OPTIMIZING THE MANAGEMENT OF PATIENTS WITH GASTRO-ESOPHAGEAL REFLUX DISEASE

Ph.D. Thesis

Floria Diana-Elena, M.D.

Translational Medicine Program

Pharmaceutical Sciences and Health Technologies Division

SEMMELWEIS UNIVERSITY

Supervisors: Prof. Vasile-Liviu Drug, M.D., Ph.D.
Bálint Erőss, M.D., Ph.D.

Official reviewers:

Head of the Complex Examination Committee: Prof. Gábor Varga, M.D., Ph.D.

Members of the Complex Examination Committee: Prof. Karl J. Oldhafer, M.D., Ph.D.

Roland Molontay, Ph.D.

Áron Vincze, M.D., Ph.D.

Zoltán Zádori, Ph.D.

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“A smooth sea never made a skilled sailor.”

Franklin D. Roosevelt

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1. LIST OF ABBREVIATIONS

CENTRAL	Cochrane Central Register of Controlled Trials
CDI	*Clostridioides difficile* infection
CI	Confidence interval
GERD	Gastro-esophageal reflux disease
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
H2RA	Histamine H2-receptor antagonist
LPR	Laryngopharyngeal reflux
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionization–Time of Flight
PPIs	Proton pump inhibitors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
ROB	Risk of bias
RR	Risk ratio
SD	Standard deviation
SEM	Standard error of the mean
SIBO	Small intestinal bacterial overgrowth
SMD	Standardized mean difference

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve the clinical management of patients with gastro-esophageal reflux disease (GERD) by advancing evidence-based care. My mission is to aid a better understanding of current and emerging diagnostic and therapeutic approaches for GERD, in relation to both typical and extra-digestive manifestations of the disease. To achieve this, my specific goals are to evaluate the efficacy of acid-suppressive therapies in treating extra-digestive symptoms of GERD, such as non-specific chronic cough; to assess the safety profile of proton pump inhibitors, with particular attention to their potential role in intestinal dysbiosis and the risk of *Clostridioides difficile* infection; and to investigate the effects of pepsin on the salivary peptidome of healthy individuals using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, with the aim of identifying proteomic signatures that may be relevant to GERD.

2.2. Scientometrics

Number of all publications:	31
Cumulative IF:	128.5
Av IF/publication:	4.15
Ranking (SCImago):	D1:6, Q1:16, Q2:6, Q3:3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	14.9
Av IF/publication:	7.45
Ranking (Sci Mago):	D1:2
Number of citations on Google Scholar:	178
Number of citations on MTMT (independent):	7
H-index:	7

The detailed bibliography of the student can be found on pages 63-69.

2.3. Future plans

I plan on completing my residency in Gastroenterology and specialized training in digestive endoscopy. As I am especially passionate about this field, I am committed to continually advancing my skills in diagnostic and therapeutic endoscopy. I intend to continue my role as a teaching assistant at Grigore T. Popa University of Medicine, contributing to the education and mentorship of medical students. I plan to remain actively involved in collaborative research projects with my team, with the goal of generating meaningful scientific evidence that translates into improved patient care.

2.4. Ongoing projects – Study III: Salivary Peptidomic Profiling as a Novel Diagnostic Approach for GERD

We are currently working on an additional third proof-of-concept study, where we investigated the effects of pepsin exposure under acidic conditions on the human salivary peptidome using Matrix-Assisted Laser Desorption/Ionization–Time of Flight (MALDI-TOF) mass spectrometry. Rather than focusing on the detection of salivary pepsin itself, our approach aimed to characterize the proteolytic peptide signatures generated by pepsin activity. Identifying reproducible peptide patterns may provide insights into reflux-related enzymatic effects and advance the discovery of potential non-invasive diagnostic tools for GERD.

3. SUMMARY OF THE THESIS

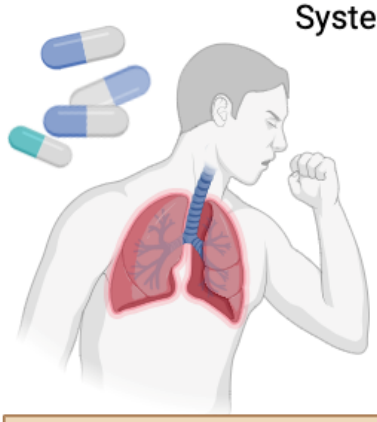
This thesis addresses the management of gastro-esophageal reflux disease (GERD), with particular focus on extra-digestive manifestations and treatment safety.

The first study is a systematic review and meta-analysis evaluating the efficacy of acid-suppressive therapy in adults with non-specific chronic cough, a recognized extra-esophageal manifestation of GERD. Placebo-controlled randomized clinical trials were analyzed to assess changes in cough severity and quality of life. The results demonstrated a rather modest clinical benefit of proton pump inhibitors (PPIs) compared to placebo. These findings support current guideline recommendations that advise cautious use of acid suppression for extra-esophageal symptoms and highlight the need for improved patient selection.

The second study investigated the safety profile of PPIs, focusing on their potential association with intestinal dysbiosis. A systematic review and meta-analysis of randomized controlled trials assessed the risk of *Clostridioides difficile* infection, other enteric infections, and small intestinal bacterial overgrowth in adults receiving PPIs. In contrast to previous observational studies, no significant increase in infection risk was identified. These results provide high-quality evidence supporting the safety of PPIs when appropriately prescribed and contribute to a more balanced interpretation of their risk–benefit profile.

4. GRAPHICAL ABSTRACT

Therapeutic Effects of Acid-Suppressive Medications in Non-specific Chronic Cough:
Systematic Review and Meta-analysis



Adults with Non-specific Chronic Cough (Suspected Extra-Esophageal GERD)

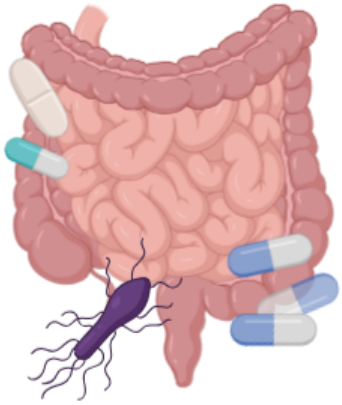
Proton Pump Inhibitors *vs.* **Placebo**

Improvement in **cough severity** (9 RCTs, 351 patients):
- SMD of 0.33 (CI: 0.05; 0.61), favoring PPIs
- Longer treatment durations were not associated with more marked symptomatic improvement

Improvement in **quality of life** (5 RCTs, 371 patients):
- SMD of 0.39 (CI: -0.51; 1.29)

Proton pump inhibitors can slightly decrease cough severity

Risk of Intestinal Dysbiosis in Patients Receiving Proton Pump Inhibitors:
Systematic Review and Meta-analysis



Risk of *Clostridioides difficile* infection (&other enteric infections, SIBO)

Proton Pump Inhibitors *vs.* **Non-users** (placebo, other drugs)

- Risk of CDI in **PPIs vs. placebo (8 RCTs,** 29,880 patients): RR=1.19, 95% CI: 0.75; 1.89
- Risk of CDI in **PPIs vs. H2RA** (4 RCTs, 27,254 patients): RR=0.72, 95% CI: 0.49; 1.07
- Risk of CDI in **PPIs vs. potassium channel acid blockers** (3 RCTs, 1,645 patients): RR=1.23, 95% CI: 0.43; 3.55

Proton pump inhibitors were **not** associated with an increased risk of *Clostridioides difficile* infection

5. INTRODUCTION

5.1. Acid-suppressive Medications for Extra-esophageal GERD

Non-specific chronic cough is commonly defined as a persistent cough for which a respiratory etiology or other known causes have been ruled out(1,2). It has a high global prevalence, estimated to be around 9.6%(3), with a significant negative impact on quality of life(4). The Montreal consensus recognizes this clinical entity as an extra-esophageal manifestation of gastro-esophageal reflux disease (GERD)(5). Epidemiologic studies report varying results, with GERD as the underlying disease in 10-41% of chronic cough patients(6). Together with asthma and post-nasal drip syndrome, GERD represents one of the three leading causes of chronic cough(6).

Given this association, acid-suppressive medications have been proposed as a therapeutic option in managing chronic cough after excluding other potential aetiologic factors. However, clinical studies investigating this intervention have yielded inconclusive results. A meta-analysis published in 2011 found insufficient data to support the beneficial effect of PPIs in patients with chronic cough(1). Even the most recent guidelines on this topic highlight the fact that the effect of acid-suppressive medication on extra-esophageal manifestations of GERD is still unclear(7–10).

5.2. Safety Profile of PPIs

Proton pump inhibitors (PPIs) rank among the most widely prescribed medications globally, and their usage is consistently on the rise(11,12). Data from a systematic literature review found that almost one in four adults were prescribed a PPI and 25% remained on acid-suppressive therapy for more than a year, with nearly one-third continuing treatment beyond three years(13). However, recent findings indicate that in over two-thirds of ambulatory patients, PPI use may be inappropriate, with no clearly documented indication for ongoing therapy(11,12,14).

Although generally considered a safe medication, PPIs have been reported to be associated with certain serious side effects, including an increased risk of intestinal dysbiosis(15). Previous meta-analyses have investigated the link between PPI treatment

and *Clostridioides difficile* infection (CDI), estimating up to twice as high odds in PPI users than in non-users(16–19). Proposed mechanisms explaining this association state that by lowering gastric acidity, PPIs may allow ingested bacteria to survive passage through the stomach and inhibit the normal conversion of salivary nitrite into reactive oxygen species that help suppress *Clostridioides difficile* spores(20). Following spore acquisition, outcomes can range from transient asymptomatic colonization to severe, life-threatening disease, including diarrheal syndrome, ileus, toxic megacolon, and even colonic perforation(21). It represents a significant challenge in clinical practice, as it remains the leading cause of hospital-acquired infections, responsible for up to 30,000 deaths in the United States annually(22,23).

Treatment with PPIs has also been hypothesised to increase the risk for developing small intestinal bacterial overgrowth (SIBO)(24). This is characterized by excessive bacterial proliferation in the small intestine, leading to various digestive symptoms, including bloating, gas, distension, and diarrhoea(25). It is estimated to be a prevalent, yet frequently overlooked condition, which can significantly impact the quality of life for those affected(26).

Notably, these conclusions were based only on observational data, which showed significant unexplained heterogeneity. The latest guidelines for managing gastroesophageal reflux disease elaborated by the American College of Gastroenterology also advocate caution in interpreting these findings(9). Furthermore, results from recent large-scale trials do not seem to substantiate these associations(27,28), and none of the previously published systematic reviews addressed this association in the context of randomised controlled trials (RCTs).

6. OBJECTIVES

6.1. Study I. – Therapeutic Effects of Acid-Suppressive Medications in Adults with Non-specific Chronic Cough: Systematic Review and Meta-analysis

The effect of acid-suppressive medication on extra-esophageal manifestations of GERD is still unclear(7–10). In the context of this knowledge gap, we aimed to assess the effects of acid-suppressive medications in adults with non-specific chronic cough, based on placebo-controlled randomized trials. Additionally, we set out to investigate the impact on quality of life.

6.2. Study II. – Risk of Intestinal Dysbiosis in Adults Receiving Treatment with Proton Pump Inhibitors: Systematic Review and Meta-analysis

Although generally considered a safe medication, PPIs have been reported to be associated with certain serious side effects, including an increased risk of intestinal dysbiosis(15). Notably, these conclusions were based only on observational data, which showed significant unexplained heterogeneity. Given the contradictory nature of the available data, we aimed to assess the risk of developing intestinal dysbiosis, more specifically CDI, other enteric infections, and small intestinal bacterial overgrowth, among adults receiving PPIs compared to non-users, based on data reported by RCTs.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

This was a systematic review and meta-analysis conducted following the recommendations of the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines(29,30). The study protocol was prospectively registered on PROSPERO (CRD42022368769) and fully adhered to.

7.1.2. Eligibility Criteria

We used the PICO (Population, Intervention, Comparator, Outcome) framework to define the eligibility criteria. The population was comprised of adult patients with non-specific chronic cough, defined as a persistent cough for which a respiratory etiology or other known causes had been excluded. Any definition for the duration of chronic cough provided by the primary studies was accepted. The intervention was acid-suppressive medication, irrespective of dose, administration frequency, or treatment duration, with placebo as the comparator. The outcomes of interest were the impact on cough severity and quality of life, assessed by comparing the means of change in questionnaire scores. Only RCTs were included. Conference abstracts were considered eligible for inclusion if they reported data on the outcomes of interest. No restrictions were applied in terms of gender or ethnicity. We excluded studies with inappropriate study design, pediatric population, and those which did not report cough severity or quality of life as an outcome.

7.1.3. Information Sources and Search Strategy

The systematic search was conducted on the 1st of November 2022 in three medical databases: MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). No restrictions were applied. Additionally, backward and forward citation searching was conducted on the 29th of November 2022, to identify other potentially relevant publications(31).

The search key was comprised of three domains: cough, acid-suppressive medication, and the concept of randomization. The detailed search key was as follows: (cough or

(laryngopharyngeal reflux) OR (LPR) or (reflux laryngitis)) AND ((acid suppress*) or (pump inhibitor) OR (ppi) OR rabeprazole OR lansoprazole OR dexlansoprazole OR pantoprazole OR esomeprazole OR omeprazole OR tenatoprazole OR (h2 receptor antagonist) OR (histamine receptor antagonist) OR (h2 blocker) OR (H2RA) OR ranitidine OR famotidine OR nizatidine or cimetidine OR revaprazan OR vonoprazan OR tegoprazan) AND (random* or RCT).

7.1.4. Study Selection and Data Extraction

The articles found through the systematic search were imported into a reference management program. Removal of duplicate entries was performed automatically and manually by overlapping the authors, titles, and publication years. Two independent reviewers (D.E.I. and S.B.K.) carried out the screening and selection process, first by title and abstract, then by full text. On both levels of selection, Cohen's kappa coefficient (κ) was calculated as a measure of inter-reviewer agreement(32). In case of conflict, a consensus was reached after discussing with a third investigator (M.O.).

Relevant information from the included articles were independently extracted by two authors (D.E.I. and S.B.K.). A third reviewer (M.O.) resolved any disagreement. Data were manually collected and entered into an Excel table (Office 365, Microsoft, USA) as preparation for statistical analysis. The following information was extracted: name of the first author, year of publication, Digital Object Identifier (DOI), country, study period and design, number of involved centers, detailed description of the study population, demographic information, details on the intervention (type of medication, dose, frequency of administration, duration of treatment), data on cough severity and quality of life (score values at baseline and at the end of treatment and/or the mean change), as well as details about the scale or scoring system used to assess them. For papers that reported information on the severity of cough or quality of life scores at multiple time points in the study, data was collected for all time points. Only data from the first period (before the switch to a different study arm) was used from cross-over studies, given the potential carry-over effect. In order to assess the effects of acid-suppressive medication on cough severity in patients with laryngopharyngeal reflux, we only selected the symptom sub-scores pertaining to cough (not the overall scores).

7.1.5. Risk of Bias and Quality of Evidence Assessment

Two reviewers (D.E.I. and S.B.K.) independently assessed the risk of bias using the 'Revised Cochrane Risk-of-bias Tool for Randomized Trials' (RoB 2)(33). Any disagreements were resolved by discussion with a third reviewer (M.O.). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach(34) and the GRADEpro tool (software) to evaluate the quality of evidence of the results.

7.1.6. Data Synthesis and Analysis

Standardized mean difference (SMD, as Hedges' g(35)) with its 95% confidence interval (CI) was used for the effect size measure. The mean, standard deviation (SD) or standard error of mean (SEM), and additionally the sample sizes were extracted, both for control and experimental groups. We reported the SMD of acid-suppressive medications compared to the placebo group using the estimated differences in cough severity and quality of life scores, from baseline to the end of treatment. As considerable between-study heterogeneity was expected, a random-effects model was used in order to pool effect sizes.

The inverse variance weighting method was used for pooling SMDs. To estimate the heterogeneity variance measure τ^2, the restricted maximum-likelihood estimator with the Q profile method for CI(36) was applied. We used a Hartung-Knapp adjustment(37,38) for CIs (if it provided a more conservative estimation compared to the classical approach, as recommended by Jackson et al.(39), as hybrid method) and prediction intervals. Additionally, between-study heterogeneity was described by means of Cochrane Q test, and the Higgins and Thompson's I^2 statistics(40).

For subgroup analyses we employed a fixed-effects "plural" model (i.e. mixed-effects model). It was assumed that all subgroups shared a common τ^2 value, as we did not anticipate differences in between-study heterogeneity in the subgroups. Moreover, the number of studies was relatively small in some subgroups. In order to assess the differences, the Cochrane Q test (an omnibus test) was used between subgroups(41). The null hypothesis was rejected on a 5% significance level. Subgroup analysis was performed based on patient population, comparing participants presenting with chronic

cough only and subjects with laryngopharyngeal reflux, which can present with accompanying chronic coughing. Results were graphically summarized using forest plots and scatter plots (for the time dependency analysis).

Outlier and influence analyses were performed following the recommendations of Harrer et al.(41) and Viechtbauer et al.(42). For assessing the small study publication bias, visual inspection of funnel-plots was carried out. Additionally, we reported the Pustejovsky test p-value(43), although it has limited diagnostic assessment below 10 studies. We performed influence analyses for the correlation coefficient assumption, used for estimating the differences from baseline to the end of treatment.

All statistical analyses were performed using the R software v4.3.0 (R Core Team, 2019, Vienna, Austria), using the meta (v6.5.0)(44), metafor (v4.2.0)(45) and dmetar (v0.0.9000)(46) packages.

7.2. Study II.

7.2.1. Methodology and Protocol

The second study was also a systematic review and meta-analysis. The protocol was prospectively registered on PROSPERO (CRD42023403322) and fully adhered to.

7.2.2. Eligibility Criteria

Eligibility criteria were defined using the PICO framework. The population comprised adult patients (over 18 years old) without limitations based on gender or ethnicity. The intervention was treatment with PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole), regardless of dose, administration route, frequency, or treatment duration. The comparison group comprised non-users who received either a placebo or different pharmaceuticals (for comparative risk assessment, we included other acid-suppressive agents, such as histamine-2 receptor antagonists and potassium-competitive acid blockers; should any medication class demonstrate an elevated risk, specific recommendations favouring an alternative agent could be formulated). Rates of CDI, other enteric infections, and SIBO were the outcomes of interest. Only RCTs were considered eligible for inclusion. We excluded studies involving paediatric populations and those lacking data on specified outcomes.

7.2.3. Information Sources and Search Strategy

On April 15th, 2025, a systematic search was performed across three medical databases: MEDLINE (via PubMed), Embase, and CENTRAL. No language or other restrictions were applied. No filters were used during the search. The detailed search key was as follows: ((pump inhibitor) OR PPI OR rabeprazole OR lansoprazole OR dexlansoprazole OR pantoprazole OR esomeprazole OR omeprazole OR tenatoprazole OR ilaprazole) AND random*.

7.2.4. Study Selection and Data Extraction

Two reviewers (D.E.F. and S.B.K.) independently screened and selected potentially relevant articles, initially assessing titles and abstracts, followed by a review of full texts. In case of disagreement, consensus was reached through consultation with a third investigator (M.O.).

Two authors (D.E.F. and S.B.K.) independently extracted information from the included studies. A third reviewer (M.O.) resolved any disagreements. The following data were extracted from studies: name of first author, year of publication, digital object identifier (DOI), country, study design, number of involved centres, detailed description of the study population, basic demographics, details of intervention, and comparator (type of medication, dose, frequency of administration, and duration of treatment), follow-up time, data on rates of CDI, other enteric infections, and SIBO in the experimental and control groups, and details of definitions of outcomes of interest. Only information from the first study period was collected for cross-over trials, given the potential for a carry-over effect.

7.2.5. Risk of Bias and Quality of Evidence Assessment

Two reviewers (D.E.F. and S.B.K.) independently evaluated the risk of bias using the RoB2(33). Any discrepancies were resolved by a third reviewer (M.O.). We employed the GRADE approach, using the GRADEpro tool (software)(34) to evaluate the quality of evidence.

7.2.6. Data Synthesis and Analysis

A random-effects model was used to pool effect sizes. The risk ratio (RR) with a 95% CI was the main effect size measure. We extracted the total number of patients and events in each group from the publications to calculate the RRs, reporting the risk in the experimental group compared to the control group. We summarized the findings of the meta-analysis in forest plots.

Heterogeneity was described by the between-study variance (τ^2) and Higgins and Thompson's I^2 statistics(40).

Potential publication bias was assessed by visual inspection of funnel plots and calculating the Harbord (modified Egger's) test p-value(47). We considered the possibility of small study bias if the p-value was below 10% while recognizing the limited utility of the test with fewer than ten studies.

Potential outlier publications were identified using various influence measures and plots following the recommendations of Harrer et al.(41)

All analyses were performed using R software(48), utilizing the *meta*(44) package for basic calculations and plots and the *dmetar*(46) package for additional influential analyses.

8. RESULTS

8.1. Study I.

8.1.1. Search, Selection and Study Characteristics

The systematic search yielded 1804 articles through the three medical databases, with 291 entries in MEDLINE (via PubMed), 1235 in Embase, and 278 in CENTRAL. Following duplicate removal, 1393 articles remained for the title and abstract selection. After the screening, 19 studies were sought for full-text evaluation (κ=0.94), of which one record could not be retrieved. In total, 18 articles were assessed for eligibility, out of which seven were excluded(49–55) (κ=1). 11 studies were finally included in the analysis(56–66). The details of the search and selection process are presented in the PRISMA 2020 flow chart (**Figure 1**).

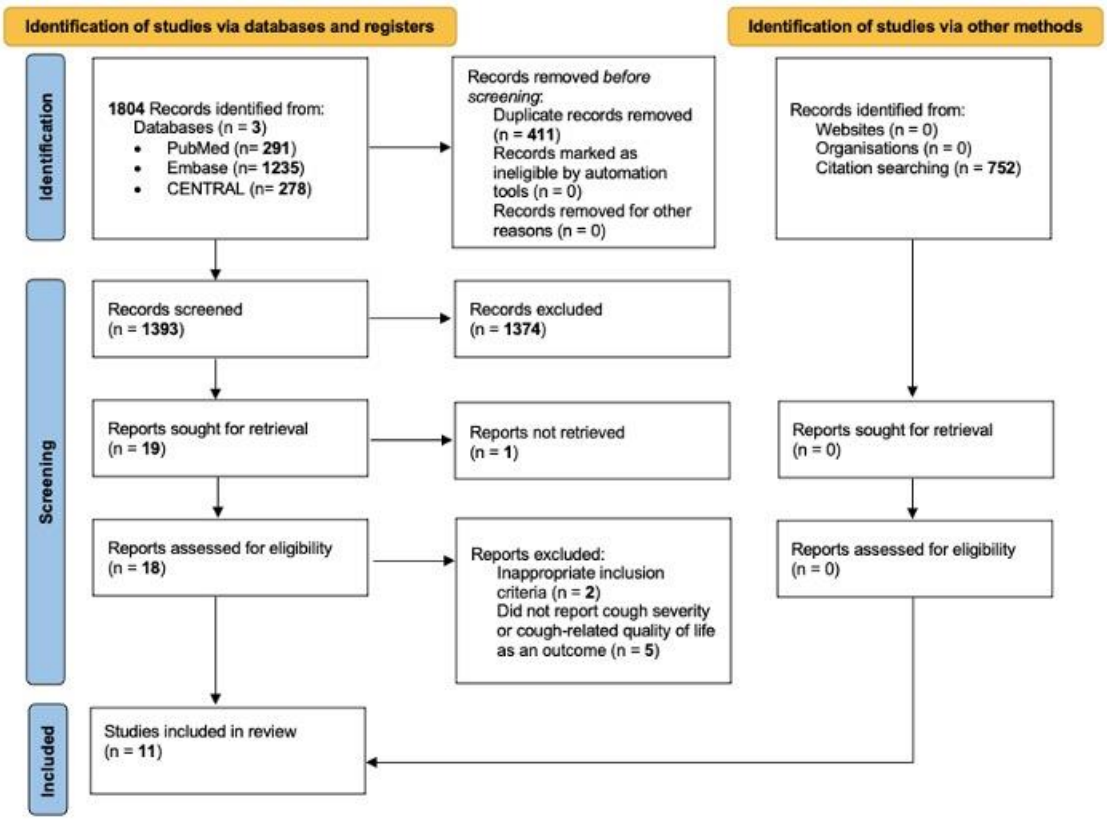


Figure 1. PRISMA 2020 flow chart detailing the search and selection process.

All the included articles were double-blinded placebo-controlled RCTs. Four studies were conducted in Europe, four in North America, two in Asia, and one in Australia. Regarding

the study population, four articles included adults presenting with non-specific chronic cough only, while the other seven studies focused on patients with laryngopharyngeal reflux (which can manifest as persistent cough). All articles used PPIs with various doses, treatment durations, and frequencies of administration. Data on the impact on cough severity were reported in nine studies, while information on changes in the quality of life was found in five articles. In total, 612 participants were included in the analyses. The basic characteristics of the studies are presented in **Table 1**.

Table 1. Basic characteristics of the included studies.

Author, Year	Country	Population	№ of patients (female%)	Mean age (years)	Intervention	Outcome and scoring system (best to worst possible values)
Faruqi et al.(56), 2011	UK	Chronic cough >8 weeks	51 (64.0)	58.1	Esomeprazole 20mg b.i.d. for 8 weeks	Cough severity: Numerical scale for severity of cough (0-9); Quality of life: Leicester Cough Questionnaire (21-3)
Kiljander et al(57), 2000	Finland	Chronic cough >8 weeks	29 (65.5)	49	Omeprazole 40mg o.d. for 8 weeks	Cough severity: Weekly cough score (0-21)
Park et al.(59), 2017	Korea	Chronic cough >8 weeks	41 (51.9)	48.1	Esomeprazole 40mg o.d./b.i.d. for 8 weeks	Cough severity: Visual Analogue Scale (0-10); Quality of life: Leicester Cough Questionnaire (21-3)
Shaheen et al.(60), 2011	USA	Chronic cough >8 weeks	40 (78.0)	50	Esomeprazole 40mg b.i.d. for 12 weeks	Cough Severity: Cough Severity Score (0-4); Quality of life: Cough-Specific Quality of Life Questionnaire (28-112)

Fass et al.(61), 2010	USA	LPR	41 (41.5)	65.1	Esomeprazole 20mg b.i.d. for 12 weeks	Quality of life: Laryngopharyngeal Reflux Health-Related Quality of Life Questionnaire – Cough section (0-36)
Havas et al.(62), 1999	Australia	Posterior pharyngo-laryngitis	15 (53.3)	53.6	Lansoprazole 30mg b.i.d. for 12 weeks	Cough severity: Cough score (0-7)
Lam et al.(63), 2010	China	LPR	82 (72.0)	46.8	Rabeprazole 20mg b.i.d. for 12 weeks	Cough severity: Reflux Symptom Index – Troublesome or annoying cough section (0-5)
Noordzij et al.(64), 2001	USA	LPR	30 (46.6)	48.5	Omeprazole 40mg b.i.d. for 8 weeks	Cough severity: Cough symptom score (0-1400)
Reichel et al.(65), 2008	Germany	LPR	62 (48.4)	48.7	Esomeprazole 20mg b.i.d. for 12 weeks	Cough severity: Reflux Symptom Index – Troublesome or annoying cough section (0-5)
Steward et al.(66), 2004	USA	LPR	42 (71.4)	49.3	Rabeprazole 20mg b.i.d. for 8 weeks	Cough severity: Dry Cough Symptom Questionnaire (0-8)

Wilson et al.(58), 2021	UK	Persistent throat symptoms (including unexplained night-time chronic cough >6weeks)	346 (57.0)	52.2	Lansoprazole 30mg b.i.d. for 16 weeks	Quality of Life: Laryngopharyngeal Reflux Health-Related Quality of Life Questionnaire – Cough section (0-36)

(o.d. – *omne in die*, once daily; b.i.d. – *bis in die*, twice daily; LPR – laryngopharyngeal reflux)

8.1.2. Primary Outcome

The primary outcome was represented by the mean change in cough severity. Nine studies reported data on the severity of cough, totaling 351 patients(56,57,59,60,62–66). For articles that reported values at multiple time points in the study, data from the end of the treatment periods were used in the calculations. The analysis of the overall change in cough severity found an SMD of 0.33 (CI: 0.05; 0.61), favoring PPIs (**Figure 2**).

Subgroup analysis was performed based on patient population. Four articles included adults presenting with non-specific chronic cough only(56,57,59,60), while the other five studies investigated patients with laryngopharyngeal reflux(62–66). In the subgroup of almost 130 participants with persistent cough only, the SMD was 0.37 (CI: -0.50; 1.24). In the laryngopharyngeal reflux subgroup, which totaled more than 220 patients, the SMD was 0.31 (CI: -0.02; 0.64). There was no statistically significant difference between the two subgroups.

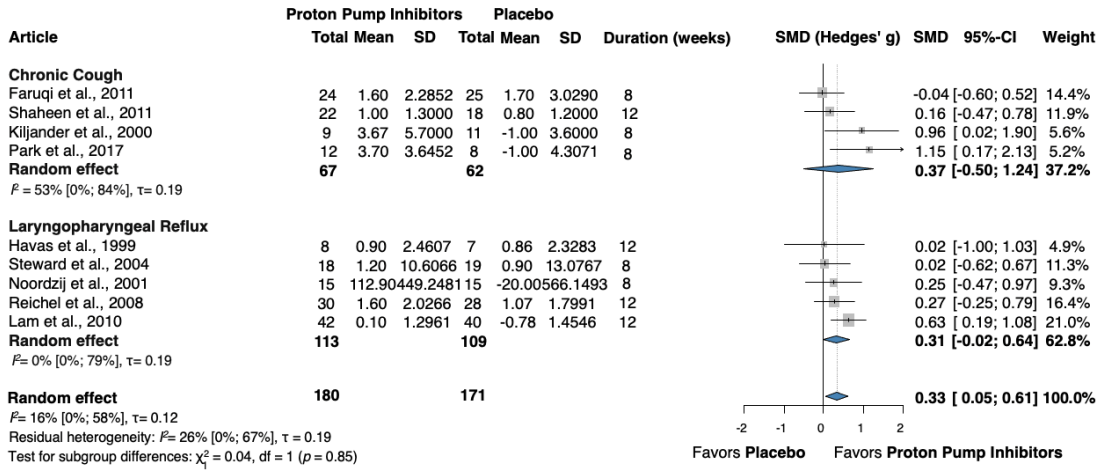


Figure 2. Forest plot demonstrating the change in mean cough severity in adults with chronic cough receiving treatment with proton pump inhibitors, compared to placebo – including subgroup analysis (*SMD, standardized mean difference; RSI, Reflux Symptom Index; CI, confidence interval; SD, standard deviation*).

The time dependency analysis found that longer treatment durations were not associated with more marked symptomatic improvement (**Figure 3**). The estimated SMDs were 0.33

(CI: -0.22; 0.88), 0.31 (CI: -1.74; 2.35), 0.32 (CI: -0.29; 0.93), 0.34 (CI: -0.16; 0.85) following 4, 6, 8 and 12 weeks of acid-suppressive therapy, respectively.

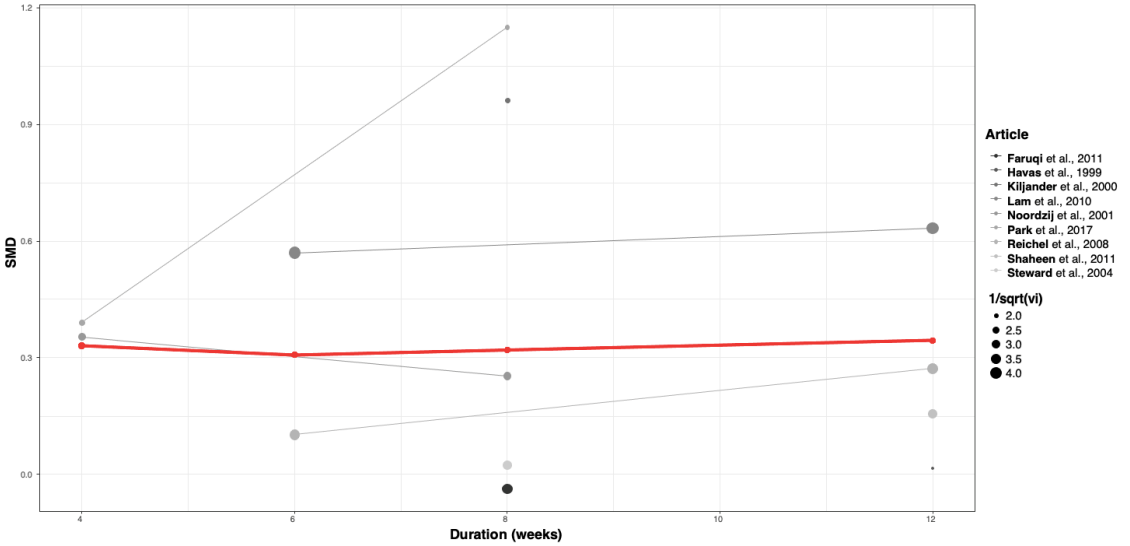


Figure 3. Time dependency analysis: improvement in mean cough severity according to the duration of acid-suppressive treatment with proton pump inhibitors (Y-axis shows the change in cough severity expressed as SMD – *standardized mean difference*; the X-axis shows the duration of acid-suppressive therapy in weeks. The point size represents the imprecision of articles expressed as the reciprocal of the sampling standard deviation).

8.1.3. Secondary Outcome

Five studies investigated the impact of PPIs on the quality of life of adults with non-specific chronic cough compared to placebo, totaling 371 patients(56,58–61). The pooled analysis found an SMD of 0.39 (CI: -0.51; 1.29) (**Figure 4**).

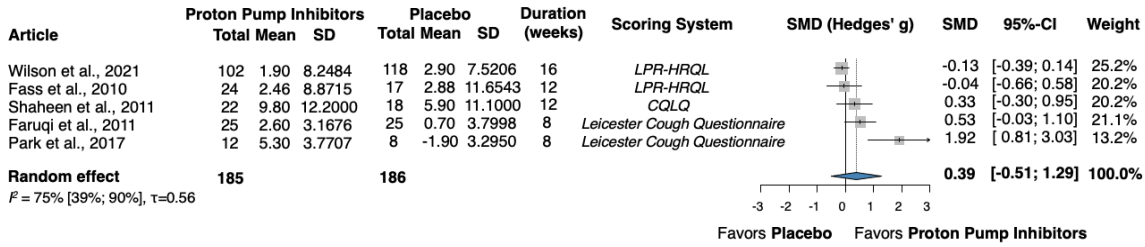


Figure 4. Forest plot demonstrating the change in mean quality of life in adults with chronic cough receiving treatment with proton pump inhibitors, compared to placebo (*SMD, standardized mean difference; LPR-HRQL, laryngopharyngeal reflux-health-*

related quality of life; CQLQ, cough-related quality of life questionnaire; CI, confidence interval; SD, standard deviation).

8.1.4. Heterogeneity

The heterogeneity was relatively low in the analysis of the overall change in cough severity (16%; CI: 0%; 58%). In order to assess the robustness of conclusions concerning the pooled effect sizes, leave-one-out sensitivity analysis was performed. It found that the study by Lam et al. (63) may have a more considerable impact on the estimation of the overall effect compared to the other articles. The omission of this study resulted in a change in SMD from 0.33 (CI: 0.05; 0.61) to 0.24 (CI: -0.05; 0.54).

In assessing the change in the cough-related quality of life following acid suppressive therapy compared to placebo, the heterogeneity was substantial (75%; CI: 39%; 90%). According to the leave-one-out sensitivity analysis, the research of Park et al.(59) may have a greater influence on the assessment of the total effect than the other publications. When this trial was omitted, the SMD changed from 0.39 (CI: -0.51; 1.29) to 0.11 (CI: -0.39; 0.62).

8.1.5. Risk of bias assessment

When the assessed outcome was cough severity, there were some concerns regarding the risk of bias in five of the articles(57,62,64–66)(**Figure 5)**. Three were considered to be at low risk for bias(56,60,63), while in one of the studies, the risk of bias was deemed high(59). Regarding the quality of life, the risk of bias was considered low in three articles(56,58,60) and high in the remaining two studies(59,61)(**Figure 6)**.

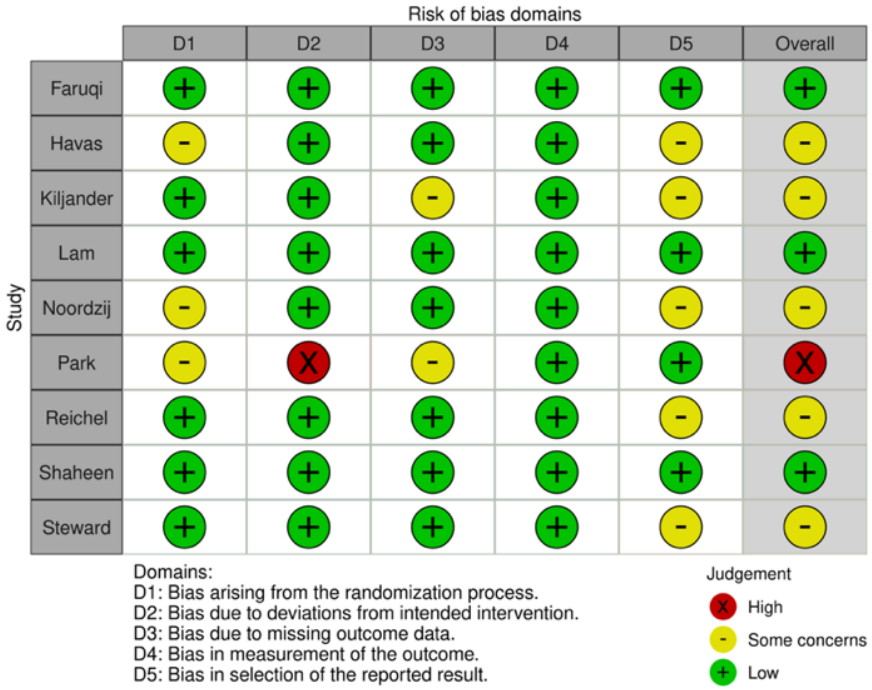


Figure 5. Risk of bias assessment results for cough severity in individual studies.

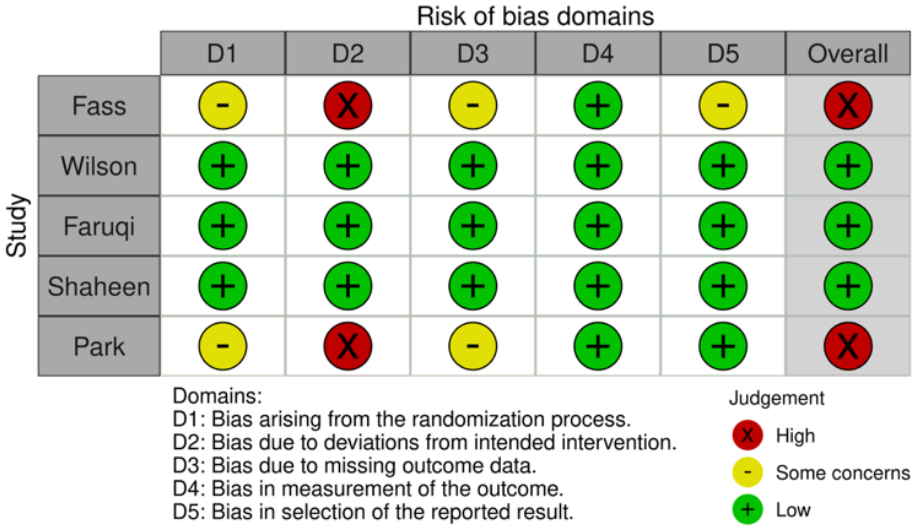


Figure 6. Risk of bias assessment results for quality of life in individual studies.

8.2. Study II

8.2.1. Search, Selection and Study Characteristics

The systematic literature search resulted in 36,443 articles identified across three medical databases: 8,723 entries in MEDLINE (via PubMed), 17,902 in Embase, and 9,818 in CENTRAL. After duplicate removal, 21,793 articles remained for the title and abstract selection. After screening, we selected 1,006 studies for full-text evaluation (κ=0.94), with 132 unretrievable publications. Finally, 19 articles were considered eligible for inclusion (κ=0.90) (**Figure 7**).

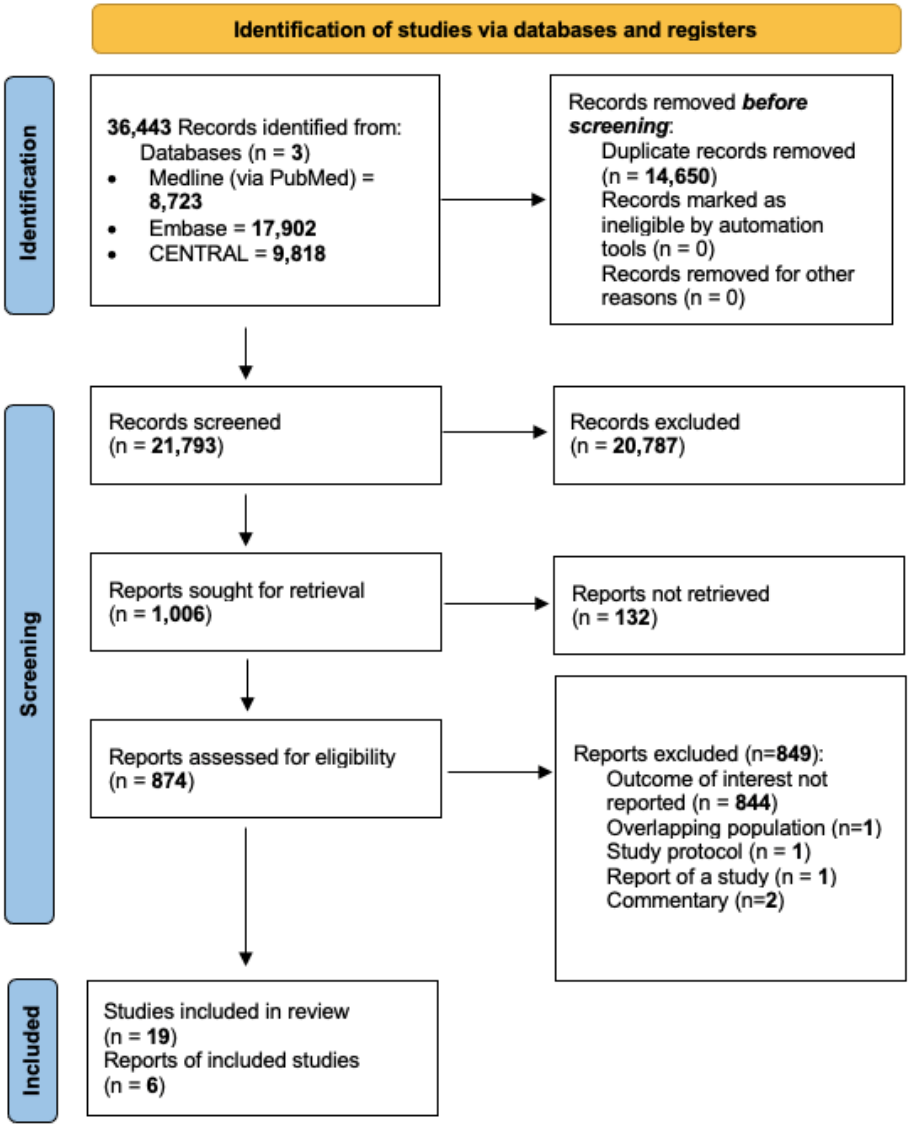


Figure 7. PRISMA Flowchart detailing the search and selection process.

The basic characteristics of the included studies are detailed in **Table 2.** All publications included were RCTs, of which 15 were multicentre studies. The authors compared the effect of PPIs to either a placebo, a histamine H2-receptor antagonist (H2RA) (cimetidine, famotidine), or a potassium-competitive acid blocker (vonoprazan). The articles eligible for inclusion used different dosages of PPIs and various treatment durations and administration frequencies. In terms of treatment indication, seven of the articles evaluated the effect of stress ulcer prophylaxis(28,67–72), four assessed patients on anticoagulants or antiplatelet medications for the prophylaxis of gastrointestinal bleeding(27,73–75), three investigated the healing of esophagitis(76–78), and the other two looked at the impact on peptic ulcer disease(79,80). The three remaining articles had various patient populations of interest, such as severe acute pancreatitis(81), individuals with hemochromatosis to assess the need for phlebotomy(82), and *Helicobacter pylori* eradication with or without acid suppression(83). In terms of outcomes, 15 of the studies reported data on the rates of CDI(27,28,67–76,78,79,83), four looked at other enteric infections(27,74,77,82), and two articles assessed the rates of SIBO(80,81).

Table 2. Basic characteristics of included studies.

Author, year	Age (years)		Intervention	Comparator	Indication	Outcome of interest
	Intervention	Comparator				
Alhazzani et al., 2017(67)	Median 61.8 (IQR 48.4-73.5)	Median 55.3 (IQR 42.2-65.5)	Pantoprazole 40mg iv once daily	Placebo	Stress ulcer prophylaxis	*Clostridioides difficile* infection
Bhatt et al., 2010(73)	Median 68.5 (IQR 60.7-74.4)	Median 68.7 (IQR 60.6-74.7)	Omeprazole 20mg po once daily	Placebo	Bleeding prophylaxis in patients with dual antiplatelet therapy	*Clostridioides difficile* infection
El-Kersh et al., 2018(68)	Median 62 (IQR 49.5-68)	Median 58 (IQR 40.5-66.5)	Pantoprazole 40mg iv once daily	Placebo	Stress ulcer prophylaxis	*Clostridioides difficile* infection
Krag et al., 2018(69)	Median 67 (IQR 56-75)	Median 67 (IQR 55-75)	Pantoprazole 40mg iv once daily	Placebo	Stress ulcer prophylaxis	*Clostridioides difficile* infection

Moayyedi et al., 2018(27)	Mean 67.6 (SD 8.1)	Mean 67.7 (SD 8.1)	Pantoprazole 40mg po once daily	Placebo	Bleeding prophylaxis in patients with aspirin or anticoagulant treatment	*Clostridioides difficile* infection, Other enteric infections
Selvanderan et al., 2016(70)	Mean 52 (SD 18)	Mean 52 (SD 17)	Pantoprazole 40mg iv once daily	Placebo	Stress ulcer prophylaxis	*Clostridioides difficile* infection
Cook et al., 2024(28)	Mean 58.2 (SD 16.4)	Mean 58.3 (SD 16.4)	Pantoprazole 40mg iv once daily	Placebo	Stress ulcer prophylaxis	*Clostridioides difficile* infection
Chen et al. (ABSTRACT), 2022(74)	NA	NA	PPI	H2blocker/ Control	Bleeding prophylaxis in patients with acute coronary syndrome	Enteric infections
Wong et al., 2020(79)	Mean 67.6 (SD 16.3)	Mean 69.6 (SD 15.8)	Lansoprazole 30mg po once daily	Famotidine 40mg po once daily	Recurrent idiopathic ulcer	*Clostridioides difficile* infection

					bleeding prophylaxis	
Young et al., 2020(71)	Mean 58.6 (SD 17)	Mean 58.2 (SD 17.1)	PPI	H2blocker	Stress ulcer prophylaxis	*Clostridioides difficile* infection
Wee et al. (ABSTRACT), 2013(72)	NA	NA	Pantoprazole 40mg iv once daily	Famotidine 20mg iv twice daily	Stress ulcer prophylaxis	*Clostridioides difficile* infection
Kawai et al., 2017(75)	Mean 68.3 (SD 9.06)	Provided for each Vonoprazan group	Lansoprazole 15mg po once daily	Vonoprazan 10/20mg po once daily/	Bleeding prophylaxis in patients with a personal history of peptic ulcer and low-dose aspirin treatment	*Clostridioides difficile* infection
Laine et al., 2023(76)	Mean 51.7 (SD 14.1)	Mean 51 (SD 13.4)	Lansoprazole 30mg po once daily	Vonoprazan 20mg po once daily	Healing of Erosive Esophagitis	*Clostridioides difficile* infection
Uemura et al., 2025(78)	Mean 61.5 (SD 12.2)	Mean 60.4 (SD 11.8)	Lansoprazole 30mg po once daily	Vonoprazan 20mg po once daily	Maintenance treatment for	*Clostridioides difficile* infection

					Erosive Esophagitis	
De Boer et al., 1995(83)	Mean 51.7	Mean 50.9	Triple therapy + Omeprazole 20mg po twice daily	Triple therapy alone (no PPI)	*Helicobacter pylori* eradication with or without acid suppression	*Clostridioides difficile* infection
Ashida et al., 2015(77)	Mean 55.8 (SD 13.92)	Provided for each Vonoprazan group	Lansoprazole 30mg po once daily	Vonoprazan 5/10/20/40 mg po once daily	Healing of Erosive Esophagitis	Other enteric infections
Vanclooster et al., 2017(82)	Mean 57.53 (SD 6.51)	Mean 53 (SD 10.5)	Pantoprazole 40mg po once daily	Placebo	Patients with hemochromatosis, assessing the need for phlebotomy	Other enteric infections
Ma et al., 2020(81)	Mean 46.12 (SD 11.14)	Mean 44.55 (SD 9.29)	Esomeprazole 40mg iv once daily	Conventional treatment	Severe acute pancreatitis	SIBO

Thorens et al., 1997(80)	NA	NA	Omeprazole 20mg po once daily	Cimetidine 800mg po once daily	Peptic disease	SIBO

(iv, intravenously; po, per orally; NA, not available; IQR, interquartile range; SD, standard deviation; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth)

8.2.2. Quantitative Synthesis

Risk of Developing CDI in PPIs versus Placebo

Eight RCTs(27,28,67–70,73,74) totalling 29,880 patients (14,946 in the PPI group, 14,934 in the placebo group) investigated the rates of CDI in individuals receiving treatment with PPIs compared to placebo. Our analysis found no significant difference in the risk of developing CDI between the two study groups (RR=1.19, 95% CI: 0.75; 1.89, I^2=0%) (**Figure 8**). Low incidence rates of CDI were reported, with 60 cases in 14,946 participants undergoing acid-suppressive therapy with PPIs (0.40%). To a similar extent, 49 cases were diagnosed out of 14,934 subjects (0.33%) receiving placebo.

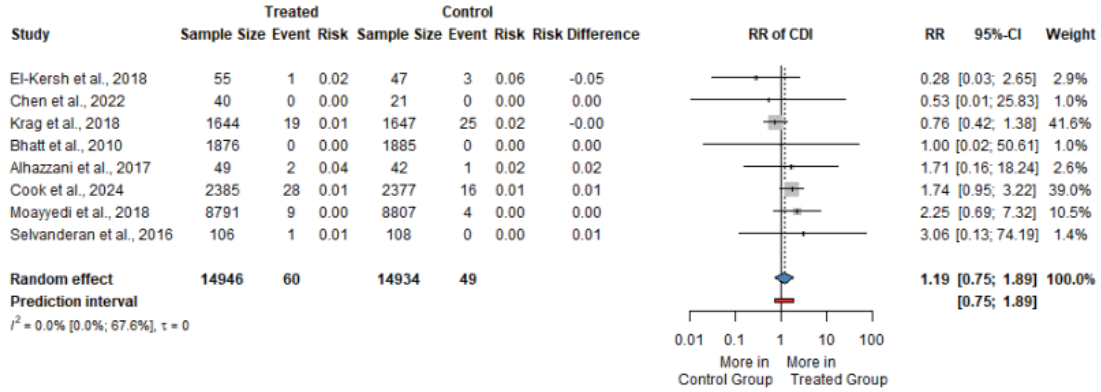


Figure 8. Forest plot showing the risk of developing *Clostridioides difficile* infection in patients receiving proton pump inhibitors compared to placebo (RR, risk ratio; CI, confidence interval; CDI, *Clostridioides difficile* infection).

Risk of Developing CDI in PPIs versus H2-Receptor Antagonists

Four studies(71,72,74,79) compared 27,254 patients treated with PPIs to H2RA (13,658 in the PPI group, 13,596 in the H2RA). The meta-analysis did not find a significant difference in the risk of developing CDI between the two study groups (RR=0.72, 95% CI: 0.49; 1.07, I^2=0%) (**Figure 9**). The incidence rates of CDI were low, with 43 cases among 13,658 participants receiving PPIs (0.32%) and 59 cases out of 13,598 subjects (0.43%) receiving H2RA.

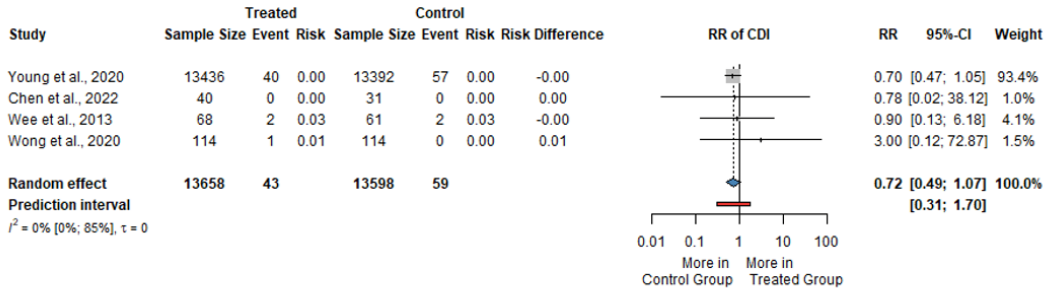


Figure 9. Forest plot showing the risk of developing *Clostridioides difficile* infection in patients receiving proton pump inhibitors compared to H2 receptor antagonists (RR, risk ratio; CI, confidence interval; CDI, *Clostridioides difficile* infection).

Risk of Developing CDI in PPIs versus Potassium-Channel Acid Blockers

Three RCTs(75,76,78) reported data on the incidence of CDI in individuals undergoing PPI therapy compared to vonoprazan. The meta-analytical calculations did not show a significant difference in the risk of developing CDI between the two study groups (RR=1.23, 95% CI: 0.43; 3.55, I^2=0%) (**Figure 10**).

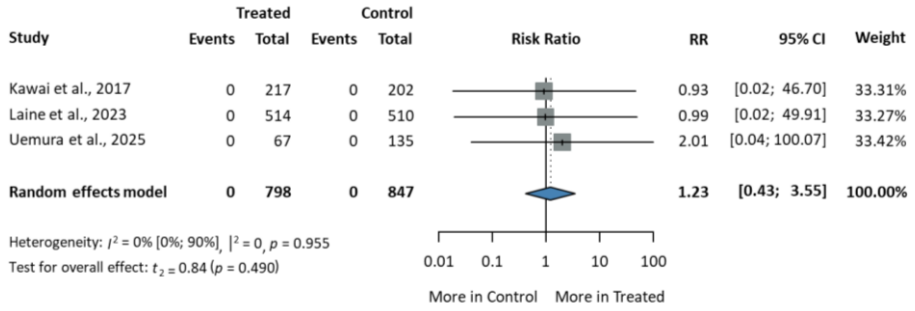


Figure 10. Forest plot showing the risk of developing *Clostridioides difficile* infection in patients receiving proton pump inhibitors compared to potassium-competitive acid blockers (RR, risk ratio; CI, confidence interval; CDI, *Clostridioides difficile* infection).

8.2.3. Qualitative Synthesis

Risk of Other Enteric Infections in PPIs versus Placebo

Three RCTs(27,74,82) reported data on the other enteric infections in patients treated with PPIs compared to placebo. A study by Moayyedi et al.(27) had a median follow-up

time of around three years and reported low incidence rates of enteric infections. There were 119 cases diagnosed in 8,791 (1,4%) individuals undergoing PPI treatment and 90 cases in 8,807 (1%) subjects receiving placebo (RR=1.33, 95% CI: 1.01–1.75). Vanclooster et al.(82) included 15 patients in each study arm and reported only one instance of enteric infection in the PPI-treated group. Chen et al.(74) assessed 61 patients, 40 receiving PPI therapy and 20 in the control arm, and reported no cases of enteric infection in the study population.

Risk of Other Enteric Infections in PPIs versus H2-Receptor Antagonists

Only one study provided information on this outcome. Chen et al.(74) conducted a comparative analysis involving 40 individuals receiving PPI treatment and 31 undergoing therapy with H2RA. No occurrences of enteric infections were observed in either study arm.

Risk of Other Enteric Infections in PPIs versus Potassium-Channel Acid Blockers

A study by Ashida et al.(77) totaling 732 participants compared the effects of lansoprazole to various doses of vonoprazan (5, 10, 20, and 40mg orally daily) for the treatment of erosive esophagitis, with an 8-week follow-up period. Only one case of enteric infection occurred in the study arm, with 40mg of vonoprazan daily.

Risk of SIBO in PPIs versus non-PPIs

Two RCTs(80,81) investigated the rates of SIBO in subjects undergoing treatment with PPIs. Ma et al.(81) studied the effect of acid suppression on duodenal microbiota in 66 patients with severe acute pancreatitis, comparing added esomeprazole to conventional therapy alone (33 in the PPI group and 33 in the conventional treatment group). Duodenal bacterial overgrowth was defined as $>10^3$ colony-forming units per milliliter (CFU/mL). In aerobic cultures, 29 out of 33 patients receiving PPIs met this criterion versus only 15 in the conventional group (RR=1.93, 95% CI: 1.30; 2.86). Anaerobic cultures showed 28 cases in the PPI group compared to 14 in the conventional group (RR=2.95% CI: 1.31; 3.05). Using a $>10^5$ CFU/mL threshold, we identified 20 cases in subjects undergoing PPI therapy, compared to 8 in the conventional treatment group in aerobic cultures (RR=2.5, 95% CI: 1.28; 4.85). Similar results were found in anaerobic cultures, with 20 cases in

the acid-suppressive group versus 7 in the conventional treatment group (RR=2.86, 95% CI: 1.4; 5.83). Thorens et al.(80) assessed 37 patients with peptic disease, randomly assigned to either omeprazole or cimetidine. The prevalence of duodenal bacterial overgrowth, defined as surpassing 10^5 CFU/ml in aerobic cultures, was higher in individuals receiving PPIs compared to H2RA (7 out of 19 patients in the PPI study arm versus 3 out of 18 participants receiving cimetidine; RR=2.21, 95% CI: 0.67; 7.25, *P*=0.19).

8.2.4. Risk of bias assessment

Concerns about the risk of bias were raised in most of the studies included, whereas some publications exhibited a high risk of bias. Notably, several studies lacked a pre-published protocol or statistical analysis plan, prompting concerns about the selection of reported results. Another critical issue was insufficient details on the definition and diagnosis of outcomes of interest. For a detailed assessment, see **Figures 11-13.**

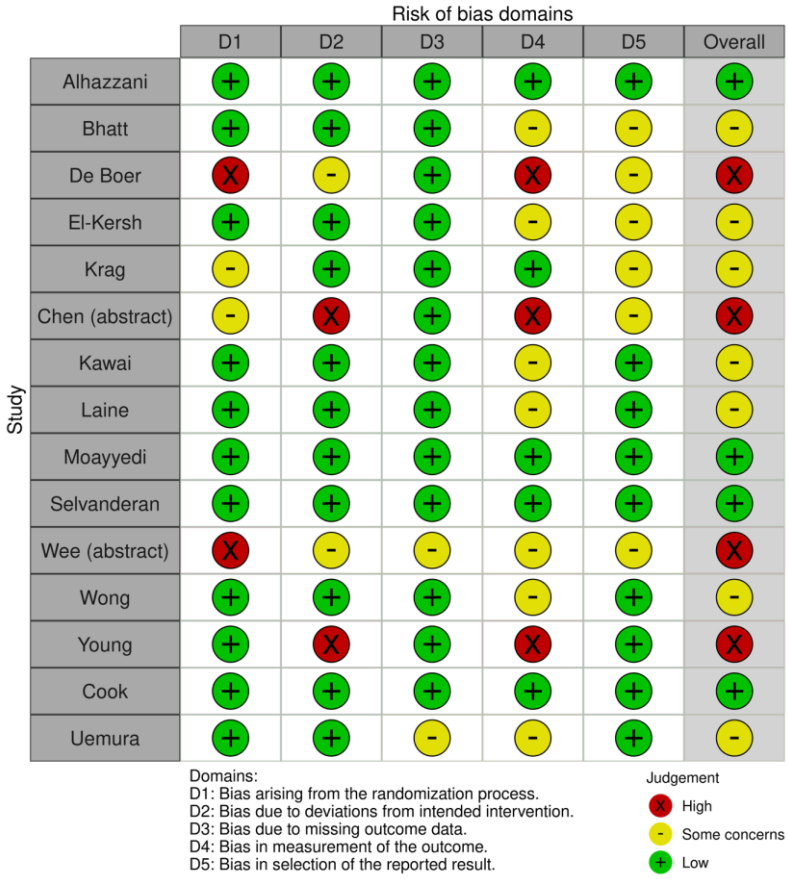


Figure 11. Detailed assessment of the risk of bias for *Clostridioides difficile* infection.

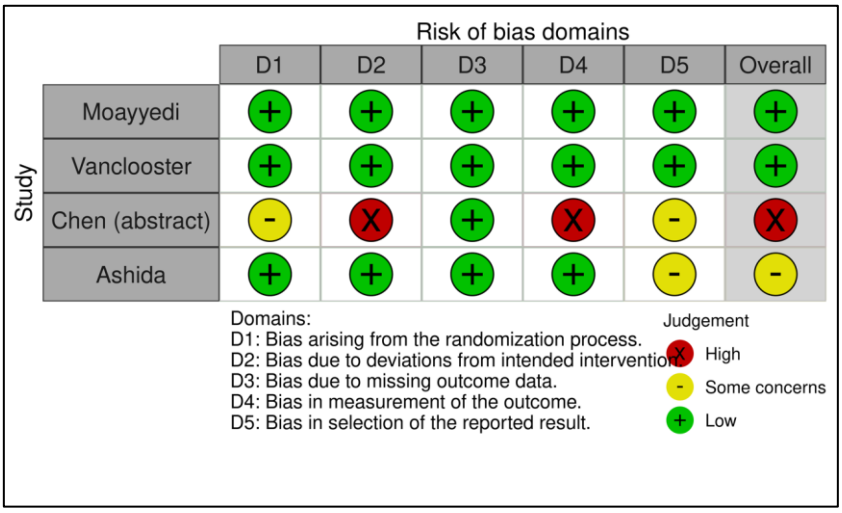


Figure 12. Detailed assessment of the risk of bias for other enteric infections.

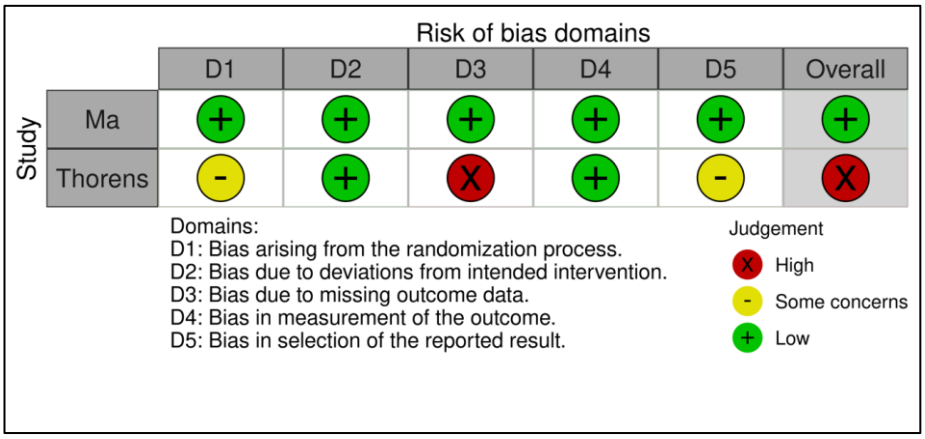


Figure 13. Detailed assessment of the risk of bias for SIBO.

8.2.5. Heterogeneity and publication bias

As the total number of studies was low and the individual study CIs were wide, the assessment of between-study heterogeneity is rather uncertain. We did not perform Egger's test for small study publication bias as fewer than 10 studies were included for the meta-analytical calculations per outcome. Although, the visual inspection of the generated funnel plots did not reveal any sign of potential publication bias (**Figure 14**).

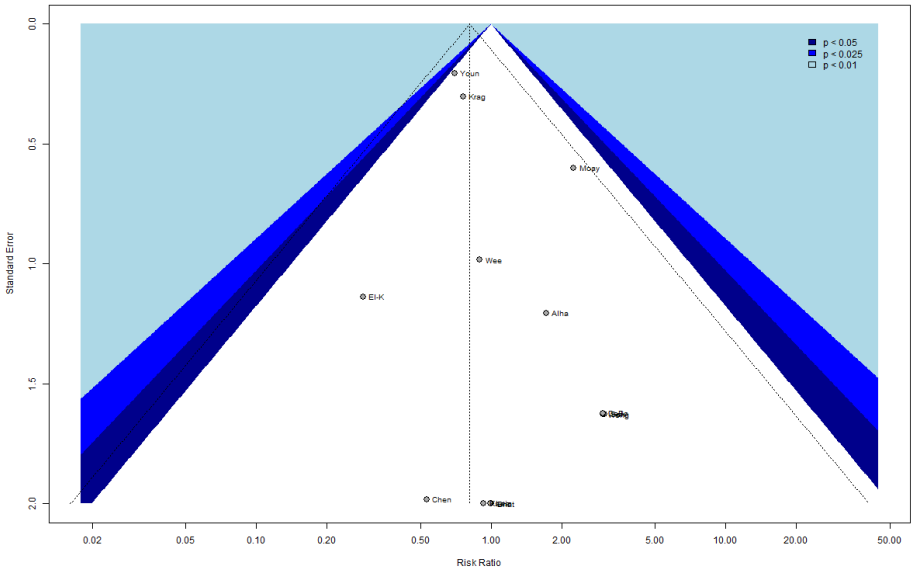


Figure 14. Funnel plot for publication bias assessment.

9. DISCUSSION

9.1. Summary of Findings, Comparisons with Other Studies

Non-specific chronic cough, which may occur as an atypical manifestation of GERD, currently represents a challenging clinical entity from a therapeutic standpoint. Acid-suppressive drugs have been proposed as a potential treatment strategy, following the appropriate exclusion of other possible aetiologic factors.

Based on the results of nine double-blinded, placebo-controlled RCTs, our study showed that acid-suppressive medications, namely PPIs, can slightly decrease cough severity. A previous meta-analysis published in 2011 by Chang et al.(1) concluded that there was insufficient evidence to support the beneficial effect of PPIs in treating chronic cough. Their analysis primarily focused on the proportion of patients who failed to respond to acid-suppressive therapy, with varying definitions of this outcome across included studies, and very limited data regarding the magnitude of the change in cough severity. Our work investigated the effect of PPIs by assessing the changes in cough scores from baseline to the end of treatment, compared to placebo. In line with the conclusion of the systematic review performed by Kahrillas et al.(2) in 2013, we showed that acid-suppressive treatment may result in some degree of symptomatic improvement. We found that the effect of acid-suppressive medication on cough severity is similar in patients presenting with non-specific chronic cough only and those with laryngopharyngeal reflux, for which persistent coughing may be a symptom. The subgroup analysis showed that the symptomatic response in these two patient populations did not differ significantly.

We also found that the magnitude of symptomatic improvement is likely unrelated to the administration duration. Based on currently available evidence, prolonged treatment durations do not seem to result in greater reductions in cough severity. Guidelines currently recommend that in patients with extra-esophageal manifestations and typical GERD symptoms, a trial of twice daily PPIs for up to 12 weeks may be advised(9,10). Data suggest that extended administration of acid-suppressive therapy will probably not result in a more pronounced symptomatic improvement compared to a treatment duration of 6-8 weeks.

Limited data was available regarding the effect of PPI therapy on cough-related quality of life. Our analysis identified the trial by Park et al.(59) as a potential outlier, showing a noticeably larger change in the group receiving acid-suppressive medication. This study's exceptionally small sample size may account for the discrepancy, and the differences in baseline characteristics between the two study arms could further explain the inconsistency. The omission of this trial resulted in a much-decreased overall effect, suggesting that the improvement in perceived well-being following acid-suppressive therapy may be rather modest. These results did not reach statistical significance, possibly due to the small number of patients. Similar to the trend observed with cough severity, extended treatment durations were not associated with a greater amelioration in quality of life.

PPIs rank among the most frequently prescribed medications worldwide. Their safety profile has generally been regarded as excellent; however, concerns have been raised regarding specific side effects associated with prolonged use(9). Among these, the increased risk of *Clostridioides difficile* infection stands out as particularly critical, given its potential for significant morbidity and mortality due to life-threatening complications. This work focused on comprehensively assessing these risks in patients on PPI treatment compared to non-users in the context of RCTs.

A number of previously reported associations between PPI use and adverse effects have been derived from observational data. These types of studies fail to establish causality and are prone to bias, such as confounding by indication and protopathic bias(84,85). In the context of PPI use, prevalent biases may include the misclassification of patients who require PPIs due to pre-existing gastrointestinal conditions, which could lead to an overestimation of the association between PPI use and enteric infections. Additionally, residual confounding may arise from unmeasured factors that contribute to both PPI use and the risk of developing infections. Several associations identified by observational research are false, whereas the minority of those that are true are often overstated(86). Specialists advise that findings from observational studies should not be deemed credible

unless RRs in cohort studies surpass two or three or odds ratios in case-control studies exceed three or four(86).

One of the most important outcomes of this study was the risk of developing CDI, given its significant morbidity, mortality, and major financial impact on healthcare systems worldwide(87). On the basis of pooled data from eight placebo-controlled RCTs totalling almost 30,000 participants, treatment with PPIs was not associated with an increased risk of acquiring CDI. A similar conclusion was reached by assessing four other RCTs comparing subjects receiving PPIs to H2RA, involving more than 27,000 patients. Additionally, treatment with PPIs did not seem to increase the risk of acquiring CDI when compared to newer acid-suppressive medications, such as potassium-competitive acid blockers. These findings stand in contrast to the conclusions of previously published meta-analyses, which estimated that patients receiving PPIs were up to twice as likely to develop CDI as those not using them(16–19,88–93). These results from previous works were based exclusively on observational data, with significant unexplained heterogeneity.

For other enteric infections, our systematic search identified one particularly representative high-quality randomized trial conducted by Moayyedi et al.(27). Some strong points of this work are the high number of patients included and the long follow-up time, with a median of three years. This study investigated subjects with stable atherosclerotic vascular disease on antithrombotic medication, randomly assigned to PPIs or placebo. A statistically significant, modestly increased risk of enteric infections was seen in those allocated to PPIs compared to non-users. Notably, this observed risk was lower than that estimated by systematic reviews of observational studies(94).

We also evaluated the occurrence of SIBO, a condition characterized by an abundance of bacteria in the small intestine, leading to gastrointestinal symptoms(25). PPI use has been described as an independent risk factor for the occurrence of SIBO(95), with a meta-analysis of 19 observational studies including over 7,000 patients reporting a potential threefold increase in the risk of SIBO (OR=1.71; 95% CI: 1.20; 2.43)(24). Two RCTs found significantly higher rates of SIBO in participants receiving PPI compared to conventional treatment without additional acid-suppression(81) and H2RA(80). These

studies employed varying threshold values to determine the presence of SIBO while including small numbers of participants. On the other hand, an extensive deep-sequencing study explored the impact of PPI use on small bowel microbiome. The findings showed that SIBO was not detected through either culture or sequencing methods, and no significant changes in microbial diversity were noted(96).

9.2. Strengths and Limitations

9.2.1. Study I.

The first study comprehensively assesses the effect of acid-suppressive medications, namely PPIs, in treating chronic cough. It focuses on the impact on cough severity and quality of life, yielding more precise insights using subgroup and time dependency analyses. Another strong point is the homogenous study design of the included articles, as we only selected double-blinded placebo-controlled RCTs. The rigorous methodological approach supports the validity of the results.

One of the main limitations of this study is the relatively small number of included patients. Given the limited number of studies, data had to be pooled irrespective of dose, administration frequency, or treatment duration. Also, the measurement of the outcomes was subjective, employing scales and questionnaires that varied widely across studies, some of which were not validated.

9.2.2. Study II.

The second meta-analysis comprehensively examines the association between PPI use and the risk of developing CDI, other enteric infections and SIBO. Results were derived only from RCTs, contributing to the reliability and validity of our findings. The use of placebo, H2RA, and potassium channel acid blockers as comparators provided additional insight, enabling a more nuanced evaluation of the safety profile. The substantial number of patients included further increased the statistical power. We adopted a rigorous methodological approach in this systematic review.

Despite the comprehensive nature of this work, certain limitations should be mentioned. None of the included studies were designed with enteric infections or SIBO as their primary outcomes. There were notable variations in treatment durations, doses, and

follow-up times across the articles included. While variability may pose challenges, it can also contribute to robust and applicable findings when accompanied by strong statistical support, such as the tight confidence intervals and low heterogeneity. Across included RCTs, CDI diagnosis was established using a range of methods (including enzyme immunoassays for toxin A/B, PCR-based detection, culture, and in some cases, colonoscopy-based diagnosis supported by histopathological confirmation). Variation in diagnostic sensitivity and specificity could have contributed to heterogeneity in reported CDI rates. However, as our analysis did not identify significant heterogeneity, this variability likely exerted only a limited effect on the pooled estimates, though it remains an important methodological consideration.

10. CONCLUSIONS

10.1. Study I

PPIs may marginally improve cough severity in some patients with non-specific chronic cough, which could be related to GERD. Longer treatment durations are not associated with a more pronounced decrease in cough severity. Therefore, extending the duration of therapy is unlikely to result in marked symptomatic improvement. The impact on the quality of life of these patients is still uncertain.

10.2. Study II

Based on data from RCTs, PPI treatment does not appear to significantly increase the already low incidence of CDI, whether compared to placebo or other acid-suppressive medications, such as H2RA or potassium channel acid blockers. However, given the limitations of available studies, including relatively short follow-up durations, heterogeneous populations, and variable diagnostic methods, a modest increase in CDI risk cannot be entirely excluded, and prompt caution interpretation is advised in interpreting the results. Other enteric infections and SIBO may be more common in patients on PPI treatment than non-users, but published data are limited. Clinicians should prescribe PPIs in the presence of a valid clinical indication, balancing benefits against potential harms.

11. IMPLICATIONS FOR PRACTICE

11.1. Study I.

We believe that PPIs can have a beneficial effect in treating non-specific chronic cough in selected cases. Excluding other potential etiologies of cough, such as respiratory disorders or systemic diseases, is essential in these patients. In case of a lack of adequate response to initial treatment with PPIs, extending the duration of therapy will probably not result in marked symptomatic improvement.

11.2. Study II.

The risk of acquiring CDI associated with PPI use may be lower than previously thought. Therefore, in the presence of a valid clinical indication for acid suppression, concerns about an increased risk of CDI should not deter physicians from prescribing PPIs.

Given the widespread use of PPIs, there are significant opportunities for targeted deprescribing efforts in order to improve patient care and reduce unnecessary treatment. As highlighted by the American Gastroenterological Association, many patients continue PPI therapy without a valid clinical indication, recommending that all patients on PPI therapy undergo regular review of their indications for use. Deprescribing strategies include dose reduction, transition to on-demand therapy, or complete discontinuation, particularly in patients without high-risk conditions such as complicated gastroesophageal reflux disease, Barrett's oesophagus, Zollinger-Ellison syndrome or eosinophilic esophagitis(12).

12. IMPLICATIONS FOR RESEARCH

12.1. Study I.

From a research standpoint, we suggest that additional high-quality double-blinded placebo-controlled RCTs should be conducted, highlighting the need for appropriate sample sizes. Future clinical studies should seek to employ validated objective cough monitoring tools, such as the Leicester Cough Monitor and VitaloJAK (97,98). Moreover, other potent acid-suppressive drugs, such as potassium-competitive acid blockers, may warrant further investigation in managing chronic cough.

12.2. Study II.

We recognize the need for further studies to refine the existing understanding of PPI safety. More high-quality RCTs with appropriate sample sizes would be useful to facilitate precise conclusions. However, we do acknowledge the practical limitations and costs associated with conducting RCTs, particularly in the context of generic drugs. Observational studies, when designed and conducted rigorously, can serve as valuable alternatives to RCTs. By utilizing advanced statistical techniques such as propensity score matching, instrumental variable analysis, and adjustment for confounding variables, observational studies can approximate the robustness of RCT findings while reflecting real-world scenarios. Furthermore, leveraging large databases and real-world evidence allows for a more comprehensive understanding of the long-term effects and potential harms of these medications.

One factor that may contribute to discrepancies across studies is geographical variation in circulating *C. difficile* strains. Our review included patients from diverse international settings, with a relatively low overall incidence of CDI. Future investigations should incorporate geographic and strain-specific analyses to clarify these associations better.

Additional secondary outcomes associated with the use of these medications should be more thoroughly investigated, such as other various enteric infections and rates of SIBO.

13. IMPLICATIONS FOR POLICY MAKERS

The findings of this thesis have several important implications for healthcare policy, particularly in the context of medication stewardship, guideline development, and resource allocation.

The modest therapeutic benefit of PPIs in non-specific chronic cough underscores the need for more evidence-based prescribing policies for extra-esophageal manifestations of GERD. Policy makers should encourage the incorporation of clearer patient selection criteria into national and international clinical guidelines, limiting empiric PPI trials to well-defined clinical scenarios and discouraging prolonged use in the absence of measurable benefit.

Second, the reassuring safety profile of PPIs with respect to *Clostridioides difficile* infection, as demonstrated by RCT evidence, supports a balanced regulatory stance. Policies should avoid overly-restrictive warnings based predominantly on observational data, which may contribute to inappropriate underuse of PPIs in patients with strong indications. Regulatory agencies should emphasize risk stratification, appropriate indication, and regular reassessment rather than firm discouragement of therapy.

Health policy makers should recognize the importance of high-quality evidence synthesis when formulating recommendations. The discrepancy between observational and randomized data highlighted in this thesis illustrates the need for guideline committees and regulatory bodies to transparently weight evidence quality, particularly when issuing safety communications that may influence prescribing behavior.

14. FUTURE PERSPECTIVES

In therapeutics, the emergence of novel acid-suppressive agents, such as potassium-competitive acid blockers, warrants further investigation not only for typical GERD symptoms, but also for extra-esophageal manifestations. Comparative effectiveness studies focusing on symptom control, safety, and patient-reported outcomes will be essential to define their role in future treatment algorithms.

From a safety perspective, expanding the use of real-world evidence and large healthcare databases, combined with advanced analytical techniques, offers an opportunity to better characterize long-term and rare adverse events associated with acid-suppressive therapy. Integrating microbiome research into these studies may also clarify the clinical relevance of intestinal dysbiosis and SIBO in patients receiving PPIs.

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16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

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