CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT

OFFICE CANADIEN DE COORDINATION DE L'ÉVALUATION DES TECHNOLOGIES DE LA SANTÉ

Summary of Findings on the Prescribing and Use of Proton Pump Inhibitors

COMPUS Interim Report

CCOHTA

March 6, 2006

FOR CONSULTATION ONLY

Note that the information presented in this document does not constitute recommendations from COMPUS on best practices for the prescribing and use of proton pump inhibitors. This document is for consultation purposes only. Feedback obtained through consultation will be part of the information used by the COMPUS Expert Review Panel on Proton Pump Inhibitors to make recommendations. Best practices recommendations and other recommendations will be included in the final report.

Foreword

In March 2004, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) was launched by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) as a service to federal, provincial, and territorial jurisdictions, and other stakeholders. COMPUS is a nationally coordinated program, funded by Health Canada.

The goal of COMPUS is to optimize drug-related health outcomes and cost-effective use of drugs by identifying and promoting best practices in drug prescribing and use. Where possible, COMPUS builds on existing applicable Canadian and international initiatives and research. COMPUS goals will be achieved through three main approaches:

1. identifying evidence-based best practices in prescribing and use of a drug;
2. identifying gaps in best practice then proposing evidence-based interventions to close these gaps; and
3. developing tools and activities to support the implementation of these interventions.

COMPUS has been asked to identify and promote best practices related to proton pump inhibitors, diabetes management, and antihypertensives. The work in this document addresses proton pump inhibitors (PPIs).

This interim report describes summary of findings from gathering and evaluating information on best practices on the prescribing and use of PPIs for indications approved in Canada. The most recent relevant clinical practice guidelines and consensus documents were used to identify current recommended practices in prescribing and using PPIs. The quality of the evidence cited in these recommended practices was assessed and extracted data are presented in tables.

This interim report is divided by conditions related to PPI use which include GERD, dyspepsia and PUD. The following information is presented on specific clinical questions:

a) synopsis of existing recommendations on the prescribing and use of proton pump inhibitors based on existing guideline recommendations or statements;
b) an evaluation of the evidence cited in the existing guideline recommendations or statements; and
c) an assessment of the available relevant cost-effectiveness information.

These detailed summary of findings are posted on the CCOHTA website for comment by stakeholders (with the use of a provided feedback form). COMPUS will also search the literature (published since 2003) for new relevant studies.The stakeholder feedback, together with the interim report and any recent, relevant evidence, will be provided to an expert panel convened by COMPUS. The expert panel will identify, based on the evidence, best practices for the prescribing and use of PPIs and areas where further research is needed. After further public consultation on the results of the expert panel, a final report will be produced.

In parallel with this work, COMPUS will also identify appropriate interventions and strategies to encourage the evidence-based best practices in prescribing PPIs, as well as develop a toolkit of information and activities to support the implementation of these interventions.

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Abbreviations

AM	in the morning
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A MeaSurement Tool to Assess Reviews
ASA	acetylsalicylic acid
BE	Barrett's Esophagus
BID	twice daily
BMT	bismuth, metronidazole and tetracycline
CanDys	Canadian Dyspepsia Working Group
CAP	capsule
CD	consensus document
CI	confidence interval
CMA	Canadian Medical Association
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
COX	cyclo-oxygenase
CPG	clinical practice guideline
DD	double dose
DoD	Department of Defence (USA)
DR CAP	delayed-release capsule
DR TAB	delayed-release tablet
DU	duodenal ulcer
ENRD	endoscopy negative reflux disease
ENT TAB	enteric-coated tablet
FD	functional dyspepsia
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GU	gastric ulcer
H2RA	histamine H_2-receptor antagonist
Hp	*Helicobacter pylori*
H. pylori	*Helicobacter pylori*
HRQOL	health related quality of life
ICSI	Institute for Clinical Systems Improvement
IMS	IMS Health
ITT	intention-to-treat
LA	Los Angeles classification system for the endoscopic assessment of esophagitis
LD	low dose
LNF	laparoscopic Nissen fundoplication
LSM	life style modification
LU	limited use
MA	meta-analysis
MCG	microgram
MG	milligram
MOS	months
NERD	non-erosive reflux disease

NICE	National Institute for Health and Clinical Excellence
NNH	number needed to harm
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
NUD	non-ulcer dyspepsia
NZGG	New Zealand Guidelines Group
OGD	oesophago-duodenoscopy
OPOT	Ontario Program for Optimal Therapeutics
OR	odds ratio
OBS	observational study
PA	prokinetic agent
PAC	PPI plus amoxicillin and clarithromycin
pH	potential hydrogen – a measure of acidity and alkalinity
PM	in the evening
PMC	PPI plus metronidazole and clarithromycin
PP	per protocol
PPI	proton pump inhibitor
PRN	when needed
Pts	patients
PUD	peptic ulcer disease
QA	quality assessment
QD	once daily
QID	four times daily
Québec CRUM	Québec Comité de revue de l'utilisation des médicaments
RBC	ranitidine bismuth citrate
RCT	randomized controlled trial
RR	relative risk
RRR	relative risk reduction
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TAB	tablet
TID	three times daily
VHA	Veterans Health Administration (US)
ZES	Zollinger-Ellison syndrome

Glossary

Alarm features of dyspepsia in primary care: dysphagia, anemia, evidence of GI blood loss, persistent vomiting, unexplained weight loss, upper abdominal mass, family history of gastric cancer (onset at <50 years old).

Anti-secretory/ acid suppression therapy: drugs that inhibit or reduce acid secretion. Two classes of drugs belong to this category: H_2RAs and PPIs.

Asymptomatic ulcer: the condition of having peptic ulcer disease, but without symptoms.

Barrett's epithelium/esophagus: abnormal esophageal epithelium that demonstrates specialized intestinal metaplasia (esophageal columnar epithelium, intestinal metaplasia positive) on histological examination.

Bismuth subsalicylate: a non-prescription medicine used to treat diarrhea, heartburn, indigestion, and nausea. It is also a component of certain *H. pylori* eradication regimens.

Case control study: a type of observational study in which past exposures to one or more putative risk factors are measured in a group of subjects with a disease or outcome of interest (cases), and in a group without this outcome (controls), in order to ascertain the degree of association between risk factor and outcome.

Case series: description of a number of cases of a particular disease or condition, or the effects of a certain treatment.

Clinical practice guideline: a set of systematically developed statements or recommendations designed to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Cohort study: a type of observational study in which the risk of disease or other outcome is compared between a group of subjects exposed to a putative risk factor, and a group that is unexposed, in order to ascertain the degree of association between risk factor and outcome.

Consensus document: a statement on the advisable course of action in a particular clinical situation developed collectively by a group of experts through either informal or formal consensus methods.

Continuous medical maintenance therapy: the daily intake of medication for an indefinite period to prevent or minimize recurrent reflux-related symptoms or injury to esophagus.

Duodenal ulcer: an ulcer in the lining of the most proximal part of the small intestine (duodenum).

Dual therapy: involves a combination of two drugs: an antibiotic and an acid suppressor (H_2RA or PPI) or bismuth for *H. pylori* eradication.

Dyspepsia: a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract. It may include any of the following symptoms: heartburn, acid regurgitation, excessive burping/belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety. The term dyspepsia can relate to several clinical contexts such as: dysmotility-like dyspepsia, functional dyspepsia, non-ulcer dyspepsia, ulcer-like dyspepsia, uncomplicated dyspepsia and uninvestigated dyspepsia.

Dysmotility-like dyspepsia: symptom complex that may include early satiety, postprandial fullness, nausea, retching and/or vomiting and upper abdominal bloating; pain is not a dominant symptom.

Empirical therapy: treatment based on experience without adequate data to support its use.

Endoscopy-negative reflux disease (ENRD): also referred to as non-erosive GERD or symptomatic GERD, applies to individuals with GERD who have normal endoscopy results while off treatment.

Esophagitis: the minimum requisite for diagnosis of esophagitis is the presence of one erosion at the junction between the columnar and squamous epithelium.

First-line therapy: preferred initial treatment for a condition or disease.

Functional dyspepsia: 12 weeks or more (within the last 12 months) of persistent or recurrent dyspepsia and lack of evidence that organic disease is likely to explain the symptoms. It includes ulcer-like dyspepsia and dysmotility-like dyspepsia. Functional dyspepsia is diagnosed after excluding all other causes of upper abdominal pain.

Gastric protection/ gastroprotection/ cytoprotective agents: protection of the gastric mucosa against ulceration with pharmacological agents.

Gastric Ulcer: an ulcer in the lining of the stomach.

Gastroesophageal reflux disease (GERD): the reflux of gastric contents into the esophagus, causing symptoms severe enough to affect the quality of life and/or cause esophageal injury.

H_2-Blocker/ H2RA: medicines that reduce the amount of acid the stomach produces by blocking histamine2 receptors. Prescription H2-blockers include cimetidine, famotidine, nizatidine, and ranitidine.

***Helicobacter pylori* (*H. pylori*):** a spiral-shaped bacterium found in the stomach that causes gastritis and is implicated in peptic ulcer disease and gastric cancer.

Intention to treat analysis: measure of association in a clinical trial in which subjects are analyzed according to the groups to which they were initially assigned, regardless of violations

of the study protocol (e.g., poor treatment compliance, use of disallowed treatments, dropping out).

Intermittent medical maintenance of GERD: the daily intake of medication for a predetermined, finite period (usually 2 to 8 weeks) to resolve reflux related symptoms or healing of esophageal lesions following the relapse of the individual's previous condition.

Maintenance treatment: long-term treatment administered for the primary or secondary prevention of disease.

Meta-analysis: statistical synthesis of a collection of results from individual studies for the purpose of integrating findings and producing a single estimate of effect.

Meta-regression: a statistical method used in meta-analysis to explore the relationship between one or more study characteristics and the outcome of interest.

Misoprostol: a cytoprotective agent.

Non-ulcer dyspepsia: presence of dyspepsia with insignificant findings at endoscopy or a barium meal; also called functional dyspepsia.

Observational study: epidemiological studies in which the investigator measures and determines associations between one or more exposures and an outcome of interest, without intervening in or manipulating the exposures experienced by study subjects.

On demand medical therapy: daily intake of a medication for a period sufficient to achieve resolution of the reflux related symptoms. Following symptoms resolution, the medication is discontinued until the symptoms recur, at which point the medication is again taken daily until the symptoms resolve.

Perforated Ulcer: an ulcer that breaks through the wall of the stomach or the duodenum. It causes stomach contents to leak into the abdominal cavity.

Per-protocol analysis: an analysis of a clinical trial from which subjects with major violations of the study protocol are omitted.

Quadruple therapy: a combination of two antibiotics, an acid suppressor (H_2RA or PPI) and a bismuth salt for *H. pylori* eradication.

Randomized controlled trial: a prospective study designed to test the effectiveness of an intervention in which the investigator randomly allocates subjects to one or more treatment groups and a control group.

Reflux esophagitis: inflammation of the esophageal mucosa resulting from exposure to gastric contents.

Refractory GERD: typical or atypical symptoms of GERD which are resistant to therapy.

Second-line Therapy: treatment that is given upon failure of initial treatment (first-line therapy).

Symptomatic ulcer/active ulcer: the condition of having peptic ulcer disease with symptoms.

Systematic review: a summary of the medical literature that uses explicit methods to identify, select, appraise, and analyze studies relevant to a particular clinical question.

Treatment Failure: the prescribed treatment fails to resolve symptoms, to improve the condition or produces intolerable side-effects.

Triple therapy: a combination of three drugs: two antibiotics and an acid suppressor (H_2RA or PPI) or bismuth salt for *H. pylori* eradication.

Ulcer bleeding: acute or chronic ulcers that enlarge and erode through a blood vessel, causing clinical evidence of bleeding.

Ulcer-like dyspepsia: symptom complex with a predominance of epigastric pain, worse before meals and relieved by food or antacids.

Ulcer relapse/recurrence: re-ulceration after initial healing.

Uncomplicated dyspepsia: dyspepsia that is not accompanied by alarm features or associated with NSAID usage

Uninvestigated dyspepsia: dyspepsia for which no cause has yet been sought, such as with imaging or endoscopy.

Table of Contents

Foreword 1

Acknowledgements 2

Abbreviations 3

Glossary 5

1 The Issue 11

2 Objective 11

3 Background 11
3.1 Proton Pump Inhibitors 11
3.2 Conditions Related to the Use of Proton Pump Inhibitors 16

4 Methods for Clinical Evaluation 18
4.1 Identification of Clinical Practice Guidelines and Consensus Documents 18
4.2 Selection of Guidelines and Consensus Documents for Literature Search 19
4.3 Stakeholder Input 20
4.4 Selection, Grouping and Synthesis of PPI Therapeutic Recommendations 20
4.5 Selection of the Evidence Cited in Recommendations 20
4.6 Quality Assessment of the Evidence 23
4.7 Data Extraction 23
4.8 Summary of the Clinical Evidence 24

5 Methods for Economic Evaluation 24
5.1 Identification and Selection of Relevant Economic Studies 24
5.2 Extraction of Economic Data 24
5.3 Assessment of Economic Studies 24

6 Results of Identification and Selection of Clinical and Economic Information 25
6.1 Quantity of Guidelines and Consensus Documents Selected 25
6.2 Quantity of Economic Studies Selected 25

7 Presentation of Results 27
7.1 Clinical Information 27
7.2 Economic Evidence 28

8 Clinical Evidence for GERD 29
8.1 Clinical Questions for GERD 29
8.2 Clinical Evidence for GERD 33

9 Summary of Economic Studies Related to GERD, Reflux Esophagitis or Barrett's Esophagus 81

10 Clinical Evidence for Dyspepsia 87
10.1 Clinical Questions for Dyspepsia 87
10.2 Clinical Evidence for Dyspepsia 90

11 Summary of Economic Studies Related to Dyspepsia 123

12 Clinical Evidence for Peptic Ulcer Disease 126
12.1 Clinical Questions for PUD 126
12.2 Clinical Evidence for PUD 128

13 Summary of Economic Studies Related to PUD 178

14 References 180

Appendix 1: Indications for Proton Pump Inhibitors in Canada 210
Appendix 2: Literature Search Strategies 214
Appendix 3: AMSTAR Instrument for Systematic Reviews 220
Appendix 4a: Adapted SIGN 50 Checklist for Randomized Controlled Trials 222
Methodology Checklist: Randomized Controlled Trials 222
Appendix 4b: Adapted SIGN 50 Checklist for Cohort Studies 224
Methodology Checklist: Cohort studies 224
Appendix 4c: Adapted SIGN 50 Checklist for Case Control Studies 226
Methodology Checklist 4: Case-control studies 226
Appendix 5: Data Extraction Table Used for Economic Studies 228
Appendix 6: List of Excluded Guidelines and Consensus Documents 231
Appendix 7: List of Selected Guidelines and Consensus Documents 237
Appendix 8: List of Excluded Economic Studies 242
Appendix 9: Selected Economic Studies and Relevant Synopsis of Existing Recommendations 247
Appendix 10: Guideline Matrix Table: GERD 248
Appendix 11: Guideline Matrix Table: Dyspepsia 251
Appendix 12: Guideline Matrix Table: Peptic Ulcer Disease 254
Appendix 13: Evidence Inventory Tables for GERD, Reflux Esophagitis and Barrett's Esophagus 256
Appendix 14: Evidence Inventory Tables for Dyspepsia 261
Appendix 15: Evidence Inventory Tables for Peptic Ulcer Disease 266
Appendix 16: Summary of Economic Studies Related to GERD 269
Appendix 17: Summary of Economic Studies Related to Dyspepsia 279
Appendix 18: Summary of Economic Studies Related to Peptic Ulcer Disease 284

1 The Issue

The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) was tasked by the federal, provincial and territorial ministries of health to identify and promote the implementation of evidence-based and cost-effective best practices in the prescribing and use of proton pump inhibitors. Since their introduction to the market, the use of this class of drugs continues to grow in Canada. Calculations performed on IMS data reveal that the estimated total number of prescriptions for proton pump inhibitors (PPIs) dispensed by the Canadian retail pharmacies increased by 15% from 10.8 million prescriptions in 2003 to 12.4 million prescriptions in 2004 with a 10% increase in total drug expenditure. (Source: IMS Health Canada, Montreal: personal communication, 2005 Jan 24). In view of the widespread and growing use of PPIs, healthcare providers, consumers and policy makers require evidence-based information that facilitates the best practices in the use of these agents.

2 Objective

The objective of this report is to identify evidence-based best practices, taking into consideration cost-effectiveness information when available, for the optimal prescribing and use of proton pump inhibitors in the management of:

1. gastroesophageal reflux disease;
2. reflux esophagitis;
3. Barrett's esophagus;
4. dyspepsia;
5. peptic ulcer disease;
6. NSAID-associated ulcer;
7. *H. pylori* eradication; and
8. Zollinger Ellison syndrome.

3 Background

3.1 Proton Pump Inhibitors

Proton pump inhibitors are compounds that suppress gastric acid secretion. They are approved for use in the treatment of conditions where the control of gastric acid is needed such as: gastric ulcers; reflux esophagitis; gastroesophageal reflux disease; and the eradication of *Helicobacter pylori*.[1] PPIs work by irreversibly inhibiting a gastric enzyme (H^+/K^+- ATPase); the proton pump system controls acid levels in the gastrointestinal system.

There are five PPI agents currently available on the Canadian market. (Table 1) Omeprazole (Losec®) was the first PPI introduced in Canada in 1989 followed by lansoprazole (Prevacid®) in 1995, pantoprazole (Pantoloc®) in 1996, and both rabeprazole (Pariet®) and esomeprazole (Nexium®) in 2001. Apo-Omeprazole, approved for marketing in 2004, is currently the only generic PPI available in Canada.[2] The other PPIs are still under patent protection.

The approved indications in Canada for these drugs are described in Appendix 1. Costs related to PPI use are listed in Table 2.

Table 1: Proton Pump Inhibitors Available in Canada

Drug	Strength	Dosage Form
Esomeprazole (Nexium, AstraZeneca)	20mg 40mg	DR tab DR tab
Lansoprazole (Prevacid, Abbott)	15mg 30mg	DR cap DR cap
Omeprazole (Losec, AstraZeneca)	10mg 20mg 40mg	DR cap DR cap DR cap
Omeprazole magnesium (Losec & Losec MUPs, AstraZeneca)	10mg 20mg	DR tab DR tab
Omeprazole (Apo-omeprazole, Apotex)	20mg	cap
Pantoprazole (Pantoloc, SolvayPharma)	20mg 40mg	EC tab EC tab
Rabeprazole Sodium (Pariet, Janssen-Ortho)	10mg 20mg	EC tab EC tab
DR: delayed release; EC: enteric coated		

Table 2: Comparable Adult Doses and Daily Costs[a] of Proton Pump Inhibitors for Approved Indications

Drug	**OMEPRAZOLE & OMEPRAZOLE Mg (Losec, Losec MUPS --AstraZeneca)**	**OMEPRAZOLE (ApoOmeprazole --Apotex)**	**LANSOPRAZOLE (Prevacid--Abbott)**	**PANTOPRAZOLE (Pantoloc--Solvay Pharma)**	**ESOMEPRAZOLE (Nexium--AstraZeneca)**	**RABEPRAZOLE (Pariet-- Janssen-Ortho)**	**LAN/CLAR/AMOX[#] (Hp-PAC--Abbott)**
Format & Strength & Price ($)	**per cap; tab; DR tab 10 mg: 1.7500 20 mg: 2.2000 40 mg: 3.0800/cap**	**20 mg: 1.2500/cap**	**15 mg: 2.000/cap 30 mg: 2.000/cap**	**20 mg: 1.7000/tab 40 mg: 1.9000/tab**	**20 mg: 2.1000/tab 40 mg: 2.1000/tab**	**10 mg: 0.6500/tab 20 mg: 2.7400/tab**	**Per 7 day pack: 78.2400**
Duodenal Ulcer Active	20 – 40 mg daily	20 – 40 mg daily	15 mg daily	40 mg daily		20 mg daily	
Cost ($)	2.2000-4.4000[§]/d	1.2500-2.5000/day	2.0000/day	1.9000/day	--	1.3000/day[b]	--
Duodenal Ulcer Maintenance	10 – 40 mg daily		15 mg daily				
Cost ($)	1.7500-4.4000[§]/d	--	2.0000/day	--	--	--	--
Gastric Ulcer Active	20 – 40 mg daily	20 – 40 mg daily	15 mg daily	40 mg daily		20 mg daily	
Cost ($)	2.2000-4.4000[§]/d	1.2500-2.5000/day	2.0000/day	1.9000/day	--	1.3000/day[b]	--
Gastric Ulcer Maintenance	20 – 40 mg daily	20 – 40 mg daily					
Cost ($)	2.2000-4.4000[§]/d	1.2500-2.5000/day	--	--	--	--	--
NSAID Associated Duodenal Ulcers Active	20 mg daily	20 mg daily					
Cost ($)	2.2000/day	1.2500/day	--	--	--	--	--
NSAID Associated Duodenal Ulcers Maintenance	20 mg daily	20 mg daily					
Cost ($)	2.2000/day	1.2500/day	--	--	--	--	--
NSAID Associated Gastric Ulcers Active	20 mg daily	20 mg daily	15 – 30 mg daily		20 mg daily		
Cost ($)	2.2000/day	1.2500/day	2.000/day	--	2.1000/day	--	--
NSAID Associated Gastric Ulcers Maintenance	20 mg daily	20 mg daily					
Cost ($)	2.2000/day	1.2500/day	--	--	--	--	--
Risk Reduction of NSAID-associated Gastric Ulcer			15 mg daily	20 mg daily	20 mg daily		
Cost ($)	--	--	2.0000/day	1.7000/day	2.1000/day	--	--
Prevention of NSAID-induced GI lesions				20 mg daily			
Cost ($)	--	--	--	1.7000/day	--	--	--
Reflux Esophagitis Acute	20 – 40 mg daily	20 – 40 mg daily	30 mg daily	40 mg daily	40 mg daily	20 mg daily	
Cost ($)	2.2000-4.4000[§]/d	1.2500-2.5000/day	2.0000/day	1.9000/day	2.1000/day	1.3000/day[b]	--
Reflux Esophagitis Maintenance	10 – 40 mg daily		15 mg daily	20 – 40 mg daily	20 mg daily	10 – 20 mg daily	
Cost ($)	1.7500-4.4000[§]/d	--	2.0000/day	1.7000–1.9000/day	2.1000/day	0.6500-1.3000/d[b]	--
Barrett's Esophagus			30 mg daily				
Cost ($)	--	--	2.0000/day	--	--	--	--
	10 – 20 mg daily	20 mg daily	15 mg daily	40 mg daily	20 mg daily	10 – 20 mg daily	

Drug	**OMEPRAZOLE & OMEPRAZOLE Mg (Losec, Losec MUPS --AstraZeneca)**	**OMEPRAZOLE (ApoOmeprazole --Apotex)**	**LANSOPRAZOLE (Prevacid--Abbott)**	**PANTOPRAZOLE (Pantoloc--Solvay Pharma)**	**ESOMEPRAZOLE (Nexium--AstraZeneca)**	**RABEPRAZOLE (Pariet-- Janssen-Ortho)**	**LAN/CLAR/AMOX[#] (Hp-PAC--Abbott)**
Format & Strength & Price ($)	**per cap; tab; DR tab 10 mg: 1.7500 20 mg: 2.2000 40 mg: 3.0800/cap**	**20 mg: 1.2500/cap**	**15 mg: 2.000/cap 30 mg: 2.000/cap**	**20 mg: 1.7000/tab 40 mg: 1.9000/tab**	**20 mg: 2.1000/tab 40 mg: 2.1000/tab**	**10 mg: 0.6500/tab 20 mg: 2.7400/tab**	**Per 7 day pack: 78.2400**
Symptomatic GERD Treatment	10 – 20 mg daily	20 mg daily	15 mg daily	40 mg daily	20 mg daily	10 – 20 mg daily	
Cost ($)	1.7500-2.2000/day	1.2500/day	2.0000/day	1.9000/day	2.1000/day	0.6500-1.3000/d[b]	--
Symptomatic GERD Maintenance	10 mg daily						
Cost ($)	1.7500/day	--	--	--	--	--	--
Dyspepsia	10 – 20 mg daily (tab & MUPS)						
Cost ($)	1.7500-2.2000/day	--	--	--	--	--	--
Zollinger-Ellison Syndrome	60 mg daily[‡] (up to 360 mg/day)	60 mg daily[‡] (up to 360 mg/day)	60 mg daily (up to 90 mg BID)			60 mg daily (up to 60 mg BID)	
Cost ($)	6.6000/day up to 39.6000/day	3.7500/day up to 22.5000/day	4.0000 up to 12.0000/day	--	--	3.9000/day up to 7.8000/day[b]	--
Eradication Therapy (DU)	20 mg BID‡‡		30 mg BID[β]	40 mg BID[ο]	20 mg BID**	20 mg BID**	Lan/Clar/Amox[#]BID
Cost ($)	4.4000/d	--	4.0000/day	3.8000/day	4.2000/day	2.6000/day[b]	11.1771/day
To ensure healing after eradication therapy (DU)	20 mg daily						
Cost ($)	2.2000/day	--	--	--	--	--	--
Eradication Therapy (GU)	20 mg BID‡‡						
Cost ($)	4.4000/day	--	--	--	--	--	--
To ensure healing after eradication therapy (GU)	20 – 40 mg daily						
Cost ($)	2.2000-4.4000[§]/d	--	--	--	--	--	--
Pediatric GERD (erosive & non-erosive esophagitis)			15 mg (≤30kg) daily 30 mg (≥30kg) daily				
Cost ($)	--	--	2.0000/day 2.0000/day	--	--	--	--
Source of Prescribing Information [Product Monograph (PM)]	Losec caps PM[3] Losec DR tabs PM[4] Losec MUPS PM[5]	Apo-Omeprazole PM[6]	Prevacid PM[7]	Pantoloc PM[8]	Nexium PM[9]	Pariet PM[10]	Hp-PAC PM[11,11]

Shaded cells: Not an approved indication

a Manufacturer's list prices used. Dispensing fees and wholesaler mark-up are not included.
b Cost for Pariet is based on using the 10mg tablets as it is the most economical form of Pariet.
§ Cost for Losec 40mg is expressed as $4.4000 (2 X 2.2000) as the Losec 40mg capsule is not commonly used in Canada.
‡ More than 90% of patients are controlled with doses of 20 to 120mg daily at a cost of $2.2000-13.2000/d for Losec and $1.2500-7.5000/day for Apo-Omeprazole.
# Lan/Clar/Amox—components of Hp-PAC include lansoprazole 30mg delayed release capsules; clarithromycin 500 mg tablets; and amoxicillin 500mg capsules

ß with amoxicillin 1000mg and clarithromycin 500mg BID x 7d, 10d or 14d
** with amoxicillin 1000mg and clarithromycin 500mg BID x 7d
º with amoxicillin 1000mg and clarithromycin 500mg BID OR metronidazole 500mg and clarithromycin 500mg BID x 7d
±± with amoxicillin 1000mg and clarithromycin 500mg BID (Losec 1-2-3 A) OR metronidazole 500mg and clarithromycin 250mg BID (Losec 1-2-3 M) x 7d

3.2 Conditions Related to the Use of Proton Pump Inhibitors

3.2.1 Gastroesophageal reflux disease (GERD)

Gastroesophageal reflux is the movement of gastric contents from the stomach back into the esophagus. The most common symptoms of patients with GERD are heartburn and regurgitation. Endoscopic examination of the esophagus may or may not show erosive esophagitis (erosion of the esophagus by acid).[12,13]

In Canada, GERD is the most prevalent acid related disease and significantly impairs health related quality of life.[12] A population-based study shows that up to 10% of Canadians have isolated heartburn.[14]

Although the complications associated with GERD are not very common they may include deep ulcer, strictures, hemorrhage, anemia and Barrett's esophagus. [15,16] Mortality associated with GERD is very low (1/100,000).[17]

3.2.2 Reflux Esophagitis

Reflux esophagitis is one of the complications of GERD and is characterized by inflammation and ulceration of the esophagus as seen with endoscopic examination. It is caused by acidic gastric contents refluxing back into the esophagus. Heartburn is a characteristic symptom of reflux esophagitis and may be associated with regurgitation or a feeling of warm fluid climbing up the throat.[18] Approximately 30% of the patients in primary care and general practice with GERD showed endoscopic evidence of esophagitis.[12]

3.2.3 Barrett's Esophagus

In Barrett's esophagus, the stratified squamous epithelium that normally lines the distal esophagus is replaced by an abnormal columnar epithelium that has intestinal features. This process is called intestinal metaplasia and it is one of the complications of GERD. It is usually detected during the endoscopic examination of the esophagus when symptoms of GERD are being evaluated. This condition does not cause any noticeable symptoms but a very small number of patients with Barrett's esophagus develop esophageal adenocarcinoma.[19]

3.2.4 Dyspepsia

Dyspepsia describes a heterogeneous group of symptoms (such as pain or discomfort centred in the upper abdomen) with many underlying causes (e.g. peptic ulcer disease, GERD, gastritis, gastric cancer, drug-induced dyspepsia, etc.). Dyspepsia is a common condition in Canada (prevalence of 29%),[14] that significantly diminishes the quality of life of patients. An estimated 7% of the average Canadian family physician's practice is devoted to the management of dyspepsia.[20] Although the Rome II definition of dyspepsia does not include reflux disease, the Canadian Dyspepsia Working Group considers that reflux disease is an integral source of uninvestigated dyspepsia.[21]

3.2.5 Peptic Ulcer Disease (PUD)

Peptic ulcer disease is a condition of the upper gastrointestinal tract characterized by erosions and/or ulcerations of the gastric or duodenal walls.[22] The mucosal ulceration seen in PUD is due to alterations in the normal defense mechanisms of the mucosa, and acid hypersecretion in

some cases. The lifetime incidence of PUD is estimated at 10% in men and 4% in women.[23] PUD may cause abdominal pain and other gastrointestinal symptoms such as heartburn, nausea, vomiting, belching and bloating. However, some patients with PUD are asymptomatic. Upper gastrointestinal bleeding, perforation, and obstruction are serious, life-threatening complications that occur in a small percentage of PUD sufferers.[22] The two major etiological factors in PUD are infection with *H. pylori* and the use of non-steroidal anti-inflammatory drugs (NSAIDs), both of which produce mucosal damage through various mechanisms.[22]

A small fraction of ulcers are associated with neither *H. pylori* infection nor NSAID use. Some of these ulcers are due to other medical conditions such as Zollinger-Ellison syndrome or Crohn's disease, or the ingestion of drugs other than NSAIDs.[24]

3.2.6 NSAID-associated Ulcers

NSAID use is a well-established risk factor for the development of ulcers. The prevalence of endoscopically-proven gastric ulcers is 12% to 30% in individuals with arthritis taking NSAIDs over several months, while that of duodenal ulcers is 2% to19%. In comparison, the prevalence estimates of gastric and duodenal ulcers in the general population are 0.3% and 1.4%, respectively.[22] NSAID users are also at higher risk for bleeding ulcers and other complications.[24] Furthermore, the risk of ulceration in NSAID-users increases with age in comparison to NSAID non-users from 1.5 fold greater risk in those age 60 or less to five times greater risk in those older than age 60.[25] Other risk factors for NSAID-associated ulcers are: concomitant comorbidity, past history of PUD, concomitant use of steroids, combined NSAID use and the type and dose of NSAID.

3.2.7 *H. pylori* Infection

H. pylori is a bacterium that infects the gastric mucosa and is associated with chronic gastritis, peptic ulcer, and gastric cancer. The prevalence of the infection is 20% to 40% in Canada. Although the majority of patients infected with the organism do not develop clinically apparent disease, the risk of peptic ulcer in those infected is about twice that of uninfected individuals.[26] More than 90% of patients with duodenal ulcers, and 70% to 84% of those with gastric ulcer, are infected with the organism. Successful eradication of the infection leads to healing and a reduction in recurrence rates to less than 5% per year.[23] *H. pylori* may also have a role in other upper gastrointestinal diseases such as non-ulcer dyspepsia.[24]

3.2.8 Zollinger-Ellison syndrome (ZES)

ZES is a syndrome of single or multiple gastrointestinal ulcerations that result from benign or malignant islet cell tumours of the pancreas (gastrinomas) that secrete high levels of gastrin. The symptoms of ZES include signs of peptic ulcers: burning pain in the abdomen; diarrhea; nausea; vomiting; fatigue; weakness; weight loss; and bleeding. It is a rare disease and its prevalence is estimated to be 0.1 to 3 per million in the US.[27]

4 Methods for Clinical Evaluation

The COMPUS approach for identifying evidence-based best practices is to build on existing work rather than initiating a systematic review of primary studies. Accordingly, the most recent clinical practice guidelines (CPGs) and consensus documents (CDs) published or generated at the time of this project which contained recommendations on the prescribing or use of PPIs were used as the main source of evidence for best practices and economic studies.

The following steps summarize the process used to identify and evaluate the clinical information related to the best practices on PPI prescribing and use:

- Identification and selection of guidelines and consensus documents related to approved PPI indications;
- Selection, grouping and synthesis of recommendations, contained within the guidelines or consensus documents, on PPIs addressing the same clinical question;
- Selection, assessment and extraction of the evidence supporting each of these recommendations; and,
- Summarizing the evidence related to each synopsis of existing recommendation around different clinical situations.

4.1 Identification of Clinical Practice Guidelines and Consensus Documents

A search strategy (Appendix 2) was designed to retrieve published, web-published and unpublished guidelines and consensus documents that focused on either PPIs or indications for the use of PPIs. MEDLINE®, BIOSIS Previews®, EMBASE® and PASCAL were searched on the DIALOG® search system. Drug registry numbers were searched in MEDLINE®, BIOSIS Previews® and PASCAL but were excluded from searching in EMBASE® to avoid large numbers of false hits. The search combined controlled vocabulary descriptors and free-text keywords, and was not limited by date or by language. A highly sensitive filter was created to restrict the results to guidelines and consensus documents. Parallel searches were run on PubMed, the Cochrane Library and CINAHL (Ovid).

Internet-based collections of guidelines were searched, including CMA Infobase, AHRQ's National Guidelines Clearinghouse, the NHS National Electronic Library of Health Guidelines Finder, and the Guidelines International Network web site.

Grey literature was retrieved by searching selected web sites and by general Internet searching using the Google™ and Yahoo! ® search engines. Specific websites of gastroenterology associations, guideline-producing bodies and organizations concerned with the creation and regulation of health information and systems were also searched. General Internet searching was executed. Grey literature searching techniques on the Internet were limited by the search options available on individual websites and search engines, but when possible MESH headings and keywords were used from the principle search strategy.

4.2 Selection of Guidelines and Consensus Documents for Literature Search

Two steps were taken to identify relevant guidelines and consensus documents: a) documents were selected from the systematic literature search and b) stakeholders were invited to provide missing documents via the CCOHTA website.

The eight indications in which PPIs are used were sorted into three groups as follows:

- GERD, reflux esophagitis, Barrett's espophagus (referred to as GERD)
- Dyspepsia
- PUD, NSAID-associated ulcer, *H. pylori* infection, and Zollinger-Ellison syndrome. (referred to as PUD)

All selected guidelines and consensus documents were sorted into these three groups. Some overlap occurred and sorting was clarified with the input of a clinical expert.

The titles and abstracts of documents obtained in the literature search were independently verified by two reviewers and a list of potentially relevant citations was identified according to the inclusion criteria described below. The full-text documents of all selected citations were retrieved.

Full-text documents were independently assessed by two reviewers to examine whether they contained relevant recommendations for the use of PPIs in GERD, reflux esophagitis, Barrett's esophagus, dyspepsia, PUD, NSAID-associated ulcer, *H. pylori* infection, or Zollinger-Ellison syndrome in adults and children. Any disagreements were resolved by consensus between the two reviewers or through the intervention of a third reviewer.

4.2.1 Selection Criteria for Guidelines and Consensus Documents

Clinical guidelines and consensus documents were selected or excluded from the results of the literature search based on the following inclusion and exclusion criteria.

a. Inclusion criteria:

- Guidelines or consensus documents prepared by professional bodies or groups in Canada, the United States, Australia, New Zealand, the UK, and Western Europe that contained recommendations on using pharmacotherapy for the management of GERD, esophagitis, Barrett's esophagus, dyspepsia, PUD, NSAID-associated ulcer, *H. pylori* infection, or ZES in adults and children.

b. Exclusion criteria:

- Documents other than guidelines or consensus documents (e.g. reviews, randomized controlled trials, observational studies, surveys, letters to the editor, and comments);
- Guidelines or consensus documents for diseases other than GERD, reflux esophagitis, Barrett's esophagus, dyspepsia, PUD, NSAID-associated ulcer, *H. pylori* infection or ZES.
- Guidelines or consensus documents for the procedure of endoscopy, pH monitoring and surgical management of acid related disorders
- Duplicate citations

- Outdated versions of guidelines that have since been updated by the same society or group.
- Non-English guidelines.

4.3 Stakeholder Input

Stakeholders were consulted to provide any missing relevant guidelines or consensus documents. The proposed list of relevant guidelines and consensus documents to be included in this project was posted on the COMPUS web site on July 27, 2005. Stakeholders were invited through the e-bulletin, the COMPUS Communiqué to identify missing CPGs or CDs. The deadline for feedback was August 12, 2005. Additional guidelines and consensus documents identified by the stakeholders that met COMPUS inclusion criteria were added to the final list of selected documents.

4.4 Selection, Grouping and Synthesis of PPI Therapeutic Recommendations

Existing recommendations in CPGs and CDs related to the clinical conditions related to the use of PPIs were identified and selected independently by two reviewers. All discrepancies in the selection of recommendations were resolved by consensus.

Two reviewers, working by consensus, grouped similar recommendations from different CPGs and CDs according to GERD, dyspepsia or PUD. These recommendations were then synthesized into one overall "synopsis of existing recommendations" and reviewed by a clinical expert to ensure appropriate grouping and wording. Based on the synthesized statements, clinical questions were developed. The clinical situations reflected in the questions, synopsis of existing recommendations and the original recommendations from CPGs and CDs were tabulated (Guideline Statements Tables).

4.5 Selection of the Evidence Cited in Recommendations

For each recommendation extracted from the CPGs and CDs, two reviewers independently identified the studies and other publications cited as supporting information (i.e., evidence). Full text articles of this evidence were obtained and classified by study design into systematic reviews, randomized controlled trials (RCTs), observational studies or others. Two reviewers independently checked the relevance of the evidence to the recommendation for which it was cited. If the evidence was deemed to be irrelevant (e.g., obvious error in referencing in the guidelines, economic studies, studies not involving PPIs), it was omitted from further evaluation.

A variety of types of evidence was cited for the extracted recommendations. For this project, systematic reviews were considered to be the highest level of evidence. Evidence was selected based upon the following hierarchy of study design: systematic reviews, RCTs, observational studies and finally narrative reviews or expert opinion. The detailed description of the decision path used to select the evidence is shown in Figures 1a to 1d. An inventory of the selected evidence cited by the recommendations was then tabulated. (Evidence Inventory Tables)

The evidence behind each synopsis of existing recommendations was selected and the quality of the studies assessed (section 4.6) as described below.

Fig 1a: Systematic Reviews

Two reviewers independently assessed the quality of each SR by applying the AMSTAR instrument for systematic reviews (Appendix 3). The relevant data was extracted by one reviewer and checked by a second reviewer.

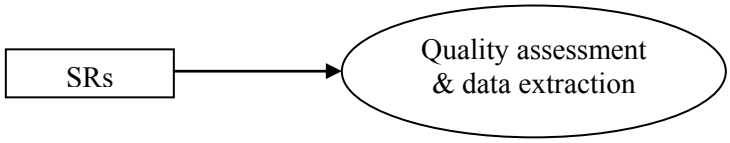
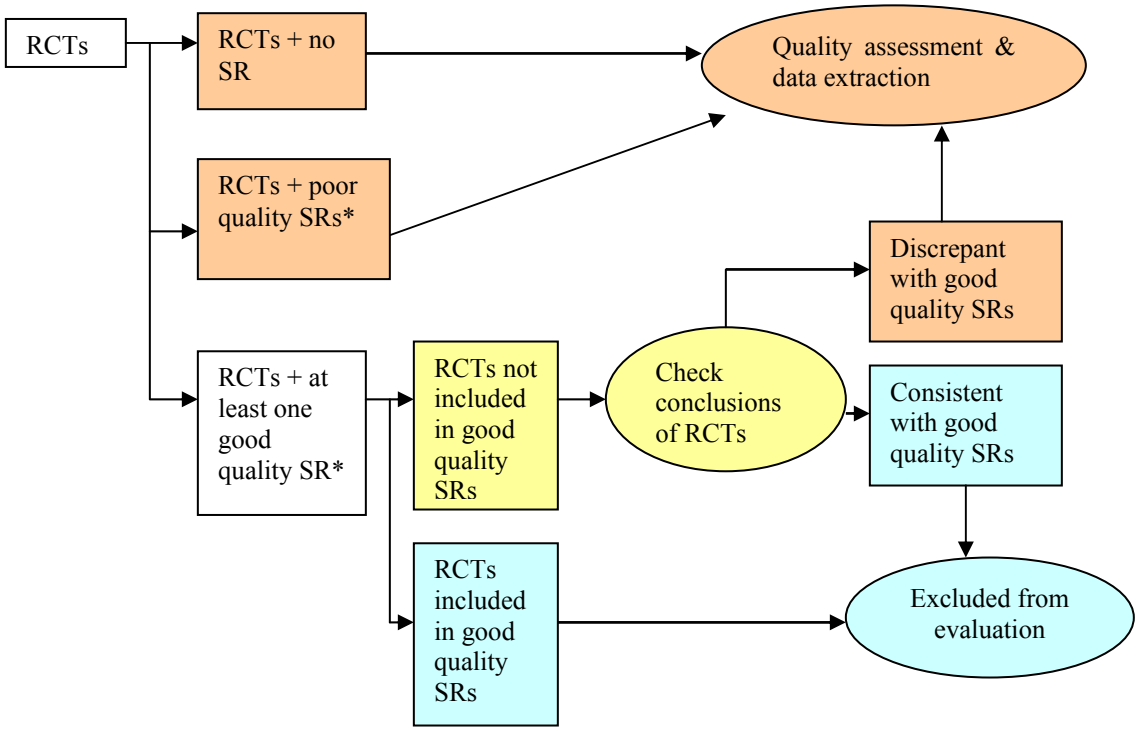


Fig 1b: Randomized controlled trials

RCTs were considered for evaluation as secondary evidence after SRs when:

- There were no SRs cited in support of a recommendation. In this case, all cited RCTs were assessed for quality and data were extracted.
- Only poor quality SRs (as determined by the AMSTAR instrument for systematic reviews (Appendix 3) were cited along with RCTs. In this case, all cited RCTs were assessed for quality and data were extracted.
- One or more good quality SRs were cited along with additional RCTs not included in these reviews. The conclusion of each of these RCTs was checked against those of the good quality SR(s) and if discrepant, the RCT was assessed for quality and data were extracted. If there was agreement, the RCT was excluded from further analysis.

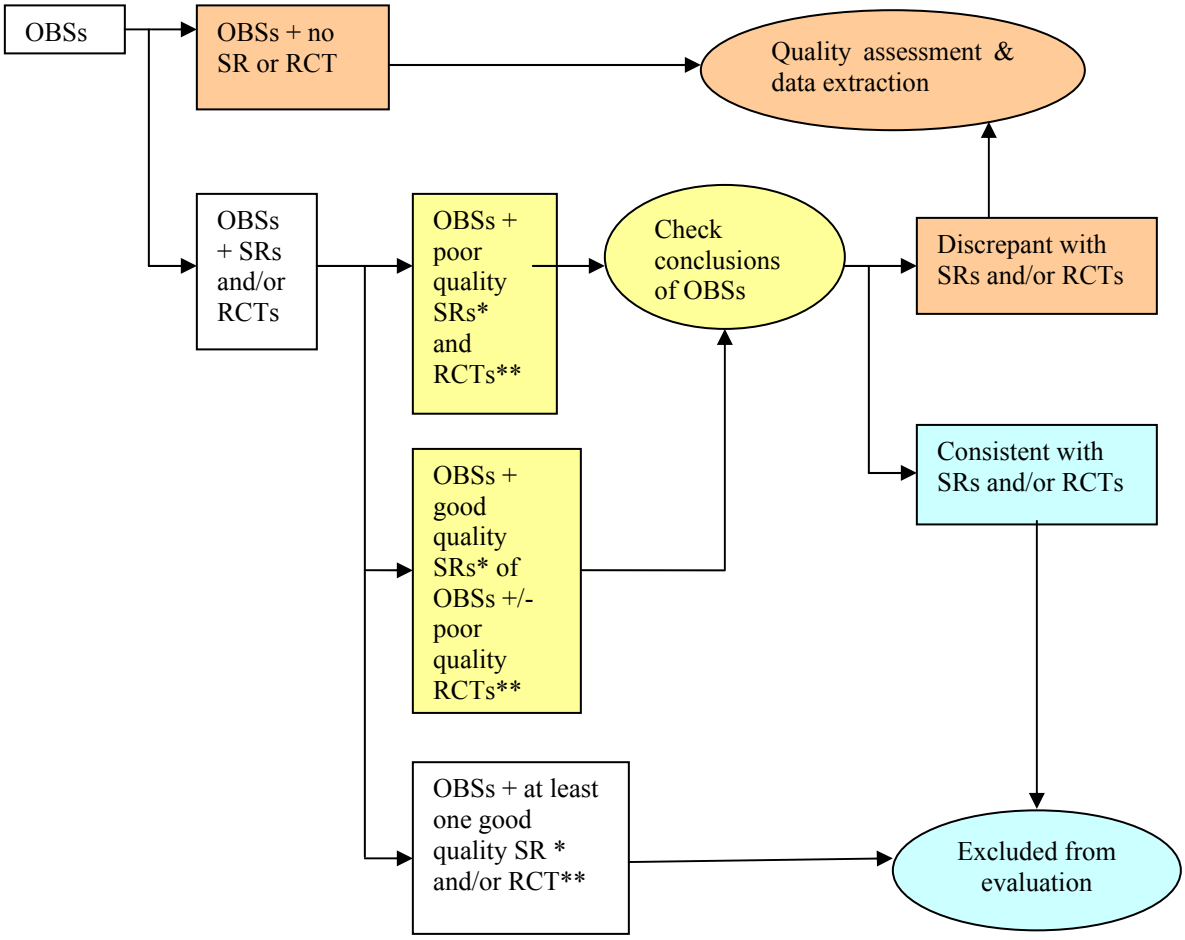


*good quality SRs (≥6), poor quality SRs (<6) (AMSTAR instrument, Appendix 3)

Fig 1c: Observational studies

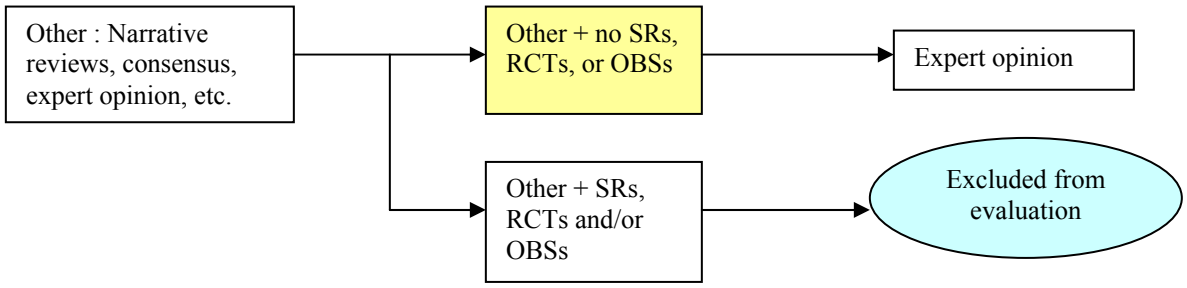
OBSs were considered for evaluation when:

- There were no SRs or RCTs cited for a recommendation. In this case, all cited OBSs were assessed for quality and data were extracted.
- All cited SRs and RCTs were of poor quality. In this case, the conclusions of all cited OBSs were checked and compared with those of the SRs and RCTs. Discrepant OBSs were assessed for quality and data extracted. OBSs consistent with the conclusions of the SRs and RCTs were excluded from further evaluation.
- The only good quality SRs cited were of OBSs, and no good quality RCTs were cited. The conclusion of each cited OBS not included in the SR(s) was checked against the conclusion of the SR(s), and if discrepant, the study was assessed for quality and data were extracted. On the other hand, if there was agreement, the OBS was excluded from further analysis.



*good quality SRs (≥6), poor quality SRs (<6) (AMSTAR, Appendix 3)
** very good quality RCTs (++), good quality RCTs (+), poor quality RCTs (-) (Adapted SIGN 50 Checklist for RCTs, Appendix 4a)

Fig 1d: Other (narrative reviews, consensus, expert opinion, etc.)
If there were no SRs, RCTs or OBSs cited for a recommendation, any narrative reviews, consensus statements and expert opinions were reported as expert opinion. Otherwise, they were excluded from the evaluation.



4.6 Quality Assessment of the Evidence

Two reviewers independently assessed the quality of all selected studies (except expert opinion, case reports and case series) and resolved any discrepancies by consensus or the intervention of a third reviewer.

The quality of systematic reviews was assessed using the 11 point AMSTAR instrument (Appendix 3). The median score of 6 was chosen in consultation with the originator of the AMSTAR instrument to differentiate good quality systematic reviews (≥6) from poor quality (<6) systematic reviews.

The quality of RCTs was assessed using the adapted SIGN 50 methodology checklist for randomized controlled trials. (Appendix 4a) The overall assessment of RCTs was classified into ++, + or – and scored as very good quality, good quality or poor quality, respectively.

Similarly, the adapted SIGN 50 methodology checklists (Appendix 4b, 4c) were used to assess the quality of cohort studies and case control studies, respectively.

4.7 Data Extraction

After identifying and assessing the evidence, one reviewer extracted the following data about each SR, RCT and OBS: the type of study, population, intervention, comparator, outcome measure, results, sample size, and source of funding. In addition, information about the objective of the study, the number and types of included studies, the databases searched, the method of data synthesis and statistical heterogeneity was collected from SRs, while the length of follow-up and sites of study were extracted from RCTs. A second reviewer checked all data extraction tables by comparing them with the original studies.

4.8 Summary of the Clinical Evidence

The clinical evidence results were summarized in various tables. The first table shows the "synopsis of existing recommendations" suggesting a best practice, with the original relevant recommendations and statements from which it is derived. The summary of evidence related to each clinical question is shown in the second table with details of the supporting studies.

5 Methods for Economic Evaluation

5.1 Identification and Selection of Relevant Economic Studies

Two approaches were taken to identify relevant economic studies related to the prescribing and use of PPIs for the approved indications defined in the objectives section. First, the titles of the final list of selected clinical practice guidelines and consensus documents from the clinical evalution and their references were checked for reference to economic studies. All potential economic studies were then retrieved in full text and selected based on the following criteria:

- the study was conducted in the Canadian health care setting
- the study was related to the "synopsis of existing recommendations".

The second approach involved a search strategy created to retrieve economic studies of PPIs in the treatment of indications for the use of proton pump inhibitors. (Appendix 2) MEDLINE®, BIOSIS Previews® and EMBASE® were searched on the DIALOG® search system. Drug registry numbers were searched in MEDLINE®, BIOSIS Previews® and PASCAL but were excluded from searching in EMBASE® to avoid large numbers of false hits. A more sensitive filter was created and used in combination with a filter to identify Canadian studies, while a less sensitive filter was created and applied to all other search results. The search combined controlled vocabulary descriptors and free text keywords, and was not limited by date or language. A parallel search was run on the Cochrane Library.

The abstracts were reviewed using the same criteria as for the hand search. Where available, the full text version was retrieved.

The two lists of selected studies from each approach were compared and duplicates removed.

5.2 Extraction of Economic Data

A summary of each selected economic study was written along with comments. The data were extracted from each study, where available, using the data extraction form as shown in Appendix 5.

5.3 Assessment of Economic Studies

The quality and relevance of the economic studies were described using key parameters identified in consultation with an external health economist expert. To assess the quality the following study parameters were examined: timelines, type of study, outcomes,

efficacy/effectiveness, cost, discounting and summary efficiency measure. To assess relevance the following parameters were examined: population, intervention, time frame and setting. (Appendix 5) Many of the parameters align with those in the 'BMJ checklist'.[28] The quality and relevance data was extracted by one economist and reviewed by another for accuracy.

6 Results of Identification and Selection of Clinical and Economic Information

6.1 Quantity of Guidelines and Consensus Documents Selected

The selection of final relevant documents is shown in the flow diagram in Fig 2. Of the 3823 citations and documents obtained from the database searches, Internet-based search and grey literature, 3668 were excluded. The remaining 155 potentially relevant documents were retrieved for further selection. Of these 155 documents, a total of 86 did not meet the selection criteria, (Appendix 6) leaving 69 unique guidelines and consensus documents that were selected for review.

At this point, the list of selected guidelines and documents was posted on the CCOHTA website for stakeholder input to identify any missing documents. From this consultation, one unique guideline document that met our selection criteria was brought to our attention.

The final selection included 70 unique guideline and consensus statement documents. (Appendix 7) A total of 28 guidelines and consensus documents were selected for GERD, reflux esophagitis and Barrett's esophagus, 20 for dyspepsia and 33 for peptic ulcer disease, NSAID-associated ulcer, and *H. pylori* eradication. Eleven documents applied to more than one disease area. No guidelines or consensus documents were found for Zollinger-Ellison syndrome.

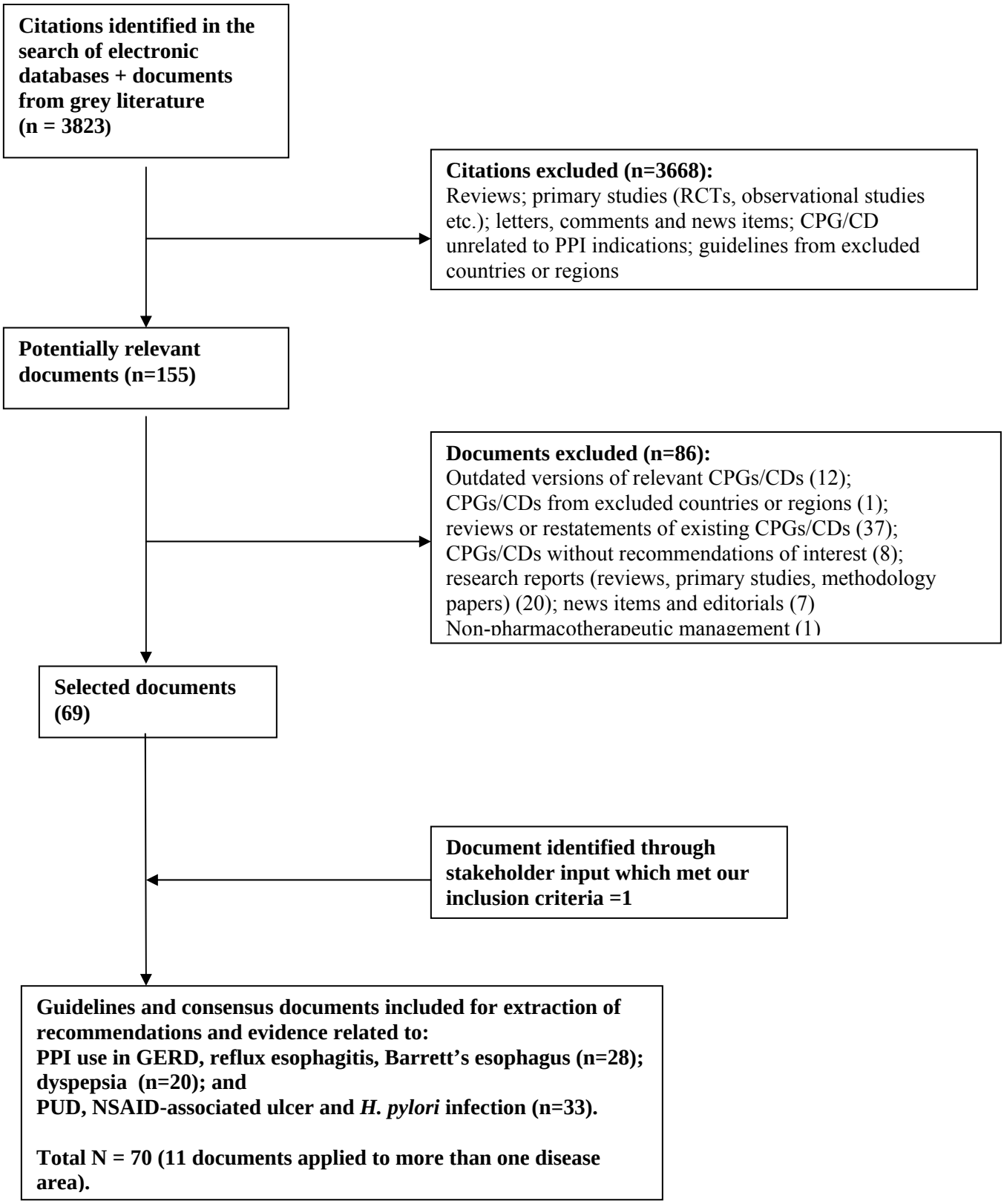
6.2 Quantity of Economic Studies Selected

Eighty-four economic studies were identified by checking the references of selected clinical practice guidelines and consensus documents and retrieved in full text. Upon review using the criteria described above, seventy-nine studies were excluded. (Appendix 8) The remaining five studies were selected: four were journal articles, and one was a CCOHTA report which contained two studies.

The literature search resulted in 843 studies. Thirteen studies were selected and retrieved in full text as potentially relevant studies. Eight studies were excluded, and three of these were duplicates of the seventy-nine already excluded above. (Appendix 8) Therefore a total of five studies were selected from the literature search.

Between these two approaches, ten studies were identified (5+5 studies) but three studies were duplicates. One study identified through the literature search was a journal publication of one of the studies contained in the CCOHTA report. Therefore, a final total of seven unique economic studies were selected. Each of these seven economic studies was linked to relevant synopsis of existing recommendations. (Appendix 9)

Figure 2: Quorum Statement for All Indications



7 Presentation of Results

7.1 Clinical Information

The results of the evaluation of the clinical information are grouped by the three clinical conditions: GERD (G), dyspepsia (D) and peptic ulcer disease (P). Each section is introduced with a list of the clinical situations that have been addressed.

Each synopsis of existing recommendations is accompanied by a table of existing guideline recommendations (Guideline Statements table) and a summary of the related evidence (Supporting Evidence table).

The Guidelines Statements table lists exact quotes of statements and recommendations from existing guidelines and consensus documents from which the synopsis of existing recommendations was derived. The originating guidelines were identified by a check mark in the Guidelines Matrix tables in Appendices 10-12.

The Supporting Evidence tables provide details of the actual studies evaluated for each clinical situation. A summary statement summarizes the quantity, quality, and consistency of the evaluated evidence. The rest of the table summarizes each of the selected studies as follows:

- Column 1: Study, Type, QA: The lead author and year are noted. The study design and overall quality assessment level is listed. Studies were identified with a * if they declared industry funding, if the author(s) were employed by industry, if the author(s) stated a conflict of interest, if industry was mentioned in the acknowledgement, or if industry monitored study process or assisted in study management.
- Column 2: Population: The number of patients in all study arms and patient characteristics. For systematic reviews and meta-analyses the number of included studies is also indicated.
- Column 3: Intervention: PPI therapy or PPI combination therapy.
- Column 4: Comparator: The comparison or control. In studies with more complex designs, the comparator is often included under the Intervention category.
- Column 5: Outcome Measure: The outcomes measured by the study pertinent to the clinical point in question.
- Column 6: Results: The results of the study pertinent to the clinical point in question. All results listed are from ITT analyses unless otherwise indicated.
- Column 7: Direction: symbols are used to indicate whether the results of the study support (+), refute (-) or neither support nor refute (0) the synopsis of existing recommendations.

Where the studies address different clinical situations of a particular recommendation, they are grouped accordingly and are presented in separate evidence tables for the sake of clarity.

An inventory of the total quantity of evidence found related to each synopsis of existing recommendations before the evidence was selected for evaluation according to Fig. 1 is shown in Appendices 13-15.

For studies with more than one outcome of relevance to a recommendation, a separate entry appears for each outcome in the evidence table. In such cases, the study citation is annotated with lower case letters to distinguish multiple entries for the same study.

7.2 Economic Evidence

The economic studies were determined to relate to one of the three clinical conditions; GERD, Dyspepsia or PUD. (Appendix 9) Each economic study is described in the Results section with a summary comment. The extracted data, the quality assessment and relevancy assessment results are tabulated for each economic study in Appendices 16-18.

8 Clinical Evidence for GERD

8.1 Clinical Questions for GERD

Question G1: Are PPIs more effective than H2RAs in patients with GERD, ENR and esophagitis?

Synopsis of Existing Recommendations G1A: PPIs are more effective than H2RAs for controlling the symptoms and improving the healing and the quality of life in GERD. H2RAs may be effective in some patients with mild to moderate symptoms of GERD.

i. PPIs are more effective than H2RAs for remission of symptoms and healing in patients with GERD.

ii. PPIs may be used in patients with GERD who had incomplete response to a previous trial of H2RAs

iii. There is a greater improvement in quality of life with PPIs than H2RAs in GERD.

iv. H2RAs may be effective in some patients with mild to moderate symptoms of GERD

Synopsis of Existing Recommendations G1B: PPIs are more effective than H2RAs for remission of heartburn and improving the quality of life in ENRD.

i PPIs are more effective than H2RAs for remission of heartburn in ENRD.

ii PPIs are more effective than H2RAs for improving quality of life in patients with ENRD

Synopsis of Existing Recommendations G1C: PPIs are more effective and faster than H2RAs for controlling the symptoms and improving the healing in patients of esophagitis.

i PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis.

ii The speed of heartburn relief and improvement of healing are faster with omeprazole than ranitidine in patients with erosive or reflux esophagitis.

Question G2: What is the status of double dose vs. single dose of PPIs in GERD and esophagitis as initial therapy?

Synopsis of Existing Recommendations G2A: Double dose of PPI is no better than standard dose for healing of GERD or esophagitis. Twice-daily, standard dose may be used for patients with severe symptoms.

i. Doubling the dose of PPI therapy is no better than standard dose PPI therapy for healing typical GERD or esophagitis.

ii. Twice-daily, standard dose PPIs may be used for patients who have severe symptoms of GERD.

Question G3: What is the duration of treatment?

Synopsis of Existing Recommendations G3A: Long-term PPI therapy is recommended for erosive esophagitis complicated by strictures with an aim of preventing recurrence.

Question G4: How do the individual drugs in the PPI category differ in controlling the initial symptoms and/or disease?

Synopsis of Existing Recommendations G4A: Standard doses of PPIs are equally effective in GERD and esophagitis

Question G5: How should long-term maintenance for GERD be conducted?

Synopsis of Existing Recommendations G5A: Long-term maintenance in GERD should be given at the lowest dose and frequency that is sufficient to achieve optimal control of the patient's symptoms.

Synopsis of Existing Recommendations G5B: Once a dose of either a H2RA, prokinetic agent, and/ or a PPI that relieves symptom has been identified, this dose should be maintained for a period of 3 months. After this time an attempt should be made to reduce the dose, with the aim of maintaining a stable clinical status. If symptoms recur, then the patient should go back to full-dose PPI and plan for long-term treatment.

Question G6: Should attempts be made to step-down and discontinue therapy or continue the current therapy?

Synopsis of Existing Recommendations G6A: Step-down therapy in patients with GERD and erosive esophagitis prevents symptomatic relapse in a majority of patients after stopping the PPI. Continued PPIs provided better heartburn relief than step-down to H2RAs. Many patients require medications other than PPI. The optimal approach of step-up, step down and no step remains to be determined.

i. Step-down therapy in patients with GERD and erosive esophagitis prevents symptomatic relapse in a majority of patients in one year after stopping the PPI. Many patients require medications other than PPI.

ii. Continued PPIs provided better heartburn relief than step-down to H2RAs. The optimal approach of step-up or step-down remains to be determined**.**

Synopsis of Existing Recommendations G6B: Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment.

i. Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy.

ii. If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment. Restart the treatment (e.g., PPI) at full dose, with a

limited number of repeat prescriptions. Encourage people to step-down treatment to the lowest dose required to control symptoms.

Synopsis of Existing Recommendations G6C: In patients with LA grade C and D esophagitis who remain symptomatic with regular dose PPIs, offer a double dose PPI for a further month, then encourage patients to step down to the lowest dose required to control symptoms.

Question G7: What is the status of "on-demand" therapy in ENRD and GERD?

Synopsis of Existing Recommendations G7A: "On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD. PPIs could be used as 'on demand' therapy.

i. "On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD.

ii. PPIs can be used as "on-demand" therapy.

Question G8: What is the status of half-dose PPI in GERD and reflux esophagitis?

Synopsis of Existing Recommendations G8A: The effect of half-dose of PPI is less than the standard dose PPI for acute treatment in ENRD.

Synopsis of Existing Recommendations G8B: The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD and esophagitis.

i. The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD.

ii. The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission in esophagitis.

Question G9: In the management of GERD, what should be preferred, PPIs or surgery?

Synopsis of Existing Recommendations G9A: Antireflux surgery was superior to PPI therapy in terms of symptomatic relapse, but if patients increased the PPI dose at relapse, there was no difference between the treatment strategies.

Synopsis of Existing Recommendations G9B: Surgical procedures could be considered if high dose PPI is ineffective, poorly tolerated, or if GERD is associated with serious complications despite therapy.

Question G10: What is the role of PPIs in the management of Barrett's Esophagus?

Synopsis of Existing Recommendations G10A: GERD can be such an insidious long-standing process, even a patient with Barrett's esophagus lacking symptoms may benefit from a trial of PPI therapy.

Synopsis of Existing Recommendations G10B: Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE.

i. Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE.

ii. Even high-dose PPI therapy will not usually result in reversal of Barrett's esophagus.

Question G11: What are the different adverse drug reactions of PPIs?

Synopsis of Existing Recommendations G11A: PPIs are generally well tolerated. Adverse effects include GI disturbances (most commonly diarrhea), headaches, and dizziness. However, long term safety is the major concern, when maintenance therapy with PPIs is considered. Increasing gastric levels as well as proliferation of endocrine cells have been shown, but no gastric carcinoids have been detected in several long-term human studies. Of more concern are those treated with a PPI with a *H. pylori* infection because they appear to be at risk of atrophic gastritis. Consequently it was suggested that it might increase the risk of *H. pylori* related gastric cancer.

8.2 Clinical Evidence for GERD

Question G1: Are PPIs more effective than H2RAs in patients with GERD, ENRD and esophagitis?

G1A: Guideline Statements

Synopsis of Existing Recommendations G1A: PPIs are more effective than H2RAs for controlling the symptoms and improving the healing and the quality of life in GERD. H2RAs may be effective in some patients with mild to moderate symptoms of GERD. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

i PPIs are more effective than H2RAs for remission of symptoms and healing in patients with GERD.

ii PPIs may be used in patients with GERD who had incomplete response to a previous trial of H2RAs

iii There is a greater improvement in quality of life with PPIs than H2RAs in GERD.

iv H2RAs may be effective in some patients with mild to moderate symptoms of GERD

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	21	PPIs are superior to H2RAs for the reduction of heartburn and healing of esophagitis. [PPIs] produce greater healing and symptom relief than do H2RAs in patients with confirmed GERD.
DeVault and Castell[13]	2005	193	Although less effective than PPIs, H2RAs given in divided doses may be effective in some patients with less severe GERD. In addition to controlling symptoms and esophagitis, PPI therapy has been shown to normalize the impaired quality of life caused by GERD.
NICE – Dyspepsia[24]	2004	96	Offer patients with GERD a full dose PPI for one or two months
NZGG[29]	2004	33, 34	A trial of empiric therapy is justified in people aged less than 50 years with typical GERD symptoms in the absence of alarm signals. In ascending order of potency and efficacy, the choice of drugs available includes: antacids/alginate, H2RAs (single then double dose, both twice daily), prokinetics, PPIs (half, standard, double dose) and combinations of PPIs and H2RAs or prokinetic agents. [In a Cochrane Review] the results showed that PPIs were significantly superior to H2RAs in controlling symptoms [of GERD]. PPIs provide more symptom relief and better healing than the other treatments.
ICSI Dyspepsia and GERD[30]	2004	34	The use of initial PPI has been shown to reduce the heartburn severity and duration compared to the use of H2RA.

Guidelines and protocol[31]	2004	2	Management of typical presentation - In the absence of alarm features or complications, the initial management should consist of diet and lifestyle medications and the intermittent use of antacids or H2RAs. Severe symptoms or poor response – In the absence of improvement with the above management strategy, the following regimens may be tried in sequence for up to 4 weeks each: a) Full dose H2RA, b) PPI. Note: GERD is a chronic disease and many patients require prolonged therapy. Refractory symptoms – Absence of response to the above regimen justifies specialist consultation and/or further investigation. [In GERD] when antacids are ineffective or required more than twice per day, H2RAs may be helpful. PPIs are the most effective but also the most expensive agents.
VHA/DoD[32]	2003	21-22	[To consider the option of H2RAs vs. PPIs] For empiric initial treatment of GERD, there is a lack of evidence and consensus to support using one treatment approach over the other. Start standard-dose PPI x 4 to 8 weeks (in patients who had an incomplete response to a previous trial of H2RA). Compared to H2RAs, PPIs have also been shown to produce greater improvement in certain measurements of health-related quality of life at various time points in patients with uninvestigated GERD and mixed populations of patients with ENRD or reflux esophagitis.
Federal Bureau of Prison[33]	2001	13	Treatment with a once daily PPI medication taken one hour before a meal provides symptomatic relief in the large majority of patients with GERD.
OPOT[23]	2000	29-33	The conventional approach to GERD therapy involves a 3-step process. Lifestyle modifications (LSM) and OTC products (i.e., alginic acid, antacids, and low-dose H2RA) are used as initial therapy (Phase I) for mild symptomatic disease. Phase IIa consists of prescription medications; namely H2RAs. If symptoms persist despite 4-8 weeks of optimal therapy, use of a PPI is recommended (Phase IIb). Phase III consists of anti-reflux surgery which may be indicated for resistant cases in eligible and willing individuals. PPIs are superior to H2RAs in GERD therapy, but are more expensive than generic H2RAs. The use of H2RAs as first-line for patients with GERD symptoms is considered appropriate for mild to moderate symptoms. PPIs are more effective than H2RAs or cisapride. In the step-up approach they are reserved for patients who have moderate-to-severe or prolonged symptoms, those with documented erosive esophagitis or other GERD complications, or for second-line use after failure of H2RAs. Cost comparisons, in the absence of rigorous economic analyses, have led to recommendations to use H2RAs initially, reserving PPIs for severe or resistant symptoms or disease
French-Belgian Consensus[34]	2000	134	[The] jury recommends treatment with PPI as single or double dose for 4-8 weeks when GERD is diagnosed or strongly suspected.
Kroes et al.[35]	1999	10	PPIs in low and normal doses were superior in relieving heartburn compared to H2RAs. Normal and high doses of PPIs have been found superior to normal or high doses of H2RAs in controlling symptoms of GERD and/or esophagitis and act twice as rapidly in this respect.

Fennerty et al.[36]	1996	481	Because of the greater antisecretory effect of PPIs, the success of this class of agent in treating GERD has been superior to H2RAs in terms of symptom relief and healing.

G1A: Supporting Evidence

G1A-i: PPIs are more effective than H2RAs for remission of symptoms and healing in patients with GERD.

Summary: PPIs are more effective than H2RAs in the resolution of symptoms in patients with heartburn/ GERD. This is supported by 1 good quality MA (Van Pinxteren et al 2004[37]) and 2 good quality RCTs (Kaplan-Machlis et al 2000[38], Wiklund et al 1998[39]).

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Van Pinxteren et al 2004[37] MA **(good)**	5 RCTs, (n=2419 GERD patients)	ome 10, 20 or 40 mg qd, pant 20 or 40 mg qd, esome 20 or 40 mg, rab 20 mg per d for 4 weeks	cim 300 or 400 mg qid, fam 20 mg bid or 40 mg qd, niz 150 mg bid, ran 150 mg bid) for 4 weeks	Heartburn remission at 4 weeks	PPIs vs. H2RAs: RR 0.69, (95% CI 0.61,0.77), (p<0.05) NNT=2.5	+
	1 RCT (n=220) patients with heartburn	pant 40 mg for 4 weeks	niz 150 mg bid for 4 weeks	Overall symptom improvement at 4 weeks	PPIs vs. H2RAs: RR: 0.29, (95% CI 0.17,0.51), (p=0.00001).	+
Caro et al 2001*[40] MA **(poor)**	18 trials containing 1592 patients with endoscopically confirmed GERD (grade 0-4, Savary-Miller classification)	lans 30 mg/day, ome 20 mg/day, pant 40 mg/day, rab 20 mg/day	ran 300 mg/day	Heartburn resolution at 4 weeks Healing proportion and rates at 4 and 8 weeks Endoscopic remission rate at 1 year Relapse at 6 and 12 months	<u>Heartburn resolution:</u> 4 week times [95% CI] : 1.53 [1.37, 1.72] time with PPIs vs ran (p<0.002). <u>Overall healing rate ratios:</u> wk 4: 1.53 [95% CI: 1.63,2.08] with PPIs vs. H2RAs 1.84 [95% CI: 1.63,2.08] lans vs. ran 1.61 [95% CI: 1.27,2.05] rab vs. ran 1.31 [95% CI: 1.03,1.73] pant vs. ran 1.87 [95% CI: 1.64,2.15] ome vs. ran wk 8: 1.62 [95% CI: 1.46,1.76] lans vs. ran 1.36 [95% CI: 1.20,1.54] rab vs. ran 1.60 [95% CI: 1.33,1.96] pant vs. ran 1.58 [95% CI: 1.41,1.78] ome vs. ran	+ + +

					<u>Endoscopic remission rate:</u> 1 year: 87% for PPI vs. 40% for ran (p<0.05). <u>Relapse rate:</u> 6 months: It was lower, varying from 6% to 42% for different PPIs vs. 42% to 69% with ran (p<0.05). 1 year: It was also better for PPIs vs. ran (p<0.05).	+ + +
Kaplan-Machlis et al 2000*[38] RCT **(good)**	268 clinically diagnosed GERD patients	ome 20 mg qd for 4 weeks	ran 150 mg bid for 4 weeks	Heartburn relief at 2-4 weeks	wk 2: 49% with ome vs. 33% with ran (p = 0.007) wk 4: 59% with ome vs. 35% with ran (p< 0.001)	+ +
Wiklund et al 1998*[39] RCT **(good)**	704 patients with heartburn without and with erosive esophagitis (A-C, LA classification)	ome 10 or 20 mg qd for 6 months	ran 150 mg bid for 6 months	Heartburn relief at 2 weeks	55% with ome 20 mg and 40% with ome 10 mg vs. 26% with ran 150 mg bid (p<0.001)	+
cim: cimitidine; esome: esomeprazole; fam: famotidine; lans: lansoprazole; niz: nizatidine; ome: omeprazole; rab: rabeprazole; ran: ranitidine, pant; pantoprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G1A-ii: PPIs may be used in patients with GERD who had incomplete response to previous trial of H2RAs

Summary: PPIs are more effective than H2RAs in patients with heartburn/ GERD resistant to H2RAs, in improving the symptoms of heartburn, regurgitation as well as improving the healing. The statement is based on 1 good and 1 poor quality RCT.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Maton et al 1999*[41] RCT **(good)**	533 patients with heartburn, poorly responsive to 6 weeks of treatment with H2RAs	ome 20 mg qd for 8 weeks	ran 150 mg bid for 8 weeks	Complete heartburn resolution Total heartburn relief Heartburn-free days at 4 and 8 weeks	Patients with complete resolution of heartburn: wk 4: 31% with ome vs. 11% with ran (p<0.0001). wk 8: 46% with ome vs. 16% with ran (p<0.0001). Total heartburn relief (patients having no or mild heartburn): wk 4: 66% with ome vs. 40% with ran (p<0.0001). wk 8: 70% with ome vs. 49% with ran (p = 0.0004) The percentage of heartburn-free	 + + + +

					days: wk 4: 69% with ome vs. 48% with ran (p<0.0001) wk 8: 76% with ome vs. 56% with ran (p<0.0001)	+ +
Richter et al 1996*[42] RCT **(poor)**	290 patients with GERD remaining symptomatic after 8 weeks of treatment with ranitidine (grade 0-4)	ome 20 mg qd for 8 weeks	ran 150 mg bid, combination (ran 150 mg bid + metoclopra-mide 10 mg qid) for 8 weeks	Symptom relief at 1, 4 and 8 weeks Endoscopic healing at 8 weeks	Symptom relief : wk 1: 13% with ome vs. 1% with ran and 3% with the combination of ran and metoclopramide (p< 0.001). wk 4: 33% with ome vs. 8% with ran and 7% with combination of ran and metoclopramide (p< 0.001) wk 8: 64% with ome vs. 28% with ran and 29% with combination of ran and metoclopramide (p< 0.001). Endoscopic healing: wk 8: 80% of patients of esophagitis (grade II or more) were healed with ome vs 40% with ran vs. 46% with the combination of ran and metoclopramide (p<0.001)	+ + + +
ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G1A-iii: There is a greater improvement in quality of life scale with PPIs than H2RAs in GERD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary:

Gastrointestinal general symptoms rating scale (GSRS): The results show that for up to 3 months, PPIs are better than H2RAs in improving the dimensions of GSRS scores in patients with GERD. However at 6 months, no differences were found between these two treatments. The data is based on 1 good quality MA (Van Pinxteren et al 2004[37]) and 3 good quality RCTs (Kaplan-Machlis et al 2000[38], Wiklund et al 1998 [39], Festen et al 1999[43]). However, Wiklund et al 1998[39] reported no improvement in the reflux dimension of GSRS with omeprazole vs ranitidine at 4 weeks, though the total score of GSRS improved with omeprazole vs ranitidine.

Psychological general well-being scale (PGWB): The data are controversial. One RCT (Wiklund et al 1998[39]) shows that PPIs are better than H2RAs for improving the score of PGWB at 4 weeks, but the other (Kaplan-Machlis et al 2000[38]) reported no difference between these two groups from 1 to 6 months. Both RCTs are of good quality.

In patients of heartburn poorly responsive to 6 months treatment with ranitidine, PPIs were better than ranitidine in improving GSRS and PGWB scores. The data are based on a good quality RCT (Revicki et al 1998[44]).

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Van Pinxteren et al 2004[37] MA **(good)**	2 RCTs, 526 patients with GERD	Pan 40 mg	Niz 150 mg bid; ran 150 mg bid	Quality of life scales, GSRS from 1-12 weeks	PPIs improve reflux dimension of GSRS better than H2RAs (p< 0.05).	+
Kaplan-Machlis et al 2000*[38] RCT **(good)**	268 GERD patients (clinically diagnosed)	ome 20 mg qd for 6 months	ran 150 mg bid for 6 months	Quality of life scales, GSRS at 12 and 24 weeks PGWS at 24 weeks	<u>GSRS:</u> At 2- and 4- week: ome groups showed lower adjusted reflux scores (adjusted 1-month mean score 2.53) vs. ran (2.89) (p=0.005) At 3 months, GSRS reflux scores, showed overall treatment difference favoring ome (adjusted 3-month mean score 2.67) vs. ran (2.95) (p<0.05) At 6 months: Adjusted mean reflux scores 2.68 with ome vs. 2.85 with ran (p = 0.2). <u>PGWS:</u> No difference in the improvement PGWB score was found between ome and ran from 1 to 6 months.	+ + - -
Wiklund et al 1998*[39] RCT **(good)**	704, endoscopy negative or positive GERD patients (grade A-C, LA classification)	ome 10 mg or 20 mg qd for 4 weeks	ran 150 mg bid for 4 weeks	Quality of life scales, GSRS, PGWS at 4 weeks	<u>GSRS:</u> At 4 weeks: No difference in improvement in reflux dimensions of the GSRS score was found between ome 20 mg vs. other groups. There was better improvement in the total GSRS score with ome 10 mg vs. ran, mean difference (95% CI) -0.18 (-0.31,-0.05) (p = 0.006). <u>PGWS:</u> At 4 weeks: Mean difference (95% CI) 4.2 (1.3, 7.1) with ome 10 mg and ran 150 mg (p = 0.005). 3.2 (0.3, 6.1) with 20 mg and ran 150 mg (p = 0.03).	- + +
Festen et al 1999*[43] RCT **(good)**	448 mild GERD patients (grade I or II, Savary Miller classification)	ome 20 mg qd for 4-8 weeks	ran 300 mg bid for 4-8 weeks	Quality of life scale, GSRS, at 4 weeks	At 4 weeks, total GSRS score showed better improvement with ome (12.28) vs. ran (9.95) (p<0.001) Reflux dimension also showed improvement with ome (4.06) vs. (2.84) ran (p<0.013).	+
Revicki et al. 1998[44] RCT **(good)**	533 GERD patients with heartburn poorly responsive to 6 weeks	ome 20 mg qd for 8 weeks	ran 150 mg bid for 8 weeks	Quality of life scale, GSRS PGWS at 8 weeks	<u>GSRS:</u> At 8 weeks, 1.60 with ome vs. 2.04 with ran (p<0.0001). Abdominal pain score and indigestion score, were also better with ome than ran (p = 0.003 and	+ +

	of treatment with ran (Clinical diagnosis)				p=0.003, respectively) <u>PGWS:</u> At 8 weeks: Adjusted PGWS: 83 with ome vs 79 with ran (p = 0.019). ome is better than ran in improving anxiety and general health (p<0.01), patient rating of overall treatment effect, and impact on daily life activity (p = 0.001).	 + +
GSRS: Gastrointestinal Symptoms Rating Scale; PGWB: Psychological General Well Being scale; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G1A-iv: H2RA may be effective in some patients of GERD with mild to moderate symptoms.						
Summary: This Synopsis of Existing Recommendations is based on expert opinion (DeVault and Castell[13], VHA/DoD[32], OPOT[23]) guidelines (DeVault and Castell[13], VHA/DoD[32], OPOT[23])						
Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G1: Are PPIs more effective than H2RAs in patients with GERD, ENRD and esophagitis?

G1B: Guideline Statements

Synopsis of Existing Recommendations G1B: PPIs are more effective than H2RAs for remission of heartburn and improving the quality of life in ENRD. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

i PPIs are more effective than H2RAs for remission of heartburn in ENRD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

ii PPIs are more effective than H2RAs for improving quality of life in patients with ENRD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update [12]	2005	21	[PPI produce] greater symptom relief [than H2RA] in patients with ENRD.
Kroes et al.[35]	1999	11	If no macroscopic esophagitis is found, one country recommends consultation with the endoscopist to consider the need for acid suppression therapy when complaints are severe and another country recommends H2RAs or other drugs. In cases of GERD without esophagitis, a PPI has been proven effective but evaluation of its superiority to other drugs is not available.
NICE – Dyspepsia [24]	2004	96	On balance, PPIs are more effective that H2RAs in ENRD. In head-to-head trials, 53% of patients became symptom free on PPI compared with 42% receiving H2RAs although the difference was not statistically significant.

Prodigy – Proven GORD[15]	2005	9	PPIs appears more effective than H2RAs in people with ENRD.
VHA/DoD[32]	2003	22- 23	Compared to H2RAs, PPIs have also been shown to produce greater improvement in certain measurements of health-related quality of life at various time points in patients with uninvestigated GERD and mixed populations of patients with ENRD or reflux esophagitis. In a mixed population of patients with ENRD or uncomplicated erosive esophagitis, PPIs were found to be superior to H2RAs in achieving heartburn remission regardless of the initial severity of heartburn.
Québec CRUM[45]	2002	13	Absence of reflux esophagitis upon exploration: when symptoms are mild to moderate and interfere with daily life activities or more importantly patients feel that the symptoms have mild to moderate impact on their quality of life; H2RAs for at least 4 weeks constitute first-line treatment; when symptoms are unresponsive to this treatment, PPIs constitute second-line treatment for 4-8 weeks. When symptoms are severe and interfere with daily acticvities or more importantly patients feel that the symptoms have a significant impact on their quality of life; first-line treatment; PPI for four to eight weeks.
Asia-Pacific Consensus[46]	2004	361	[In ENRD] PPIs are significantly superior to prokinetic agents in heartburn remission and superior to H2RAs in overall symptom improvement. In terms of heartburn remission there is a trend in favor of PPI.

G1B-i: PPIs are more effective than H2RAs for remission of heartburn in ENRD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: The results from a good quality MA do not support the main recommendation. PPIs are not more effective than H2RAs in patients with ENRD for the relief of heartburn. For overall symptoms improvement, PPIs are better than H2RAs. The data are based on the same SR, but containing only one RCT (different from the RCTs for heartburn remission).

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Van Pinxteren et al 2004[37] SR/MA **(good)**	3 RCTs (n=854, patients with ENRD) for heartburn remission	ome 10, 20 or 40 mg, qd, pant 20 or 40 mg qd, esome 20 or 40 mg, qd, rab 10 and 20 mg qd) for 8 weeks	cim 300 or 400 mg qid, fam 20 mg bid or 40 mg qd, niz 150 mg bid, ran 150 mg bid for 8 weeks	Heartburn remission at 8 weeks	Heartburn remission RR PPIs vs H2RAs: 0.74, (95% CI: 0.53, 1.03). NNT = 9.1 (p = 0.08)	-
	1RCT (n=831, patients with ENRD) for overall symptom improvement	lans 15, 30 mg	ran 150 mg bid	Overall symptom improve-ment at 8 weeks	Overall symptom improvement: lans vs ran RR: 0.83 (95% CI: 0.76, 0.91), (p = 0.00006).	+

lans: lansoprazole; ome: omeprazole; esome: esomeprazole; rab: rabeprazole; cim: cimetidine; ran; ranitidine; fam: famotidine; niz: nizatidine; pant; pantoprazole

G1B-ii: PPIs are more effective than H2RAs for improving quality of life in patients with

ENRD. *The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

Summary: The data do not support the recommendation in ENRD. There is no difference in improvement of reflux dimension of the GSRS between the PPIs or H2RAs. The data are based on a single RCT contained in a good quality MA.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Van Pinxteren et al 2004[37] MA **(good)**	1 RCT (n= 220 patients with ENRD)	Pan 40 mg qd	Niz 150 mg bid	Quality of life scales, GSRS from 1-12 weeks	No difference in improvement in reflux dimension of the GSRS was found for PPIs vs. H2RAs	-

Pan: pantoprazole; niz: nizatidine

Question G1: Are PPIs more effective than H2RAs in patients with GERD, ENRD and esophagitis?

G1C: Guideline Statements

Synopsis of Existing Recommendations G1C: PPIs are more effective and faster than H2RAs for controlling the symptoms and improving the healing in patients of esophagitis.

i PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

ii The speed of heartburn relief and improvement of healing are faster with omeprazole than ranitidine in patients with erosive or reflux esophagitis.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	21	PPIs are superior to H2RAs for the reduction of heartburn and healing of esophagitis.
DeVault and Castell[13]	2005	193	PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients.
NICE – Dyspepsia[24]	2004	96, 106	PPIs are more effective than H2RAs at healing esophagitis in trials. Healing occurred in 22% of patients on placebo, 39% of patients on H2RAs (a number needed to treat of 6), and 76% of patients on PPIs (a number needed to treat of 2). There is considerable variation in findings of trials.
University of Michigan[47]	2002	6	PPIs are more effective than both H2RAs and placebo in controlling symptoms from erosive reflux disease over a 4 to 8 week period. In the treatment of erosive esophagitis, PPIs had faster healing rates than either H2RAs or placebo over a 4 to 8 week period.
Québec CRUM[45]	2002	14	Severe reflux esophagitis; first-line treatment; PPIs for four to eight weeks.
Asia-Pacific Consensus[46]	2004	361	PPIs are the most effective for the control of symptoms and healing of esophagitis and erosive esophagitis.
Prodigy – Proven GORD[15]	2005	8	PPIs are more effective than H2RAs at healing esophagitis in trials.

NZGG[29]	2004	34	PPIs provide more symptom relief and better healing than the other treatments
North American[48]	2003	3	H2RAs produce relief of symptoms and mucosal healing. PPIs [are] most effective acid suppressant medications. [PPIs] are superior to H2RAs in relieving symptoms and healing esophagitis [in children].
Digetive Health Foundation[49]	2001	3	There is an evolving switch of strategy for the initial treatment of reflux disease from the more traditional step-up approach to high level (more potent) initial therapy, on the grounds of outcomes, speed of response and the total cost, in the majority of patients. Traditonal step-up: Antacids [followed by] H2RAs [followed by] PPIs. High level: daily PPI at standard dose.
Rudolph et al.[50]	2001	S10	PPIs are superior to H2RAs in relieving symptoms and healing esophagitis [in adults].
French-Belgian Consensus[34]	2000	133	PPI have a superior efficacy to any other therapeutic class for symptom relief and treatment of esophagitis, whatever the severity.
Kroes et al.[35]	1999	10	PPIs in low and normal doses were superior in relieving heartburn compared to H2RAs. Normal and high doses of PPIs have been found superior to normal or high doses of H2RAs in controlling symptoms of GERD and/or esophagitis and act twice as rapidly in this respect.

G1C-i: PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

a) PPIs vs. H2RAs (single or double dose) or the combination of H2RAs with metoclopramide.

Summary: PPIs are more effective than H2RAs alone (single or double dose) or the combination of H2RAs with metoclopramide in controlling symptoms in patients with esophagitis (grade 1-4). The data are based on 2 poor quality MAs, 3 very good, 3 good and 2 poor quality RCTs.

The data on the superiority of PPIs over the combination of ranitidine and metoclopramide is based on a poor quality RCT.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Chiba et al 1997[51] MA **(poor)**	2,123 patients with erosive esophagitis (grade II-IV), 16 studies	lans 30, 60 mg qd, ome 20, 40 mg qd, pant 40 mg qd	cim 800-1600 mg/day, fam 40 or 80 mg/day, niz 300-600 mg/day, ran 300-1200 mg/day	Heartburn relief ≤12 week Healing proportion 1- 12 weeks	Mean overall heartburn proportion: 77±10.4% with PPIs vs. 48±15.5% with H2RAs ($p<0.0001$). Healing proportion: 84±11.4% with PPIs vs. 52±17.1% with H2RAs ($p< 0.0005$)	+ +
Carlsson et al 1997*[52] MA **(poor)**	4 trials, 1154 patients with erosive esophagitis	ome 10 and 20 mg qd	ran 150 mg bid and placebo	Endoscopic remission at 6 months	Endoscopic remission : 82.4% (95%CI: 78.2%, 86.6%) with ome 20 mg vs. 72% (95%CI: 65.5%, 78.3%) with ome 10 mg vs. 52.3% (95%CI: 44.4%, 60.1%) with ran 150 mg vs.	+ +

					10.6% (95 CI: 5.0%, 16.3%) with placebo. <u>Time to remission:</u> ome 20 mg was superior to ome 10 mg (p=0.04) and ran (p<0.0001) and placebo (p<0.0001). Ome 10 mg is superior to ran (p<0.0001).	+
Jansen et al 1999*[53] RCT **(very good)**	133 patients with reflux esophagitis (grade II or III, Savary-Miller classification)	lans 30 mg qd for 4-8 weeks	ran 300 mg bid for 4-8 weeks	Symptom resolution at 4 and 8 weeks	wk 4: 84% with lans vs. 43% with ran (p<0.001) wk 8: 88% with lans vs. 66% with ran (p<0.003).	+ +
Bardhan et al. 1995*[54] RCT **(very good)**	229 patients with reflux esophagitis (grade 1-3)	lans 30 mg qd or lans 60 mg qd for 4-8 weeks	ran 150 mg bid for 4-8 weeks	Symptom relief Antacid consumption Healing rate at 4-8 weeks	<u>Symptom relief:</u> Patients in lans groups had significantly better improvement in heartburn relief at 4 and 8 weeks than pts in ran group (p<0.001). <u>Regurgitation and dysphagia:</u> No differences were found for relief of regurgitation and dysphagia between the lans 30, 60 mg or ran 150 mg groups at 4 or 8 weeks. <u>Antacid consumption:</u> Patients in lans 30 mg group took antacids on fewer days than those in ran group (19% vs 33% p<0.01) and a similar trend was found with lans 60 mg and ran group (22% vs 33%, p<0.01). <u>Healing rates:</u> wk 4: 84% (lans 30 mg) vs. 39% (ran) (p<0.01); 72% (lans 60 mg) vs. 39% (ran) (p<0.01) wk 8: 92% (lans 30 mg) vs. 53% (ran) (p<0.02); 90% (lans 60 mg) vs. 53 % (ran) (p<0.02).	+ - + +

					<u>The difference in healing between lans 30 mg and ran:</u> wk 4: 44.8% (95% CI: 29.6%, 60%) wk 8: 39.2% (95% CI: 24.7%, 53.8%). <u>The difference between lans 60 mg and ran:</u> wk 4: 32.9% (95% CI: 16%, 49.7%) wk 8: 37.9% (95% CI: 22.8%, 53%) The difference between lans 30 mg and lans 60 mg rates was NS.	+ +
Koop et al. 1995*[55] RCT **(good)**	249 patients with acute symptomatic reflux esophagitis (grade II and III, Savary-Miller classifiication)	pant 40 mg qd for 4-8 weeks	ran 150 mg bid for 4-8 weeks	Symptom relief at 2 and 4 weeks. Healing rate at 4 and 8 weeks	<u>Symptom relief:</u> wk 2: 46 % (95% CI: 38%,54%) with pant vs. 37 % (95% CI: 65%,80%) with ran (NS) wk 4: 72% (95% CI: 65%,80% with pant vs. 52% (95% CI: 40%,63%) with ran ($p<0.01$). <u>Healing rates (pant vs ran):</u> wk 4 : 62% (95%CI: 55%, 70%) (pant 40 mg) vs. 47% (95%CI: 36%, 58%) (ran), ($p<0.05$) wk 8 : 74% (95%CI: 67%, 80%) (pant 40 mg) vs. 55% (95%CI: 45%, 66%) (ran), ($p<0.01$) .	- + + +
Bate et al 1990*[56] RCT **(poor)**	272 patients with reflux esophagitis (grade I-IV).	ome 20 mg qd for 4 weeks	cim 400 mg qid for 4 weeks	Symptom relief at 4 weeks. Healing (endoscopic and/or histological) proportions at 4 weeks and 8 weeks Patients both asymptomatic and healed of	<u>Symptom relief:</u> at 4 weeks: 46% with ome vs. 22% with cim ($p<0.001$). <u>Endoscopic healing:</u> wk 4: 56% with ome vs. 26% with cim ($p<0.001$) wk 8: 71% with ome vs. 35% with cim ($p<0.001$)	+ +

				esophagitis assessed by endoscopy and or histology.	Both asymptomatic and healed of esophagitis: 38% of patients with ome vs. 12% with cim were (p<0.001). Abnormal histology: About 60% of the patients had at entry. At 8 weeks, 33% of patients taking ome vs. 52% with cim continued to have abnormal histology (p<0.001). Endoscopy and histology healed and symptoms relief: 45% with ome vs. 22% with cim (p<0.01)	+ + +
Sandmark et al 1988*[57] RCT **(good)**	152 patients with reflux esophagitis (grade 2-4)	ome 20 mg qd for 4-8 weeks	ran 150 mg bid for 4-8 weeks	Symptom relief at 1 and 4 weeks Endoscopic healing at 4 and 8 weeks	Symptom relief (PP analysis): wk 1: 57% with ome vs. 27% ran (p<0.009) wk 4: 73% with ome vs. 46% with ran (p<0.002). Endoscopic healing: wk 4: 67% with ome vs. 31% with ran (p<0.0001) wk 8: 85% with ome vs. 50% with ran (p<0.0001)	+ +
Zeitoun et al. 1989*[58] RCT **(very good)**	156 patients with erosive or ulcerative esophagitis (grade 2-4)	ome 20 mg for 4-8 weeks	ran 150 mg bid for 4-8 weeks	Healing rates at 4 and 8 weeks	At 29+/- 6 days: 74% with ome vs. 41 % with ran (p<0.001) At 57+/- 6 days: 87% with ome vs. 56% with ran (p<0.001)	+
Green et al. 1995*[59] RCT **(good)**	198 patients with reflux esophagitis (1-IV)	ome 20 mg qd, (or 40 mg qd if needed) for 4-16 weeks	ran 150 mg bid) for 4-16 weeks	Healing rates (PP analysis) at 4, 8, 12 and 16 weeks	wk 4: 35% with ome vs. 7% with ran (p<0.0001) wk 8: 55% with ome vs. 25% with ran (p<0.001) wk 12: 71% with ome vs. 33% with ran (P<0.001) wk 16: 72% with ome	+ + +

					vs. 33% with ran (p<0.0001)	+
Frame 1991*[60] RCT **(poor)**	172 patients with erosive or ulcerative esophagitis (grade 2-3)	ome 20 mg qd for 4-8 weeks	ran 150 mg bid for 4-8 weeks	Healing rates at 4 and 8 weeks	wk 4: 72% with ome vs. 54% with ran, Diff (95%CI): 18% (1%, 34%), p=0.042. wk 8: 90% with ome vs. 76% with ran, Diff (95%CI): 14% (2%, 27%), p=0.03.	+ +
Robinson et al 1993*[61] RCT **(poor)**	184 patients with erosive esophagitis (grade II-IV)	ome 20 mg qd for 8 weeks	ran 150 mg bid + metoclopram-ide 10 mg qid combination for 8 weeks	Heartburn and symptom relief 1-8 weeks Regurgitation	<u>Improvement in night time heartburn wk 4:</u> 64% with ome 20 mg vs 25.1% in the combination group (p<0.01). wk 8: 73% with ome vs. 52% with the combination group (p<0.01). <u>Night-time and day-time heartburn relief</u> Over the 8 week, the night-time and day-time heartburn relief were better with ome than with ran and metoclopramide combination (p<0.01). <u>Complete relief of acid regurgitation</u> wk 4: 68% with ome vs. 35% in combination (p<0.01). wk 8: 78% with ome vs. 57% with combination (p<0.01).	+ + + + +
cim: cimetidine; fam: famotidine; lans: lansoprazole; pant: pantoprazole; niz: nizatidine; rab: rabeprazole; ran: ranitidine, ome; omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G1C-i: PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

b) PPIs vs. H2RAs for erosive GERD (grade 0-4)

Summary: The results indicate better improvement of symptoms relief and healing with PPIs than H2RAs in patients with erosive GERD (grade 0-4). The data are based on 1 poor quality MA (Caro et al 2001[40]) and 2 good quality RCTs (Dettmer et al. 1998[62], Farley et al. 2000[63]).

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Dettmer et	209	pant 20 mg qd	ran 300 mg qd	Symptom relief	<u>Symptom relief:</u>	

al. 1998[62] RCT **(good)**	endoscopically established GERD (stage I, Savary-Miller)	for 8 weeks	for 8 weeks	at 2 and 4 weeks. Healing rate at 4 and 8 weeks	wk 2: 69% with pant vs. 48% with ran (p<0.01) wk 4: 80% with pant vs. 65% with ran (p<0.05). <u>Healing rate:</u> wk 4: 67% with pant vs. 53% with ran (p<0.05) wk 8: 74% with pant vs. 61% with ran (p<0.05)	+ + + +
Farley et al. 2000*[63] RCT **(good)**	338 erosive GERD (Modified Hetzel-Dent esophagitis 2-4)	rab 20 mg qd for 4- 8 weeks	ran 150 mg bid for 4- 8 weeks	Symptom improvement at 4 and 8 weeks. Heartburn relief at 4 and 8 weeks Healing rate at 4 and 8 weeks	<u>Symptom relief:</u> wk 4: 75% with rab vs. 58% with ran (p<0.001) wk 8: 79% with rab vs. 68% with ran (p = 0.032) <u>Heartburn relief:</u> There were no differences in improvement of severity of heartburn symptoms between the groups for either time point. <u>Healing rates:</u> wk 4: 59% with rab vs. 36% with ran; the difference of 23% was statistically significant (95% CI: 13%-23%) (p<0.001) wk 8: 87% with rab vs. 66% with ran; the difference of 21% was statistically significant (95% CI: 12%– 30%) (p<0.001)	 + + + + +

Lans: lansoprazole; ome: omeprazole; Pant: pantoprazole; rab: rabeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

G1C-i: PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

c) PPIs vs. H2RAs for H2RA resistant esophagitis.

Summary: The results show that PPIs are more effective than H2RAs, in improving heartburn, regurgitation and healing in patients with erosive and/or ulcerative esophagitis resistant to H2RAs. The

data are supported by 2 very good quality and 1 good quality RCTs.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Porro et al 1992*[64] RCT **(very good)**	60 patients with erosive / ulcerative esophagitis (grade 2-4) despite previous treatment with H2RA for 8 weeks	Phase I: ome 20 mg qd for 4-8 weeks Phase II: If patients still showing esophagitis after Phase I, ome 40 mg qd for 4-8 weeks	Phase I: ran 150 mg bid for 4-8 weeks Phase II: If patients still showing esophagitis after Phase I, ran 300 mg bid for 4-8 weeks	Symptoms relief 4-8 weeks Endoscopic assessment at 4, 8 and 12 weeks	<u>Heartburn relief:</u> wk 4: 60% with ome vs. 21% with ran ($p<0.006$). wk 8: 64% with ome vs. 44% with ran ($p>0.05$). <u>Relief of regurgitation:</u> wk 4: 23% in ome vs. 48% in ran groups ($p=0.05$). wk 8: regurgitation was absent in ome groups vs. 17% of patients in ran group ($p>0.05$). <u>Endoscopic healing:</u> wk 4: 50% with ome vs. 21% with ran ($p<0.01$) wk 8: 79% with ome vs. 35% with ran ($p<0.05$) wk 12: 97% with ome vs. 64% with ran ($p<0.05$).	+ - + - + + +
Lundell et al 1990*[65] RCT **(very good)**	98 patients with erosive and / or ulcerative esophagitis (grade 2-4) not responding to standard doses of H2RA for 3 months	ome 40 mg qd for 4-12 weeks	ran 300 mg bid for 4-12 weeks	Symptom relief at 4 weeks. Healing rates at 4, 8, and 12 weeks	<u>Heartburn relief:</u> wk 4: 86% with ome vs. 32% with ran ($p<0.001$). <u>Relief of regurgitation:</u> It was also better with ome than ran ($p<0.05$). <u>Healing rates:</u> wk 4: 63% with ome vs. 17% with ran ($p<0.0001$) wk 8: 86% with ome vs. 38% with ran ($p<0.0001$). wk 12: 90% with ome vs. 47% with ran ($p<0.0001$).	+ + + + +
Lundell et al 1991*[66] RCT **(good)**	98 patients with erosive and/ or ulcerative esophagitis (grade ≥ 2), unhealed after treatment with cim ≥1200 mg or ran ≥300 mg daily.	Phase I: ome 40 mg qd for 12 weeks. Phase II: Patients healed after treatment with ome or ran given Ome 20 mg qd for 12 weeks	Phase I: ran 300 mg bid for 12 weeks Phase II: Patients healed after treatment with ome or ran given Ran 150 bid for 12 weeks	Phase I: Healing rates at 12 weeks Phase II: Healing rates at further 12 weeks	<u>Phase I: Healing rates:</u> wk 12: 90% with ome vs. 47% with ran. <u>Phase II: Healing rates</u> Weeks 12:, 70% with ome vs 10% with ran ($p<0.0001$)	0 +

ome: omeprazole; ran: ranitidine; cim: cimetidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

G1C-i: PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

d) PPIs vs. H2RAs in maintaining remission of reflux esophagitis

Summary: The results show that PPIs are better than H2RAs in maintaining remission at 12 months in patients with reflux esophagitis. The data are supported by 6 RCTs, 4 of good quality and 2 of poor quality.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Hallerback et al 1994*[67] RCT **(good)**	426 patients with reflux esophagitis (grade ≥ 2)	Phase I ome 20-40 mg qd for 8-12 weeks. Phase II maintenance ome 10 mg or 20 mg qd for 12 months	ran 150 mg bid for 12 months	Proportion of patients in remission after 12 months	72% for ome 20 mg, 62% for ome 10 mg vs. 45% for ran ($p<0.005$ and $p<0.005$ respectively)	+
Lundell et al 1991*[66] RCT **(good)**	98 patients with erosive and /or ulcerative esophagitis (grade ≥ 2) resistant to H2RAs	ome 40 mg qd for 12 months	ran 300 mg bid for 12 months	Remission of esophagitis after 12 months	67% of patients taking ome vs. 10% taking ran at 12 months ($p<0.0001$)	+
Metz et al 2003*[68] RCT **(poor)**	371 patients with erosive esophagitis (grade 2-4, Hetzel-Dent scale)	pant 10, 20, 40 mg qd for 12 months	ran 150 mg bid for 12 months	Maintenance of healing at 12 months	All pant groups (82% with pant 40 mg, 68% with pant 20 mg, 40% with pant 10 mg) vs. 33% with ran 150 mg ($p<0.001$).	+
Vigneri et al 1995[69] RCT **(good)**	175 patients with reflux esophagitis (grade 1-3, Savary Miller Classification)	ome 20 mg qd for 12 months ome 20 mg qd, cis 10 mg tid for 12 months	ran 150 mg, cis 10 mg tid, ran 150 mg + cis 10 mg tid	Remission rate at 12 months	89% with ome+cis vs. 80% with ome vs. 66% with ran+cis vs. 54% with cis vs. 49% with ran. ome significantly more effective than cis ($p<0.02$), or ran ($p<0.003$)	+ +
Gough et al 1996*[70] RCT **(poor)**	419 patients with reflux esophagitis (grade 2-3)	lans 15 mg, 30 mg qd for 12 months	ran 300 mg bid for 12 months	Relapse rate at 12 months	20% with lans 30 mg vs. 31% with lans 15 mg, vs. 68% with ran ($p<0.001$ for both ome groups vs. ran)	+
Dent et al 1994 [71] RCT **(poor)**	204 patients with reflux esophagitis (grade 2-4)	ome 20 mg qd am/day, Weekend ome 20 mg (3 day a week) for 12 months	ran 150 mg bid for 12 months	Remission rate at 12 weeks	89% with ome vs. 25% with ran vs. 32% receiving weekend ome ($p<0.001$ and $p<0.001$ respectively)	+

cis : cisapride; lans : lansoprazole; ome : omeprazole; pant : pantoprazole; ran : ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

G1C-ii: The speed of heartburn relief and improvement of healing was faster with omeprazole than ranitidine in patients with erosive esophagitis.

Summary: PPIs produce faster relief of heartburn and improvement of healing than H2RAs in patients with erosive or reflux esophagitis. The data are based on a poor quality MA and a good quality RCT.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Chiba et al 1997[51] MA **(poor)**	2,123 patients with erosive esophagitis (grade II-IV) , 16 studies.	lans 30-60 mg qd, ome 20-40 mg qd, pant 40 mg qd for 12 weeks	H2RAs, cim 800-1600 mg/day, fam 40 or 80 mg/day, niz 300-600 mg/day, ran 300-1200 mg /day for 12 weeks	The rate of heartburn improvement. Speed of healing/week 1- 12 weeks; overall healing rates	<u>Rate of heartburn improvement</u>: (12±1%/week) with PPIs vs. (6±1%/week) with H2RAs ($p<0.05$). <u>Healing rates:</u> wk 2: 32±3%/week with PPIs vs. 15±6%/week with H2RAs wk 4: 17±3%/week with PPIs vs. 9±3%/week with H2RAs wk 6: 15±1%/week with PPIs vs. 6±2%/week with H2RAs wk 8: 11±1%/week with PPIs vs. 7±2%/week with H2RAs. wk 12: 8±0.1%/week with PPIs vs. 5±1%/week with H2RAs <u>Overall healing rates:</u> 12±1%/week with PPIs vs. 6±0.2%/week with H2RAs The r^2 for regression slopes (0.91 for PPIs vs. 0.89 for H2RAs) ($p<0.0001$).	+ +
Green et al. 1995*[59] RCT **(good)**	198 patients with reflux esophagitis (1-IV)	ome 20mg qd, (or 40 mg qd if needed)	ran 150mg bid	Median time to report no heartburn and to consume no antacid	7 days with ome vs. 19 days with ran ($p<0.001$).	+

cim: cimetidine; lans: lansoprazole; niz: nizatidine; ome: omeprazole, pant; pantoprazole, fam; famotidine; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question G2: What is the status of double dose vs. single dose of PPIs in GERD and esophagitis as initial therapy?

G2A: Guideline Statements

Synopsis of Existing Recommendations G2A: Double dose of PPI is no better than standard dose for healing of GERD or esophagitis. Twice-daily, standard dose may be used for patients with severe symptoms.

The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.

i. Doubling the dose of PPI therapy is no better than standard dose PPI therapy for healing typical GERD or esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

ii. Twice-daily, standard dose PPIs may be used for patients who have severe symptoms of GERD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	22	Twice-daily PPI therapy is not generally required as initial therapy for typical GERD symptoms. Twice-daily, standard dose PPI may be used for patients who have severe symptoms despite standard once daily PPI therapy. Twice-daily standard dose PPI therapy may be used for patients who have severe esophagitis (LA grade C or D or stricture). Doubling the dose of a PPI reduced esophageal acid exposure in patients in whom single dose therapy was not adequate. There is little clinical evidence to support the use of double dose or twice-daily PPI therapy for initial therapy. However, several trials have shown that a proportion of patients who had not responded to standard dose PPI therapy experienced symptom relief with double dose PPI or a longer duration of therapy.
Prodigy – Proven GORD[15]	2005	9	Doubling the dose of PPI has only a small effect on healing of esophagitis at 4 weeks. Pooled data found that the average healing rate in full-dose PPI groups was 72%, and doubling the dose resulted in an absolute increase of 5%. However, post-hoc subgroup analysis suggests that the absolute increase in healing is greatest in people with LA grade C and D esophagitis.
Toward optimized Practice[72]	2005	3	For those few patients [with GERD] who fail therapy with a [standard dose of] PPI for 8 weeks, a trial of twice-daily PPI for 4 weeks may be tried.
NICE – Dyspepsia[24]	2004	96	If patients have severe esophagitis and remain symptomatic, double dose PPI for a further month may increase the healing rate.
MAMSI[73]	2003	2	[For PPIs] if once daily dosing does not control symptoms [of GERD], the dose may be increased to twice a day.
Johnson DA.[16]	2000	S52	[For GERD] partial responders or non-responders with persistent acid exposure on BID therapy it was agreed that higher trial doses of the PPI therapy may be warranted (e.g., 40 mg bid of omeprazole, 60 mg bid of lansoprazole, 40 mg bid or rabeprazole or 80 mg bid for pantoprazole).
First Muli-disciplinary[74]	1997	149S	The committee members were in agreement that high dose PPI therapy is the initial treatment of choice in patients with suspected supraesophageal complications of GERD.
Marzo et al[75]	2002	2	PPIs have demonstrated efficacy in curing esophagitis. Before considering the drugs to be a therapeutic failure, the doubling of the dose should be considered.

G2A: Supporting Evidence

G2A-i: Doubling the dose of PPI therapy is no better than standard dose PPI therapy for healing of typical GERD or esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: The data reflux or erosive esophagitis are controversial. Three good quality RCTs (Van Resenburg et al 1996, Bardhan et al 1995, Sontag et al. 1992) and two poor quality RCTs (Hetzel et al 1988, Earnes et al. 1998) reported no benefit of using the double dose over the standard dose of PPIs for healing in patients of reflux or erosive esophagitis. However, two poor quality RCTs (Bate et al 1993, Richter et al 2000) reported a better healing with the double dose than the standard dose of PPI in patients with reflux or erosive esophagitis. There is no data on the role of double-dose of PPIs in typical GERD, hence the data does not fully support the recommendation.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
van Resenburg et al. 1996*[76] RCT **(very good)**	192 patients with reflux esophagitis	pant 40 mg qd for 8 weeks	pant 80 mg qd for 8 weeks	Healing at 4 and 8 weeks	wk 4: 69% (pant 40 mg) vs. 66% (pant 80 mg) wk 8 : 85% (pant 40 mg) vs. 86% (pant 80 mg)	+
Bardhan et al 1995*[54] RCT **(very good)**	229 patients with endoscopically confirmed reflux esophagitis (grade 1-3)	lans 30 mg qd or lans 60 mg qd for 4-8 weeks	ran 150 mg bid for 4-8 weeks	Healing rate at 4 and 8 weeks	wk 4: 84% (lans 30 mg) vs. 72% (lans 60 mg) wk 8: 92% (lans 30 mg) vs. 90% (lans 60 mg) The difference between lans 30 mg and lans 60 mg rates was NS.	+ +
Sontag et al. 1992*[77] RCT **(good)**	230 patients with symptomatic erosive esophagitis (grade ≥ 2)	ome 20 mg qd or ome 40 mg qd for 4-8 weeks	Placebo for 4-8 weeks	Healing rates at 4 and 8 weeks. Symptom relief.	<u>Healing rates:</u> wk 4: 44% (ome 40 mg) vs. 38% (ome 20 mg) wk 8: 72.5% (ome 40 mg) vs. 73% (ome 20 mg) There were no significant differences in healing rates between the two dose groups when adjusting for baseline severity of esophagitis. <u>Heartburn relief:</u> 82.1% (ome 40 mg) vs. 80% (ome 20 mg).	+ +
Hetzel et al 1988*[78] RCT **(poor)**	132 patients of severe peptic esophagitis (grade 2-4)	ome 20 mg qd for 4 weeks	ome 40 mg qd for 4 weeks	Healing rates at 4 weeks	<u>Grade II:</u> 87% (ome 20 mg) vs. 97% (ome 40 mg) <u>Grade III:</u> 67% (ome 20 mg) vs. 88% (ome 40 mg) <u>Grade IV:</u> 48% (ome 20 mg) vs. 44% (ome 40 mg)	+
Earnest et al. 1998*[79] RCT **(poor)**	292 patients with reflux esophagitis (grade ≥ 2)	lans 15mg qd, 30mg qd or 60mg qd for 4-8	Placebo for 4-8 weeks	Healing rates at 4, 6 and 8 weeks	wk 4: 73% (lans 30 mg) vs. 76% (lans 60 mg) wk 6: 87% (lans 30 mg) vs. 86% (lans 60 mg)	+

		weeks			wk 8: 87% (lans 30 mg) vs. 89% (lans 60 mg)	
Bate et al 1993*[80] RCT **(poor)**	313 patients with reflux esophagitis (grade 2-4)	ome 20 mg qd for 8 weeks	ome 40 mg qd for 8 weeks	Healing rates at 8 weeks	45% (ome 20 mg) vs. 64% (ome 40 mg) (p<0.02)	-
Richter et al 2000*[81] RCT **(poor)**	603 patients with erosive esophagitis (grade 2-4)	pant 10, 20, 40 mg for 4-8 weeks	pant 40 mg or placebo for 4-8 weeks	Healing rates of esophagitis at 4 and 8 weeks	wk 4: 72% (pant 40 mg) vs. 55% (pant 20 mg) vs. 42% (pant 10 mg) vs. 14% (placebo) (p<0.001 all doses of pant vs. placebo). pant 20 mg produced better healing than 10 mg (p=0.022). pant 40 mg produced better healing than pant 20 mg and pant 10 mg (p ≤0.001). wk 8: 88% (pant 40 mg) vs. 78% (pant 20 mg) vs. 59% (pant 10 mg) vs. 33% (placebo) (p<0.001 all doses of pant vs. placebo) pant 20 mg produced better healing than 10 mg (p=0.001). pant 40 mg produced better healing than pant 20 mg and pant 10 mg at (p ≤0.001)	- - - - -
ome: omeprazole; pant: pantoprazole; lans: lansoprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G2A-ii: Twice-daily, standard dose PPIs may be used for patients who have severe symptoms of GERD. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Summary: This Synopsis of Existing Recommendations is based on expert opinion[12,15,16,24,72,73,74,75] and further research is required.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G3: What is the duration of treatment?

G3A: Guideline Statements

Synopsis of Existing Recommendations G3A: Long-term PPI therapy is recommended for erosive esophagitis complicated by strictures with an aim of preventing recurrence. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline

Canadian Consensus Update[12]	2005	23	Long-term therapy is recommended for erosive esophagitis with an aim of preventing recurrent esophageal injury or mucosal breaks, in addition to complications such as strictures.

G3A: Supporting evidence

G3A: Long-term therapy is recommended for erosive esophagitis complicated by strictures with an aim of preventing recurrence. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: The results from the 3 RCTs (one good quality and two poor quality) are inconsistent. The results of two poor quality RCTs (Smith et al. 1994, Marks et al. 1994) showed that long term treatment (6-12 months) with PPIs (or H2RAs) is effective in reducing the need for redilatation and symptom relief and PPIs are superior to ranitidine in the long term treatment for relieving dysphagia and reducing the need for redilatation in patients with esophageal strictures. However, one of the above poor quality RCTs (Marks et al. 1994) did not find any benefit with omeprazole over ranitidine at 3 months in these patients. In addition, the results of another good quality RCT (Swarbrick et al. 1996) showed no superiority of PPIs over double dose of ranitidine in patients with esophageal stricture.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Smith et al. 1994*[82] RCT **(poor)**	366 patients with esophageal strictures (grade 1-2), esophagitis (grade 0-4), mean age 71 years	ome 20 mg qd for 1 year	ran 150 mg bid for 1 year	Stricture recurrence (redilat-ation), symptom occurrence, adverse events at 1 year	<u>Patients requiring redilatation:</u> 30% in ome arm vs. 46% in ran arm, (p<0.01) <u>Patients requiring redilatation:</u> 0.48 in ome arm vs. 1.08 in ran arm, (p<0.01) <u>Symptoms relief:</u> <u>No dysphagia:</u> 76% in ome arm vs. 64% in ran arm (p<0.05) <u>Able to eat normal diet:</u> 83% in ome arm vs. 69% in ran arm (p< 0.01) <u>Asymptomatic:</u> 65% in ome arm vs. 43% in ran arm (p<0.001)).	+ + + + +
Marks et al. 1994*[83] RCT **(poor)**	37 patients with esophageal strictures (stricture 1, 2), esophagitis (grade ≥ 2) age 57-64 years.	ome 20 mg qd for 6 mos	(ran 150 mg bid or fam 120 mg bid) for 6 mos	Esophagitis healing; dysphagic relief; Need for dilatation at 3 and 6 months	<u>Healing:</u> At 3 months, 61% in ome arm and 47% in ran arm (NS). At 6 months, 100% of patients in ome arm and 53% in ran arm were healed (p<0.01). <u>Patients requiring dilatation:</u> At 6 months: 41% with ome vs. 73% with ran (p=0.07) <u>Dysphagia relief:</u> At 3 months: 50% with ome vs 33% with ran (p = 0.34).	- + - -

					At 6 months: 94% with ome vs 40% with ran (p<0.01).	+
Swarbrick et al. 1996*[84] RCT **(good)**	158 patients of esophageal strictures (grade 1-4), esophagitis (present or absent, but not graded, present in 80% of patients) (mean age 68 years)	lans 30 mg qd for 1 year	ran 300 mg bid for 1 year	Time to redilatation; proportion of pts needing redilatation; number of redilatations. dysphagia relief; reduction in stricture grade presence of esophagitis at 1 year	Time to redilatation and probability of no redilatations: These were higher in lans group than ran group (P = 0.053); Redilatation: At 12 months, fewer redilatations 30.8% in lans group vs. 43.8% in ran group (NS). # of redilatation: No significant difference between groups in # of redilatations. Dysphagia grade: Significantly lower dysphagia grades in lans group at 6 months (p = 0.009) but not at 12 months (p = 0.074). Reduction in stricture grade: There is more reduction for lans group than ran at both 6 months and 12 months. (p=0.11 and 0.33, respectively). Esophagitis present at 12 months: 30% with lan vs 52% with ran groups.	- - - + - - 0
fam: famotidine; lans: lansoprazole; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G4: How do the individual drugs in the PPI category differ in controlling the initial symptoms and/or disease?

G4A: Guideline Statements

Synopsis of Existing Recommendations G4A: Standard doses of PPIs are equally effective in GERD and esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy – Proven GORD[15]	2005	9,10	There is no evidence that any PPI is more effective than another for healing of esophagitis when PPIs are compared at equivalent doses. Differences between the PPIs in clinical efficacy and safety are minimal.
Canadian Consensus Update[12]	2005	21,22	In general, 24 h intragastric pH studies suggest that standard dose omeprazole, lansoprazole, pantoprazole and rabeprazole are similar with respect to their effect on the duration of the 24 h period during which gastric pH remains above 4.0. However, 24 h intragastric pH studies suggest greater suppression of gastric acidity with esomeprazole 40 mg compared with lansoprazole 30 mg, omeprazole 20 mg and 40 mg, pantoprazole 40 mg and rabeprazole 20 mg, although these differences do not

			necessarily lead to differences in esophageal acid exposure. The standard dose of omeprazole, lansoprazole, pantoprazole and rabeprazole are equivalent to each other with respect to healing esophagitis. Esomeprazole 40 mg produces somewhat higher four and eight week healing rates than standard dose omeprazole, lansoprazole or pantoprazole, particularly in more severe (LA grades C and D) erosive esophagitis, overall differences in healing proportions at eight weeks are small ranging from just over 3% to just over 6%. Furthermore, although the differences are statistically significant, their clinical relevance is debated and the results have not been replicated consistently in other studies.
Marzo et al[75]	2002	1	[For GERD] the comparison of different PPIs at standard doses (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and rabeprazole 20 mg) has not demonstrated significant differences, although recent studies with esomeprazole note a small superiority relative to omeprazole.
Fennerty et[36]	1996	481	[In GERD] the PPIs appear equally effective when used in equivalent doses.

G4A: Supporting Evidence

G4A: Standard doses of PPIs are equally effective in GERD and esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

a) Studies on PPIs doses for healing of GERD

Summary: In GERD (grade 0-4), the results show no significant difference among lansoprazole, omeprazole, pantoprazole, and rabeprazole on the healing of reflux esophagitis in patients with erosive or ulcerative esophagitis and GERD. The data is based on 2 poor quality MAs.

Esomeprazole produces significantly better healing as compared to omeprazole. This effect may be dose-related as the effect of 40 mg of esomeprazole was compared with the standard dose of omeprazole. The data are supported by one poor quality MA **(**Klok et al 2003[85])

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Caro et al 2001*[40] MA **(poor)**	8 studies for healing involving 1298 patients with endoscopically confirmed GERD (grade 0-4)	lans 30 mg/day, ome 20 mg/day, pant 40 mg/day, rab 20 mg/day	ran 300 mg/day	Healing proportion and symptom relief and rates at 4 and 8 weeks Relapse at 1 year	<u>RR healing rates (PPIs (lans, pant, rab) vs. ome 20 mg):</u> wk 4 : 1.04 (95%CI : 0.99, 1.10) for lans, 0.92 (95%CI : 0.85, 1.00) for rab, 0.96 (95%CI : 0.85, 1.08) for pant wk 8: 1.02 (95%CI: 0.98, 1.06) for lans; 0.93 (95%CI: 0.87, 1.00) for rab, 0.98 (95%CI : 090, 1.07) for pant. <u>Overall heartburn relief RR PPIs (lans, pant, rab) compared with ome 20 mg</u>: At 4 wk: 1.02 (95%CI: 0.94, 1.11). <u>Relapse</u>: at 1 year: lans vs. rab (4.1% vs.	+

					5%, respectively)	
Klok et al 2003[85] MA **(poor)**	pant vs. ome 4, studies (n=604), lans vs. ome 6, studies (n=1881), rab vs. ome, 2 studies (n=409), esome vs ome, 2 studies (n=3729) with endoscopically determined GERD.	ome 20 mg qd	pant 40 mg qd, lans 30 mg qd, rab 20 mg qd, esome 40 mg qd	Endoscopic healed GERD	wk 4: other PPIs vs. ome: 0.97 (95%CI: 0.88, 1.06) for pant, 1.02 (95%CI: 0.96, 1.08) for lans, 0.98 (95%CI: 0.91, 1.06) for rab. esome 40 mg vs. ome RR : 1.18, (95%CI: 1.14, 1.23),.NNT = 7.7.	+ - -
esome : esomeprazole; lans: lansoprazole; ome: omeprazole; pant: pantoprazole; ran: ranitidine; rab: rabeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G4A Supporting Evidence

G4A: Standard doses of PPIs are equally effective in GERD and esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***
b) Intragastric pH studies in GERD

Summary: On compiling the data of 4 poor quality RCTs, no significant differences were found among lansoprazole, omeprazole, pantoprazole, and rabeprazole on the increase of intragastric pH in patients with symptomatic GERD. Esomeprazole produces slightly better effect when compared to other PPIs. This effect may be dose-related as 40 mg of esomeprazole has been compared with standard doses of other PPIs (Miner et al 2003, Lind et al 2000, Röhss et al 2002). However, the effect of esomeprazole 40 mg is similar to pantoprazole 40 mg on intragastric pH. (Simon et al 2003). In addition, all the RCTs are comparing the effect of short term treatment (less than a week), but whether the better effect of esomeprazole on intragastric pH is maintained on long term use is not known. Considering the above findings from 3 poor quality RCTs in patients with symptoms of GERD, there is no justification for favouring one PPI over the others.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Miner et al 2003*[86] RCT **(poor)**	34 patients of *H. pylori* negative with symptoms of GERD	esome 40 mg qd for 5 days	lans 30 mg qd, ome 20 mg, or pant 40 mg qd, or rab 20 mg qd for 5 days	Intragastric pH on day 5	The mean number of hours of maintenance with intragastric pH >4 14.0 h with esome vs. 12.1 h with rab vs. 11.8 h with ome vs. 11.5 h with lans vs. 10.1 h with pant ($p \leq 0.001$) % of pts with intragastric pH >4.0: esome provided higher % of patients for >12 h vs. other PPIs ($p<0.05$)	- -
Lind et al 2000*[87] RCT **(poor)**	36 patients with suspected or confirmed GERD	esome 20 mg and 40 mg qd for 5 days	ome 20 mg qd for 5 days	Intragastric pH at day 5	Intragastric pH: >4 maintained (mean): 16.8 h with esome 40 mg and 12.7 h with esome 20mg vs. 10.5 h with ome 20 mg ($p<0.001$ and $p<0.01$, respectively)	-

					24 h intragastric pH: 4.9 with esome 40 mg and 4.1 with esome 20 mg vs. 3.6 with ome 20mg ($p<0.001$ and $p<0.01$, respectively)	-
Röhss et al 2002*[88] RCT **(poor)**	130 patients of *H. pylori* negative with symptoms of GERD	esome 40 mg qd for 5 days	ome 40 mg qd for 5 days	Intragastric pH on day 1 and 5	Mean % of 24 h >4: Day 1: 48.6% with esome 40 mg vs 40.6% with ome ome 40 mg (48.6% vs. 40.6%) ($p<0.001$) On day 5, 68.4% with esome 40 mg vs. 62.0% ($p<0.001$).	- -
Simon et al 2003*[89] RCT **(poor)**	48 patients with symptomatic GERD	esome 40 mg qd for 7 days	pant 40 mg qd for 7 days	Intragastric pH and total number of reflux episodes for 7 days	Both esome and pant decreased the mean total number of reflux episodes and reduced the % of reflux time within 24 h to <3% (2.6% with pant and 0.9% with esome) to almost similar extent; The time of pH <4.0 was also similar between the two treatments.	+
esome : esomeprazole; lans : lansoprazole; ome : omeprazole; pant : pantoprazole; rab : rabeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G4A Supporting Evidence

G4A: Standard doses of PPIs are equally effective in GERD and esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***
c) Studies on the healing of esphagitis

Summary: In GERD (grade BC or ≥ 2), the effects of omeprazole 20 mg vs. rabeprazole 20 mg; pantoprazole 40 mg vs. esomeprazole 40 mg are similar on the healing and symptoms improvement. The data is supported by 2 good quality RCTs (Dekkers et al. 1999[90], Gillessen et al 2004[91]) .
In erosive or reflux esophagitis (grade 1-4) the effect of omeprazole, pantoprazole and rabeprazole are similar on the healing and symptoms. This is supported by 2 poor quality RCTs (Vcev et al. 1999[92], Delchier et al 2000[93]). Esomeprazole 40 mg produces significantly better healing as compared to Esomeprazole 20 mg, omeprazole 20 mg, and lansoprazole 30 mg. The data are supported by 3 very good RCTs. This effect may be dose-related as the effect of 40 mg of esomeprazole was compared with the standard doses of omeprazole, lansoprazole and esomeprazole. A good quality RCT (Labenz et al 2005)[94] reported better healing of esophagitis with esomeprazole 40 mg as compared to pantoprazole 40 mg, indicating that the effect may be PPI-specific.
The effect of PPI may also be indication-specific since in peptic ulcer disease, pantoprazole 40 mg was superior to omeprazole 20 mg in ulcer healing RR 1.07, (95%CI: 1.02, 1.13). All other PPIs showed no significant difference.[85] *H pylori* eradication studies found no difference among the PPIs.[85] However, the real differences among the PPIs remains to be determined.
On analyzing the data, the overall differences in healing proportions at 8 weeks are small ranging from 3% to 6%. The results, though statistically significant, may not be clinically relevant.
** A heartburn rating of 'none' on a 4-point scale was considered resolution whereas 7 consecutive days with a rating of 'none' was considered sustained resolution.

Study Typ(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Dekkers et al. 1999[90] RCT **(good)**	202 patients with erosive or ulcerative GERD (≥2)	rab 20 mg qd	ome 20 mg qd	Healing rates and symptom relief at 4 and 8 weeks.	<u>Healing rates:</u> wk 4: 81% with rab vs. 81% with ome (95%CI: ±11%) (NS) wk 8: 92% with rab vs. 94% with ome (95%CI: -9%, 5%) (NS) <u>Heartburn improvement:</u> wk 4: 68% with rab vs. 75% with ome (p=0.36) wk 8: 73% with rab vs. 76% with ome (p=0.66)	+ + + +
Gillessen et al 2004*[91] RCT **(good)**	227 patients with GERD grade B/C (LA classification)	esome 40 mg qd for 10 weeks	pant 40 mg qd for 10 weeks	Healing at 4, 6, 8, 10 weeks and overall relief from symptoms	<u>Healing rates</u> : Overall healing rates: 95% (pant 40 mg) vs. 90% (esome 40 mg) wk 4: 58% (pant 40 mg) vs. 66% (esome 40 mg) wk 6: 84% (pant 40 mg) vs. 75% (esome 40 mg) wk 8: 100% (pant 40 mg) vs. 89% (esome 40 mg) wk 10: 91% (pant 40 mg) vs. 97% (esome 40 mg) No significant difference between pant and esome <u>Overall relief from symptoms:</u> 55% with pant vs. 51% with esome (per-protocol population).	+ + +
Vcev et al. 1999[92] RCT **(poor)**	120 patients with reflux esophagitis (grade 1-4, Savary-Miller classification)	pant 40 mg qd	ome 20 mg qd	Healing rates at 4 and 8 weeks	wk 4:pant 75% vs. ome 70% (NS) wk 8: pant 90% vs. ome 87% (NS)	+
Delchier et al 2000*[93] RCT **(poor)**	310 patients with erosive esophagitis ≥2	rab 20 mg qd (rab 20 mg) or rab 10 mg bid (rab 10 mg)	ome 20 mg qd (ome 20 mg)	Esophageal mucosal healing; symptom reduction; QOL scores improvement.	<u>Healing rates (ome vs. rab):</u> (difference between all groups are not significant) Diff between ome 20 mg qd and rab 20 mg qd: wk 4: 4% (95%CI : -2%, 10%) (NS) wk 8: 3% (95%CI : -1%, 6%) (NS) Difference between ome 20 mg qd and rab 10 mg bid: wk 4: 5% (95% CI -1%, 6%) wk 8: 3% (95%CI -2%, 12%) Multiple regression analysis also showed no sig differences. <u>Quality of life:</u> At 4 and 8 weeks, no significant differences between any groups for	+ + + +

					symptom relief or QOL scores.	
Castell et al 2002*[95] RCT **(very good)**	5241 patients with endoscopically documented erosive esophagitis (grade A-D)	esome 40 mg qd for 8 weeks	lans 30 mg qd for 8 weeks	Healing rates and heartburn resolution at 4 and 8 weeks	<u>Healing rates:</u> wk 8: 92.6% (95%CI: 91.5%, 93.6%) for esome vs. 88.8% (95%CI: 87.5%, 90.0%) for lans, (p=0.0001, life table estimates) wk 4: 76% esome vs. 72% lans (p<0.01) <u>Complete resolution of heartburn:</u> 63% esome vs. 60% lans (p<0.05)	- - - -
Kahrilas et al 2000*[96] RCT **(very good)**	1960 patient with endoscopy-confirmed reflux esophagitis (grade A-D)	esome 40 mg qd for 8 weeks	esome 20 mg or ome 20 mg qd for 8 weeks	Healing rates; heartburn resolution at 8 week	<u>Healing rates (cumulative life table estimates:</u> wk 8: 94.1% (esome 40mg) vs. 89.9% (esome 20 mg) vs. 86.9% (ome 20 mg) (each p<0.05) wk 4: esome 40mg more effective vs. ome for healing and all secondary measures evaluating heartburn resolution (p<0.05).	- - -
Richter et al 2001*[97] RCT **(very good)**	2425 patients with erosive esophagitis (*H. pylori* negative) (grade A-D)	esome 40 mg qd for 8 weeks	ome 20 mg qd for 8 weeks	Healing rates; heartburn resolution at 8 weeks	<u>Healing rates:</u> wk 8: 93.7% (esome 40 mg) vs. 84.2% (ome 20 mg) (p<0.001) wk 4: 81.7% (esome 40 mg) vs. 68.7% (ome 20 mg) (p<0.001) <u>Resolution of heartburn</u>: (rating of 'none' for 7 days)** was higher for esome 40 mg vs. ome 20 mg at wk 4. (p=0.0005).	- - -
Labenz et al 2005*[94] RCT **(good)**	3161 patients with erosive esophagitis and endoscopy performed to grade erosive esophagitis (grade A-D)	esome 40 mg qd for 8 weeks	pant 40 mg qd for 8 weeks	Healing at 4 and 8 weeks	wk 4: 81% (esome 40 mg) vs. 75% (pant 40 mg) (p<0.001). wk 8: 96% (esome 40 mg) vs. 92% (pant 40 mg) (p<0.001)	- -
esome: esomeprazole; lans: lansoprazole; ome: omeprazole; pant: pantoprazole; rab: rabeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G5: How should long-term maintenance for GERD be conducted?

G5A: Guideline Statements

Synopsis of Existing Recommendations G5A: Long-term maintenance in GERD should be given at the lowest dose and frequency that is sufficient to achieve optimal control of the patient's symptoms.

The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel

Guideline/ Consensus	Year	Page	Recommendation within the guideline

Canadian Consensus Update[12]	2005	23	Long-term maintenance should be given at the lowest dose and frequency that is sufficient to achieve optimal control of the patient's symptoms.
DeVault and Castell[13]	2005	194	Because GERD is a chronic condition, continuous therapy to control symptoms and prevent complications is appropriate.
NICE – Dyspepsia[24]	2004	108	Sixty to eighty percent of patients with successfully treated GERD will have a symptomatic relapse within one year if not provided with maintenance therapy. While a trial without medication is appropriate, many patients will require a further course of treatment.
OPOT[23]	2000	30,35	Maintenance therapy using the drug that treated the acute episode effectively is appropriate for patients whose symptoms recur after the initial treatment course. Full doses of H2RAs and PPIs are generally necessary for maintenance therapy, although lower doses may be effective in some patients, H2RAs and PPIs can be recommended for maintenance therapy for GERD. The choice of maintenance therapy should mirror the initial agent that successfully improved symptoms. PPIs are more effective for more severe, erosive disease.

G5A: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[12] and further research is required.[13,23,24]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G5: How should long-term maintenance for GERD be conducted?

G5B: Guideline Statements

Synopsis of Existing Recommendations G5B: Once a dose of either a H2RA, prokinetic agent, and/ or a PPI that relieves symptom has been identified, this dose should be maintained for a period of 3 months. After this time an attempt should be made to reduce the dose, with the aim of maintaining a stable clinical status. If symptoms recur, then the patient should go back to full-dose PPI and plan for long-term treatment. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel. The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Guideline/ Consensus	Year	Page	Recommendation within the guideline

OPOT[23]	2000	34	Long-term maintenance therapy should be considered for patients with GERD in whom symptoms recur after the completion of an initial course of therapy. Many experts believe that serious underlying pathology (e.g., Barrett's esophagus) should be ruled out endoscopically before committing a patient to long-term acid suppression therapy (i.e., >6 months).
Yale Consensus[98]	1998	11	It was felt that the addition of a prokinetic agent to therapy in conjunction with PPI was likely to be of only marginal benefit for GERD. Once a dose of either H2RA, prokinetic agent, and/ or PPI that relieves symptoms is identified, this dose should be maintained for a period of 3 months. After this time, an attempt should be made to reduce the dose, with the aim of maintaining a stable clinical status (asymptomatic) on a half-dose PPI or alternatively on alternate days. If symptoms recur, then the patient should go back to the full dose of PPI and a plan formulated for long-term treatment.

G5B: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[98] and further research is required.[23]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G6: Should attempts be made to step-down and discontinue therapy or continue the current therapy in GERD and erosive esophagitis?

G6A: Guideline Statments

Synopsis of Existing Recommendations G6A: Step-down therapy in patients with GERD and erosive esophagitis prevents symptomatic relapse in a majority of patients after stopping the PPI. Continued PPIs provided better heartburn relief than step-down to H2RAs. Many patients require medications other than PPI. The optimal approach of step-up, step down and no step remains to be determined. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

i. Step-down therapy in patients with GERD and erosive esophagitis prevents symptomatic relapse in a majority of patients in one year after stopping the PPI. Many patients require medications other than PPI. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

ii. Continued PPIs provided better heartburn relief than step-down to H2RAs. The optimal approach of step-up or step-down remains to be determined**.** ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Asia-Pacific Consensus[46]	2004	362	With this [step-down] strategy, after 1 year of stopping PPI, 58% of patients with reflux esophagitis were asymptomatic and

			75% of these patients require medication other than PPI (H2RA, prokinetic, antacid). An earlier study reported that heartburn remission after stopping treatment was 85% among patient with grade I erosive esophagitis.
VHA/DoD[32]	2003	26,28	There is currently no definite evidence to support a particular approach in the maintenance therapy for DoD or VA patients with uninvestigated GERD. PPIs are superior to H2RAs and a no-step PPI approach may be superior to a step-down or no-step H2RA approach for the maintenance therapy in a population of patients. The optimal approach to maintenance therapy is unclear.
Prodigy – Proven GORD[15]	2005	9	The relapse rates without treatment is 60-80%. Full-dose PPIs are more effective that H2RAs. Full-dose PPIs are more effective than placebo. Full dose PPIs are slightly more effective than low-dose PPIs.

G6A-i: Supporting Evidence

G6A-i: Step-down therapy in patients with erosive esophagitis prevents symptomatic relapse in a majority of patients in one year after stopping the PPI and many patients require medications other than PPIs. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Summary: This Synopsis of Existing Recommendations is based on expert opinion[46] and further research is required.[32]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

G6A-ii: Supporting Evidence

G6A-ii: Continued PPIs provide better heartburn relief than step-down to H2RAs. The optimal approach of step-up or step-down remains to be determined.

Summary: The results indicate that PPI treatment provides more consistent heartburn relief than step-down to H2RAs in patients with GERD. Regarding step-down and step-up therapy, the results show that at week 1-8, step-down therapy is better than step-up and continued use of ranitidine. However, at week 9-20, step-up is better than step-down and continued use of ranitidine. At week 1-20, step-up is equally effective to step-down and step-up is better than ranitidine. This indicates that the real status of step-up or step-down therapy in GERD remains to be determined. The data are supported by one good quality RCT.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Howden et al 2001*[99] RCT **(good)**	593 patients with symptomatic GERD	L= lans 30 mg qd	R= ran, 150 mg, bid for 20 weeks RL = ran 150 mg bid for 8 weeks and then switch to lans 30 mg qd for the following 12 weeks	Heartburn relief at 20 weeks	L had significantly less heartburn than R L (82%) had significantly higher 24-h heartburn relief than R (66%), RL (74%), and LR (67%), $p<0.001$ Median heartburn severity during study on scale 0-3 (0=none, 1=mild, 2=moderate, 3=severe): Pre-treatment period: 1.88 for R,	+ +

			LR = lans 30 mg qd for 8 weeks and then switch to ran 150 mg bid for the following 12 weeks		1.75 for L, 1.75 for RL, 1.70 for LR Week 1-8: 0.57 for R, 0.29 for L, 0.56 for RL, 0.34 for LR; L vs. R p<0.001, L vs. RL p<0.001, LR vs. R p<0.001, RL vs. LR p<0.001 Week 9-20: 0.36 for R, 0.17 for L, 0.19 for RL, 0.49 for LR ; L vs. R p<0.001, L vs. LR p<0.001, LR vs. RL p<0.001, RL vs. R p<0.05 Week 1-20: 0.46 for R, 0.25 for L, 0.35 for RL, 0.44 for LR; L vs. R p<0.001, L vs. RL p<0.05, L vs. LR p<0.001, RL vs. R p<0.05, LR vs. R not significant, LR vs. RL not significant	
lans: lansoprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G6: Should attempts be made to step-down and discontinue therapy or continue the current therapy?

G6B: Guideline Statements

Synopsis of Existing Recommendations G6B: Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment.

- **i.** Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***
- **ii.** If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment. Restart the treatment (e.g., PPI) at full dose, with a limited number of repeat prescriptions. Encourage people to step-down treatment to the lowest dose required to control symptoms. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***
- **iii.** PPIs or ranitidine could be used as intermittent therapy for GERD.

Guideline/ Consensus	Year	Page	Recommendation within the guideline

Canadian Consensus Update[12]	2005	23	An individual whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. Intermittent medical maintenance therapy is defined as the daily intake of a medication for a predetermined, finite period (usually 2-8 weeks) to produce resolution of reflux-related symptoms or healing of esophageal lesions following relapse of the individual's condition.
Prodigy – Proven GORD[15]	2005	7	Stepping down or stopping treatment is not appropriate for people with complicated esophagitis (past strictures, ulcers, or hemorrhage).
VHA/DoD[32]	2003	26	If a patient has an adequate, sustained response to initial therapy, this guideline suggests two possible options for maintenance therapy: (1) step-down management with attempted discontinuation of therapy (preferred); or (2) no-step management (i.e., continuation of the current medication regimen).
NICE-Dyspepsia[24]	2004	114	[For intermittent therapy for GERD] The study found that patients randomized to the omeprazole groups [10 mg or 20 mg] had faster symptoms relief but there was no difference in outcome between the there groups [omeprazole 10 mg or 20 mg or raniditine 150 mg bid] in terms of time off treatment, time to failure of intermittent treatment or willingness to continue.

G6B-i: Supporting Evidence

G6B-i: Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. Stepping-down is not appropriate in complicated esophagitis. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Summary: This Synopsis of Existing Recommendations is based on expert opinion [12,15,32] and further research is required.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

G6B-ii: Supporting Evidence

G6B-ii: If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment. Restart the treatment (e.g., PPI) at full dose, with a limited number of repeat prescriptions. Encourage people to step-down treatment to the lowest dose required to control symptoms. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Summary: This Synopsis of Existing Recommendations is based on expert opinion [12,15,32] and further research is required.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Supporting Evidence

G6B-iii: PPIs or ranitidine could be used as intermittent therapy for GERD.

Summary: The results show that intermittent therapy with a PPI or ranitidine is effective in managing symptoms of heartburn in half of patients with uncomplicated GERD. The data are supported by one poor quality RCT.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Bardhan et al 1999*[100] RCT **(poor)**	677 patients with symptomatic GERD with normal endoscopy or mucosal breaks (grade A-C)	ome 10 mg and 20 mg qd	ran 150 mg	Symptoms Time to failure of intermittent treatment	<u>Patients not requiring treatment:</u> Half of the patients did not require treatment and this was similar in all the treatment groups <u>Patients asymptomatic at week 2:</u> 26% for ran vs. 40% for ome 10 mg and 55% for ome 20 mg ($p<0.001$) <u>Patients completed intermittent treatment:</u> 47% for ran vs. 46% for ome 10 mg and 48% for ome 20 mg <u>% transferred to maintenance treatment</u>: 27% for ran vs 22% for ome 10 mg and 22% for ome 20 mg.	 + + +

ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

G6C: Guideline Statements

Synopsis of Existing Recommendations G6C: In patients with LA grade C and D esophagitis who remain symptomatic with regular dose PPIs, offer a double dose PPI for a further month, then encourage patients to step down to the lowest dose required to control symptoms. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy – Proven GORD[15]	2005	6	If the person has LA grade C and D esophagitis and still remains symptomatic [with regular dose PPIs], offer a double-dose PPI for a further month, then encourage patients to step down treatment to the lowest dose required to control symptoms.

* The Los Angles classification system for the endoscopic assessment of esophagitis:

(A) One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds.

(B) One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds.

(C) Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference.

(D) Mucosal breaks which involve at least 75% of the esophageal circumference.

G6C: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion [15] and further research is required.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G7: What is the status of "on-demand" therapy in ENRD and GERD?

G7A: Guideline Statements

Synopsis of Existing Recommendations G7A: "On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD. PPIs could be used as 'on demand' therapy.

i. "On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

ii. PPIs can be used as "on-demand" therapy

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	23	On-demand acid suppression therapy is a reasonable long-term medical strategy for selected patients with GERD
Prodigy – Proven GORD[15]	2005	10	NICE recommend 'on demand' therapy as this promotes patient involvement in the management of their disease and should in theory be most cost-effective as, on average, patients take therapy once every 3 days. However, therapy can (and should) be individualized as a proportion of people will continue to take their PPI daily.
NICE – Dyspepsia[24]	2004	114	[For trials comparing on demand with continuous PPI therapy] Trials reported that the willingness to continue of patients allocated to on demand PPI was either similar to continuous PPI therapy or superior to continuous therapy.
Asia-Pacific Consensus[46]	2004	362	On-demand therapy with a standard dose of PPI is an effective treatment strategy in ENRD patients.
Baldi et al.[101]	1998	110	The cost/ benefit ratio of on-demand treatment is better than that of continuous maintenance treatment in patients without severe esophagitis or frequent recurrences.

G7A-i: Supporting Evidence

G7A-i: "On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Summary: This Synopsis of Existing Recommendations is based on expert opinion[12] and further research

is required.[15,24,46,101]						
Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

G7A-ii: Supporting Evidence

G7A-ii: PPIs can be used as "on-demand" therapy in ENRD

Summary: The results show that PPIs are better than placebo as 'on-demand' therapy in patients with ENRD. The data are supported by 3 poor quality RCTs. For the dose of PPI to be used, the data is controversial. Talley et al 2002,[102] reported no difference between esome 20 mg and esome 40 mg as on-demand therapy. However, Lind et al 1999[103] reported better response with ome 20 mg than with ome 10 mg.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Talley et al 2002*[102] RCT **(poor)**	721 endoscopy-negative GERD patients having resolution of heartburn after PPI	esome 40 mg, 20 mg on demand (maximum one dose/ day) for 6 mos	Placebo (maximum one dose/ day) for 6 mos	Time to study discontinuation due to unwillingness to continue and inadequate control of heartburn Mean daily intake Antacid consumption at 6 months	<u>Rate of study discontinuation due to unwillingness to continue</u>: 11% with esome 40 mg and 8% with esome 20 mg vs. 42% with placebo ($p<0.0001$) <u>Rate of study discontinuation due to inadequate control of heartburn</u>: 9% with esome 40 mg and 5% with esome 20 mg vs. 36% with placebo. ($p<0.0001$) <u>Patients free of heartburn, regurgitation and epigastric pain after 6 months</u>: It was better with esome 20 and 40 mg vs. placebo ($p<0.005$) No difference between esome 20 mg and 40 mg. <u>Mean daily drug intake:</u> 0.29 with esome 40 mg, 0.33 with esome 20 mg and 0.40 with placebo. <u>Average antacid consumption per day:</u> 0.48 tablet for esome 40, 0.44 for esome 20 mg vs 1.07 with placebo ($p<0.001$).	+ + + +
Lind et al 1999*[103] RCT **(poor)**	424 patients with heartburn without endoscopic esophagitis	ome 10 and 20 mg on demand qd for 6 mos	Placebo on demand for 6 mos	Time to study discontinuation due to unwillingness to continue and inadequate control of heartburn at 6 months. Quality of life,	<u>Remission rate at</u> 6 months crude, (95% CI): 83% (76%, 89%) ome 20 mg vs. 70% (62%, 78%) ome 10 mg vs. 56% (48%, 64%) placebo <u>Rate of remission</u>: at 6 months Life table analysis, (95% CI): 83% (77%, 89%) ome 20 mg vs. 69% (61%, 77%) ome	

				GSRS. Drug consumption Antacid consumption	10 mg vs. 56% (46%, 64%) placebo Differences were significant ($p<0.01$) between all three groups in both APT and PP analyses. Quality of life: for the reflux dimension of GSRS, the deterioration of score was greater in placebo compared to ome group. Difference between placebo and ome 20 mg was 0.6 (95% CI: 0.3-0.9) and between placebo and ome 10 mg 0.4 (95% CI: 0.1-0.7). Difference between the ome 10 mg and 20 mg was not significant. Antacids consumption per day: with ome 20 mg, ome 10 mg and placebo were 0.8 ± 0.7, 0.9 ± 0.9 and 1.1 ± 1.0 respectively. Average antacid consumption per day Mean (SD): 0.43 (0.3) for ome 20 mg, 0.41 (0.3) for ome 10 mg and 0.47 (0.3) for placebo.	+ + +
Talley et al 2001*[104] RCT **(poor)**	342 patients with ENRD demonstrating resolution of complete heartburn during final week for 4 week treatment with PPI	esome 20 mg (maximum one dose/ day) for 6 mos	Placebo (maximum one dose/ day) for 6 mos	Frequency and severity of heartburn, other GERD symptoms at 2, 4 and 6 months Mean intake of medication Antacid consumption	Rate of study discontinuation due to unwillingness to continue: 14% (esome 20 mg) vs. 51% (placebo) ($p<0.0001$) Completion of 6 month follow up: 82% (esome 20 mg) vs. 46% (placebo) Completion of 6 month follow up with no more than one day of heartburn in previous 7 days: 50% (esome 20 mg) vs. 27% (placebo) ($p<0.0001$). Mean intake of medication: 0.34 for esome 20 mg vs. 0.41 inplacebo ($p<0.01$). Antacid consumption: 1.1 tablet/day with placebo vs 0.4 with esome 20 mg	+ + +
esome: esomeprazole; ome: omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G8: What is the status of half-dose PPI in ENRD?

G8A: Guideline Statements

Synopsis of Existing Recommendations G8A: The effect of half-dose of PPI is less than the standard dose PPI for acute treatment in ENRD.			
Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	22, 23	Half dose PPI therapy (e.g., esomeprazole 20 mg, lansoprazole 15 mg, omeprazole 10 mg, pantoprazole 20 mg, or rabeprazole 10 mg daily) is less effective than standard dose therapy for acute treatment in erosive esophagitis and ENRD and is not generally recommended for initial therapy. Half-dose 'on-demand' PPI therapy produces acceptable symptoms control in 83 to 92% of ENRD, who have responded previously to acute PPIs, though half-dose omeprazole (10 mg/d) was less effective than standard-dose omeprazole (20 mg/d). On the other hand, half-dose esomeprazole (20 mg/d) was comparable to its standard-dose (40 mg/d). Although, most patient with more severe symptoms or esophagitis require ongoing daily standard dose therapy to maintain healing and symptom relief.

G8A: Supporting Evidence

G8A: The effect of half-dose of PPI is less than the standard dose PPI for acute treatment in ENRD.						
Summary: In ENRD, one very good and one good quality RCT reported better heartburn resolution with standard vs half dose of PPI.						
Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Lind et al 1997*[105] RCT **(very good)**	509 patients with heartburn without esophagitis	ome 10 mg qd for 4 wks	ome 20 mg qd for 4 wks	Heartburn resolution at 4 weeks	Heartburn resolution: 31% (ome 10 mg) vs. 46% (ome 20 mg) ($p<0.002$)	+
Richter et al 2000*[106] RCT **(poor)**	359 patients with heartburn without esophagitis	ome 10 mg qd for 4 wks	ome 20 mg qd, for 4 wks	Complete eradication of heartburn at 1 week	Complete eradication of heartburn: 27% (ome 10 mg) vs. 48% (ome 20 mg) ($p<0.002$)	+
ome: omeprazole; pant: pantoprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G8: What is the status of half-dose PPI in GERD and reflux esophagitis?

G8B: Guideline Statements

Synopsis of Existing Recommendations G8B: The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD and esophagitis.
i. The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***
ii. The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission in esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	22, 23	Half dose PPI therapy is sufficient to maintain endoscopic remission in about 35% to 95% of patients with erosive esophagitis. Half dose PPI therapy (e.g., esomeprazole 20 mg, lansoprazole 15 mg, omeprazole 10 mg, pantoprazole 20 mg, or rabeprazole 10 mg daily) is less effective than standard dose therapy for acute treatment in erosive esophagitis and ENRD and is not generally recommended for initial therapy. Half-dose 'on-demand' PPI therapy produces acceptable symptoms control in 83 to 92% of ENRD, who have responded previously to acute PPIs, though half-dose omeprazole (10 mg/d) was less effective than standard-dose omeprazole (20 mg/d). On the other hand, half-dose esomeprazole (20 mg/d) was comparable to its standard-dose (40 mg/d). Although, most patient with more severe symptoms or esophagitis require ongoing daily standard dose therapy to maintain healing and symptom relief.
NICE – Dyspepsia[24]	2004	96	PPIs at full dose were more effective than PPIs at low dose in trials of 6 to 12 months duration. Relapse of esophagitis occurred in 28% of patients on low dose PPI and 15% of patients on full dose PPI (a number needed to treat of 8). There is considerable variation in the findings of trials.

G8B-i: Supporting Evidence

G8B-i: The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: In patients with GERD (grade 1-4) the data are controversial. One good quality and 1 poor quality RCT reported better healing and less relapse with the standard vs half-dose of PPI at 6 months and 1 year, whereas 3 good quality RCTs reported similar healing or relapse at 1 year between these two treatments.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Caos et al 2000*[107] RCT **(poor)**	209 patients with erosive or ulcerative GERD (grade 2-4)	rab 10 mg qd for 1 year	rab 20 mg qd for 1 year	Endoscopic relapse rates at 1 year	rab 10 and 20 mg were superior to placebo for relapse prevention ($p<0.001$). The relapse rate with rab 20 mg was lower than with rab 10 mg ($p<0.04$)	+
Laursen et al	168 patients with	ome 10 mg	ome 20 mg qd	Endoscopic	Proportion of patients	+

1995*[108] RCT **(good)**	GERD (grade 1-4)	qd for 4-8 weeks	for 4-8 weeks	healing at 6 months	maintained macroscopically normal mucosa at 6 months was 35% with ome 10 mg vs. 59% with ome 20 mg (P<0.002).	
Plein et al 2000*[109] RCT **(good)**	433 patients with GERD previously diagnosed as stage II and III (Savary-Miller classification)	pant 20 mg qd for up to 1 yr	pant 40 mg qd for up to 1 yr	Endoscopic remission at 12 months	Endoscopic remission : 75% (pant 20 mg) vs. 78% (pant 40 mg)	-
Thjodleifsson et al 2000*[110] RCT **(good)**	243 patients with erosive or ulcerative GERD	rab 10 mg qd for 4 weeks	rab 20 mg qd and ome 20 mg qd for 4 weeks	Patients remaining free of relapse at 1 year	Cumulative proportion remaining free of relapse in daytime heartburn: 90% (rab 10 mg) vs. 94% (rab 20 mg) Patients remaining free of relapse of nighttime heartburn: 88% (rab 10 mg) vs. 85% (rab 20 mg) Relapse rate: 5% (rab 10 mg) vs. 4% (rab 20 mg)	-
Birbara et al 2000*[111] RCT **(good)**	288 patients with erosive or ulcerative GERD	rab 10 mg qd for 52 weeks	rab 20 mg qd for 52 weeks	Endoscopically demonstrated GERD relapse rate and heartburn relapse at 12 months.	Endoscopically demonstrated GERD relapse rates of erosive GERD: 23% (rab 10 mg) vs. 14% (rab 20 mg) (p=NS) Heartburn relapse: No significant difference between these two doses in preventing relapse of heartburn (21% with rab 20 mg vs. 31% with rab 10 mg, p=NS)	-
ome: omeprazole; pant: pantoprazole; rab : rabeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

G8B-ii: The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission of reflux esophagitis. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: The data are controversial. One MA (poor quality) and 4 RCTs (3 good quality and 1 poor quality) reported better maintenance of remission with standard vs half-dose of PPIs in patients with erosive or ulcerative esophagitis. However, 2 RCTs (1 very good and 1 poor) reported almost similar response with standard vs half dose of PPIs in these patients.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Carlsson et al 1997*[52] MA **(poor)**	4 trials, 1154 patients with erosive esophagitis	ome 10 and 20 mg qd for 6 mos	ran 150 mg bid for 6 months	Endoscopically-verified relapse at 6 months Time to	<u>Relapse:</u> 82.4% (95%CI: 78.2%, 86.6%) ome 20 mg vs. 72% (95%CI: 65.5%, 78.3%) ome 10 mg	+

				remission	Time to remission: ome 20 mg is superior to 10 mg (p<0.04).	
Richter et al 2000*[81] RCT **(good)**	603 patients with endoscopically confirmed erosive esophagitis; grade 2 or more	pant 10 mg qd For 4-8 weeks	pant 20 mg qd for 4-8 weeks	Endoscopic healing of esophagitis at 4 and 8 weeks	wk 4: 42% (pant 10 mg) vs. 55% (pant 20 mg) (p<0.02) wk 8: 59% (pant 10 mg) vs. 78% (pant 20 mg) (p<0.01)	+
Castell et al 1996*[112] RCT **(poor)**	1284 erosive reflux esophagitis ≥ grade 2	lans 15 mg qd for 8 weeks	lans 30 mg qd for 8 weeks	Healing rates at 8 weeks	75% (lans 15 mg) vs. 87% (lans 30 mg) (p<0.05)	+
Escourrou et al 1999*[113] RCT **(good)**	396 patients with reflux esophagitis (grade II and III)	pant 20 mg qd for up to 1 year	pant 40 mg qd for up to 1 year	Endoscopic relapse rates and symptom relapse at 6 and 12 months	Endoscopic relapse rates: 6 months:16% (pant 20 mg) vs. 7% (pant 40 mg) 12 months: 29% (pant 20 mg) vs. 19% (pant 40 mg) (p=0.037) Symptom relapse rates: 6 months: 14% (pant 20 mg) vs. 10% (pant 40 mg) 12 months: 21% (pant 20 mg) vs. 17% (pant 40 mg)	+
Hallerbäck et al 1994*[67] RCT **(good)**	392 patients with reflux esophagitis (grade 2-4)	ome 10 mg qd for 8 -12 weeks	ome 20 mg qd for 8 -12 weeks	Endoscopic healing and remission proportion at 12 weeks	Healing rates: 72% (ome 20 mg) vs. 62% (ome 10 mg) (p=0.06) Endoscopic remission: 77% with ome 20 mg vs. 58.1% with ome 10 mg (p=0.003)	+
Bate et al 1995*[114] RCT **(poor)**	190 patients with reflux esophagitis (grade 2-4)	ome 10 mg qd for 1 yr	ome 20 mg qd for 1 yr	Endoscopic relapse rates and proportion asymptom-atic at 12 months	Endoscopic relapse rates (Life table estimates) proportions without ≥2 esophagitis: 50% (ome 10 mg) vs. 74% (ome 20 mg) (p=NS) Proportion asymptomatic: 77% (ome 10 mg) vss 83% (ome 20 mg) (p=NS) Half-dose is effective in long term treatment and prolonging remission.	-
Robinson et al 1996*[115] RCT **(very good)**	173 patients with erosive esophagitis (grade 2-4)	lans 15 mg qd for 12 months	lans 30 mg for 12 months	Healing and symptom relief at 1 year	Healing rates: 79% (lans 15 mg) vs. 90% (lans 30 mg) (p=NS) Patients asymptomatic: 72% (lans 15 mg) vs. 67% (lans 30 mg) (p=NS)	-
lans: lansoprazole; ome: omeprazole; rab: rabeprazole; ran: ranitidine; pant: pantoprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G9: In the management of GERD, what should be preferred, PPIs or surgery?

G9A: Guideline Statements

Synopsis of Existing Recommendations G9A: Antireflux surgery was superior to PPI therapy in terms of symptomatic relapse, but if patients increased the PPI dose at relapse, there was no difference between the treatment strategies.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	24	In a randomized trial, antireflux surgery was superior to PPI therapy in terms of symptomatic relapse, but if patients increased the PPI dose at relapse, there was no significant difference between the treatment strategies at three and five years follow up.

G9A: Supporting Evidence

G9A: Surgical antireflux therapy is an alternative to medical therapy for the long-term management of selected patients with GERD.

Summary: The results from these 2 good quality RCTs support that if the dose of omeprazole is adjusted in cases of relapse the responses of the two strategies (surgery or PPI) are almost equal for the management of esophagitis.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Lundell et al 2000*[116] RCT **(good)**	298 patients with esophagitis (grade 0-1), with or without Barrett's esophagus and strictures	ome (either 20 mg or 40 mg qd)	Antireflux surgery (ARS)	Relpse, esophagitis, symptoms, quality of life scales for 3 years	Relapse: 17 experienced symptom relapse in ARS vs. 50 in ome group, Esophagitis: 14 had esophagitis and endoscopy in ARS group vs. 18 in ome group; 6 in ARS group required ome therapy vs. 2 required ARS in ome group; Clinical remission: 97 remained in study and in clinical remission after 3 years in ARS group vs. 77 remission in ome group (p=0.0016). Quality of life (PGWB score): 12 months: 103.7 (16.7) ome vs. 102.1 (19.0) ARS 24 months: 103.5 (17.0) ome vs. 103.1 (19.4) ARS 36 months: 103.2 (17.8) ome vs. 104.7 (17.1) ARS GSRS score: 12 months: 1.9 (0.7) ome vs. 1.9 (0.6) ARS 24 months: 1.9 (0.7) ome vs. 1.9 (0.7) ARS 36 months: 1.8 (0.7) ome vs. 1.7 (0.5) ARS	+

					GSRS reflux dimension score: 12 months: 1.8 (1.0) ome vs. 1.4 (0.7) ARS 24 months: 1.7 (0.8) ome vs. 1.3 (0.7) ARS 36 months: 1.7 (0.9) ome vs. 1.3 (0.6) ARS	
Lundell et al 2001*[117] RCT **(good)**	310 patients with erosive esophagitis, grade ≥ 2, with or without Barrett's esophagus and strictures.	ome (either 20 mg or 40 mg qd)	Antireflux surgery (ARS)	Relapse, esophagitis, remission and quality of life scales	<u>Relapse:</u> 122 ARS vs. 133 ome patients completed the 5 year follow-up. 20 relapse in ARS group vs. 49 in ome group; <u>Esophagits:</u> 18 esophagitis and endoscopy ARS group vs 20 in ome group; 7 required ome in ARS group vs. 16 in ome group submitted to ARS <u>Remission:</u> 83 remissions after 5 years in ARS group vs. 65 remission in ome group. P<0.001. <u>Quality of life (PGWB score):</u> 48 months: 102.7 (17.6) ome vs. 103.2 (18.8) ARS 60 months: 104.4 (16.7) ome vs. 103.5 (19.1) ARS <u>GSRS score:</u> 48 months: 1.9 (0.7) ome vs. 1.9 (0.7) ARS 60 months: 1.9 (0.7) ome vs. 2.0 (0.9) ARS <u>Total GSRS reflux dimension score:</u> 48 months: 1.7 (0.8) ome vs. 1.4 (0.8) ARS 60 months: 1.6 (0.8) ome vs. 1.4 (0.9) ARS	+
ARS: antireflux surgery; GSRS: Gastrointestinal Symptom Rating Scale; ome: omeprazole; PGWB: Psychological General Well-Being score; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question G9: In the management of GERD, what should be preferred, PPIs or surgery?

G9B: Guideline Statements

Synopsis of Existing Recommendations G9B: Surgical procedures could be considered if high dose PPI is ineffective, poorly tolerated, or if GERD is associated with serious complications despite therapy. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Federal Bureau of Prison[33]	2001	14	Specialized surgical procedures can be considered if high dose PPI suppressive therapy is ineffective, poorly tolerated, or if GERD is associated with serious complications despite therapy. Surgical interventions may not prevent the development of adenocarcinoma associated with Barrett's esophagus.

G9B: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion [32] and further research is required.						
Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G10: What is the role of PPIs in the management of Barrett's Esophagus?

G10A: Guideline Statements

Synopsis of Existing Recommendations G10A: GERD can be such an insidious long-standing process, even a patient with Barrett's esophagus lacking symptoms may benefit from a trial of PPI therapy. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***			
Guideline/ Consensus	Year	Page	Recommendation within the guideline
Sampliner[118]	2002	1892	Patients with Barrett's esophagus may be found incidentally and may deny symptoms of reflux. There is suggestive evidence that many more patients have Barrett's esophagus are detected by symptoms. This undetected group of patients is a result of factors including patient threshold for seeking medical attention and presumed elevated threshold to the perception of acid exposure of Barrett's patients. Because GERD can be such an insidious long-standing process, even a patient with Barrett's esophagus lacking symptoms may benefit from a trial of PPI therapy.

G10A: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion [118] and further research is required.						
Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question G10: What is the role of PPIs in the management of Barrett's Esophagus?

G10B: Guideline Statements

Synopsis of Existing Recommendations G10B: Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE. **i.** Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE. **ii.** Even high-dose PPI therapy will not usually result in reversal of Barrett's esophagus.			
Guideline/ Consensus	Year	Page	Recommendation within the guideline
Canadian Consensus Update[12]	2005	26	Neither medical nor surgical therapy has been proven to prevent the development of Barrett's epithelium or the subsequent development of esophageal adenocarcinoma.

			Acid suppression was associated with symptom control but not disappearance of Barrett's epithelium despite some reports of regression.
Sampliner[118]	2002	1892	As a group, patient with Barrett's have greater esophageal acid exposure than other GERD patients and control of symptoms may require higher than usual doses of PPIs. If once-a-day dosing of a PPI fails to control symptoms, then increasing the dose to b.i.d. is rational given the pharmacology of the effect on the parietal cells. The goals of therapy of Barrett's esophagus are the same as GERD: the control of symptoms of GERD and the maintenance of healed mucosa. Even high dose PPI therapy nearly eliminating esophageal acid exposure will not usually result in reversal of Barrett's esophagus.
Prodigy – Proven GORD[15]	2005	7	PPIs are used for symptom control. It is unknown whether acid suppression can reduce the risk of developing esophageal cancer, so it is currently unclear whether there is any value in continuing PPIs in people with asymptomatic Barrett's esophagus.

G10B-i: Supporting Evidence

G10B-i: Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE.

Summary: On comparing the management with medical and surgical treatment in patients with BE, no definite answer can be obtained from these RCTs. One RCT is of good quality and the other, poor quality. Acid suppression controls symptoms but does not cause the disappearance of BE. Surgery did not prevent the progression of dysplasia development. For medical management, different acid suppressants have been used (PPIs, H2RAs) in these RCTs. The role of PPIs or H2RAs alone has not been reported in these RCTs.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Ortiz et al 1996 [119] RCT **(poor)**	59 patients with BE and GERD symptoms	Medical treatment antisecretory drugs (H2RAs) initially and ome from 1992 onwards and periodical dilatations in patients with stenosis.	Surgical antireflux surgery (ARS)	Clinical outcomes and endoscop-ic and histolog-ical data	<u>Clinical outcome:</u> Treatment excellent for 56% of patients for medical treatment vs. 78% of patients for ARS; good for 33% of patients for medical vs. 13% of patients for ARS , fair for 11% of patients for medical vs. 9% of patients for ARS; 11% required a median of 3 dilatations in medical vs. 3% required 2 dilatations with ARS. <u>Endoscopic and histological Data</u> <u>Esophagitis</u> Before treatment: 13 for medical, 22 for surgery After treatment: 7 for medical, 1 for surgery <u>Barrett's ulcer</u> Before treatment: 4 for medical, 4 for surgery After treatment: 0 for medical, 0 for surgery <u>Stricture</u>	+

					Before treatment: 17 for medical, 13 for surgery After treatment: 8 for medical, 2 for surgery <u>Length of Barrett's segment (cm):</u> Before treatment: median(range): 4 (3-12) for medical, 5 (3-14) for surgery After treatment: median(range): 5 (3-12) for medical, 4.5 (3-13) for surgery ($p<0.01$) <u>Mild dysplasia</u> Before treatment: 0 for medical, 0 for surgery After treatment: 5 for medical, 0 for surgery <u>Severe dysplasia</u> Before treatment: 0 for medical, 0 for surgery After treatment: 1 for medical, 1 for surgery.	
Parrilla et al 2003[120] RCT **(good)**	101 patients with BE	Medical treatment, hygiene, diet and postural measures associated with antisecretory drugs: ran (150 mg bid) initially and ome (20 mg bid) from 1992 onwards for all patients, and periodical dilations in patients with stenosis	Surgical antireflux surgery (ARS)	Clinical outcomes and endoscop-ic and histolog-ical data	<u>Clinical outcome:</u> Medical treatment: excellent to good for 91%, fair 9%; 5% required a median of 3 dilatations Surgical: excellent to good for 91%, fair for 7%, poor for 2%; 2% needed 3 dilatations <u>Endoscopic and histological data</u> <u>Esophagitis</u> Before treatment: 58% for medical, 55% for surgical After treatment: 19% for medical, 3% for surgical; $p<0.05$ <u>Barrett's ulcer:</u> Before treatment: 12% for medical, 14% for surgical After treatment: 0% for medical, 0% for surgical <u>Stricture</u> Before treatment: 42% for medical, 28% for surgical After treatment 21% for medical, 7% for surgical <u>Length of Barrett's segment (cm)</u> Before treatment: median(range): 4 (2-16) for medical, 5 (2-14) for surgical After treatment: median(range): 5 (2-16) for medical, 4 (2-12) for surgical *length before vs. after treatment $p<0.05$.	+
ARS: Anti Reflux Surgery; BE: Barrett's Esophagus; ome: omeprazole; ran: ranitidine.						

G10B-ii: Supporting Evidence

G10B-ii: Even high-dose PPI therapy will not usually result in reversal of Barrett's esophagus.

Summary: This recommendation is supported by guidelines [12,15] and a good quality RCT. The finding in the RCT supports that the use of PPIs is associated with the control of symptoms in patients with BE. Large dose PPIs, though better than standard doses of ranitidine, are not able to reverse BE.

Study Type QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Peters et al 1999*[121] RCT **(good)**	68 patients of Barrett's esophagus and GERD symptoms	ome 40 mg bid for 24 months	ran 150 mg bid for 24 months	reflux symptoms, change in BE size, 24-hour pH-measurement at 3 months	Change in symptom score 0-24 months - mean (95%CI): Heartburn: -1.08 (-1.65, -0.51) for ome vs. -0.67 (-1.10, -0.23) for ran, p=0.13 Regurgitation: -0.50 (-0.90 to -0.10) for ome vs. -0.70 (-1.16 to -0.25) for ran, p=0.48 Dysphagia: 0.0 (-0.15, 0.15) for ome vs. -0.11 (-0.31, 0.09) for ran, p=0.30 Odynophagia: -0.19 (-0.43, 0.05) for ome vs. -0.11 (-0.31, 0.09) for ran, p=0.73 Change in length of BE (area under the curve) Absolute change (cm/month) = -6.4 (-15.8, -0.8) for ome vs. -0.0 (-4.5, 4.5) for ran; p=0.06 Relative change (%/month) = -4.8 (-11.6, -0.8) for ome vs. -0.0 (-4.7, 3.7) for ran; p=0.07 Change in surface area for BE (area under the curve): Absolute change (cm^2/month) =-862 (-1466, -302) for ome vs. -11 (-312, 236) for ran; p=0.02 Relative change (%/month) = -9.0 (-15.0, -3.0) for ome vs. +0.1 (-3.6, 2.8) for ran; p=0.02 24-hr pH-metry at 3 months (% reflux with pH<4) - mean (95%CI): Total = 0.1 (0, 1.2) for ome vs. 9.4 (6.2, 13.0) for ran; p<0.0001 Erect = 0.1 (0, 1.3) for ome, 8.5 (5.5, 13.3) for ran; p<0.0001 Supine = 0.0 (0, 0.05) for ome vs. 9.2 (4.1, 15.5) for ran, p<0.001	+

BE: Barrett's Esophagus; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question G11: What are the different adverse drug reactions of PPIs?

G11A: Guideline Statements

Synopsis of Existing Recommendations G11A: PPIs are generally well tolerated. Adverse effects include GI disturbances (most commonly diarrhea), headaches, and dizziness. However, long term safety is the major concern, when maintenance therapy with PPIs is considered. Increasing gastric levels as well as proliferation of endocrine cells have been shown, but no gastric carcinoids have been detected in several long-term human studies. Of more concern are those treated with a PPI with a *H. pylori* infection because they appear to be at risk of atrophic gastritis. Consequently it was suggested that it might increase the risk of *H. pylori* related gastric cancer. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy – Proven GORD[15]	2005	10	PPIs are generally well tolerated. Adverse effects include GI disturbances (mostly commonly diarrhea), headaches, and dizziness.
DeVault and Castell[13]	2005	193	PPIs are safe, effective, and have been used for more than a decade in the United States and much longer in Europe and Australia. It is becoming increasingly clear that the benefit of chronic PPI therapy in patients with chronic and/or complicated GERD outweighs any theoretical risk.
Canadian Consensus Update[12]	2005	24	Long term PPI therapy has not been associated with any clinically significant adverse events.
Kroes et al.[35]	1999	12	Long term safety is the major concern, when maintenance therapy with a PPI is considered. Increasing serum gastrin levels as well as proliferation of endocrine cells have been shown, but no gastric carcinoids have been detected in several long term human studies. Of more concern are those treated with a PPI with a *H. pylori* infection because they appear to be at risk of atrophic gastritis. Consequently it is suggested that this might increase the risk of *H. pylori* related gastric cancer.

G11A: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[12] and further research is required.[13,15,35] The concern of atrophic gastritis and gastric cancer requires more evidence.

Study Type QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

9 Summary of Economic Studies Related to GERD, Reflux Esophagitis or Barrett's Esophagus

1. Goeree et al. (2002)[122]

This study compares, over a one-year period, the expected costs and outcomes of seven alternative primary care strategies for the management of adult patients with moderate-to-severe heartburn in Canada. Outcomes are expressed in terms of symptomatic recurrences averted, weeks without heartburn and quality adjusted life years (QALYs). Costs are expressed in 2001 Canadian dollars and calculated from the perspective of the provincial government.

A decision-analytic model was developed. The information on the management of patients is based on survey responses from 55 family physicians and 48 gastroenterologists randomly selected from across Ontario. A systematic review of published controlled clinical trials was undertaken to derive pooled estimates of symptom relief and recurrence probability for each strategy.

The seven strategies modeled are as follows:

Strategy 1: Intermittent short course H2RA. Acute treatment with an H2RA (e.g., ranitidine 150 mg twice daily) for 4 weeks and no further treatment with prescription medications until recurrence.

Strategy 2: Intermittent long course H2RA. Acute treatment with an H2RA (e.g., ranitidine 150 mg twice daily) for 4 weeks followed by another 4 weeks if symptoms persist, and no further treatment with prescription medications until recurrence.

Strategy 3: Intermittent PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks and no further treatment with prescription medications until recurrence.

Strategy 4: Maintenance H2RA. Acute treatment with an H2RA (e.g., ranitidine 150 mg twice daily) for 4 weeks followed by continuous maintenance treatment with an H2RA (same dose).

Strategy 5: Maintenance PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks followed by continuous maintenance treatment with a PPI (same dose).

Strategy 6: Step-down maintenance H2RA. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks followed by continuous maintenance treatment with an H2RA (e.g., ranitidine 150 mg bid).

Strategy 7: Step-down maintenance PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg or lansoprazole 30 mg once daily) for 4 weeks followed by continuous maintenance treatment with a low dose PPI (e.g., omeprazole 10 mg or lansoprazole 15 mg once daily).

In the base case, no strategy was strictly dominated; however strategies "*Maintenance H2RA*" and "*Step-down maintenance PPI*" were dominated through principles of extended dominance. The efficient frontier is represented by strategies "*Intermittent long course H2RA*", "*Intermittent short course H2RA*", "*Intermittent PPI*", "*Step-down maintenance H2RA*", and "*Maintenance PPI*".

Moving from strategy "*Intermittent long course H2RA*" to "*Intermittent short course H2RA*" costs an additional $26 per heartburn symptom week averted, or $7,515 per QALY gained. Moving from strategy "*Intermittent short course H2RA*" to "*Intermittent PPI*" costs an additional $42 per symptom week averted, or $12,206 per QALY; from strategy "*Intermittent PPI*" to "*Step-down maintenance H2RA*" costs an additional $81 per symptom week averted, or $23,367 per QALY; and finally from "*Step-down maintenance H2RA*" to "*Maintenance PPI*" costs an additional $341 per symptom week averted, or $98,422 per QALY.

This analysis showed that the best way of managing patients with heartburn depends upon how much society is willing to pay to achieve health improvements. Based on a commonly quoted threshold of $50,000 per QALY, the optimal primary care strategy for managing patients with moderate-to-severe heartburn symptoms is to treat the symptoms with a PPI followed by maintenance therapy with an H2RA to prevent symptomatic recurrence.

The results of the probabilistic sensitivity analysis reveal a fair amount of variation from the base case analysis, different strategies having different probability of being cost-effective at different ceiling ratios per QALY.

The one-year time frame may be too short to capture long-term complications but was chosen due to the lack of long-term follow-up studies. This study uses inputs (i.e., costs), which are specific to the province of Ontario.

Comment:
This study was conducted about five years ago, in a Canadian health care setting from the perspective of a provincial (Ontario) government; uses the inputs specific to Ontario, and the costs are in 2001 Canadian dollars. The information on the management of patients is based on a survey of family physicians and gastroenterologists. The effectiveness data (heartburn relief rates and symptomatic recurrence rates for each drug dose at different duration) were estimated from the systematic review and meta-analysis of the studies published to January 2000. The data from the single arms of trials are pooled together, which might not be the most appropriate method as within-study randomization is lost in the process.

2. Romagnuolo et al. (2002)[123]

This study compares, over the five-year period, the cost and utility of healing and maintenance regimens of omeprazole, and laparoscopic Nissen fundoplication (LNF) in the framework of the Canadian medical system. The outcome measure is quality adjusted life years (QALYs). Discounted direct costs in Canadian dollars were estimated from the perspective of a provincial (Alberta) health ministry.

A two-stage Markov model (healing and maintenance phases) was constructed, which included the creation of five separate Markov chains stemming from the five regimens required for successful healing. The base case was a 45-year-old man with endoscopically proven grade II to IV erosive reflux esophagitis, refractory to H2RAs. The simulation considered two treatment options: medical therapy with omeprazole versus surgery using LNF. Rates derived from medical literature were converted to transition probabilities. Transitions were allowed at the end of each three-month cycles. The proportions of patients assigned to each of the five healing regimens are based primarily on probabilities derived from one published study. Discounted quality-of-life estimates were derived from the medical literature. All utilities and costs are discounted at 3% per annum in the maintenance phase.

For the 5-year period studied, LNF was less expensive than omeprazole ($3,520 vs $5,464 per patient) and became the more cost-effective option at 3.3 years of follow-up. The incremental cost for medical therapy was $129,665 per QALYs gained.

This analysis illustrates that LNF is a cost-effective option for middle-aged patients with erosive esophagitis when the expected time of medical maintenance therapy is more than 3.1 years.

Sensitivity analyses were performed to test the robustness of the model and to determine thresholds. A Monte Carlo simulation of 10,000 patients was used to estimate variances and 95% interpercentile ranges. One-way sensitivity analysis demonstrated that the model's conclusions were most dependent on the values of three variables: the cost of medical therapy, the cost of surgery, and time.

Comment:
This study was conducted in a Canadian health care setting from the perspective of a provincial (Alberta) government; uses the inputs specific to Alberta, and the costs are in Canadian dollars. The effectiveness data were derived from the literature but there is no mention about any systematic search in identifying those studies. This is a mathematical simulation so must be regarded as such and should in no way replace real life experience as authors have correctly pointed out. Another note of caution is that the literature likely reflects the experience of the best centers and may not apply specifically to every surgeon; and the well-known bias in the literature leaning toward the reporting of favourable results hence questioning the validity of the available data on long-term LNF success.

3. Goeree et al. (1999)[124]

This study compares, over a one-year period, the expected costs and outcomes of six alternative strategies for the management of patients with erosive esophagitis (grades II to IV in the Savary-Miller Scale) confirmed by endoscopy but without complications such as Barrett's esophagus or stricture, in Canada. Outcomes are quantified in terms of GERD recurrence and weeks per year without GERD. The viewpoint for the study was that of a provincial government and all costs are presented in 1998 Canadian dollars.

A decision model was constructed. The information on clinical practice patterns and resource utilization are based on convening an expert physician panel (4 gastroenterologists, 2 family physicians). Healing and recurrence rates by drug regimen were derived from the systematic review and meta-analysis of the published studies.

The six strategies modeled are as follows:

Strategy 1: Intermittent PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg once daily) for 8 weeks and then no further treatment with prescription medications until recurrence.

Strategy 2: Maintenance PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg once daily) for 8 weeks and then continuous maintenance treatment with a PPI (same dose).

Strategy 3: Maintenance H2RA. Acute treatment with an H2RA (e.g., ranitidine 150 mg twice daily) for 8 weeks and then continuous maintenance treatment with an H2RA (same dose).

Strategy 4: Step-down maintenance PA. Acute treatment with a prokinetic agent (PA) (cisapride 10 mg 4 times daily) for 12 weeks and then continuous maintenance treatment with a lower dose of PA (e.g., cisapride 10 mg bid).

Strategy 5: Step-down maintenance H2RA. Acute treatment with a PPI (e.g., omeprazole 20 mg once daily) for 8 weeks and then continuous maintenance treatment with an H2RA (e.g., ranitidine 150 mg bid).

Strategy 6: Step-down maintenance PPI. Acute treatment with a PPI (e.g., omeprazole 20 mg once daily) for 8 weeks and then continuous maintenance treatment with a lower dose PPI (e.g., omeprazole 10 mg once daily).

In the base case, "*Step-down maintenance PA*" was dominated, and "*Step-down maintenance PPI*" was dominated through principles of extended dominance. The "efficient frontier" is represented by "*Maintenance H2RA*", "*Intermittent PPI*", "*Step-down maintenance H2RA*" and "*Maintenance PPI*". The incremental cost effectiveness of "*Intermittent PPI*" is $8 per week free of GERD, "*Step-down maintenance H2RA*" higher at $44 and "*Maintenance PPI*" is higher still at $256.

The price of H2RA is an important factor in determining whether "*Step-down maintenance PPI*" forms part of, or is contained within, the "efficient frontier" of long term management for erosive esophagitis.

Comment:
This study was conducted about seven years ago, in a Canadian health care setting from the perspective of a provincial (Ontario) government; uses the inputs specific to Ontario, and the costs are in 1998 Canadian dollars. The information on clinical practice patterns and resource utilization are based on convening an expert physician panel. The effectiveness data were derived from the systematic review and meta-analysis of the studies published to November 1997. The data from the single arms of trials are pooled together, which might not be the most

appropriate method as within-study randomization is lost in the process. The one-year time horizon may to too short to capture long-term complications. The model is sensitive to the price of H2RA (brand name versus generic ranitidine). This should not be of a huge concern since 90% of prescriptions for ranitidine in Canada are generic, which is used in the base case. For the prokinetic agent, cisapride was used, which has now been withdrawn from the Canadian market.

4. O'Brien et al. (1996)[125]

This study compares, over a one-year period, the expected costs and outcomes of four alternative strategies for the management of patients with endoscopically confirmed reflux esophagitis of grades II to IV (Savary-Miller) without complications such as Barrett's or stricture, in Canada. Outcomes are quantified in terms of GERD (esophagitis) recurrence, and GERD healed weeks in a one-year period. The viewpoint of the study was that of a provincial government and the costs are reported in 1995 Canadian dollars.

A technique of decision analysis is used. The information on clinical practice patterns and resource utilization are based on convening an expert physician panel (4 gastroenterologists, 2 family physicians). Healing and recurrence rates by drug regimen were derived from the systematic review and meta-analysis of the published studies.

The four strategies modeled are as follows:

Strategy 1: Intermittent PPI. Acute treatment with a PPI for 8 weeks then no further treatment until recurrence.

Strategy 2: Maintenance PPI. Acute treatment with a PPI for 8 weeks and then start continuous maintenance treatment with a PPI.

Strategy 3: Maintenance H2RA. Acute treatment with an H2RA for 8 weeks then start continuous maintenance treatment with an H2RA.

Strategy 4: Maintenance PA. Acute treatment with a prokinetic agent (PA) for 12 weeks then start continuous maintenance treatment with a PA.

In the base case analysis, "*Maintenance H2RA*" and "*Maintenance PA*" were dominated. The incremental analysis indicates that the implied cost per additional week without GERD in switching from "*Intermittent PPI*" to "*Maintenance PPI*" is $142.

The sensitivity analysis shows that the model is not very sensitive (rankings do not change) with the upper and lower 95% CIs for GERD healing probabilities, regional variation in drug prices. However, it is sensitive to the price of H2RA (generic ranitidine (base case), generic cimetidine, and brand name ranitidine).

Comment:
This study was conducted about ten years ago, in a Canadian health care setting from the perspective of a provincial (Ontario) government; uses the inputs specific to Ontario, and the costs are in 1995 Canadian dollars. The information on clinical practice patterns and resource utilization are based on convening an expert physician panel. The data from the single arms of trials are pooled together, which might not be the most appropriate method as within-study randomization is lost in the process, which the authors acknowledge and provide some justification. The one-year time horizon may be too short to capture long-term complications, but was chosen due to the lack of data beyond one year for estimates of probability for recurrence of GERD. The model is sensitive to the price of H2RAs (brand name versus generic ranitidine). But is should not be of a huge concern since 90% of prescriptions for ranitidine in Canada are for the generic product, which is used in the base case. For the prokinetic agent, cisapride was used, which has now been withdrawn from the Canadian market.

10 Clinical Evidence for Dyspepsia

10.1 Clinical Questions for Dyspepsia

Question D1: What is the role of PPIs in empiric therapy for uninvestigated dyspepsia?

i: As first-line therapy

Synopsis of Existing Recommendations D1A: PPI empirical therapy or testing and treating for *H. pylori* are recommended for uninvestigated dyspepsia as initial therapeutic strategies. There is currently no sufficient evidence to guide which should be offered first. Early endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment.Prompt endoscopy plus test for *H. pylori* has not been shown to produce better patient outcomes than empirical treatment.

Synopsis of Existing Recommendations D1B: PPIs are more effective than alginates/antacids at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia.

Synopsis of Existing Recommendations D1C: PPIs are more effective than H2RAs at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia.

Synopsis of Existing Recommendations D1D: PPIs or H2RAs or prokinetics for up to four weeks is recommended in uninvestigated dyspepsia patients whose dominant symptoms are heartburn and acid regurgitation.

Synopsis of Existing Recommendations D1E: PPIs should be used as a first-line initial treatment for four to eight weeks when symptoms mimic those of GERD and are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patient feels the symptoms have a significant impact on their quality of life.

Synopsis of Existing Recommendations D1F: PPIs should be used as a first line maintenance treatment at regular customized dosages when symptoms mimic those of GERD and are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patient feels the symptoms have a significant impact on their quality of life.

ii: As second-line and maintenance

Synopsis of Existing Recommendations D1G: PPIs for four to eight weeks constitute second-line treatment in uninvestigated dyspepsia whose manifestations mimic those of gastroesophageal reflux if the symptoms are unresponsive to first line H2RA treatment for at least 4 weeks, when symptoms are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, the patient feels the symptoms have a mild to moderate impact on their quality of life.

Synopsis of Existing Recommendations D1H: PPIs should be used for maintenance therapy when symptoms have been relieved by an initial second-line PPI treatment, when symptoms mimic those of GERD and are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, the patient feels the symptoms have a mild to moderate impact on their quality of life.

Question D2: What is the role of *H. pylori* "test and treat" strategy for un-investigated dyspepsia?

i. in younger adults

Synopsis of Existing Recommendations D2A: *H. pylori* "test and treat" strategy is recommended for uninvestigated/uncomplicated dyspepsia in younger patients (50-55 years or less) who have no alarm features.

ii. in older patients

Synopsis of Existing Recommendations D2B: *H. pylori* "test and treat" may be as appropriate as early endoscopy for the initial investigation and management of patients over the age of 55 years presenting with uncomplicated dyspepsia.

iii. in adults of all ages

Synopsis of Existing Recommendations D2C: *H. pylori* "test and treat" strategy is recommended as an initial step in the management of patients with uninvestigated/uncomplicated dyspepsia.

iv. role of PPIs in Hp negative dyspeptics

Synopsis of Existing Recommendations D2D: PPIs or H2RAs or prokinetics for four weeks are recommended for patients with dyspepsia with negative *H. pylori* testing but without endoscopy and imaging done.

Synopsis of Existing Recommendations D2E: PPI therapy for four to eight weeks constitutes a second-line treatment for *H. pylori* negative dyspepsia without endoscopy and imaging done, if the symptoms are unresponsive to first-line (H2RA) treatment.

Question D3: What is the role of PPIs for NSAID-induced dyspepsia?

i. in low risk patients

Synopsis of Existing Recommendations D3A: PPIs constitute a second-line treatment in uninvestigated dyspepsia patients with a low risk of severe gastrointestinal events when the symptoms are unresponsive to first-line H2RA treatment (for at least 4 weeks) and NSAIDs cannot be discontinued.

ii. in high risk patients

Synopsis of Existing Recommendations D3B: PPIs should be used as the first line treatment in dyspepsia patients with a high risk of gastrointestinal events.

Question D4: What is the role of PPIs for functional dyspepsia?

i. role of H. pylori eradication

Synopsis of Existing Recommendations D4A: For proven functional dyspepsia, the results from *H. pylori* eradication are controversial (no consensus)

ii. first-line therapy

Synopsis of Existing Recommendations D4B: A trial of acid suppression (i.e., H2RAs or PPIs) therapy may be considered in the management of functional dyspepsia.

Synopsis of Existing Recommendations D4C: PPIs are superior to placebo for the disappearance or improvement of symptoms in functional dyspepsia.

Synopsis of Existing Recommendations D4D: PPIs or H2RA or antacids should not be used on a regular/long term basis for functional dyspepsia since functional dyspepsia can have various causes.

iii. role of long-term therapy

Synopsis of Existing Recommendations D4E: PPI therapy should be stepped down to the lowest dose required to control symptoms and discuss using the treatment on an "on-demand" basis with patients to manage their own symptoms for those patients with symptom relapse after initial care strategies.

Synopsis of Existing Recommendations D4F: High-dose PPIs is one of the three recommended options (or switch therapy or endoscopy) if dyspepsia symptom persists.

Question D5: What are the differences among PPIs in terms of clinical efficacy and safety? What is the recommended PPI dose for non-ulcer dyspepsia?

i. differences among PPIs

Synopsis of Existing Recommendations D5A: Differences between the PPIs in clinical efficacy and safety are minimal.

ii. recommended doses of PPIs

Synopsis of Existing Recommendations D5B: PPI doses for non-ulcer dyspepsia as recommended by the PRODIGY guideline are Omeprazole Low Dose (LD) 10 mg od, *H. pylori* eradication double dose 20 mg bid; Lansoprazole LD 15 mg od, *H. pylori* eradication double dose 30 mg bid; Pantoprazole LD 20 mg od, *H. pylori* eradication double dose 40 mg bid; Rabeprazole LD 10 mg od, *H. pylori* eradication double dose 20 mg bid; Esomeprazole LD not available, *H. pylori* eradication double dose 20 mg bid.

10.2 Clinical Evidence for Dyspepsia

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

i. as first-line therapy

D1A: Guideline Statements

Synopsis of Existing Recommendations D1A: PPI empirical therapy or testing and treating for *H. pylori* are recommended for uninvestigated dyspepsia as initial therapeutic strategies. There is currently no sufficient evidence to guide which should be offered first. Early endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment.Prompt endoscopy plus test for *H. pylori* has not been shown to produce better patient outcomes than empirical treatment

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NICE[24]	2004	84	[Interventions for uninvestigated dyspepsia] Initial therapeutic strategies for dyspepsia are empirical treatment with a PPI or testing for and treating *H. pylori*. There is currently insufficient evidence to guide which should be offered first. ▪ Offer empirical full dose PPI therapy for one month to patients with dyspepsia. ▪ Offer *H. pylori* 'test and treat' to patients with dyspepsia. ▪ Early endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment. ▪ Test and endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment
Talley NJ[126]	1999	1136	There are at least four major strategies for the management of dyspepsia: 1) Reassurance and over-the-counter antacids or H2RAs. 2) Empirical therapy strategy (e.g., prescribing an antisecretory or prokinetic agent), reserving endoscopy or other testing for those who are unresponsive or have an early relapse. 3) Stratified approach based on symptom patterns and *H.pylori* status. 4) Refer all patients with dyspepsia for prompt endoscopy.

D1A: Supporting Evidence

Summary: The statement is based on two good quality RCTs.[127,128] The data from the two RCTs indicate that there is no statistically significant difference between PPI empirical therapy and prompt endoscopy strategy in the symptom relief and impact on the management strategy for

patients with uninvestigated dyspepsia. Therefore, there is currently insufficient evidence to guide which should be offered first.						
Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Lewin van den Broek et al. 2001*[127] RCT **(good)**	N=349 1) age: (mean) 43.5 yrs 2) all pts presenting with new episode of dyspepsia in the past 34 mos 3) primary care setting 4) Hp(+): 43-44% pts in both groups (Hp serological test) 5) endoscopy: not done before entering the study 6) no PPI use in the past 2 wks before entering the study	Empirical treatment with: ome 20 mg qd for 8 wks	prompt endoscopy followed by the treatment of disorder found. 1): no treatment 2) H2RA 3) ome, 20 mg qd for 8 wks 4) Hp eradication 5) refer to a specialist	percentage of pts without strategy failure: (strategy failure defined as the following: need to change medication; use of medication longer than eight wks; need an additional investigation or a second endoscopy; or refer to a specialist;	(Not ITT) percentage of pts without strategy failure): no statistically significant difference btw groups. OR calculated with non-specific symptom subgroup as reference category PPI vs. prompt endoscopy group: At wk 8: (reflux-like subgroup: OR (95%CI):1.4 (0.58, 3.47) vs. 1.0 (0.44, 2.33); ulcer-like subgroup: 0.8 (0.27, 2.6) vs. 1.0 (0.37, 2.63). At wk 52: OR (95%CI): reflux-like subgroup: 1.5 (0.41, 5.78) vs. 1.8 (0.57, 5.52); ulcer-like subgroup: 2.1 (0.5, 8.5) vs. 1.3 (0.32, 4.83)	+
Laheij et al. 1998*[128] RCT **(good)**	N=84 1) age (mean) 43-44 yrs in both groups 2) pts with persistent dyspeptic symptoms of sufficient severity as judged by the GP, were referred for upper GI endoscopy 3) tertiary setting 4) Hp status: not available 5) endoscopy: not done before entering the study 6) no PPI use history	ome, 20 mg qd for two wks)	Prompt endoscopy + appropriate treatment (no further detail info)	# of pts undergoing endoscopy; dyspeptic symptom-free days; QOL (10 wks & 1 year)	Pts undergoing endoscopy: PPI vs. prompt endoscopy: 31% vs. 100%. (p value, not reported) Dyspeptic symptom-free days (mean): PPI vs. endoscopy: 166 d (95% CI: 128d, 204d) vs. 159 d (95% CI: 119d, 198d): (p value: not provided) QOL score at 1 yr: PPI vs endoscopy: 15 (95% CI: 13, 17) vs. 16 (95% CI: 14, 17). (P value : not provided)	+

ome: omeprazole; QOL: Quality of Life; Rx: prescription; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

i. as first-line therapy

D1B: Guideline Statements

Synopsis of Existing Recommendations D1B: PPIs are more effective than antacids/alginats at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NICE[24]	2004	84	PPIs are more effective than antacids at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia. The average rate of response taking antacid was 37% and PPI therapy increased this to 55%; a number needed to treat for one additional responder of 6.
Talley[129]	2002	iv 74	Several large studies with omeprazole have now shown that proton pump inhibition is more effective than H2RAs as well as placebo and antacid-alginate in relieving symptoms in uninvestigated dyspepsia, and lansoprazole has also been shown to be superior to ranitidine.
Mascort et al[130]	2003	78	[Empiric antisecretory treatment for patients with dyspepsia]: The results of a systematic review have demonstrated that the PPIs , compared with H2RAs and with antacids, has a greater efficacy in symptom resolution with a risk reduction calucated, from the original data, respectively as 1.62 (95%CI 1.40 to 1.87) and 1.48 (95%ci 1.30 to 1.68).

D1B: Supporting Evidence

Summary: The statement is based on a good quality SR.[131] The data indicates that PPIs are more effective than antacids/alginates at reducing dyspeptic symptoms (for global assessment, and heartburn, but not episgastric pain) in uninvestigated dyspepsia patients.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Delaney et al. 2003*[131] SR **(good)**	2 RCTs (Total n=1186) 1) age: (RCT1) >18 yrs and (RCT2) 18-75 yrs 2) pts presenting with dyspeptic	ome 10-20 mg qd for 2 and 4 weeks	Gaviscon 10 ml qid for 2 and 4 weeks; placebo (antacids as needed)	Symptom relief by global and individual symptom assessment (at 2 or/and 4 wks)	PPI vs. antacids/alginates: Symptom relief (global assessment) : RR 0.72 (95% CI 0.64, 0.80) NNT 5.7 (95% CI 4.6, 7.9), using a control event rate of 60%. Heartburn: PPI significantly more effective RR 0.52 (95% CI 0.44, 0.61) NNT 3.5 (95% CI 3.0, 4.2)	+ +

	symptoms 3) primary care setting or an endoscopy unit 4) Hp status: not available 5) endoscopy: not done before entering the study				Epigastric pain: RR was nonsignificant RR 0.84 (95% CI 0.63, 1.13) NNT 10.42 (95% CI 4.1 benefiting, 8.8 harmed). No significant benefit over antacids in the epigastric pain arm. However, there was statistically significant heterogeneity btw studies in this arm (Q=4.5 (df=1) p=0.03)	–
ome: omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

i. as first-line therapy

D1C: Guideline Statements

Synopsis of Existing Recommendations D1C: PPIs are more effective than H2RAs at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Talley[129]	2002	iv 74	Several large studies with omeprazole have now shown that proton pump inhibition is more effective than H2RAs as well as placebo and antacid-alginate in relieving symptoms in uninvestigated dyspepsia, and lansoprazole has also been shown to be superior to ranitidine.
NICE[24]	2004	84	PPIs are more effective than H2 receptor antagonists (H2RAs) at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia. The average response rate in H2RA groups was 36% and PPI increased this to 58%. A number needed to treat for one additional responder of 5.
Mascort et al[130]	2003	78	[Empiric antisecretory treatment for patients with dyspepsia]: The results of a systematic review have demonstrated that the PPIs , compared with H2RAs and with antacids, has a greater efficacy in symptom resolution with a risk reduction calucated, from the original data, respectively as 1.62 (95%CI 1.40 to 1.87) and 1.48 (95%ci 1.30 to 1.68).
ICSI[30]	2004	26	The PPIs have been compared to H2RAs for treatment of dyspepsia. There are a total of 3 trials with a total of 1,267 patients. All three studies show global improvement scores favouring PPIs. The advent of generic PPIs improves the cost-benefit considerations for this application.

D1C: Supporting Evidence

Summary: This statement is based on one good quality SR.[131] The data indicate that PPIs are more effective than H2RAs at reducing dyspeptic symptoms in uninvestigated dyspepsia patients (global assessment, heartburn and episgastric pain). In theRCTs included in the SR, the dose of omeprazole ranged from low dose (10 mg) to high dose (40mg).

Study	Population	Intervention	Comparator	Outcome	Results	Dir

Type(QA)				measure		
Delaney et al. 2003*[131] SR **(good)**	3 RCTs (n=1,267 pts) 1) age 18-80 yrs 2) dyspepsia pts without definite previous diagnosis of PUD and esophagitis 3) primary care setting 4) Hp status: not available 5) endoscopy: not available	lans 30 mg/d; or ome 10-40 mg/d	cim 800 mg/d; ran 150 mg/d	Symptom relief by global and individual symptom assessment	(PPIs vs. H2RA) <u>Symptom relief (global assessment)</u> RR: 0.64 (95% CI 0.49, 0.82) NNT 4.5 (95% CI 3.1, 11.1) <u>Epigastric pain</u>: RR 0.77 (95% CI 0.62, 0.95); NNT 5.6 (95% CI 4.1, 11.1) <u>Heartburn</u>: RR 0.45 (95% CI 0.37, 0.57) NNT 3.1 (95% CI 2.7, 3.9)	+ + +
cim: cimetidine; lans: lansoprazole; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

i. as first-line therapy

D1D: Guideline Statements

Synopsis of Existing Recommendations D1D: PPIs or H2RAs or prokinetics for up to four weeks is recommended in uninvestigated dyspepsia patients whose dominant symptoms are heartburn and acid regurgitation. ***The evidence cited in support of the existing recommendations does not reflect the population being referred to in the statements. Therefore the existing recommendations could be considered as being based on expert opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
CanDys[21]	2000	s15,s16	Treatment recommendations for patients with a dominant symptom of heartburn or acid regurgitation or both are as follows: A: PPI; B: H2RA; C: Prokinetic agents (data for cisapride* only). Patient should be reassessed after 4 weeks of therapy. *There are reported adverse cardiac events related to the use of cisapride, and sometimes this can result in serious ventricular arrhythmia and possible death. This must be taken into consideration before prescribing cisapride).
Hungin et al.[132]	1997	278	Empirical treatment with anti-secretory drugs [for patients with apparent dyspepsia].
MAMSI[73]	2003	5	For dyspepsia symptoms with no alarm symptoms: initial trial of OTC H2RAs or OTC PPIs for two to four weeks
Federal Bureau of Prisons[33]	2001	14	Inmates with dyspepsia associated with GERD should be given a trial of a PPI for 4 wks. [Note: this was extracted from a treatment algorithm].

D1D: Supporting Evidence

Summary: Statements from the guidelines are based on outcomes from two good quality RCTs. However, the study population in these trials did not include patients with uninvestigated dyspepsia (i.e., patients underwent endoscopy in these studies). Therefore the Synopsis of Existing Recommendations could be considered as being based on expert opinion[21] and further research being required.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Venables et al 1997*[133] RCT **(good)**	N=994 1) age: mean (SD):51 (14) y 2) pts ≥18 y presenting to GP with heartburn as predominant symptom of GERD for at least 3 previous mos, 3) primary setting 4) Hp status: not available 5) endoscopy: done to exclude peptic ulcer disease.	OME 20 mg/qd for 4 wks	OME 10 mg/qd for 4 wks RAN 150 mg/qid for 4 wks	Symptom relief, Adverse event	<u>Relief of Heartburn for all pts</u>: <u>after 4 wks: % of pts</u> achieved heartburn relief: 61% (OME 20), 49% (OME 10), and 40% (RAN). [OME 20 vs. OME 10, p<0.0167; OME 20 vs. RAN, p<0.0001; OME 10 vs. RAN, p<0.01]. <u>Severity of Heartburn improvement:</u> <u>at 4 wks:</u> OME 20 experienced > improvement in heartburn severity vs. RAN (p<0.001). Improvement in OME 10 > than in RAN ; p<0.0167), (no actualy data provided); No significant diff. in improvement in pts in OME 20 or OME 10 (actual data and p value not provided) Pts presenting with moderate to severe heartburn more likely relieved by OME 20 (59%) or OME 10 (52%) than with RAN (38%): OME 20 vs RAN p<0.001; OME 10 vs RAN p<0.01.	The study population did not include patients with univestigated dyspepsia. 0

					Frequency of heartburn: at 4 wks OME 20 experienced less frequent heartburn vs. OME 10 or RAN: OME 20 vs. OME 10: p<0.001; OME 20 vs. RAN: p=0.0001. (no actual data provided) After 4 wks: OME 20 provided relief for 55% of pts presenting with daily heartburn, representing therapeautic advantage over OME 10 (43%, p<0.0167) or RAN (29%, p<0.0001). OME 10 more effective vs RAN, p<0.0167) OME 10 also experienced less frequent heartburn vs RAN , p<0.01.	
Galmiche et al 1997*[134] RCT **(good)**	N=424 1) age: Mean ±SD: 51±15 y 2) pts with heartburn as predominant symptom of GERD; ≥18 y; normal esophagus or non-circumferential EO, according to endoscopy 3) Multiple centre 4): Hp status::	OME 20 mg/qd for 4 wks	OME 10 mg/qd for 4 wks Cisapride 10 mg/qid –for 4 wks all with matched placebo group.	heartburn resolution (GSRS); GERD Symptoms [GSRS reflux scores]; HRQL	Heartburn resolution: at 4 wks, heartburn resolved in 65% (95%CI: 57%, 73%), 56% (95%CI: 48%, 64%) and 41% (95%CI: 32%, 49%) of pts treated with OME 20 mg, OME 10 mg and cisapride, respectively. Both OME doses significantly more effective vs. cisapride (p<0.01). Cumulative symptom resolution	The study population did not include patients with uninvestigated dyspepsia. 0

	not available 5) Endoscopy: done to exclude esophagitis and PUD				rates at 8 wks with OME 20 mg qd, OME 10 mg qd and cisapride 10 mg qid, were 79%, 71% and 61%, respectively. (p value not provided) % of pts with complete absence of heartburn: OME 20 vs OME 10 vs cisapride: 54.6% vs 42.5% vs 29%, respectively OME 20 vs OME 10, (p =0.04); OME 20 vs Cisapride, (p<0.01); OME 10 vs Cisapride, (p =0.02). Incidence of regurgitation at 4 wks: 31.2%, 40.3%, 49.2% for OME 20, OME 10, and cisapride, respectively (p values not stated) Incidence of epigastric pain at 4 wks: 20.6%, 20.2%, 26.8% for OME 20, OME 10, and cisapride, respectively (p values not stated) Quality of Life: improved in all groups (PGWB score) but no significant differences between groups. No difference between groups for global GSRS score. Improvement of all items in GSRS	

					greater in OME groups vs cisapride Reflux dimension of GSRS - significantly different between OME groups vs. cisapride, (p=0.002). OME 20 vs cisapride (p=0.001), OME 20 vs OME 10 (p=0.19).	

Ome: omeprazole; ran: ranitidine; PGWB: Psychological General Well Being; GSRS: Gastrointestinal Symptom Rating Scale; * studies that declared industry funding

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?
i) as first line

D1E: Guideline Statements

Synopsis of Existing Recommendations D1E: PPIs should be used as a first-line initial treatment for four to eight weeks when symptoms mimic those of GERD and are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patient feels the symptoms have a significant impact on their quality of life. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	9	In unexplored dyspepsia whose primary manifestations mimic those of gastroesophageal reflux - when symptoms are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patients feel that the symptoms have significant impact on their quality of life. Initial treatment: First-line treatment: PPI for four to eight weeks.

D1E: Supporting Evidence

Summary: This statement is based on two good quality RCTs.[38,99,135] Howden et al[99] demonstrated that lansoprazole is more effective than ranitidine in relief of heartburn at 20 wks. But, in Kaplan-Machlis et al[38] showed that PPIs are more effective than ranitidine in relief of heartburn only at two and four weeks, but not at 12 and 24 weeks. In terms of HRQL, there is no difference between lansoprazole and ranitidine treatment.[38]

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Howden et al. 1998*[99] RCT	N=593 1) age: mean± SD (range): 48±13.1(18-85) yrs 2) symptoms of	lans 30 mg qd 20 wks	ran 150 mg bid 20 wks	heartburn severity; % of heartburn-free symptom	Heartburn-free days: lans vs. ran: % of 24-h heartburn-free days (median):	+

(good)	daytime and/or night time heartburn. Pts required to experience heartburn on at least 50% of d, including at least 1 moderate to severe episode in the 7-10 d preRx period. 3) participants were screened in primary care setting and the study was done in health care centre settings 4) Hp status: not available 5) endoscopy: not used in this study.			days	82% vs. 66%, p<0.01	
Kaplan-Machlis et al. 2000*[38] RCT **(good)**	N=268 1) age: > 18 yrs; mean± SD: 45.3 ±13.4 yrs 2) pts with clinical diagnosis of GERD (not endoscopically confirmed) requiring medication Rx, despite nonprescription Rx for ≥ 2 wks 3) multiple university-based family medicine clinic setting 4) Hp status: not available 5) endoscopy: not used in this study	ome 20 mg qd up to six mons	ran 150 mg/bid up to six mons	heartburn resolution (GSRS) & GERD Symptoms (GSRS reflux scores), HRQL	<u>Heartburn resolution</u>: (ome vs. ran): % of pts improved <u>at 2 wks</u>: 49% vs. 33.3%; P=0.007; <u>at 4 wks</u> 58.6% vs. 35%; P<0.001 <u>At 12 and 24 wks</u> No significant differences in heartburn resolution (no actual data reported for 12 and 24 wks, reported as figure) at 12 wks (P=0.14) or 24 wks (P=0.18) <u>GERD Symptoms: (GSRS reflux scores)</u>: ome vs. ran at 3 mos: 2.67 vs. 2.95 (p<0.04); <u>HRQL: ome vs ran</u> no difference between ome and ran: <u>Short form-36 mental component summary score</u>, mean(SD): 39.2 911.1) vs 37.8 (10.2) (p-value not reported); <u>Short form-36 physical component score</u>:	+ + _ + _ 0 0

					41.5 (13.1) vs 42.0(13.4) (p-value not reported)	

GSRS: Gastrointestinal Symptoms Rating Scale; HRQL: Health Related Quality of Life; lans: lansoprazole; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

i. First line

D1F: Guideline Statements

Synopsis of Existing Recommendations D1F: PPIs should be used as a first-line maintenance treatment at regular customized dosages when symptoms mimic those of GERD and are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patient feels the symptoms have a significant impact on their quality of life. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	9	In unexplored dyspepsia whose primary manifestations mimic those of gastroesophageal reflux - when symptoms are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patients feel that the symptoms have significant impact on their quality of life. Maintenance treatment: PPI regular customized dosages.

D1F: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[45] and further research is required.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

ii. Second-line and maintenance

D1G: Guideline Statements

Synopsis of Existing Recommendations D1G: PPIs for four to eight weeks constitute second-line treatment in uninvestigated dyspepsia whose manifestations mimic those of gastroesophageal reflux if the symptoms are unresponsive to first line H2RA treatment for at least 4 weeks, when symptoms are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, the patient feels the symptoms have a mild to moderate impact on their quality of life.
The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	8	In unexplored dyspepsia whose primary manifestations mimic those of gastroesophageal reflux – when symptoms are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, patients feel that the symptoms have mild to moderate impact on their quality of life. Initial treatment: H2RAs for at least 4 weeks constitute the first line treatment; when symptoms are unresponsive to this treatment, PPIs constitute the second-line treatment for four to eight weeks. However, It is undesirable to substitute an initial or maintenance H2RA treatment with a PPI (or vice versa) if symptom relief is observed.

D1G: Supporting Evidence

Summary: This statement is based on one good quality SR[136] and one good quality RCT. In the SR, Delaney et al[136] demonstrated that PPIs were more effective than H2RAs in symptom relief for dyspeptic patients in primary care. Kaplan-Machlis et al [38] demonstrated that PPIs were more effective than H2RAs in relief of heartburn at 4 weeks, but there was no difference at 2 weeks and 12 to 24 weeks and there was no difference in health related quality of life between PPIs and H2RAs.

Study Type(QA)	Sample Size	Intervention	Comparator	Outcome measure	Results	Dir
Delaney BC et al, 2000*[136] SR **(good)**	3 RCTs (N=1,267) ; 5 study arms (PPIs); 3 study arms (H2RAs) 1): age: 18-80 years 2): Patients presenting with dyspeptic symptoms 3): primary care setting 4): Hp status: not provided 5): Endoscopy:	lans 30 mg/d; ome 10-40 mg/d	H2RAs: cim 400 mg po bid; ran 150 mg po qd	Global symptom scores (dichotomous format), heartburn, epigastric pain, patient satisfaction.	PPIs vs H2RAs Global symptom scores (dichotomous format) at 2-4 wks: ▪ RRR = 36% (95% CI: 51%, 18%) ▪ NNT = 4.5 (95% CI: 3.1, 11.1) Heartburn at 2-4 wks: ▪ RRR = 31% (95% CI: 42%, 19%; z=-4.3); p<0.0005 ▪ NNT = 3.1 (95% CI: 2.7, 3.9) Epigastric pain at 2-4 wks: ▪ RRR = 54% (95% CI: 43%, 63%; z=-7.38); p<0.0000001	_ _ _

	not provided				▪ NNT = 5.6 (95% CI: 4.1, 11.4)	
Kaplan-Machlis et al. 2000*[38] RCT **(good)**	N=268 1) age: > 18 yrs; mean± SD: 45.3 ±13.4 yrs 2) pts with clinical diagnosis of GERD (not endoscopically confirmed) requiring medication Rx, despite nonprescription Rx for ≥ 2 wks 3) multiple university-based family medicine clinic setting 4) Hp status: not available 5) endoscopy: not used in this study	ome 20 mg qd up to six months	ran 150 mg/bid up to six months	heartburn resolution (GSRS) & GERD Symptoms (GSRS reflux scores), HRQL	<u>Heartburn resolution</u>: (ome vs. ran): % of pts improved <u>at 2 wks</u>: 49% vs. 33.3%; p=0.007; <u>at 4 wks</u> 58.6% vs. 35%; p<0.001 <u>At 12 and 24 wks</u> No significant differences in heartburn resolution (no actual data reported for 12 and 24 wks, reported as figure) at 12 wks (p=0.14) or 24 wks (p=0.18) <u>GERD Symptoms: (GSRS reflux scores)</u>: ome vs. ran at 3 mos: 2.67 vs. 2.95 (p<0.04); <u>HRQL:</u> no difference between ome and ran: <u>Short form-36 mental component summary score,</u> mean(SD): 39.2 911.1) vs 37.8 (10.2) (p-value not reported); <u>Short form-36 physical component score</u>: 41.5 (13.1) vs 42.0(13.4) (p-value not reported)	0 - 0 - 0 0 0

GSRS: Gastrointestinal Symptoms Rating Scale; HRQL: Health Related Quality of Life; lans: lansoprazole; ome: omeprazole; ran: ranitidine; cim: cimetidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question D1: What is the role of PPIs for empiric therapy for uninvestigated dyspepsia?

ii. Second line and maintenance

D1H: Guideline Statements

Synopsis of Existing Recommendations D1H: PPIs should be used for maintenance therapy when symptoms have been relieved by an initial second-line PPI treatment, when symptoms mimic those of GERD and are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, the patient feels the symptoms have a mild to moderate impact on their quality of life. ***The existing recommendations are only based upon consensus opinion. A***

potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.			
Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	9	In unexplored dyspepsia whose primary manifestations mimic those of gastroesophageal reflux – when symptoms are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, patients feel that the symptoms have mild to moderate impact on their quality of life. Maintenance treatment: first-line treatment, when symptoms have been relieved by an initial second line PPI treatment: PPI, intermittent customized dosages.

D1H: Supporting evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[45] and further research is required.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question D2: What is the role of *H. pylori* "test and treat" strategy for uninvestigated dyspepsia?

i. In younger adults

D2A: Guideline Statements

Synopsis of Existing Recommendations D2A: *H. pylori* "test and treat" strategy is recommended for uninvestigated/uncomplicated dyspepsia in younger patients (50-55 years or less) who have no alarm features.
Note: the cut off age for this varies between guidelines
The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
CanDys[21]	2000	S12	A test-and-treat strategy for uninvestigated dyspepsia in younger patients (aged 50 years or less) who have no alarm features is recommended.
SIGN 68[137]	2003	9	A non-invasive *H. pylori* test and treat strategy is as effective as endoscopy in the initial management of patients with uncomplicated dyspepsia who are less than 55 years old.
British Society of Gastroenterology[138]	2002	8	We now favour a "*H. pylori* test and treat" strategy for uncomplicated dyspepsia in patients under 55.

D2A: Supporting Evidence

Summary: The statement is based on one good quality SR[131] and four RCTs, one of good quality[139] and three of poor quality.[140-142]. Data from the Delaney et al[131] are not stratified by age and therefore may not be applicable to this Synopsis of Existing Recommendations. Manes et al [139] showed that *H. pylori* test and treat

strategy is more effective than PPI treatment alone in symptom relief. Heaney et al[140] demonstrated empirical Hp eradication strategy is more effective than prompt endoscopy strategy in symptom relief for younger (<50 years old) patients with uninvestigated dyspepsia. Jones et al[141] revealed the comparable clinical outcomes at one year between test and treat group and prompt endoscopy. McColl et al[142] found no difference in the clinical outcomes between non-invasive test and treat group and endoscopy test and treat group. Jones et al showed a significantly lower cost in test and treat strategy than prompt endoscopy plus appropriate treatment strategy.[141,142]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Delaney et al. 2003*[131] SR **(good)**	2 RCTs (Total n=1186) 1) age: (RCT1) >18 yrs and (RCT2) 18-75 yrs 2) pts presenting with dyspeptic symptoms 3) primary care setting or an endoscopy unit 4) Hp status: not available 5) endoscopy: not done before entering the study	ome 10-20 mg qd for 2 and 4 weeks	Gaviscon 10 ml qid for 2 and 4 weeks; placebo (antacids as needed)	Symptom relief by global and individual symptom assessment (at 2 or/and 4 wks)	**[NOTE: Data from this trial are not stratified by age]** PPI vs. antacids/alginates: <u>Symptom relief (global assessment) :</u> RR 0.72 (95% CI 0.64, 0.80) NNT 5.7 (95% CI 4.6, 7.9), using a control event rate of 60%. <u>Heartburn</u>: PPI significantly more effective RR 0.52 (95% CI 0.44, 0.61) NNT 3.5 (95% CI 3.0, 4.2) <u>Epigastric pain:</u> RR was nonsignificant RR 0.84 (95% CI 0.63, 1.13) NNT 10.42 (95% CI 4.1 benefiting, 8.8 harmed). No significant benefit over antacids in the epigastric pain arm. However, there was statistically significant heterogeneity btw studies in this arm (Q=4.5 (df=1) p=0.03)	0 0 0
Manes et al. 2003[139] RCT **(good)**	N=219 1) age: mean (range): 38 (18-45) yrs 2) presenting with uninvestigated upper abdominal symptoms 3) hospital GI unit 4) Hp status: assessed with C-UBT, if (+), go eradication, if (-), go PPI-only therapy 5) control group (PPI empirical treatment) no Hp test done 6) endoscopy: not done	Hp test and treat: 1 wk triple eradication (ome 20 mg, clar 500 mg, & tini 500 mg all bid)	PPI: ome 20 mg qd for 4 wks	Symptom relief assessed by dyspepsia severity score every 2 mos.; use of medical resources; clinical outcome	Test and treat vs. PPI alone: <u>Symptom improvement at 4 wks:</u> 71% (95% CI : 61%, 79%) vs. 83% (95% CI : 74%, 89%) (P=0.05); <u>Overall Endoscopy rates:</u> 55% (95% CI, 46-65%) vs. 88% (95% CI : 80%, 93%), (P<0.0001) <u>Dyspepsia symptom scores at 6 and 12 mos:</u> Hp test and treat significantly better scores at 6 & 12 mos vs. PPIs alone (P<0.001 for both 6 & 12 mos comparisons). (the result was presented in the figure, no actual value reported) <u># of days w/o symptoms</u>: Hp test-and-treat vs. PPIs: (mean, 95% CI) 231.5 (95% CI: 205.7, 257.5) vs. 139.3 (95% 117.9-160.7); P<0.0001)	+ + + +
Heaney et al. 1999[140] RCT **(poor)**	N=104 1) age: mean (range): 32 (18-45) yrs 2) pts presenting	Empirical eradication - 1 wk triple (ome 20 mg bid, clar 250	Prompt endoscopy + appropriate treatment based on the	Glasgow dyspepsia severity score at 1 year	<u>Dyspeptic symptoms score</u> Eradication vs. prompt endoscopy: mean (SEM): 3.37 (0.54) vs. 5.08 (0.62), p<0.05	+

	complaint of ulcer-like dyspepsia; 3) hospital clinic setting 4) Hp status : assessed with C-UBT, positive pts randomized to two groups 5) endoscopy: not done	mg bid & tini 500 mg bid)	endoscopic finding			
Jones et al 1999[141] RCT **(poor)**	N=165 1) pts <45 yrs, mean age = 34.1 yrs 2) pts presenting ulcer-like dyspeptic symptoms (≥4wks), without alarm symptoms and in whom GP deemed further investigation appropriate 3) "Test and treat" in primary care setting and endoscopy group in hospital setting 4) Hp status: assessed with serological test, if (+), then Hp eradication therapy 5) endoscopy: for control group	Hp test-and-treat (PPI or bis-based triple therapy at least for one wk)	Prompt endoscopy + appropriate treatment based on the endoscopic finding	Clinical outcomes at end of 1 year	<u>Clinical outcomes at 1 year:</u> comparable in both groups (no actual data reported) (note: the cost in Hp test and treat group is cheaper than prompt endoscopy group, p<0.0001)	0
McColl et al. 2002[142] RCT **(poor)**	N=708 1) age <55 yrs 2) pts referred for endoscopic investigation of dyspepsia 3) hospital setting 4) Hp status: assessed with non-invasive breath test or endoscopy plus *H. pylori* testing	non-invasive Hp test and treat ome 20 mg bid, clar 250 mg tid, amox 500 mg tid (or met 400 mg tid if pts allergic) for 7 days	endoscopy (plus Hp test) and treat ome 20 mg bid, clar 250 mg tid, amox 500 mg tid (or met 400 mg tid if pts allergic) for 7 days	Glasgow dyspepsia severity score at 1 year	The use of endoscopy over 12 mos was reduced by 94% in non-invasive Hp test and treat group. <u>Glasgow dyspepsia severity score at one year</u>: Non-invasive test and treat vs. endoscopy plus test: Mean: (SD range) 5.4 (3.4, 0-15) vs. 5.6 (3.4, 0-15) (p-value not reported) <u>The mean change in score was also similar:</u> non-invasive test and treat vs. endoscopy plus test: 4.6 and 4.8 (95% CI: for difference: -0.7, 0.5; P=0.69)	0
clar: clarithromycin; ome: omeprazole; SEM: Standard Error of the Mean; tini: tinidazole; bis: bismuth; amox: amoxicillin; met: metronidazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D2: What is the role of *H. pylori* "test and treat" strategy for uninvestigated

dyspepsia?

ii. In older adults

D2B: Guideline Statements

Synopsis of Existing Recommendations D2B: *H. pylori* "test and treat" may be as appropriate as early endoscopy for the initial investigation and management of patients over the age of 55 years presenting with uncomplicated dyspepsia. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
SIGN 68[137]	2003	9	A non-invasive *H. pylori* test and treat policy may be as appropriate as early endoscopy for the initial investigation and management of patients over the age of 55 years presenting with uncomplicated dyspepsia.

D2B: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[24,137] and further research is required.

Study	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question D2: What is the role of *H. pylori* "test and treat" strategy for uninvestigated dyspepsia?

iii. In adults of all ages

D2C: Guideline Statements

Synopsis of Existing Recommendations D2C: *H. pylori* "test and treat" strategy is recommended as an initial step in the management of patients with uninvestigated/uncomplicated dyspepsia. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel. The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
CanDys[21]	2000	s11	[in uninvestigated dyspepsia] The Canadian *H. pylori* Consensus Conference recommended that eradication thearpy be offered to all patients with a positive result of testing for *H. pylori.*
Québec CRUM[45] (translated)	2002	9	For unexplored dyspepsia whose primary manifestations do not mimic those of gastroesophogeal reflux: Positive *H. pylori* test: Eradication of *H. pylori*.
Talley[129]	2002	iv 74	Consequently, there is growing support for the use of a test and treat strategy as an initial step in the management of patients with uninvestigated dyspepsia.
NICE[24]	2004	84	Offer *H. pylori* "test and treat" to patients with dyspepsia;

			H pylori testing and treatment is more effective than empirical acid suppression at reducing dyspeptic symptoms after 1 year in trials of selected patients testing positive for *H. pylori*. The average response rate receiving empirical acid suppression was 47% and *H. pylori* eradication increased this to 60%: a number needed to treat for one additional responder of 7.
Prodigy (Dyspepsia-symptoms)[143]	2004	9	A [*H. pylori*] "test and treat " strategy is recommended for uncomplicated dyspepsia in any person

D2C: Supporting Evidence

Summary: This statement is based on one very good quality RCT[144] and one good quality SR.[131] In the SR,[131] there was no difference in clinical outcomes between "Hp test and treat" and prompt endoscopy or acid suppression strategies. Chiba et al showed that *H. pylori* "test and treat" as an initial therapeutic strategy is more effective than placebo in overall symptom relief at one year, but the significance of treatment success in the subgroups was not tested

Study	Population	Intervention	Comparator	Outcome measure	Results	Dir
Delaney et al. 2003*[131] SR **(good)**	1-8 RCTs (n=294-1,412) in different arms Hp test and treat vs. endoscopy: 4 RCTs (n=1412) Hp test and treat vs. acid suppression: two RCTs (n=563) Patients with dyspeptic symptoms presenting to their primary care or an endoscopy unit	*H. pylori* "test and treat"	Initial endoscopy or acid suppression	Dyspepsia symptom score, dyspepsia dichotomous outcome, quality of life, patient satisfaction	*H. pylori* "test and treat" vs. Initial endoscopy Dyspepsia symptom score: Standardized Mean difference (random) 95% CI : -0.14 (-0.58, 0.31) Dyspepsia dichotomous outcome: RR (random) 95% CI: 0.94 (0.71, 1.25) Patients satisfaction: Weighted mean difference (fixed) 95% CI. 0.00 (-0.27, 0.27) *H. pylori* "test and treat" vs. acid suppression Dyspepsia dichotomous outcome: RR (random) 95% CI: 0.87 (0.65, 1.18) # of endoscopies: Odds Ratio (Fixed) 95% CI. 0.68 (0.31, 1.53)	– – – –
Chiba et al. 2002*[144] RCT **(very good)**	N=294 1) age ≥18 yrs mean (range) = 50 (18-82) yrs 2) uninvestigated symptoms of dyspepsia for at least previous 3 mos 3) primary care	eradication arm : ome 20 mg bid + met 500 mg + clar 250 mg	placebo : ome 20 mg + placebo met + placebo clar	Therapy success (no symptoms or minimal symptoms of dyspepsia) at end of 1 year - Healthcare costs	Therapy success Eradication vs. placebo : 50% (95% CI, 42-58) vs. 36% (28%, 44%); difference 14% (95% CI, 2%, 25%), P=0.02; NNT = 7 (95% CI, 4-63) In multiple logistic regression analysis including age, sex and treatment as predictors, only	+

	setting 4) (+) Hp results (Helisal test) & (+) C-urea breath test pre-randomisation 5) endoscopy: not done				eradication treatment was significantly (P=0.009) associated with treatment sucess. Pts completely asympotmatic eradication vs. Placebo : 28% (95% CI, 21%, 36%) vs. 15% (95%CI : 9%, 20%); difference 13% (95% CI, 4%, 24%), P=0.008 Therapy success of reflux predominant dyspepsia subgroup eradication vs. placebo : 43% (95% CI, 29%, 56%) vs. 32% (95% CI, 20%, 45%); difference 11% (95% CI: not reported; no statistical test) Therapy success of non-reflux predominant dyspepsia: Eradication vs placebo: 54% (95% CI, 44%, 64%) vs. 39% (95% CI: 29%, 48%); difference 15% (95% CI, not reported; no statistical test)	+ 0 0
clar: clarithromycin; met: metronidazole; ome: omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D2: What is the role of H. pylori "test and treat" strategy for uninvestigated dyspepsia?

iv: Role of PPIs in Hp negative dyspeptics

D2D: Guideline Statements

Synopsis of Existing Recommendations D2D: PPIs or H2RAs or prokinetics for four weeks are recommended for patients with dyspepsia with negative *H. pylori* testing but without endoscopy and imaging done. ***The evidence cited in support of the existing recommendations does not reflect the population being referred to in the statements. Therefore the existing recommendations could be considered as being based on expert opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
CanDys[21]	2000	s17-18	Treatment recommendations for patients who present with uninvestigated dyspepsia and who subsequently have negative results of testing for *H. pylori* are as follows: A: PPI (most of the data are for omeprazole 20 mg once daily,

			some for lansoprazole 30 mg once daily); B: H2RA; C: Prokinetic agent. Treat for 4 weeks.
BC Guidelines and Protocols Advisory Committee[145]	2004	1	Test for *H. pylori* infection: This approach is most appropriate for patients in whom the predominant symptom is epigastric pain that is alleviated by food or that awakens the patient at night. If the test is positive, treat using a currently recommended regimen. If negative, follow empiric therapy as below: Empiric therapy: A 4-week course of treatment with a H2RA or PPI may be prescribed.

D2D: Supporting Evidence

Summary: Talley et al[146] was cited as a reference in support of the recommendations from the guidelines. However, the study population in this RCT was not limited to *H. pylori* negative patients. Therefore the Synopsis of Existing Recommendations could be considered as being based on expert opinion[21,145] and further research being required.

Study	Population	Intervention	Comparator	Outcome measure	Results	Dir
Talley et al. 1998*[146] RCT **(very good)**	N=1262 1) age mean (range) 43 (18-80) yrs 2) pts presenting with functional dyspepsia (endoscopically normal) with persistent or recurrent epigastric pain and/or epigastric discomfort experienced on at least one of 3 days immediately prior to study entry; pts also required to have at minimum 1 mo history of dyspeptic symptoms, with symptoms having had to occur at minimum 25% of days during that month. 3) health care centre setting, both GP and GI specialist recruiting patients 4) Hp status: 38%, 42% and 44.6% Hp(+) in ome 20 mg, ome 10 mg, and	ome 20 mg qd; ome 10 mg qd	Placebo	Symptom relief	**[NOTE: Study population was not limited to Hp negative patients]** <u>pts with complete symptom relief (combined studies):</u> ome 20 mg vs. placebo: 38% vs. 28% (P=0.002) ome 10 mg vs. placebo : 36% vs. 28% (P= 0.02) ome 20 mg vs. placebo NNT = 10 (95% CI:6, 27); RRR = 14% (95% CI:5.3%, 21.9%) <u>pts with complete symptom relief (ulcer-like dyspepsia):</u> ome 20 mg = 40%; ome 10 mg = 35%; placebo = 27% (P=0.006 ome 20 mg vs. placebo; P=0.08 ome 10 mg vs. placebo) <u>pts with complete symptom relief (reflux-like dyspepsia):</u> ome 20 mg = 54%; ome 10	0

	placebo groups respectively 5) endoscopy: used for diagnosis of functional dyspepsia (FD)				mg = 45%; placebo = 23% (P=0.002 ome 20 mg vs. placebo; P=0.02 ome 10 mg vs. placebo) pts with complete symptom relief (dysmotility-like symptoms): ome 20 mg = 32%; ome 10 mg = 37%; placebo = 31% (P=0.92 ome 20 mg vs. placebo; P=0.33 ome 10 mg vs. placebo).	
Ome: omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D2: What is the role of *H. pylori* "test and treat" strategy for uninvestigated dyspepsia?

iv: Role of PPI in Hp negative dyspeptics:

D2E: Guideline Statements

Synopsis of Existing Recommendations D2E: PPI therapy for four to eight weeks constitutes a second-line treatment for *H. pylori* negative dyspepsia without endoscopy and imaging done, if the symptoms are unresponsive to first-line (H2RA) treatment. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	9	For unexplored dyspepsia whose primary manifestations do not mimic those of gastroesophogeal reflux: Negative *H. pylori* test or when an *H. pylori* test is impossible: H2 receptor antagonists for at least four weeks constitute first-line treatment; when symptoms are unresponsive to this treatment, PPIs constitute second-line treatment for four to eight weeks

D2E: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[45] and further research is required

Study Type(QA)	Sample Size	Intervention	Comparator	Outcome measure	Results	Dir

Question D3: What is the role of PPIs for NSAID-induced dyspepsia ?

i. In low risk patients

D3A: Guideline Statements

Synopsis of Existing Recommendations D3A: PPIs constitute a second-line treatment in uninvestigated dyspepsia patients with a low risk of severe gastrointestinal events* when the symptoms are unresponsive to first-line H2RA treatment (for at least 4 weeks) and NSAIDs cannot be discontinued. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

* Low risk patients do not present any of high risk factors listed in D3B.[45]

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	9-10	In unexplored dyspepsia whose primary manifectations do not mimic those of gastroesophageal reflux: NSAIDs-related dypepsia: In patients with a low risk of undesirable severe gastrointestinal events, an H2RA for at least four weeks constitute first-line treatment; when symptoms are unresponsive to this treatment and the NSAID cannot be discontinued; PPIs constitute the second-line treatment for four to eight weeks

* Low risk patients do not present any of high risk factors listed in D3B.[45]

D3A: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[45] and further research is required

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir

Question D3: What is the role of PPIs for NSAID-induced dyspepsia ?

ii. In high risk patients

D3B: Guideline Statements

Synopsis of Existing Recommendations D3B: PPIs should be used as first-line treatment in dyspepsia patients with a high risk of gastrointestinal events*. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

* High risk individuals have the following risk factors : history of ulcer complications, concurrent anticoagulant therapy, a years or older, concurrent oral corticosteroid therapy, or two of the following factors: taking several NSAIDs in combin high NSAID dosages, age 60-74 years, history of cardiovascular disease.[45]

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Talley[129]	2002	iv 74	A large programme of trials in patients taking concomittant NSAID therapy has shown that proton pump inhibition is superior for both healing and prophylaxis of NSAID associated gastroduodenal damage

			compared with placebo, misoprostol, and ranitidine. The need for prophylactic therapy should be based on the presence of risk factors for complications. The two major risk factors are a pervious hitory of peptic ulcer disease and old age, with the risk increasing as the patient's age increases over 60 years. Other risk factors include glucocorticosteroid intake and comcomitant use of anticoagulants.
Québec CRUM[45] (translated)	2002	9-10	In unexplored dyspepsia whose primary manifectations do not mimic those of gastroesophageal reflux: NSAIDs-related dypepsia: Prevention of dyspepsia in patients with a high risk of undesirable gastrointestinal events: First-line treatment: PPIs in combination with NSAIDs. High risk individuals have the following risk factors : history of ulcer complications, concurrent anticoagulant therapy, age 75 years or older, concurrent oral corticosteroid therapy, or two of the following factors: taking several NSAIDs in combination, high NSAID dosages, age 60 to 74 years, history of cardiovascular disease

D3B: Supporting Evidence

Summary: The statement is based on one good quality SR.[147] PPIs are more effective than placebo and ranitidine but no better than misoprostol for the prophylaxis of gastric ulcer in patients taking NSAIDs and are more effective for the prophylaxis of duodenal ulcers than placebo, misoprostol and ranitidine.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Rostom et al. 2002[147] SR **(good)**	8 RCTs (n=2,529) 1) age 58 yrs (age info not provided in all studies) 2) patients taking NSAIDs for longer than 3 weeks. 3) Hp status, not available 4) endoscopy: ulcers were assessed endoscopically.	lans 15 or 30 mg/d x 12 wks, ome 20 mg/d x 6-12 wks, pant 40 mg/d x 12 wks	placebo, mis (400-800 mcg/d), ran (150 mg bid)	# of pts with ulcers or ulcer complications	Gastric ulcers: PPIs vs. placebo, n=1,187 (5 studies): RR: 0.40 (95% CI: 0.32, 0.51) PPIs vs. mis, n=917 (2 studies) : RR: 0.59 (95% CI: 0.27, 1.25) random effects model used due to heterogeneity PPIs (ome) vs. ran, n=425 (1 study): RR: 0.32 (95% CI: 0.17, 0.62) Duodenal ulcers: PPIs vs. placebo, n=840 (4 studies): RR: 0.19 (95% CI: 0.09, 0.37) PPIs vs. mis, n=570 (1 study) RR: 0.29 (95% CI: 0.15, 0.56) PPIs (ome) vs. ran, n=425 (1 study): RR: 0.11 (95% CI: 0.01, 0.89)	+ – + + + +
lans: lansoprazole; mis: misoprostol; ome: omeprazole; pant: pantoprazole; ran: ranitidine.						

Question D4: What is the role of PPIs for functional dyspepsia?

i. Role of *H. pylori* eradication

D4A: Guideline Statements

Synopsis of Existing Recommendations D4A: For proven functional dyspepsia, the results from *H. pylori* eradication are controversial (no consensus). ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NICE[24]	2004	146	*H. pylori* eradication was more effective than placebo at reducing symptoms of dyspepsia (NUD): risk ratio for symptom persisting: Risk Ratio = 0.90 (95% CI: 0.86, 0.95).
NZGG[29]	2004	25	In people with proven functional dyspepsia (where organic pathology has been excluded), the results from *H. pylori* eradication are controversial. Current data indicate that from 1 in 15 to 1 in 20 may benefit from such eradication, while one meta-analysis found no benefit at all.
SIGN 68[137]	2003	14, 13	*H. pylori* eradication therapy should be considered in the management of functional dyspepsia. Overall, because about 50% patients with functional dyspepsia will be positive for *H. pylori*, eradication treatment will be symptomatically beneficial for slightly less than 5% of all functional dyspepsia patients. Three meta-analyses on the effect of *H. pylori* eradication on functional dyspepsia have differed in their conclusions.
Hellenic Society of Gastroenterology[148]	1999	16	Eradication therapy is recommended also in patients with functional dyspepsia that did not respond to any other empirical treatment and afterwards, were subjected to an endoscopy, where no lesions were observed, but urease test was found positive.

D4A: Supporting Evidence

Summary: The statement is based on three good quality SRs.[149-151] The two SRs (Moayyedi et al) [149,150] showed that eradication was more effective than non-eradication in symptom relief. But the SR (Laine et al. 2001)[151] found no difference between Hp eradicaton and non-eradication treatment at one month. There is no sufficient evidence to conclude that Hp eradication is more effective than non-eradication therapy (PPIs, H2RA empirical therapy) in symptom relief for non-ulcer dyspepsia.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Moayyedi et al. 2005*[149] SR **(good)**	13 RCTs (n=3,186) Adult pts presenting to secondary care with *H. pylori* infection and dyspepsia who have negative or insignificant finding	Hp eradication (with either PPI or H2RA in combination with antibiotics)	Non-eradication: placebo; PPIs (ome 20 mg po bid; lans 15 mg po bid); placebo antibiotics)	Symptom relief by global assessment	Global symptom scores (dichotomous format): eradication vs. non-eradication: RRR: 8% (95% CI: 3%, 12%) at 12 months eradication vs. non-eradication: NNT: 18 (95% CI: 12-48)	+

	endoscopically or barium studies					
Moayyedi et al. 2000*[150] SR **(good)**	9 RCTs (n=2,541) Dyspepsia pts with no ulcer and esophagitis found endoscopically. Hp status: not available.	Hp eradication treatment (PPI + antibiotics or H2RAs + antibiotics)	Non-eradication: placebo or non-eradication drug	RRR for remaining dyspeptic symptoms (same or worse) at 12 months	RRR: Hp eradication vs. placebo (or non-eradication): 9% (95% CI: 4%, 14%) at 12 months NNT: 15 (95% CI: 10, 31)	+
Laine et al. 2001[151] MA **(good)**	7 RCTs (n=1,544) pts with non-ulcer dyspepsia and Hp infection.	Hp eradication (ome 20 mg orally bid or 40 mg bid) + antibiotics	Non-eradication : (ome; ran or sucralfate)	Improvement in symptoms	<u>Treatment success (symptom relief) (dichotomous format):</u> Hp eradication vs. non-eradication Odds ratio (OR) : 1.29 (95% CI: 0.89, 1.89) at 1 month post therapy	+
lans: lansoprazole; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D4: What is the role of PPIs for functional dyspepsia?

ii. First-line therapy

D4B: Guideline Statements

Synopsis of Existing Recommendations D4B: A trial of acid suppression (i.e., H2RAs or PPIs) therapy may be considered in the management of functional dyspepsia. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy[152]	2005	6	Offer a low-dose PPI or an H2RA, with a limited number of repeat prescriptions. There is no evidence to guide which of these therapies should be tried first. PPIs offer more powerful acid suppression, but H2RAs are cheaper.
SIGN 68[137]	2003	14	A trial of acid suppression therapy may be considered in the management of functional dyspepsia. Acid suppression therapy can be separated into H2RAs and PPIs and the results of treatment with either in functional dyspepsia are broadly similar. There are no meaningful trials comparing the effects of PPIs and H2RAs.
Talley[129]	2002	iv 76	Full dose PPI therapy for example, with omeprazole 20 mg once daily, should therefore be the first choice of therapy in patients with "ulcer-like" dyspepsia [for 2-4 weeks]. In addition, full dose PPI therapy is to be recommended in *H. pylori* negative patients to ensure healing of peptic ulcer.
Toward Optimized	2005	1-2	If UBT [Urease Breath Test] negative, consider trial of empiric therapy. If patient is less than 50 years of age, has no alarm

Practice Program[153]			features and the *H. pylori* test is negative, consider functional disease of UGI (i.e., non-ulcer dyspepsia). Consider trial of empiric therapy. Empiric Therapy: PPI for 4 wks or H2RA for 4 weeks. There is little evidence to guide therapeutic choice. A 4 week trial of empiric therapy has been recommended by expert panels, followed by reassessment.
Talley NJ[154]	1998	340	Patients who are younger than the cut off age for investigation, who have no alarm features, and who are not chronic users of NSAIDs are at very low risk of serious disease. A provisional diagnosis of functional dyspepsia is reasonable in this setting. If their symptoms have persisted for more than 4 weeks, a treatment trial may be started. Anti-secretory drugs such as H2RAs and PPIs may be prescribed in these cases. H2RAs are often prescribed for patients with functional dyspepsia but the data supporting their value is equivocal with both positive and negative trials in the literature. PPIs show greater promise than H2RAs but futher trials are needed to confirm their efficacy in functional dyspepsia; they may be more efficacious in ulcer-like than dysmotility like dyspepsia. Prokinetics have been shown to be effective in the treatment of functional dyspepsia and, in particular, dysmotility like dyspepsia.

D4B: Supporting Evidence

Summary: This statement is based on three RCTs, one of very good quality[146] and two of poor quality.[155,156] Talley et al[146] showed omeprazole was more effective than placebo in symptom relief of reflux-like dyspepsia, but not in dysmotility-like dyspepsia. For ulcer-like dyspepsia, only 20 mg (but not 10 mg) of omeprazole was more effective than placebo. Farup et al[155] found that ranitidine was more effective than placebo in dyspeptic symptom relief. Meineche-Schmidt et al[156] also demonstrated that omeprazole responders had improved quality of life, fewer clinic visits and fewer days on medication than non-responders in three months follow up period, but no difference in absence from work. Overall, The data from the three RCTs indicated that acid suppression agents (i.e.H2RA or PPI) are more effective than placebo in symptom relief for patients with functional dyspepsia.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Talley et al. 1998*[146] RCT **(very good)**	N=1262 1) age mean (range) 43 (18-80) yrs 2) pts presenting with functional dyspepsia (endoscopically normal) with persistent or recurrent epigastric pain and/or epigastric discomfort	ome 20 mg qd; ome 10 mg qd	Placebo	Symptom relief	pts with complete symptom relief (combined studies): ome 20 mg vs. placebo: 38% vs. 28% (P=0.002) ome 10 mg vs. placebo : 36% vs. 28% (P= 0.02) ome 20 mg vs. placebo NNT = 10 (95% CI:6, 27); RRR = 14% (95% CI:5.3%, 21.9%)	 + +

	experienced on at least one of 3 days immediately prior to study entry; pts also required to have at minimum 1 mo history of dyspeptic symptoms, with symptoms having had to occur at minimum 25% of days during that month. 3) health care centre setting, both GP and GI specialist recruiting patients 4) Hp status: 38%, 42% and 44.6% Hp(+) in ome 20 mg, ome 10 mg, and placebo groups respectively 5) endoscopy: used for diagnosis of functional dyspepsia (FD)				pts with complete symptom relief (ulcer-like dyspepsia): ome 20 mg = 40%; ome 10 mg = 35%; placebo = 27% (P=0.006 ome 20 mg vs. placebo; P=0.08 ome 10 mg vs. placebo) pts with complete symptom relief (reflux-like dyspepsia): ome 20 mg = 54%; ome 10 mg = 45%; placebo = 23% (P=0.002 ome 20 mg vs. placebo; P=0.02 ome 10 mg vs. placebo) pts with complete symptom relief (dysmotility-like symptoms): ome 20 mg = 32%; ome 10 mg = 37%; placebo = 31% (P=0.92 ome 20 mg vs. placebo; P=0.33 ome 10 mg vs. placebo).	+/_ + _
Farup et al, 1997[155] RCT **(poor)**	N=226 1) age ≥18 yrs (mean ± SD: 43 ±14.8) 2) pts with FD (endoscopic diagnosis) symptoms > 6 mos duration with symptoms during the week prior to inclusion 3) GI unit 4) Hp status: not available 5) Endoscopy: used for diagnosis of FD	ran 150 mg bid	Placebo	symptoms (VAS score)	Overall symptoms (VAS Scores) ran vs. placebo : median (25% -75% range) : 19 mm (-31mm, 80mm) vs. 12 mm (-52mm, 71mm) (P<0.03)	+
Meineche-Schmidt et al, 1999*[156] RCT **(poor)**	N=567 1) age >18 yrs 2) all pts with FD who had completed RCT comparing ome to placebo; normal endoscopy and history of epigastric pain and/or discomfort for at least 1 mo and who had experienced symptoms on at least 1 of 3 previous days were randomized to Rx ome or placebo 3) health care centre setting	Follow up after PPI for 4 wks therapy	Follow up after placebo	GI symptoms, absence from work, concomitant medicat-ions and QOL	Clinic visits: Over 3 mos, responders to PPI had fewer visits vs. non-responders (1.5 vs. 2.0 mean visits), P<0.001) Medication: over 3 mos, responders to PPIs had fewer days on medication vs. non-responders (mean, 9 d vs. 23 d), P<0.001. Absence from work: mean # of hours absent was higher for non-responders but NS (P=0.38) QOL: better for responders to PPI at study	+ + _ +

	4) Hp status: not available 5) endoscopy: used for diagnosis of FD				entry and persisted over 3 mos (P<0.001) [responders had sig. < symptom score on GSRS and sig. > level of well being (PGWB total score)].	

GSRS: Gastrointestinal Symptoms Rating Scale; ome: omeprazole; PGWB: Psychological General Well-Being scale; ran: ranitidine; VAS: Visual Analog Scale; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question D4: What is the role of PPIs for functional dyspepsia?

ii. First line therapy

D4C: Guideline Statements

Synopsis of Existing Recommendations D4C: PPIs are superior to placebo for the disappearance or improvement of symptoms in functional dyspepsia.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NICE[24]	2004	142	PPIs were more effective than placebo at reducing symptoms of dyspepsia: the risk ratio for symptoms persisting was 0.86 (95%CI: 0.77 to 0.95).
Mascort et al[130]	2003	87	[For functional dyspepsia] The available systematic reviews indicate that the PPIs are superior to placebo in the disappearance or improvement of symptoms, with a RR calculation from the original data as 1.21 (95%CI: 1.12, 1.31).

D4C: Supporting Evidence

Summary: The statement is based on two good quality SRs.[157] The data from both SR indicate that PPIs are better than placebo in symptom relief for functional dyspepsia.[158]

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Moayyedi et al. 2005*[157] SR **(good)**	8 RCTs (n=3293) 1) adults presenting with dyspepsia symptoms who have had negative or insignificant findings on endoscopy or barium studies 2) Hp status: not	ome 10 or 20 mg qd x 2-4 weeks or lans 15 or 30 mg qd x 4-8 weeks	Placebo	Treatment success in symptom relief	Treatment success (dichotomous outcomes) at 2-8 weeks: PPIs vs. placebo RRR: 14% (95% CI: 5%, 23%) NNT: 9 (95% CI: 6, 26)	+

	available					
Shiau et al. 2002[158] SR **(good)**	6 RCTs (n=2368) 1) adults with functional dyspepsia (no evidence of organic disease, including at upper endoscopy, to explain the symptoms) 2) Hp status: not available 3) endoscopy: used for diagnosis of functional dyspepsia.	PPI for at least 1 week	Placebo	# of patients experiencing symptom relief	PPIs vs. placebo Excellent outcome OR: 1.81 (95% CI: 1.49, 2.20) Combined good and excellent response OR: 1.53 (95% CI: 1.29, 1.81) NNT: 10 (95% CI: 6.67, 16.67)	+
lans: lansoprazole; ome: omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D4: What is the role of PPIs for functional dyspepsia?

ii. First line therapy

D4D: Guideline Statements

Synopsis of Existing Recommendations D4D: PPIs or H2RA or antacids should not be used on a regular/long term basis for functional dyspepsia since functional dyspepsia can have various causes. ***The evidence cited in support of the existing recommendations does not reflect the situation (i.e., duration of therapy) being referred to in the statements. Therefore the existing recommendations could be considered as being based on expert opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Québec CRUM[45] (translated)	2002	11	Treatment of functional (or non-ulcer) dyspepsia is one of the recognized indications in the monograph of some PPIs. However, functional dyspepsia symptoms can have various causes. As such, these symptoms should not be treated with PPIs on a regular basis. Besides, it is unlikely that PPIs would be efficient for long-term treatment of functional dyspepsia.
Talley NJ[159]	1991	154	However, in uninvestigated ulcer-like dyspepsia, where there is more likely to be a concentration of cases with PUD, the committee recommends that a patient who warrants empiric drug therapy should be treated initially with antacids or a H2RA for one month. Although lacking a firm scientific basis, it appears appropriate to use a similar approach in ulcer-like functional dyspepsia. If treatment fails here, the committee believes it is acceptable to consider switching to a prokinetic agent. Long-term drug treatment should be avoided in almost all cases.

D4D: Supporting Evidence

Summary: The recommendations from the guidelines are based on three good quality SRs. Both Moayyedi et al[157] and Shiau et al[158] showed that PPIs are more effective than placebo and Delaney et al[136] demonstrated that PPIs are more effective than H2RAs for the management of functional dyspepsia. The recommendations from the guidelines discuss long term management of functional dyspepsia, but the evidence cited demonstrate only short term efficacy (i.e., 1-8 weeks). Therefore this Synopsis of Existing Recommendations could be considered as being based on expert opinion[45,159] and further research being required.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Moayyedi et al. 2005*[157] SR **(good)**	8 RCTs (n=3293) 1) adults presenting with dyspepsia symptoms who have had negative or insignificant findings on endoscopy or barium studies 2) Hp status: not available	ome 10 or 20 mg qd x 2-4 weeks or lans 15 or 30 mg qd x 4-8 weeks	Placebo	Treatment success in symptom relief	Treatment success (dichotomous outcomes) at 2-8 weeks: PPIs vs. placebo RRR: 14% (95% CI: 5%, 23%) NNT: 9 (95% CI: 6, 26)	0
Shiau et al. 2002[158] SR **(good)**	6 RCTs (n=2368) 1) adults with functional dyspepsia (no evidence of organic disease, including at upper endoscopy, to explain the symptoms) 2) Hp status: not available 3) endoscopy: used for diagnosis of functional dyspepsia.	PPI for at least 1 week	Placebo	# of patients experiencing symptom relief	PPIs vs. placebo Excellent outcome OR: 1.81 (95% CI: 1.49, 2.20) Combined good and excellent response OR: 1.53 (95% CI: 1.29, 1.81) NNT: 10 (95% CI: 6.67, 16.67)	0
Delaney et al, 2000*[136] SR **(good)**	3 RCTs (N=1,267) ; 5 study arms (PPIs); 3 study arms (H2RAs) 1) age Patients presenting to primary care with dyspeptic symptoms but not selected on	lans 30 mg/d; ome 10-40 mg/d	H2RAs: cim 400 mg po bid; ran 150 mg po qd	Global symptom scores (dichotomous format), heartburn, epigastric pain, patient satisfaction.	PPIs vs H2RAs <u>Global symptom scores (dichotomous format) at 2-4 wks:</u> ▪ RRR = 36% (95% CI: 51%, 18%) ▪ NNT = 4.5 (95% CI: 3.1, 11.1) <u>Heartburn at 2-4 wks:</u> ▪ RRR = 31%	0

	the basis of any previous investigative results.				(95% CI: 42%, 19%; z=-4.3); p<0.0005 ▪ NNT = 3.1 (95% CI: 2.7, 3.9) <u>Epigastric pain at 2-4 wks:</u> ▪ RRR = 54% (95% CI: 43%, 63%; z=-7.38); p<0.0000001 ▪ NNT = 5.6 (95% CI: 4.1, 11.4)	0 0
Lans: lansoprazole; ome: omeprazole; ran: ranitidine; cim: cimetidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question D4: What is the role of PPIs for functional dyspepsia?

iii. Role of long-term therapy

D4E: Guideline Statements

Synopsis of Existing Recommendations D4E: PPI therapy should be stepped down to the lowest dose required to control symptoms and discuss using the treatment on an "on-demand" basis with patients to manage their own symptoms for those patients with symptom relapse after initial care strategies. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NICE[24]	2004	84, 85	▪ If symptoms return after initial care strategies. Step down PPI therapy to the lowest dose required to control symptoms. Discuss using the treatment on an "on demand" basis with patients to manage their own symptoms. ▪ Evidence is taken from patients with endoscopy negative reflux disease. Patients using PPI therapy as needed (waiting for symptoms to develop before taking treatment) reported similar "willingness to continue" to those on continuous PPI therapy. ▪ Patients taking therapy as needed used about 0.4 [PPI] tablets per day, averaged across studies of 6 to 12 months duration. Taking therapy when symptoms occur may help patients to tailor their treatment to their needs. ▪ It is argued that 'on-demand' use of a PPI may be effective, but less costly than continuous therapy. This step extrapolates evidence from recent trials of on-demand therapy for endoscopy negative reflux disease to the care of patients with uninvestigated dyspepsia.
Talley[129]	2002	iv 76	Long term treatment: If the symptoms recur after the full dose PPI controlled the symptoms, repeat the successful therapy. [Note

			information was extracted from a treatment algorithm].
Prodigy[152]	2005	10	On-demand therapy is where treatment is taken only when symptoms recur. Once symptoms are relieved (often after a few days) treatment is stopped again. The PPI doses most commonly studies as on-demand therapy are rabeprazole 10 mg, pantoprazole 20 mg, esomeprazole 20 mg, omeprazole 20 mg, and lansoprazole 15 mg.

D4E: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[24,129,152] and further research is required.

Study Type(QA)	Sample Size	Intervention	Comparator	Outcome measure	Results	Dir

Question D4: What is the role of PPIs for functional dyspepsia?

iii. Role of long-term therapy

D4F: Guideline Statements

Synopsis of Existing Recommendation D4F: High-dose PPIs is one of the three recommended options (or switch therapy or endoscopy) if dyspepsia symptom persists. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Talley[129]	2002	iv 76	If the symptom persists, switch therapy or consider endoscopy or high dose PPI use. [Note this information was extracted from a treatment algorithm].

D4F: Supporting evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[129] and further research is required.

Study Type(QA)	Sample Size	Intervention	Comparator	Outcome measure	Results	Dir

Question D5: What are the differences among PPIs in terms of clinical efficacy and safety?
What is the recommended PPI dose for non-ulcer dyspepsia?

i. What are the differences among PPIs in terms of clinical efficacy and safety?

D5A: Guideline Statements

Synopsis of Existing Recommendation D5A: Differences between the PPIs in clinical efficacy and safety are minimal. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy[152]	2005	9	Differences between the proton pump inhibitors (PPIs) in clinical efficacy and safety are minimal. On present evidence, PPIs do not have any serious contraindications for most users, and have been in common use for over a decade.

D5A: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[152] and further research is required.

Study Type(QA)	Sample Size	Intervention	Comparator	Outcome measure	Results	Dir

ii. What are the recommended PPI doses for non-ulcer dyspepsia?

D5B: Guideline Statements

Synopsis of Existing Recommendation D5B: PPI doses for non-ulcer dyspepsia as recommended by the PRODIGY guideline are Omeprazole Low Dose (LD) 10 mg qd, *H. pylori* eradication double dose 20 mg bid; Lansoprazole LD 15 mg od, *H. pylori* eradication double dose 30 mg bid; Pantoprazole LD 20 mg qd, *H. pylori* eradication double dose 40 mg bid; Rabeprazole LD 10 mg qd, *H. pylori* eradication double dose 20 mg bid; Esomeprazole LD not available, *H. pylori* eradication double dose 20 mg bid. ***The existing recommendations are only based upon consensus opinion. A potential gap in research-based evidence has been identified. Interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy[152]	2005	10	PRODIGY-recommended proton pump inhibitor doses for non-ulcer dyspepsia are Omeprazole Low Dose (LD) 10mg od, double dose (DD) 20mg bid; Lansoprazole LD 15mg od, DD 30mg bid; Pantoprazole LD 20mg od, DD 40mg bid; Rabeprazole LD 10mg od, DD 20mg bid; Esomeprazole LD not available, DD 20mg bid. [Note double dose (DD) are recommended only for H. pylori eradication regimen. Also information was extracted from a table].

D5B: Supporting Evidence

Summary: This Synopsis of Existing Recommendations is based on expert opinion[152] and further research is required.

Study Type(QA)	Sample Size	Intervention	Comparator	Outcome measure	Results	Dir

11 Summary of Economic Studies Related to Dyspepsia

1. Chiba et al. (2004)[160]

This study provides a detailed economic analysis of the CADET-Hp study, a double-blind, placebo-controlled, parallel-group, multicentre, randomized controlled trial, performed in 36 family practitioner centres across Canada. *H. pylori*–positive patients by ^{13}C-urea breath test, 18 years and over with uninvestigated dyspepsia of at least moderate severity and without alarm symptoms were randomized to one-week eradication treatment with omeprazole, metronidazole and clarithromycin (OMC) versus omeprazole and placebo antimicrobials (OPP). Following the initial week of treatment, patients were managed by their own family practitioner according to each physician's standard practice.

Cost data were collected prospectively for each patient every 4 weeks using a Health Resource Utilization Questionnaire to capture all relevant health care costs associated with dyspepsia over one year. Mean costs per patient with 95% CIs were calculated.

The primary clinical outcome measure, treatment success was defined as a score of either 1 (none) or 2 (minimal) on a 7-point Likert scale measuring overall global severity of dyspepsia symptoms at the final visit.

The incremental cost-effectiveness ratio of OMC versus OPP was -$387 per treatment success (90% CI: -$1,707, $607), indicating a lower cost with treatment success. The incremental net benefit analysis showed that *H. pylori* eradication was cost-effective if the willingness-to-pay value exceeded a nominal figure of $100 from a health service perspective or $607 from the societal perspective. This study shows that the "test and eradicate" strategy is cost-effective in *H. pylori*-positive patients.

Comment:
This study was conducted in a Canadian health care setting from the perspective of both a ministry of health perspective and societal perspective. The effectiveness data were derived from the single study. Costs were calculated prospectively for each patient on the same sample of patients from whom effectiveness data were derived. The cost estimates were specific to the study setting and no sensitivity analysis was conducted. Although small, this study is important because of its prospective nature, its naturalistic design as well as the fact that it was performed within a primary care setting.

2. Makris et al. (2003)[161]

This study assesses, over a one-year period, the cost-effectiveness of seven alternative initial strategies in the management of uninvestigated dyspepsia in adult patients presenting to a primary care physician in Canada. The analysis is separated into two age ranges, 18 to 45 years, and over 45 years. The primary outcome of the analysis was defined as the proportion of patients remaining symptom-free over a twelve-month period after initial therapy. Costs were analyzed over a one-year period after initial presentation, including consideration of a single

relapse of symptoms. The chosen cost perspective was that of a public payer, with only direct medical expenses included.

A decision-tree was developed to simulate possible choices confronting physicians in the investigation of dyspepsia. The sequence of events adopted for each of the seven strategies was based on Western consensus conferences. The baseline estimates and ranges of the clinical data used in the model are derived from the literature from 1966 to 1999; and where such data were unavailable, assumptions were made based on an expert panel of gastroenterologists.

The seven initial management strategies modeled are as follows:

Strategy 1: Initial endoscopy.

Strategy 2: Barium examination.

Strategy 3: Empirical eradication therapy. Without performing any *H. pylori* test, dyspeptic patients are empirically prescribed eradication therapy.

Strategy 4: Empirical antisecretory therapy. Without performing any *H. pylori* test, dyspeptic patients are empirically prescribed a 4-week antisecretory regimen.

Strategy 5: Urea breath test. Patients begin the investigation with a UBT and pharmacotherapy is then chosen according to the presence or absence of *H. pylori* infection.

Strategy 6: Laboratory serology testing. Patients begin the investigation with a laboratory serology testing and pharmacotherapy is then chosen according to the presence or absence of *H. pylori* infection.

Strategy 7: Sequential testing. Confirm an *H. pylori*-positive serology test with a UBT before initiating appropriate treatment.

In the younger patients (between 18 and 45 years old), no single strategy was cost-effective over all others in the base case analysis. The strategies "*Initial endoscopy*" and "*Sequential testing*" were dominated, and "*Barium examination*" were dominated through principles of extended dominance. The remaining four strategies "*Empirical antisecretory therapy*", "*Laboratory serology testing*", "*Empirical eradication therapy*" and "*Urea breath test*" were cost-effective. Compared with "*Empirical antisecretory therapy*", "*Laboratory serology testing*" can provide an additional cure at an extra cost of $2,970. Compared with "*Laboratory serology testing*", "*Empirical eradication therapy*" can provide an additional cure at an extra cost of $6,412. Compared with "*Empirical eradication therapy*", "*Urea breath test*" can provide an additional cure at an extra cost of $10,429.

In patients over age 45, the strategies "*Initial endoscopy*" and "*Sequential testing*" were dominated, and "*Laboratory serology testing*" were dominated through principles of extended dominance. The remaining four strategies "*Empirical antisecretory therapy*", "*Barium examination*", "*Empirical eradication therapy*" and "*Urea breath test*" were cost-effective.

Compared with "*Empirical eradication therapy*", "*Urea breath test*" can provide an additional cure at an extra cost of $10,835. Although not cost-effective when considering symptomatic cure rates, early endoscopy resulted in the best early detection rate of gastric cancers.

Clinical variables that impacted these findings were the probability of symptomatic relapse in patients with non-ulcer dyspepsia (NUD) after successful versus failed *H. pylori* eradication, the probability of finding a duodenal ulcer (DU) in a young dyspeptic patient, the specificity of Urea breath test, and the prevalence of *H. pylori* in patients with DU.

The study results were very sensitive to the impact of eradication on symptoms in patients with NUD. The more likely a patient with NUD is to become asymptomatic after successful *H. pylori* eradication, the more test-and-treat strategies are favoured and vice versa. The choice of the most cost-effective approach is dependent on the benefits of *H. pylori* eradication in patients with NUD.

Comment:
This study was conducted in a Canadian health care setting from the perspective of a provincial (Quebec) government; uses the inputs specific to Quebec, and the costs are in Canadian dollars. The sequence of events adopted for each of the seven strategies was based on Western consensus conferences. The effectiveness data was derived mainly from literature by averaging study results. The analysis was conducted separately for younger (18 to 45 years old) and older patients (over 45 years).

12 Clinical Evidence for Peptic Ulcer Disease

12.1 Clinical Questions for PUD

Question P1: What is the optimal use of PPIs in the treatment of *H. pylori* positive PUD?

Synopsis of Existing Recommendations P1A: *H. pylori* eradication therapy is recommended for patients diagnosed with gastric or duodenal ulcer who are infected with *H. pylori*.

Synopsis of Existing Recommendations P1B: Acid-suppression therapy following *H. pylori* eradication may be required until healing is documented in patients with complicated ulcers, or when ulcer symptoms persist. Follow-up acid-suppression therapy after *H. pylori* eradication is not required in uncomplicated duodenal ulcer that is asymptomatic.

Question P2: What is the optimal use of PPIs in *H. pylori* eradication regimens?

Synopsis of Existing Recommendations P2A: A PPI-based triple therapy regimen is recommended as a first-line therapy for adults in whom *H. pylori* eradication is indicated.

i. The following triple therapy regimens provide optimal eradication rates: a twice daily course of standard dose PPI, amoxicillin 1 g and clarithromycin 500 mg (PAC regimen) OR a twice daily course of standard dose PPI, metronidazole 500 mg and clarithromycin 250 mg-500 mg (PMC regimen).
ii. Various PPIs have similar efficacy when used in triple therapy.
iii. PPI dose in triple therapy regimens: Optimal eradication rates are achieved with double-dose PPIs (a standard dose administered twice daily) in triple-therapy regimens.
iv. PPI-triple therapy duration: 7-14 days. Factors other than eradication rates, such as cost, may be taken into account when choosing between 7 and 14 days duration.

Synopsis of Existing Recommendations P2B: A combination of standard dose PPI twice daily, 262 mg bismuth subsalicylate four times daily, 375-500 mg metronidazole four times daily and 500 mg tetracycline four times daily (PBMT quadruple therapy), given for 7-14 days can be considered for first-line eradication therapy.

Synopsis of Existing Recommendations P2C: Patients who remain *H. pylori* positive after an initial attempt at eradication with a first-line regimen can be treated with a 7-14 day course of PPI quadruple therapy (PBMT), or an alternative PPI-triple therapy with different antibiotics from the initial attempt.

Synopsis of Existing Recommendations P2D: For children in whom *H. pylori* eradication is indicated, a PPI-triple therapy can be used as in adults with appropriate dose adjustment, for a duration of 7-14 days.

Question P3: What is the optimal use of PPIs in the treatment of *H. pylori* negative PUD?

Synopsis of Existing Recommendations P3A: PPI or H2RA therapy is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs.

Synopsis of Existing Recommendations P3B: Maintenance treatment with H2RA or PPI therapy may be required in *H. pylori* negative patients with a history of frequent ulcers, previous ulcer complications, or for whom co-morbid factors may cause ulcer complications to be life-threatening.

Question P4: What is the optimal use of PPIs in the treatment and prevention of NSAID-induced ulcer?

Synopsis of Existing Recommendations P4A: Full-dose H2RA, PPI or misoprostol therapy is recommended for ulcer healing in patients with NSAID-associated duodenal or gastric ulcers. PPIs are more effective than H2RAs in healing large or complicated ulcers, or when NSAID therapy must be continued. PPIs are better tolerated than high dose misoprostol.

Synopsis of Existing Recommendations P4B: Offer eradication therapy to *H. pylori* positive NSAID users with previous or current peptic ulcer.

Synopsis of Existing Recommendations P4C: Offer *H. pylori* eradication therapy to reduce ulcer risk in *H. pylori* positive patients without peptic ulcer who are initiating long-term therapy with conventional NSAIDs or ASA.

Synopsis of Existing Recommendations P4D: Offer ulcer prophylaxis with a PPI, H2RA, or misoprostol to all long-term NSAID or ASA users at high risk for the development of ulcer and/or ulcer complications. Risk factors include: age, history of PUD, previous GI bleeding, history of cardiovascular diseases, use of high NSAID doses, and concurrent use of corticosteroids or anticoagulants. Standard dose PPIs, double dose H2RAs, and 800 mcg/day of misoprostol are all effective for the prevention of NSAID-associated gastric and duodenal ulcers while single dose H2RAs and lower misoprostol doses are less effective. The use of misoprostol may be limited by adverse effects.

12.2 Clinical Evidence for PUD

Question P1: What is the optimal use of PPIs in the treatment of *H. pylori* positive PUD?

P1A: Guideline Statements

Synopsis of Existing Recommendations P1A: *H. pylori* eradication therapy is recommended for patients diagnosed with gastric or duodenal ulcer who are infected with *H. pylori*. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Hunt et al[162] Canadian *H. pylori* consensus conference	1999	215	All *H. pylori*-positive patients with duodenal or gastric ulcer, whether symptomatic or asymptomatic, should receive eradication treatment.
Prodigy[163]	2005	4	For people with a gastric ulcer or duodenal ulcer: if *H. pylori* positive, eradicate *H. pylori* using triple therapy.
NZGG[29]	2004	43	*H. pylori* eradication is effective in healing peptic ulcers and also very significantly reduces ulcer recurrence (rare) and complications.
NICE[24]	2004	121	Offer *H. pylori* eradication therapy to *H. pylori*-positive patients who have peptic ulcer disease: *H. pylori* eradication therapy increases duodenal ulcer healing in *H. pylori*-positive patients. After 4 to 8 weeks, patients receiving acid suppression therapy average 69% healing: eradication increases this by a further 5.4%, a number needed to treat for one patient to benefit from eradication of 18. *H. pylori* eradication therapy reduces duodenal ulcer recurrence in *H. pylori* positive patients. After 3–12 months, 39% of patients receiving short-term acid suppression therapy are without ulcer: eradication increases this by a further 52%, a number needed to treat for one patient to benefit from eradication of 2. Trials all show a positive benefit for *H. pylori* eradication but the size of the effect is inconsistent. *H. pylori* eradication therapy does not increase gastric ulcer healing in *H. pylori*-positive patients, when compared with acid suppression alone in trials of 4 to 8 weeks duration. *H. pylori* eradication therapy reduces gastric ulcer recurrence in *H. pylori*-positive patients. After 3–12 months, 45% of patients receiving short-term acid suppression therapy are without ulcer; eradication increases this by a further 32%, a number needed to treat for one patient to benefit from eradication of 3. Trials all show a positive benefit for *H. pylori* eradication but the size of the effect is inconsistent. *H. pylori* eradication therapy is a cost-effective treatment for *H. pylori*-positive patients with peptic ulcer disease. Eradication therapy provides additional time free from dyspepsia at acceptable

			cost in conservative models and is cost-saving in more optimistic models.
Malfertheiner et al.[164] Maastricht 2-2000 consensus	2002	171	The recommendation to eradicate *H. pylori* in patients with peptic ulcer disease includes active and inactive disease.
Québec CRUM[45] (translated)	2002	12	Eradication is recommended in the presence of a known *H. pylori* infection.
OPOT[23]	2000	21	Eradication therapy for *H. pylori* –associated ulcers is highly recommended.
Gold et al[165] North American Society for Pediatric Gastroenterology and Nutrition Position Statement	2000	491	Eradication treatment is recommended for children who have duodenal or gastric ulcer identified at endoscopy and *H. pylori* detected on histology. A prior history of documented duodenal or gastric ulcer disease is an indication for treatment if active *H. pylori* infection is documented.
SIGN 7[166,167]	1996, updated in 1999	10	Patients with duodenal ulcer confirmed by barium meal or endoscopy should receive eradication therapy. This includes both newly diagnosed cases and patients previously confirmed to have duodenal ulcer who have persistent or recurrent ulcer symptoms and/or requirement for ulcer therapy. Patients with endoscopically confirmed benign gastric ulcer who are H. pylori positive should receive eradication therapy. It is recommended that infection is checked before commencing eradication.
Deltenre et al[168] Belgian consensus meeting	1998	300	All Hp positive gastric or duodenal ulcer diseases active or not, regardless of NSAID intake, of first presentation or relapse, of present or past complication(s) are an absolute indication for Hp eradication.

P1A: Supporting Evidence

P1A: *H. pylori* eradication therapy is recommended for patients diagnosed with gastric or duodenal ulcer who are infected with *H. pylori*. *The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

a) Evidence supporting the benefit of *H. pylori* eradication on ulcer healing in adults diagnosed with DU and GU

Summary: Results from one good quality systematic review by Ford et al.[169] (a and b) and another poor quality systematic review by Veldhuyzen van Zanten and Sherman[170] showed that *H. pylori* eradication was superior to ulcer healing drugs and no treatment in the healing of duodenal ulcers. However, Ford et al. (c) also showed that there was no benefit to adding *H. pylori* eradication to ulcer healing drugs in the healing of gastric ulcers.[169] A good quality meta-analysis by Leodolter et al.[171] found that eradication of *H. pylori* cures both duodenal and gastric ulcers and that healing rates for the two ulcer types are similar.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Ford et al. - a 2003*[169] SR & MA **(good)**	34 RCTs (n= 3,910) Adults with diagnosed PUD & Hp positive	Hp eradication therapy: (PPI dual/triple therapy; H2RA triple therapy; bismuth triple/quadruple therapy; RBC dual/triple therapy; clarithromycin monotherapy) plus ulcer healing drugs (UHD)	UHD	DU healing after 1-4 months	RR of ulcer persisting with Hp eradication therapy plus UHD versus UHD alone was 0.66 (95% CI: 0.58, 0.76); NNT = 14 (95% CI: 11, 20)	+
Ford et al. - b 2003*[169] SR & MA **(good)**	2 RCTs (n=207) Adults with diagnosed PUD & Hp positive	Hp eradication therapy	No treatment	DU healing after 2-3 months	RR of ulcer persisting with Hp eradication vs. no treatment was 0.37 (95% CI: 0.26, 0.53); NNT = 2.5 (95% CI: 2,4)	+
Veldhuyzen van Zanten & Sherman 1994*[170] SR **(poor)**	8 RCTs (n= 644) Adults with DU & Hp positive	Various Hp eradication regimens including PPI, H2RA (dual, triple and quadruple) in DU		DU healing rate and time required for healing	DU: when Hp eradication therapy was added to conventional ulcer treatment acute ulcers healed more rapidly. Ulcer healing rate ranged from 76% with cim-dual therapy to 95% with ome-quadruple therapy (pooled data for all Hp eradicated subjects not provided)	+
Ford et al. - c 2003*[169] SR & MA **(good)**	13 RCTs (n= 1,469) Adults with diagnosed PUD & Hp positive	Hp eradication therapy plus UHD	UHD	GU healing after 1-3 months	RR of ulcer persisting with Hp eradication therapy plus UHD vs. UHD alone was 1.32 (95% CI: 0.92, 1.90) - NNH = 33 (95% CI: NNT=33, NNH=11)	-
Leodolter et al. 2001[171] MA **(good)**	11 RCTs and non-RCTs (n= 1,119) Patients with DU or GU & Hp positive	Exclusive use of PPI-based eradication therapy (dual, triple and quadruple) in DU or GU		Ulcer healing rate after 1-3 months	Ulcer healing rate was 87.4% (95% CI: 84.2%, 90.5%) for GU and 92.5% (95% CI: 90.5%, 94.4%) for DU, p-value not reported	+
cim: cimetidine; ome: omeprazole; UHD: ulcer healing drugs; RBC: ranitidine bismuth citrate; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P1A: *H. pylori* eradication therapy is recommended for patients diagnosed with gastric or duodenal ulcer who are infected with *H. pylori*. *The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

b) Evidence supporting the benefit of *H. pylori* eradication in preventing ulcer recurrence in adults diagnosed with DU and GU

Summary: Results from a good quality systematic review by Ford et al.[169] (d and e) and a poor quality review by Hopkins et al.[172]showed that *H. pylori* eradication is superior to no treatment in preventing both duodenal and gastric ulcer recurrence. However, Ford et al.(f), a good quality systematic review, also showed that there was no significant difference between *H. pylori* eradication therapy and maintenance ulcer healing drug therapy for the prevention of duodenal ulcer recurrence.[169] According to Leodolter et al.,[171] a good quality meta-analysis, there was no difference in the pooled ulcer remission rates of gastric and duodenal ulcers when both were treated with *H. pylori* eradication therapy. The pooled ulcer remission rate for both gastric and duodenal ulcers was higher in Hp-eradicated patients than in unsuccessfully eradicated patients or in those treated with ulcer healing drug alone.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Ford et al. - d 2003*[169] SR & MA **(good)**	27 RCTs (n= 2,509) Adults with diagnosed PUD & Hp positive	Hp eradication therapy	No treatment	DU recurrence following initial healing after 2 months to 5 years	RR of ulcer recurrence in Hp alone vs. no treatment was 0.20 (95% CI: 0.15-0.26) - NNT was 2 (95% CI: 1.6, 2.2)	+
Ford et al. - e 2003*[169] SR & MA **(good)**	10 RCTs (n= 1,029) Adults with diagnosed PUD & Hp positive	Hp eradication therapy	No treatment	GU recurrence following initial healing after 3 months to 5 years	RR of ulcer recurrence in Hp alone vs. no treatment was 0.28 (95% CI: 0.18, 0.43) - NNT was 3 (95% CI: 2,5)	+
Ford et al. - f 2003*[169] SR & MA **(good)**	4 RCTs (n= 319) Adults with diagnosed PUD & Hp positive	Hp eradication therapy	UHD	DU recurrence following initial healing after 6 months to 2 years	RR of ulcer recurrence in Hp alone vs. UHD was 0.73 (95% CI: 0.42-1.25) - NNT was 25 (95% CI: NNT=8, NNH=33)	-
Leodolter et al. 2001[171] MA **(good)**	11 RCTs & non RCTs (n= 1,119) Patients with DU or GU & Hp positive	PPI-based eradication therapy (dual, triple and quadruple) in DU or GU		Ulcer remission rate after 12 months	Ulcer remission rates in Hp eradicated patients were 97.1% (95% CI: 95.1%, 99.1%) for GU and 98% (95% CI: 96.9%, 99.0%) for DU, p-values not reported Ulcer remission rates in unsuccessfully eradicated or UHD-treated patients were 60.9% (95% CI: 51.9%, 69.8%) for GU and 57.5% (95% CI: 50.1%, 64.8%) for DU, p-values not reported	+

Hopkins et al. 1996[172] MA **(poor)**	19 studies† on Hp eradication and DU or GU recurrence (14 studies for DU, n= 892); (5 studies for GU, n=222)	Patients with DU or GU cured of Hp infection with eradication therapy	Non-eradicated Hp patients with DU or GU	DU and GU recurrence rate	Duodenal recurrence rate in Hp-eradicated vs. non-eradicated patients was 6% vs. 67%. Study-weighted OR: 24.1 (95% CI: 13.9, 41.7). Gastric recurrence rate in Hp- eradicated vs. non-eradicated patients was 4% vs. 59%. Study-weighted OR: 28.1 (95% CI: 10.0, 79.0)	+
†The types of studies included in this meta-analysis were not defined. UHD: ulcer healing drugs; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P1A: *H. pylori* eradication therapy is recommended for patients diagnosed with gastric or duodenal ulcer who are infected with *H. pylori*. *The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

c) Evidence supporting the benefit of *H. pylori* eradication in preventing peptic ulcer bleeding in adults

Summary: Results from a good quality RCT by Rokkas et al.[173] and a poor quality RCT by Jaspersen et al.[174] showed that eradication of *H. pylori* in patients with gastrointestinal bleeding due to peptic ulceration reduces the risk of future re-bleeding as compared to PPI therapy alone. The rate of re-bleeding with *H. pylori* eradication therapy was zero, compared to 33% and 27% in those treated with PPIs alone. Another two poor quality RCTs by Sung et al.[175] and Graham et al.[176] showed that there was no significant difference between *H. pylori* eradication therapy (with ranitidine + BMT) and ranitidine alone in reducing the rate of re-bleeding at 9-12 months, although the rate of re-bleeding in the *H. pylori* eradication arms was zero in both studies.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Rokkas et al. 1995[173] RCT **(good)**	31 adults with current bleeding, history of bleeding & Hp positive	OA group: ome 20 mg tid, amox 500 mg qid for 2 wks	O group: ome 20 mg tid for 2 wks	Rate of re-bleeding after 12 months	Rate of re-bleeding was: OA group: 0% vs. O group: 33%, p=0.018	+
Sung et al. 1997[175] RCT **(poor)**	250 pts (≥16yrs) with confirmed bleeding related to PUD +/- stigmata of recent hemorrhage & Hp-positive	RBMT group: bis 120 mg qid, met 400 mg qid, tet 500 mg qid, ran 300 mg/day for 1wk	R group: ran 300 mg/day for 6 wks	Number of patients with re-bleeding after 9-12 months	Number of patients with re-bleeding: RBMT group: 0 vs. R group: 3, p=0.08 (NS)	-
Jaspersen et al. 1995[174] RCT **(poor)**	51 adults with DU with stigmata of recent bleeding & Hp positive	OA group: ome 40 mg qd, amox 1 g bid for 2 wks	O group: ome 40 mg qd for 2 wks	Rate of re-bleeding after 12 months	Rate of re-bleeding was: OA group: 0% vs. O group: 27.3%, p<0.01	+
Graham et al. 1993*[176] RCT **(poor)**	36 adults with GI bleeding from PUD & Hp-positive	RBMT group: bis 5-8tbs/day, met 250 mg tid, tet 500 mg qid for 2wks plus ran 300 mg/day until	R group: ran 300 mg/day until ulcer healed	Rate of re-bleeding after 9-12 months	Rate of re-bleeding: RBMT group: 0% vs. R group: 12.9%, p>0.2 (NS)	-

		ulcer healed				

amox: amoxicillin; bis: bismuth; met: metronidazole; ome: omeprazole; ran: ranitidine; tet: tetracycline; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Question P1: What is the optimal use of PPIs in the treatment of *H. pylori* positive PUD?

P1B: Guideline Statements

Synopsis of Existing Recommendations P1B: Acid-suppression therapy following H. pylori eradication may be required until healing is documented in patients with complicated ulcers, or when ulcer symptoms persist. Follow-up acid-suppression therapy after H. pylori eradication is not required in uncomplicated duodenal ulcer that is asymptomatic.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy[163]	2005	7	If symptoms have responded to eradication treatment, then no further course of treatment is needed
Malfertheiner et al.[164] Maastricht 2-2000	2002	174	In uncomplicated duodenal ulcer patients, it is strongly recommended that H. pylori eradication therapy does not need to be followed by further antisecretory treatment, based on level 1 evidence and this approach has recently been approved by the European regulatory authorities.
OPOT[23]	2000	19	Follow-up acid suppression therapy after eradication is not necessary unless symptoms persist, the patient has had a serious complication (e.g., hemorrhage), or is at risk in the event of a complication because of comorbid illness.
Gisbert et al.[177]	2000	192	To obtain a high rate of duodenal ulcerous scar, it is sufficient to use a PPI for one week, that is, for the period of administration of the two antibiotics. On the other hand, with a complicated gastroduodenal ulcer, it seems prudent that antisecretories be administered until confirmation of the eradication of H. pylori.
Agence Française de Sécurité Sanitaire des Produits de Santé[178]	1999	23, 25 (Table V)	In case of Helicobacter pylori infection, eradication therapy is recommended (grade A). There are two phases to the treatment: - the first eradication phase consists of a triple therapy administered orally: Initial triple therapy for 1 week - the second phase consists of a monotherapy by antisecretory at a standard dose administered orally: • Duodenal ulcer: PPI (lansoprazole 30 mg/d or omeprazole 20 mg/d or pantoprazole 40 mg/d for 3 weeks) OR ranitidine 300 mg/d for 2 weeks. • Gastric ulcer: PPI (lansoprazole 30 mg/d or omeprazole 20 mg/d or pantoprazole 40 mg/d for 5 weeks) OR ranitidine 300 mg/d for 4 weeks.
Jovell et al.[179] CAHTA	1998	13	If there exists a background of complicated duodenal ulcer, antisecretive therapy should be maintained after the eradication triple therapy until confirmation of eradication by means of breath test or endoscopy.
Buckley et al.[180] Irish *H. pylori* group	1996	3, 4	Duodenal ulcer-endoscopically confirmed – uncomplicated: no need for other treatment Gastric ulcer-endoscopically confirmed – uncomplicated: At present it is unknown if a course of eradication therapy is adequate to heal active gastric ulcers. Accordingly, it is recommended that in addition, an

			antisecretory drug be prescribed until healing is documented at follow up Duodenal ulcer bleeding: This is still a controversial area and there are no definitive studies to suggest the optimal treatment. The authors recommend that an antisecretory drug be continued until healing of ulcer has been proven.

P1B: Supporting Evidence

P1B: Acid-suppression therapy following *H. pylori* eradication may be required until healing is documented in patients with complicated ulcers, or when ulcer symptoms persist. Follow up acid suppression therapy after *H. pylori* eradication is not required in uncomplicated duodenal ulcer that is asymptomatic.

Summary: This recommendation is based on results from seven RCTs cited in the guidelines. Four RCTs of good quality[181-184] and one of poor quality[185] compared eradication therapy alone with eradication therapy plus follow-up acid suppression in healing active duodenal ulcers. These RCTs demonstrated that *H. pylori* eradication therapy alone is sufficient to heal active, uncomplicated duodenal ulcers.
Two RCTs provided indirect evidence that *H. pylori* eradication alone is sufficient to heal duodenal ulcers. The first was a poor quality RCT[186] in which the rate of duodenal ulcer healing was higher in subjects successfully cleared of *H. pylori* infection as compared to those who remained infected despite treatment. The high rate of healing in the *H. pylori* eradicated group suggested that acid suppression after successful eradication was unnecessary. The second RCT,[187] of good quality, compared two different *H. pylori* eradication regimens without follow-up acid suppression and found high rates of ulcer healing with both treatments.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Tulassay et al. 2001*[181] RCT **(good)**	446 adults with active DU ≥5mm & Hp positive	OAC group: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 1 wk, followed by ome 20 mg qd for 3 wks	EAC group: esome 20 mg bid, amox 1 g bid, clar 500 mg bid for 1 wk	DU healing rate at 4 wks	DU healing rate (95% CI): OAC group: 92% (88%, 95%) vs. EAC group: 91% (87%, 95%), p > 0.05, NS	+
Dupas et al. 2000*[182] RCT **(good)**	343 adults with symptomatic DU ≥5mm & Hp positive	RMC followed by ran: ran 300 mg/d, met 1 g/d, clar 500 mg/d for 7 days, followed by ran 300 mg/d for 21 days	RMC alone: ran 300 mg/d, met 1 g/d, clar 500 mg/d for 7 days	DU healing rate at 4 wks	DU healing rate: RMC followed by ran: 86% vs. RMC alone: 83%, difference was 2.7% (95% CI: - 3.8%, 9.2%)	+
Labenz et al. 1997*[183] RCT **(good)**	59 adults with DU ≥5mm & Hp positive	OMC followed by ome: ome 20 mg bid, met 400 mg bid, clar 250 mg bid for 1wk; followed by ome 20 mg/d for 3wks	OMC alone: ome 20 mg bid, met 400 mg bid, clar 250 mg bid for 1wk	DU healing rate at 4 wks	DU healing rate: OMC followed by ome: 100% vs. OMC alone: 100%	+
Wurzer et al. 1997*[187]	267 adults with active DU & Hp positive	OAC group: ome 20 mg qd, amox 1 g bid, clar	OC group: ome 40 mg/d, clar 500 mg tid	DU healing rate at 4-6 wks	DU healing rate (95% CI): OAC: 90% (83.3%, 94.3%) vs. OC:	+

RCT **(good)**		500 mg bid for 10 days	for 14 days		85% (78.1%, 91.0%); p = 0.35, NS	
Hosking et al. 1994[184] RCT **(good)**	160 pts (16 - 75 yrs) with dyspepsia & DU & Hp positive	OBMT: ome 20 mg for 4 wks plus [bis 120 mg, met 400 mg, tet 500 mg, all qid for 1 wk]	BMT: bis 120 mg, met 400 mg, tet 500 mg, all qid for 1 wk	DU healing rate at 4 wks	DU healing rate (95% CI): OBMT: 91.7% (85.3%, 98.1%) vs. BMT: 92.8% (86.6%, 98.9%), NS difference	+
Ge et al. 2000[185] RCT **(poor)**	115 adults with active DU & Hp positive	OBTC: ome 20 mg qd for 4wks plus [bis 220 mg bid, tini 500 mg bid, clar 250 mg bid for 1wk]	BTC: bis 220 mg bid, tini 500 mg bid, clar 250 mg bid for 1wk	DU healing rate at 4 wks	DU healing rate (95% CI): OBTC: 90% (82%, 98%) vs. BTC: 86% (77%, 95%), NS difference	+
Goh et al. 1996*[186] RCT **(poor)**	66 Adults with uncomplicated DU & Hp positive	Hp eradicated patients treated with OC: ome 40 mg/d clar 1.5 g/d for 2 weeks or FC: fam 80 mg/d, clar 1.5 g/d for 2 wks	Hp non-eradicated patients after treatment with OC: ome 40 mg/d and clar 1.5 g/d for 2 weeks, or FC: fam 80 mg/d, clar 1.5 g/d for 2 wks	DU healing rate at 6 wks	DU healing rate : Hp eradicated: 95.5% vs. Hp non-eradicated: 36.8%, p<0.001	+
amox: amoxicillin; bis: bismuth; clar = clarithromycin; esome: esomeprazole; fam: famotidine; met: metronidazole; ome: omeprazole; ran: ranitidine; tet: tetracycline; tini: tinidazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						
Comments: Some guidelines[23,177-180] recommended that antisecretory medication should be continued after *H. pylori* eradication in patients who had complications due to peptic ulcer, however, no evidence was cited to support this recommendation.						

Question P2: What is the optimal use of PPIs in *H. pylori* eradication regimens?

P2A: Guideline Statements

Synopsis of Existing Recommendations P2A: A PPI-based triple therapy regimen is recommended as first-line therapy for adults in whom *H. pylori* eradication is indicated. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

i. The following triple therapy regimens provide optimal eradication rates: a twice daily course of standard dose PPI, amoxicillin 1 g and clarithromycin 500 mg (PAC regimen) OR a twice daily course of standard dose PPI, metronidazole 500 mg and clarithromycin 250 mg-500 mg (PMC regimen). ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

ii. Various PPIs have similar efficacy when used in triple therapy. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

iii. PPI dose in triple therapy regimens: Optimal eradication rates are achieved with double-dose (standard dose administered twice daily) PPIs in triple-therapy regimens. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

iv. PPI-triple therapy duration: 7-14 days. Factors other than eradication rates, such as cost, may be taken into account when choosing between 7 and 14 days duration.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Hunt et al[162] Canadian *H. pylori* consensus conference	1999	216	• Twice daily, seven-day regimen of a proton pump inhibitor (PPI) (Omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) or ranitidine bismuth citrate (RBC) 400 mg, clarithromycin 500 mg and amoxicillin 1000 mg; OR • A twice daily, seven-day regimen of a PPI or RBC, clarithromycin 500 mg or 250 mg, and metronidazole 500 mg
Prodigy[163]	2005	12	First-line eradication therapy: NICE recommends that one of the following one-week triple therapy regimens is used: • A'PAC' regimen (a PPI plus amoxicillin 1 g and clarithromycin 500 mg, all given twice a day) • Or (for people with penicillin hypersensitivity) a 'PMC' regimen (a PPI plus metronidazole 400 mg and clarithromycin 250 mg, all given twice a day) • Note: an alternative antibiotic should be used in the eradication regimen, if a course of clarithromycin or metronidazole has previously been given (for any indication). (See second-line triple therapy choices.)
NZGG[29]	2004	44	Give triple therapy: regimens containing PPI, clarithromycin, and amoxicillin or metronidazole, have consistently high eradication rates after one week. Substitute metronidazole for amoxicillin in penicillin-allergic individuals.
NICE[24]	2004	149	For patients who test positive, provide a seven day, twice daily course of treatment consisting of a full-dose proton pump inhibitors, with either metronidazole 400 mg and clarithromycin 250 mg or amoxicillin 1 g and clarithromycin 500 mg: • Eradication is effective in 80–85% of patients. • Eradication may reduce the long term risk of ulcer and gastric cancer. • Clarithromycin 250 mg twice-daily is as effective as 500 mg twice-daily when combined with metronidazole. • PPI, amoxicillin, clarithromycin 500 mg (PAC_{500}) regimens and PPI, metronidazole, clarithromycin 250 mg (PMC_{250}) regimens achieve the same eradication rate. • PMC_{250} used as a first-line therapy may induce resistance to both clarithromycin and metronidazole, whereas amoxicillin resistance does not seem to increase after use of a PAC regimen. • Per course of treatment PAC_{500} costs about £36, while PMC_{250} costs £25. • Although 14-day therapy gives an almost 10% higher eradication rate, the absolute benefit of *H. pylori* therapy is relatively modest in non-ulcer dyspepsia and undiagnosed dyspepsia and the longer duration of therapy does not appear cost-effective. • In patients with peptic ulcer, increasing the course to 14 days

			duration improves the effectiveness of eradication by nearly 10% but does not appear cost-effective.
British Society of Gastroenterology[1] [38]	2002	10, 12	HP+ve duodenal ulcer: One week triple therapy: First Line (no continued Antisecretory required): PPI (standard dose twice daily) or RBC (ranitidine bismuth citrate) plus amoxicillin 500-1000 mg twice daily or metronidazole 400-500 mg twice daily, plus clarithromycin 500 mg twice daily. It is sensible to avoid metronidazole if the patient has had a previous course of treatment with this agent. HP+ve gastric ulcer: Anti *H. pylori* therapy as for duodenal ulcer followed by antisecretory therapy for two months. The reason for this latter recommemdation is the lack of evidence that gastric ulcers heals as quickly as DU after *H. pylori* eradication alone.
Malfertheiner et al.[164] Maastricht 2-2000	2002	173, 174	First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole (for a minimum 7 days). (clarithromycin plus amoxicillin is preferred to clarithromycin plus metronidazole as it may favour best results with second-line PPI quadruple therapy)
Québec CRUM[45] (translated)	2002	12	First-line treatment: triple therapy for seven days. The strongest recommended treatment regimens are a PPI (bid) in combination with amoxicillin and clarithromycin or with metronidazole and clarithromycin.
OPOT[23]	2000	20, 21	All of the first-line regimens appear similar in efficacy: • PPI or RBC plus C & M: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid OR Ranitidine Bismuth Citrate 400 mg bid PLUS Clarithromycin 250 mg bid AND Metronidazole 500 mg bid • PPI or RBC plus C & A: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid OR Ranitidine Bismuth Citrate 400 mg bid PLUS Clarithromycin 500 mg bid AND Amoxicillin 1 g bid • PPI plus A & M: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid PLUS Amoxicillin 1 g bid AND Metronidazole 500 mg bid • H2RA plus B & M & T: Cimetidine 400 mg bid OR Famotidine 20 mg bid OR Nizatidine 150 mg bid OR Ranitidine 150 mg bid PLUS Bismuth subsalicylate 2 tabs qid AND Metronidazole 500 mg tid or 250 mg qid AND Tetracycline 500 mg tid or 250 mg qid • PPI plus B & M & T: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid PLUS BMT (dose as above).
Peterson et al[188] USA	2000	1287, 1288	No therapy is 100% effective for *H. pylori* infection. However, several regimens have been devised that attain cure rates between 80% and 90%. These regimens consist of twice daily triple therapy with a PPI or or ranitidine bismuth citrate along with 2 antimicrobial agents such as clarithromycin and either amoxicillin or metronidazole…… Therefore, we recommed that PPI or ranitidine bismuth citrate-based triple therapy be administrated for 10 -14 days.

Gisbert et al[177] Spanish Consensus (translation)	2000	191	• Omeprazole, lansoprazole or pantoprazole can be used indistinctively along with two antibiotics as part of one week triple therapies. • The combination of a PPI, amoxicillin and a nitroimidazole when used in a 7 day regimen every 12 hours is less efficient than other therapeutic alternatives and should not be advised as the first option. • Ranitidine bismuth citrate in association with two antibiotics (clarithromycin and amoxicillin or a nitroimidazole) can be included in first-line eradication treatments. • The guidelines recommend, for first-line use in Spain, a PPI with amoxicillin and clarithromycin, or ranitidine bismuth citrate with these same antibiotics; in the case of an allergy to penicillin, metronidazole should be substituted for amoxicillin. • A duration of one week with triple therapy with a PPI in combination with clarithromycin and amoxicillin is probably the best option at this time, though this recommendation is based on studies of cost-effectiveness.
SIGN 7[166,167]	Developed in 1996 and updated in 1999	Quick Reference Guide	Eradication rate of over 80% is achieved with triple therapy for seven days: PPI* plus metronidazole 400 mg tid plus amoxicillin 500 mg tid OR PPI* plus clarithromycin 250 mg tid plus amoxicillin 500 mg tid OR PPI* plus clarithromycin 250 mg bid plus metronidazole 400 mg bid (if allergic to amoxicillin). * Suitable doses for PPIs are: Omeprazole 20 mg bid or 40 mg od, lansoprazole 30 mg bid or pantoprazole 40 mg od)
Agence Française de Sécurité Sanitaire des Produits de Santé[178] (translated)	1999	7-11	When and how should anti-ulcer agents be prescribed for duodenal ulcer? 1) In case of Helicobacter pylori infection, eradication therapy is recommended (grade A). There are two phases to the treatment: - the first eradication phase consists of a triple therapy administered orally: • either a double dose of proton pump inhibitor (PPI), combined with 2 antibiotics for 7 days; • or a double dose of ranitidine, combined with 2 antibiotics for 14 days. - the second phase consists of a monotherapy by antisecretory at a standard dose administered orally. The total duration of the treatment (triple therapy and then monotherapy) is 4 weeks. Only three PPIs (lansoprazole, omeprazole and pantoprazole) and ranitidine have a MA for the indication Helicobacter pylori eradication therapy in association with antibiotic therapy. Antisecretories and antibiotics must be administered in two doses per day. The antibiotic regimens combine clarithromycin with amoxicillin or with an imidazole (metronidazole or tinidazole) whether the PPI or anti-H2 option is chosen. The clarithromycin and tetracycline combination may be used with ranitidine. The amoxicillin-imidazole combination is one possible alternative in cases where the previous

			regimens are inapplicable. The suggested dosages are amoxicillin 2 x 1 g/d, imidazole 2 x 0.5 g/d, clarithromycin 2 x 0.5 g/d and tetracycline 2 x 1 g/d. When and how should anti-ulcer agents be prescribed for gastric ulcer? 1) In case of Helicobacter pylori infection: Helicobacter pylori eradication consists of a triple therapy (an antisecretory combined with two antibiotics), as in the case of duodenal ulcer. However, the total duration of treatment (triple therapy and then monotherapy) is longer; it lasts 6 to 8 weeks (grade A)
Deltenre et al[168] Belgian consensus meeting	1998	301	The first choice, recommended for a 7-day course minimum to a 10-day course maximum, is PPI one dose before meal morning and evening, clarithromycin 500 mg and amoxicillin 1000 mg after meal morning and evening.
Howden et al[189] American College of Gastroenterology	1998	2335	The highest eradication rates are achieved with the following regimens: • a PPI, clarithromycin and either amoxicillin or metronidazole for 2 weeks. • Ranitidine bismuth citrate, clarithromycin and either amoxicillin, metronidazole or tetracycline for 2 weeks • a PPI, bismuth, metronidazole and tetracycline for 1 to 2 weeks.
Jovell et al[179] CAHTA	1998	1	The results of this study made it possible to elaborate a clinical practice guideline that recommends as first choice eradicating therapy the 7-day treatment with triple therapy, that is a proton pump inhibitor (standard dose), plus clarithromycin (500 mg/12h) , plus amoxicillin (1000 mg/12h) or metronidazole (500 mg/12h).
Buckley et al[180] Irish *H. pylori* group	1996	8,9	Triple therapy regimen, combining a proton pump inhibitor and two antibiotics, have yielded the highest eradication rates to date. The two triple treatment regimens that this panel recommended for eradication of *H. pylori* are: (a PPI 1 bid + clarithromycin 500 mg bid + amoxicillin 1 g bid) AND (a PPI 1 bid + clarithromycin 250 mg bid+ metronidazole 400 mg bid (or tinidazole 500 mg bid)

P2A: Supporting Evidence

P2A-i: The following triple therapy regimens provide optimal eradication rates: a twice daily course of standard dose PPI, amoxicillin 1 g and clarithromycin 500 mg (PAC regimen) OR a twice daily course of standard dose PPI, metronidazole 500 mg and clarithromycin 250 mg-500 mg (PMC regimen). ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

a) PPI-based triple therapy vs. other *H. pylori* eradication regimens

Summary: Five poor quality meta-analyses[190] evaluated various *H. pylori* eradication regimens consisting of PPIs, H2RAs or bismuth in combination with one or more antibiotics. Although no statistical analyses were provided in any of these studies, PPI triple therapies were shown to produce higher eradication rates than H2RA-triple therapies, bismuth-containing regimens, and PPI dual therapies. The highest eradication rates were obtained by PPI triple therapy regimens containing clarithromycin and either amoxicillin or a nitroimidazole (metronidazole or tinidazole).

Study Type(QA)	Population	Interventions	Outcome measure	Results	Dir

Laheij et al. 1999[191] MA **(poor)**	666 studies (n= 53,228) Hp positive patients	Various Hp eradication regimens containing PPIs or H2RAs (dual, triple and quadruple)	Adjusted Hp eradication rates	Adjusted Hp cure rates were: 78.96% for (PPI+ pen+ nit); 80.09% for (PPI + pen + mac); 82.85% for (PPI + mac + nit); 66.09% to 78.39% for H2RA triple therapy; <70% for dual therapy, p-values not reported	+
Schmid et al. 1999*[192] MA **(poor)**	74 studies (n= 4,769) Patients with GU, DU or NUD and Hp positive	OA: ome, amox OC: ome,clar OAC: ome, amox, clar OAN: ome, amox, nit OCN: ome, clar, nit	Hp eradication rate	Hp eradication rates: OA: 65%, OC: 76%, OAC: 82%, OAN: 83% and OCN: 89%, p-values not reported	+
Unge 1998[193] MA **(poor)**	686 study arms (No. of studies and total n not reported) Patients with Hp infection +/- complications	Various Hp eradication regimens: PPI-dual therapy: PPI & amox or clar H2RA- triple & quadruple therapies PPI-triple therapies: PAC: PPI, amox, clar PNC: PPI, nit, clar PAN: PPI, amox, nit	Hp eradication rate	Overall eradication rates: PPI-dual therapies: 55-65%. PAC regimen: with ome was 83%, with lans or pant was 77%. PNC regimen: with ome was 90%, lans was 80% and pant was 83%. PAN: with ome was 80%, lans was 74% and pant was 77%. H2RA triple: 63%-65%, p-values not reported	+
Unge 1997[194] MA **(poor)**	380 reports (total n not reported) Patients with Hp infection	Various Hp eradication regimens: PPI-triple therapy: PAC: PPI, amox, clar PNC: PPI, nit, clar PPI dual therapy: PPI & amox or nit or clar H2RA triple therapy	Hp eradication rate	Hp eradication rates (95% credibility values (CV) are reported here for triple therapies only): PAC regimen: with ome was 83% (80%, 86%); with lans was 78% (73%, 83%) PNC regimen with ome was 90% (89%,91%); with pant was 87% (82%,92%) PPI dual: with ome was 57%-61% H2RA triple: 60%-70%, p-values not reported	+
Unge & Berstad 1996[190] MA **(poor)**	515 studies (total n not reported) Patients with Hp infection	Various Hp eradication regimens PPI-triple therapy: PAC: PPI, amox, clar PNC: PPI, nit, clar PPI dual therapy: PPI & amox or nit or clar H2RA triple therapy	Hp eradication rate	Hp eradication rates (95% CI): PAC regimen: with lans 82% (67%, 97%); with ome 85% (82%, 89%) PNC regimen: with lans or pant was 82% (72%, 92%); with ome was 87% (83%, 90%); PPI dual with ome was: 54% - 66% H2RA triple: 65% (59% - 71%), p-values not reported	+
amox: amoxicillin; bis: bismuth; clar: clarithromycin; lans: lansoprazole; mac: macrolide; met: metronidazole; nit: nitroimidazole; ome: omeprazole; pant: pantoprazole; pen: penicillin; tet: tetracycline; tini: tinidazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)					
Comments: All six papers were pooled analyses of treatment arms from controlled and uncontrolled studies that studied the regimens of interest. None consisted of direct comparisons between the various regimens.					

P2A-i: The following triple therapy regimens provide optimal eradication rates: a twice daily course of standard dose PPI, amoxicillin 1 g and clarithromycin 500 mg (PAC regimen) OR a twice daily course of standard dose PPI, metronidazole 500 mg and clarithromycin 250 mg-500 mg (PMC regimen). ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

b) Head-to-head comparisons between PAC and PMC regimens

Summary: Results from two poor quality meta-analyses by Moayyedi and Murphy[195] and Gisbert et al.[196] revealed that both PAC and PMC regimens were effective in eradicating *H. pylori* and that there was no statistically significant difference between them. The two regimens produced similar *H. pylori* eradication rates in 11 RCTs, five of good quality[197-201] and five of poor quality,[202-206] although statistical significance was not reported in three trials.[198,199,201]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Moayyedi and Murphy 2001[195] MA **(poor)**	14 RCTs (n=2,532) Patients with Hp infection	PAC: therapeutic doses of PPI, amox, and at least 500 mg clar bid for at least 1wk	PNC: any dose of PPI, nit, and clar for at least 1wk	Hp eradication rate	0.6% improvement in eradication rate with PNC (95% CI: -2.2, 3.4); p=0.68, NS	+
Gisbert et al. 2000[196] MA **(poor)**	22 RCTs (n= 2,862) Patients with Hp infection	PAC: standard dose PPI bid + clar (any dose) bid + amox (any dose) bid for 7 days	PNC: standard dose PPI bid + clar (any dose) bid + nit (any dose) bid for 7 days	Hp eradication rate	Mean Hp eradication efficacy (95% CI) for PAC vs. PNC was: 81% (79%, 83%) vs. 81% (78%, 83%); OR PAC vs. PNC (95% CI) was 1.00 (0.83, 1.22), NS	+
Neville et al. 2001*[197] RCT **(good)**	221 adults with Hp infection	OAC group: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days	OMC group: ome 20 mg bid, clar 250 mg bid, met 400 mg bid for 7 days	Hp eradication at 4 wks	Hp eradication rate (95% CI): OMC vs. OAC was 84% (77%, 91%) vs. 87% (81%, 94%); Difference = 3% in favour of OCM (95% CI: -6%, 13%); p = 0.461, NS	+
Lind et al. 1999*[198] RCT **(good)**	514 adults with history of ≥1 DU & Hp positive	OAC group ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days OMC group ome 20 mg bid, met 400 mg twice daily, clar 250 mg bid for 7	AC group amox 1 g bid, clar 500 mg bid for 7 days MC group met 400 mg bid, clar 250 mg bid for 7 days	Hp eradication at 4 & 8 wks	Hp eradication rate (95%CI): OMC vs. OAC vs. MC vs. AC: 87% (79%, 92%) vs. 94% (88%, 97%) vs. 69% (60%, 77%) vs. 26% (19%, 34%), p<0.001 for AC vs. OAC and MC vs. OMC, p-value not reported for OAC vs. OMC	0

		days				
Malfertheiner et al. 1999*[199] RCT **(good)**	145 adults with GU & Hp positive	OAC group: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days OMC group: ome 20 mg bid, met 400 mg bid, clar 250 mg bid for 7 days	O group: ome 20 mg qd x 7 days	Hp eradication at 4 wks	Hp eradication rate (95% CI): OMC vs. OAC vs. O: 86% (73%, 94%) vs. 79% (65%, 90%) vs. 4% (0%,14%), p<0.001 for OMC and OAC vs. O, p-value not reported for OMC vs. OAC	0
Veldhuzen Van Zanten et al. 1999*[200] RCT **(good)**	146 adults with DU & Hp positive	OAC group: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days, then ome 20 mg qd for 3 weeks OMC group: ome 20 mg bid, met 400 mg bid, clar 250 mg bid for 7 days, then ome 20 mg qd for 3 weeks	O group: ome 20 mg qd for 4 weeks	Hp eradication at 4 wks	Hp eradication rate (95% CI): OMC vs. OAC vs. O: 85% (72%, 94%) vs. 78% (64%, 88%) vs. 0% (0%,7%), p<0.001 for OMC vs, O and OAC vs. O, p>0.05 (NS) for OMC vs. OAC	+
Lind et al. 1996*[201] RCT **(good)**	787 adults with DU & Hp positive	OAC_{250} group: ome 20 mg, amox 1 g, clar 250 mg, all bid for 7 days OAC_{500} group: ome 20 mg, amox 1 g, clar 500 mg, all bid for 7 days OMC_{250} group: ome 20 mg, met 400 mg, clar 250 mg, all bid for 7 days OMC_{500} group: ome	O: ome 20 mg bid for 7 days	Hp eradication at 4 wks	Hp eradication rate (95% CI): OMC_{250} vs. OMC_{500} vs. OAC_{250} vs. OAC_{500} vs. OAM vs. O: 89.7% (84.3%, 95.2%) vs. 85.5% (79.3%, 91.7%) vs. 79.5% (72.2%, 86.8%) vs. 90.6% (85.3%, 95.9%) vs. 75.8% (68.3%, 83.3%) vs. 0.8% (0.0%, 2.5%), p-values not reported	0

		20 mg, met 400 mg, clar 500 mg, all bid for 7 days OAM group: ome 20 mg, amox 1 g, met 400 mg, all bid for 7 days				
Bazzoli et al. 2002*[202] RCT **(poor)**	134 adults with NUD & Hp positive	LAC: lans 30 mg qd, clar 500 mg bid, amox 1g bid for 7 days	LMC: lans 30 mg qd, clar 250 mg bid, met 500 mg bid for 7 days	Hp eradication at 4 to 12 wks	Hp eradication rate (95% CI): LMC vs. LAC was: 92.4% (84.8%, 98.9%) vs. 83.1% (73.9%, 92.3%); Difference = 9.35% (-1.78%, 20.5%), NS	+
Laurent et al. 2001*[203] RCT **(poor)**	323 adults with dyspeptic symptoms & Hp positive	OAC: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days	OMC: ome 20 mg bid, met 500 mg bid, clar 250 mg bid for 7 days	Hp eradication at 4 to 6 wks	Hp eradication rate (95% CI): OMC vs. OAC was: 61.4% (50.0%, 72.8%) vs. 71.8% (61.8%, 81.8%), NS	+
Fock et al. 2000*[204] RCT **(poor)**	241 adults with ≥1 DU ≥ 5 mm & Hp positive	OAC group: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days OAM group: ome 20 mg bid, amox 1 g bid, met 400 mg bid for 7 days	OMC group: ome 20 mg bid, met 400 mg bid, clar 500 mg bid for 7 days	Hp eradication at 4 wks	Hp eradication rate (95% CI): OMC vs. OAC vs. OAM was: 85.0% (77%, 93%) vs. 86.7% (80%, 94%) vs. 79.5% (70%, 89%); p=0.419 (X^2 for trend), NS difference btween groups	+
Frevel et al. 2000*[205] RCT **(poor)**	331 adults with active DU 1 or 2 DUs (5-20 mm) & Hp positive	PAC group: pant 40 mg bid, amox 1 g bid, clar 500 mg bid for 7 days, then pant 40 mg / day for 7 days	PMC group: pant 40 mg bid, met 500 mg bid, clar 500 mg bid for 7 days, then pant 40 mg / day for 7 days	Hp eradication at 4 wks	Hp eradication rate (95% CI): PMC vs. PAC was: 90% (84%, 94%) vs. 90% (84%, 94%); OR = 0.98 (95% CI: 0.52, 1.84), NS	+
Misiewicz et al. 1997*[206] RCT **(poor)**	508 adults with DU or gastritis, or both, who were Hp positive	LMC : lans 30 mg bid, met 400 mg bid, clar 250 mg bid for 7 days OAM : ome	LAC : lans 30 mg bid, amox 1 g bid, clar 250 mg bid for 7 days LAM : lans 30 mg bid,	Hp eradication at 4 wks	Eradication rate (95% CI): LAC vs. LAM vs. LMC vs. OAM was: 86% (82.3%, 94.3%) vs. 66.4% (63.5%, 80.1%) vs. 87.5% (83.0%, 94.8%) vs. 74.6%	+

		20 mg bid, amox 1 g bid, met 400 mg bid for 7 days	amox 1 g bid, met 400 mg bid for 7 days		(73.2%, 88.1%); p < 0.001 for LMC and LAC vs. LAM	

amox: amoxicillin; clar: clarithromycin; lans: lansoprazole; met: metronidazole; nit: nitroimidazole; ome: omeprazole; tini: tinidazole; NS: not statistically significant; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

P2A-i: The following triple therapy regimens provide optimal eradication rates: a twice daily course of standard dose PPI, amoxicillin 1 g and clarithromycin 500 mg (PAC regimen) OR a twice daily course of standard dose PPI, metronidazole 500 mg and clarithromycin 250 mg-500 mg (PMC regimen). ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

c) Head-to-head comparisons between PPI-triple therapy containing clarithromycin and either amoxicillin or metronidazole (PAC/PMC) vs. PPI-triple therapy containing amoxicillin and metronidazole (PAM)

Summary: Five RCTs,[204,206-209] only one of which was of good quality,[207] demonstrated that PPI, amoxicillin and metronidazole (PAM) provide a lower *H. pylori* eradication rate than regimens containing clarithromycin (either PAC or PMC), although the difference was not statistically significant in all studies.[204,209]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Katelaris et al. 2000*[207] RCT **(good)**	220 adults with active DU (≥5mm) & Hp positive	OAM group: ome 40 mg am, amox 500 mg tid, met 400 mg tid for 7 days, then ome 20 mg qd for 7 days	OMC group: ome 20 mg bid, met 400 mg bid, clar 250 mg bid for 7 days, then ome 20 mg qd for 7 days	Hp eradication at 4 wks	Hp eradication rate (95% CI): OMC vs. OAM: 82% (74%,89%) vs. 58% (49%, 67%); Difference= 24%, p=0.0001	+
Gisbert et al. 1998[208] RCT **(poor)**	88 adults with active DU > 0.5 cm, & Hp positive	OAM group: ome 20 mg bid, amox 1 g bid, met 500 mg bid for 7 days	OMC group: ome 20 mg bid, met 500 mg bid, clar 500 mg bid for 7 days	Hp eradication at 4 wks	Hp eradication rate (95%CI): OMC vs. OAM: 90.5% (78%, 95%) vs. 57% (42%, 71%); p<0.001	+
Misiewicz et al. 1997*[206] RCT **(poor)**	508 adults with DU or gastritis, or both, who were Hp positive	LMC group: lans 30 mg bid, met 400 mg bid, clar 250 mg bid for 7 days OAM : ome 20 mg bid, amox 1 g bid, met 400 mg bid for 7 days	LAC group: lans 30 mg bid, amox 1 g bid, clar 250 mg bid for 7 days LAM : lans 30 mg bid, amox 1 g bid, met 400 mg bid for 7 days	Hp eradication at 4 wks	Eradication rate (95% CI): LAC vs. LAM vs. LMC vs. OAM: 86% (82.3%, 94.3%) vs. 66.4% (63.5%, 80.1%) vs. 87.5% (83.0%, 94.8%) vs. 74.6% (73.2%, 88.1%); p < 0.001 for LMC and LAC vs. LAM	+
Fock et al. 2000*[204]	241 adults with 1 or	OAC group: ome 20 mg bid,	OMC group: ome 20 mg	Hp eradication	Hp eradication rate (95% CI):	-

RCT **(poor)**	more DU ≥ 5 mm & Hp positive	amox 1 g bid, clar 500 mg bid for 7 days OAM group: ome 20 mg bid, amox 1 g bid, met 400 mg bid for 7 days	bid, met 400 mg bid, clar 500 mg bid for 7 days	at 4 wks	OMC vs. OAC vs. OAM: 85.0% (77%, 93%) vs. 86.7% (80%, 94%) vs. 79.5% (70%, 89%); p=0.419 (X^2 for trend), no significant difference b/w groups	
Sito et al. 1996[209] RCT **(poor)**	90 adults with DU 5-20mm & Hp positive	OTC group: ome 20 mg bid, tini 500 mg bid, and clar 250 mg bid for 7 days	LAM group: lans 15 mg bid, amox 750 mg bid, met 500 mg bid for 7 days	Hp eradication at 4 wks	Eradication rate: OTC vs. LAM: 91% vs. 87%; p>0.05, NS	-
amox: amoxicillin; clar: clarithromycin; lans: lansoprazole; met: metronidazole; ome: omeprazole; tini: tinidazole; NS: not statistically significant; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P2A-ii: Supporting Evidence

P2A-ii. Various PPIs have similar efficacy when used in triple therapy. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: A poor quality meta-analysis by Moayyedi and Murphy[195] showed that there was no significant difference between omeprazole and lansoprazole in PPI-based triple therapy of seven days or more. However, in a good quality RCT by Spinzi et al.,[210] lansoprazole was found to be somewhat more effective than omeprazole in the PAC regimen, although the difference was of only marginal statistical significance. Three good quality RCTs by Hawkey et al.,[211] Wong et al.[212], Tulassay et al.[181] compared omeprazole with rabeprazole, esomeprazole and pantoprazole in 7-day PPI-based triple therapy regimens. There were no significant differences in Hp eradication rates between omeprazole and other PPIs in these studies.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Moayyedi and Murphy 2001[195] MA **(poor)**	10 RCTs (n=1,348) Patients with Hp infection (ulcer status not provided)	PPI-triple therapy with ome	PPI-triple therapy with lans	Hp eradication rate	2% difference in eradication rate in favour of ome; p=0.35, NS	+
Hawkey et al. 2003*[211] RCT **(good)**	348 adults with PUD & Hp positive	RAC (rab 40 mg/d + amox 2 g/d + clar 1 g/d) RMC (rab 40 mg/d + met 800 mg/d + clar 1 g/d) for 7 days	OAC: (ome 40 mg/d + amox 2 g/d + clar 1 g/d) for 7 days OMC: (ome 40 mg/d + met 800 mg + clar 1 g/d) for 7 days	Hp eradication rate at 4 wks	Hp eradication rate: RAC + RMC pooled rate: 77% vs. OAC + OMC pooled rate: 75%; difference (95% CI) = 1.5% (-7.4%, 10.4%), NS	+
Tulassay et al. 2001*[181] RCT **(good)**	433 adults with DU & Hp positive	EAC group: esome 20 mg, amox 1 g and clar 500 mg, all bid for 7	OAC group: ome 20 mg, amox 1 g, clar 500 mg, all bid for 7 days,	Hp eradication at 4 to 6 wks	Hp eradication rate and (95% CI): EAC vs. OAC was: 86% (81%, 90%) vs. 88% (83%, 92%); p>0.05, NS	+

		days	then ome 20 mg qd for 3 wks			
Wong et al 2001*[212] RCT **(good)**	173 adults with Hp infection & no active bleeding	RAC7: rab 10 mg, amox 1 g, clar 500 mg, each bid for 7 days RAC3: rab 20 mg, amox 1 g, clar 500 mg, each bid for 3 days	7-day OAC: ome 20 mg, amox 1 g, clar 500 mg, each bid for 7 days	Hp eradication at 6 wks	Hp eradication rate and (95% CI): RAC7 vs. RAC3 vs. OAC was: 88% (77%, 95%) vs. 72% (59%, 83%) vs. 82% (70%, 91%), NS difference b/w groups	+
Spinzi et al. 1998[210] RCT **(good)**	356 adults with DU or GU & Hp positive	LAC group: lans 30 mg bid, amox 1 g bid, clar 500 mg bid for 7 days	OAC group: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days	Hp eradication at ≥ 6 wks	Hp eradication rate and (95% CI): LAC vs. OAC was: 72% (65%, 78%) vs. 62% (54%, 69%), p=0.043	-
amox: amoxicillin; clar: clarithromycin; esome: esomeprazole; lans: lansoprazole; met: metronidazole; ome: omeprazole; rab: rabeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P2A-iii: Supporting Evidence

P2A-iii. PPI dose in triple therapy regimens: Optimal eradication rates are achieved with double-dose (standard dose administered twice daily) PPIs in triple-therapy regimens. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: A good quality meta-analysis by Vallve et al.[213] showed that the *H. pylori* eradication rate was significantly higher with double dose PPI than single dose in the PAC regimen, but not in the PMC regimen containing 250 mg bid clarithromycin and 500 mg bid metronidazole. However, the meta-analysis for the latter consisted of only 2 studies with a total of 304 patients. One poor quality RCT by Miwa et al.[214] showed that there was no difference in eradication rates between rabeprazole 20 mg bid and 10 mg bid in the PAC regimen.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Vallve et al. 2002[213] MA **(good)**	11 RCTs (n=2,391) Patients with Hp infection (ulcer status not provided)	Double doses of PPI (ome, lans, pant or rab), clar (any dose) bid, and either amox or met (any doses) bid for any duration	Single doses of PPI (ome, lans, pant or rab), clar (any dose) bid, and either amox or met (any doses) bid for any duration	Hp eradication rate	Overall Hp eradication rate and (95% CI): double dose PPI vs. single dose: 83.9% (81%, 85%) vs. 77.7% (72%, 77%). Odds ratio was 1.51 (95% CI: 1.23, 1.85); p<0.01 Hp eradication rate (95% CI) in PMC (PPI, clar 250 mg bid, met 500 mg bid): double dose PPI vs. single dose: 74.8% (67%, 81%) vs. 74.5% (67%, 81%). Odds ratio was 1.01 (95% CI: 0.60, 1.69); p>0.05, NS.	+ -
Miwa et al.	308 adults with	RAC group: rab	R1/2AC group:	Hp	Hp eradication rate (95%	-

1999[214] RCT **(poor)**	PUD or NUD & Hp positive	20 mg bid, amox 500 mg tid, clar 200 mg bid for 7 days	rab 10 mg bid, amox 500 mg tid, clar 200 mg bid for 7 days LAC group: lans 30 mg bid, amox 500 mg tid, clar 200 mg bid for 7 days	eradication rate at 4 to 8wks	CI): LAC vs. RAC vs. R1/2AC: 82.7% (74%, 89%) vs. 85.6% (77%, 92%) vs. 87.0% (79%, 93%), NS difference b/w groups	
amox: amoxicillin; clar: clarithromycin; lans: lansoprazole; met: metronidazole; ome: omeprazole; pant: pantoprazole.						

P2A-iv: Supporting Evidence

P2A-iv. PPI-triple therapy duration: 7-14 days. Factors other than eradication rates, such as cost, may be taken into account when choosing between 7 and 14 days duration.

Summary: A poor quality meta-analysis by Calvet et al.[215] showed that the *H. pylori* eradication rate was significantly higher with a 14-day PPI triple therapy as compared to 7 days. However, there were no significant differences in eradication rates between 7 and 10-day, or 10 and 14-day regimens. Seven RCTs,[216] only one of which was of good quality,[217] reported that the eradication rate was slightly higher with 14-day PPI triple therapy versus 7-day, but the results were not significant in any trial. Two RCTs, one of very good quality[218] and the other of poor quality[219] compared PPI triple therapy of 7-day and 10-day duration. Both reported that there was no significant difference between the two durations. A third RCT,[220] of good quality, found no significant difference between 10 and 14-day therapy.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Calvet et al. 2000[215] MA **(poor)**	13 RCTs (n=906) Patients with Hp infection	PPI, clar, and either amox or met for 10 to 14 days (doses not specified)	PPI, clar, and either amox or met for 7 days (doses not specified)	Hp eradication rate	Hp eradication rate and (95%CI): 14 days vs. 7 days was: 81% (77%, 85%) vs. 72% (68%, 76%). Overall OR and (95% CI) = 0.62 (0.45, 0.84) Hp eradication rate and (95% CI): 10 days vs. 14 days: 82% (77%, 86%) vs. 84% (79%, 89%); p>0.05, NS Hp eradication rate and (95% CI): 7 days vs. 10 days was: 80% (71%, 86%) vs. 83% (75%, 89%); p>0.05, NS NNT for 10-14 days as compared to 7 days to obtain one extra cure = 6 to 23	+ + + +
Vakil et al. 2004*[218]	803 adults with GI symptoms &	RAC-7: rab 20 mg bid ,amox	RAC-10: rab 20 mg bid,	Hp eradication	Hp eradication rate and (95%CI): RAC-7 vs.	+

RCT **(very good)**	Hp positive	1 g bid, clar 500 mg bid for 7 days	amox 1 g bid, clar 500 mg bid for 10 days OAC ome 20 mg bid, amox 1 g, clar 500 mg bid for 10 days	rate at 8 wks	RAC-10: 77% (71%, 83%) vs. 78% (72%, 84%); p>0.05, NS	
Dammann et al. 2000*[217] RCT **(good)**	244 adults with active DU (≤ 2 ulcers) & Hp positive	PCM-14: pant 40 mg bid, clar 500 mg bid, met 500 mg bid for 10 days, then pant 40 mg bid and clar 500 mg bid for 4 days	PCM-7: pant 40 mg bid, clar 500 mg bid, met 500 mg bid for 7 days	Hp eradication rate at 6 wks	Hp eradication rate and (95% CI): PCM-7 vs. PCM-14 was: 73.6% (64.8%, 81.2%) vs. 74.8% (66.2%, 82.2%); p > 0.05, NS	+
Fennerty et al. 1998*[220] RCT **(good)**	284 adults with active DU or history of DU in the past yr & Hp positive	LAC: lans 30 mg bid, amox 1 g bid, clar 500 mg bid for 10 days	LAC for 14 days	Hp eradication rate at 4 to 6 wks	Hp eradication rate and (95% CI):10 days vs. 14 days: 81% (73.9%, 87.6%) vs. 82% (73.9%, 88.1%); p>0.05, NS	+
Maconi et al. 2001[221] RCT **(poor)**	142 adults with PUD or NUD & Hp positive	LAC: lans 30 mg bid, amox 1 g bid, clar 500 mg bid for 14 days	LAC: lans 30 mg bid, amox 1 g bid, clar 500 mg bid for 7 days	Hp eradication rate at 4 to 12 wks	Hp eradication rate: 7 days vs. 14 days was: 74.6% vs. 85.9%; OR=0.51(95% CI, 0.21-1.22); p=0.09, NS	+
Kiyota et al. 1999[222] RCT **(poor)**	147 adults with PUD & Hp positive	OAC: ome 20 mg bid, amox 1 g bid, clar 400 mg bid for 14 days, then ran 300 mg daily for 4 weeks	OAC: ome 20 mg bid, amox 1 g bid, clar 400 mg bid for 7 days, then ran 300 mg daily for 4 weeks	Hp eradication rate at 4 wks	Hp eradication rate and (95% CI): 7 days vs. 14 days was: 78.2% (69%-87%) vs. 88.4% (81%-96%); p>0.05, NS	+
Ching et al. 1998[219] RCT **(poor)**	186 adults with PUD or NUD & Hp positive	OAC: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 10 days	OAC: ome 20 mg bid, amox 1 g bid, clar 500 mg bid for 7 days	Hp eradication rate at 5 wks	Hp eradication rate and (95% CI): 7 days vs. 10 days was 94.6% vs.94.6%; p>0.05, NS	+
Dal Bo et al. 1998[223] RCT **(poor)**	129 dyspeptic adults with Hp positive gastritis	OMC: ome 20 mg bid, met 250 mg qid, clar 250 mg bid for 14 days.	OMC: ome 20 mg bid, met 250 mg qid, clar 250 mg bid for 7 days.	Hp eradication rate at 4 wks	Hp eradication rate: 7 days vs. 14 days was: 68.1% vs. 75.7%; p>0.05, NS	+
Louw et al. 1998*[224] RCT **(poor)**	134 adults with NUD & Hp positive	LAC: lans 30 mg qd, amox 1g bid, clar 500 mg bid for 14 days	LAC: lans 30 mg qd, amox 1g bid, clar 500 mg bid for 7 days	Hp eradication rate at 4 wks	Hp eradication rate and (95% CI): 7 day vs. 14 days was: 93% (73%, 98%) vs. 93% (78%, 99%); p>0.05, NS	+
Laine et al. 1996*[216]	150 adults with Hp infection	OAC: ome 20 mg bid, amox	OAC: ome 20 mg bid, amox	Hp eradication	Hp eradication rate and (95% CI): 7 days vs. 10	+

RCT **(poor)**		1 g bid, and clar 500 mg bid) for 10 or 14 days	1 g bid, and clar 500 mg bid) for 7 days	rate at 4 wks	days vs. 14 days was: 86% (73%, 94%) vs. 90% (78%, 97%) vs. 92% (81%, 98%); p>0.20 by X^2 test for trend, NS	
Moayyedi et al. 1996*[225] RCT **(poor)**	70 adults with Hp infection	LAC: lans 30 mg bid, amox 1 g bid, and clar 500 mg bid for 14 days	LAC: lans 30 mg bid, amox 1 g bid, and clar 500 mg bid for 7 days	Hp eradication rate at 4 to 6 wks	Hp eradication rate and (95% CI): 7 days vs. 14 days was: 86% (71%, 96%) vs. 91% (76%, 98%); p=1.0, fisher extract test, NS	+
amox: amoxicillin; clar: clarithromycin; lans: lansoprazole; met: metronidazole; ome: omeprazole; pant: pantoprazole; rab: rabeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question P2: What is the optimal use of PPIs in *H. pylori* eradication regimens?

P2B: Guideline Statements

Synopsis of Existing Recommendations P2B: A combination of standard dose PPI twice daily, 262 mg bismuth subsalicylate four times daily, 375-500 mg metronidazole four times daily and 500 mg tetracycline four times daily (PBMT quadruple therapy), given for 7-14 days can be considered for first-line eradication therapy.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Hunt et al[226] Canadian *H. pylori* consensus conference	2004	549	A quadruple combination of a PPI, bismuth, tetracycline and metronidazole for 10 to 14 days can be considered first-line therapy for the eradication of *H. pylori*. The quadruple therapy recommended for consideration as first-line therapy by the consensus panel was standard dose of PPI twice daily, 375 mg or 500 mg of metronidazole four times daily, 375 mg or 500 mg of tetracycline four times daily, and 262 mg of bismuth subsalicylate (two tablets of Pepto-bismol, Procter & Gamble, USA) four times per day.
OPOT[23]	2000	20, 21	All of the first-line regimens appear similar in efficacy: • PPI or RBC plus C & M: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid OR Ranitidine Bismuth Citrate 400 mg bid PLUS Clarithromycin 250 mg bid AND Metronidazole 500 mg bid • PPI or RBC plus C & A: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid OR Ranitidine Bismuth Citrate 400 mg bid PLUS Clarithromycin 500 mg bid AND Amoxicillin 1 g bid • PPI plus A & M: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid PLUS Amoxicillin 1 g bid AND Metronidazole 500 mg bid • H2RA plus B & M & T: Cimetidine 400 mg bid OR Famotidine 20 mg bid OR Nizatidine 150 mg bid OR Ranitidine 150 mg bid PLUS Bismuth subsalicylate 2 tabs qid AND Metronidazole 500 mg tid or 250 mg qid AND

			Tetracycline 500 mg tid or 250 mg qid • PPI plus B & M & T: Lansoprazole 30 mg bid OR Omeprazole 20 mg bid OR Pantoprazole 40 mg bid PLUS BMT
Howden et al[189] American College of Gastroenterology	1998	2335	The highest eradication rates are achieved with the following regimens: • a PPI, clarithromycin and either amoxicillin or metronidazole for 2 weeks. • Ranitidine bismuth citrate, clarithromycin and either amoxicillin, metronidazole or tetracycline for 2 weeks • a PPI, bismuth, metronidazole and tetracycline for 1 to 2 weeks.

P2B: Supporting Evidence

P2B: A combination of standard dose PPI twice daily, 262 mg bismuth subsalicylate four times daily, 375-500 mg metronidazole four times daily and 500 mg tetracycline four times daily (PBMT quadruple therapy), given for 7-14 days can be considered for first-line eradication therapy.

Summary A good quality meta-analysis by Gené et al.[227] showed that PPI triple (with the PAC regimen) and quadruple therapies had similar *H. pylori* eradication rates. A poor quality meta-regression by Fischbach et al.[228] showed that both triple and quadruple therapies are more effective than double therapy.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Gené et al. 2003[227] MA **(good)**	4 RCTs (n= 981) Patients with Hp infection	Triple regimens: PAC regimen (PPI + amox + clar) with either ome or pant (doses and duration not specified)	Quadruple regimens: PBMT (PPI + bis + met + tet) regimen with either ome or pant (doses and duration not specified)	Hp eradication rate	Hp eradication rate (95% CI) PBMT vs. PAC was: 81% (77%, 84%) vs. 78% (74%, 81%). Odds ratio was 0.83 (0.61, 1.14); p=0.3, NS	+
Fischbach et al. 2002[228] MR **(poor)**	Not reported	Nit-based therapies: dual, triple, and quadruple therapy with and without PPI Non-nit-based therapies: dual and triple therapy with and without PPI	NA	Hp eradication rates	Overall, triple and quadruple therapies are more effective than double therapy; longer treatment was more successful than shorter treatment duration.	+
Calvet et al. 2000[215] MA **(poor)**	13 RCTs (n=906) Patients with Hp infection	PPI, clar, and either amox or met for 7 days (doses not specified)	PPI, clar, and either amox or met for 10 to 14 days (doses not specified)	Hp eradication rate	Hp eradication rate (95% CI): 14 days vs. 7 days: 81% (77%, 85%) vs. 72% (68%, 76%). Overall OR (95% CI) = 0.62 (0.45, 0.84) Hp eradication rate (95% CI): 10 days vs. 14 days: 82% (77%, 86%) vs. 84% (79%, 89%), p>0.05, NS	0 0

					Hp eradication rate (95% CI): 7-days vs. 10 days: 80% (71%, 86%) vs. 83% (75%, 89%), p>0.05, NS	0
amox: amoxicillin; bis: bismuth; clar: clarithromycin; met: metronidazole; nit: nitroimidazole; ome: omeprazole; pant: pantoprazole; tet: tetracycline; MR: meta-regression; NS: not statistically significant; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						
Comments: None of the studies cited in the guidline addressed the optimal duration of PBMT quadruple therapy (7 or 14 days). A poor quality meta-analysis by Calvet et al.[215], which was cited by one of the guidelines, only compared various durations in triple therapy regimens.						

Question P2: What is the optimal use of PPIs in *H. pylori* eradication regimens?

P2C: Guideline Statements

Synopsis of Existing Recommendations P2C: Patients who remain *H. pylori* positive after an initial attempt at eradication with a first-line regimen can be treated with a 7-14 day course of PPI quadruple therapy (PBMT), or an alternative PPI-triple therapy with different antibiotics from the initial attempt. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Hunt et al[162] Canadian *H. pylori* consensus conference	1999	216	Treatment failure in patients who received metronidazole in the first course: • A twice daily, seven- to 14-day regimen of PPI or RBC, amoxicillin 1000 mg and clarithromycin 500 mg; or • A 14-day course of PPI plus BMT Treatment failure in patients who received amoxicillin in the first course: • PPI or RBC, metronidazole 500 mg and clarithromycin 500 mg; or • A 14-day course of PPI plus BMT
Prodigy[163]	2005	12	Second-line eradication therapy: if first-line eradication therapy fails, PRODIGY recommends that one of the following one-week eradication regimens is used. • Quadruple therapy (a PPI twice a day, bismuth 120 mg four times a day, metronidazole 400 mg three times a day, and oxytetracycline 500 mg four times a day) • If quadruple therapy is not tolerated, consider using a triple-therapy regimen that contains antibiotics that have not been used before. Second-line eradication therapy should use different antibiotics to first-line therapy. The HPA Helicobacter Working Group recommends that two antibiotics are chosen from the following options: amoxicillin, clarithromycin, metronidazole, or oxytetracycline. Other antibiotics can be considered, but advice should be sought from the Helicobacter Reference Laboratory.

NZGG[29]	2004	45	For initial treatment failure, use either of the following for 1 week: • an alternative triple therapy regimen (PPI plus two of the following: clarithromycin, amoxicillin, metronidazole, tinidazole, tetracycline and bismuth), OR • quadruple therapy (standard triple therapy plus bismuth). Repeated treatment failure: • review compliance factors and consider testing for bacterial resistance • consider re-treatment for 2 weeks
NICE[24]	2004	149, 157	For patients requiring a second course of eradication therapy, a regimen should be chosen that does not include antibiotics given previously. There are inadequate data on the optimum second line therapy but quadruple therapy such as a PPI, once daily DeNol 120mg qds, tetracycline 500 mg qid and metronidazole 400 mg tid for one week is sometimes recommended.
Québec CRUM[45] (translated)	2002	12	Persistent or recurring infection: Triple therapy or quadruple therapy for 14 days. The strongest recommended treatment regimens are a PPI in association with two different antibiotics from those of the first triple therapy attempt or a PPI (bid) in association with bismuth, metronidazole and tetracycline.
British Society of Gastroenterology[138]	2002	10	Quadruple therapy: second line: PPI (standard dose twice daily), plus bismuth subcitrate 120 mg qid, plus metronidazole 400-500 mg tid and tetracycline 500 mg qid.
Malfertheiner et al.[164] Maastricht 2-2000	2002	173	• Subsequent second-line therapy should use quadruple therapy: with a proton pump inbibitor, bismuth, metronidazole and tetracycline (for a minimum 7 days). • Where bismuth is not available, second-line therapy should be with proton pump inhibitor triple therapy.
OPOT[23]	2000	21	Recurrences: For *H. pylori* positive ulcer recurrences, an alternate regimen that does NOT include the same two antimicrobial agents should be selected and treatment should be extended to 14 days.
Peterson et al[188] USA	2000	1289	The choice of an alternative treatment should be based on the initial treatment regimen.
Gisbert et al[177] Spanish Consensus (translation)	2000	192	When treatment with a PPI, clarithromycin and amoxicillin has failed, a "rescue" therapy of 7 days with a PPI, bismuth, tetracycline and metronidazole is recommended. It is probable that ranitidine bismuth citrate in combination with said antibiotics represents a valid alternative "rescue" therapy in the future.
Agence Française de Sécurité Sanitaire des Produits de Santé[178] (translated)	1999	27	Should eradication fail, three approaches may be discussed: • either a second probabilistic course of eradication using the same treatment regimen; • or a second course adapted to the data from the antibiogram on the strain of *Helicobacter pylori* responsible; • or long-course treatment by antisecretory at half dose

Deltenre et al[168] Belgian consensus meeting	1998	301	The second choices, recommended in case of allergy or known intolerance to first choice compounds are : 1) PPI bid, colloidal bismuth subcitrate qid, tetracycline 500 mg bid or amoxicillin 1000 mg bid, metronidazole 500 mg tid, for 7 days; or 2) PPI bid, clarithromycin 500 mg bid, metronidazole 500 bid, for 7-10 days (if primary imidazole-resistance is below 20% in the local community)
Buckley et al[180] Irish *H. pylori* group	1996	9	The second line treatment should be guided by the antimicrobial sensitivity of the organism. If the antimicrobial sensitivity is not available, an effective regimen that consists of different antibiotic(s) should be used as a second-line treatment.

P2C: Supporting Evidence

P2C: Patients who remain *H. pylori* positive after an initial attempt at eradication with a first-line regimen can be treated with a 7-14 day course of PPI quadruple therapy (PBMT), or an alternative PPI-triple therapy with different antibiotics from the initial attempt. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: Laheij et al.[191] and Unge[193], two poor quality meta-analyses, reported that PPI-quadruple therapy consisting of bismuth, a nitroimidazole derivative and tetracycline provided a high eradication rate similar to that of PPI triple therapy. The only studies conducted in patients failing initial eradication therapy were three case series. They showed that PPI quadruple therapy for seven days is effective in treating patients who failed initial *H. pylori* eradication therapy. Eradication rates of between 83% and 93% were observed.

Study	Population	Intervention	Comparator	Outcome measure	Results	Dir
Laheij et al. 1999[191] MA **(poor)**	666 studies (n= 53,228) Patients with Hp infection	Various Hp eradication regimens (dual, triple and quadruple therapies)		Adjusted Hp cured rate	Adjusted Hp cure rate was: PPI-triple therapy: (PPI+ pen+ nit): 78.96%; (PPI + pen + mac): 80.09%; (PPI + mac + nit): 82.85% PPI-quadruple therapy: (PPI+bis+nit+tet): 81.73% p-values not reported	+
Unge 1998[193] MA **(poor)**	Not reported (686 study arms) Patients with Hp infection	Various Hp eradication regimens; PPI-dual therapy: PPI & amox or clar H2RA- triple & quadruple therapies PPI-triple therapies: PAC: PPI, amox, clar PNC: PPI, nit, clar		Hp eradication rate	Overall eradication rate: PAC regimen: with ome was 83%, with lans or pant was 77%. PPI given once or twice did not change the efficacy, duration >7 days gave small increase in efficiency and higher dose of clar 1 g daily was more effective. PNC regimen: with ome was 90%, lans was 80% and pant was 83%. PAN: with ome was 80%, lans was 74% and pant was 77%. Increasing PPI dose from once to twice or	+

		PAN: PPI, amox, nit			increasing duration to > 7 days did not increase the efficacy. Lower clar dose, 500 mg daily, was more effective than higher dose PPI quadruple: PBMT (ome, bis, nit, tet): 81%; PBNA (ome, bis, nit, amox): 70% p-values not reported	
Lin et al. 2002[229] Case Series **(NA)**	78 patients who failed Hp therapy	LBCA quadruple therapy: lans 30 mg bid, bis 120 mg qid, clar 500 mg bid, amox 1 g bid for 7 days	No Comparator	Hp eradication rate at 7wks	Hp eradication rate (95% CI): 83% (75%, 91%)	+
Borda et al. 1998[230] Case Series **(Abs)**	30 patients who failed Hp therapy	OBMT quadruple therapy: ome 20 mg bid, bis 120 mg qid, met 500 mg tid, tet 500 mg tid for 7 days	No Comparator	Hp eradication rate	Hp eradication rate: 87.1%	+
Huelin Bénitez et al. 1997[231] Case Series **(Abs)**	30 patients who failed Hp therapy	OBMT quadruple therapy: ome 20 mg bid, bis 120 mg qid, met 500 mg qid, tet 500 mg qid for 7days	No Comparator	Hp eradication rate	Hp eradication rate: 93%	+
bis: bismuth; mac : macrolide; met: metronidazole; nit: nitroimidazole; ome: omeprazole; pen : penicillin; pant: pantoprazole; tet: tetracycline, clar : clarithromycin.						
Comments: No systematic reviews, meta-analyses or RCTs addressing the best treatment following the failure of initial eradication therapy were cited in the guidelines.						

Question P2: What is the optimal use of PPIs in *H. pylori* eradication regimens?

P2D: Guideline Statements

Synopsis of Existing Recommendations P2D: For children in whom *H. pylori* eradication is indicated, a PPI-triple therapy can be used as in adults with appropriate dose adjustment, for a duration of 7-14 days.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Jones et al[232] Canadian Helicobacter Study Group consensus conference	2005	405	• First-line therapy for *H. pylori* infection is a twice daily, triple-drug regimen comprised of a PPI plus two antibiotics (clarithromycin plus amoxicillin or metronidazole) • Optimal treatment duration is 14 days
Gold et al[165]	2000	495 & Table 3	It is recommended that initial treatment consist of three medications, administered twice daily for 1 or 2 weeks. Three first-line therapy options are recommended for use in children and adolescents: • Amoxicillin 50 mg/kg/day up to 1 g bid, clarithromycin 15 mg/kg/day up to 500 mg bid, proton pump inhibitor (omeprazole 1 mg/kg/day up to 20 mg bid or comparable acid inhibitor doses of another PPI.) • Amoxicillin 50 mg/kg/day up to 1 g bid, metronidazole 20 mg/kg/day

			up to 500 mg bid, proton pump inhibitor (omeprazole 1mg/kg/day up to 20 mg bid or comparable acid inhibitor doses of another PPI.) • Clarithromycin 15 mg/kg/day up to 500 mg bid, metronidazole 20 mg/kg/day up to 500 mg bid, proton pump inhibitor (omeprazole 1 mg/kg/day up to 20 mg bid or comparable acid inhibitor doses of another PPI
Sherman et al[233] Canadian Helicobacter Study Group consensus conference	1999	557	The first-line treatment for H. pylpri infection is a twice-daily, triple-drug regimen comprising a proton pump inhibitors (PPI) plus two antibiotics. In combination with a PPI, the acceptable antibiotic combinations are clarithromycin plus amoxicillin or clarithromycin plus metronidazole. The optimal period of treatment is seven to 14 days

P2D: Supporting Evidence

P2D: For children in whom *H. pylori* eradication is indicated, a PPI-triple therapy can be used as in adults with appropriate dose adjustment, for a duration of 7-14 days.

Summary: A poor quality systematic review by Oderda et al.[234] reported that bismuth-based dual or triple therapy when given for two weeks were as effective as one week PPI-based triple therapy. A very good quality RCT by Gottrand et al.[235] demonstrated that PPI-based triple therapy (PAC) is significantly more effective than PPI-based dual (AC) therapy when given for seven days. A case series[236] also showed that PPI-based triple therapy (PMC) is effective in eradicating *H. pylori*.

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Oderda et al. 2000[234] SR **(poor)**	30 full articles (n=870) & 17 abstracts (n=1,579) Children with Hp Infection (age not specified)	Hp eradication therapy: mono; dual; or triple therapy qd bis-based or PPI-based. (8 different combinations)		Hp eradication rate	<u>Full articles summary:</u> Dual therapies: amox + met, bis + amox or met: 73%-76% PPI+amox+met: 79%; PPI+amox+clar: 83%; PPI+met+clar: 89%; Bis-triple therapy: 95.5% No statistically significant differences in eradication rates with these regimens. <u>Abstracts:</u> PPI+amox+clar similar in efficacy to dual therapy; PPI+amox+met significantly superior to dual therapy (OR = 5.07 p<0.001) Bis-based triple therapy: 82% vs. 73% for PPI+amox+clar (p<0.0005); PPI+amox+tin: 95%, better than both PPI+amox+clar (OR = 6.5, p<0.001) and bis- based triple therapy (OR = 3.8, p<0.05). Therapy duration: Bis-dual therapy less effective when given for 1 wk vs 2 or more wks (74% vs 84%, p<0.05); similar results for bis-based triple therapy; PPI-based triple therapy obtained similar results with 1 or 2 weeks (75% vs. 77%, p>0.05 (NS).	0 +
Gottrand et al. 2001*[235] RCT	63 children with dyspeptic symptoms and Hp positive, mean age	OAC: ome 10 mg bid (15-30 kg) or 20 mg bid (>30 kg), amox 25	AC: amox 25 mg/kg bid, clar 7.5 mg/kg bid for 7 days	Hp eradication rate at 4 wks	Hp eradication rate (95% CI): OAC vs. AC: 74.2% (58.7%, 89.6%) vs. 9.4% (0%, 19.5%); Difference = 64.8% (46.4%, 83.2%), p<0.01	+

(very good)	(range) 10.8 years (3.3-5.4)	mg/kg bid, clar 7.5 mg/kg bid for 7 days				
Dohil et al. 1997[236] Case Series **(NA)**	15 children with DU & Hp positive, mean age (range) 12.4 years (9-16)	OMC: ome 20 mg qd; met 500 mg bid, clar 250 mg bid		Hp eradication rate at 6 to 8 weeks	Hp eradication rate was 93%	+
amox: amoxicillin; bis: bismuth; clar: clarithromycin; met: metronidazole; ome: omeprazole; tin: tinidazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question P3: What is the optimal use of PPIs in the treatment of *H. pylori* negative PUD?

P3A: Guideline Statements

Synopsis of Existing Recommendations P3A: PPI or H2RA therapy is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy[163]	2005	4	If the *H. pylori* test is negative, offer a course of a full-dose proton pump inhibitor for one or two months
NZGG[29]	2004	46	• Treat duodenal ulcers with H2RAs or PPIs for 4 – 8 weeks. • Treat gastric ulcers with PPIs or H2RAs for 8 – 12 weeks and confirm healing with OGD.
NICE[24]	2004	121	Offer full-dose PPI therapy to *H. pylori*-negative patients not taking NSAIDs for one or two months . • Full-dose PPI therapy heals peptic ulcers in the majority of cases.
Québec CRUM[45] (translated)	2002	16	• Duodenal Ulcer: First-line treatment: PPI for four to eight weeks • Gastric Ulcer: First-line treatment: PPI for six to twelve weeks • Confirmed gastroduodenal ulcer complications (gastrointestinal hemorrhage, perforation): first-linr treatment: PPI bid for 8 weeks
OPOT[23]	2000	26	Standard anti-ulcer therapy is recommended. High-dose PPI therapy is superior to H2RA therapy in healing refractory DUs. It is not recommended to combine PPIs with other acid suppressants (e.g., H2RAs). Concomitant use of H2RAs may impair PPI efficacy.
Agence Française de Sécurité Sanitaire des Produits de Santé[178] (translated)	1999	10, 11	<u>When and how should anti-ulcer agents be prescribed for duodenal ulcer?</u> 2) In the absence of *Helicobacter pylori:* The antisecretories are all effective against duodenal ulcer (grade A). The different meta-analyses comparing PPIs and anti-H_2s in initial treatment have shown that PPIs have a better rate of healing at two and four weeks. No difference in efficacy has been demonstrated between the PPIs. For duodenal ulcer attacks, the duration of antisecretory treatment is 4 weeks for PPIs and 4 to 6 weeks with anti-H_2s, varying depending on the products (professional agreement).

			<u>When and how should anti-ulcer agents be prescribed for gastric ulcer?</u> 2) In the absence of Helicobacter pylori infection: PPIs are more effective than anti-H2s in healing gastric ulcers (grade A). The rate of healing of the different PPIs is similar. For the same therapeutic class, the duration of treatment in order to achieve healing is longer than for duodenal ulcer. The recommended duration is 4 to 6 weeks for PPIs and 6 to 8 weeks for anti-H2s. The duration may be extended if there are factors that delay healing, such as smoking or a large ulcer size (> 10 mm) (professional agreement).

P3A: Supporting Evidence

P3A: PPI or H2RA therapy is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs. *The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

a) Evidence on the relative efficacy of PPIs vs. H2RAs for duodenal ulcer healing. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: In all meta-analyses, PPI therapy was superior to H2RAs in producing duodenal ulcer healing and pain relief at 2 and 4 weeks.[237] All MAs except one[238] were of poor methodological quality. The two RCTs, one of good quality[239] and the other[240] of very good quality, also found that PPIs were more effective than H2RAs in producing duodenal ulcer healing at two weeks, however in the trial by Misra et al.[240] the 4-week healing rate was not significantly different between treatment arms.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Poynard et al. 1995*[238] MA **(good)**	5 studies (n = 848) Patients with endoscopically-verified DU	lans 30 mg/day	ran 300 mg/day or fam 40 mg/day	DU healing rate, proportion w/o pain at 2 and 4 weeks	Healed at wk 2 (lans vs. H2RA): 60% vs. 40%, p < 0.01 Healed at wk 4 (lans vs. H2RA): 85% vs. 75%, p < 0.01 Difference in % pain-free at wk 2 (lans vs. H2RA) = 8%, p < 0.02. No significant difference b/w groups in pain-free proportion at wk 4.	+ + + -
Eriksson et al. 1995*[241] MA **(poor)**	16 studies (n = 3504; n for DU = 1532) Patients with endoscopically-verified DU or GU	ome 20 mg qd	ran 300 mg/day or cim 800-1200 mg/day	DU and GU healing, symptom resolution at 2 and 4 weeks (for DU)	DU healed at wk 2 (ome vs. ran): 61.7% vs. 46.5%, p < 0.001; (ome vs. cim): 62.5% vs. 41.9%, p < 0.001 DU healed at wk 4 (ome vs. ran): 87.4% vs. 76.5%, p < 0.001; (ome vs. cim): 86.2% vs. 73.9%, p < 0.001 Symptom-free at wk 2 (ome vs. ran): 72.1% vs. 58.0%, p < 0.001; (ome vs. cim): 72.6% vs.	+ + +

					59.3%, p < 0.001.	
Bamberg et al. 1992*[237] MA **(poor)**	5 studies (n = 1057) Asian pts with ≥1 symptomatic, endoscopically-verified DU ≥5mm	ome 20 mg qd	ran 300mg/day or cim 800 mg/day	DU healing rate at 2 and 4 weeks	DU healed at wk 2 (ome vs. H2RA): 72% vs. 42%, p < 0.0001 DU healed at wk 4 (ome vs. H2RA): 96% vs. 83%, p < 0.0001 Symptom-free at wk 2 (ome vs. H2RA): 79% vs. 65%, p < 0.001	+ + +
Mulder & Schipper 1990[242] MA **(poor)**	10 studies (n = 2225) Patients with endoscopically-verified DU	ome 20 mg qd	ran 300 mg/day	DU healing rate and symptom resolution at 2 and 4 weeks	DU healed at wk 2 (ome vs. ran): 69.3% vs. 52.8%, p < 0.0001 DU healed at wk 4 (ome vs. ran): 92.8% vs. 83.1%, p < 0.0001 Symptom-free at wk 2 (ome vs. ran): 71.1% vs. 57.6%, p < 0.001	+ + +
Judmaier et al. 1994[239] RCT **(good)**	202 patients with 1-2 endoscopically-verified DU of size 5-20mm	pant 40 mg/day	ran 300 mg/day	DU healing rate, symptom relief at 2 and 4 weeks	DU healed at wk 2 (pant vs. ran): 75% vs. 48%, p < 0.001 DU healed at wk 4 (pant vs. ran): 89% vs. 76%, p < 0.05 Pain at wk 2 (pant vs. ran): 23% vs. 42%, p < 0.01	+ + +
Misra et al. 1993*[240] RCT **(very good)**	60 patients with endoscopically verified DU ≥5mm, symptomatic for ≥ 3 months	ome 20 mg/day	fam 40 mg/day	DU healing rate at 2 and 4 weeks, pain relief, ulcer relapse rate at 6 months	DU healed at wk 2 (ome vs. fam): 77% vs. 40%, p < 0.001 DU healed at wk 4 (ome vs. fam): 93% vs. 80%, p = 0.2 Complete relief of day pain at wk 2 (ome vs. fam): 90% vs 40%, p = 0.001 Complete relief of day pain at wk 4 (ome vs. fam): 100% in both groups	+ - + -
cim: cimetidine; fam: famotidine; lans: lansoprazole; ome: omeprazole; pant: pantoprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						
Comments: None of the studies cited in the guidelines as evidence for the treatment of *H. pylori* negative ulcers reported *H. pylori* status. This may be because most were conducted prior to the issuance of recommendations for *H. pylori* testing and eradication in peptic ulcer disease. No study specifically addressed the treatment of *H. pylori* negative duodenal ulcers.						

P3A: PPI or H2RA therapy is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs. *The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

b) Evidence on the relative efficacy of PPIs vs. H2RAs for gastric ulcer healing. ***The evidence is not in***

agreement, therefore interpretation for practice is to be determined by the expert review panel.

Summary: Two meta-analyses,[241,243] both of poor quality, found that PPI therapy produced significantly higher ulcer healing rates at 4 and 8 weeks than H2RA, except for the comparison between omeprazole and cimetidine, in which statistical significance was not achieved. [241] PPI therapy was more effective at providing symptom-relief at 4 weeks, although the difference was of marginal statistical significance.[241] Healing rates in the 5 RCTs, all of good quality, were higher at 4 weeks in the PPI treatment arms, although Michel et al. found no significant difference between lansoprazole and ranitidine at 4 weeks.[244] At 8 weeks, healing rates between PPI and H2RA arms tended to converge, such that 3 trials detected no significant difference in healing at this time point.[244-246] Where symptom relief was assessed, PPIs did not confer a consistent benefit over H2RAs.

Study	Population	Intervention	Comparator	Outcome measure	Results	Dir
Di Mario et al. 1996[243] MA **(poor)**	52 studies total; 6 studies (n = 1273) for ome vs. H2RA Previously untreated, endoscopically verified GU, w/o DU	ome 20-40 mg/day or	ran 300 mg/day or cim 800-1000 mg/day	GU healing rate at 8 weeks	Pooled OR for healing (ome vs. H2RA) (95% CI) = 2.00 (1.57, 2.55) at 4 weeks, and 2.16 (1.51, 3.08) at 8 weeks	+
Eriksson et al. 1995*[241] MA **(poor)**	16 studies (n = 3504; n for GU = 374) DU or GU patients	ome 20 mg qd	ran 300 mg/day or cim 800-1200 mg/day	GU healing rate	GU healed at wk 4 (ome vs. ran): 68.7% vs. 58.8%, p = 0.005; (ome vs. cim): 62.5% vs. 41.9%, p < 0.001 GU healed at wk 8 (ome vs. ran): 85.6% vs. 78.9%, p = 0.02; (ome vs. cim): 84.3% vs. 74.7%, p = 0.1 (NS) Symptom-free at wk 2 (ome vs. ran): 65.3% vs. 56.4%, p = 0.04	+ - +
Hotz et al. 1995*[247] RCT **(good)**	248 patients with 1-2 endoscopically verified GU of size 5-20mm	pant 40 mg/day for up to 8 weeks depending upon healing	ran 300 mg/day for up to 8 weeks depending upon healing	Ulcer healing at 2, 4, 8 weeks, symptom relief at 2 weeks	GU healed at wk 2 (pant vs. ran): 33.1% vs. 17.1%, p < 0.01 GU healed at wk 4 (pant vs. ran): 77.1% vs. 52.4%, p < 0.001 GU healed at wk 8 (pant vs. ran): 85.5% vs. 72.0%, p < 0.01 Without ulcer pain at wk 2 (pant vs. ran): 71.9% vs. 67.7%, p > 0.05 (NS)	+ + + -
Bardhan et al. 1994*[245] RCT **(very good)**	250 patients with endoscopically verified GU of 3-25 mm	lans 30 mg/day, lans 60 mg/day, both x 28 days	ran 300 mg/day x 28 days	Ulcer healing rate and symptom relief at 4 and 8 weeks	GU healed at wk 4 (lans 30 mg vs. lans 60 mg vs. ran): 78.4% vs. 83.8% vs. 60.6%, p < 0.05 and p < 0.01 for lans 30 mg and lans 60 mg vs. ran	+

					GU healed at wk 8 (lans 30 mg vs. lans 60 mg vs. ran): 98.6% vs. 97.3% vs. 91.4%, p > 0.05 (NS) for all pairwise comparisons	-
Michel et al. 1994*[244] RCT **(good)**	132 patients with endoscopically verified GU of ≥5 mm	lans 30 mg/day for up to 8 weeks depending upon healing	ran 150 mg/day for up to 8 weeks depending upon healing	Ulcer healing rate and symptom relief at 4 and 8 weeks	GU healed at wk 4 (lans vs. ran): 68% vs. 56%, p > 0.05 (NS) GU healed at wk 8 (lans vs. ran): 81% vs. 76%, p > 0.05 (NS) Symptoms at wk 4 (lans vs. ran): 27% vs. 28%, p > 0.05 (NS) Symptoms at wk 8 (lans vs. ran): 5% vs. 8%, p > 0.05 (NS)	- - - -
Bate et al. 1989*[246] RCT **(good)**	197 patients with endoscopically verified symptomatic GU or ulcer within 3cm of pylorus	ome 20 mg/day x 8 weeks	cim 400 mg bid x 8 weeks	Ulcer healing rate at 4 and 8 weeks	GU healed at wk 4 (ome vs. cim): 73% vs 58%, p < 0.05 GU healed at wk 8 (ome vs. cim): 84% vs 75%, p = 0.1 (NS)	+ +
Walan et al. 1989*[248] RCT **(good)**	602 patients with GU ≥5mm	ome 20 mg/day, ome 40 mg/day for up to 8 weeks depending upon healing	ran 300 mg/day for up to 8 weeks depending upon healing	Ulcer healing rate at 4 and 8 weeks, symptom relief at 2 weeks	<u>GU healed at wk 4</u> (ome 20 mg vs. ome 40 mg vs. ran): 69% vs. 80% vs. 59% ome 40mg vs. ran: p < 0.0005 ome 20mg vs. ran: p = 0.01 ome 20mg vs. ome 40mg: p = 0.05 <u>GU healed at wk 8</u> (ome 20 mg vs. ome 40 mg vs. ran): 89% vs. 96% vs. 85%; ome 40mg vs. ran: p = 0.001 ome 20mg vs. ran: p > 0.05 (NS) Symptom-free at wk 2 (ome 20 mg vs. ome 40 mg vs. ran): 62% vs. 69% vs. 55%, ome 40mg vs. ran: p = 0.02 ome 20mg vs. ran: p > 0.05 (NS)	 + + 0 + - + -
cim: cimetidine; lans: lansoprazole; ome: omeprazole; pant: pantoprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						
Comments: None of the studies cited in the guidelines as evidence for the treatment of *H. pylori* negative ulcers reported *H. pylori* status. This may be because most were conducted prior to the issuance of recommendations for *H. pylori* testing and eradication in peptic ulcer disease. No study specifically addressed the treatment of *H. pylori* negative gastric ulcers.						

P3A: PPI or H2RA is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

c) Evidence for the relative efficacy of one PPI over another PPI for ulcer healing.

Summary: Two good quality RCTs[249,250] showed that pantoprazole and omeprazole had similar efficacy in terms of healing rates in gastric and duodenal ulcer, as well as for symptom relief.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Rehner et al. 1995[249] RCT **(good)**	286 patients with 1-2 endoscopically confirmed DU of 5 - 20 mm	pant 40 mg/day for up to 4 weeks depending upon healing	ome 20 mg/day for up to 4 weeks depending upon healing	DU healing at 2 and 4 weeks, pain relief at 2 weeks	DU healed at wk 2 (pant vs. ome): 68% vs. 72%, p > 0.05 (NS) DU healed at wk 4 (pant vs. ome): 92% vs. 89%, p > 0.05 (NS) Pain-free at wk 2 (pant vs. ome): 85% vs. 86%, p > 0.05 (NS)	+ + +
Witzel et al. 1995*[250] RCT **(good)**	243 patients with endoscopically verified GU or intrapyloric ulcer	pant 40 mg/day for up to 8 weeks depending upon healing	ome 20 mg/day for up to 8 weeks depending upon healing	GU healing at 4 and 8 weeks, symptom relief at 2 and 4 weeks	GU healed at wk 4 (pant vs. ome): 78.5% vs. 70.0%, p > 0.05 (NS) GU healed at wk 8 (pant vs. ome): 87.1% vs. 87.5%, p > 0.05 (NS) Pain-free at wk 4 (pant vs. ome): 88.2% vs. 81.0%, p > 0.05 (NS)	+ + +

ome: omeprazole; pant: pantoprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)

Comments: Neither study reported *H. pylori* status. No study specifically addressed the relative efficacy of one PPI over another for the treatment of *H. pylori* negative ulcers.

P3A: PPI or H2RA therapy is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

d) Evidence for the relative efficacy of PPIs vs. H2RAs for ulcer healing in H2RA-refractory ulcer.

Summary: In this study of good methodological quality[251], PPI therapy for 4 weeks was more effective than continued H2RA therapy for the healing of H2RA-refractory ulcers.

Study	Population	Intervention	Comparator	Outcome measure	Results	Dir
Bardhan et al. 1991*[251] RCT **(good)**	107 patients with duodenal bulb, pyloric channel, or gastric ulcer ≥ 0.5 cm after ≥ 2 months treatment with cimetidine	ome 40 mg/day	Pre-trial dose of cim or ran	Ulcer healing and symptom relief at 8 weeks	Ulcers healed at wk 2 (ome vs. H2RA): 85% vs. 34%, p < 0.0001 Ulcers healed at wk 4	+ +

	(0.8 or 1 g/d) or ranitidine (0.3 g/d)				(ome vs. H2RA): 96% vs. 57%, p < 0.0001 Overall symptom relief at wk 4 (ome vs. H2RA): 83% vs. 51%, p < 0.001	+
cim: cimetidine; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						
Comments: This study did not report *H. pylori* status, possibly because it was conducted prior to the issuance of recommendations for *H. pylori* testing and eradication in peptic ulcer disease. No study specifically addressed the treatment of *H. pylori* negative ulcers refractory to H2RAs.						

Question P3: What is the optimal use of PPIs in the treatment of *H. pylori* negative PUD?

P3B: Guideline Statements

Synopsis of Existing Recommendations P3B: Maintenance treatment with H2RA or PPI therapy may be required in *H. pylori* negative patients with a history of frequent ulcers, previous ulcer complications, or for whom co-morbid factors may cause ulcer complications to be life-threatening.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NZGG[29]	2004	46	Use maintenance treatment with H2RA or PPI if: • ulcer recurrences are frequent (eg, more than once per 12 months) or severe • previous peptic ulcer complication • there are comorbid factors that might make any complications life threatening.
Agence Française de Sécurité Sanitaire des Produits de Santé[178] (translated)	1999	10,27	DU (HP negative): Long-course antisecretory treatment reduces the frequency of recurrences, hemorrhagic complications and perforations. Long-course half-dose anti-H2 or adapted dose PPI treatment is recommended for patients who have had complications, recurrences or who have an at-risk background (anticoagulants, visceral defects) (grade A).

P3B: Supporting Evidence

P3B: Maintenance treatment with H2RA or PPI therapy may be required in *H. pylori* negative patients with a history of frequent ulcers, previous ulcer complications, or for whom co-morbid factors may cause ulcer complications to be life-threatening.

Summary: One very good quality RCT showed that omeprazole 10 mg/day and 20 mg three times per week were more effective than placebo in preventing DU ulcer recurrence.[252] This trial and another of good quality[253] showed that there was no significant difference between omeprazole 10 mg daily and 20 mg three times per week in reducing duodenal ulcer recurrence. A third poor quality RCT[254] showed that ranitidine was superior to placebo in reducing the rate of duodenal ulcer recurrence when administered at a daily dose of 600 mg for 12 months.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Lauritsen et al 1991*[252]	195 patients with healed DU ≥ 5mm	ome 10 mg qd for 6 months	ome 20 mg 3 times per wk (Group	Ulcer relapse at 6 months	Crude relapse rates at 3 months: Group A: 21% vs. Group B: 16% vs. Group C: 50%	

RCT **(very good)**	and complete pain relief with 2-8 weeks of ome	(Group A)	B) vs. placebo for 6 months (Group C)		Group A vs. Group C: Difference (95% CI): -29% (-45, -13); p < 0.00005 Group B vs. Group C at 3 months: Difference (95% CI): -34% (-49, -19), p < 0.00001 Group B vs. Group A at 3 months: Difference (95% CI): -5% (-19, 9); p > 0.05, NS <u>Crude relapse rates at 6 months</u>: Group A: 27% vs. Group B: 23% vs. Group C: 67% Group A vs. Group C at 6 months: Difference (95% CI): -40% (-56, -24); p < 0.00005 Group B vs. Group C at 6 months: Difference (95% CI): -44% (-60, -28); p<0.00001 Group B vs. Group A at 6 months: Difference (95% CI): -4% (-19, 11); p > 0.05, NS	+ + 0 + + 0
Bianchi Porro et al 1994*[253] RCT **(good)**	81 patients healed of DU ≥ 5mm with ome 20 mg/day, and a history of ≥ 3 DU relapses in the past 2 yrs	ome 10 mg qd for 6 months (Group A)	ome 20 mg/3 times per wk for 6 months (Group B)	Rate of ulcer relapse and symptom relief at 3 & 6 months	Rate of ulcer relapse at 3 months: Group A: 14% vs. Group B: 26%; p > 0.05, NS Rate of ulcer relapse at 6 months: Group A: 19% vs. Group B: 31%; p > 0.05, NS	0 0
Mignon et al 1990*[254] RCT **(good)**	399 DU patients for whom maintenance therapy was indicated in the absence of active ulcer	ran 150 mg qd for 12 months	placebo for 12 months	Rate of endoscopic ulcer recurrence	Rate of endoscopic ulcer recurrence (≥ 1 recurrence): placebo: 29.2% vs. ran: 8.6%; p < 0.05	+
ome: omeprazole; ran: ranitidine; NS: not statistically significant; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						
Comments: Only duodenal ulcer recurrence was addressed by the three RCTs cited in the guidelines. No studies comparing PPIs with H2RAs in preventing ulcer recurrence were cited in the guidelines. Only the study by Bianchi Porro et al.[253] assessed patients with frequent recurrences (3 relapses over 2 years). No other studies regarding the indications for which ulcer prevention therapy may be beneficial were cited. None of the studies cited in the guidelines as evidence for the maintenance treatment of *H. pylori* negative ulcers reported *H. pylori* status. This may be because they were conducted prior to the issuance of recommendations for *H. pylori* testing and eradication in peptic ulcer disease. No study specifically addressed the maintenance treatment of *H. pylori* negative ulcers.						

Question P4: What is the optimal use of PPIs in the treatment and prevention of NSAID-associated ulcer?

P4A: Guideline Statements

Synopsis of Existing Recommendations P4A: Full-dose H2RA, PPI or misoprostol therapy is recommended for ulcer healing in patients with NSAID-associated duodenal or gastric ulcers. PPIs are more effective than H2RAs in healing large or complicated ulcers, or when NSAID therapy must be continued. PPIs are better tolerated than high dose misoprostol

Guideline/ Consensus	Year	Pages	Recommendation within the guideline
Prodigy[163]	2005	6	People with an NSAID-induced ulcer • Stop the NSAID where possible • Test for *H pylori* • Give a 2-month course of a full-dose proton pump inhibitor (PPI) to heal the ulcer • Subsequently, if the *H. pylori* result was positive, eradicate it using triple therapy to reduce the risk of ulcer recurrence
NZGG[29]	2004	66	• If NSAID can be stopped, treat with an H2RA (ranitidine 150 mg twice daily or famotidine 20 mg twice daily) or PPI (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) for 8 weeks for duodenal ulcers and 12 weeks for gastric ulcers. • If NSAID is needed, treat with PPI for 8 weeks for duodenal ulcer and 12 weeks for gastric ulcer; if unsuccessful increase dose. Ongoing maintenance treatment is advised (as for individuals at increased risk of NSAID-induced GI complications)
NICE[24]	2004	121	For patients using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full dose PPI for two months to these patients and if *H. pylori* is present, subsequently offer eradication therapy.
Québec CRUM[45] (translated)	2002	16	For active ulcers, particularly when the NSAID cannot be discontinued: First-line treatment: PPI for eight weeks
OPOT[23]	2000	23 Table 3	Anti-ulcer therapy can be recommended to heal NSAID-related ulcers preferably in combination with discontinuation of the NSAID. First Line Therapy: <u>PPIs:</u> Lansoprazole 30mg daily x 4 weeks*; Omeprazole 20mg daily x 4 weeks*; Pantoprazole 40mg daily x 4 weeks*. * Duration of treatment based on assumption that NSAID is discontinued. PPIs are all considered to be safe and effective. Pantoprazole is the least expensive: <u>H2RAs:</u> Cimetidine 400mg bid x 8 weeks*; Famotidine 20mg bid x 8 weeks*; Nizatidine 150mg bid x 8 weeks*; Ranitidine 150mg bid x 8 weeks* * Duration of treatment based on assumption that NSAID is discontinued H2RAs are considered equally effective; cimetidine is the H2RA of choice because of its low cost. If patient is taking theophylline, henytoin,

			or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H2RA). Misoprostol: Misoprostol 200 µg tid or qid x 4 weeks*. * Duration of treatment based on assumption that NSAID is discontinued
Lanza et al[25] American College of Gastroenterology	1998	2041	NSAID-induced ulcer disease may be treated with any approved therapy for ulcer disease. It is preferable to stop NSAID therapy when ulcer disease occurs. A proton pump inhibitor is the agent of choice when NSAID must be continued in the presence of ulcer disease and for large ulcers.

P4A: Supporting Evidence

P4A: Full-dose H2RA, PPI or misoprostol therapy is recommended for ulcer healing in patients with NSAID-associated duodenal or gastric ulcers. PPIs are more effective than H2RAs in healing large or complicated ulcers, or when NSAID therapy must be continued. PPIs are better tolerated than high dose misoprostol

a) Evidence supporting the superiority of PPIs over H2RAs in NSAID-associated ulcer. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: Three RCTs,[248,255,256] all of good quality, showed that PPIs were significantly better than ranitidine in healing NSAID-associated gastric ulcers at 8 weeks. A higher gastric ulcer healing rate was obtained at 8 weeks compared to 4 weeks. There were no significant differences in healing rates between omeprazole 40mg and 20mg,[248,256] and lansoprazole 30 mg and 15 mg.[255]
Only one of the three RCTs[256] compared PPI with H2RA for the healing of both duodenal and gastric ulcers associated with NSAID use. Omeprazole 20 mg and 40 mg healed a greater proportion of total ulcers than ranitidine 300 mg/day. Duodenal ulcer healing rates were somewhat higher with the two omeprazole doses than ranitidine, although the difference was not statistically significant for omeprazole 40mg. There was no significant difference in duodenal ulcer healing rates between omeprazole 20 mg and 40 mg.

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Agrawal et al. 2000*[255] RCT **(good)**	353 patients with GU ≥ 5 mm, using NSAIDs ≥ 1month	lans: 15 mg/day; lans 30 mg/day	ran 300 mg/day	GU healing rate at 4 and 8 wks	<u>Rate of ulcer healing at wk 4</u>: lans 15 mg: 47% vs. lans 30 mg: 57% vs. ran: 30%; lans 15 mg vs. ran: $p < 0.01$ lans 30 mg vs. ran: $p < 0.001$ lans 15 mg vs. lans 30 mg: $p > 0.05$ (NS) <u>Rate of ulcer healing at wk 8</u>: lans 15 mg: 69% vs. lans 30 mg: 73% vs. ran: 53%; lans 15 mg vs. ran: $p = 0.01$ lans 30 mg vs. ran: $p < 0.01$ lans 15 mg vs. lans 30 mg: $p > 0.05$ (NS)	 + + - + + -
Yeomans et al. 1998*[256] RCT **(good)**	541 patients with DU or GU > 3 mm or >10 erosions, receiving NSAIDs	ome 20 mg/day; ome 40 mg/day	ran 300 mg/day	Treatment success rate at 8 weeks (healing of ulcer, < 5 erosions, no more than mild	<u>Overall success rate</u>: ome 20 mg: 80% vs. ome 40 mg: 79% vs. ran: 63%; ome 20 mg vs. ran: $p < 0.001$ ome 40mg vs. ran: $p = 0.001$ ome 40mg vs. ome 20mg: $p > 0.05$ (NS)	 + + +

				dyspepsia)	% with DU healing: ome 20 mg: 92% vs. ome 40 mg: 88% vs. ran: 81%; ome 20 mg vs ran: p < 0.03 ome 40 mg vs. ran: p > 0.05 (NS) ome 40mg vs. ome 20mg: p > 0.05 (NS) % with GU healing: ome 20 mg: 84% vs. ome 40 mg: 87% vs. ran: 64%; ome 20 mg vs ran: p < 0.001 ome 40 mg vs. ran: p < 0.001 ome 40mg vs. ome 20mg: p > 0.05 (NS)	 + - + + + +
Walan et al. 1989*[248] RCT **(good)**	602 patients with GU≥5 mm (68 of these were regular NSAID users)	ome 20 mg/day, ome 40 mg/day	ran 300 mg/day	GU healing rate at 4 and 8 wks	Rate of ulcer healing in NSAID users at wk 4: ome 20 mg: 61% vs. ome 40 mg: 81% vs. ran: 32%; ome 40 mg vs. ran: p = 0.02 ome 20 mg vs. ran: p > 0.05 (NS) ome 40mg vs. ome 20mg: p > 0.05 (NS) Rate of ulcer healing in NSAID users at wk 8: ome 20 mg: 82% vs. ome 40 mg: 95% vs. ran: 53%; ome 40 mg vs. ran: p = 0.02 ome 20 mg vs. ran: p > 0.05 (NS) ome 40mg vs. ome 20mg: p > 0.05 (NS)	 + - + + - +
lans: lansoprazole; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P4A: A full-dose H2RA, PPI or misoprostol is recommended for ulcer healing in patients with NSAID-associated duodenal or gastric ulcers. PPIs are more effective than H2RAs in healing large or complicated ulcers, or when NSAID therapy must be continued. PPIs are better tolerated than high dose misoprostol

b) Evidence supporting the superiority of PPIs over misoprostol or sucralfate in NSAID-associated ulcer. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: Omeprazole and misoprostol produced similar ulcer healing rates in a good quality RCT.[257] Another RCT, of poor quality, showed that omeprazole was superior to sucralfate in healing gastric ulcers.[258]

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Hawkey et al. 1998*[257]	935 NSAID users with DU, GU or	ome 20 mg/day, ome 40 mg/day	mis 800 mcg/day	Success rate: (ulcer healed, <5 erosions,	Success rate at wk 8: ome 20 mg: 76% vs. ome 40 mg: 75% vs. mis 800 mcg: 71%;	

RCT **(good)**	both (≥ 3 mm) or >10 erosions			no more than mild dyspepsia), DU and GU ulcer healing at 8 weeks	ome 40 mg vs. mis: p > 0.05 (NS) ome 20 mg vs. mis: p > 0.05 (NS) ome 40mg vs. ome 20mg: p > 0.05 (NS) <u>Rate of DU healing at wk 8</u>: ome 20 mg: 93% vs. ome 40 mg: 89% vs. mis 800 mcg: 77%; ome 40 mg vs. mis: p < 0.001 ome 20 mg vs. mis: p < 0.001 ome 40mg vs. ome 20mg: p-value not reported <u>Rate of GU healing at wk 8</u>: ome 20 mg: 87% vs. ome 40 mg: 80% vs. mis 800 mcg: 73%; ome 40 mg vs. mis: p > 0.05 (NS) ome 20 mg vs. mis: p = 0.004 ome 40mg vs. ome 20mg: p-value not reported	- - + + + 0 - + 0
Bianchi Porro et al. 1998[258] RCT **(poor)**	98 NSAID users with GU ≥5 mm	ome 20 mg/day	suc 2 g bid	Ulcer healing rate at 4 and 8 wks	Rate of ulcer healing at wk 4: ome: 82% vs. suc: 51%, p = 0.004 Rate of ulcer healing at wk 8: ome: 96% vs. suc: 78%, p = 0.01	+ +
mis:misoprostol; ome: omeprazole; suc: sucralfate; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

Question P4: What is the optimal use of PPIs in the treatment and prevention of NSAID-associated ulcer?

P4B: Guideline Statements

Synopsis of Existing Recommendations P4B: Offer eradication therapy to *H. pylori* positive NSAID users with previous or current peptic ulcer. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
NZGG[29]	2004	67	Eradicate *H. pylori* if testing is positive.
NICE[24]	2004	121	For patients using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full dose PPI for two months to these patients and if *H. pylori* is present, subsequently offer eradication therapy: • In patients using NSAIDs with peptic ulcer, *H. pylori* eradication does not increase healing when compared with acid suppression therapy alone in trials of 8 weeks duration. • In patients using NSAIDs with previous peptic ulcer, *H. pylori* eradication reduces recurrence of peptic ulcer. In a single trial of 6 months duration, recurrence was reduced from 18% to 10%. • In patients using NSAIDs without peptic ulcer disease, *H. pylori* eradication reduces the risk of a first occurrence of peptic ulcer. In a single trial of 8 weeks duration, first occurrence was reduced from 26% to 7% of patients

Lanza et al[25] American College of Gastroenterology	1998	2041	Treatment of *H. pylori* is recommended for patients taking NSAIDs who have ulcers and are infected with this organism.

P4B: Supporting Evidence

P4B: Offer eradication therapy to H. pylori positive NSAID users with previous or current PUD. The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.

a) Evidence for H. pylori eradication for healing NSAID-associated ulcer. **The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.**

Summary**: Hp eradication was found to have no effect on overall NSAID-associated ulcer healing rates in all three trials.[259-261] One of these trials, of good quality, found that gastric ulcer healing was impaired by Hp eradication,[259] while two others (one of good and one of poor quality) found no difference.[260,261]**

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Chan et al. 1998[260] RCT **(good)**	195 Hp-infected patients with NSAID/ASA-ulcer	ome 20 mg/day for 8 wks, Hp eradication therapy (bis 480 mg/day, tet 2 g/day, met 1.6 mg/day for 1 week)	ome 20 mg/day for 8 wks	Ulcer healing rate at 8 wks	Total healing rate at 8 wks: Hp erad: 83% vs. ome: 86%, p > 0.05 (NS) DU healing rate at 8 wks: Hp erad: 90%. vs. ome: 92%, p > 0.05 (NS) GU healing rate at 8 wks: Hp erad: 72%. vs. ome: 84%, p > 0.05 (NS)	- - -
Hawkey et al. 1998*[259] RCT **(good)**	285 Hp-infected patients with NSAID-ulcer	Hp eradication therapy: ome 40 mg/day, amox 2 g/day, clar 1 g/day for 7 days	ome 40 mg/day for 7 days	Ulcer healing rate at 4 and 8 wks	Total healing rate at 4 wks: Hp erad: 75% vs. ome: 86%, p > 0.05 (NS) Total healing rate at 8 wks: Hp erad: 89% vs. ome: 100%, p > 0.05 (NS) Rate of GU healing at 4 wks: Hp erad: 50% vs. ome: 88%, p = 0.006 Rate of GU healing at 8 wks: Hp erad 72% vs. ome: 100%, p = 0.006	- - - -
Bianchi Porro et al. 1996[261] RCT **(poor)**	70 Hp-infected patients with NSAID-ulcer	Hp eradication therapy: ome 40 mg for 4 wks , amox 2 g/day for 2 wks	ome 40 mg/day for 4 wks	Ulcer healing rate at 4 and 8 wks	Total healing rate at 4 wks: Hp erad: 75% vs. ome: 74%, p > 0.05 (NS) Total healing rate at 8 wks: Hp erad: 80% vs. ome: 88%, p > 0.05 (NS) GU healing rate at 4 wks: Hp erad: 68% vs. ome: 65%, p >	- - -

					0.05 (NS) GU healing rate at 8 wks: Hp erad: 76% vs. ome: 90%, p > 0.05 (NS) DU healing rate at 4 wks: Hp erad: 86% vs. ome: 91%, p > 0.05 (NS) DU healing rate at 8 wks: Hp erad: 86% vs. ome: 91%, p > 0.05 (NS)	- - -
amox: amoxicillin; bis: bismuth; clar: clarithromycin; met: metronidazole; ome: omeprazole; tet: tetracycline; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P4B: Offer eradication therapy to *H. pylori* positive NSAID users with previous or current PUD. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

b) Evidence for *H. pylori* eradication for prevention of NSAID-associated ulcer recurrence. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: Neither of the two trials[259,261] found that Hp eradication reduced the rate of ulcer recurrence in Hp positive patients. Only one of these trials was of good methodological quality.[259]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Hawkey et al. 1998*[259] RCT **(good)**	285 Hp-infected patients with NSAID-ulcer	Hp eradication therapy: ome 40 mg/day, amox 2 g/day, clar 1 g/day for 7 days	ome 40 mg/day, placebo antibiotics for 7 days	Ulcer remission rate at 6 months	Ulcer remission rate at 6 months: Hp erad: 56% vs. ome: 53%, p > 0.05 (NS)	-
Bianchi Porro et al. 1996[261] RCT **(poor)**	62 patients with healed NSAID-ulcer, both Hp –ve and +ve	ome 40 mg for 4 wks , amox 2 g/day for 2 wks (for Hp eradication)	ome 40 mg/day for 4 wks	Ulcer recurrence rate at 6 months	Ulcer recurrence rate at 6 months: Hp negative: 27% vs. Hp successfully eradicated: 46% vs. Hp not eradicated: 31%, p > 0.05 (NS)	-
amox: amoxicillin; clar: clarithromycin; ome: omeprazole; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

P4B: Offer eradication therapy to *H. pylori* positive NSAID users with previous or current PUD. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

c) Evidence for *H. pylori* eradication to prevent recurrent NSAID-associated ulcer bleeding. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: A good quality RCT showed that *H. pylori* eradication was equivalent to maintenance therapy with omeprazole for the prevention of recurrent GI bleeding due to ASA, and inferior to maintenance therapy for the prevention of recurrent upper GI bleeding due to NSAIDs.[262]

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Chan et al. 2001[262] RCT **(good)**	400 users of NSAIDs or ASA for ≥ 6 months (ASA users = 250; naproxen users = 150)	Hp eradication therapy (bis 480 mg/day, met 1.6 g/day, tet 2 g/day for 7 days), then placebo for 6 months	ome 20 mg/day for 6 months	Recurrent upper GI bleeding at 6 months	Recurrent bleeding at 6 months (ASA users): Hp erad: 1.9% vs. ome: 0.9%, difference = 1.0% (95% CI: -1.9%, 3.9%) Recurrent bleeding at 6 months (naproxen users): Hp erad: 18.8% vs. ome: 4.4%, difference = 14.4% (95% CI: 4.4%, 24.4%)	- +
bis: bismuth; met: metronidazole; ome: omeprazole; tet: tetracycline.						

P4B: Offer eradication therapy to *H. pylori* positive NSAID users with previous or current PUD.
The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.

d) Evidence for the relationship between *H. pylori* status and the risk of NSAID ulcer and bleeding ulcer

Summary: NSAID use and Hp infection independently and synergistically increased the risk of peptic ulcer and bleeding ulcer in this good quality meta-analysis of observational studies.[263]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Huang et al. 2002 - a[263] SR/MA **(good)**	16 studies (n = 1625) NSAID-users and non-users	N/A	N/A	Prevalence of PUD by *H. pylori* status in NSAID users	Ulcer risk for Hp +ve vs. Hp –ve NSAID users, OR = 3.52, 95% CI: (2.16, 5.75) Ulcer risk for Hp +ve NSAID users vs. Hp-ve non-users, OR = 61.1, 95% CI: (10.0, 373)	+ +
Huang et al. 2002 - b[263] SR/MA **(good)**	9 studies (n = 893) Patients with bleeding ulcers and controls	N/A	N/A	Prevalence of Hp infection and NSAID use in bleeding ulcer cases vs. controls	Summary OR for Hp infection in case-control studies = 1.67, 95% CI: (1.02, 2.72) Summary OR for NSAID use in case-control studies = 4.79, 95% CI: (3.7, 6.06) Risk of ulcer bleeding in Hp +ve NSAID users vs. Hp –ve non-users = 6.13, 95% CI: (3.93, 9.56)	+ + +

Question P4: What is the optimal use of PPIs in the treatment and prevention of NSAID-associated ulcer?

P4C: Guideline Statements

Synopsis of Existing Recommendations P4C: Offer *H. pylori* eradication therapy to reduce ulcer risk in *H. pylori* positive patients without peptic ulcer who are initiating long-term therapy with conventional NSAIDs or ASA. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Hunt et al[226] Canadian *H. pylori* consensus conference	2004	550	• Patients initiating long-term nonsteroidal anti-inflammatory drug (NSAID) therapy should be tested for *H. pylori* infection and treated if positive. • Patients initiating long-term acetylsalicylic acid (ASA) prophylaxis for cardiovascular disease should be tested for *H. pylori* infection and treated if positive.
Malfertheiner et al.[164] Maastricht 2-2000	2002	172	Maastricht 2-2000 recognised that *H. pylori* eradication reduces the incidence of peptic ulcers and concomitant symptoms when given prior to NSAID use. However *H. pylori* eradication does not enhance the healing of gastric or duodenal ulcers in patients receiving antisecretory therapy who continue to take NSAIDs. H. pylori eradication is advisable if NSAID therapy is planned in order to eliminate the infectiom as a confounding explanation of subsequent peptic ulcers and dyspeptic symptoms. In patients with a history of peptic ulcer disease who are on low-dose aspirin, testing for *H. pylori* and eradication were recommended as advisable based on a level 2 evidence.
OPOT[23]	2000	22	Routine testing for and eradicating *H. pylori* in patients embarking on NSAID therapy or with NSAID-related PUD is not currently recommended
Deltenre et al[168] Belgian consensus meeting	1998	300	Despite the uncertainty on the interaction of HP and NSAID in the genesis of peptic ulcer disease, it is acceptable to prescribe eradication treatment in known HP carriers before a long-term treatment with NSAID

P4C: Supporting Evidence

P4C: Offer *H. pylori* eradication therapy to reduce ulcer risk in *H. pylori* positive patients without peptic ulcer who are initiating long-term therapy with conventional NSAIDs or ASA. ***The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

a) Evidence for the benefit of *H. pylori* eradication for prevention of NSAID ulcer in patients initiating long-term ASA or NSAID therapy. ***The evidence is not in agreement, therefore interpretation for practice is to be determined by the expert review panel.***

Summary: One very good quality RCT[264] and a second of good quality RCT[265] demonstrated that Hp eradication prior to the initiation of long-term NSAID therapy decreases the overall risk of ulcer. However, there was no significant difference in the individual rates of DU and GU in the Hp eradicated group versus the control group in the second trial.[265]

Study	Population	Intervention	Comparator	Outcome	Results	Dir

Type (QA)				measure		
Chan et al. 2002[264] RCT **(very good)**	102 arthritic Hp-positive patients requiring long-term NSAID therapy, with at least moderate dyspepsia or a hx of PUD	Hp erad therapy (ome 40 mg/day, amox 2 g/day, clar 1 g/day for 7 days); dicl 100 mg/day slow-release for 6 months	ome 40 mg/day, placebo antibiotics for 7 days; dicl 100 mg/day slow-release for 6 months	Ulcer rate at 6 months, ulcer complication	Ulcer rate at 6 months: Hp erad: 12.1% vs. ome: 34.4%, log-rank test p = 0.008 Ulcer complication rate at 6 month: Hp erad: 4.2% vs. ome: 27.1%, log-rank test p = 0.003	+ +
Chan et al. 1997[265] RCT **(good)**	100 Hp-positive NSAID-naïve patients requiring long-term NSAIDs, w/o ulcer hx	Hp erad therapy: bis 480 mg/day, tet 2 g/day, met 1.6 g/day for 1 week; nap 750 mg/day for 8 weeks	nap 750 mg/day for 8 weeks	Ulcer rate at 8 weeks	Ulcer rate at wk 8: Hp erad: 7% vs. no erad: 26%, p = 0.01 No. of GU at 8 weeks: Hp erad: 3 vs. no erad: 9, p > 0.05 (NS) No. of DU at wk 8: Hp erad: 0 vs. no erad: 2, p > 0.05 (NS)	+ - -
amox: amoxicillin; bis: bismuth; clar: clarithromycin; dicl: diclofenac; met: metronidazole; nap: naproxen; ome: omeprazole; tet: tetracycline.						

P4C: Offer *H. pylori* eradication therapy to reduce ulcer risk in *H. pylori* positive patients without peptic ulcer who are initiating long-term therapy with conventional NSAIDs or ASA. *The existing recommendations are not in agreement, therefore interpretation for practice is to be determined by the expert review panel.*

b) Evidence for the relationship between *H. pylori* status and the risk of NSAID ulcer and bleeding ulcer

Summary: A good quality meta-analysis of observational studies showed that NSAID use and Hp infection independently and synergistically increased the risk for peptic ulcer and bleeding ulcer[263].

Study Type (QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Huang et al. 2002 - a[263] SR/MA **(good)**	16 studies (n = 1625) NSAID-users and non-users	N/A	N/A	Prevalence of PUD by *H. pylori* status in NSAID users	Ulcer risk for Hp +ve vs. Hp –ve NSAID users, OR (95% CI) = 3.52 (2.16,5.75) Ulcer risk for Hp +ve NSAID users vs. Hp-ve non-users, OR (95% CI) = 61.1 (10.0, 373)	+ +
Huang et al. 2002 - b[263] SR/MA **(good)**	9 studies (n = 893) Patients with bleeding ulcers and controls	N/A	N/A	Prevalence of Hp infection and NSAID use in bleeding ulcer cases	Summary OR (95% CI) for Hp infection in case-control studies = 1.67 (1.02, 2.72) Summary OR (95% CI) for NSAID use in case-	+ +

				vs. controls	control studies = 4.79 (3.78, 6.06) Risk (95% CI) of ulcer bleeding in Hp +ve NSAID users vs. Hp – ve non-users = 6.13 (3.93, 9.56)	+ +

Question P4: What is the optimal use of PPIs in the treatment and prevention of NSAID-associated ulcer?

P4D: Guideline Statements

Synopsis of Existing Recommendations P4D: Offer ulcer prophylaxis with a PPI, H2RA, or misoprostol to all long-term NSAID or ASA users at high risk for the development of ulcer and/or ulcer complications. Risk factors include: age, history of PUD, previous GI bleeding, history of cardiovascular diseases, use of high NSAID doses, and concurrent use of corticosteroids or anticoagulants. Standard dose PPIs, double dose H2RAs, and 800 mcg/day of misoprostol are all effective for the prevention of NSAID-associated gastric and duodenal ulcers while single dose H2RAs and lower misoprostol doses are less effective. The use of misoprostol may be limited by adverse effects.

Guideline/ Consensus	Year	Page	Recommendation within the guideline
Prodigy[163]	2005	8,12,14	Offer gastroprotection to all people with a previous peptic ulcer who require continued use of standard NSAIDs, as these people are at high risk of recurrent ulceration: • Proton pump inhibitors at full dose are generally the preferred choice for gastroprotection. Omeprazole, lansoprazole, pantoprazole, and esomeprazole are all licensed for prophylaxis of nonsteroidal anti-inflammatory drug-associated ulcers. Rabeprazole is not licensed for this indication. • Misoprostol is an alternative, but its place is limited by its adverse effects. The full dose (800 micrograms per day) should be used as lower doses (e.g. 400 micrograms per day) are less effective. • Double doses of H2-receptor antagonists are also effective at reducing the risk of endoscopic gastric and duodenal ulcers, but this is an off-licence use Standard doses only reduce the risk of endoscopic duodenal ulcers.
NZGG[29]	2004	75, 76	Co-prescription of cytoprotective agents to increase risk individuals is recommended for those aged >65 years with one additional risk factor, or those aged <65 years with two or more risk factors. It is not cost effective to co-prescribe to all those on NSAID: • misoprostol, PPIs and double doses of H2RAs are effective at reducing the risk of both endoscopically verified gastric and NSAID-induced duodenal ulcers • H2RAs and PPIs are better tolerated than misoprostol, and reduce NSAID-related dyspeptic symptoms. However, PPIs are recommended over H2RAs**.** No economic or therapeutic advantages have been shown in using double doses of H2RAs, rather than standard doses of PPIs which provide more potent and reliable acid

			inhibition • Misoprostol 800 mcg/day is more effective at reducing gastric ulcers than 400 mcg/day. Although it is associated with statistically significant adverse effects, which are more common at higher doses, the evidence for the effectiveness of low doses (400 mcg/day) in the reduction of clinical ulcer complications is controversial.
NICE[24]	2004	122	In patients at high risk (previous ulceration) and for whom NSAID continuation is necessary, offer gastric protection or consider substitution to a COX-2-selective NSAID. • In patients using NSAIDs without peptic ulcer disease, double-dose H2 receptor antagonist therapy or proton pump inhibitors significantly reduce the incidence of endoscopically detected lesions. • In patients using NSAIDs without peptic ulcer disease, misoprostol at low dose is less effective than proton pump inhibitors at reducing the incidence of endoscopically detected lesions, and has greater side-effects. • In patients using NSAIDs without peptic ulcer disease, substitution to a COX-2-selective NSAID is associated with a lower incidence of endoscopically detected lesions. The promotion of healing and prevention of recurrence in those with existing ulcer disease is unclear.
Dubois et al[266] US consensus panel	2004	203, Table 7	The use of PPIs with NSAIDs is appropriate in patients who are on ASA or have had a previous GI event. The use of PPIs with NSAIDs is inappropriate in patients <65 years, not on ASA and no previous GI event
Québec CRUM[45] (translated)	2002	17	Primary prevention of ulcers in individuals with a high risk of undesirable gastrointestinal events: First-line treatment: PPI in combination with NSAIDs Secondary prevention of ulcers in individuals with a history of NSAID-related ulcers: First-line treatment: PPI in combination with NSAIDs

OPOT[23]	2000	24,25	Anti-ulcer therapy is recommended for prevention of NSAID-associated peptic ulcer in high-risk. If possible, NSAIDs should be avoided in patients thought to be at high risk of serious GI events. Factors that independently increase the risk for NSAID-related ulcers include: 1. Previous GI bleeding; 2. Previous peptic ulcer; 3. Age >75 years; 4. History of cardiovascular disease. Risk increases significantly for patients with 2 or more risk factors and preventive therapy should be considered in such cases. Having the single risk factor of age or cardiovascular disease alone does not appear to increase risk excessively and may not warrant prophylaxis First Line Therapy: Misoprostol: Misoprostol 200µg tid. diarrhea (4% discontinuation rate); avoid in women of child-bearing potential who are not receiving adequate birth control, or in those who are pregnant. PPI: Lansoprazole 30mg daily; Omeprazole 20mg daily or Pantoprazole 40mg daily. PPIs are all considered to be safe and effective. Pantoprazole is the least expensive. H2RA: Cimetidine 800mg bid; Famotidine 40mg bid; Nizatidine 300mg bid; Ranitidine 300mg bid. H2RAs are considered equally effective; cimetidine is the H2RA of choice because of its low cost. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H2RA). Only one study using high-dose famotidine supports the use of an H2RA for prevention of NSAID-associated ulcers. Equivalent doses are listed for other H2RAs.
Lanza et al[25] American College of Gastroenterology	1998	2037, 2038	Patients at high risk for hemorrhagic and perforation from aspirin and other NSAID-ulcers should be considered for prophylaxis with misoprostol. Proton pump inhibitors are an acceptable alternative for prevention of NSAID-related complications. H2 receptors antagonists have been shown to prevent only duodenal ulcer and therefore cannot be recommended for prophylaxis. Factors that have been identified as placing patients at increased-risk for NSAID-related GI complications include the following: 1. Prior history of gastrointestinal events (ulcer, hemorrhage); 2. Age >60 years; 3. High dosage of NSAID; 4. Concurrent use of corticosteroids; 5. Concurrent use of anticoagulant.

P4D: Supporting Evidence

P4D: Offer ulcer prophylaxis with a PPI, H2RA, or misoprostol to all long-term NSAID or ASA users at high risk for the development of ulcer and/or ulcer complications. Risk factors include: age, history of PUD, previous GI bleeding, history of cardiovascular diseases, use of high NSAID doses, and concurrent use of corticosteroids or anticoagulants. Standard dose PPIs, double dose H2RAs, and 800 mcg/day of misoprostol are all effective for the prevention of NSAID-associated gastric and duodenal ulcers while single dose H2RAs and lower misoprostol doses are less effective. The use of misoprostol may be limited by adverse effects.

Summary: According to a good quality systematic review, PPIs, double-dose H2RAs, and misoprostol were all effective for the prevention of NSAID-associated endoscopic gastric and duodenal ulcers, as

compared to placebo (Rostom et al. a,b,c).[147] In the same systematic review, the results of one RCT showed that standard dose omeprazole was superior to standard dose ranitidine in preventing both duodenal and gastric ulcer recurrence (Rostom et al.-d). Another two RCTs (Rostom et al-e) demonstrated that PPIs are superior to misoprostol for preventing NSAID-associated duodenal ulcer but not gastric ulcer.

A good quality RCT by Lai et al., showed that PPI therapy reduces recurrence rates of ulcer complications due to low-dose ASA.[267]

Study Type(QA)	Population	Intervention	Comparator	Outcome measure	Results	Dir
Rostom et al.-a 2002[147] SR **(good)**	5 RCTs (n = 1,216) Subjects requiring chronic NSAID use taking NSAIDs > 3 weeks, w/ or w/o past ulcer	PPI	Placebo	Ulcer recurrence or ulcer complication	DU RR (95% CI) = 0.19 (0.09, 0.37) GU RR (95% CI) = 0.40 (0.32, 0.51)	+ +
Rostom et al-b 2002[147] SR **(good)**	3 RCTs (n=298) Subjects requiring chronic NSAID use taking NSAIDs > 3 weeks, w/ or w/o past ulcer	double dose H2RA	Placebo	Prevention of NSAID induced upper GI toxicity	DU RR (95% CI) = 0.26 (0.11, 0.65) GU RR (95% CI) = 0.44 (0.26, 0.74)	+ +
Rostom et al-c 2002[147] SR **(good)**	11 RCTs (n=3,641) Subjects requiring chronic NSAID use taking NSAIDs > 3 weeks, w/ or w/o past ulcer	mis 400 mcg/day or 800 mcg/day	Placebo	Ulcer recurrence or ulcer complication after at least 3 months	Both mis doses : DU RR (95% CI) = 0.47 (0.33, 0.69) GU RR (95% CI) = 0.26 (0.17, 0.39) mis 400 mcg/day: GU RR (95% CI) = 0.42 (0.28, 0.67) mis 800 mcg/day: GU RR (95% CI) = 0.17 (0.11, 0.24)	+ - +
Rostom et al-d 2002[147] SR **(good)**	1 RCT (n = 425) Subjects requiring chronic NSAID use taking NSAIDs > 3 weeks, w/ or w/o past ulcer	ome 20 mg/day	ran 150 mg bid	Ulcer recurrence or ulcer complication	DU RR (95% CI) = 0.11 (0.01, 0.89) GU RR (95% CI) = 0.32 (0.17, 0.62)	+ +
Rostom et al-e 2002[147] SR **(good)**	2 RCTs (n = 838) Subjects requiring chronic NSAID use taking NSAIDs > 3 weeks, w/ or w/o past ulcer	ome 20 mg daily & lans 15 or 30 mg daily	mis 400 mcg/day and mis 800 mcg/day	Ulcer recurrence or ulcer complication	DU RR (95% CI) = 0.29 (0.15, 0.56) GU RR (95% CI) = 0.59 (0.27, 1.25)	+ -
Lai et al. 2002*[267] RCT **(good)**	123 Hp-infected patients with complicated ulcer ≥5 mm, receiving ASA	lans 30 mg/day for 1 yr; ASA 100 mg/day	placebo for 1 yr; ASA 100 mg/day	Ulcer complication rate at 12 months	Ulcer complication rate at 12 months: lans: 1.6% vs. placebo:14.8%; p =	+

	≤325mg/day for ≥ 1 month before ulcer complications occurred				0.008 Hazard ratio (95% CI) (placebo vs. lans): 10.6 (1.3, 86)	
lans: lansoprazole; mis: misoprostol; ome: omeprazole; ran: ranitidine; * indicates industry involvement (see Section 7.1 Clinical Information under Presentation of Results)						

13 Summary of Economic Studies Related to PUD

1. O'Brien et al. (1997)[268]

(This paper is a summarized version of the CCOHTA report, so details of methods and results are available from the report "Bernie O'Brien, Ron Goeree, Richard Hunt, Joanne Wilkinson, Mitchell Levine, Andrew Willan. Economic evaluation of alternative therapies in the long-term management of peptic ulcer disease and gastroesophageal reflux disease. CCOHTA 1996. Project #1: Cost-effectiveness of alternative therapies for the long-term management of peptic ulcer disease (PUD)")

This study compares, over a one-year period, nine alternative strategies for the management of patients diagnosed with uncomplicated duodenal ulcer. The primary outcome was time free from ulcer. The viewpoint of the study was that of a provincial ministry of health in Canada. Costs are expressed in 1995 Canadian dollars.

A decision analytic model was used. The information on clinical practice patterns and resource utilization are based on convening an expert physician panel (4 gastroenterologists, 2 family physicians). The probabilities of ulcer healing and recurrences rates were derived using the principles of quantitative literature review. *H. pylori* eradication rates were based on one recent meta-analysis.

The nine strategies modeled are as follows:

Strategy 1: Heal with an H2RA and wait. Heal ulcer with ranitidine (150 mg bid, 8 weeks). No further treatment until ulcer recurrence, then heal with ranitidine (150 mg bid, 8 weeks).

Strategy 2: Heal with a PPI and wait. Heal ulcer with omeprazole (20 mg/day, 28 days). No further treatment until ulcer recurrence, then heal with omeprazole (20 mg/day, 28 days).

Strategy 3: Heal and maintenance H2RA. Heal ulcer with ranitidine (150 mg bid, 8 weeks) followed by continuous maintenance therapy with half-dose (150 mg/day) ranitidine. Recurrences treated with full-dose ranitidine (150 mg bid, 8 weeks).

Strategy 4: Heal and eradicate H. pylori with OA. Heal ulcer and eradicate *H. pylori* with omeprazole and amoxicillin.

Strategy 5: Heal and eradicate H. pylori with OC. Heal ulcer and eradicate *H. pylori* with omeprazole and clarithromycin.

Strategy 6: Heal and eradicate H. pylori with OAM. Heal ulcer and eradicate *H. pylori* with omeprazole, amoxicillin and metronidazole.

Strategy 7: Heal and eradicate H. pylori with OAC. Heal ulcer and eradicate *H. pylori* with omeprazole, amoxicillin and clarithromycin.

Strategy 8: Heal and eradicate H. pylori with OMC. Heal ulcer and eradicate *H. pylori* with omeprazole, metronidazole and clarithromycin.

Strategy 9: Heal and eradicate H. pylori with RBMT. Heal ulcer and eradicate *H. pylori* with ranitidine, bismuth, metronidazole and tetracycline.

In the base case analysis, six strategies "*Heal with an H2RA and wait*", "*Heal and eradicate H. pylori with OAC*", "*Heal with a PPI and wait*", "*Heal and maintenance H2RA*", "*Heal and eradicate H. pylori with OA*" and "*Heal and eradicate H. pylori with OC*" were dominated. The remaining three strategies "*Heal and eradicate H. pylori with RBMT*", "*Heal and eradicate H. pylori with OAM*", and "*Heal and eradicate H. pylori with OMC*" were cost–effective. The incremental cost per week without ulcer for the strategy "*Heal and eradicate H. pylori with OAM*" versus "*Heal and eradicate H. pylori with RBMT*" is calculated as $38; and for the strategy "*Heal and eradicate H. pylori with OMC*" versus "*Heal and eradicate H. pylori with OAM*" is calculated as $140.

The one-way sensitivity analyses show that the results are sensitive to eradication rates.

Comment:
This study was conducted about ten years ago, in a Canadian health care setting from the perspective of a provincial (Ontario) government; uses the inputs specific to Ontario, and the costs are in 1995 Canadian dollars. The modeled strategies are based on practices prevailing in 1995 and may not be reflective of current practice. The information on clinical practice patterns and resource utilization are based on convening an expert physician panel. The effectiveness data were derived from the systematic review and meta-analysis (crude form) of the published studies (no date given, however the latest study included is 1995).

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Appendix 1: Indications for Proton Pump Inhibitors in Canada

A. Apo-Omeprazole

omeprazole – 20mg capsules
Information from product monograph revised September 3, 2004 from Apotex Inc.[6]

Apo-Omeprazole is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

1. duodenal ulcer;
2. gastric ulcer;
3. reflux esophagitis;
4. symptomatic gastroesophageal reflux disease (GERD);
5. Zollinger-Ellison Syndrome (pathological hypersecretory conditions);
6. NSAID-associated gastric and duodenal ulcers.

Use in Children: The safety and effectiveness of omeprazole in children has not yet been established.

B. Losec and Losec MUPS

omeprazole magnesium – 10mg and 20mg delayed released tablets
Information from product monograph revised September 23, 2003 from AstraZeneca Canada Inc.[4]
omeprazole magnesium – 10mg and 20mg delayed release tablets [MUPS formulation]
Information from product monograph revised September 23, 2003 from AstraZeneca Canada Inc.[5]
omeprazole – 10mg, 20mg and 40 mg delayed release capsules
Information from product monograph revised June 22, 2004 from AstraZeneca Canada Inc. [3]

Losec tablets/capsules are indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

- Duodenal ulcer;
- Gastric ulcer;
- NSAID-associated gastric and duodenal ulcers;
- Reflux esophagitis;
- Symptomatic gastroesophageal reflux disease (GERD) i.e., heartburn and regurgitation;
- Dyspepsia: a complex of symptoms which may be caused by any of the organic diseases listed above, or upon investigation no identifiable organic cause is found (i.e., functional dyspepsia) [omeprazole capsules 10mg, 20mg and 40 mg are not indicated for dyspepsia];
- Zollinger-Ellison syndrome (pathological hypersecretory condition);
- Eradication of *H. pylori*.

Losec, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with peptic ulcer disease associated with Helicobacter infection. The optimal timing for eradication therapy in patients whose ulcer is not clinically active (i.e. asymptomatic) remains to be determined.

Use in Children: The safety and effectiveness of Losec tablets in children have not yet been established.

C. Nexium
esomeprazole magnesium trihydrate – 20mg and 40mg delayed release tablets.
Information from product monograph revised November 23, 2005 from AstraZeneca Canada Inc.[9]

Nexium is indicated for treatment of conditions where a reduction in gastric acid secretion is required such as:

- Reflux esophagitis
- Maintenance treatment of patients with reflux esophagitis
- Symptomatic gastroesophageal reflux disease (i.e. heartburn and regurgitation)
- Healing of NSAID-associated gastric ulcers
- Reduction of risk of NSAID-associated gastric ulcers
- *Helicobacter pylori* (*H. pylori*) eradication

Nexium, in combination with clarithromycin and amoxicillin, is indicated for the treatment of patients with duodenal ulcer disease associated with *Helicobacter pylori* infection to eradicate the *H. pylori* and heal ulcers. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.
Pediatrics: The safety and effectiveness of Nexium tablets in children have not yet been established.

D. Pantoloc
pantoprazole sodium – 20mg and 40mg enteric-coated tablets.
Information from product monograph revised May 17, 2005 from Solvay Pharma Inc.[8]

Pantoloc is indicated for the treatment of conditions where a reduction of gastric acid secretion is required, such as the following:

- Duodenal ulcer
- Gastric ulcer
- Reflux esophagitis
- Symptomatic gastro-esophageal reflux disease (such as, acid regurgitation and heartburn).
- Prevention of gastrointestinal lesions induced by non-steroidal anti-inflammatory drugs (NSAIDs) in patients with a need for continuous NSAID treatment, who have increased risk to develop NSAID-associated upper gastrointestinal lesions.
- *Helicobacter pylori* associated duodenal ulcer
  Pantoprazole, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with an active duodenal ulcer who are *H. pylori* positive. Clinical trials using combinations of pantoprazole with appropriate antibiotics have indicated that such combinations are successful in eradicating *H. pylori*

For the maintenance treatment of patients with reflux esophagitis and the rapid resolution of symptoms associated with reflux esophagitis, such as heartburn, regurgitation and dyspepsia, 20 mg pantoprazole once daily in the morning has been used for up to 12 months in controlled clinical trials, and in continuous maintenance treatment, in a limited number of patients for up to eight years.
Pediatrics**:** The safety and effectiveness of pantoprazole in children have not yet been established.

E. Pariet
rabeprazole sodium – 10mg and 20mg enteric-coated tablets
Information from product monograph revised January 26 2005 from Janssen-Ortho Inc.[10]

Pariet is indicated for:
- Treatment of conditions where a reduction of gastric acid secretion is required, such as:
  1. Symptomatic relief and healing of erosive or ulcerative gastroesophageal reflux disease (GERD).
  2. Long-term maintenance of healing of erosive or ulcerative gastroesophageal reflux disease (GERD).
  3. Treatment of symptoms (i.e. heartburn and regurgitation) in symptomatic gastroesophageal reflux disease (GERD), also called non-erosive reflux disease (NERD).
  4. Symptomatic relief and healing of duodenal ulcers.
  5. Symptomatic relief and healing of gastric ulcers.
  6. Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.
  7. Eradication of *H. pylori* associated with duodenal ulcer disease (active or history within the past 5 years). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. Clinical trials using combinations of rabeprazole with appropriate antibiotics have indicated that such combinations are successful in eradicating *H. pylori*.

Pediatrics (< 18 years of age): The safety and efficacy of rabeprazole have not been established in children under the age of 18 years.

F. Prevacid
lansoprazole – 15mg and 30mg delayed release capsules
Information from product monograph revised June 15, 2005 from TAP Pharmaceuticals Inc. (Distributed by Abbott Laboratories, Limited)[7]

Prevacid is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:
1. Duodenal ulcer.
2. Gastric ulcer.
3. Reflux esophagitis including patients with Barrett's esophagus, and patients poorly responsive to an adequate course of therapy with histamine H_2-receptor antagonists.

4. Healing of NSAID-Associated Gastric Ulcer; treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. (Controlled studies did not extend beyond 8 weeks).
5. Reduction of Risk of NSAID-Associated Gastric Ulcers in patients with a history of gastric ulcers who require to continue taking a NSAID. (A controlled study did not extend beyond 12 weeks).
6. Symptomatic Gastroesophageal reflux disease (GERD); treatment of heartburn and other symptoms associated with GERD.
7. Pathological hypersecretory conditions including Zollinger-Ellison Syndrome.
8. Eradication of *Helicobacter pylori* (*H. pylori*).

Triple Therapy: Lansoprazole, in combination with clarithromycin plus amoxicillin as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and active duodenal ulcer disease. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Pediatric GERD (erosive and non-erosive esophagitis) (1 to 17 years of age): Prevacid is indicated for treatment of erosive and non-erosive GERD in children, aged 1 to 17 years. The clinical trial treatment period did not extend beyond 12 weeks.
Dose safety and effectiveness have not been established in patients <1 year.

Appendix 2: Literature Search Strategies

Guide to DIALOG® Search Syntax

?	Truncation symbol. Retrieves plural and variant endings.
n	Proximity operator. Words can be in any order.
w	Proximity operator. Words must be adjacent, in given order.
l	Proximity operator. Subject heading must be linked to subject subheading.
ti	Title. Search in article titles.
ab	Abstract. Search in article abstracts.
de	Descriptor (i.e. subject heading). Search in subject headings.
!	Explode descriptor (i.e. retrieve the search concept plus all narrower terms).
dt	Publication type.
rn	Registry number.

GUIDELINES SEARCH

Search Logic

#1 Indications for the use of proton pump inhibitors
#2 Proton pump inhibitors
#3 Guidelines and/or consensus statements
#4 (#1 OR #2) AND #3
#5 Apply human limit

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
DIALOG One Search® (May 18, 2005) MEDLINE® (1955-present) BIOSIS Previews® (1969-present) EMBASE® (1974-present) PASCAL	Human	#1 INDICATIONS FOR THE USE OF PROTON PUMP INHIBITORS (gastrointestinal hemorrhage OR peptic ulcer hemorrhage)/de from MEDLINE OR (gastrointestinal hemorrhage OR peptic ulcer bleeding OR upper gastrointestinal bleeding)/de from EMBASE OR (gastrointestinal hemorrhage OR upper gastrointestinal bleeding)/de from BIOSIS Previews OR ((gastrointestinal OR gastro(w)intestinal OR gi)(2n)(hemorrhag? OR haemorrhag? OR perforat? OR bleed? OR rebleed?))/ti,ab OR (ulcer?(2n)((hemorrhag? OR haemorrhag? OR perforat? OR bleed? OR rebleed?) OR (gastrointestinal OR gastro(w)intestinal OR gi)))/ti,ab OR gastric mucosa(l)in from MEDLINE OR stomach mucosa injury/de from EMBASE OR gastric mucosal injury/de from BIOSIS Previews OR mucosa?(2n)injur?/ti,ab

		OR peptic ulcer!/de from MEDLINE, EMBASE, BIOSIS Previews OR peptic ulcer disease/de from BIOSIS Previews OR ((peptic OR stomach OR duoden? OR gastroduoden? OR gastric)(2n)ulcer?)/ti,ab OR gastroesophageal reflux/de from MEDLINE,EMBASE,BIOSIS Previews OR barrett esophagus/de from MEDLINE,EMBASE OR barrett's esophagus/de from BIOSIS Previews OR (gastro-esophageal reflux OR gastro-esophageal reflux disease OR gastroesophageal reflux disease)/de from BIOSIS Previews OR (esophageal(w)reflux OR gastro(w)oesophageal(w)reflux OR gastroesophageal(w)reflux OR gerd OR gord OR gastric(w)regurgitation OR acid(w)reflux OR barrett?(w)esophagus OR barrett?(w)oesophagus)/ti,ab OR (dyspepsia OR heartburn)/de from MEDLINE, EMBASE, BIOSIS Previews OR (dyspepsia? OR indigestion OR heartburn)/ti,ab OR helicobacter infections/de from MEDLINE OR helicobacter infection/de from EMBASE OR (helicobacter pylori gastritis OR helicobacter pylori infection)/de from BIOSIS Previews OR (helicobacter OR h(w)pylori OR campylobacter)(n4)(infection OR infections) OR gastric acid(l)se from MEDLINE OR stomach acid secretion/de from EMBASE OR gastric acid secretion/de from BIOSIS Previews OR (gastric(2n)hypersecret?) OR idiopathic(w)hypersecretion/ti,ab OR zollinger-ellison syndrome/de from BIOSIS Previews OR (zollinger(w)ellison OR ellison(w)zollinger OR zes)/ti,ab OR esophagitis!/de from MEDLINE, EMBASE, BIOSIS Previews OR (esophagitis OR esophagitides OR oesophagitis OR oesophagitides)/ti,ab #2 PROTON PUMP INHIBITORS

		proton pumps(l)ai/de from MEDLINE OR proton pump inhibitor!/maj from EMBASE OR proton pump inhibitors/de from BIOSIS Previews OR (proton(w)pump(w)inhibitor? OR ppi OR ppis)/ti,ab OR omeprazole/de from MEDLINE, BIOSIS Previews OR (omeprazole OR Antra OR Audazol OR Aulcer OR Belmazol OR CCRIS(w)7099 OR Ceprandal OR Danlox OR Demeprazol OR Desec OR Dizprazol OR Dudencer OR Elgam OR Emeproton OR Epirazole OR Erbolin OR Exter OR Gasec OR Gastrimut OR Gastroloc OR Gibancer OR H(w)168(w)68 OR HSDB(w)3575 OR Indurgan OR Inhibitron OR Inhipump OR Lensor OR Logastric)/ti,ab OR (Lomac OR Losec OR Mepral OR Miol OR Miracid OR Mopral OR Morecon OR Nilsec OR Nopramin OR OMEP OR OMP OR OMZ OR Ocid OR Olexin OR Omapren OR Omebeta(w)20 OR Omed OR Omegast OR Omepral OR Omeprazol OR Omeprazole OR Omeprazolum OR Omeprazon OR Omeprol OR Omesek OR Omezol OR Omezolan OR Omid OR Omisec)/ti,ab OR (Omizac OR Ompanyt OR Ortanol OR Osiren OR Ozoken OR Paprazol OR Parizac OR Pepticum OR Pepticus OR Peptilcer OR Prazentol OR Prazidec OR Prazolit OR Prilosec OR Procelac OR Proclor OR Prysma OR Ramezol OR Regulacid OR Sanamidol OR Secrepina OR Tedec Ulceral OR Ulceral OR Ulcesep OR Ulcometion OR Ulcozol OR Ulcsep OR Ulsen OR Ultop OR Ulzol)/ti,ab OR (Victrix OR Zefxon OR Zegerid OR Zepral OR Zimor OR Zoltum OR Zanprol OR Ufiprazole OR Ufiprazol OR Ufiprazolum OR Andra)/ti,ab OR s rn=(73590-58-6 OR 73590-85-9 OR 88546-55-8 OR 95382-33-5 OR 95510-70-6 OR 102332-89-8 OR 120003-84-1) from MEDLINE,BIOSIS Previews,PASCAL OR esomeprazole/de from BIOSIS Previews OR (esomeprazole OR Nexium OR Perprazole OR Nexiam OR Inexium OR Sompraz OR Axagon OR Esopral OR Lucen OR Axiago)/ti,ab OR rn=(119141-88-7 OR 161796-78-7 OR 161973-10-0 OR 217087-09-7) from MEDLINE, BIOSIS Previews, PASCAL OR lansoprazole/de from BIOSIS Previews OR (lansoprazole OR A(w)65006 OR AG(w)1749 OR Agopton OR Alexin OR Amarin OR Aprazol OR BRN(w)4333393 OR Bamalite OR Blason OR Compraz OR Dakar OR Estomil OR Fudermex OR Gastrex OR Gastride OR

		Gastroliber OR HSDB(w)7204 OR Ilsatec OR Ketian OR Keval)/ti,ab OR (Lancid OR Lanfast OR Lanproton OR Lansopep OR Lansoprazol OR Lansoprazole OR Lansoprazolum OR Lansox OR Lanston OR Lanz OR Lanzo OR Lanzogastro OR Lanzol OR Lanzol(w)30 OR Lanzopral OR Lanzor OR Lasoprol OR Limpidex OR Lizul OR Mesactol)/ti,ab OR (Monolitum OR Ogast OR Ogasto OR Ogastro OR Opiren OR Pampe OR Peptomil OR Prevacid OR Prezal OR Pro(w)Ulco OR Promp OR Prosogan OR Suprecid OR Takepron OR Ulcertec OR Uldapril OR Ulpax OR Unival OR Zoprol OR Zoton)/ti,ab OR rn=(103577-45-3) from MEDLINE, BIOSIS Previews, PASCAL OR pantoprazole/de from BIOSIS Previews OR (pantoprazole OR BY(w)1023 OR Pantoprazol OR Pantoprazole OR Pantoprazolum OR SK&F(w)96022 OR Controloc OR Pantoloc OR Protonix OR Angastra OR Apton OR Eupantol OR Inipomp OR Gastromax OR Noprop OR Pamgest OR Pantecta OR Panto OR Pantoc)/ti,ab OR (Pantocal OR Pantocarm OR Pantodac OR Pantop OR Pantopan OR Pantopaz OR Pantorc OR Pantozol OR Pantozol(w)Rifun OR Pantus OR Peptazol OR Protium OR Rifun OR Singastril OR Somac OR Supracam OR Ulcemex OR Ulcotenal OR Ulserch OR Ziprol OR Zurcal OR Zurcale OR Zurcazol)/ti,ab OR rn=(102625-70-7 OR 138786-67-1 OR 164579-32-2) from MEDLINE, BIOSIS Previews, PASCAL OR rabeprazole/de from BIOSIS Previews OR (rabeprazole OR Aciphex OR E(w)3810 OR Gastrodine OR LY(w)307640(w)sodium OR Pariet OR Rabec OR Rabeloc)/ti,ab OR rn=(117976-90-6) from MEDLINE, BIOSIS Previews, PASCAL #3 GUIDELINES AND/OR CONSENSUS STATEMENTS guidelines!/de from MEDLINE, BIOSIS Previews OR (clinical guidelines OR clinical practice guidelines)/de from BIOSIS Previews OR (critical pathways OR health planning guidelines)/de from MEDLINE OR consensus development conferences!/de from MEDLINE OR practice guideline!/de from EMBASE OR dt=(practice guideline OR guideline OR consensus development conference OR consensus development conference, nih) OR

		(cpg OR cpgs OR (critical OR clinical OR practice)(w)(path OR paths OR pathway OR pathways OR protocol OR protocols OR guideline OR guidelines) OR care(w)(path OR paths OR pathway OR pathways OR map OR maps OR plan OR plans) OR consensus)/ti,ab
The Cochrane Library 2005, issue 2 (May 19, 2005)		Same search logic, MeSH descriptors and keywords as DIALOG® MEDLINE search; adapted search commands for Wiley InterScience® search interface.
PubMed (May 17, 2005)	Human	Same search logic, MeSH descriptors and keywords as DIALOG® MEDLINE® search; adapted search commands for PubMed search interface.
CINAHL (May 19, 2005)		Same search logic and keywords as DIALOG® MEDLINE® search; converted MeSH descriptors for CINAHL thesaurus; adapted search commands for Ovid search interface.
Searched online guidelines collections (including CMA Infobase, AHRQ's National Guidelines Clearinghouse, the NHS National Electronic Library of Health Guidelines Finder, Guidelines International Network) as well as the web sites of guideline producing bodies, relevant professional associations and other online databases and web sites.		

HEALTH ECONOMICS STUDIES SEARCH

Search Logic

#1 Indications for the use of proton pump inhibitors (as above)
#2 Proton pump inhibitors (as above)
#3 Health economics studies – more sensitive filter
#4 Canada filter
#5 Health economics studies – less sensitive filter
#6 #1 AND #2 AND #3 AND #4
#7 #1 AND #2 AND #5
#8 #6 OR #7

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
DIALOG One Search® (October 3, 2005) MEDLINE® (1955-present) BIOSIS Previews® (1969-present) EMBASE® (1974-present)		#3 HEALTH ECONOMICS MORE SENSITIVE FILTER cost?/ti,ab,de OR ec/de from MEDLINE OR pharmacoeconomics/de from EMBASE OR health care costs!/de from MEDLINE OR health care cost!/de from EMBASE, BIOSIS Previews OR (costs OR cost(w)effective OR economic)/ti,ab OR economic evaluation!/de from EMBASE OR economic value/de from BIOSIS Previews

		#4 CANADA FILTER Canada!/de from MEDLINE, EMBASE OR Canad?/ti,ab OR British(w)Columbia/ti,ab OR Alberta/ti,ab OR Saskatchewan/ti,ab OR Manitoba/ti,ab OR Ontario/ti,ab OR Quebec/ti,ab OR Nova(w)Scotia/ti,ab OR New(w)Brunswick/ti,ab OR Prince(w)Edward(w)Island/ti,ab OR Newfoundland/ti,ab OR Yukon/ti,ab OR Northwest(w)Territories/ti,ab OR Nunavut/ti,ab OR (Canada OR British(w)Columbia OR Alberta OR Saskatchewan OR Manitoba OR Ontario OR Quebec OR New(w)Brunswick OR Nova(w)Scotia OR Newfoundland OR Prince(w)Edward(w)Island OR Yukon(w)Territory OR Yukon OR Northwest(w)Territories OR Nunavut OR Nunavut(w)Territory)/de from BIOSIS Previews OR (Vancouver OR Victoria OR Calgary OR Edmonton OR Winnipeg OR Hamilton OR Toronto OR Ottawa OR Montreal OR Quebec OR Halifax)/ti,ab #5 HEALTH ECONOMICS LESS SENSITIVE FILTER (cost(w)effective? OR sav?)/ti,ab OR cost-benefit analysis/de from MEDLINE,BIOSIS Previews OR cost analysis/de from BIOSIS Previews OR (cost(w)effective OR sensitivity(w)analys? OR cost(w)effectiveness)/ti,ab OR economic evaluation!/de from EMBASE OR economic value/de from BIOSIS Previews
The Cochrane Library 2005 issue 3 (October 4, 2005)		Search logic: (PPIs AND Indications) AND Canada filter Same MeSH descriptors and keywords as DIALOG® MEDLINE search; adapted search commands for Wiley InterScience® search interface.

Appendix 3: AMSTAR Instrument for Systematic Reviews

A MeaSurement Tool to Assess Reviews (AMSTAR), 2005

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and the consensus procedure for disagreements should be reported.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases (e.g. Central, EPOC, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an exclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and reported? 'A priori' methods of assessment should be reported (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess the homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot) and statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

AMSTAR 2005 (Beverley Shea, CIET, Institute of Population Health, Ottawa: personal communication, 2005 Oct)

Appendix 4a: Adapted SIGN 50 Checklist for Randomized Controlled Trials[269]

Indication:	Recommendation #:	Lead Author:
Title:		
Reviewer:	Date:	RefMan #:

SIGN	Methodology Checklist: Randomized Controlled Trials

Section 1: Internal validity

In a well conducted RCT study…..		In this study this criterion is:		
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.3	*An adequate concealment method is used*	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?			
1.9	*All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)*	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed

Section 2: Overall Assessment Of The Study

2.1	*How well was the study done to minimise bias?* Code ++, +, or –	

Section 3: Others		
3.1	*How was this study funded?* *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	

Appendix 4b: Adapted SIGN 50 Checklist for Cohort Studies[270]

Indication:	Recommendation #:	Lead Author:
Title:		
Reviewer:	Date:	RefMan #:

SIGN

Methodology Checklist: Cohort studies

Section 1: Internal validity

In a well conducted cohort study:		**In this study the criterion is:**		
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
SELECTION OF SUBJECTS				
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.			
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
ASSESSMENT				
1.7	The outcomes are clearly defined.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.8	The assessment of outcome is made blind to exposure status.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed

1.10	The measure of assessment of exposure is reliable.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.12	Exposure level or prognostic factor is assessed more than once.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
CONFOUNDING				
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
STATISTICAL ANALYSIS				
1.14	Have confidence intervals been provided?			
Section 2: Overall Assessment Of The Study				
2.1	How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code ++, +, or –*			
Section 3: Others				
3.1	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*			

Appendix 4c: Adapted SIGN 50 Checklist for Case Control Studies[271]

Indication:	Recommendation #:	Lead Author:
Title:		
Reviewer:	Date:	RefMan #:

SIGN Methodology Checklist 4: Case-control studies

Section 1: Internal validity

	In an well conducted case control study:	***In this study the criterion is:***		
1.1	The study addresses an appropriate and clearly focused question	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
SELECTION OF SUBJECTS				
1.2	The cases and controls are taken from comparable populations	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.3	The same exclusion criteria are used for both cases and controls	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.4	What percentage of each group (cases and controls) participated in the study?		Cases: Controls:	
1.5	Comparison is made between participants and non-participants to establish their similarities or differences	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.6	Cases are clearly defined and differentiated from controls	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.7	It is clearly established that controls are non-cases	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
ASSESSMENT				
1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
1.9	Exposure status is measured in a standard, valid and reliable way	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
CONFOUNDING				
1.10	The main potential confounders are identified and taken into account in the design and analysis	Well covered Adequately addressed	Poorly addressed Not reported	Not applicable Not addressed
STATISTICAL ANALYSIS				
1.11	Confidence intervals are provided			

Section 2: *Overall Assessment Of The Study*		
2.1	How well was the study done to minimise the risk of bias or confounding? *Code ++, +, or –*	
Section 3: *Others*		
3.1	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	

Appendix 5: Data Extraction Table Used for Economic Studies

Data Extraction Table

Category	Alternatives
Background	
Source of funding	1. Government (foundations) 2. Industry 3. Private 4. Not specified
Year to which study applies	
Country	
Currency used	
Description of population	
Indication	
Comparators Drug dose intensity / duration etc	
Methods	
Time horizon	
Perspective	1. Ministry of health (province) 2. Societal 3. Private patient
Type of study	1. Cost effectiveness 2. Cost utility 3. Cost benefit 4. Cost minimization (effectiveness proven) 5. Cost comparison
Approach used	1. Economic study applied to RCT 2. Observational 3. Modeling 4. Others
Modeling approach	1. Decision analytic model 2. Markov model 3. Other
Modeling features	
Outcome used	1. Life years 2. QALY 3. Clinical indicator 4. Other (list)
Source of effectiveness data	1. Single study (RCT, meta-analysis) 2. Meta-analysis of RCTs with systematic search 3. Meta-analysis of RCTs with non-systematic search 4. Systematic review with systematic search 5. Non-systematic review with systematic search 6. Non-systematic review with non-systematic search 7. Retrospective study 8. Professional opinion 9. Other

Resources included	1. Hospital 2. Physician 3. Drugs 4. Diagnostic tests 5. Work loss 6. Personal out-of pocket expenses 7. Other
Physical resource use	1. Clinical trial data 2. Surveys of patients 3. Administrative data (including hospital records) 4. Literature 5. Professional opinion 6. Other 7. Not reported
Sources of unit cost data	
Hospital	1. MIS (including CIHI) 2. Micro-costing 3. Professional opinion 4. Literature (secondary sources) 5. Other
Medical doctor	1. Fee schedule 2. Other
Pharmaceuticals (drugs only)	1. Provincial formulary 2. Manufacturers list price 3. IMS or other data provider 4. Survey of pharmacies 5. Other
Pharmaceuticals (dispensing fee)	1. Pharmacy associations 2. Provincial drug plan 3. Other 4. Not specified 5. Not included
Sensitivity analysis	1. Deterministic One–way 2. Deterministic Two–way 3. Probabilistic One–way 4. Probabilistic Two–way 5. Other 6. None
Other	
Results	
Summary of efficiency (cost effectiveness etc)	
Stochastic results	
Key sensitivity variables	

Quality Assessment Table

Item	Criteria	BMJ #	Source from Data
Timelines	Are the timelines appropriate?	22	Time horizon
Type of study	Was the type of study justified?	6, 7	Type of study
Outcomes	Are the outcome indicators appropriate to the intervention?		Outcome used
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	8, 9	Source of effectiveness data
	Was adjustment made to estimate effectiveness?		Not currently used
Cost	Are the appropriate resources included?	3	Resources included
	Were quantities of resources measured appropriately?		Physical resource use
	Were unit costs appropriately measured?		Source of unit cost data
Discounting	Was discounting done and justified?		Discounting
Summary efficiency measure	Was an incremental measure used?		Summary of efficiency

Relevancy Assessment Table

Item	Criteria	BMJ #	Source from Data
Population	Is the population relevant to the intervention(s) being studied?	1, 13	Description of population
Intervention	Are the interventions relevant?	1, 5, 30	Comparators
Time frame	Is the time frame of the study sufficiently current?		Year to which the study applies
Setting	Is the setting relevant to Canadian practice?		Country, Perspective

Notes:

BMJ #: the related numbers in the standard BMJ (British Medical Journal) checklist.[28]
Source: the location of this information in the data extraction table.

Appendix 6: List of Excluded Guidelines and Consensus Documents

A. Outdated versions of included guidelines and consensus statements

1. Institute for Clinical Systems Improvement, Corrections Health Service. *Clinical practice guideline for dyspepsia*. Bloomington (MN): The Institute; 2002 Jan.

2. National Institute for Clinical Excellence. *The appropriate use of proton pump inhibitors in the treatment of dyspepsia: summary of evidence*. London: The Institute; 2000 Mar. Available: http://www.nice.org.uk/pdf/ppi_hta_report.pdf (accessed 2005 Dec 7).

3. Pharmacy Benefits Management Strategic Healthcare Group, Medical Advisory Panel. *The pharmacologic management of gastroesophageal reflux disease*. Updated. Washington: Veterans Health Administration; 2000. Available: http://www.pbm.va.gov/pocketcards/gerdpocketcard.pdf (accessed 2005 Dec 7).

4. Beck IT, Connon J, Lemire S, Thomson AB, Bourdages R, Carmichael C, et al. Canadian consensus conference on the treatment of gastroesophageal reflux disease. *Can J Gastroenterol* 1992;6(5):277-89.

5. Beck IT, Champion MC, Lemire S, Thomson AB, Anvari M, Armstrong D, et al. The second canadian consensus conference on the management of patients with gastroesophageal reflux disease. *Can J Gastroenterol* 1997;11 Suppl B:7B-20B.

6. Beck IT. Guidelines of the previous consensus conference and recent developments. *Can J Gastroenterol* 1997;11(Suppl B):21B-7B.

7. Copeland R. Implementation of NICE guidance: guidance on the use of proton pump inhibitors in the treatment of dyspepsia. *Pharmacy in Practice* 2002;12(3):119-26.

8. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Practice Parameters Committee of the American College of Gastroenterology. *Arch Intern Med* 1995;155(20):2165-73.

9. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999;94(6):1434-42.

10. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1998;93(7):1028-32.

11. Schroeder BM. Evaluation of epigastric discomfort and management of dyspepsia and GERD. *Am Fam Physician* 2003;68(6):1215-20.

12. Thomson AB, Chiba N, Armstrong D, Tougas G, Hunt RH. The second Canadian gastroesophageal reflux disease consensus: moving forward to new concepts. *Can J Gastroenterol* 1998;12(8):551-6.

B. Guidelines and consensus statements developed in excluded countries or regions

1. Sung J, Russell RI, Nyeomans, Chan FK, Chen S, Fock K, et al. Non-steroidal anti-inflammatory drug toxicity in the upper gastrointestinal tract. *J Gastroenterol Hepatol* 2000;15 Suppl:G58-G68.

C. Reviews or restatements of existing guidelines or consensus statements

1. NIH Consensus Conference: Helicobacter pylori in peptic ulcer disease: NIH consensus development panel on Helicobacter pylori in peptic ulcer disease. *JAMA* 1994;272(1):65-9.

2. Summary of the NIH consensus: Helicobacter pylori in peptic ulcer disease. *Md Med J* 1994;43(10):923-4.

3. Helicobacter pylori: guidelines for health care providers. *Mod Med Aust* 1996;39(1):45-52.

4. APhA drug treatment protocols: uncomplicated gastroesophageal reflux disease. *J Am Pharm Assoc (Wash)* 1997;NS37(5):507-9.

5. Refluxkrankheit der speiserohre und peptisches ulkus [Therapy recommendations for esophageal reflux disease and peptic ulcer]. *Fortschr Med* 1998;116(34):35-8.

6. National Institute for Clinical Excellence. *Guidance on the use of proton pump inhibitors in the treatment of dyspepsia* [Technology appraisal guidance no 7]. London: The Institute; 2000 Mar. Available: http://www.nice.org.uk/page.aspx?o=15945 (accessed 2005 Dec 9).

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Appendix 7: List of Selected Guidelines and Consensus Documents

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Appendix 9: Selected Economic Studies and Relevant Synopsis of Existing Recommendations

Economic Study	Synopsis of Existing Recommendations
Romagnuolo et al. (2002)[123]	G9A
Goeree et al. (2002)[122]	G1A G1B G1C G5A G5B G5C G6A G8A
Goeree et al. (1999)[124]	G1A G1C G5B G6A
O'Brien et al. (1996)[125]	G1A G1C G5A G5B G6A G8A
Makris et al. (2003)[161]	D1A D2A D2B D2C
Chiba et al. (2004)[160]	D1A D2C
O'Brien et al. (1997)[268]	P1A P2A

Appendix 10: Guideline Matrix Table: GERD

Synopsis of Existing Recommendations / CPG/CD	G 1A	G 1B	G 1C	G 2A	G 3A	G 4A	G 5A	G 5B	G 6A	G 6B	G 6C	G 7A	G 8A	G 8B	G 9A	G 9B	G 10 A	G 10 B	G 11 A
Canadian Guidelines and Consensus Documents																			
Armstrong et al. 2005[12]	✓	✓	✓	✓	✓	✓	✓			✓		✓	✓	✓	✓			✓	✓
TOPP (AB) 2005[72]				✓															
GPAC (BC) 2004[31]	✓																		
Quebec CRUM 2002[45]		✓	✓																
OPOT (ON) 2000[23]	✓						✓	✓											
Other Guidelines and Consensus Documents																			
DeVault & Castell (USA) 2005[13]	✓		✓				✓												✓
Prodigy (UK) 2005[15]		✓	✓	✓		✓			✓	✓	✓	✓						✓	✓
NZGG (New Zealand) 2004[29]	✓		✓																
NICE 2004[24]	✓	✓	✓	✓			✓			✓		✓		✓					
ICSI (USA) 2004[30]	✓																		
Fock et al. (Asia-Pacific)		✓	✓						✓			✓							

Synopsis of Existing Recommendations / CPG/CD	G 1A	G 1B	G 1C	G 2A	G 3A	G 4A	G 5A	G 5B	G 6A	G 6B	G 6C	G 7A	G 8A	G 8B	G 9A	G 9B	G 10 A	G 10 B	G 11 A
2004[46]																			
VHA/DoD (USA) 2003[32]	✓	✓							✓	✓									
MAMSI (USA) 2003[73]				✓															
NASPGHN (N. America) 2003[48]			✓																
U. of Michigan (USA) 2002[47]			✓																
Sampliner (USA) 2002[118]																	✓	✓	
Marzo et al. (Spain) 2002[75]				✓		✓													
Digestive Health Foundation (Australia) 2001[49]			✓																
Rudolph et al. (N. America) 2001[50]			✓																

Synopsis of Existing Recommendations / CPG/CD	G 1A	G 1B	G 1C	G 2A	G 3A	G 4A	G 5A	G 5B	G 6A	G 6B	G 6C	G 7A	G 8A	G 8B	G 9A	G 9B	G 10 A	G 10 B	G 11 A
Federal Bureau of Prisons (USA) 2001[33]	✓															✓			
French/ Belgian Consensus 2000[34]	✓		✓																
Johnson 2000[16]				✓															
Kroes et al. (Europe) 1999[35]	✓	✓	✓																✓
Moss et al. (USA) 1998[98]								✓											
Baldi et al. (Italy) 1998[101]												✓							
First International Symposium 1997[74]				✓															
Fennerty et al. (USA) 1996[36]	✓					✓													

Appendix 11: Guideline Matrix Table: Dyspepsia

Synopsis of Existing Recommendations / CPG/CD	D 1A	D 1B	D 1C	D 1D	D 1E	D 1F	D 1G	D 1H	D 2A	D 2B	D 2C	D 2D	D 2E	D 3A	D 3B	D 4A	D 4B	D 4C	D 4D	D 4E	D 4F`	D 5A	D 5B
TOPP (AB) 2005[153]																	✓						
GPAC (BC) 2004[145]												✓											
Quebec CRUM 2002[45]					✓	✓	✓	✓			✓		✓	✓	✓				✓				
Veldhuyzen van Zanten et al. 2000[21]				✓					✓		✓	✓											
Prodigy (UK) 2005[152]																	✓			✓		✓	✓
Prodigy (UK) 2004[143]											✓												
NZGG (New Zealand) 2004[29]																✓							
NICE 2004[24]	✓	✓	✓								✓					✓		✓		✓			
ICSI (USA) 2004[30]			✓																				
SIGN 68 (Scotland)									✓	✓						✓	✓						

Synopsis of Existing Recommendations / CPG/CD	D 1A	D 1B	D 1C	D 1D	D 1E	D 1F	D 1G	D 1H	D 2A	D 2B	D 2C	D 2D	D 2E	D 3A	D 3B	D 4A	D 4B	D 4C	D 4D	D 4E	D 4F`	D 5A	D 5B
2003[137]																							
MAMSI (USA) 2003[73]				✓																			
Mascort et al. (Spain) 2003[130]		✓	✓															✓					
British Soc. Gastroenterology 2002[138]									✓														
Talley 2002[129]		✓	✓								✓				✓		✓			✓	✓		
Federal Bureau of Prisons (USA) 2001[33]				✓																			
Hellenic Soc. Of Gastroenterology 1999[148]																✓							
Talley et al. (Asia-Pacific) 1998[154]																	✓						
Talley et al. (World	✓																						

Synopsis of Existing Recommendations / CPG/CD	D 1A	D 1B	D 1C	D 1D	D 1E	D 1F	D 1G	D 1H	D 2A	D 2B	D 2C	D 2D	D 2E	D 3A	D 3B	D 4A	D 4B	D 4C	D 4D	D 4E	D 4F`	D 5A	D 5B
congress) 1998[126]																							
Hungin et al. (UK) 1997[132]				✓																			
Talley 1991[159]																			✓				

Appendix 12: Guideline Matrix Table: Peptic Ulcer Disease

Synopsis of Existing Recommendations / CPG / CD	P 1A	P 1B	P 2A	P 2B	P 2C	P 2D	P 3A	P 3B	P 4A	P 4B	P 4C	P 4D
Canadian Guidelines and Consensus Documents												
Jones et al. 2005[232]						✓						
Hunt et al. 2004[226]				✓							✓	
Quebec CRUM 2002[45]	✓		✓		✓		✓		✓			✓
OPOT 2000[23]	✓	✓	✓	✓	✓		✓		✓		✓	✓
Hunt et al. 1999[162]	✓		✓		✓							
Sherman et al. 1999[233]						✓						
Other Guidelines and Consensus Document												
Prodigy (UK) 2005[163]	✓	✓	✓		✓		✓		✓			✓
NZGG (New Zealand) 2004[29]	✓		✓		✓		✓	✓	✓	✓		✓
NICE 2004[24]	✓		✓		✓		✓		✓	✓		✓
Dubois et al. (USA) 2004[266]												✓
Maastricht 2-2000 Consensus (Europe) 2002[164]	✓	✓	✓		✓						✓	
British Soc. Gastroenterology 2002[138]			✓		✓							
Gisbert et al. (Spain) 2000[177]		✓	✓		✓							
Peterson et al. (USA) 2000[188]			✓		✓							
Gold et al. (N. America) 2000[165]	✓					✓						
SIGN 7 (Scotland) 1999, 1996 [167,166]	✓		✓									

Synopsis of Existing Recommendations / CPG / CD	P 1A	P 1B	P 2A	P 2B	P 2C	P 2D	P 3A	P 3B	P 4A	P 4B	P 4C	P 4D
Agence Française de Sécurité Sanitaire des Produits de Santé (France) 1999[178]		✓	✓		✓		✓	✓				
Deltenre et al. (Belgium) 1998[168]	✓		✓		✓						✓	
Jovell et al. (Spain) 1998[179]		✓	✓									
Howden et al. (USA) 1998[189]			✓	✓								
Lanza et al. (USA) 1998[25]									✓	✓		✓
Buckley et al. (Ireland) 1996[180]		✓	✓		✓							

Appendix 13: Evidence Inventory Tables for GERD, Reflux Esophagitis and Barrett's Esophagus

Question G1: Are PPIs more effective than H2RAs in patients with GERD, ENRD and esophagitis?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G1A	PPIs are more effective than H2RAs for controlling the symptoms and improving the healing and the quality of life in GERD. H2RAs may be effective in some patients with mild to moderate symptoms of GERD. ***i.*** PPIs are more effective than H2RAs for remission of symptoms and healing in patients with GERD. ***ii.*** PPIs may be used in patients with GERD who had incomplete response to a previous trial of H2RAs ***iii.*** There is a greater improvement in quality of life with PPIs than H2RAs in GERD. ***iv.*** H2RAs may be effective in some patients with mild to moderate symptoms of GERD	4 [37,51,85,272]	11 [38,43,44,56,57,61,64,65,273-275]		1 [276]
G1B	PPIs are more effective than H2RAs for remission of heartburn and improving the quality of life in ENRD. **i.** PPIs are more effective than H2RAs for remission of heartburn in ENRD. **ii.** PPIs are more effective than H2RAs for improving quality of life in patients with ENRD	21 [37,272]	3 [39,43,44]		
G1C	PPIs are more effective and faster than H2RAs for controlling the symptoms and improving the healing in patients of esophagitis. **i.** PPIs are more effective than H2RAs for remission of symptoms and improving the healing of esophagitis. **ii.** The speed of heartburn relief and improvement of healing are faster with omeprazole than ranitidine in patients with erosive or reflux esophagitis.	2 [51,85]	8 [66-71,135,277]		1 [278]

QuestionG 2: What is the status of double-dose vs single-dose of PPIs as initial therapy in GERD?

COMPUS Synopsis of Existing Recommendations	Evidence Inventory			
	SR/MA	RCT	Obs	Other

G2A	Double dose of PPI is no better than standard dose for healing of GERD or esophagitis. Twice-daily, standard dose may be used for patients with severe symptoms. **i.** Doubling the dose of PPI therapy is no better than standard dose PPI therapy for healing typical GERD or esophagitis. **ii.** Twice-daily, standard dose PPIs may be used for patients who have severe symptoms of GERD.		20 41,42,56,64,65,71,76,78,80,84,107,110,111,114,115,279-283		

Question G3: What is the duration of treatment for esophagitis?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G3A	Long-term PPI therapy is recommended for erosive esophagitis complicated by strictures with an aim of preventing recurrence.		3 82-84		2 284,285

Question G4: How do the individual drugs in the PPI category differ in controlling the initial symptoms and/or disease?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G4A	Standard doses of PPIs are equally effective in GERD and esophagitis.	2 40,85	11 86-89,91,95-97,280,286,287		

Question G5: How should the long-term maintenance for GERD be conducted?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G5A	Long-term maintenance in GERD should be given at the lowest dose and frequency that is sufficient to achieve optimal control of the patient's symptoms.				4 12,13,23,24
G5B	Once a dose of either a H2RA, prokinetic agent, and/ or a PPI that relieves symptom has been identified, this dose should be maintained for a period of 3 months. After this time an attempt should be made to reduce the dose, with the aim of maintaining a stable clinical status. If symptoms recur, then the patient should go back to full-dose PPI and plan for long-term treatment.				2 23,98

Question G6: Should attempts be made to step-down and discontinue therapy or continue the current therapy?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G6A	Step-down therapy in patients with GERD and erosive esophagitis prevents symptomatic relapse in a majority of patients after stopping the PPI. Continued PPIs provided better heartburn relief than step-down to H2RAs. Many patients require medications other than PPI. The optimal approach of step-up, step down and no step remains to be determined. **i.** Step-down therapy in patients with GERD and erosive esophagitis prevents symptomatic relapse in a majority of patients in one year after stopping the PPI. Many patients require medications other than PPI. **ii.** Continued PPIs provided better heartburn relief than step-down to H2RAs. The optimal approach of step-up or step-down remains to be determined**.**		1 [99]		2 [32,46]
G6B	Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment. **i.** Individuals whose symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy. **ii.** If there is an initial response to treatment, but symptoms have now returned, offer maintenance treatment. Restart the treatment (e.g., PPI) at full dose, with a limited number of repeat prescriptions. Encourage people to step-down treatment to the lowest dose required to control symptoms.		1 [99]		3 [12,13,10 1]
G6C	In patients with LA grade C and D esophagitis who remain symptomatic with regular dose PPIs, offer a double dose PPI for a further month, then encourage patients to step down to the lowest dose required to control symptoms.				1 [15]

Question G7: What is the status of "on-demand" therapy in ENRD and GERD?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G7A	"On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD. PPIs could be used as 'on demand' therapy. **i.** "On-demand" acid suppression therapy is a reasonable long-term medical strategy for selected patients with ENRD and GERD. **ii.** PPIs can be used as "on-demand" therapy.		6 [69,100,102-104,115]		

Question G8: What is the status of half-dose PPI in GERD and reflux esophagitis?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G8A	The effect of half-dose of PPI is less than the standard dose PPI for acute treatment in ENRD.		4 [105,106,108,109]		
G8B	The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD and esophagitis. **i.** The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission and healing in GERD. **ii.** The effect of half-dose PPIs is less than the standard dose PPIs in the maintenance of remission in esophagitis.	1 [52]	17 [66,67,69,71,81,102-106,108-110,112,113,283,288]		

Question G9: In the management of GERD, what should be preferred, PPIs or surgery?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G9A	Antireflux surgery was superior to PPI therapy in terms of symptomatic relapse, but if patients increased the PPI dose at relapse, there was no difference between the treatment strategies.		3 [116,117,289]		
G9B	Surgical procedures could be considered if high dose PPI is ineffective, poorly tolerated, or if GERD is associated with serious complications despite therapy.				

Question G10: What is the role of PPIs in the management of Barrett's esophagus?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G10A	GERD can be such an insidious long-standing process, even a patient with Barrett's esophagus lacking symptoms may benefit from a trial of PPI therapy.				
G10B	Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE. **i.** Neither medical nor surgical therapy has been proven to prevent the development of, or progression of BE. **ii.** Even high-dose PPI therapy will not usually result in reversal of Barrett's esophagus.		4 [119-121,289]		

Question G11: What are different adverse drug reactions of PPIs?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	Obs	Other
G11A	PPIs are generally well tolerated. Adverse effects include GI disturbances (most commonly diarrhea), headaches, and dizziness. However, long term safety is the major concern, when maintenance therapy with PPIs is considered. Increasing gastric levels as well as proliferation of endocrine cells have been shown, but no gastric carcinoids have been detected in several long-term human studies. Of more concern are those treated with a PPI with a *H. pylori* infection because they appear to be at risk of atrophic gastritis. Consequently it was suggested that it might increase the risk of *H. pylori* related gastric cancer.				4 [12,13,15,35]

Appendix 14: Evidence Inventory Tables for Dyspepsia

Question D1: What is the role of PPIs in empiric therapy for uninvestigated dyspepsia?

i. First-line

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D1A	PPIs are recommended for empiric therapy for uninvestigated dyspepsia as initial therapeutic strategies. Early endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment. There is currently no sufficient evidence to guide which should be offered first.	0	2 [127,128]	0	0
D1B	PPIs are more effective than alginates/antacids at reducing dyspeptic symptoms in trials of pts with uninvestigated dyspepsia.	1 [131]	2 [290,291]	0	0
D1C	PPIs are more effective than H2RAs at reducing dyspeptic symptom in trials of patients with uninvestigated dyspepsia.	1 [131]	3 [291-293]	0	1 [30]
D1D	PPIs (or H2RAs or prokinetics) for four weeks in uninvestigated dyspepsia patients whose dominant symptoms are heartburn and acid regurgitation is recommended	0	0	0	4 [21,33,73,132]
D1E	PPIs should be used as a first-line initial treatment for four to eight weeks when symptoms mimic those of GERD and are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patient feels the symptoms have a significant impact on their quality of life.	0	2 [38,99]	0	5 [21,294-297]
D1F	PPIs should be used as a first-line maintenance treatment at regular customized dosages when symptoms mimic those of GERD and are present three or more days per week, are severe, and interfere with daily activities or, more importantly, the patient feels the symptoms have a significant impact on their quality of life.	0	0	0	1 [296]

ii. Second-line and maintenance

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D1G	PPIs constitute second-line treatment for four to eight weeks in uninvestigated dyspepsia whose manifestations mimic those of gastroesophageal reflux if the symptoms are unresponsive to first line H2RA treatment for at least four weeks, when symptoms mimic those of GERD and are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, the patient feels the symptoms have a mild to moderate impact on their quality of life.	1 [136]	1 [38]	0	8 [294-296,298-302]
D1H	PPIs should be used for maintenance therapy when symptoms have been relieved by an initial second-line PPI treatment, when symptoms are present three or more days per week, are mild to moderate, and interfere with daily activities or, more importantly, the patient feels the symptoms have a mild to moderate impact on their quality of life.	0	0	0	1 [296]

Question D2: What is the role of *H. pylori* "test and treat" strategy for uninvestigated dyspepsia?

i. In younger adults

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D2A	*H. pylori* "test and treat" strategy for uninvestigated dyspepsia in younger patients (50 years or less) who have no alarm features is recommended. Note: the cut off age for this varies between guidelines	1 [131]	4 [139-142]	4 [303-306]	2 [307,308]

ii. In older adults

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D2B	*H. pylori* "test and treat" may be as appropriate as early endoscopy for the initial investigation and management of patients over the age of 55 years presenting with uncomplicated dyspepsia.	0	0	0	1 [137]

iii. In adults of all ages

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D2C	*H. pylori* "test and treat" strategy is recommended as an initial step in the management of patients with uninvestigated dyspepsia.	1 [131]	1 [144]	0	9 [21,24,45,126,143,164,309-311]

iv. Role of PPI in Hp negative dyspeptics

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D2D	PPIs for four weeks are recommended for patients with dyspepsia with negative *H. pylori* testing but without endoscopy and imaging done. If symptoms are not relieved, increase dose or switch to another therapy.	1 [146]	0	0	2 [21,145]
D2E	PPIs constitute a second-line treatment for four to eight weeks for *H. pylori* negative dyspepsia without endoscopy and imaging done, if the symptoms are unresponsive to first-line (H2RA) treatment.	0	0	0	1 [312]

Question D3: What is the role of PPIs for NSAIDs-induced dyspepsia (ulcer prophylaxis)?

i. In low risk patients

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D3A	PPIs constitute a second-line treatment in uninvestigated dyspepsia patients with a low risk of severe gastrointestinal events when the symptoms are unresponsive to first-line H2RA treatment (for at least 4 weeks) and NSAIDs cannot be discontinued.	0	0	0	2 [154,313]

ii. In high-risk patients

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D3B	PPIs should be used as the first line treatment in dyspepsia patients with a high risk of gastrointestinal events.	1 [147]	0	0	7 [21,23,31 3-317]

Question D4: What is the role of PPIs for functional dyspepsia?

i. Role of *H. pylori* eradication

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D4A	For proven functional dyspepsia, the results from *H. pylori* eradication are controversial (no consensus)	3 [149-151]	4 [318-321]	0	1 [148]

ii. First-line therapy

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D4B	A trial of acid suppression (i.e., H2RAs or PPIs) therapy may be considered in the management of functional dyspepsia.	0	3 [146,155, 156]	0	1 [126]
D4C	PPIs are superior to placebo for the disappearance or improvement of symptoms in functional dyspepsia.	2 [157,158]	0	0	1 [152]
D4D	PPIs should not be used on a regular basis for functional dyspepsia since functional dyspepsia can have various causes.	3 [136,157,15 8]	0	0	2 [45,159]

iii. Role of long-term therapy

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D4E	PPI therapy should be stepped down to the lowest dose required to control symptoms and discuss using the treatment on an "on-demand" basis with patients to manage their own symptoms for those patients with symptom relapse after initial care strategies.	0	0	0	3 [24,129,1 52]
D4F	High-dose PPIs is one of the three recommended options (or switch therapy or endoscopy) if dyspepsia symptom persists.	0	0	0	1 [129]

Question D5: Which PPI should be used for patients with dyspepsia? What are the differences among PPIs in terms of clinical efficacy and safety? What is the recommended PPI dose for non-ulcer dyspepsia?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory			
		SR/MA	RCT	OBS	Other
D5A	Differences between the PPIs in clinical efficacy and safety are minimal.	0	0	0	1 [152]
D5B	PPI doses for non-ulcer dyspepsia as recommended by the PRODIGY guideline are Omeprazole Low Dose (LD) 10mg od, *H. pylori* eradication double dose (DD) 20mg bid; Lansoprazole LD 15mg od, DD 30mg bid; Pantoprazole LD 20mg od, DD 40mg bid; Rabeprazole LD 10mg od, DD 20mg bid; Esomeprazole LD not available, DD 20mg bid.	0	0	0	1 [152]

Appendix 15: Evidence Inventory Tables for Peptic Ulcer Disease

Question P1: What is the optimal use of PPIs in the treatment of *H. pylori* positive PUD?

	COMPUS Synopsis of Existing Recommendations	Evidence Inventory SR/MA	RCT	Obs	Other
P1A	*H. pylori* eradication therapy is recommended for patients diagnosed with gastric or duodenal ulcer who are infected with *H. pylori*.	4 169-172	9 173-176,322-326	4 327-330	3 317,331, 332
P1B	Acid-suppression therapy following *H. pylori* eradication may be required until healing is documented in patients with complicated ulcers, or when ulcer symptoms persist. Follow-up acid-suppression therapy after *H. pylori* eradication is not required in uncomplicated duodenal ulcer that is asymptomatic.	0	8 181,183-187,198, 333	1 334	2 332,335

Question P2: What is the optimal use of PPIs in *H. pylori* eradication regimens?

	COMPUS Synopsis of Existing Recommendations	Evidence Inventory SR/MA	RCT	Obs	Other
P2A	A PPI-based triple therapy regimen is recommended as a first-line therapy for adults in whom *H. pylori* eradication is indicated. i. The following triple therapy regimens provide optimal eradication rates: a twice daily course of standard dose PPI, amoxicillin 1 g and clarithromycin 500 mg (PAC regimen) OR a twice daily course of standard dose PPI, metronidazole 500 mg and clarithromycin 250 mg-500 mg (PMC regimen). ii. Various PPIs have similar efficacy when used in triple therapy. iii. PPI dose in triple therapy regimens: Optimal eradication rates are achieved with double-dose PPIs (a standard dose administered twice daily) in triple-therapy regimens. iv. PPI-triple therapy duration: 7-14 days. Factors other than eradication rates, such as cost, may be taken into account when choosing between 7 and 14 days duration.	10 190-196,213,215,336	50 181,197-199,201-204,206, 207,214, 216,221, 222,224, 337-343 184,200, 208-210,212, 220,223, 225,344-362	17 219,231, 363-377	14 317,378-390
P2B	A combination of standard dose PPI twice daily, 262 mg bismuth subsalicylate four times daily, 375-500 mg metronidazole four times daily and	3 215,227,228	0	1 391	3 392-394

P2C	500 mg tetracycline four times daily (PBMT quadruple therapy), given for 7-14 days can be considered for first-line eradication therapy. Patients who remain *H. pylori* positive after an initial attempt at eradication with a first-line regimen can be treated with a 7-14 day course of PPI quadruple therapy (PBMT), or an alternative PPI-triple therapy with different antibiotics from the initial attempt.	4 169,191,193,395	0	4 229-231,396	10 21,164,386,396-402
P2D	For children in whom *H. pylori* eradication is indicated, a PPI-triple therapy can be used as in adults with appropriate dose adjustment, for a duration of 7-14 days.	1 234	1 235	1 236	6 400,403-407

Question P3: What is the optimal use of PPIs in the treatment of *H. pylori* negative PUD?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory SR/MA	RCT	Obs	Other
P3A	PPI or H2RA therapy is recommended for ulcer healing in *H. pylori* negative patients diagnosed with a duodenal or gastric ulcer. PPIs provide higher ulcer healing rates as compared to H2RAs.	6 237,238,241-243,408	10 239,240, 244-251	1 409	7 410-416
P3B	Maintenance treatment with H2RA or PPI therapy may be required in *H. pylori* negative patients with a history of frequent ulcers, previous ulcer complications, or for whom co-morbid factors may cause ulcer complications to be life-threatening.	0	3 252-254	0	2 414,415

Question P4: What is the optimal use of PPIs in the treatment and prevention of NSAID-induced ulcer?

COMPUS Synopsis of Existing Recommendations		Evidence Inventory SR/MA	RCT	Obs	Other
P4A	Full-dose H2RA, PPI or misoprostol therapy is recommended for ulcer healing in patients with NSAID-associated duodenal or gastric ulcers. PPIs are more effective than H2RAs in healing large or complicated ulcers, or when NSAID therapy must be continued. PPIs are better tolerated than high dose misoprostol.	0	5 248,256-258,417	0	4 21,313,418,419
P4B	Offer eradication therapy to *H. pylori* positive NSAID users with previous or current peptic ulcer.	1 263	5 259-262,420	1 421	6 313,422-426
P4C	Offer *H. pylori* eradication therapy to reduce ulcer risk in *H. pylori* positive patients without peptic ulcer who are initiating long-term therapy with	1 263	3 264,265, 427	0	1 423

P4D	conventional NSAIDs or ASA. Offer ulcer prophylaxis with a PPI, H2RA, or misoprostol to all long-term NSAID or ASA users at high risk for the development of ulcer and/or ulcer complications. Risk factors include: age, history of PUD, previous GI bleeding, history of cardiovascular diseases, use of high NSAID doses, and concurrent use of corticosteroids or anticoagulants. Standard dose PPIs, double dose H2RAs, and 800 mcg/day of misoprostol are all effective for the prevention of NSAID-associated gastric and duodenal ulcers while single dose H2RAs and lower misoprostol doses are less effective. The use of misoprostol may be limited by adverse effects.	1 147	6 256,257, 267,428- 430	0	5 21,313,3 17,418,4 31

Appendix 16: Summary of Economic Studies Related to GERD

1. Goeree et al. (2002)[122]

Data Extraction Table

Background		
Source of funding	Industry (Abbot Laboratories Limited)	
Year to which study applies	2001	
Country	Canada	
Currency used	2001 Canadian dollars	
Description of population	Adult patients with moderate-to-severe heartburn	
Indication	Heartburn	
Comparators Drug dose intensity / duration etc	Strategy 1: Intermittent short course H_2RA	Ranitidine 150mg bid / 4 wks, no further treatment until recurrence
	Strategy 2: Intermittent long course H_2RA	Ranitidine 150mg bid / 4 wks, another 4 wks if symptoms persist, no further treatment until recurrence
	Strategy 3: Intermittent PPI	Omeprazole 20mg or lansopazole 30mg od / 4 wks, no further treatment until recurrence
	Strategy 4: Maintenance H_2RA	Ranitidine 150mg bid / 4 wks, continuous maintenance treatment w/ an H_2RA (same dose)
	Strategy 5: Maintenance PPI	Omeprazole 20mg or lansoprazole 30mg od / 4 wks, continuous maintenance treatment w/ a PPI (same dose)
	Strategy 6: Step-down maintenance H_2RA	Omeprazole 20mg or lansoprazole 30mg od / 4 wks, continuous maintenance treatment w/ an H_2RA (ranitidine 150mg bid)
	Strategy 7: Step-down maintenance PPI	Omeprazole 20mg or lansoprazole 30mg od / 4 wks, continuous maintenance treatment w/ low dose (omeprazole 10mg or lansoprazole 15mg od)
Methods		
Time horizon	1 year	
Perspective	Ministry of health (province)	
Type of study	Cost effectiveness, Cost utility	
Approach used	Modeling	
Modeling approach	Decision analytic model	
Modeling features	Step-up, step-down, & switching algorithms conditional upon symptomatic relief & recurrence. A state-transition w/ three 4-months cycles.	

Outcome used	QALY, Clinical indicator (Symptom–free weeks, Heartburn recurrences)	
Source of effectiveness data	Meta-analysis of RCTs with systematic search	
Resources included	Hospital, Physician, Drugs, Diagnostic tests	
Physical resource use	Professional opinion (survey of family physicians & gastroenterologists)	
Sources of unit cost data		
Hospital	MIS (A hospital participating in Ontario Case Costing Project in South-western Ontario)	
Medical doctor	Fee schedule (Ontario Schedule of Benefits for insured medical services)	
Pharmaceuticals (drugs only)	IMS or other data provider	
Pharmaceuticals (dispensing fee)	Provincial drug plan (Ontario)	
Sensitivity analysis	Probabilistic One–way, Probabilistic Two–way	
Other		
Results		
Summary of efficiency (cost effectiveness etc.)		<u>Incremental cost per QALY</u> (relative to the next less costly non-dominated strategy)
	Strategy 2: Intermittent long course H_2RA	-
	Strategy 1: Intermittent short course H_2RA	CAD $7,515
	Strategy 3: Intermittent PPI	CAD $12,206
	Strategy 6: Step-down maintenance H_2RA	CAD $22,367
	Strategy 5: Maintenance PPI	CAD $98,422
	Strategy 4: Maintenance H_2RA	Dominated (E)
	Strategy 7: Step down maintenance PPI	Dominated (E)
Stochastic results	Fair amount of variation	
Key sensitivity variables		

Quality Assessment Table

Item	Criteria	Goeree et al. Value in Health 2002
Timelines	Are the timelines appropriate?	Longer time horizon would have been better but the 1-year time horizon was chosen due to the lack of longer term follow up studies.
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	Data from single arms of trials pooled together
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Professional opinion used
	Were unit costs appropriately measured?	Yes (Ontario)
Discounting	Was discounting done and justified?	N/A
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	Criteria	Goeree et al. Value in Health 2002
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	Yes
Time frame	Is the time frame of the study sufficiently current?	Yes
Setting	Is the setting relevant to Canadian practice?	Yes

2. Romagnuolo et al. (2002)[123]

Data Extraction Table

Background		
Source of funding	Government (foundations) (Dr Romagnuolo was sponsored by the Alberta heritage foundation for medical research)	
Year to which study applies	Not stated	
Country	Canada	
Currency used	Canadian dollars	
Description of population	Base case: A 45-year old man with endoscopically proven grade II to IV erosive reflux esophagitis, refractory to H_2-blockers.	
Indication	Erosive reflux esophagitis	
Comparators Drug dose intensity / duration, etc	Strategy 1: Medical therapy	w/ omeprazole In the healing phase, patients assigned to one of five treatment arms, each one representing different dose &/or duration of therapy required to accomplish successful endoscopic healing. In the maintenance phase, omeprazole 20mg od for those requiring > 4 months of therapy or > 60mg od omeprazole to achieve healing. In case of relapse, maintenance dose escalated by 20mg od increments to a maximum of 60mg od.
	Strategy 2: Surgery using LNF	
Methods		
Time horizon	5 years	
Perspective	Ministry of health (Alberta)	
Type of study	Cost utility	
Approach used	Modeling	
Modeling approach	Markov model	
Modeling features	A two-stage Markov model (healing & maintenance phases) Five separate Markov chains stemming from the five regimens required for successful healing Transitions allowed at the end of each 3-month cycle A Monte Carlo simulation of 10,000 patients in each arm to estimate the mean costs & utilities for each strategy; & the variances & 95% interpercentile ranges for each parameter. In the simulation, each patient passes thru the model from beginning to end (5 years), w/ transitions at each cycle decided by a random generator & the probabilities associated w/ that transition.	
Outcome used	QALY	
Source of effectiveness data	Meta-analysis of RCTs with non-systematic search, Non-systematic reviews with non-systematic search, Retrospective study, Professional opinion	
Resources included	Hospital, Physician, Drugs, Diagnostic tests	
Physical resource use	Other	

Sources of unit cost data		
Hospital	Other (A local costing study carried out at the Grey Nuns Hospital in Edmonton, Per-diem costs estimated from charges billed to non Alberta residents (Grey Nuns Hospital))	
Medical doctor	Fee schedule (Alberta Health Care Insurance Plan Fee schedule)	
Pharmaceuticals (drugs only)	Other (Local pharmacy)	
Pharmaceuticals (dispensing fee)	Other (Local pharmacy)	
Sensitivity analysis	Deterministic One-way, Deterministic Two-way, Other (Threshold analysis)	
Other		
Results		
Summary of efficiency (cost effectiveness etc.)	 Strategy 2: Surgery Strategy 1: Medical therapy	<u>Incremental cost per QALY</u> - CAD $129,667
Stochastic results	Substantial variation	
Key sensitivity variables	Cost of medical therapy, Cost of surgery, and Time	

Quality Assessment Table

Item	**Criteria**	**Romagnuolo et al. 2002**
Timelines	Are the timelines appropriate?	Yes
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	MA w/ non-systematic search, non-SR, retrospective study, professional opinion used
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Not clear
	Were unit costs appropriately measured?	Yes (Alberta)
Discounting	Was discounting done and justified?	Yes
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	Criteria	Romagnuolo et al. 2002
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	Yes
Time frame	Is the time frame of the study sufficiently current?	Yes
Setting	Is the setting relevant to Canadian practice?	Yes

3. Goeree et al. (1999)[124]

Data Extraction Table

Background		
Source of funding	Industry (Astra Pharma Inc., Ontario, Canada)	
Year to which study applies	1998	
Country	Canada	
Currency used	1998 Canadian dollars	
Description of population	Patients with erosive oesophagitis (i.e., grades II to IV using the Savary-Miller Scale endoscopic classification) confirmed by endoscopy but without complications such as Barrett's oesophagus or stricture.	
Indication	Erosive oesophagitis	
Comparators Drug dose intensity / duration etc	Strategy 1: Intermittent PPI	Omeprazole 20mg od / 8 wks, no further treatment until recurrence
	Strategy 2: Maintenance PPI	Omeprazole 20mg od / 8 wks, continuous maintenance treatment w/ a PPI (same dose)
	Strategy 3: Maintenance H_2RA	Ranitidine 150mg bid / 8 wks, continuous maintenance treatment w/ an H_2RA (same dose)
	Strategy 4: Step-down maintenance PA	Cisapride 10mg qid / 12 wks, continuous maintenance treatment w/ a lower dose PA (cisapride 10mg bid)
	Strategy 5: Step-down maintenance H_2RA	Omeprazole 20mg od / 8 wks, continuous maintenance treatment w/ an H_2RA (ranitidine 150mg bid)
	Strategy 6: Step-down maintenance PPI	Omeprazole 20mg od / 8 wks, continuous maintenance treatment w/ a lower dose PPI (omeprazole 10mg od)
Methods		
Time horizon	1 year	
Perspective	Ministry of health (Ontario)	

Type of study	Cost effectiveness	
Approach used	Modeling	
Modeling approach	Decision analytic model	
Modeling features	Step-up & switching algorithms conditional upon oesophagitis healing failure or recurrence. Model recursive in two 6-month periods.	
Outcome used	Clinical indicator (GORD–free weeks, GORD recurrences)	
Source of effectiveness data	Meta-analysis of RCTs with systematic search	
Resources included	Hospital, Physician, Drugs, Diagnostic tests	
Physical resource use	Professional opinion	
Sources of unit cost data		
Hospital	MIS (A hospital participating in Ontario Case Costing Project in South-western Ontario)	
Medical doctor	Fee schedule (Physician fee schedule for Ontario)	
Pharmaceuticals (drugs only)	Provincial formulary, Manufacturers list price (for omeprazole 10mg, a non-formulary benefit)	
Pharmaceuticals (dispensing fee)	Provincial drug plan (Ontario)	
Sensitivity analysis	Deterministic One-way	
Other		
Results		
Summary of efficiency (cost effectiveness etc.)		<u>Incremental cost per GORD wk averted</u> (relative to the next less costly non-dominated strategy)
	Strategy 3: Maintenance H_2RA	-
	Strategy 1: Intermittent PPI	CAD $8
	Strategy 5: Step-down maintenance H_2RA	CAD $44
	Strategy 2: Maintenance PPI	CAD $256
	Strategy 4: Step-down maintenance PA	Dominated
	Strategy 6: Step-down maintenance PPI	Dominated (E)
Stochastic results	Substantial variation	
Key sensitivity variables	Price of H_2RA (generic cimetidine, brand name ranitidine)	

Quality Assessment Table

Item	Criteria	Goeree et al. 1999
Timelines	Are the timelines appropriate?	Longer time horizon (>1 year) would have been better.
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	Data from single arms of trials pooled together
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Professional opinion used
	Were unit costs appropriately measured?	Yes (Ontario)
Discounting	Was discounting done and justified?	N/A
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	Criteria	Goeree et al. Pharmacoeconomics 1999
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	For PA, cisapride is used, which has been withdrawn from the Canadian market.
Time frame	Is the time frame of the study sufficiently current?	No (about 7 years old)
Setting	Is the setting relevant to Canadian practice?	Yes

4. O'Brien et al. (1996)[125]

Data Extraction Table

Background		
Source of funding	Government (foundations) (CCOHTA)	
Year to which study applies	1995	
Country	Canada	
Currency used	1995 Canadian dollars	
Description of population	Patients with endoscopically confirmed reflux esophagitis of grades II to IV (Savary-Miller) without complications such as Barrett's or stricture.	
Indication	Gastroesophageal reflux disease (GERD)	
Comparators Drug dose intensity / duration etc	Strategy 1: Intermittent PPI	Omeprazole 20mg od / 8 wks, no further treatment until recurrence
	Strategy 2: Maintenance PPI	Omeprazole 20mg od / 8 wks, continuous maintenance treatment w/ a PPI
	Strategy 3: Maintenance H_2RA	Ranitidine 150mg bid / 8 wks, continuous maintenance treatment w/ an H_2RA
	Strategy 4: Maintenance PA	Cisapride 10mg qid / 12 wks, continuous maintenance treatment w/ a PA
Methods		
Time horizon	1 year	
Perspective	Ministry of health (Ontario)	
Type of study	Cost-effectiveness	
Approach used	Modeling	
Modeling approach	Decision analytic model	
Modeling features	Step-up & switching algorithms conditional upon healing failure or GERD recurrence. Model recursive in two 6-month periods.	
Outcome used	Clinical indicator (GORD–free weeks, GORD recurrence)	
Source of effectiveness data	Meta-analysis of RCTs with systematic search	
Resources included	Hospital, Physician, Drugs, Diagnostic tests	
Physical resource use	Professional opinion	
Sources of unit cost data		
Hospital	MIS (Corporate cost model for Chedoke-McMaster hospitals in Hamilton, Ontario)	
Medical doctor	Fee schedule (Physician fee schedule for Ontario)	
Pharmaceuticals (drugs only)	Provincial formulary (Best available price from the ODB program), Survey of pharmacies (for omeprazole, a non-formulary benefit), IMS or other data provider (to construct drug price index for selected drugs relative to Ontario for sensitivity analysis)	
Pharmaceuticals (dispensing fee)	Other (Survey of local pharmacies)	
Sensitivity analysis	Deterministic One-way	

Other		
Results		
Summary of efficiency (cost effectiveness etc.)		Incremental cost per week without GERD
	Strategy 1: Intermittent PPI	-
	Strategy 2: Maintenance PPI	CAD $142
	Strategy 3: Maintenance H_2RA	Dominated
	Strategy 4: Maintenance PA	Dominated
Stochastic results	Substantial variation	
Key sensitivity variables	Price of H_2RA (generic cimetidine, brand name ranitidine)	

Quality Assessment Table

Item	**Criteria**	**O'Brien et al. 1996**
Timelines	Are the timelines appropriate?	Longer time horizon (>1 year) would have been better.
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	Data from single arms pooled together
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Professional opinion used
	Were unit costs appropriately measured?	Yes (Ontario)
Discounting	Was discounting done and justified?	N/A
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	**Criteria**	**O'Brien et al. CCOHTA 1996**
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	For PA, cisapride is used, which has been withdrawn from the Canadian market.
Time frame	Is the time frame of the study sufficiently current?	No (almost 10 years old)
Setting	Is the setting relevant to Canadian practice?	Yes

Appendix 17: Summary of Economic Studies Related to Dyspepsia

1. Chiba et al. (2004)

Data Extraction Table

Background		
Source of funding	Industry (AstraZeneca Canada Inc.)	
Year to which study applies	Not stated	
Country	Canada	
Currency used	Canadian dollars	
Description of population	Patients 18 years and over with uninvestigated dyspepsia of at least moderate severity (≥ 4 of 7) over the preceding month and without alarm symptoms, and H. pylori positive (confirmed by ^{13}C-urea breath test)	
Indication	Uninvestigated dyspepsia and H. pylori positive	
Comparators Drug dose intensity / duration etc	H. pylori eradication	Omeprazole 20 mg bid / 7 days Metronidazole 500 mg bid / 7days Clarithromycin 250 mg bid / 7 days
	Empirical PPI	Omeprazole 20 mg bid / 7 days Metronidazole placebo bid / 7days Clarithromycin placebo bid / 7 days
Methods		
Time horizon	1 year	
Perspective	Ministry of health (Ontario), Societal	
Type of study	Cost-effectiveness	
Approach used	Economic study applied to RCT	
Modeling approach	Other	
Modeling features		
Outcome used	Clinical indicator (treatment success defined as a score of either 1 (none) or 2 (minimal) on the global severity of dyspepsia symptoms in a seven-point Likert scale at the final visit)	
Source of effectiveness data	Other (double-blind, placebo-controlled, parallel-group, multi-centre, randomized controlled trial, performed in 36 family practitioner centres across Canada using computer randomization and allocation concealment)	
Resources included	Hospital, Physician, Drugs, Diagnostic tests, Work loss, Personal out-of-pocket expenses, Other (transportation)	
Physical resource use	Other (collected prospectively)	
Sources of unit cost data		
Hospital	MIS (CCOHTA, A manual of standard costs for pharmacoecoomic studies in Canada: feasibility study, Ottawa, 1995)	
Medical doctor	Fee schedule (1999 OHIP Schedule of benefits)	
Pharmaceuticals (drugs only)	Provincial formulary (ODB formulary), IMS or other data provider (Medis Distributing	

	Catalogue)		
Pharmaceuticals (dispensing fee)	Provincial drug plan		
Sensitivity analysis	N/A		
Other			
Results			
Summary of efficiency (cost effectiveness etc.)		MOH perspective	
		ICER per treatment success (90% CI)	N
	Empirical PPI	-	146
	H. pylori eradication	-$387 (-$1,707 to $607)	142
Stochastic results	Wide confidence intervals		
Key sensitivity variables	No sensitivity analysis conducted		

Quality Assessment Table

Item	**Criteria**	**Chiba et al. 2004**
Timelines	Are the timelines appropriate?	Yes
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	Yes
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Yes
	Were unit costs appropriately measured?	Yes (Ontario)
Discounting	Was discounting done and justified?	N/A
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	**Criteria**	**Chiba et al. 2004**
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	Yes
Time frame	Is the time frame of the study sufficiently current?	Yes
Setting	Is the setting relevant to Canadian practice?	Yes

2. Makris et al. (2003)

Data Extraction Table

Background		
Source of funding	Industry (supported in part by an "at arms length grant from AstraZenecca)	
Year to which study applies	Not stated	
Country	Canada	
Currency used	Canadian dollars	
Description of population	Adult patients presenting to a primary care physician in Canada (excludes patients presenting with symptoms suggestive of GERD, alarm symptoms, biliary pain, irritable bowel syndrome, or use of NSAID).	
Indication	Dyspepsia	
Comparators Drug dose intensity / duration etc	Strategy 1: Initial endoscopy	
	Strategy 2: Barium examination	
	Strategy 3: Empirical eradication therapy	Omeprazole 20mg bid, amoxicillin 1000 mg bid, and Clarithromycin 500mg bid / 1 wk /
	Strategy 4: Empirical antisecretory therapy	Omeprazole / 4 wks /
	Strategy 5: Urea breath test (UBT)	
	Strategy 6: Laboratory serology testing	
	Strategy 7: Sequential testing	Laboratory serology followed, if H. pylori positive, by UBT
Methods		
Time horizon	1 year	
Perspective	Ministry of health (Public payer, Quebec)	
Type of study	Cost effectiveness	
Approach used	Modeling	
Modeling approach	Decision analytic model	
Modeling features	Two separate models for patient groups: 18 to 45 years old, and over age 45	
Outcome used	Clinical indicator (Symptomatic cure)	
Source of effectiveness data	Single study, Non-systematic review with systematic search, Professional opinion	
Resources included	Hospital, Physician, Drugs, Diagnostic tests	
Physical resource use	Professional opinion	
Sources of unit cost data		
Hospital	MIS (Quebec ministry of health and social services), Micro-costing (Microcosting time-motion study at the Montreal general hospital for the cost of endoscopy)	
Medical doctor	Fee schedule (Quebec physician fee schedule, 1998)	
Pharmaceuticals (drugs only)	Provincial formulary (The Quebec drug plan (RAMQ), Conseil Consultatif de Pharmacologie, Capsules Pharmacothérapeutiques, April of 1998)	

Pharmaceuticals (dispensing fee)	Provincial drug plan (Quebec)	
Sensitivity analysis	Deterministic One-way	
Other		
Results		
Summary of efficiency (cost effectiveness etc.)	<u>Patients 18-45 years of age</u> Strategy 4: Empirical antisecretory therapy Strategy 6: Laboratory serology testing Strategy 3: Empirical eradication therapy Strategy 5: Urea breath test Strategy 2: Barium examination Strategy 1: Initial endoscopy Strategy 7: Sequential testing <u>Patients over age 45</u> Strategy 4: Empirical antisecretory therapy Strategy 2: Barium examination Strategy 3: Empirical eradication therapy Strategy 5: Urea breath test Strategy 6: Laboratory serology testing Strategy 1: Initial endoscopy Strategy 7: Sequential testing	<u>ICER</u> (relative to the next less costly non-dominated strategy) - CAD $2,970 CAD $6,412 CAD $10,429 Dominated (E) Dominated Dominated - Not reported Not reported CAD $10,835 Dominated (E) Dominated Dominated
Stochastic results	Substantial variation	
Key sensitivity variables	Impact of H. pylori eradication on symptoms in patients w/ NUD	

Quality Assessment Table

Item	Criteria	Makris et al. 2003
Timelines	Are the timelines appropriate?	Longer time horizon (>1 year) would have been better.
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	Single study, non-SR, professional opinion used
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Professional opinion used
	Were unit costs appropriately measured?	Yes (Quebec)
Discounting	Was discounting done and justified?	N/A
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	Criteria	Makris et al. 2003
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	Yes
Time frame	Is the time frame of the study sufficiently current?	Yes
Setting	Is the setting relevant to Canadian practice?	Yes

Appendix 18: Summary of Economic Studies Related to Peptic Ulcer Disease

1. O'Brien et al. (1997)

Data Extraction Table

Background		
Source of funding	Government (foundations) (CCOHTA)	
Year to which study applies	1995	
Country	Canada	
Currency used	1995 Canadian dollars	
Description of population	Patients with confirmed and uncomplicated DU	
Indication	Duodenal ulcer (DU)	
Comparators Drug dose intensity / duration etc	Strategy 1: Heal with an H_2RA and wait	Ranitidine 150mg bid / 8 wks, no further treatment until recurrence, then heal w/ an H_2RA (same dose)
	Strategy 2: Heal with a PPI and wait	Omeprazole 20mg od / 4 wks, no further treatment until recurrence, then heal w/ a PPI (same dose)
	Strategy 3: Heal and maintenance H_2RA	Ranitidine 150mg bid / 8 wks, continuous maintenance w/ half dose H_2RA (ranitidine 150mg od), full dose H_2RA for recurrences
	Strategy 4: Heal and eradicate H. pylori with OA	Omeprazole 20mg bid / 1-14 days Amoxicillin 1g bid / 1-14 days Omeprazole 20mg od / 14-28 days
	Strategy 5: Heal and eradicate H. pylori with OC	Omeprazole 20mg bid / 1-14 days Clarithromycin 500mg tid / 1-14 days Omeprazole 20mg od / 14-28 days
	Strategy 6: Heal and eradicate H. pylori w/ OAM	Omeprazole 20mg bid / 1-14 days Metronidazole 500mg bid / 1-7 days Amoxicillin 1g bid / 1-7 days Omeprazole 20mg od / 14-28 days
	Strategy 7: Heal and eradicate H. pylori w/ OAC	Omeprazole 20mg bid / 1-14 days Amoxicillin 1g bid / 1-7 days Clarithromycin 500mg bid / 1-7 days Omeprazole 20mg od / 14-28 days
	Strategy 8: Heal and eradicate H. pylori w/ OMC	Omeprazole 20mg bid / 1-14 days Clarithromycin 500mg bid / 1-7 days Metronidazole 500mg bid / 1-7 days Omeprazole 20mg od / 14-28 days
	Strategy 9: Heal & eradicate H. pylori w/ RBMT	Ranitidine 150mg bid / 1-56 days Bismuth subsalicylate 151mg qid/ 42-56 days Metronidazole 500mg qid / 42-56 days Tetracycline 500mg qid / 42-56 days
Methods		
Time horizon	1 year	

Perspective	Ministry of health (Ontario)	
Type of study	Cost effectiveness	
Approach used	Modeling	
Modeling approach	Decision analytic model	
Modeling features		
Outcome used	Clinical indicator (Ulcer-free weeks, Ulcer recurrences)	
Source of effectiveness data	Single study (meta-analysis), Meta-analysis of RCTs with systematic search	
Resources included	Hospital, Physician, Drugs, Diagnostic tests	
Physical resource use	Professional opinion	
Sources of unit cost data		
Hospital	MIS (Corporate cost model for Chedoke-McMaster hospitals in Hamilton, Ontario)	
Medical doctor	Fee schedule (Physician fee schedule for Ontario)	
Pharmaceuticals (drugs only)	Provincial formulary (Best available price from the ODB program), Survey of pharmacies	
Pharmaceuticals (dispensing fee)	Not included	
Sensitivity analysis	Deterministic One-way	
Other		
Results		
Summary of efficiency (cost effectiveness etc.)		<u>Incremental cost per wk w/o ulcer</u> (relative to next less costly non-dominated strategy)
	Strategy 9: Heal & eradicate H. pylori w/ RBMT	-
	Strategy 6: Heal and eradicate H. pylori w/ OAM	CAD $38 (calculated)
	Strategy 8: Heal and eradicate H. pylori w/ OMC	CAD $140 (calculated)
	Strategy 1: Heal with an H_2RA and wait	Dominated
	Strategy 7: Heal and eradicate H. pylori w/ OAC	Dominated
	Strategy 2: Heal with a PPI and wait	Dominated
	Strategy 3: Heal and maintenance H_2RA	Dominated
	Strategy 4: Heal and eradicate H. pylori with OA	Dominated
	Strategy 5: Heal and eradicate H. pylori with OC	Dominated
Stochastic results	A fair amount of variation	
Key sensitivity variables	Eradication rate	

Quality Assessment Table

Item	Criteria	O'Brien et al. 1997
Timelines	Are the timelines appropriate?	Yes
Type of study	Was the type of study justified?	Yes
Outcomes	Are the outcome indicators appropriate to the intervention?	Yes
Efficacy / effectiveness	Were sources of efficacy high quality, using clinical standards?	Data from single arms pooled together
	Was adjustment made to estimate effectiveness?	No
Cost	Are the appropriate resources included?	Yes
	Were quantities of resources measured appropriately?	Professional opinion used
	Were unit costs appropriately measured?	Yes (Ontario)
Discounting	Was discounting done and justified?	N/A
Summary efficiency measure	Was an incremental measure used?	Yes

Relevancy Assessment Table

Item	Criteria	O'Brien et al. CCOHTA 1997
Population	Is the population relevant to the intervention(s) being studied?	Yes
Intervention	Are the interventions relevant?	Not all
Time frame	Is the time frame of the study sufficiently current?	No (about 10 years old)
Setting	Is the setting relevant to Canadian practice?	Yes