

# Anti-inflammatory Drugs and GI Safety

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## ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) confer a gastrointestinal (GI) side effect profile associated with considerable morbidity and mortality. COX-2 inhibitors were developed as GI safer alternatives to traditional NSAIDs—providing equivalent analgesic and anti-inflammatory efficacy. Recent data confirms their GI sparing is significantly impaired by concomitant aspirin use, and concerns regarding adverse cardiovascular outcomes for patients using these medications have become paramount. The withdrawal of rofecoxib and valdecoxib from the market has focused attention on the key issue currently facing clinicians: how can we achieve the right balance to maximize benefits and minimize cardiovascular (CV) and GI risks when treating patients who need anti-inflammatory therapy? This update discusses our current understanding of the risks and benefits of NSAIDs therapies and suggested approaches leading to improved outcomes for patients with and without CV and GI risks requiring these medications.

## STATE OF THE ART—2005

Gastroenterologists recognize that the widespread use of over-the-counter (OTC) and prescription nonsteroidal anti-inflammatory drug (NSAID) tablets to treat arthritis and pain has a gastrointestinal (GI) side-effect profile associated with considerable morbidity and mortality.<sup>1</sup> NSAIDs achieve their effects by blocking prostaglandin endoperoxide synthase (cyclooxygenase, COX). The discovery in the 1990s of 2 isoforms COX, COX-1 and COX-2, led to the opportunity to selectively block COX-2, theoretically providing an anti-inflammatory effect without increasing bleeding risk from GI or other sites.<sup>2</sup> COX-2 inhibitors were developed as GI safer alternatives to traditional NSAIDs—providing equivalent analgesic and anti-inflammatory efficacy. Consequently, there was a rapid rise in prescriptions for these drugs.<sup>3</sup> At the same time, evolving data suggested the GI sparing effect could be significantly impaired by concomitant aspirin use, and concerns regarding adverse cardiovascular (CV) outcomes for patients using these medications became paramount. The voluntary withdrawal of rofecoxib from the market on Sept 30, 2004, led to great consternation and focused attention on the key issue currently facing clinicians: how, then, can we achieve the right balance to maximize benefits and minimize CV and GI risks when treating patients who need anti-inflammatory therapy?

### Gastroprotective Agents Versus Safer Anti-inflammatory Drug?

The major risk factors for NSAID-related GI events are listed in Table 1. A prior bleed or perforation confers the highest risk for an NSAID-related GI complication. At what age risk substantially increases is not clear, but those over age 50 have a significantly higher GI risk than their younger counterparts. Patients 75 and over may have a GI risk that is comparable to having a prior clinical event. Certain drugs may potentiate NSAID GI toxicity, such as combining an NSAID with an anticoagulant or corticosteroid. Most important-

ly, high doses and/or multiple NSAIDs (*including an NSAID plus low-dose aspirin*), significantly raises risk.<sup>4</sup>

What about a COX-2-selective inhibitor plus aspirin co-therapy? In a 12-week, double-blind, placebo-controlled, endoscopic trial of 1,615 patients with osteoarthritis (OA), low-dose aspirin (81 mg/day) plus the COX-2-selective inhibitor rofecoxib (25 mg/day) significantly increased ulcer incidence to a rate similar to that of the nonselective NSAID ibuprofen.<sup>5</sup> The Celecoxib Long-term Arthritis Safety Study (CLASS)<sup>6</sup> and the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) trial (N = 18,325)<sup>7</sup> provide additional insight into this question. In CLASS (N = 8059), aspirin use ( $\leq 325$  mg) was found to significantly increase the incidence of upper GI ulcer complications in celecoxib-treated patients (400 mg bid). Among low-dose aspirin users, those who took celecoxib had a relative risk of 2.01 for an upper GI ulcer complication, which was comparable to the relative risk of 2.21 in NSAID using counterparts. In TARGET, lumiracoxib was compared with 2 traditional NSAIDs, naproxen and ibuprofen. Lumiracoxib was associated with a 79% relative risk reduction in ulcer complications compared with NSAID therapy. However, with concomitant low-dose aspirin, there was a nonsignificant 21% relative risk reduction for lumiracoxib compared with NSAIDs (RR, 0.79; 95% CI, 0.40–1.55), suggesting that the gastrointestinal benefit of lumiracoxib was diminished substantially.

Aspirin, a classic antiplatelet drug (when given at low doses,  $\leq 325$  mg/day), is widely used for cardioprotection, but the trade-off between CV benefits and GI risks of low-dose aspirin therapy must be taken into consideration. Clinicians should dissuade otherwise healthy patients from using aspirin as a “lifestyle drug.” Advocating aspirin for the secondary prevention of CV events is justified because the benefits in preventing recurrent CV events outweigh the risk of GI hemorrhage. The use of aspirin for the primary prevention of CV events, however, may be ill-advised (especially in those patients with no known CV risk) because the potential CV benefits are outweighed by the increased risk of GI bleeding.<sup>8</sup>

For patients with GI risk who require aspirin for cardioprotection, data strongly support prophylactic treatment with a proton pump inhibitor (PPI). The efficacy of lansoprazole for prevention of recurrent ulcer complications associated with low-dose aspirin

**Table 1.** Risk Factors for NSAID-associated Ulcer Complications (In Order of Relative Importance)

1. Personal history of complicated ulcer disease
2. Concurrent use of more than 1 NSAID (including aspirin)
3. Use of high NSAID doses
4. Concurrent use of an anticoagulant
5. Personal history of uncomplicated peptic ulcer disease
6. Advanced age
7. Concurrent use of steroids

was demonstrated in patients (N = 123) with ulcer bleeding and *Helicobacter pylori* infection. All patients received eradication therapy and were randomized to either aspirin (100 mg) plus lansoprazole (30 mg) or aspirin (100 mg) plus placebo for 12 months. Ulcer bleeding recurred in 1.6% and 14.8% of patients in the lansoprazole and placebo groups, respectively ( $P = .008$ ).<sup>9</sup> Of the 14.8% of patients who had recurrent ulcer complications at 1 year, two thirds had failed *H pylori* eradication or had used concomitant NSAIDs for arthritis. Given these findings, it is uncertain whether *H pylori* eradication alone can prevent recurrent ulcer complications in high-risk aspirin users.

NSAID users at risk benefit from the utilization of a safer agent or addition of a gastroprotective agent, such as a PPI or misoprostol. In a head-to-head comparison of misoprostol versus the lansoprazole, both therapies demonstrated significant reduction in the risk of ulcer relapse in comparison with placebo, while the PPI was better tolerated.<sup>10</sup> COX-2 inhibitors should not be considered devoid of GI risk. In a population-based study using a large administrative health care database, a 41% increase in NSAID use—entirely due to an increase in COX-2 inhibitor use—was accompanied by a 10% increase in hospitalization for upper GI bleeding. COX-2 inhibitors were likely given to those who might not have otherwise received these agents.<sup>11</sup> Furthermore, COX-2 inhibitor monotherapy may be insufficient for such very high-risk patients. In a randomized trial of 287 patients with NSAID-related ulcer bleeding, celecoxib (200 mg twice daily) was shown to be as effective as treatment with diclofenac (75 mg twice daily) plus omeprazole (20 mg/day) for 6 months at preventing recurrent ulcer bleeding (4.9% vs. 6.4%, respectively;  $P = .6$ ).<sup>12</sup> The incidence of recurrent gastroduodenal ulcers was also high in the follow-up endoscopy study among patients without recurrent gastrointestinal complications within the study period: 19% of patients receiving celecoxib and 26% of patients receiving diclofenac plus omeprazole had recurrent ulcers in 6 months.<sup>13</sup> These data suggest that neither treatment regimen was sufficient for these very high-risk patients. Hence, very high-risk patients may benefit from co-therapy using a COX-2 inhibitor and a PPI.

## NEW INSIGHTS IN 2005

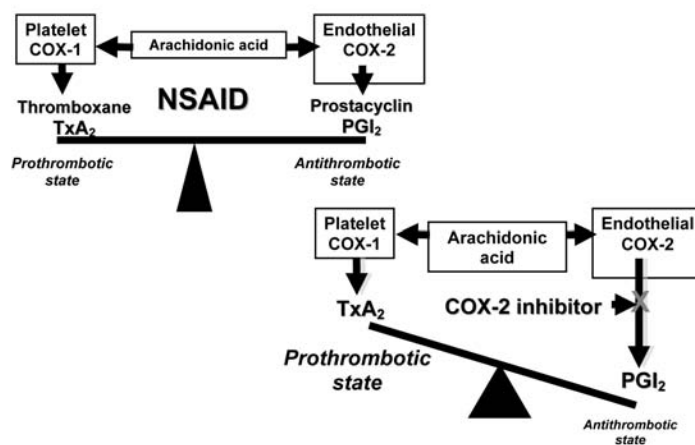
### CV Effects of COX-2–Selective Inhibitors

The increased risk of CV events with COX-2 inhibitors has been hypothesized to relate to an imbalance between the effects of COX-1 and COX-2. In platelets, COX-1 mediates thromboxane A<sub>2</sub> (TxA<sub>2</sub>) synthesis, which promotes platelet aggregation and vasoconstriction. In endothelial cells, COX-1 and COX-2 both mediate production of prostacyclin (PGI<sub>2</sub>), which acts as an “anti-TxA<sub>2</sub>” to inhibit platelet aggregation and promote vasodilation. In theory, the ability of aspirin and conventional NSAIDs to inhibit both COX-1 and COX-2 maintains a balance between reductions in PGI<sub>2</sub> and TxA<sub>2</sub>. In contrast, COX-2 inhibitors selectively suppress the production of PGI<sub>2</sub> without influencing TxA<sub>2</sub> synthesis, theoretically causing relative imbalance in PGI<sub>2</sub> and TxA<sub>2</sub> production leading to a prothrombotic state.<sup>14</sup> (Figure 1)

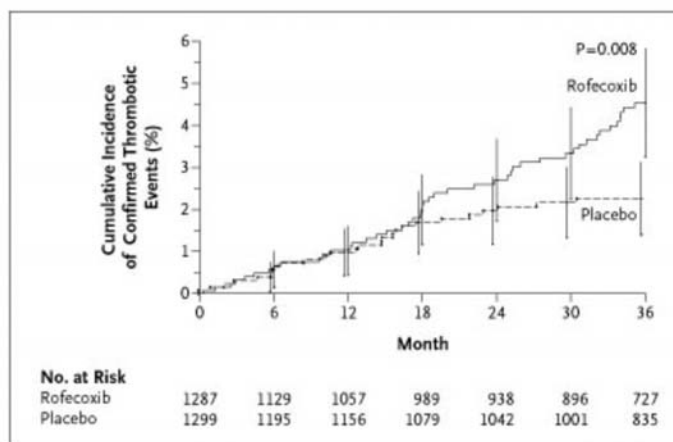
The COX-2–inhibitor cardiovascular story began with the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, where it was noted that the rheumatoid arthritis (RA) patients randomized to receive naproxen (500 mg twice daily) had a significantly lower rate of myocardial infarction than those receiving rofecoxib (50 mg/day), although the 2 groups did not

differ significantly in the CV deaths or stroke.<sup>15</sup> Subsequently, randomized controlled studies published in 2005 have demonstrated an increased risk of CV events with 3 COX-2–selective inhibitors placebo-controlled trials. These include the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial,<sup>16</sup> studies of parecoxib/valdecoxib in patients after coronary artery bypass graft (CABG) surgery,<sup>17</sup> and the Adenoma Prevention with Celecoxib (APC) trial.<sup>18</sup>

In the APPROVe trial (N = 2,586), patients with a history of colorectal adenomas were randomized to receive either rofecoxib (25 mg/day) or placebo. The study was designed to evaluate the efficacy of rofecoxib in reducing the risk of recurrent adenomatous polyps; CV events were part of the safety assessment. In this study, a 1.9-fold increase in risk of thrombotic events was noted in patients assigned to the rofecoxib group (25 mg/day) compared with placebo.<sup>16</sup> (Figure 2) This divergence in event rates did not



**Figure 1.** FitzGerald Hypothesis for the mechanism of prothrombotic action of COX-2–selective inhibitors. By affecting vascular prostacyclin only, the balance toward thrombosis may be altered. Both selective and nonselective agents may cause salt and water retention, increasing further the risk of adverse cardiovascular outcomes.



**Figure 2.** Kaplan–Meier estimates of the cumulative incidence of confirmed serious thrombotic events in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.

occur until after 18 months of therapy.

In a double-blind study (N = 1,671), patients with postoperative pain following CABG were randomized to therapy with intravenous parecoxib (20 mg) for at least 3 days, followed by oral valdecoxib (20 mg) through day 10; intravenous placebo followed by oral valdecoxib (20 mg); or placebo alone for 10 days. There was a 3.7-fold increase in CV risk in the group given parecoxib plus valdecoxib compared with the placebo group (2.0% vs. 0.5%, respectively;  $P = .03$ ), suggesting that even short-term COX-2 inhibition is associated with an elevated risk of CV events in very high-risk patients.<sup>16</sup> Subsequently, valdecoxib was withdrawn from the market in April 2005.

Figure 3 illustrates the key finding of the APC trial (N = 2,035).<sup>18</sup> This placebo-controlled trial was designed to assess celecoxib (200 mg or 400 mg twice daily) for the prevention of adenomatous polyps. During 2.8 to 3.1 years of follow-up, an increase in the risk of serious CV events was noted, including CV death, myocardial infarction, stroke, and heart failure compared with placebo. The increased risk of CV events appeared to be dose related and appeared in a shorter time frame than the APPROVe trial. A post hoc analysis did not find aspirin to be protective for the subgroup taking cardioprotective doses. Data from a sister study, the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial, were discussed in this paper. PreSAP evaluated celecoxib (400 mg once daily) compared to placebo. Unlike APC, this study did not show a significant CV risk associated with celecoxib. Given the wide confidence intervals obtained from the PreSAP study, the data cannot refute a hazard with celecoxib. The differences in results obtained from APC and PreSAP may be attributed to the differences in doses used in the study (since celecoxib has a shorter half-life than the other coxibs removed from the market) and the patient population.<sup>18</sup>

The Food and Drug Administration (FDA) convened an advisory committee meeting to discuss the CV issues of COX-2-selective inhibitors and NSAIDs in February 2005. These studies and others, including observational studies of nonselective NSAIDs, were reviewed. The FDA Joint Advisory Committee concluded coxibs as a class were associated with CV risks, but with the

exception of high-dose (>25 mg/day) rofecoxib, not dissimilar from the known effects of nonselective NSAIDs. Until further data for nonselective NSAIDs are available, some committee members suggested that patients in need of pain relief first try naproxen, since it has the longest lasting antiplatelet effect and its CV safety was supported by meta-analysis.<sup>19</sup> Subsequent Conclusions of the FDA analysis after this meeting included the following: 1) COX-2 inhibitors increase CV risks compared with placebo; 2) however, long-term clinical trials have not yet clearly demonstrated that the COX-2 inhibitors confer greater CV risks than nonselective NSAIDs; 3) data from long-term, placebo-controlled trials that assess the CV risk of nonselective NSAIDs are unavailable; and 4) the available data are best interpreted as consistent with a class effect of all NSAIDs.<sup>20</sup> Consequently, the FDA issued a directive that all NSAIDs should include a boxed warning regarding potentially serious CV events.

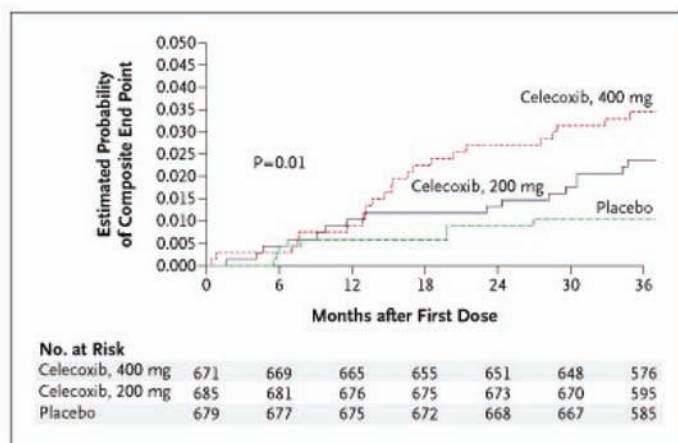
### Antiplatelet Therapy and GI Risk

Replacing aspirin with another antiplatelet drug such as clopidogrel, although recommended by the American College of Cardiology and American Heart Association may not protect patients from developing upper or lower GI complications. This question was addressed in a 12-month, randomized, prospective, double-blind trial of cardiac and stroke patients (N = 320), comparing clopidogrel (75 mg) with aspirin (80 mg) plus esomeprazole (20 mg) twice daily for the prevention of recurrent ulcer bleeding.<sup>21</sup> Patients who had a recent history of bleeding ulcer all were treated for ulcers and *H pylori* eradication (for those who tested positive). The cumulative incidence of recurrent bleeding during the 12-month period was 8.6% in the clopidogrel group versus 0.7% in the aspirin plus esomeprazole treatment group ( $P = .001$ ).<sup>10</sup> In addition, the incidence of lower GI bleeding in the 2 treatment groups remained high, indicating that antiplatelet agents may precipitate bleeding beyond the upper gut that PPI therapy cannot ameliorate. These data also suggest that for such high-risk patients, clopidogrel alone is not a safer alternative and the addition of a PPI might benefit these patients as well; this concept deserves further study.

### To What Extent Should We Be Concerned Regarding the “Lower GI” Toxicity of NSAIDs?

NSAIDs are associated with small-bowel lesions, including ulceration. Lower rates of gastroduodenal ulcers, and “lower GI events” as well, have been observed with the use of COX-2-specific inhibitors, but the effects of these drugs on the small-bowel mucosa have not been well characterized. Goldstein et al. confirmed less small intestinal injury observed by video capsule endoscopy among healthy, non-aspirin using volunteers taking a coxib compared to the competing strategy to reduce gastroduodenal ulcers, an NSAID + PPI.<sup>22</sup> These data raised more questions than answers.<sup>23</sup> Are these lesions the source of the reduction in fecal blood loss seen with coxibs compared to NSAIDs? The investigators noted many lesions in healthy subjects apparently off NSAIDs—why? Are these lesions a surrogate marker that predicts clinically important events—the source of anemia or significant bleeding?

These data do provide an additional consideration for clinicians making the very difficult choice between a coxib and NSAID + PPI for at-risk patients. Until well-designed studies address the clinical relevance of these differences, clinicians should think about the CV risk first (considering aspirin and its impact on coxib safety, as well) before a coxib is prescribed. In a low-cardiac-risk patient (not using aspirin) with significant GI risk, the additional benefit



**Figure 3.** Kaplan-Meier estimates of the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction, stroke, or heart failure among patients who received celecoxib (200 mg twice daily or 400 mg twice daily) or placebo in the Adenoma Prevention with Celecoxib (APC) trial.

for the entire GI tract suggested by this study may influence medication selection for this small group of patients.<sup>24</sup>

Lanas et al. provided further insight into the issue of the clinical relevance of the upper versus lower GI toxicity of NSAIDs.<sup>25</sup> In a national cohort of mortality associated with hospitalization in Spain in 2001, hospitalizations due to upper tract events were 6-fold more common than lower GI events. Furthermore, when he extrapolated the death rates observed in Spain to the U.S. population, they were far less than previous estimates from the ARAMIS database—the widely quoted 10–20,000 deaths per annum. The authors hypothesized the widespread use of PPI and safer anti-inflammatory agents may be one explanation for the more contemporary observation. The next paper, a large database study from the UK further supports this contention.

#### What Risk-Reduction Strategies Improve Clinical Outcomes?

A large observational study from a British general-practice database indicated COX-2 inhibitors and traditional NSAIDs were less risky in patients at high risk for GI events *only* when taken in combination with ulcer-healing drugs such as PPIs.<sup>26</sup> The study showed that, for example, taking an ulcer-healing drug in addition to celecoxib reduces the risk of an adverse upper GI event by 27%, while in patients taking rofecoxib the risk is reduced by 55%, and with naproxen the risk goes down by 69%.

Hippisley-Cox et al. examined records of 9,407 general-practice patients with an adverse upper GI event and 88,867 patients without such an event in the QRESEARCH database between August 1, 2000, and July 31, 2004.<sup>26</sup> They found the highest adjusted odds ratio for an adverse GI event was associated with a recent prescription of naproxen (OR, 2.12), followed by diclofenac (OR, 1.96), other NSAIDs besides ibuprofen, diclofenac and naproxen (OR, 1.67), aspirin (OR, 1.60), rofecoxib (OR, 1.56), ibuprofen (OR, 1.42) and celecoxib (OR, 1.1). The risk of an adverse event was all significantly lower in patients recently prescribed a PPI or misoprostol; however, with diclofenac there was still an elevated risk. The authors suggested that COX-2 inhibitors may not provide the magnitude of GI benefit expected by many clinicians. While this observational study cannot entirely correct for the possibility that patients given COX-2s may have been higher risk and/or were using other nonprescription drugs, this study emphasizes that COX-2s are not gastroprotective and importantly demonstrates the value of ulcer-healing drugs, whether added to a traditional NSAID or a COX-2. Most gastroenterologists have been using PPIs in high-risk patients irrespective of the NSAID selected, and these data support that approach.

#### What About Economic Considerations?

Several economic analyses evaluated whether the reduction in risk of GI events provided by COX-2 inhibitors were worth the higher acquisition costs of these drugs. Our previous work<sup>27</sup> revealed that the unrestricted use of the safer drug resulted in a 6-fold reduction in the costs of complications, which only partially offset the added drug acquisition cost. Restricting them to average risk patients who fail traditional NSAIDs results in lower overall costs in relation to the cost differential of the medications, but the added cost to prevent an NSAID-related complication fell dramatically as the patients' risk for NSAID-related adverse event increased.

A recent study, also using a Markov model, incorporated recent CV adverse event data, and confirmed that cost effectiveness is strongly linked to GI risk.<sup>28</sup> Coxibs were found to be economically favorable only in high-risk patients; in average-risk patients they

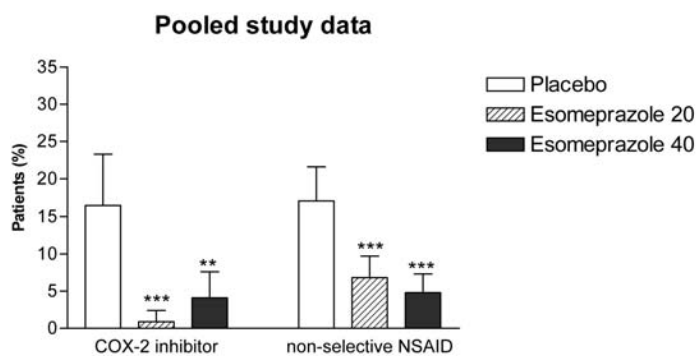
were not a worthwhile investment. The authors allowed for the use of concurrent aspirin, and evaluated varying combinations of GI and CV risks simultaneously. Their model estimated the cost effectiveness of NSAIDs alone, NSAID + PPI, and coxib alone. The analysis accounted for both GI and CV risk among patients eligible for aspirin prophylaxis. The coxib strategy was less effective and more expensive than the NSAID + PPI strategy. Sensitivity analysis revealed that the NSAID + PPI strategy became the dominant approach in patients at high risk for an NSAID adverse event (i.e., patients taking aspirin with >1 risk factor for a GI complication). The authors concluded that generic nonselective NSAIDs are most cost effective in low-risk patients; however, the addition of a PPI to a nonselective NSAID may be the preferred strategy in patients taking aspirin or otherwise at high risk for a GI or CV adverse event.

#### A LOOK TO THE FUTURE

Esomeprazole effectively reduces the incidence of gastric and duodenal ulcers in at-risk patients who are taking chronic therapy with nonselective NSAIDs or coxibs (Figure 4). Patients with arthritis who were aged  $\geq 60$  years and/or had a previous history of ulcers within the past 5 years were randomly assigned to receive placebo or esomeprazole (20 or 40 mg qd) for 6 months while continuing on NSAID therapy. Interestingly, the incidence of ulcers in those on placebo was the same irrespective of whether they were taking a COX-2 selective or traditional NSAID.<sup>29</sup> These data support the value of the costly combination of a COX-2 selective drug + a PPI, and additional data addressing the issue will be presented at Digestive Disease Week (DDW) 2006.

Finally, the comprehensive GI safety benefit (sparing of the upper and lower gut) of a COX-2 inhibitor versus a PPI with a nonselective NSAID is currently being tested in the CONDOR trial. The study will compare celecoxib to combination therapy with diclofenac and omeprazole and will assess the incidence of clinically significant upper and/or lower GI events in 4,402 patients with OA and/or RA. Patients aged 60 years with or without history of gastroduodenal ulceration or adults with evidence of ulceration 90 days prior to screening will be studied, but patients with vascular disease or those requiring aspirin therapy will be excluded.<sup>30</sup>

A large CV outcomes study with celecoxib has been initiated as



**Figure 4.** Cumulative proportion of patients developing a gastric ulcer or duodenal ulcer at 6 months, split by nonsteroidal anti-inflammatory drug (NSAID) type for the pooled study data from 2 identically designed trials: the PLUTO (Prevention of Latent Ulceration Treatment Options) and VENUS (Verification of Esomeprazole for NSAID Ulcers and Symptoms) studies. \*\* $P < .002$ ; \*\*\* $P < .001$ . Reprinted with permission from Scheiman, Yeomans, Talley, et al. *Am J Gastroenterol* 2006;100:701-710.

well.<sup>31</sup> This 20,000 patient worldwide study, the PRECISION Trial—Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen will enroll patients with OA who have known coronary heart disease or who have multiple risk factors for heart disease. Some patients with RA also will be included. This trial will be run by the Cleveland Clinic and will exclusively study those with or at high risk for heart disease; consequently, all patients will receive low dose of aspirin as indicated by current guidelines. The results should provide insight into the impact of aspirin and gastroprotective therapy on GI outcomes, in addition to anxiously awaited CV outcome data. The lack of a placebo (or non-NSAID) control group will leave lingering uncertainties on the absolute CV risk of any NSAID, and therefore clinicians will likely need to continue to integrate their best understanding of limited data when balancing the comprehensive risk benefit tightrope of anti-inflammatory therapy.

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