Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Proton Pump Inhibitors for Gastrointestinal Conditions: A Review of Clinical Effectiveness and Cost-Effectiveness

DATE: 19 June 2015

CONTEXT AND POLICY ISSUES

Proton pump inhibitors (PPIs) reduce acid secretion by irreversibly inhibiting the hydrogen potassium ATPase (also known as proton pump) in the gastric parietal cells. They are the most effective agents available for reducing acid secretion, and they are widely used to treat various acid-related disorders such as peptic ulcer disease, eradication of *Helicobacter pylori* (*H. pylori*), treatment and prevention of gastroduodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs), Zollinger-Ellison syndrome, and management of gastroesophageal reflux disease (GERD).[1]

H. pylori infection is associated with chronic gastritis, most peptic ulcers, and gastric adenocarcinoma and lymphoma.[2] PPI treatment reduces gastric acidity, which affects the stability of antibiotics used in the treatment of *H. pylori* infection, thereby increasing effectiveness of the antibiotic for eradication.[3] Furthermore, PPIs protect the stomach from the effects of excessive gastric acid levels.[3] Common regimens recommended for *H. pylori* eradication include triple, quadruple, or sequential therapy regimens, in which PPIs are used in combination with several antibiotics such as clarithromycin, amoxicillin, and metronidazole.[2]

Up to one-third of adults suffer from GERD, with many experiencing symptoms of heartburn and/or regurgitation at least monthly.[1,4] The prevalence of GERD in Canada was reported in 2010 to be 3.4 to 6.8 million person, with incidence of 170,000 per year among adults, and 56,000 in the pediatric population.[5] Besides the gastrointestinal/abdominal symptoms, GERD has also been associated with extra-esophageal symptoms such as cough, hoarseness, laryngeal problems, ear disease, and dental erosion.[4,6]

Gastroesophageal reflux disease (GERD) symptoms and sequelae are associated with reduced quality of life, causing considerable morbidity which contribute to substantial medication use and economic burden.[4,7] The Canadian health care system spent a total of $52,235,910 in 2004/2005 on 7554 patients who had a primary diagnosis of diseases of the esophagus and associated complications.[5]

The aim of the current review is to summarize current evidence on clinical and cost-effectiveness of PPIs for the treatment of gastrointestinal diseases, which may be used to update knowledge mobilization tools developed based on earlier evidence.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of proton pump inhibitors for the treatment and prevention of gastrointestinal conditions?

2. What is the comparative clinical effectiveness of proton pump inhibitors for the treatment and prevention of gastrointestinal conditions?

3. What is the cost-effectiveness of proton pump inhibitors for the treatment of gastrointestinal conditions?

4. What is the comparative cost-effectiveness of proton pump inhibitors for the treatment of gastrointestinal conditions?

KEY FINDINGS

Overall, PPIs are reported to be more effective than placebo or H2 receptor antagonists (H2RAs) for resolution of symptoms associated with GERD and to improve healing of esophagitis. However, PPIs were not found to be effective for the relief of GERD-related cough in both adults and children, and the use of PPIs in infants is associated with adverse events. PPIs were reported to be more cost-effective that H2RAs, placebo, or no treatment. The evidence on cost-effectiveness between PPIs and surgery was inconsistent. No consistent differences were reported on the effectiveness of one PPI versus another, and therefore it was reported that the least costly PPI is likely to be the most cost-effective, especially for long-term therapy.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and April 27, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for

inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with gastrointestinal conditions including: • Gastroesophageal reflux disease (GERD) • GERD-associated symptoms (e.g., cough, asthma, laryngeal symptoms) • *Helicobacter pylori* infection • NSAID related ulcers • Dyspepsia • Peptic ulcer disease
Intervention	Proton pump inhibitors
Comparator	Q1 and 3: Placebo, other active comparators, no treatment, no comparator Q2 and 4: Other PPIs
Outcomes	Q1 and 2: Clinical effectiveness (e.g., symptom relief or reduction, prevention of NSAID related ulcers) Harms (e.g., gastrointestinal symptoms, headache, nutrient deficiencies, *Clostridium difficile* infection) Q3 and 4: Cost-effectiveness outcomes
Study Designs	Health technology assessments, systematic reviews, meta-analyses, Randomized Controlled Trials (RCTs)*, non-RCTs* and economic evaluations

*In view of the large number of systematic reviews, non-RCTs were excluded and titles of randomized controlled trials have been listed as additional references of potential interest in Appendix 5.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR measurement tool to assess the methodological quality of systematic reviews, and the economic studies were assessed using the Drummond checklist. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described. The strengths and limitations of the individual studies are summarized and presented in Appendix 3

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 524 citations were identified in the literature search. Following screening of titles and abstracts, 501 citations were excluded and 23 potentially relevant reports from the electronic search were retrieved for full-text review. A grey literature search yielded no potentially relevant publications. Of these potentially relevant articles, 7 publications were excluded for various reasons, while 16 publications met the inclusion criteria and were included in this report. All the

included studies were systematic reviews. In view of the large number of systematic reviews, non-RCTs were excluded and titles of RCTs have been listed in Appendix 5 as additional references of potential interest. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study design
All the included studies were systematic reviews.

Country of origin
Three of the included systematic reviews were from China,[8-10] three from The Netherlands[11-13] two from the USA,[7,14] and one each from Australia,[6] Germany,[4] Korea,[15] Singapore,[16] Spain,[3] Switzerland,[17] Taiwan,[18] and the United Kingdom.[19] Eight of them stated the countries of origin of their included studies,[4,6-8,10,13,14,17] while 7 others did not.[3,11,12,16,18-20] One systematic review stated that the included studies were from Asian countries only.[9]

Patient population
Two of the studies[12,19] included children (0 to 17 years) and one included both adults (≥ 18years) and children.[6] The remaining systematic reviews included studies in the adult population. Information on patients' characteristics was generally limited.

Interventions and comparators
The PPIs that were commonly used in the included systematic reviews were esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Dexlansoprazole was an intervention in four systematic reviews,[4,8,18,20] while ilaprazole was the intervention in one study.[9] Comparators were mainly placebo, H2RAs, or other PPIs.

Outcomes

Outcomes of interest included resolution rate of GERD symptoms such as heartburn, healing rate of peptic ulcer, eradication rate of *H. pylori* in infected patients, and resolution of chronic non-specific cough in patients GERD.

Summary of Critical Appraisal

Appendix 3 provides further details of the critical appraisal of individual studies. All the included systematic reviews had well-defined objectives and they all clearly described the inclusion and exclusion criteria of their primary studies, except in one case[3] where the specific exclusion criteria were not provided. All of the included systematic reviews were based on comprehensive literature searches, and in most cases, study selection and data collection were performed independently by two reviewers who resolved differences by consensus to reduce potential for selection bias Potential for publication bias in the primary studies was assessed by the majority of the systematic reviews. Where studies were pooled for meta-analysis, appropriate methods including assessment of heterogeneity were applied. In most of the systematic reviews the conclusions were related to the quality of the primary studies. Two investigators in one systematic review[12] declared that they received grants from a pharmaceutical company, and another investigator was a member of an advisory board of the same company. In the majority of the included systematic reviews, information about population characteristics and settings of

the primary study was either lacking or limited. Therefore, it was not possible to assess generalizability of the findings to the Canadian setting.

Summary of Findings

A total of 16 systematic reviews[3,4,6-19] were included in this report, of which 14 covered clinical effectiveness while two[7,13] were on cost-effectiveness of PPIs. PPIs were compared to placebo in five systematic reviews[4,6,8,12,17] and to H2 receptor antagonists (H2RAs) in four systematic reviews[4,6,8,14]. Seven systematic reviews[3,9,10,14,16,18,19] compared PPIs to other PPIs, while one compared clinical effectiveness of PPI therapy to surgery.[14] One systematic review compared rates of *H. pylori* eradication over time with PPI co-treatment[15] and one compared PPI treatment in two different conditions[11] Of the two cost-effectiveness systematic reviews, both compared PPIs to surgery[7,13] and one also compared PPIs to medical interventions.[7] Further details on individual study findings and authors' conclusions are reported in Appendix 4, and Appendix 5 has a list of randomized controlled trials (RCT) of potential interest, which were not included in this report owing to the large number of systematic reviews produced by the literature search.

What is the clinical effectiveness of proton pump inhibitors for the treatment and prevention of gastrointestinal conditions?

Three systematic reviews[4,8,17] reported that PPIs were more effective than placebo for remission of symptoms associated with GERD. Two systematic reviews[6,12] found that PPI was not more effective than placebo for the symptomatic relief of GERD in infants, with one of the studies adding further that PPI use in infants increased adverse events.

Three systematic reviews[4,8,14] reported that PPIs are more effective than H2RAs for the relief of GERD symptoms, with one[14] also reporting that PPIs were superior to H2RAs for improvement of the healing rate of GERD-related esophagitis. However, one study[12] found that PPI was equally effective as H2RAs for the reduction of GERD symptoms in children, although PPI was reported to be ineffective for the relief of GERD symptoms in infants and was associated with adverse events. Another study[14] found insufficient evidence of the effectiveness of PPIs or H2RAs to improve asthma symptoms, and lung capacity; or to reduce nocturnal asthma, or eradicate dry cough.

A systematic review[14] reported that surgery (laparoscopic fundoplication) was similarly effective as medical treatment with PPIs to improve GERD symptoms in patients whose symptoms were already well controlled by medical therapy for at least the first 1 to 3 years following surgery.

One systematic review[11] investigated treatment with a PPI for non-erosive reflux disease (NERD) compared to treatment in erosive reflux disease (ERD) and found that PPIs are equally effective in NERD as they are in ERD. According to the authors, this finding contrasts with previously held notion that PPIs had lower effectiveness when used to treat NERD patients.

Another systematic review[15] published in 2014 reported that *H. pylori* eradication rate had declined since the late 1990s, using the triple therapy approach involving a PPI and two antibiotics. However, the study did not compare PPIs to any treatment, was limited to one country, and the authors suggested that one of the reasons for the decline could be resistance to antibiotics.

What is the comparative clinical effectiveness of proton pump inhibitors for the treatment and prevention of gastrointestinal conditions?

Seven systematic reviews[3,9,10,14,16,18,19] reported that overall, there were no consistent differences in effectiveness between PPIs for gastrointestinal conditions. Furthermore, effectiveness was not found to vary significantly on account of the different formulations of PPIs.[14] One, systematic review[14] reported that continuous intake of PPIs provided greater improvement in symptom control, endoscopic remission, and quality of life than on-demand therapy with PPIs.

What is the cost-effectiveness of proton pump inhibitors for the treatment of gastrointestinal conditions?

One systematic review[7] reported the costs of treatment of patients with symptoms of GERD, including PPIs, H2RAs, endoscopy stratification, and surgery. The study stated that in populations with *H. pylori* prevalence below 40%, empiric PPI was most effective and least costly than initial endoscopy or *H. pylori* testing ahead of initial medical management of GERD in patients with reflux symptoms. Another systematic review[13] compared the long-term cost-effectiveness of PPI therapy to laparoscopic Nissen fundoplication (LNF) and found inconclusive evidence to support either treatment.

What is the comparative cost-effectiveness of proton pump inhibitors for the treatment of gastrointestinal conditions?

One systematic review[7] stated that because "there is very little evidence that any one PPI is superior in terms of efficacy, use of the cheapest PPI available dominated specific PPI therapeutic regimens."

Limitations

Due to the large number of published systematic reviews, RCTs were not included. Relevant primary studies are provided in Appendix 5, but due to the nature of rapid reviews, they are not summarized.

Limitations of included studies have been summarized in Appendix 3. Many of the systematic reviews included only a few studies (< 10) that focused on PPI therapy. Secondly, majority of them either did not provide information about population characteristics and settings of their primary studies, or where provided, the information was not sufficiently detailed to allow inference about generalizability of findings in the Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence from the systematic reviews indicates that PPIs are superior to placebo for treatment of symptoms associated with GERD.[4,8,17] However, in infants, PPIs were not more effective than placebo for treating symptoms of GERD, and was associated with adverse events.[6,12] Overall, PPIs are also more effective than H2RAs for the relief of GERD symptoms, and in the improvement of the healing rate of GERD-related esophagitis.[4,8,14] However, some evidence was found indicating that PPI was equally effective as H2RAs for the reduction of GERD symptoms in children.[12] Where GERD was associated with cough and asthma symptoms, there was insufficient evidence for the effectiveness of PPIs or H2RAs to improve

these symptoms.[14] The majority of the included studies which compared PPIs to each other found that in general, there was no consistent advantage of one PPI over another. Surgery and medical treatment with PPI are similarly effective for GERD symptoms in patients whose symptoms were already well controlled by medical therapy for at least the first 1 to 3 years following surgery.[14] PPI was reported to be more cost-effectiveness for empiric treatment of GERD symptoms compared with initial *H. pylori* test or endoscopy directed treatment for eradication of *H. pylori* infection. However, evidence on comparative cost-effectiveness between PPI therapy and surgery was not consistent.

Overall, treatment with PPIs for GERD symptoms appears to be more effective for gastrointestinal symptoms than placebo and H2RAs, and may be more cost-effective. Specific patient symptoms and the cost of the various PPIs may be a consideration for PPI use.

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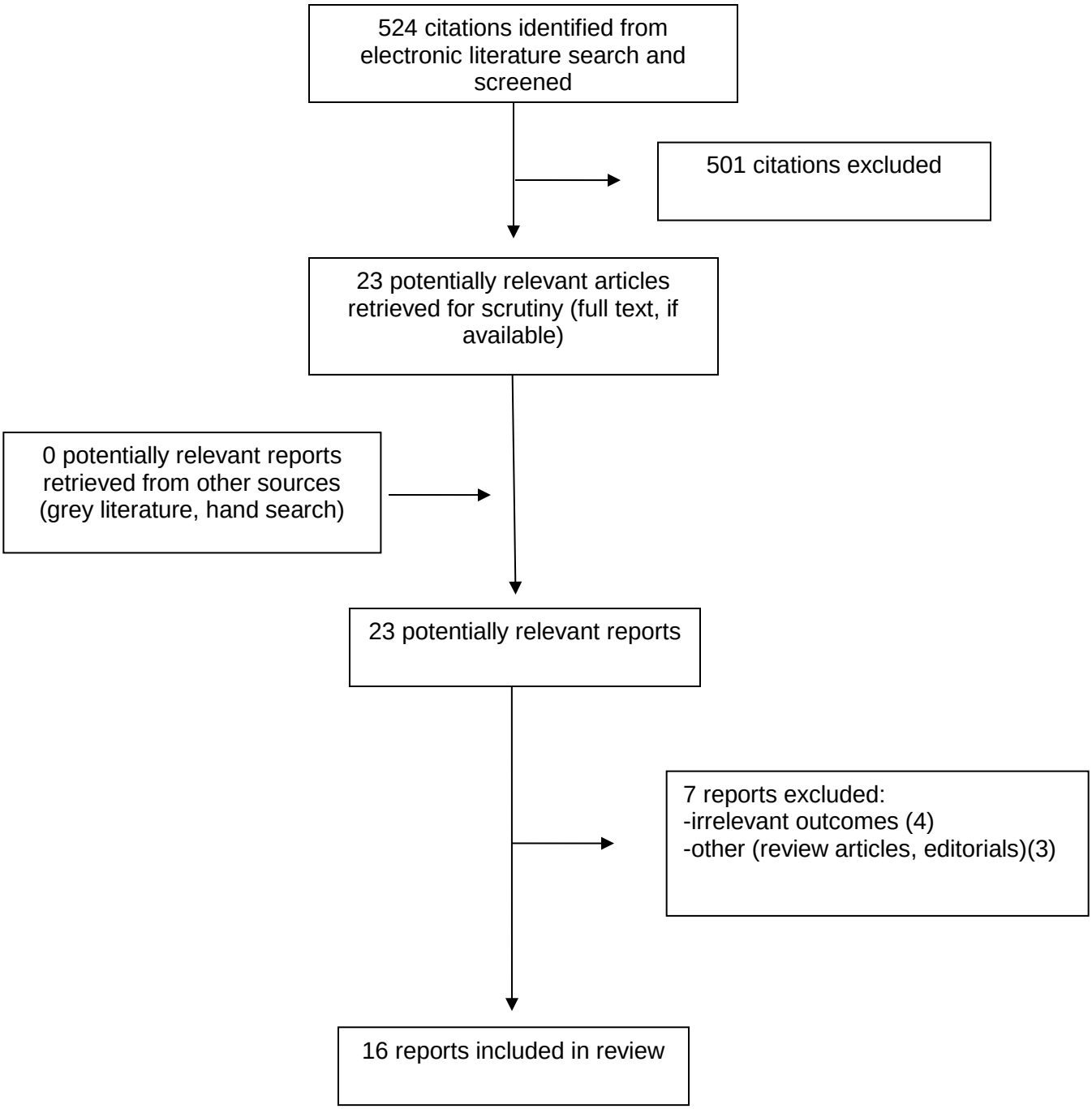
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Length of Follow-Up
Teng et al. 2015,[16] Singapore	15 RCTs (GERD = 7 RCTs, *H. pylori* infection = 8 RCTs)	9491 adult patients (≥18 years), with GERD (N=9893, age range 45 to 58 years old; *H. pylori* infection, N = 2588, age range 39 to 59 years old)	Esomeprazole 40 mg or 20 mg, once daily	Omeprazole 20 mg once daily	Resolution rate in patients with of GERD, peptic ulcer healing rate and eradication rate of *H. pylori* in patients with PUD, quality of life and adverse effects
Burgstaller et al. 2014,[17] Switzeland	30 RCTs total (5 RCTs on GERD)	192 GERD-positive NCCP patients (≥18 years)	Esomeprazole 20 mg, Lansoprazole 30 mg or 60 mg, Omeprazole 10 mg, 20 mg or 40, Pantoprazole 20 mg, Rabeprazole 20 mg	Placebo	NCCP treatment efficacy
Gong et al. 2014,[15] South Korea	104 studies (38 RCTs and 66) observational studies	42,124 patients with *H. pylori* infection	Triple therapy (PPI + plus two antibiotics)	Unclear or no comparator	Eradication rate of *H. pylori* infection, and adverse events
Ji et al. 2014,[9] China	5 RCTs	1481 Patients with duodenal ulcer	Ilaprazole 10 mg in triple therapy with two antibiotics	Omeprazole 20 mg; or esomeprazole 40 mg	Ulcer healing after 4 weeks therapy, safety
Tighe et al. 2014,[19] The United Kingdom	24 RCTs (N = 1201)	Children (birth to 16 years) with GER or GERD	All drugs for GER or GERD, including PPIs, H2RAs, antacids, prokinetics (domperidone), and alginates	Placebo or other drugs for GER or GERD	Improvement in symptom scores, Improvements in clinical symptoms (e.g. vomiting, back arching, regurgitation, failure to thrive, feeding difficulties, heartburn, abdominal pain, and epigastric pain), pH indices and endoscopic/ histological appearances
Sigterman et al. 2013,[4] Germany	34 RCTs (N = 1314)	Adults with predominant heartburn diagnosed as GERD or reflux-like dyspepsia, empirically determined or	Dex-lansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole,	Placebo, H2RAs (cimetidine, famotidine, nizatidine and ranitidine) or prokinetics (cisapride,	Heartburn remission (defined as no more than one day per week with mild heartburn)

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator**	**Clinical Outcomes, Length of Follow-Up**
		having ENRD		domperidone and meto-clopramide)	
Wu et al. 2013,[18] Taiwan	11 RCTs, N= 14145	Patients with GERD, including erosive esophagitis and NERD	Dexlansoprazole 30 mg	Esomeprazole 20 mg or 40 mg	Complete healing rate of patients with erosive esophagitis, comparative efficacy in maintaining healed erosive esophagitis over 6 months, complete resolution of NERD-associated heartburn
Xia and Wang 2013,[10] China	6 RCTs (N = 1895)	Adults (> 18 years) with erosive GERD	Rabeprazole 20 mg once daily	omeprazole 20 mg once daily	Rate of endoscopic relief and symptom (heartburn) relief rate
Zhang et al. 2013,[8] China	17 RCTs (N = 6072)	Patients with NERD	Dex-lansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Placebo or H2RAs (famotidine, nizatidine, ranitidine, and roxitidine)	Rates of symptomatic relief and AEs
McNicholl et al. 2012,[3] Spain	35 RCTs (N = 5998)	Patients with *H. pylori*	Rabeprazole or esomeprazole plus two antibiotics	Omeprazole, lansoprazole, pantoprazol, (known as first-generation PPIs), or esomeprazole rabeprazole, plus two antibiotics	*H. pylori* eradication rates as determined by histology and/or urea breath test at least 4 weeks after the end of treatment
Weijenborg et al. 2012,[11] The Netherlands	59 RCTs (N = 26,885)	Adult patients with NERD (diagnosis confirmed by endoscopy with or without pH testing), and ERD (diagnosed or empirically treated)	Esomeprazole, omeprazole, pantoprazole rabeprazole	NR	Complete or partial heartburn relief
Chang et al. 2011,[6] Australia	19 RCTs (6 for pediatric, n=536; 13 for adult, n=485)	Adults and children with GERD and chronic cough	Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Placebo, H2RAs, Cisapride	Relief of non-specific chronic cough
Ip et al. 2011,[14] USA	166 studies total; unspecified number of studies for PPI	Adults with chronic GERD	Dex-lansoprazole, esomeprazole, lansoprazole,	Surgical intervention, different PPI dosing	Treatment effectiveness and symptom relief of gastrointestinal

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator**	**Clinical Outcomes, Length of Follow-Up**
	and H2RA comparison		omeprazole, pantoprazole, rabeprazole	regimens, H2RAs,	diseases.
van der Pol et al. 2011,[12] The Netherlands	12 RCTs and crossover studies. N=895	Children (ages 0 to 17 years) with GERD	Esomeprazole,lansoprazole, omeprazole, pantoprazole	Placebo, alginates, ranitidine, or alternate PPI dose, and hydrolyzed formula,	Reduction in GERD symptoms, safety

AE = adverse event; ENRD = endoscopy-negative reflux disease; ERD = erosive reflux disease; GER = gastrointestinal reflux; GERD = gastrointestinal reflux disease; H2RA = H2-receptor antagonist; H. pylori = Helicobacter pylori; ITT = intention to treat; mg = milligrams; N = number of patients; NCCP = non-cardiovascular chest pain; NERD = non-erosive reflux disease; NR = none reported; OR = odds ratio; PP = per-protocol; PPI = proton pump inhibitor; PUD = peptic ulcer disease; QALY = quality adjusted life year; RCT = randomized controlled trial; vs. = versus.

Table A2: Characteristics of Included Cost Studies					
First author, Publication Year, Country	**Type of Analysis, Perspective**	**Intervention, Comparator**	**Study Population**	**Time Horizon**	**Main Assumptions**
Gawron et al. 2014,[7] USA	Cost-effectiveness Decision analysis or Markov models (12 studies), cost outcomes related to randomized trials (5 studies), retrospective incremental annualized healthcare costs (1 study), Perspectives: Public health system (n=15), societal (n=1), Third-party (n=1), and Employer (n=1)	PPIs vs. different PPIs; or PPIs vs.H2RAs, endoscopic or management (diagnostic or therapy) or surgery	Adult patients with GERD symptoms	Ranged from 5 (n =1) months to a lifetime (n = 3)	NR
Thijssen et al. 2011,[13] The Netherlands	Cost-effectiveness, analysis using on decision analytic and Markov modeling (for all studies, n=4), Perspective: third-party payer (direct cost only)	PPIs vs. LNF	Adult patients with GERD	≥ 5years	Lifetime cost of medication, lifetime benefit of surgery

GERD = gastrointestinal reflux disease; H2RA = H2-receptor antagonist; LNF = laparoscopic Nissen fundoplication; PP = per-protocol; PPI = proton pump inhibitor; vs. = versus. None reported.

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[21]

Strengths	Limitations
Teng et al. 2015,[16]	
• Clearly defined study design with well-defined inclusion and exclusion criteria, and a comprehensive literature search • Study selection, data collection, and assessment of methodological quality of included studies were done independently by two reviewers who resolved differences by consensus. This reduced potential for selection bias • Characteristics of included studies and ranks of methodological quality in terms of risk of bias were provided • Meta-analysis used appropriate method and approach to assessment of heterogeneity was well described • Author's conclusions were appropriately linked to the scientific quality of the included studies • The authors declared they had no conflict of interest, which makes it unlikely that the review process may be biased by such interest	• Publication bias of the included studies was not assessed; therefore the extent of reporting bias is unclear • The systematic review focused on treatment in children therefore it is unknown whether its findings are generalizable to the adult population
Burgstaller et al. 2014,[17]	
• The study question was well-defined and inclusion and exclusion criteria were clearly described. Characteristics of included studies were provided • A comprehensive literature search was done, and study selection and quality appraisal, as well as data collection were performed independently by two reviewers who resolved differences by consensus to reduced potential for selection bias • All the included studies were of high or moderate quality suggesting minimum flaws and reduced potential for bias • Studies were pooled for meta-analysis using appropriate methods including assessment of heterogeneity • Author's conclusions were appropriately linked to the scientific quality of the included studies • The authors declared they had no support or funding to report and no competing interest, which makes it unlikely that the review process may be biased due to such interest	• Of the 30 RCTs included in the review, only eight involved the use of PPIs, and 7 out of these compared PPIs to placebo which is not a likely treatment choice in clinical practice.
Gong et al. 2014,[15]	
• Inclusion and exclusion criteria were clearly described and the study question was well-defined. • The literature search was comprehensive, and two reviewers performed the study selection with differences resolved by a third reviewer. The decision to include an article was based on consensus. • The systematic review involved a large number of studies (n = 104) with a total of 42124 patients. The large scale reduces the potential of reporting findings due chance. • Many of the included RCTs (24 out of 38) were of	• Because of its focus (to analyze the eradication rate of *H. pylori* infection and adverse events of triple therapy in Korea, and to evaluate practices in that country) it is unknown whether the study finding are generalizable in other countries, in particular Canada. • No details were provided on how the meta-analysis involving RCTs and observational studies were performed. Thus the appropriateness and methodological quality of the analysis is unknown. • Many factors can affect the effectiveness of eradicating *H. pylori* infection using triple therapy

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[21]

Strengths	Limitations
high or moderate quality with reduced potential for bias, although the quality of the included observational studies (n = 66) were not ranked. • The authors declared they had no competing conflicts of interest to disclose, which makes it unlikely that the review process may be biased due to such interest.	approach (a PPI plus two antibiotics). Examples include antibiotic resistance, patient's compliance, and reinfection after previous successful treatment. Therefore determining the clinical effectiveness of PPIs from such studies is problematic. • The scientific quality of the included observational studies (n = 66) were evaluated and publication bias was not assessed for any of the included studies.
Ji et al. 2014,[9]	
• A comprehensive literature search was done based on a well-defined study question and the inclusion and exclusion criteria were clearly described. • Two reviewers independently performed the study selection and quality appraisal, as well as data collection and resolved differences by consensus to reduced potential for selection bias. • Four out of the five included studies were of high based on the Jadad composite scale suggesting minimum flaws and reduced potential for bias. • Appropriate methods were used to assess heterogeneity of included studies and to perform the meta-analysis. • The authors declared they had no support or funding to report and no competing interest, which makes it unlikely that the review process may be biased due to such interest.	• A limited number of studies (n = 5) were included in this studies. Of these, one showed some asymmetry suggesting the possibility of publication bias (although rank high on the quality scale used) and the other was an abstract. Therefore, although the systematic review followed processes and the meta-analysis used appropriate analytical methods, it is unclear whether there were sufficient high quality studies to allow firm conclusions. • All the included studies came from Asian countries. Therefore, it is unknown whether similar results will be produced among the Canadian population.
Tighe et al. 2014,[19]	
• Clearly defined study question and objective were provided. The literature search was comprehensive and inclusion and exclusion criteria were well-defined • Study selection, data collection, and assessment of methodological quality of included studies were done independently by two reviewers who resolved differences by consensus. This reduced potential for selection bias • Characteristics of included studies and ranks of methodological quality in terms of risk of bias were provided • Meta-analysis of qualifying studies used appropriate method and assessment of heterogeneity was well described • Author's conclusions were appropriately related to the scientific quality of the included studies • The authors declared they had no known conflict of interest,	• Publication bias of the included studies was not assessed; therefore the extent of reporting bias is unclear • The systematic review focused on treatment in children therefore it is unknown whether its findings are generalizable to the adult population
Sigterman et al. 2013,[4]	
• Clearly defined study question and objective were provided. The literature search was comprehensive and inclusion and exclusion criteria were well-defined • Study selection, data collection, and assessment of methodological quality of included studies were done independently by two reviewers who resolved differences by consensus to reduced potential for selection bias • Characteristics of included studies and ranks of	• According to the authors, the quality of the data reporting of most included studies was poor, and the trials provided little or no information on allocation concealment. • The systematic review focused on short-term drug efficacy therefore it is unknown whether its findings will be generalizable in patients who require long-term disease management.

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[21]

Strengths	Limitations
methodological quality in terms of risk of bias were provided • The settings of the included studies covers North America, Europe, Australia, South Africa, China, and Japan; increasing the probability that the study findings may be generalizable across many regions • Meta-analysis of qualifying studies used appropriate method and assessment of heterogeneity was well described • Author's conclusions were appropriately related to the scientific quality of the included studies • The authors declared they had no known conflict of interest,	
Wu et al. 2013,[18]	
• The study objective was well-defined and inclusion and exclusion criteria were clearly described. • Two reviewers independently performed study selection and quality assessment, as well as data collection and resolved disagreements through consensus to reduced potential for selection bias. • The included studies had Jadad score of 4 to indicating high quality, with minimal potential for bias. • Author's conclusions were appropriately linked to the scientific quality of the included studies. • The authors declared they had no support or funding to report and no competing interest, which makes it unlikely that the review process may be biased due to such interest.	• On account of this study being an indirect treatment comparison, it may be biased by cross-trial differences in patient populations, sensitivity to modeling assumptions, and differences in the definitions of outcome measures. • Only fully published studies in peer-reviewed journals written in English were included in this systematic review. Therefore, it is likely that potentially relevant articles from other sources were missed, although 3 electronic sources (Medline, Embase, and Cochrane Library) were searched. • Characteristics of included studies were not provided in sufficient details. For example the number of patients involved in the studies and their demographic characteristics are unknown. However, relative risk with 95% CI was calculated based on the number of events. • Publication bias was not assessed for the included studies, therefore reporting bias cannot be ruled out. • The study was funded in part by the pharmaceutical company that markets the PPI of interest (dexlansoprazole). In addition, two out of the three authors served as consultants for this and other pharmaceutical companies.
Xia and Wang 2013,[10]	
• The study objective is well-defined inclusion and exclusion criteria were provided, a comprehensive literature search was done, and characteristics of included studies were listed. • Publication bias of included studies was assessed. • Analyses were performed in parallel by two people blinded to each other's status. • The authors declared they had no conflict of interest, which makes it unlikely that the review process may be biased by such interest.	• Details of study selection, and data collection, were not provided. Therefore, potential for selection bias cannot be excluded • Assessment of methodological quality of included studies was not reported. Therefore, the robustness of the study findings based on scientific quality of the source articles is unknown • Five of the included studies were conducted in Europe and the sixth was conducted in Japan. Therefore, the generalizability of the study findings in Canada is uncertain
Zhang et al. 2013,[8]	
• A clearly defined study objective was provided. The literature search was comprehensive and inclusion and exclusion criteria were well-defined, and characteristics of included studies were listed in detail in a table • Study selection was done independently by two reviewers, while three reviewers performed the data	• The primary endpoint of the study (relief of symptoms/heartburn) depends on the feelings of patients. This outcome is subjective and reduces the objectivity of the study findings. • Two out of six of the included studies were open-label trials without blinding of participants and personnel. Together with the fact that none of the

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[21]

Strengths	Limitations
extraction. Differences were resolved through discussion involving four reviewers. This helped to reduced potential for selection bias • Included studies were assessed for risk of bias using Cochrane handbook 4.2.2. Egger's test and Begg's test were used to check for publication bias • The settings of the included studies covers North America (including Canada), Europe, Australia, Lebanon, and Japan; increasing the probability that the study findings may be generalizable across many regions • Meta-analysis of qualifying studies used appropriate method and assessment of heterogeneity was well described • Univariate meta-regression analysis was performed to explore factors influencing the efficacy and adverse events of PPI • Author's conclusions were appropriately related to the scientific quality of the included studies • The authors declared they had no known conflict of interest,	studies study carried out allocation concealment, there was high potential for bias. • While the studies which compared PPIs to H2RAs did not exhibit publication bias, assessment revealed that publication bias may exist in the outcome of studies which compared PPIs with placebo. • According to the authors, the analytical results were influenced by the reviewers, although they attempted to overcome this drawback. Details of how the reviewers' influence played out and the extent of its impact were not provided.
McNicholl et al. 2012,[3]	
• The objective of the study was clearly stated, and a comprehensive literature search was conducted. • Study selection, (following clearly defined inclusion criteria) and data extraction were conducted independently by two reviewers, with disagreements resolved by a third reviewer. • Statistical analysis was robust and included determination and report of number needed to treat (NNT) for more clinical applicability. • The authors declared they had no personal interest and the study was not funded by pharmaceutical industry. Thus it was unlikely that the review process was biased by competing interest.	• Patient characteristics of included study were not reported. Therefore, assessment of the generalizability of the findings was not possible. • Exclusion criteria were not clearly stated, although a flow chart of the meta-analysis process stated the number of excluded articles with reason. • It is unknown if the scientific quality of the included studies was assessed. Therefore the robustness of study findings is unknown. • It was not possible to isolate the unique contribution of individual PPIs to the outcomes reported because of the diversity of regimens, the antibiotics used, the number of intakes per day, the doses and the treatment duration. • Although esomeprazole 40mg given twice daily showed the best improvement in outcome, the meta-analysis which produced the finding was based on only four studies which demonstrated high heterogeneity. It is unclear how this influenced the outcome.
Weijenborg et al. 2012,[11]	
• A comprehensive literature search was conducted based on a clearly defined objective. • Inclusion criteria were clearly describes, and two reviewers independently extracted data and assessed study quality of selected articles. • Quality of included studies was performed according to the Jadad scoring system. • Statistical analysis and reporting were rigorous, and included assessment for heterogeneity and potential association between placebo response and study quality. • Publication bias of included studies was assessed.	• The manner in which studies were selected for inclusion was not described, and exclusion criteria were not specified. Therefore the possibility of selection bias cannot be ruled out. However, a flowchart listed the number of excluded studies with three reasons-no randomization, different design, and data not extractable. • Patient characteristics of included study were not reported. Therefore, assessment of the generalizability of the findings was not possible.

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[21]

Strengths	Limitations
Chang et al. 2011,[6]	
• Clearly defined study question and objective were provided. The literature search was comprehensive and inclusion and exclusion criteria were well-defined • Study selection, data collection, and assessment of methodological quality of included studies were done independently by two reviewers who resolved differences by consensus. This reduced potential for selection bias • Characteristics of included studies and ranks of methodological quality in terms of risk of bias were provided • The included studies involved both pediatric and adult populations. Therefore the findings of this systematic review are potentially generalizable across a wider range of age groups • Meta-analysis of qualifying studies used appropriate method and assessment of heterogeneity was well described • Author's conclusions were appropriately related to the scientific quality of the included studies • The authors declared they had no known conflict of interest	• Majority of the included studies had small sample sizes and it is unknown is they were sufficiently powered to detect relevant clinical differences. • Not all participants had cough, GERD criteria varied between studies, and the exclusion criteria had no mechanism to not ensure all patients with lung disease were excluded. All these factors had potential to influence results, although it is uncertain if they did. • The disparate nature of the interventions used in the included studies makes review challenging. Only six (all adult studies) out of the 19 included studies were used in the meta-analysis, leaving one to question if the results would be different if the analysis had been possible with all the studies. • According to the authors, lack of validated scales and objective data on cough as well as a lack of allocation concealment data and possibly clinical heterogeneity of participants and medications were limitations of the review.
Ip et al. 2011,[14]	

• Study questions were clearly defined and the literature search was comprehensive and inclusion and exclusion criteria were well described.
• The methodological quality of studies was assessed using predefined criteria based on AHRQ methods guide.
• A draft version of this report was reviewed by a panel of expert reviewers, and revisions of the draft were made based on their comments where appropriate.
• Author's conclusions were appropriately related to the scientific quality of the included studies.
• The authors declared they had no known conflict of interest
	• Only existing systematic reviews were included in the study so it is unknown whether important relevant primary studies were excluded
	• Although it was stated that inclusion criteria were used, details about selecting studies to be included in the systematic review were not described. Therefore the possibility of selection bias cannot be ruled out
	• The following were among limitations listed by the author:
	  ○ There was a great deal of variability in the rigor of how the outcomes were evaluated across studies, particularly in subjective endpoints
	  ○ Most studies were non-randomized or lacked a suitable control group
	  ○ The majority of the included studies had a relatively short follow-up (typically no longer than 1 year), particularly those concerned with medical treatments
	  ○ Pharmacologically equivalent doses of various PPIs have not been well established (or universally agreed upon), thus clouding interpretation of existing comparative PPI studies

van der Pol et al. 2011,[12]	
• A comprehensive search was conducted based on a clearly defined objective • Inclusion and exclusion criteria were clearly stated • Two independent reviewers performed article selection, data extraction, and assessment of risk of bias; and resolved disagreements by consensus • The methodological quality of included studies was	• The level of heterogeneity between the included studies prevented meta-analysis. Thus discussion of outcomes was limited to the individual studies without the benefit of a pooled effect estimate. • Two investigators declared that they have received grants from a pharmaceutical company, and another was a member of an advisory board of the same

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[21]	
Strengths	**Limitations**
assessed by independently by two reviewers using the Delphi list, who resolved differences by consensus to reduced potential for selection bias • Author's conclusions were appropriately related to the scientific quality of the included studies	company. The other authors indicated they have no financial relationships relevant to this article to disclose. • Although the Delphi list is a validated study quality assessment tool, it does not consider sample size on included studies. This is particular important for this systematic review since the investigators could not conduct pooled analysis, and the power of the individual studies to determine relevant clinical differences in outcomes is unknown.

Table A4: Strengths and Limitations of Economic Studies using Drummond[22]	
Strengths	**Limitations**
Gawron et al. 2014,[7]	
• The objective of the research was clearly stated and its economic importance of the was outlined in a manner that considers both costs and treatment outcomes • A comprehensive literature search was conducted based on the stated question, and clearly defined inclusion and exclusion criteria were applied • Two independent reviewers assessed included studies according to the CHEERS task force guidelines on good reporting practices for economic evaluations • The type of analysis performed and the viewpoints of the included studies were clearly stated, as well as the primary outcome measure for the economic evaluation	• Details about the characteristics of the study population and settings of the included studies were scanty. Therefore, assessing generalizability to Canadian patient population and health system was not possible. • There was no discussion about the justification of the modeling methods used in the included studies. Thus it is unknown whether the models used in the source studies were likely to lead to the credible outcomes given the time horizons that were applied. • Data could not be pooled due to the different time horizons and comparisons made in individual studies.
Thijssen et al. 2011,[13]	
• The objective of the research was clearly stated and its economic importance of the was outlined in a manner that considers both costs and treatment outcomes • A comprehensive literature search was conducted based on the stated question, and clearly defined inclusion and exclusion criteria were applied • Two independent reviewers screened titles and abstracts for relevance read full texts of potentially relevant articles and selected studies to be included • The levels of evidence of the data for economic analyses were awarded using the Oxford Centre for Evidence-Based Medicine criteria • The quality of the economic evaluations of the included studies was assessed with a modified version of the Drummond checklist for assessing economic • The primary outcome measures for the economic evaluation were clearly stated	• Data could not be pooled due to the different time horizons and comparisons made in individual studies, and the inconsistent nature of the individual findings prevented a firm conclusion to be made on the comparative cost-effectiveness of PPI to LNF.

CHEERS = Consolidated Health Economic Evaluation Reporting Standards; LNF = laparoscopic Nissen fundoplication;

APPENDIX 4: Main Study Findings and Author's Conclusions

• Table A5: Summary of Findings of Included Studies	
• Main Study Findings	• Author's Conclusions
Teng et al. 2015,[16]	
• At week 8, both esomeprazole 40 mg and 20 mg improved healing of GERD-related esophagitis: • Esomeprazole 40 mg versus omeprazole 20 mg: RR = 1.07 (95% CI: 1.02 to 1.12), NNT = 17 • Esomeprazole 20 mg versus omeprazole 20 mg: RR = 1.04 (95% CI: 1.01 to 1.08), NNT = 30 • Only esomeprazole 40 mg achieved significant improvement in GERD-related esophagitis at week 4 compared to omeprazole 20 mg, RR = 1.13 (95% CI: 1.04 to 1.22), NNT = 12 • At week 4, heartburn resolution rate was higher among patients on esomeprazole 40 mg (64% to 68%) compared with those on omeprazole 20 mg (57% to 63%) • In 7-day triple therapy regimen involving a PPI co-administered with 2 antibiotics (either amoxicillin and clarithromycin or metronidazole and clarithromycin), *H. pylori* eradication rates were higher with esomeprazole (70% to 96%, regardless of dose) compared with omeprazole (65% to 88%). The RRs for esomeprazole 40 mg and 20 mg compared with omeprazole 20 mg twice daily were 1.16 (95% CI: 1.01 to 1.32) and 1.01 (95% CI: 0.96 to 1.05), respectively	"Esomeprazole provided a statistically significant but marginal degree of improvement in esophagitis healing when compared with omeprazole. However, this clinical advantage in patients with GERD diminished when the treatment duration was within 4 weeks. There was no difference in the *H. pylori* eradication rates when esomeprazole and omeprazole were given at the same doses."[16] page 7
Burgstaller et al. 2014,[17]	
• Among patient with GERD-related NCCP, PPI treatment was more effective than placebo: pooled OR = 11.7 (95% CI: 5.5 to 25.0) • In GERD-negative NCCP patients, PPI treatment showed no difference in effectiveness compared to placebo: pooled OR = 0.8 (95% CI: 0.2 to 2.8)	Esomeprazole provided a statistically significant but marginal degree of improvement in esophagitis healing when compared with omeprazole. However, this clinical advantage in patients with GERD diminished when the treatment duration was within 4 weeks. There was no difference in the *H. pylori* eradication rates when esomeprazole and omeprazole were given at the same doses."[16] page 7
Gong et al. 2014,[15]	
• Using a standard triple therapy (PPI + amoxicillin + clarithromycin), the *H. pylori* eradication rates of 7-day and 14-day treatments were 81.1% (95% CI, 79.8 to 82.3%) and 85.3% (95% CI: 83.5 to 87.1%) for PP analysis, respectively. • The pooled overall eradication rate of 74.6% (95% CI: 72.1% to 77.2%) showed a decreasing tendency from the years 1998 to 2013 based on ITT and PP analysis (P< 0.001 and *P* = 0.0003, respectively). • The pooled *H. pylori* eradication rates following standard triple therapy are lower than the set standard (>80% in ITT analysis and >90% in PP analysis) considered by the Asia-Pacific Consensus Guidelines for a regimen to be suitable for first-line eradication therapy	"In conclusion, conflicting results have been reported worldwide with regard to *H. pylori* eradication with standard triple therapy. Our data support the evidence for a decreased eradication rate of *H. pylori*, suggesting that a novel therapeutic strategy is warranted to improve first-line treatment for *H. pylori* infection in Korea".[15] page 708
Ji et al. 2014,[9]	
• At 4 weeks, ilaprazole showed no difference in the healing rate duodenal ulcer compared with other PPIs (89.7% vs 87.0%; RR = 1.02; 95% CI: 0.98-	"In conclusion, conflicting results have been reported worldwide with regard to *H. pylori* eradication with standard triple therapy. Our data support the evidence for a

• Table A5: Summary of Findings of Included Studies	
• Main Study Findings	• Author's Conclusions
1.06). The results did not change in the sensitivity analyses showed no change in the results	decreased eradication rate of *H. pylori*, suggesting that a novel therapeutic strategy is warranted to improve first-line treatment for *H. pylori* infection in Korea".[15] page 708
Tighe et al. 2014,[19]	
• Improvements in GERD symptoms related to nocturnal acid breakthrough were observed after three weeks of treatment with omeprazole • There was poor quality evidence for symptom improvements in infants with 'likely' GERD • Moderate quality evidence showed significantly better GERD-symptom improvement following lansoprazole and alginate treatment than with treatment with either of them alone • Similar improvements were observed for both high dose and low dose lansoprazole groups in one study • Both low and high dose esomeprazole resulted in improvement in symptoms for infants with reflux symptoms and abdominal reflux • GERD-symptom scores improved significantly in children treated with either high dose or low dose pantoprazole	"Moderate evidence was found to support the use of PPIs, along with some evidence to support the use of H antagonists in older children with GORD, based on improvement in symptom scores, pH indices and endoscopic/histological appearances. However, lack of independent placebo-controlled and head-to-head trials makes conclusions as to relative efficacy difficult to determine. Further RCTs are recommended." "Better evidence has been found to support the use of PPIs in infants with GORD, but heterogeneity in outcomes and in study design impairs interpretation of placebo-controlled data regarding efficacy." "Studies of omeprazole and lansoprazole in infants with functional GOR have demonstrated variable benefit, probably because of differences in inclusion criteria."[19] page 2 No PPIs were superior over alternate PPIs
Sigterman et al. 2013,[4]	
• Empirical treatment with PPIs for the remission of heartburn associated with GERD is more effective than H2RAs (RR = 0.66; 95% CI: 0.60 to 0.73) or placebo (RR = 0.37; 95% CI: 0.32 to 0.44). • Treatment with PPIs better improves heartburn remission in patients with ENRD than H2RAs (RR = 0.78; 95% CI: 0.62 to 0.97), or placebo (RR = 0.71; 95% CI: 0.65 to 0.78)	"Proton pump inhibitors (PPIs) are more effective than H2-receptor antagonists (H2RAs) for treatment of heartburn in patients treated empirically and in patients with endoscopy-negative reflux disease (ENRD), althoughH2RAs are also effective." "Both a PPI and an H2RA are therefore reasonable options for achieving short-term symptom relief in patients with ENRD. However, this review did not address the relative efficacy of these drugs in the long-term management of ENRD."[4] page 18
Wu et al. 2013,[18]	
• Indirect comparison showed that dexlansoprazole 30 mg was significantly more effective than both esomeprazole 20 mg (RR: 2.01, 95% CI: 1.15 to 3.51); or esomeprazole 40 mg (RR: 2.17, 95% CI: 1.39 to 3.38) at controlling symptoms of heartburn in NERD at 4 weeks. Dexlansoprazole 60 mg was also more effective than both doses of esomeprazole. • For healing of erosive esophagitis and maintenance of healed erosive esophagitis, there were no statistically significant differences between dexlansoprazole and esomeprazole for over 6 months	"Adjusted indirect comparisons based on currently available randomized controlled trials suggested that patients treated with dexlansoprazole 30 mg would have higher rate with significant difference of symptom control than esomeprazole 20 mg or 40 mg in the management of NERD at 4 weeks, although there were no statistically significant differences between dexlansoprazole and esomeprazole in other outcomes for the treatment and maintenance of healed EO. However, these study findings need to be interpreted with caution due to small number of studies and other limitations"[18] page 199
Xia and Wang 2013,[10]	
• Endoscopic relief of GERD was not significantly different between rabeprazole 20 mg and omeprazole 20 mg for up to 8 weeks of treatment (RR = 1.02; 95% CI: 0.99 to 1.05; P = 0.282). • Once daily rabeprazole 20mg showed a statistically significantly greater improvement than once daily omeprazole 20mg in heartburn relief for up to 8 weeks of treatment (RR = 1.13; 95% CI: 1.03 to 1.25; *P* = 0.012)	"In summary, these data suggest a clinical advantage of rabeprazole over omeprazole in symptomatic relief, but no significant difference in endoscopic relief, of erosive GERD for up to 8 weeks of treatment. Rabeprazole and omeprazole were both tolerated by GERD patients."[10] page 5

• Table A5: Summary of Findings of Included Studies	
• Main Study Findings	• Author's Conclusions
Zhang et al. 2013,[8]	
• Overall, PPIs showed symptomatic relief rate for NERD of 51.4% (95%CI: 0.43 to 0.59)The results of the meta-analysis showed that PPI treatment was significantly superior to H2RA treatment for the symptomatic relief of NERD (RR = 1.63; 95%CI: 1.42 to 1.87,) and placebo (RR = 1.90; 95%CI: 1.57 to 2.30) • The results were consistent in both the short-term (RR = 1.52, 95%CI: 1.30 to 1.78, and the long-term (RR = 2.06, 95%CI: 1.54 to 2.76, PPI relief of NERD symptoms was significantly superior compared with placebo (RR = 1.90, 95%CI: 1.57 to 2.30,) • There were no obvious differences among different doses, durations, and PPI types	"In conclusion, our meta-analysis showed that PPI is more effective than H2RA or placebo for the treatment of NERD. However, there was no significant difference between the safeties of PPI and H2RA or placebo. In addition, the effective rate of PPI for NERD was associated with hiatal hernia, while the adverse rate was associated with hiatal hernia and drinking." "More multi-center, high quality randomized controlled trials with larger samples and longer terms of follow-up visits are desirable."[8] page 8417
McNicholl et al. 2012,[3]	
• Overall, esomeprazole showed higher *H. pylori* eradication rates than first-generation PPIs (82.3% vs. 77.6%); OR = 1.32 (95% CI: 1.01 to 1.73); NNT = 21. • A subgroup analysis revealed that improved results were driven by only esomeprazole 40 mg twice daily, which had 83.5% improvement compared with 72.4% for the first-generation PPIs (OR = 2.27 [95% CI: 1.07 to 4.82]; NNT = 9) while esomeprazole 20 mg twice daily obtained lower efficacy. • Overall, rabeprazole showed better *H. pylori* eradication rates than first-generation PPIs (80.5% vs. 76.2%; OR = 1.21(95% CI: 1.02 to 1.42); NNT = 23), with both rabeprazole 10 and 20 mg twice daily having similar results • no significant differences were found in *H. pylori* eradication rates between esomeprazole and rabeprazole (78.7% vs. 76.7%, respectively; OR = 0.90 [95% CI: 0.70 to 1.17])	"In conclusion, esomeprazole and rabeprazole obtained an overall higher eradication rate than omeprazole, lansoprazole and pantoprazole, although this difference was more marked in esomeprazole, especially when given in double doses."[3] page 423
Weijenborg et al. 2012,[11]	
• After 4 weeks of PPI therapy, the estimated proportion of patients with ERD reporting complete heartburn relief was 0.72 (95% CI: 0.69 to 0.74) compared with 0.50 (95% CI: 0.43 to 0.57) in empirically treated patients; 0.49 (95% CI: 0.44 to 0.55) in endoscopy-defined NERD patient, and 0.73 (95% CI: 0.69 to 0.77) in patients with NERD confirmed by endoscopy and a positive pH-test • Partial heartburn relief rates after 4 weeks of PPI therapy was 0.75 (95% CI, 0.71 to 0.78) in ERD patients compared with 0.71 (95% CI, 0.59 to 0.81) in NERD cases confirmed by heartburn symptoms only, 0.65 (95% CI, 0.61 to 0.69) in NERD cases confirmed by heartburn symptoms and endoscopy, and 0.85 (95% CI, 0.55 to 0.96) in NERD cases confirmed by heartburn symptoms, endoscopy, and a positive pH-test • After 8 weeks of PPI therapy, the estimated proportion of patients with ERD reporting complete heartburn relief was 0.73 (95% CI, 0.59 to 0.84)	"In conclusion, our analyses support the conclusion that when NERD is well defined with functional studies, PPI therapy is as effective in NERD patients as it is in patients with ERD and the PPI failure rate is only around 20%. We argue that the previously reported lower response rates in patients with NERD are the result of contamination of the NERD study populations with subjects with functional heartburn and functional dyspepsia."[11] page 754

• Table A5: Summary of Findings of Included Studies	
• Main Study Findings	• Author's Conclusions
compared with 0.47 (95% CI, 0.43 to 0.51) in NERD confirmed by heartburn symptoms only. No studies reported complete symptom relief at 8 weeks in NERD groups defined by endoscopy or by pH measurement • Partial heartburn relief rates after 8 weeks of PPI therapy was 0.76 (95% CI 0.72 to 0.80) in ERD patients compared with 0.69 (95% CI 0.64 to 0.74) for empirically treated NERD patients, and 0.76 (95% CI 0.66 to 0.84) in NERD cases confirmed endoscopy. No studies classifying NERD by a normal endoscopy and a positive pH measurement reported partial symptom relief at 8 weeks	
Chang et al. 2011,[6]	
• The single RCT found that PPI was not efficacious for cough outcomes compared with placebo (OR = 1.61; 95% CI: 0.57 to 4.55, in favor of placebo). However, AEs in infants who were treated with PPI significantly increased (OR = 5.56; 95% CI: 1.18 to 26.25) • In adults, pooled data based on ITT showed no significant difference between treatment with PPI and placebo in total resolution of cough (OR = 0.46; 95% CI: 0.19 to 1.15) in two to three months.	In very young children including infants, PPI is not efficacious for cough associated with GORD symptoms and should not be used for cough outcomes. A valid conclusion could not be drawn in older children because of insufficient data. Evidence in adults is insufficient and does not support a definite conclusion that GERD treatment with PPI is universally beneficial for the relief of cough associated with GERD.
Ip et al. 2011,[14]	
• Based on moderate evidence, PPIs were superior to H2RAs in resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. Furthermore, PPIs are more effective at maintenance treatment than H2RAs • No comparative efficacy difference was observed between omeprazole, lansoprazole, pantoprazole, and rabeprazole for symptom relief at 8 weeks • No comparative efficacy difference was observed between esomeprazole 40 mg, lansoprazole 30 mg or pantoprazole 40 mg for symptom relief at 4 weeks • No comparative efficacy difference was observed between esomeprazole 20 mg versus omeprazole 20 mg for symptom relief at 4 weeks. However, a significantly higher rate of esophagitis healing at 4 weeks was observed with esomeprazole 40 mg taken once a day compared with esomeprazole 20 mg taken once a day. • Moderate evidence suggests no consistent difference in symptom resolution or esophagitis healing rates between various doses of pantoprazole, esomeprazole, lansoprazole, and dexlansoprazole for duration on therapy ranging from 1 to 12 months. However, there is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and pantoprazole 40 mg better relief than esomeprazole 40 mg over 24 weeks • Continuous intake appeared to provide better improvement over 6 months in symptom control, endoscopic remission, and quality of life than on-	"PPIs (esomeprazole 20 mg taken once daily or on-demand, lansoprazole 15 mg taken once daily and omeprazole 20 mg taken once daily) were superior to H2RAs (ranitidine 150 mg and famotidine 20 mg both taken twice daily) for resolution of GERD symptoms at 6 months."[14] page 153 "Based on analysis of 10 RCTs, no consistent comparative difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months."[14] page 153 "Based on analysis of 12 RCTs, no consistent difference in doses and dosing regiments with different PPIs in relation to symptom resolution and esophagitis healing rates."[14] page 154 "Three RCTs comparing continuous daily intake of esomeprazole 20 mg appears to provide better symptom control and quality of life relative to on-demand dosing over a period of 6 months."[14] page 154 "Based on analysis of eight RCTs, no consistent comparative difference in symptom relief and esophagitis healing rates was observed between esomeprazole (20 to 40 mg), lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg with omeprazole 20 mg or lansoprazole 15 mg over a period ranging from 4 weeks to 1 year."[14] page 154

• Table A5: Summary of Findings of Included Studies	
• Main Study Findings	• Author's Conclusions
demand dosing using rabeprazole 10 mg or 20 mg, and esomeprazole 20 mg or 40mg • There was either insufficient or no evidence to support a benefit of PPIs or H2RAs in improving asthma symptoms, lung capacity, use of asthma medications, or reducing hoarseness and nocturnal asthma, and complete eradication of non-specific dry cough • Surgery (laparoscopic fundoplication) was similarly effective as medical treatment with PPI in improving GERD symptoms in patients whose symptoms were already well controlled by medical therapy for at least the first 1 to 3 years following surgery	
van der Pol et al. 2011,[12]	
• The level of heterogeneity related to participants, interventions and outcome measures precluded meta-analysis of the included studies and results were reported on individual study basis. • In infants, five placebo-controlled studies showed no significant difference between PPIs and placebo in effectiveness to reduce GERD symptoms, although two studies reported significant reductions in gastric acidity with omeprazole compared to placebo. • In children, five studies found that PPIs effectively improved clinical symptoms or endoscopic healing. Two of the studies reported that PPIs were more effective at reducing gastric acidity than alginate or ranitidine but the reduction of macroscopic or histologic scores did not differ. • In adolescents, two dose-finding studies found no significant difference in effectiveness between pantoprazole 20 mg versus 40 mg, or between esomeprazole 20 mg versus 40 mg in reducing GERD symptoms	"If the primary aim is to treat GERD symptoms in infants, PPIs should not be prescribed. Despite PPIs seeming to be well tolerated in the short-term, there is insufficient evidence to support the effectiveness and safety of PPIs in the treatment of GERD in children and adolescents. Therefore, physicians should be careful when prescribing PPIs, medications that are not approved for infants and have potential adverse effects, unless there is documented disease or with careful monitoring. Large, well-designed, placebo-controlled, randomized trials with well-chosen end points are necessary to evaluate the effect and safety of PPIs in the entire pediatric age range."[12] page 933
Gawron et al. 2014,[7]	
• Overall, empiric PPI therapy was most effective and least costly than initial endoscopy stratification or *H. pylori* testing for initial GERD medical management in patients with reflux symptoms, except in populations with *H. pylori* prevalence greater than 40%. • An extensive evaluation of seven different PPIs and a variety of treatment regimens found that generic omeprazole (20–40 mg daily) was the least costly and most effective strategy for the medical management of GERD. • Initial PPI therapy in patients with endoscopically confirmed reflux esophagitis was less costly and more effective than first using an H2RA, or no therapy. • Both standard-dose PPI and low-dose PPI treatment dominated standard-dose H2RA treatment with more symptom-free patient-years gained and a lower cost per patient. • The results were due to a lower relapse probability with stronger therapy (standard-dose PPI) leading	"As there is very little evidence that any one PPI is superior in terms of efficacy, use of the cheapest PPI available dominated specific PPI therapeutic regimens." "There is very little evidence that more expensive PPIs offer additional major benefits over less costly PPIs for most GERD patients, especially for initial therapy. Therefore, practitioners in countries or settings without fixed formularies should be encouraged to use the least costly PPI formulation." [7] page 752

• Table A5: Summary of Findings of Included Studies	
• Main Study Findings	• Author's Conclusions
to overall lower long-term healthcare costs • In six studies, surgery was more cost effective than long-term PPI therapy (3 years to lifetime), however PPI therapy was found to be more effective and less costly than surgery at a 10-year time horizon in another study.	
Thijssen et al. 2011,[13]	
Findings from this systematic review were not pooled but reported on the basis of individual studies. The findings were not consistent for all studies. • One study found that after 5 years of follow-up medical therapy is associated with lower costs and higher utility than the surgical strategy • Another study reported although PPIs dominate LNF surgery with respect to symptom-free months, the LNF yielded a somewhat higher utility. Overall, PPIs were the most cost-effective therapy in this study • One study found LNF was more effective and more expensive compared with medical management • One study found that LNF was slightly less effective than PPIs but less expensive	"In summary, the evidence on long-term cost-effectiveness of LNF compared to PPIs is equivocal. The included economic analyses were performed at a time when trial data with a sufficient length of follow-up were not yet available. The long-term costs and effects of the competing treatment strategies were instead estimated by way of decision analytic modeling. The evidence to populate these models was, however, of varying quality. More reliable estimates of effectiveness, based on meta-analysis of long-term randomized controlled trials, are needed to improve the evidence on cost-effectiveness."[13] page 3133

AE = adverse event; CI = confidence interval; ENRD = endoscopy-negative reflux disease; ERD = erosive reflux disease; GERD = gastroesophageal reflux disease; GOR = gastro-oesophageal reflux; GORD = gastro-oesophageal reflux disease; H2RA = H2-receptor antagonist; *H. pylori* = Helicobacter pylori; ITT = intention to treat; mg = milligrams; LNF = laparoscopic Nissen fundoplication; NNT = number needed to treat; NCCP = non-cardiovascular chest pain; NERD = non-erosive reflux disease; OR = odds ratio; PP = per-protocol; PPI = proton pump inhibitor; RCT = randomized controlled trial. RR = relative risk

APPENDIX 5: Additional References of Potential Interest

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