ECONOMIC EVALUATION OF PROTON PUMP INHIBITORS, RELATIVE TO ALTERNATIVE GASTROPROTECTIVE AGENTS, FOR PREVENTION OF GASTROINTESTINAL COMPLICATIONS IN ELDERLY PATIENTS TAKING NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

by

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ABSTRACT

A cost-utility analysis of proton pump inhibitors (PPIs), relative to alternative gastroprotective agents, in preventing gastrointestinal complications among elderly patients (age≥65years) that require non-selective non-steroidal anti-inflammatory drugs (nsNSAID) therapy was conducted. The analysis adopted the perspective of a provincial healthcare system and used a decision analytical model over a 1-year time horizon. Clinical outcomes, costs, and utilities for the model were derived from recently published studies. Results from the analysis suggest that routine prescription of PPIs in all elderly patients (age≥65y) taking nsNSAIDs may not be warranted, as incremental cost-utility ratios (ICURs) exceeded commonly cited thresholds in the range $50,000-$100,000 per quality-adjusted life-years gained. However, co-prescribing PPIs among elderly patients taking nsNSAIDs and with a history of a complicated/uncomplicated ulcer was associated with more favorable ICURs and may be considered an efficient use of finite healthcare resources.

LIST OF ABBREVIATIONS AND SYMBOLS USED

ASA	Acetylsalicyclic acid
bid	Twice daily
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CLASS	Celecoxib Long-Term Arthritis Safety Study
COMPUS	Canadian Optimal Medication Prescrbing and Utilization Service
COX	Cyclooxygenase
CUA	Cost-utility analysis
DALY	Disability adjusted life year
DSA	Deterministic sensitivity analysis
EQ-5D	EuroQol
GDP	Gross domestic product
GI	Gastrointestinal
GPA	Gastroprotective agent
H_2RA	H_2 Receptor anatagonist
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IWB	Index of Well being
JW	Johannesson and Weinstein
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-term
MUCOSA	Misoprostol Outcome Safety Assessment
NB	Net benefits
NICE	National Institute of Clinical Excellence
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drug
NsNSAID	Non-selective Non-steroidal anti-inflammatory drug
NSSPP	Nova Scotia Senior Pharmacare Program
od	Once daily
OR	Odds ratio
PBMA	Program budgeting and marginal analysis
PPI	Proton pump inhibitor
POB	Strict ulcer complication (Perforation, obstruction, or bleed)
PUB	Clinical ulcer complication (symptomatic ulcer or POB)
QALY	Quality adjusted life year
qid	Four times daily
RCT	Randomized controlled trial
RR	Relative risk
RUGBE	Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endsocopy
TARGET	Therapeutic Arthritis Research and Gastrointestinal Event Trial
US	United States

VIGOR	Vioxx Gastrointestinal Outcomes Research
WTP	Willingness to Pay
y	Year
λ	cost-effectiveness threshold
μ	micro

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CHAPTER 1 INTRODUCTION

1.1 BACKGROUND

Non-steroidal anti-inflammatory drugs (nsNSAID) are widely prescribed as anti-inflammatory agents or analgesics to relieve symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), bursitis, gout, painful menstruation, headache, and other diseases. NSAIDs are among the leading classes of prescribed drugs in Canada. [1-3] In 2004, the per capita expenditure on anti arthritic* agents was $21 per capita. [1,2]

Although NSAIDs alleviate pain and inflammation, there is unequivocal evidence that NSAIDs increase the risk of gastrointestinal (GI) and other complications including: dyspepsia, gastric and duodenal ulcers, which can lead to bleeding, perforations, surgery and death.[4-12] In adult patients (age≥ 18y) taking NSAIDs for at least 2 months, the risk of developing an endoscopic ulcer is 1 in 5, a symptomatic ulcer is 1 in 70, bleeding or perforated ulcer is 1 in 150, or death is 1 in 1200.[4-7,12,13,13,14]

The magnitude of GI risk increases with the presence of risk factors.[14-17] Well documented risk factors for NSAID-induced GI complications include advanced age, history of complicated or uncomplicated ulcers, frailty, use of high doses of NSAIDs, and concomitant use of use of anti-platelet agents, acetylsalicylic acid (ASA), anticoagulants, corticosteroids.[14-17]

There is convincing evidence that advanced age is an independent risk factor for NSAID induced GI complications.[14,15] The relative risk of a GI event increases from 2.37 in patients age ≥ 65y to 3.87 in patients' age ≥ 75y relative to all patients age ≥ 50y.[4,14] Several studies have shown that individuals age ≥ 75y have a similar risk of a GI event to patients age≥50 and with a history of a GI Bleed, one of the strongest recognized risk factors. [4,14]

* The majority of expenditures on agents in this treatment category were for selective cyclooxygenase-2 (COX-2) inhibitors (70%) and non-selective non-steroidal anti-inflammatory agents (20%)

To prevent adverse GI events, individuals are often co-prescribed a gastroprotective agent. Proton Pump Inhibitors (PPI) (e.g. omeprazole 20mg *od*), double dose H2-Receptor Antagonists (H2RA) (e.g. ranitidine 300mg *bid*), and Misoprostol (200μg, qid) are efficacious in preventing both gastric and duodenal ulcers in patients that require NSAID therapy.[8-11] Single dose H2RA (e.g. ranitidine 150mg *bid*) and Misoprostol (200μg, bid) are less efficacious. [8-11]

Standard dose PPI is considered the therapy of choice by many physicians, in terms of efficacy, fewer side effects, and ease of use (once daily dose which enhances patient compliance); albeit an increased cost. [18,19]As a result, PPI prescriptions dispensed by Canadian retail pharmacies increased from 10.8 million in 2003 to 12.4 million prescriptions in 2004.[11] Accordingly, the per capita expenditure on gastrointestinal drugs in Canada also increased from $24 in 1998 to $45 in 2004.[1]

To promote apprpriate therapy and curb growth in expenditures, public drug plans adopted different policies surrounding reimbursement of PPIs.[11] In many jurisdictions in Canada, PPIs are classified as exception status drugs, where physicians must provide documentation demonstrating that a patient satisfies the criteria for reimbursement.[11,20] There are concerns that these reimbursement policies may be restricting the frequency of PPI use in high risk patients and in turn increasing the number of preventable GI events, particularly in the elderly.[11,28,91] Moreover, acquisition costs of PPIs have decreased considerably since these policies were implemented.[20,21] For instance, in the Ontario Drug Benefits Program, the price of apo-omeprazole (20mg od) dropped from $1.25 in 2006 to $1.10 in 2008.

It is therefore crucial that an economic evaluation is conducted to examine the cost-effectiveness of PPIs relative to alternative gastroprotective strategies in elderly patients. This information will enable decision makers and healthcare providers to make informed judgments on reimbursement of PPIs in elderly patients, including which patients, represents an efficient use of limited healthcare resources.

1.2 STRUCTURE OF THESIS

The individual components of this thesis, that is, the literature review of clinical and economic evidence, the theoretical foundation of economics in health care, and cost-effectiveness analysis, form an integreated whole, resulting in a thesis that consists of eight chapters. Details of each chapter are discussed below.

Chapter 1 presents the general background and the context for this topic. Chapter 2 presents a review of relevant clinical and economic evidence. Chapter 3 provides the theoretical foundations and underlying limitations of the use of economic evaluation in healthcare. Chapter 4 presents the research questions to be addressed in this thesis. Chapter 5 provides a comprehensive discussion of the methods used to carry out the economic analysis. Chapters 6 and 7 present the results from the base-case, sensitivity, and variability analyses. In Chapter 8, findings are integreated to address and answer the main goals of the thesis. Furthermore, limitations of the analysis are presented, along with recommendations for future research.

CHAPTER 2 LITERATURE REVIEW

2.1 ARTHRITIS AND RELATED MEDICATIONS IN CANADA

According to the 2000 Canadian Community Health Survey, nearly 4 million Canadians (16%) aged 15y and older are affected by arthritis and related conditions. [2] The age-sex standardized prevalence of arthritis is projected to increase to over 6 million (20.6%) in Canada by the year 2026.[2] The standardized rate of arthritis varies considerably across jurisdictions throughout Canada[2]; residents of Nova Scotia reported a prevalence of 23% whereas residents of Quebec reported a prevalence of 12% in 2000.[2] The prevalence is also much higher among the elderly population; approximately 40% of individuals aged 65 and older have chronic arthritis, compared with 15% of individuals under the age of 35.[22]

Approximately 80% of Canadians with arthritis and related conditions take medicines to alleviate pain and inflammation. Simple analgesics, such as acetaminophen, are first line of therapy among patients with mild osteoarthritis.[23] Non steroidal anti-inflammatory agents (NSAIDs) are considered the therapy of choice in patients with moderate to severe osteoarthritis.[23]

NSAIDs selectively block prostaglandin formation, thereby reducing pain and inflammation.[24-26] Evidence has shown that NSAIDs reduce short term pain in patients with osteoarthritis; however, there is a paucity of evidence demonstrating the long-term effects of NSAIDs in reducing pain. [24-26] There are two main classes of NSAIDs: non-selective NSAIDs and selective COX-2 inhibitors. Selective COX 2 inhibitors are associated with a reduced risk of upper GI complications.[27] Selective COX-2 inhibitors inhibit the COX 2 enzyme; the COX 2 enzyme is considered the primary enzyme responsible for pain and inflammation, while inhibition of COX-1 enzyme is considered to be the primary cause of GI toxicity. [8,27]

NSAID use among elderly residents of Ontario increased from 14% before introduction of COX-2 inhibitors in April 2000 to 19.8% after the introduction in February 2002.[28] In

2000/2001, 173 people per 1000 aged 65y and older had a prescription for a non-selective NSAID while 111 per 1000 had a prescription for a selective COX-2 inhibitor in Ontario.[22] Interestingly, the increased use of COX-2 agents (safer GI profile at patient-level) was also associated a 10% increase in GI hospitalizations among Ontario seniors, as a greater number of patients at the population-level were prescribed NSAIDs.[28]

2.2 EPIDEMIOLOGY

Although NSAIDs reduce pain and inflammation, they do so at an increased risk of GI and other complications.[4,6,7,15,27,29-31] The majority of NSAID induced GI complications occur in the upper GI tract, especially gastric and duodenal ulcers, which can lead to bleeding, perforations, surgery and death. Dyspepsia due to NSAIDs also occurs commonly, in 5-15% of patients.[32] The remainder of serious GI complications occur in the small and large bowel and bleeding is the most frequent one. In adult patients (age≥18y) on oral NSAIDs for at least 2 months, the risk of developing an endoscopic ulcer is 1 in 5, a symptomatic ulcer is 1 in 70, bleeding or perforated ulcer is 1 in 150, or death is 1 in 1200. [4-10,12-14]

Given the widespread use of NSAIDs, large numbers of GI complications have been observed, despite the low absolute risk. NSAID induced ulcer complications are estimated to cause 3897 hospitalizations and 365 deaths each year in Canada.[33] It is estimated that for each dollar spent on NSAIDs in Canada, an additional $0.66 was spent on the treatment of side effects.[34,35]

The likelihood of an NSAID-induced GI complication increases with the presence of one or more risk factors- with advanced age being one of the more important risk factors. In the MUCOSA trial, patients age ≥ 75y had a similar risk (RR, 2.48; 95% CI, 1.48 to 4.14) to individuals with history of a GI bleed (RR, 2.56; 95% CI, 1.30 to 5.03) and patients with a history of a peptic ulcer (RR, 2.29; 95% CI, 1.28 to 4.12).[7,16] These results are similar to results from a sub-analysis of the VIGOR trial where patients' age ≥ 75y had a similar risk (RR, 3.87; 95% CI, 2.41 to 6.22) to patients with a prior complicated GI event (RR, 3.73; 95% CI, 2.25 to 6.17).[4,14] In this study, the number needed to treat

(NNT) in 1 year to prevent an adverse clinical event in patients age ≥ 75y was 10 while the NNT in patients with a prior complicated GI event was 11.[4,14]

2.3 RECOMMENDATIONS FOR CLINICAL PRACTICE

Current clinical practice in preventing GI events among at-risk patients requiring NSAIDs is to co-prescribe a gastroprotective agent. The Canadian Optimal Medication Prescribing & Utilization Service (COMPUS) recommends co-prescribing either standard dose (e.g. omeprazole 20 mg once daily) Proton Pump Inhibitors (PPI), double dose (e.g. ranitidine 150mg twice daily) H2-Receptor Antagonists (H2RA), and Misoprostol (200μg, qid) for prevention of NSAID-induced ulcers in high risk patients.[11,36] A proton pump inhibitor (PPI) is also recommended for patients at increased GI risk that require NSAID therapy by the The third Canadian Consensus Conference group on prescribing NSAIDs.[23]

2.4 OVERVIEW OF THERAPEUTIC OPTIONS

2.4.1 Proton Pump Inhibitors

PPIs (Appendix B) act by irreversibly blocking the proton pump of the parietal cell; the proton pump is the terminal stage of gastric acid secretion, making it the ideal target for inhibiting acid secretion.[37] PPIs are efficacious in reducing (OR, 0.23; 95% CI, 0.18-0.31) NSAID induced gastroduodenal endoscopic ulcers.[8] PPIs are also efficacious in reducing dyspeptic symptoms (OR, 0.43; 95% CI, 0.24-0.77) in patients taking NSAIDs.[8] It is generally accepted that endoscopic results will translate into a reduction in clinical ulcer complications, despite no randomized clinical outcome study to prove this.[38]

Rodriguez and colleagues [39] found that users of omeprazole had a reduced risk of upper GI complications (RR, 0.6; 95% CI, 0.4 to 1.0) after adjusting for several risk factors including age, sex, ulcer history, use of steroids, anticoagulants, NSAIDs, and ASA use. Similarly, Lanas and colleagues[40] found that concomitant use of PPI with an NSAID reduced the risk (RR, 0.3; 95% CI, 0.3 to 0.4) of upper GI complications.

PPIs are considered by many physicians the therapy of choice in terms of efficacy, few side effects, and ease of use (once daily dose which enhances patient compliance), albeit an increased cost [17,19,41] In a recent survey of physicians from across Canada, 67.3% stated that they would prescribe a PPI for prevention of NSAID induced ulcer complications.[19]

PPI prescriptions dispensed by Canadian retail pharmacies increased from 10.8 million in 2003 to 12.4 million prescriptions in 2004.[11] This has resulted in a corresponding increase in costs; per capita in expenditures on gastrointestinal drugs[†] in Canadian retail pharmacies increased from $24 in 1998 to $45 in 2004. [1]

2.4.2 H2-Receptor Antagonists

H_2 receptor antagonists, reduce acid secretion by binding to H_2 receptors on parietal cells and blocking the action of histamine. Standard dose H_2 receptor antagonists (i.e. Ranitidine 150mg bid) are efficacious in reducing endoscopic duodenal ulcers (OR, 0.36; 95% CI, 0.18-0.74), but not endoscopic gastric ulcers (OR, 0.73 ; 95% CI, 0.50-1.08) in patients taking NSAIDs.[8] Evidence surrounding standard dose H2 receptors antagonists ability to reduce gastrointestinal symptoms, such as dyspepsia is weak[8,9]; no statistically significant reductions in dyspepsia (OR, 0.59; 95% CI, 0.29-1.19) and drop-outs due to gastrointestinal symptoms (OR, 0.86 ; 95% CI,0.58, 1.28) were observed in patients taking H2 receptor antagonists, relative to placebo.[8] Double dose H2 receptors antagonists (i.e. Ranitidine 300mg bid) are efficacious in reducing gastroduodenal ulcers (OR, 0.41; 95% CI, 0.26-0.63) in patients taking NSAIDs. [8]

While evidence from endoscopic outcome trials exist, no RCTs have been conducted to examine whether H2-receptor antagonists reduce clinical ulcer complications.[8] Furthermore, evidence of the effectiveness of H2RAs in preventing GI complications among NSAID users from epidemiological studies is poor. Rodriguez et al[39] found that users of H2RAs, omeprazole, and misoprostol, each in combination with NSAID therapy, had relative risks of upper GI complications of 1.4 (95% CI, 1.2 to 1.8), 0.6 (95% CI=,

[†] The majority of expenditure in this treatment cataegory is for PPIs (80%) and H2RAs (20%)

0.4 to 1.0), and 0.6 (95% CI, 0.4 to 1.0) respectively, after adjusting for several risk factors including age, sex, ulcer history, use of steroids, anticoagulants, type of NSAIDs, and ASA use. Similarly, patients who were taking NSAIDs plus H2-RAs had an increased risk[‡] of clinically significant GI events (RR, 1.31; 95% CI, 1.04 to 1.65) in a recent case-control study, while patients on celecoxib, paracetamol or concomitant use of PPI with an NSAID had a decreased risk (RR, 0.3; 95% CI, 0.3 to 0.4).[40] The lack of effectiveness of H2RA to prevent GI complications[42] coincides with results from a sub-group of adult patients (age≥52y) from the VIGOR trial[14] but differ from results in an earlier study by Lanas et al[42], where the adjusted odds ratio for upper gastrointestinal bleeding was 0.6 (95% CI, 0.4 to 0.8) and 0.6 (95% CI, 0.6 to 0.9) for H2RA and PPI respectively, in adult patients from the general population receiving NSAIDs.

Despite the lack of strong evidence for prevention of nsNSAID induced GI complications, H2RAs are still widely prescribed agents in Canada for this indication. A recent physician survey in Canada found that 19.1% of physicians prescribe H2RAs as the gastroprotective agent of choice for prevention of NSAID induced ulcer complications.[19] Apo-Ranitidine® remains one of the top 100 prescription drugs dispensed across Canada; over one million prescriptions were filled for Apo-Ranitidine across Canada in 2005.[3] In some provinces, the number of prescriptions filled for H2RA is much higher.[1] In Nova Scotia Senior Pharmacare Program (NSSPP) from 1998-2002, 92.63% of beneficiaries co-prescribed a gastroprotective agent, received a H2RA while only 6% and ~1% were co-prescribed PPI and misoprostol, respectively.[43]

2.4.3 Misoprostol

Misoprostol, a synthethic prostaglandin analogue, stimulates mucus secretion in the upper GI tract; it has modest inhibitory effects on gastric acid secretion. [37] Misoprostol is the only gastroprotective agent that has been shown to reduce clinical ulcer complications in a large prospective randomized clinical outcome trial.[7] Silverstein et al found that serious upper GI complications were reduced by 40% (OR, 0.60; 95% CI, 0.34-0.98) among

[‡] H2RAs do not cause clinically significant GI events; patients prescribed H2RAs are at higher baseline risk and GI benefits conferred by H2RAs are not offsetting increased GI risk

patients co-prescribed misoprostol. [7] Similarly, Rostom et al (2002) found that misoprostol (200 μg qid) reduces both gastric (OR, 0.20 ; 95% CI, 0.15-0.27) and duodenal ulcers (OR, 0.28; 95% CI, 0.15-0.52). Lower doses of misoprostol (i.e. 200μg bid) are less efficacious in reducing gastric (OR, 0.35; 95% CI, 0.26-0.46) and duodenal ulcers (OR, 0.54; 95% CI, 0.37-0.79), relative to nsNSAID alone. [8]

Although misoprostol reduces clinical ulcer complications, it also causes diarrhea, dyspepsia, nausea, vomiting, and abdominal pain.[7,8] Accordingly, Rostom and colleagues found a large increase in drop-outs in the misoprsotol arm, relative to NSAID, in a meta-analysis of endoscopic outcome trials. Similarly, significant drop-outs were also observed among all patients (placebo and treatment arm) in the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial.[7] Large drop-out rates in the placebo arm may be attributable to multiple (4x) daily dosing regimens. Claxton et al found that compliance of oral medications (in general) decreased to 50% in patients taking 4 times daily dosing regimens. [44]

Misoprostol is seldom recommended in clinical practice[37], despite strong evidence of efficacy from a large clinical outcomes trial.[7] Only 11.7% of Canadian physicians in a recent survey stated that Misoprostol was their therapy of choice in preventing NSAID induced ulcer complications.[19] In Australian retail pharmacies, prescriptions of misoprostol decreased by 84% from 1992 to 1998, while prescriptions for H2RAs and PPIs increased by 52% and 1228%, respectively.[45] Less than 1% of patients co-prescribed a GPA in the NSSPP, were given misoprostol.[43]

2.4.4 Selective COX-2 Inhibitors

Although COX-2 inhibitors are commonly prescribed in clinical practice, they were not included in the present evaluation. Selective COX-2 inhibitors are a form of NSAID that specifically inhibit the COX-2 enzyme; the primary enzyme responsible for pain and inflammation. [24-26] Accordingly, selective COX-2 Inhibitors decrease the risk of GI complications, relative to nsNSAIDs. However, COX-2 inhibitors increase the risk of gastrointestinal complications relative to placebo, and therefore, are not gastroprotective

agents. Furthermore, there have been concerns that selective COX-2 inhibitors may increase the risk of myocardial infacrtion, relative to nsNSAIDs. However, recent reports suggest that this may not be the case for celecoxib at doses less than 400mg per day.[121]

2.5 REVIEW OF ECONOMIC EVIDENCE

Economic analysis is increasingly being used to inform health policy decisions. To date, several economic evaluations have been conducted to determine the cost-effectiveness of alternative gastroprotective strategies in preventing NSAID induced GI toxicity. Results from economic evaluations identified are presented in chronological order. Costs are converted to Canadian currency using Bank of Canada annual exchange rates.

Maetzel et al (1998)[46]developed a decision analytical model to examine the cost-effectiveness of misoprostol compared to no prophylaxis in Canada using clinical outcomes data from the Misoprostol Outcome Safety Assessment Trial (MUCOSA).[7] In this analysis, Maetzel and colleagues[46] found that prescribing misoprostol to all patients with Rheumatoid arthritis (RA) who are age $\geq$ 52 years of age would cost C $94,766 for each additional GI event averted. However, for patients with previous history of a peptic ulcer, the additional cost per GI event avoided would be C $14,943 and for patients with a history of peptic ulcer disease and age $\geq$ 75, the additional cost per GI event avoided is C $4,101.

Zabinski et al[47] developed a model to estimate downstream resource use associated with alternative gastrointestinal strategies in the management of adult patients with osteoarthritis and rheumatoid arthritis in Canada. The model demonstrated that an NSAID-alone strategy was associated with the lowest cost (C$262 per-patient per 6 months), followed by celecoxib (C$ 273 per-patient per 6 months). NSAID plus PPI was assicaited with the highest costs ($C 731 per patient per 6 months). They concluded that an NSAID alone regimen is associated with the lowest cost but celecoxib could lead to a reduction of GI complications at an increased cost that would not impose an excessive impact on Canadian provincial healthcare budgets.

Maetzel and colleagues (2003)[48] conducted a cost-effectiveness analysis of rofecoxib and celecoxib in adult patients with osteoarthritis or rheumatoid arthritis in Canada, based on a 5-year Markov model. This model included both upper GI events and myocardial infarctions in the analysis. Maetzel et al[48] found that rofecoxib was associated with an incremental cost of $C 271,188 per QALY gained, relative to naproxen in average risk patients. They also found that celecoxib was more expensive and less effective (dominated) by diclofenac in average risk patients. However, both rofecoxib and celecoxib became more economically attractive with advanced age. Assuming a threshold of $50,000 per QALY, they concluded that rofecoxib and celecoxib are cost-effective in patients over 76 and 81, respectively, without additional risk factors.

In 2004, Moore et al[49] developed an economic evaluation, based on a 3rd party payer-perspective in the UK, comparing etoricoxib to alternative gastroprotective strategies in adult patients with osteoarthritis or rheumatoid arthritis. They found that etoricoxib was associated with and incremental cost of £19 766 (C$46,608) per QALY gained, relative to non-selective NSAID alone. The ICUR is less than £30,000 (C$70,740) per Quality Adjusted Life Year (QALY), which is within the National Institute of Clinical Excellence (NICE) stated range of acceptable cost-effectiveness of £ 25,000- £ 35,000 (C$58,950-C$82,530).[50]

Spiegel et al[51] developed a cost-effectiveness decision analysis in the US among adult patients of varying risk groups receiving NSAIDs. This analysis incorporated both cardiovascular and serious GI complications into their model that compared non-selective NSAIDs to non-selective NSAID + PPI and selective COX-2 inhibitors. Spiegel et al [51] found that NSAID plus PPI strategy was associated with an incremental cost of $309,666 (C$486,186) per QALY gained, relative to NSAID alone strategy. However, ICURs became more economically attractive with the presence of risk factors. They concluded that the NSAID alone regimen is cost-effective in patients at low risk for an adverse event but NSAIDs plus PPI is cost-effective in patients at high risk for GI or cardiovascular events.

Elliot et al[52] conducted a cost-effectiveness analysis among the general adult population (age≥18y) in the UK. This analysis compared six gastroprotective strategies including: no prophylaxis, PPIs, misoprostol, H2RA, COX-2 preferential, and selective COX-2 inhibitors. A systematic review of outcomes was used to generate adverse event rates for this decision analytical model[9] Elliot and colleagues found that a treatment strategy of NSAID and H2RA was less costly and more effective than NSAID alone. Furthermore, coxibs were associated with an incremental cost of £670,000 (C$1,532,960) per QALY, relative to NSAID and H2RA, while NSAID plus PPI was associated with an incremental cost of £26,000 (C$59,488) per QALY, relative to coxib. Based on these results, Elliot et al[52] concluded that " there may be a case for prescribing all H2RAs in all patients requiring NSAIDs".

Leontiadis and colleagues[53] developed a Markov model to examine the cost-effectiveness of PPIs, relative to alternative strategies in prevention of GI ulcers among patients taking NSAIDs in the UK. The following six treatment strategies were included in their analysis: do nothing, PPI, misoprostol, *Helicobacter pylori* eradication, *Helicobacter pylori* eradication followed by a PPI, and *Helicobacter pylori* eradication followed by misoprostol. They concluded that at willingness to pay threshold of £100 (C$215) per QALY, the most cost-effective strategy is *Helicobacter pylori* eradication, and at a threshold of £1000 (C$ 2,158) per QALY, *Helicobacter pylori* eradication followed by misoprostol, if tolerated, was the most cost effective strategy.

CHAPTER 3 ECONOMIC EVALUATION IN HEALTHCARE

Economic evaluation is increasingly used in health-care, as escalating costs and rapid technological advances have prompted a search for greater efficiency.[54,55] Healthcare agencies and regulating bodies across the globe have embraced economic evaluation as a technique to support resource allocation decisions.[54,55]

In the following chapter, I review the theoretical foundation for economic evaluation in healthcare and discuss current applications and short-comings. I begin by discussing how cost-effectiveness analysis (CEA) has emerged, and the theoretical underpinnings of CEA. Subsequently, we describe current applications of economic evaluation in healthcare and inherent limitations with these approaches. I conclude the chapter by introducing emerging approaches that are more consistent with the concept of opportunity cost, or the benefits associated with foregone opportunities.[54-56]

3.1 FOUNDATIONS OF ECONOMIC EVALUATION IN HEALTH CARE

Economics is concerned with how society allocates scarce resources to satisfy the greatest number of needs and wants.[56] Accordingly, health economics is a branch of economics concerned with issues related to scarcity in the allocation of health and healthcare.[54-56]

The theoretical foundation of health economics rests on welfare economics, a branch of economics that is concerned with maximizing social welfare.[54] Neoclassical welfare economics is built on four key tenets[57]:

i. Utility maximization- rationale individuals maximize their welfare or utility
ii. Consumer sovereignty- individuals are the best judges of their individual welfare or utility
iii. Consequentialism- any action or choice must be judged in terms of outcomes rather than the processes or intentions that led to the outcomes.
iv. Welfarism- "goodness" of resource allocation is judged solely on welfare or utility levels attained by individuals in that situation.

Under a welfare economics framework, policy changes can only be deemed an unambiguous improvement when at least one person feels better off and all other persons feel no worse off, which is referred to in economics as the Pareto criterion.[57,58] This criterion is very restrictive and few situations meet the criteria. Consequently, an alternative form, the potential Pareto criterion, was developed to widen its applicability. A Potential Pareto improvement, requires that the gains related to some policy change to outweigh the losses caused by it.[57,58]

Under this criterion, it assumed that individual utility can be compared in monetary terms and the aggregate welfare of a society is a summation of individual utilities. [54-56] Consequently, welfare economics is fundamentally utilitarian in philosophy, as decisions are made on the basis of achieving the greatest welfare for the greatest number, without making intrinsic value judgement about the decision itself.[57,58]

Cost-benefit analysis (CBA), a technique where both costs and benefits are measured in commensurate terms (usually monetary units), has emerged from neoclassical welfare economics.[54,56-58] CBA represents one of the earliest approaches used to evaluate programs funded by the public sector. [54,56] Under a neoclassical welfare economics framework, a CBA is used in making resource allocation decisions.[54,56,59,60] CBA takes a societal perspective and attempts to include all relevant costs (financial and non-financial) and benefits borne by the patients. [54,55,57,58] Interventions with the highest net benefit (benefit expressed in monetary terms minus cost) are adopted in descending order until budget is exhausted [54,56,59,60] The main advantage of CBA is that it allows comparison of interventions across different fields of social policy (e.g., education, criminal justice, health, housing, poverty reduction). [54,55]

Despite the strong theoretical foundation and wide applicability, the use of CBA in the healthcare sector has been limited.[54,55] The subjective nature in the judgement of personal welfare makes aggregate level comparison of social policies difficult. [54] Furthermore, some suggest that the limited use of CBA is attributable to ethical concerns in placing monetary values on health or life-years saved[54,55] while others have expressed concern

surrounding the methods for which to convert benefits to monetary values, as willingness to pay methodology, gives greater weight to preferences of the wealthy.[54,55] In light of these issues, more practical approaches have been developed, specifically, cost-effectiveness analysis (CEA).[54,55]

The widespread use of the more pragmatic CEA has challenged traditional welfare economic theory. Consequently, an alternative conceptual view- the extra-welfarist approach has emerged.[54,57-59] Extra-welfarist health economics "transcends traditional welfare"[59], as general utility has been replaced with health utility (e.g., quality adjusted-life years (QALYs)) as the primary outcome measure. Furthermore, extra-welfarism incorporates the concept of need, as opposed to demand, as an outcome of concern, as some consider health to be a merit good. The incorporation of ethical criteria, like need, lie outside the traditional Paretian welfare economics framework.[57,58]

Thus, rather than basing recommendations on neo-classical welfare economic theory, adherents of the extra-welfarist approach base recommendations on more relaxed and practical, but not well formulated "rules of thumb". [58] Under this framework, the use of CEA, where the narrower concept of health-related QALYs, as opposed to welfare is considered, in combination with costs. [57-59,61].

3.2 COST-EFFECTIVENESS ANALYSIS

CEA has emerged as the most popular technique in evaluation of interventions in the healthcare sector. [54,55] A CEA is a systematic comparison of two or more treatment alternatives, in terms of costs and consequences of each intervention.[54,55] A distinguishing feature of CEA is that consequences of interventions are measured in natural units of the clinical objective (i.e., life-years gained, GI bleed averted, etc.) Results from CEA, comparing intervention A and B in terms of life-years gained, are expressed in terms of ratio of incremental costs and life-years gained of B, relative to A. [54,55] That is,

$$ICER = \frac{C_2 - C_1}{LY_2 - LY_1}$$

A special case of CEA, termed a cost-utility analysis (CUA), is becoming more increasingly used.[62] A CUA is a systematic comparison of treatment alternatives, in terms of cost and consequences, where consequences are measured in units of utility or preference, often a Quality-adjusted life year (QALY). [54,55] Results from CUA, comparing interventions C and D, are expressed in terms of ratio of incremental costs and QALYs gained of D, relative to a C. That is,

$$ICER = \frac{C_2 - C_1}{QALY_2 - QALY_1}.$$

A CUA enables standardization and comparability of economic results across disease states. [54,55]

In recent years, a net-benefits framework has emerged, as an alternative method of estimating cost-effectiveness results. The incremental net benefit (INB) of an intervention is a transformation of ICER calculation:

$$INB_i = \lambda * \Delta E_i - \Delta C_i$$

where E_i represents effectiveness (e.g., QALYs); C represents costs, and λ represents the monetary value per unit of effectiveness.[63-65] The main advantages of using a NB approach is that an intervention is considered more cost-effective, relative to an alternative intervention, if the INB>0, at a specified decision maker's cost-effectiveness threshold.[63,66,67] Second, when describing uncertainty in CE calculations with small mean differences in effectiveness, NB are not as unstable, as ICERs can be, as INB is a linear relationship rather than a ratio.[63] Third, the NB framework is the basis for acceptability curves and value of information analysis, which are becoming more widely used in healthcare research.[63]

3.3 THEORETICAL FOUNDATION OF COST-EFFECTIVENESS ANALYSIS

The general aim of CEA is to aid decision making in healthcare with the goal of maximizing health benefits within a finite budget from the decision makers specified

perspective. [54,55] Traditionally, the costs and effectiveness of a new intervention, are compared with that of the status quo, to determine whether the new intervention is less costly and at least as effective as the status quo (more technically efficient), or more costly and more effective, in which a decision has to be made as to whether the extra cost is worth the extra gains received (allocative efficiency).[68]

CEA is routinely applied in healthcare decisions, however, often without regard to its origin and underlying assumptions.[54] Lord and colleagues[61] recently outlined the basic methodology and underlying assumptions in the conventional approach to CEA. In the following section, we provide a brief overview of findings by Lord and colleagues[61], which is based upon seminal work by Johannesson and Weinstein. [69]

Table 1 presents a healthcare decision problem, adopted from Lord and colleagues[61], where a decision maker must choose between 6 treatment alternatives (P_1, P_2, P_3, P_4, P_5, P_6) in the management of single group of patients. Costs and QALYs associated with each treatment alternative are provided in Table 1, and ordered by ascending cost (Column 3). Incremental costs and effects (QALYs gained), along with the ICER for each strategy, with respect to previous non-dominated strategies are presented. (Column 7-9).

Table 1 Costs and effects of health care programs for one patient group, adapted from *Lord et al*[61]

Patient group (number of people)	Programs	Mean per patient		Total for group		Incremental Analysis		
		Cost ($)	QALYs	Cost ($)	QALYs	Cost ($)	QALYs	ICER* ($ per QALY)
P-type (n=10,000)	P1	2000	0.0500	20	500	Baseline		
	P2	3200	0.0600	32	600	Dominated (simple)		
	P3	2400	0.0700	24	700	4	200	20,000
	P4	4200	0.1060	42	1060	18	360	50,000
	P5	4800	0.1070	48	1070			
	P6	5000	0.1100	50	1100	8	40	200,000

QALY=quality adjusted life year; ICER= incremental cost effectiveness ratio
*Defined with respect to previous non-dominated option

Data from Table 1 is graphically illustrated in Figure 1. A rational decision maker, one that wishes to maximize health gains subject to a finite budget, will select from alternatives that lie along the "cost-effectiveness frontier". The cost-effectiveness frontier is the line that connects feasible and non-dominated treatment alternatives (P_1, P_3, P_4, P_5). In Figure 1, P_2 and P_5 do not lie on the cost-effectiveness frontier, as these options are eliminated by simple and extended dominance, respectively. P_2 is eliminated by simple dominance, as P_2 lies to the northwest of P_3. Thus, P_2 is more expensive and less effective (dominated), relative to P_3. In Figure 1, P_5 also does not lie along the cost-effectiveness frontier. This strategy is eliminated by extended dominance, as P_5 lies to the northwest of the line joining P_4 and P_6. Consequently, treating a group of patients with a combination P_4 and P_6 (which both lie on cost-effectiveness frontier) will yield a higher overall health gain than treating all patients with P_5.

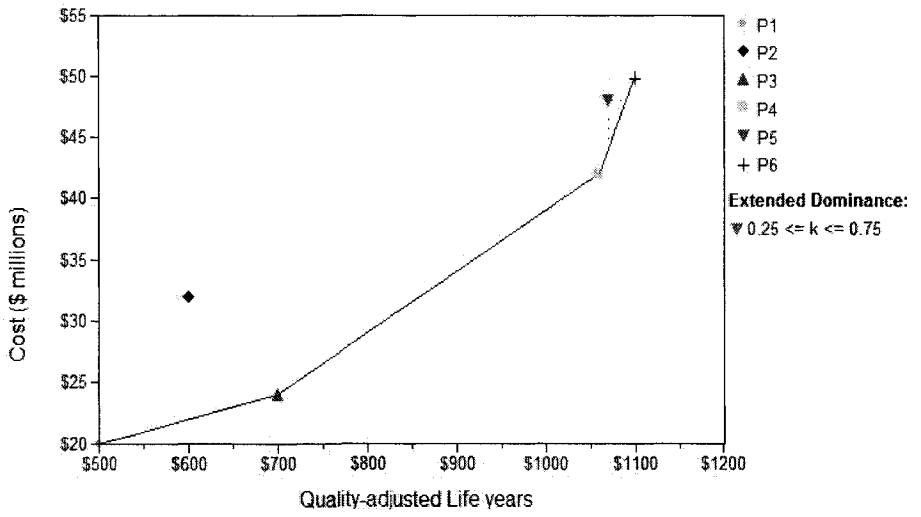

Figure 1 Cost and effects of programmes for P-type patient group[61]

The theoretical foundation for the aforementioned approach is based upon a seminal paper by Johannesson and Weinstein (JW).[69] In this publication, JW highlight two key assumptions. The first assumption that all programs are divisible, while the second assumption is that all programs exhibit constant returns to scale. [69]

Divisibility means that programs can be partially implemented, with different patients receiving different treatment options (i.e., 5000 patients receiving P_1 and 5000 receive

P_3). Constant returns to scale means that costs and effects are proportional to the scale of implementation.[69] Thus, treating half of patients with P3 costs ½ C3 ($12 million) and yields ½ E3 units of health (350 QALYs). However, in the real world, these assumptions may be violated. For instance, some programs have large fixed costs and must be implemented in their entirety. Furthermore, the assumption of constant or linear returns to scale, may not be appropriate in many situations in the real world. For instance, there are clinical situations where there is diminishing returns to scale. For instance, a physician may prioritize treatment of patients by those who receive the greatest net-benefit. If the cost of the treatment is constant, this may result in a non-linear expansion path, with diminishing returns to scale for each successive patient treated. [61,69]

If the following assumptions are violated in the real world, they may have effects on the opportunity cost of resources at the margin, and in turn effect the cost-effectiveness threshold. [61,69]

3.4 COMPREHENSIVE RESOURCE ALLOCATION

In the previous section, we described how decision makers systematically compare treatment alternatives in the management of a single group of patients. However, in the real world, health-care decision makers must allocate scarce resources between, as well as within, multiple patient groups.

Table 2 expands the decision problem presented in Table 1, to reflect greater complexity that is more representative of a decision makers' reality. The decision problem presented is this section is derived from Lord and colleagues.[61] Costs and treatment effects across treatment alternatives for each patients group are presented, as described in section 2.3.[61] The following sections describe theoretical approaches used to allocate scarce resources to maximize health benefits, between multiple patient groups.

Table 2 Costs and effects of health care programs for four patient groups, obtained from *Lord et al*[61]

Patient group (number of people)	Programs*	Mean per patient		Total for group		Incremental Analysis		
		Cost ($)	QALYs	Cost ($)	QALYs	Cost ($)	QALYs	ICER† ($ per QALY)
P-type (n=10,000)	P1	2,000	0.0500	20	500	Baseline		
	P2	3,200	0.0600	32	600	Dominated (simple)		
	P3	2,400	0.0700	24	700	4	200	20,000
	P4	4,200	0.1060	42	1,060	18	360	50,000
	P5	4,800	0.1070	48	1,070			
	P6	5,000	0.1100	50	1,100	8	40	200,000
Q-type (n=1,000)	Q1	10,000	5.0000	10	5,000	Baseline		
	Q2	26,000	5.3120	26	5,312	16	312	51,282
	Q3	41,000	5.3620	41	5,362	15	50	300,000
R-type (n=50,000)	R1	1,500	0.2000	75	10,000	Baseline		
	R2	1,600	0.2100	80	10,500	5	500	10,000
	R3	1,680	0.2115	84	10,578	4	76	52,632
S-type (n=100,000)	S1	100	0.0050	10	500	Baseline		
	S2	180	0.0075	18	750	8	250	32,000
	S3	200	0.0077	20	770	4	200	100,000

QALY=quality adjusted life year; ICER= incremental cost effectiveness ratio
* Programs are mutually exclusive for patient group
† Defined with respect to previous non-dominated option

3.4.1 League Table Approach

Theoretically, if costs and effects of all potential programs are available, a cost-effectiveness league table approach can be used to allocate scarce healthcare resources.[55,61] Table 3 presents a league table for programs provided in Table 2. In the league table, combinations of mutually exclusive non-dominated programs are presented, ranked in order of increasing ICER of the marginal program. Rational decision makers, will be "QALY maximizing".[61] Accordingly, they will move down the list until their budget is exhausted, and select the respective combination of programs.

Table 3 Cost effectiveness league table, from *Lord et al* [61]

Set of programs* provided	Marginal program	Incremental Analysis†			Total for set of programs	
		Cost ($ million)	QALYs	ICER ($ per QALY)	Cost ($ million)	QALYs
P1,Q1,R1,S1	-	-	-	-	115	16,000
P1,Q1,R2,S1	R2	5	500	10,000	120	16,500
P3,Q1,R2,S1	P3	4	200	20,000	124	16,700
P3,Q1,R2,S2	S2	8	250	32,000	132	16,950
P4,Q1,R2,S2	P4	18	360	50,000	150	16,950
P4,Q2,R2,S2	Q2	16	312	51,282	166	17,310
P4,Q2,R3,S2	R3	4	76	52,632	170	17,622
P4,Q2,R2,S3	S3	2	20	100,000	172	17,718
P6,Q2,R2,S3	P6	8	40	200,000	180	17,758
P6,Q3,R2,S3	Q3	15	50	300,000	195	17,808

QALY=quality adjusted life year; ICER= incremental cost effectiveness ratio
* Excludes any programs that are dominated
† Defined with respect to programs in previous row

For instance, a QALY maximizing decision maker with a budget of $150 million would implement the following set of programmes: P_4, Q_1, R_2, and S_2. However, a decision maker with a larger budget, would be able to descend further down the table. For instance, a region with a budget of $180 million would implement P_6, Q_2, R_3, S_3.

A cost-effectiveness threshold, or λ, can be theoretically derived using this league table approach. However, as discussed previously, λ is bounded by assumptions of divisibility and constant returns to scale. The cost-effectiveness threshold, or λ, is the ICER for the marginal programme, i.e., the next programme upon which any additional money would be spent. For instance, if a decision maker has a budget of $150 million, Q_2 would be the marginal programme, upon which any additional money would be spent. Consequently, the ICER would be representative of the marginal ICER for Q_2, or $51,282 per QALY gained (Table 2).

3.4.2 Mathematical Programming

Alternatively, the league table approach can be represented as a mathematical linear program, with an automated algorithm used to solve the decision problem described in section 2.4.1.[61,70-72] Moreover, advanced mathematical programming techniques can be

used to accommodate resource allocation decisions, when JW assumptions are thought to be unrealistic. [61,70-72] Integer programming can be used to accommodate indivisible programs[73]; non-linear programming can allow non-constant returns to scale[71]; while mixed integer programming can accommodate both.[74]

3.5 From Theory to Practice: The Threshold Approach

3.5.1 The Acceptable Threshold Approach

In the real world, information on costs and benefits of all existing and future programs within a system are not readily available. Hence, comprehensive resource allocation decision allocation, using league table and mathematical programming techniques are not practical. Consequently, alternative approaches have emerged to assist policy makers in allocation of scarce healthcare resources. Most commonly, an incremental cost-utility ratio (ICUR) is calculated, where:

$$ICER = \frac{C_2 - C_1}{QALY_2 - QALY_1}$$

The ICUR is subsequently compared to λ, which represents an estimate of how much a decision maker is willing to pay for an additional year in perfect health. If the ICUR$\leq\lambda$, a program may be considered "good value for money" and adopted under this decision rule. This is the approach that is currently adopted by most health technology assessment agencies throughout the world.[54,55]

3.5.2 What is the Value of λ?

Despite the central role of λ in methods and application of CEA, little attention has been given in determination of the value of λ.[75-77] As discussed previously, the theoretical value of λ is based on the ICER of the marginal programme beyond a fixed budget.[61] However, due to practical considerations, estimates of λ based on this approach are not readily available. In contrast, most estimates of λ that are widely cited in the literature are

based on expert opinion and past experience.[76-80] Consequently, this has resulted in a large variation in estimates of the value of λ. [76-80]

Ubel and colleagues[81] have traced the origin of the widely cited λ =US$50,000 back to a 1982 decision to cover renal dialysis for patients with chronic renal failure under the US Medicare programme.[81] The logic goes: as renal dialysis is a federal entitlement in the US, "interventions with similar or better cost-effectiveness should likewise be offered to everyone"[81]. Consequently, this λ value has propagated through the literature, resilient to inflation and generalizable, irrespective of currency.

In 1992, Laupacis and colleagues[78] published explicit, yet opinion-based, guidelines to assist policy makers in making reimbursement decisions. Laupacis and colleagues[78] state that evidence for adoption of a new technology is weak if λ exceeds C$100,000; moderate if λ is between C$20,000 and C$100,000, and strong if λ is less than C$20,000.[78] Consequently, these threshold values have been widely cited in the literature.

In 2000, Hirth et al[80] conducted a literature search to determine the value of λ, as implied using estimates from the value-of-life literature. Hirth et al[80] found tremendous variation in the value of λ, depending upon methods, study population and data source utilized. Estimates of λ ranged from a median of $24,777 using the human capital approach to $428,286 using job-risk studies. Revealed preference based studies and contingent valuation studies yielded median values of $93,402 and $161,305 for a QALY, respectively. [80]

The value of λ has also been estimated by exploring past reimbursement recommendations from the National Institute of Clinical Excellence (NICE).[50] Rawlins and colleagues[50] examined the relationship between likelihood of a technology being considered cost-ineffective against the cost-effectiveness ratio. Based on this analysis, Rawlins and colleagues concluded that NICE is unlikely to reject a technology with a ratio in the range of £5000 to £15,000. However, NICE would need special reasons to

accept technologies with ratios over £25,000 to £35,000. Consequently, others have concluded that NICE has an implicit threshold of λ = £25,000 to £35,000.[81,82] This threshold coincides with an implicit threshold in the Phamaceautical Benefits Scheme in Australia, where the highest cost per QALY at which a drug was recommended was $52,400 beteen 1994 and 2003.[83]

More recently, some reports have suggested that λ be a function of GDP, as GDP varies across time and space. The Commission of macroeconomics and Health from the World Health Organization suggest that an intervention is highly cost-effective if the incremental cost per disability-adjusted life year (DALY) is less than the GDP per capita; an intervention is cost-effective between one and three time GDP per capita; an intervention is not cost-effective if greater than three times the GDP.[84] Similarly, Williams argues that GDP could be utilized to determine λ. However, Williams suggests that WHO estimates are too high, and suggests that λ should not exceed the GDP per capita, which provides all the needs for the average citizen (i.e., food, shelter, transport, and education).[85]

3.6 INCREMENTALIST REALLOCATION

Several authors have expressed concern regarding the origin of widely cited "acceptable cost-effectiveness thresholds".[75-77] Sendi, Birch and Gafni argue that widely cited λ values are arbitrary, and have no empirical or theoretical basis. [75-77] They suggest that a single λ value for determining the efficiency of interventions across different settings and over time is unlikely to exist, as λ is based upon the ICER of the marginal program within a fixed budget. Furthermore, they suggest that λ is dynamic and stochastic in nature, as the range of programs within a budget are ever-changing and the cost and effects of all programs are subject to uncertainty. [75-77]

Birch and Gafni conclude that there is no evidence to suggest that the application of the ICER threshold approach has resulted in an efficient use of limited resources. [75-77] In fact, they suggest that adoption of an ICER approach, based on an ill-calibrated generous

λ value (too high), may have led to decisions that resulted in increased healthcare expenditures. [75-77] Moreover, they express concern over introducing thresholds substantially in excess of currently cited thresholds[81], as this is likely to further fuel cost escalation generated by the use of a threshold as a decision rule. [75-77]

Sendi, Gafni and Birch acknowledge[75-77] that a comprehensive approach, requiring information on the incremental cost and effects of all current and potential interventions, is not plausible in the real world. Consequently, they recommend a less data hungry approach, consistent with the concept of opportunity costs. Their approach, coined the "SBG decision rule"[61], requires that for program A to be implemented, a program B must be found where: $\Delta C(B) \geq \Delta C(A)$ and $\Delta E(B) < \Delta E(A)$. [75-77]

Consequently, the "SBG decision rule", in theory, facilitates unambiguous improvements of efficiency in resource use.[75,76,86] However, the "SBG" rule provides no guidance on allocation of resources, if a budget were to increase.[76,77] Recently, a Bayesian form of the "SBG rule" has been developed, where parameters are ascribed distributions, to reflect uncertainty associated with their value.[86]

Program Budgeting and Marginal Analysis (PBMA) has also been presented as a process that helps decision makers maximize the impact of healthcare resources on health needs of a local population.[68,87,88] PBMA incorporates many features of the SBG approach, as this approach considers opportunity cost, or the benefits associated with foregone opportunities. For instance, if a budget is fixed within a PBMA framework, "opportunity costs is accounted for by recognizing that the items for service growth can only be funded if resources are taken from elsewhere." [68,87,88]The PBMA framework has been used in over 60 healthcare organizations around the globe. [68,87,88]

3.7 CHAPTER SUMMARY

The theoretical foundation of health economics rests on welfare economics, a branch of economics where a policy is judged based on its impact on total welfare of individuals. A

welfarist approach requires the use of a CBA to evaluate programs across different fields of social policy. However, due to practical and ethical considerations, more flexible approaches have emerged. The extra-welfarist approach transcends traditional welfare economics, as it is not concerned with overall welfare of people, but with a narrower concept of health-related QALYs. [59,61] Under an extra-welfarist approach, a CEA may be used to evaluate policies or interventions in the healthcare sector.

The conventional CUA approach, based on work by Johannesson and Weinstein[69], is bounded by assumptions of divisibility and constant returns to scale. Furthermore, it requires information on costs and benefits (QALYs) of all available programs.[61,69] Consequently, comprehensive resource allocation, using the league table approach or mathematical programming, may not be practical in the real world. Accordingly, less data hungry approaches have emerged.

The most common approach, the acceptable threshold, uses a decision rule where a treatment strategy may be adopted if it is less than an "acceptable cost-effectiveness threshold."[54,55] This is the method used, implicitly or explicitly, by most health technology assessment agencies around the world. [54,55] In theory, the ICUR approach will result in an efficient use of limited resources, if λ is well-calibrated and programs are divisible with constant returns to scale.[61]

However, there are concerns that widely cited λ values are not well-calibrated,[76,77,86,89] which may in-turn increase expenditures (λ set too high) or decrease health (λ set too low). Commonly cited "accepted cost-effectiveness thresholds" have been described as arbitrary, with no empirical or theoretical basis. [76,77,86,89] Furthermore, it is argued that single λ value is unlikely to exist for determining the efficiency of interventions across different settings and over time, as λ is based upon the ICER of the marginal program within a fixed budget. [76,77,86,89] Thus, λ is dynamic and stochastic in nature, as the range of programs within a budget is constantly changing, and the cost and effects of all programs are subject to uncertainty. [76,77,86,89] Consequently, we cannot be certain that decision rules based on the ICUR approach result in efficient resource allocation. [76,77,86,89]

Alternative approaches have been proposed[76,77,86,87,89], more consistent with the concept of opportunity cost. The "SBG rule" [76,77,86,87,89], and PBMA[87], if widely adopted, should facilitate improvements of efficiency in healthcare resource use.

CHAPTER 4 RESEARCH QUESTIONS

In the previous chapter, we discussed the theoretical foundations for economic evaluation in healthcare. Despite its underlying limiations, the use of decision modeling with economic evaluation in healthcare is widespread.[54,55,67,90]Accordingly, several economic evaluations have examined the cost-effectiveness of gastroprotective agents in preventing NSAID induced GI complications. However, previous analyses have focused on the general population.[10,47,52] Furthermore, acquisition costs of PPIs in Canada have dropped considerably in recent years. Thus, the main objecticve of this paper is to:

1.) examine the cost-effectiveness of PPIs relative to alternative gastroprotective therapies among elderly patients (age≥65y) requiring non-selective NSAID therapy in Canada
2.) determine how the cost-effectiveness of PPIs, relative to alternative gastroprotective therapies, varies with age and presence of additional risk factors

CHAPTER 5 STUDY DESIGN AND METHODS

5.1 MODEL STRUCTURE

A model was developed to simulate progression of GI complications among a cohort of elderly patients (age≥65y) taking nsNSAIDs and alternative gastroprotective agents. The model (Figure 2) employs a decision tree approach to forecast GI complications over a 1-year time horizon. Base-case simulations and subsequent sensitivity analyses (deterministic and probabilistic) were calculated using TreeAge ProSuite 2005 (TreeAge Software Inc., Williamson, MA, USA).

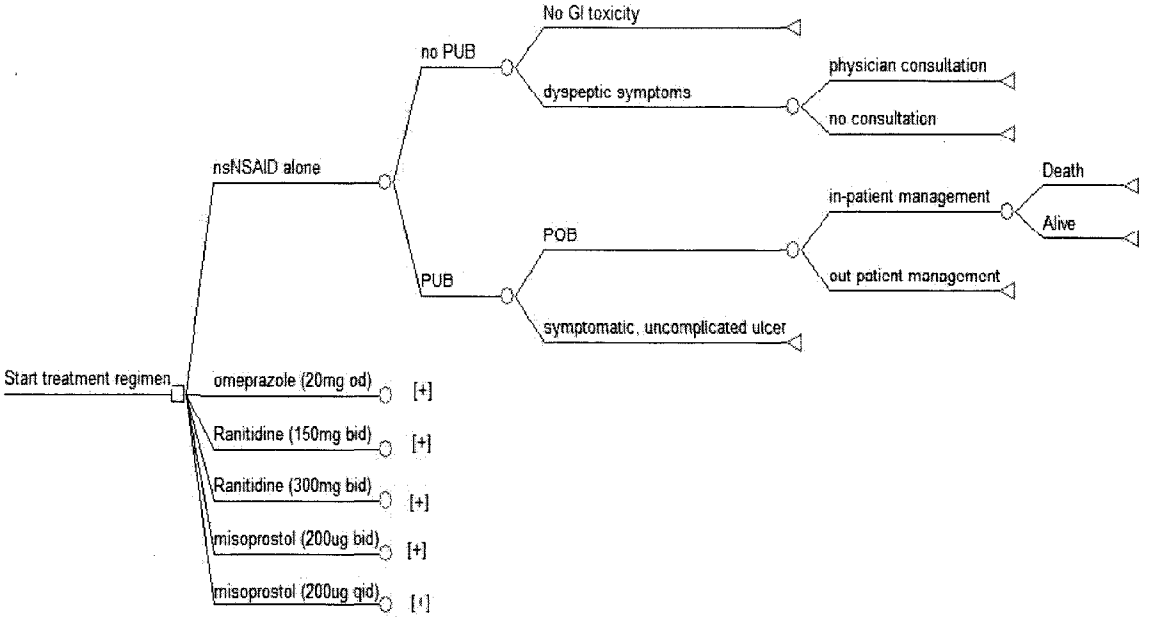

Figure 2 Decision analytical model used to examine the cost-utility of proton pump inhibitors (omeprazole 20mg od) compared with alterative gastroprotective agents for prevention of gastrointestinal complications in elderly.

bid= twice daily; od= once daily; GI= gastrointestinal; mg= milligram; POB= perforation, obstruction, bleed; PUB= perforation, obstruction, bleed, or symptomatic uncomplicated ulcer; qid=four times daily; µg=microgram

The models' architecture was reviewed by a gastroenterologist (SZV) to ensure that structure is reflective of Canadian clinical practice. The identify potential programming errors, the model was programmed separately using TreeAge ProSuite 2005 (TreeAge Software Inc., Williamstown, Mass) and Microsoft Excel® (Microsoft Corp., Redmond,

WA, USA). Inconsistencies were identified by the analyst (CC) and errors were corrected. To confirm the external validity of the model, event rates for GI bleeding and dyspepsia were compared with estimates from clinical outcome trials[4-7,12,16] and published Canadian epidemiological studies. [28,91]

5.2 EFFICACY OF TREATMENT COMPARATORS

Efficacy of treatment comparators in preventing gastrodoudenal endoscopic ulcers and dyspeptic symptoms were obtained from a meta-analysis.[8] Results from this meta-analysis were presented as odds ratios. As odds ratios are more difficult to handle in modeling [92-94], we repeated the meta-analysis using relative risk (RR) as the outcome measure in Comprehensive Meta-Analysis® (Biostat, Englewood, NJ, USA). Results are presented in Table 4. To examine heterogeneity of meta-analyses, an I^2 statistic was computed. I^2 values range from 0%-100% with values of 25%, 50%, and 75% representing low, moderate, and high levels of heterogeneity.[95,96] For our analysis, RR values were used from the fixed effects model if I^2 <50% and a random effects model if $I^2 \geq 50\%$.[95,96]

Table 4 Results from repeated meta-analysis examining the efficacy of treatment comparators in preventing gastroduodenal ulcers by Rostom and collegues[8] using relative risk (RR) as outcome measure.

Treatment Comparison	Relative Risk Estimate	95% CI	P-value	I^2	Model
Misoprostol (800ug day) plus NSAID versus NSAID alone	0.219	(0.142, 0.339)	0.0000	0%	Fixed Effects Model
Misoprostol (400ug day) plus NSAID versus NSAID alone	0.524	(0.331, 0.829)	0.0051	56.7%	Random Effects Model
Standard dose PPI plus NSAID versus NSAID alone	0.363	(0.295, 0.447)	0.0000	0%	Fixed Effects Model
Low dose- H2RA plus NSAID versus NSAID alone	0.631	(0.450,0.884)	0.0075	0%	Fixed Effects Model
High dose H2RA plus NSAID versus NSAID alone	0.416	(0.271, 0.637)	0.0000	0%	Fixed Effects Model

CI=confidence interval; H2RA= H2 Recptor antagonist; I^2= measure of heterogeneity (i.e., how comparable studies in meta-analysis are); NSAID= non-selective non-steroidal anti-inflammatory agent; PPI= proton pump inhibitor; ug= microgram

A subsequent regression model (Appendix A) was developed to project the relative risk reduction of clinical ulcer complications, based upon the relative risk reduction of gastroduodenal endoscopic ulcers. Data to populate the regression model was obtained from a recent meta-analysis of COX-2 inhibitors.[27] A power regression model[§], $y=x^{0.672}$, yielded the best fit, with a coefficient of determination (R^2) value of 0.970.

5.3 PERSPECTIVE

The primary target audiences for this evaluation are healthcare providers and decision makers in the Canadian healthcare system. Consequently, the economic evaluation takes the perspective of publicly funded provincial healthcare system, as recommended by Canadian Agency for Drugs and technologies in Health (CADTH) economic guidelines.[97], Therefore, only direct costs to the healthcare system are considered.

5.4 MODELLING HEALTH OUTCOMES

Baseline probabilities of GI complications among patients taking nsNSAIDs were obtained from a recently published meta-analysis[27] and a large prospective clinical outcome RCT.[5] These baseline probabilities were subsequently converted to rates (and later back to probabilities), as rates possess mathematical properties that enable multiplication by risk factors (i.e. advanced age, history of GI complications, concomitant aspirin use). [67,98,99] The age-related increase in risk of GI events was obtained from a regression equation derived by Maetzel and colleagues[48], based upon data from a meta-analysis of epidemiological studies.[15] Parameters inputs and distributions for other risk factors, along with clinical input parameters used in the analysis, are presented in Table 5.

5.4.1 Clinical Ulcer Complications

A one-arm meta-analysis of event rates in the control arm of a recent meta-analysis[27] (30,177 patients in 8 studies) was conducted using Comprehensive Meta-Analysis® (Biostat, Englewood, NJ, USA). We found that 1.7% of patients taking nsNSAIDs

[§] Power Regression model, $y=x^{0.672}$, where y=relative risk of clinical ulcer complication; x=relative risk of gastroduodenal endoscopic ulcer.

experienced ulcer complications and/or ulcer related symptoms that lead to identification of an ulcer.[27] We subsequently conducted a meta-analysis for the conditional probability of patients' experiencing strict ulcer complications (i.e. perforation, obstruction or bleeding), given they experienced an ulcer complication and/or ulcer related symptoms that lead to identification of an ulcer (PUB**)).We found that 41.8% of patients experiencing a PUB had strict ulcer complications (i.e. perforation, obstruction, or bleeding). Therefore, we assumed an annualized incidence of strict ulcer complications of 0.71% among patients taking nsNSAIDs. This event rate seems to coincide with rates observed from several recent randomized clinical outcome trials[5,12] and published Canadian epidemiological studies.[28,30,91]

Data from the Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endsocopy (RUGBE)[101] demonstrated that 11.7% of bleeding patients were directly discharged from the emergency room, following upper GI endoscopy. We therefore assumed that 88.3% of patients experiencing a POB received in-patient management.

5.4.2 Symptoms Leading to Identification of an Ulcer

We assumed that 58.2% of patients experiencing a PUB developed ulcer related symptoms that lead to identification of an ulcer with upper GI endoscopy. Therefore, the annualized incidence of ulcer-related symptoms leading to identification of an ulcer is 0.99%.

** PUB collectively refers to a strict ulcer complication (perforation, obstruction, or bleeding) and/or ulcer related symptoms that lead to identification of an ulcer

Table 5 Clinical Parameters used in economic evaluation.

Parameter	Value	Reference	Distribution for PSA	Distribution Parameters for PSA
Annual Risk of PUB in patients taking nsNSAID alone	0.0174	27	Beta	alpha=445.25. beta=25,144.01
Probability of a POB given a patient experiences a PUB	0.418	27	Beta	alpha = 155.78, beta = 216.71
Annual Risk of Dyspeptic symptoms among a patient taking nsNSAID	0.2544	4-6	Beta	alpha = 2324, beta = 6808
Probability that a patient experiencing dyspeptic symptoms will consult physician	0.105	100	Beta	alpha = 168.37, beta = 1435.14
Probability that a patient with dyspepsia is referred to gastroenterology	0.132	100	Beta	alpha = 13, beta = 85
Risk of Death in patients experiencing a POB	0.0537	101	Beta	alpha = 102, beta = 1796
Probability of out-patient management of a POB	0.117	101	Beta	alpha = 222, beta = 1674
RR of Dyspepsia for omeprazole compared with nsNSAID alone	0.506	8	log-normal	u = -0.7133, sigma = 0.25
RR of Dyspepsia for Misoprostol (200ug bid) compared with nsNSAID alone	0.953	8	log-normal	u = -0.0513, sigma= 0.075
RR of Dyspepsia for Misoprostol (200ug qid) compared with nsNSAID alone	1.25	8	log-normal	u = 0.2070, sigma = 0.199
RR of Dyspepsia for Ranitidine (150mg bid) compared with nsNSAID alone	0.653	8	log-normal	u = -0.4943, sigma = 0.37
RR of Dyspepsia for Ranitidine (300mg bid) compared with nsNSAID alone*	0.506	8	log-normal	u = -0.7133, sigma = 0.25
RR of gastroduodenal endoscopic ulcers for omeprazole compared with nsNSAID alone	0.362	8	log-normal	u = -1.0217, sigma = 0.10
RR of gastroduodenal endoscopic ulcers for Misoprostol (200ug bid) compared with nsNSAID alone	0.535	7	log-normal	u = -0.6539, sigma = 0.24
RR of Clinical ulcer complications for Misoprostol (200ug qid) compared with nsNSAID alone	0.529	8	log-normal	u = -0.6539, sigma = 0.18
RR of gastroduodenal endoscopic ulcers for Ranitidine (150mg bid) compared with nsNSAID alone	0.639	8	log-normal	u = -0.4620, sigma = 0.17
RR of gastroduodenal endoscopic ulcers for Ranitidine (300mg bid) compared with nsNSAID alone	0.43	8	log-normal	u = -0.8675, sigma = 0.22
RR, history of uncomplicated ulcer	3.08	4	log-normal	u = 1.1249, sigma= 0.2243
RR, history of complicated ulcer	3.73	4	log-normal	u = 1.316408234, sigma = 0.2573
RR, use of low-dose aspirin	2.07	102	log-normal	u = 0.7275, sigma = 0.1281
Median time to PUB (Days)	62	103	Fixed	NA
Parameter in regression equation to estimate efficacy of gastroprotective agents in preventing clinical ulcer complications	0.673	Appendix A	Normal	Mean=0.673, standard error=0.037

bid= twice daily; od= once daily; GI= gastrointestinal; mg= milligram; nsNSAID= non-selective non-steroidal anti-inflammatory drugs; POB= perforation, obstruction, bleed; PUB= perforation, obstruction, bleed, or symptomatic uncomplicated ulcer; PSA= probabilistic sensitivity analysis; sigma= standard deviation of logs; qid=four times daily; u=mean of logs; µg=microgram

5.4.3 Dyspepsia

Dyspepsia was defined as "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.[41]" The model assumed that 26% of patients taking nsNSAIDs experience dyspeptic symptoms, as 2234 of 9127 patients experienced dyspeptic symptoms in the nsNSAID arm of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[5]. We assumed that 10.5% (95% CI, 9-12%) of these patients will contact their primary care physician annually for dyspeptic symptoms, with a median of 1 consultation (range 1-7).[100] Therefore, 2.73% of patients experiencing dyspeptic symptoms will have contact with a primary care physician each year. Due to the consultation rate[100] for dyspepsia being derived from a younger population (age 50-59 years) who were not taking NSAIDs specifically (42% were taking NSAID therapy), we compared our estimate to recent epidemiological and clinical studies. Rahme and colleagues (2007) found that 2.9% of elderly patients (age≥65 years) consulted their physician for dyspepsia or heartburn in the prior year. Similarily, data from the MEDAL trial found that 2.5% of patients taking nsNSAID discontinued the trial due to dyspeptic related symptoms.

We assumed that 23% (95% CI, 18-28%) of patients that sought care for dyspepsia, were referred to gastroenterology.[82] As per the Canadian Dyspepsia Working Group[41], we assumed that patients with uninvestigated dyspepsia, who are regular users of NSAIDs (including ASA) and have no alarm features[††], are managed without initial GI endoscopy.

5.4.3 Death

The model assumes a probability of death of 5.4%, as noted in previous study using data from the Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUBGE).[101] The model assumes that all deaths result after in-patient

[††] Alarm features include persistent vomiting, evidence of gastrointestinal bleeding or anemia, presence of an abdominal mass or unexplained weight loss, or dysphagia (Velhuyzen and colleagues)

management, as the rate of out-patient deaths due to GI bleeding is very low (0.1 per 1000 patient-years).[91]

5.5 VALUING OUTCOMES

Osteoarthritis patients experiencing no GI toxicity were assumed to have a utility of 0.778 with a marginal impact of aging of -0.00029 per year, based upon EQ-5D[‡‡] scores from a catalogue by Sullivan et al 2006.[104] A utility is a quatitative expression of an individuals preference for a particular health state.[54] Utility decrements for GI events were also obtained from this preference-based EQ-5D catalogue[104,105], when available. The disutility of dyspepsia was estimated to be 0.0228[§§] (se=0.0001), based upon 1211 patients with a mean age of 53y.[104] The disutility associated with a chronic uncomplicated ulcer was estimated to be 0.0269 (SE=0.0002), based upon 244 patients a gastric ulcer and mean age=57y.[104] These disutilities were applied over the 1-year time horizon. Utilities for acute events in the model, such as experiencing an endoscopy or inpatient management of an ulcer complication, were obtained from a study by *Ebell et al.*[106] This study elicited preferences for health states using the Index of Well-Being (IWB), a well validated multi-attribute measure of health status.[54] Patients undergoing in-patient management of a complicated ulcer were applied a utility of 0.4902, over 5 days.[107] Patients experiencing an upper GI endoscopy were applied a utility of 0.5675, over 1 day. Although preference scores were not generated in Canada, they should be generalizable to Canada, as instrument scores travel well and are applicable in other countries.[55,108,109] Utilities and disutilities for health states in the model, parameter distributions, and the measurement instruments utilized, are provided in Table 6.

[‡‡] The EQ-5D (or EuroQol) is a indirect measurement technique used to obtain utilities without direct measurement (i.e. standard gamble, time trade-off), a very time consuming and complex task. It is a questionnaire with several sections where respondents are asked to describe their health states based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, there are three levels of severity from which the respondents can choose. Respondents are also asked to indicate their own health state on a visual analog scale (or "thermometer") calibrated from zero ("worst imaginable health state") to 100 ("best imaginable health state").

[§§] This disutility translates into approximately 200 hours per year in a health state with a utility of 0 or death.

Table 6 Utilities/disutilities for health states in the model, along with parameters distributions, measurement instruments utilized, population from which utilities/disutilities were elicted, and references

Parameter	Value	Reference	Utilities derived from	Technique	Distribution for PSA	Distribution Parameters for PSA
Utility (EQ-5D) score for patients with arthritis	0.778	104,105	US survey - 38,678 adults	EQ-5D	Beta	alpha = 14.36, beta = 4.10
Disutility (EQ-5D) for patients with arthritis experiencing chronic dyspepsia	0.0228	104,105	US survey - 38,678 adults	EQ-5D	Gamma	alpha = 51984, lambda = 2280000
Disutility (EQ-5D) for patients with arthritis that have been diagnosed with a gastric ulcer	0.0268	104,105	US survey - 38,678 adults	EQ-5D	Gamma	alpha = 17956, lambda = 670000
Utility of patients experiencing inpatient management for a POB	0.4642	106	Not Provided	Index of Well-Being (IWB)	Fixed	NA
Utility of patients experiencing an upper GI Endoscopy	0.5675	106	Not Provided	Index of Well-Being (IWB)	Fixed	NA

EQ-5D=EuroQol; IWB= Index of well being; POB= perforation, obstruction, bleed; PUB= perforation, obstruction, bleed, or symptomatic uncomplicated ulcer; PSA= probabilistic sensitivity analysis; PSA= Probabilistic sensitivity analysis; EQ-5D=EuroQol; US=United States

5.6 RESOURCE USE AND COSTING

Medication costs were based on unit costs from the Nova Scotia Senior Pharmacare Program 2007, plus an allowable markup of 10% and appropriate pharmacy fees. The lowest generic cost was used for each alternative, where possible (Table 7).

Table 7 Acquisition cost of medications used in analysis

Product	Brand Name	Unit Cost*†
Ompeprazole 20mg Tab/Cap *od*	Apo-omeprazole	$1.10
Ranitidine 150mg Tab *bid*	Apo-Ranitidine	$0.81
Ranitidine 300mg Tab *bid*	Apo-Ranitidine	$1.56
Misoprostol 200ug Tab *qid*	Apo-Misoprostol	$1.14
Arthrotec 75‡ *bid*	Arthrotec	$1.70
Naproxen 500mg Tab *bid*	Apo-Naproxen	$0.42

*Nova Scotia Pharmacare Programs List- November 2007; † Prices listed are for generic drugs and maximum allowable cost (MAC) under the Nova Scotia Senior Pharmacare Program (NSSPP) ‡ Arthrotec= 75mg of diclofenac and 200μg of misoprostol; bid= twice daily; od= once daily; qid= four times daily; mg= milligram; Tab= tablet; ug= microgram

Costs for physician fees and procedures were obtained from the College of Physicians and Surgeons of Nova Scotia Fee Schedule 2006. In-patient and out-patient costs for management of GI complications were obtained from the Health Costing in Alberta 2006 Annual Report.[107] Costing data for the Alberta Case Costing Report 2006[107] was generated from the cost of cases in 2 health authorities and 12 sites in Alberta from April 1, 2004 to March 31, 2005. Associated costs per case for in-patient and out-patient management of GI complications are presented in Table 8.[107]

Table 8 Cost for physicians fees/procedures, management costs of gastrointestinal complications, along with parameter distributions used in analysis

Parameter	Value	Reference	Distribution for PSA	Distribution Parameters for PSA
Management, general gastrointestinal, adult patients	134	107	Gamma	alpha = 1.00, lambda = 0.007463
Endoscopy	453	107	Gamma	alpha = 3.231, lambda = 0.007133
Out-patient management GI bleed/Perforation/Obstruction	231	107	Gamma	alpha = 1.103, lambda = 0.004773
In-patient management of GI hemmorrhage	4006	107	Gamma	alpha = 1.238, lambda = 0.000309
Endoscopy Fee	92	110	Fixed	NA
General Practioner (GP) Physician Fee	56	110	Fixed	NA
Gastroenterologist Fee	128	110	Fixed	NA

GI= gastrointestinal; GP= general practioner; NA= not applicable; PSA= probabilistic sensitivity analysis

5.7 OUTCOME ASCERTAINMENT

The main outcome for this economic evaluation is the incremental cost per QALY gained (ICUR).

5.8 HANDLING UNCERTAINTY

A probabilistic sensitivity analysis[67,90,111] using second-order Monte Carlo Simulation was used to examine uncertainty of results. A probabilistic sensitivity analysis enables simultaneous sensitivity analysis of all uncertain variables by replacing parameter point estimates with realistic probability distributions.[54,67,67,111] Mean estimates of costs and QALYs were generated based on results from 10,000 iterations; where each iteration randomly samples parameter values from specified distributions. Distributions used for each parameter in the model are presented in Tables 5-8. Costs, probabilities, and relative risks were assigned gamma, beta, and log-normal distributions as outlined by Briggs and colleages. [67]

A net-benefits cost-effectiveness acceptability [54,67,90] curve was subsequently generated to convey uncertainty of results. A net-benefits acceptability curve graphs the probability that a comparator is most cost-effective (highest net monetary benefit) relative to all other strategies, across willingness to pay per QALY thresholds Acceptability curves have been advocated as an approach to convey uncertainty to health care decision makers.[90,90,111,112]

In addition to the probabilistic sensitivity analysis, we conducted a detailed univariate sensitivity analysis.[54,55,90] Uni-variate sensitivity analyses were conducted, where parameters in the model were varied across plausible ranges, while other variables were held constant. A Tornado Diagram was generated to identify key parameters and schematically present results from the uni-variate sensitivity.[54,97] All sensitivity analyses were conducted using TreeAge ProSuite 2005 (TreeAge Inc., Williamstown, PA, USA.)

CHAPTER 6 BASE-CASE RESULTS

The expected values for cost, QALYs gained, incremental costs and QALYs, and incremental cost-utility ratios (ICUR) across treatment strategies are presented in Table 9. Treatment with nsNSAID alone is the least expensive alternative, albeit the least effective (lowest QALYs). Treatment with nsNSAID plus ranitidine (150mg bid) is projected to improve QALYs gained by 0.00084, relative to treatment with nsNSAID alone. However, the incremental benefit (0.00084 QALYs) is associated with an incremental cost of $349 per patient per year. Treatment of patients with omperazole (20mg od) is associated with an incremental cost ($180) and incremental benefit (0.00053), relative to nsNSAID alone plus ranitidine (150mg bid).

Table 9 Expected Values (QALYs and costs) across alternative gastroprotective strategies for prevention of nsNSAID induced GI complications in adult patients with no additional risk factors

Strategy	Cost	ΔCost	QALY	ΔQALY	ICUR
nsNSAID alone	$383		0.77052		
nsNSAID + Ranitidine (150mg bid)	$732	$349	0.77136	0.00084	$416,425*
nsNSAID + omeprazole (20mg od)	$822	$91	0.77189	0.00053	$170,132
nsNSAID + Misoprostol (200ug bid)	$824	$2	0.77104	-0.00085	Dominated
nsNSAID + Misoprostol (200ug qid)	$843	$21	0.77078	-0.00112	Dominated
nsNSAID + Ranitidine (300mg bid)	$1,003	$180	0.77181	-0.00008	Dominated

*nsNSAID + Ranitidine (150mg bid) is extendedly dominated by nsNSAID + generic omeprazole (20mg od). Δ= change; nsNSAID= non-selective non-steroidal anti-inflammatory agent

Three treatment strategies are considered to be dominated (Table 9). A strategy is considered to be dominated when it is more costly and less effective than a treatment alternative. For instance, nsNSAID plus Misoprostol (200ug qid) is more expensive and less effective (less QALY) than a strategy of nsNSAID plus omeprazole (20mg od). Therefore, it is dominated. Similarly, Misoprostol (200ug bid) and nsNSAID + Ranitidine (300mg bid) are dominated.

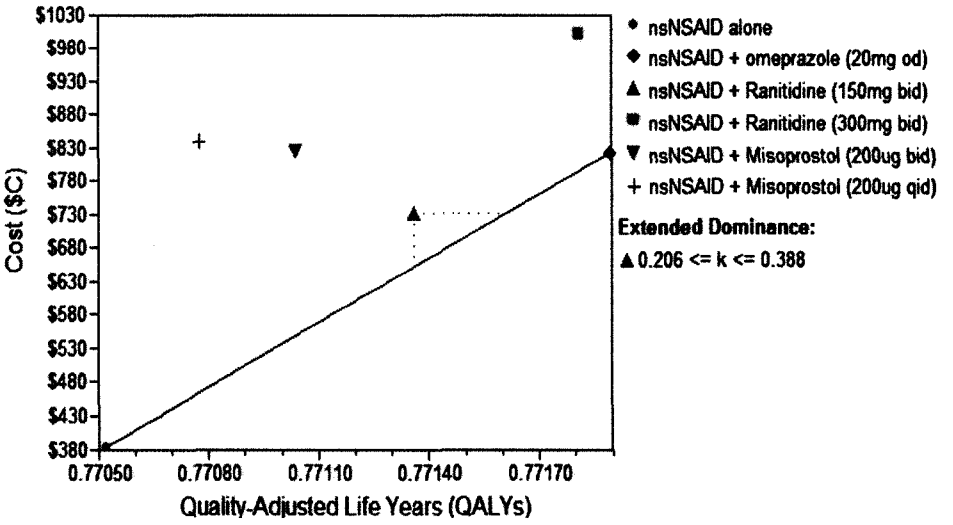

Figure 3 Expected Values for QALYs and costs associated with the treatment of patients with alternative gastroprotective strategies for prevention of nsNSAID induced GI complications.

A strategy of nsNSAID plus Ranitidine (150mg bid) is considered to be extendedly dominated. The concept of extended dominance is derived from a key rule of thumb "Lower ICERs correspond to better value for money". In Figure 3, if a slope was drawn between nsNSAID alone and nsNSAID plus Ranitidine (150mg bid), it would have a "steeper slope" (or higher ICUR) than the slope between nsNSAID alone and nsNSAID plus omeprazole (20mg od). For instance, the ICUR for nsNSAID plus Ranitidine (150mg bid), relative to nsNSAID alone, is $416,425, whereas the ICUR of nsNSAID plus omeprazole (20mg od), relative to nsNSAID alone, is $320,742. Figure 3 demonstrates that nsNSAID plus Ranitidine (150mg bid) is dominated by a blend of nsNSAID alone and nsNSAID plus omeprazole (20mg od) with a coefficient of inequity of between 0.206 and 0.388. Consequently, treatment of between 20.6%-38.8% of patients with nsNSAID + PPI and the remainder with nsNSAID would result in higher QALYs gained at an equivalent cost, as opposed to treating all patients with plus Ranitidine (150mg bid) and nsNSAID.

Table 10 Expected Values for QALYs and costs associated with non-dominated treatment strategies (simple and extended) for prevention of nsNSAID induced GI complications.

Strategy	Cost	ΔCost	QALY	ΔQALY	ICUR
nsNSAID alone	$383	NA	0.77052	NA	NA
nsNSAID + generic omeprazole (20mg od)	$732	$439	0.77189	0.00137	$320,743

Δ= change; nsNSAID= non-selective non-steroidal anti-inflammatory agent

Table 10 presents results remaining strategies without simple or extendedly dominated treatment alternatives. A treatment strategy of nsNSAID plus omeprazole (20mg od) is associated with an incremental cost of $439 and an incremental benefit of 0.00137 QALYs. As each day in perfect health represents 0.0027 QALYs (1/365), this translates in approximately a ½ day in perfect health. Consequntly, the incremental cost per QALY gained for PPIs is $320,743, relative to nsNSAID alone.

CHAPTER 7 SENSITIVITY AND VARIABILITY ANALYSES

There are two main forms of sensitivity analysis used to examine robustness of results; 1.) probabilistic sensitivity analysis and (2.) deterministic sensitivity analysis. A probabilistic sensitivity analysis uses Monte Carlo simulation to take random draws from plausible probability distributions in the model.[54] In a deterministic sensitivity analysis, one or more parameters are varied (not randomly sampled from a distribution) within plausible ranges, while all other parameters are left constant. [54]

7.1 PROBABILISTIC SENSITIVITY ANALYSIS

The cost-effectiveness (CE) scatter-plot is presented in Figure 4, where results from 10,000 iterations for costs and QALYs for each strategy are plotted on the cost-effectiveness plane. Each point in the CE Scatter-plot represents the cost and QALYs for each treatment strategy associated with one iteration (of 10,000 total iterations) in the 2nd order Monte Carlo Simulation. From Figure 4, it can been seen that nsNSAID is the least expensive strategy while ranitidine (300mg bid) is clearly the most expensive strategy.

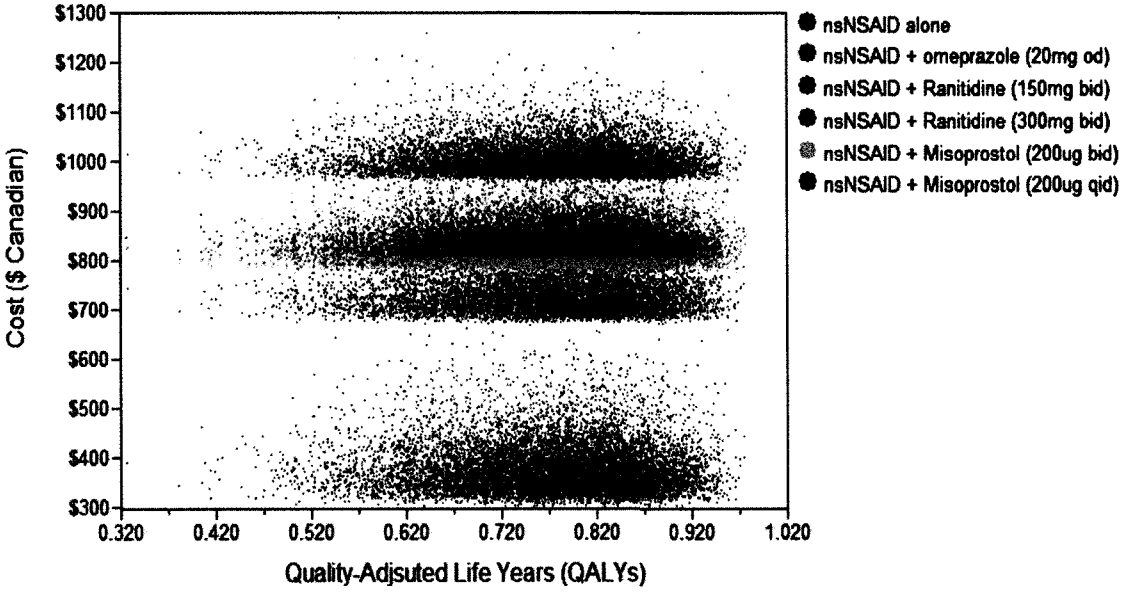

Figure 4 Cost-Effectiveness Scatter-Plot where each point on the scatter-plot represents the cost and QALYs for each treatment strategy associated with one iteration from the Monte Carlo simulation.

bid= twice daily; od= once daily; mg= milligram; nsNSAID= non-selective non-steroidal anti-inflammatory drugs; qid=four times daily; µg=microgram

A net-benefits acceptability curve is presented in Figure 5, where the changing percentage of iterations that are cost-effective (relative to all other strategies) are plotted against a Willingness to pay per QALY threshold. Figure 5 demonstrates that nsNSAID alone strategy is has the highest probability of being the most cost-effective strategy for WTP thresholds less than ~$320,000 per QALY gained. Beyond this WTP threshold, nsNSAID plus PPI has the highest probability of being the most cost-effective strategy.

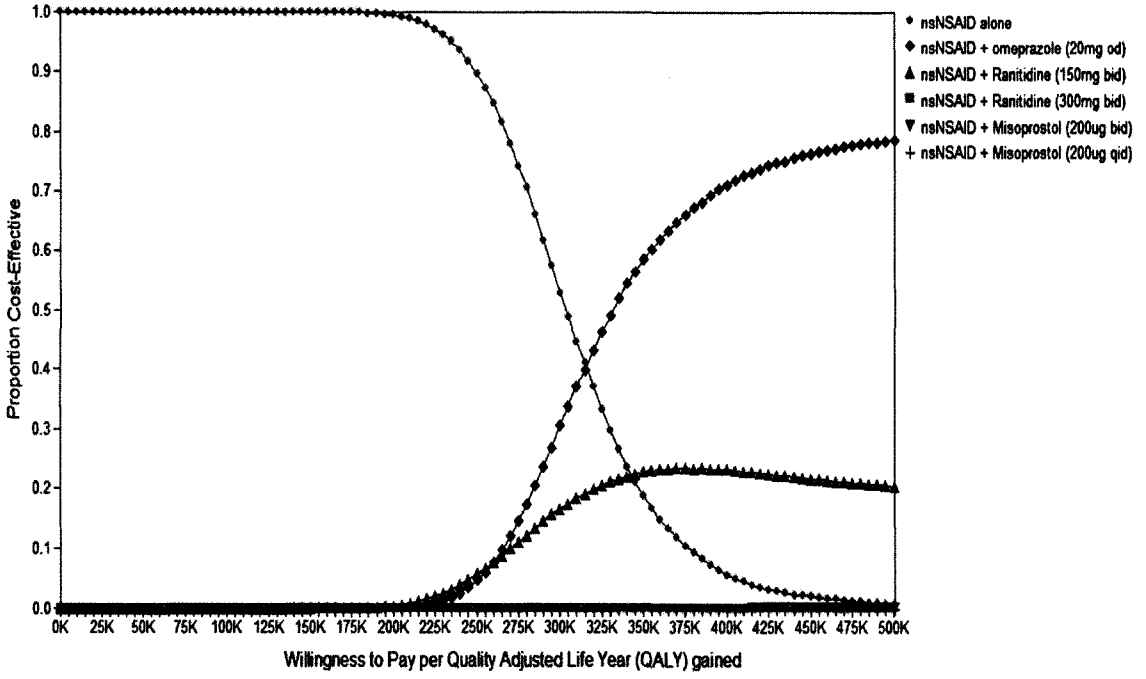

Figure 5 Net-benefits cost-effectiveness acceptability curve that plots the probability that each treatment strategy is cost-effective strategy, relative to all other strategies, across Willingness to pay per QALY thresholds.

bid= twice daily; od= once daily; mg= milligram; nsNSAID= non-selective non-steroidal anti-inflammatory drugs; qid=four times daily; µg=microgram

7.2 DETERMINISTIC SENSITIVITY ANALYSIS

A tornado diagram is illustrated in Figure 6. A tornado diagram is a set of one-way sensitivity analyses brought together in a single graph. A one-way sensitivity analysis is a form of sensitivity analysis where one parameter is varied within plausible ranges while

all other parameters are held constant. The horizontal axis of the Tornado diagram depicts the incremental cost-utility ratio (ICUR) and the vertical axis presents the parameters and ranges examined in the analysis. The dotted line represents an incremental cost-utility ratio value of $50,000 per QALY gained. This figure demonstrates that results in our analysis were sensitive to variation of many parameters in deterministic sensitivity analysis. Parameters for which the model was most sensitive include: probability of consulation for dyspepsia, disutility associated with experiencing dyspepsia, age, baseline probability of clinical ulcer complication, and acquisition cost. It should be noted that directionality in the Tornado diagram depends on the nature of the parameter. For age, an increase results in a decrease in the ICUR (left), while an increase in utility of a patient experiencing upper endoscopy, will result in a decrease in the ICUR.

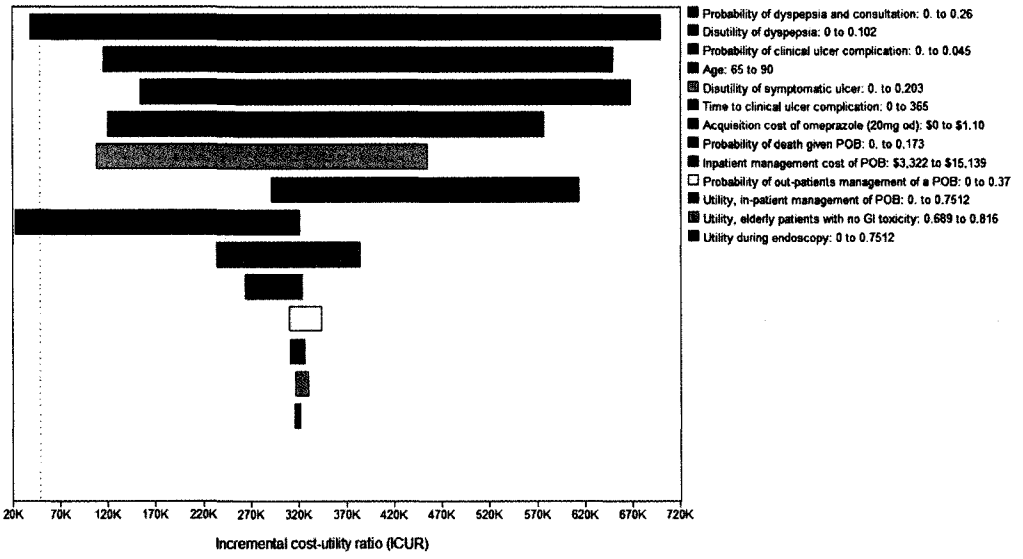

Figure 6 A tornado diagram that illustrates a series of uni-variate sensitivity analyses, where parameters in the model are varied within plausible ranges while all other parameters are held constant. The horizontal axis of the Tornado diagram depicts the incremental cost-utility ratio (ICUR) for PPIs relative to nsNSAID alone, and the vertical axis presents the parameters and ranges examined in the analysis.

GI= gastrointestinal; ICUR= incremental cost-utility ratio; mg=milligram; Mngt=management; od=once daily; POB= perforation, obstruction, bleed; PUB=perforation, obstruction, bleed, or symptomatic uncomplicated ulcer

One-way sensitivity analyses presented in Figure 7 demonstrate how the incremental cost-utility ratio (ICUR) for PPIs, relative to nsNSAID, varies with age and relative risk. For patients with no additional risk factors, the ICUR for PPIs decreases from $577,000 per QALY gained in patients that are 65y to $121,000 per QALY gained in patients aged 90y. ICURs decrease further with the presence of additional risk factors. In individuals aged 65y and at an increased risk of complications (RR=3), the ICUR is $260,721 per QALY gained while the ICUR is $35,000 per QALY gained in patients 90y with equivalent risk.

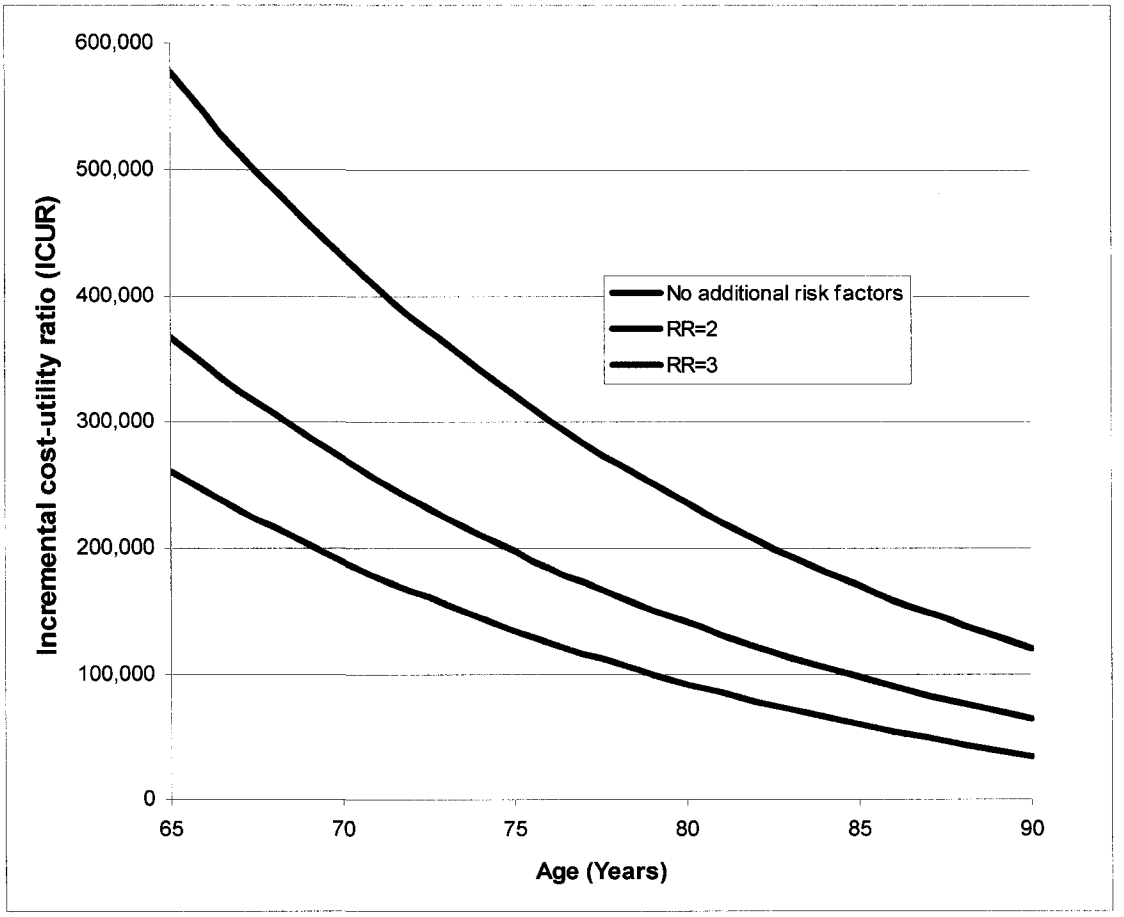

Figure 7 A one-way sensitivity analysis illustrating how the incremental cost-utility ratio (ICUR) for PPI, relative to nsNSAID, varies with age and relative risk. The horizontal axis presents age, in years, while the ICUR for PPIs are presented on the vertical axis. The blue line represents a group of patients with no additional risk factors, while the red and green line represents cohorts of patients with a relative risk (RR) of 2 and 3, respectively.

A one-way sensitivity analysis is presented in Figure 8 that demonstrates how the incremental cost-utility ratio (ICUR) for PPIs, relative to nsNSAID, varies with age and decreases in acquisition cost of PPIs. At the current acquisition cost and in patients with no additional risk factors, the ICUR is $577,000 per QALY gained for patients aged 65y and $121,000 per QALY gained in patients 90y. ICURs decrease further when the acquisition cost of PPIs decrease. If costs were decreased by 50%, ICUR would decrease to $320,605 and $56,000 per QALY gained in patients with no additional risk factors and aged 65y and 90y, respectively.

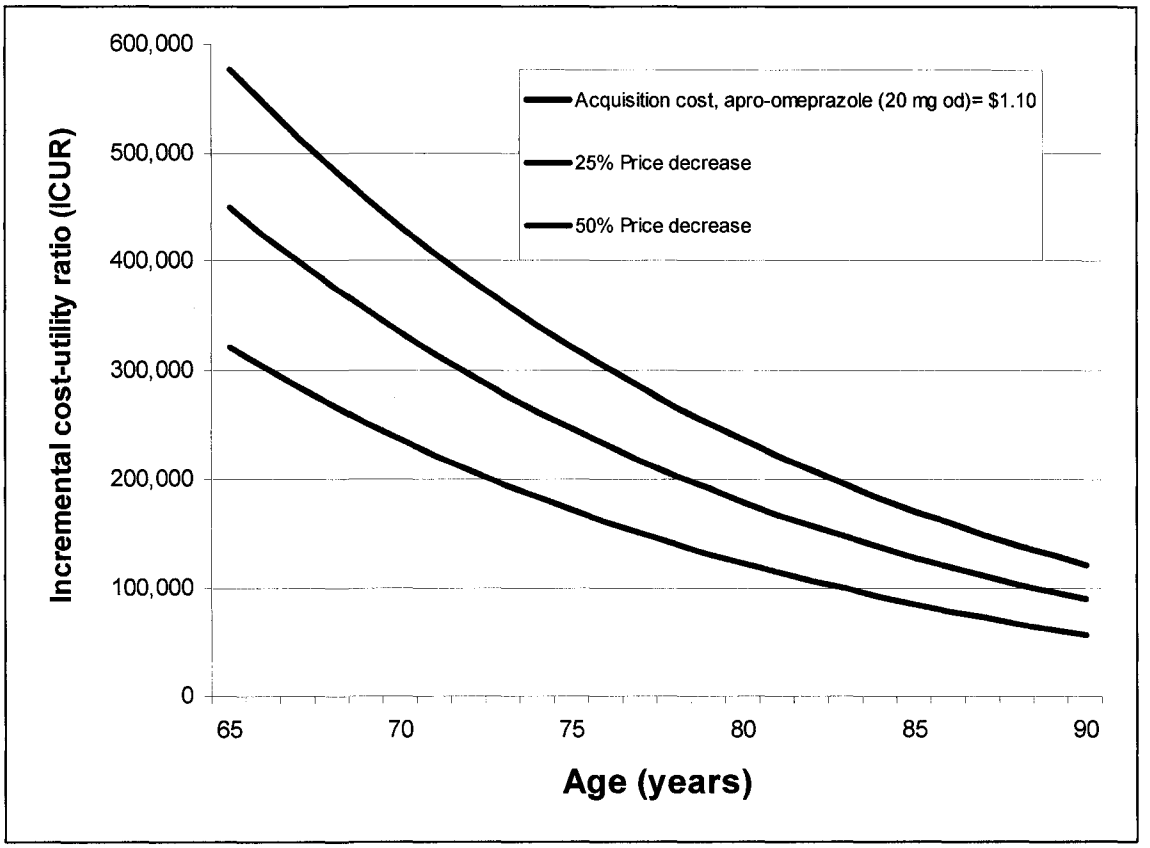

Figure 8 A one-way sensitivity analysis that illustrates how the incremental cost-utility ratio (ICUR) for PPI, relative to nsNSAID, varies with age and acquisition cost of PPI. The horizontal axis presents age, in years, while the ICUR for PPIs are presented on the vertical axis. The blue line represents the ICUR at the present acquisition cost, while the red and green line represents 25% and 50% decreases in costs, respectively.

7.3 VARIABILITY ANALYSIS

Figure 9 provides a bar-chart illustrating the incremental cost-utility ratios (ICUR) for nsNSAID plus omeprazole (20mg od), relative to nsNSAID alone, for sub-groups of patients with various risk factors. ICUR values range from $320,553 per QALY in a sub-group of elderly patients with no additional risk factors to Cost Saving ($33 per person-year) in individuals with advanced age (age≥75y) and history of a prior complication. Variability analyses assume that patients with all patients with a history of a complicated/uncomplicated ulcer develop strict ulcer complications (POB), and are managed as in-patients.

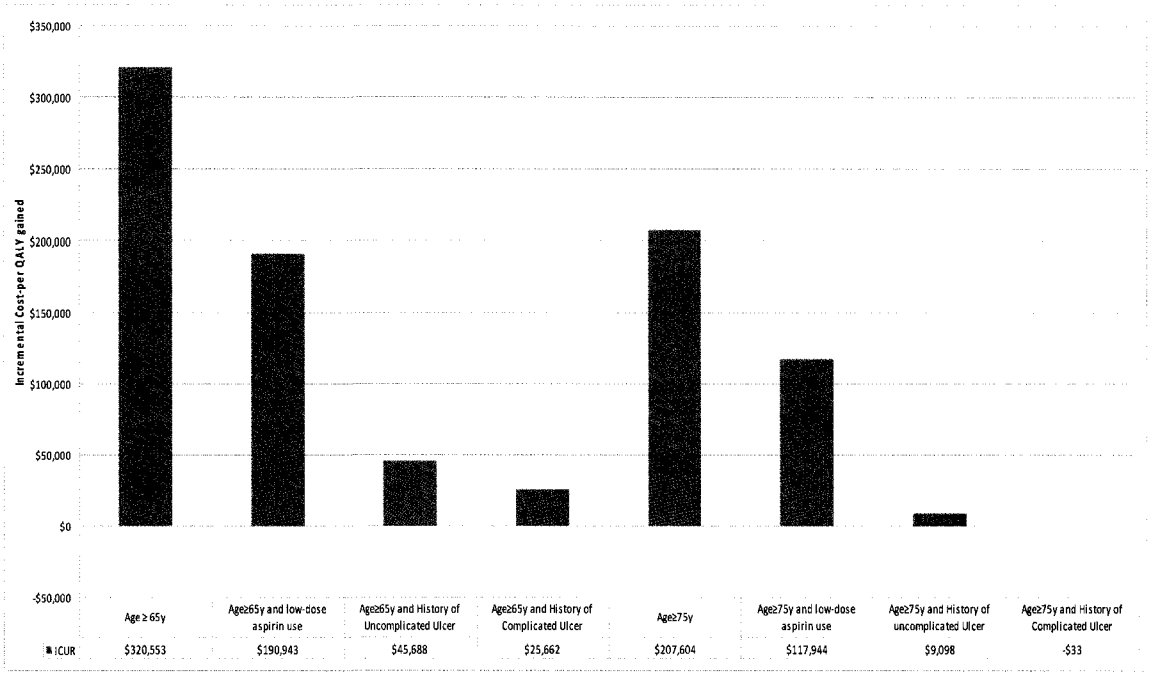

Figure 9 Bar-chart illustrating the incremental cost-utility ratio (ICUR) for nsNSAID plus omeprazole (20mg once daily), relative to non-selective non-steroidal anti-inflammatory drugs (nsNSAID) alone, for sub-group of patients with various risk factors.

Figure 10 presents the probability that a treatment strategy is most cost-effective (i.e., highest net monetary benefit) at a willingness to pay threshold of $50,000 per QALY gained. In elderly patients (age≥65y) with no additional risk factors, there is a 0% chance

that routine prescription of PPIs in all patients represents the most efficient treatment at this WTP threshold. In contrast, the probability that PPIs are the most efficient strategy in patients with advanced age (age≥75y) and history of a complicated ulcer is 63%. However, it should be noted that decisions should be based on expected values (Figure 9), as opposed to using information derived from cost-effectiveness acceptability curves.

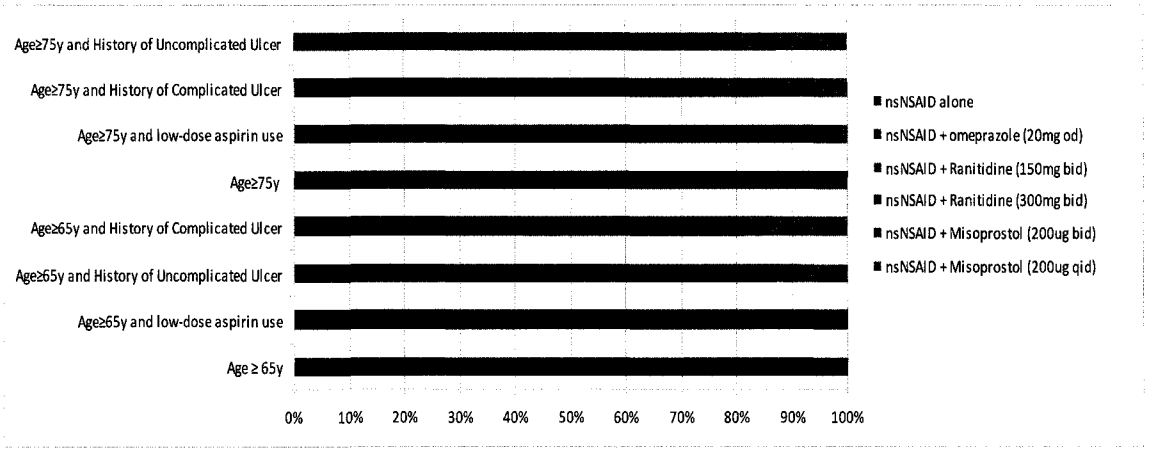

Figure 10 Net-Benefits Optimality Bar-chart illustrating the probability that each treatment strategy is most cost-effective (i.e., highest net monetary benefit) at a willingness to pay threshold of $50,000 per QALY gained across sub-groups of patients with various risk factors

bid= twice daily; od= once daily; mg= milligram; nsNSAID= non-selective non-steroidal anti-inflammatory drugs; qid=four times daily; µg=microgram

Figure 11 presents the probability the net-benefits acceptability curve for elderly patients with a history of a complicated ulcer. It can be seen that PPIs have the highest probability of being the most cost-effective strategy beyond a willingness to pay threshold of $20,000 per QALY gained. At a willingness to pay threshold of $50,000 per QALY gained, treatment with nsNSAID alone has only a 13% chance of being the most cost-effective strategy.

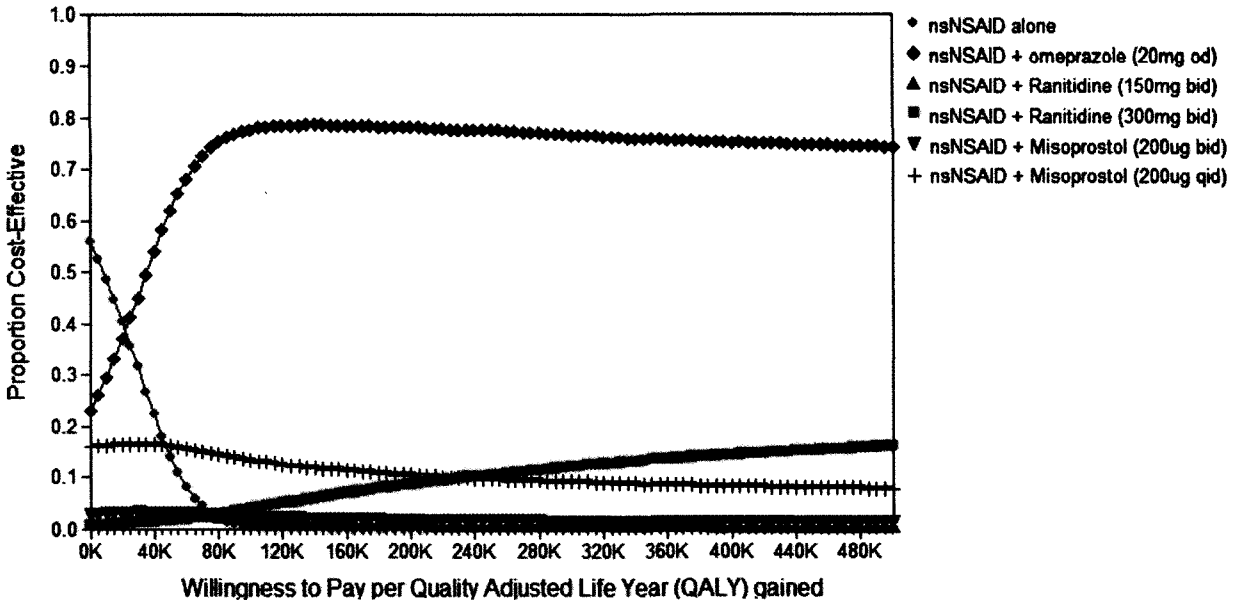

Figure 11 Net-benefits cost-effectiveness acceptability curve for elderly patients with a history of a complicated ulcer.

bid= twice daily; od= once daily; mg= milligram; nsNSAID= non-selective non-steroidal anti-inflammatory drugs; qid=four times daily; µg=microgram

CHAPTER 8 DISCUSSION

Drug policy is a complex mix of scientic evidence, alongside economic, ethical, political and legal considerations. Consequently, results derived from the present economic evalaution represent one piece of the ultimate policy decision. Results from the present economic evaluation suggest that the most efficient strategy for prevention of GI complications in patients taking nsNSAIDs is dependent upon age and presence of risk factors (i.e., history of complicated ulcer, history of uncomplicated ulcer, and low-dose aspirin use). Among elderly patients (age≥65y) with no additional risk factors, our analysis suggests that treatment with nsNSAID alone is the most efficient strategy. Although other treatment strategies yielded a more pronounced decrease in GI complications relative to nsNSAID alone treatment strategy, the incremental cost associated with the benefit may not be justified in a healthcare system with limited resources. For instance, nsNSAID plus omeprazole (20mg *od*) was associated with an ICUR of $320,743 per QALY gained, relative to nsNSAID alone in elderly (age≥65y) patients with no additional risk factors. Laupacis and colleagues[78] suggest that therapies which have yielded incremental cost-effectiveness ratios of between $20,000 and $100,000 per QALY gained warrant consideration for adoption and utilization. Similarly, Rawlins and Cuyler[50] have highlighted that treatment alternatives with incremental cost-effectiveness ratios beyond £25,000-£35,000 would need special reasons to merit acceptance and adoption. However, as discussed in Chapter 3, the use of commonly cited "accepted cost-effectiveness thresholds" has been debated considerably in the literature.[76,77,86,89]

Similar results were observed among patients aged≥75y and in elderly patients (age≥65y and age≥75y) taking concomitant low-dose aspirin. Although omeprazole (20mg *od*) reduced the incidence of GI complications in these cohorts of patients, ICURs still exceeded commonly cited thresholds of between $20,000 to $100,000 per QALY gained. In contrast, ICURs in the present model yielded acceptable cost per QALY thresholds in cohorts of patients with advanced age (age≥65y) and history of complicated or uncomplicated ulcer. Consequently, co-prescribing omeprazole (20mg od) among elderly patients (age≥65) taking nsNSAIDs with a history of a complicated or uncomplicated

ulcer may be considered good value for money in a healthcare system with finite resources.

These findings are consistent with results observed in an US cost-utility analysis of competing gastroprotective strategies in patients with varying risk groups. Spiegel and colleagues[51] found that treatment of patients with nsNSAID alone is the preferred strategy in average-risk patients, as nsNSAID plus PPI therapy was associated with a cost of US $309,666 (C$486,186) per QALY gained, compared with nsNSAID alone in this patient population. Similarly, they found that in patients with additional risk factors, the ICURs for PPIs, relative to NSAID dropped significantly.

Interestingly, results from the present analysis differ from several recent economic evaluations[10,52] from which the model was derived. A recent cost-utility analysis conducted in the UK [52] suggested that "there may be a case for prescribing H2RAs in all patients that require nsNSAID therapy" in the general population (age≥18y). In contrast, our analysis suggests that a blend of nsNSAID alone and nsNSAID alone plus omeprazole is preferred to the routine prescription of H2RA (Ranitidine, 150mg bid) in all elderly patients (age≥65y) taking nsNSAIDs. Results derived from our variability analysis further suggest that treatment with nsNSAID alone in low-risk (i.e., elderly patients with no additional risk factors) patients and nsNSAID alone plus omeprazole in high risk patients (age≥65 plus history of complicated or uncomplicated events) should result in a more efficient use of limited healthcare resources.

Differences in results observed between the present evaluation and the evaluation by Elliott and colleagues[52] are attributable to differences in event rates across treatment arms. Elliott and colleagues[52] assume that low-dose H2RA therapy is more efficacious (RR, 0.33; 95%CI, 0.01-8.14) than standard dose PPI therapy (RR, 0.46; 95% CI, 0.07-2.92) in preventing clinical ulcer complications.[9,10] This assumption is not reflective of results observed in several recent epidemiological studies. Rodriguez et al (2001)[29] found that users of H_2RAs, omeprazole, and misoprostol had RRs of 1.4 (95% CI= 1.2-1.8), 0.6 (95% CI= 0.4-1.0), and 0.6 (95% CI= 0.4-1.0) after adjusting several risk factors

including age, sex, ulcer history, use of steroids, anticoagulants, NSAIDs, and ASA use. Similarly, Rahme and colleagues[91] found that elderly patients taking nsNSAIDs and PPI had a 53% reduction in hazard rate of hospitalization while patients taking nsNSAID plus other GPAs (H2RA or misoprostol) had a 29% increase in hazard rate for GI hospitalization. In contrast, event rates for the present model have been validated against a large prospective clinical outcome trial[12] and Canadian epidemiological studies. [30,91]

Detailed probabilistic and deterministic sensitivity analyses were performed to test the robustness of results in the present evaluation. Results from the probabilistic sensitivity analysis demonstrate that generic omeprazole (20mg *od*) has a 0% chance of being the optimal strategy among elderly patients (age≥65y) taking nsNSAIDs, at willingness to pay thresholds of $50,000 and $100,000 per QALY gained. nsNSAID plus omeprazole becomes the optimal treatment strategy (highest net benefit) beyond a willingness to pay threshold of ~$320,000 per QALY gained.

Deterministic sensitivity analyses highlight that results are sensitive to probability of consultation for dyspeptic symptoms, disutility associated with dyspepsia, age, and event rate of clinical ulcer complications. The tornado diagram (Figure 6) demonstrates that probability of consultation for dyspeptic symptoms is the key driver in the analysis. If the consultation rate for dyspepsia increases, routine use of PPIs becomes more cost-effective, relative to NSAID alone. Our analysis assumes that 26% of patients taking nsNSAIDs will experience dyspepstic symptoms.[4-6] Among these patients, we assume that ~10.5% will consult their physician each year.[82,100] This consultation rate coincides with results observed in a recent Canadian epidemiological study and a large prospective clinical outcome study. Rahme and colleagues found that 2.9% of patients taking nsNSAID consulted their physician in the previous year.[91] Similarly, 2.4% of patients in the MEDAL trial dropped out after experiencing dyspeptic symptoms.[12] The disutility associated with dyspepsia is also a major driver in the analysis. The estimate for this parameter was derived from an EQ-5D catalogue in the US.[104,105] The methodological rigor of the catalogue developed by Sullivan and colleages has been discussed extensively in the literature.[104,105,113] Further research may be warranted to identify more

precise estimates for these parameters, as they have a significant impact on the cost-effectivenes of PPIs, relative to NSAID alone.

This analysis also demonstrates that ICURs for PPIs would become considerably more favorable, if acquisition costs were decreased. For instance, in elderly patients (age≥65y) with no additional risk factors, the ICUR would decrease from $320,743 to $171,743 if the acquisition cost were decreased by 50%. This decrease becomes even more pronounced (<$50,000 per QALY) when additional risk factors are applied (Figure 8). Consequently, as the acquisition cost of PPIs decrease, more widespread use of PPIs may be warranted. However, the decision to prescribe a PPI should also factor in other considerations, i.e., potential safety risks. Recent reports suggest that PPIs may increase the risk of community acquired pneumonia[114] and *Campylobactor Enteritis*, along with *Clostridium Difficile*. Fortunately, such side effects confer a small absolute risk increase.[114]

8.1 Strengths and Limitations of Approach

There are a number of strengths associated with our approach. First, model predictions were validated against recent Canadian epidemiological studies, as recommended by the International Society of Pharmacoeconomics for Outcomes Research (ISPOR) Principles of Good Practice for Decision Analytic Modeling in Health Care Evaluation.[115] Results forecasted by our model closely correlate with results observed in these recently published Canadian epidemiological studies.[30,91]

Second, when available, disutility estimates were obtained from a nationally representative, community-based EQ-5D Catalogue in the US.[104,105] The catalogue by Sullivan and colleagues provides mean EQ-5D scores for various health states while controlling for other chronic conditions and determinants of health including age gender, income, and education. Given the methodological rigor (i.e., sample size, control for confounding variables) undertaken in the generation of this catalogue, it has been described as "about at good as it gets" in providing preference-based score for cost-utility analyses.[113]

Third, unlike previous models[47,49,51,52,116], we did not assume patients with arthritis were in perfect health (i.e., utility=1). In contrast, our analysis assumed that a patient with arthritis had a median EQ-5D score of 0.778 with a marginal impact of aging of -0.00029 per year.[104,105] In doing so, our model should not overemphasize the benefit of treatment with gastroprotective agents, like previous models[47,49,51,52,116,117]

Fourth, our model incorporated dose-response relationships for misoprostol and ranitidine. We felt it was important to capture this element as many agents are available in different dosing regimens and these doses have different treatment effects and costs. Finally, detailed sensitivity analyses (deterministic and probabilistic) were performed to test the robustness of results. Although various cost-effectiveness analyses have been conducted on gastroprotective agents[46-49,51,52,116],earlier studies have not examined uncertainty in a high level of detail.

As with all modeling studies, there are a number of limitations to present. First, the efficacy of PPI and H_2RA therapy in preventing NSAID induced GI complications was derived from a meta-analysis of endoscopic outcome trials[8], as no long-term RCTs have been conducted to determine the efficacy of these agents in preventing clinical outcomes. The validity of surrogate outcomes has been debated considerably in the literature.[118]

Second, a regression equation was used to project efficacy in preventing clinical outcomes, based upon results from endoscopic outcome studies. This approach is not as methodologicaly rigorous as using estimates obtained directly from clinical outcome trials.[119] Third, the efficacy of treatment alternatives were derived from RCTs, often of short duration, under conditions that may not be reflective of the real world. For instance, patients in the real world may not be adherent to dual therapies, which would in-turn increase present cost-effectiveness estimates for PPIs.

Fourth, the present analysis was limited to gastroprotective agents. Consequently, celecoxib, despite the benefit it confers in reducing GI complications is not a

gastroproective agent as it increases the risk of GI complications relative to placebo.[27] Furthermore, there have been concerns that celecoxib may increase the risk of myocardial infarction in patients taking celecoxib, relative to nsNSAIDs. [120] Moreover, inclusion of celecoxib as a comparator in the analysis would have limited the generaliazibility of the analysis, as data from RCTs suggest that aspirin, a widely used agent in elderly patients, attenuates the GI benefits of selective COX-2 inhibitors.[5,6]

Fifth, the model takes a one-year time horizon to coincide with drug reimbursement budgets, despite patients taking NSAIDs often require therapy for longer than a year. CADTH Guidelines for the Economic Evaluation of Health Technologies[97] suggest that the time horizon should be sufficient to capture meaningful differences between comparators. As the median time to an ulcer complication in patients taking NSAID therapy is 60 days,[103] a one-year time horizon should be sufficient. Adoption of a longer time horizon should not significantly alter cost-effectiveness results, as many patients that experience a GI bleed will discontinue NSAID therapy altogether[53] due to increased risk of GI complications.

Sixth, the present model does not account for patients that have a symptomatic ulcer but do not seek medical attention. Amongst these patients, there would be a decrease in health-related quality of life that is not currently captured. Consequently, the present analysis may bias against Proton Pump Inhibitors, relative to nsNSAID alone (yieled less favorable cost-effectiveness estimates). However, given the low absolute risk of symptomatic uncomplicated ulcers,[4,5,6,7,12] this limitation should not significantly alter cost-effectiveness estimates.

Finally, we assume that our base-case cohort is representative of an elderly cohort, with no additional risk factors. However, many studies upon which event rates were derived[4-6] include patients with risk factors. This should bias results in favour of PPIs. (result in lower ICURs).

8.2 IMPLICATIONS FOR CLINICIANS AND POLICY MAKERS

The optimal prescribing of PPIs in patients taking nsNSAIDs is paramount. Over-prescription of PPIs in patients at low risk for GI complications may increase health care costs unnecessarily and increase the risk of other complications, while under prescription of these agents in high risk patients' results in an increase of preventable GI ulcer complications.

Thus, a challenge exists for healthcare providers and policy makers to prescribe PPIs appropriately and cost-consciously. Results from the present analysis may assist healthcare providers and decision makers in identifying patients for which co-prescribing a PPI represents and efficient use of limited healthcare resources.

Results from the present analysis suggest that routine use of PPIs in all elderly patients taking nsNSAID therapy should not be recommended, as ICURs exceed widely cited cost-effectiveness thresholds. Results from this analysis suggest that PPIs should be used in elderly patients (age≥65y) with additional risk factors, i.e., history of uncomplicated or complicated ulcers.

These results contradict those from a recent health technology assessment conducted on by NICE, where routine use of HR_2A was recommended in all patients requiring nsNSAID therapy.[10,52] In contrast, in the present analysis, a blend of nsNSAID alone and nsNSAID + PPI, as opposed to routine use of H2RA, represents a more efficient use of resources. Furthermore, results from the present variability analyses suggest that there are few clinical situations where H2RAs are the most efficient strategy, if the main clinical objective is prevention of NSAID induced GI complications.

8.3 UNANSWERED QUESTIONS AND FUTURE RESEARCH

The present analysis was limited to gastroprotective agents. Consequently, celecoxib, despite the benefit it confers in reducing GI complications relative to nsNSAIDs, was not included, as it increases the risk of GI complications relative to placebo.[27] Furthermore, there are concerns that celecoxib may increase the risk of myocardial infarction, relative

to nsNSAIDs.[120] However, recent reports suggest that this may not be the case at doses less than 400mg per day.[121] Consequently, a large RCT is needed to assess the efficacy naproxen (500mg bid) plus a PPI compared with celecoxib (200mg *od*), in terms of cardiovascular and gastrointestinal clinical outcomes.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen (PRECISION) trial[122] is currently underway and has an expected completion date of 2011. The PRECISION trial is a large RCT with 20,000 arthritis patients that will examine cardiovascular, gastrointestinal and renal safety benefits, in patients treated with celecoxib (100mg to 200mg bid), relative to ibuprofen (600 mg to 800 mg tid) or naproxen (naproxen 375mg to 500 mg twice daily). To enhance generalizability, the PRECISION trial will permit PPI use and include patients with cardiovasucular risk or an established need for aspirin or both. [122]

8.4 CONCLUSION

Within the limitations of cost-effectiveness modeling and available data, results from this economic analysis suggest that use of PPIs, compared with alternative gastrprotective strategies, in patients that require nsNSAID therapy, is associated with incremental cost-effectiveness ratios that exceed widely cited thresholds. In contrast, use of PPIs among elderly patients with a history of a complicated or uncomplicated ulcer was associated with more favorable ICURs. Consequently, prescribing and use of PPIs in elderly patients taking nsNSAIDs with history of complicated and uncomplicated ulcers may represent an efficient use of limited healthcare resources. However, it should be noted that efficacy estimates are based upon endoscopic outcome trials. Consequently, large RCTs that examine clinical endpoints are needed, particularly in at-risk elderly patients. This information will enable a more accurate estimation of the cost-effectiveness of PPIs, relative to alternative gastroprotective startegies, in prevention of GI complications in elderly patients that require NSAID therapy.

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APPENDIX A Extrapolating Clinical Outcomes

Surrogate outcomes are widely used medical research to support the approval of new pharmacological treatments, as conducting RCTs on clinical endpoints outcomes sometimes require a large investment in both time and financial resources. [123-125] Surrogate outcomes usually consist of a laboratory measurement or a physical sign that acts as a substitute for a direct measure of how a patient feels, functions, or survives. The use of surrogate outcomes enables clinical studies to have smaller sample sizes and shorter follow-up periods that would otherwise not be possible. [123-125]

In instances where clinical outcome evidence is unavailable, guidelines for economic submissions require that relationships between surrogates and final outcomes be defined, i.e., forecast changes in a clinical outcome based upon incremental changes in a surrogate.[97] The aim of co-prescribing gastroprotective agents among patients taking NSAIDs is to reduce clinical ulcer complications. Randomized controlled trials have demonstrated that co-prescribing a PPI reduces the presence of both gastric and duodenal endoscopic ulcers. [8]Similarly, co-prescribing high dose H2RA reduces gastric and duodenal endoscopic ulcers.[8] In contrast, co-prescribing low dose H2RA reduces duodenal, but not gastric ulcers.[8] It is generally accepted that reduction in endoscopic ulcers will translate into reductions in clinical outcomes, despite the absence of prospective randomized clinical outcome trials to prove this. [38]

A recent meta-analysis presented results surrounding reduction in both endoscopic and clinical ulcer complications, across selective COX-2 inhibitors.[27] The relative risk reduction of endoscopically detected ulcers was more drastic than reduction in clinical ulcer complications.[27] Table 11 presents results from the meta-analysis analysis.

Table 11 Relative Risk of endoscopically detected gastroduodenal ulcers and clinical ulcer complications (perforations, obstruction or bleed) across selective COX-2 inhibitors

Treatment comparison	RR (Gastroduodenal endoscopic ulcers)	RR (POB)
Celecoxib versus nsNSAID	0.21 (95% CI, 0.16-0.28)	0.42 (95% CI, 0.22-0.80)
Rofecoxib versus nsNSAID	0.26 (95% CI, 0.21-0.32)	0.42 (95% CI, 0.24-0.73)
Etoricoxib versus nsNSAID	0.37 (95% CI, 0.18-0.77)	0.57 (95% CI, 0.31-1.04)
Valdecoxib versus nsNSAID	0.30 (95% CI, 0.24-0.39)	0.35 (95% CI, 0.14-0.87)
Lumiracoxib versus nsNSAID	0.26 (95% CI, 0.18-0.39)	0.36 (95% CI, 0.24-0.55)

RR=relative risk; nsNSAID=non-selective non-steroidal anti-inflammatory drug; POB= perforation, obstruction or bleed

A scatter-plot of relative risk point estimates (and inverse point estimates, i.e., nsNSAID versus Celecoxib) are presented in Figure 11. An additional point (1,1) was subsequently added to the figure, as it assumed that a strategy that does not reduce gastroduodenal ulcers will not result in a decrease in strict ulcer complications (perforation, obstruction or bleed).

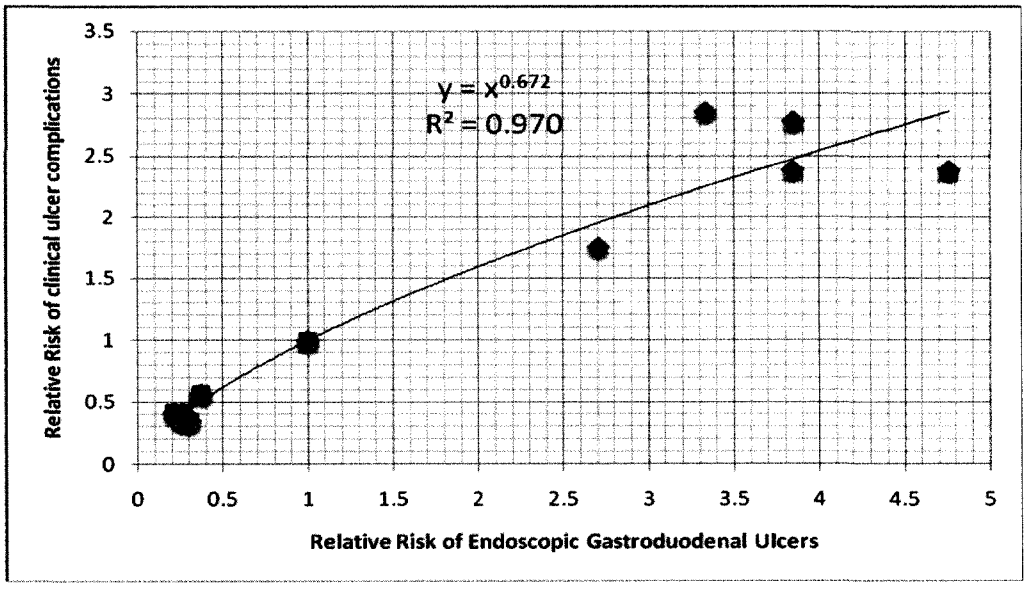

Figure 12 Scatterplot depicting relationship between relative risk of endoscopic gastroduodenal ulcers and relative risk of clinical ulcer complications

A series of regression models (logarithmic, power, linear, nth polymomial) were fit between pairs of relative risk point estimates on the scatter-plot. A power regression

model yielded the best fit, with a coefficient of determination (R^2) value of 0.970, indicating strong correlation between point estimates of relative risk.

The regression equation, $y=x^{0.672}$, can be used to determine the relative risk of clinical ulcer complications (relative to no prophylaxis) across treatment strategies. Table 12 presents the relative risk of endoscopic ulcers across treatment strategies. From this, we can calculate the relative risk of clinical ulcer complications across strategies. For instance, PPIs would have a RR of 0.50 ($y=0.36^{0.672}$).

Table 12 Relative Risk of endoscopic ulcers across treatment strategies in patients taking nsNSAIDs

Treatment	RR	95% CI
PPI	0.36	(0.30,0.45)
Low dose-H2RA	0.63	(0.45,0.88)
High dose-H2RA	0.42	(0.27,0.64)
Misoprostol 200 µg bid	0.52	(0.33,0.83)
Misoprostol 200 µg qid	0.22	(0.14,0.34)

RR=Relative risk; CI=confidence interval; PI=Proton pump inhibitor, H2RA=H2 receptor antagonist; µg=microgram; bid=twice; Daily; qid=four times daily

To test the validity of our regression equation, we compared model projections with results from published epidemiological and clinical studies.[7,29] Model projections slightly overestimate the relative risk reduction observed in these studies. Our regression equation projected a 64% (RR=0.36) relative risk reduction (RRR) in clinical ulcer complications (perforation obstruction, or bleed) in patients taking nsNSAID + misoprostol (200ug *qid*). Results from the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial demonstrated that misoprostol reduced the risk of ulcer complications by 44% (RR=0.56).[7] However, 27.9% of patients in the Misoprostol arm were prescribed doses of 400µg per day. Incorporating this into our regression model, our model produced a RRR of 54% (RR=0.46), a slightly higher RRR than that observed in the MUCOSA trial. Similarly, our regression model projected that ulcer complications would be reduced by 50% (RR=0.50) in patients taking nsNSAID + standard dose PPI. A case-control study by Rodriquez and Hernandez-Diaz found that patients co-prescribed PPIs

had a reduced risk (RR, 0.6; 95% CI, 0.4-0.9) of upper GI complications, after adjusting for several well known risk factors.[15]

APPENDIX B Public Drug Plan Listings for PPIs

Table adapted from Canadian Optimal Medication, Prescribing & Utilization Service (COMPUS) Scientific Report[11] and updated to May 2008 (Canadian Optimal Medication Prescribing and Utilization Service: Personal Communication, May 2008)

Drug	Strength & dosage	BC	AB	SK	MB	ON	QC	NWB	NS	PE	NL	YK	NW	NIHB /Nunavut
Omeprazole (Losec)	10mg	RES	RES	RES	RES	FB	FB	FB	FB	RES	RES	RES	RES	RES
	20mg	RES	FB	RES	RES	RES	FB	RES	FB	RES	RES	RES	RES	RES
Omeprazole (Apotex)	20mg	NB	FB	RES	RES		FB	RES	FB	RES	RES	RES	FB	FB
Rabeprazole (Pariet)	10mg	RES	FB	RES	RES	FB	FB	RES	FB	RES	RES	RES	FB	FB
	20mg	RES	FB	RES	RES	FB	FB	RES	NB	NB	NB	NB	NB	NB
Pantoprazole (Pantoloc)	20mg	NB	NB	NB	NB	NB	NB	NB	RES	NB	NB	RES	NB	
	40mg	RES	FB	RES	RES	RES	FB	RES	RES	RES	RES	RES	RES	RES
Lansoprazole (Prevacid)	15mg	RES	FB	RES	RES	RES	FB	RES	RES	RES	RES	RES	RES	RES
	30mg	RES	FB	RES	RES	RES	FB	RES	RES	RES	RES	RES	RES	RES
Esomeprazole	20mg	NB	NB	RES	NB	NB	FB	NB	NB	NB	NB	NB	NB	NB
	40mg	RES	NB	RES	NB	NB	FB	NB	NB	NB	NB	NB	NB	NB

AB=Alberta; BC=British Columbia; FB=Full benefit; NB= Not a benefit; NIHB= non-insured health benefits; NL=Newfoundland; NS=Nova Scotia; NW=Northwest Territories; NWB=New Brunswick; ON=Ontario; PE=Prince Edward Island; SK=Saskatechwan; MB=Manitoba; ON=Ontario; QC-Quebec; RES= restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit) YK=Yukon