# COXIBs In Clinical Practice

***Towards a Saskatchewan Consensus***

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**RxFiles**

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**HIGHLIGHTS**

***1. Studies generally show that COXIBs are equal but not superior in efficacy to other NSAIDS.***

***2. COXIBs reduce the incidence of serious adverse GI events in patients not taking ASA. {Relative Risk Reductions >40%; Absolute Risk Reductions ≥0.78%; Number Needed to Treat ≥120*** (*high-dose trials*)***}.***

***3. Concomitant ASA largely attenuates the GI advantage of celecoxib (and possibly rofecoxib) compared to traditional NSAIDs.***

***4. In high-GI-risk patients on ASA, conventional NSAIDs or COXIBs should be used together with a gastroprotective agent (ie. a proton pump inhibitor or misoprostol).***

***5. The advantage of COXIBs is particularly justifiable in patients at high risk of GI complications. For low risk patients, their high cost compared to conventional NSAIDS may not justify the routine use of COXIBs.***

***6. COXIBs have better GI tolerability than NSAIDs, and one can expect better compliance and lower drop-out rates with their use in select patients.***

***7. COXIBs share similar adverse renal effects with conventional NSAIDs; caution is warranted in high risk patients such as the very elderly.***

***8. Patients at high risk of cardio-renal complications (see Table 5) should be reassessed within 7-14 days. Evaluation for any respiratory insufficiency, edema and measurement of blood pressure and weight could be useful. SCr and electrolytes may provide additional information.***

***9. Some studies have observed an increase in cardiovascular risk in patients on COXIBs; this has not been conclusively studied in well designed clinical trials. Caution is warranted; further safety studies are planned.***

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### Introduction

The risk of adverse effects with NSAIDs has led to a search for safer anti-inflammatories. Thus, agents with highly selective inhibition of cyclooxygenase-2 (COX-2) have been developed in hopes of greater safety. The interpretation of studies measuring relative COX-2 to COX-1 selectivity is subject to much debate due to differences in the various assays used. This paper will limit discussion to celecoxib *CELEBREX* and rofecoxib *VIOXX*, which have outcome evidence for decreasing gastrointestinal risk.

## EFFICACY

### *1. Studies generally show that COXIBs are equal but not superior in efficacy to other NSAIDS.*

**Osteoarthritis (OA):** Celecoxib has been compared to placebo, naproxen and diclofenac in the treatment of OA. [1,2] All active treatment arms had greater efficacy than placebo. Efficacy between celecoxib and comparator NSAIDS were similar in both studies. The 100mg bid dose of Celecoxib has been most studied although the commonly used 200mg daily dose also appears to be effective.[3]

Rofecoxib has been compared to placebo, ibuprofen, diclofenac, and nabumetone in the treatment of OA. [4,5,6,7,8] Active treatment groups consistently did better than placebo groups. No differences were found between rofecoxib 12.5 or 25mg groups compared to ibuprofen 800mg tid[6] and diclofenac 50mg tid[7]. One study found rofecoxib 12.5mg od to be superior to nabumetone 1,000mg od in patient global response over 6 weeks.[8] A recent study compared rofecoxib 12.5 or 25mg daily to celecoxib 200mg daily and acetaminophen 4g/day in OA of the knee. The higher dose of rofecoxib appeared most efficacious.[9]

**Rheumatoid Arthritis (RA):** Celecoxib has been compared to placebo, naproxen and diclofenac in the treatment of RA.[10,11] Celecoxib was consistently more efficacious than placebo. Celecoxib at varying dosages had similar efficacy to naproxen 500mg bid and diclofenac SR 75mg bid.

Rofecoxib has also been studied in the treatment of RA. Both 25 and 50mg doses of rofecoxib had higher response rates than 5mg daily rofecoxib or placebo.[12] Rofecoxib has just recently been granted an FDA indication for use in RA.

**Acute Pain (AP):** Rofecoxib at a dose of ≥50mg has been compared to ibuprofen, celecoxib and placebo in the **single dose** treatment of dental pain.[13,14] Efficacy for rofecoxib 50mg was equivalent to ibuprofen 400mg. Rofecoxib and ibuprofen both provided **earlier** pain relief than celecoxib.[13] The duration of effect with rofecoxib has been shown to be longer than celecoxib and ibuprofen, although this is somewhat misleading as ibuprofen and celecoxib require multiple daily dose regimens.[14] Celecoxib 100mg and 400mg have been compared to ASA 650mg in the treatment of acute dental pain.[15] Celecoxib had similar efficacy to ASA and was superior to placebo.

**Other conditions:** COXIBs have been studied in both primary dysmenorrhea and acute fever[16]. Effects appear similar, but not superior to standard NSAID treatment. Celecoxib at a dose of 400mg bid has also been effective in reducing the number of polyps in familial adenomatous polyposis (FAP).

See also Table 1: Summary of Clinical Efficacy Studies

**Table 1: Summary of Clinical Efficacy Studies for Celecoxib and Rofecoxib**

| Authors | Type | Weeks | Treatment | Pts | Results & Comments |
|---|---|---|---|---|---|
| Bensen et al[1] | **OA** | 12 | Celecoxib 200mg bid<br>Celecoxib 100mg bid<br>Celecoxib 50mg bid<br>Naproxen 500mg bid<br>Placebo | 202<br>197<br>203<br>198<br>203 | Celecoxib and naproxen more efficacious than placebo. Celecoxib 100mg and 200mg appeared more effective than celecoxib 50mg group. |
| McKenna et al[2] | **OA** | 6 | Celecoxib 100mg bid<br>Diclofenac 50mg tid<br>Placebo | 201<br>199<br>200 | Celecoxib and diclofenac more efficacious than placebo. Celecoxib better tolerated. |
| Ehrich et al[4] [abstract] | **OA** | 6 | Rofecoxib 50mg od<br>Rofecoxib 25mg od<br>Rofecoxib 12.5mg od<br>Rofecoxib 5mg od<br>Placebo | 97<br>137<br>144<br>149<br>145 | Rofecoxib more efficacious than placebo. A dose-response curve showed 12.5mg, 25mg, and 50mg all superior to 5mg. |
| Ehrich et al[5] | **OA** | 6 | Rofecoxib 125mg od<br>Rofecoxib 25mg od<br>Placebo | 74<br>73<br>72 | Rofecoxib more efficacious than placebo.<br>Dose dependent side effects: e.g. edema: 6.8% in 125mg arm. |
| Day et al[6] | **OA** | 6 | Rofecoxib 25mg od<br>Rofecoxib 12.5mg od<br>Ibuprofen 800mg tid<br>Placebo | 242<br>244<br>249<br>74 | Rofecoxib and ibuprofen more efficacious than placebo. No differences in efficacy or incidence of 'any clinical adverse event' between active treatment groups. |
| Cannon et al[7] | **OA** | 26 | Rofecoxib 25mg od<br>Rofecoxib 12.5mg od<br>Diclofenac 50mg tid | 257<br>259<br>268 | All showed similar efficacy. Most frequent adverse event for rofecoxib was upper respiratory infection (≥23.9% vs 17.9%). |
| Geba et al[8] | **OA** | 6 | Rofecoxib 12.5mg od<br>Nabumetone 1000mg od<br>Placebo | 424<br>410<br>208 | Rofecoxib and nabumetone more efficacious than placebo; rofecoxib more efficacious than nabumetone. |
| Geba et al[9] | **OA** | 6 | Rofecoxib 25mg od<br>Rofecoxib 12.5mg od<br>Celecoxib 200mg od<br>Acetaminophen 1g qid | 95<br>96<br>97<br>94 | Rofecoxib 25mg more efficacious than rofecoxib 12.5mg, celecoxib 200mg, acetaminophen 4g. (Note: rofecoxib 25mg dose may be more fairly compared to celecoxib 200mg bid) |
| Simon et al[10] | **RA** | 12 | Celecoxib 400mg bid<br>Celecoxib 200mg bid<br>Celecoxib 100mg bid<br>Naproxen 500mg bid<br>Placebo | 218<br>235<br>240<br>225<br>231 | All celecoxib arms similar in efficacy to the naproxen arm and superior in efficacy to the placebo. |
| Emery et al[11] | **RA** | 24 | Celecoxib 200mg bid<br>Diclofenac SR 75mg bid | 326<br>329 | Similar response in both groups. |
| Schnitzer et al[12] | **RA** | 8 | Rofecoxib 50mg od<br>Rofecoxib 25mg od<br>Rofecoxib 5mg od<br>Placebo | 161<br>171<br>158<br>168 | Rofecoxib 50mg and 25mg had greater efficacy than rofecoxib 5mg and placebo. A potential drug interaction with methotrexate did not appear to cause any safety problems. |
| Hubbard et al[15] [abstract] | **AP** | single dose | Celecoxib 400mg<br>Celecoxib 100mg<br>ASA 650mg<br>Placebo | 50<br>50<br>50<br>50 | Celecoxib efficacy similar to ASA and superior to placebo. |
| Morrison et al[14] | **AP** | single dose | Rofecoxib 50mg<br>Ibuprofen 400mg<br>Placebo | 50<br>51<br>50 | Initial efficacy for rofecoxib and ibuprofen similar; both better than placebo. Effect duration longer with rofecoxib. |
| Malmstrom et al[13] | **AP** | single dose | Rofecoxib 50mg<br>Celecoxib 200mg<br>Ibuprofen 400mg<br>Placebo | 90<br>91<br>46<br>45 | Efficacy for rofecoxib, celecoxib & ibuprofen greater than placebo. Initial response with rofecoxib & ibuprofen greater than celecoxib. Effect duration longer with rofecoxib. |
| Morrison et al[17] | **AP**<br>Dysmenorrhea | 3 days | Rofecoxib 50mg od<br>Rofecoxib 25mg od<br>Naproxen sodium 550mg bid<br>Placebo | 118<br>115<br>122<br>118 | Pain relief in both rofecoxib groups and the naproxen group similar and greater than placebo group. |
| Schwartz et al[16] | **AP** | 6 hours | Rofecoxib 25mg<br>Rofecoxib 12.5mg<br>Ibuprofen 400mg<br>Placebo | 23<br>24<br>21<br>21 | Rofecoxib and ibuprofen both reduced naturally occurring fever more than placebo. Duration of effect was longer with rofecoxib. |

**AP**= acute pain; **OA**= osteoarthritis; **RA**= rheumatoid arthritis

## GI SAFETY

Gastrointestinal (**GI**) toxicity has been a major adverse effect of NSAIDs. Perforation, obstruction and bleeding (**POB**) are the hallmarks of serious toxicity. Other GI complaints such as symptomatic ulcer can also create substantial management difficulties.

The annual rate of severe gastrointestinal adverse effects with the use of traditional NSAIDs is 2-4%.[18,19,20] Ulcers caused by NSAIDs are usually asymptomatic. In this group up to 80% of cases present initially as a severe complication (POB), rather than any symptom indicating ulcer.[21,22,23] This risk varies considerably depending on the presence of risk factors (see Table 2). While the risk of developing POB in young individuals without risk factors is only 0.4%[24], elderly patients with one or more risk factors have a POB risk in the range of 5%. Anti-inflammatory drugs with lower GI toxicity would be of great value, particularly in the latter group if not offset by other adverse effects (e.g. cardio-renal complications).

**Table 2: Risk Factors for GI toxicity** [25,26]

- advanced age (e.g. over 75years)
- previous history of ulcer or peptic ulcer disease (PUD)
- concomitant use of corticosteroids, ASA, or warfarin (e.g. Coumadin)
- use of multiple NSAIDs (including low-dose ASA)
- alcoholism
- co-morbid illness (especially cardiovascular, renal & hepatic failure)

### *2. COXIBs reduce the incidence of serious adverse GI events in patients <u>not</u> taking ASA. {Relative Risk Reductions >40%; Absolute Risk Reductions ≥0.78%; Number Needed to Treat ≥120* (*high-dose trials*)*}.*

Preliminary trials with the COXIBs demonstrated substantial reduction of both endoscopic ulcer and ulcer complications compared to traditional NSAIDs. They were also somewhat better tolerated.[12,27]

Two large trials have been published which address the safety of COXIBs administered for a period of six months or longer. These are the Celecoxib Long Term Arthritis Safety Study (**CLASS**)[28] and the Vioxx Gastrointestinal Outcomes Research (**VIGOR**).[29] Each study was designed differently with regards to patient selection, study end points, duration of therapy, comparator NSAIDs, and allowable administration of aspirin during the study. Thus, these studies cannot be directly compared. Both showed a decrease, but not disappearance, of GI toxicity.

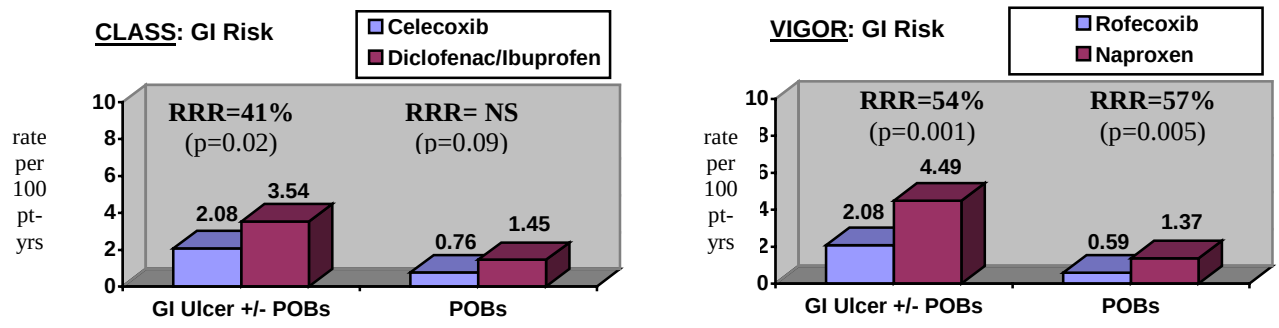
Compared to traditional NSAIDs, the incidence of symptomatic ulcers and ulcer complications was reduced from 3.54% to 2.08% in CLASS and from 4.49% to 2.08% in VIGOR. **In VIGOR, severe complications (POBs) were reduced from 1.37% to 0.59% (ARR=0.78%; RRR=41%)**. In the CLASS study, reduction in POB did not reach a level of statistical significance, likely due to insufficient statistical power. The inclusion of patients on ASA and the high dropout rate in diclofenac patients were also limitations in CLASS. **See Table 3 & Figure 1**.

**Table 3: Adverse GI Events from CLASS and VIGOR** [30,31]

| Study | Drug & Dose | Duration & type of patients in trial | # patients | GI Ulcer Complications* & Symptomatic Ulcers per 100 patient years | | | GI Ulcer Complications* (POBs) per 100 patient years | | |
|---|---|---|---|---|---|---|---|---|---|
| **CLASS** | **Celecoxib** 400mg BID | **≤6mo; ave 4.2mo** OA[72%] or RA | 3987 | **2.08** | RRR= 41% ARR= 1.46% NNT= 69 | p= 0.02 | **0.76** | RRR= NS ARR= 0.69% NNT= NS | p= 0.09 **NS** |
| | **Ibuprofen** 800mg TID or **Diclofenac** 75mg BID | | 3981 | **3.54** | | | **1.45** | | |
| **VIGOR** | **Rofecoxib** 50mg OD | **≤13mo; mean 8mo** RA | 4047 | **2.08** | RRR= 54% ARR= 2.41% NNT= 42 | p= 0.001 | **0.59** | RRR= 41% ARR= 0.78% NNT= 128 | p= 0.005 |
| | **Naproxen** 500mg BID | | 4029 | **4.49** | | | **1.37** | | |

**ARR=** absolute risk reduction; **NNT=** number needed to treat to prevent one event; **NS**= not statistically significant; **OA**= osteoarthritis; **RA**= rheumatoid arthritis; **RRR**= relative risk reduction ***GI Ulcer Complications** consisted of perforation, obstruction and bleeding (**POB**)
**Note**: the selective reporting of **<u>6-month</u>** data for CLASS has been criticized due to **"entire study period"** data (**<u>12-16 month</u>**) also submitted to the FDA[32]

**Figure 1: Adverse GI Events from CLASS and VIGOR**



In both studies, COXIBs were administered in supra-therapeutic doses, twice the maximum recommended for rheumatoid arthritis (celecoxib 400 mg bid and rofecoxib 50mg od) as opposed to standard doses of comparative NSAIDs. Thus the advantage over NSAIDs might have been even higher had COXIBs been used in their usually recommended dose.

A post-marketing report to the FDA reviewed 3.6 million celecoxib prescriptions filled over a 3-month period. It showed a remarkably low incidence of serious GI bleeding events of 0.0015 per 100 patient years.[33]

***3. Concomitant ASA largely attenuates the GI advantage of celecoxib (and possibly rofecoxib) compared to traditional NSAIDs.***
***4. In high-GI-risk patients on ASA, conventional NSAIDs or COXIBs should be used together with a gastroprotective agent (ie. a proton pump inhibitor or misoprostol).***

In the CLASS study, 21% of patients were on a cardioprotective dose of ASA. Sub-group analysis demonstrated that a reduction in the GI toxicity of celecoxib was largely attenuated by aspirin (ASA).[30] This suggests there may be very little advantage to using celecoxib (and possibly rofecoxib) in patients who require ASA. ASA did not increase the risk of GI complications in NSAID groups. This question was not tested in the VIGOR study, but caution should be exercised with all COXIBs in the setting of combination ASA use. Adding a gastroprotective agent such as a proton pump inhibitor or misoprostol (200mcg BID-TID) may be considered for high-GI risk patients requiring both ASA and an NSAID/COXIB.

***5. The advantage of COXIBs is particularly justifiable in patients at high risk of GI complications. For low risk patients, the high cost compared to conventional NSAIDS may not justify routine use.***

The risk of ulcer complications in young patients without risk factors is estimated to be in the range of 0.5% per year.[34] Provided COXIBs reduce this risk by 40%, 333 patients must be treated with COXIBs for one year to save one POB. The price difference between one-month treatment with generic ibuprofen and COXIBs is in the range of $40 - $80. Therefore, the expense of preventing one complication in this low-risk patient group would be approximately $13,000 to $26,000. The cost of managing a gastrointestinal event has been estimated to range from $1,200 (outpatient, uncomplicated) to $6,127 (hospitalized, requiring surgery).[35] The substantial expense of COXIBs, together with the low risk of complications with conventional NSAIDs in lower risk patients makes conventional NSAIDs a perfectly acceptable mode of treatment in this patient population.

***6. COXIBs have better GI tolerability than NSAIDs, and one can expect better compliance and lower drop-out rates with their use in select patients.***

Dropout rates (from VIGOR and CLASS) due to upper GI symptoms such as dyspepsia, abdominal pain, nausea and heartburn are shown in Table 4. One should again note that patients in the COXIB arms were on supratherapeutic doses and one would expect lower dropout rates due to GI side effects with normal doses. Lower GI dropout rates did not always translate into reductions in rates of withdrawal from any cause. In CLASS the rate of withdrawal from any cause (entire study period) was 22.4% for celecoxib and 23% for ibuprofen. In VIGOR, the rate of withdrawal from any cause was15.9% for rofecoxib and 15.8% for naproxen.

**Table 4: Dropout rates due to GI symptom/event**[30,31]

| Study | Drug | Rate | Risk Reduction |
|---|---|---|---|
| **VIGOR** | rofecoxib<br>naproxen | 7.6%<br>10.3% | RRR= 26.2%<br>ARR=2.7% p<0.001<br>◆NNT= 37 |
| **CLASS** (entire study period) | celecoxib<br>ibuprofen | 12.2%<br>13.4% | RRR= 8.95%<br>ARR=1.2% p<0.05<br>◆NNT=84 |
| | celecoxib<br>diclofenac | 12.2%<br>**16.6**% | RRR= 26.5%<br>ARR=4.4% p<0.05<br>◆NNT= 23 |

◆*VIGOR: For every 37 patients treated with rofecoxib, there was1 less dropout due to GI symptoms compared to naproxen.*
◆*CLASS: For every 84 patients treated with celecoxib, there was1 less dropout due to GI symptoms compared to ibuprofen.*

## RENAL / CARDIOVASCULAR EFFECTS

The hope that COXIBs would have fewer adverse renal effects has not been realized. Recent studies have shown that COX-2 is constitutively expressed in renal tissue and that COXIBs have the potential to cause similar renal effects as seen with conventional NSAIDs.[36]

Renal syndromes caused by conventional NSAIDs are numerous. Fluid retention with the development of **edema**, worsening of **congestive heart failure** or aggravating **hypertension** are the most common complications. Other less frequent side effects are **hyperkalemia** and **acute renal failure**. In a few rare instances, nephrotic syndrome or papillary necrosis may occur, the latter a long-term complication.[37]

***7. COXIBs share similar adverse renal effects with conventional NSAIDs; caution is warranted in high risk patients such as the very elderly.***
***8. Patients at high risk of cardio-renal complications (see Table 5) should be reassessed within 7-14 days. Evaluation for any respiratory insufficiency, edema and measurement of blood pressure and weight could be useful. SCr and electrolytes may provide additional information.***

Renal effects of COXIBs have been examined by several studies as well as postmarketing surveillance. The physiologic effects of COXIBs in individuals with normal renal function showed that with glomerular filtration, both celecoxib and rofecoxib had similar effects to NSAIDs in salt-depleted subjects; that is, a small decrease in glomerular filtration rate.[38] Swan studied elderly subjects (60-80yrs) with mild renal impairment (creatinine clearance 30-80 ml/min) who were placed on sodium restriction for 6 days and found that GFR decreased 10-12ml compared with placebo, similar to conventional NSAID effect.[39]

CLASS and VIGOR provide useful information regarding cardio-renal side effects. However the cardio-renal aspects of these studies were not the primary endpoints and therefore the cardio-renal results are observational and await further study. These studies differed greatly in their design and results can not be directly compared. In CLASS, hypertension occurred in 2% of patients taking celecoxib vs 2.6% in the NSAID group and SCr rose in 1.3% of patients on celecoxib vs 1.6% in the NSAID group.[30] In VIGOR, adverse renal events were reported as one overall category; the incidence was 1.2% with rofecoxib and 0.9% with naproxen.[31,40] Hypertension precipitated discontinuation in 0.7% of rofecoxib patients and 0.1% of naproxen patients ($p<0.001$).[31]

One large study has attempted to differentiate between these COXIBs with respect to edema and hypertension. Whelton (SUCCESS VI study group) did a randomized prospective 6-week study comparing celecoxib 200mg/day and rofecoxib 25mg/day in elderly (≥65 yrs) osteoarthritic hypertensive patients.[41] The results for rofecoxib vs celecoxib were as follows: edema 9.5% vs 4.9% ($p= 0.014$); systolic blood pressure rise (>20mmHg) of 17% vs 11% ($p=0.032$); and diastolic rise (>15mmHg) 2.3% vs 1.5% (not significant; $p=0.44$). Of note, the mean rise in systolic blood pressure was only 2.6 mmHg for rofecoxib and –0.5 mmHg for celecoxib ($p=0.007$).

This study suggested there was a difference in edema and hypertension between the two agents; however, there were several shortcomings that call for caution in interpreting results. Firstly, the study did not include any data on the anti-inflammatory efficacy of the agents used and it is not clear whether the renal COX-2 inhibiting effects of the two doses of drugs used in this trial (celecoxib 200mg/day; rofecoxib 25mg/day) were equivalent. Secondly, baseline SCr is not reported for either arm, so it is unclear if patient groups were similar. Finally, antihypertensive therapy in the two groups was variable and changes made to antihypertensive treatment during the studies was unknown. The large number of sites (101) increases the possibility of site variability in data collection.

Acute hemodynamically mediated renal failure can occur with NSAIDs especially in susceptible individuals (see Table 5). Since normal renal physiology is dependent on COX-2, it is expected that acute renal failure will be seen with the COXIBs in the same susceptible individuals. In fact, several cases of COXIB induced acute renal failure have been reported.[42] The VIGOR and CLASS trials did not see an increase in renal failure compared to traditional NSAIDs. Post-marketing data to date also confirms this.

Hyperkalemia is another concern with NSAIDs. In a review of COX-2 and renal function, Breyer noted that two studies in patients on salt-restricted diets showed a decrease in urinary potassium secretion. In subpopulations of patients at risk, the development of hyperkalemia with COXIBs appears likely, although studies documenting its frequency are lacking.[43]

There have been a few case reports of nephrotic syndrome and papillary necrosis with both COXIBs. These preliminary reports come from data voluntarily submitted which has not been scientifically verified. Causality has not been established for most reports.

Because COXIBs share similar adverse renal effects with traditional NSAIDs, patients at high risk of cardio-renal complications (see Table 5) should be reassessed within 7-14 days. Measurement of SCr, electrolytes, weight, blood pressure, and evaluation of respiratory difficulty (due to edema/precipitation of heart failure) is useful.

**Table 5: Risk Factors for Adverse Renal Effects**

- underlying volume depletion (e.g. patients on diuretics, especially high-dose loop diuretics e.g. furosemide)
- pre-existing renal insufficiency
- congestive heart failure
- cirrhosis
- elderly (age over 75years)
- previous long-term daily use of NSAIDs/ASA

***9. Some studies have observed an increase in cardiovascular risk in patients on COXIBs; this has not been conclusively studied in well designed clinical trials. Caution is warranted; further safety studies are planned.***

Prostaglandins are intimately involved in platelet function. ASA irreversibly acetylates COX-1 in platelets, inhibiting the production of thromboxane A2, a promoter of platelet adhesion. The platelet cannot re-synthesize COX-1 and the effect of ASA endures for the lifespan of the platelet (≥7 days). All other NSAIDs inhibit platelet COX-1 reversibly. By contrast COXIBs do not have this effect on platelets and thus lack cardiovascular protective properties. A thrombotic tendency has been postulated because the COX-2 isoenzyme has an important role in the increase in prostacyclin that occurs in clinical syndromes of platelet activation. Prostacyclin is thought to be part of a homeostatic defense mechanism that limits platelet activation in vivo. COXIBs may therefore decrease the production of prostacyclin and potentially affect thrombosis.[44]

A meta-analysis by Mukherjee[45] suggests that COXIBs have a higher incidence of cardiovascular events such as myocardial infarction (MI). Four studies were included in this meta-analysis, but only CLASS and VIGOR were of significant size. The authors suggested that the annualized rate of MI for the VIGOR trial (rofecoxib) was 0.74% and CLASS (celecoxib) was 0.80%. This was compared to four separate ASA prevention trials (ASA vs placebo) where the annualized rate was 0.52%.

Unfortunately this meta-analysis has many shortcomings and does not answer whether COXIBs increase clinical thrombotic events. Deficiencies of this analysis were:

- a heterogenous group of patients in VIGOR and CLASS were compared to a general population
- in VIGOR, ASA patients were excluded; however about 4% of patients could have benefited from ASA for cardio-prophylaxis; naproxen but not rofecoxib has some potentially cardio-protective antiplatelet effects
- doses of both rofecoxib and celecoxib used in VIGOR and CLASS were supratherapeutic
- in CLASS, Mukherjee compared all patients including those who were on low dose ASA for cardio-protection (a high risk group for cardiac events). If they are removed from analysis and only the non-aspirin users are evaluated, the annualized rate of heart attacks was 0.33%, a number less than the "control" group quoted at 0.52%. In spite of these limitations, this study indicates that from the cardiovascular standpoint, **individuals on ASA for cardiovascular prophylaxis should remain on this agent when COXIBs are added even though the benefit of gastrointestinal protection may be lessened**. COXIBs should be used with caution in patients at high cardiovascular risk**. Well-designed studies** focussing on cardiovascular risk as the primary endpoint **are needed**.

**Serious Adverse Events Data**

A recent review of VIGOR trial data requested by the FDA concluded that "This risk reduction in relevant GI events did not translate into an overall safety benefit of rofecoxib over naproxen. GI safety must be assessed within the overall safety profile of a drug. Evaluation of safety by routine parameters showed no advantage of rofecoxib over naproxen". [46] This statement was made after reviewing serious adverse events which were higher for rofecoxib than for naproxen (See Table 6). Similar results were found in the CLASS study. **Additional study has been recommended to clarify these important safety issues**.

**Table 6: Total Serious Adverse Events – [FDA 30, 31,44]**

| Study | Drug | Rate | Risk Increase |
|---|---|---|---|
| **VIGOR** | rofecoxib<br>naproxen | 9.3%<br>7.8% | RRI= 19.2%<br>ARI=1.5%<br>NNH= 67 |
| **CLASS**<br>(entire study period) | celecoxib<br>diclofenac<br>ibuprofen | 11.6%<br>10.3%<br>10.6%<br>10.5% | RRI=10.5%<br>ARI=1.1<br>NNH=91 |

**RRI**= relative risk increase **ARI**= absolute risk increase
**NNH**= number needed to harm

## MISCELLANEOUS-RECENT Q&As

### What is acetaminophen's role in OA (osteoarthritis)?

The "first-line" role of acetaminophen (≤4g/day) in OA has come into question with the growing use of COXIBs. It is still an option for mild joint pain in OA, although some studies have suggested patient preference for NSAIDs.[47] Some clinicians favor COXIBs for their efficacy and relative GI safety; conversely acetaminophen is less costly, may be safer from a GI and cardio-renal point of view but is only effective in a subset of patients. Glucosamine may also be considered in high risk patients.

### Can COXIBs be used in patients with ASA allergy?

ASA induces asthma in ~20% of asthmatics. Rofecoxib has been safely used in ASA-sensitive asthma patients.[48,49]

### Does celecoxib cause sulfa-like adverse reactions?

Serious sulfonamide reactions with celecoxib are rare; however a recent review of the WHO database found that the relative reporting rate of sulfonamide-like adverse reactions was higher with celecoxib than rofecoxib, 375 vs 238 per million patient-years respectively (RR 1.8; 95% CI 1.6-1.9).[50] Rates for rash, urticaria, Stevens-Johnson syndrome and photosensitivity were statistically significantly higher for celecoxib compared to rofecoxib.

### What about reports of meningitis with rofecoxib?

In March-2002, the FDA issued a warning that 5 cases of meningitis had been reported in new rofecoxib patients. Patients showed symptoms within 1-12 days of starting treatment. Aseptic meningitis has also been reported in patients on naproxen and ibuprofen.

### Has there been a Canadian economic assessment for COXIB use?*

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) recently published an economic assessment of COXIB use in OA and RA (excluding patients also requiring ASA).[51] It suggests that COXIBs:

- are not cost-effective treatments in patients at average risk of upper GI events
- are cost-effective for patients at high risk for GI events
- become less cost-effective in high risk patients as rates of co-prescription for proton pump inhibitors (PPIs) increase
- become cost-effective for patients without risk factors only in the very elderly (age >76yr rofecoxib; >81yr celecoxib)

***Caution**: economic assessments are not an *exact science* and are controversial given the potential variability in factors evaluated and dollar values assigned to outcomes.

**NSAIDS & Other Analgesics: Comparison Chart** Prepared by: Loren Regier, Brent Jensen - ***www.sdh.sk.ca/RxFiles*** - **MAY/02**

| Generic Name | TRADE | Products/Comments* | Usual Dosage | Max/d | ≅ Dose | $/30d | *Class* / Comments |
|---|---|---|---|---|---|---|---|
| ASA-Plain<br>**ASA-Enteric Coated** | **ASPIRIN** OTC✘<br>**ENTROPHEN** | 150✘ & 650✘ mg supp; 80✘,325✘ mg tab; 81✘,325,650,975✘ mg EC tab | 325-650mg q4-6h<br>325-975mg QID | 4g | 650mg EC po QID | **$11** | ***Salicylates***<br>◆ASA: **irreversible** platelet inhibition |
| Diflunisal | **DOLOBID** | 250,500mg tab | 250-500mg BID | 1.5g | 250mg po BID | $37 | |
| Salsalate | **DISALCID** ✘ | 500,750mg tab | 1000mg TID | 3g | 1500mg po BID | $54 | ***Non-acetylated Salicylates*** - less adverse GI reactions, less cross-allergy in NSAID allergic patients |
| Choline Mg Trisalicylate | **TRILISATE** ✘ | 500mg tab | 1-1.5g BID | 3g | 1000mg po BID | $33 | |
| Indomethacin | **INDOCID** | 25,50mg cap; 50,100mg supp | 25-50mg TID | 200mg | 25mg po TID | $17 | ***Indole Acetic Acids***<br>Note: INDOCID SR available by Special Access (Ph.613-941-2108) for ankylosing spondylitis only |
| Sulindac | **CLINORIL** | 150,200mg tab; PD | 150-200mg BID | 400mg | 150mg po BID | $34 | |
| Tolmetin | **TOLECTIN** | 200✘ ,600mg tab | 200-600mg TID-QID | 2g | 600mg po TID | $93 | |
| Diclofenac | **VOLTAREN** | 25,50mg EC tab; 50,100mg supp; 75,100mg SR tab | 25-50mg BID-TID | 200mg | 50mg po TID | $27 | ***Phenylacetic Acids***<br>(♣ Voltaren Rapide 50mg tab ✘ $72; generic diclofenac K 50mg ✘ $46 )<br>◆diclofenac 75mg BID ↑LFTs AST >4% in CLASS |
| **Diclofenac + Misoprostol ✚** | **ARTHROTEC-50**<br>**ARTHROTEC-75** | (50mg + 200µg) tab<br>(75mg + 200µg) tab | 1 tab BID-TID<br>1 tab OD-BID | 200mg/ 800µg | One tab po BID<br>One tab po BID | **$47**<br>$61 | |
| Ketorolac | **TORADOL** ✘ | #; 10mg tab; 30mg injectable<br>IM formulation available | 10mg po q6h x7d max<br>10-30mg **IM** q4-6h | 40mg<br>120mg | 10mg po QID | $67# | ***Pyrolizine Carboxylic Acids*** |
| Etodolac | **ULTRADOL** | ~COX-2 selective; 200,300mg cap | 200-600mg BID | 1.2g | 300mg po BID | $50 | ***Pyranocarboxylic Acids*** |
| Fenoprofen | **NALFON** | 600mg tab | 300-600mg TID-QID | 3.2g | 600mg po TID | $63 | ***Propionic Acids***<br>◆ibuprofen & naproxen: similar overall withdrawal rates as celecoxib CLASS & rofecoxib VIGOR respectively<br>◆naproxen less HTN causing withdrawal (0. 1 vs 0.7%) vs rofecoxib VIGOR |
| Flurbiprofen | **ANSAID** | 50, 100mg tab | 50-100mg TID-QID | 300mg | 100mg po BID | $32 | |
| **Ibuprofen** | **MOTRIN** OTC✘ | 200mg tab OTC; 100mg/5ml **susp** ✘; 300,400,600mg tab | 200-800mg TID-QID<br>(**Peds: ≤50mg/kg/day**) | 3.2g | 400mg po TID<br>600mg po TID | **$12**<br>$13 | |
| Ketoprofen | **ORUDIS** | 50,100mg EC; 200mg SR tab<br>50mg cap; 50,100mg supp | 25-100mg TID-QID | 300mg | 50mg po TID | $25 | |
| **Naproxen** | **NAPROSYN** | 125,250,375,500mg; 750mg SR;<br>125mg/5ml **susp**; 500mg supp | 125-500mg BID<br>**>2yr =≤10mg/kg/day** | 1.5g | 375mg po BID<br>500mg po BID | **$16**<br>$20 | naproxen EC available ✘ : 375mg BID $41;<br>♣Anaprox ✘ 275-550mg BID $45-80 (naproxen sodium) |
| Oxaprozin | **DAYPRO** ✘ | 600mg caplet; long t1/2 (50h) | 600-1800mg OD | 1.8g | 600mg po OD | $30 | |
| Tiaprofenic Acid | **SURGAM** | 200,300mg tab | 200-300mg BID | 600mg | 200mg po BID | $32 | |
| Piroxicam | **FELDENE** | 10,20mg cap & 10,20mg supp | 10-20mg OD | 20mg | 20mg po OD | $33 | ***Oxicams***- long t½ (>50h) |
| Piroxicam-beta-cyclodextrin | **BREXIDOL** ✘ | 20mg tab (may give 40mg x1 initially) | 20mg OD x 7d max | 20mg | 20mg po OD ♣ | $97# | |
| Meloxicam | **MOBICOX** | ~COX-2 selective; 7.5,15mg tab | 7.5-15mg OD | 15mg | 7.5mg po OD | $32 | |
| Tenoxicam | **MOBIFLEX** ✘ | 20mg tab | 20-40mg OD | 40mg | 20mg po OD | $48 | |
| Nabumetone | **RELAFEN** | ~COX-2 selective; PD; 500,750mg tab | 1-2g OD | 2g | 1g po OD | $43 | ***Naphthylalkanones***- long t½ (>24h) |
| Floctafenine | **IDARAC** | 200,400mg tab | 200-400mg TID-QID | 1.2g | 200mg po QID | $49 | **Anthranilic Acids** |
| Mefenamic Acid | **PONSTAN** | 250mg cap; (initially 500mg x1) | 250mg QID x 7d max | 1.5g | 250mg po QID | $54# | |
| **Celecoxib** | **CELEBREX** ▼ | 100,200mg cap<br>{Rare SULFA-type reactions} | 100mg BID (OA) **$52** -<br>200mg BID (RA) | 800mg | 200mg OD<br>200mg BID | **$52**<br>**$97** | ***COXIBs*** – **highly COX-2 selective:**<br>equal efficacy & similar renal toxicity to other NSAIDs; less GI ulcer/bleed Non-ASA pts; minimal platelet effects; concerns regarding ??↑cardiac/serious events FDA; warfarin DI |
| **Rofecoxib** | **VIOXX** ▼ | 12.5, 25mg tab; 2.5mg/ml **susp** | 12.5 OA-25mg OA/RA OD<br>acute pain: ≤50mg/d x5d | 50mg | 12.5mg OD<br>25mg OD | **$52** | |
| **Acetaminophen** Pregnancy category B<br>(= paracetamol) | **TYLENOL** OTC✘<br>TYLENOL ARTHRITIS=ER Tab | 80,160,325,500mg **tab** ✘;<br>650mg **ER tab** ✘; various **susp's** ✘<br>120,325,650mg **supp** ✘ | (**Peds: ≤65mg/kg/day**)<br>325-1000mg TID-QID | 4g | 650mg po QID<br>1,300mg ER Q8H | **$12**<br>$27 | **Non-Antiinflammatory Analgesic**<br>lowest risk GI ulcer/bleed; option in OA; monitor **LFTs** in chronic use |

**EDS**=**E**xception **D**rug **S**tatus ✘ Non-formulary SK ▼=prior approval required for Department of Indian Affairs coverage **DI**=drug interaction **EC**=enteric coated **ER**=extended release **HTN**= hypertension **LFT**=liver function tests **OA**=osteoarthritis **OTC**=over the counter (& non-formulary in SK) **PD**=Pro-drug **RA**=rheumatoid arthritis **SK**=Saskatchewan **SR**=sustained release **supp**=suppository **susp**=suspension **COST** to consumer based on acquisition cost (generic if avail.), markup & dispensing fee. **Cost comparison** based on **lowest usual anti-inflammatory dose**. Lower doses of NSAIDs often effective for analgesia.

**#** Monthly cost for ketorolac,mefenamic acid & Brexidol shown for comparison only; Recommended maximum length of oral treatment is **7 day.** **Suppository** form does **NOT** prevent ulcers from occurring.

♣ **Fast-acting formulation** available but non-formulary in SK (Anaprox, Brexidol, Voltaren Rapide, Novo-Difenac-K ); slightly faster onset, but more expensive.

* Possible gastric bleeding; antiplatelet effects of NSAIDs may ↑ this risk during **anticoagulant therapy**. ✚ Misoprostol Cytotec 200mcg po bid-tid is cytoprotective. **PDA / PALM** version available; see **www.sdh.sk.ca/RxFiles**

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**New COXIBs on the Horizon:**

| Generic | TRADE | Company | Comments |
|---|---|---|---|
| cox-189 | PREXIGE | Novartis | Very large Phase III trials are under way |
| etoricoxib | ARCOXIA | Merck | Submitted to FDA for approval |
| parecoxib | DYNASTAT | Pharmacia | A pro-drug that is rapidly converted in the body to the active valdecoxib; available as injection |
| valdecoxib | BEXTRA | Pharmacia/Pfizer | Approved by FDA & available in USA. See also Medical Letter April 29, 2002 |