

Recommendations for Use of Selective and Nonselective Nonsteroidal Antiinflammatory Drugs: An American College of Rheumatology White Paper

AMERICAN COLLEGE OF RHEUMATOLOGY AD HOC GROUP ON USE OF SELECTIVE AND NONSELECTIVE NONSTEROIDAL ANTIINFLAMMATORY DRUGS

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INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) provide important analgesic and antiinflammatory benefits to mil-

lions of patients. Although the most common serious toxicities associated with NSAID use are gastrointestinal (GI) effects, concerns about cardiovascular safety have caused many patients to discontinue their use (1). There is cur-

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rently only 1 selective NSAID, celecoxib, available on the US market. Rofecoxib and valdecoxib were both withdrawn from the US market, the former in 2004 voluntarily by the manufacturer and the latter in 2005 at the request of the Food and Drug Administration (FDA). The FDA has linked all cyclooxygenase 2 (COX-2) selective NSAIDs and nonselective NSAIDs to potential cardiovascular risk and has required changes in labeling, even for the over-the-counter preparations (2). Moreover, the American Heart Association recently issued a Position Statement on the use of analgesics that specifically singled out the selective NSAIDs and proposed a prescribing algorithm (3).

With the ongoing controversy over the role of selective and nonselective NSAIDs in the treatment of arthritis and other inflammatory musculoskeletal conditions, the Board of Directors of the American College of Rheumatology (ACR) recommended a state-of-the-art review pertaining to selective and nonselective NSAIDs that would be most useful for those interested in treating rheumatic diseases. This "White Paper" does not pursue new systematic analyses nor does it cover all analgesics or antiinflammatory drugs. Instead, the authors relied on methodologically-rigorous reviews supplemented with more recent literature to encapsulate the critical issues regarding NSAID effectiveness, toxicity (cardiovascular, GI, renal, and other areas), and economics. This "White Paper" has been endorsed by the ACR Board of Directors and provides summary recommendations wherever supported by sufficient evidence.

EFFICACY AND EFFECTIVENESS

Salicylates have been used to treat inflammatory and non-inflammatory pain for thousands of years. Aspirin became available in pill form in 1899, phenylbutazone in 1949, and more than 40 other NSAIDs were subsequently introduced, most recently, the selective NSAIDs. At least 20 NSAIDs are available for adult use in the US and 5 NSAIDs, ibuprofen, tolmetin sodium, naproxen, meloxicam, and celecoxib, are FDA-approved for use in children with juvenile idiopathic arthritis (JIA). All medications in this class work through inhibition of cyclooxygenase, decreasing the production of prostaglandin E_2 (PGE₂) and PGI₂ that sensitize sensory fibers to painful stimuli (4). The 2 isoforms of cyclooxygenase, COX-1 and COX-2, catalyze the synthesis of prostaglandins from arachidonic acid. COX-1 is present in many tissues and produces prostaglandins that predominantly regulate normal cellular processes (5,6). COX-2 activity is usually undetectable in most tissues, but can be rapidly induced by proinflammatory cytokines or by growth factors. Inhibition of COX-2 prevents high levels of local production of prostanoids, which results in reduced pain, edema, inflammation, and fever (7). The selective NSAIDs inhibit COX-2 preferentially, thus reducing the unwanted effects of nonselective NSAIDs on the upper GI tract mucosa and platelet function mediated by COX-1–derived prostaglandins (8).

Acetaminophen versus nonselective NSAIDs. The relative efficacy of acetaminophen and nonselective NSAIDs

in the treatment of osteoarthritis (OA) pain has been an area of great interest and extensive study (9–21). Results of The Cochrane review of 15 randomized control trials (RCTs) reported that NSAIDs were more effective in treating OA pain (pain at rest, pain at night, and a trend toward superiority in controlling pain after activity) than acetaminophen (at dosages ≤ 4 gm/day), but the differences were small when averaged over a large group, and toxicity was higher with NSAID use (22). After a review of available data, the authors of the ACR OA Treatment Guidelines (23) noted that acetaminophen appeared to be comparable with nonselective NSAIDs in the treatment of mild to moderate OA pain. However, several studies suggest that nonselective NSAIDs are more effective in severe OA pain (23). Because of the cost and toxicity associated with NSAID use, the ACR OA Treatment Guidelines suggest an initial trial of acetaminophen before NSAIDs for treatment of OA pain. The European League Against Rheumatism (EULAR) guidelines for treatment of OA pain give similar recommendations (24).

Selective NSAIDs versus nonselective NSAIDs. Individual patients may find that one particular nonselective NSAID is more effective than another; however, studies of large groups of patients fail to demonstrate differences in efficacy in the treatment of OA and rheumatoid arthritis (RA) pain (25,26). Depending on formulation and metabolism, some nonselective NSAIDs have a quicker onset of analgesia and others have a longer duration of effect, making them more or less appropriate for the treatment of acute or chronic pain.

Selective and nonselective NSAIDs also have comparable efficacy in treating pain and improving function in clinical trials (27). In numerous studies, OA patients treated with celecoxib and nonselective NSAIDs have had similar decreases in pain and improvements in physical function (28–33). In a meta-analysis of data from short-term studies, the dropout rate for lack of efficacy was slightly higher in patients treated with celecoxib at dosages of 200–400 mg/day than those treated with nonselective NSAIDs (34).

The Celecoxib Long-Term Arthritis Safety Study (CLASS), although not designed to assess efficacy, followed more than 7,000 patients with both OA and RA over 6–13 months. This trial found a slightly higher dropout rate in patients treated with celecoxib compared with those receiving ibuprofen or diclofenac (14.8% versus 12.6%; $P = 0.005$) (32). The Successive Celecoxib Efficacy and Safety Study I (SUCCESS-1), a 12-week trial that included more than 13,000 OA patients, found no difference in efficacy between celecoxib (100–200 mg/day) and diclofenac or naproxen (35). The efficacy of rofecoxib and valdecoxib was quite similar compared with nonselective NSAIDs in various clinical settings (29,36–50). These data suggest that inhibition of COX-1 is not required to achieve the analgesic or antiinflammatory effects of NSAIDs.

Comparative efficacy of selective NSAIDs. The few available head-to-head studies of selective NSAIDs are generally small, limiting the power to find differences in

efficacy. Although rofecoxib is far more selective toward COX-2 than celecoxib, rofecoxib and celecoxib have similar potency in the treatment of pain from knee OA (28,51–55). The Vioxx, Acetaminophen, Celecoxib Trial (VACT), funded by the makers of rofecoxib, found that rofecoxib was more effective than celecoxib (28), but another trial, funded by the makers of celecoxib, found no difference in efficacy or toxicity between the 2 drugs (55). These data suggest that more specific inhibition of COX-2 does not necessarily translate into increased efficacy.

SIDE EFFECTS

Cardiovascular risk. In considering the cardiovascular issues pertaining to NSAIDs, it is useful to review the possible mechanisms underlying potential cardiovascular effects. Low-dose aspirin has a clear cardioprotective effect and is recommended for prevention of myocardial infarction, cardiovascular death, and stroke (56). The mechanism for the antithrombotic effect of low-dose aspirin is the irreversible inhibition of platelet COX-1 and thromboxane A₂ (TBA₂) production. Because circulating platelets cannot regenerate COX-1, even brief exposure to aspirin renders platelets dysfunctional for the remainder of their lifespan. Low-dose aspirin is inefficient as an inhibitor of COX-2 for several reasons: the half-life of aspirin is extremely brief, the expression of COX-2 is low in most tissues unless stimulated, and the COX-2 protein can be replenished rapidly when expression is stimulated.

It is important for clinicians to recognize that there is evidence that some NSAIDs, such as ibuprofen, may block the antiplatelet effect of aspirin (57). The clinical significance of this interaction is not entirely clear. Data are more limited for other nonselective NSAIDs, but at least 1 study reports that naproxen interferes with the effect of aspirin (58). However, there are no published data indicating that selective NSAIDs interfere with aspirin.

Although all nonselective NSAIDs also inhibit COX-1, this inhibition is reversible and the effect diminishes over the dosing interval. From a pharmacokinetic standpoint, only naproxen inhibits platelet function over the majority of its dosing interval. Nevertheless, there are no RCT data suggesting that naproxen or any other nonselective NSAID is effective in the prevention of cardiovascular outcomes.

The effect of aspirin on vascular function serves as a starting point for understanding cardiovascular effects of other NSAIDs. As in many biologic systems, there are multiple mechanisms that are involved in the promotion and restraint of thrombosis. Early in the development of specific COX-2 inhibitors, it became apparent that COX-2 was involved in the production of prostaglandins in the vasculature (59). Furthermore, COX-2 is up-regulated during inflammation and vascular damage, and is likely to be the principal enzyme involved in producing both detrimental and protective prostaglandins in the setting of atherosclerotic disease. There is strong expression of COX-2 in atherosclerotic plaque, particularly in infiltrating macrophages. Inhibition of COX-2–dependent production of prostacyclin in vascular endothelial cells and PGD₂ associated with plaque stability in macrophages are plausible

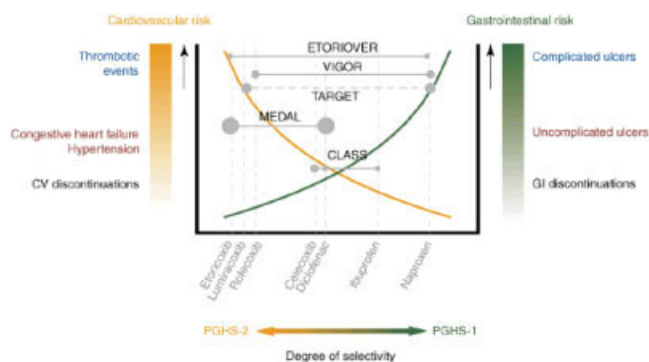


Figure 1. Relative cyclooxygenase 1 (COX-1) and COX-2 inhibition and associated cardiovascular and gastrointestinal (GI) risk. ETORIOVER = Overview of Phase II and Phase III trials of etoricoxib; VIGOR = Vioxx Gastrointestinal Outcomes Research; TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial; MEDAL = Multinational Etoricoxib and Diclofenac Arthritis Long-term; CLASS = Celecoxib Long-term Arthritis Safety Study; CV = cardiovascular; PGHS = prostaglandin H synthase. Adapted, with permission, from ref. 59.

mechanisms for increased cardiovascular risk, although inhibition of COX-2-dependent PGE₂ production associated with plaque rupture may be beneficial (60). It is certainly likely that factors, including specific polymorphisms of the COX-2 gene, related to the individual are important determinants of cardiovascular risk associated with COX-2 inhibition (60). All NSAIDs, including nonselective NSAIDs, inhibit COX-2, thereby potentially increasing cardiovascular hazard.

There is insufficient evidence from placebo-controlled trials to demonstrate increased cardiovascular risk with nonselective NSAIDs (61). Analyses of observational data sets have been inconclusive. Some authors have suggested that naproxen may pose less hazard and diclofenac may pose more hazard than other nonselective NSAIDs (62). A meta-analysis of observational studies examining the risk of myocardial infarction among individuals receiving selective and nonselective NSAIDs found pooled relative risks of 0.96 for celecoxib (95% confidence interval [95% CI] 0.90–1.02), 0.98 for naproxen (95% CI 0.92–1.05), 1.07 for ibuprofen (95% CI 1.02–1.12), 1.26 for rofecoxib (95% CI 1.17–1.36), and 1.44 for diclofenac (95% CI 1.32–1.56) (63). Diclofenac is one of the nonselective NSAIDs with the greatest COX-2 selectivity, whereas naproxen is the most potent inhibitor of COX-1 (64). These observations suggest that relative COX-1/COX-2 inhibition may be important for cardiovascular hazard.

Selective NSAIDs might pose increased cardiovascular risk compared with nonselective NSAIDs through several potential mechanisms, including inhibition of the protective PGI₂ without concomitant inhibition of TBA₂, leading to a magnification of the adverse cardiovascular effects of TBA₂ (59) (Figure 1). Many other factors, however, promote and attenuate cardiovascular risk, and the perception that selective COX-2 inhibition simply alters the balance between vasoactive prostaglandins is an oversimplification. Furthermore, there are insufficient data to ascertain if low-dose aspirin eliminates the cardiovascular risk associated with inhibition of COX-2 (65).

COX-2 selectivity *in vivo* can be viewed as a continuous

variable that has cardiovascular consequences on the basis of altered vascular function, blood pressure regulation, and cardioprotection (59). Rofecoxib is a highly selective inhibitor of COX-2, more so than celecoxib. There is strong evidence of increased cardiovascular risk for rofecoxib as demonstrated in placebo-controlled trials, trials with non-selective NSAIDs as comparators, and observational studies (66–69). Of the selective NSAIDs, rofecoxib has the greatest risk for adverse hypertension events as well as the longest half-life (70). In some studies of low-risk groups, detection of cardiovascular hazard was delayed, leading to the hypothesis that increased blood pressure over time could be a contributing factor for cardiovascular events (71,72). Interestingly, rofecoxib inhibits prostacyclin synthase as well as COX-2, perhaps providing an additional mechanism for cardiovascular hazard (73).

Beyond the increased cardiovascular risk of rofecoxib demonstrated in RCTs and observational data sets, the magnitude of overall risk for selective NSAIDs remains a contentious issue (62,68). It is important for clinicians to recognize that both the baseline risk of the study population and the specific comparator NSAIDs are likely to influence the ability to detect separation in cardiovascular risk between a selective and nonselective NSAID. The strict entry criteria for many RCTs of selective NSAIDs exclude patients with prior myocardial infarction, revascularization procedures, coronary artery bypass graft (CABG), or heart failure (HF) from being enrolled. Because these are the patients at highest risk for future cardiovascular outcomes, many trials are unable to detect a significant difference between selective and nonselective NSAIDs due to the low number of cardiovascular outcomes.

The choice of comparator nonselective NSAIDs is also critical in the analysis of available data. For instance, diclofenac is used as one of the comparator nonselective NSAIDs in the pivotal trials for celecoxib and etoricoxib (74). Because diclofenac is associated with a higher cardiovascular risk than some of the other nonselective NSAIDs, a comparison between a selective NSAID and diclofenac may not show the same magnitude of difference in risk. In contrast, those studies in which naproxen is used as a comparator are more likely to show differences between the nonselective NSAID naproxen and the selective NSAIDs, even when studies are underpowered to detect cardiovascular events (65).

The data demonstrating increased cardiovascular risk with selective NSAIDs other than rofecoxib have been difficult to ascertain. In a study of post-CABG patients receiving aspirin, the combination of valdecoxib and parecoxib was compared with placebo. There were more cardiovascular events among the valdecoxib and parecoxib groups compared with placebo (relative risk [RR] 3.7, 95% confidence interval [95% CI] 1.0–13.5) (75). However, in another study of the utilization of RCTs to evaluate higher-risk patients, a post hoc analysis of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) study compared lumiracoxib with ibuprofen or naproxen in a subset of patients at high risk of cardiovascular events, including patients with a prior event or Framingham risk equations or diabetes and ≥ 1 risk factor,

which included 16.6% of the participants (76). Of this group, ~60% were taking aspirin. The highest risk was seen for ibuprofen in those patients taking aspirin (2.14% per annum), again raising concerns that use of ibuprofen could negate the protective effects of low-dose aspirin. Event rates were similar between naproxen and lumiracoxib at 1.58% and 1.48% per year, respectively, in patients taking aspirin. In patients not taking aspirin, those receiving naproxen were less likely than those taking lumiracoxib to have a cardiovascular event.

Data on the cardiovascular safety of celecoxib in RCTs are limited by the patient-years of exposure and the small number of events, reflecting a relatively low-risk population studied in these trials. A systematic review of observational studies suggests that celecoxib, in commonly used doses, does not significantly increase cardiovascular risk (62). However, it is likely that higher doses, particularly when administered twice daily, increase the cardiovascular risk associated with celecoxib as seen in 2 placebo-controlled trials for the prevention of colorectal adenomas (72). In those studies, the hazard ratio was 2.6 (95% CI 1.1–6.1) in patients taking celecoxib 200 mg twice daily, 3.4 (95% CI 1.5–7.9) in patients taking celecoxib 400 mg twice daily, and 1.3 (95% CI 0.6–2.6) in patients taking celecoxib 400 mg once daily. These data point out the importance of considering dose and dosing interval when interpreting studies for risk and when counseling patients regarding cardiovascular risk.

Another strategy for evaluating and informing patients about cardiovascular risk is calculation of absolute annualized event rates. This type of calculation, using data from meta-analyses of RCTs of nonselective NSAIDs, selective NSAIDs, and placebo, revealed absolute event rates of 0.9–1.97% serious cardiovascular end points per year (77). There were no significant differences between nonselective NSAIDs and selective NSAIDs.

In addition to myocardial infarction, stroke, and cardiovascular death, an increased risk of HF can be seen in patients taking NSAIDs. There is a small increased risk of first hospital admission for HF in patients receiving NSAIDs (RR 1.3, 95% CI 1.1–1.6) (78). In elderly patients with preexisting HF, the risk of hospital admission for recurrent HF is increased among those taking NSAIDs (79). This is likely related to renal effects of these agents, such as interaction with other medications used to treat HF including diuretics and angiotensin-converting enzyme inhibitors, as well as independent effects of NSAIDs on prostaglandin and renin–angiotensin–aldosterone interactions. It is important to recognize this relationship and discontinue NSAIDs in patients with a new onset or exacerbation of HF. There is some suggestion that celecoxib may be safer than other NSAIDs in this group of patients, but compelling evidence is still lacking (79).

Another important aspect of cardiovascular risk with NSAIDs is the incidence of arrhythmias. A meta-analysis of 114 randomized trials evaluating selective NSAIDs assessed more than 100,000 participants for the outcome of arrhythmia (atrial fibrillation, ventricular fibrillation, tachycardia, cardiac arrest, sudden cardiac death, or unspecified arrhythmia) (80). The relative risk of arrhythmia in patients taking rofecoxib compared with controls was

Table 1. Meta-analyses of nonselective nonsteroidal antiinflammatory drug use with GI end points*

Author (ref.), year	End point	No. of studies pooled	GI risk, OR/RR (95% CI)
Ofman (85), 2002	PUBs	16 placebo RCT	5.4 (1.8–16.0)
		9 cohort	2.7 (2.1–3.5)
		23 case-control	3.0 (2.5–3.7)
Bollini (82), 1992	GI tract disease†	34 studies (7 cohort and 27 case-control)	3.0 (1.9–4.7)
Gabriel (83), 1991	GI AEs‡	16 studies (7 cohort and 9 case-control)	2.7 (2.5–3.0)
Hernandez-Diaz (84), 2000	Upper GI bleed§	18 studies (3 cohort and 15 case-control)	3.8 (3.6–4.1)

* GI = gastrointestinal; OR = odds ratio; RR = relative risk; 95% CI = 95% confidence interval; PUBs = perforations, ulcers, and GI bleeds; RCT = randomized controlled trial; AEs = adverse events.
† Hematemesis, melena, peptic ulcer, ulcer perforation, and death attributable to these outcomes (RR adjusted for study design and methodologic strength).
‡ Bleeding, perforation, or other adverse GI events resulting in hospitalization or death.
§ Bleeding, perforation, or other serious upper GI tract events resulting in hospitalization or visit to a specialist.

increased, even though there were few arrhythmia events (RR 2.90, 95% CI 1.07–7.88). In addition, the arrhythmias occurring in the rofecoxib-treated patients appeared more clinically significant, as they included ventricular fibrillation, cardiac arrest, and sudden cardiac death. There was no increased risk of arrhythmias noted in patients receiving celecoxib, valdecoxib, or parecoxib.

GI risk. NSAIDs are associated with GI adverse events, including peptic ulcer disease, gastritis, esophagitis, and their complications. NSAID-associated GI adverse events are best assessed in studies of serious end points such as ulcers, bleeding, perforations, and obstruction. The relationship between endoscopic ulcers and clinically significant GI adverse events is not well established (81), and studies with this outcome provide a lower level of evidence. Exposure to nonselective NSAIDs has been associated with a 2.7–5.4-fold increased risk of various GI adverse events (Table 1) (82–85). Current NSAID users have a 4.3-fold greater risk of upper GI bleeding compared with controls taking placebo (95% CI 3.7–5.0). The case fatality rate for upper GI bleeds is 5% (86,87).

Among patients with RA receiving NSAID therapy, there is a 1.58% hospitalization incidence and a 0.19% per year risk of GI-related death (88). A variety of demographic characteristics, comorbidities, and cotherapies may predispose NSAID users to GI adverse events. Major risk factors include female sex, older age (>75 years), history of prior GI adverse events, significant cardiovascular disease, RA, and concomitant therapy with either anticoagulants or glucocorticoids (82–85,89,90).

Etodolac, nabumetone, meloxicam, and diclofenac are partially selective NSAIDs. These agents have been reported to be less toxic to the gastric mucosa, particularly at lower doses, in some studies (91–94) but not all studies (95,96). A recent federally funded evidence synthesis concluded that there was either no significant difference or insufficient evidence to judge a significant GI safety difference between these partially selective NSAIDs and nonselective NSAIDs (27). Nonacetylated salicylates (salsalate, magnesium choline salicylate) have not been subjected to large GI outcomes studies. A smaller RCT has indicated superior GI safety (97).

Several selective NSAIDs, including rofecoxib, etori-

coxib, lumiracoxib, and valdecoxib, as well as celecoxib (a slightly less selective NSAID), have been approved previously for use either in the US or internationally. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study and CLASS were the first large, multicenter RCTs designed specifically to compare the upper GI toxicity of COX-2 selective and nonselective NSAIDs using clinically relevant end points (Table 2) (32,89).

More recently, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study followed persons with RA and OA for an average of 18 months (98), and the TARGET study examined lumiracoxib compared with ibuprofen or naproxen in more than 9,000 patients with OA (99). In the MEDAL study, although uncomplicated GI adverse events were reduced with etoricoxib, complicated ulcers, perforation, and bleeds did not differ significantly between the groups (0.30 per 100 person-years with etoricoxib and 0.32 per 100 person-years with diclofenac) (98). In the TARGET study, lumiracoxib showed a 3–4-fold reduction in ulcer complications (bleeding, perforation, or obstruction) compared with ibuprofen or naproxen but showed no difference in ulcer complication risk among aspirin users (99). In only 2 of these 4 large RCTs (VIGOR and TARGET) was the incidence of prespecified clinically meaningful upper GI bleeding significantly lower among the selective NSAIDs than nonselective comparators for the primary study end points. In fact, the National Institute for Clinical Excellence recommends considering the use of selective NSAIDs only in patients with OA or RA who are at high risk of developing serious GI events (100).

In the CLASS study, celecoxib 400 mg twice daily did not decrease serious ulcer complications overall, compared with diclofenac and ibuprofen. At 6 months, an analysis of the patients not taking aspirin showed that the risk of serious GI events was lower than with ibuprofen but not diclofenac (101). A 12-month analysis of data showing no relative risk reduction of serious upper GI and endoscopic ulcers was presented to the FDA. The individual comparisons between celecoxib versus ibuprofen and celecoxib versus diclofenac were not reported in the main publication (102); ulcer complication rates at either 6 months or the end of followup did not differ between treatment groups (32). For the secondary outcome of ulcer complications or symptomatic ulcers, celecoxib was supe-

Table 2. Randomized controlled trials of selective nonsteroidal antiinflammatory drugs and clinically relevant GI end points*

Study (ref.)	Subjects	GI end point	Annualized incidence of GI events (per 100 patient-years)	
			COX-2	Active comparator drug
VIGOR (89) CLASS (32)	8,076 RA patients 7,968 RA and OA patients	Confirmed upper GI events† Upper GI ulcer complications (primary), symptomatic gastroduodenal ulcer (secondary)§	Rofecoxib (50 mg/day): 2.1 Celecoxib (400 mg bid): 0.8 (primary), 2.1 (secondary)	Naproxen (500 mg bid): 4.5‡ Ibuprofen (800 mg tid), diclofenac (75 mg bid): 1.4 (primary), 3.5 (secondary)¶
MEDAL (98)	34,701 RA and OA patients	Upper GI events (secondary)#	Etoricoxib (60 or 90 mg/day): 0.3 (complicated), 0.37 (uncomplicated)	Diclofenac (150 mg/day): 0.32 (complicated), 0.65 (uncomplicated)
TARGET (99)	18,244 OA patients	Upper GI ulcer complications (primary)**	Lumiracoxib (400 mg/day): 0.32	Naproxen (500 mg bid), ibuprofen (800 mg tid): 0.91

* GI = gastrointestinal; COX-2 = cyclooxygenase 2; VIGOR = Vioxx Gastrointestinal Outcomes Research; RA = rheumatoid arthritis; bid = 2 times per day; CLASS = Celecoxib Long-term Arthritis Safety Study; OA = osteoarthritis; tid = 3 times per day; MEDAL = Multinational Etoricoxib and Diclofenac Arthritis Long-term; TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial, reduction in ulcer complications.
† Indicates gastroduodenal ulcers, perforations or obstructions, upper GI bleeding, and symptomatic gastric or duodenal ulcers.
‡ $P = 0.005$ versus rofecoxib.
§ Indicates gastric or duodenal perforation, gastric outlet obstruction, upper GI bleeding (primary); endoscopic/radiographic evidence of a gastric or duodenal ulcer (secondary).
¶ $P =$ nonsignificant versus celecoxib (primary); $P = 0.02$ versus celecoxib (secondary).
Indicates bleeding, perforation, obstruction, or ulcer diagnosed on clinical evaluation (secondary).
** Indicates bleeding, perforation, or obstruction.

rior to ibuprofen, but not to diclofenac at either 6 months or the end of followup (103). However, no significant difference was observed in the frequency of upper GI complications between the celecoxib and nonselective NSAID groups among 581 patients who were taking concomitant low-dose aspirin in the CLASS study. Thus, the interaction of celecoxib with low-dose aspirin may negate the potential GI safety benefits of celecoxib. Results of the 4 major RCTs are summarized in Table 2 (32,89,98,99).

In addition to comparing the incidence of clinically relevant end points among selective versus nonselective NSAID users, several pooled analyses allow comparison with placebo (33,104,105). In a meta-analysis of data from 4 double-blind RCTs, the annualized incidence rate of serious upper GI tract adverse events was 2.7 per 100 patient-years for placebo and 2.5 for rofecoxib (P value nonsignificant) (104). Another meta-analysis of 14 RCTs of patients treated with celecoxib compared with those receiving placebo or an active comparator found an annualized incidence rate of upper GI ulcer complications of 0.20% in celecoxib-treated patients, 1.68% in NSAID-treated patients, and 0% in placebo-treated patients ($P < 0.05$ for the difference between celecoxib and NSAID) (105).

The gastroprotective effects of proton-pump inhibitors (PPIs), misoprostol, and H_2 receptor antagonists on NSAID-related GI events have been reasonably well explored. In a meta-analysis and the Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) trial, 2 important outcomes were seen: a significant protective effect of misoprostol cotherapy in patients taking nonselective NSAIDs on the incidence of endoscopically determined gastric and duodenal ulcers, and a protective effect of H_2 receptor antagonists in the prevention of duodenal ulcers alone (90,106). Standard-dose H_2 receptor antagonists have not been associated with a reduction in the risk

for gastric ulcers, but full double-dose H_2 receptor antagonists (i.e., famotidine 40 mg twice daily) decrease endoscopic gastric and duodenal ulcers relative to placebo (107).

The misoprostol meta-analysis and MUCOSA trial focused solely on primary prevention of NSAID-related gastric and duodenal ulceration. In contrast, the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) (108) and Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) (109) studies examined the effects of misoprostol, PPIs, and H_2 receptor antagonists on treatment of secondary endoscopically-confirmed ulcers and erosions in patients receiving NSAID therapy. Patients randomized to omeprazole treatment had the highest rate of healing and approximately half of all patients remained ulcer free across each treatment arm.

The role of GI prophylaxis for selective NSAIDs has been considered an important avenue of research, but until recently there were few studies to guide therapeutic decision making (110). A review of 5 strategies to prevent NSAID-induced GI toxicity found that misoprostol, selective NSAIDs, and PPIs all reduced the risk of symptomatic ulcers; however, standard-dose H_2 receptor antagonists did not (111). However, an RCT demonstrated that in high-risk patients with a history of nonselective NSAID-induced ulcer bleeding, celecoxib plus a PPI was more effective in preventing recurrent ulcer bleeding compared with celecoxib plus placebo (8.9% probability of recurrent ulcer bleeding in celecoxib plus placebo; 95% CI 4.1–13.7; $P = 0.0004$) (112). Another study of peptic ulcer hospitalizations in Medicaid enrollees demonstrated an approximately 50% risk reduction in peptic ulcer hospitalization among both nonselective NSAIDs with PPIs and selective NSAIDs with PPIs (113). These new data may provide some evidence in favor of the concomitant use of PPIs with

Table 3. Summary of gastrointestinal outcomes of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study (36,39)*

	Etoricoxib†	Diclofenac†	Hazard ratio (95% CI)
No aspirin or proton-pump inhibitor	0.49	0.80	0.60 (0.43–0.86)
Proton-pump inhibitor only	0.35	0.59	0.59 (0.36–0.98)
Aspirin only	1.58	1.69	0.93 (0.65–1.35)
Aspirin and proton-pump inhibitor	0.84	1.31	0.64 (0.44–0.93)

* Any upper gastrointestinal clinical event (complicated or uncomplicated) in patients receiving aspirin and/or proton-pump inhibitor therapy. 95% CI = 95% confidence interval.
† Events per 100 patient-years.

selective NSAIDs in high-risk patients when the patient and provider have agreed to use a selective NSAID.

Balancing cardiovascular and GI risk. How can the clinician assess the risks of NSAID use for a particular patient? An analysis of data from the MEDAL study, a carefully selected RCT population, provides insight into the risks associated with etoricoxib and diclofenac as representative selective and nonselective NSAIDs (98,114). By extrapolating from the analysis of events in different risk groups in this trial (Tables 3 and 4), the clinician can estimate the risks for a particular patient taking selective and nonselective NSAIDs based on concomitant medications and comorbidities. For example, the risk of a GI event in patients not taking aspirin or a PPI but taking a nonselective NSAID is <1% per year. This risk is reduced ~40% for those taking a selective NSAID. Using a PPI reduces the risk for both types of NSAIDs by approximately 15–20%. For both selective and nonselective NSAIDs, concomitant aspirin use increases the risk to ~1.6% per year and the advantage of

using a selective NSAID disappears. In patients receiving aspirin and an NSAID, concomitant use of a PPI reduces the risk of a GI event, and there may be an advantage to the use of a selective NSAID. The risk of cardiovascular events in patients taking both types of NSAIDs without preexisting cardiovascular risk factors and with <2 risk factors is approximately <1% per year. The risk may increase to ~3% per year in older patients, men, those with known cardiovascular disease, or those with multiple risk factors. The cardiovascular risks are likely to vary significantly among specific drugs (98,114).

In a patient with cardiovascular risk and low GI risk who is receiving aspirin therapy, naproxen with or without a PPI might be used. In a patient with both cardiovascular risk and high GI risk receiving aspirin therapy, a PPI should be utilized with either naproxen (if cardiovascular risk is greater than GI risk) or a selective NSAID, especially in those with a prior history of GI bleeding (115). However, in each case, the patient and provider must come to a mutual decision about the use of an NSAID in that partic-

Table 4. Summary of cardiovascular outcomes of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study (36,39)

	Etoricoxib*	Diclofenac*	Hazard ratio
Characteristics of cardiovascular event			
Fatal thrombotic event	0.17	0.17	0.96
Other events†	0.71	0.78	0.90
Patient characteristics			
Age <65	0.85	0.88	0.96
Age 65–75	1.63	1.64	0.99
Age >75	2.51	3.10	0.81
Male	1.94	2.32	0.83
Female	1.00	0.95	1.04
Established cardiovascular disease	3.12	3.33	0.94
No established cardiovascular disease	1.02	1.06	0.96
Established cardiovascular disease or >2 cardiac risk factors	2.00	1.93	1.04
No established cardiovascular disease or >2 cardiac risk factors	0.81	0.95	0.85
Baseline low-dose aspirin use	1.67	1.87	0.89
No baseline low-dose aspirin use	1.01	1.01	1.00

* Events per 100 patient-years.
† Myocardial infarction, sudden cardiac death, cardiac arrest, unstable angina, and cardiac thrombus.

ular case, as individual circumstances and overall risk may vary.

Renal adverse events. The nephrotoxicity of nonselective NSAIDs and selective NSAIDs is well recognized and has several different clinical manifestations, including pre-renal azotemia, hyporeninemic hypoaldosteronism (a low renin, angiotensin II, and aldosterone state characterized by mild hyperkalemia), hypertension, sodium retention, acute interstitial nephritis, and nephrotic syndrome (116). Pre-renal azotemia is quite common in persons with a preexisting reduction in renal blood flow and appears to be due to inhibition of the prostaglandin-mediated counter-regulatory mechanisms of the kidney. Edema, hypertension, and acute renal failure are several manifestations of pre-renal azotemia. Pre-renal azotemia can evolve into acute tubular necrosis if untreated. In addition, hyporeninemic hypoaldosteronism is not uncommon in patients with diabetes taking NSAIDs, with clinical features including a higher degree of hyperkalemia and a mild metabolic acidosis.

Acute renal dysfunction has been noted to be increased with most agents in many studies, including nonselective NSAIDs and selective NSAIDs (117–121). In addition, many of the nonselective NSAIDs have been implicated as causing chronic renal failure. Relative risks range from 2–8 in 2 well-done epidemiologic studies (122,123). However, the existence of a chronic NSAID nephropathy has been debated by some.

Hypertension is a well-described side effect of the nonselective NSAIDs (124) and selective NSAIDs (52). Hypertension may occur in previously normotensive patients and may worsen in those with a preexisting diagnosis of hypertension. To answer the question of how nonselective NSAIDs compare with the newer selective NSAIDs with respect to the outcome of hypertension, a meta-analysis scrutinized 19 RCTs of selective NSAIDs involving more than 45,000 participants. A slightly greater elevation in blood pressure was found among patients taking selective NSAIDs when compared with patients taking nonselective NSAIDs and those receiving placebo; however, the findings were not statistically significant (1.61, 95% CI 0.91–2.84; $P = 0.10$ for selective NSAIDs versus placebo and 1.25, 95% CI 0.87–1.78; $P = 0.23$ for selective NSAIDs versus nonselective NSAIDs) (70).

The role of hypertension in the pathogenesis of NSAID-related cardiovascular risk remains less well understood. Analysis of combined data from the Prevention of Spontaneous Adenomatous Polyps (PreSAP) and Adenoma Prevention with Celecoxib (APC) trials demonstrated a dose-related increase in blood pressure. In the PreSAP study, the 400 mg once daily dosing had a hazard ratio of 1.3 (95% CI 0.6–2.6) with no difference in blood pressure. In the APC study, the 200 mg twice daily dosing had a hazard ratio of 2.6 (95% CI 1.1–6.1) with a difference in blood pressure of 2.0 mm Hg ($P = 0.04$) at 1 year, and the 400 mg twice daily dosing had a hazard ratio of 3.4 (95% CI 1.5–7.9) with a difference in blood pressure of 2.9 mm Hg ($P = 0.005$) at 1 year (72). The authors postulated that perhaps the short half-life of celecoxib, the timing of the

blood pressure measurements with respect to the celecoxib dosing, and the once daily versus twice daily dosing may explain these findings.

Hepatotoxicity. Liver toxicity is a rare adverse event related to both nonselective NSAIDs and selective NSAIDs. There is a paucity of data regarding the risk of individual NSAIDs (125). A general estimate for clinically relevant liver toxicity is 1 per 10,000 patient courses of either nonselective NSAIDs or selective NSAIDs (126). A systematic review of population-based epidemiologic studies examining the risk of NSAID-related hepatotoxicity revealed an increased nonsignificant risk (absolute incidence 3.1–23.4 per 100,000 patient-years of exposure), but no fatal hepatotoxicity cases (127). In the CLASS study, the incidence of serum elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) that were more than 3 times the upper limit of normal were increased in patients receiving nonselective NSAIDs (diclofenac and ibuprofen) compared with those receiving celecoxib. In addition, 97% of the ALT and AST abnormalities were observed in patients treated with diclofenac (32). In the TARGET study, 2.6% of patients treated with high-dose (400 mg daily) lumiracoxib had a reversible increase in transaminases of more than 3 times the upper limit of normal (99). A recent systematic review of the NSAIDs that were withdrawn from the market due to hepatotoxicity showed that there are significant challenges in assessing predictors of severe hepatocellular injury in clinical trials, but flu-like symptoms and jaundice may be the initial features (128).

On August 13, 2007, lumiracoxib was taken off the Australian market due to reports of serious liver adverse reactions associated with this selective NSAID in 8 patients (129). Of these 8 patients, 2 died and 2 required liver transplantation. In the clinical trial data on lumiracoxib, if elevations in the liver function tests occurred, they were likely to normalize once the medication was discontinued. However, in the postmarketing surveillance of lumiracoxib in Australia, these new severe reports of hepatotoxicity led to removal of these agents from the market. Subsequently, lumiracoxib was removed from the Canadian market and several European countries, including the UK and Germany. Although liver toxicity associated with NSAIDs is a highly unusual event, hepatotoxicity as an adverse event is the most common reason for either lack of approval or market withdrawal of NSAIDs (128). Overall, it seems that these liver toxicities are idiosyncratic and that the risk of hepatotoxicity with NSAID use is not high. In comparison, acetaminophen hepatotoxicity can lead to acute liver failure and is one of the leading causes of liver transplantation in the US (130).

Cutaneous. Almost every type of cutaneous drug reaction has been described with NSAIDs, including morbilliform eruptions, fixed drug eruptions, erythema multiforme (Stevens-Johnson syndrome or toxic epidermal necrolysis), pseudoporphyria, and photosensitivity. The epidemiology of these reactions has not been extensively studied, but one estimate is that 27% of all adverse drug

eruptions result from NSAIDs (131). Although most of these reactions are mild, Stevens-Johnson syndrome has been described in a relatively large number of patients taking valdecoxib and is one of the reasons the FDA requested that the manufacturer of valdecoxib remove the drug from the market (132). In children with JIA, pseudoporphyria is a much more common skin eruption than in adults taking NSAIDs (occurring in 10–12% of all JIA patients receiving NSAID therapy). Pseudoporphyria is much more common with the use of naproxen, with younger age and fair complexion being additional risk factors (133,134).

Pulmonary. Aspirin-exacerbated respiratory disease, or aspirin-induced asthma is characterized by asthma and rhinitis triggered by ingestion of aspirin and NSAIDs. Aspirin-exacerbated respiratory disease is associated with upper and lower respiratory tract mucosal inflammation, progressive sinusitis, nasal polyposis, and asthma, regardless of whether or not patients avoid the triggering drugs. The mechanism underlying the propensity of aspirin and NSAIDs to cause this reaction involves inhibition of the synthesis of protective prostaglandins resulting in an increase in synthesis of cysteinyl leukotrienes by eosinophils and mast cells. Clinical data suggest that protective prostaglandins are derived from COX-1, because studies have now confirmed that drugs specifically inhibiting COX-2 are not cross-reactive with aspirin in patients with aspirin-exacerbated respiratory disease and suggest that celecoxib might be safe to use in these patients (135–138).

Hematologic. Anemia associated with NSAID use primarily reflects GI bleeding and blood loss and should prompt immediate investigation. Aplastic anemia or agranulocytosis due to NSAID use has very rarely been reported with piroxicam, sulindac, naproxen, diclofenac, indomethacin, ibuprofen, fenoprofen, fenbufen, tolmetin, meclofenamate, and phenylbutazone. However, the commonly used diclofenac may be the most often reported among these very rare reports of aplastic anemia or agranulocytosis. The attributable incidence of diclofenac agranulocytosis has been estimated to be 0.14 (95% CI 0.01–0.28) events per 1 million patient-years of exposure (139). Other very rare hematologic events (e.g., eosinophilia, neutropenia, thrombocytopenia, or hemolytic anemia) have not been conclusively linked to NSAID use and may be attributed to concomitant drugs or diseases (140).

Anticoagulant effects are the most common hematologic effects of NSAID use. Nonselective NSAIDs inhibit COX-1 on platelets and decrease TBA₂ release and may thus inhibit platelet aggregation. Therefore, aspirin and nonselective NSAIDs prolong bleeding time and may have a significant anticoagulant effect. Symptoms of easy bruising and, less commonly, epistaxis can occur. These effects are significantly worsened by the concomitant use of anticoagulants or combined aspirin and nonselective NSAID use. Aspirin and nonselective NSAID therapy is contraindicated in patients receiving anticoagulants. Because platelets use only the COX-1 isoform, pure COX-2 inhibitors do not affect platelet function and may be used in circum-

stances in which nonselective NSAIDs should not. As such, if there are situations in which the patient and provider have agreed that NSAID therapy may provide therapeutic benefit, selective NSAIDs may be used with caution in patients receiving warfarin. Close monitoring of the international normalized ratio is needed because minor ulcers may occur. Overall, the risk of bleeding gastric ulcers is greater when NSAIDs and warfarin are used together.

Central nervous system side effects. Aseptic meningitis is well recognized among persons taking almost all NSAIDs. Many of the reported cases involve ibuprofen in patients with autoimmune diseases. However, normal hosts taking NSAIDs other than ibuprofen have developed well-documented cases of aseptic meningitis. In elderly patients, there may be a risk of psychosis and other mental status changes with the use of indomethacin (141).

PHARMACOECONOMICS

The advent of selective NSAIDs has created great controversy over the appropriate use of NSAIDs. Selective NSAIDs were developed to improve the GI toxicity profile of NSAIDs but were then marketed widely and used beyond high-risk GI patients (142). Although much of the marketing frenzy quieted down when the potential cardiovascular toxicities of selective NSAIDs were revealed, the controversy regarding which patients should receive which agents and the implications for health care costs provides an important pharmacoeconomic lesson.

NSAID utilization. NSAIDs are extremely popular medications. Investigators from the Nurses Health Study found that among women 52–77 years of age, 10.8% reported using NSAIDs ≥ 6 days per week and 26.7% at least 1 day per week (143). The recognition of how large a public health problem NSAID-associated GI toxicity has become and the advent of selective NSAIDs focused attention on NSAID utilization patterns. Some patients with OA are prepared to tolerate the additional risk of GI bleeding or myocardial infarction resulting from their pain or antiinflammatory medications in exchange for greater pain relief (144).

Investigators using several different data sources have observed that many coxib users do not have clear indications for these drugs (145,146). Much of the use of selective NSAIDs appears to have been driven by physician preferences and specialty, which may have been influenced by nonclinical factors (145,147). One study found that patients who received concomitant aspirin were more likely to receive a nonselective NSAID (148). It is also interesting to note that many patients receiving nonselective NSAIDs have risk factors for NSAID-associated GI toxicity (145,149). Thus, there appears to be both an overuse of selective NSAIDs and an underuse of strategies to reduce NSAID-associated GI toxicity.

The variation in practice regarding selective NSAIDs and nonselective NSAIDs prompted the Arthritis Foundation's Quality Indicator Project to develop a group of evi-

Table 5. Results of a cost-utility analysis of selective nonsteroidal antiinflammatory drug use under varying conditions (151)*

Analysis	Strategy	Cost (\$)	Effectiveness (QALYs gained)	Incremental cost-effectiveness (\$)
Base-case analysis (3% discount rate)	Naproxen	4,859	15.2613	–
	Coxib	16,443	15.3033	275,809
Base-case analysis (5% discount rate)	Naproxen	4,238	12.6933	–
	Coxib	13,820	12.7282	274,555
Including cardiovascular events	Naproxen	5,037	15.2539	–
	Coxib	16,620	15.2832	395,324
Using VA prices	Naproxen	1,917	15.2613	–
	Coxib	7,885	15.3033	142,095
Assuming high-risk cohort (previous ulcer hemorrhage)	Naproxen	14,294	14.7235	–
	Coxib	19,015	14.8081	55,803

* QALYs = quality-adjusted life years; VA = Veterans Administration.

dence-based prescribing measures for this group of agents (150). These measures are based on the best available evidence. Although still untested, it is likely that if these measures were put in place, there would be fewer adverse events.

Pharmacoeconomics of selective NSAIDs. Several different groups have investigated the economics of coxib use. These agents can cost from 5 to 10 times more than a generic NSAID and do not confer greater benefits to patients. In selected groups at high risk for GI toxicity, coxibs may be a good deal from an economic standpoint. Analyses by 2 groups suggested that using selective NSAIDs in patients with at least 1 risk factor for an NSAID-associated GI adverse event was economically reasonable (151,152). However, selective NSAID use in young patients without risk factors is associated with cost-effectiveness ratios that are much higher than accepted limits (Table 5) (151).

One analysis simultaneously compared the GI and cardiovascular benefits and risks of rofecoxib with naproxen (153). This analysis assumed that the GI benefits and cardiovascular risks would mirror data observed in the VIGOR trial and applied those event rates to a 58-year-old patient with RA. In this analysis, patients taking naproxen had a more than 90% likelihood of a longer life expectancy. Although this analysis has some appeal because it brings the competing GI and cardiovascular risks into the same model, it is based on use of a high dose of rofecoxib in patients with RA and may not generalize to a broader population.

DISCUSSION

Despite clinical expertise of practicing physicians, observational studies, RCTs, and postmarketing surveillance data on NSAIDs, there are still several key areas in which there is an inadequate amount of information to guide clinical decision making. Patients who are candidates for NSAID therapy for the relief of musculoskeletal pain and inflammation are often at high risk of the myriad complications of NSAIDs due to their underlying comorbid medical conditions and age. The typical patient with knee OA may be an elderly woman with cardiovascular risk factors such as hypertension and hypercholesterolemia and de-

clining renal function. To determine the best approach for the treatment of her conditions, her other medications (calcium-channel blocker or angiotensin-converting enzyme inhibitor for hypertension, statin for hypercholesterolemia, aspirin for cardioprotection) and the overall risk/benefit of adding an NSAID must be considered.

Currently, there is insufficient evidence to guide decision making on NSAID use in patients with a history of GI complications and cardiovascular disease. For example, if a patient has had a previous upper GI bleed with ulceration that has been treated and has a high cardiovascular risk, and use of an NSAID is truly necessary, is it preferable to use a nonselective NSAID plus a PPI or a selective NSAID plus a PPI? If this same patient would benefit from low-dose aspirin for cardioprotection, then should one even consider a selective NSAID since the gastroprotective benefit of the selective NSAID would be abolished with the concomitant use of aspirin? One recent review comparing the safety of nonselective NSAIDs with selective NSAIDs in patients at high risk of a cardiovascular event who were receiving low-dose aspirin therapy argued that selective NSAIDs are preferable to nonselective NSAIDs for the management of chronic pain in this population (154).

Part of this uncertainty derives from the fact that most RCTs of selective NSAIDs systematically exclude patients with a history of significant cardiovascular disease. Thus, one cannot accurately calculate the risk of cardiovascular outcomes because the events are few. There is a lack of NSAID trials either comparing one nonselective NSAID with another or using a placebo control. This leads to the inability to ascertain the degree of significant cardiovascular risk associated with these agents.

RECOMMENDATIONS

Individual treatment decisions may supercede general recommendations because the scientific evidence does not address all aspects of clinical practice. The role of patient preference and risk-taking behavior differs between individuals, but there are patients who may be willing to accept the risk of GI complications or myocardial infarctions in exchange for pain relief from their musculoskeletal diseases (144).

Based on the currently available data, we propose the

following recommendations aimed at the practicing clinician.

Efficacy/effectiveness. If a patient and provider agree to utilize an NSAID for arthritis pain relief and the patient does not respond to one agent, then other agents may be tried. Some patients respond differently to different NSAIDs.

If a patient and provider agree to utilize an NSAID for arthritis pain relief and the patient is at low risk for toxicity, then the lowest effective dose of the least expensive agent should be considered first line. Low doses of NSAIDs are safer than high doses. There are no compelling data to support the selection of one agent over another if there are no significant toxicity concerns.

Toxicity. If a patient and provider agree to utilize an NSAID (nonselective or selective) for arthritis pain relief, then the patient should be advised of the potential toxicities and relevant monitoring (complete blood cell count, renal function, liver function, and blood pressure) should be pursued.

If a patient is taking aspirin for cardioprotective benefit, then selective and nonselective NSAIDs should be avoided. This combination is associated with an elevated risk of GI bleeding. However, if a patient is educated about this risk and wants to take the drugs concomitantly, then a PPI or misoprostol should be added to the regimen.

If a patient is at moderate-to-high risk of a future cardiovascular event, is taking low-dose aspirin for cardioprotection, and the patient and provider agree that continuous treatment for arthritis pain relief is needed, then the patient should be managed initially with acetaminophen or naproxen. Selective NSAIDs and other nonselective NSAIDs have been associated with an increased cardiovascular risk. Note that naproxen may also confer cardiovascular risk when used intermittently or at low doses that do not inhibit platelet aggregation.

If a patient and provider agree to utilize an NSAID for arthritis pain relief, and the patient is taking low-dose aspirin for cardiovascular prevention, then continuous use of ibuprofen should be avoided. There is a potential drug-drug interaction between aspirin and ibuprofen that reduces cardioprotective benefit. This may be true for other nonselective NSAIDs, but there are insufficient data to assess the interaction. Selective NSAIDs do not appear to have relevant drug-drug interactions with the anticoagulant effects of aspirin.

If a patient and provider agree to utilize an NSAID for arthritis pain relief, and the patient has risk factors for GI bleeding, then the patient should be treated concomitantly with either misoprostol or a PPI. These agents will reduce the risk of GI bleeding.

If a patient has renal insufficiency, then use of both selective and nonselective NSAIDs should be avoided.

If a patient has compromised liver function, then the risks of selective and nonselective NSAID use should be carefully considered. Although severe hepatotoxicity with NSAIDs is rare, NSAIDs are associated with liver function

abnormalities. Diclofenac should be avoided in patients with liver disease.

If a patient is fully anticoagulated with warfarin, heparin, or other anticoagulants or is thrombocytopenic, then use of nonselective NSAIDs should be avoided because they can increase the risk of bleeding.

The modified RAND/UCLA Appropriateness Method on an expert multidisciplinary panel was not utilized in the preparation of this White Paper. The context for the style of these recommendations is the Arthritis Foundation's Quality Indicator Set for osteoarthritis (150).

AUTHOR CONTRIBUTIONS

Dr. Solomon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Lovell, Solomon.

Acquisition of data. Desai, Cush, Saag.

Analysis and interpretation of data. Desai, Abramson, Lovell, Saag, Solomon.

Manuscript preparation. Desai, Abramson, Buckley, Crofford, Cush, Lovell, Saag, Solomon.

Collaboration. Solomon.

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