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Proton Pump Inhibitor Use Is Not Strongly Associated With SARS-CoV-2 Related Outcomes: A Nationwide Study and Meta-analysis

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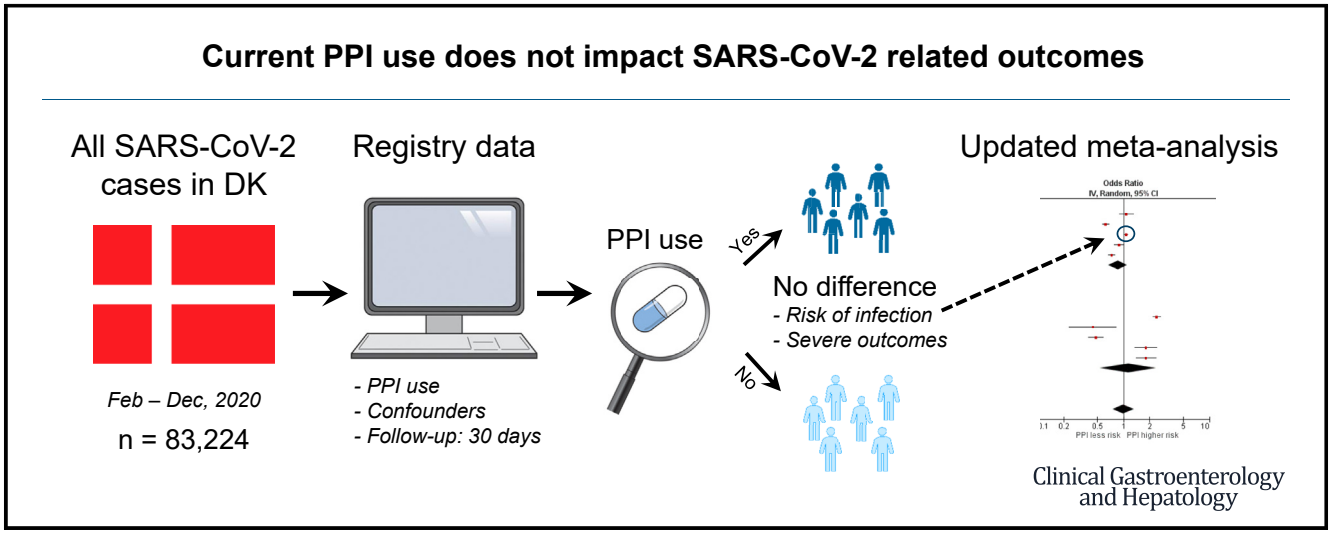

BACKGROUND & AIMS: **Proton pump inhibitor (PPI) use has been associated with increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe outcomes. However, meta-analyses show unclear results, leading to uncertainty regarding the safety of PPI use during the ongoing coronavirus disease 2019 (COVID-19) pandemic.**

METHODS: **We conducted a nationwide observational study including all SARS-CoV-2 cases (n = 83,224) in Denmark as of December 1, 2020. The association of current PPI use with risk of infection was examined in a case-control design. We investigated the risk of severe outcomes, including mechanical ventilation, intensive care unit admission, or death, in current PPI users (n = 4473) compared with never users. Propensity score matching was applied to control for confounding. Finally, we performed an updated meta-analysis on risk of SARS-CoV-2 infection and COVID-19 mortality attributable to PPI use.**

Abbreviations used in this paper: CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standardized mean difference.

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RESULTS: **Current PPI use was associated with increased risk of infection; adjusted odds ratio, 1.08 (95% confidence interval [CI], 1.03–1.13). Among SARS-CoV-2 cases, PPI use was associated with increased risk of hospital admission; adjusted relative risk, 1.13 (1.03–1.24), but not with other severe outcomes. The updated meta-analysis showed no association between PPI use and risk of infection or mortality; pooled odds ratio, 1.00 (95% CI, 0.75–1.32) and relative risk, 1.33 (95% CI, 0.71–2.48).**

CONCLUSIONS: **Current PPI use may be associated with an increased risk of SARS-CoV-2 infection and hospital admission, but these results with minimally elevated estimates are most likely subject to residual confounding. No association was found for severe outcomes. The results from the meta-analysis indicated no impact of current PPI use on COVID-19 outcomes.**

Keywords: PPI; COVID-19; Risk of Infection; Mortality.

Acid suppressive drugs, especially proton pump inhibitors (PPI), are hypothesized to influence the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and affect outcomes in patients diagnosed with coronavirus disease 2019 (COVID-19). This concern is based on their suppression of stomach acid and an association with an increased risk of infection and, in particular, with a risk of pneumonia.[1–3] SARS-CoV-1 has been reported to be inactivated by acidic conditions,[4] and SARS-CoV-2 may directly invade the gastrointestinal epithelium of infected patients.[5]

In July 2020, a large survey found that individuals using PPI had higher odds of reporting a positive SARS-CoV-2 test.[6] In contrast, Lee et al[7] reported that current PPI use was associated with an increased risk of severe outcomes of COVID-19 but not with risk of infection. Similarly, Zhou et al[8] reported an association with severe outcomes, including need for intensive care unit (ICU) admission, intubation, or death.

Subsequently, 2 meta-analyses[9,10] including 14 further observational studies of PPI use in patients with COVID-19 found that PPI use was associated with an increased risk of severe outcomes. However, most of the studies had low statistical precision of estimates, only some controlled fully for confounding, and they were all quite heterogenous, with study populations from different countries, including patients with few or many comorbidities and with or without requiring hospitalization. Currently, use of PPI and its possible association with risk of infection and disease severity remain uncertain.

In this nationwide study of all individuals tested in Denmark as of December 1, 2020, we examined the association between current use of PPI and risk of SARS-CoV-2 infection and the risk of hospital admission, ICU admission, mechanical ventilation, or death among individuals with current PPI use and a positive SARS-CoV-2 RNA test. In addition, we performed an updated meta-analysis of studies reporting risk of SARS-CoV-2 infection and COVID-19 mortality in current PPI users.

Methods

Study Register

The original study protocol and analysis plan are available from the EU PAS Register with identification number EUPAS35835: http://www.encepp.eu/encepp/viewResource.htm?id=37050.

Data Source

Data on all Danish residents tested for SARS-CoV-2 RNA as of December 1, 2020 were retrieved from the Danish Microbiology Database and individually linked to other nationwide health care registries, as described previously.[11]

SARS-CoV-2 infection was verified by a positive real-time polymerase chain reaction on an oropharyngeal or nasopharyngeal swab or lower respiratory tract specimen. The individuals' medical history included International Classification of Diseases, 10th Revision diagnoses registered within 10 years before the date of first positive SARS-CoV-2 test (index date). Comorbidities included were peptic ulcer, chronic obstructive pulmonary disease, asthma, ischemic heart disease, stroke, heart failure, diabetes mellitus, renal failure, and cirrhosis. Lifestyle factors included smoking- and alcohol-related diagnoses (Table 1).

Major psychiatric disorders (schizophrenia, schizoaffective disorders, manic episodes, and bipolar disorder) were added along with available frailty markers based on health care utilization (number of admissions within the past 3 years).

Data on patients' medications included current use (within 90 days before index date) of inhaled corticosteroids and bronchodilators, systemic corticosteroid treatment, immunomodulating treatment, H2-receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), anticholinergic agents, antibiotics, blood pressure lowering drugs, lipid lowering drugs, glucose lowering drugs, antiplatelets, anticoagulants, treatment to support alcohol abstinence and smoking cessation,

and antipsychotic agents (Supplementary Table 1). Finally, the total burden of comorbidity was assessed on the basis of the Charlson Comorbidity Index and classified as 0, 1–2, or ≥3.

Study Design and Population

The case-control study included all individuals tested for SARS-CoV-2 RNA and examined the risk of infection with current PPI use in cases (test-positive) vs controls (test-negative). Cases were matched on sex and birth year with up to 4 controls each. Control subjects were Danish residents alive at the index date of the case and who had been tested negative for SARS-CoV-2 RNA. To account for changing testing criteria and in-hospital capacity during the study period, cases were matched with controls on the week wherein the test was performed.

The cohort study included the test-positive population and investigated the risk of hospital admission and severe outcomes, including ICU admission, mechanical ventilation, and death, within 30 days of the first positive SARS-CoV-2 RNA test. Patients were followed from date of first positive test until death, migration, or end of follow-up (30 days).

Exposure

Current PPI use was defined as having redeemed a prescription of PPI within 90 days before the first positive SARS-CoV-2 RNA test (index date), although only including prescriptions before possible hospitalization. Individuals were classified as former users if they had redeemed a prescription more than 90 days before the index date. Never use was defined as never having redeemed a prescription since 2005. The specific PPI (pantoprazole, lansoprazole, omeprazole, or esomeprazole) was registered for each user. Dose levels were defined as low or high dose if the prescribed tablet strength was either below or equal to/above 30 mg, respectively. The choice of dose level cutoff was based on usual tablet sizes and a standard once-daily dosing regimen.

Outcomes

In the case-control study, the outcome was a positive SARS-CoV-2 RNA test during the study period.

In the cohort study, the primary outcome was hospital admission within 30 days after a positive test for SARS-CoV-2 RNA or a positive test for SARS-CoV-2 RNA within 48 hours of hospital admission if hospitalized before the date of testing. Secondary outcomes included ICU admission, mechanical ventilation, and death within 30 days of a positive SARS-CoV-2 RNA test. Finally, a composite of severe outcomes, including ICU admission or death, was added as a post hoc analysis to compare with recent studies.

What You Need to Know

Background

To date, uncertainty prevails regarding the safety of proton pump inhibitor use in relation to SARS-CoV-2 infection because existing evidence has indicated both protective and harmful effects.

Findings

In this nationwide observational study, we found a slightly increased risk of infection and hospital admission in 4473 current proton pump inhibitor users but no association with other severe outcomes. Our updated meta-analysis showed no association with risk of infection or mortality.

Implications for patient care

Our findings show that current proton pump inhibitor use does not have a significant clinical impact on risk of SARS-CoV-2 infection or related severe outcomes. Therefore, they suggest that previous conflicting results rather arise from between-study differences.

Meta-analysis

To put our study results in context with other studies, we performed a literature search in the global search engine maintained by World Health Organization, WHO COVID-19 database, https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/. Li et al[10] recently reported a comprehensive meta-analysis of PPI use and clinical outcomes including 16 studies. Therefore, we applied the same search strategy for the remaining period (September 23–December 14) (Supplementary Table 2). Studies examining the impact of current PPI use compared with never use on risk of SARS-CoV-2 infection or COVID-19 mortality were included. However, in contrast to Li et al, we did not include the composite outcome of ICU admission or mortality because we find it difficult to interpret the clinical meaning of this result.

Two authors (AL, TB) independently extracted outcome data from study publications and assessed studies for risk of bias. High risk of bias was defined as studies not dealing with confounding at either study design level or in the included analyses or if studies had other important biases, eg, high risk of selection bias.

Statistical Analyses

Continuous variables are presented as median with interquartile range, whereas categorical variables are presented as count with percentage. Baseline characteristics are reported separately for the case-control and the cohort study populations.

Table 1. Baseline Characteristics of Individuals With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection (Case-Control Study)

	Cases (n = 83,224)	Controls (n = 332,799)	*P* value
Age, *y*, median (IQR)	36 (21–53)	36 (21–53)	.85
Sex (male), N (%)	41,501 (49.9)	165,946 (49.9)	.99
Exposure to proton pump inhibitors, N (%)			
Non-use	59,413 (71.4)	241,536 (72.6)	<.001
Current use	4473 (5.4)	17,553 (5.3)	.25
Former use	19,338 (23.2)	73,710 (22.1)	<.001
No. of prior admissions, N (%)[a]			
0	66,144 (79.5)	267,533 (80.4)	<.001
1	10,497 (12.6)	40,240 (12.1)	<.001
2	3235 (3.9)	12,234 (3.7)	.004
3+	3348 (4.0)	12,792 (3.8)	.02
Charlson Comorbidity Index, N (%)			
0	74,797 (89.9)	299,207 (89.9)	.79
1–2	7099 (8.5)	28,225 (8.5)	.65
3+	1328 (1.6)	5367 (1.6)	.73
Diagnoses, N (%)[b]			
Peptic ulcer	400 (0.5)	1639 (0.5)	.68
Asthma	2574 (3.1)	9726 (2.9)	.010
Chronic obstructive pulmonary disease	957 (1.1)	4775 (1.4)	<.001
Cirrhosis	71 (0.1)	445 (0.1)	<.001
Ischemic heart disease	4020 (4.8)	15,537 (4.7)	.05
Diabetes	2452 (2.9)	8308 (2.5)	<.001
Renal failure	769 (0.9)	2905 (0.9)	.16
Heart failure	773 (0.9)	2943 (0.9)	.22
Stroke	1241 (1.5)	5272 (1.6)	.05
Alcohol-related diagnoses	785 (0.9)	5156 (1.5)	<.001
Smoking-related diagnoses	581 (0.7)	3801 (1.1)	<.001
Major psychiatric disorders	305 (0.4)	1977 (0.6)	<.001
Medication, N (%)[c]			
Systemic corticosteroids	738 (0.9)	3428 (1.0)	<.001
Inhaled corticosteroids	2674 (3.2)	11,086 (3.3)	.09
Bronchodilators	1657 (2.0)	7638 (2.3)	<.001
H2-receptor antagonists	—	—	<.001
Nonsteroidal anti-inflammatory drugs	3650 (4.4)	14,984 (4.5)	.15
Anticholinergic agents	325 (0.4)	1631 (0.5)	<.001
Immunosuppressants	210 (0.3)	936 (0.3)	.16
Antipsychotic agents	859 (1.0)	4919 (1.5)	<.001
Antibiotics	6546 (7.9)	24,494 (7.4)	<.001
Alcohol abstinence treatment	62 (0.1)	480 (0.1)	<.001
Smoking cessation treatment	70 (0.1)	528 (0.2)	<.001
Blood pressure lowering drugs	8353 (10.0)	35,053 (10.5)	<.001
Lipid lowering drugs	5011 (6.0)	19,929 (6.0)	.72
Glucose lowering drugs	3090 (3.7)	10,356 (3.1)	<.001
Antiplatelets	2447 (2.9)	10,450 (3.1)	.003
Anticoagulants	1526 (1.8)	6163 (1.9)	.74

IQR, interquartile range.
[a]During the past 3 years.
[b]Diagnoses within 10 years before inclusion.
[c]Use within 90 days before inclusion.

In the case-control study, conditional logistic regression was performed to examine a possible association between current PPI use and risk of SARS-CoV-2 infection. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Confounding by age, sex, and calendar time were handled by the risk set sampling and the matched analysis, as described above. Other potential confounders, including comorbidity and current medication use, are listed in Table 1 and included in the multivariable modelling. Comparisons between groups were performed using Fisher exact test or *t* test, as appropriate.

In the cohort study, an individual propensity score of drug exposure was estimated by logistic regression based on age, sex, comorbidities, and current medication use, as listed in Table 2. Propensity scores were used to match the exposed and unexposed groups to adjust for preexisting differences in risk factors. Covariate balance was quantified by standardized mean differences (SMDs), with values below 0.1 considered acceptable. Relative risks (RRs) for hospital admission and severe outcomes in the exposed (current PPI use) vs the unexposed (never PPI use) groups were calculated by log binomial regression and presented as crude (unmatched)

Table 2. Characteristics of Individuals Infected With Severe Acute Respiratory Syndrome Coronavirus 2 According to Current or Never Use of Proton Pump Inhibitors Before and After Propensity Score Matching (Cohort Study)

	Use of proton pump inhibitors					
	Unmatched			Matched		
	Current (n = 4473)	Never (n = 59,413)	Standardized mean difference	Current (n = 3955)	Never (n = 3955)	Standardized mean difference
Age, *y*, median (IQR)	60 (48–73)	29 (18–47)	1.42	58 (46–71)	59 (47–73)	0.07
Sex (male)	1989 (44.5)	31,224 (52.6)	0.16	1770 (44.8)	1758 (44.5)	0.01
No. of prior admissions, N (%)[a]						
0	2416 (54.0)	50,230 (84.5)	0.70	2353 (59.5)	2568 (64.9)	0.11
1	781 (17.5)	6466 (10.9)	0.19	710 (18.0)	695 (17.6)	0.01
2	425 (9.5)	1596 (2.7)	0.29	375 (9.5)	274 (6.9)	0.09
3+	851 (19.0)	1121 (1.9)	0.58	517 (13.1)	418 (10.6)	0.08
Charlson Comorbidity Index, N (%)						
0	2980 (66.6)	55,696 (93.7)	0.72	2846 (72.0)	2920 (73.8)	0.04
1–2	1077 (24.1)	3328 (5.6)	0.54	871 (22.0)	814 (20.6)	0.04
3+	416 (9.3)	389 (0.7)	0.41	238 (6.0)	221 (5.6)	0.02
Diagnoses, N (%)[b]						
Peptic ulcer	147 (3.3)	16 (0.0)	0.26	22 (0.6)	16 (0.4)	0.02
Asthma	329 (7.4)	1378 (2.3)	0.24	222 (5.6)	203 (5.1)	0.02
Chronic obstructive pulmonary disease	287 (6.4)	289 (0.5)	0.33	170 (4.3)	143 (3.6)	0.04
Cirrhosis	31 (0.7)	10 (0.0)	0.11	12 (0.3)	9 (0.2)	0.01
Ischemic heart disease	623 (13.9)	699 (1.2)	0.50	404 (10.2)	393 (9.9)	0.01
Diabetes	564 (12.6)	891 (1.5)	0.44	378 (9.6)	353 (8.9)	0.02
Renal failure	231 (5.2)	222 (0.4)	0.30	118 (3.0)	107 (2.7)	0.02
Heart failure	209 (4.7)	247 (0.4)	0.27	134 (3.4)	125 (3.2)	0.01
Stroke	296 (6.6)	463 (0.8)	0.31	210 (5.3)	200 (5.1)	0.01
Alcohol-related diagnoses	118 (2.6)	410 (0.7)	0.15	79 (2.0)	77 (1.9)	0.00
Smoking-related diagnoses	85 (1.9)	218 (0.4)	0.15	57 (1.4)	58 (1.5)	0.00
Major psychiatric disorders	50 (1.1)	140 (0.2)	0.11	32 (0.8)	34 (0.9)	0.01
Medication, N (%)[c]						
Systemic corticosteroids	235 (5.3)	237 (0.4)	0.30	147 (3.7)	120 (3.0)	0.04
Inhaled corticosteroids	513 (11.5)	1276 (2.1)	0.38	354 (9.0)	333 (8.4)	0.02
Bronchodilators	322 (7.2)	775 (1.3)	0.30	226 (5.7)	201 (5.1)	0.03
H2-receptor antagonists	—	—	—	—	—	—
Nonsteroidal anti-inflammatory drugs	691 (15.4)	1707 (2.9)	0.45	565 (14.3)	582 (14.7)	0.01
Anticholinergic agents	92 (2.1)	96 (0.2)	0.18	62 (1.6)	49 (1.2)	0.03
Immunosuppressants	36 (0.8)	94 (0.2)	0.09	30 (0.8)	24 (0.6)	0.02
Antipsychotic agents	195 (4.4)	357 (0.6)	0.24	137 (3.5)	134 (3.4)	0.00
Antibiotics	971 (21.7)	3487 (5.9)	0.47	705 (17.8)	713 (18.0)	0.01
Alcohol abstinence treatment	15 (0.3)	25 (0.0)	0.07	10 (0.3)	12 (0.3)	0.01
Smoking cessation treatment	20 (0.4)	30 (0.1)	0.08	10 (0.3)	9 (0.2)	0.01
Blood pressure lowering drugs	1737 (38.8)	3598 (6.1)	0.85	1401 (35.4)	1438 (36.4)	0.02
Lipid lowering drugs	1093 (24.4)	1987 (3.3)	0.64	875 (22.1)	903 (22.8)	0.02
Glucose lowering drugs	635 (14.2)	1245 (2.1)	0.45	473 (12.0)	466 (11.8)	0.01
Antiplatelets	597 (13.3)	902 (1.5)	0.46	446 (11.3)	442 (11.2)	0.00
Anticoagulants	368 (8.2)	588 (1.0)	0.35	272 (6.9)	259 (6.5)	0.01

IQR, interquartile range.
[a]During the past 3 years.
[b]Diagnoses within 10 years before inclusion.
[c]Use within 90 days before inclusion.

and adjusted (propensity score matched) estimates with 95% CI.

To determine the robustness of the estimates, sensitivity analyses on the chosen PPI exposure window were performed in both studies and included comparisons of current vs former use and former vs never use. Finally, a post hoc analysis of the dose-effect of PPI was computed comparing low-dose vs high-dose regimens, as defined above.

In the meta-analyses, we preferred adjusted estimates to unadjusted estimates. To include as much information as possible, we extracted estimates for the effect measure most frequently reported in the studies, eg, OR. For studies using a different effect measure, unadjusted results based on reported events were calculated. Inverse variance random-effects models were applied to estimate either OR or RR with 95% CI. We described statistical heterogeneity using I^2 and explored our results in subgroup analysis stratified by risk of bias. Meta-analyses were conducted in RevMan 5.4.1.

Results

Between February 27 and December 1, 2020, 83,224 cases with SARS-CoV-2 infection were identified. Of these, 4473 (5%) were current users of PPI, and 19,338 (23%) were former users. Among current users, pantoprazole accounted for 57% of prescriptions, whereas users of lansoprazole, omeprazole, and esomeprazole numbered 833 (19%), 749 (17%), and 324 (7%), respectively.

Characteristics of Cases and Controls

Cases (n = 83,224) and controls (n = 332,799) had a median age of 36 years and an equal sex distribution. Less than 15% had a score of 1 or more in the Charlson Comorbidity Index (Table 1). The predominant comorbidity was ischemic heart disease, followed by asthma, diabetes, stroke, and chronic obstructive pulmonary disease. Blood pressure lowering drugs were the most common drugs used in both cases and controls. Other common medications used included lipid lowering drugs, glucose lowering drugs, antibiotics and NSAIDs.

Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Current PPI users had a crude OR of 1.04 (95% CI, 1.00–1.08) of SARS-CoV-2 infection compared with never PPI users. After including all the covariates in the regression model, the adjusted OR was 1.08 (95% CI, 1.03-1.13). The sensitivity analyses (current vs former use and former vs never use) yielded similar results with crude and adjusted ORs around 1.0 (Table 3).

In the dose-response analysis, individuals with current low-dose PPI use had an adjusted OR of 1.04 (95% CI, 0.98–1.11) of SARS-CoV-2 infection, whereas individuals with current high-dose PPI use had an adjusted OR of 1.11 (95% CI, 1.05–1.16) when compared with never PPI use (Table 3). When comparing the different classes of PPI, lansoprazole, omeprazole, and esomeprazole had adjusted ORs below 1.0 compared with pantoprazole, but all estimates had low statistical precision (Supplementary Table 3).

Characteristics of Current and Never Users of Proton Pump Inhibitor Among Patients With Positive Severe Acute Respiratory Syndrome Coronavirus 2 RNA

In the unmatched SARS-CoV-2 RNA positive population, current users of PPI (n = 4473) were compared with never users of PPI (n = 59,413). Current users were older (median 60 vs 29 years), fewer were male (45% vs 53%), and they had a greater comorbidity burden with a larger proportion of registered diagnoses across all the included comorbidities (Table 2). Use of other medications was also consistently more frequent in current users compared with never users (Table 2).

After propensity score matching, 3955 individuals persisted in each group, and the difference in characteristics was significantly reduced, with 89% of the SMDs below 0.05 and none with SMD above 0.11 (Table 2). However, important comorbidities and prior health care utilization remained more frequent in current users.

Hospital Admission and Severe Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

In the propensity score matched analyses, current PPI users had an increased risk of hospital admission compared with never PPI users (19% vs 16%), corresponding to an adjusted RR of 1.13 (95% CI, 1.03–1.24)

Table 3. Odds of Infection With Severe Acute Respiratory Syndrome Coronavirus 2 for Cases Compared With Controls According to Current, Former, or Never Use of Proton Pump Inhibitors

Proton pump inhibitor use	Crude odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Current versus never	1.04 (1.00–1.08)	1.08 (1.03–1.13)
Current low dose versus never	1.01 (0.95–1.07)	1.04 (0.98–1.11)
Current high dose versus never	1.06 (1.01–1.11)	1.11 (1.05–1.16)
Current versus former	0.98 (0.93–1.02)	1.00 (0.95–1.05)
Former versus never	1.08 (1.06–1.10)	1.08 (1.06–1.10)

CI, confidence interval.
[a]Adjusted for age, sex, comorbidities, current medication use, Charlson Comorbidity Index, and number of hospital admissions within the last 3 years.

(Table 4). Current and never PPI users had comparable risks of ICU admission, mechanical ventilation, death, and severe outcomes (ICU or death) at around 2%, 1%, 4%, and 6%, respectively. The RR for these secondary outcomes in the matched analysis had estimates just below or at 1.0, with 95% CIs on both sides of 1 (Table 4).

The sensitivity analysis comparing current and former users showed risks of 21% and 19% for hospital admission with a similar adjusted RR of 1.08 (95% CI, 1.00-1.18). When comparing former users with never users, the risks of hospital admission were comparable between the groups (Supplementary Table 4).

In the dose-response analysis, the risk of hospital admission for current PPI users with a high-dose regimen was increased with an adjusted RR at 1.19 (95% CI, 1.07-1.32), whereas current users with a low-dose regimen had an adjusted RR of 1.03 (95% CI, 0.90–1.17), when compared with never PPI users. All secondary outcomes were not statistically significant (Supplementary Table 5).

When comparing the different classes of PPI, neither consistent nor statistically significant differences were observed in risk of hospital admission or severe outcomes (Supplementary Table 6).

Meta-analysis of Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

In the updated literature search, 8 studies,[6,7,12–16] including our current study, investigated the association between current PPI use and risk of SARS-CoV-2 infection. In addition, a recent nationwide study was included alongside a relevant preprint not detected in the initial search.[17,18] Study characteristics are shown in Supplementary Table 7. Analysis of these studies, comprising 730,941 individuals, resulted in a pooled OR of 1.00 (95% CI, 0.75-1.32), with considerable between-study heterogeneity ($I^2 = 98\%$) (Figure 1). When divided into subgroups on the basis of risk of bias, the analysis of the 5 studies with high risk of bias showed an OR of 1.13 (95% CI, 0.53–2.41) for current PPI use compared with never use (Figure 1). Furthermore, the 5 studies with low risk of bias showed a decreased risk of infection, although with low statistical precision, OR of 0.86 (95% CI, 0.67–1.10) (Figure 1).

Meta-analysis of Coronavirus Disease 2019 Mortality

Only 4 studies[12,19,20] reported the association between current PPI use and mortality alone, including 4150 current PPI users (Supplementary Table 7). The overall analysis showed an RR of 1.33 (95% CI, 0.71–2.48) in current PPI users compared with never users, although estimates differed between studies with low risk of bias, RR 0.85 (95% CI, 0.70–1.03), and high risk of bias, RR 2.37 (1.53–3.67) (interaction test: $P < .0001$) (Figure 2). The between-study heterogeneity was substantial ($I^2 = 84\%$).

Discussion

Overall, current use of PPI was associated with an increased risk of SARS-CoV-2 infection in the case-

Table 4. Relative Risk of Hospital Admission, Intensive Care Unit Admission, Mechanical Ventilation, or Death for Current and Never Users of Proton Pump Inhibitors

	Current proton pump inhibitor use		Never proton pump inhibitor use		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Hospital admission	995/4473	22.2 (21.0–23.5)	2145/59,413	3.6 (3.5–3.8)	6.16 (5.75–6.60)
ICU admission	118/4473	2.6 (2.2–3.1)	254/59,413	0.4 (0.4–0.5)	6.17 (4.97–7.66)
Mechanical ventilation	68/4473	1.5 (1.2–1.9)	145/59,413	0.2 (0.2–0.3)	6.23 (4.68–8.30)
Death	269/4473	6.0 (5.3–6.7)	280/59,413	0.5 (0.4–0.5)	12.76 (10.82–15.04)
ICU or death	353/4473	7.9 (7.1–8.7)	487/59,413	0.8 (0.7–0.9)	9.63 (8.42–11.00)
Matched					
Hospital admission	734/3955	18.6 (17.3–19.8)	650/3955	16.4 (15.3–17.6)	1.13 (1.03–1.24)
ICU admission	92/3955	2.3 (1.9–2.8)	95/3955	2.4 (1.9–2.9)	0.97 (0.73–1.29)
Mechanical ventilation	55/3955	1.4 (1.0–1.8)	55/3955	1.4 (1.0–1.8)	1.00 (0.69–1.45)
Death	166/3955	4.2 (3.6–4.8)	189/3955	4.8 (4.1–5.4)	0.88 (0.72–1.08)
ICU or death	235/3955	5.9 (5.2–6.7)	260/3,955	6.6 (5.8–7.3)	0.90 (0.76–1.07)

ICU, intensive care unit.

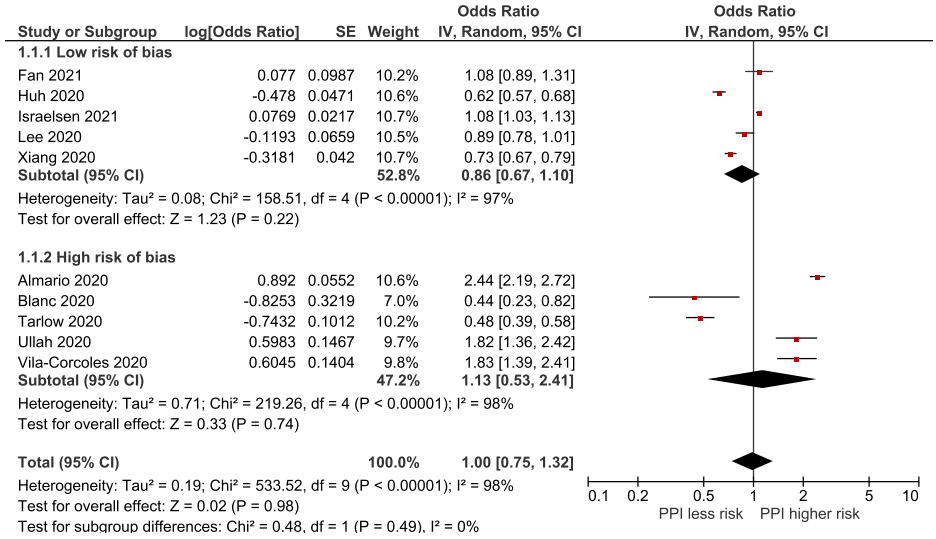

Figure 1. Forest plot of the association between proton pump inhibitor use and risk of SARS-CoV-2 infection. CI, confidence interval; df, degrees of freedom; IV, inverse variance; PPI, proton pump inhibitor; SE, standard error.

control study and an increased risk of hospital admission in the cohort study including test-positive individuals. However, both estimates were close to 1.0 and may be caused by residual confounding. Moreover, current use of PPI was not associated with increased risk of severe outcomes that included ICU admission or death.

The lack of a clinically significant association with increased risk of infection in current PPI users in our study is consistent with most previous reports and our updated meta-analysis. In contrast, the meta-analysis by Li et al[10] showed that current PPI use was associated with increased odds of infection, although the estimate was statistically uncertain.

Our results show a possible association between current PPI use and increased risk of hospital admission in SARS-CoV-2 RNA positive individuals. However, we could not confirm the association with increased risk of severe outcomes of COVID-19 with current PPI use as reported in previous meta-analyses.[9,10,21,22] In addition, a multicenter study from North America and a nationwide United Kingdom study, not included in any of the meta-analyses, did not find an association between PPI use and severe outcomes either.[18,23]

Notably, all the studies reporting the impact of PPI use in SARS-CoV-2 infected individuals differ substantially. First, the study populations are rather heterogenous including different nationalities and ranging from young resourceful individuals[6] to elderly with several comorbidities[12,13] and between hospitalized patients and residents without hospital contact. The SARS-CoV-2 RNA positive population in our study had comorbidities corresponding to previous reports of diagnoses commonly present in infected individuals[24] and included both residents without hospital contact and hospitalized patients. Second, the study designs vary from small single center studies[19,20] to large nationwide cohorts,[7,18] and study results are presented as only crude estimates[14] or after adjustment for possible confounders, some by use of propensity score matched methods.[7,8,18] Third, current use of PPI was defined in different ways and in some studies not reported at all.

The associations with increased risk of infection and hospital admission for current PPI use identified here may have arisen from limitations associated with an observational design. Although a wide range of relevant comorbidity and medication was used to adjust our analyses, there may inherently remain residual confounding by

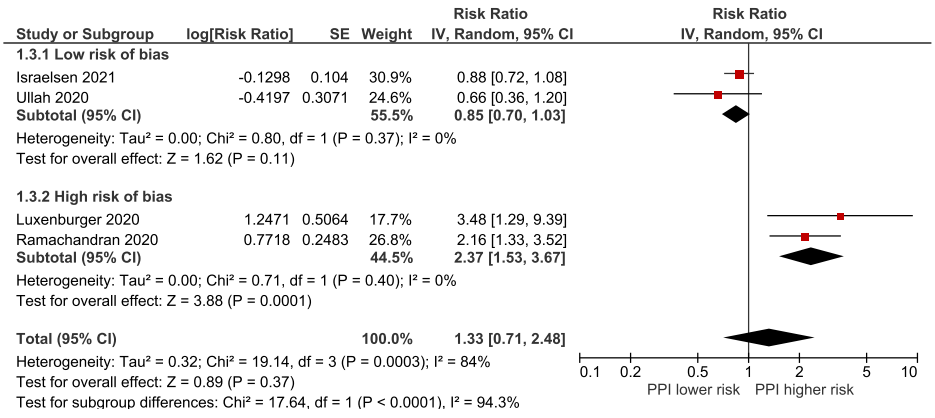

Figure 2. Forest plot of the association between proton pump inhibitor use and COVID-19 mortality. CI, confidence interval; df, degrees of freedom; IV, inverse variance; PPI, proton pump inhibitor; SE, standard error.

imperfectly measured, unmeasured, or unknown factors. In addition, the propensity score matching failed to fully account for important differences in comorbidities and prior health care use between current and never users. Use of PPI has been associated with socioeconomic deprivation and frailty, but this information was not available through the applied registries. Similarly, information on the indication for use of PPI was unavailable except for a prior diagnosis of peptic ulcer. Interestingly, Luxenburger et al[20] found that gastroesophageal reflux disease was independently associated with severe courses of COVID-19, thereby raising the question whether the indication for the drug prescription accounts for the association rather than the drug per se. Furthermore, PPI is linked to overprescribing, which could be another (unknown) marker of frailty.[25] Low-dose PPI is available as over-the-counter medicine in Denmark, which could give rise to information bias, affecting the results toward the null.

Finally, for the test-negative case-control study of PPI use as risk factor for contracting SARS-CoV-2-infection, there is a potential bias if PPI affects the chance of becoming a control, ie, being tested negative. In the early stages of the pandemic, most test-negative individuals had other viral upper respiratory infections, which to our knowledge is not associated with PPI use in general.

Our updated meta-analysis showed a possible increased risk of COVID-19 mortality, but no risk of SARS-CoV-2 infection. However, neither of these results were statistically significant. Indeed, when we restricted our analyses to studies with low risk of bias, the point estimates decreased to below 1.0 in both analyses, indicating that the conflicting results from the included studies and former meta-analyses arise from between-study differences rather than an actual impact of current PPI use on COVID-19 outcomes.

In conclusion, our data support that PPI use in general is safe with regard to risk of SARS-CoV-2 infection and severe COVID-19 outcomes. The risk of hospital admission was increased for current PPI users, but this minimally elevated RR is seemingly explained by residual confounding. Following hospital admission there was no association with severity of COVID-19 and use of PPI. Finally, our updated meta-analysis indicated no impact of current PPI use on COVID-19 outcomes, thereby suggesting that previous conflicting results are more likely due to differences in study design and population.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.05.011.

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Thomas Benfield (Conceptualization: Equal; Funding acquisition: Equal; Investigation: Equal; Methodology: Equal; Supervision: Lead; Writing – review & editing: Equal)

Conflicts of interest

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Supplementary Table 1. Covariates and Corresponding ATC/Diagnoses Codes Included in the Propensity Score Model

Type of information	Variables	Time frame/diagnosis codes
Demographics	Sex	
	Date of birth	
Health care utilization	No. of hospital admissions	Within 3 years before index date
Charlson Comorbidity Index	0	Since 1994 (ICD-10)
	1–2	
	3+	
Comorbidities	Peptic ulcer	K25, K26, K27
	Asthma	J45
	COPD	J44
	Cirrhosis	K703, K717A, K717B, K743, K744, K745, K746, K746B, K746C, K746D, K746E, K746F, K746G, K746H, DP788A
	Ischemic heart disease	I20, I21, I22, I23, I24, I25, N02BA, C01DA, B01AC24
	Diabetes mellitus	E10, E11, E13, E14
	Renal failure	I12, I13, N00-N05, N07, N08, N11, N14, N18, N19, E102, E112, E142
	Heart failure	I099A, I110, I130, I132, I50
	Stroke	I60, I61, I62, I63, I64, I69
	Alcohol-related diagnosis or drug use	F10, E244, G312, G621, G721, I426, K292, K70, K852, K860, Q860, Z502, Z714, Z721
	Smoking-related diagnosis	DF17, DZ716, DZ720
	Major psychiatric disorder	F20, F25, F30, F31
Medication	Systemic corticosteroids	H02AB
	Inhaled corticosteroids	R03AK, R03AL, R03BA
	Bronchodilators	R03AA, R03AC
	H2RA	A02BA
	NSAID	M01A (excluding M01AX)
	Anticholinergic agents	R03BB
	Immunosuppressants	L04AA, L04AB, L04AC, L04AD, L04AX, L01XC02
	Antipsychotic agents	N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN, N05AX
	Antibiotics	J01
	Alcohol abstinence treatment	N07BB
	Smoking cessation treatment	N07BA
	Blood pressure lowering drugs	C03A, C07, C08, C09
	Lipid lowering drugs	C10
	Glucose lowering drugs	A10A, A10B
	Antiplatelets	B01AC
	Anticoagulants	B01AA, B01AE07, B01AF

COPD, chronic obstructive pulmonary disease, H2RA, H2-receptor antagonists; ICD-10, International Classification of Diseases version 10, NSAID, nonsteroidal anti-inflammatory drug.

Supplementary Table 2. Search Strategy for Meta-analysis

World Health Organization COVID-19 database September 23–December 14.
(tw:(proton pump inhibitor*)) OR (tw:(ppi*)) OR (tw:(h2-receptor antagonist*)) OR (tw:(hypochlorhydria)) OR (tw:(gastric acid)) OR (tw:(gastric ph)) OR (tw:(omeprazole)) OR (tw:(rabeprazole)) OR (tw:(esomeprazole)) OR (tw:(pantoprazole)) OR (tw:(lansoprazole)) OR (tw:(gastrointestinal))

Supplementary Table 3. Odds of Infection With SARS-Cov-2 for Cases Compared With Controls According to Use of Different Classes of Proton Pump Inhibitors

Proton pump inhibitor use	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Lansoprazole versus pantoprazole	0.85 (0.70–1.02)	0.84 (0.69–1.02)
Omeprazole versus pantoprazole	0.85 (0.69–1.04)	0.83 (0.67–1.03)
Esomeprazole versus pantoprazole	0.84 (0.61–1.15)	0.82 (0.59–1.14)

CI, confidence interval; ICD-10, International Classification of Diseases version 10; OR, odds ratio; SARS-Cov-2, Severe Acute Respiratory Syndrome Coronavirus 2.

[a]Adjusted for age, sex, comorbidities (peptic ulcer, asthma, chronic obstructive pulmonary disease, cirrhosis, ischemic heart disease, diabetes, renal failure, heart failure, stroke, alcohol-related diagnoses, smoking-related diagnoses, major psychiatric disorders), other current medication use (systemic and inhaled corticosteroids, bronchodilators, H2-receptor antagonists, nonsteroidal anti-inflammatory drugs, anticholinergic agents, immunosuppressants, antipsychotic agents, antibiotics, alcohol abstinence treatment, smoking cessation treatment, blood pressure lowering drugs, lipid lowering drugs, glucose lowering drugs, antiplatelets, anticoagulants), Charlson Comorbidity Index (0, 1–2, 3+), and number of hospital admissions within the last 3 years (0, 1, 2, 3+).

Supplementary Table 4. Relative Risk of Hospital Admission, Intensive Care Unit Admission, Mechanical Ventilation, or Death for Current, Former, or Never Use of Proton Pump Inhibitors

	Current PPI use		Former PPI use		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Death	269/4473	6.0 (5.3–6.7)	297/19,338	1.5 (1.4–1.7)	3.92 (3.33–4.60)
ICU admission	118/4473	2.6 (2.2–3.1)	203/19,338	1.0 (0.9–1.2)	2.51 (2.01–3.15)
ICU or death	353/4473	7.9 (7.1–8.7)	454/19,338	2.3 (2.1–2.6)	3.36 (2.94–3.85)
Mechanical ventilation	68/4473	1.5 (1.2–1.9)	130/19,338	0.7 (0.6–0.8)	2.26 (1.69–3.03)
Hospital admission	995/4473	22.2 (21.0–23.5)	1848/19,338	9.6 (9.1–10.0)	2.33 (2.17–2.50)
Matched					
Death	232/4326	5.4 (4.7–6.0)	205/4326	4.7 (4.1–5.4)	1.13 (0.94–1.36)
ICU admission	107/4326	2.5 (2.0–2.9)	106/4326	2.5 (2.0–2.9)	1.01 (0.77–1.32)
ICU or death	311/4326	7.2 (6.4–8.0)	282/4326	6.5 (5.8–7.3)	1.10 (0.94–1.29)
Mechanical ventilation	63/4326	1.5 (1.1–1.8)	70/4326	1.6 (1.2–2.0)	0.90 (0.64–1.26)
Hospital admission	905/4326	20.9 (19.7–22.1)	835/4326	19.3 (18.1–20.5)	1.08 (1.00–1.18)

	Former PPI use		Never PPI use		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Death	297/19,338	1.5 (1.4–1.7)	280/59,413	0.5 (0.4–0.5)	3.26 (2.77–3.83)
ICU admission	203/19,338	1.0 (0.9–1.2)	254/59,413	0.4 (0.4–0.5)	2.46 (2.04–2.95)
ICU or death	454/19,338	2.3 (2.1–2.6)	487/59,413	0.8 (0.7–0.9)	2.86 (2.52–3.25)
Mechanical ventilation	130/19,338	0.7 (0.6–0.8)	145/59,413	0.2 (0.2–0.3)	2.75 (2.18–3.49)
Hospital admission	1848/19,338	9.6 (9.1–10.0)	2145/59,413	3.6 (3.5–3.8)	2.65 (2.49–2.81)
Matched					
Death	177/18,381	1.0 (0.8–1.1)	256/18,381	1.4 (1.2–1.6)	0.69 (0.57–0.84)
ICU admission	170/18,381	0.9 (0.8–1.1)	182/18,381	1.0 (0.8–1.1)	0.93 (0.76–1.15)
ICU or death	312/18,381	1.7 (1.5–1.9)	401/18,381	2.2 (2.0–2.4)	0.78 (0.67–0.90)
Mechanical ventilation	109/18,381	0.6 (0.5–0.7)	106/18,381	0.6 (0.5–0.7)	1.03 (0.79–1.34)
Hospital admission	1471/18,381	8.0 (7.6–8.4)	1381/18,381	7.5 (7.1–7.9)	1.07 (0.99–1.14)

ICU, intensive care unit; PPI, proton pump inhibitor use.

Supplementary Table 5. Relative Risk of Hospital Admission, Intensive Care Unit Admission, Mechanical Ventilation, or Death According to Dose of Proton Pump Inhibitors

	Current PPI use		Never PPI use		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Death					
Low dose	90/1631	5.5 (4.4–6.6)	280/59,413	0.5 (0.4–0.5)	11.71 (9.28–14.77)
High dose	179/2842	6.3 (5.4–7.2)	280/59,413	0.5 (0.4–0.5)	13.36 (11.12–16.06)
ICU admission					
Low dose	29/1631	1.8 (1.1–2.4)	254/59,413	0.4 (0.4–0.5)	4.16 (2.84–6.09)
High dose	89/2842	3.1 (2.5–3.8)	254/59,413	0.4 (0.4–0.5)	7.33 (5.77–9.30)
ICU or death					
Low dose	112/1631	6.9 (5.6–8.1)	487/59,413	0.8 (0.7–0.9)	8.38 (6.86–10.23)
High dose	241/2842	8.5 (7.5–9.5)	487/59,413	0.8 (0.7–0.9)	10.35 (8.91–12.02)
Mechanical ventilation					
Low dose	13/1631	0.8 (0.4–1.2)	145/59,413	0.2 (0.2–0.3)	3.27 (1.86–5.75)
High dose	55/2842	1.9 (1.4–2.4)	145/59,413	0.2 (0.2–0.3)	7.93 (5.83–10.79)
Hospital admission					
Low dose	319/1631	19.6 (17.6–21.5)	2145/59,413	3.6 (3.5–3.8)	5.42 (4.87–6.03)
High dose	676/2842	23.8 (22.2–25.4)	2145/59,413	3.6 (3.5–3.8)	6.59 (6.10–7.12)
Matched					
Death					
Low dose	64/1479	4.3 (3.3–5.4)	189/3955	4.8 (4.1–5.4)	0.91 (0.69–1.19)
High dose	102/2476	4.1 (3.3–4.9)	189/3955	4.8 (4.1–5.4)	0.86 (0.68–1.09)
ICU admission					
Low dose	26/1479	1.8 (1.1–2.4)	95/3955	2.4 (1.9–2.9)	0.73 (0.48–1.12)
High dose	66/2476	2.7 (2.0–3.3)	95/3955	2.4 (1.9–2.9)	1.11 (0.81–1.51)
ICU or death					
Low dose	84/1479	5.7 (4.5–6.9)	260/3955	6.6 (5.8–7.3)	0.86 (0.68–1.10)
High dose	151/2476	6.1 (5.2–7.0)	260/3955	6.6 (5.8–7.3)	0.93 (0.76–1.13)
Mechanical ventilation					
Low dose	13/1479	0.9 (0.4–1.4)	55/3955	1.4 (1.0–1.8)	0.63 (0.35–1.15)
High dose	42/2476	1.7 (1.2–2.2)	55/3955	1.4 (1.0–1.8)	1.22 (0.82–1.82)
Hospital admission					
Low dose	250/1479	16.9 (15.0–18.8)	650/3955	16.4 (15.3–17.6)	1.03 (0.90–1.17)
High dose	484/2476	19.5 (18.0–21.1)	650/3955	16.4 (15.3–17.6)	1.19 (1.07–1.32)

ICU, intensive care unit; PPI, proton pump inhibitor.

Supplementary Table 6. Relative Risk of Hospital Admission, Intensive Care Unit Admission, Mechanical Ventilation, or Death According to Use of the Different Classes of Proton Pump Inhibitors

	Lansoprazole		Pantoprazole		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Death	40/833	4.8 (3.3–6.3)	187/2607	7.2 (6.2–8.2)	0.67 (0.48–0.93)
ICU admission	25/833	3.0 (1.8–4.2)	71/2607	2.7 (2.1–3.3)	1.10 (0.70–1.73)
ICU or death	55/833	6.6 (4.9–8.3)	237/2607	9.1 (8.0–10.2)	0.73 (0.55–0.96)
Mechanical ventilation	12/833	1.4 (0.6–2.2)	41/2607	1.6 (1.1–2.1)	0.92 (0.48–1.73)
Hospital admission	180/833	21.6 (18.8–24.4)	633/2607	24.3 (22.6–25.9)	0.89 (0.77–1.03)
Matched					
Death	38/829	4.6 (3.2–6.0)	37/829	4.5 (3.1–5.9)	1.03 (0.66–1.60)
ICU admission	24/829	2.9 (1.8–4.0)	23/829	2.8 (1.7–3.9)	1.04 (0.59–1.83)
ICU or death	53/829	6.4 (4.7–8.1)	52/829	6.3 (4.6–7.9)	1.02 (0.70–1.48)
Mechanical ventilation	12/829	1.4 (0.6–2.3)	15/829	1.8 (0.9–2.7)	0.80 (0.38–1.70)
Hospital admission	178/829	21.5 (18.7–24.3)	195/829	23.5 (20.6–26.4)	0.91 (0.76–1.09)

	Omeprazole		Pantoprazole		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Death	22/749	2.9 (1.7–4.1)	192/2616	7.3 (6.3–8.3)	0.40 (0.26–0.62)
ICU admission	14/749	1.9 (0.9–2.8)	73/2616	2.8 (2.2–3.4)	0.67 (0.38–1.18)
ICU or death	34/749	4.5 (3.0–6.0)	242/2616	9.3 (8.1–10.4)	0.49 (0.35–0.70)
Mechanical ventilation	11/749	1.5 (0.6–2.3)	41/2616	1.6 (1.1–2.0)	0.94 (0.48–1.81)
Hospital admission	126/749	16.8 (14.1–19.5)	640/2616	24.5 (22.8–26.1)	0.69 (0.58–0.82)
Matched					
Death	22/747	2.9 (1.7–4.2)	37/747	5.0 (3.4–6.5)	0.59 (0.35–1.00)
ICU admission	14/747	1.9 (0.9–2.8)	14/747	1.9 (0.9–2.8)	1.00 (0.48–2.08)
ICU or death	34/747	4.6 (3.1–6.0)	44/747	5.9 (4.2–7.6)	0.77 (0.50–1.19)
Mechanical ventilation	11/747	1.5 (0.6–2.3)	9/747	1.2 (0.4–2.0)	1.22 (0.51–2.93)
Hospital admission	126/747	16.9 (14.2–19.6)	125/747	16.7 (14.1–19.4)	1.01 (0.80–1.26)

	Esomeprazole		Pantoprazole		
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude					
Death	21/324	6.5 (3.8–9.2)	192/2614	7.3 (6.3–8.3)	0.88 (0.57–1.36)
ICU admission	8/324	2.5 (0.8–4.2)	73/2614	2.8 (2.2–3.4)	0.88 (0.43–1.82)
ICU or death	28/324	8.6 (5.6–11.7)	242/2614	9.3 (8.1–10.4)	0.93 (0.64–1.36)
Mechanical ventilation	NA	NA	NA	NA	0.79 (0.28–2.18)
Hospital admission	65/324	20.1 (15.7–24.4)	639/2614	24.4 (22.8–26.1)	0.82 (0.65–1.03)
Matched					
Death	21/324	6.5 (3.8–9.2)	22/324	6.8 (4.1–9.5)	0.95 (0.54–1.70)
ICU admission	8/324	2.5 (0.8–4.2)	8/324	2.5 (0.8–4.2)	1.00 (0.38–2.63)
ICU or death	28/324	8.6 (5.6–11.7)	27/324	8.3 (5.3–11.3)	1.04 (0.63–1.72)
Mechanical ventilation	NA	NA	NA	NA	0.80 (0.22–2.95)
Hospital admission	65/324	20.1 (15.7–24.4)	63/324	19.4 (15.1–23.8)	1.03 (0.76–1.41)

ICU, intensive care unit; NA (not applicable), refers to no observed events or number of events below 5 not presented because of patient confidentiality considerations.

Supplementary Table 7. Characteristics of Studies Included in the Meta-analyses

Study	Design	Population-based	Country or region	Timing of data collection	Mean or median age (*y*)	No. of subjects	Current PPI users, n (%)	Confounder control in design	Confounder adjustment in analysis	Outcomes
Vila-Corcoles	Cohort	Yes	Spain	May 1–Apr 3, 2020	71	34,936	11,807 (34%)	No	No	Risk of infection
Huh	Case-control	Yes	Korea	Up to Apr 8, 2020	49	65,149	14,827 (23%)	No	Yes	Risk of infection
Xiang	Cohort	Yes	UK	Jan–Nov 6, 2020	68	30,835	10,724 (33%)	No	Yes	Risk of infection
Almario	Cohort	Yes	USA	May 3–Jun 24, 2020	NR	53,130	16,547 (31%)	No	Yes	Risk of infection
Tarlow	Cohort	No	USA	NR	NR	84,325	18,240 (22%)	No	No	Risk of infection
Blanc	Case-control	No	France	Up to Apr 8, 2020	84	179	63 (35%)	No	No	Risk of infection
Ullah	Cohort	No	UK	Feb 12–Jun 12, 2020	57 67	15,586 212	4533 (29%) 87 (41%)	No No	Yes Yes	Risk of infection; mortality
Lee	Matched case-control	Yes	Korea	Jan 1–May 15, 2020	56	27,746	13,873 (50%)	Yes	Yes	Risk of infection
	Cohort				50	534	267 (50%)	Yes	Yes	Severe clinical outcomes[a]
Israelsen	Matched case-control	Yes	Denmark	Feb–Dec 1, 2020	36	416,023	22,026 (5%)	Yes	Yes	Risk of infection
	Cohort				60	7910	3955 (50%)	Yes	No	Severe clinical outcomes; mortality
Ramachandran	Cohort	No	USA	Mar 1–Apr 25, 2020	66	295	46 (48%)	No	No	Severe clinical outcomes; mortality
Luxenburger	Cohort	No	Germany	NR	65	152	62 (41%)	No	No	Secondary infection; ARDS; mortality
Fan	Cohort	Yes	UK	Mar 16–Jun 29, 2020	NR	3032	1354 (45%)	Yes	No	Risk of infection; mortality

ARDS, acute respiratory distress syndrome; NR, not reported; PPI, proton pump inhibitor.
[a]Severe clinical outcomes include mechanical ventilation, intensive care unit admission, or death.