

## Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: Systematic review and meta-analysis

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**Author contributions:** Trifan A and Stanciu C designed the study, contributed to the selection of studies, analyzed the data and wrote the manuscript; Stoica OC, Maxim R, Singeap AM, Girleanu I, Chiriac SA and Ciobica A were involved in the acquisition of data and contributed to the analysis and interpretation of data; Girleanu I, Stoica OC, Maxim R and Singeap AM drafted the manuscript; Boiculese L and Girleanu I contributed to the statistical analysis; all authors have read and approved the final version of the manuscript; all authors accept responsibility for its content.

**Conflict-of-interest statement:** The authors deny any conflict of interest.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Unsolicited manuscript

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**Received:** July 13, 2017

**Peer-review started:** July 17, 2017

**First decision:** August 10, 2017

**Revised:** August 11, 2017

**Accepted:** August 25, 2017

**Article in press:** August 25, 2017

**Published online:** September 21, 2017

### Abstract

#### AIM

To perform a systematic review and meta-analysis on proton pump inhibitors (PPIs) therapy and the risk of *Clostridium difficile* infection (CDI).

#### METHODS

We conducted a systematic search of MEDLINE/PubMed and seven other databases through January 1990 to March 2017 for published studies that evaluated the association between PPIs and CDI. Adult case-control and cohort studies providing information on the association between PPI therapy and the development of CDI were included. Pooled odds ratios (ORs) estimates with 95% confidence intervals (CIs) were calculated using the random effect. Heterogeneity was assessed by  $I^2$  test and Cochran's  $Q$  statistic.

Potential publication bias was evaluated *via* funnel plot, and quality of studies by the Newcastle-Ottawa Quality Assessment Scale (NOS).

## RESULTS

Fifty-six studies (40 case-control and 16 cohort) involving 356683 patients met the inclusion criteria and were analyzed. Both the overall pooled estimates and subgroup analyses showed increased risk for CDI despite substantial statistical heterogeneity among studies. Meta-analysis of all studies combined showed a significant association between PPI users and the risk of CDI (pooled OR = 1.99, CI: 1.73-2.30,  $P < 0.001$ ) as compared with non-users. The association remained significant in subgroup analyses: by design-case-control (OR = 2.00, CI: 1.68-2.38,  $P < 0.0001$ ), and cohort (OR = 1.98, CI: 1.51-2.59,  $P < 0.0001$ ); adjusted (OR = 1.95, CI: 1.67-2.27,  $P < 0.0001$ ) and unadjusted (OR = 2.02, CI: 1.41-2.91,  $P < 0.0001$ ); uncenter (OR = 2.18, CI: 1.72-2.75,  $P < 0.0001$ ) and multicenter (OR = 1.82, CI: 1.51-2.19,  $P < 0.0001$ ); age  $\geq 65$  years (OR = 1.93, CI: 1.40-2.68,  $P < 0.0001$ ) and  $< 65$  years (OR = 2.06, CI: 1.11-3.81,  $P < 0.01$ ). No significant differences were found in subgroup analyses (test for heterogeneity):  $P = 0.93$  for case-control *vs* cohort,  $P = 0.85$  for adjusted *vs* unadjusted,  $P = 0.24$  for uncenter *vs* multicenter,  $P = 0.86$  for age  $\geq 65$  years and  $< 65$  years. There was significant heterogeneity across studies ( $I^2 = 85.4\%$ ,  $P < 0.001$ ) as well as evidence of publication bias (funnel plot asymmetry test,  $P = 0.002$ ).

## CONCLUSION

This meta-analysis provides further evidence that PPI use is associated with an increased risk for development of CDI. Further high-quality, prospective studies are needed to assess whether this association is causal.

**Key words:** Proton pump inhibitors; *Clostridium difficile* infection; Risk; Systematic review; Meta-analysis

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**Core tip:** A possible association between the use of proton pump inhibitors (PPIs) and the risk of *Clostridium difficile* infection (CDI) have been suggested by several studies. This meta-analysis, including the largest number of studies published to date found the risk of CDI almost two-times higher in PPIs users than in nonusers. Because all the studies analyzed were observational, the causality could not be confirmed. Nevertheless, clinicians should be aware of such potential association and prescribe the PPIs only where they are clearly indicated.

Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculescu L. Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: Systematic review and meta-analysis. *World J Gastroenterol* 2017;

23(35): 6500-6515 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i35/6500.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i35.6500>

## INTRODUCTION

Over the past two decades *Clostridium difficile* (*C. difficile*) infection (CDI) has registered an increasing trend worldwide both in incidence and severity<sup>[1-5]</sup>, with healthcare costs varying between 1.2 and 4.7 billion dollars each year in the United States alone<sup>[6-9]</sup>. In addition to the broad-spectrum antimicrobial therapy which has been the most prominent causative factor for CDI<sup>[10,11]</sup>, other potential risk factors have been identified such as: advanced age, hospitalization [particularly in intensive care units (ICU)], immunosuppression, renal insufficiency, hypoalbuminemia, lengthy hospital stay, the use of nasogastric tubes, invasive gastrointestinal procedures, chemotherapy, the presence of comorbidities, environment-related factors, and the emergence of a hypervirulent strain of the bacterium known as North American pulso-type 1 in some areas<sup>[12-21]</sup>. However, there might be some other risk factors for the CDI epidemic in the recent years despite tighter control on the use of antibiotics and stricter control policies on hospital-related infections<sup>[17]</sup>. A possible association between the use of proton pump inhibitors (PPIs) and the development of CDI has been suggested and numerous studies have examined it, reporting conflicting results<sup>[22-43]</sup>.

Since their release in the late 1980s, PPIs have become some of the most widely prescribed agents both in outpatient and inpatient settings throughout the world<sup>[44-53]</sup>, with sales totalling billions dollars worldwide<sup>[54,55]</sup>. These drugs have proven effective in the treatment of ulcer disease (including bleeding peptic ulcer), gastroesophageal reflux disease, *Helicobacter pylori* (in combination with antibiotics), Zollinger-Ellison syndrome, in the prophylaxis of upper gastrointestinal complications with nonsteroidal anti-inflammatory drugs (NSAIDs) therapy, stress ulcer prophylaxis in ICU patients, and functional dyspepsia<sup>[50,53,56-60]</sup>. The widespread use of PPIs during the last 25 years in clinical practice is the result not only of their high efficacy but also of their excellent safety profile, proving to be one of the safest class of medication used in gastroenterology<sup>[57,61-64]</sup>.

Nevertheless, like in the case of other drugs, PPIs are not as safe as it has been thought and more recently, concerns have been raised about their potential association with pneumonia<sup>[65-67]</sup>, bone fractures<sup>[68-70]</sup>, interstitial nephritis and acute kidney injury<sup>[71]</sup>. More recently, reports of other potential PPIs adverse events such as risk for chronic kidney disease<sup>[72,73]</sup>, dementia<sup>[74]</sup>, spontaneous bacterial peritonitis<sup>[75,76]</sup>, acute myocardial infarction<sup>[77,78]</sup>, micronutrient

deficiency (magnesium, calcium, iron)<sup>[79,80]</sup> were published, although the quality of evidence for these is consistently low to very low<sup>[81]</sup>.

An association between PPIs use and CDI is, at least theoretically, rational. Thus, intestinal homeostasis is maintained by host defense mechanisms in which gastric acid plays an important role as a barrier to ingested bacteria and bacterial overgrowth<sup>[82]</sup>. PPIs therapy profoundly inhibits gastric acid production leading to the proliferation of spores and their ability to convert to a vegetative form of *C. difficile*<sup>[83]</sup>. Moreover, PPIs impair leukocyte function by inhibiting phagocytosis and acidification of phagolysosome<sup>[84]</sup>.

Several systematic reviews and meta-analyses have reported conflicting results regarding the association between PPIs use and increased risk of CDI. Thus, no less than six meta-analyses<sup>[85-90]</sup> found a significant association between PPIs therapy and increased risk of CDI. These findings were also supported by several studies<sup>[19,22-26,39,91-114]</sup> which reported a risk for CDI two or three times higher in PPIs users than in nonusers. Moreover, the United States Food and Drug Administration (FDA) informed the public about a possible correlation between PPIs use and CDI<sup>[115]</sup>. Still, other studies and meta-analyses have failed to associate PPIs use with the development of CDI<sup>[11,27,34,38,40-43,116-123]</sup>. It should be mentioned that PPIs continue to be among the most used drugs despite the above mentioned concerns about long-term side effects. Furthermore, beside a marked overuse of PPIs, over half of prescriptions are for non-indicated reasons<sup>[29]</sup>. One study reported that 60.7% of patients with CDI used PPIs, of whom only 47.1% had an evidence-based indication<sup>[30]</sup>.

The aim of this systematic review and meta-analysis is to summarize data on the association between PPIs use and the risk of CDI as presented in the published studies.

## MATERIALS AND METHODS

### Information sources

A systematic literature search was independently conducted by four study investigators (Girleanu I, Stoica OC, Singeap AM and Chiriac SA) using a variety of databases including MEDLINE/PubMed, Web of Science (ISI Web of Knowledge), Scopus, EMBASE, Science Direct, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database, and Cochrane Library, from January 1990 (the first PPI received FDA approval in 1989) to March 2017. The database searches were performed using the following medical subject heading (MeSH) terms: "proton pump inhibitors", "acid suppressive therapy", "omeprazole", "pantoprazole", "lansoprazole", "rabeprazole", "esomeprazole", combined with "*C. difficile* infection", "*C. difficile*-associated diarrhea", "pseudomembranous colitis". Reference lists of all

retrieved papers were hand-searched to identify any additional studies that may have been missed in the computed-assisted literature search. The investigation was limited to studies performed in adult human beings, written and published in English, French, and German, in any geographic region.

### Inclusion and exclusion criteria

Selection of the studies. Inclusion and exclusion criteria were established a priori by two authors (Trifan A and Stanciu C). First, duplicate citations were identified and removed, then three of us (Ciobica A, Maxim R and Singeap AM) independently reviewed the titles and abstracts of the studies and excluded those which did not answer the search question. Adult case-control and cohort studies providing information on the association between PPI therapy and the development of CDI were included. Studies conducted on pediatric patients, systematic reviews and meta-analyses, consensus documents, studies using PPIs simultaneously with H2 receptor antagonists (H2RA) or reporting exclusively on H2RA, case reports, editorials, protocols, and studies presented only as abstracts were excluded. There was no restriction related to the type of PPI regimen or diagnostic methods of CDI. Any disagreements about study inclusion were resolved in consensus with a third author (Stanciu C or Trifan A) after the full-text of the potential study had been reviewed; all eligible studies were assessed in full. They were subsequently included in this meta-analysis only if reported odds ratios (ORs) or risk ratios (RRs) for (adjusted or unadjusted) case-control and cohort studies, respectively, or data for their calculation were available.

### Data extraction

Extracted data were cross-checked independently by four authors (Girleanu I, Stoica OC, Chiriac SA and Ciobica A) from each included study using a standardized data extracting sheet which included the last name of first author, journal and year of publication, country where the study was carried out, study design, sample size, age (mean or median) and gender distribution of patients, duration of the PPI treatment, effect estimates ORs or RRs, and 95% confidence intervals (CIs) of PPI exposure with and without adjustment for confounding variables. Any disagreement between reviewers was resolved in consensus with a third reviewer (Stanciu C or Trifan A).

### Study quality assessment

Assessment of study quality was made independently by two authors (Boiculese L and Girleanu I) using the Newcastle-Ottawa Quality Assessment Scale (NOS; ranging 0-9)<sup>[124]</sup> as recommended by the Cochrane Handbook for Systematic Reviews of Interventions<sup>[125]</sup>. The NOS comprises three domains: selection, comparability, and outcome for cohort studies or exposure for case-control studies. A maximum of

four stars were awarded for selection, two stars for comparability, and three stars for exposure/outcome. Studies with cumulative score  $\geq 7$  were considered high quality, 6 stars to be of moderate quality, and less than 6 stars to be of low quality. When disagreement, after discussion with the third author (Trifan A or Stanciu C) a consensus was reached. The final analysis included 56 high and moderate quality studies.

As none of the studies was randomized, and all were observational (case-control and cohort), the methods used in our systematic review and meta-analysis followed the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) criteria<sup>[126]</sup>.

### Statistical analysis

Meta-analyses were performed both for all studies together and separately for case-control and cohort studies using DerSimonian and Laird<sup>[127]</sup> random effects model due to expected heterogeneity between studies. Our primary analysis focused on the association between PPIs therapy and the risk for developing CDI and because all of PPIs have similar efficacy we have not performed meta-analyses stratified by type of PPIs. The results are reported as pooled ORs with 95% CIs for primary and subgroup analyses.

Heterogeneity between studies was assessed by  $I^2$  statistic and Cochran's  $Q$ -statistic. The level of heterogeneity was considered as high when  $I^2 > 75\%$  or  $P < 0.10$  for the  $Q$  statistic<sup>[128]</sup>.  $I^2$  values between 61%-75%, 30%-60%, and  $< 30\%$  were considered to represent substantial, moderate and low level of heterogeneity, respectively<sup>[129]</sup>. Seven potential confounders were considered: study design, effect estimate (adjusted vs unadjusted), setting (community vs inpatient), number of centers (single center vs multicenter), age, study quality, and geographical region.

Publication bias was assessed quantitatively using Egger's regression asymmetry test<sup>[130]</sup> and a  $P < 0.1$  was considered statistically significant for asymmetry, and qualitatively by visual inspection of funnel plots of the logarithmic OR vs their standard errors<sup>[131]</sup>. Asymmetrical funnel plots were regarded to indicate high risk of publication bias.

Number needed to harm (NNH) estimates the number of patients needed to be treated with PPI for one additional person to have a CDI, and was calculated using the pooled OR (95%CI) from the meta-analysis and Patient Expected Event Rate (1.67%)<sup>[120]</sup>.

All statistical tests were two tailed, and results associated with  $P < 0.05$  (except for heterogeneity and publication bias) were considered significant. All analyses were performed using R version 3.2.3 software for the metaphor package 1.9-8, which provides a comprehensive collection of validated functions<sup>[132]</sup>. The statistical analyses of this study were performed by an expert in biostatistics from

"Grigore T. Popa" University of Medicine and Pharmacy, Department of Medical Informatics and Biostatistics.

## RESULTS

### Search results

The initial online databases search identified 944 studies and 12 more were found from the reference lists of the articles retrieved. After reviewing all titles and abstracts, 216 studies were selected for full-text review, from which 56 studies were found to fulfill the inclusion criteria and were included in meta-analysis. Five of the 56 studies were published after the last meta-analysis (Figure 1).

### Characteristics of included studies

The characteristics of the included studies are shown in Table 1. Of the included 56 studies, 40 (71.4%) were case-control, and 16 (28.6%) cohort studies, addressed to hospital-acquired ( $n = 43$ ), community-acquired ( $n = 6$ ), and both hospital and community-acquired CDI ( $n = 7$ ). Most of the studies ( $n = 31$ ) were single-center. The size of the study population ranged from 40 to 101796. In total, 356683 subjects were included, most of them from North-American and European studies ( $n = 46$ ).

### Quality assessment

The median value of NOS quality assessment was 7, with a mean  $6.67 \pm 0.74$ , range 6-8. In studies reporting gender, the proportion of men ranged from 47% to 67%, and from those that reported the age, the average age ranged between 18 and 82.2 years. Thirty-eight studies identified confounding factors (sex, age, antibiotic use, comorbidities) used for adjustment of the association between PPI therapy and risk of CDI. The majority of the studies were retrospective (85.7%) and only 8 were prospective (14.3%). None of the studies was randomized.

### Meta-analysis

Meta-analysis of all studies combined. The results of pooled analysis for all 56 studies showed a significant association between PPI therapy and the risk of CDI as compared with non-PPI users (OR = 1.99, CI: 1.73-2.30,  $P < 0.001$ ) (Figure 2). There was significant heterogeneity of effects across studies ( $I^2 = 85.41\%$ ;  $P < 0.001$ ).

Subgroup analyses of case-control and cohort studies also showed a significant higher risk of CDI with PPI use (Table 2). There was no significant difference of effects between cohort and case-control studies ( $P = 0.931$ ). The pooled OR for the cohort studies was 1.98 similar to OR for case-control that was 2.0.

The association remained also significant after limiting meta-analysis to studies with both adjusted (OR = 1.95, CI: 1.67-2.27,  $P < 0.001$ ) and unadjusted

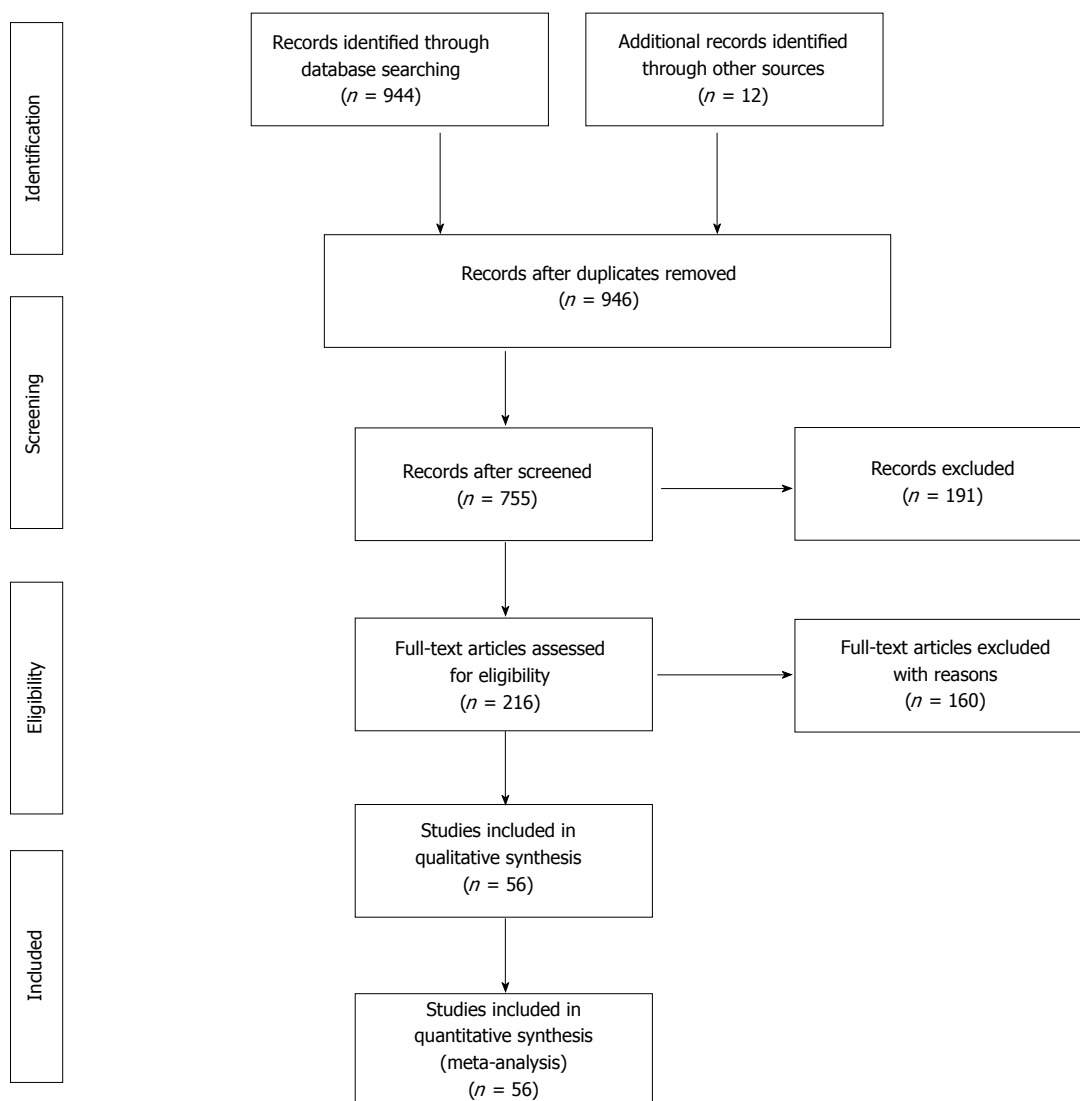


Figure 1 Study selection process.

data (OR = 2.02, CI: 1.41-2.91,  $P < 0.001$ ). There was also no significant difference of effects between adjusted and unadjusted studies ( $P = 0.856$ ).

PPIs use was found to be associated with an increased risk of CDI in both single-center studies (OR = 2.18, 95%CI: 1.72-2.75) and multicenter studies (OR = 1.82, 95%CI: 1.51-2.19).

There was no significant difference between inpatients and outpatients regarding CDI risk ( $P = 0.868$ ). For both inpatients and outpatients the PPIs use almost doubled the risk of CDI (OR = 1.95, OR = 2.10, respectively).

When grouped by region, a direct association was found in the European group (OR = 1.78, 95%CI: 1.35-2.34), the North American group (OR = 2.00, 95%CI: 1.67-2.40), while the highest risk of CDI after PPI treatment was demonstrated in the Asian group (OR = 2.31, 95%CI: 1.96-2.72).

The subgroup of high-quality studies (NOS  $\geq 7$ ) showed a direct association (OR = 1.88, 95%CI:

1.55-2.28) between PPIs and risk of CDI, and this association was also significant in the medium-quality group (OR = 2.11, 95%CI: 1.69-2.62), with no difference between the two groups ( $P = 0.441$ ).

There was no statistical difference regarding the risk for CDI for elderly ( $\geq 65$  years) compared with younger group ( $< 65$  years) ( $P = 0.860$ ).

#### Publication bias

We have drawn the funnel plot for 3 levels of confidence interval (90%, 95% and 99% corresponding to shades white, gray and dark gray) (Figure 3). The Egger's test of asymmetry proved no significance ( $Z = 0.3699$ ,  $P = 0.711$ ).

#### Number needed to harm

Based on reported incidence of CDI (at 14 d after hospital admission) of 1.67% in patients who have not used PPI, we estimate a NNH of 63 (95%CI: 48-78), if these patients will receive PPIs.

**Table 1 Characteristics of studies included in the meta-analysis**

Author, yr	Region	Study design	Centers	Setting	Sample size, n	Mean age, yr	Identified confounders	OR (95%CI)
Akhtar <i>et al</i> Shaheen <sup>[91]</sup> , 2007	America	Case-control	Unicenter	Inpatient	1290		Adjusted for age, sex, comorbidities, antibiotics, chemotherapy	2.1 (1.6-2.7)
Al-Tureihi <i>et al</i> <sup>[91]</sup> , 2005	America	Case-control	Unicenter	Inpatient	53		Adjusted for age, antibiotics	3.1 (1.0-9.7)
Aseeri <i>et al</i> <sup>[23]</sup> , 2008	America	Case-control	Unicenter	Inpatient	188		Adjusted for admission date, sex, age group, antibiotic use, patient location, and room type	4.4 (2.3-8.2)
Bajaj <i>et al</i> <sup>[133]</sup> , 2010	America	Case-control	Multicenter	Mixt	162		Adjusted for antibiotics, PPI	37.6 (6.2-227.6)
Barletta <i>et al</i> <sup>[92]</sup> , 2014	Asia	Case-control	Unicenter	Inpatient	408		Adjusted for PPI exposure, antibiotics, immunosuppression	2.1 (1.2-3.8)
Baxter <i>et al</i> <sup>[93]</sup> , 2008	America	Case-control	Multicenter	Inpatient	4493		Adjusted for antibiotics, age, hospital stay, other infections	1.2 (1.0-1.4)
Beaulieu <i>et al</i> <sup>[27]</sup> , 2007		Cohort	Unicenter	Inpatient	827		Adjusted for age, sex, length of stay, comorbidities, APACHE score, NGT feeding, tracheal tube placement, antibiotics	1.3 (0.9-2.0)
Branch <i>et al</i> <sup>[94]</sup> , 2007	America	Case-control	Unicenter	Inpatient	787	66.02	No	13.0 (7.5-22.7)
Buendgens <i>et al</i> <sup>[95]</sup> , 2014	Europe	Case-control	Multicenter	Inpatient	3286		Adjusted for age, sex, antibiotics, comorbidities, other treatment	3.1 (1.1-8.7)
Campbell <i>et al</i> <sup>[38]</sup> , 2013	America	Case-control	Unicenter	Inpatient	96		Adjusted for antibiotics, hospitalization	2.2 (0.6-8.0)
Cunningham <i>et al</i> <sup>[96]</sup> , 2003	Europe	Case-control	Unicenter	Inpatient	320		Adjusted for antibiotics and chemotherapy	2.5 (1.5-4.1)
Dalton <i>et al</i> <sup>[22]</sup> , 2009	America	Cohort	Multicenter	Inpatient	14719	74.7	Adjusted for number of medication groups, antibiotic days, age, length of stay, medical service, PPI days	1.9 (1.4-2.7)
Debast <i>et al</i> <sup>[116]</sup> , 2009	Europe	Case-control	Unicenter	Inpatient	154		Adjusted for age, hospital stay, comorbidities, antibiotics	1.1 (0.5-2.4)
Dial <i>et al</i> <sup>[26]</sup> , 2004 (case-control)	America	Case-control	Multicenter	Inpatient	188		Adjusted for age, antibiotics	2.6 (1.3-5.0)
Dial <i>et al</i> <sup>[26]</sup> , 2004 (cohort)	America	Cohort	Multicenter	Inpatient	1187		Adjusted for age, antibiotics	2.1 (1.2-3.5)
Dial <i>et al</i> <sup>[98]</sup> , 2005	Europe	Case-control	Multicenter	Outpatient	13563		Adjusted for age, sex, antibiotics	2.9 (2.4-3.5)
Dial <i>et al</i> <sup>[97]</sup> , 2006	Europe	Case-control	Multicenter	Outpatient	3484		Adjusted for PPI and antibiotics	3.5 (2.3-5.3)
Dial <i>et al</i> <sup>[134]</sup> , 2008	America	Case-control	Multicenter	Outpatient	9196	79.8	Adjusted for age, sex, antibiotics, comorbidities, physician visits, hospital admissions, length of stay	1.6 (1.3-1.9)
Dubberke <i>et al</i> <sup>[99]</sup> , 2007	America	Cohort	Unicenter	Inpatient	36086		Adjusted for age, admissions, antibiotics, albumin level, leukemia/lymphoma, mechanical ventilation, antimotility agents	1.6 (1.3-2.1)
Elseviers <i>et al</i> <sup>[100]</sup> , 2015	Europe	Case-control	Multicenter	Inpatient	743	71.9	Adjusted for age, co-morbidity, endoscopic procedures	1.9 (1.1-3.4)
Faleck <i>et al</i> <sup>[42]</sup> , 2016	America	Cohort	Unicenter	Inpatient	11230	66	Adjusted for age, sex, antibiotics, comorbidities, length of stay	0.6 (0.4-0.8)
Garzotto <i>et al</i> <sup>[43]</sup> , 2015	Europe	Case-control	Multicenter	Inpatient	225		No	0.4 (0.2-0.8)
Hebbard <i>et al</i> <sup>[135]</sup> , 2017	Asia	Case-control	Unicenter	Inpatient	200	59.7	Adjusted for age, chemotherapy, abdominal surgery, antibiotics	2.4 (1.0-5.7)
Hensgens <i>et al</i> <sup>[117]</sup> , 2011	Europe	Case-control	Unicenter	Inpatient	169		Adjusted for age, co-morbidity, antibiotics, ICU stay	1.1 (0.5-2.5)
Howell <i>et al</i> <sup>[136]</sup> , 2010	America	Cohort	Unicenter	Inpatient	101796	65.4	Adjusted for age, comorbidities, antibiotics	1.7 (1.3-2.1)
Ingle <i>et al</i> <sup>[40]</sup> , 2011	Asia	Cohort	Unicenter	Mixt	99	47	Adjusted for immunosuppression	1.8 (0.4-7.4)
Ingle <i>et al</i> <sup>[118]</sup> , 2013	Asia	Case-control	Unicenter	Community	150	45.3	no	2.3 (0.6-9.2)
Jayatilaka <i>et al</i> <sup>[101]</sup> , 2007	America	Case-control	Unicenter	Inpatient	366		Adjusted for PPI	2.7 (1.6-4.8)

Kazakova <i>et al</i> <sup>[102]</sup> , 2006	America	Case-control	Unicenter	Mixt	195		Adjusted for antibiotics, PPI, length of stay, psychosis, depression	5.0 (1.3-19.3)
Khan <i>et al</i> <sup>[39]</sup> , 2012	Asia	Cohort	Unicenter	Inpatient	123		Adjusted for surgery, PPI, antibiotics, hospitalization, Underlying debilitating conditions	3.2 (1.2-8.5)
Khanafer <i>et al</i> <sup>[119]</sup> , 2013	Europe	Cohort	Unicenter	Inpatient	40			2.5 (0.6-9.6)
Kuntz <i>et al</i> <sup>[2]</sup> , 2011	America	Case-control	Unicenter	Mixt	3344		no	2.3 (1.5-3.3)
Kurti <i>et al</i> <sup>[3]</sup> , 2015	Europe	Case-control	Multicenter	Inpatient	979	72.4	Adjusted for antibiotics, PPI, length of stay,	1.6 (1.1-2.2)
Kutty <i>et al</i> <sup>[41]</sup> , 2010	America	Case-control	Multicenter	Outpatient	144	62	No	1.7 (0.7-4.0)
Lewis <i>et al</i> <sup>[103]</sup> , 2016	America	Cohort	Unicenter	Inpatient	41663		No	6.4 (3.6-11.5)
Lin <i>et al</i> <sup>[137]</sup> , 2013	Asia	Case-control	Multicenter	Inpatient	86	59	Age, sex, unit, antibiotics, length of stay	10.1 (1.2-87.4)
Linney <i>et al</i> <sup>[24]</sup> , 2010	America	Case-control	Unicenter	Inpatient	284		Age, sex, discharge date and hospital unit, antibiotics, diabetes mellitus, IBD, cancer, enteral feeding, length of stay	2.4 (1.4-4.3)
Loo <i>et al</i> <sup>[120]</sup> , 2005	America	Case-control	Multicenter	Inpatient	474		no	1.0 (0.7-1.4)
Loo <i>et al</i> <sup>[138]</sup> , 2011	America	Cohort	Multicenter	Inpatient	4143	67.4	Adjusted for age, PPI, antibiotics, chemotherapy	2.6 (1.7-4.0)
Lowe <i>et al</i> <sup>[121]</sup> , 2006	America	Case-control	Multicenter	Inpatient	13692	78.7	Adjusted for antibiotics, other medications, and comorbidities	0.9 (0.7-1.0)
McFarland <i>et al</i> <sup>[122]</sup> , 2007	America	Case-control	Multicenter	Mixt	368		No	0.8 (0.5-1.4)
Mizui <i>et al</i> <sup>[104]</sup> , 2013	Asia	Case-control	Multicenter	Inpatient	2716	71.7	No	3.2 (1.4-7.3)
Modena <i>et al</i> <sup>[105]</sup> , 2005	America	Case-control	Unicenter	Inpatient	250		Adjusted for macrolides, ICU, length of stay, infections	3.3 (1.6-6.8)
Mori <i>et al</i> <sup>[123]</sup> , 2015	Asia	Case-control	Unicenter	Outpatient	78	58.2	No	0.4 (0.1-2.0)
Muto <i>et al</i> <sup>[106]</sup> , 2005	America	Case-control	Multicenter	Inpatient	406		Adjusted for PPI, antibiotics, diabetes mellitus, organ transplantation	2.4 (1.3-4.4)
Pakyz <i>et al</i> <sup>[107]</sup> , 2014	America	Case-control	Multicenter	Inpatient	14164		No	1.4 (1.3-1.5)
Peled <i>et al</i> <sup>[108]</sup> , 2007	America	Cohort	Unicenter	Inpatient	217		Adjusted for PPI, low albumin level,	3.7 (1.5-9.3)
Pepin <i>et al</i> <sup>[11]</sup> , 2005	America	Cohort	Unicenter	Inpatient	5619		Adjusted for age, length of stay, antibiotics	1.0 (0.7-1.2)
Ro <i>et al</i> <sup>[139]</sup> , 2016	Asia	Cohort	Unicenter	Inpatient	1005	64.8	Adjusted for age, antibiotics, comorbidities	3.3 (1.5-7.2)
Roughead <i>et al</i> <sup>[109]</sup> , 2016	Asia	Cohort	Multicenter	Mixt	54957		Adjusted for antibiotics, PPI, length of stay,	2.4 (1.9-3.1)
Shah <i>et al</i> <sup>[34]</sup> , 2000	Europe	Case-control	Unicenter	Inpatient	252		No	0.8 (0.4-1.5)
Southern <i>et al</i> <sup>[110]</sup> , 2010	Europe	Cohort	Multicenter	Inpatient	3904	65.5	No	2.3 (1.1-4.5)
Vesteinsdottir <i>et al</i> <sup>[111]</sup> , 2012	Europe	Case-control	Multicenter	Mixt	333		No	1.6 (1.0-2.6)
Yang <i>et al</i> <sup>[112]</sup> , 2011	Asia	Case-control	Multicenter	Inpatient	1420	67.12	No	1.9 (1.3-2.7)
Yearsley <i>et al</i> <sup>[25]</sup> , 2006	Europe	Case-control	Unicenter	Inpatient	308	79.1	Adjusted for PPI, antibiotics, female sex	1.9 (1.1-3.2)
Yip <i>et al</i> <sup>[140]</sup> , 2001	America	Case-control	Unicenter	Inpatient	54		No	3.0 (0.8-11.1)

CI: Confidence interval; IBD: Inflammatory bowel disease; ICU: Intensive care unit; PPI: Proton pump inhibitor; NGT: Naso-gastric tube; OR: Odds ratio.

## DISCUSSION

This systematic review and meta-analysis which includes 56 studies and 356683 subjects<sup>[2,3,11,19,22-27,34,38-43,91-112,116-123,133-140]</sup> found a significant association between PPI therapy and the risk for CDI development. Both the overall pooled estimates (OR = 1.99, CI: 1.73-2.30,  $P < 0.001$ ) and subgroup analyses showed a significant increased risk for CDI in patients on PPI therapy compared to nonusers, despite substantial statistical heterogeneity among studies and evidence of publication bias. Thus, in line with previous meta-analyses, our results add further evidence to

PPIs use as a risk factor for development of CDI<sup>[85-89]</sup>.

Since 2001, when Yip *et al*<sup>[140]</sup> first suggested a possible association between PPIs use and the risk of CDI, other studies, systematic reviews, and meta-analyses have reported such an association. It should be mentioned that a decade earlier (1993), Walker *et al*<sup>[141]</sup> suggested that the H2RAs therapy was a potential risk factor for CDI. In an earlier systematic review which included 11 studies with 126999 patients, Leonard *et al*<sup>[113]</sup> reported a significant association between PPI therapy and CDI (OR = 2.05, 95%CI: 1.47-2.85) although there was significant heterogeneity among the studies ( $\chi^2 = 50.9$ ,  $P <$

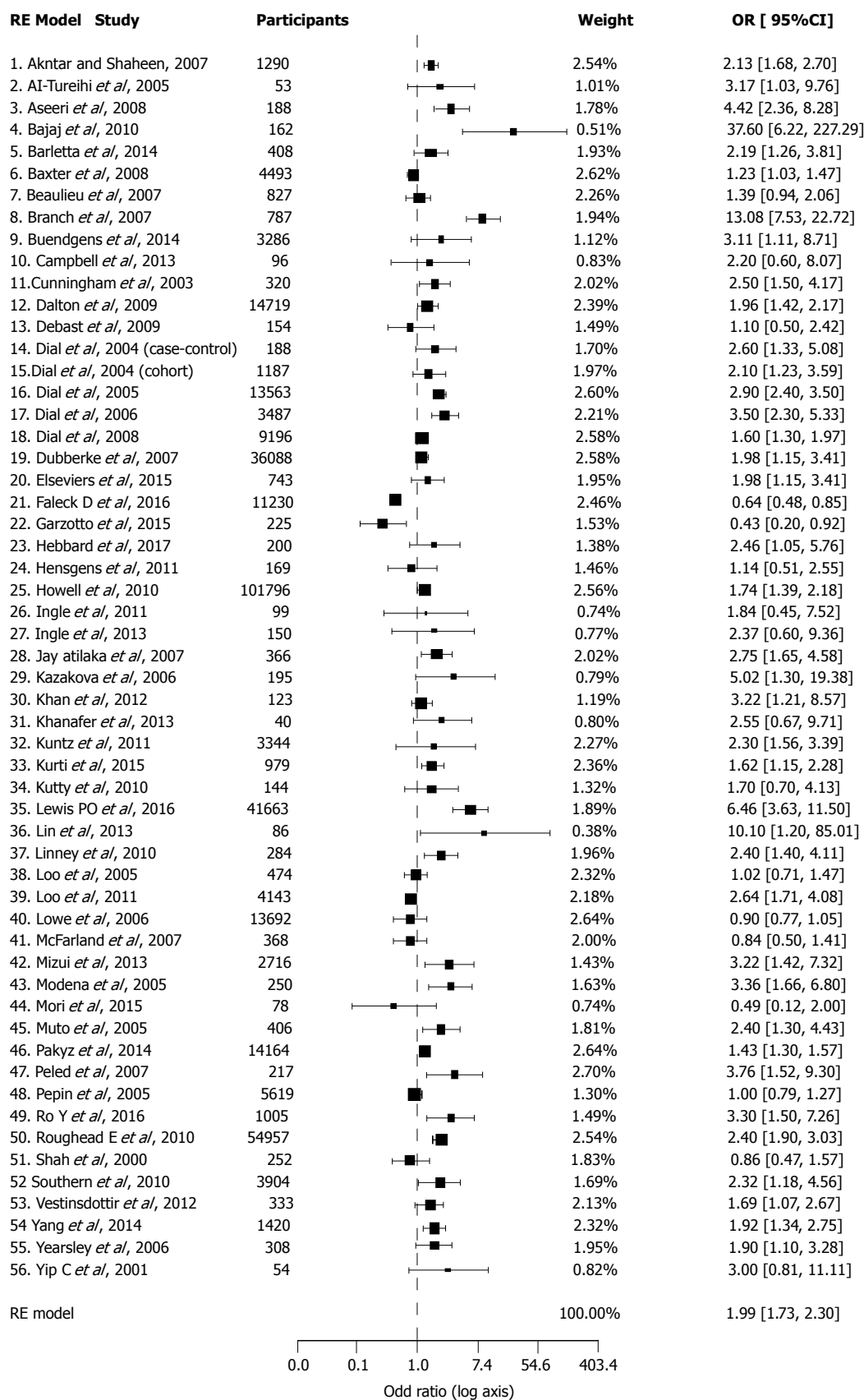


Figure 2 Forest plot of the meta-analysis.

0.0001). During the last years, six meta-analyses have been published on this topic, and all reported a positive

association between PPIs use and the risk for CDI. Thus, Janarthanan *et al*<sup>[88]</sup> in a meta-analysis including



Table 2 Subgroup analysis

Subgroup analysis	No. of studies ( <i>n</i> = 56)	ORs	95%CI	Heterogeneity, <i>I</i> <sup>2</sup> , %	Heterogeneity between groups, <i>P</i> value
Study design					
Case-control	40	2	1.68-2.38	85.54	0.931
Cohort	16	1.98	1.51-2.59	85.99	
Study type					
Adjusted	38	1.95	1.67-2.27	85.02	0.856
Unadjusted	18	2.02	1.41-2.91	85.58	
Centers					
Unicentric	31	2.18	1.72-2.75	83.99	0.241
Multicentric	25	1.82	1.51-2.19	86.97	
Type					
Inpatient	43	1.95	1.67-2.29	84.99	0.868
Outpatient	6	2.1	1.36-3.24	84.84	
Mixt	7	2.19	1.39-3.45	76.77	
Region					
Europe	14	1.78	1.35-2.34	74.33	0.231
America	31	2	1.67-2.40	88.58	
Asia	11	2.31	1.96-2.72	89.18	
Age					
Age < 65 yr	6	2.06	1.11-3.81	35.39	0.86
Age ≥ 65 yr	13	1.93	1.40-2.68	92.11	
NOS					
NOS ≥ 7	26	1.88	1.55-2.28	87.65	0.441
NOS < 7	30	2.11	1.69-2.62	81.98	

CI: Confidence interval; NOS: Newcastle-Ottawa Quality Assessment Scale; ORs: Odds ratio.

23 observational studies with nearly 300000 patients found a 65% increase in the incidence of CDI among PPIs users with an estimated risk of 1.69 and 95%CI from 1.395 to 1.974. In another meta-analysis (30 studies, 202965 patients), Desphande *et al*<sup>[85]</sup> reported that PPI therapy was associated with a 2-fold increase in risk for CDI, but their study is limited by unadjusted risk estimates. Recently, the same team<sup>[90]</sup> performed a meta-analysis examining the relationship between PPI therapy and the risk for recurrent CDI, and found a positive association with the pooled risk ratio of 1.58 (95%CI: 1.13-2.21). A third meta-analysis by Kwok *et al*<sup>[87]</sup> including 42 studies (313000 participants) also found a statistically significant association between PPIs use and the risk for CDI compared with nonusers (OR = 2.51; 95%CI: 1.47-2.85; *P* = 0.05). Tleyjeh *et al*<sup>[86]</sup> in a systematic review and meta-analysis including 51 observational studies (37 case-control and 14 cohort) examining healthcare and community-associated CDI, found a very low quality evidence for an association between PPI therapy and CDI not supporting a cause-effect relationship. Authors reported a pooled OR of 1.65 (95%CI: 1.47-1.85) with evidence of publication bias and significant statistical heterogeneity among the studies (*I*<sup>2</sup> = 89.9%). More recently, Arriola *et al*<sup>[89]</sup> suggest, in a meta-analysis including only inpatients, that PPIs use significantly increases the risk of hospital-acquired CDI (OR = 1.81). Bavishi *et al*<sup>[114]</sup> in a systematic review regarding the use of PPI and increased susceptibility to enteric infection found 27 studies evaluating an association between PPI therapy and the risk of CDI, 17 of which

reported a significant association. Based on an analysis of 28 studies, US FDA issued a warning on the risk of CDI with PPIs use<sup>[115]</sup>, and similar warnings are found in CDI treatment guidelines<sup>[142]</sup>.

Several studies reported that PPIs use is also a risk factor for community-acquired CDI. Dial *et al*<sup>[26]</sup>, in a study including over 1000 cases of community-acquired CDI, found that patients who had received PPIs within the previous 90 d had a nearly 3-fold increased risk for CDI. A similar result was reported by Kutty *et al*<sup>[41]</sup> who found a 2-3-fold increased for community-acquired CDI in patients treated with PPIs within the previous 6 mo. Marwick *et al*<sup>[143]</sup> in a study including patients aged 65 years or older identified all cases of community-acquired CDI and found that patients prescribed PPIs within the previous 6 mo had a 1.7-fold increased risk for CDI compared to matched controls. A study assessing the epidemiology of community-acquired CDI found rates of PPI use of nearly 30% among patients with this infection compared to less than 3% in the general population<sup>[144]</sup>. These results indicate a similar degree of association between PPIs use and CDI risk, be it community-acquired CDI or hospital-acquired CDI<sup>[145]</sup>.

Nevertheless, the association between PPIs use and the risk for CDI remains to a certain extent controversial despite the results reported above, as several studies failed to find such an association<sup>[11,27,34,94,122]</sup>. Beaulieu *et al*<sup>[27]</sup> found that the use of gastric acid-suppression therapy does not predispose to development of CDI, while McFarland *et al*<sup>[122]</sup> reported no relation between CDI and the use of PPIs. Branch *et al*<sup>[94]</sup> found that

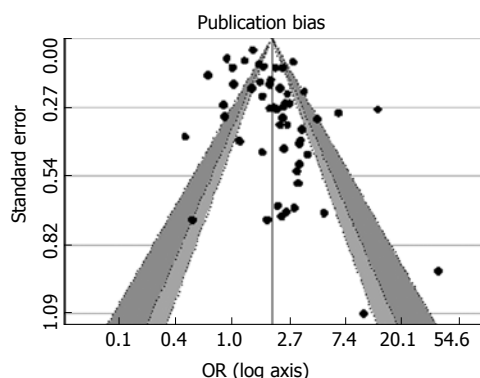


Figure 3 Funnel plot with 95% confidence limits.

PPI use did not increase the incidence of CDI in hospitalized patients.

The mechanism by which PPI therapy contributes to an increased risk of CDI is unclear. It has been proposed that a vegetative form of *C. difficile* survives in conditions of gastric pH greater than 4<sup>[114]</sup>-the threshold for enteric infections acquisition, including *C. difficile*. Howell *et al*<sup>[136]</sup> reported that the risk of nosocomial CDI rose with increasing levels of acid suppression. Hegarty *et al*<sup>[146]</sup> reported that PPI therapy decreased the expression of genes holding an important role in colonocyte integrity, thus favoring the development of CDI. Other studies show that long-term use of PPIs decreases microbial diversity, a condition found in patients with CDI<sup>[147]</sup>.

As we have already mentioned, our subgroup analyses also showed an increased risk for CDI. There were no significant differences of effects between cohort and case-control studies, adjusted and unadjusted data, single-center and multicenter studies, hospitalized-and community-acquired CDI or among geographic regions. Advanced age is a well-known risk factor for CDI. To our surprise, we found no increased risk of CDI in elderly patients ( $\geq 65$  years) using PPIs compared with younger (OR = 1.93 vs OR = 2.06,  $P = 0.860$ ). A possible explanation is that many of such patients may have atrophic gastritis with low gastric acid output<sup>[148]</sup> and PPIs use cannot further lower gastric acid secretion, without any additional risk of CDI<sup>[32]</sup>.

As data regarding the association between PPI therapy and risk of CDI are supported only by observational studies, a final estimation of the real risk is not possible. It should be mentioned that randomized placebo-controlled clinical trials evaluating the association of PPIs use and the risk for CDI are ethically unfeasible and therefore, such studies could not be performed in the future. Thus, a weak association between PPI therapy and CDI does not confirm causality and could be the result of bias and uncontrolled confounding (*e.g.*, comorbidities, comedication use, *etc.*) which were lacking in most studies.

Our meta-analysis has some strengths such as the

largest number of studies published to date, adjusted effect estimates concerning the association between PPI use and the risk of CDI, and subgroup analyses based on age, region, type, design and quality of the study. However, it also has several limitations: the included studies were observational, influenced by confounding variables despite statistical adjustment, the significant heterogeneity among most of them and lack of information regarding the dose and duration of PPI use as well as patient compliance to PPI therapy.

Although the above presented data from several meta-analyses and many studies demonstrated an association between PPI therapy and the risk for development of CDI, PPIs continue to be overused even in patients who are at high risk of CDI, because they are still considered "safe" drugs by most physicians. There is evidence that over half of PPI users who developed CDI had no valid indications for such therapy<sup>[25]</sup>. While in many countries PPIs are now totally available as over-the-counter medication, clinicians should inform their patients about the risk of CDI when PPIs are used on the long-term and without valid indication.

In spite of the aforementioned limitations of our and several other meta-analyses, clinicians should be aware of the risk of CDI when prescribing long-term PPI therapy, particularly in patients at high risk (*e.g.*, hospitalized patients on antibiotics). It should be underlined that PPIs remain, on the whole, a safe group of drugs<sup>[149]</sup>, providing enormous benefits when prescribed for well-established indications. Unfortunately, many prescriptions fall outside accepted indications<sup>[90]</sup>.

In conclusion, this systematic review and meta-analysis provides further evidence that PPI use significantly increases the risk for developing CDI, despite the substantial heterogeneity and publication bias present among studies. Due to the fact that all the studies included in our analysis are observational and cannot confirm causality, further large, high quality, prospective studies are needed to assess the association between PPI use and the risk of CDI.

## COMMENTS

### Background

Proton pump inhibitors (PPIs) are among the most widely prescribed agents by gastroenterologists because of their high efficacy and excellent safety profile. However, more recently, concerns have been raised about association between PPI therapy and several potentially serious adverse events including *Clostridium difficile* (*C. difficile*) infection (CDI). This systematic review and meta-analysis explored the existing evidence regarding the association of PPI therapy and CDI.

### Research frontiers

Many observational studies and meta-analyses have reported conflicting results regarding the association between PPI therapy and the risk for CDI.

### Innovations and breakthroughs

This systematic review and meta-analysis, including the largest number

of studies published to date, provides further evidence that PPI therapy is associated with an increased risk for development of CDI. Because all the studies analyzed were observational, with inherent limitations, the causality could not be confirmed.

### Applications

Although our systematic review and meta-analysis, in line with previous studies and meta-analyses, reported an association between PPI therapy and the risk for development of CDI, such association remains controversial and a final estimation of the real risk has not been established. Further high-quality, prospective studies are needed to assess whether this association is causal. Until then, clinicians should be aware that long-term PPI therapy may be associated with the risk of CDI, and prescribe the PPIs in the lowest effective dose only to patients with a clear indication.

### Terminology

PPIs are a group of potent inhibitors of gastric acid secretion. CDI is a symptomatic infection due to the spore-forming bacterium *C. difficile*.

### Peer-review

This manuscript is an interesting, informative and well-presented meta-analysis on PPI therapy and risk of *C. difficile* infection.

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ISSN 1007-9327

