-2.06) compared with nonusers [102]. A prospective cohort study showed that bivariable analyses revealed significant associations between being-dispensed PPIs in relation to severe cognitive impairment [103]. Prospective population-based cohort study (N=3,484) showed that PPIs exposure was not associated with risk of dementia (P=0.66) or Alzheimer's disease (P=0.77) [104]. Moayyedi et al. reported that there was no association between PPIs use and Alzheimer's dementia and there was no increased risk of dementia with long-term use of PPIs or higher doses of PPIs [105]. In analyzing data from 2 large population-based studies of twins in Denmark, Wod et al. found no association between PPIs use and cognitive decline [106]. A systematic review identified that the reported association between PPIs use and dementia was limited by methodological issues and conflicting results [107]. A prescription sequence symmetry analysis on a nationwide South Korean database showed that the adjusted sequence ratio (aSR) of dementia and PPIs (7342 pairs, aSR 1.21, 95% CI: 1.16-1.27) was not higher than that for dementia and H2RAs (6170 pairs, aSR 1.91, 95% CI: 1.80-2.02) [108]. The SR was calculated as the number of patients first diagnosed with dementia after initiating PPIs (or H2RAs) (causal group) divided by the number of patients first diagnosed with dementia before the initiation of PPIs (or H2RAs) (non-causal group) [108].

Cardiovascular events and mortality: Some *in vitro* studies on muscle strips and cardiomyocytes showed that PPIs might have negative inotropic effects [109,110]. When results from 3761 patients were analyzed, there was no difference in the cardiovascular event rate between omeprazole-clopidogrel (4.9%) compared to clopidogrel alone (5.7%) [111]. It was found that gastroesophageal reflux disease patients exposed to PPIs to have a 1.16 fold increased association (95% CI: 1.09-1.24) with myocardial infarction (MI) [112]. Survival analysis in a prospective cohort found a two-fold (HR 2.00, 95% CI: 1.07-3.78) increase in association with cardiovascular mortality [112]. An increased risk of cardiovascular events (MI, stroke, etc.) and deaths has also been reported in older patients receiving long-term PPIs therapy [113-117]. PPIs use was associated with a higher risk of hospitalization due to ischemic stroke with a HR of 1.36 (95% CI: 1.14-1.620) [118]. An association between PPIs use and increased cerebrovascular risks was identified, and the AOR for PPIs use were 1.77 (95% CI: 1.45-2.18) within 30 days, 1.65 (95% CI: 1.31-2.08) between 31 and 90 days, and 1.28 (95% CI: 1.03-1.59) between 91 and 180 days before the onset of first-time ischemic stroke [118]. A study reported that current PPIs exposure was associated with significantly higher rates of both ischemic stroke (HR 1.13, 95% CI: 1.08-1.19) and MI (HR 1.31, 95% CI: 1.23-1.39) after adjusting for age, sex, comorbidities and concomitant medication [119]. High-dose PPIs was associated with increased rates of ischemic stroke (HR 1.31, 95% CI: 1.21-1.42) and MI (HR 1.43, 95% CI: 1.30-1.57) [119]. Long-term users of PPIs, compared with nonusers, had a 29% (95% CI: 5%-59%) greater absolute risk of ischemic stroke and a 36% (95% CI: 7%-73%) greater risk of MI within a 6-month period [119]. In an analysis of administrative claims from commercial and Medicare Supplemental plans, Landi et al. found no evidence that prescription PPIs increased risk of MI compared with prescription H2RAs (more than 5 million new users of prescription PPIs and H2RAs) [120]. A systematic review reported that all-cause mortality (OR 1.68, 95% CI 1.53-1.84; p<0.001) and rate of major cardiovascular events (OR 1.54, 95% CI 1.11-2.13; p=0.01) were significantly higher for patients taking PPIs [121]. The use of PPIs did not predict mortality of hospitalized patients for complications of cirrhosis in 339 consecutive patients (636 admissions) [122]. In a large cohort of real-world patients, the combination of PPIs with dual antiplatelet therapy was not associated with increased risk of major adverse cardiovascular and cerebrovascular events in patients who underwent percutaneous coronary intervention at up to 2 years of follow-up [123]. In an analysis of data from the Nurses' Health Study (68,514 women) and the Health Professionals Follow-up Study (28,989 men), Nguyen et al. did not find a significant association between PPIs use and ischemic stroke, after accounting for indications for PPI use [124]. Nguyen et al. reported that prior reports of an increased risk of stroke might be due to residual confounding related to chronic conditions associated with PPIs use [124]. Malhotra et al. conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies, reporting following outcomes among patients treated with thienopyridine and PPIs versus thienopyridine alone [125]. In adjusted analyses, concomitant use of PPIs with thienopyridines was associated with increased risk of stroke (adjusted HR 1.30, 95% CI: 1.04-1.61; P=0.02), composite stroke/MI/cardiovascular death (adjusted HR 1.23, 95% CI: 1.03-1.47; P=0.02), but not with MI (adjusted HR 1.19, 95% CI: 0.93-1.52; P=0.16) [125]. A review showed that PPIs were associated with long QT syndrome [126]. A meta-analysis including 33,492 patients showed that patients

taking PPIs had statistical differences in major adverse cardiovascular events (OR 1.17, 95% CI: 1.07-1.28; P=.001; I=28.3%), GIB (OR 0.58, 95% CI: 0.36-0.92; P=.022; I=80.6%), stent thrombosis (OR 1.30, 95% CI: 1.01-1.68; P=.041; I=0%), and revascularization (OR 1.20, 95% CI: 1.04-1.38; P=.011; I=5.1%), compared those not taking PPIs and there were no significant differences in MI (OR 1.03, 95% CI: 0.87-1.22; P=.742; I=0%), cardiogenic death (OR 1.09, 95% CI: 0.83-1.43; P=.526; I=0%), or all-cause mortality (OR 1.08, 95% CI: 0.93-1.25; P=.329; I=0%) [127].

Mortality: Patients with PPIs treatment had significantly higher index mortality compared to patients without PPIs treatment (30.0% *vs.* 11.1%, P=0.003) in patients with pyogenic liver abscesses [128]. After adjusting for comorbidities PPIs remained an independent predictive factor with an OR of 2.56 (1.01-6.46; P=0.036) [128].

Yoshihisa et al. reported that cardiac mortality was significantly lower in the PPIs group than in the H2RAs and non-acid suppressive therapy groups in the Kaplan-Meier analysis (11.0% versus 21.3% and 16.8%, respectively; log-rank P=0.004) and cardiac mortality was significantly lower in the PPIs group than in the H2RAs group in the postmatched cohort (log-rank P=0.025) in heart failure patients [129].

A large longitudinal observational cohort study reported that PPIs use was associated with increased risk of death compared with H2RAs use (HR 1.25, CI: 1.23-1.28) [130]. The risk of death was increased when considering PPIs use versus no PPIs (HR 1.15, CI: 1.14-1.15), and PPIs use versus no PPIs and no H2RAs (HR 1.23, CI: 1.22-1.24). Risk of death associated with PPIs use was increased among participants without gastrointestinal conditions: PPIs versus H2RAs (HR 1.24, CI: 1.21-1.27), PPIs use versus no PPIs (HR 1.19, CI: 1.18-1.20) and PPIs use versus no PPIs and no H2RAs (HR 1.22, CI: 1.21-1.23). Among new PPIs users, there was a graded association between the duration of exposure and the risk of death.

Drug interaction: Kawayama et al. reported that the average trough blood dabigatran concentration (DC) was significantly higher without PPIs than with PPIs (83 ± 42.3 *vs.* 55.5 ± 24.6 ng/mL, respectively; P<0.001) and the average peak DC was significantly higher without PPIs than with PPIs (184.1 ± 107.7 *vs.* 124 ± 59.2 ng/mL, respectively; P=0.0029) in patients withnon-valvular atrial fibrillation (NVAF) [131]. Therefore, when prescribing PPIs for patients with NVAF in a clinical setting, the possibility that the bioavailability of dabigatran may decrease should be considered [131].

Hassan et al. reported that omeprazole increased tigecycline minimum inhibitory concentrations by 4-128-fold [132].

When PPIs are co-administered with dasatinib, absorption is significantly reduced [133]. Dasatinib is used in the management of chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia [133].

Przespolewski et al. reported that the addition of PPIs might have a weak effect on clopidogrel's antiplatelet properties, and might only be relevant in specific clinical circumstances [134].

Yokota et al. reported that the combination of gefitinib and PPI should be avoided if the plasma concentrations of gefitinib cannot be monitored [135]. Because the total area under the observed plasma concentration-time curve (AUC0-24) and the maximum and trough plasma concentrations of gefitinib with the PPIs were significantly lower than those without the PPIs [135].

Low total motile sperm count: A case-control study of a population-based registry showed that the use of PPIs in the period 12 to 6 months preceding semen analysis was associated with a threefold higher risk of low total motile sperm count (OR 2.96, 95% CI: 1.26-6.97) [136].

Micronutrient deficiencies: Despite marked changes in gastric pH due to omeprazole treatment, no change in the intestinal absorption of calcium, phosphorus, magnesium or zinc from a standard test meal was evident [137]. A randomized crossover trial showed that PPIs would decrease calcium absorption [138]. Administration of PPIs to patients with hereditary haemochromatosis could inhibit the absorption of non-haem iron from a test meal and the habitual diet [139]. Long-term PPIs use caused iron deficiency anemia [140]. Liu et al. reported that PPIs usage (p=0.027) was associated with a decreased serum ω-3 polyunsaturated fatty acid (PUFAs) concentration [141]. Liu et al. concluded that serum concentrations of ω-3 PUFAs might associate with a decreased coronary artery disease proportion [141].

Vitamin B12 deficiency: Den Elzen et al. reported that no association between long-term PPIs use and vitamin B12 status was observed [142]. A clinical examination of the Canadian Study of Health and Aging reported that antiulcer medication (H2RAs or PPIs) use at baseline was significantly associated with the initiation of cobalamin therapy during the 5 year follow-up period. (OR 2.56, 95% CI: 1.30-5.05), even after adjusting for age, gender and institutional residence (OR 2.61, 95% CI: 1.31-5.23) [143]. A retrospective case-control study using a state-wide Medicaid population reported that initiation of vitamin B12 supplementation was associated with chronic gastric acid suppression therapy (H2RAs or PPIs) [144]. A case-control study reported that controlling for age, gender, multivitamin use, and *Helicobacter pylori* infection, chronic (≥ 12 months) current use of H2RAs/PPIs was associated with a significantly increased risk of vitamin B(12) deficiency among patients aged 65 years or older (OR 4.45, 95% CI: 1.47-13.34) [145]. No association was found between past or short-term (<12 months) current use of H2RA/PPI and vitamin B12 deficiency [145]. A case-control study within the Kaiser Permanente Northern California population reported that previous and current gastric acid inhibitor (PPIs and H2RAs) use was significantly associated with the presence of vitamin B12 deficiency [146].

Hypomagnesemia: Many articles showed that PPIs caused hypomagnesemia [147-153]. A systematic review and meta-analysis of observational studies showed that the association between the use of PPIs and hypomagnesemia remained significant after the sensitivity analysis including only studies with high quality score with a pooled RR of 1.63 (95% CI: 1.14-2.23) [154]. Another systematic review and meta-analysis

showed that pooled OR for hypomagnesemia was 1.775 (95% CI: 1.077-2.924) [150]. Current evidence suggests that the mechanism of PPIs induced hypomagnesemia is impaired intestinal magnesium absorption [152]. A retrospective review of patient records at time of hospitalization showed that regardless of PPIs dosage or concomitant diuretics prescribed, magnesium levels were unaffected [155].

Malignancy: Studies in humans have not confirmed an association between PPIs and digestive cancer or digestive neuroendocrine tumors [156].

However, a nationwide population-based cohort study showed that the standardised incidence ratios (SIR) of gastric cancer was over threefold increased among 797,067 individuals on maintenance PPIs therapy, (SIR 3.38, 95% CI: 3.23-3.53) [157].

A population-based prospective cohort study reported that PPIs use was associated with an increased risk of colorectal cancer within the low-risk population, although the association did not weigh the effects of conventional risk factors [158].

A population-based cohort study included all 796,492 adults exposed to maintenance therapy with PPIs [159]. Among all individuals using maintenance PPIs therapy, the overall SIR of oesophageal adenocarcinoma was 3.93 (95% CI: 3.63-4.24) [159]. The SIRs among participants using maintenance PPIs therapy because of maintenance treatment with NSAIDs and aspirin were 2.74 (95% CI: 1.96-3.71) and 2.06 (95% CI: 1.60-2.60), respectively [159].

A systematic review and meta-analysis reported that no dysplasia or cancer-protective effects of PPIs usage in patients with Barrett's esophagus were identified [160].

Hypergastrinemia: A multivariate analysis revealed that hypergastrinemia (over 150 pg/mL) was significantly associated with PPIs use (OR 5.30, 95% CI: 3.32-8.47) [161].

Barrett's esophagus: A systematic review and meta-analysis showed that use of PPIs (4 studies; OR 0.55, 95% CI: 0.32-0.96) or statins (3 studies; OR 0.48, 95% CI: 0.31-0.73) were associated with lower risk of Barrett's esophagus progression [162]. The data in the literature showed that although the PPIs treatment did not reduce the Barrett's segment length, it could reduce dysplasia or the development of early-stage adenocarcinoma (OR 0.46) [163].

Eosinophilic esophagitis: A prospective study reported that up to 70% of children with PPIs-responsive eosinophilic esophagitis remained in histological and clinical remission on a low-dose maintenance treatment at 1-year follow-up, with adequate safety profile [164].

Chemosensitivity: A retrospective clinical study of colorectal cancer patients receiving the FOLFOX or CapeOx regimen indicates that PPIs increase the chemosensitivity of colorectal cancer patients [165]. Patients who received the FOLFOX regimen with PPIs had better overall survival and progression-free survival than patients who did not receive PPIs during FOLFOX chemotherapy [165]. Ikemura et al. suggested that PPIs enhanced the efficacy and safety of anticancer agents [166].

Unexplained chronic cough: A double-blind, placebo-controlled, randomized clinical trial revealed significant effects of PPIs in patients suffering from unexplained chronic cough [167]. The main finding of the study was that the significant effect of PPIs therapy in chronic cough was consistent even in subjects without evidence of reflux [167].

Microbial translocation and immune activation: In human immunodeficiency virus-infected persons, long-term use of PPIs was associated with increased microbial translocation, innate immune activation, and reduced immune reconstitution [168].

Chronic rejection after lung transplantation: A retrospective cohort study showed that post-lung transplant exposure to persistent PPIs therapy resulted in the greatest protection against rejection in lung transplant recipients [169].

Increased frequency of hospitalization in patients with cystic fibrosis: A longitudinal retrospective review showed that exposure to PPIs therapy was independently associated with a higher number of hospitalizations for pulmonary exacerbation in cystic fibrosis patients [170].

Functional dyspepsia: The Cochrane Database Systematic Review reported that there was evidence that PPIs were effective for the treatment of functional dyspepsia, independent of the dose and duration of treatment compared with placebo [171].

Gastric acid rebound: A narrative review showed that daily PPIs exposure for more than 4 weeks was likely to trigger a rebound of acid hypersecretion about 15 days after discontinuation, and lasting from a few days to several weeks depending on the duration of the exposure [172].

Sustained virologic response: A systematic review and meta-analysis reported that a significantly increased risk of failure to achieve sustained virologic response (SVR) in chronic hepatitis C virus (HCV)-infected patients taking direct-acting antiviral (DAA) with PPIs compared to non-PPIs users [173]. Eradication of HCV is predicted by the attainment of an SVR 12 weeks following DAA therapy [173].

Histamine-2 receptor antagonists (H2RAs)

Gastrointestinal complications: Based on the Cochrane Database Systematic Review [3], standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36, 95% CI: 0.18-0.74) but not gastric ulcers (RR 0.73, 95% CI: 0.50-1.09). Double dose H2RAs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44, 95% CI: 0.26-0.74 for gastric ulcer), and were better tolerated than misoprostol [3]. The Cochrane Database Systematic Review conclude that standard doses of H2RAs should not be used for the prevention of NSAIDs related upper GI toxicity, since they are ineffective at preventing NSAIDs related gastric ulcers [3]. A network meta-analysis of randomized clinical trials showed that there were no convincing differences among H2RAs, sucralfate, and placebo for preventing clinically important GIB [4]. A systematic review and net-work meta-analysis reported that H2RAs were not recommended for upper GI hemorrhage patients as patients treated with H2RAs were associated with an

increased risk of adverse events including rebleeding, need for surgery and all-cause mortality [9]. Moreover, patients treated with H2RAs exhibited an increased length of average hospital stay and blood transfusion amount compared to those treated with PPIs [9]. A systematic review and meta-analysis reported that the use of H2RAs instead of PPIs (OR, 2.13) was the procedural factors associated with bleeding after endoscopic resection [174].

A systematic review and meta-analysis reported that PPIs were superior to H2RAs for prevention of low-dose aspirin-associated GI erosion/ulcer (OR 0.28, 95% CI: 0.16-0.50) and bleeding (OR 0.28, 95% CI: 0.14-0.59) [20].

Lower gastrointestinal complications: H2RAs usage (OR 3.95, 95% CI: 1.28-12.25) was independent risk factors for severe small intestinal damage [11].

Asthma: A systematic review and meta-analysis showed that acid-suppressive drug use in pregnancy was associated with an increased risk of asthma in childhood (RR 1.45, 95% CI 1.35-1.56; I2=0%; P<.00001) and the overall risk of asthma in childhood increased among H2RAs users (RR 1.57, 95% CI 1.46-1.69; I2=0%; P<.00001) [65].

Pneumonia and gut microbiota: A meta-analysis of eight databases indicated that H2RAs were not associated with an increased risk of hospitalization for CAP (AOR 0.95, 95% CI: 0.75-1.21) [50]. A network meta-analysis reported that H2RAs bolus was associated with increased risk of gastric colonization and pneumonia [6].

Fracture: A systematic review and meta-analysis showed that the pooled OR for fracture was 1.10 (95% CI: 0.99-1.23) with use of H2RAs and long-term H2RAs use was not significantly associated with fracture risk [78].

Kidney disease: A systematic review and meta-analysis showed that there was no association between the use of H2RAs and CKD with a pooled RR of 1.02 (95% CI: 0.83-1.25) [91].

Klatte et al. reported that initiation of PPIs therapy and cumulative PPIs exposure was associate with increased risk of CKD progression in a large, North European healthcare system, but this was not the case for cumulative H2RAs use [98].

Depression: A population-based study reported that no association was found between use of H2RAs or antacids and the Geriatric Depression Scale score [100].

Cardiovascular events: One study reported that H2RAs use was not significantly associated with ischemic stroke (HR 1.02, 95% CI: 0.84-1.24) or MI (HR 1.15, 95% CI: 0.92-1.43) [119].

Malignancy: A nationwide population-based cohort study showed long-term users of H2RAs were not at any increased risk gastric cancer [157].

Infection and mortality: A retrospective cohort study reported that ranitidine use in neonates was associated with an increased risk of infections and mortality, but not with necrotising enterocolitis [175].

Drug interaction: Yokota et al. reported that the combination of gefitinib and H2RAs should be used carefully [135]. Because the AUC0-24 of gefitinib with H2RAs tended to be lower than that without H2RAs [135].

Vitamin B12 deficiency: The aforementioned literatures reported that H2RAs were associated with an increased risk of vitamin B12 deficiency [143-146].

Misoprostol

High price and four times a day prescription is demerit of misoprostol.

Gastrointestinal complications: Based on the Cochrane Database Systematic Review [3], all doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively) [3]. A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhoea at all doses, although significantly more at 800 ug/day than 400 ug/day [3]. A network meta-analysis demonstrated that nonselective NSAIDs+misoprostol (RR, 95% CI: ulcer complications 0.47, 0.24-0.81; symptomatic ulcer 0.41, 0.13-1.00) were associated with significantly lower risk of clinical GI events compared with nonselective NSAIDs [176].

Lower gastrointestinal complications: A small single-blind, randomized controlled study showed that misoprostol (600 ug/day) prevented small intestinal injuries associated with the use of diclofenac (75 mg/day) and omeprazole (20 mg/day) for a period of two-week in healthy male volunteers [177]. Low-dose enteric-coated aspirin frequently damaged the small intestine, and misoprostol 800 mg/day was effective in the treatment of aspirin-induced enteropathy [178]

Rebamipide

Gastrointestinal complications: Rebamipide is not described in the Cochrane Database Systematic Review in 2002 [3]. A systematic review and meta-analysis showed that rebamipide acted better than placebo against short-term NSAIDs-induced gastroduodenal injury and rebamipide was equal to or not superior to traditional strategies (including PPIs, H2RAs and misoprostol treatment) [179]. A systematic review and meta-analysis showed that significant symptom improvement was observed both in pooled RR and standardized mean difference (SMD) in subjects with organic dyspepsia (peptic ulcer disease, reflux esophagitis or NSAIDs-induced gastropathy) (RR 0.72, 95% CI: 0.61-0.86; SMD -0.23, 95% CI: -0.4 to -0.07), while symptom improvement in FD was observed in pooled SMD but not RR (SMD -0.62, 95% CI: 1.16 to -0.08; RR 1.01, 95% CI: 0.71-1.45) [180]. A randomized double-blind controlled trial reported that 200 mg/day rebamipide did not protect against naproxen-induced gastric damage in healthy volunteers [181]. A randomized controlled study showed that 300 mg rebamipide improved the clinical symptoms, gastric mucosal lesions, and pathological grades of chronic gastritis patients and decreased the expression rates of CDX2 and TFF3 (intestinal metaplasia markers) in gastric cells [182].

Lower gastrointestinal complications: Rebamipide showed a beneficial effect against the small bowel damage (total RR 2.70, 95% CI: 1.02-7.16) when compared with placebo group [179]. A multicenter, randomized, double-blind, placebo-controlled trial showed that the triple dose of rebamipide (900 mg/day) was effective for the treatment of low-dose aspirin-induced moderate-to-severe small intestinal damage (rebamipide group: n=25, placebo group: n=13) [183]. A randomized, double-blinded, placebo-controlled, multicenter trial showed that rebamipide had not only the healing effect for low-dose aspirin and/or NSAIDs-induced small bowel injury compared with placebo, but the improvement of nutritional condition (rebamipide group: n=31, placebo group: n=30) [184]. A prospective, randomized, double-blinded, placebo-controlled, cross-over study with 10 healthy subjects showed that the number of subjects with NSAIDs-induced small-intestinal mucosal injuries was lower in the rebamipide group (2/10) than in the placebo group (8/10) (P=0.023) [185]. The occurrence rate of gastric ulcers of 300 mg rebamipide was similar to that of 600 mg misoprostol, but rebamipide was superior to misoprostol in terms of the withdrawal rate and the total severity score of the GI symptoms in a 12-week randomized, double-blind study (rebamipide group: n=242, misoprostol group: n=237) [186]. Ota et al. reported that standard-dose (300 mg) rebamipide is sufficient for preventing mucosal injury of the small intestine induced by low-dose (100 mg) aspirin, indicating that high-dose (900 mg) rebamipide is not necessary [187].

Safety: The triple dose of rebamipide was well tolerated [183]. Based on my experience, rebamipide has few adverse effects.

Mechanism of anti-ulcer effects: The exact mechanism by which rebamipide exerts anti-ulcer effects is unclear. The protective effect may be related to inhibition of lipid peroxidation in the gastric mucosa [188]. Rebamipide could exert its effect of gastric mucosal protection to maintain mucosal integrity through the simulation of endogenous prostaglandins mechanisms [189]. Rebamipide may prevent indomethacin-induced gastric mucosal lesion formation by inhibiting neutrophil activation [190]. Rebamipide may prevent NSAIDs-induced small intestinal damage by regulating the intestinal microbiota [191].

Gastrointestinal symptoms of type 2 diabetes mellitus: An open study showed that 300mg rebamipide treatment for 12 weeks improved atypical GI symptoms in patients with type 2 diabetes mellitus [192].

Combination: Hong et al. reported that 40 mg esomeprazole and 300 mg rebamipide combination therapy was more effective in decreasing the symptoms of reflux esophagitis than 40 mg esomeprazole monotherapy [193].

Nakamura et al. reported that combination therapy with 300 mg rebamipide and PPIs (10 mg rabeprazole) had limited benefits compared with PPIs monotherapy (10 mg rabeprazole) in the treatment of post-endoscopic submucosal dissection gastric ulcer [194].

A systematic review and meta-analysis showed that the combined therapeutic use of PPIs and mucosal protective agents improved healing rates of endoscopic submucosal dissection-induced ulcers compared to treatment with PPIs monotherapy (11 studies OR 2.28, 95% CI: 1.57–3.31; p<0.0001: 6 [300 mg/day] rebamipide OR 2.4, 95% CI: 1.68–3.44: 2 ecabet OR 2.18, 95% CI: 0.49–9.70: 2 polaprezinc OR 1.89, 95% CI: 0.44–7.91: 1 irsogladine OR 5.24, 95% CI: 1.08–25.4) [195].

Discussion

The best medicine has been discussed to prevent GI events due to NSAIDs in patients requiring long-term NSAIDs therapy. NSAIDs should be used at the lowest effective dosage and for the shortest time. Although NSAIDs are not effective for neuropathic pain such as fibromyalgia, application of NSAIDs is not discussed in this review. Tai et al. reported that if NSAIDs cessation is not possible, selective cyclooxygenase 2 (COX-2) inhibition without PPIs therapy should be considered in patients with upper GI risk factors [18]. A systematic review with network meta-analysis reported that the combination of selective COX-2 inhibitors plus PPIs provided the best gastrointestinal protection, followed by selective COX-2 inhibitors, and thirdly by nonselective NSAIDs plus PPIs [176]. The difference of application between traditional NSAIDs and selective COX-2 inhibitors and application of combined usage of gastroprotective agent and NSAIDs are not discussed in this review.

Aspirin is usually prescribed for a prolonged period, often for the entire lifetime. It is very important to prevent GI events due to aspirin.

Nehra et al. reported that most of the published evidence is inadequate to establish a definite association between PPIs use and the risk for development of serious adverse effects [196]. Maes et al. conducted systematic reviewed about adverse effects of PPIs in older adults and concluded that PPIs had been associated with an increased risk of a number of adverse effects including osteoporotic-related fractures, CDI, CAP, vitamin B12 deficiency, kidney disease, and dementia, demonstrated by a number of case-control, cohort studies, and meta-analyses [197]. Many adverse effects were provided in this review. We have to recognize that PPIs cause many serious adverse effects. Given the widespread use of PPIs, even small adverse effects could result in large public health burden [92]. Timely cessation of PPIs therapy might reduce the population burden of many kinds of diseases [92]. Some physicians have noticed adverse effects of PPIs and discontinued PPIs. An online survey of a representative sample of the American College of Physicians in 2013 showed that 63% reported sometimes/often reducing the PPIs dose, 52% switching to H2RAs, and 44% discontinuing PPIs [198]. If other medicines alleviate GI symptoms, PPIs should not be prescribed in all cases. PPIs should not be prescribed for the ambiguous purpose. Even if only PPIs alleviate GI symptoms, PPIs should be prescribed for the shortest time. Periodical evaluation for the need for continued use of PPIs therapy is necessary.

PPIs are considered the best medicine to prevent GI events due to NSAIDs. It may be a fact based on efficacy on upper GI events alone. The articles that mentioned safety and risks of PPIs excluded the adverse effects except lower GI tract disturbance

[199,200]. Guidelines for prevention of NSAIDs-related ulcer complications were published in collaboration with the Practice Parameters Committee of the American College of Gastroenterology [201]. The guidelines reported as follows: Patients requiring NSAIDs therapy who is at high risk (e.g., prior ulcer bleeding or multiple GI risk factors) should receive alternative therapy, or if anti-inflammatory treatment is absolutely necessary, a COX-2 inhibitor, and co-therapy with misoprostol or high-dose PPIs (Level of evidence 1. Strength of recommendation 2.) [201]. However, the guidelines excluded aforementioned adverse effects including lower GI tract disturbance [201]. A meta-analysis about NSAIDs-related upper GI toxicity excluded aforementioned adverse effects including lower GI tract disturbance [202]. If we discuss efficacy and risks of PPIs, the adverse effects including lower GI tract disturbance should be included. It is irrational that only adverse effects proved by systematic review and meta-analysis are accepted.

Efficacy of H2RAs for GI complications due to NSAIDs is weak and H2RAs are associated with an increased risk of some serious adverse effects. Therefore, H2RAs are not recommended as a first-line therapy

Tai et al. reported that mucoprotective agents such as misoprostol and rebamipide show promise and probiotics may have a future role [18]. Based on these literatures, rebamipide is the best medicine to prevent GI events due to NSAIDs. Rebamipide is not described in the Cochrane Database Systematic Review in 2002 [3], however, a systematic review and meta-analysis showed that rebamipide acted better than placebo against short-term NSAIDs-induced gastroduodenal injury [179]. Moreover, rebamipide prevented NSAIDs-induced small bowel damage [179,183,184]. Rebamipide was equal to or not superior to traditional strategies (including PPIs, H2RAs and misoprostol treatment) against short-term NSAIDs-induced gastroduodenal injury [179]. To my knowledge, at this time the adverse effects such as dementia, fracture, renal dysfunction, cardiovascular events, infection, low total motile sperm count, and deaths have not reported, however, these adverse effects will be reported in the future. The biggest disadvantage of rebamipide is that it is available only in some Asian countries (Philippines, Thailand, Vietnam, the Republic of Korea, China, Cambodia, Indonesia, and Japan) and Egypt.

Combination therapy with PPIs and rebamipide is not recommended because the combination therapy probably provides aforementioned adverse effects of PPIs.

In the countries where rebamipide is not available, PPIs or misoprostol is not recommended as a first-line therapy. If efficacy is given priority over adverse effects, PPIs are recommended as a first-line therapy. If fewer adverse effects are given priority over efficacy, misoprostol is recommended as a first-line therapy and PPIs as a second-line therapy.

The common classification of the adverse effects is based on severity (mild, moderate, and severe). There are other classifications, the adverse effects that are easily or hardly recognized, or the adverse effects that are easily or hardly recovered after discontinuation of medication. For example, diarrhoea, common adverse effect of misoprostol, is easily noticed and it easily disappears after discontinuation of medication. However, fracture, renal dysfunction, dementia, cardiovascular events, infection, low total motile sperm count, and deaths, common adverse effects of PPIs, are noticed only in a study; however, these are not noticed in an individual level. Improvement of them is impossible or difficult after discontinuation of PPIs. The adverse effects of PPIs are not often noticed, and their improvement after discontinuation of medication is impossible or difficult. PPIs are believed to be safe. However, the adverse effects were repeatedly reported from 2004. Regardless of indication, the adverse effects of PPIs are suspected to be similar. PPIs alone may prevent upper GI events due to NSAIDs in some patients. PPIs are important medicine for the treatment of gastroesophageal reflux disease [203], although it is different from the purpose of this review. Some patients require long-term PPIs therapy. When we have to use PPIs, we should explain aforementioned adverse effects and obtain the patient's agreement. It is hoped that many countries approve rebamipide for the treatment of patients requiring long-term NSAIDs therapy.

This review is written from the viewpoint of gastroprotective agent. From the viewpoint of analgesic agent, analgesic agent should be prescribed taking into account the adverse effects of gastroprotective agent.

Limitation

Rebamipide is available only in some Asian countries and Egypt. Therefore, there are a few articles about rebamipide. Serious adverse effects have not been reported, however, they will be reported in the future. Moreover, three studies that showed efficacy for lower GI complications were conducted in small number of patients [183-185]. The protective effects of rebamipide against small bowel injury due to NSAIDs have not been directly comported with that of other medications to date. Efficacy of rebamipide for upper GI complications due to NSAIDs may not be similar to that of PPIs.

Among the adverse effects of PPIs, CDI [29-39,42,45,46], fracture [73,75,78], fall [83], CAP [52,56] , pneumonia (either community or hospital acquired) [53,4], gastric colonization and pneumonia [6], community-acquired enteric infection [28], small intestinal bacterial overgrowth [61,62], spontaneous bacterial peritonitis and bacterial infection in patients with cirrhosis and ascites [23], hypomagnesemia [142,150,154], gastric atrophy [19], asthma [65], CKD [91], AKI [96,97], hepatic encephalopathy in patients with liver dysfunction [99], cardiovascular events and deaths [121,125,127], and failure to achieve SVR in HCV-infected patients taking DAA [173] were shown with meta-analysis. However, we should not underestimate many adverse effects.

In this narrative review, the best medicine has been discussed to prevent upper and lower GI events due to NSAIDs. This conclusion does not apply to other diseases such as gastroesophageal reflux disease.

Conclusion

In the countries where rebamipide is available, rebamipide is recommended as a first-line therapy to prevent GI events due to NSAIDs. In the countries where rebamipide is not available, PPIs or misoprostol is recommended as a first-line therapy. If efficacy is given priority over adverse effects, PPIs are recommended as a first-line therapy. If fewer adverse effects are given priority over efficacy, misoprostol is recommended as a first-line therapy and PPIs as a second-line therapy.

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