Economic Assessment: Celecoxib and Rofecoxib for Patients with Osteoarthritis or Rheumatoid Arthritis

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Economic Assessment:
Celecoxib and Rofecoxib for Patients with Osteoarthritis or Rheumatoid Arthritis

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Bruce Brady and Michel Boucher (CCOHTA) are acknowledged for their significant contribution in the preparation of this Overview.

CCOHTA takes sole responsibility for the final form and content.
Highlights

What is already known about this topic?

• About NSAIDs
  − Nonsteroidal anti-inflammatory drugs (NSAIDs) are a core modality for the management of rheumatoid arthritis (RA) and are a valuable alternative for patients with osteoarthritis (OA).
  − However, some users of NSAIDs experience gastrointestinal side effects and a few develop stomach and duodenal ulcers.
  − A new generation of NSAIDs that more selectively inhibit cyclo-oxygenase type-2, called COX2 NSAIDs, have been promoted as being associated with fewer upper gastrointestinal (UGI) side effects when compared with therapy using other NSAIDs.

• About rofecoxib (Vioxx®) and celecoxib (Celebrex®)
  − Both drugs are approved for acute and chronic treatment of OA in Canada. At the time of this review, only celecoxib had been approved for the treatment of RA.
  − Their analgesic activity is similar to that of other NSAIDs.
  − Concern exists about an increase in cardiovascular events from celecoxib and rofecoxib vs comparator NSAIDs.

Assessment Objective

To determine the cost-effectiveness of:
  1. celecoxib in comparison to the “traditional” NSAIDs diclofenac and ibuprofen, and
  2. rofecoxib in comparison to the “traditional” NSAID naproxen,
in patients with OA and RA who are not on low-dose aspirin for the prevention of cardiovascular disease. The findings are based on the clinical outcomes in the CLASS and VIGOR trials.

What new information does this assessment provide?

• Average risk patients
  − Rofecoxib and celecoxib were not found to provide cost-effective therapy in patients who are at average risk of UGI events or in a population with a typical mix of average risk and high risk patients. Average risk patients are those who have not experienced UGI events, defined as either (i) prior complicated UGI events (GI perforation, obstruction or major bleeding) or (ii) prior clinical symptomatic ulcers, as shown by endoscopy.
  − The two drugs provide cost-effective therapy for patients without additional risk factors when these patients are over the age of 76 yr for rofecoxib and age 81 yr for celecoxib.

• High risk patients
  − Rofecoxib and celecoxib were found to provide cost-effective therapy for patients with proven histories of UGI events (as defined above).
  − However, these drugs may no longer be cost-effective in comparison to therapy combining a traditional NSAID with a proton pump inhibitor (PPI) if a low priced PPI becomes available, with the threshold PPI price dependent on the particular treatments being compared.
Executive Summary

The Issue

Nonsteroidal anti-inflammatory drugs (NSAIDs) are core therapeutics in the management of inflammatory musculoskeletal conditions such as rheumatoid arthritis (RA). They are also a valuable therapeutic alternative for patients with osteoarthritis (OA) who fail to respond to acetaminophen or non-pharmaceutical interventions. The gastrointestinal (GI) adverse effects are hypothesized to be due to the inhibition of cyclo-oxygenase 1 and the therapeutic effects due to the inhibition of cyclo-oxygenase 2.

The synthesized NSAIDs, rofecoxib and celecoxib, have demonstrated a selective COX2 inhibition with sparing of COX1 that may prevent the development of GI adverse effects. Both rofecoxib and celecoxib have shown clinical efficacy similar to regular NSAIDs and an improved GI safety profile, but concerns exist about an increase in CV adverse events. While sparing of COX1 leads to less GI adverse events, the inhibition of COX2 produces therapeutic analgesic, anti-inflammatory and anti-pyretic effects, and may also lead to an increase in cardiovascular (CV) thrombotic events by inhibiting prostacyclin.

Objective

The purpose of this assessment is to evaluate the long-term cost-effectiveness of the COX2 NSAID celecoxib, in comparison to diclofenac and ibuprofen, and rofecoxib in comparison to naproxen, in patients with OA and RA who are not on low-dose aspirin for the prevention of CV disease. Analyses are performed for patients at average risk of upper gastrointestinal (UGI) events, and for higher risk patients with a history of a UGI event that is either (a) a clinical UGI event (a symptomatic ulcer), as shown by endoscopy, or (b) a complicated UGI event (a GI perforation, obstruction or major bleeding).

Methods

A decision-analysis model was constructed where GI and CV events were modelled as a consequence of NSAID-intake. The model used the Markov technique and extrapolated clinical trial results over a 5-year timeframe. Major events were 1) clinical UGI events, 2) complicated UGI events (excluding symptomatic ulcers), and 3) nonfatal myocardial infarctions (MIs). Key estimates of event rates, and the relative effectiveness of COX2 NSAIDs in reducing these, were based on data from two key clinical trials, which were submitted to the US Federal Drug Administration. These trials were the Vioxx® Gastrointestinal Outcomes Research (VIGOR) study and the Celecoxib Long-Term Arthritis Safety Study (CLASS). In the VIGOR study, rofecoxib was used to treat patients with RA, although it is not currently approved by Health Canada for the treatment of RA. Remaining probability estimates were obtained through a comprehensive literature search of MEDLINE®, supplemented by bibliographies of relevant articles. Standard gamble utility estimates for arthritis health states that are complicated by GI events were gathered through a separate study of 60 randomly selected members of the general public. Cost estimates were obtained from provincial databases.

Incremental cost-effectiveness, defined as the additional cost of the COX2 strategy divided by its additional clinical benefit, was calculated from the perspective of the Ontario Ministry of Health in 1999 dollars. COX2 NSAIDs were priced at dosages consistent with the proportion of RA and
OA populations in the respective trials: (i) celecoxib 100 – 200mg bid was compared to
diclofenac 50mg tid and ibuprofen 800mg tid, and (ii) rofecoxib 25mg qd was compared to
naproxen 500mg bid. A number of other assumptions were made, including: 1) patients who
were considered at high risk of recurrent GI bleeding received a co-prescription of proton pump
inhibitors (PPIs); 2) the relative GI benefit of PPIs is the same in patients treated with COX2s
and regular NSAIDs; and 3) the cost/day of rofecoxib in RA patients was assumed to be that of
25mg qd in the absence of a regulatory-approved dosage regimen. The sensitivity of the cost-
effectiveness results to changes in individual variables was tested, as well as the effect of an
additional risk factor.

Results
For average-risk patients, base case results were more than $200,000 per quality-adjusted life-
year (QALY) gained for rofecoxib vs naproxen and for celecoxib vs ibuprofen. Diclofenac was
more effective and less costly than celecoxib in average-risk patients. Cost-effectiveness results
for average-risk patients did not fall below $86,000 per QALY gained for either COX2 NSAID
in any sensitivity analysis performed. For high risk patients, the base case results showed the
COX2 NSAIDs to be more effective and less costly for rofecoxib vs naproxen + PPI and for
celecoxib vs ibuprofen + PPI. Diclofenac had a cost per QALY gained of $255,000 compared to
celecoxib in high risk patients. In a sensitivity analysis, results fall below $50,000 per QALY
gained when high risk patients are treated with regular NSAIDs + a low priced PPI (< $1.90 per
day) compared to COX2 NSAIDs, with the threshold PPI price dependent on the particular
treatments being compared. Analysis by age group showed that the results for rofecoxib and
celecoxib fall below $50,000 per QALY gained in patients without additional risk factors over
age 76 and 81, respectively.

Conclusions
The findings are based on the clinical outcomes (including upper gastrointestinal events and
myocardial infarctions) in the CLASS and VIGOR trials and pertain only to patients with OA
and RA who do not require low-dose aspirin therapy. In the analysis, rofecoxib and celecoxib:

(i) are not cost-effective treatments in patients at average risk of upper gastrointestinal
    events (symptomatic ulcers or complicated UGI events) or in a population with a
    typical mix of average risk and high risk patients;
(ii) are cost-effective treatments for patients who are considered at high risk for
    gastrointestinal events by having a history of upper gastrointestinal events;
(iii) become less cost-effective in high risk patients as the rate of co-prescription of PPIs
    increase, and may lose their cost-effective advantage altogether if the price of PPIs was
    to decrease, with the threshold PPI price dependent on the particular treatments being
    compared; and
(iv) become cost-effective treatments for patients without additional risk factors over the
    age of 76 yr for rofecoxib and 81 yr for celecoxib.

It is noted that rofecoxib is currently not approved in Canada for the treatment of RA.
Uncertainty remains about the correct method for deriving utilities for short-term health states.
1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed on a long-term basis for patients with rheumatoid arthritis (RA), and are recommended in therapeutic guidelines as an option for individuals with osteoarthritis (OA). However, NSAIDs are generally prescribed with some hesitation due to the possibility of rare but “complicated” upper gastrointestinal (UGI) events (defined as gastrointestinal perforation, obstruction or major bleeding). NSAID-users are at almost four times greater risk than non-users of developing a “clinical” UGI event (i.e. a complicated UGI event or a symptomatic ulcer, as shown by endoscopy).

Standard NSAIDs are believed to inhibit the activity of two isoforms of the enzyme cyclooxygenase (COX). Inhibition of COX1 is associated with gastrointestinal events and inhibition of platelet aggregation. Inhibition of COX2 has beneficial pain-reducing and anti-inflammatory effects, but might also lead to an increase in cardiovascular thrombotic events.

Two recently approved NSAIDs, rofecoxib (Vioxx®) and celecoxib (Celebrex®), are believed to interact with only the COX2 isoform of the COX enzyme. Rofecoxib and celecoxib have been demonstrated to have similar analgesic activity to standard NSAIDs, while being somewhat less likely to precipitate a UGI event. However, the reduction in UGI events is questionable in patients who are also on low-dose aspirin for the prevention of cardiovascular (CV) disease. In addition, there is concern that these COX2 drugs may lead to an increased risk of CV thrombotic events.

Celecoxib and rofecoxib are approved by Health Canada for acute and chronic treatment of the signs and symptoms of OA in adult patients. In Canada, celecoxib is also approved for the treatment of the signs and symptoms of RA, while rofecoxib is not currently approved for this indication.

2. Objectives

The objective of this assessment is to evaluate the cost-effectiveness of:

1. celecoxib in comparison to diclofenac and ibuprofen, and
2. rofecoxib in comparison to naproxen,

in patients with OA and RA who are not on low-dose aspirin for the prevention of CV disease. Analyses are performed for patients at average risk of upper gastrointestinal events, and for higher risk patients with a history of a UGI event that is either (i) a prior complicated UGI event (GI perforation, obstruction or major bleeding) or (ii) a prior clinical symptomatic ulcer, as shown by endoscopy.
3. Clinical Review

Our primary estimates of efficacy and side effects were taken from two large trials, the Celecoxib Long-Term Arthritis Safety Study (CLASS),\textsuperscript{10} and the Vioxx\textsuperscript{®} Gastrointestinal Outcomes Research (VIGOR)\textsuperscript{11} study. Table 1 shows the main results from these two studies that were used in this analysis. For the purpose of this analysis, we adopted the definitions of UGI events used in the CLASS and VIGOR studies, where gastrointestinal perforation, obstruction or major bleeding were classified as a “complicated UGI event”, and all complicated UGI events including symptomatic ulcers, were classified as a “clinical UGI event”.

In CLASS,\textsuperscript{10} celecoxib 400mg bid (2 – 4 times maximum recommended doses) was compared to diclofenac 75mg bid or ibuprofen 800mg tid in about 8,000 patients over a period of 12 months. The study population included: 28% with RA and 72% with OA; 22% receiving aspirin; average age 60 years; 30% on corticosteroids. No significant difference was observed between celecoxib vs diclofenac and ibuprofen (at the doses studied in these trials) in treating the signs and symptoms of OA and RA.

In the VIGOR study,\textsuperscript{11} rofecoxib 50mg qd (2 times maximum recommended dose) was compared to naproxen 500mg bid in about 8,000 patients over a period of 12 months. The study population included: 100% with RA; none receiving low-dose aspirin; 80% female; 56% on corticosteroids. Discontinuations due to NSAID-related adverse events (AEs) such as renal, liver, HTN and edema-related AEs were numerically higher (and some statistically significantly higher) in the rofecoxib group. No differences could be observed in efficacy parameters. In the VIGOR study, rofecoxib was used to treat patients with RA, although it is not currently approved by Health Canada for this indication.

| Table 1: Incidences for clinical and complicated UGI events and for myocardial infarctions as observed in the patients recruited into the VIGOR\textsuperscript{13} and CLASS\textsuperscript{14} studies |
|-----------------------------------------------|-----------------|-----------------|-----------------|
|                                | Rofecoxib | Naproxen | Celecoxib | Diclofenac | Ibuprofen |
| **Total patient years**           | 2697      | 2694     | 1804      | 841        | 874        |
| **Clinical UGI events**          |           |          |           |            |            |
| Number                          | 56        | 121      | 22        | 10         | 29         |
| Rate / 100 patient-years        | 2.08      | 4.49     | 1.16      | 1.19       | 3.20       |
| RRR COX2 vs. regular NSAID       | --        | 53.7%*   | --        | 2.5%       | 63.8%*     |
| **Complicated UGI events**       |           |          |           |            |            |
| Number                          | 16        | 37       | 9         | 4          | 11         |
| Rate / 100 patient-years        | 0.59      | 1.37     | 0.44      | 0.48       | 1.14       |
| RRR COX2 vs. regular NSAID       | --        | 56.9%*   | --        | 8.3%       | 61.4%*     |
| **MIs**                         |           |          |           |            |            |
| Number                          | 20        | 4        | 6         | 2          | 2          |
| Rate / 100 patient-years        | 0.74      | 0.15     | 0.33      | 0.24       | 0.23       |
| RRR COX2 vs. regular NSAID       | --        | 4.93%*   | --        | 1.39%      | 1.44%      |

RRR: relative risk reduction; RR: relative risk; UGI: upper gastrointestinal; MI: myocardial infarction
*: p<0.05
4. Methods

Two types of economic evaluations were performed: a cost-effectiveness analysis and cost-utility analysis. Effectiveness was reported in terms of changes in clinical UGI events and complicated UGI events, and changes in life-years, as a consequence of taking COX2 NSAIDs as compared to regular NSAIDs. Results for the cost-utility analysis were reported in terms of quality-adjusted life-years (QALYs), as determined for the relevant clinical events associated with the different treatment strategies.

**Strategies and model**

To assess the cost-effectiveness of treatment with celecoxib or rofecoxib vs regular NSAIDs, a decision analysis model (Figure 1) was used to compare the health outcomes, resource use and costs of the different treatment strategies. The Markov model simulates the clinical events and clinical management pathways for treating OA and RA patients.

Model cycles are three months in duration, during which time a patient might experience the following GI or cardiovascular events:

- **dyspeptic symptoms** (symptoms severe enough to require a medical consultation, with or without prescription of antacids);
- **clinical UGI events** (symptomatic ulcers);
- **complicated UGI events** (symptomatic ulcers with bleeding, requiring treatment that ranges from hospitalization with surgery to simple outpatient management); and
- **myocardial infarctions**, as well as the respective increase in mortality post MI.

![Figure 1: Decision Tree used for the cost-effectiveness and cost-utility evaluation](image)

Repetitive subtrees [1] and [2] are represented once. PPI: Proton Pump Inhibitor; MI: myocardial infarctions; GI: gastrointestinal. *: patients in post MI states will go through subtree 1 without further MIs.
Recurrent bleeding was also modeled since patients who bleed are at a higher risk of recurrent GI bleeding. A small fraction of patients with a bleed, but no recurrence, was modeled to receive NSAIDs again with co-prescription of PPIs. The large majority of patients with a bleed, and all those with a recurrence, were switched to non-NSAID analgesics. At each cycle, patients are subject to age-specific mortality.

Patients with a complicated UGI event were taken off NSAIDs, except for the few that continued NSAIDs because of their particular clinical circumstances. Patients who experienced an MI were modeled to continue their respective NSAID with co-prescription of low-dose aspirin.

The expected costs and consequences of each treatment strategy were estimated by multiplying the relevant probabilities with their associated costs and health outcomes. These were then summed to arrive at the total expected costs and health outcomes for each strategy. The incremental results are based on the differences in the expected values of the treatment strategies.

A summary of the key features of the economic evaluation are given below:

a) Analytical perspective
A government payer (e.g. Ministry of Health) perspective is presented, so only the direct costs borne by the health care system were considered in the analysis.

b) Populations
The target populations are patients with RA or OA, who do not require low-dose aspirin for the prevention of cardiovascular disease. An analysis was performed for patients at average risk of a clinical UGI event, as well as those at high risk. High-risk patients were those with a positive history of clinical UGI events.

c) Time horizon
We adopted a 5-year horizon to capture the long-term consequences of the different treatment strategies on cardiovascular and GI outcomes.

d) Treatment comparators
Celecoxib (100-200mg bid) was compared to diclofenac (75mg bid) and ibuprofen (800mg tid) in patients with OA or RA and rofecoxib (25mg qd) was compared to naproxen (500mg bid) in patients with RA. While twice the recommended doses were required for COX2 to be used in these safety trials, the lower dosages of COX2 NSAIDs as recommended in patients with OA and RA were used for this analysis. High-risk patients in the standard NSAID strategy were given a proton pump inhibitor (PPI) as gastroprotective medication, while patients in the COX2 strategy were evaluated with and without PPIs.

e) Clinical data:
Estimates of UGI and MI event rates (whether statistically significant or not) associated with the different treatment strategies were taken from VIGOR® and CLASS® documents submitted to the Federal Drug Administration Arthritis Advisory Panel (Table 1).

Remaining probability estimates were obtained through a comprehensive literature search of MEDLINE®, supplemented by bibliographies of relevant articles. Estimates were only selected
from studies that included patients who receive long-term NSAIDs, preferentially with a diagnosis of OA or RA. The study providing the best evidence was used to provide the baseline estimate. Confidence intervals (95%) or estimates from other studies were used to support the lower and upper plausible range for each variable for the purposes of sensitivity analysis.

f) Utility estimates:
Utilities for the gastrointestinal health states described in the model were elicited from the general public by surveying 60 randomly selected residents of the city of Sudbury, Ontario. Rating scale and standard gamble methods were used to elicit utilities for short-term and long-term health states, as shown in Table 2.

Short-term utilities were translated into quality adjusted life-year (QALY) values for a 3-month cycle by two alternative methods: 1) assuming that the QALY equivalent of short-term events can not be less than zero (standard QALYs) and 2) by allowing negative QALY penalties that directly resulted from the measured values provided by the survey participants (health path QALYs). Standard QALY values were used in the Base Cases.

Table 2: Standard Gamble values obtained for hypothetical short-term and lifetime arthritis health states from 60 members of the general public and calculated QALY estimates according to the standard and health path method

<table>
<thead>
<tr>
<th></th>
<th>SG Utilities 3-Month*</th>
<th>Life*</th>
<th>Standard QALYs Estimate (95% CI)</th>
<th>Health path QALYs Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfect Health</td>
<td>n/a</td>
<td>1</td>
<td>0.25</td>
<td>0.250</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1</td>
<td>0.688 (0.207)</td>
<td>0.172</td>
<td>0.159, 0.185</td>
</tr>
<tr>
<td>Arthritis &amp; dyspepsia</td>
<td>0.734 (0.204)</td>
<td>0.677</td>
<td>0.126</td>
<td>0.108, 0.145</td>
</tr>
<tr>
<td>Arthritis &amp; unconfirmed ulcer</td>
<td>0.669 (0.214)</td>
<td>0.675</td>
<td>0.115</td>
<td>0.098, 0.134</td>
</tr>
<tr>
<td>Arthritis &amp; confirmed ulcer</td>
<td>0.555 (0.208)</td>
<td>0.670</td>
<td>0.095</td>
<td>0.080, 0.112</td>
</tr>
<tr>
<td>Arthritis &amp; complicated UGI, medical</td>
<td>0.454 (0.260)</td>
<td>0.666</td>
<td>0.078</td>
<td>0.062, 0.096</td>
</tr>
<tr>
<td>Arthritis &amp; complicated UGI, surgical</td>
<td>0</td>
<td>0.648 (0.251)</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Immediate Death</td>
<td>n/a</td>
<td>0</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*: values are means (standard deviation); **: values in italics are indirectly calculated

g) Resource use and costs:
The costs of the drugs are shown in Table 3. Other costs, associated with managing the clinical events included: consultation for dyspepsia; outpatient management of symptomatic ulcers and complicated UGI events; medical and surgical management of complicated UGI events; and managing MI events. All costs are reported in 1999 dollars. Costs were based on provincial data, where possible.

Drug costs were those allowed under the Ontario Drug Benefit Plan, and were supplemented by the allowable mark-up and prescription fee. Costs of celecoxib are different for OA and RA dosages and were thus weighted based on the percentage of patients with OA and RA recruited into CLASS. As rofecoxib is not currently approved for use by Health Canada for treatment of RA, the cost per day of rofecoxib in RA was assumed to reflect double the dosage used in OA patients and has not been derived from a regulatory-approved dosage regimen.
### Table 3: Drug cost estimates used in the decision analysis model (Base Case)\textsuperscript{15}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Costs per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen (800mg tid)</td>
<td>$0.22</td>
</tr>
<tr>
<td>Naproxen (500mg bid)</td>
<td>$0.42</td>
</tr>
<tr>
<td>Diclofenac (75mg bid)</td>
<td>$1.14</td>
</tr>
<tr>
<td>Rofecoxib (12.5mg qd / 25mg qd / 50mg qd)</td>
<td>$1.25 / $1.25 / $2.50</td>
</tr>
<tr>
<td>Celecoxib (100mg bid / 200mg bid / 400mg bid)</td>
<td>$1.25 / $2.50 / $5.00</td>
</tr>
<tr>
<td>Acetaminophen (1g qid)</td>
<td>$0.37</td>
</tr>
<tr>
<td>Cimetidine (400mg bid)</td>
<td>$0.27</td>
</tr>
<tr>
<td>Pantoprazole (40mg qd)</td>
<td>$1.90</td>
</tr>
</tbody>
</table>

### h) Discounting:
Future costs and QALYs were discounted at an annual rate of 5%, as recommended in CCOHTA’s Guidelines.\textsuperscript{16} Rates of 0% and 3% were tested in sensitivity analyses.

### i) Handling uncertainty:
Uncertainty was tested through one-way and multi-way sensitivity analyses of model parameters, including the probability and utility of clinical events, the dosage of celecoxib and rofecoxib, the costs of managing clinical events and the PPI price.

### j) Other assumptions:
1) We assumed a constant protective effect of COX2 inhibitors on GI complications, which may favour COX2 inhibitors, as the population of NSAID users over time is likely to eventually include mainly NSAID-tolerant patients.
2) Congruent with our \textit{a priori} exclusion of patients on low-dose aspirin, we assumed that COX2 NSAIDs would have no GI benefit in patients who experienced an MI in the model and then received low dose aspirin.
3) We assumed that PPIs co-prescribed with NSAIDs were associated with a constant relative risk reduction in the rate of UGI events, irrespective of whether the NSAID was COX2-specific or not.
4) Trial doses of COX2 NSAIDS were 2-4 times higher than recommended, however, we assumed that the efficacy and GI safety profile of COX2 NSAIDs was identical at the lower recommended doses, which we used for the purpose of this analysis. Cost-effectiveness analysis was also performed for the higher doses of COX2 NSAIDs as used in the VIGOR and CLASS studies.

### 5. Results
Below are the key results for the base cases (Table 4) and the sensitivity analysis of rofecoxib and celecoxib (vs comparators) over the 5-year period of analysis. Results are presented separately for average risk and high risk patients.
**Base Case**

a) **Average Risk Patients**

For patients at average risk, rofecoxib increased costs relative to naproxen ($3,173 vs $1,576), and increased quality-adjusted life expectancy by 0.006 QALYs, approximately 2.2 days of life in full health. The marginal cost for each QALY gained was high, at $271,188.

Use of the CLASS data generated similar results. Celecoxib increased costs relative to diclofenac and ibuprofen ($3,371 vs $2,503 vs $1,141). However, in the CLASS study, celecoxib reduced GI events by a very modest amount in comparison with diclofenac. In addition, cardiovascular events were in fact slightly more common in the celecoxib group, albeit not statistically significantly. Thus, neither of the more effective strategies (celecoxib and diclofenac) appear to be economically attractive in comparison with the least costly strategy (ibuprofen). The incremental cost effectiveness ratio for diclofenac in comparison with ibuprofen is unattractive (> $100,000/QALY), and celecoxib is even less attractive (dominated by) than diclofenac, because of its similar efficacy and worse cardiovascular profile.

**Table 4:** Baseline cost-effectiveness ratios (Canadian dollars) for the 5-year comparison of 1) rofecoxib to naproxen in patients with rheumatoid arthritis and 2) celecoxib to diclofenac and ibuprofen in patients with osteoarthritis (72%) or rheumatoid arthritis (28%)

<table>
<thead>
<tr>
<th>Average-risk patients</th>
<th>Costs*</th>
<th>QALYs*</th>
<th>Life-years*</th>
<th>Cost/QALY gained*</th>
<th>Cost/life-year gained*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIGOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen (500mg bid)</td>
<td>$1,576</td>
<td>2.894</td>
<td>4.358</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Rofecoxib (25mg qd)</td>
<td>$3,173</td>
<td>2.900</td>
<td>4.361</td>
<td>$271,188</td>
<td>$455,071</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (800mg tid)</td>
<td>$1,141</td>
<td>2.899</td>
<td>4.360</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Diclofenac (75mg bid)</td>
<td>$2,503</td>
<td>2.910</td>
<td>4.365</td>
<td>$119,395</td>
<td>$236,510</td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid)</td>
<td>$3,371</td>
<td>2.909</td>
<td>4.365</td>
<td>dominated by diclofenac **</td>
<td></td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid) vs. Ibuprofen</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>$212,593</td>
<td>$402,545</td>
</tr>
<tr>
<td>High-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VIGOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd)</td>
<td>$4,090</td>
<td>2.885</td>
<td>4.354</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Naproxen (500mg bid) + PPI</td>
<td>$4,766</td>
<td>2.882</td>
<td>4.352</td>
<td>dominated by rofecoxib **</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (25mg qd) + PPI</td>
<td>$6,486</td>
<td>2.894</td>
<td>4.359</td>
<td>$281,244</td>
<td>$567,820</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid)</td>
<td>$4,327</td>
<td>2.900</td>
<td>4.360</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ibuprofen (800mg tid) + PPI</td>
<td>$4,414</td>
<td>2.889</td>
<td>4.354</td>
<td>dominated by celecoxib **</td>
<td></td>
</tr>
<tr>
<td>Diclofenac (75mg bid) + PPI</td>
<td>$5,881</td>
<td>2.906</td>
<td>4.363</td>
<td>$254,803</td>
<td>$487,241</td>
</tr>
<tr>
<td>Celecoxib (100/200mg bid) + PPI</td>
<td>$6,746</td>
<td>2.906</td>
<td>4.363</td>
<td>dominated by diclofenac **</td>
<td></td>
</tr>
</tbody>
</table>

Strategies are ordered by increasing cost. The more expensive strategy is compared to the less expensive, non-dominated strategy.

UGI: Upper Gastrointestinal events; QALY: Quality Adjusted Life Year; PPI: proton pump inhibitor (lansoprazole)

*: future QALYs and life-years are discounted by 5%

**: i.e. is a more costly and less efficacious strategy
b) High risk patients
In patients with a prior history of a clinical UGI event, rofecoxib alone is both less costly and more effective than naproxen, co-prescribed with a PPI. Adding a PPI to rofecoxib is not an economically attractive strategy in comparison with rofecoxib alone, in view of the high cost-utility ratios of $281,244 per QALY gained. Similarly, celecoxib alone is less costly and more effective in comparison to ibuprofen. Celecoxib alone is the most economically attractive strategy, as the strategies which are marginally more effective (celecoxib + PPI, diclofenac + PPI) are not economically attractive.

Sensitivity Analysis
a) Average Risk Patients
Most single variable sensitivity analyses for the comparison of rofecoxib and naproxen in RA patients at average-risk showed only a relatively minor impact on the cost-effectiveness ratios. Results for rofecoxib in RA patients of average-risk were sensitive to the relative risk reduction in clinical UGI events and complicated UGI events, but were still not cost-effective (Table 5). Sensitivity analysis around the utility for coronary artery disease showed that assuming a utility for Class III coronary artery disease would increase the cost-effectiveness ratio for rofecoxib to $651,033. On the other hand, assuming no difference in MI event rates between rofecoxib and naproxen would lower the cost-effectiveness ratio to $86,054 per QALY gained. A much less dramatic effect is seen for the comparison of celecoxib to ibuprofen for the same variables. Celecoxib is also unlikely to be cost-effective for average risk patients in all other sensitivities examined.

Table 5: Average risk patients: sensitivity analysis of selected model estimates

<table>
<thead>
<tr>
<th>Variables changed in sensitivity analysis</th>
<th>Cost per QALY gained *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Range</td>
</tr>
<tr>
<td><strong>Rofecoxib 25mg qd vs. Naproxen 500mg bid</strong></td>
<td></td>
</tr>
<tr>
<td>RRR clinical UGI events (36.0% - 67.0%)</td>
<td>$536,852</td>
</tr>
<tr>
<td>Utility for coronary artery disease (0.875 - 1)</td>
<td>$651,033</td>
</tr>
<tr>
<td>No difference in MI event rates</td>
<td></td>
</tr>
<tr>
<td><strong>Celecoxib 100/200mg bid vs. Ibuprofen 800mg tid</strong></td>
<td></td>
</tr>
<tr>
<td>Utility for coronary artery disease (0.875 - 1)</td>
<td>$226,276</td>
</tr>
<tr>
<td>No difference in MI event rates</td>
<td></td>
</tr>
<tr>
<td><strong>Trial dosages of COX2 NSAIDs</strong></td>
<td></td>
</tr>
<tr>
<td>Average risk: Rofecoxib 50mg qd vs. Naproxen 500mg bid</td>
<td>$638,240</td>
</tr>
<tr>
<td>High risk: Rofecoxib 50mg qd vs. Naproxen 500mg bid + PPI</td>
<td>$420,112</td>
</tr>
<tr>
<td>Average risk: Celecoxib 400mg bid vs. Ibuprofen 800mg tid</td>
<td>$774,929</td>
</tr>
<tr>
<td>High risk: Celecoxib 400mg bid vs. Ibuprofen 800mg tid + PPI</td>
<td>$526,236</td>
</tr>
<tr>
<td>High risk: Celecoxib 400mg bid vs. Diclofenac 75mg bid + PPI</td>
<td>diclofenac dominates</td>
</tr>
</tbody>
</table>

RRR: relative risk reduction; PPI: proton pump inhibitor; UGI: upper gastrointestinal event;
*: future QALYs discounted by 5%.
b) High risk patients

Sensitivity analyses results limited to high risk patients revealed that cost-effectiveness ratios were sensitive to the price of PPI and the percentage of patients receiving rofecoxib plus a concomitant PPI. Specifically, prescription of rofecoxib to RA patients at high risk is more expensive than naproxen plus a PPI, if the daily price of PPIs (before mark-up and prescription fee) drops below $1.35. It would achieve reasonable cost-effectiveness thresholds of $50,000 per QALY gained as long as PPIs cost no less than $1.20. Prescribing rofecoxib would also become more expensive than prescribing naproxen if more than 28% of RA patients on rofecoxib were co-prescribed PPIs. Likewise, celecoxib is cost-saving compared to ibuprofen in combination with PPIs down to a daily price of $1.83 for PPIs and would still be reasonably cost-effective ($50,000 / QALY), as long as PPIs cost no less than $1.38 per day. Diclofenac becomes cost-effective ($50,000 / QALY) compared to celecoxib when the price of PPIs falls below $0.90 and diclofenac is a cost savings strategy when the PPI price falls below $0.65. Furthermore, cost-effectiveness ratios would be higher, if COX2 NSAIDs were costed according to dosages used in the clinical trials.

The influence of age was examined in a sensitivity analysis of average-risk patients. The results showed that rofecoxib became reasonably cost-effective in comparison to naproxen below thresholds of $100,000 and $50,000 per QALY gained in patients aged greater than 68 and 76 years, respectively. Analysis of age for celecoxib in comparison to ibuprofen in patients with RA or OA led to age thresholds of 70 and 81 yr for cost-effectiveness ratios of $100,000 and $50,000 per QALY gained.

When values for short-term events, which were estimated using the Health-Path approach, were utilized in the model, more favourable cost-utility ratios were observed in all scenarios. In average-risk patients, use of the Health-Path approach results in lower cost-utility ratios for COX2 inhibitors, although celecoxib is dominated by diclofenac. The analysis appears to be somewhat sensitive to values placed on short-term events.

6. Discussion and Limitations

The findings of the economic analysis are closely influenced by the rates of certain adverse events (specifically, clinical and complicated UGI events and MI events) reported in two major trials of celecoxib\(^6\) and rofecoxib.\(^{11}\) In view of the fact that the cost of both drugs is similar at OA doses, and that the absolute risk reduction in GI events was similar in both CLASS and VIGOR, we believe that the qualitative results observed in this analysis (economically attractive in high risk patients, not so in average risk patients) most likely apply to both celecoxib and rofecoxib for OA patients. We also believe that the qualitative results of this analysis also apply to RA patients, although celecoxib may be somewhat less attractive at the higher doses (200mg bid) suggested for RA patients [which, in Ontario, is twice as expensive as the recommended dose of rofecoxib (25mg qd)].

Two large new trials of celecoxib and rofecoxib for patients with OA have been recently published, each of three months duration: the SUCCESS\(^\dagger\)\(^{17}\) study compared celecoxib to naproxen or diclofenac, and the ADVANTAGE\(^\dagger\)\(^{18}\) trial compared naproxen and rofecoxib. However, the data of these two large studies have been published in abstract form only and do
not invalidate the findings of this cost-effectiveness analysis, but rather corroborate the present results.

We are less confident about the extrapolation of the rate of UGI events observed in the study populations to specific age strata. Precise estimates for the relationship between age and UGI event rates were not available from the VIGOR and CLASS studies. Hence, conclusions about precise age thresholds should be viewed with caution. Similarly, extrapolation to patients on aspirin is uncertain. Our baseline analysis assumes that the gastroprotective effect of COX2 NSAIDs does not extend to aspirin. This is because aspirin increases bleeding risk and because clinical UGI events in the CLASS study were not different, and were in fact slightly higher in aspirin users who took celecoxib versus those who took ibuprofen or diclofenac. However, this conclusion must be regarded as uncertain, as this interpretation is based on results from a small subgroup of the CLASS study.

Event rates of nonfatal MIs were incorporated in the analyses exactly as reported for each drug in its respective trial. Although the pathophysiologic mechanisms of COX2 inhibition may lend some credibility to differing event rates, an evaluation of cardiovascular safety was not the primary objective of either study and it would require larger sample sizes to address this issue properly. The results may thus be overly conservative, if, in truth, there were no added cardiovascular risks due to COX2 NSAIDs.

This analysis also specifically excluded the consideration of adverse events other than MIs and UGI events. In fact, higher event rates of so-called serious adverse events were reported for celecoxib and rofecoxib, and higher withdrawal rates due to NSAID-related adverse events were reported for rofecoxib. However, while UGI events and MIs (VIGOR only) were classified according to their clinical relevance, this was not the case for other adverse events which precluded their use in this analysis.

Some controversy has arisen about the adequacy of measuring QALYs for short-term states using conventional methods because they do not allow for values less than zero for the period of the short-term. We used a second method to derive utilities for the short-term states that resulted in negative utilities. Substitution of the baseline short-term QALYs with these negative QALYs would have led to more favourable cost-effectiveness ratios. This method is not commonly accepted and results should, therefore, be regarded as preliminary.

In order to judge the cost-effectiveness of the COX2 drugs from the perspective of public health care payers and decision-makers in Canada, the following benchmarks were loosely inferred from previous reimbursement decisions of health technologies: (i) “likely to be cost-effective” if below $50,000 per QALY gained; (ii) “marginally cost-effective” if between $50,000 and $100,000 per QALY gained; and (iii) “unlikely to be cost-effective” if above $100,000 per QALY gained. Caution should be used when interpreting these benchmarks. These are not strict thresholds but reflect, in general terms, what is considered to be the current judgements of Canadian decision-makers. In addition, other factors such as confidence in the clinical results, are often taken into account by decision-makers when considering whether to reimburse a health technology.

For high risk patients, the cost-effectiveness of both celecoxib and rofecoxib were shown to be sensitive to the cost of PPIs used in combination with a regular NSAID. However, these findings
should be viewed cautiously as they are based on modeling techniques and not on actual head-to-head trials comparing COX2 NSAIDs to PPIs used in combination with a regular NSAID.

7. Conclusions
The findings are based on the clinical outcomes (including upper gastrointestinal events and myocardial infarctions) in the CLASS and VIGOR trials and pertain only to patients with OA and RA who do not require low-dose aspirin therapy. In the analysis, rofecoxib and celecoxib:

- are not cost-effective treatments in patients at average risk of upper gastrointestinal events (symptomatic ulcers or complicated UGI events) or in a population with a typical mix of average risk and high risk patients;
- are cost-effective treatments for patients who are considered at high risk for gastrointestinal events by having a history of upper gastrointestinal events;
- become less cost-effective in high risk patients as the rate of co-prescription of PPIs increases; and may lose their cost-effective advantage altogether if the price of PPIs was to decrease, with the threshold PPI price dependent on the particular treatments being compared; and
- become cost-effective treatments for patients without additional risk factors over the age of 76 yr for rofecoxib and 81 yr for celecoxib.

It is noted that rofecoxib is currently not approved in Canada for the treatment of RA. Uncertainty remains about the correct method for deriving utilities for short-term health states.
8. References


