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Review

Potential Risks Associated With Long-term Use of Proton Pump Inhibitors and the Maintenance Treatment Modality for Patients With Mild Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) significantly affects the health-related quality of life and healthcare costs. The prevalence of this disease is increasing in Asia, leading to a rapid increase in the demand of proton pump inhibitors (PPIs). Despite effective symptom management during initial treatment, relapse rates after PPI cessation remain high in patients with GERD, warranting long-term maintenance therapy. Concerns regarding potential side effects related to the long-term use of PPIs are escalating with increased usage. Studies have reported diverse side effects of PPIs, such as increased fracture risk, cardiovascular concerns, enteric infections, neurological diseases, and potential associations with gastric cancer. However, definitive causal relationships remain unclear. This review comprehensively summarizes the latest knowledge on the potential risks associated with long-term use of PPIs. Continuous or noncontinuous therapy can be used as a maintenance treatment modality for GERD. For patients with mild GERD, including those with nonerosive and mildly erosive reflux disease, on-demand therapy following a sufficient period of continuous maintenance therapy is recommended as a long-term maintenance treatment option.
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Key Words
Adverse effects; Gastroesophageal reflux; Maintenance; Proton pump inhibitors

Introduction

Gastroesophageal reflux disease (GERD) is a prevalent disorder, with an average global prevalence reported to be approximately 14%.[1] As compared to the global average of GERD, West Asia has a higher prevalence, whereas South-East and East Asia have a lower prevalence.[1] However, recent studies have reported an increasing trend of the GERD prevalence in Asia.[2] Based on the presence of endoscopic mucosal injury, GERD is classified into erosive and nonerosive reflux diseases (ERD and NERD). ERD is found in approximately 25.0% of individuals with GERD symptoms, whereas NERD is identified in approximately 70.0% of patients.[3,4] A large-scale prospective study reported that the prevalence of endoscopic erosive esophagitis in Korean patients undergoing checkups was 8.0%, with 58.0% of them being asymptomatic. In

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Table 1. Prevalence of Gastroesophageal Reflux Disease Reported in Population-based Studies From East Asia Since 2010

First author	Year	Country	Sample size	GERD definition	Mean age (yr)	Men (%)	Prevalence (%)
Liu[14]	2023	China	50183	GERD-Q ≥ 8	49.4	42.0	5.6
Zhang[15]	2019	China	5680	GERD-Q ≥ 8	38.9	55.3	10.8
Tan[16]	2016	Hong Kong	2074	Montreal definition[a]	48.1	36.9	3.8
Cai[17]	2015	China	2950	GERD-Q ≥ 8	42.4	50.5	4.8
Murase[18]	2014	Japan	9643	GERD-Q ≥ 8	54.0	32.8	22.9
Min[19]	2014	Korea	5000	Any troublesome heartburn and/or acid regurgitation at least once a week during 3 months preceding the interview	43.2	51.1	7.1
Niu[20]	2012	China	1995	GERD-Q ≥ 8	43.5	71.9	31.3
Hung[21]	2011	Taiwan	1238	Chinese GERD-Q ≥ 12	59.1	45.6	25.0
He[22]	2010	China	16091	Montreal definition[a]	42.5	47.8	3.1

[a]According to the Montreal definition, a diagnosis of gastroesophageal reflux disease (GERD) is defined as mild symptoms occurring on ≥ 2 days of the week, or moderate to severe (troublesome) symptoms occurring on ≥ 1 day of the week.
GERD-Q, gastroesophageal reflux disease questionnaire.

those with erosive esophagitis, grade A, B, C, and D according to Los Angeles (LA) classification were observed in 74.1%, 23.3%, 2.3%, and 0.2%, respectively.[5] In a systematic review of Japanese studies, 87% of erosive esophagitis were grade A or B.[6] In a cross-sectional study conducted in one region of China, 93.7% of erosive esophagitis were grade A or B.[7] Thus, most ERD in countries of East Asia is LA-A or LA-B, suggesting that mild GERD is the most common form in those Asian countries.

The severity of symptoms correlates with esophageal acid exposure, and acid-suppressive agents such as a proton pump inhibitor (PPI) are generally prescribed for the treatment of GERD.[8-10] GERD is a chronically recurrent disease, and the majority of patients with GERD require long-term maintenance treatment.[11,12] The chronic nature of the disease can be associated with a considerable economic burden and decreased quality of life.[13] Furthermore, many patients and physicians are still concerned about the potential adverse effects of long-term PPI use. However, to date, data on this issue is controversial. Moreover, only a few studies have been conducted in Asian countries. Therefore, in the present review, we aim to evaluate data on the potential adverse effects associated with long-term PPI use, particularly in Asian countries. We also tried to suggest the long-term maintenance treatment modality appropriate for patients with mild GERD, which is the most prevalent type of GERD in Asian countries.

Gastroesophageal Reflux Disease Prevalence in Asia

The prevalence of GERD in Asia has been increasing. In a meta-analysis of population-based studies in Asia, the prevalence of GERD was reported to significantly increase from 11.0% in 2000-2009 to 15.0% in 2010-2019.[2] Similarly, in observational studies for participants who underwent a medical check-up, the prevalence of GERD was significantly increased (6.0% vs 15.0%) in the same period (2000-2009 to 2010-2019). In this meta-analysis, a high heterogeneity was noted among the studies included. In another meta-analysis of 102 studies performed around the world, the prevalence of GERD was 13.9% and varied depending on the regions.[1] In 54 studies from Asia, the prevalence was 12.9%; the highest prevalence was noted in Turkey (22.4%) and the lowest in China (4.2%). In that study, the prevalence of GERD in South Korea was 5.8%. The prevalence in population-based studies performed in East Asia since 2010 is listed in Table 1.[14-22] In a large-scale prospective study based on data from the health checkup centers of 40 hospitals in Korea, the prevalence of GERD, including ERD and NERD, was reported to be 12.0%.[5]

Maintenance Treatment Appropriate for Mild Gastroesophageal Reflux Disease

Despite adequate symptom control and mucosal healing by the initial treatment using PPIs, relapse occurs in approximately 50.0-80.0% of patients with NERD or mild erosive esophagitis with GERD.[23,24] A randomized controlled trial of maintenance therapy for NERD patients found that 83.0% of patients using 20 mg omeprazole were in remission at 6 months, compared to 56.0% of those in the placebo group.[25] This suggests that approximately half of patients with NERD may require long-term acid suppressive

therapy to maintain a normal quality of life. Moreover, in cases of LA grade C esophagitis, the relapse rate is almost 100.0% within 6 months.[26] Therefore, the current guidelines recommend maintenance therapy for individuals experiencing persistent or recurrent symptoms after discontinuing PPIs, as well as for those with severe erosive esophagitis or complications, such as Barrett's esophagus.[2,27,28]

Several approaches for maintenance therapy have been proposed for the long-term management of GERD. These include continuous therapy, which refers to the daily intake of PPIs, on-demand therapy, which involves taking PPIs when symptoms arise and stopping them once the symptoms subside, intermittent therapy, which involves the use of PPIs for a specific duration, typically 1-2 weeks, in response to the symptoms, and threshold therapy, which indicates a gradually increasing interval between PPI intakes as long as symptoms do not reappear.[29] The latter 3 methods can be described as noncontinuous therapies or broadly categorized as on-demand therapies. Studies comparing on-demand and continuous therapy for the maintenance treatment of GERD have yielded inconsistent results in terms of symptom relief, satisfaction with the present treatment, or the willingness to continue current therapy (Table 2).[30-38] While some studies have reported the superior effect of continuous therapy, on-demand therapy is noninferior to or not significantly different from continuous therapy in other studies. The latest meta-analysis, comprising 11 studies (9 from the West and 2 from Asia), indicates no significant difference in treatment failure rates between the 2 groups (9.1% vs 7.3%) with an RR of 1.26 (95% CI, 0.76-2.07; $P = 0.372$). However, the advantage of on-demand therapy is the fact that the total amount of PPIs used in the on-demand treatment group is approximately half, compared with that of the continuous group.[39]

A prospective multicenter randomized study involving 304 patients with NERD or mild erosive esophagitis who underwent maintenance treatment using a half dose of PPIs following symptom improvement with a standard dose of PPIs for the comparison between the on-demand and continuous maintenance treatment was recently reported.[30] Continuous and on-demand therapies were compared for a 6-month maintenance period. Unlike the findings of the recent meta-analysis,[39] the results failed to show the noninferiority of on-demand treatment over continuous treatment. There is a significant difference in the proportion of patients unwilling to continue the assigned treatment modality between the on-demand and continuous treatment groups (45.9% vs 36.1%). Regarding the reasons for reluctance to continue the assigned maintenance treatment, poorly controlled symptoms were notably more common in the on-demand group than in the continuous treatment group (35.8% vs 17.0%, $P = 0.009$). Furthermore, compared with the on-demand group, the GERD symptom and health-related quality of life scores significantly more improved and the overall satisfaction score was significantly higher in the continuous treatment group, particularly at week 8 and 16 of maintenance treatment. However, at week 24 of maintenance treatment, there was no significant difference in the GERD symptom score or overall satisfaction between the 2 groups.[30] Therefore, as a long-term maintenance treatment modality for mild GERD, a sequential maintenance treatment, that is switching to on-demand therapy after a sufficient period of continuous maintenance treatment using a half-dose PPI, may be desirable.

In a real-world survey conducted in patients receiving long-term PPIs for maintenance treatment of GERD, no significant differences were observed in overall satisfaction, degree of GERD symptom control, or preference for the current maintenance therapy modality among the continuous, on-demand, and intermittent therapy groups.[40] However, the convenience score of taking PPIs was reported to be higher in the continuous therapy group than in the noncontinuous therapy group (31.6% vs 18.8%, respectively; $P = 0.025$). This preference is likely attributable to the perception that taking one pill daily without specific considerations is more convenient than providing instructions for self-administering the medication based on symptoms. Interestingly, patients with longer duration of GERD tended to receive noncontinuous therapy, such as on-demand therapy. Moreover, the noncontinuous therapy group was demonstrated to show significantly higher awareness of potential adverse effects associated with PPIs than the continuous therapy group.[40] Therefore, for GERD patients who requires maintenance treatment using a PPI, physicians or medical staffs need to actively educate the advantages and disadvantages of continuous and noncontinuous maintenance treatment modalities. The benefits of noncontinuous therapy may be associated with concerns about potential adverse effects of long-term PPI use and cost effectiveness.

Taking all these findings into consideration, as a maintenance treatment modality following initial treatment using PPIs for patients with mild esophagitis or NERD, step-by-step sequential maintenance therapy is recommended, which is initially continuous maintenance treatment for a sufficient period of time until adequate control of symptoms, followed by noncontinuous treatment with carefully monitoring the patient's symptoms.

Table 2. Studies Comparing Continuous Versus On-demand Therapy in the Maintenance Treatment of Gastroesophageal Reflux Disease

First author	Year	Country	Institutions	Enrolled patients	Maintenance treatment	Continuous (n)	On-demand (n)	Primary outcome	Outcome results (%, continuous / on-demand, *P*-value or interpretation)	Conclusion
Jung[30]	2023	Korea	Multi-center	NERD and mild EE	Pantoprazole 20 mg daily or on-demand for 6 mo	147	146	Unwillingness to continue the present treatment	36.1/45.9, failed to confirm the noninferiority of on-demand treatment	Continuous treatment seems to be more appropriate for the initial maintenance treatment of mild GERD than on-demand treatment.
Cho[31]	2018	Korea	Single-center	GERD (severe EE 2.5%)	Esomeprazole 20 mg daily or esomeprazole 40 mg on-demand for 12 wk	41	39	Heartburn resolution rate at 12 wk	87.8/82.1, $P = 0.471$	On-demand therapy with esomeprazole 40 mg appears to be sufficient for maintenance treatment in GERD patients.
Bayerdörffer[32]	2016	Austria, France, Germany, South Africa and Spain	Multi-center	NERD	Esomeprazole 20 mg daily or on-demand for 6 mo	297	301	Proportion of patients who discontinue the study due to unsatisfactory treatment	9.8/6.3, NS	On-demand treatment with esomeprazole 20 mg is non-inferior to continuous maintenance treatment.
Nagahara[33]	2014	Japan	Single-center	GERD	Omeprazole 20 mg daily or on-demand for 6 mo	59	58	Symptom relief at 6 mo	66.7/74, NS	On-demand therapy appears to be sufficient as maintenance therapy for NERD patients.
Szucs[34]	2009	Switzerland	Multi-center	GERD	Esomeprazole 20 mg daily or on-demand for 6 mo	420	484	Heartburn relief at 6 mo	86/80, $P < 0.001$	The adjusted direct medical costs of on-demand treatment are significantly lower compared with a continuous treatment.
Morgan[35]	2007	Canada	Multi-center	GERD	Rabeprazole 20 mg daily or on-demand for 6 mo	137	131	Proportions of heartburn-free days	90.3/64.8, $P < 0.001$	Continuous therapy is associated with an increased number of medication intake days with less heartburn episodes versus on-demand therapy.
Bour[36]	2005	France	Multi-center	NERD and mild EE	Rabeprazole 10 mg daily or on-demand for 6 mo	81	71	Symptom relief at 6 months	86.4/74.6, $P = 0.065$	On-demand therapy provides an alternative to continuous therapy.
Janssen[37]	2005	Germany, France, Switzerland and Hungary	Multi-center	NERD and mild EE	Pantoprazole 20 mg daily or on-demand for 6 mo	217	215	Treatment failure	18.6/30.7, confirm the noninferiority of on-demand treatment	On-demand treatment is noninferior to continuous therapy with regard to symptom control.
Tsai[38]	2004	UK	Multi-center	NERD	Lansoprazole 15 mg daily or Esomeprazole 20 mg on-demand for 6 mo	311	311	Unwillingness to continue the present treatment	13/6, $P = 0.001$	On-demand therapy is more acceptable and economically more effective than continuous therapy.

GERD, gastroesophageal reflux disease; NERD, non-erosive reflux disease; EE, erosive esophagitis; NS, not significant.

Potential Adverse Effects Associated With Proton Pump Inhibitor Use

Acid-suppressive therapy with PPIs is established as the most efficacious approach for treating patients with GERD and has been used as the first-line treatment.[26] PPIs are widely used for long-term maintenance treatment of GERD and acid-related diseases such as peptic ulcers. Therefore, they are known to be one of the most commonly used drugs in the US, and PPI use is reported to be increasing in the United States (US) population.[41] The Health Insurance data of Korea estimating based on the number of GERD patients taking PPIs also showed increased prescription of PPIs for more than 12 weeks in Korea.[13] As the use of PPIs increases, concerns regarding adverse effects are raised. The safety profile of PPIs is generally considered to be good, with less than 1% to 2% patients experiencing adverse effects and requiring discontinuation of the medication.[42] However, several studies, which mainly include case-control studies and meta-analyses, have raised concerns about the adverse effects associated with long-term use of PPIs. These include alterations in the gut microbiome, enteric infections, micronutrient deficiencies, fundic gland polyps, gastrointestinal malignancy, chronic kidney disease, cognitive dysfunction, myocardial infarction, bacterial overgrowth, bacterial peritonitis, pneumonia, bone fracture, drug interactions, and even death.[43] In addition, the US Food and Drug Administration (FDA) has issued several warnings regarding these adverse effects, including those related to bone fractures, interactions with clopidogrel, enteric infections, and hypomagnesemia.[42] However, many of these associations need further investigation for causal relationship. Residual confounding factors and other analytical biases cannot be excluded. Furthermore, there is a lack of explanation for possible mechanisms. Randomized controlled trials reporting adverse events associated with PPI use are rare.[44] In a recent meta-analysis evaluating the certainty of evidence on PPI use and adverse effects, the association between PPI use and risk of all-site fracture and chronic kidney disease in the elderly population was found to have convincing evidence. However, none of these associations remained supported by convincing evidence after sensitivity analyses. In meta-analyses of randomized controlled trials, none of statistically significant associations were supported by high or moderate-quality evidence.[45] Therefore, high-quality evidence is still required to confirm putative adverse effects associated with PPI use. Particularly, further research on the causal relationship for some adverse effects with convincing evidence is necessary.

Bone Fracture

The relationship between PPIs and bone health has been a research topic of interest for a long time. Based on several potential mechanisms including hypochlorhydria-associated malabsorption of calcium or vitamin B_{12}, gastrin-induced parathyroid hyperplasia, and osteoclastic vacuolar proton pump inhibition, a possible link between PPI use and increased fracture risk has been proposed.[46] Numerous studies have examined this association; some found a positive association, while others did not. Additionally, several meta-analyses have indicated a positive association with an increased risk of fracture (Table 3).[47-50] A recent meta-analysis demonstrated that PPI users had an increased risk of developing any site fractures (hazard ratio [HR], 1.30; 95% CI, 1.16-1.45), hip fracture (HR, 1.22; 95% CI, 1.15-1.31), spine fracture (HR, 1.49; 95% CI, 1.31-1.68), and osteoporosis (HR, 1.23; 95% CI, 1.06-1.42) compared to nonusers. However, the risk is small and there is no correlation of PPI use with developing bone mineral density loss.[49] Another meta-analysis also reported a significant association of PPI use with an increased fracture risk (OR, 1.28; 95% CI, 1.22-1.35), but not with bone mineral density loss.[48] Although the results suggest that PPI therapy may increase fracture risk, confounding factors may be involved in the overall outcomes. Moreover, most of the included studies were retrospective observational studies, and moderate-to-high heterogeneity was observed. Observational data are affected by unmeasured and/or residual confounding factors, and data related to a dose- or duration-based response have been inconsistent. Thus, because of these limitations of current data, long-term and well-designed randomized controls are needed to confirm the association between PPI use and bone fractures or osteoporosis.

Cardiovascular Risk

PPIs are primarily metabolized by the cytochrome P450 isoenzyme, CYP2C19. The antiplatelet drug clopidogrel is activated by CYP2C19, and there is concern that PPIs may decrease clopidogrel's antiplatelet effect. Several retrospective studies have suggested an association between the use of PPIs and an increased rate of cardiovascular events.[51,52] The FDA has also warned against the combination of clopidogrel with PPIs, particularly omeprazole. There are differences in the influence on CYP2C19 metabolism between PPIs. Thus, omeprazole and esomeprazole seem to have more effect on CYP2C19 metabolism, whereas lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole are likely to have less

effect.[53,54] However, evidence on the interaction between the use of PPIs and cardiovascular risk is inconsistent. A randomized controlled study of PPIs vs placebo in patients with coronary artery disease who were receiving dual antiplatelet therapy reported that there was no clinically significant interaction between clopidogrel and omeprazole.[55] However, a recently published meta-analysis found a significant increase in cardiovascular-related events in patients who took clopidogrel and PPIs (Table 4).[56-58] However, the number of randomized controlled trials included is small, and the increase in risk was not significant when only randomized controlled trials were analyzed.[56] Additionally, a subgroup analysis including 7 studies conducted in Asia did not show a significant association. Therefore, the relationship between PPI use and cardiovascular risk is not clear yet.[57]

Enteric Infection

As gastric acid kills ingested microorganisms, PPIs may potentially contribute to an increased susceptibility to enteric infections. Enteric infections are attributed to alterations in the composition of the gut microbiota, particularly affecting the acid-sensitive organisms such as *Vibrio cholera, Salmonella, Campylobacter,* and *Noro-*

Table 3. Association of Proton Pump Inhibitor Use With Risk of Bone Diseases

First author	Year	Included studies	Outcomes	No. of included studies	Heterogeneity I^2 (%)	Metrics (95% CI)	
Hussain[47]	2018	Observational studies	Hip fracture	17	68.0	RR	1.26 (1.17-1.35)
Nassar[48]	2018	Population-based studies	Fracture of any site	22	78.6	OR	1.24 (1.18-1.31)
			Hip fracture	15	89.6	OR	1.34 (1.24-1.46)
			Spine fracture	10	91.5	OR	1.18 (0.93-1.42)
			BMD loss	5	72.0	SMD	0 (−0.18-0.19)
Liu[49]	2019	Observational studies	Fracture of any site	13	78.6	HR	1.3 (1.16-1.45)
			Hip fracture	17	72.5	HR	1.22 (1.15-1.31)
			Spine fracture	5	22.2	HR	1.49 (1.31-1.68)
			Osteoporosis	7	90.6	HR	1.23 (1.06-1.42)
			Femoral BMD loss	3	47.4	SMD	−0.27 (−0.62-0.09)
			Spine BMD loss	3	70.4	SMD	−0.06 (−0.04-0.99)
Poly[50]	2019	Observational studies	Hip fracture	24	76.7	RR	1.21 (1.14-1.28)

CI, confidence interval; RR, risk ratio; OR, odds ratio; BMD, bone mineral density; SMD, standardized mean difference; HR, hazard ratio.

Table 4. Clinical Outcomes of Concomitant Use of Proton Pump Inhibitors and Clopidogrel

First author	Year	Included studies	Outcomes	No. of included studies	Heterogeneity I^2 (%)	Metrics (95% CI)	
Luo[56]	2022	2 RCTs and 16 observational studies	MACEs	18	59	HR	1.15 (1.06-1.26)
			MI	13	18	HR	1.18 (1.11-1.24)
			Cardiac death	5	80	HR	1.09 (0.80-1.48)
			All-cause mortality	13	78	HR	1.15 (0.94-1.41)
			GI complication	3	19	HR	0.44 (0.30-0.64)
Shi[57]	2021	18 observational studies, ≥ 12 mo follow-up	MACCEs	18	42	OR	1.38 (1.28-1.62)
			MI	12	41	OR	1.30 (1.19-1.41)
			Cardiac death	13	57	OR	1.35 (1.19-1.53)
			All-cause mortality	8	39	OR	1.54 (1.31-1.80)
			GI bleeding reduction	4	73	OR	1.50 (1.21-1.87)
Demsack[58]	2018	10 RCTs and 17 observational studies	MACEs	23	90	RR	1.22 (1.06-1.39)
			MI	14	66	RR	1.43 (1.24-1.66)
			CV death	10	67	RR	1.21 (0.97-1.50)

CI, confidence interval; RCTs, randomized controlled trials; MACEs, major adverse cardiovascular events; MI, myocardial infarction; GI, gastrointestinal; MACCE, major adverse cardiovascular and cerebrovascular events; CV, cardiovascular; HR, hazard ratio; OR, odds ratio; RR, risk ratio.

virus.[59] In a previous study in patients with stable cardiovascular and peripheral artery disease using aspirin or rivaroxaban, those given either a PPI or a placebo did not exhibit a significant increase in the risk of *Clostridium difficile* infection (CDI), but showed a significant increase in the risk of other enteric infections.[60] In the US, FDA issued a warning regarding the use of PPIs and the risk of developing CDI. In meta-analyses of studies reporting the risk of CDI related to the use of PPIs, the risk of community-associated or hospital-acquired CDI and recurrent CDI was found to be significant (Table 5).[61-66] A recent comprehensive analysis based on meta-analyses of eight studies on the risk of CDI in PPI users revealed a significant elevation in the likelihood of developing CDI compared to nonusers. In the majority of included studies, a moderate risk for the development of CDI was identified, with ORs between 1.5 and 2.0.[67] Although current evidence supports a positive link between PPI use and the development of CDI, clear recommendations are not established yet. Thus, the use of PPIs in patients at risk for CDI needs to be personalized.

Neurological Diseases

Inconsistent and conflicting findings have been observed in studies examining the potential association between the use of PPIs and cognitive decline or dementia. Recent population-based observational studies on the risk of dementia in PPI users are summarized in Table 6.[68-78] Studies using the database from Korean National Health Insurance Service have shown variable results; some studies reported a significant increase in the risk of dementia, while others did not.[73,74] This discrepancy is thought to be due to manipulative definitions for dementia and wash-out periods, and differences in analytical methods. A recent meta-analysis of nine observational studies did not provide supporting evidence for this association.[79] Several studies investigating the relationship between the use of PPIs and Parkinson's disease (PD) consistently suggest

Table 5. Risk of *Clostridium difficile* Infection in Proton Pump Inhibitor Users

First author	Year	Population	Outcome	No. of included studies	Heterogeneity I^2 (%)	OR (95% CI)
Metha[61]	2021	Hospitalized patients	Recurrent CDI	7	83.4	1.84 (1.18-2.85)
Arriola[62]	2016	Hospitalized patients	CDI	23	82.0	1.81 (1.52-2.14)
D'Silva[63]	2021	Overall patients	Recurrent CDI	16	55.6	1.69 (1.46-1.96)
Oshima[64]	2018	Overall patients	CDI	49	94.0	2.30 (1.89-2.80)
		Overall patients	Recurrent CDI	12	52.0	1.73 (1.39-2.15)
Cao[65]	2018	Overall patients	CDI	50	80.6	1.26 (1.12-1.39)
Trifan[66]	2017	Overall patients	CDI	56	85.4	1.99 (1.73-2.30)

OR, odds ratio; CI, confidence interval; CDI, *Clostridium difficile* infection.

Table 6. Risk of Dementia in Proton Pump Inhibitor Users

First author	Year	Country	Follow-up durations (yr)	Age (yr)	PPI users (n)	Non-users (n)	Outcome	Metrics (95% CI)	
Ahn[68]	2022	Germany	median 4.3	median 56.0	674 544	2023 632	Dementia	HR	1.56 (1.50-1.63)
Lin[69]	2021	Taiwan	max 10	mean 55.0	494	6711	Dementia	HR	1.84 (1.35-2.51)
Wu[70]	2020	Taiwan	mean 4	mean 56.0	2580	2583	Dementia	HR	0.72 (0.50-1.03)
Torres-Bondia[71]	2020	Spain	max 14	mean 66.9	36 360	99 362	AD	OR	1.06 (0.93-1.21)
							non-AD dementia	OR	1.20 (1.05-1.37)
Chen[72]	2020	Taiwan	max 12	≥ 65	9348	9348	Dementia	HR	1.42 (1.07-1.84)
Park[73]	2018	Korea	max 11	≥ 60	7342	7342	Dementia	SR	1.21 (1.16-1.27)
Hwang[74]	2018	Korea	max 6	≥ 60	1947	68 086	Dementia	HR	0.99 (0.70-1.39)
Gray[75]	2018	USA	mean 7.5	mean 74.0	402	3082	Dementia	HR	1.13 (0.82-1.56)
Tai[76]	2017	Taiwan	mean 9	mean 55.6	7863	7863	Dementia	HR	1.22 (1.05-1.42)
Gomm[77]	2016	Germany	max 6	mean 83.8	2950	70 729	Dementia	HR	1.44 (1.36-1.52)
Haenisch[78]	2015	Germany	max 4	mean 79.6	713	2363	Dementia	HR	1.38 (1.04-1.83)

PPI, proton pump inhibitor; OR, odds ratio; CI, confidence interval; AD, Alzheimer's disease; HR, hazard ratio; SR, sequence ratio.

a weak positive association (Table 7).[80-83] PD is a chronic neurodegenerative disorder, and its underlying mechanism remains poorly understood. A recent investigation using the population-based database from Korean National Health Insurance Service demonstrated an association between PPI use and PD after applying a 2-year or 3-year lag window before diagnosis, with evidence of a dose-response relationship. Moreover, older individuals aged ≥ 50 years were found to be more susceptible to the risk of PD related to the use of PPIs.[81] It is presumed that PPIs can pass through the blood-brain barrier and inhibit lysosomal acidification through the inhibition of vacuolar proton pumps, preventing the degradation ability of fibrillar amyloid-β, an amyloid-β degradation product.[84,85] Therefore, PPIs are likely to increase the risk for neurodegenerative diseases. Nevertheless, diverse confounders were not considered in the analysis. Thus, future studies with adjustments for the potential confounding factors are necessary to confirm this association.

Kidney Disease

Following the publication of the first observation regarding the association of PPIs with acute interstitial nephritis (AIN) in 1992, numerous case series have described this association.[86] The largest case series is a study reporting 133 biopsy-proven cases of AIN in US, where 71.0% of the cases are drug-related; antibiotics are

Table 7. Risk of Parkinson's Disease in Proton Pump Inhibitor Users

First author	Year	Study design	Country	Follow-up durations (yr)	Age (yr)	Cohort study (n)		Case-control study (n)		HR/OR (95% CI)
						PD cases/ PPI users	PD cases/ non-PPI users	PPI users/ PD cases	PPI users/ control	
Chen[80]	2023	Retrospective cohort	Taiwan	median 5	mean 47.1	366/56 785	258/56 785			1.76 (1.48-2.08)
Hong[81]	2023	Nested case-control	Korea	max 9	mean 67.7			15 467/31 326	55 407/125 304	1.10 (1.07-1.13)
Kim[82]	2022	Nested case-control	Korea	max 12	≥ 50			562/5993	1817/23 972	1.12 (1.01-1.25)
Lai[83]	2020	Nested case-control	Taiwan	max 12	mean 76.5			997/4280	895/4280	1.15 (1.04-1.27)

PD, Parkinson's disease; PPI, proton pump inhibitor; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

Table 8. Risk of Kidney Disease in Proton Pump Inhibitor Users

First author	Year	Study design	Country	Follow-up durations	Age (yr)	Outcome	Cohort study (n)		Case-control study (n)		HR/OR (95% CI)
							KD cases/ PPI users	KD cases/ non-PPI users	PPI users/ KD cases	PPI users/ control	
Klesper[89]	2013	Nested case-control	USA	within 1 yr	mean 21.1	AKI			126/854	191/3289	1.72 (1.27-2.32)
Antoniou[90]	2015	Retrospective cohort	Canada	median 120 day	≥ 65	AKI	1269/290 592	518/290 592			2.52 (2.27-2.79)
Hart[91]_AKI	2019	Retrospective cohort	USA	median 90 day	mean 44.1	AKI	115/13 889	29/13 889			3.93 (2.61-5.93)
Hart[91]_CKD	2019	Retrospective cohort	USA	median 6.8 yr	mean 44.2	CKD	1710/12 093	1500/12 093			1.20 (1.11-1.29)
Lazarus[92]_ARIC	2016	Prospective cohort	USA	median 13.9 yr	mean 63.0	CKD	56/322	1224/9204			1.35 (1.17-1.55)
Lazarus[92]_ Geisinger	2016	Retrospective cohort	USA	median 6.2 yr	mean 50.0	CKD	1921/16 900	27 204/225 221			1.22 (1.19-1.25)
Peng[93]	2016	Nested case-control	Taiwan	mean 3.9 yr	mean 65.4	ESRD			2647/3808	2104/3808	1.88 (1.71-2.06)

KD, kidney disease; PPI, proton pump inhibitor; HR, hazard ratio; OR, odds ratio; CI, confidence interval; AKI, acute kidney injury; CKD, chronic kidney disease; ARIC, atherosclerosis risk in communities; ESRD, end-stage renal disease.

most commonly implicated (49%), followed by PPIs (14.0%) and NSAIDs (11.0%).[87] However, the precise mechanism by which PPIs induce AIN is not clearly known. PPIs and/or their metabolites are presumed to be deposited within the tubulointerstitium of the kidney, that act as either haptens or directly stimulate T cells to mediate AIN.[88] PPIs are known to be associated with both acute kidney injury and chronic kidney disease. Recent reports showed that over half of patients with PPI-induced AIN did not fully recover, suggesting that PPIs may lead to chronic kidney disease through progression of AIN.[87] Inflammation and damage to the tubulointerstitium may result in interstitial fibrosis and chronic interstitial nephritis, potentially leading to chronic kidney disease.[88] Several studies support an association between PPI use and renal diseases (Table 8).[89-93] A systematic review and meta-analysis revealed an increased risk of both AKI and chronic kidney disease associated with PPI use, with a number needed to harm of 27 (risk ratio, 1.44) for AKI and 20 (risk ratio, 1.36) for chronic kidney disease.[94] In summary, the existing literature indicates an association between the use of PPIs and kidney diseases. Although there are no official warnings in the guidelines or PPI labeling, it seems desirable that healthcare providers consider periodic renal monitoring in patients on chronic PPI therapy.

Gastric Cancer

An increasing number of observational studies have documented the risk of gastric cancer in patients receiving long-term PPI therapy. Nevertheless, current evidence on the association between PPI use and gastric cancer remains inconclusive. Recent observational studies on the risk of gastric cancer in PPI users are summarized in Table 9.[95-103] Some investigations have reported an elevated risk of gastric cancer in PPI users,[95,100] whereas others have failed to establish any significant link between PPI use and the development of gastric cancer.[98,99] Several mechanisms have been proposed to elucidate how PPIs may contribute to the development of gastric cancer. First, the use of PPIs leads to a reduction in gastric acid production, resulting in hypergastrinemia.[104] Gastrin, a trophic hormone, can act as a growth factor, thereby inducing hyperplasia and potentially functioning as a carcinogen in the stomach.[105] Hypergastrinemia may induce hyperplasia of the enterochromaffin-like

Table 9. Risk of Gastric Cancer in Proton Pump Inhibitor Users

First author	Year	Study design	Country	PPI exposure	Cohort study (n)		Case-control study (n)		HR/OR (95% CI)	HR/OR in patients with *H. pylori* eradication
					GC cases/ PPI users	GC cases/ non-PPI user	PPI users/ GC cases	PPI users/ control		
Tamim[95]	2008	Nested case-control	Canada	At least one			234/1071	837/7158	1.46 (1.22-1.74)	
Wennerstrom[96]	2017	Nested case-control	Denmark	At least one					3.34 (2.99-3.73)	
Lai[97]	2019	Nested case-control	Taiwan	> 6 mo			308/649	341/649	2.0 (1.36-2.95)	
Liu[98]_PCCIU	2020	Nested case-control	UK	At least one			329/1117	1213/5394	1.49 (1.24-1.8)	
Liu[98]_Biobank	2020	Nested case-control	UK	At least one	44/20 887 person-year	206/1949 341 person-year			1.28 (0.86-1.90)	
Lee[99]	2020	Nested case-control	USA	≥ 2 yr			164/1233	773/10 543	1.07 (0.81-1.42)	
Seo[100]	2021	Retrospective cohort	Korea	≥ 30 day	118/11 741	40/11 741			2.37 (1.56-3.68)	1.35 (0.79-2.31)
Niikura[101]	2018	Retrospective cohort	Japan	At least one	13/118	8/415			-	3.61 (1.49-8.77)
Cheung[102]	2018	Retrospective cohort	Hong Kong	At least weekly	NA/3271	NA/60 126				2.44 (1.45-4.2)
Kim[103]	2023	Retrospective cohort	Korea	≥ 180 day	1117/144 091	1020/144 091				1.15 (1.06-1.25)

GC, gastric cancer; PPI, proton pump inhibitor; HR, hazard ratio; OR, odds ratio; CI, confidence interval; *H. pylori, Helicobacter pylori;* PCCIU, primary care clinical information unit.

cells and increase the risk of cell proliferation.[106,107] A possibility that chronic gastrin elevation may act as a potential factor during gastric carcinogenesis has been suggested.[108] Another plausible mechanism is bacterial overgrowth and dysbiosis in the stomach, resulting from the reduction of gastric acidity due to PPI therapy. Alterations in the gut microbiota have been suggested to increase the risk of gastric cancer.[109]

Helicobacter pylori infection is known to be the principal causative agent for peptic ulcer disease and gastric cancer.[110,111] Many studies reporting the association between long-term PPI use and gastric cancer development often lack accurate documentation of *H. pylori* status. Thus, whether *H. pylori* infection and PPIs exert synergistic effects on gastric cancer development remains unclear. A previous population-based study from Hong Kong who received eradication therapy demonstrated that long-term use of PPIs was still associated with an increased risk of gastric cancer even in subjects after *H. pylori* eradication therapy.[102] Another population-based study using Korean National Health Insurance Services Database for patients aged > 40 years who received *H. pylori* eradication therapy also revealed that long-term PPI use after *H. pylori* eradication therapy increased the risk of gastric cancer, with a positive dose-response relationship.[103] Furthermore, in patients who underwent endoscopic resection for gastric neoplasms and received *H. pylori* eradication therapy using the Korean National Health Insurance Services database, the incidence of metachronous gastric cancer was reported to be significantly elevated in the PPI user group than in the non-user group, indicating that long-term PPI use is associated with an increased risk of metachronous gastric cancer in patients who undergo *H. pylori* eradication therapy.[112] These observations imply that PPIs may increase the risk of gastric cancer in individuals with *H. pylori*-associated chronic gastritis and atrophy. Thus, the long-term use of PPIs seems to require caution for the development of gastric neoplasms, particularly in *H. pylori*-infected subjects.

Conclusions

The increasing prevalence of GERD in Asia has led to the common long-term use of PPIs, accompanied by increased concerns about their possible adverse effects. Although most studies are observational and clear causative relationships are lacking, warnings or potential of adverse effects related to the long-term use of PPIs continue to be published. Since GERD tends to relapse after discontinuation of medication, long-term maintenance therapy is commonly necessitated. Both patient's satisfaction associated with symptom control and concerns regarding the possible side effects of PPIs should be considered for maintenance treatment of GERD. For patients with mild esophagitis or NERD, sequential step-by-step maintenance therapy, that means noncontinuous therapy with monitoring of the patient's symptoms following continuous maintenance therapy for a sufficient period until adequate control of symptoms, is recommended.

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