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COMPUS

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Economic Models and Conclusions for the Treatment of Dyspepsia; and Gastroesophageal Reflux Disease-Related Heartburn and the Prevention of Non-steroidal Anti-inflammatory Drug-Induced gastrointestinal Complications

Supporting Informed Decisions

À l'appui des décisions éclairées

This report is prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH) with the advice and assistance of economic and clinical experts.

This report is a comprehensive review of the existing public literature available to CADTH at the time this report was prepared and is an adaptation and updating of economic studies with input and advice throughout the preparation of this report. The conclusions are provided by experts. The authors have also considered input from other stakeholders. The information in this report should not be used as a substitute for the application of professional judgement in any decision making process. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this Report.

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SUMMARY

1 PROTON PUMP INHIBITOR ECONOMIC ANALYSIS

The objective of the economic component of this Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) project was to compare expected costs and outcomes of various primary care strategies for the:

- management of moderate-to severe heartburn in patients with uninvestigated gastroesophageal reflux disease (GERD)
- management of non-heartburn predominant symptoms in patients with uninvestigated dyspepsia (UD)
- prevention of gastrointestinal (GI) complications associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) for more than three weeks.

2 METHODS

The economic studies build upon three previously published decision analytic models. In collaboration with the COMPUS Expert Review Panel (ERP) on Proton Pump Inhibitors (PPIs), modifications were made to update the original models. Members of the COMPUS ERP validated model structure, resource utilization, outcomes, and transition probabilities. In addition, stakeholder feedback was incorporated into the each of the models. Analyses covered a period of up to one-year, and were conducted from a third-party payer perspective. Sensitivity analyses were conducted to determine the robustness of the results of each model.

2.1 Moderate-to-severe heartburn in patients with uninvestigated GERD

In this model, five strategies were compared:

- two on-demand approaches (standard-dose histamine H2-receptor antagonist (H2RA) or standard-dose PPI for up to four weeks until resolution of symptoms, with no further treatment until a recurrence of symptoms)
- two maintenance approaches (acute treatment for four weeks with a standard dose of H2RA followed by continuous maintenance treatment with a H2RA at the same dose; or standard-dose PPI followed by continuous maintenance treatment with a PPI at the same dose)
- one step-down maintenance approach (acute treatment with a standard-dose PPI for four weeks, followed by continuous maintenance treatment with a H2RA to prevent recurrences).

Separate analyses were conducted for erosive esophagitis (EE), endoscopy-negative reflux disease (ENRD), and uninvestigated GERD (UG) patients.

2.2 Non-heartburn predominant uninvestigated dyspepsia (UD)

Six strategies were compared in this model:

- two test and treat approaches (*Helicobacter pylori* (*H. pylori*) eradication with triple therapy if *H. pylori* positive; four weeks of antisecretory therapy with either generic omeprazole 20 mg daily or ranitidine 150 mg twice daily if *H. pylori* negative) in the treatment of UD patients
- four weeks of empirical antisecretory therapy in all patients with either omeprazole 20 mg daily or ranitidine 150 mg twice daily

- prompt upper gastrointestinal endoscopy of all patients (subsequent management primarily with PPI or H2RA-based acid suppression).

2.3 Prevention of GI complications associated with the use of NSAIDs

Three gastroprotective strategies were compared to a strategy of no prophylaxis in patients using a non-selective NSAID (diclofenac 50mg tid):

- H2RAs (ranitidine 300 mg bid)
- PPIs (omeprazole 20 mg qd)
- Misoprostol 200 µg qid.

3 RESULTS

3.1 Moderate-to-severe heartburn in patients with uninvestigated GERD

In uninvestigated GERD, the heartburn condition most commonly treated in primary care, on-demand PPI was the least costly strategy. Strategies involving either on-demand or continuous H2RA therapy were shown to be less effective and more costly than on-demand or continuous PPI therapy (i.e., H2RAs as initial therapy were dominated). Continuous PPI therapy was both more effective and more expensive, costing about $28,000 per additional quality-adjusted life years (QALY) gained over on-demand therapy. All other strategies were less effective and more costly (i.e., they were dominated). At a willingness-to-pay (WTP) threshold of up to $28,000 per QALY gained, on-demand PPI therapy was most likely to be a cost-effective strategy in uninvestigated GERD. For WTP greater than $28,000 per QALY gained, continuous maintenance PPI was most likely to be cost-effective.

CONTEXT

On-demand therapy - Acute treatment (PPI or H2RA) for up to four weeks until resolution of symptoms with no further treatment until a recurrence of symptoms.

Maintenance therapy - Acute treatment with (PPI or H2RA) for four weeks followed by continuous maintenance therapy (same drug and dose) to prevent recurrences

H2RA – generic ranitidine 150 mg twice daily; $0.81 daily.

PPI – generic omeprazole 20mg once daily; $1.25 daily.

3.1.1 Synthesis of Clinical and Economic Results

For GERD, the clinical evidence and economic findings are consistent. That is, initial treatment with standard-dose PPI for four weeks is both more efficacious and cost-effective than standard-dose H2RA for the improvement of reflux symptoms in patients with moderate to severe symptoms of UG; decreasing symptom occurrence over one year in patients with moderate to severe UG. Similarly, PPI maintenance therapy is both more efficacious and cost-effective than H2RA in the management of patients with moderate to severe UG.

3.2 Non-heartburn predominant uninvestigated dyspepsia (UD)

Standard-dose H2RA therapy for four weeks, given either empirically or only to *H. pylori*-negative patients within a strategy of test-and-treat, was shown to be less efficacious and more costly than other strategies for heartburn non-dominant dyspepsia (i.e. H2RAs were dominated). H2RA-based strategies were therefore eliminated from further analysis. Among the remaining alternatives, empirical PPI therapy was the least expensive and least effective approach. Test-and-treat PPI was estimated to cost an additional $10,000 per QALY gained over empirical PPI. The two endoscopy-based strategies were estimated to cost in excess of $200,000 per QALY gained over test-and-treat PPI.

At a WTP threshold of up to $25,000 per QALY gained, empirical standard-dose PPI for four weeks was most likely to be a cost-effective strategy. The strategy test-and-treat PPI had the highest probability of being cost-effective between WTP thresholds of $25,000 and $125,000 per QALY gained. For WTP thresholds exceeding $125,000 per QALY gained, treatment strategies based on prompt endoscopy were most likely to be cost-effective.

CONTEXT

Standard-dose PPI: generic omeprazole 20 mg daily; $1.25 per day

Standard-dose H2RA: generic ranitidine 150 mg twice daily; $0.81 per day

3.2.1 Synthesis of Clinical and Economic Results

In terms of uninvestigated dyspepsia, the economic and clinical conclusions are consistent in that an initial course of standard-dose PPI is both more efficacious and cost-effective than a course of standard-dose H2RA as a management strategy in *H. pylori* negative patients. Prompt endoscopy is not a preferred strategy in non-heartburn dominant dyspeptic patients.

3.3 Prevention of GI complications associated with the use of NSAIDs

Misoprostol was less effective and more costly than the other gastroptotective strategies (i.e., it was dominated) and was therefore eliminated from further analysis. Non-selective NSAID therapy alone (i.e., no prophylaxis) was the least costly but least effective strategy. Compared to NSAID therapy alone, the use of standard-dose PPI prophylaxis would cost approximately $64,000 per additional QALY gained. Double-dose H2RA therapy was associated with an additional cost of more than $2 million per QALY gained when compared to the use of a non-selective NSAID plus a PPI.

NSAID alone had the highest likelihood of being cost-effective up to a WTP threshold of $52,000 per QALY gained. Above a WTP threshold of $52,000, standard-dose PPI prophylaxis was most likely to be cost-effective. It should be noted that the economic model consisted of a mixed population of patients who had both average and high risk for NSAID-associated ulcer. It is likely that the cost per additional QALY gained associated with PPI prophylaxis would be lower if the analysis was restricted to patients within the high-risk group.

CONTEXT

Misoprostol: misoprostol 200 µg four times daily; $0.91 per day

Standard-dose PPI: generic omeprazole 20 mg daily; $1.25 per day

Double-dose H2RA: generic ranitidine 300 mg twice daily; $1.56 per day

3.3.1 Synthesis of Clinical and Economic Results

Although standard-dose PPIs in combination with non-selective NSAIDs may be similar in efficacy to misoprostol in terms of NSAID-ulcer prevention, the latter alternative was eliminated in the analysis due to higher costs. Furthermore, standard-dose PPI therapy was both more efficacious and more cost-effective than double-dose H2RAs for NSAID-ulcer prevention. Nevertheless, PPI prophylaxis is associated with a significant cost per additional QALY, and is not likely to be cost-effective compared to NSAID alone when the WTP is below $52,000 per QALY gained. It should be noted, however, that incremental cost-effectiveness ratios would be more attractive in high-risk patients.

4 POLICY IMPLICATIONS

4.1 Moderate to severe[*] heartburn in patients with uninvestigated GERD[†]

Key Economic Messages (summarized from the economic technical report):

- On-demand PPI therapy[‡] is the most cost-effective maintenance strategy at a willingness to pay (WTP) below $ 28,000 per QALY gained.
- Continuous PPI maintenance therapy is the most cost-effective strategy when the WTP exceeds $ 28,000 per QALY gained.

Key Clinical Messages (summarized from scientific report):

- Although H2RA therapy is effective in managing many patients, standard-dose PPIs are more efficacious compared to H2RAs in the initial (i.e., four to eight weeks) and maintenance (on-demand or continuous) management of patients with uninvestigated GERD.
- Alternatives (PPI discontinuation, H2RAs, on-demand therapy) to long-term regular use of standard-dose PPIs for GERD may be appropriate in selected patients.

Policy Implications:

- PPIs (at a price equal to or less than $1.25 per day) are the optimal therapy choice both clinically and economically.
- Whether PPI maintenance therapy should be given continuously or on-demand is dependent upon the decision-makers' WTP.

[*] Data are not available for cases of mild GERD, therefore no conclusions on mild GERD can be made

[†] Uninvestigated GERD = patients who have not undergone endoscopy (i.e. diagnosed by a general practitioner and not referred to a gastroenterologist). Precludes patients with endoscopic negative reflux disease (ENRD) or erosive esophagitis.

[‡] On-demand = daily standard-dose PPI until symptom resolution or a maximum of 4 weeks.

4.2 Non-heartburn predominant uninvestigated dyspepsia*

Key Economic Messages (summarized from the economic technical report):
- Empiric daily standard-dose PPI therapy for four weeks is the most cost-effective strategy at a WTP below $25,000 per QALY gained.
- A strategy of *test-and-treat* PPI is the most cost-effective strategy when the WTP exceeds $25,000 per QALY gained.†

Key Clinical Messages (summarized from scientific report):
- PPIs are more efficacious for the initial short-term management of uninvestigated dyspepsia
- For ongoing maintenance treatment of uninvestigated dyspepsia, therapeutic options include no drug, on-demand H2RA and on-demand PPI

Policy Implications:
- PPIs (at a price equal to or less than $1.25 per day) are the optimal therapy choice for initial management of uninvestigated dyspepsia.
- Whether PPI initial therapy should be empirical PPI or test and treat PPI is dependent upon the decision-makers' WTP.

4.3 Prevention of GI complications associated with the use of NSAIDs‡

Key Economic Messages (summarized from the economic technical report):
- No prophylaxis is the most cost effective strategy at a WTP below $52,000 per QALY gained.
- Standard-dose PPIs are the most cost-effective strategy when the WTP exceeds $52,000 per QALY gained.

Key Clinical Messages (summarized from scientific report):
- Standard-dose PPIs are efficacious for the prevention of NSAID-associated ulcers.

Policy Implications:
- Whether therapy should be given for the prevention of NSAID-associated complications is dependent upon the decision-makers' WTP.§
- If drug therapy is to be used, PPI therapy (at a price equal to or less than $1.25 per day) is the optimal choice both clinically and economically.

5 SUMMARY

The clinical and economic evidence for the treatment of common GI ailments (i.e., uninvestigated GERD, uninvestigated dyspepsia, and NSAID ulcer prophylaxis) in the general practice setting suggests that PPIs (at a price equal to or less than $1.25 per day) may be cost-effective depending on the willingness to pay per QALY gained.

* Uninvestigated dyspepsia = patients who have not undergone endoscopy (i.e. diagnosed by a general practitioner and not referred to a gastroenterologist). Precludes patients with functional dyspepsia

† Data are not available to guide maintenance management. Patients were followed for a one-year period as per usual care after initial treatment.

‡ Efficacy data used in this study was not limited to high-risk patients, hence these conclusions do not address the high-risk population.

§ If acceptable WTP is less than $52,000 per QALY gained, no prophylaxis is the recommended action.

Definitions

WTP - willingness to pay. The amount a third-party payer would be willing to pay in order to obtain a specified outcome.

QALY - quality adjusted life year. An outcome that attempts to combine both the quantity and quality of life that results from a given treatment.

TABLE OF CONTENTS

ECONOMIC EVALUATION OF ALTERNATIVE STRATEGIES FOR THE MANAGEMENT OF PATIENTS WITH HEARTBURN PREDOMINANT GASTROESOPHAGEAL REFLUX DISEASE SYMPTOMS IN CANADA

PREVENTING NSAID INDUCED GASTROINTESTINAL COMPLICATIONS: AN ECONOMIC EVALUATION OF ALTERNATIVE STRATEGIES IN CANADA

Economic evaluation of alternative strategies in the medium-term management of patients with non-heartburn predominant dyspepsia in Canada

A Markov Analysis Evaluating Test and Treat for *H. pylori*, Prompt Endoscopy and Empiric Antisecretory Therapy in Terms of Cost, Symptom-free Months and Quality-adjusted Life-Years over a 12-Month Period in a reconstituted sample of patients with non-heartburn predominant uninvestigated dyspepsia

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Alan N. Barkun, M.D., C.M., F.R.C.P.(C), M.Sc
Ralph Crott, Ph.D., MPH
Carlo A. Fallone, M.D., C.M., F.R.C.P.(C)
Wendy A. Kennedy, Ph.D., MBA, LLB
Jean Lachaine, Ph.D., BPharm.
Carey Levinton, MSc.

ABBREVIATIONS

BID	twice daily
CanDys	Canadian Dyspepsia Working Group
DU	duodenal ulcer
GERD	gastroesophageal reflux disease
GSRS	Gastrointestinal Symptom Rating Scale
GU	gastric ulcer
H2RA	histamine-2 receptor antagonist
H. pylori	*helicobacter pylori*
ICER	incremental cost-effectiveness
mg	milligram
NSAID	non-steroidal anti-inflammatory drug
NUD	non-ulcer dyspepsia
PPI	proton pump inhibitor
PO	by mouth
QALY	quality-adjusted life year
qd	once daily
UBT	Urea Breath Test
UD	uninvestigated dyspepsia

1 EXECUTIVE SUMMARY

This study, performed at the request of CADTH, compares the efficacy, cost, and cost-effectiveness of six alternative strategies for medium-term (one year) management of patients with uninvestigated non-heartburn predominant dyspepsia (UD) by the family physician or general practitioner. Efficacy and resource use data were derived from a subgroup of patients in the Canadian clinical (CADET) studies who reported UD*. Efficacy was measured as the number of symptom-free months over the twelve months after the start of treatment, as well as quality –adjusted life years (QALY). Medication and other health care resource use was collected from patients in these studies through the use of structured questionnaires. The first and second treatment strategies were based on testing for *H. pylori* and treating according to test results. Comparator approaches were empirical treatment with antisecretory medication and prompt endoscopy to determine the presence of demonstrated upper GI mucosal abnormalities. Initial treatments in these alternatives were:

1. A stratification of patients into two groups according to the presence of *Helicobacter pylori* infection using a Urea Breath Test (UBT), i.e.: a test and treat approach. If found to be negative patients were treated with omeprazole 20 mg once daily for four weeks; if positive patients were treated with one week of triple therapy (omeprazole 20 mg twice daily, metronidazole 500 mg twice daily and clarithromycin 250 mg twice daily).

2. The same approach as (1) but replacing the use of omeprazole with ranitidine 150 mg twice daily, except for the triple therapy, which remains the same.

3. Empirical antisecretory therapy using omeprazole 20 mg once daily for four weeks.

4. Empirical antisecretory therapy using ranitidine 150 mg twice daily for four weeks.

5. Prompt endoscopy to determine the underlying disorder. Patients negative for *H. pylori* were treated primarily with a proton pump inhibitor (PPI); patients positive for *H. pylori* were treated with a form of triple therapy.

6. Prompt endoscopy to determine the underlying disorder. Patients negative for *H. pylori* were treated primarily with an H2 antagonist (H2RA); patients positive for *H. pylori* were treated with a form of triple therapy.

The clinical question was formally structured into a Markov Monte Carlo model representing the major clinical pathways and their consequences. The model was validated by a team of Canadian gastroenterologist experts. Modeling was done using TreeAge Pro 2005 (Release 1.6). Estimates of disease prevalence, efficacy rates and resource use were derived from patient-specific data on file with AstraZeneca of clinical trial results (CADET program) (Dr. Alan Barkun, Division of Gastroenterology, McGill University, Montreal: personal communication, 2007 Mar). Efficacy and resource use estimates were entered into the model as distributions based on the parameters of clinical trial data. The primary perspective was that of the health care system, and only costs to the health system were included, whoever the payer. Most costs were based on 2006 costs in the province of Ontario.

* Three months or more history of epigastric pain/discomfort, with or without associated heartburn, nausea or other symptoms thought to originate in the proximal alimentary tract.

In the base-case analysis, using expected values of cost and effectiveness for each strategy, two strategies were dominated when the outcome was symptom-free months: test and treat (ranitidine) and empirical antisecretory therapy (ranitidine). Of the four non-dominated strategies, least costly and least effective was the empirical antisecretory therapy (omeprazole) approach. Test and treat (omeprazole) was $20.44 more per subject and yielded 0.27 more symptom-free months per subject than the empirical antisecretory approach using omeprazole. More effective and more costly than both were the two prompt endoscopy approaches; the most costly and most effective was that with PPI therapy.

In terms of incremental cost-effectiveness, the use of test and treat (omeprazole) was estimated to cost $75 per symptom-free month more than the use of empirical antisecretory (omeprazole) therapy in this patient group. Similarly, the use of prompt endoscopy (ranitidine) was estimated to cost $1236 per symptom-free month more than test and treat (omeprazole), and the use of prompt endoscopy (PPI) $5167 more per symptom-free month than that prompt endoscopy (H2RA). Empirical antisecretory therapy (ranitidine) and test and treat (ranitidine) strategies were dominated.

The use of QALYs as measure of outcome yielded the same basic conclusions as those using symptom-free months. Test and treat (omeprazole) was estimated to cost $10,004 more per additional QALY than the empirical antisecretory therapy (omeprazole) approach. Both prompt endoscopy approaches were considerably more costly: H2RA therapy was estimated to cost $205,643 per QALY compared to test and treat (omeprazole), while prompt endoscopy (PPI) was estimated to cost $688,989 more per QALY than prompt endoscopy (H2RA). Empirical antisecretory therapy (ranitidine) and test and treat (ranitidine) strategies were dominated.

Expected values were subject to variations in costs and probabilities associated with the patient data. Although base-case cost-effectiveness results of empirical antisecretory therapy (ranitidine) and test and treat (ranitidine) strategies were dominated in deterministic analysis, the observed differences in cost-effectiveness that these conclusions were based on were generally not statistically significant in the probabilistic sensitivity analysis of the Monte Carlo simulation. The range of ICERs of each strategy in the Monte Carlo simulations were extremely wide, and no significant difference was observed between pairs of strategies. In those terms, we could not conclude that the ICERs between pairs of approaches were different ($p<0.05$).

2 INTRODUCTION

Dyspepsia is a common medical condition. In Canada its prevalence was recently estimated to be 29%.[1] It monopolizes a significant portion of physician consultations. It was estimated that 7% of the average Canadian family physician time is devoted to the management of dyspepsia,[2] although it was found that only 25% of patients in the general population with dyspeptic symptoms will consult their physician for medical advice.[3] An American study of dyspepsia patients who were followed for one year found they were heavy users of health care, averaging 14 visits and $US 3850 in charges.[4]
The term "dyspepsia" describes a heterogeneous group of symptoms with numerous underlying causes.[5] It has been defined as the presence of chronic or recurrent epigastric discomfort, post-prandial fullness, early satiety, sour stomach, nausea, vomiting, bloating, and/or abdominal distension.[6] Over the years, many other definitions of dyspepsia have been proposed.[7-11] International panels of clinical investigators issued consensus statements, commonly referred to as the Rome Criteria (I and II), that defined dyspepsia as "persistent or recurrent abdominal pain or abdominal discomfort centered in the upper abdomen."[12,13] Because of the differing symptom-driven perspective in the primary care setting, the Canadian Dyspepsia (CanDys) working group recently agreed on the

following definition of dyspepsia that also includes possible symptoms of gastro-esophageal reflux disease: "Dyspepsia is a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, and 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."[5]

Dyspepsia can be caused by a variety of underlying conditions. The main organic causes of dyspepsia are gastroesophageal reflux disease (GERD), duodenal ulcer (DU) and gastric ulcer (GU). In many patients no organic causes can be found for their dyspepsia. These patients are considered to have functional dyspepsia or non-ulcer dyspepsia (NUD). They differ from the uninvestigated patients with dyspepsia that includes all possible causes mentioned above.

Within functional dyspepsia, it has been suggested that three symptom groups can be identified: ulcer-like, dysmotility-like and reflux-like dyspepsia. The value of such a classification, especially when dealing with patients in the primary care setting in uninvestigated dyspepsia has recently been questioned.[14]

The recognition of the role of *Helicobacter pylori* in the pathogenesis of peptic ulcer disease has forced a re-evaluation of the clinical approach to dyspepsia as questions have arisen as to the role of testing for this bacterium in primary care. Eradication of *H. pylori* in the context of dyspepsia reduces symptoms[14] and improves quality of life,[15] could impact the cost-effectiveness of symptom resolution,[16] may reduce risk of ulcer and perhaps gastric cancer and also possibly decrease the risk of certain adverse effects* should long-term antisecretory treatments become otherwise necessary.[19] On the other hand it may induce side effects associated with the eradication treatment, and a considerable proportion of patients may still need prescription anti-ulcer medication treatment even after successful eradication.[20,21]

2.1 Treatment Strategies For Dyspepsia

Over the years, different treatment strategies for dyspepsia have been proposed. Some advocate immediate endoscopy for all patients with dyspepsia symptoms while others recommend empirical therapy with various medications or combinations of different drug treatments. There are also many proponents of testing for the presence of *H. pylori* to subsequently select an appropriate treatment strategy. All these approaches eventually involve the use of medications. Drug therapies used for dyspepsia can be classified as either antisecretory or eradicative.

The aim of antisecretory therapy is to reduce acid secretion permitting healing of the lesion and reducing symptoms associated with the disease. Antisecretory agents used in Canada include antacids, H2RA such as cimetidine, ranitidine, famotidine or nizatidine and proton pump inhibitors (PPI) such as omeprazole, lanzoprazole, pantoprazole, esomeprazole or rabeprazole.

Eradication treatments are used to cure ulcer disease, possibly alleviate dyspepsia symptoms and to eradicate *H. pylori*. Eradication treatments are combinations of three to four agents comprising

* Although the monograph for omeprazole (Losec™)[17] reports the most common adverse reactions to be minor, (diarrhoea, headache, flatulence, abdominal pain, constipation and dizziness/vertigo), there were also more severe incidents reported, in adverse events from clinical trials or routine use. In the monograph for ranitidine (Zantac™)[18] adverse reactions reported as events in clinical trials or in the routine management of patients, were also mainly minor, but more severe effects were also mentioned.

generally one antisecretory drug and two or more antibiotics. The most frequently used eradicative combinations include: a PPI + metronidazole + clarithromycin or a PPI + amoxicillin + clarithromycin. Efficacy of the different treatments has been tested in numerous trials. Clinical outcomes to compare approaches are most often healing of the lesion as seen on endoscopic examination. Although this type of outcome is relevant in the context of the randomized clinical trial, it is of more limited use in the context of current primary care practice, where symptoms resolution would be a more appropriate marker of effectiveness considering costs and availability of the procedure.

In a recent review performed by the Canadian Coordination Office for Health Technology Assessment,[22] efficacy of the different treatments for functional dyspepsia can be summarized as follows: Antacids have not been found to be better than placebo; reviews on eradication therapy of *H. pylori* in reducing symptoms of functional dyspepsia have not reached a definitive conclusion; prokinetic agents and H2RAs have been found to be more effective than placebo; and PPIs have limited efficacy in functional dyspepsia. In uninvestigated dyspepsia, although the literature is scanty, there is some evidence of benefit with *H. pylori* eradication.

Although dyspepsia, like other gastrointestinal diseases, is characterized by potential recurrences of the initial disease, many studies were limited to a short time horizon. In most cases treatment outcomes were measured after four or eight weeks of therapy, but a few recent studies report follow-up of up to one year. After one year, the proportion experiencing treatment failure (i.e. a SODA Pain Intensity score of ≥29) among dyspepsia patients who received an initial 6-week course of PPI was not significantly different as compared to placebo.[23] Two studies of dyspepsia patients receiving endoscopy versus non-invasive *H. pylori* testing saw similar results after one-year follow-up.[24,25]
A Cochrane systematic review of 25 trials reporting 27 comparisons, concluded that a strategy of PPI therapy was significantly more effective than either H2RAs or antacids.[26] A strategy of test and treat for *H. pylori* infection may also be more effective than acid suppression alone.[14] Initial endoscopy was associated with a small reduction in the risk of recurrent dyspeptic symptoms compared with *H. pylori* test and treat, but was not cost effective. Indeed, an individual patient meta-analysis from the same group suggested that prompt endoscopy conferred a small benefit in terms of cure of dyspepsia, but cost more than "test and treat" and was not a cost-effective strategy for the initial management of dyspepsia (with prompt endoscopy eventually became cost-effective only when the willingness to pay per patient symptom-free of dyspepsia reached $180,000).[27]

A recent cluster randomized trial compared empirical antisecretory therapy with testing for *H. pylori*, or a combination of the two. The strategies based on *H. pylori* testing led to similar symptom resolution, but reduced endoscopic workload and lower one-year total costs compared with empirical antisecretory therapy.[28] Unfortunately, all aforementioned studies, whether related to effectiveness or costs, suffer from heterogeneity in the clinical source data.
Because no randomized trial has been large enough to compare all viable initial strategies in patients with uninvestigated upper GI symptoms, investigators have also turned to decision models. However, disparate modeling methodologies, variations in study parameters such as study design, strategies (some now outdated), patient populations, base case assumptions, measurements of outcome, and time horizons have limited analytical conclusions. This is especially true since decision models generally incorporate data from disparate trials, and are highly influenced by parameters such as: costs of endoscopy, treatment, and physician visits, the prevalence of *H. pylori*, the specificity of diagnostic tests, as well as the short and long-term benefits of *H. pylori* eradication in patients with functional non-ulcer dyspepsia.[29]

We thus attempted to better characterize the cost-effectiveness of competing initial strategies in the management of patients with uninvestigated upper GI symptoms in the primary care setting using coherent data drawn from the CADET studies (described below).

This report, commissioned by CADTH, specifically assessed patients with non-heartburn predominant symptoms, and complemented a separate decision model exercise produced by another group that specifically assesses a non-CADET theoretical cohort of patients with gastroesophageal reflux disease.

2.2 Economic Aspects Of Dyspepsia

Considering the widespread prevalence of dyspepsia and the health resources deployed for its treatment and prevention of recurrence, dyspepsia represents a significant economic burden to the health care system and to society in general. Although studies have evaluated the economic impact of treatment strategies, very few studies have evaluated more globally the overall economic burden of dyspepsia.[30-35] Only one of these studies was performed in a Canadian context.[35]

The many available treatment strategies for dyspepsia have generated numerous clinical trials to explore the relative efficacy of the different options. As well, many economic evaluations have been performed to help identify the most efficient approaches. In a recent review of economic evaluation of treatment strategies for functional dyspepsia, 18 studies were identified.[36] Most of the studies performed some kind of cost analysis or cost-minimization analysis (n=10), several performed a cost-effectiveness analysis (n=7), one performed a cost-utility analysis, and one a cost benefit analysis. Decision analysis techniques were used in ten of these studies. The variability in compared alternatives identified in this review rendered it impossible to identify the most efficient treatment strategy. Many of the economic evaluations utilizing clinical trials of dyspepsia treatments were limited to a short time horizon.

Key medical costs related to the management of dyspepsia may include the following (depending on the adopted treatment strategy):

- Physician honorarium for initial and subsequent visits to a general practitioner and eventually to a gastroenterologist;
- Cost for endoscopy, which includes professional honorarium, and costs related to facilities and materials used to performed this examination;
- Cost of medications and pharmacist fees for antisecretory or eradicative treatment;
- Cost for testing the presence of H. pylori;
- Cost of other diagnostic tests;
- Cost related to the management of medication side effects (in some instances).

From a Canadian perspective most of these costs are assumed by the public health care system. For some categories of patient, medications are paid for by the patient or by a private third party payer. Costs for *H. pylori* testing may also be at the expense of the patient or a third party payer. Other costs, such as expenses to, travel to and from physician visits are also part of the economic burden of dyspepsia. Potential loss of patient productivity due to the disease itself or to the time diverted to medical visits or medical interventions may also be included in the burden of the disease.

In light of what is found in the literature on the economic impact of dyspepsia and its different treatment strategies, it was difficult to identify which treatment approach would be most efficient in a Canadian context.

2.3 Canadian Dyspepsia Management Approach

The CADET series of clinical studies examined alternative strategies for initial and long-term management of uninvestigated dyspepsia (UD), using the Canadian Dyspepsia Management (CAN/Dys) Approach for the initial treatment of UD by the family physician or general practitioner. The CAN/Dys approach (Strategies 1 and 2 in this study) recommended an initial screening by the physician on the basis of certain criteria. The approach applied to adult patients under the age of 50 presenting with symptoms indicative of dyspepsia (three months or more history of epigastric pain/discomfort, with or without associated heartburn, nausea or other symptoms thought to originate in the proximal alimentary tract). Individuals presenting with alarm symptoms (bleeding etc), are referred for endoscopy directly, and those using (non-steriodal anit-inflammatory drugs) NSAIDs are regularly excluded from this management scheme. The CAN/Dys approach recommended that the remaining patients be stratified into two groups (a) individuals presenting with a predominance of heartburn or reflux symptoms, or b) others. In the case of (a) the approach recommended initial treatment with empirical antisecretory therapy (as first choice, a PPI, or as second choice, an H2RA). In the case of (b) the recommendation was to test the patient for the presence of *H. pylori* infection using a Urea Breath Test (UBT), and to treat according to the findings. Patients found to be negative were treated with empirical antisecretory therapy (PPI or an H2RA), whereas those found to be positive were treated with a PPI-based triple therapy.

2.4 Alternatives Compared To Test and treat Approach

In this analysis, we focused on the group (b) patients with non-heartburn predominant UD. Two test and treat strategies using initial treatment of omeprazole 20 mg by mouth (PO) once daily (qd) for four weeks (strategy 1) or ranitidine 150 mg PO twice daily (BID) for four weeks (strategy 2) as antisecretory therapies and eradication therapy in *H. pylori* positive patients were compared to four other initial treatment strategies for UD: prompt upper gastrointestinal endoscopy of all patients, with predominant treatment with PPI if *H. pylori* negative (strategy 3), prompt upper gastrointestinal endoscopy of all patients predominant treatment with H2RA if *H. pylori* negative (strategy 4), empirical antisecretory treatment using omeprazole PO qd for four weeks (strategy 5) and empirical antisecretory treatment using ranitidine 150 mg PO BID for four weeks (strategy 6). Patient-reported health resources accounted for subsequent treatment. We estimated two outcomes a) symptom-free months over 12 months, and b) QALYs over 12 months.

Table 1: Medium-term treatment strategies for the management of non-heartburn predominant UD (uninvestigated dyspepsia)

Strategy 1: Test and Treat Omeprazole
If *H. pylori* positive: Triple therapy bid for seven days (PPI, clarithromycin and amoxicillin); if *H. pylori* negative: omeprazole 20 mg qd for 4 weeks

Strategy 2: Test and Treat Ranitidine
If *H. pylori* positive: Triple therapy bid for seven days (PPI, clarithromycin and amoxicillin); if *H. pylori* negative: 150 mg ranitidine bid for four weeks

Strategy 3: Prompt endoscopy, PPI
Treatment based on endoscopic findings. *H. pylori* testing performed and mainly antisecretory treatment with PPI in *H. pylori* negative subjects, triple therapy in *H. pylori* positive subjects

Strategy 4: Prompt endoscopy, H2RA
Treatment based on endoscopic findings. *H. pylori* testing performed and mainly antisecretory treatment with H2RA in *H. pylori* negative subjects, triple therapy in *H. pylori* positive subjects

Strategy 5: Empirical Antisecretory therapy, omeprazole
Omeprazole 20 mg qd for four weeks

Strategy 6: Empirical Antisecretory therapy, ranitidine
Ranitidine 150 mg bid for four weeks

3 OBJECTIVES

The purpose of this study was to compare, using a modeling approach and over a period of 12 months, in terms of efficacy, cost and cost-effectiveness, the test and treat approaches in the treatment of patients with non-heartburn predominant UD presenting to a physician to four other approaches: 1) empirical antisecretory therapy in all patients (omeprazole or ranitidine) and 2) prompt upper gastrointestinal endoscopy of all patients (with PPI or H2RA-based acid suppression).

4 METHODS

4.1 General Methodology

The clinical question was formally structured into a clinical Markov model, representing the major clinical pathways and their consequences. In a Markov model, patients move between defined health states according to transition probabilities. Attached to those health states are certain health outcomes (in this case symptom-free months or quality-adjusted months) and cost outcomes. A three-month cycle was chosen, with discrete probabilities and costs associated with the first cycle. Probabilities and costs associated with a further three-month cycle were repeated three times to approximate the 12-month outcomes. Two health states were defined, symptomatic and non-symptomatic, and transition was assumed to occur at mid-cycle. Modeling was done using TreeAge Pro 2005, version 1.6 (TreeAge Software, Inc.). The validation of the basic model was previously done by presenting the structure to a team of Canadian gastroenterologists (the CADET steering committee) consisting of Drs. D. Armstrong, A. N. Barkun, N. Chiba, A.B.R. Thomson, and S. Veldhuyzen van Zanten. A healthcare system perspective was taken in the analysis.

It was assumed that the patient presenting to the family practitioner was an adult with symptomatic UD (chronic or recurrent pain or discomfort in the upper abdomen), not presenting with alarm symptoms (weight loss, recurrent vomiting, dysphagia, bleeding, anaemia), without heartburn or acid reflux as the primary symptom. Clinical and health resource utilization data from the patient-specific clinical trial data of the CADET series of trials were used to populate the Markov model, presented in Figure 1. The model is set forth in greater detail in Appendix A. The main outcome of interest was estimated symptom-free months at the end of four three-month cycles (12 months), or as an alternate outcome QALYs at the end of the four cycles. From the patient-specific trial data, we estimated symptom-free days using the transition probabilities derived from the proportion of patients reported to be free of symptoms (or with very minor symptoms) at the beginning and the end of a cycle. QALY estimates were derived from existing literature.

4.1.1 Clinical Data

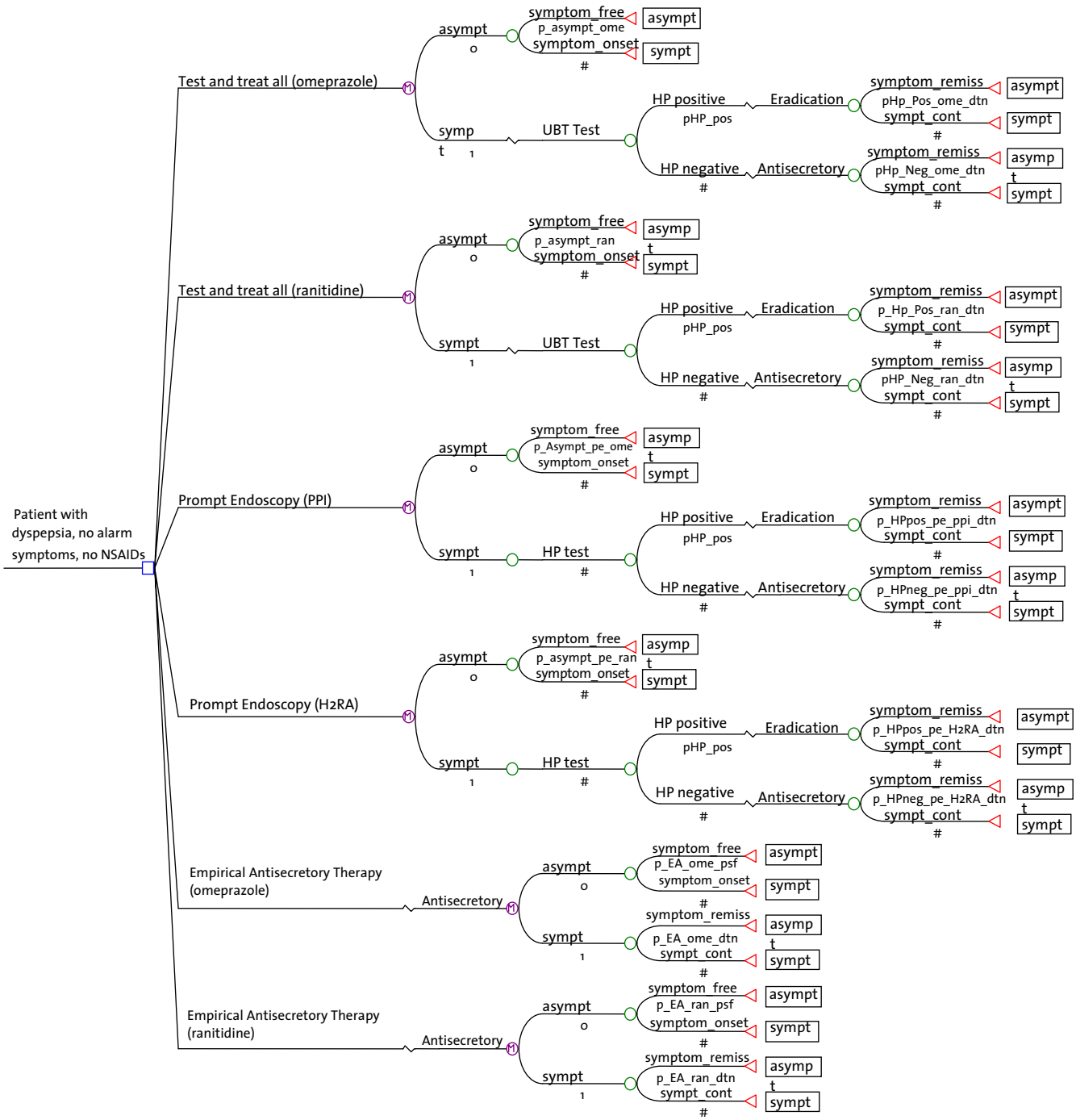
Estimates of transition probabilities were based on results of treatment effectiveness from the CADET series of trials. Clinical data for test and treat approach and treatments (based upon symptom presentation and *H. pylori* status) were drawn from patient-specific data from two CADET studies (CADET-HN and CADET-HP), data on file with AstraZeneca Canada (Dr. Alan Barkun, Division of Gastroenterology, McGill University, Montreal: personal communication, 2007 Mar). (See items A, B and C in Tables 2, 3 and 4.) Clinical data for the effectiveness of prompt endoscopy were drawn from patient-specific data (on file with AstraZeneca (Dr. Alan Barkun, Division of Gastroenterology, McGill University, Montreal: personal communication, 2007 Mar)) from the CADET-PE study, data on file with AstraZeneca Canada (Dr. Alan Barkun, Division of Gastroenterology, McGill University, Montreal: personal communication, 2007 Mar).

(See items D, E and F in Tables 2, 3 and 4.) Results of these studies were previously published.[14,37-40] Clinical data of the effectiveness of empirical antisecretory treatment with ranitidine and omeprazole in uninvestigated dyspepsia were derived from a constituted sample of patients from the CADET HN and HP studies. (See items G and H in Tables 2, 3 and 4.) Because these studies did not contain a group of *H. pylori* positive patients taking a four-week course of antisecretory therapy, the efficacy was assumed to be the same as in the control arm of the CADET-HP trial, in which subjects were treated with seven days of daily omeprazole. Proportions of the constituted samples were based on prevalence of *H. pylori* in the non-heartburn predominant subjects from the CADET-PE study. Information required to assign patients to each of the health states was collected throughout the clinical trials by way of patient responses to questions and reported in case report forms. Results were taken from reporting patients.

Estimates of *H. pylori* prevalence in UD patients with non-heartburn predominant symptoms were drawn from the CADET-PE study (clinical data on file with AstraZeneca) (Dr. Alan Barkun, Division of Gastroenterology, McGill University, Montreal: personal communication, 2007 Mar).

This study recruited adult patients with UD through family practice centres in Canada in order to explore the underlying pathology. Recruited patients who consented were referred for prompt endoscopy, and questioned about their initial symptoms, symptoms after two months, and symptoms after six months. Treatment by the family practitioner followed his/her usual practice after receipt of the endoscopy results. After excluding subjects reporting reflux or heartburn as the primary symptom or with alarm symptoms, those patients positive for *H. pylori* and noted in the records as receiving one or another form of triple therapy were selected for the eradication arm, subjects negative for *H. pylori* and reporting mainly proton pump inhibitor therapy were selected for the prompt endoscopy (PPI) arm, and those noted as receiving mainly H2RAs for the prompt endoscopy (H2RA) arm. Subjects negative for *H. pylori* and treated with eradication therapy and subjects positive for *H. pylori* and not treated with eradication therapy were not selected for the analysis. For the purposes of transition probabilities over a three-month cycle, we used the proportion of patients reporting no/minimal problems to questions about stomach ache and heartburn on the Gastrointestinal Symptom Rating Scale (GSRS) at two months and six months. (See item E in Tables 2, 3 and 4.)

Figure 1: Markov model of medium-term treatment strategies for the management of non-heartburn predominant UD.



The CADET-HP study compared the efficacy of omeprazole 20 mg qd (plus placebo tablets) for one week and a triple-therapy treatment of omeprazole 20 mg, clarithromycin 250 mg and metronidazole 500 mg, all bid for seven days in *H. pylori* positive patients with UD. During the follow-up treatment period (after initial one-week treatment) treatment was at the discretion of the investigator in

accordance with normal clinical routine. For the purposes of transition probabilities over a three-month cycle, we selected the subgroup of patients that did not report predominantly reflux or heartburn symptoms at baseline, and used the proportion of patients reporting no/minimal problems on the Global overall symptom score at three months and five months. (See items D, E and F in Tables 2, 3 and 4.)

The CADET-HN study compared the efficacy of various treatment alternatives, including omeprazole 20 mg qd and ranitidine 150 mg bid in UD patients testing negative for *H. pylori*. Patients randomized to this study received a four-week course of treatment, followed by on-demand medication. For the purposes of transition probabilities over a three-month cycle, we selected the subgroup of patients in the omeprazole and ranitidine arms that did not report predominantly reflux or heartburn symptoms at baseline, and used the proportion of patients reporting no/minimal problems on the Global overall symptom score* at three months and six months. (See items A and B in Tables 2, 3 and 4.)

After health states were attributed to each patient, we counted transitions from one state to another for patients in each treatment arm in each cycle. The total for all patients per arm per cycle were summed. No zero probabilities were observed. In all cases, we used a modified per protocol approach, analyzing all patients who completed a relevant three-month cycle.

Tables 2, 3 and 4 report the transition variables used in the analysis, together with 95% confidence intervals. The probability to be *H. pylori* positive in subjects with non-heartburn predominant symptoms as drawn from the CADET-PE trial was 29.2% (95% confidence interval from 25.7 to 32.8), based on 633 subjects for which *H. pylori* status was available.
We incorporated the following utility weights for health states in the model taken from recent literature:[41,42] a) symptomatic dyspepsia: 0.91, b) Non-symptomatic: 1.00, and outpatient endoscopy: 0.5675 for one day. We did not account for hospitalization in the QALY analysis. No subjects in any of the original study data were diagnosed with cancer and none died during the study period.

Table 2: Transition probabilities‡ from symptomatic to symptom-free, cycle 1 (zero to three months) non-heartburn predominant UD

Percentage symptom-free at 3 months		% (95% CI)	
A)	*H. pylori* negative treated with omeprazole	47.5	(37-58)
B)	*H. pylori* negative treated with ranitidine	43.2	(33-53)
C)	*H. pylori* positive treated with OMC †	53.7	(43-65)
D)	Prompt endoscopy *H. pylori* negative treated with PPI	53.6	(46-61)
E)	Prompt endoscopy *H. pylori* positive treated with eradication	57.6	(48-68)
F)	Prompt endoscopy *H. pylori* negative treated with H2RA	57.0	(48-66)
G)	Empirical antisecretory treated with omeprazole	45.2	(34-56)
H)	Empirical antisecretory treated with ranitidine	42.1	(32-52)

† OMC: omeprazole, metronidazole, clarithromycin triple therapy

* A question administered to patients using a now validated 7-point Likert scale measuring the intensity of epigastric pain
‡ Confidence intervals were truncated at a lower value of zero.

Table 3: Transition probabilities from symptomatic to symptom-free, cycle 2 (three to six months) non-heartburn predominant UD

Percentage symptom-free at 6 months given symptom-free at 3 months		% (95% CI)	
A)	*H. pylori* negative treated with omeprazole	71.1	(57-86)
B)	*H. pylori* negative treated with ranitidine	60.0	(45-75)
C)	*H. pylori* positive treated with OMC †	73.8	(61-87)
D)	Prompt endoscopy *H. pylori* negative treated with PPI	78.1	(69-88)
E)	Prompt endoscopy *H. pylori* positive treated with eradication	92.3	(84-100)
F)	Prompt endoscopy *H. pylori* negative treated with H2RA	77.6	(66-89)
G)	Empirical antisecretory treated with omeprazole	68.9	(54-84)
H)	Empirical antisecretory treated with ranitidine	61.1	(46-77)

† OMC: omeprazole, metronidazole, clarithromycin triple therapy

Table 4: Transition probabilities from symptomatic to symptom-free, cycle 3 (six to nine months) non-heartburn predominant UD

Percentage symptom-free at 6 months given symptomatic at 3 months		% (95% CI)	
A)	*H. pylori* negative treated with omeprazole	22.5	(10-35)
B)	*H. pylori* negative treated with ranitidine	24.0	(12-36)
C)	*H. pylori* positive treated with OMC †	26.3	(12-40)
D)	Prompt endoscopy *H. pylori* negative treated with PPI	26.4	(15-38)
E)	Prompt endoscopy *H. pylori* positive treated with eradication	36.4	(16-57)
F)	Prompt endoscopy *H. pylori* negative treated with H2RA	11.4	(1-22)
G)	Empirical antisecretory treated with omeprazole	24.9	(12-38)
H)	Empirical antisecretory treated with ranitidine	26.0	(14-38)

† OMC: omeprazole, metronidazole, clarithromycin triple therapy

4.1.2 Costs

Data were analyzed from the perspective of the health care system, consequently, only medical costs were included (excluding over-the-counter medication), whoever the payer. Resource use was based on extraction of patient-reported data from the respective CADET trials. In accordance with responses to a questionnaire on the use and cost of health resources that asked subjects about their use of certain resources over the previous four-week period, we attributed a total per-cycle cost to each patient. The CADET-PE study administered the questionnaire after two months and six months, so responses to these questionnaires were tripled to estimate resource use for the first and the subsequent cycles, respectively. Responses to the questionnaire by subjects in the CADET-HP study at one month and three months were used for the first cycle, with the three-month response repeated twice, and responses at the five-month visit were tripled to estimate costs for the subsequent cycle. The CADET-HN study administered the questionnaire monthly, and the first to third responses were used to estimate costs for the first cycle, the fourth to sixth responses to estimate costs for the subsequent cycle. Added to these resources in the first cycle for the test and treat and empirical antisecretory approaches were attributed costs for initial therapies and treatments. For all subjects, we added the cost of an initial visit with a general practitioner. For patients in the test and treat approaches, the cost of a UBT test was added. In the PE arms, we also assumed an initial consultation with a gastroenterologist, together with the cost and fees for an upper GI endoscopy testing for H. pylori. Other trial-driven costs were not included. Most prices are based on 2006 costs from the province of Ontario and summarized in Table 5. Laboratory tests are based on the Ontario schedule.

The total for all patients per arm per cycle were summed, and an average cost per patient per cycle was estimated for each transition. In all cases, we used a modified per protocol approach, analyzing all patients who completed a relevant three-month cycle. The cost parameters used in the model are found in Appendix B.

4.1.3 Markov model - medical costs, sensitivity analyses and total costs analysis

Estimates of:

a) Base-case analysis: symptom free months over the 12-month period following initial treatment
b) Alternate case analysis: QALYs over the same 12-month period,
c) costs ($ to treat a non-heartburn predominant dyspeptic patient for 12 months),
d) cost-effectiveness ($ per symptom-free month or $ per QALY),
e) incremental symptom-free months, incremental QALYs incremental costs, and
f) ICERS: incremental cost per symptom-free month and incremental QALYs

were calculated for each strategy using the Markov Model (Figure 1).

Probabilistic sensitivity analyses were conducted using first and second-order Monte Carlo simulation technique (a random number generator seed* of 1000 was used). The *H. pylori* prevalence estimate was entered as a point estimate. All other probability variables were entered as Beta distributions, and all cost variables were entered as Gamma distributions based on clinical trial data. Details on the conversion to the appropriate distributions are found in Appendix C. Once the distributions were fitted to the model parameters, the TreeAge program randomly selects values from each distribution to create a sample and evaluates the model for that sample; the process is then repeated for another sample with a different combination of randomly selected values. The simulation was run using 1000 samples containing 1000 trials per sample.† The result was a range of cost and effect pairs of values for each approach, which can be presented as distributions. It was from these 1000 distributions that ranges and confidence intervals of efficacy, cost, cost-effectiveness ratios and incremental cost, efficacy and cost-effectiveness ratios (ICERs) were derived.

Cost-effectiveness acceptability curves were also produced comparing the strategies. These curves represented, at each cost level, the percentage of the simulations for which each strategy was cost-effective relative to the others.

Table 5: Price data for resource use – COMPUS Markov analysis

Unit Cost Variable		Cost Per Unit ($)
A)	omeprazole 20 mg od x 28 days (28 tablets of apo-omeprazole @ $1.25 per tablet with 10% upcharge plus ODB pharmacy fee of $7.00)	45.50*
B)	ranitidine 150 mg bid x 28 days (56 tablets of generic ranitidine @ $0.4042 per tablet with 10% upcharge plus ODB pharmacy fee of $7.00)	31.90*
C)	Triple therapy bid 7 days (HP-Pac @ $73.60 with 10% upcharge plus ODB pharmacy fee of $7.00)	87.96*
	GP consultation (A005)	56.10‡

* This ensures a predictable set of simulation results so our analyses are reproducible. Choosing a key value in TreeAge Pro will produce the same set of results for analyses performed at the root node of the Markov model for the medium term management of non-heartburn predominant uninvestigated dyspepsia.[43]

† This number was considered adequate to reasonably represent the results; running much larger samples takes considerably longer and should not change the results to any extent.

Unit Cost Variable	Cost Per Unit ($)
GP follow-up visit (A004)	30.70‡
Gastroenterologist, visit with consultation (A415)	127.50‡
Gastroenterologist, repeat consult (A416)	75.35‡
Surgeon, special surgical consult (A935)	127.50‡
Surgeon, repeat visit (A036)	46.30‡
Endoscopy	545.10***
Nursing visit (1 hour average nursing salary for an RN in Ontario in 2003)	26.34**
Test for HP during endoscopy (L628 Microbiology other swabs 25 LMS @ $0.517 per LMS)	12.925‡
Day in hospital for stomach problem	956.97‡‡
Barium meal (X104 diagnostic radiology of oesphagus, stomach and duodenum)	86.90‡
Urea breath test (G166 and G167 Hydrogen Breath Test)	17.20‡
Barium enema (X112 diagnostic radiology)	73.90‡
Value of 1 day's work	153.72‡‡‡
Blood test (L393 13 LMS plus L700 15 LMS)	14.48‡
Urine test (L633 20 LMS plus L700 15 LMS)	18.10‡
Stool culture (L630 34 LMS plus L700 15 LMS)	25.33‡
Physiotherapist visit	24.40****
Other type of visit	54.10

* Based on Ontario Drug Plan 2006[44] costs. Consists of the drug cost, together with a wholesale upcharge of 10% and a pharmacy fee of $7.00 for every 28 days' supply

‡ Ontario physician fee schedule, 2007[45]

‡‡ weighted average (weighted by number of cases reported) of per diem cost of CMGs from 255 to 297 inclusive from *Health Costing in Alberta 2006 Annual Report*,[46] the cost for 2004/2005)

** Pyper 2004[47]

*** $453 (28.2 Endoscopy GI med from *Health Costing in Alberta 2006 Annual Report*[46]), plus professional fee of $92.10

****OHIP-insured physiotherapy services effective April 1, 2005 (V822), initial home visit (Bulletin 3070 MOH[48])

‡‡‡ Based on average weekly earnings, all industries Ontario, 2005[49]

5 RESULTS

Table 6 reports the average results of the four-cycle (12-month) Monte Carlo analysis using symptom-free months as the outcome, and Table 7 reports the same results for QALYs. Figures 2 and 3 graphically present the results.

5.1 Expected values (point estimates) for effectiveness and cost

In the base-case analysis, using expected values of cost and effectiveness for each strategy, two strategies were dominated when the outcome was in terms of symptom-free months: Test and treat (ranitidine) and empirical antisecretory therapy (ranitidine).* Of the four non-dominated strategies, least costly and least effective over a 12-month period was the empirical antisecretory therapy (omeprazole) approach. Test and treat (omeprazole) was $20.44 more costly per subject and yielded 0.27 more symptom-free months per subject than the empirical antisecretory approach using omeprazole. More effective and more costly than both of these strategies were the two prompt endoscopy approaches, of which prompt endoscopy (PPI) is most effective and most costly.

* A strategy is strictly dominated if it is more costly than another of equal or greater efficacy, or if it is less effective than one which is of equal or lesser cost

In terms of incremental cost-effectiveness, the use of test and treat (omeprazole) was estimated to cost $75 per symptom-free month more than the use of empirical antisecretory therapy in this patient group. Similarly, the use of prompt endoscopy (ranitidine) was estimated to cost $1236 per symptom-free month than test and treat (omeprazole), and the use of prompt endoscopy (PPI) $5167 more per symptom-free month than that prompt endoscopy (H2RA).

The use of QALYs as outcome yielded the same basic conclusions as that using symptom-free months. Test and treat (omeprazole) was estimated to cost $10,004 more per additional QALY than the empirical antisecretory therapy (omeprazole) approach. Both prompt endoscopy approaches were considerably more costly: that using H2RA was estimated to cost $205,643 per QALY more than test and treat (omeprazole); prompt endoscopy (PPI) was estimated to cost $688,989 more per QALY than prompt endoscopy (H2RA).

These results were based on minor differences in effectiveness in terms of symptom-free months and QALYs and in cost for many of the comparisons; therefore the sensitivity analysis was of interest.

Table 6: Expected values for symptom-free months and costs associated with medium term treatment of non-heartburn predominant UD.

Strategy	Cost	Incremental Cost	Symptom Free Months	Incremental SF Months	Cost per SF Month	ICER†††
A) ordered by increasing cost						
Empirical Antisecretory Therapy (omeprazole)	218.91		4.73		46.30	
Test and treat (omeprazole)	239.35	20.44	5.00	0.27	47.86	75.03
Empirical Antisecretory Therapy (ranitidine)	259.09	19.73	4.27	-0.73	60.68	(Dominated†)
Test and treat (ranitidine)	290.70	51.34	4.59	-0.42	63.40	(Dominated****)
Prompt Endoscopy (H2RA)	1221.63	982.28	5.80	0.79	210.78	1235.77
Prompt Endoscopy (PPI)	3083.37	1861.75	6.16	0.36	500.87	5167.42
B) without dominated options						
Empirical Antisecretory Therapy (omeprazole)	218.91		4.73		46.30	
Test and treat (omeprazole)	239.35	20.44	5.00	0.27	47.86	75.03
Prompt Endoscopy (H2RA)	1221.63	982.28	5.80	0.79	210.78	1235.77
Prompt Endoscopy (PPI)	3083.37	1861.75	6.16	0.36	500.87	5167.42

††† Incremental cost-effectiveness ratio (incremental cost per symptom-free month)

† The strategy "Empirical Antisecretory Therapy (ranitidine)" is dominated by "Test and treat (omeprazole)"

**** The strategy "Test and treat (ranitidine)" is dominated by "Test and treat (omeprazole)"

Table 7 : Expected values for QALYs and costs associated with medium-term treatment of non-heartburn predominant UD.

Strategy	Cost	Incremental Cost	Symptom Free Months	Incremental SF Months	Cost per SF Month	ICER†††
A) ordered by increasing cost						
Empirical Antisecretory Therapy (omeprazole)	218.91		0.9455		231.54	
Test and treat all (omeprazole)	239.35	20.44	0.9475	0.0020	252.61	10004.07
Empirical Antisecretory Therapy (ranitidine)	259.09	19.73	0.9420	-0.0055	275.03	(Dominated†)
Test and treat all (ranitidine)	290.70	51.34	0.9444	-0.0031	307.81	(Dominated****)
Prompt Endoscopy (H2RA)	1221.63	982.28	0.9523	0.0048	1282.84	205643.49
Prompt Endoscopy (PPI)	3083.37	1861.75	0.9550	0.0027	3228.71	688989.77
B) without dominated options						
Empirical Antisecretory Therapy (omeprazole)	218.91		0.9455		231.54	
Test and treat all (omeprazole)	239.35	20.44	0.9475	0.0020	252.61	10004.07
Prompt Endoscopy (H2RA)	1221.63	982.28	0.9523	0.0048	1282.84	205643.49
Prompt Endoscopy (PPI)	3083.37	1861.75	0.9550	0.0027	3228.71	688989.77

††† Incremental cost-effectiveness ratio (incremental cost per QALY)

† The strategy "Empirical Antisecretory Therapy (ranitidine)" is dominated by "Test and treat (omeprazole)"

**** The strategy "Test and treat (ranitidine)" is dominated by "Test and treat (omeprazole)"

Figure 2: Symptom-free months and costs associated with alternative strategies over 12 months: Markov analysis of medium-term treatment of non-heartburn predominant UD.

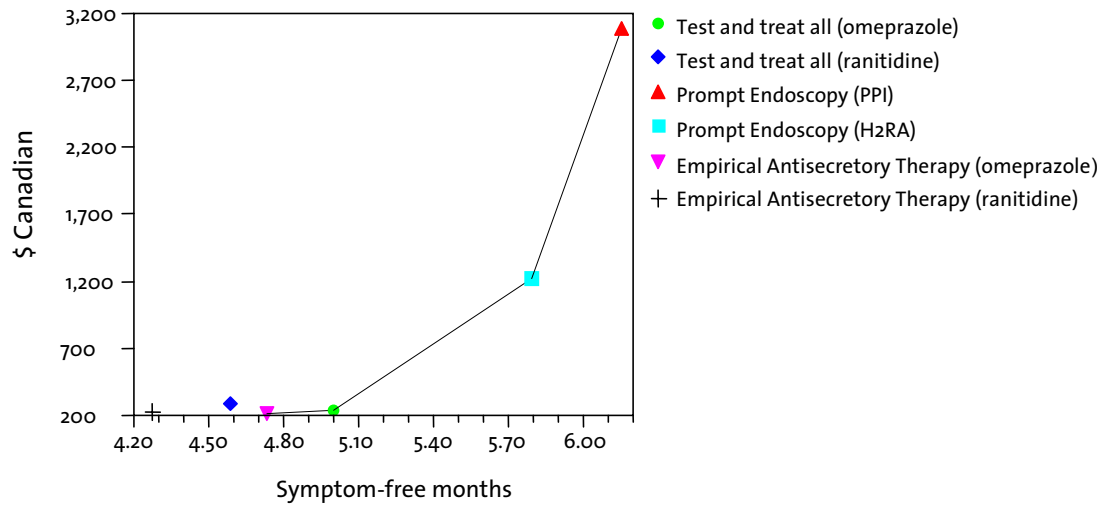
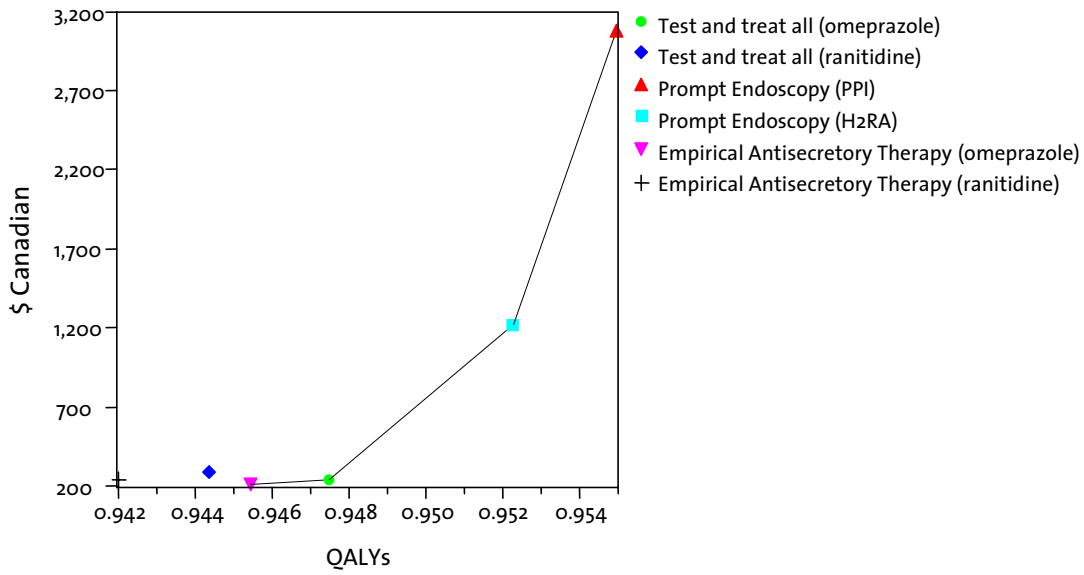


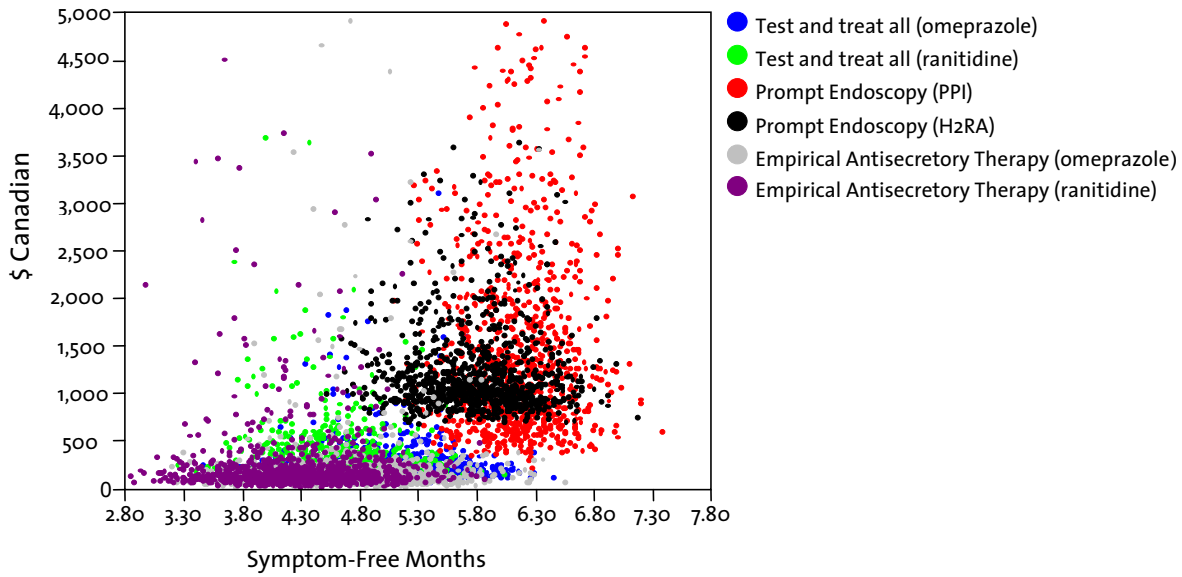
Figure 3: QALYs and costs associated with alternative strategies over 12 months: Markov analysis of medium-term treatment of non-heartburn predominant UD.



5.2 Sensitivity analyses

An estimate of 95% confidence intervals for the average and incremental cost, effect and cost-effectiveness of each approach calculated from the Monte Carlo simulation allowed us to determine whether differences between treatment strategies were statistically significant. We have presented the results of the simulation in graphical and tabular form in Figure 4 and Table 8, respectively, using symptom-free months as the effectiveness measure. Similar data were presented in Figure 5 and Table 9 for QALYs as the measure of effectiveness. Note that in both cases, the Y-axis was truncated to better illustrate the results; most of the points found above the truncation line represent the co-ordinates of Prompt Endoscopy (PPI), the most costly alternative.

Figure 4: Scatterplot of cost-effectiveness of COMPUS Markov Monte Carlo analysis: Costs and symptom-free months



As can be seen both graphically (Figure 4) and in Table 8, most 95% confidence intervals for costs and symptom-free months overlap. Similar results were found in the simulation incorporating QALYs as the outcome effect.

Table 8: Mean costs and effectiveness in symptom-free months for alternative strategies over 12 months: Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD

Strategy	Mean cost (95% CI) [median]	Mean SF months (95% CI) [median]
Test and treat (ome)	$239 (97-784) [182]	5.00 (4.12-5.94) [5.00]
Test and treat (ran)	$291 (99-1077) [204]	4.59 (3.82-5.40) [4.58]
Empiric (ome)	$219 (42-960) [141]	4.73 (3.62-5.83) [4.74]
Empiric (ran)	$259 (41-1347) [148]	4.27 (3.27- 5.23) [4.28]
Endoscopy+H2RA	$1222 (769-2551) [1070]	5.80 (4.92-6.59) [5.82]
Endoscopy+PPI	$3083 (439-16,052) [1302]	6.16 (5.45-6.86) [6.14]

ome=omeprazole, ran=ranitidine, SF=symptom-free.

Figure 5: Scatterplot of cost-effectiveness estimates from Markov Monte Carlo analysis: Costs and QALYs

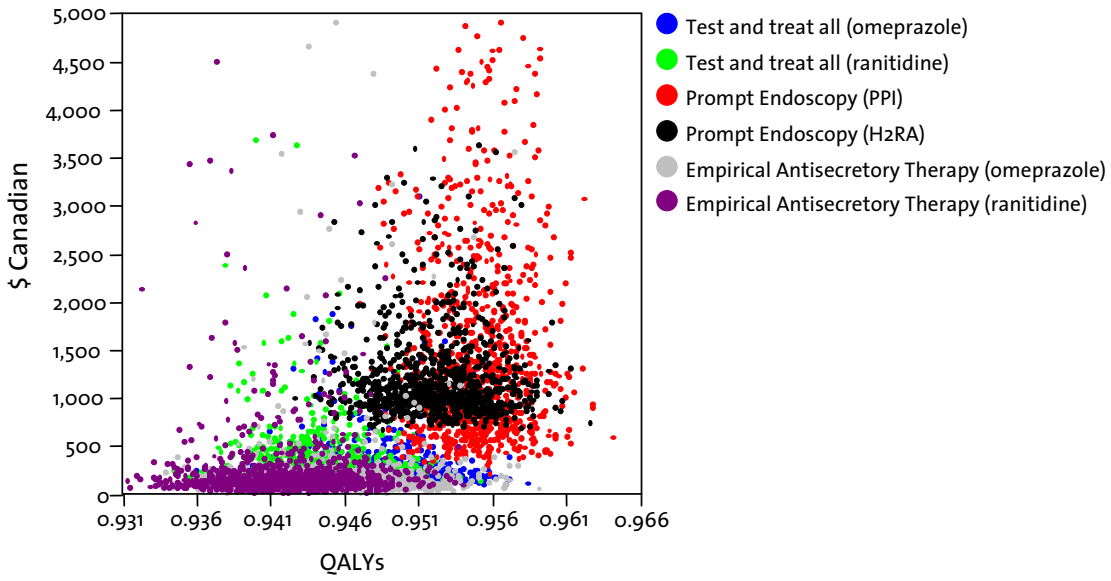


Table 9: Mean costs and effectiveness in QALYs for alternative strategies over 12 months: Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD

Strategy	Mean cost (95% CI) [median]	Mean QALYs (95% CI) [median]
Test and treat (ome)	$239 (97-784) [182]	0.9475 (0.9409-0.9546) [0.9475]
Test and treat (ran)	$291 (99-1077) [204]	0.9444 (0.9386-0.9505) [0.9444]
Empiric (ome)	$219 (42-960) [141]	0.9455 (0.9371-0.9537) [0.9455]
Empiric (ran)	$259 (41-1347) [148]	0.9420 (0.9345- 0.9492) [0.9421]
Endoscopy+H2RA	$1222 (769-2551) [1070]	0.9523 (0.9457-0.9583) [0.9525]
Endoscopy+PPI	$3083 (439-16,052) [1302]	0.9550 (0.9497-0.9603) [0.9549]

ome=omeprazole; ran=ranitidine; QALY=quality-adjusted life-year.

Incremental effects, costs, and cost-effectiveness ratios (ICERs) and corresponding 95% confidence intervals were calculated for different pairs of strategies. Differences that were statistically significant, based on the 95% confidence intervals of the simulations, are highlighted in yellow. Results are found in Tables 10 to 13.

When paired comparisons are made, a few strategies were estimated to be more costly than their comparator, based upon the 95% confidence intervals of the incremental cost. These include the prompt endoscopy approaches, both of which were more costly than Empirical antisecretory (omeprazole) and Test and treat (omeprazole).

Table 10: Incremental costs and symptom-free months for different pairs of strategies over 12 months: Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD

Strategy	Baseline	Incremental cost (95% CI) [median]	Incremental symptom-free months (95% CI) [median]
T&T-ran	Empiric-ome	+$72 (-803 to +949) [+73]	-0.14 (-1.55 to +1.22) [-0.15]
T&T-ome	Empiric-ome	+$20 (-778 to +594) [+48]	+0.27 (-1.16 to +1.71) [+0.28]
Empiric- ran	Empiric-ome	+$40 (-854 to +1218) [+9]	-0.46 (-1.89 to +1.02) [-0.45]
Endoscopy-H2RA	Empiric-ome	+$1003 (+143 to +2340) [+919]	+1.07 (-0.28 to +2.41) [+1.06]
Endoscopy-PPI	Empiric-ome	+$2864 (+150 to +15825) [+1132]	+1.43 (+0.16 to +2.69) [+1.44]
T&T-ome	T&T-ran	-$51 (-490 to +128) [-21]	+0.42 (-0.65 to +1.42) [+0.43]
T&T-ome	Empiric-ran	-$20 (-1125 to +552) [+38]	+0.73 (-0.57 to +2.05) [+0.74]
Endoscopy-PPI	Endoscopy- H2RA	+$1862 (-1367 to +14110) [+209]	+0.36 (-0.53 to +1.25) [+0.37]
Endoscopy-H2RA	T&T-ome	+$982 (+312 to +2278) [877]	+0.79 (-0.43 to +1.94) [+0.81]
Endoscopy-PPI	T&T-ome	+$2844 (+115 to +15884) [+1102]	+1.16 (-0.02 to +2.25) [+1.16]

T&T=test and treat; ran=ranitidine; ome=omeprazole; yellow highlighting=significant (p<0.05)

Table 11: Incremental QALYs for different pairs of strategies over 12 months: Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD

Strategy	Baseline	Incremental QALYs (95% CI) [median]
T&T-ran	Empiric-ome	-0.0011 (-0.0116 to +0.0091) [-0.0011]
T&T-ome	Empiric-ome	+0.0020 (-0.0087 to +0.0128) [+0.0021]
Empiric-ran	Empiric-ome	-0.0034 (-0.0142 to +0.0076) [-0.0034]
Endoscopy-H2RA	Empiric-ome	+0.0068 (-0.0033 to +0.0169) [+0.0068]
Endoscopy-PPI	Empiric-ome	+0.0095 (0.0000 to +0.0190) [+0.0096]
T&T-ome	T&T-ran	+0.0031 (-0.0048 to +0.0106) [+0.0033]
T&T-ome	Empiric-ran	+0.0055 (-0.0043 to +0.0154) [+0.0056]
Endoscopy-PPI	Endoscopy-H2RA	+0.0027 (-0.0040 to +0.0094) [+0.0028]
Endoscopy-H2RA	T&T-ome	+0.0048 (-0.0044 to +0.0134) [+0.0049]
Endoscopy-PPI	T&T-ome	+0.0075 (-0.0014 to +0.0157) [+0.0075]

T&T=test and treat; ran=ranitidine; ome=omeprazole; yellow highlighting=significant ($p<0.05$)

Only one paired comparison was estimated to show a significant difference in the measured effectiveness outcomes: Prompt endoscopy (PPI) was estimated to yield more symptom-free months and more QALYs than empirical antisecretory (omeprazole).

As illustrated in Tables 12 and 13, the range of ICERs of each strategy in the Monte Carlo simulations were extremely wide, and no significant difference was observed between pairs of strategies.

Table 12: Incremental cost-effectiveness ratios (ICERs) for different pairs of strategies from Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD: Cost per additional Symptom-free month over 12 months

Strategy	Baseline	Mean Incremental $/ Incremental SF month (95% CI) [median]
T&T-ran	Empiric-ome	-$406 (-4412 to +3781) [-23]
T&T-ome	Empiric-ome	+$96 (-4934 to +3803) [+30]
Empiric-ran	Empiric-ome	-$57 (-4312 to +2741) [-4]
Endoscopy-H2RA	Empiric-ome	+$1025 (-5756 to +11124) [+844]
Endoscopy-PPI	Empiric-ome	+$2822 (-199 to +22369) [+871]
T&T-ome	T&T-ran	-$88 (-1819 to +1513) [-27]
T&T-ome	Empiric-ran	-$66 (-2547 to +1723) [+28]
Endoscopy-PPI	Endoscopy-H2RA	+$555 (-31223 to +63922) [+208]
Endoscopy-H2RA	T&T-ome	+$1107 (-10771 to +14186) [+953]
Endoscopy-PPI	T&T-ome	+$2907 (-1270 to +21957) [+951]

T&T=test and treat; ran=ranitidine; ome=omeprazole

Table 13: Incremental cost-effectiveness ratios (ICERs) for different pairs of strategies from Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD: Cost per additional QALY over 12 months

Strategy	Baseline	Mean Incremental $/ Incremental QALY (95% CI) [median]
T&T-ran	Empiric-ome	-$54,151 (-588326 to +504103) [-3128]
T&T-ome	Empiric-ome	+$12,825 (-657924 to +507042) [+3978]
Empiric-ran	Empiric-ome	-$7,610 (-574887 to +365464) [-534]
Endoscopy-H2RA	Empiric-ome	+$243,824 (-1475455 to +1162018) [+119264]
Endoscopy-PPI	Empiric-ome	+$1,592,733 (-151321 to +3568585) [+128729]
T&T-ome	T&T-ran	-$11,703 (-242547 to +201765) [-3544]
T&T-ome	Empiric-ran	-$8,851 (-339541 to +229793) [+3788]
Endoscopy-PPI	Endoscopy-H2RA	+$73,987 (-4163005 to +8522959) [+27729]
Endoscopy-H2RA	T&T-ome	+$192,370 (-2147286 to +2603653) [+134108]
Endoscopy-PPI	T&T-ome	+$464,014 (-348580 to +4076217) [+145964]

T&T=test and treat; ran=ranitidine; ome=omeprazole

Cost-effectiveness acceptability curves showing the proportion of simulations of each of the strategies cost-effective at a given willingness-to-pay were seen as Figure 6 using the outcome of symptom-free months and in Figure 7 using QALYs. We have truncated the x-axis of both these figures to better illustrate the results: the relative positions of the curves remain essentially the same at higher costs in the case of Figure 6, and in the case of Figure 7, the axis was truncated at $500,000 to focus on pertinent levels of willingness-to-pay. In both cases, it was seen that at lower levels of willingness-to-pay the preferred strategy was empirical antisecretory therapy (omeprazole), superceded at a relatively low cost point by test and treat (omeprazole) and later by prompt endoscopy (PPI).

Figure 6: Cost-effectiveness acceptability curves of incremental cost per symptom-free month gained: Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD

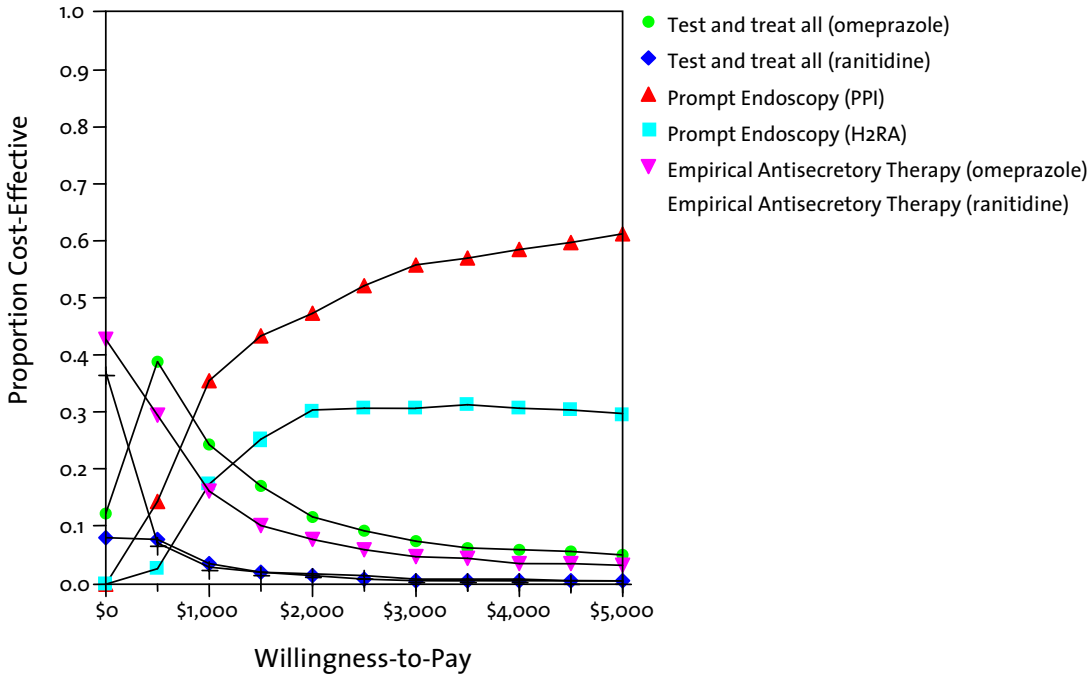
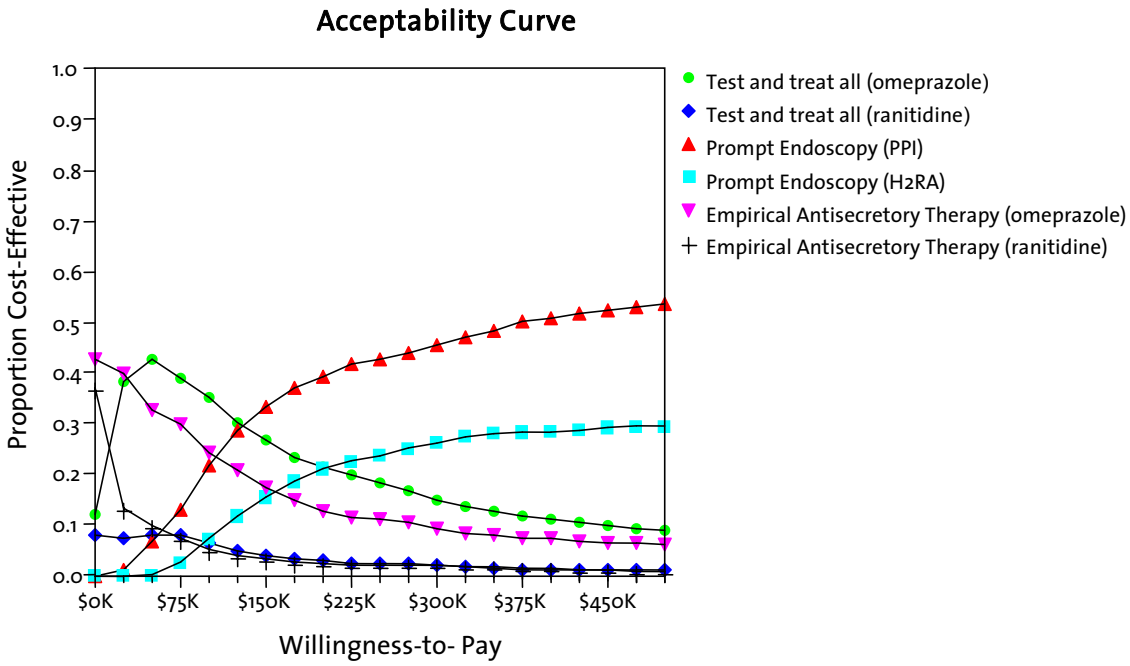


Figure 7: Cost-effectiveness acceptability curves of incremental cost per QALY gained: Markov Monte Carlo analysis of medium-term treatment of non-heartburn predominant UD



6 DISCUSSION AND LIMITATIONS

This study compared the cost and the effectiveness (based on clinical trial data) of six approaches to the treatment of the non-heartburn-predominant uninvestigated dyspepsia patient, without alarm symptoms or history of major NSAID use, by the general practitioner. The time frame for the outcome measurement was medium-term, 12 months, and the outcomes measured included that thought to be most relevant to general practice: the number of symptom free months, defined as no or minimal symptoms, and the outcome most easily compared to other cost-effectiveness evaluations: QALYs.

Using a model created in TreeAge Pro and comparing the alternative strategies each modeled as a Markov cycle, two types of cost-effectiveness results were produced, the first based on point estimates of the cost and effectiveness of each strategy (expected value) and the second a sensitivity analysis based on the Monte Carlo simulation. The latter produced a series of simulations incorporating the distribution parameters for subjects transiting between symptom states, and for the costs of medical resources used in each subgroup.

Conclusions based upon expected values estimated from the Markov model estimated four of the strategies to be cost-effective (and non-dominated): starting with the least costly and least effective was the empirical antisecretory therapy (omeprazole) approach, followed by test and treat (omeprazole) and the two prompt endoscopy approaches, with the most costly and most effective endoscopic approach being that using PPI. The order of the results was the same whether measured in symptom-free months or QALYs.

As this study used a Monte Carlo analysis sampling from distributions of variables potentially influencing the cost or effect outcome of the strategies, we were able to explore the variability of the outcomes (i.e., robustness of point estimates and respective ranges). Testing the robustness of these results using the Monte Carlo sensitivity analysis, the differences were found to be largely statistically non-significant (i.e., $p<0.05$). In particular, comparisons revealed no pairs of compared approaches to have significantly different ICERs.

Health states and resource use were taken from those patients who reported this information; it is assumed that results would be similar for patients who dropped out of the trial. It should also be noted that the patient-reported resources used in the PE study were markedly higher than resource use reported in the CADET-HN and CADET-HP studies.

A major strength of this study was the coherence of the data sources. This model was developed using information from three different sources, which lends itself to criticism when we expect it to behave in a predictable manner.[50] As O'Brien suggests: "This approach...pulls together the many needed pieces of information from multiple sources and then stitches them together into a (hopefully) cohesive whole." However, all these sources were clinical trials conducted in the Canadian population over the same time period. Resource utilization came from the same questionnaire repeated over all the trials. We confidently compared the two test and treat approaches, as the results came from head-to-head comparisons of the two treatments in clinical trials. The antisecretory approaches were artificial samples constituted from these trials and were also comparable. The only limitation related to the group deemed to be *H. pylori* positive and treated with antisecretory therapy; we used the placebo population for this estimate. Although the placebo population was treated with only one week of omeprazole rather than a longer course, this should not significantly influence the definition of the symptom-free month that determined the efficacy in this group, as the measure was at three months after the start of treatment, several weeks past the end of initial therapy.

It was also important to note that we could not assess the actual CanDys approach using this analysis since patients with heartburn predominant symptoms were removed from the analysis. A separate decision model had suggested the superiority of the CanDys approach using omeprazole as acid suppressing agent across a clinically relevant willingness-to-pay range.[51]

Because of the wide confidence intervals of the probabilities and the resource use estimates from the clinical trials, few differences were statistically significant in probabilistic sensitivity analyses. Our major conclusions were very sensitive to the variability in the clinical data. This data had come from clinical trials, and the cohorts of subjects in which transition probabilities and resource use were measured were often rather small, thus the large confidence intervals.

Another strength of this study was its long time horizon. In an earlier model of four-week treatment of UD, where the empirical antisecretory approaches were seen to be the least costly, we suggested an important limitation associated with such a short time period for a chronic problem. It was only over the longer term that drug treatment costs may differ markedly among strategies.

From the point of view of the decision-maker, the choice of the preferred approach will depend upon particular priorities and constraints. The decision-maker bent on using the best technology with the highest effectiveness and no consideration for cost would choose the prompt endoscopy strategy incorporating PPI as the antisecretory therapy. For the decision maker whose only criterion is least cost, the choice is empirical antisecretory therapy (omeprazole); however the results of the sensitivity analysis could not allow a conclusion based on statistical significance that this option was less costly

than many of the other options. The results of the cost acceptability curves raised the issue of what was an acceptable willingness-to-pay range; such data were sparse in the literature and their validity remains controversial. In an attempt to frame the results of the current study, one may have considered the data from Kleinman et al. suggesting that GERD sufferers were willing to pay up to $182 to obtain complete relief in a short period of time without side effects.[52]

We have not incorporated any probability of cancer in this population, but if detection of cancer in the older population was of interest, we would need to adjust the model accordingly. As patients got older, the prompt endoscopy strategies became increasingly favorable, despite the low overall incidence of esophageal or gastric cancer in Canada.

The question of interest, when choosing an appropriate strategy, was whether the additional cost was worth the additional gain. The response to this and similar questions depended on a number of criteria, including the implicit willingness to pay threshold and certainty threshold of the decision maker. The ICER of one approach compared to another can guide the decision-maker who must determine the most appropriate strategy based on available funds. As discussed above, no reliable estimates of willingness to pay for symptom-free months in dyspepsia existed in the literature; therefore outcome measured in QALYs was also incorporated in the analysis. An ICER of $10,000 per QALY to implement test and treat (omeprazole) in the population compared to the least costly and least effective approach of empirical antisecretory (omeprazole) was generally seen to be within the range of acceptable costs per QALY found in the literature (i.e. under $50,000 per QALY). Some may have considered the two prompt endoscopy approaches, with ICERs of several hundred thousand dollars per QALY compared with other approaches, to be excessive. However, the confidence intervals of costs and outcomes were seen to be wide in the sensitivity analyses, demonstrating that conclusions based on point estimate values were subject to question.

7 CONCLUSIONS

When comparing approaches, the most appropriate measure was said to be that of incremental cost-effectiveness.[53] The "lowest cost" approach was thus estimated to be empirical antisecretory therapy (omeprazole) at a cost of $46 per symptom-free month. In these terms, the approach of test and treat (omeprazole) costs an estimated $75 per added symptom-free month more than does the least costly approach. For an estimated additional $1236 per additional symptom-free month subjects could have been treated by prompt endoscopy (H2RA) compared to test and treat (omprazole). Using the prompt endoscopy (PPI) approach costs $5167 more per additional symptom-free month than prompt endoscopy (H2RA). In QALY terms, test and treat (omeprazole) costs an estimated $10,004 more per added QALY than does empirical antisecretory (omeprazole). For an estimated additional $205,644 per additional QALY, subjects could be treated by prompt endoscopy (H2RA) compared to test and treat (omprazole). Using the prompt endoscopy (PPI) approach would cost almost $690,000 more per additional QALY than prompt endoscopy (H2RA).

However, these value estimates were subject to the variability in the costs and probabilities associated with the patient data. Although the cost-effectiveness results showed some of the approaches to be dominated, of differing effect and differing cost, these differences were generally not robust to the tests of statistical significance using the probabilistic sensitivity analysis of the Monte Carlo simulation. In those terms, we could not conclude that the ICERs between pairs of approaches were significantly different ($p<0.05$).

When results were presented as cost-effectiveness acceptability curves, it was observed that at lower levels of willingness-to-pay the preferred strategy was empirical antisecretory therapy (omeprazole), superceded at a relatively low cost point by test and treat (omeprazole) and later by prompt endoscopy (PPI). This was true for both symptom-free months and QALYs. For example, up to a willingness-to-pay level of approximately $25,000 per additional QALY, empirical antisecretory (omeprazole) appeared to be the preferred strategy. Test and treat (omeprazole) was the preferred strategy for willingness-to-pay in the range of approximately $25,000 to $125,000 per QALY gained. Above this level, prompt endoscopy (PPI) was the preferred strategy.

8 ACKNOWLEDGEMENTS

The investigators were free to publish their results, and to make decisions regarding methodology at all times independent of the study sponsor.

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APPENDIX A: DETAILS OF COMPUS MODEL OF MEDIUM-TERM TREATMENT STRATEGIES FOR THE MANAGEMENT OF NON-HEARTBURN PREDOMINANT UD

Figure 8*:* Root node showing six alternative treatment strategies in model of medium-term treatment strategies for the management of non-heartburn predominant UD

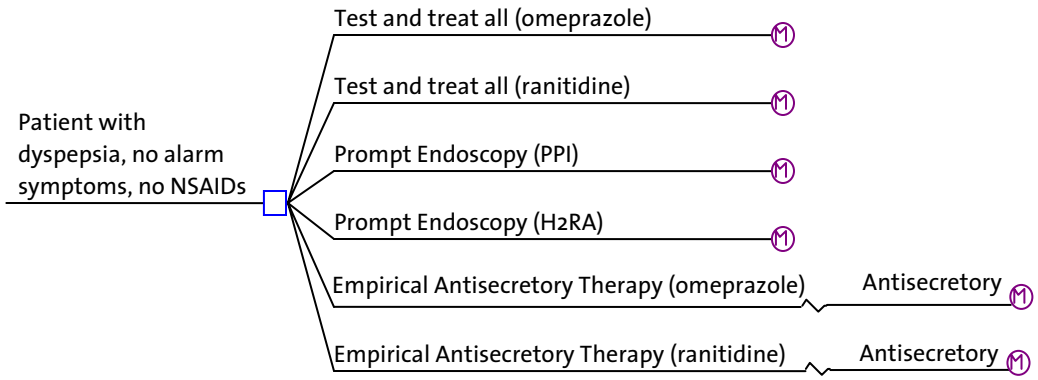


Figure 9: Test and treat (omeprazole) Markov subtree in the model of medium-term treatment strategies for the management of non-heartburn predominant UD

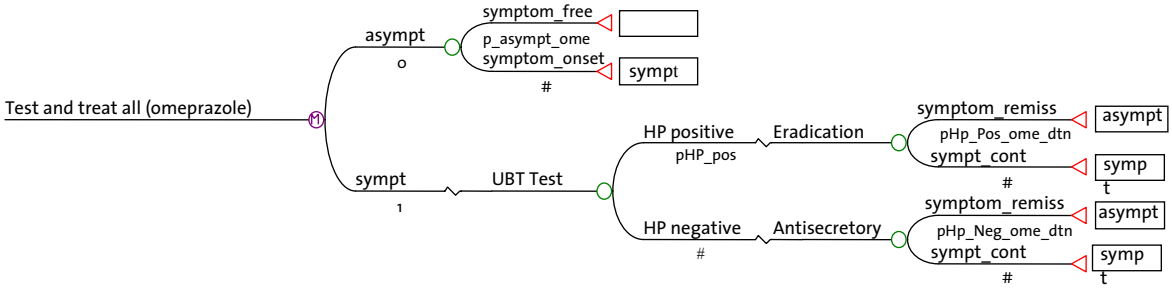


Figure 10: Test and treat (ranitidine) Markov subtree in the model of medium-term treatment strategies for the management of non-heartburn predominant UD

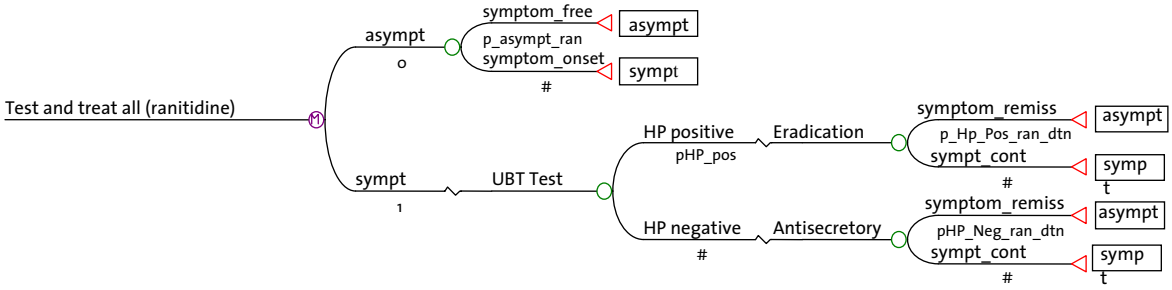


Figure 11: Prompt endoscopy (PPI) Markov subtree in the model of medium-term treatment strategies for the management of non-heartburn predominant UD

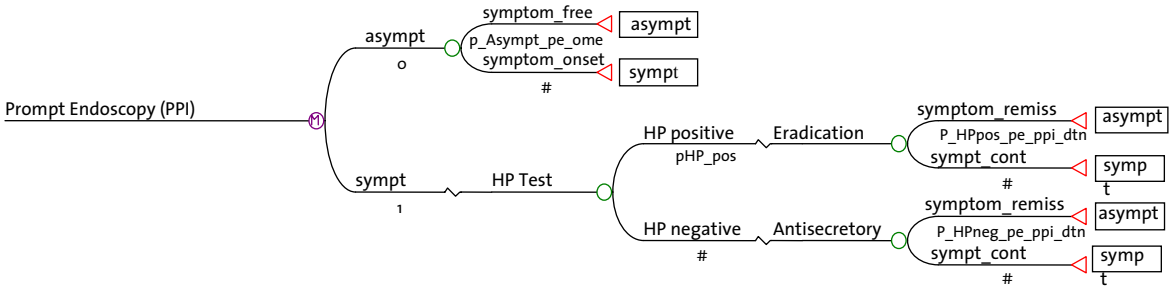


Figure 12: Prompt endoscopy (H2RA) Markov subtree in the model of medium-term treatment strategies for the management of non-heartburn predominant UD

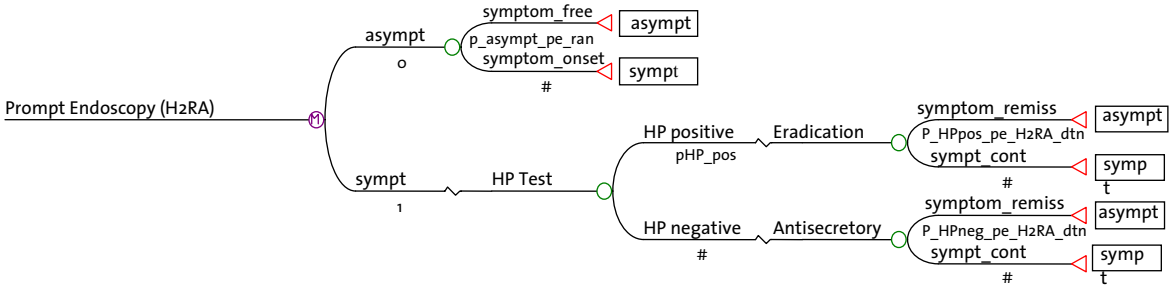


Figure 13: Empirical antisecretory therapy (omeprazole) Markov subtree in the model of medium-term treatment strategies for the management of non-heartburn predominant UD

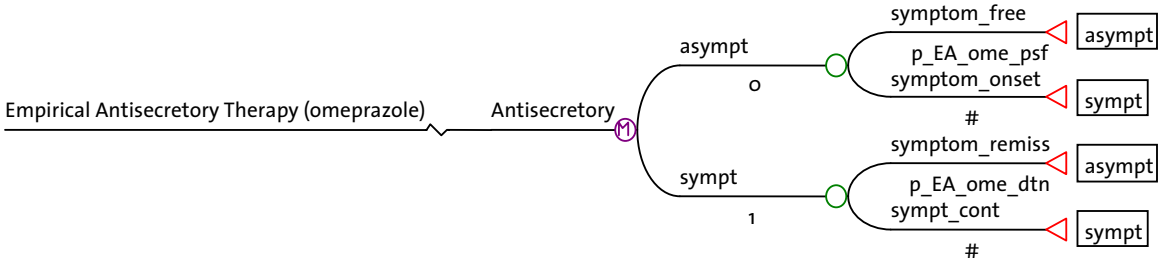
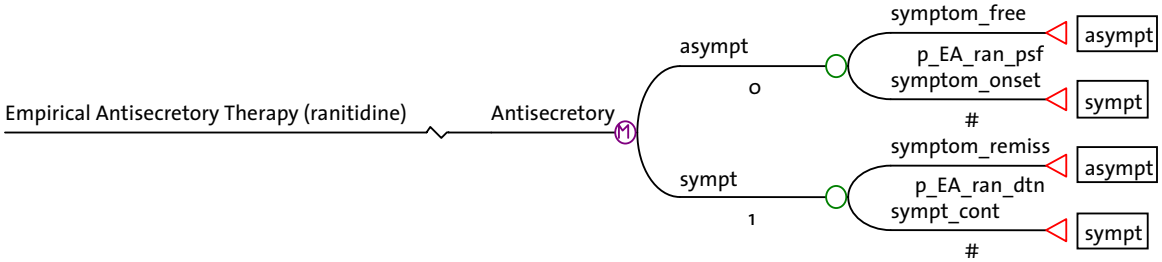


Figure 14: Empirical antisecretory therapy (ranitidine) Markov subtree in the model of medium-term treatment strategies for the management of non-heartburn predominant UD



APPENDIX B: COSTS

Table 14: Cost parameters in the Markov Monte Carlo analysis

Cohort	Costs ($)	
	Mean	St Dev
T&T HP+ So to SF3	175.71	46.42
T&T HP+ So to S3	245.73	224.26
T&T ome HP- So to SF3	137.31	114.09
T&T ome HP- So to S3	119.53	4.74
T&T rani HP- So to SF3	123.40	73.42
T&T rani HP- So to S3	118.31	53.96
PE HP+ So to SF3	950.79	215.69
PE HP+ So to S3	910.13	145.70
PE PPI HP- So to SF3	950.17	891.00
PE PPI HP- So to S3	1069.38	1639.68
PE H2RA HP- So to SF3	857.31	133.06
PE H2RA HP- So to S3	863.30	302.11
EAS ome So to SF3	124.00	101.65
EAS ome So to S3	114.69	67.21
EAS rani So to SF3	110.18	79.19
EAS rani So to S3	109.86	74.03
T&T HP+ SF3 to SF6	12.41	49.16
T&T HP+ SF3 to S6	16.75	37.26
T&T HP+ S3 to SF6	1.69	5.34
T&T HP+ S3 to S6	174.49	553.56
T&T ome HP- SF3 to SF6	7.15	31.56
T&T ome HP- SF3 to S6	11.59	38.44
T&T ome HP- S3 to SF6	26.62	79.86
T&T ome HP- S3 to S6	0.99	5.51
T&T rani HP- SF3 to SF6	18.47	81.40
T&T rani HP- SF3 to S6	15.09	60.37
T&T rani HP- S3 to SF6	28.17	75.69
T&T rani HP- S3 to S6	49.34	173.18
PE HP+ SF3 to SF6	178.33	387.41
PE HP+ SF3 to S6	36.32	49.03
PE HP+ S3 to SF6	24.46	27.28
PE HP+ S3 to S6	159.67	229.09
PE PPI HP- SF3 to SF6	281.74	888.89
PE PPI HP- SF3 to S6	107.23	141.30
PE PPI HP- S3 to SF6	2508.59	8208.56
PE PPI HP- S3 to S6	2068.99	11872.34
PE H2RA HP- SF3 to SF6	130.92	203.11
PE H2RA HP- SF3 to S6	135.46	161.34
PE H2RA HP- S3 to SF6	82.67	147.89
PE H2RA HP- S3 to S6	165.16	407.95
EAS ome SF3 to SF6	11.96	68.55

Cohort	Costs ($)	
	Mean	St Dev
EAS ome SF3 to S6	13.73	38.01
EAS ome S3 to SF6	31.49	86.30
EAS ome S3 to S6	64.75	411.76
EAS rani SF3 to SF6	19.97	89.16
EAS rani SF3 to S6	16.21	51.86
EAS rani S3 to SF6	32.59	83.99
EAS rani S3 to S6	98.98	410.97

Legend : T&T= Test and treat, ome = omeprazole, rani = ranitidine, HP+ = H. pylori positive, HP- = H. pylori negative, So = symptomatic at month 0, SF3 = symptom-free at month 3, S3 = symptomatic at month 3, SF6 = symptom-free at month 6, S6 = symptomatic at month 6, PE = prompt endoscopy, EAS = empirical antisecretory therapy

APPENDIX C: BETA AND GAMMA DISTRIBUTIONS

A beta distribution was fitted to the parameters of the probabilities to be symptom-free. For the beta function, the conversions for μ (proportion) and σ (standard deviation) are:

$$\alpha = (\mu^2 / \sigma^2)*(1-\mu) - \mu$$

$$\beta = (\alpha/\mu)*(1-\mu)$$

A gamma distribution was fitted to the parameters of the costs of each branch. For the gamma distribution, the conversions for μ (mean) and σ (standard deviation) are:

$$\alpha = (\mu^2 / \sigma^2)$$

$$\lambda = \sigma^2 / \mu$$

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Economic Evaluation of Alternative Strategies for the Management of Patients with Heartburn Predominant Gastroesophageal Reflux Disease Symptoms in Canada

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Gord Blackhouse[1,2]
Avtar Lal[3]
Sameer Rajbhandary[3]
Dénis Belanger[3]
Daria O'Reilly[1,2]
Ron Goeree[1,2]

[1] Program for Assessment of Technology in Health (PATH), St. Joseph's Healthcare Hamilton, Hamilton, Canada
[2] Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada
[3] Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, Canada

Corresponding author:

Ron Goeree
Program for the Assessment of Technology in Health (PATH)
25 Main St. W., Suite 2000
Hamilton, ON L8P 1H1
E-mail: goereer@mcmaster.ca
Tel. (905) 523-7284 ext.5266
Fax. (905) 522-0568

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ABBREVIATIONS

CEAFs	cost-effectiveness acceptability frontiers
CMD	Canadian Medical Directory
EE	erosive esophagitis
ENRD	endoscopy-negative reflux disease
GERD	gastroesophageal reflux disease
GI	gastroenterologists
H. pylori	Helicobacter pylori
H2RA	H_2-receptor antagonists
OTC	Over-the-counter medications
PPIs	Proton Pump Inhibitors
QALYs	quality adjusted life years
SF	Short Form
UG	Uninvestigated gastroesophageal reflux disease
WTP	Willingness-to-pay

1 INTRODUCTION

Over the past several years, health care professionals and health care decision makers are increasingly concerned about gastroesophageal reflux disease (GERD). Not only is GERD a complex condition to diagnose and manage, but symptoms characteristic of GERD (i.e. heartburn) occur monthly in almost 50% of adults, and it is estimated that 17 million patients in the United States suffer from GERD.[1] It should be noted that not all patients with GERD-like symptoms have GERD, however, offsetting this is the fact that patients are generally not referred to a gastroenterologist for confirmatory diagnosis unless symptoms become resistant to treatment and that a number of patients with symptoms treat themselves with over-the-counter (OTC) medications, without consulting a physician. Therefore, although an accurate estimate of the prevalence of GERD in the community is difficult, community-based studies suggest the prevalence of GERD is at least 5-7%.[2]

In addition to being highly prevalent, GERD is shown to be associated with impaired health-related quality of life and significant health care costs. Using the Short Form (SF) 36 health survey, Ronkainen et al.[3] found clinically relevant impairment of health-related quality of life in people with reflux symptoms compared to patients without symptoms. Furthermore, the direct and indirect costs attributed to GERD are substantial.[4] Although GERD is mostly managed in primary care, it accounts for 17% of all visits to gastroenterologists[5] and drugs used to treat GERD patients are widely prescribed and impose a significant burden on government and private insurance drug plans.[6] And this does not even account for the OTC reflux remedy market which is substantial.[7] The American Gastroenterological Association[8] estimated the direct and indirect cost of GERD to be over $10 billion per year in the United States in 2001, and a recent direct-cost estimate places the burden of GERD at over $9 billion per year.[9]

For the most part, clinical trials emphasize the healing and prevention of esophageal erosions as the dominant metric of treatment efficacy in the management of more severe GERD. However, the management of GERD in primary care is guided by the presence and absence of symptoms, often without prior referral to a specialist or endoscopic evaluation. The most common GERD-like symptoms include heartburn, acid reflux, regurgitation, chest pain, coughing and wheezing, hoarseness and laryngitis, and difficulty swallowing. Although the symptoms of GERD are notoriously non-specific, heartburn as a dominant complaint is predictive of underlying gastroesophageal reflux.[10,11] A recent systematic review of prevalence studies[12] found that in Western populations 25% of people report having heartburn once a month, 12% once a week, and 5% report daily symptoms.

Patients with GERD symptoms may have one of two underlying conditions: erosive esophagitis (EE), characterized by breaks in the esophageal mucosa; or endoscopy-negative reflux disease (ENRD), characterized by the absence of esophageal mucosal disease. EE is associated with an increased risk for certain complications (i.e., hemorrhage, stricture formation, Barrett's esophagus, and esophageal cancer), but also demonstrates better responsiveness to therapy than ENRD. Part of the challenge in managing patients with heartburn-predominant symptoms in the primary care setting is that only some patients are investigated, endoscopically, to determine the presence of EE, while the majority remain uninvestigated.

Regardless of the underlying cause, current Canadian guidelines endorse primary care empiric management of uncomplicated heartburn symptoms without referral or prior investigation.[13] However, given the potential long-term nature of drug treatment for these patients, it is imperative that primary-care management approaches be evaluated, systematically, for their effectiveness in relieving and preventing heartburn symptoms and their overall cost-effectiveness. Furthermore, this

assessment should be based on strategies geared at managing patient symptoms as this bears greater relevance to clinical practice in primary care where the majority of heartburn predominant reflux symptoms are managed.

Despite the importance of such assessments, there continues to be controversy regarding the optimal acute treatment and maintenance strategies for managing heartburn predominant symptoms. Proton pump inhibitors (PPI) are superior to H_2-receptor antagonists (H2RA) in their degree and speed of healing,[1] however, they also have higher acquisition costs. PPIs are one of the fastest growing drug classes and are second only to cholesterol-lowering drugs in drug cost among all paid prescription claims in Canada.[14] Payers and decision makers need to determine whether the additional cost of PPI therapy is justified by its benefits in relieving symptoms and preventing recurrence and whether this value for money assessment is different for EE, ENRD or uninvestigated GERD (UG) heartburn predominant patients.

The objective of this study was to compare, over a 1-year period, the expected costs and outcomes of alternative primary care strategies for the management of patients with moderate-to-severe heartburn. Separate analyses are conducted for EE, ENRD and UG patients. Outcomes are expressed in terms of symptomatic recurrences averted, weeks without heartburn symptoms and quality adjusted life years (QALYs) over a one-year period. The analysis is taken from a third party payer perspective and all costs are expressed in 2006 Canadian dollars.

2 METHODS

2.1 Model overview

This study builds upon a previously published model.[15] In collaboration with the PPI Expert Review Panel (ERP) of the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), several updates and modifications to the original model were undertaken. A new systematic review of studies reporting heartburn symptomatic relief and recurrence was completed and costs were updated to 2006 Canadian dollars. The analysis was undertaken for different patient populations based upon evidence of erosive esophagitis (i.e. EE, ENRD, UG). And finally, the treatment strategies considered in the model was updated to reflect current treatment patterns as suggested by the PPI ERP of COMPUS. The costs and effects of five treatment strategies for adults with moderate to severe heartburn were estimated using a probabilistic Markov model and the model was run for the three different patient populations (EE, ENRD, UG).

2.2 Treatment Strategies

The treatment strategies in the model were based on a review of the literature, two surveys completed by family physicians and gastroenterologists, and the PPI ERP of COMPUS. Strategies differed according to both initial heartburn treatment and treatment following heartburn symptomatic relief for prevention of recurrences. Descriptions of the five treatment strategies are provided below.

Strategy A: H2RA on demand. Acute treatment with a standard-dose H2RA for up to four weeks until resolution of symptoms with no further treatment until a recurrence of symptoms.
Strategy B: PPI on demand. Acute treatment with a standard-dose PPI for up to four weeks until resolution of symptoms with no further treatment until a recurrence of symptoms.

Strategy C: H2RA maintenance. Acute treatment with a standard-dose H2RA for four weeks followed by continuous maintenance therapy with an H2RA (same dose) to prevent recurrences.
Strategy D: PPI maintenance. Acute treatment with a standard-dose PPI for H2RA or four weeks followed by continuous maintenance treatment with a PPI (same dose) to prevent recurrences.
Strategy E: PPI with step-down H2RA maintenance. Acute treatment with a standard-dose PPI for four weeks followed by continuous maintenance treatment with an H2RA to prevent recurrences.

These strategies do not simply represent single drug treatments, but rather overall primary care treatment strategies for patients with heartburn. For example, when patients fail to achieve symptom relief, patients are assumed to be prescribed either a higher dosage of a medication or switched to a different medication. The logic of patient management for each strategy is shown in Table 1. Failure to achieve symptom relief after 4 weeks of treatment results in a step-up in medication in all strategies. For example, failure to achieve symptomatic with an H2RA leads to an attempt to relieve symptoms with a PPI. Failure to achieve relief with a PPI leads to an attempt to relieve symptoms with a double dose of a PPI. If symptom relief requires a double-dose PPI, it is assumed that patients will be prescribed continuous maintenance therapy with a standard-dose PPI. This is the case for all strategies regardless of initial therapy intention. Finally if a patient on maintenance therapy experiences a symptomatic relapse, it is assumed that a step up to a higher dosage or more effective medication would be prescribed. The duration of medication treatment for a symptomatic recurrence differs between continuous maintenance strategies (C, D & E) and on-demand strategies (A&B). For continuous maintenance strategies, it is assumed patients will finish an entire course of therapy regardless of when their symptoms subside. For the on-demand strategies, it is assumed that patients stop taking their medication when symptoms subside.

2.3 Model structure

Figure 1 provides a simplified representation of the structure of the Markov model. The model uses the step-up, step-down, and switching strategies shown in Table 1. The model is comprised of three 4 month cycles. After initial heartburn relief, patients are at risk of recurrence of symptoms in each cycle. The expected costs and outcomes estimated by the model incorporate not only the initial heartburn relief therapy, but also maintenance therapy and heartburn recurrence.

2.4 Outcome Measures

A number of outcome measures were used in the analysis. The primary outcome was quality adjusted life years (QALYs) over the 12 month time horizon. QALYs were estimated by applying a utility weight (0.82) to each day of heartburn symptoms.[16] Secondary outcome measures included the number of weeks with heartburn symptoms and number of heartburn recurrences. Symptom weeks have commonly been used in economic evaluation of gastroenterologic interventions as they combine the number of symptom recurrences and the speed with which symptoms are relieved.

2.5 Systematic review

A systematic review of published controlled clinical trials was undertaken to derive pooled estimates of symptom relief and recurrence probability for each strategy. Studies published through 2006 were identified from Medline, and EMBASE. Search terms were exhaustive and included a combination of MeSH (Medical Subject Headings) and keywords for Proton Pump Inhibitors, H2RAs (H2 Receptor Antagonists), and heartburn, gastroesophageal reflux disease, and other indications where heartburn is a significant factor. A compete summary of the search terms are provided in Appendix A. Study

inclusion criteria were: English language; adult subjects (i.e. over 16 years old); randomized controlled trial; single or double-blind studies; and data presented as heartburn relief, improvement and or relapse.

2.6 Symptomatic Relief Analysis

For studies meeting the inclusion criteria, the number of patients initially at risk, along with the number of patients with relief of heartburn symptoms was extracted for the various time points reported in the study. For purposes of analysis, the absence of heartburn symptoms was defined as none to mild symptoms, and the presence of heartburn symptoms was defined as moderate to severe heartburn symptoms. In addition, the patient population (i.e. EE, ENRD, UG) was abstracted for each study. In a number of studies, results were presented separately for EE and ENRD patients. For these cases, data was abstracted separately for the EE and ENRD patients. Rates of symptomatic relief by drug regimen for each patient population were estimated by pooling single arms of trials using random effects meta-analysis.[17] Rates of heartburn relief were calculated separately for standard-dose H2RA, standard-dose PPI and double-dose PPI. There was an additional inclusion criterion for the double-dose PPI relief studies in that only studies that looked specifically at patients who had previously failed on a PPI were included. This is because in the model only patients who had failed a course with standard-dose PPI were prescribed double- dose PPI for heartburn relief. Time with heartburn symptoms over the acute relief period for each drug regimen was calculated as the area under the relief curve using standard principles of mathematical integration.

2.7 Recurrence Analysis

For studies meeting the inclusion criteria, the number of patients initially at risk, along with the number of patients with a recurrence of symptoms (defined as moderate to severe heartburn) was extracted for the various time points reported. In addition, the patient population (i.e. EE, ENRD, UG) was abstracted for each study. Within each patient population, rates of symptomatic recurrence by drug regimen were estimated by pooling single arms of trials using random effects meta-analysis.[17] Rates of heartburn recurrence were calculated separately for placebo (for on-demand strategies), standard-dose H2RA and standard-dose PPI.

2.8 Management of Initial and Recurring Symptoms

Two surveys were conducted in 2001 to estimate the non-drug costs associated with the management of initial and recurrent heartburn symptoms. These included costs for tests, procedures and doctor visits related to heartburn management. Two different survey questionnaires were developed, one for family physicians and one for gastroenterologists. Physicians listed in the Canadian Medical Directory (CMD) were selected at random to participate in the survey. A total of 100 questionnaires were mailed out to family physicians and 65 to gastroenterologists. There were 55 family physician and 48 gastroenterologist questionnaires completed and returned for a response rate of 56% and 76% respectively. Since we assumed that all patients would initially be managed by their family physician, the family physician survey responses were used to determine initial patient management. The gastroenterologist survey responses were used only when the family physician indicated that they would make a referral.

The survey questionnaires were designed to capture information about the management of patients at initial presentation with heartburn symptoms, after failure with initial therapy, and upon recurrence of heartburn symptoms. A summary of the findings from the surveys for initial

management and upon treatment failure are shown in Table 2. The proportions listed in the second column of Table 2 were used to assign costs to the tests and procedures associated with initial patient management. The third and the fifth columns were used to cost tests and procedures ordered by the family physician if initial treatment was not effective in relieving symptoms. Finally, the fourth and sixth columns of Table 2 were used to cost out tests and procedures ordered by the gastroenterologist after initial treatment failure and upon referral from the family physician.

A summary of the findings from the surveys of management of symptomatic heartburn recurrence is presented in Table 3. Since physician management of a recurrence might depend on previous diagnosis, we asked about tests and procedures ordered under four different scenarios in both the family physician and gastroenterologist questionnaires: 1) maintenance therapy for patients with previous testing indicating ENRD; 2) maintenance therapy with previous evidence of EE; 3) no maintenance therapy for patients with previous evidence of ENRD; 4) no maintenance therapy for patients with previous evidence of EE.

The columns in Table 3 were used to estimate the costs of tests and procedures ordered for symptomatic recurrence. Which column was used for any particular recurrence depended on whether the patient was on maintenance therapy or not, whether the patient was previously diagnosed as ENRD, EE or UG, and whether the patient was being managed by a family physician or a gastroenterologist. ENRD and EE specific recurrence costs were used in the analysis of ENRD and EE populations respectively. For patients with UG, we assumed that 32% had underlying EE, whereas the remaining 68% had ENRD.[18]

2.9 Unit costs for Health Care Resources

A list of the unit costs used in the model is provided in Table 4. The 2006 Ontario Drug Benefit (ODB) formulary was used to estimate the daily cost of medications.[19] The cost of ranitidine 150mg twice a day was used for daily H2RA cost. The daily cost of standard-dose PPI was based upon 20mg omeprazole once a day, while double-dose PPI costs were based on 20mg omeprazole twice a day. We assumed a standard 10% pharmacy markup charge and a $4.54 dispensing fee for all prescriptions. These are the maximum allowable amounts under the ODB program. Physician fees for visits and procedures were based upon the 2006 Ontario Schedule of Benefits for physicians.[20] The costs of tests and procedures were provided by a hospital participating on the Ontario Case Costing Project.[21]

2.10 Probabilistic Analysis

The model used in this analysis is fully probabilistic. In probabilistic models, input variables are specified as distributions around mean values, instead of a single point estimate. The model is run a large number of times in what is referred to as Monte Carlo simulations. Each time the model is run, a different set of values from all model parameters are chosen based on the specified distributions and a set of random numbers. Different expected costs and outcomes are estimated in each simulation. The expected costs and outcomes of the model are then estimated as the mean of the costs and outcomes across all simulations. This allows for the uncertainty of all model variables to be incorporated into the model results. We ran 1,000 Monte Carlo simulations for all analyses.

The distributions specified in the model depended upon the type of variable. Variables whose values are constrained between 0 and 1 were assigned Beta distributions. These included symptomatic relief and recurrence variables, the utility weight for heartburn symptoms, and all the test and procedure probability variables derived from the physician survey. When appropriate, cost variables were

assigned Gamma distributions. Gamma distributions were chosen because cost variables must be greater than zero. For certain cost variables, distributions were not assigned and single point estimates were used instead. These included drug costs and physician fees which were based upon set provincial reimbursement schedules.

2.11 Cost-Effectiveness analysis

The analysis of the probabilistic Markov model provides expected costs, expected recurrences, expected weeks with heartburn symptoms, and expected QALYs over a 12 month time horizon. General principles of cost-effectiveness analysis with multiple comparators were applied to these results.[22] First, it was determined whether certain strategies were strictly dominated by other strategies. A strategy is strictly dominated if it has higher cost and lower effectiveness (i.e. QALYs) compared to another strategy. Second, it was determined whether any strategies were dominated through principles of extended dominance. Finally, among non-dominated alternatives, incremental cost-effectiveness ratios were calculated using the ratio of the difference in cost to the difference in outcomes between two strategies. Beginning with the least costly strategy, alternatives were compared with the next most costly strategy to calculate incremental ratios. This process produces an efficiency frontier of increasingly more costly and more effective strategies. The slope of this frontier reflects incremental cost-effectiveness, the additional cost at which additional units of effect can be purchased.

2.12 Assessment of Uncertainty

The parameter uncertainty of the model was assessed using the simulation results from the probabilistic analysis. Utilizing the net benefit framework,[23] parameter uncertainty was expressed as both cost-effectiveness acceptability curves (CEACs) and as cost-effectiveness acceptability frontiers (CEAFs).[24] CEACs show the proportion of Monte Carlo simulations that a treatment strategy has the highest net benefit (i.e. is the most cost-effective), as a function of societies' willingness to pay (WTP) for a unit of outcome (i.e. cost per QALY). CEAFs show the proportion of simulations in which a treatment has the highest net benefit (i.e. is the most cost-effective) as a function of societies' WTP, given that the strategy has the highest average net benefits across all simulations. CEAFs are preferred for decision making because they show which strategy should be chosen based upon having the highest average net benefit.

3 RESULTS

3.1 Symptomatic relief

Studies of heartburn symptomatic relief meeting the study inclusion criteria are shown in Appendix B by patient population and drug regimen. The total number of patients at risk along with the number of patients with symptomatic relief is shown at baseline and week 4 for each study. Applying meta-analytic techniques to these studies, pooled estimates of symptom relief after 4 weeks of treatment were estimated by drug regimen for each patient population. Table 5 summarizes the 4 week relief rates along with the associated 95% confidence intervals. The number of trials that were used in each estimate is also provided. Based on trials of EE patients, heartburn relief rates after 4 weeks of treatment were estimated to be 48.0% for H2RA and 75.4% for standard-dose PPI. The probability of relief after four weeks of double-dose PPI, conditional on having failed a 4-week course of standard-dose PPI, was estimated to be 55.4%. All three studies that investigated symptom relief from double-dose PPI after failure on standard- dose PPI were conducted on patients whose GERD status was

uninvestigated. Therefore, the 55.4% relief rate was assumed for all patient populations. In the ENRD population, relief with H2RA was estimated to be 42.7% while relief after 4 weeks of PPI was estimated to be 52.6%. H2RA and PPI symptomatic relief was estimated to be 35.2% and 58.3% respectively in the UG population. Less than 10% of patients in all strategies remain unhealed after 8 weeks of double-dose PPIs. Therefore, we made the simplifying assumption that all patients achieve symptomatic relief after 8 weeks of double-dose PPIs. Alternatively, we could have assumed that patients continue therapy until all achieve symptom relief, or that patients who are not relieved of symptoms are referred to surgery. In the original published model, the latter assumption was used. However, ERP members felt that this assumption was no longer valid. Using the assumption that patients continue therapy until all have symptom relief is problematic because there will always be a proportion of patients remaining unrelieved if 100% relief is not assumed at some point. Because slightly more patients in the PPI treatment strategies (B, D, and E) remain unrelieved after 8 weeks of double-dose PPIs, cost effectiveness results would be less favorable for these strategies under alternate assumptions.

3.2 Symptomatic recurrence

Studies reporting recurrence of heartburn symptoms at 3 or 12 months are shown in Appendix C. The number of patients at risk along with the number of patients experiencing recurrences is shown for baseline, 3 months, and 12 months. These studies were used to estimate pooled recurrence rates for each drug regimen. These rates are summarized in Table 6. Because all studies reporting recurrence data included the same patient population (i.e. EE), the same recurrence rate was assumed for all populations. As shown in Table 6, the fewest recurrences are estimated for patients on PPI maintenance therapy (strategy D). Recurrence rates are estimated to be 16.6% at 3 months and 19.7% at 12 months. Recurrence rates for H2RA maintenance therapy (strategies C and E) are estimated to be 32.1% at 3 months and 39.7% at 12 months. Recurrence rates are highest for patients that are not on any maintenance therapy (strategies A and B). Recurrence rates at 3 and 12 months are estimated to be 62.6% and 68.9% respectively.

3.3 Cost-Effectiveness for EE population

Table 7 displays the expected costs, and outcomes for patients with confirmed EE by treatment strategy. As shown, PPI on demand had the lowest expected 1-year costs ($537) while the PPI Maintenance strategy had the highest expected costs ($776). The PPI Maintenance strategy also had the most favorable outcomes, whether measured as recurrences (0.201), time with symptoms (4.19), or QALYS (0.909). By contrast, the H2RA on-demand strategy had the highest number of recurrences (0.834), the highest number of weeks with heartburn symptoms (8.24) and the lowest number of expected QALYs (0.895).

The last two columns of Table 7 show, respectively, the incremental cost per heartburn week avoided and incremental cost per QALY gained. Figure 2 presents the cost-effectiveness efficiency frontier for the primary cost-effectiveness QALY outcome. The efficiency frontier for the incremental cost per heartburn week avoided is not presented diagrammatically as these results are similar as the cost per QALY analysis. As shown, there are three strategies that comprise the efficiency frontier, PPI on-demand (B), PPI with step down H2RA Maintenance (E), and PPI Maintenance (D). The other 2 strategies (A and C) are dominated because they are more costly and less effective than another strategy. Moving from strategy B to strategy E, costs $115 per symptom week averted or $33,692 per QALY gained, moving from strategy E to strategy D costs $151 per symptom week averted or $44,168 per QALY gained.

3.4 Cost-Effectiveness for ENRD population

Table 8 displays the expected costs, and outcomes for patients with confirmed ENRD by treatment strategy. H2RA on-demand had the lowest expected costs ($641) while the H2RA Maintenance strategy had the highest expected costs ($772). The PPI Maintenance strategy had the most favorable outcomes (0.196 recurrences, 5.48 symptom weeks, 0.904 QALYs). H2RA on-demand had the least favorable expected outcomes (0.6896 recurrences, 9.46 symptom weeks, 0.890 QALYs) amongst the 5 strategies. Compared to the EE population, expected costs are higher for all strategies in the ENRD population, while symptoms weeks and QALYs are less favorable in all strategies. This is because the symptomatic relief rates for both PPI and H2RA are estimated to be lower (Table 6) for both H2RA and PPI in the ENRD population. Lower relief rates lead to more time with symptoms along with costlier treatment to relieve initial and recurrent heartburn episodes. This change in relief rates are more pronounced for PPI than it is for H2RA.

The last two columns of Table 8 show, respectively, the incremental cost per heartburn week avoided and incremental cost per QALY gained. Figure 3 presents the cost-effectiveness efficiency frontier for the incremental cost per QALY outcome. The three strategies comprising the efficiency frontier are H2RA on-demand (A), PPI on-demand (B) and PPI Maintenance (D). Strategy C is dominated by B and strategy E is extendedly dominated by linear combinations of B and D. Moving from strategy A to strategy B, costs $9 per symptom week averted or $2,505 per QALY gained, moving from strategy B to strategy D costs $93 per symptom week averted or $26,986 per QALY gained.

3.5 Cost-Effectiveness for UG population

Table 9 displays the expected costs, and outcomes for heartburn patients whose GERD status is uninvestigated. The lowest expected costs were estimated for the PPI on-demand strategy ($635), while the highest expected costs were estimated for the PPI Maintenance strategy. The PPI Maintenance strategy had the most favorable outcomes (0.197 recurrences, 5.17 symptom weeks, 0.905 QALYs) and H2RA on-demand had the least favorable expected outcomes (0.686 recurrences, 9.64 symptom weeks, 0.889 QALYs).

The last two columns of Table 9 show, respectively, the incremental cost per heartburn week avoided and incremental cost per QALY gained. Figure 4 presents the cost-effectiveness efficiency frontier for the incremental cost per QALY outcome. The two strategies comprising the efficiency frontier are PPI on demand (B) and PPI Maintenance (D). Strategies A and C are dominated by B and E, and strategy E is extendedly dominated by linear combinations of strategies B and D. The incremental cost-effectiveness of strategy D compared to strategy B was estimated to be $97 per symptom week and $27,848 per QALY.

3.6 Cost-effectiveness Acceptability Curves and Cost-effectiveness Acceptability Frontiers

Figures 5 through 10 show the CEACs and the CEAFs for the 3 patient populations analyzed after accounting for parameter uncertainty in the model. As shown in Figure 6 for the EE population, PPI on-demand (B) has the is the most cost-effective strategy for willingness-to-pay (WTP) values below $34,000 per QALY, PPI with step-down maintenance H2RA (E) is the most cost effective between $34,000 and $44,000 per QALY and PPI maintenance (D) is the most cost-effective for WTP values above $44,000 per QALY. The results are different for the ENRD population, where H2RA on-demand (A) is the most cost-effective for WTP values below $3,000 per QALY, PPI on-demand (B) is the most

cost effective between $3,000 and $27,000 per QALY and PPI maintenance (D) is the most cost-effective for WTP values above $27,000 per QALY. And finally, the results are different again for the UG population, where PPI on-demand (B) is the most cost effective for WTP values below $28,000 per QALY and PPI maintenance (D) is the most cost-effective for WTP values above $28,000 per QALY.

4 CONCLUSIONS

Based on a systematic review and meta-analysis of the symptomatic relief literature on acute and maintenance treatment for patients with heartburn predominant reflux symptoms, physician surveys regarding patient management and expert opinion regarding appropriate treatment strategies, we developed a Markov model to estimate the cost-effectiveness of 5 alternative management strategies. In addition, since treatment effectiveness varies not only be type of drug, but by type of patient population, we estimated the cost-effectiveness separately for three patient populations (i.e. EE, ENRD and UG patients).

It was found that which strategies were considered cost-effective depended on the decision maker's threshold (i.e. WTP per QALY gained) and that the results varied across the three patient populations. Which strategy was considered cost-effective was very sensitive over the range typically discussed as being cost-effectiveness thresholds (i.e. $20,000 to $100,000 per QALY).[25] As such, which strategies were cost-effective depended on both the threshold WTP and the patient population. However, some patterns did emerge across all three patient populations. For example, at a WTP threshold of $25,000 per QALY, PPI on-demand (B) is the most cost-effective strategy for all three populations (EE, ENRD,UG). Similarly, for a WTP threshold of $50,000 or greater, PPI maintenance (D) is the most cost-effective strategy for all three populations. Decision-makers can use the results from this analysis, and based on their own thresholds and local circumstances, determine which management strategy is most appropriate for their own local jurisdiction.

5 DISCUSSION

There are a number of strengths associated with our analysis. The model used in the analysis was based upon a previously published validated Markov model. In addition rigorous methodology was used to derive key model input variables. A systematic literature review along with meta-analysis were used to estimate heartburn relief and recurrence probabilities. Physician surveys were conducted to help determine the non-drug related management of initial and recurrent symptomatic heartburn. Also, because the model was fully probabilistic, the expected costs and outcomes estimated by the model incorporated the uncertainty of model input variables. Finally, analyses were completed for different populations of patients depending on their GERD status.

It is difficult to compare our study results with many economic evaluations of symptomatic GERD treatment options. There is a lot of variation in the treatment strategies that are included in the various analyses making comparisons difficult. Additionally, most other economic models have used endoscopic endpoints to judge treatment success, and not specifically heartburn symptoms.

Three recent studies have focused specifically on heartburn predominant GERD symptoms Heudebert et al.[16] reported a cost and QALY trade-off of $10,440 between strategies most similar to our H2RA on demand and PPI on-demand strategies. This compares with our current analysis, where PPI on demand dominates (less costly , more QALYs) compared to H2RA on demand. A direct comparison of the Heudebert analysis is difficult as the structure of this model is quite different from ours. In their

analysis, recurrence and relief rates were dependent upon the presence of peptic ulcer disease and reflux status.

Our results do not support the findings by Gerson et al.[26] who found PPI-on-demand to dominate intermittent H2RA, maintenance H2RA and maintenance PPI strategies. The main reason for these discrepant findings is that these authors assumed a lower recurrence rate for PPI-on demand (42% versus 63%), a higher failure rate for maintenance H2RA (50% versus 32%) and a higher failure rate for maintenance PPI (20% versus 17%).

The results from our previous publication (Goeree et al. 2002[15]) is somewhat similar to our current results. In our previous model, PPI Maintenance had the highest expected costs and QALYs. The incremental cost-effectiveness of PPI Maintenance relative to PPI with step-down H2RA Maintenance was $98,422 per QALY. In our current analysis, the incremental cost effectiveness of PPI Maintenance compared to the next least dominated strategy is smaller. The incremental cost of moving to PPI maintenance varies from $27,000 per QALY to $48,000 depending on the population analyzed. In fact the PPI with step-down H2RA Maintenance strategy is not part of the efficiency frontier in either the EE or uninvestigated GERD population. These differences are due to a couple of reasons. Since our previous publication, generic PPI's have become available in Ontario. Therefore the cost of PPIs are now lower, therefore cost-effectiveness for PPI strategies are more favourable. In addition, relief and recurrence rates have been updated and specified for different populations.

As with all modeling studies, a number of limitations of the present study are worth noting. First, we have assumed standardized management strategies for patients presenting with heartburn symptoms based on survey responses from 55 family physicians and 48 gastroenterologists. Although physicians who participated in the survey were randomly selected from across Ontario, it is unclear how generalizable are their responses. It is likely that there are geographic differences in practice patterns, in waiting times for specialist referral, and in the timely availability of diagnostic tests and procedures such as endoscopy. Also, since the survey was conducted in 2001, it is possible that current management strategies, and hence costs, differ from those modeled here. Second, we used moderate-to-severe heartburn as our primary measure of GERD symptoms. This was primarily because of differences across studies in how GERD symptoms are measured and which symptoms are included in the analysis. Since heartburn is the predominant GERD symptom, most studies include a separate reporting of heartburn symptoms. It is uncertain how the results of this study might change if a more inclusive symptom definition was used, such as one that included mild heartburn or other GERD symptoms. Third, all studies in our review that reported symptomatic heartburn recurrence were conducted in patients with erosive esophagitis. Therefore our analyses of ENRD and uninvestigated populations did not include population specific recurrence rates. Fourth, the 1-year time horizon chosen for the study may be too short to capture long-term complications such as Barrett's esophagus or esophageal stricture. Given the lack of long-term follow-up studies, we did not feel it was appropriate to extrapolate the model much beyond 1-year. Finally, this study uses inputs (i.e. costs) which are specific to the province of Ontario. Price weights and surveys of practice patterns from other geographic areas would be needed in order to fully explore the potential impact of regional variations in cost and practice pattern.

Finally, it should be noted that, although a strategy of on-demand PPI use has been investigated in several clinical trials of GERD, on-demand use has not been approved by Health Canada for any of the PPIs available in Canada.[27]

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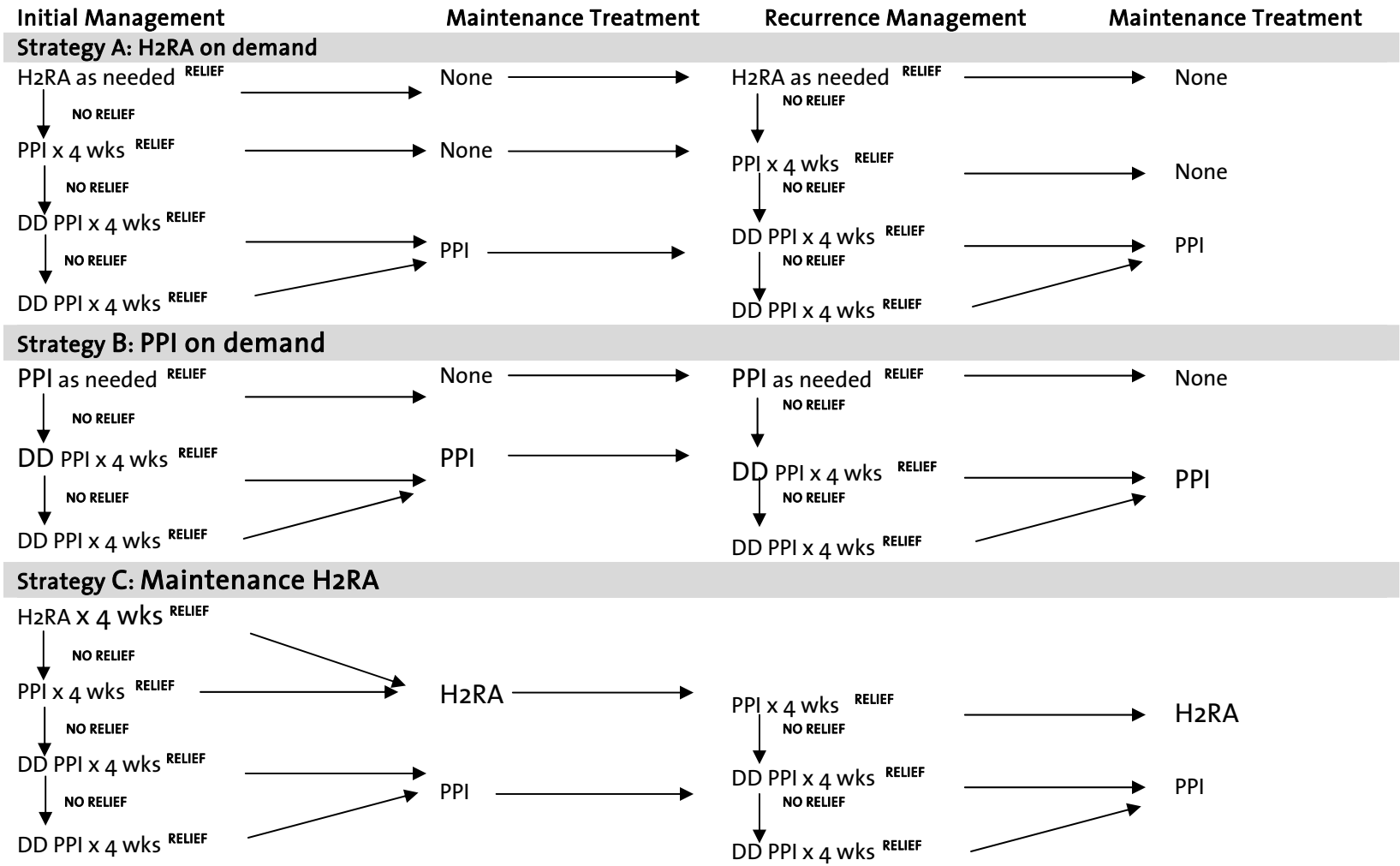
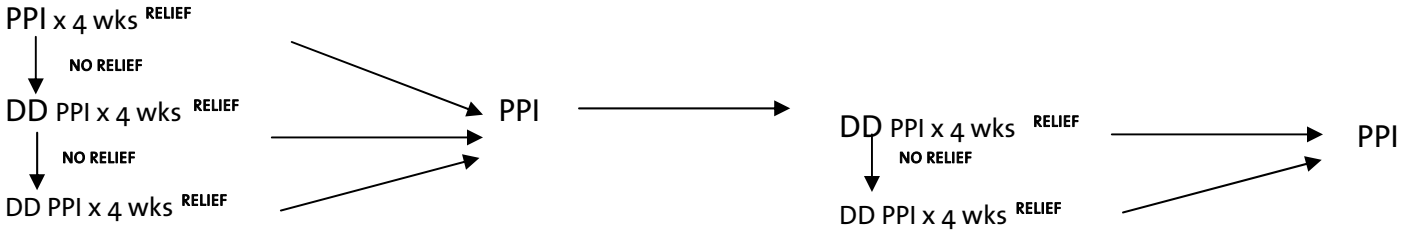
Table 1: Step-up and switching algorithms conditional upon symptomatic relief and recurrence



Strategy D: Maintenance PPI



Strategy E: Step-down Maintenance H2RA

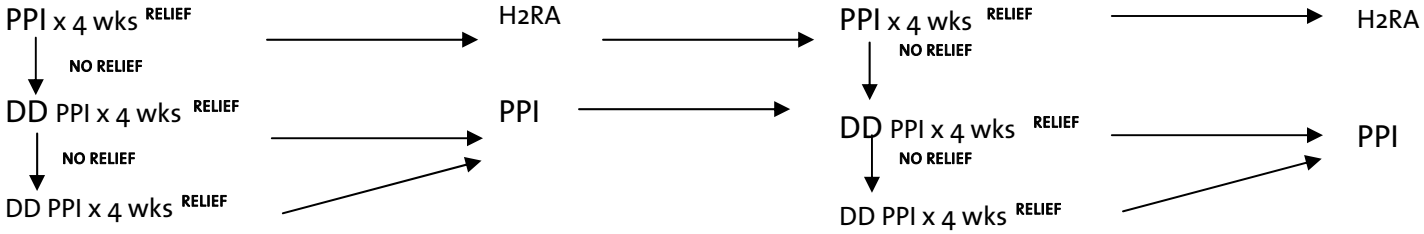


Table 2: Summary of findings from the family physician and gastroenterologist surveys for initial patient management of heartburn symptoms

		Failure of H2RA (%)		Failure of PPI (%)	
Test/Procedure Ordered	**Initial Treatment (%)**	**FP***	**GI†**	**FP***	**GI†**
CBC	25.5	21.8	37.5	25.0	39.6
Upper GI series	27.3	41.8	6.3	32.7	2.1
Upper GI endoscopy	1.8	21.8	64.6	23.1	89.6
24-hr pH study	0.0	0.0	2.1	1.9	10.4
Testing for *H.pylori*	16.4	27.3	4.2	34.6	4.2
Motility study	0.0	1.8	2.1	0.0	6.3
Referral to GI	0.0	5.5	--	42.3	--

*FP=family physicians (n=55)
†GI=gastroenterologists (n=48)

Table 3: Summary of findings from the family physician and gastroenterologist surveys for management of symptomatic heartburn recurrence

	Patients Assumed to be on Maintenance Therapy (%)				Patients Assumed not to be on Maintenance Therapy (%)			
Test/Procedure	**ENRD**		**EE**		**ENRD**		**EE**	
Ordered	**FP**	**GI**	**FP**	**GI**	**FP**	**GI**	**FP**	**GI**
CBC	40.0	22.9	65.5	39.6	40.0	25.0	60.0	35.4
Upper GI series	20.0	2.1	18.2	0.0	18.2	2.1	16.4	0.0
Upper GI endoscopy	16.4	2.1	38.2	27.1	9.1	8.3	40.0	25.0
24-hr pH study	7.3	18.8	7.3	8.3	7.3	20.8	7.3	0.0
Test for *H.pylori*	43.6	6.3	41.8	2.1	38.2	4.2	32.7	2.1
Motility study	7.3	12.5	5.5	4.2	7.3	12.5	3.6	2.1
Referral to GI	12.7	--	32.7	--	12.7	--	27.3	--

FP = Family Physicians (n=55)
GI = gastroenterologists (n=48)
ENRD = previous testing indicated non-erosive gastroesophageal reflux disease
EE = previous testing indicated erosive gastroesophageal reflux disease

CBC – complete blood count
GI - gastrointestinal
H. pylori – Helicobacter pylori

Table 4: Unit costs for healthcare resources

Health care resource	Cost[1] (Cdn$)
H2RA regular dose daily (Novo-Ranitidine 150 mg b.i.d.)[1]	0.89
PPI regular dose daily (Apo-Omperazole 20 mg q.d.)[1]	1.38
Family physician general assessment	58.20
Gastroenterologist re-assessment	45.90
CBC	12.04
Upper GI series	111.23
Upper GI endoscopy	238.52
24-hr pH study	120.50
Urea breath test for *H.pylori*	17.20
Motility study	106.40

[1]Including pharmacy mark-ups

Table 5: Heartburn symptomatic relief at 4 weeks by patient population

Drug Regimen	n	EE relief (%)	n	ENRD relief (%)	n	UG relief (%)
H2RA	21	48.0 (38.0, 58.0)	8	42.7 (26.3, 59.1)	5	35.2 (26.9, 43.5)
PPI	26	75.4 (68.9, 82.1)	14	52.6 (42.2, 63.0)	4	58.3 (52.9, 63.6)
PPI double dose[1]					2	55.4 (48.3, 62.5)

[1] after failure on regular dose PPI

Table 6: Heartburn symptomatic recurrence at three and 12 months for all patient populations

		Symptomatic Recurrence (%)	
Drug Regimen	**n**	**3 months**	**12 months**
Placebo	8	62.6 (58.5, 66.7)	68.9 (64.6, 73.2)
H2RA	3	32.1 (23.9, 40.1)	39.7 (33.8, 45.6)
PPI	9	16.6 (13.7, 19.4)	19.7 (16.7, 22.7)

Table 7: Expected cost, recurrences, weeks with heartburn symptoms and incremental cost-effectiveness: EE population

Strategy	Expected 1-year cost per patient	Expected recurrences per patient in 1 year	Expected weeks with heartburn symptoms	Expected QALYs	Incremental cost per heartburn week averted[1] (Cdn$)	Incremental cost per QALY[1] (Cdn$)
B: PPI on-demand	537	0.774	6.09	0.902	--	--
E: PPI with step-down H2RA maintenance	692	0.379	4.74	0.907	$115	$33,692
D: PPI maintenance	776	0.201	4.19	0.909	$151	$44,168
A: H2RA on-demand	560	0.834	8.24	0.895	Dominated by B	
C: H2RA maintenance	717	0.392	6.42	0.901	Dominated by E	

[1]Relative to the next less costly non-dominated strategy. Values have been rounded
QALY=quality-adjusted life-year

Table 8: Expected cost, recurrences, weeks with heartburn symptoms and incremental cost-effectiveness: ENRD population

Strategy	Expected 1-year cost per patient	Expected recurrences per patient in 1 year	Expected weeks with heartburn symptoms	Expected QALYs	Incremental cost per heartburn week averted[1] (Cdn$)	Incremental cost per QALY[1] (Cdn$)
A: H2RA on demand	641	0.689	9.46	0.890	--	--
B: PPI on demand	660	0.558	7.27	0.898	$9	$2,505
D: PPI maintenance	827	0.196	5.48	0.904	$93	$26,986
E: PPI with step-down H2RA maintenance	770	0.313	6.13	0.902	Extendedly Dominated	
C: H2RA maintenance	772	0.349	7.66	0.897	Dominated by E	

[1]Relative to the next less costly non-dominated strategy. Values have been rounded
QALY=quality-adjusted life-year

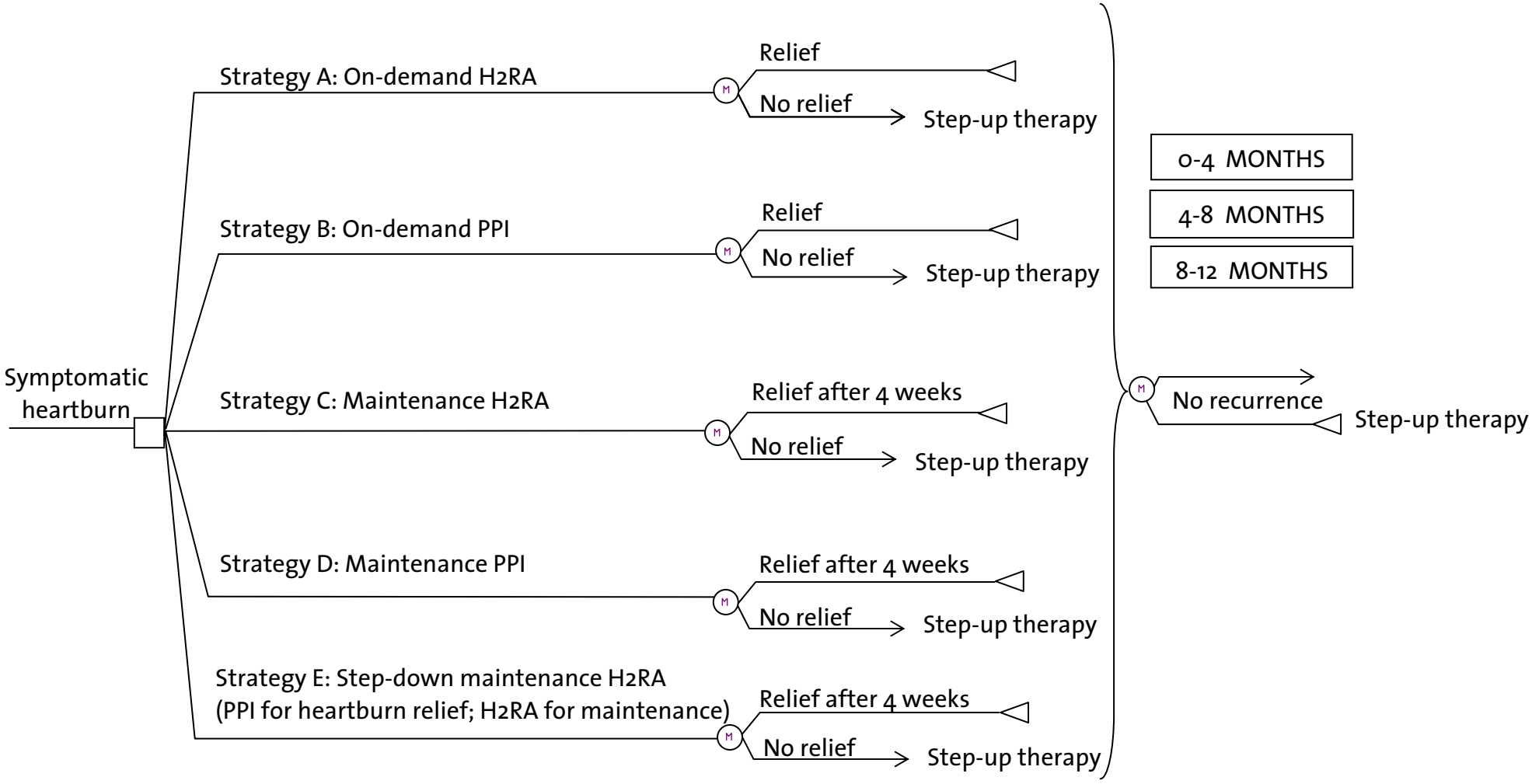
Table 9: Expected cost, recurrences, weeks with heartburn symptoms and incremental cost-effectiveness: UG population

Strategy	Expected 1-year cost per patient	Expected recurrences per patient in 1 year	Expected weeks with heartburn symptoms	Expected QALYs	Incremental cost per heartburn week averted[1] (Cdn$)	Incremental cost per QALY[1] (Cdn$)
B: PPI on-demand	$635	0.605	7.05	0.899	--	--
D: PPI maintenance	$816	0.197	5.17	0.905	$97	$27,848
A: H2RA on demand	$665	0.686	9.64	0.889	Dominated by B	
E: PPI with step-down H2RA maintenance	$754	0.329	5.83	0.903	Extendedly dominated	
C: H2RA maintenance	$789	0.349	7.89	0.896	Dominated by E	

[1]Relative to the next less costly non-dominated strategy. Values have been rounded
QALY=quality-adjusted life-year

ILLUSTRATIONS: FIGURES

Figure 1: State transition model for the management of symptomatic heartburn



All patients are symptomatic and are provided treatment to relieve symptoms in the first cycle of the model. Patients who do not achieve symptom relief after the initial 4 weeks of treatment, are given additional courses of therapy. The drug regimen that unrelieved patients are 'stepped up' to, varies by treatment strategy. These are specified in Table 1. In subsequent cycles of the model, patients either remain symptom free or have a relapse of symptoms. Details of specific drug regimens after symptomatic relief for each strategy are provided in Table 1.

Figure 2: Cost-effectiveness efficiency frontier: EE population

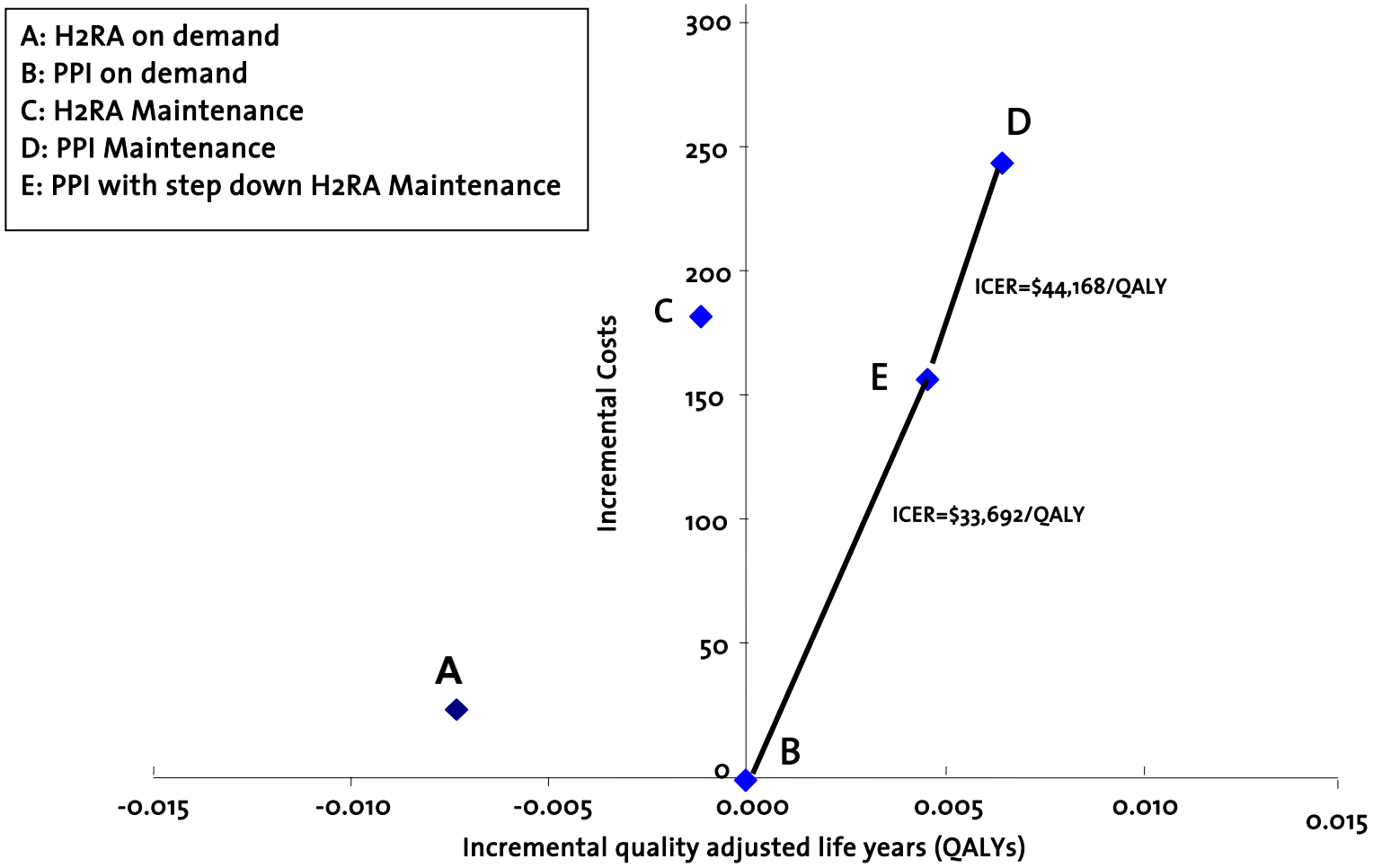


Figure 3: Cost-effectiveness efficiency frontier: ENRD population

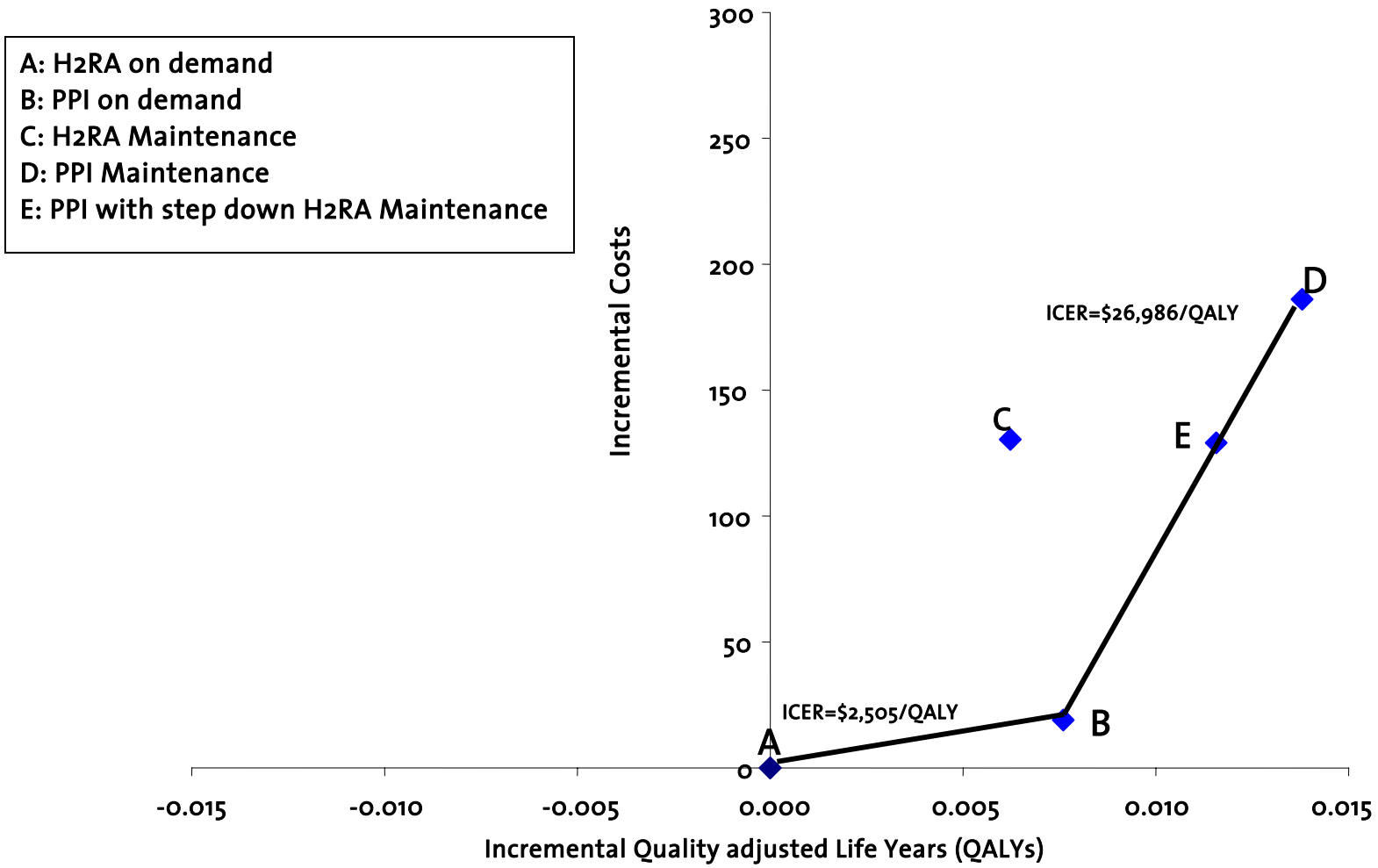


Figure 4: Cost-effectiveness efficiency frontier: UG population

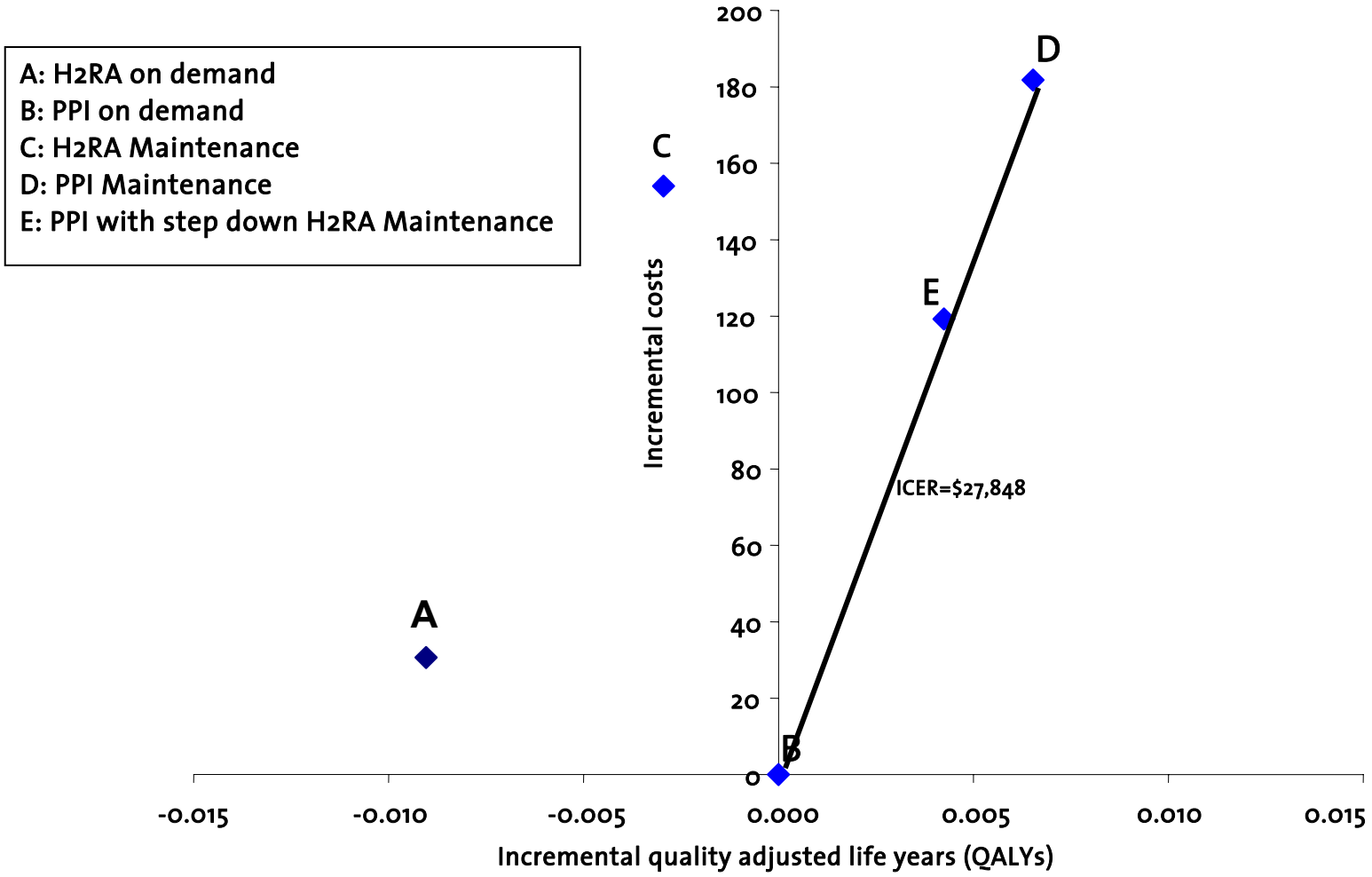


Figure 5: Cost-effectiveness acceptability curves: EE population

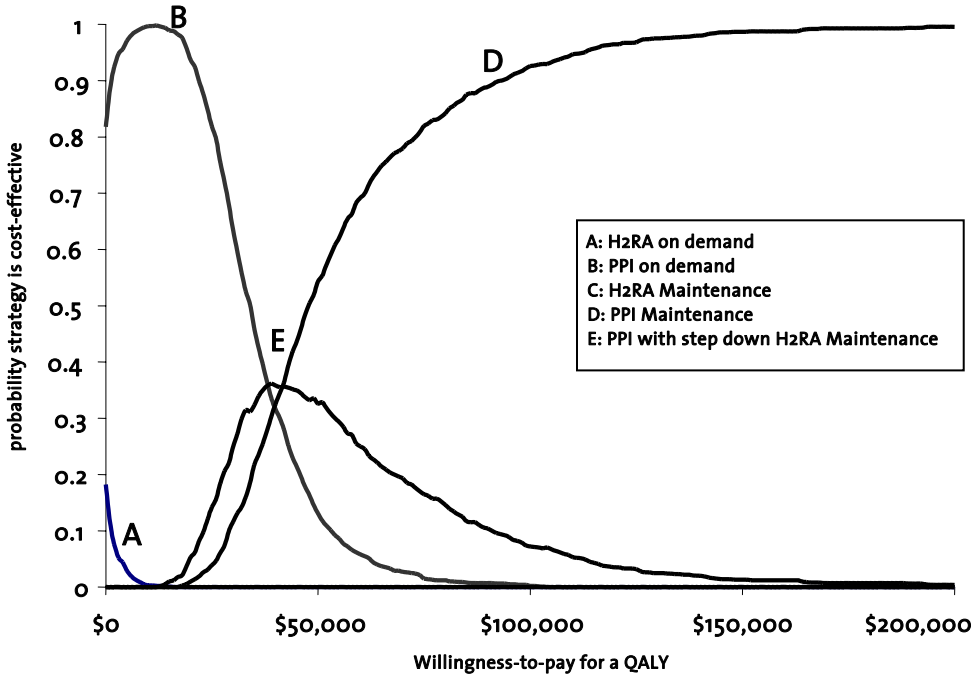


Figure 6: Cost-effectiveness acceptability frontier: EE population

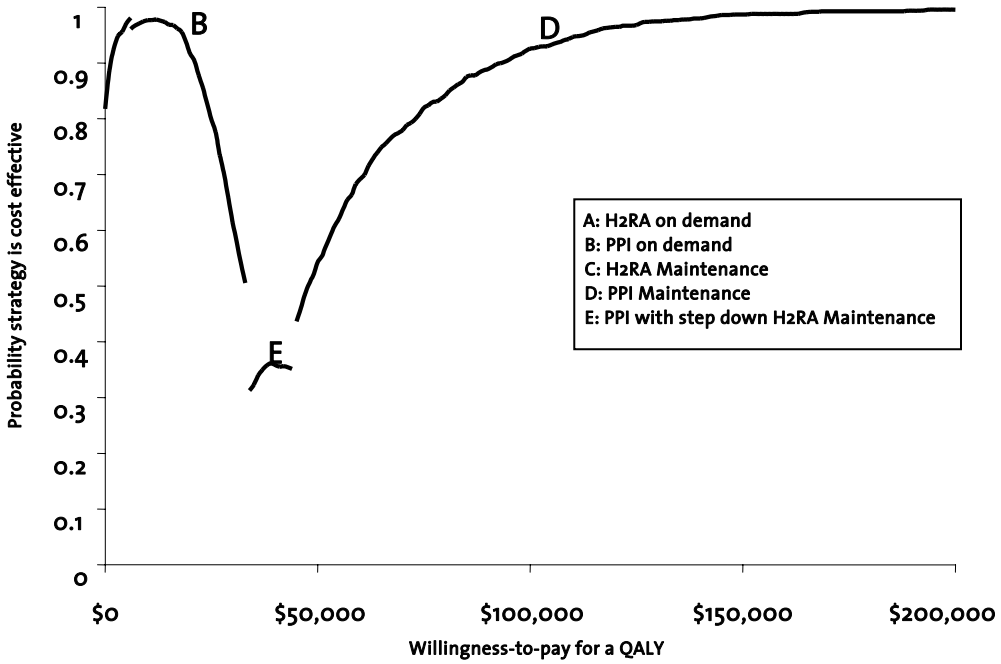


Figure 7: Cost-effectiveness acceptability curves: ENRD population

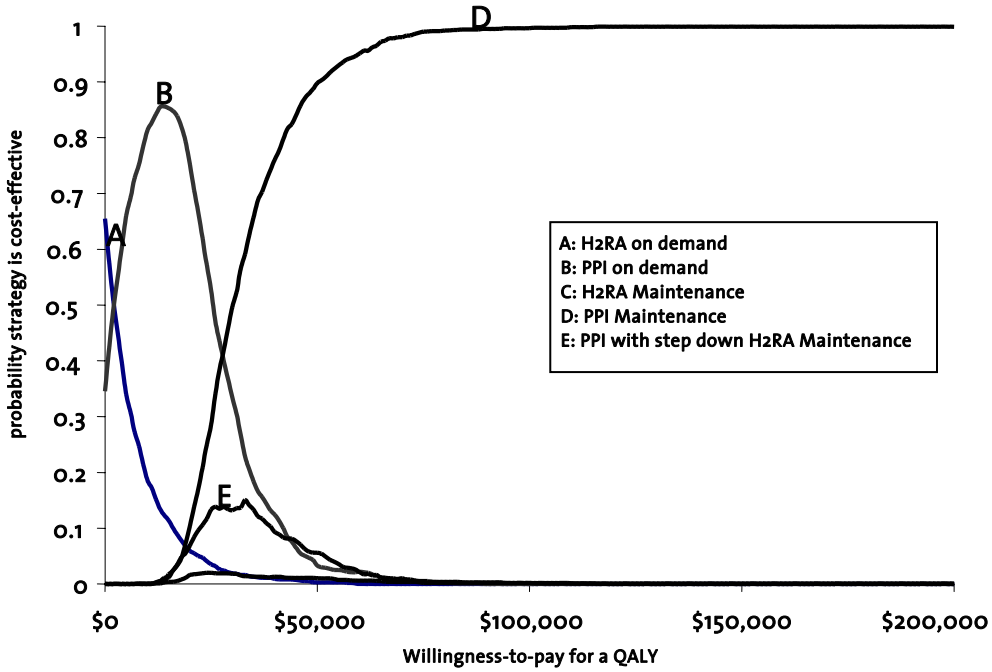


Figure 8: Cost-effectiveness acceptability frontier: ENRD population

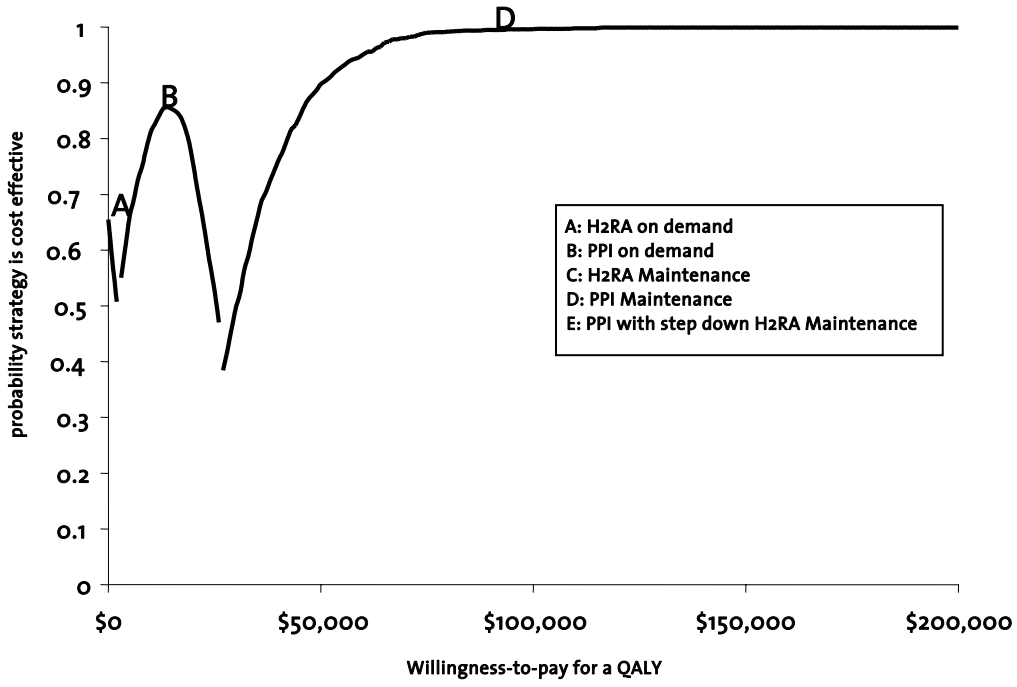


Figure 9: Cost-effectiveness acceptability curves: UG population

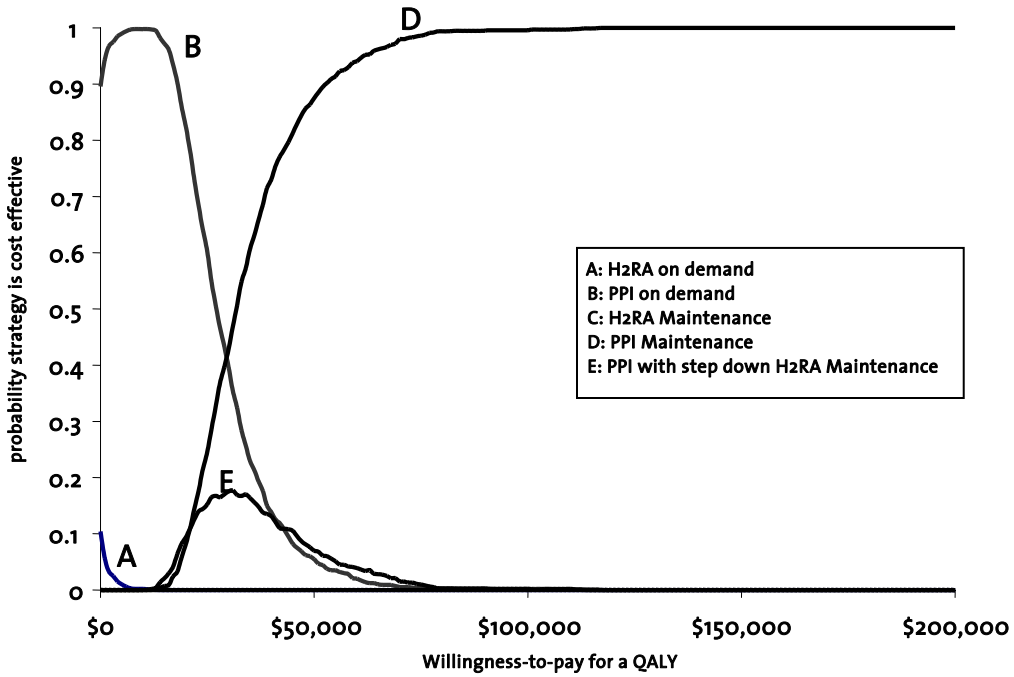
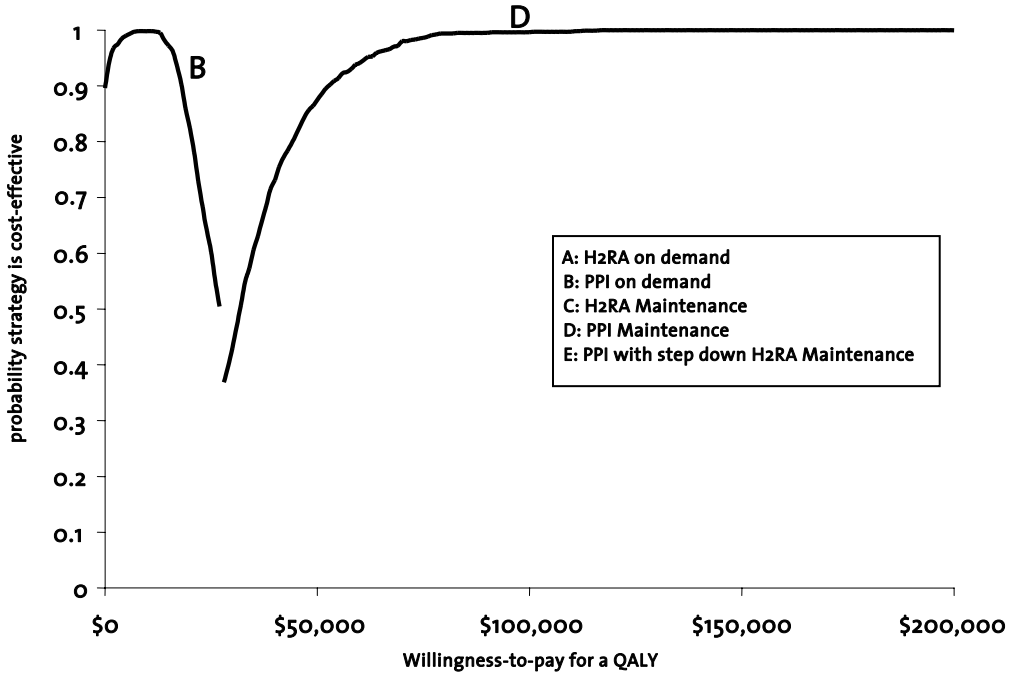


Figure 10: Cost-effectiveness acceptability frontier: UG population



APPENDIX A: SEARCH STRATEGY FOR STUDIES REPORTING SYMPTOMATIC HEARTBURN RELIEF OR RECURRENCE

Search combinations:

1. Indications AND PPIs AND (H2RA Inhibitors OR Placebo) AND RCT filter
2. Indications AND H2RA Inhibitors AND Placebo AND RCT filter

Search Key	
term/	Subject heading (MeSH or Emtree)
*	Major MeSH or Emtree term
ti,ab	Terms are searched in title and abstract fields
ai	Antagonists and inhibitors subheading
rn	CAS Registry/EC Number/Name of Substance
?	Single character truncation
$	Unlimited truncation
adj	requires search terms to be next to each other, in any order
adj2	Requires search terms to be within 2 words of each other, in any order

Search terms:

Indication:[†††]

exp Gastroesophageal Reflux/

(gord or gerd or ((gastroesophageal or (gastro adj esophageal) or (gastro adj oesophageal) or gastrooesophageal or acid) adj reflux)).ti,ab.

exp Esophagitis/

(enrd or ENRD or erd).ti,ab.

(esophagitis or oesophagitis).ti,ab.

((Peptic or reflux or regurgitation or erosive or ulcerative) adj (gastric or oesophagitis or esophagitis or esophageal or oesophageal)).ti,ab.

Heartburn/

(heartburn or pyrosis).ti,ab.

[†††] Searching heartburn alone would have omitted relevant results such as those where heartburn is discussed in conjunction with other indications, e.g. GERD, esophagitis, etc.

PPI Search Terms:

exp Proton Pump Inhibitor/

(proton pump inhibitor? or ppi or ppis).ti,ab.

(pantoprazole or Pantoprazol or Pantoprazole or Pantoprazolum or (SK&F adj "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 or Pantocal or Pantocarm or Pantodac or Pantop or Pantopan or Pantopaz or Pantorc or Pantozol or (Pantozol adj 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.

omeprazole or Antra or Audazol or Aulcer or Belmazol or (CCRIS adj "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 adj "168" adj "68") or (HSDB adj "3575") or Indurgan or Inhibitron or Inhipump or Lensor or Logastric 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 adj "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 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 or Ulceral or Ulceral or Ulcesep or Ulcometion or Ulcozol or Ulcsep or Ulsen or Ultop or Ulzol or Victrix or Zefxon or Zegerid or Zepral or Zimor or Zoltum or Zanprol or Ufiprazole or Ufiprazol or Ufiprazolum or Andra).ti,ab

(lansoprazole or (AG adj "1749") or Agopton or Alexin or Amarin or Aprazol or (BRN adj "4333393") or Bamalite or Blason or Compraz or Dakar or Estomil or Fudermex or Gastrex or Gastride or Gastroliber or (HSDB adj "7204") or Ilsatec or Ketian or Keval 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 adj "30") or Lanzopral or Lanzor or Lasoprol or Limpidex or Lizul or Mesactol or Monolitum or Ogast or Ogasto or Ogastro or Opiren or Pampe or Peptomil or Prevacid or Prezal or (Pro adj Ulco) or Promp or Prosogan or Suprecid or Takepron or Ulcertec or Uldapril or Ulpax or Unival or Zoprol or Zoton).ti,ab

(esomeprazole or Nexium or Perprazole or Nexiam or Inexium or Sompraz or Axagon or Esopral or Lucen or Axiago).ti,ab.

pantoprazole or Pantoprazol or Pantoprazole or Pantoprazolum or (SK&F adj "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 or Pantocal or Pantocarm or Pantodac or Pantop or Pantopan or Pantopaz or Pantorc or Pantozol or (Pantozol adj 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.

(rabeprazole or Aciphex or (E adj "3810") or Gastrodine or (LY adj "307640" adj sodium) or Pariet or Rabec or Rabeloc).ti,ab

H2RA

exp Histamine H2 Receptor Antagonist/
((H2RA# or histamine) adj h2 adj receptor adj antagonist#).ti,ab.
((h2 or (h adj "2") or (histamine adj h2)) adj (antagonist# or blocker# or (blocking adj agent#) or (receptor adj antagonist#) or (receptor adj blockader#) or (receptor adj blocker#))).ti,ab.

(cimetidine or (apo adj cimetine) or (gen adj cimetidine) or (novo adj cimetine) or (nu adj cimet) or altramet or biomet or biomet400 or eureceptor or histodil or (sk&f adj "92334") or (skf adj "92334") or tagamet or Acibilin or Acinil or (CCRIS adj "3247") or Cimal or Cimetag or Cimetidina or Cimetidine or Cimetidinum or Cimetum or (DRG adj "0150") or Dyspamet or (EINECS adj "257" adj "232" adj "2") or Edalene or Eureceptor or Gastromet or (HSDB adj "3917") or Metracin or (SKF adj "92334") or Tagamet or Tametin or Tratul or Ulcedine or Ulcimet or Ulcomet).ti,ab.

(famotidine or Amfamox or Antodine or Apogastine or Bestidine or Blocacid or Brolin or Cepal or Confobos or Cronol or Cuantin or (Dibrit adj "40") or Digervin or Dinul or Dipsin or Dispromil or Dispronil or Duovel or Durater or Evatin or Fadin or Fadine or Fadyn or Fagastine or Famo or Famocid or Famodar or Famodil or Famodin or Famodine or Famogard or Famonit or Famopsin or Famos or Famosan or Famotal or Famotep or Famotidina or Famotidinum or Famotin or Famovane or Famowal or Famox or Famoxal or Famtac or Famulcer or Fanobel or Fanosin or Fanox or Farmotex or Ferotine or Fibonel or Fudone or Ganor or Gaster or Gastridan or Gastridin or Gastrion or Gastro or Gastrodomina or Gastrofam or Gastropen or Gastrosidin or (H2 adj Bloc) or (HSDB adj "3572") or Hacip or Huberdina or Ingastri or Invigan or (L adj "643341") or Lecedil or Logos or (MK adj "208") or Mensoma or Midefam or Mosul or Motiax or Muclox or (Mylanta adj AR) or Neocidine or Nevofam or Notidin or Nulceran or Nulcerin or Panalba or Pepcid or Pepcidac or Pepcidin or Pepcidina or Pepcidine or Pepdif or Pepdine or Pepdul or Pepfamin or Peptan or Peptidin or Peptifam or

Pepzan or Purifam or Quamatel or Quamtel or Renapepsa or Restadin or Rogasti or Rubacina or (Sedanium adj R) or Sigafam or Supertidine or Tairal or Tamin or Tipodex or Topcid or Ulcatif or Ulceprax or Ulcofam or Ulfagel or Ulfam or Ulfamid or Ulfinol or Ulgarine or Vagostal or Weimok or Whitidin or (YM adj "11170") or Yamarin).ti,ab.

(nizatidine or Acinon or Antizid or Axid or (BRN adj "4846056") or Calmaxid or Cronizat or Distaxid or Galitidin or Gastrax or (HSDB adj "3574") or (LY adj "139037") or Naxidine or Nizatidina or Nizatidine or Nizatidinum or Nizax or Nizaxid or Panaxid or Splendil ER or Tazac or Ulcosol or Ulxid or (ZE adj "101") or (ZL adj "101") or Zanizal or Zinga).ti,ab.

(ranitidine or (nu adj ranit) or zantac or Achedos or Acidex or Atural or Axoban or Coralen or Curan or Duractin or (EINECS adj "266" adj "332" adj "5") or Ezopta or Gastrial or Gastrosedol or (HSDB adj "3925") or stomar or Logast or Mauran or Microtid or Ptinolin or Quantor or Quicran or RND or Radinat or Randin or Ranidine or Ranin or Raniogas or Ranisen or Raniter or Ranitidina or Ranitidinum or Ranitiget or Rantacid or Ratic or Raticina or Sampep or Taural or (Ul adj Pep) or lceranin or Urantac or Verlost or Vesyca or Vizerul or Weichilin or Weidos or Xanidine or Zantab or Zantadin or (AH adj "19065") or Alquen or (Alter adj H2) or Alvidina or (Apo adj Ranitidin) or Artomil or Azuranit or (CCRIS adj "5268") or Coralen or (DRG adj "0114") or Digestosan or (EINECS adj "266" adj "333" adj "0") or Ergan or Esofex or Fendibina or Gastridina or Gastrolav or Kuracid or Label or Lake or Logat or Mideran or Neugal or Noktome or Normon or (Novo adj Radinine) or (Nu adj Ranit) or (Pep adj Rani) or Quadrin or Quantor or RAN or Radin or (Ran adj H2) or (Ran adj Lich) or (Rani adj "2") or (Rani adj AbZ) or (Rani adj BASF)).ti,ab.

((Rani adj (Puren or Q or Sanorania or nerton)) or Raniberl or Raniberta or Ranibloc or Ranicux or Ranidil or Ranidin or Ranidura or Ranifur or Ranigasan or Ranigast or Ranigen or Ranilonga or Ranimerck or Ranisan or Ranitab or Ranitic or Ranitidin or Ranitin or Ranitine or Ranobel or Ranuber or Regalil or Renatac or Rozon or Rubiulcer or Santanol or Serviradine or Tanidina or Toriol or Trigger or Ulcecur or Ulcirex or Ulcodin or (Ulcolind adj Rani) or Ulcosan or Ulsaven or Viserul or Zandid or Zantac or Zantarac or ranic).ti,ab.

(Azamplus or Elicodil or Helirad or Pylorisan or Tritec).ti,ab.

Placebo:

placebo/

placebo$.ti,ab.

RCT Filter:

exp Clinical Trial/

(random$ or sham$ or placebo$).ti,ab.

((singl$ or doubl$ or tripl$ or trebl$) adj (blind$ or dumm$ or mask$)).ti,ab.

((control$ adj (study or studies or trial$)) or rct$).ti,ab.

((multicent$ or (multi adj cent$)) adj (study or studies or trial$)).ti,ab.

APPENDIX B: STUDIES REPORTING RELIEF OF MODERATE-TO-SEVERE HEARTBURN SYMPTOMS AT FOUR WEEKS

DRUG	Reference	Drug Class	N	Relief at Baseline (%)	Relief at 4 weeks (%)
EE					
Cim 400 mg q.i.d.	Bate *et al.* 1997[28]	H2RA	55	0 (0)	19 (35)
Cim 400 mg q.i.d.	Dehn *et al.* 1990[29]	H2RA	31	14 (45)	28 (90)
Niz 50 mg b.i.d.	Bochenek *et al.* 2004 [30]	H2RA	82	0 (0)	16 (20)
Niz 50 mg b.i.d.	Kovacs *et al.* 2002[31]	H2RA	72	0 (0)	9 (13)
Niz 50 mg b.i.d.	Armstrong *et al.* 2002[32]	H2RA	56	0 (0)	19 (34)
Rab 20 mg q.d.	Farley *et al.* 2000[33]	H2RA	167	18(11)	118 (70)
Ran 150 mg b.i.d.	Bardhan *et al.* 1995[34]	H2RA	77	14 (18)	30 (39)
Ran 150 mg b.i.d.	Frame 1991[35]	H2RA	86	18 (21)	77 (90)
Ran 150 mg b.i.d.	Havelund *et al.* 1988[36]	H2RA	72	11 (15)	53 (74)
Ran 150 mg b.i.d.	Hungin *et al.* 1993[37]	H2RA	191	118 (62)	164 (86)
Ran 150 mg b.i.d.	Klinkenberg-Knol *et al.* 1987[38]	H2RA	26	4 (16)	17 (65)
Ran 150 mg b.i.d.	Koop *et al.* 1995[39]	H2RA	83	2 (2)	49 (59)
Ran 150 mg b.i.d.	Meneghelli *et al.* 2002[40]	H2RA	128	8 (6)	74 (58)
Ran 150 mg b.i.d.	Porro *et al.* 1992[41]	H2RA	30	0 (0)	6 (21)
Ran 150 mg b.i.d.	Richter *et al.* 1996[42]	H2RA	61	0 (0)	4 (7)
Ran 150 mg b.i.d.	Sontag *et al.* 1987[43]	H2RA	119	0 (0)	71 (60)
Ran 150 mg b.i.d.	Vantrappen *et al.* 1988[44]	H2RA	30	7 (23)	25 (84)
Ran 150 mg b.i.d.	Zeitoun *et al.* 1989[45]	H2RA	80	6 (7)	36 (45)
Ran 150 mg b.i.d.	Venables *et al.* 1997[18]	H2RA	113	0 (0)	37 (33)
Ran 300 mg q.d.	Van Zyl *et al.* 2000[46]	H2RA	100	5 (5)	58 (58)
Ran 300 mg q.d.	Green *et al.* 1995[47]	H2RA	97	39 (40)	68 (70)
Lan 30 mg q.d.	Bardhan *et al.* 1995[34]	PPI	77	7 (9)	61 (79)

DRUG	Reference	Drug Class	N	Relief at Baseline (%)	Relief at 4 weeks (%)
EE					
Lan 30 mg q.d.	Castell *et al.* 2002[48]	PPI	2617	310 (12)	1575 (60)
Lan 30 mg q.d.	Jansen *et al.* 1999[49]	PPI	68	0 (0)	57 (84)
Lan 30 mg q.d.	Sontag *et al.* 1996[50]	PPI	54	0 (0)	47 (87)
Ome 20 mg q.d.	Hetzel *et al.* 1988[51]	PPI	31	10 (32)	28 (90)
Ome 20 mg q.d.	Bate *et al.* 1990[52]	PPI	138	44(32)	102 (74)
Ome 20 mg q.d.	Bate *et al.* 1997[28]	PPI	63	0 (0)	49 (78)
Ome 20 mg q.d.	Carlsson *et al.* 1998[53]	PPI	138	42 (30)	110 (80)
Ome 20 mg q.d.	Dekkers *et al.* 1999[54]	PPI	97	0 (0)	74 (76)
Ome 20 mg q.d.	Frame 1991[35]	PPI	86	20 (23)	82 (95)
Ome 20 mg q.d.	Green *et al.* 1995[47]	PPI	99	43 (43)	91 (92)
Ome 20 mg q.d.	Hungin *et al.* 1993[37]	PPI	204	118 (58)	194 (95)
Ome 20 mg q.d.	Lundell *et al.* 1990[55]	PPI	51	17 (34)	51 (100)
Ome 20 mg q.d.	Porro *et al.* 1992[41]	PPI	30	0 (0)	18 (60)
Ome 20 mg q.d.	Richter *et al.* 1996[42]	PPI	63	0 (0)	23 (36)
Ome 20 mg q.d.	Sontag *et al.* 1992[56]	PPI	93	0 (0)	62 (66)
Ome 20 mg q.d.	Zeitoun *et al.* 1989[45]	PPI	76	6 (8)	71 (94)
Ome 20 mg q.d.	Hetzel *et al.* 1988[51]	PPI	82	32 (39)	78 (95)
Ome 20 mg q.d.	Venables *et al.* 1997[18]	PPI	101	0 (0)	80 (79)
Pan 40 mg q.d.	Armstrong *et al.* 2002[32]	PPI	66	0 (0)	46 (70)
Pan 40 mg q.d.	Kovacs *et al.* 2002[31]	PPI	76	0 (0)	32 (42)
Pan 40 mg q.d.	Richter *et al.* 2000[57]	PPI	173	26 (15)	114 (66)
Pan 40 mg q.d.	Bochenek *et al.* 2004[30]	PPI	254	0 (0)	163 (64)
Pan 40 mg q.d.	Koop *et al.* 1995[39]	PPI	166	5 (3)	143 (86)
Pan 40 mg q.d.	Meneghelli *et al.* 2002[40]	PPI	128	5 (4)	116 (91)
Rab 20 mg q.d.	Dekkers *et al.* 1999[54]	PPI	97	0 (0)	78 (80)

DRUG	Reference	Drug Class	N	Relief at baseline (%)	Relief at 4 weeks (%)
ENRD					
Cim 400 mg q.i.d.	Bate *et al.* 1997[28]	H2RA	43	0 (0)	17 (40)
Fam 20 mg b.i.d.	Wada *et al.* 2005[58]	H2RA	21	0 (0)	12 (56)
Fam 20 mg b.i.d.	Robinsen *et al.* 1991[59]	H2RA	158	6 (4)	30 (19)
Niz 150 mg b.i.d.	Armstrong *et al.* 2001[60]	H2RA	42	0 (0)	18 (43)
Ran 150 mg b.i.d.	Kaspari *et al.* 2001[61]	H2RA	132	1 (1)	91 (69)
Ran 150 mg b.i.d.	Richter *et al.* 1996[42]	H2RA	36	0 (0)	4 (11)
Ran 150 mg b.i.d.	Venables *et al.* 1997[18]	H2RA	212	0 (0)	94 (44)
Ran 300 mg q.d.	Dettmer *et al.* 1998[62]	H2RA	102	2 (2)	66 (65)
Eso 20 mg q.d.	Fock *et al.* 2005[63]	PPI	38	0 (0)	30 (79)
Eso 20 mg q.d.	Katz *et al.* 2003[64] (study 1)	PPI	121	1 (1)	41 (34)
Eso 20 mg q.d.	Katz *et al.* 2003[64] (study 2)	PPI	113	0 (0)	47 (42)
Ome 20 mg q.d.	Richter *et al.* 2000[65]	PPI	118	17 (14)	87 (74)
Ome 20 mg q.d.	Carlsson *et al.* 1998[53]	PPI	87	7 (8)	49 (56)
Ome 20 mg q.d.	Lind *et al.* 1997[66]	PPI	205	77 (38)	125 (61)
Ome 20 mg q.d.	Hatlebakk *et al.* 1999[67]	PPI	161	32 (20)	114 (71)
Ome 20 mg q.d.	Wada *et al.* 2005[58]	PPI	18	0 (0)	7 (41)
Ome 20 mg q.d.	Bate *et al.* 1996[68]	PPI	98	0 (0)	88 (90)
Ome 20 mg q.d.	Richter *et al.* 1996[42]	PPI	37	0 (0)	10 (28)
Ome 20 mg q.d.	Bate *et al.* 1997[28]	PPI	43	0 (0)	27 (63)
Ome 20 mg q.d.	Venables *et al.* 1997[18]	PPI	229	0 (0)	120 (52)
Pan 40 mg q.d.	Armstrong *et al.* 2001[60]	PPI	36	0 (0)	19 (53)
Rab 20 mg q.d.	Miner *et al.* 2002[69]	PPI	65	0 (0)	18 (28)

DRUG	Reference	Drug Class	N	Relief at baseline (%)	Relief at 4 weeks (%)
Uninvestigated					
Ran 150 mg b.i.d.	Armstrong *et al.* 2005[70]	H2RA	194	14 (7)	53 (27)
Ran 150 mg b.i.d.	Kaplan-Machlis *et al.* 2000[71]	H2RA	121	0 (0)	42 (35)
Ran 150 mg b.i.d.	Maton *et al.* 1999[72]	H2RA	161	0 (0)	64 (40)
Ran 150 mg b.i.d.	Talley *et al.* 2002[73]	H2RA	153	24 (16)	73 (48)
Ran 300 mg q.d.	Van Zyl *et al.* 2004[74]	H2RA	171	3 (2)	74 (43)
Eso 20 mg q.d.	Johnson *et al.* 2005[75]	PPI	220	0 (0)	122 (56)
Ome 20 mg q.d.	Armstrong *et al.* 2005[70]	PPI	196	6 (3)	108 (55)
Ome 20 mg q.d.	Kaplan-Machlis *et al.* 2000[71]	PPI	130	0 (0)	76 (59)
Ome 20 mg q.d.	Maton *et al.* 1999[72]	PPI	156	0 (0)	103 (66)
Eso 40 mg q.d.	Fass *et al.* 2006[76]	DDPPI	138	45 (33)	92 (67)
Lan 30 mg b.i.d.	Fass *et al.* 2006[76]	DDPPI	144	48 (33)	105 (73)

DRUG	Reference	Drug Class	N	Relief at baseline (%)	Relief at 4 weeks (%)
Uninvestigated					
Placebo	Bate *et al.* 1995[77]	Placebo	62	23 (37)	41 (66)
Placebo	Birbara *et al.* 2000[78]	Placebo	79	0 (0)	57 (72)
Placebo	Caos *et al.* 2000[79]	Placebo	70	43 (62)	43 (62)
Placebo	Caos *et al.* 2005[80]	Placebo	169	115 (68)	122 (72)
Placebo	Johnson *et al.* 2001[81]	Placebo	77	49 (64)	
Placebo	Robinson *et al.* 1996[82]	Placebo	55	27 (48)	36 (65)
Placebo	Sontag *et al.* 1996[50]	Placebo	47	37 (79)	47 (100)
Placebo	Laursen *et al.* 1995[83]	Placebo	47	21 (70)	
Ran 150 mg b.i.d.	Dent *et al.* 1994[84]	H2RA	51	0 (0)	12 (24)
Ran 150 mg b.i.d.	Hallerback *et al.*1994[85]	H2RA	128	41 (32)	70 (55)
Ran 150 mg b.i.d.	Gough *et al.* 1996[86]	H2RA	67	0 (0)	20 (30)
Eso 20 mg q.d.	Johnson *et al.* 2001[81]	PPI	82	22 (27)	
Lan 30 mg q.d.	Gough *et al.* 1996[86]	PPI	77	0 (0)	6 (8)
Lan 30 mg q.d.	Sontag *et al.* 1996[50]	PPI	49	7 (15)	17 (34)
Lan 30 mg q.d.	Robinson *et al.* 1996[82]	PPI	56	11 (20)	18 (33)
Ome 20 mg q.d.	Hallerback *et al.* 1994[85]	PPI	131	14 (11)	37 (28)
Ome 20 mg q.d.	Laursen *et al.* 1995[83]	PPI	67	7 (10)	
Rab 20 mg q.d.	Birbara *et al.* 2000[78]	PPI	72	0 (0)	15 (21)
Rab 20 mg q.d.	Caos *et al.* 2000[79]	PPI	67	8 (12)	5 (8)
Rab 20 mg q.d.	Caos *et al.* 2005[80]	PPI	163	49 (30)	57 (35)

APPENDIX C: STUDIES REPORTING RECURRENT MODERATE-TO-SEVERE HEARTBURN SYMPTOMS

DRUG	Reference	Drug Class	N	Recurrence at 3 months (%)	Recurrence at 12 months (%)
Placebo	Bate *et al.* 1995[77]	Placebo	62	23 (37)	41 (66)
Placebo	Birbara *et al.* 2000[78]	Placebo	79	0 (0)	57 (72)
Placebo	Caos *et al.* 2000[79]	Placebo	70	43 (62)	43 (62)
Placebo	Caos *et al.* 2005[80]	Placebo	169	115 (68)	122 (72)
Placebo	Johnson *et al.* 2001[81]	Placebo	77	49 (64)	
Placebo	Robinson *et al.* 1996[82]	Placebo	55	27 (48)	36 (65)
Placebo	Sontag *et al.* 1996[50]	Placebo	47	37 (79)	47 (100)
Placebo	Laursen *et al.* 1995[83]	Placebo	47	21 (70)	
Ran 150 mg b.i.d.	Dent *et al.* 1994[84]	H2RA	51	0 (0)	12 (24)
R 150 mg b.i.d.	Hallerback *et al.*1994[85]	H2RA	128	41 (32)	70 (55)
R 150 mg b.i.d.	Gough *et al.* 1996[86]	H2RA	67	0 (0)	20 (30)
Eso 20 mg qd	Johnson *et al.* 2001[81]	PPI	82	22 (27)	
Lan 30 mg q.d.	Gough *et al.* 1996[86]	PPI	77	0 (0)	6 (8)
Lan 30 mg q.d.	Sontag *et al.* 1996[50]	PPI	49	7 (15)	17 (34)
Lan 30 mg q.d	Robinson *et al.* 1996[82]	PPI	56	11 (20)	18 (33)
Ome 20 mg q.d.	Hallerback *et al.* 1994[85]	PPI	131	14 (11)	37 (28)
Ome 20 mg q.d.	Laursen *et al.* 1995[83]	PPI	67	7 (10)	
Rab 20 mg q.d.	Birbara *et al.* 2000[78]	PPI	72	0 (0)	15 (21)
Rab 20 mg q.d.	Caos *et al.* 2000[79]	PPI	67	8 (12)	5 (8)
Rab 20 mg q.d.	Caos *et al.* 2005[80]	PPI	163	49 (30)	57 (35)

PREVENTING NSAID INDUCED GASTROINTESTINAL COMPLICATIONS: AN ECONOMIC EVALUATION OF ALTERNATIVE STRATEGIES IN CANADA

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Sameer Rajbhandary[1]
Chris Cameron[2]

[1] Canadian Agency for Drugs and Technologies in Health, Ottawa ON
[2] Department of Community Health and Epidemiology, Faculty of Medicine, Dalhousie University, Halifax ON

ABBREVIATIONS

ACCS	Ambulatory Case Classification System
ASA	acetylsalicylic acid
bid	twice daily
CE	cost-effectiveness
CMG	case mix groupings
COX	cyclo-oxygenase
GI	gastrointestinal
GPA	gastrointestinal prophylaxis agent
H2RA	histamine2-receptor antagonist
ICE	incremental cost-effectiveness
MUCOSA	Misoprostal Ulcer Complications Outcomes Safety Assessment
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
QALY	quality-adjusted life year
qd	once daily
qid	four times daily
QWB	Quality of Well Being Scale
RA	rheumatoid arthritis
RCT	randomized controlled trial
RR	relative risks
RUGBE	The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy
tid	three times daily
µg	microgram
WTP	Willingness-to-Pay

1 INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAID) are widely prescribed to prevent pain and inflammation in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). In 2004, approximately 13 million NSAID prescriptions were dispensed in Canada.[1] It is estimated that per capita expenditure on oral anti-arthritic agents increased from $9 in 1998 to $21 in 2004.[1]

Although NSAIDs are effective anti-inflammatory and analgesic agents, overwhelming evidence links NSAID use to a variety of gastrointestinal (GI) complications including gastric and duodenal ulcers, dyspepsia, GI bleeding, perforations, gastric outlet obstructions, and death.[2-5] The risk of a NSAID-induced GI event increases with the presence of risk factors including advanced age, previous GI ulcer or bleed, and concomitant use of corticosteroids, anticoagulants or anti-platelet agents.[2-5]

NSAID induced complications are estimated to cause 3,897 hospitalizations and 365 deaths each year in Canada.[6] It is estimated that for each dollar spent on NSAIDs in Canada, an additional $0.66 was spent on the treatment of side effects.[7] Therefore, optimal prescribing of gastrointestinal prophylaxis agents in patients receiving NSAIDs is paramount.

To prevent NSAID-induced GI complications, patients taking NSAIDs are often prescribed a gastrointestinal prophylaxis agent (GPA). The GPAs available in Canada include proton pump inhibitors (PPIs), histamine2-receptor antagonists (H2RAs), and misoprostol. According to the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) *Evidence for PPI use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease: Scientific Report*,[8] standard dose PPIs in combination with non-selective NSAIDs are more efficacious than standard dose H2RAs, and equally efficacious as misoprostol for ulcer prevention. However, there have been no recent evaluations that have adequately addressed the economic question of the use of gastroprotective strategies within a Canadian context. Therefore, a need existed to conduct an economic evaluation in order to provide information on the relative cost-effectiveness of the available strategies.

2 OBJECTIVE

The objective of this study was to assess the cost-utility of PPIs, compared with H2RAs and with misoprostol for the prevention of NSAID-associated GI complications in patients with chronic musculoskeletal conditions (primarily RA and OA) who required NSAID therapy for more than three weeks.

3 METHODS

Given that we did not identify any recent economic evaluations that adequately addressed our study question within a Canadian context; we conducted our own economic evaluation, adapted from previous economic analyses.[9,10]

3.1 Analytical Approach

To evaluate the cost-utility of gastrointestinal prophylaxis in preventing NSAID-associated GI complications, a decision-analytic model was developed (Figure 1). The model was adapted from recently published economic analyses that were conducted in the United Kingdom.[9,10] To minimize the

need for unsubstantiated assumptions, while adequately accounting for essential GI consequences resulting from NSAID use, a static decision tree model was selected.

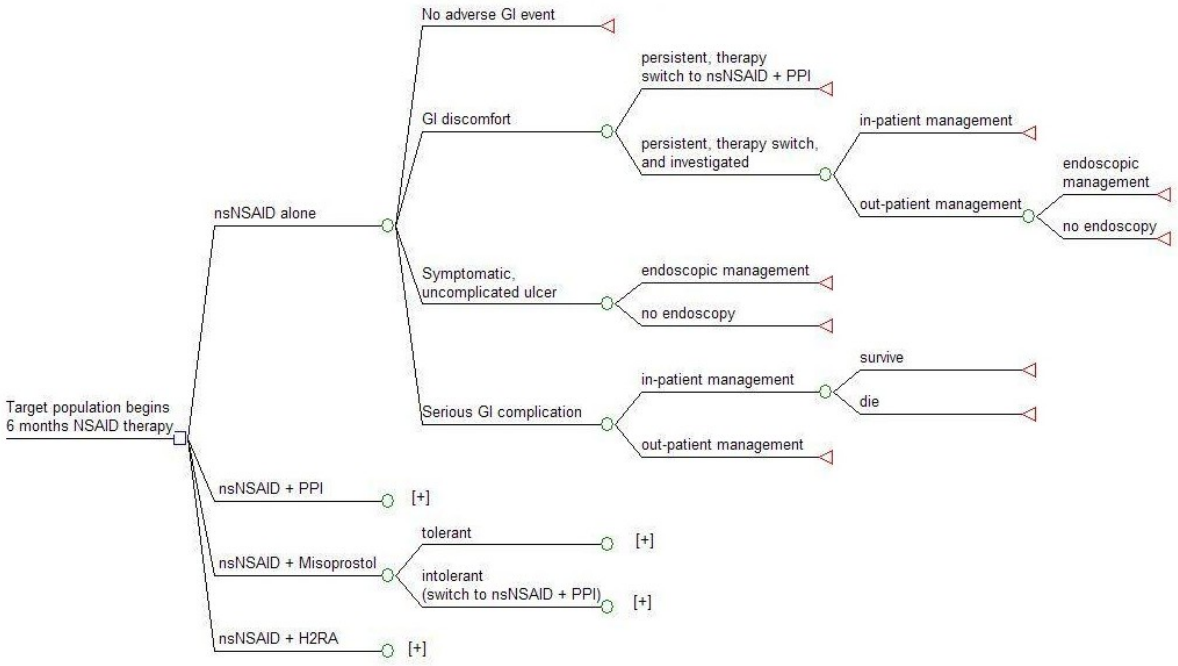
The three main events in the model (i.e., GI discomfort, symptomatic ulcer, and serious GI complication) were assumed to occur independently and to be mutually exclusive. The time-horizon of the model was six months which was based upon a Quebec study that reported NSAID use for patients ≥ 65 years to be between 34 and 90 days.[11] Additionally, the time-horizon reflects the maximum length of clinical trials used to generate model inputs, thereby minimizing the need for assumptions. To ensure that the model was reflective of the Canadian context model structure and resource utilization were validated by gastroenterologists from the COMPUS Expert Review Panel on Proton Pump Inhibitors (PPIs).

The outputs for the model were cost, quality adjusted life year (QALYs) gained, and incremental cost per QALY gained. A probabilistic sensitivity analysis was conducted to incorporate uncertainty of the inputs in the model using TreeAge ProSuite 2005 (TreeAge Software Inc., Williamson, MA, USA).

3.2 Patient Population

The patient population for this study included patients with chronic musculoskeletal conditions (primarily RA and OA) who required NSAID therapy for more than three weeks.[9,12] A mean age of 58 years was used in the model. This age is representative of patient populations included in a recent meta-analysis[10] and two large (16,135 patients) prospective RCTs.[2,5] The populations studied in those trials were heterogeneous in terms of their baseline risk of NSAID-associated ulcer.

Figure 1: Decision analytic model used in the economic analysis. [+] represents a sub-tree not shown in figure that is identical to sub-tree for NSAID alone.



3.3 Treatment Comparators

As shown in Figure 1, patients entering the model were treated with one of the following:

- Non-selective NSAID alone
- Non-selective NSAID+ Double Dose H2RA
- Non-selective NSAID+ Standard Dose PPI
- Non-selective NSAID+PPI to COX-2 selective NSAID (i.e. celecoxib 200 mg qd)
- Non-selective NSAID+ misoprostol 800 µg/day

Acetylsalicylic acid (ASA) was excluded from the definition of NSAID for the purpose of this study. The cost of generic diclofenac, a widely used NSAID in Canada, was used as the input for the cost of non-selective NSAIDs in all treatment arms. Lowest cost generic alternatives were chosen to represent each of the three gastroprotective strategies; the dose for each agent was obtained from pooled efficacy data for NSAID-ulcer prevention.[9] Drug therapies and doses used in the model were:

- NSAID: diclofenac 50 mg tid
- H2RA: ranitidine 300 mg bid
- PPI: omeprazole 20 mg qd
- Misoprostol 200 µg qid

In the case of persistent GI discomfort (i.e. dyspepsia) patients were switched to alternative gastroprotective therapies. Switching patterns, which were based on those modeled in previous economic analyses, were as follows:[9,10]

- Non-selective NSAID alone to Non-selective NSAID+PPI
- Non-selective NSAID+ H2RA to Non-selective NSAID+PPI
- Non-selective NSAID+ misoprostol to Non-selective NSAID+PPI

3.4 Audience and Perspective

The target audience for this economic evaluation was decision-makers in public drug benefit programs. The economic evaluation took the perspective of a third party provincial payer, as recommended in guidelines issued by the Canadian Agency for Drugs and Technologies in Health (CADTH).[13]

3.5 Clinical Events and Treatment Pathways

GI event rates for the NSAID-alone arm were derived from a pooled analysis of clinical trials that measured the efficacy of three gastroprotective agents in the prevention of non-ASA NSAID-ulcer.[9] The GI event rate associated with each gastroprotective strategy was determined by multiplying the pooled relative risk (versus placebo or no prophylaxis) across trials of each strategy,[9] by the corresponding baseline risks for the NSAID-alone arm. Rates in the NSAID-alone arm were assigned beta distributions and relative risks log-normal distributions according to Brown et al.[9]

Events included in the model were:

GI discomfort - persistent moderate to severe discomfort requiring visit to general practitioner (GP). Patients experiencing GI discomfort were switched to alternative therapy as outlined in section 3.03. Based on results from the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial, a small proportion of such patients (2.2% in the NSAID-alone arm and 1.8% in the NSAID+GPA arm) were investigated and subsequently managed either as inpatients or outpatients.[9] GI discomfort was assumed to occur after one month of initial treatment.

Symptomatic Uncomplicated Ulcer- a symptomatic, uncomplicated, clinically significant gastric or duodenal ulcer. It was assumed that patients could be diagnosed and treated as having a symptomatic, uncomplicated ulcer with or without endoscopy based on data from the MUCOSA trial.[9] It was assumed that 15% of all endoscopic ulcers would be symptomatic based on data from the MUCOSA trial.[4] Symptomatic ulcers were assumed to occur after three months of initial treatment.

Serious GI complication - GI hemorrhage, perforated ulcer, or gastric outlet obstruction. Serious GI complications were assumed to occur after three months of initial treatment. Management of serious GI complications (as inpatient or outpatient) was based on the respective proportions observed in the MUCOSA trial.[9]

GI-related death- mortality associated with serious GI ulcer complication requiring inpatient management. This rate was assumed to be 5.5% based on Canadian observational data.[14] GI complications managed in the outpatient setting were presumed to be associated with a zero probability of death.[9]

Rates for GI discomfort, symptomatic ulcers, and serious GI complications for the four strategies modeled are presented in Table 1.

Table 1: Six-month adverse event rates for alternative gastroprotective strategies in patients taking NSAIDs for more than three weeks.[9]

Strategy	GI discomfort	Symptomatic uncomplicated ulcer	Serious GI complications
NSAID	0.284	0.0320	0.00550
NSAID+H2RA	0.205	0.0176	0.00182
NSAID+PPI	0.122	0.0118	0.00253
NSAID+Misoprostol	0.276	0.0106	0.00314

Notes:

1. The probability of no GI adverse event = 1 - (p(GI discomfort) + p(symptomatic uncomplicated ulcer) + p(serious GI complication))
2. The estimates for the baseline risk of each event were calculated from the MA assuming that the control arm represented using an NSAID alone.
   Probability = (number of events in control group NSAID plus H2RA studies + number of events in control group NSAID plus PPI studies + number of events in control group NSAID plus misoprostol studies + number of events in control group Cox2 studies + number of events in control group Cox2 preferential studies) / (sample size in control group NSAID plus H2RA studies + sample size in control group NSAID plus PPI studies + sample size in control group NSAID plus misoprostol studies + sample size in control group Cox2 studies + sample size in control group Cox2 preferential studies)
3. The probability of symptomatic uncomplicated ulcer = 0.15*p(endoscopic ulcer)
   (Based on MUCOSA [4] study estimate of 85% of endoscopic ulcer remained silent)
4. The probability of each event = baseline risk of each event from NSAID arm * RR ratio from MA

Tables 2 and 3 present treatment pathway probabilities for the NSAID-alone treatment arm and NSAID + GPA treatment arms, respectively. Treatment pathway probabilities were derived from the MUCOSA trial[4] and The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE) study.[14] Treatment pathway probabilities for PPI and H2RA were unavailable in the literature and were assumed to be equivalent to those observed in the MUCOSA study for misoprostol.[4] All probabilities are conditional, that is, they are dependent upon a previous event occurring in the decision tree (Figure 1).

Table 2: Estimated treatment pathway probabilities for patients treated with NSAID alone.

Treatment Pathway•	Probability (95% CI)
Investigation after GI discomfort**	0.0223 (0.0179- 0.0267)
Inpatient management of GI discomfort**	0.24 (0.17 - 0.34)
Outpatient endoscopy of GI discomfort**	0.35 (0.25 - 0.46)
Endoscopy, given ulcer**	0.27 (0.20 - 0.36)
Inpatient management of GI complication**	0.67 (0.52 - 0.81)
Death, given inpatient management of GI complication*	0.054

* The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy RUGBE study[14]
** Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial [4]
• Treatment pathway probabilities are conditional, e.g. only 0.15% (0.28*0.0223*0.24) of patients in the NSAID-alone arm would undergo inpatient management for GI discomfort.

Table 3: Estimated treatment pathway probabilities for patients treated with NSAID + GPA.

Treatment Pathway•	Probability (95% CI)
Investigation after GI discomfort**	0.0176 (0.0137- 0.0215)
Inpatient management of GI discomfort**	0.39 (0.29 - 0.50)
Outpatient endoscopy of GI discomfort**	0.15 (0.07 - 0.28)
Endoscopy, given ulcer**	0.27 (0.20 - 0.36)
Inpatient management of GI complication**	0.56 (0.36 - 0.76)
Death, given inpatient management of GI complication*	0.054

* The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy RUGBE study[14]
** Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial [4]
• Treatment pathway probabilities are conditional, e.g. only 0.19% (0.276*0.0176*0.39) of patients in the NSAID-alone arm would undergo inpatient management for GI discomfort.

In their pooled analysis of gastroprotective strategies, Brown et al. reported that misoprostol was associated with a statistically significant risk of drop-out due to GI symptoms as compared to placebo or no prophylaxis.[9] Conversely, there was no significant risk associated with H2RAs, while PPIs were associated with a significantly lower risk of drop-out. Those findings were reflected in the current model by assuming that misoprostol was associated with a drop-out rate of 5.11%. This was calculated as the difference between the pooled rates of drop-out due to GI symptoms in the misoprostol and control arms of clinical trials.[9] The PPI and H2RA arms were assigned an equivalent drop-out rate to control (i.e. zero).

3.6 Resource Use

Identification and quantification of resource use for each treatment strategy (e.g., numbers of physician visits and endoscopies) was derived from a recent United Kingdom economic evaluation[10] and adapted to reflect the Canadian setting. Costs associated with inpatient and outpatient management of GI events were obtained from the Alberta Case Costing Project.[15] Resource use was validated by gastroenterologists from the COMPUS Expert Review Panel on PPIs to ensure that it reflected the Canadian context. Table 4 presents the resource use associated with each treatment pathway.

Table 4: Resource use associated with each treatment pathway.*

Treatment Pathway	Resource Use Estimation
No GI adverse Event	six months of treatment with initial strategy
GI Discomfort: therapy switch, with no investigation	one month of treatment with initial strategy, one GP visit, five months switched treatment[1]
GI Discomfort: investigated, inpatient management	one month of treatment with initial strategy, two inpatient days for stomach problem, two visits with GP, PPI for 28 days, diagnostic endoscopy, one outpatient visit, outpatient general gastrointestinal management, age• 18, five months switched treatment
GI Discomfort; outpatient management with endoscopy	one month of treatment with initial strategy, two visits with GP, PPI for 28 days, one outpatient visit, diagnostic endoscopy, therapeutic endoscopy[3], outpatient general gastrointestinal management, age• 18, five months switched treatment
GI Discomfort; outpatient management- no endoscopy	one month of treatment with initial strategy, two visits with GP, PPI for 28 days, one outpatient visit, outpatient general gastrointestinal management, age• 18, five months switched treatment
Symptomatic, uncomplicated ulcer: endoscopy	three months of treatment with initial strategy, diagnostic endoscopy, therapeutic endoscopy[3], two visits with GP, PPI for 28 days, two outpatient visits, outpatient general gastrointestinal management-Age • 18, three months acetaminophen treatment
Symptomatic, uncomplicated ulcer: no endoscopy	three months of treatment with initial strategy, two visits with GP, PPI for 28 days, two outpatient visits, two outpatient Gastrointestinal Management Age • 18, three months acetaminophen treatment
Serious GI complication: outpatient management ‡	three months of treatment with initial strategy, 42 days oral PPI, two visits with GP, two outpatient visits, diagnostic endoscopy, therapeutic endoscopy[3], outpatient management GI Bleed/Perforation/Obstruction, three months acetaminophen treatment
Serious GI complication: inpatient medical management ‡	three months of treatment with initial strategy, 42 days oral PPI, two visits with GP, two outpatient visits, GI bleed: inpatient management of serious GI event costs‡, three months acetaminophen treatment

[1] Patients were switched to alternative therapy as outlined in Section 2.03
[2] The associated cost of an outpatient visit was assumed to be equivalent to the weighted cost of outpatient management[4], gastroenterology age • 18 from Alberta Case Costing Report and outpatient physician fee[15]
[3] The associated cost of a therapeutic endoscopy is assumed to be equivalent to the cost of an endoscopy from the Alberta 2006 Case Costing Ambulatory Care[15] statistics and endoscopy fee from the Ontario Fee Schedule[4]
These costs included all indirect and direct costs (salaries, drugs, medical, and surgical supplies) and other expenses in patient care centers. They exclude payments made to physicians and other allied health professionals
*adapted from Elliott et al.[10]

3.7 Costs

Only direct medical costs were considered. Costs were calculated and presented in 2006 Canadian dollars.

Drugs

Drug costs were calculated based on unit costs from the Ontario Drug Benefit e-Formulary,[16] plus an allowable markup of 10% and a pharmacy fee of $7.00. The lowest generic cost was used for each alternative, where possible. Daily drug costs are presented in Table 5.

Physician Fees and Procedures

Costs for physician fees and procedures were obtained from the Ontario Ministry of Health and Long Term Care Schedule of Benefits, October 1, 2006. Costs of physician fees and procedures are provided in Table 5.

Inpatient and Outpatient Management

Inpatient and outpatient costs were obtained from the Health Costing in Alberta 2006 Annual Report.[15] Data for the Alberta Case Costing Report were generated from the cost of cases in two health authorities and 12 sites in Alberta from April 1, 2004 to March 31, 2005. Payments made to physicians and other allied health professions were not included. Associated costs per case for inpatient and outpatient management of GI complications are presented in Table 4, along with Case Mix Groupings (CMG) and Ambulatory Case Classification System (ACCS) codes. Inpatient and outpatient costs were assigned a gamma distribution in the analysis. The gamma distribution is commonly assigned to costing estimates in economic evaluations because it is constrained to be positive and continuous.[17]

Table 5: Cost data used in economic analysis

Parameter	Cost Estimate (2006 $CAD)
Drug Treatments (daily dose)	
Diclofenac 50 mg tid §	0.94
Omeprazole 20 mg qd §	1.25
Misoprostol 200 µg qid §	0.91
Ranitidine, 300 mg bid §	1.56
Celecoxib 200mg qd §	1.30
Acetaminophen (1gm qid)	0.06
Physician Fees and Procedures **	
GP Visit	56.10
Gastroenterologist, visit with consultation	127.50
Subsequent Inpatient visit with Gastroenterologist	29.20
Endoscopic treatment fee	92.10
Inpatient and outpatient costs	
Diagnostic Endoscopy¤	157.46
Therapeutic Endoscopy ¥	453 (s.d = 252)
Outpatient, gastroenterology	
Management, general gastrointestinal, Age 18+ζ	134 (s.d = 134)
Outpatient Management GI	231 (s.d = 220)

Parameter	Cost Estimate (2006 $CAD)
Bleed/Perforation/Obstruction[ρ]	
GI Hemorrhage- Inpatient medical management [φ]	4006 (s.d = 3600)
Inpatient day for GI symptoms [ώ]	956.97

§ Drug Costs based on Ontario Drug Benefit Formulary[16]
ɗ Crott et al.[18]
** Ontario Ministry of Health and Long Term Care, January 2007[19]
¥ Health Costing in Alberta 2006 Annual Report, Ambulatory Care Costs, ACCS Code=28.2[15]
ζ Health Costing in Alberta 2006 Annual Report, Ambulatory Care Costs, Weighted average of ACCS Code= 409, 410, and 413[15]
ρ Health Costing in Alberta 2006 Annual Report, Ambulatory Care Costs, ACCS Code=413[15]
φ Health Costing in Alberta 2006 Annual Report, Inpatient Costing Data, CMG Group= 281[15]
ώ Health Costing in Alberta 2006 Annual Report, Inpatient Costing Data, Weighted Average of GI CMG Groups[15]

3.8 Utilities

Utilities were adopted from a recent economic model.[10] Table 6 presents 1) the utility of each GI adverse event health state, 2) the duration of health state in days; and 3) QALYs lost over six months, for each of the ten health states in the model. Given the lack of data surrounding variance of GI utility estimates, QALYs lost over six months were assigned a triangular distribution; such that the mean of published values comprised the apex of the distribution, while the lowest and highest published values comprised the minimum and maximum, respectively. In instances where the range around the mean was wide a beta distribution was assigned.

Utilities were derived from studies that reported on varying patient populations and used differing measurement methodologies. For example, utilities for dyspepsia were elicited from patients using time-trade off interviews[20] while HRQOL associated with inpatient and outpatient management of GI conditions was obtained using the Quality of Well Being Scale (QWB).[21] QALYs lost over six months were subtracted from the average life expectancy of individuals taking NSAIDs. Estimated life expectancy at age 58 for the Canadian population was obtained from Statistics Canada.[22] Life years were discounted by 5% as recommended by CADTH guidelines.[13]

Table 6: Utility and Duration of GI Events, adopted from Elliott et al., (2006)[10]

Treatment pathway	Utility	Duration	QALY lost over 6 months
No GI adverse event	1.0000	0	0
GI discomfort, switch therapy:			0.0049
moderate dyspepsia before seeking help	0.9100	10	
GI discomfort, inpatient medical management:			0.0318
severe dyspepsia before seeking help	0.8700	10	
inpatient days with endoscopy	0.5675	2	
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	
GI discomfort, outpatient medical management, endoscopy:			0.0295
severe dyspepsia before seeking help	0.8700	10	
outpatient endoscopy	0.5675	1	

Treatment pathway	Utility	Duration	QALY lost over 6 months
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	
GI discomfort, outpatient medical management, no endoscopy:			0.0271
severe dyspepsia before seeking help	0.8700	10	
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	
Symptomatic ulcer, endoscopy:			0.0318
severe dyspepsia before seeking help	0.8700	10	
outpatient endoscopy (2)	0.5675	2	
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	
Symptomatic ulcer, no endoscopy:			0.0271
severe dyspepsia before seeking help	0.8700	10	
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	
Serious GI complication, inpatient management, survive:			0.0410
severe dyspepsia before seeking help	0.8700	10	
inpatient treatment of complicated ulcer	0.4900	5*	
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	
serious GI complication, inpatient management, die	0.0000		0.5
Serious GI complication, outpatient management:			0.0318
severe dyspepsia before seeking help	0.8700	10	
outpatient endoscopy (2)	0.5675	2	
severe dyspepsia after therapy	0.8700	12	
moderate dyspepsia after therapy	0.9100	23	

* Average length of stay for inpatient management of serious GI complication (hemorrhage, perforation, gastric outlet obstruction) in Canadian setting (Alberta Case Costing Report).[15]

3.9 Sensitivity Analysis

A probabilistic sensitivity analysis using Monte Carlo Simulation was used to incorporate uncertainty of parameters. Monte Carlo simulation enables simultaneous sensitivity analysis of all uncertain variables[23] by replacing point estimates of probabilities, utilities, and costs with probability distributions. The probabilistic analysis sums the results of 10,000 iterations in which each iteration represents a combination of parameter values randomly sampled from specified distributions. Probability distributions for this model were derived from a previously published economic analysis.[9] Cost-effectiveness scatter plots and cost-effectiveness acceptability curves were generated to convey uncertainty of results. The simulation software used to conduct the sensitivity analysis was TreeAge Pro 2005 (TreeAge Software Inc., Williamson, MA, USA

4 RESULTS

4.1 Base Case Analysis

The results of the base case analysis are provided in Table 7 and Figure 2.

Of the non-dominated strategies, NSAID therapy alone (i.e., with no prophylaxis) was the least costly but least effective strategy. NSAID + misoprostol (200µg qid) was removed from the results by extended dominance. NSAID + misoprostol (200µg qid) was cheaper than NSAID +PPI; however, NSAID + PPIs was better value for money (i.e., this strategy had a lower ICER as compared to no prophylaxis than did misoprostol).

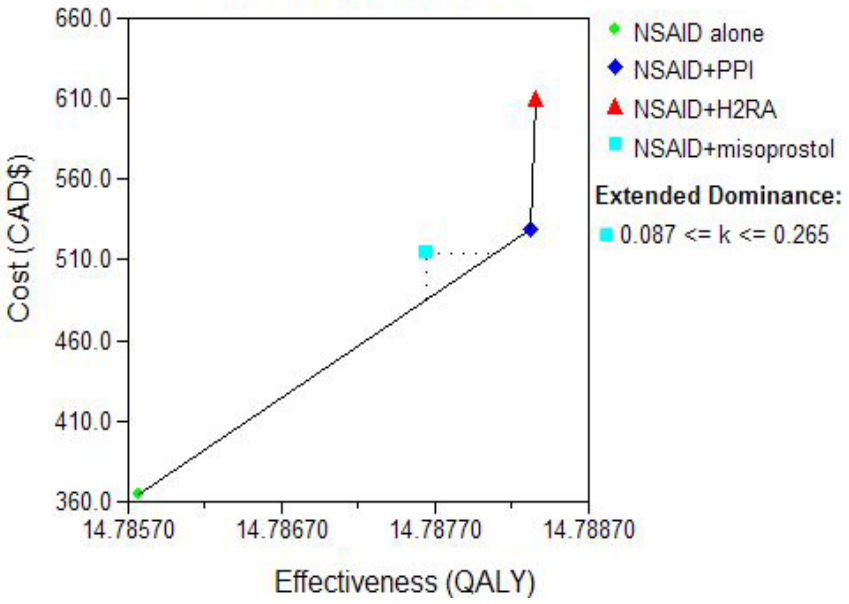
NSAID + PPI was $163 was more costly per person and yielded 0.00255 additional QALYs relative to NSAID alone. NSAID+PPI was estimated to cost $63,835 per QALY gained over NSAID alone.

Table 7: Expected costs, QALYs, costs per QALY and incremental costs per QALY gained for alternative gastrointestinal prophylaxis therapies in Canada

Strategy	Cost ($CAD)	Incr Cost	Effectiveness (QALY)	Incr Eff	Incr C/E (ICER)*
A) All options ordered by increasing cost					
NSAID alone	366	N/A	14.7858	N/A	N/A
NSAID+misoprostol	515	149	14.7876	0.00188	79,274
NSAID+PPI	529	14	14.7883	0.00068	20, 981
NSAID+H2RA	610	81	14.7884	0.00004	2,112,862
B) Without dominated options (simple or extended)					
NSAID alone	366		14.7858		
NSAID+PPI	529	163	14.7883	0.00255	63,835
NSAID+H2RA	610	81	14.7884	0.00004	2,112,862

* Incremental cost per QALY gained

Figure 2: Cost-effectiveness plane of gastroprotective strategies in Canada



4.2 Probabilistic Sensitivity Analysis

Figure 3 displays the cost-effectiveness (CE) scatter plot for all iterations in the Monte Carlo simulation. Each point in the CE scatterplot represents the cost and effectiveness (QALYs) for each strategy associated with a particular iteration of the Monte Carlo simulation. The Y-axis is truncated in the CE scatter plot to better illustrate results.

Figure 3: Cost-effectiveness scatter plot of COMPUS model from Monte Carlo simulation: Costs and QALYs

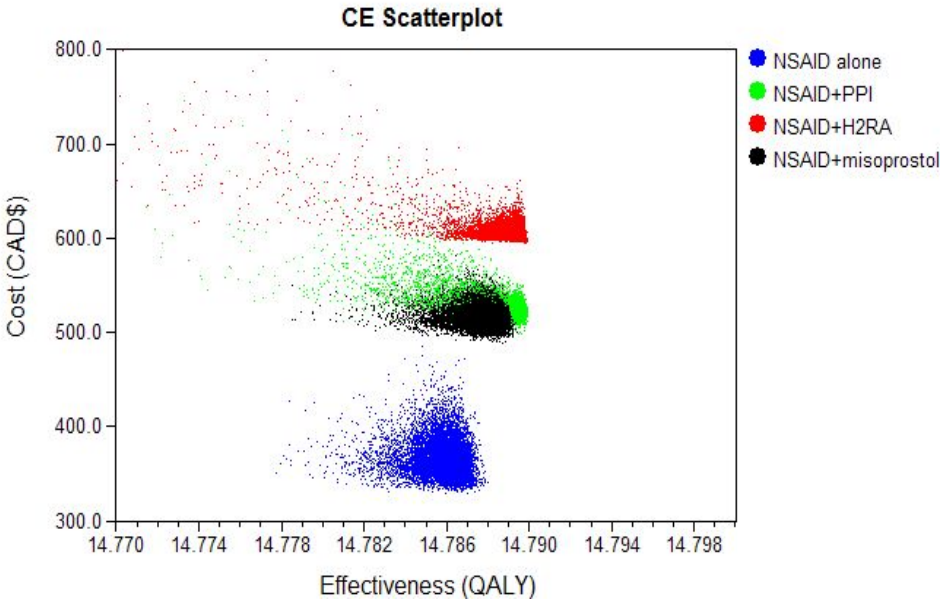


Figure 4 provides the incremental cost-effectiveness (ICE) scatter plot from the Monte Carlo simulation for NSAID+PPI versus NSAID alone. Each point represents the incremental cost and effectiveness of PPIs relative to no prophylaxis for a particular iteration. Table 8 shows the proportion of samples in each component region of the ICE scatterplot. The table illustrates that 42.78% of the PPI samples in the Monte Carlo simulation were cost-effective relative to no prophylaxis at a willingness to pay threshold of $50,000 per QALY gained.

Figure 4: Incremental cost-effectiveness scatter plot of PPIs relative to no prophylaxis in Monte Carlo simulation: Costs and QALYs at WTP = $50,000. Vertical dashed line represents incremental effectiveness of zero, diagonal dashed line indicates WTP threshold of $50,000 per QALY gained.

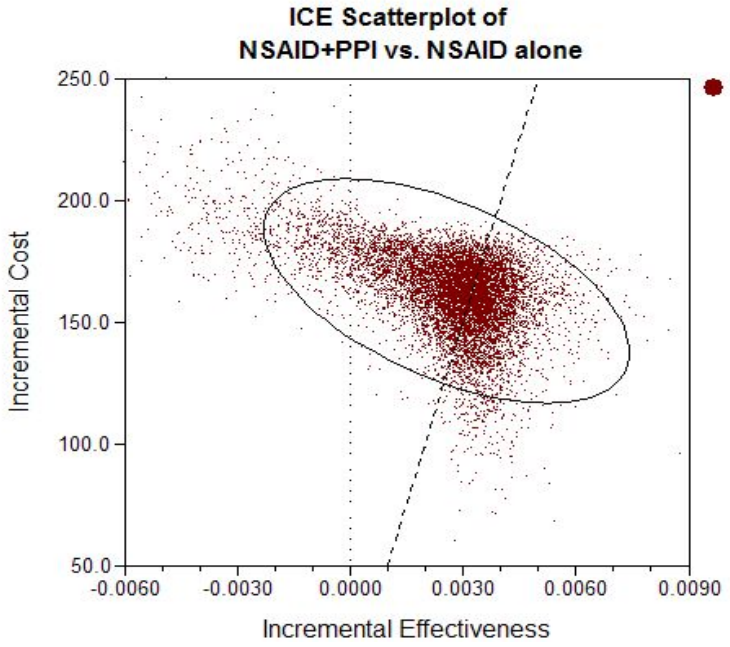


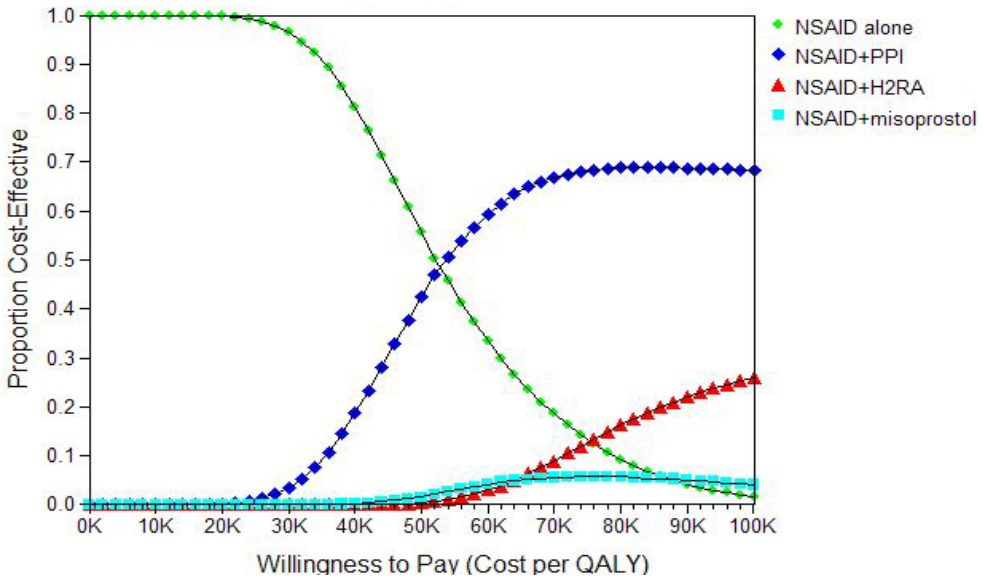
Table 8: Proportion of samples in each component region of ICE scatter plot

Component	Quadrant	Incr. Eff.	Incr. Cost	ICER	# Points	Percent
C1	IV	IE>0	IC<0	Superior	0	0.00%
C2	I	IE>0	IC>0	<50000	4278	42.78%
C3	III	IE<0	IC<0	>50000	0	0.00%
C4	I	IE>0	IC>0	>50000	4876	48.76%
C5	III	IE<0	IC<0	<50000	0	0.00%
C6	II	IE<0	IC>0	Inferior	846	8.46%

**To identify cost-effective points, a different component labeling system is used. Cost-effective points for "NSAID+PPI" lie below the WTP line ($50,000 per QALY), in components 1-3.
Component 1 (C1) is where NSAID+PPI is dominant ('Superior')
Component 2 (C2) is where NSAID+PPI is more costly, but lies below the WTP
Component 3 (C3) is where NSAID+PPI is less costly, but lies below the WTP
Component 4 (C4) is where NSAID+PPI is more costly, and lies above the WTP.
Component 5 (C5) is where NSAID+PPI is less costly, and lies above the WTP.
Component 6 (C6) is where NSAID+PPI is dominated ('Inferior').

Figure 5 provides the cost-effectiveness acceptability curve for all strategies in the economic analysis. NSAID alone was the strategy most likely to be cost-effective up to a WTP threshold of $52,000 per QALY gained, beyond which NSAID+PPI was most likely to be cost-effective.

Figure 5: Cost-effectiveness acceptability curve of COMPUS Economic model



5 LIMITATIONS

The interpretation of results in this economic evaluation is limited by several key assumptions/limitations:

- This model did not evaluate the cost-utility of selective COX-2 inhibitors as an alternative to non-selective NSAIDs in combination with a GPA. Although the COX-2s must be included for an economic analysis of NSAID-ulcer prevention to be considered complete, this required a more complex model in which cardiovascular outcomes were also incorporated. Such a model was not found in the literature, therefore the present work was restricted to non-selective NSAIDs in combination with GPAs. COMPUS's future work in this area will focus on the development of a *de novo* model that incorporates all relevant outcomes associated with both non-selective and COX-2 selective NSAIDs.
- The efficacy of PPIs and H2RAs in reducing the risk of serious GI complications was estimated from trials with very low event rates, thus the relative risks (RR) associated with these strategies were highly imprecise and not statistically significant.[9] The degree of imprecision in these key data had repercussions on the economic analysis. For example, the point estimate for the pooled RR of serious GI complications associated with H2RAs was lower than that for PPIs. This resulted in H2RAs appearing more effective than PPIs in the analysis, a finding that is not corroborated by the clinical evidence.
- There was a lack of data to model patients at high-risk for NSAID-induced ulcer complications, a group in which gastroprotection may be most cost-effective.
- The time horizon of the analysis was six months. However, it has been reported that the greatest risk of NSAID-induced ulcer complications may exist early in therapy.[24] It is possible, therefore, that over a longer time horizon, gastroprotective strategies would be less cost-

effective than estimated in the current study. A study of cost-effectiveness in long-term NSAID users is therefore required.

- The face validity of the model was assessed by gastroenterologists from the COMPUS Expert Review Panel on PPIs. However, independent validation of the model and results of the analysis are necessary.
- The incremental difference in QALYs across alternatives was small, i.e. • 0.001 QALYS which was equivalent to about eight hours. Interpretation of the importance of such small differences in effect was difficult.
- Indirect comparisons were used to generate event rates rather than direct comparisons. Because different study populations may differ in their baseline risk and responsiveness to treatment, indirect comparisons may not appropriately estimate differences in treatment effects.
- The cost of the H2RA strategy was based on double-dose therapy (ranitidine 300 mg bid), and that of misoprostol on a daily dose of 800 µg qd. Although higher than routinely used in clinical practice, those doses have been shown to be efficacious in reducing the risk of both gastric and duodenal ulcers.
- GI event probabilities in the NSAID-alone arm were based on pooled results of NSAIDs as a class. The cost of diclofenac was chosen to be representative of the cost of the NSAID class. However, other agents in this class differ in cost and propensity to cause gastropathy. Therefore, the cost-effectiveness of various gastroprotective strategies versus NSAID alone may differ for NSAIDs other than diclofenac. Also, the risks of GI events associated specifically with diclofenac may differ from the pooled risks associated with NSAIDs as a class.
- Dose response relationships of strategies were not incorporated into the analysis. Estimates surrounding the efficacy of strategies were based on pooled results from RCTs employing different dosages.
- There is a lack of data surrounding utilities of GI states. Thus, utilities were obtained from sources that studied different populations and utilized varying methods to derive utility estimates. The degree to which these utility values pertain to the population modeled in this study was uncertain.
- Probabilities for treatment pathways were obtained primarily from the MUCOSA study, a RCT conducted in the early 1990s.[4] These probabilities may not reflect current clinical practice in Canada. This may be of particular concern for the probabilities of inpatient management following adverse GI events, since the costs of inpatient management are a major driver of total costs in the model. Also, the study population, and hence the treatment probabilities, in the MUCOSA trial may have differed from the pooled population in the meta-analysis from which GI event rates were derived.
- The model incorporates a drop-out rate for misoprostol that was estimated by pooling misoprostol RCTs. However, those studies varied in dose, duration, design, population, NSAID prescribed, and methodological quality. The degree to which the pooled drop-out rate reflects the true drop-out rate for the population and misoprostol dose modeled in this study is unknown.
- Non-compliance due to factors other than intolerance was not modeled due to the lack of reliable data on the degree of non-compliance with GPAs and its effect on the efficacy of these agents. This may have resulted in overestimation of the effectiveness and cost-effectiveness of the GPAs, since there was evidence that a significant proportion of patients prescribed H2RAs or PPIs as GPAs had suboptimal compliance with therapy.[25]
- Data on resource use associated with NSAID-related GI events was of poor quality. The model assumes that Canadian resource utilization is the same as in recent economic models from the UK.[9,10] If resource utilization in Canada were to differ substantially, this would impact

the estimates of cost-effectiveness.

- In the absence of trial data on the rate of symptomatic ulcers, it was assumed that 15% of endoscopic ulcers become symptomatic uncomplicated ulcers, as observed in the MUCOSA trial.[4] If the true rate of symptomatic ulcers differs substantially from this estimate, it could impact the estimated cost-effectiveness of the various strategies.

6 DISCUSSION

Despite the limitations as discussed above, this model generated some useful information that may be used to aid decision-makers and healthcare managers. Among non-dominated strategies, our analysis found that the use of non-selective NSAID+PPI or NSAID+H2RA therapy may reduce the risk of serious GI complications, albeit at an increased cost to the healthcare system relative to NSAIDs alone.

In the base case analysis, compared to NSAID therapy alone, NSAID+PPI therapy was associated with a cost of $63,835 per QALY gained, while NSAID+ H2RA therapy was associated with an incremental cost of $2,112,862 per QALY gained relative to NSAID+PPI. Misoprostol was eliminated based on the principle of extended dominance, such that a combination of no prophylaxis and NSAID+PPI therapy demonstrated greater efficacy at a lower cost. The probabilistic sensitivity analysis and corresponding cost-effectiveness acceptability curves indicated that a strategy of no prophylaxis was most likely to be cost-effective up to a WTP threshold of approximately $52,000 per QALY gained. For a WTP threshold above $52,000 per QALY gained, NSAID+PPI was most likely to be cost-effective.

The risk of a NSAID-induced GI event was likely to increase in the presence of risk factors such as age or the concomitant use of ASA. That increased risk may affect the relative cost-effectiveness of the various strategies modeled. For example, it was likely that gastroprotection would be more economically attractive in high-risk populations. However, due to a lack of data, the cost-effectiveness of gastroprotective strategies in such populations was not assessed. Future studies examining the effect of risk factors or stratifying patients by risk will provide useful information for decision-makers.

To date, no large, prospective, randomized, controlled clinical outcome studies have been conducted to examine the efficacy of PPIs or H2RAs in preventing NSAID-associated clinical GI complications. Given the widespread use of these therapies, a large prospective RCT and economic evaluation examining clinically important outcomes across strategies would yield more precise estimates of efficacy and cost-effectiveness than are currently available, and thus provide valuable information to decision makers and healthcare managers.

Finally, this analysis did not examine the cost-utility of selective COX-2 inhibitors in preventing NSAID associated GI complications. A complete understanding of the costs and effects of strategies to prevent NSAID-associated ulcers requires more intricate models that compare the cost-utility of selective COX-2 inhibitor therapies to non-selective NSAID in combination with GPAs in terms of cardiovascular, rheumatological and gastrointestinal outcomes.

Acknowledging its limitations, this model generated some useful results for decision makers. These findings highlight the relative cost-utility of gastrointestinal prophylaxis strategies in preventing NSAID-associated GI complications in the Canadian context. The results can be utilized to aide decision makers, physicians, and other health professionals on how to prescribe gastroprotective agents appropriately and cost-effectively.

7 CONCLUSIONS

The economically preferred gastroprotective strategy for patients receiving NSAIDs will be dependent upon decision makers' willingness to pay. A strategy of no prophylaxis (i.e., NSAID alone) was the least costly, but also the least effective, strategy in a cohort of patients (age≥18) beginning a six-month course of NSAID therapy.

All three gastroprotective strategies tested in this analysis may reduce the risk of serious GI complications, albeit at an increased cost to the healthcare system. Compared to no prophylaxis, PPI therapy is cost-effective as a gastroprotective strategy in NSAID users when a cost exceeding $63,835 per QALY gained is acceptable. With an incremental cost per QALY exceeding $2 million as compared to NSAID+PPI, NSAID + H2RA therapy is not a cost-effective strategy. Misoprostol is a dominated alternative.

When uncertainty is incorporated in the analysis through the use of a Monte Carlo simulation, the strategy with the highest likelihood of being cost-effective is NSAID alone up to a WTP threshold of $52,000 per QALY gained. Beyond this threshold, NSAID+PPI is most likely to be a cost-effective strategy.

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