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ORIGINAL ARTICLE—ALIMENTARY TRACT

Effects of proton pump inhibitor use on risk of *Clostridium difficile* infection: a hospital cohort study

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Abstract

Background Although there are several studies on the association between use of proton pump inhibitors (PPIs) and increased *Clostridium difficile* infection (CDI) risk, detailed studies analyzing the effects of PPI use on CDI risk are lacking. The present study investigated the association of the dose, duration, and types of PPIs with CDI risk.

Methods A single-center, cohort study was conducted on patients admitted to a hospital. The exposed cohort comprised patients who were prescribed PPIs at least once during the study period, and a control cohort was prepared by randomly assigning an index date to patients who did not use PPIs ensuring the same distribution of index dates as in the exposed cohort and matching sex, age, hospitalization period, and date of admission.

Results PPI use increased the risk of CDI by 1.8-fold [95% confidence interval (CI) 1.5–2.2]. CDI risk increased by 1.8-fold with esomeprazole (95% CI 1.4–2.2) and 2.0-fold with pantoprazole (95% CI 1.5–2.8). Patients who used a high dose had a higher risk than those who used a medium dose [adjusted hazard ratio (HR) 2.0 vs 1.3]. The risk of CDI increased 4.2-fold when the PPI exposure period was 6 days or shorter than 6 days.

Conclusions Our study showed that PPI use was associated with an increased risk of developing CDI and the risk of CDI was dose dependent. Therefore, PPIs should only be used at proper doses and only for the necessary indications to avoid CDI risk.

Keywords Proton pump inhibitor · *Clostridium difficile* · Diarrhea

Introduction

Proton pump inhibitors (PPIs) are gastric acid secretion inhibitors used for the management of various gastrointestinal diseases including peptic ulcer disease, gastroesophageal reflux disease, and for *Helicobacter pylori* eradication. The use of PPIs has become increasingly widespread because of their high efficacy, good safety profile, and low cost. However, the popularity of PPIs has led to their improper use such as overdose or long-term use [1–3]. Various adverse drug events due to overuse or misuse have been reported, with some problems related to poor absorption of electrolytes and changes in intestinal bacterial flora because of increased gastric pH [4–7]. Inhibition of gastric acid secretion by PPIs affects the intestinal microbial environment and facilitates intestinal germination and growth of *Clostridium difficile* spores, increasing the risk of developing gastroenteritis [8–10].

Yoon Hee Park and Jong Mi Seong equally contributed to this work.

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Clostridium difficile infection (CDI) is a significant cause of hospital-associated infections, and its incidence and severity have markedly increased in recent years. CDI increases the length of hospital stay, readmission, morbidity, and mortality [11]. Risk factors for CDI include advanced age, hospitalization, severity of illness, and concurrent use of drugs such as antibiotics and acid-suppressive agents including PPIs [12].

Although conflicting results regarding the association between use of PPIs and increased risk of CDI have been reported in several studies, recent large-scale cohort studies, systematic reviews, and meta-analyses have demonstrated that the use of PPIs increases the risk of developing CDI [13–18]. In addition, the US Food and Drug Administration has informed the public that PPIs may be associated with an increased risk of CDI, and that a diagnosis of CDI should be considered when diarrhea occurs while taking PPIs [19].

There have been many studies on the use of PPIs and CDI risk, but there have been no detailed analyses on the association of dose, duration, and types of PPIs with risk of CDI. Therefore, the present study aimed to investigate CDI occurrence and patterns of PPI use, and to evaluate the risk of CDI depending on PPI usage patterns.

Methods

Study design and patients

The present study followed a single-center, cohort study design and assessed the association of PPI exposure with occurrence of CDI among patients admitted to Asan Medical Center, a 2700-bed tertiary care hospital located in Seoul, South Korea. This study conformed to the provisions of the Declaration of Helsinki 2013 and was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2018-0453).

The cohort included all patients over 18 years old who had been hospitalized for more than 3 days during the study period of January 2013–December 2017, regardless of their history of CDI. Patients with inflammatory bowel disease, bowel cancer, or gastrointestinal surgery were excluded. Patients with the culture test before the index date and those with less than 3 days of follow-up period were also excluded.

The study database contains information on patient age, sex, date and duration of admission, prescription drugs including PPIs, indication of PPI use, antibiotics use, histamine-2 receptor antagonists (H2RAs), and probiotics, CDI check date and results of CDI check. The exposed cohort comprised patients who were prescribed PPIs at least once during the study period. An index date was defined as the date of first PPI exposure in each patient. A control cohort was prepared by matching sex, age (± 5 years), hospitalization period, and date of admission (± 30 days). To make comparable groups of patients in terms of follow-up time, we assigned an index date to patients who did not use PPIs, ensuring the same distribution of index dates as in the exposed.

Outcomes and covariate definition

The primary outcome was occurrence of CDI, as determined by a positive result in tests for *C. difficile* toxin. The diagnostic tests for *C. difficile* toxin in stool were performed using enzyme-linked fluorescent assay (C. DIFFICILE TOX A/B II, TECHLAB, Blacksburg, VA, USA) or polymerase chain reaction (BD MAX Cdiff assay, GeneOhm Sciences Canada Inc., Quebec, Canada). If one or more positive results were recorded for a patient, the first result during the study period was used as the index event. The secondary outcome was the presence of diarrhea, which was defined as the prescription of the *C. difficile* toxin test.

Covariates included sex, age, hospitalization period, and date of admission. To account for drug exposure affecting CDI development, we evaluated use of antibiotics, H2RAs, or probiotics before CDI occurrence. The antibiotics included clindamycin, ampicillin, amoxicillin, first- and second-generation cephalosporins, fluoroquinolones, monobactams, carbapenems, sulfonamides, trimethoprim/sulfamethoxazole, macrolide antibiotics, aminoglycoside, metronidazole, teicoplanin, rifampin, tetracyclines, tigecycline, vancomycin, colistimethate, fosfomycin, linezolid, and pentamidine isethionate [20].

Definition of PPI exposure

All types of PPIs used in our hospital were included in evaluating PPI exposure. The PPI exposure period was calculated from the date of initiating PPIs (index date) to the end date (CDI development or end of the observation period). The daily dose was calculated as the average daily dose during the exposure period or the maximum daily dose in case of multiple component use. The daily dose of PPIs was standardized to the esomeprazole dose in proportion to the usual daily dose of each ingredient for the same indications based on previous reports [13, 21–24] (Supplement 1). The dose distribution was categorized into low, medium, and high dose based on an 18–25 mg range.

Statistical analysis

In the PPI use group and the control comparison group, we assessed characteristics using the Chi-square test for categorical variables and the t-test for continuous variables. The association between PPI use and CDI risk was

analyzed using the Cox proportional hazard regression models, adjusting for co-administered medications (antibiotics, H2RA, or probiotics) in addition to age, sex, hospitalization period, and date of admission, which were controlled by matching. To assess whether the proportional hazard assumption was met, we examined whether the log–log survival curves were constant over time. To evaluate whether antibiotics and H2RAs affected CDI risk as covariates, subgroup analyses were carried out in patients with or without use of antibiotics and H2RAs, respectively. We also performed sensitivity analyses to evaluate outcomes when the study cohort was restricted to patients who did not take metronidazole or vancomycin orally, since those medications are frequently prescribed for diarrhea.

Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). A two-tailed p value < 0.05 was considered statistically significant.

Results

The study included a total of 309,073 patients after exclusion of ineligible patients during the 5-year study period. Of these, 125,922 patients were prescribed PPIs at least once. After matching patients who did not use PPIs with PPI-exposed patients based on the sex, age, hospitalization period, and date of admission, 101,396 PPI-exposed patients remained. Then, except for cases in which culture tests were performed before the index date or the follow-up period was less than 3 days, the final PPI-exposed cohort consisted of 78,722 patients. The control cohort consisted of 78,971 patients (Fig. 1).

The PPI-use group had more males than females (59% vs. 41%) and a mean age of 59.5 years. Age distribution showed the highest number of individuals in the 60 s, followed by the 50 s, 70 s, and 40 s. The number of patients using PPIs increased up to 30% from 2013 to 2017. The mean and median values of hospitalization period were 9.0 and 7.0 days, respectively. Because age, gender, hospitalization period, and date of admission were used as matching variables, the values in the control group were similar to those in the PPI-use group. Antibiotics were used less frequently in the PPI-use group than in the control group (80.3% vs. 89.6%). The frequency of H2RA use was relatively high in the control group (64.9% vs. 37.3%). Probiotics were used more frequently in the control group (10.8% vs. 7.2%; Table 1).

As shown in Table 2, the most frequently used PPI was esomeprazole, followed by pantoprazole and lansoprazole. More than three quarters of the PPI-use group used a high

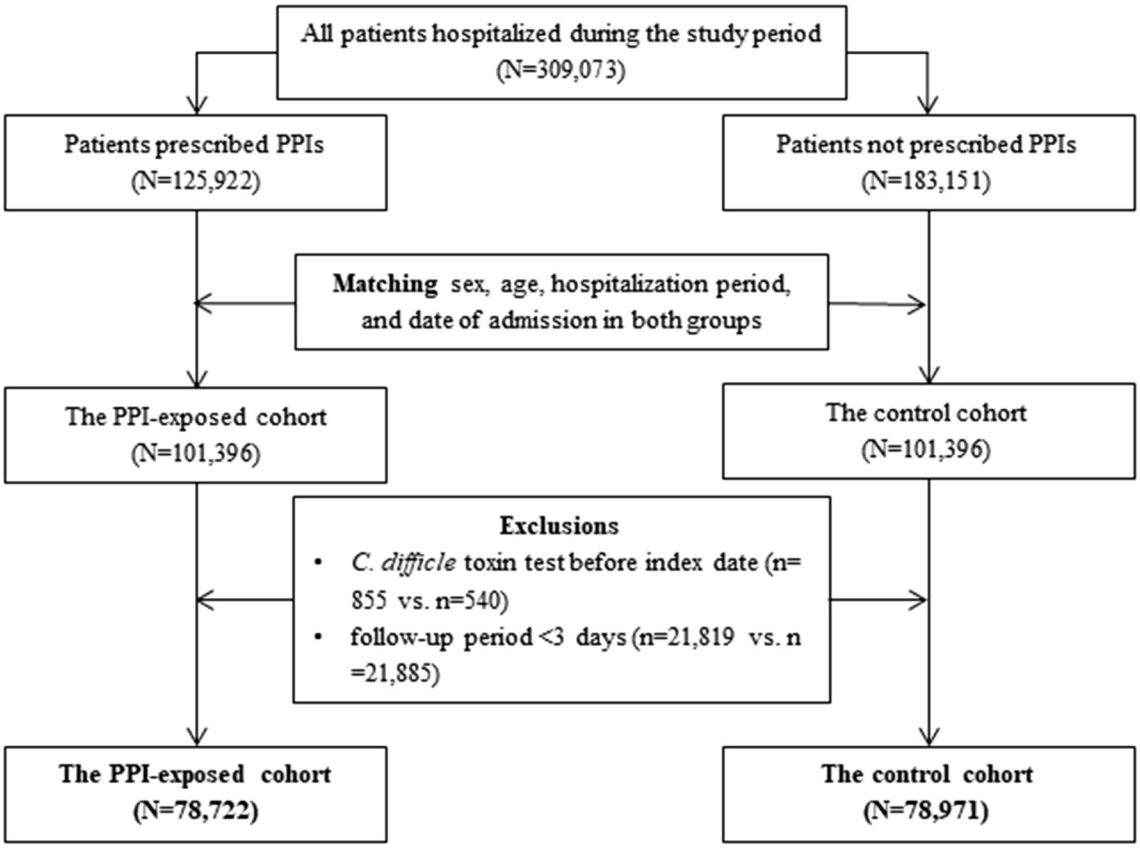

Fig. 1 Patients included in the final cohort

Table 1 Baseline characteristics of the PPI-use group and the control group

	Total (N = 157,693)		PPIs use group (N = 78,722)		Control group (N = 78,971)	
	N	%	*N*	%	*N*	%
Gender						
Male	92,768	58.8	46,320	58.8	46,448	58.8
Female	64,925	41.2	32,402	41.2	32,523	41.2
Mean age ± SD (years)	59.5 ± 13.5 (median 60)		59.5 ± 13.5 (median 60)		59.5 ± 13.5 (median 60)	
Age group						
18–19	541	0.3	269	0.3	272	0.3
20–29	3787	2.4	1910	2.4	1877	2.4
30–39	9073	5.7	4491	5.7	4582	5.8
40–49	19,363	12.2	9545	12.1	9818	12.4
50–59	41,271	26.2	20,748	26.4	20,523	26.0
60–69	44,845	28.4	22,508	28.6	22,337	28.3
70–79	31,681	20.1	15,531	19.7	16,150	20.5
80–89	6838	4.3	3553	4.5	3285	4.2
≥ 90	294	0.2	167	0.2	127	0.2
Hospitalization period (days)	9.0 ± 6.7 (median 7)		9.0 ± 6.7 (median 7)		9.1 ± 6.7 (median 7)	
Admission year						
2013	26,111	16.6	13,022	16.5	13,089	16.6
2014	29,165	18.5	14,535	18.5	14,630	18.5
2015	32,868	20.8	16,427	20.9	16,441	20.8
2016	34,861	22.1	17,415	22.1	17,446	22.1
2017	34,688	22.0	17,323	22.0	17,365	22.0
Co-prescribed drugs						
Antibiotic use extent	133,926	84.9	63,207	80.3	70,719	89.6
H2RA use extent	80,637	51.1	29,382	37.3	51,255	64.9
Probiotic use extent	14,215	9.0	5,704	7.2	8,511	10.8

PPIs proton pump inhibitors, *H2RAs* histamine-2 receptor antagonists, *SD* standard deviation

dose. The mean PPI exposure period was 7.5 days, and the median period was 6 days. The rate of use for ≤ 6 days (median) was 56.1%, and the frequency of use decreased as the duration increased. The mean time from PPI exposure to the *C. difficile* test was 6.7 days (median, 5 days).

More than 38% of patients used PPIs for stress ulcer prophylaxis. Other indications of PPI use were, in the order of frequency, gastritis and duodenitis (n = 6912), gastro-esophageal reflux disease (n = 1615), peptic ulcer disease (n = 1308), gastrointestinal bleeding (n = 629), and esophagitis (n = 565). Almost 40% of patients used PPIs due to gastrointestinal symptoms such as heartburn, dyspepsia, hypersalvation, regurgitation, epigastric pain, and nausea/vomiting or at the prescriber's discretion without specific indications. PPIs were frequently prescribed in the department of gastroenterology (32.5%), oncology (13.3%), neurosurgery (10.9%), hepato-biliary-pancreas (8.2%), liver transplantation surgery (7.2%), cardiology (3.5%), orthopedics (2.8%), urology (2.5%), pulmonology (2.5%), thoracic surgery (2.2%), and others (14.5%).

The incidence of CDI in the PPI-use group was 6.48 per 10,000 person-days (391/78,722) compared to 3.24 (197/78,971) in the control group. The HR for the PPI-use group versus the control group was 2.00 (95% CI 1.69–2.37). After adjusting for covariates, the adjusted HR was 1.81 (95% CI 1.51–2.18). The log–log survival curves for CDI development in the PPI-use group and the control group are shown in Fig. 2.

In analyzing the risk of CDI depending on PPI types, the adjusted HR of esomeprazole was 1.79 (95% CI 1.44–2.21) and that of pantoprazole was 2.02 (95% CI 1.47–2.76), which was similar to that in the PPI-use group. The use of high-dose PPIs increased the risk of CDI by approximately 1.95-fold compared to the control group (adjusted HR, 1.95, 95% CI 1.62–2.36), and CDI risk increased as the dose increased. When the cut-off of the PPI exposure period was set to 6 days (median value), the risk of CDI

Table 2 PPI prescription patterns

	N	%
Types (includes duplicate use)		
Esomeprazole	56,876	62.1
Pantoprazole	20,008	21.9
Lansoprazole	10,812	11.8
Rabeprazole	2219	2.4
Dexlansoprazole	1190	1.3
Ilaprazole	260	0.3
Omeprazole	148	0.2
s-Pantoprazole	28	0.0
Revaprazan	11	0.0
Daily dose (mg), mean ± SD	35.30 ± 8.48 (median 40)	
Daily dose distribution		
Low dose	33	0.0
Medium dose	18,420	23.4
High dose	60,269	76.6
Days of PPI exposure (days), mean ± SD	7.51 ± 5.85 (median 6)	
Distribution of days of PPI exposure		
1–6	44,156	56.1
7–12	24,525	31.2
13–18	6225	7.9
19–24	1769	2.2
> 25	1823	2.3

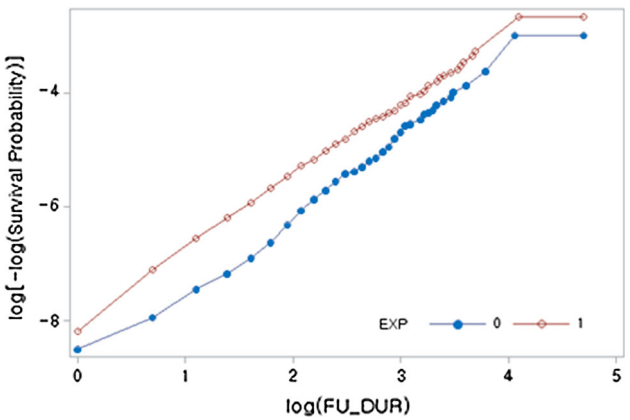

Fig. 2 Log–log survival curve for CDI development. *EXP = 0* control group, *EXP = 1* PPIs use group, *FU_DUR* follow-up duration (days)

increased by 4.2-fold in those who used PPIs for ≤ 6 days compared to non-users (95% CI 3.42–5.25). On the other hand, a statistically significant difference was not present between patients using PPIs for > 6 days and non-users (Table 3).

Regarding the presence of diarrhea as a secondary outcome, the *C. difficile* toxin test was performed at a rate of 63.49 per 10,000 individuals in the PPI-use group (3667/78,722), and 37.05 per 10,000 individuals in the control group (2193/78,971). The HR for diarrhea was 1.72 (95% CI 1.63–1.81), which was similar to that for CDI. After adjusting for covariates, the adjusted HR was 1.92 (95% CI 1.81–2.03).

Stratification analysis was performed in patients with or without antibiotic use. As shown in Table 4, the adjusted HRs for CDI and diarrhea in patients using antibiotics were 1.53 (95% CI 1.27–1.86) and 1.34 (95% CI 1.26–1.42), respectively. On the other hand, the adjusted HRs for CDI (2.25, 95% CI 1.35–3.76) and diarrhea (1.95, 95% CI 1.61–2.34) in patients not using antibiotics were higher than those in patients with antibiotics. There were 2081 and 314 patients who took metronidazole and vancomycin, respectively. Results of sensitivity analysis using only patients without metronidazole or vancomycin were similar to those using the whole study population; the adjusted HRs for CDI and diarrhea were 1.63 (95% CI 1.32–2.01) and 1.35 (95% CI 1.27–1.44), respectively.

Table 5 reveals results of stratification analysis using patients with or without H2RA use. The adjusted HRs for CDI and diarrhea in patients using H2RAs were 1.79 (95% CI 1.36–2.36) and 2.10 (95% CI 1.92–2.29), respectively. On the other hand, the adjusted HRs for CDI and diarrhea in patients not using H2RAs were 1.74 (95% CI 1.35–2.26) and 1.67 (95% CI 1.54–1.82).

Table 3 HRs of PPI prescription patterns as a risk factor for CDI in PPI users compared to non-users

	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Control group (PPI non-user)	1		1	
PPI types				
Esomeprazole	1.98 (1.63–2.40)	< 0.01	1.79 (1.44–2.21)	< 0.01
Pantoprazole	2.07 (1.54–2.80)	< 0.01	2.02 (1.47–2.76)	< 0.01
Lansoprazole	1.40 (0.83–2.37)	0.21	1.32 (0.77–2.25)	0.31
Dexlansoprazole	0.86 (0.12–6.11)	0.88	0.86 (0.12–6.13)	0.88
PPI dose				
Low dose	N/A		N/A	
Medium dose	1.34 (0.99–1.81)	0.06	1.28 (0.94–1.74)	0.11
High dose	2.17 (1.82–2.59)	< 0.01	1.95 (1.62–2.36)	< 0.01
PPIs exposure period				
1–6 days	4.25 (3.47–5.20)	< 0.01	4.24 (3.42–5.25)	< 0.01
> 6 days	1.22 (0.99–1.49)	0.06	1.05 (0.85–1.30)	0.67

N/A not applicable because no event occurred

Table 4 Comparisons of incidence rate of CDI and diarrhea between the PPI-use group and the control group in patients with or without antibiotic use

	PPI-use group (*N* = 78,722)			Control group (*N* = 78,971)			Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	No. of events	Person-days	IR[a]	No. of events	Person-days	IR[a]		
Incidence of CDI								
Patients using antibiotics (*n* = 114,907)	348	496,568	7.01	172	470,765	3.65	1.91 (1.59–2.29)	1.53 (1.27–1.86)
Patients using antibiotics II[b] (*n* = 112,938)	301	479,775	6.27	138	461,722	2.99	2.09 (1.71–2.56)	1.63 (1.32–2.01)
Patients not using antibiotics (*n* = 42,786)	43	107,108	4.01	25	136,831	1.83	2.21 (1.34–3.62)	2.25 (1.35–3.76)
Incidence of diarrhea								
Patients using antibiotics (*n* = 114,907)	3,358	471,874	71.16	1,995	456,118	43.74	1.63 (1.54–1.72)	1.34 (1.26–1.42)
Patients using antibiotics II[b] (*n* = 112,938)	2,867	460,249	62.29	1,691	449,756	37.60	1.66 (1.56–1.76)	1.35 (1.27–1.44)
Patients not using antibiotics (*n* = 42,786)	309	105,662	29.24	198	135,864	14.58	1.95 (1.63–2.34)	1.95 (1.61–2.34)

[a]Incidence rate per 10,000 person-days

[b]Patients not taking metronidazole or vancomycin orally

Discussion

One of the main findings of the present study is that PPI use increased the risk of CDI by 1.8-fold and the risk of diarrhea by 1.9-fold. Patients using higher doses were at higher risk of developing CDI. The risk of CDI increased by 4.2-fold in those who used PPIs for 6 days or shorter than 6 days compared to non-users.

Compared to other cohort studies investigating the association of CDI risk with PPI use, the adjusted HR in the PPI-use group compared to that in the non-users in our study was 1.81 (95% CI 1.51–2.18), which was similar to the finding of a study by Dalton et al. [25] (OR 1.96; 95% CI, 1.42–2.72). A recent systematic review and meta-analysis also showed a statistically significant association between PPI use and CDI risk (OR 2.34; 95% CI 1.94–2.82), which was higher than the risk found in our study. Unlike our study, the above meta-analysis included patients of all ages including children; therefore, their results may have differed from ours because of the higher risk in pediatric patients (OR 3.00; 95% CI 1.44–6.23) [17].

Table 5 Comparisons of incidence rate of CDI and diarrhea between the PPI-use group and the control group in patients with or without H2RAs use

	PPI-use group (N = 78,722)			Control group (N = 78,971)			Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	No. of events	Person-days	IR[a]	No. of events	Person-days	IR[a]		
Incidence of CDI								
Patients using H2RAs (n = 80,637)	135	263,491	5.12	114	412,786	2.76	1.74 (1.36–2.23)	1.79 (1.36–2.36)
Patients not using H2RAs (n = 77,056)	256	340,185	7.53	83	194,810	4.53	1.79 (1.39–2.29)	1.74 (1.35–2.26)
Incidence of diarrhea								
Patients using H2RAs (n = 80,637)	1415	251,705	56.22	1376	402,537	34.18	1.61 (1.50–1.74)	2.10 (1.92–2.29)
Patients not using H2RAs (n = 77,056)	2252	325,831	69.11	817	189,445	43.12	1.60 (1.48–1.74)	1.67 (1.54–1.82)

[a]Incidence rate per 10,000 person-days

Our study evaluated CDI risk based on PPI prescription patterns (types, daily dose, and duration of PPI use). CDI risk was increased by 1.8-fold with esomeprazole (95% CI 1.44–2.21) and by 2.0-fold with pantoprazole (95% CI 1.47–2.76). It was challenging to evaluate other PPI types because the number of events was low, but it appeared that no other PPI types presented a higher risk for CDI. When assessing CDI risk depending on daily dose, patients taking a higher dose had a higher risk than those taking a medium dose (adjusted HR, 1.95 vs. 1.28, respectively).

Unexpectedly, our results showed that the risk of CDI increased by 4.2-fold when they were used for $\leq$ 6 days, but the risk was not higher than control when they were used for $>$ 6 days. There are no studies on the association between PPI use duration and CDI in clinical settings. Only one study reported that the risk of developing CDI due to PPI use increased with long-term use over 3 months [26]. However, the study had a small sample size (n = 10) and employed healthy volunteers. We studied the risk of CDI during hospitalization in a large cohort, and found that CDI occurred early after PPI exposure. Further prospective studies are required to confirm our results.

We also analyzed the risk of developing diarrhea due to PPI use as a secondary outcome. Generally, testing stools for the presence of *C. difficile* toxin is prescribed when patients have diarrhea; therefore, it is considered a surrogate for symptoms of diarrhea [27]. The risk of diarrhea associated with the use of PPIs was 1.92 (95% CI 1.81–2.03), which was similar to CDI risk.

Antibiotic exposure is an important risk factor for the development of CDI, and there have been several studies based on antibiotic use patterns. Several antibiotic classes (i.e., clindamycin, cephalosporins, and fluoroquinolones) appear to increase the risk of CDI [28, 29]. Based on these facts, we conducted stratification analysis of the risk of CDI in the presence or absence of antibiotic use. The PPI use significantly increased the risk of CDI regardless of the presence or absence of antibiotic use. The impact of PPI use on CDI or diarrhea was higher in patients not taking antibiotics. This may have been because the significant effect of high-risk antibiotics on the development of CDI masked the effect of concurrent PPI use; the effect of PPIs in the group not using antibiotics may have thus appeared greater.

Since antibiotics could be used for diarrhea, we conducted sensitivity analyses only using patients without medications for diarrhea. In our institution, oral metronidazole and oral vancomycin are used for treating diarrhea. Results excluding patients who used metronidazole or vancomycin were similar to those using the whole study population, while the association between PPI use and higher risk of incident CDI or diarrhea remained significant.

As PPIs and H2RAs are the two most commonly prescribed anti-acid secreting agents, H2RA use was higher in the control group compared to PPI use group in our study because H2RAs would be prescribed to the control group instead of PPIs. Since H2RAs are known to be associated with CDI [30, 31], we performed stratification analysis of the risk of CDI in the presence or absence of H2RA use. PPI use significantly increased the risk of CDI regardless of the presence or absence of H2RA use. In specific, the adjusted HR for CDI in patients taking H2RAs was almost the same as that of the whole study population, indicating that the concomitant use of PPI and H2RA did not have a significant effect on CDI compared to the use of PPI alone.

Of the total 309,073 patients hospitalized during the study, 125,922 were prescribed PPIs (40.7%), similar to that in a report by Lewis et al. [32] (41.9%). The number of patients using PPIs has increased annually up to 30% over 5 years. The problem with PPI overuse has been addressed in several studies (2, 3, 30–32). One study reported that 37% of elderly individuals were on PPIs at admission, and 61% had been prescribed PPIs inappropriately [33]. Our study showed that patients using a higher dose of PPIs had a higher risk of developing CDI, indicating that PPIs should be used at appropriate doses.

Our study was limited by its retrospective and single-center design, but the size of the study population was large, allowing for the assumption of normally distributed data. In addition, it was not possible to distinguish if PPI was associated with initial or recurrent CDI, since we included all patients who had CDI during the study period regardless of their previous history of CDI. The results of our study lacked information regarding PPI exposure prior to hospitalization or *C. difficile* diagnosis post-discharge, but are meaningful in assessing the risk of CDI in a hospital setting. To overcome these limitations, we included a matching control group with similar distributions of variables.

In conclusion, PPI use was associated with an increased risk of developing CDI. The risk of CDI was PPI dose dependent and higher within a shorter period of PPI exposure. Therefore, PPIs should be used only at proper doses and only in patients with necessary indications. Given the retrospective study design in a single center, our hypothesis requires further independent validation using more robust prospective and multi-center designs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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