Review

Cardiovascular and gastrointestinal effects of COX-2 inhibitors and NSAIDs: achieving a balance

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Published: 15 September 2005
This article is online at http://arthritis-research.com/content/7/S4/S14

Arthritis Research & Therapy 2005, **7(suppl 4):**S14-S22
(DOI 10.1186/ar1794)

Abstract

Conventional 'nonselective' nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation; however, the potential gastrointestinal risks associated with their use can be a cause for concern. In response to the adverse effects that can accompany nonselective NSAID use, selective cyclo-oxygenase (COX)-2 inhibitors were developed to target the COX-2 isoenzyme, thus providing anti-inflammatory and analgesic benefits while theoretically sparing the gastroprotective activity of the COX-1 isoenzyme. Data from large-scale clinical trials have confirmed that the COX-2 inhibitors are associated with substantial reductions in gastrointestinal risk in the majority of patients who do not receive aspirin. However, some or all of the gastrointestinal benefit of COX-2 inhibitors may be lost in patients who receive low, cardioprotective doses of aspirin, and recent evidence suggests that some of these agents, at some doses, may be associated with an increased risk for cardiovascular adverse events compared with no therapy. The risks and benefits of conventional NSAIDs and of COX-2 inhibitors must be weighed carefully; in clinical practice many patients who might benefit from NSAID or COX-2 therapy are likely to be elderly and at relatively high risk for gastrointestinal and cardiovascular adverse events. These patients are also more likely to be taking low-dose aspirin for cardiovascular prophylaxis and over-the-counter NSAIDs for pain. Identifying therapies that provide relief from arthritis related symptoms, confer optimum cardioprotection, and preserve the gastrointestinal mucosa is complex. Factors to consider include the interference of certain NSAIDs with the antiplatelet effects of aspirin, differences in the adverse gastrointestinal event rates among nonselective NSAIDs and selective COX-2 inhibitors, emerging data regarding the relative risks for cardiovascular events associated with these drugs, and the feasibility and cost of co-therapy with proton pump inhibitors.

Introduction

Conventional nonsteroidal anti-inflammatory drugs (NSAIDs; relatively nonselective in their inhibition of cyclo-oxygenase [COX]-1 and COX-2) are widely used for the treatment of pain and inflammation. However, the deleterious gastrointestinal effects potentially associated with their use can be a cause for concern, accounting for approximately 21% of adverse drug reactions reported in the USA [1]. Studies of the COX-2 selective agents (COX-2 inhibitors) have demonstrated that they are associated with a significantly reduced risk for upper and lower gastrointestinal complications compared with conventional NSAIDs, although recent evidence indicates that this effect is partially or totally ameliorated in patients who are receiving concomitant aspirin. Furthermore, recent evidence suggests that at least some of the COX-2 inhibitors are associated with cardiovascular adverse effects at certain doses; fewer relevant data are available for conventional NSAIDs (generally studied many years ago), although accumulating information suggests that at least some of these also increase risk for cardiovascular events.

In clinical practice, patients who require NSAID or COX-2 inhibitor therapy most frequently are those at the highest risk for cardiovascular events and are also likely to be taking prophylactic low dose aspirin. Given the interaction between certain NSAIDs, COX-2 inhibitors, and aspirin, balancing the benefits and risks of each of these agents is of considerable importance. This article summarizes the effects of aspirin, nonaspirin NSAIDs, and COX-2 inhibitors on the gastrointestinal tract and cardiovascular system that must be considered when making treatment decisions in patients who require these therapies.

Gastroprotective effects of COX-2 inhibitors

The gastrointestinal adverse effects of aspirin and traditional NSAIDs are well known. Clinically important NSAID related events, such as bleeding, result in more than 100,000

CI = confidence interval; COX = cyclo-oxygenase; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PPI = proton pump inhibitor; RA = rheumatoid arthritis.

hospitalizations and up to 16,500 excess gastrointestinal event related deaths each year in the USA alone. Endoscopic studies indicate that gastric or duodenal ulcers develop in 15–30% of patients who regularly take these agents [2]. Recent studies have indicated that the risk for serious NSAID gastropathy has declined substantially during the past decade as a result of a number of factors, including lower doses of NSAIDs, use of proton pump inhibitors (PPIs), and the introduction of the selective COX-2 inhibitors [3].

The gastrointestinal toxicity of traditional NSAIDs is thought to be the result of nonselective inhibition of both COX-1 and COX-2 isoenzymes involved in prostaglandin synthesis [4]. COX-1 is constitutively expressed and generates prostanoids that are involved in the maintenance of gastrointestinal mucosa and platelet aggregation. In contrast, COX-2 is primarily induced to generate prostaglandins that mediate inflammation and pain [5]. As a result, COX-2 inhibitors were developed to suppress prostaglandin production by the COX-2 enzyme selectively, thus providing anti-inflammatory and analgesic benefits while sparing the gastroprotective activity of COX-1. Data from large-scale clinical trials have confirmed that the COX-2 inhibitors are associated with substantial reductions in gastrointestinal risk in the majority of patients who do not receive aspirin.

The evidence for reduced gastrointestinal risk with COX-2 inhibitors

Clinical studies suggest that the COX-2 inhibitors are associated with a reduction in risk for gastrointestinal adverse events that is approximately equivalent to the reduction achieved by adding PPI therapy to traditional NSAIDs.

Endoscopic evidence indicates that COX-2 inhibitors are associated with a reduced incidence of gastroduodenal ulcers compared with conventional NSAIDs. In a study conducted by Laine and colleagues [6] 742 patients with osteoarthritis (OA) were randomly assigned to therapy with rofecoxib (25 or 50 mg/day), ibuprofen, or placebo. Patients were allowed to take acetaminophen, non-NSAIDs, or an antacid during the trial. Patients in the rofecoxib and placebo groups had lower rates of endoscopic ulcers than did patients in the ibuprofen group at 12 weeks; patients in both rofecoxib groups also had lower rates of endoscopic ulcers at 24 weeks ($P < 0.001$ for comparisons with ibuprofen). The rofecoxib and placebo groups did not differ for any gastrointestinal outcome, whereas efficacy or relief of arthritis related symptoms was similar in the rofecoxib and ibuprofen groups.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial [7] was the first large-scale trial to provide evidence that COX-2 inhibitors minimize the risk for upper gastrointestinal adverse effects. The study enrolled 8076 patients with rheumatoid arthritis (RA) aged 50 years or older (or at least 40 years of age and receiving glucocorticoid therapy) to treatment with either rofecoxib 50 mg/day or naproxen 500 mg twice daily. Over 9 months of follow up the efficacy of rofecoxib and naproxen were equivalent; however, the incidence of confirmed upper gastrointestinal adverse events per 100 patient-years in the rofecoxib group was less than half that observed in the naproxen group. In a *post hoc* analysis of the trial, about 40% of the gastrointestinal bleeding events were in the lower gastrointestinal tract; these were also reduced by more than half in patients who received rofecoxib [8].

The Celecoxib Long-term Arthritis Safety Study (CLASS) [9] provided additional evidence that COX-2 inhibitors minimize risk for gastrointestinal events. In this study 8059 patients with OA or RA aged 18 years or older were randomly assigned to therapy with celecoxib 400 mg twice daily (two times the maximum recommended dose for RA and four times the maximum recommended dose for OA), ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily. Patients were permitted to receive aspirin if indicated for cardiovascular prophylaxis. During the 6-month treatment period, among patients receiving celecoxib, the annualized incidence of upper gastrointestinal complications alone and in combination with symptomatic ulcers was half that observed in patients who received the conventional NSAIDs.

Recently released data also suggest that, in addition to minimizing ulcers and their complications, COX-2 inhibitors improve the tolerability of anti-inflammatory therapy compared with that achieved with conventional NSAIDs plus a PPI. A multicenter, double blind, placebo controlled trial of healthy adults that employed video capsule endoscopy [10] found an average of only 0.32 (± 0.10) small bowel mucosal breaks among patients receiving celecoxib 200 mg twice daily compared with 2.99 (± 0.51) for those taking naproxen 500 mg twice daily plus omeprazole 20 mg once daily ($P < 0.001$).

Similar reductions in gastrointestinal risk were observed with the newer COX-2 inhibitors valdecoxib, etoricoxib, and lumiracoxib [11-13].

It is important to note that in comparative trials, no differences in efficacy were observed between the COX-2 selective agents and the NSAID comparators. These data indicate that COX-2 inhibitors should not be viewed as more efficacious replacements for traditional NSAIDs; instead, following a careful risk/benefit analysis they should be considered appropriate in some patients at high risk for gastrointestinal adverse effects or in patients who require anti-inflammatory therapy for arthritis who do not tolerate the gastrointestinal effects of nonselective NSAIDs.

Cardioprotective effects of aspirin

The benefits of aspirin in the secondary prevention of cardiovascular events are well established; highly suggestive data also support the use of aspirin for primary prevention. Meta-analyses of randomized trials indicate that antiplatelet therapy prevents serious cardiovascular events across a

broad range of high risk patients [14]. The 1994 Antiplatelet Trialists' Collaboration [14] found that aspirin therapy resulted in an approximately 25% reduction in the risk for subsequent vascular events regardless of age, sex, blood pressure, or diabetes. In absolute terms, this benefit translated to avoidance of between 20 and 40 vascular events per 1000 high risk patients treated for 1 year. A second meta-analysis of 287 randomized studies, enrolling a total of 212,000 patients, confirmed the same results [15].

Large-scale studies have also shown that aspirin confers a substantially reduced risk for myocardial infarction (MI) in the primary prevention of cardiovascular events [16]. These studies have led to recommendations for aspirin therapy as a primary prevention strategy for the majority of at-risk patients, and as secondary prevention for nearly all patients with prior evidence of cardiovascular disease [17]. Indeed, many persons at low risk for cardiovascular events take low dose aspirin in response to publicity surrounding the results of these trials. However, recent data from the Women's Health Study [18] suggest that, although aspirin lowers the risk for stroke in women, it does not significantly reduce the risk for MI or death from cardiovascular causes.

Cardiovascular risk in patients receiving NSAIDs and COX-2 inhibitors

Current data do not support extrapolation of the cardioprotective effects of aspirin to other NSAIDs. Aspirin exerts its antiplatelet effects by irreversibly acetylating a serine residue in platelet COX-1, inhibiting the production of thromboxane A_2 for the lifetime of the platelet because the platelet lacks the machinery to synthesize new COX [19,20]. In contrast, conventional NSAIDs bind reversibly at the active site of the enzyme, depressing thromboxane A_2 production for only part of the dosing interval [21]. Case–control analyses confirm that the incomplete and reversible inhibition of COX by NSAIDs is unlikely to produce clinically detectable cardiovascular protection comparable to that achieved by low-dose aspirin [22-24].

Data from the VIGOR trial [7] were the first to suggest unusual cardiovascular risk among patients receiving rofecoxib. In this study, patients with RA received a mean of 9 months of rofecoxib 50 mg/day – a dose that is two to four times higher than that usually recommended for long-term treatment of arthritis. It should be noted that patients enrolled in the VIGOR trial were not permitted to take aspirin and other NSAIDs after randomization. Although the overall mortality rate and rate of death from cardiovascular causes were similar in the rofecoxib and naproxen arms, the rate of nonfatal MI was significantly lower in the naproxen treated group (0.1%) than in the rofecoxib group (0.4%). This difference was largely due to a high rate of MI among patients at high risk for coronary events. Among patients who did not have an indication for secondary prophylaxis with aspirin, the rates of MI were similar in the two treatment groups.

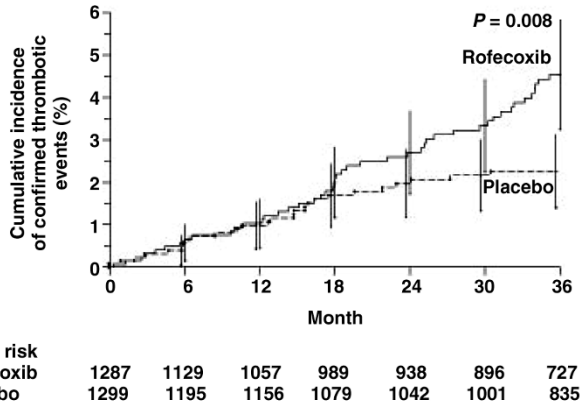
Some have attributed this difference in risk to a cardioprotective effect associated with naproxen, but this interpretation has been controversial [25,26]. In interpreting results of VIGOR it is important to be aware that this randomized controlled trial was designed to assess gastrointestinal effects. Cardiovascular events were not prespecified as outcomes and therefore were recorded only from spontaneous reports of investigators, without any standardized definitions and without prospective balancing of treatment arms for cardiovascular risk. Hence, strictly speaking, the data are hypothesis generating rather than hypothesis testing with respect to cardiovascular risk.

However, a recent meta-analysis of 18 randomized controlled trials and 11 observational studies of rofecoxib [27] support the cardiovascular findings of VIGOR. Overall, patients who received rofecoxib in these studies were at a 2.3-fold increased risk for MI compared with those receiving placebo or other NSAIDs. Importantly, the findings of the meta-analysis were largely driven by the VIGOR data and, like VIGOR, none of the other trials included in the meta-analysis had prespecified documentation or definition of cardiovascular events.

Nonetheless, the results of VIGOR gain credibility because similar results were reported in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial [28], a study of patients with a history of colorectal adenomas in which cardiovascular events were prospectively defined and collected. The 2586 study subjects were randomly assigned to therapy with rofecoxib 25 mg/day or placebo. Among patients assigned to rofecoxib, 46 patients had a confirmed cardiovascular event (acute MI, stroke, or sudden death) during 3059 patient-years of follow up, as compared with 26 patients in the placebo group during 3327 patient-years of follow up, representing a 1.92-fold increase in risk for cardiovascular events associated with rofecoxib. A divergence in risk for serious cardiovascular events was observed after 18 months of therapy (Fig. 1), primarily reflecting a greater number of MIs and strokes in the rofecoxib group.

An increase in cardiovascular events has also been observed in patients who received valdecoxib and its intravenous prodrug parecoxib as treatment for postoperative pain following coronary artery bypass grafting [29]. After an initial, small study (CABG-1) suggested increased cardiovascular risk with sequential therapy consisting of intravenous parecoxib followed by oral valdecoxib, a second study (CABG-2) was undertaken in 1671 patients, who were randomly assigned to one of the following groups: intravenous parecoxib for at least 3 days, followed by oral valdecoxib through to day 10; intravenous placebo followed by oral valdecoxib; and placebo alone for 10 days. Compared with the group receiving placebo alone, a higher proportion of patients receiving parecoxib and valdecoxib or placebo and valdecoxib suffered at least one confirmed adverse event (4.0% in the placebo

Figure 1



No. at risk							
Rofecoxib	1287	1129	1057	989	938	896	727
Placebo	1299	1195	1156	1079	1042	1001	835

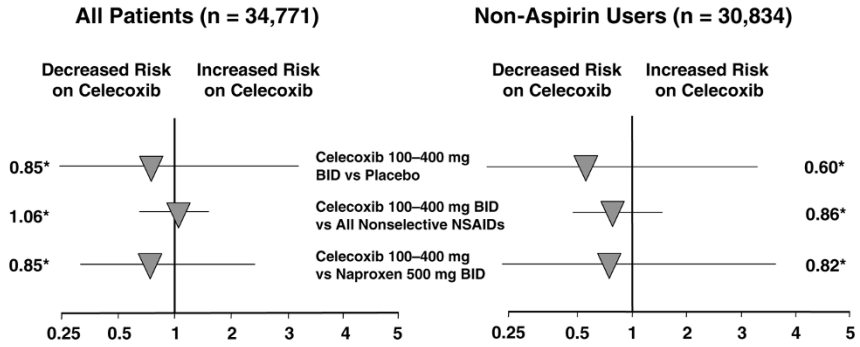
Cumulative incidence of confirmed serious thrombotic events. Vertical lines indicate 95% confidence intervals. Data are from the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial [28]. Reproduced with permission from [28]. Copyright © 2005 Massachusetts Medical Society. All rights reserved.

group versus 7.4% in the parecoxib + valdecoxib and valdecoxib alone groups). Cardiovascular adverse events (e.g. MI, cardiac arrest, stroke, and pulmonary embolism) were significantly more frequent in the group of patients who received parecoxib plus valdecoxib than in those who received placebo (2.0% versus 0.5%; $P = 0.03$). These data indicate that even short-term COX-2 inhibition, with the drugs and doses employed in this study, is associated with an increase in cardiovascular events in some subsets of patients with coronary artery disease.

In contrast to the results observed in the VIGOR and APPROVe trials, no between group differences were detected in the incidence of cardiovascular events among patients enrolled in the CLASS trial [9], regardless of aspirin use. Similarly, in a meta-analysis of multiple trials involving more than 31,000 patients with arthritis [30] there was no significant difference in MI frequency between patients taking celecoxib and those receiving placebo, any nonselective NSAID, or, specifically, naproxen, regardless of concomitant aspirin use. Celecoxib use was associated with a tendency toward a lower risk for MI in all patients (relative risk = 0.85, 95% confidence interval [CI] 0.23–3.15) and in those not receiving aspirin (relative risk = 0.60, 95% CI 0.11–3.29) compared with placebo (Fig. 2) [30]. However, like VIGOR and the rofecoxib meta-analysis, CLASS and the celecoxib studies included in the meta-analysis did not prospectively define cardiovascular events or their documentation; moreover, like the rofecoxib studies (other than VIGOR and, later, APPROVe), the randomized controlled celecoxib studies were of relatively short duration.

Based on experience with VIGOR and APPROVe, cardiovascular event documentation and adjudication were prospectively mandated before trial completion in the several randomized trials of celecoxib for prevention of colonic adenomas and for retardation of progression of Alzheimer's disease. In one of these trials (Adenoma Prevention with Celecoxib [APC]) [31], cardiovascular events segregated significantly with celecoxib among 2035 patients with a history of colorectal neoplasia. In this study patients were randomly assigned to 200 mg or 400 mg celecoxib twice daily or to placebo. During a follow-up period of 2.8–3.1 years, the composite end-point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure was reached by 7 out of 679 patients in the placebo group (1.0%), 16 out of 685 patients in the celecoxib 200 mg twice daily group (2.3%, 95% CI 0.9% to 5.5%; $P < 0.05$), and 23 out of 671 patients in the celecoxib 400 mg twice daily group (3.4%, 95% CI 1.4% to 7.8%; $P < 0.05$). Approximately half of the events in the celecoxib groups were MI [31]. These findings led the trial's data and safety monitoring board to recommend study discontinuation before its planned completion.

Figure 2



Cardiovascular risk in patients with arthritis: celecoxib versus NSAIDs, naproxen, or placebo. Shown is a summary of the risk for death, myocardial infarction, and stroke for celecoxib relative to nonsteroidal anti-inflammatory drugs (NSAIDs), naproxen, or placebo in patients with arthritis [30]. *P = nonsignificant. Reproduced with permission from Elsevier [30].

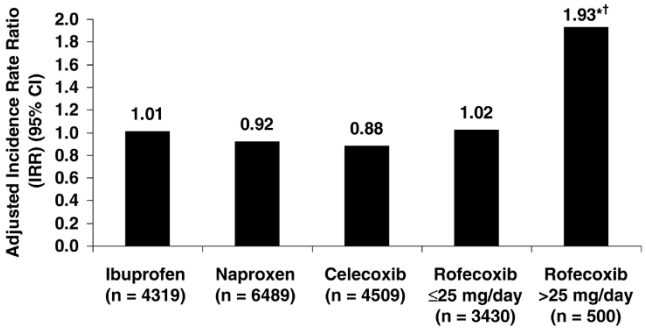
The results of the other randomized trials have not yet been published, fully adjudicated, or presented in public in their entirety, but a recent presentation to the US Food and Drug Administration indicated that in one of them (Prevention of Spontaneous Adenomatous Polyps [PreSAP] trial) no difference was seen in the frequency of cardiovascular events among patients receiving placebo and those receiving celecoxib (total dose 400 mg/day). In the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), stopped prematurely because of cessation of APC, there also was no evidence that either naproxen 220 mg twice daily or celecoxib 200 mg twice daily was associated with an increased risk for cardiovascular events. The results of such trials are difficult to interpret because of the small numbers of events that occur in each; interpretation may be facilitated by pooling the data from all the relevant trials when these are fully adjudicated and are made publicly available.

An additional source of useful data on cardiovascular risk is available from large epidemiologic studies that have been facilitated in recent years by massive medical insurance databases on drug prescriptions and discharge diagnoses following hospitalizations. These epidemiologic studies suffer from lack of randomization and the resulting potential for unintentional channeling biases, from lack of rigorous documentation of drug actually taken and of nonprescription drugs administered concomitantly, and from dependence on diagnoses defined to meet coding requirements for insurance payments, without supporting documentation or detailed event descriptions. However, they have an advantage over randomized clinical trials in that, unlike randomized trials, which typically exclude 90% of the population at risk so as to avoid influences that might confound unambiguous data interpretation, the large databases include a highly representative proportion of the populations of interest. As a result, estimates of absolute event risk drawn from these database studies are likely to reflect more realistically the expectations for the population at large than do event rates drawn from randomized clinical trials.

Several recent epidemiologic studies indicate that the cardiovascular risk associated with COX-2 inhibitors generally is similar to that in patients receiving conventional nonselective NSAIDs, although small but potentially important within-group and between-group variability in cardiovascular risk may exist. For example, among high risk patients receiving non-naproxen NSAIDs, Shaya and colleagues [32] collected medical and prescription claims data on 1005 patients using COX-2 inhibitors and 5245 patients using nonselective NSAIDs. Overall, the odds of experiencing a cardiovascular event among patients who were using COX-2 inhibitors was 1.09 compared with patients using nonnaproxen NSAIDs.

Another retrospective cohort study using a large state Medicaid database [33] illustrates the differences in risk that may be associated with usage of individual NSAIDs and COX-2 inhibitors (Fig. 3). In this study the risk for acute MI and fatal coronary heart disease was compared between patients receiving rofecoxib, celecoxib, ibuprofen, and naproxen. Patients aged between 50 and 84 years who did not have life-threatening noncardiovascular illnesses were eligible for inclusion in the analysis. Of the new drug users in the study, patients who received more than 25 mg/day rofecoxib exhibited a significantly higher incidence of serious cardiovascular events than did those receiving other NSAID treatments, including low-dose rofecoxib (≤25 mg/day; $P = 0.024$). Compared with celecoxib, the high-dose (>25 mg/day) rofecoxib group exhibited 2.2 times the rate of serious coronary heart disease events ($P = 0.014$).

Figure 3



Deaths associated with NSAID induced gastrointestinal damage versus other causes. Data from Ray and coworkers [33]. Numbers (*n*) are person-years. *$P = 0.024$ versus reference; †$P = 0.014$ versus celecoxib (2.20 [1.17–4.10]). CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug. Reproduced with permission from Elsevier [33].

Among the largest epidemiologic studies was a nested case–control analysis of information from the Kaiser-Permanente database [34]. This study, involving data from more than 1.3 million patients and 2.3 person-years of follow up, found that rofecoxib at doses above 25 mg/day was associated with a threefold higher incidence of MI and/or cardiac deaths than were recorded among nonusers or remote users of anti-inflammatory drugs. Rofecoxib at doses of 25 mg/day or less was also associated with significantly more events than among remote drug users, with an absolute rate comparable to those of several conventional NSAIDs. Interestingly, in this study celecoxib nominally was associated with a lower event rate than that seen in remote drug users (not a statistically significant finding, although the celecoxib event rate was significantly lower than that associated with naproxen, among other conventional NSAIDs).

Increased cardiovascular risk in patients receiving NSAIDs and COX-2 inhibitors: some plausible pathophysiologic bases

All NSAIDs, conventional and COX-2 selective, have the capacity to increase sodium and water retention and thereby

to increase blood pressure and cause or potentiate congestive heart failure. Blood pressure has an important influence on cardiovascular event rates; hypertension is a primary risk factor for cardiovascular events. Epidemiologic data indicate that an average blood pressure increase of even 2–3 mmHg, which is achievable with some NSAIDs and COX-2 inhibitors, can have a measurable impact on cardiovascular risk. Admission rates for heart failure in elderly patients are substantially higher among those who receive rofecoxib or nonselective NSAIDs than among those not receiving these drugs; however, celecoxib has not been associated with an increase in risk of admission for heart failure [35]. Heart failure risk also may be related to NSAID associated increases in blood pressure. An early meta-analysis [36] found that, when data from all nonselective NSAIDs (including aspirin) were pooled, supine mean blood pressure was increased by 5.0 mmHg compared with non-use.

The Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) investigators [37] reported that patients with hypertension, OA, and type 2 diabetes treated with rofecoxib 25 mg/day, but not those treated with celecoxib 200 mg/day or naproxen 500 mg twice daily, had a significant increase in 24 hour systolic blood pressure (130.3 increasing to 134.5 mmHg; $P < 0.001$) after 6 weeks of therapy. This suggests that use of these agents may result in different rates of cardiovascular adverse events.

A more recent meta-analysis of COX-2 inhibitors [38] found that, overall, these agents were associated with a higher relative risk for hypertension than placebo. In comparison with celecoxib, rofecoxib was associated with a 50% greater risk for developing clinically important systolic blood pressure elevation. It appears that all NSAIDs – both conventional and COX-2 selective – have the capacity to increase sodium and water retention and to cause or potentiate hypertension and heart failure, although celecoxib appears to have a lower propensity to cause blood pressure elevations than does rofecoxib. These data suggest that a plausible explanation for the apparent association of NSAIDs and COX-2 inhibitors with cardiovascular risk is the effect of these drugs on blood pressure. Fortunately, this is a remediable problem because the blood pressure effects of the drugs can usually be reversed with appropriate therapy.

Another mechanistic hypothesis has been advanced for the adverse cardiac effects of COX-2 inhibitors [39]. Data indicate that COX-2 activity, rather than COX-1, is the dominant source of prostaglandin I_2 in the human epithelium. Prostaglandin I_2 is involved in inhibiting platelet aggregation, in causing vasodilation, and in preventing the proliferation of vascular smooth muscle cells. In contrast, thromboxane A_2, which is largely produced by the COX-1 enzyme, is involved in platelet aggregation, vasoconstriction, and smooth muscle proliferation. Although aspirin and traditional NSAIDs suppress the activities of both COX-1 and COX-2, and therefore reduce both thromboxane A_2 and prostaglandin I_2, COX-2 inhibitors selectively suppress the production of prostaglandin I_2 without affecting thromboxane A_2 synthesis. As a result, patients in whom COX-2 is selectively suppressed might be expected to have elevated blood pressure, accelerated atherogenesis, and an exaggerated thrombotic response to plaque rupture. This attractive hypothesis does not easily account for the observation from clinical trials, discussed above, that aspirin use does not appear to have influenced the relation of cardiovascular event rates observed between COX-2 inhibitors and comparators among patients in randomized trials. In addition, pharmacoepidemiologic studies show approximately similar event rates with the nonselective NSAIDs and with at least some doses of certain COX-2 selective inhibitors. Thus, any relation between COX-2 inhibition and cardiovascular events is likely to be more complex than can be explained solely by an imbalance between COX-1 and COX-2 inhibition.

An additional hypothesis suggests that at least some anti-inflammatory drugs may prevent cardiovascular events at some doses because of salutary effects on vascular endothelium or on the inflammatory components of atherosclerosis. One study, conducted by Chenevard and colleagues [40], found that COX-2 inhibition improved endothelium dependent vasodilation and reduced low-grade chronic inflammation and oxidative stress in patients with severe coronary artery disease. Indeed, this may be particularly important in systemic inflammatory conditions, such as adult RA, that appear to enhance the risk for cardiovascular events, presumably by potentiating vascular inflammation.

‘Class’ effects of NSAIDs and COX-2 inhibitors

Taken together, data from clinical trials and epidemiologic studies suggest that NSAIDs as a group may potentiate cardiovascular risk at some doses, whether they are selective for COX-2 or not. The data also suggest some interdrug variability in these effects, and a potentially important relation of cardiovascular effects and dose with at least some of these drugs. The problem seems most apparent when rofecoxib is employed at doses above 25 mg/day, but conventional NSAIDs at some commonly used doses may be associated with similar problems. Among the COX-2 agents tested thus far at their labeled doses, cardiovascular and gastrointestinal safety profiles generally have been similar, although studies suggest that celecoxib may have a slightly better safety profile than other COX-2 inhibitors or NSAIDs. A possible basis for this is suggested by the study conducted by Whelton and colleagues [41], in which 810 elderly patients with OA and hypertension were randomly assigned to therapy with once daily celecoxib 200 mg or rofecoxib 25 mg. Nearly twice as many patients who received rofecoxib experienced edema compared with those who received celecoxib. Moreover, systolic blood pressure increased significantly in 17% of patients who received rofecoxib, compared with 11% of patients who received celecoxib.

Mean blood pressure after 6 weeks of therapy was increased by 2.6 mmHg in patients who received rofecoxib; in contrast, blood pressure was reduced by 0.5 mmHg in the celecoxib group.

Consequences of co-therapy with aspirin

Among patients at high risk for cardiovascular events, 46% of women and 59% of men take aspirin; even among low-risk patients, more than 20% may be taking aspirin [42]. The ready availability of over-the-counter NSAIDs and aspirin inevitably means that many patients take aspirin, conventional NSAIDs, and/or COX-2 selective agents concomitantly. A telephone survey [43], conducted in patients enrolled in CLASS, indicated that the majority of patients, regardless of age, were taking aspirin, acetaminophen, and/or conventional NSAIDs during the study (Table 1).

Gastrointestinal risk

The gastroprotective benefit of COX-2 inhibitors is partially or, in some patients, totally ameliorated if aspirin is used for cardiovascular prophylaxis. In a study conducted by Schnitzer and colleagues [44] 18,325 patients aged 50 years or older were randomly assigned to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily for 1 year. Patients were stratified by low dose aspirin use and age. Consistent with the results of previous studies of COX-2 inhibitors, the cumulative incidence of ulcer complications was reduced by 79% among patients who received lumiracoxib ($P < 0.0001$), but the reduction was smaller and did not reach statistical significance among patients who received concomitant aspirin. More than 20% of patients enrolled in the CLASS study [9] were receiving concomitant low dose aspirin.

Recent evidence suggests that gastrointestinal benefits may also be lost in patients who receive warfarin together with anti-inflammatory drugs. In a nested case–control analysis, Battistella and colleagues [45] quantified the gastrointestinal risk in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. During the study period, 361 (0.3%) out of 98,821 elderly patients who had received warfarin were admitted with gastrointestinal hemorrhage. These patients were 1.9-fold more likely to be receiving NSAIDs, 1.7-fold more likely to be receiving celecoxib, and 2.4-fold more likely to be taking rofecoxib than to be taking no anti-inflammatory drugs before hospitalization.

Paradoxically, the introduction of COX-2 inhibitors has been associated with an increase in hospitalization rates for upper gastrointestinal hemorrhage. In an epidemiologic study conducted by Mamdani and colleagues [46], billing records for more than 1.3 million patients were assessed for the interval between late 1994 and early 2002. During this time, there was a 41% rise in NSAID use, which was entirely attributable to increased use of COX-2 inhibitors. This increase in NSAID use was accompanied by a 10% increase in hospitalization rates for upper gastrointestinal hemorrhage (Fig. 4). However, the increase in hospitalization rate was less than one-quarter the increase in NSAID use. Moreover, it cannot be inferred that hospitalization rates directly reflect the impact of COX-2 inhibitor introduction; increased NSAID use and increasing use of aspirin for cardiovascular prophylaxis occurred during the same interval and might have importantly influenced the hospitalization data.

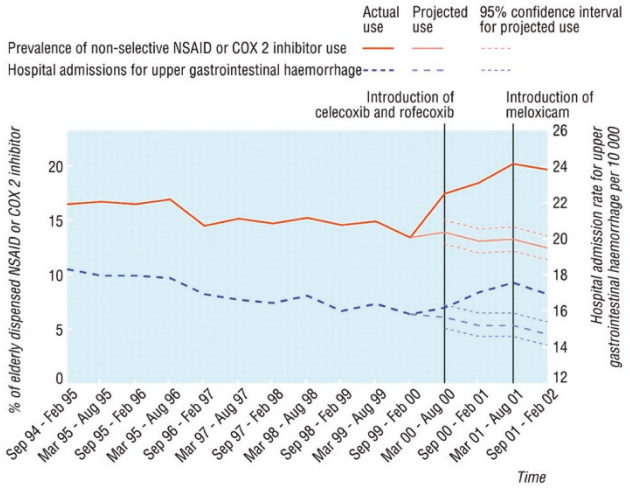
Table 1

Aspirin use

	%		
Age (years)	Aspirin	Acetaminophen	Nonaspirin NSAIDs[a]
37–55 ($n = 20$)	25	35	20
56–65 ($n = 58$)	50	45	10
66–75 ($n = 127$)	51	40	10
≥76 ($n = 119$)	48	45	8
Total ($n = 324$)	48	43	10

Shown are the percentages of long-term cyclo-oxygenase (COX)-2 inhibitor users taking aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) by age group [43]. [a]Naproxen, sodium, or ibuprofen. Reproduced with permission from [43].

Figure 4



Prevalence of NSAID use and rate of hospitalization for upper gastrointestinal hemorrhage. Data from Mamdani and coworkers [46]. NSAID, nonsteroidal anti-inflammatory drug. Reproduced with permission from [46].

Cardiovascular risk

Ibuprofen prevents the irreversible platelet inhibition induced by aspirin [47]. This effect may be responsible for a statistically and clinically significant increase in risk for mortality in users of aspirin plus ibuprofen compared with

users of ibuprofen alone [48]. In contrast, sustained exposure to diclofenac, rofecoxib, or acetaminophen did not influence the effects of aspirin on platelet function.

Conclusion

The data summarized here suggest that the risks and benefits of conventional NSAIDs and COX-2 inhibitors must be carefully weighed before making therapeutic decisions. In clinical practice, the majority of patients with moderate to severe arthritis who might benefit from NSAID or COX-2 inhibitor therapy are likely to be elderly, and therefore at relatively higher risk for gastrointestinal and cardiovascular adverse events than would younger individuals. These patients are also more likely to be taking low-dose aspirin and using over-the-counter NSAIDs for pain relief.

Selecting a combination of therapies that provides relief from arthritis related symptoms, minimizes cardiovascular risk, and preserves the gastrointestinal mucosa is a complex challenge. Factors to consider include the interference of certain NSAIDs, such as ibuprofen, with the antiplatelet effects of aspirin; direct effects of nonselective NSAIDS and of COX-2 inhibitors on fluid retention and blood pressure; emerging data about cardiovascular risks associated with these drugs; differences in the adverse gastrointestinal event rates among NSAIDs and COX-2 inhibitors; and the feasibility of co-therapy with gastroprotective agents.

Competing interests

JSB is a paid consultant to Pfizer, Inc. LSS is a consultant to AstraZeneca, Pfizer, Sanofi-Aventis and TAP.

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