A balancing act

Coxibs and cardiovascular/GI risks

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In this article:

1. **Are coxibs safe?**
2. **Can coxibs be used in combination with ASA or other drugs?**

The nonsteriodal anti-inflammatory drug (NSAID) market underwent a real boom in 1999 with the launching of cyclooxygenase-2 inhibitors (coxibs). More than 6.5 million coxib prescriptions were written in Canada in 2002.[1] The number of anti-inflammatory drug prescriptions has doubled since 1999 in Quebec, reaching approximately 600,000 prescriptions written annually; more than two-thirds of those prescriptions were written for coxibs.[2] This boom in coxib use will have a major impact on the economy. In fact, only very restricted use of coxibs is considered cost-efficient for elderly patients who are at risk for ulcer conditions, or young patients with a history of ulcer complications.[3,4] Recent data suggests that coxibs should be administered to patients who have no risk or history of ulcer conditions.[3]

What about Mary?

Mary, 79, recently suffering from rheumatoid arthritis, comes to clinic reporting acute exacerbation of the disease.

She is not taking any medication and has a history of arterial hypertension and dyslipidemia. You decide to start treatment with methotrexate and, to relieve the symptoms more quickly, also prescribe a traditional nonsteroidal anti-inflammatory drug (NSAID).

Which would *you* choose?
- **A traditional NSAID or**
- **A selective anti-inflammatory (cyclooxygenase 2 inhibitor)?**

To find out what we did, please go to page 53.

Coxibs

Table 1
General safety of coxibs

Issues	CLASS Study					VIGOR Study				
	Celecoxib %	Other NSAID %	RR (CI 95 %)	ARR ARI %	NNT NNH 9 months	Rofecoxib %	Naproxen %	RR (CI 95 %)	ARR ARI %	NNT NNH 9 months
Mortality	0.48	0.43	1.12 (0.58-2.14)	NS	NS	0.54	0.37	1.46 (0.76-2.81)	NS	NS
Complicated ulcers	0.50	0.60	0.83 (0.46-1.5)	NS	NS	0.40	0.92	0.43 (0.24-0.78)	0.52	192
Other serious side-effects	5.8	4.8	1.22 (1.01-1.47)	1.0	100	8.4	6.5	1.28 (1.10-1.50)	1.9	53
Serious side-effects total	6.8	5.8	1.17 (0.99-1.39)	NS	NS	9.3	7.8	1.21 (1.04-1.40)	1.5	66

RR: Relative risk; CI: Confidence interval; ARR: Absolute risk reduction; ARI: Absolute risk increase; NNT: Number needed to treat; NNH: Number needed to harm. NS: Not significant; Serious side effects include mortality, hospitalization, life-threatening side-effects
Adapted from: Therapeutics Letter, issue 43, November/December 2001 and January 2002 (www.ti.ubc.ca)

Does the GI safety of coxibs justify its use?

Considering their clinical efficacy in comparison to traditional NSAIDs, the theoretical advantage of coxibs lies in their gastrointestinal (GI) safety, which was evaluated in two studies: the Celecoxib Long-term Arthritis Safety Study (CLASS), which compared celecoxib to ibuprofen and diclofenac; and the Vioxx® Gastrointestinal Outcomes Research (VIGOR) study, which compared rofecoxib to naproxen.[5,6] The results show a reduction of approximately 50% in complications associated with ulcer conditions with rofecoxib, while celecoxib was similar to the traditional NSAIDs in terms of the occurrence of complications. A part of the CLASS study results may be attributed, however, to the fact that 27% of the patients were also taking acetylsalicylic acid (ASA) during the study. In fact, a subgroup analysis proved that patients using the celecoxib/ASA combination were at the same risk of ulcer complications than patients who were taking the traditional NSAID/ASA combinations. None

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Table 2
Pharmacokinetics of Coxibs and known drug interactions

	Rofecoxib	Celecoxib	Valdecoxib
Metabolism	Liver via reduction	Liver via *Cytochrome P450 and 2C9*	Liver via *Cytochrome P450, 3A4, and 2C9*
Drug interactions	Antacids Rifampin Methotrexate Warfarin (INR increased) ACEI	Zafirlukast Fluconazole Fluvastatin Beta blockers Antidepressants Antipsychotic drugs	ASA Warfarin (INR) Lithium (lithemia increased) ACEI Diuretic

ASA: Acetylsalicylic acid; ACEI: Angiotensin-converting enzyme inhibitors; INR: International normalized ratio
Adapted from: Lettre Médicale 1999; 22:101; Lettre Médicale 1999; 23:31; Medical Letter 2002; 44:39

of these two studies showed a reduction in mortality associated with GI ulcer complications or total mortality. The benefits, in terms of coxib GI safety, seem to be lower than what had been expected and offset completely for patients on ASA.

Are coxibs safe?

Data from the VIGOR study are instrumental in better evaluating the safety of this new class of NSAIDs. In this study, there is an increased risk of cardiovascular events, mainly of myocardial infarction (MI), in 0.6% of patients treated with rofecoxib. Although naproxen may have cardioprotective effects, the amplitude of this cardioprotection is not sufficient to fully justify the results.[7] The hypothesis that coxibs may induce a vascular homeostatic imbalance is a highly plausible pharmacologic theory, as these molecules, which have no antiplatelet effect, stimulate the endothelial cells and encourage vasoconstriction. Celecoxib also seems to increase the risk of cardiovascular effects, although this effect has not been described in the CLASS study, which has not yet been published in its entirety. According to results obtained from the Food and Drug Administration (FDA), which were not published in the original study, celecoxib is also associated with a 0.6% increase in MI. The FDA also reports that the collective morbidity and mortality rates are significantly higher with coxibs than with non-traditional NSAIDs, as are the rates of kidney failure risk, edema, arterial hypertension, and even fractures.[8,9] The data provided by the FDA highlight the importance of publishing the serious side-effects of a new class of drugs—especially if the drug will be massively prescribed—to help the clinician better evaluate the overall risk. According to the number of patients treated to reduce ulcer complications and the number of patients treated before discovering serious side-effects, the GI safety of coxibs seems to be offset by the cardiovascular risk (Table 1).

What happened to Mary?

Mary has two cardiovascular risk factors (age, rheumatoid arthritis) and only one gastrointestinal risk factor (age); it would be preferable to prescribe a traditional NSAID with a cytoprotective agent.

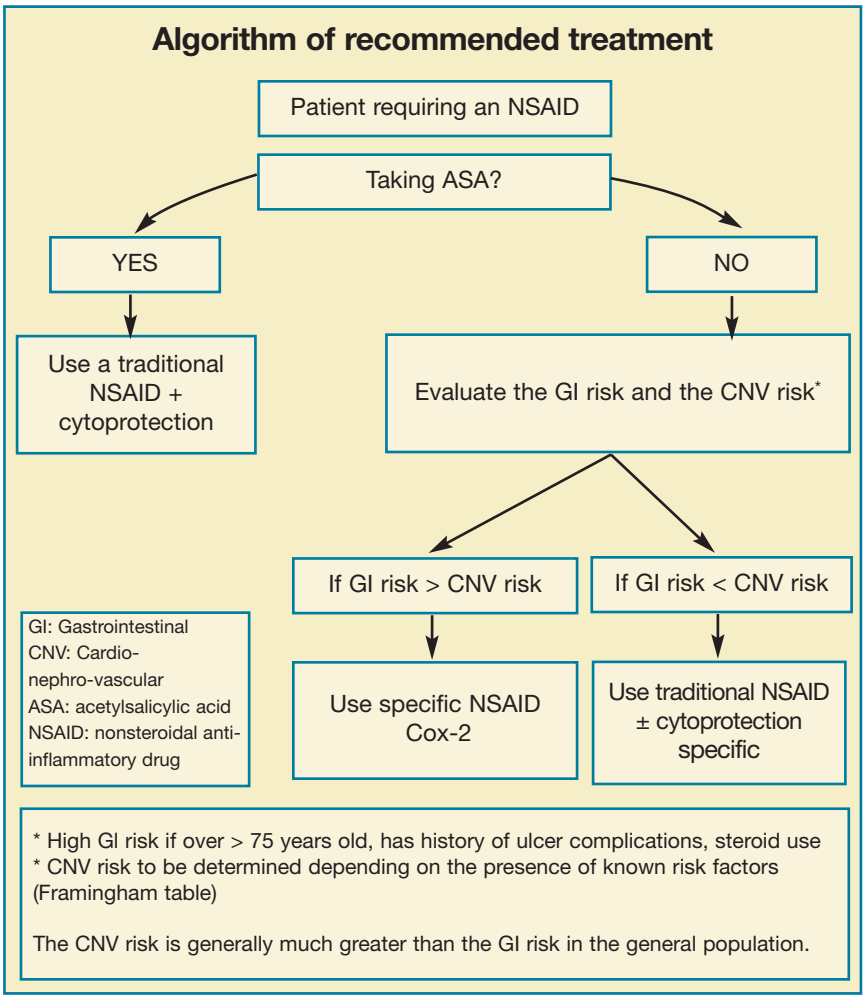

Figure 1.

Can patients take ASA/NSAID combinations?

Patients who have an ASA indication and who must take an NSAID have the same risk of ulcer complications than if they were taking a traditional NSAID or a coxib. Furthermore, for a vast number of pathologies where ASA is indicated, there is no safety data regarding coxibs, especially concerning the risk of cardiac failure, arterial hypertension, or kidney failure. Concurrently, there is very little data on possible drug interactions with a vast array of drugs that have clearly proven to be efficient in treating heart disease (angiotensin-converting enzyme inhibitors, statins, *etc.*) (Table 2). Since coxib/ASA combinations seem to be prescribed particularly to elderly patients with several pathologies and who are often taking many medications simultaneously, the potential for complications induced by this combination may pose a major public health safety problem. Finally, in contrast to the traditional ASA/NSAID combination, which has proven to be safe with cytoprotective drugs, there is no data available on the safety of cytoprotectors for the ASA/coxib combination; this alternative is also very expensive.

Patients who require an analgesic should undergo a trial with acetaminophen. If it is necessary to administer an NSAID, patients taking ASA should be prescribed a traditional NSAID with a cytoprotector (proton pump inhibitor, misoprostol). For patients who are not taking ASA, the attending physician should evaluate the individual cardio-nephro-vascular and GI risk based on the known risk factors for each condition. Since the cardiovascular risk is generally higher than the GI risk in patients with osteoarthritis or rheumatoid arthritis, and considering the patient's older age, the associated comorbidity, and the inherent risk of cardiovascular events connected with rheumatoid arthritis, the use of coxibs should be restricted.

Coxibs should be used conservatively, according to proven indications, and for the shortest possible period. It is important to keep in mind that the maximum duration of major studies is 15 months; the risks and benefits are unknown for longer periods (Figure 1). CME

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Web sites

1. The Arthritis Society of Canada: www.arthritis.ca
2. Health Canada advisories: www.hc-sc.gc.ca
3. FDA Vioxx® GI safety: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc
4. FDA Celebrex® capsules: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf

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Point of view

- Although some experts recommend using coxibs in combination with a cytoprotector in patients who are at higher risk of ulcer complications, we disagree with this recommendation, as it is not based on proof and because this type of treatment is very expensive.
- As with all medication, coxibs have a major toxicity potential, a concept that is sometimes forgotten when we hear these new molecules advertised. Nothing actually justifies the enormous increase in the use of coxibs since 1999; these agents are not more efficient than the traditional NSAIDs, nor are they safer.
- According to the data available, the serious side-effects of coxibs are probably higher than the GI benefits. Major studies on celecoxib and rofecoxib, imperfect on several levels, should not reassure the physician who prescribes these drugs. With regards to valdecoxib, it is perplexing that it was even put on the market, despite the lack of efficacy data regarding solid clinical issues and cardiovascular safety in large-scale published studies!
- We believe that prudence and reservation should be used when prescribing NSAIDs, including coxibs. Remember: *First, do no harm!*

Take-home message

The advantage

- The advantage of coxibs over traditional NSAIDs lies only in their possible GI safety.

The disadvantages

- Coxibs have not been proven to be more effective than traditional NSAIDs, nor are they safer.
- There is no data regarding the safety of coxibs in terms of the risk of cardiac failure, arterial hypertension, and kidney failure.
- Coxibs are more expensive than traditional NSAIDs.

Coxibs