Managing the Adverse Effects of Nonsteroidal Anti-inflammatory Drugs

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Abstract and Introduction

Abstract

Conventional medical treatment for rheumatoid arthritis and osteoarthritis includes the use of NSAIDs (traditional and selective inhibitors of cyclooxygenase [COX]-2), because they provide unmistakable and significant health benefits in the treatment of pain and inflammation. However, they are associated with an increased risk of serious gastrointestinal (GI) and cardiovascular (CV) adverse events. Both beneficial and adverse effects are due to the same mechanism of action, which is inhibition of COX-dependent prostanoids. Since CV and GI risk are related to drug exposure, a reduction in the administered dose is recommended. However, this strategy will not eliminate the hazard owing to a possible contribution of individual genetic background. Further studies will be necessary to develop genetic and/or biochemical markers predictive of the CV and GI risk of NSAIDs.

Mechanism of Action of Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are a chemically heterogeneous group of compounds that provide unmistakable and significant health benefits in the treatment of pain and inflammation.[1] However, their use is associated with increased risk of gastrointestinal (GI) and cardiovascular (CV) effects.[2–5] Both therapeutic and adverse effects of NSAIDs are mainly due to the inhibition of prostanoid biosynthesis.[1] Prostanoids (i.e., prostaglandin [PG]E_2, PGD_2, $PGF_{2\alpha}$, thromboxane A2 [TXA_2] and prostacyclin [PGI_2]) are special second messengers owing to their ability to cross the cell membrane, diffuse through the extracellular space, and interact with high-affinity G-protein-coupled receptors located on the same cell or in neighboring cells.[6] Prostanoids play important roles in many cellular responses and pathophysiologic processes, such as modulation of the inflammatory reaction and its resolution, erosion of cartilage and juxta-articular bone, GI cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics and progression of kidney disease, as well as atheroprotection and progression of atherosclerosis.[7]

Prostanoids are generated intracellularly from arachidonic acid (AA) mainly through, but not exclusively, the activity of phospholipase A2.[8] Once released, intracellular free AA is transformed to PGH_2 by the activity of prostaglandin H (PGH) synthases (named cyclooxygenase [COX]-1 and COX-2); then, PGH_2 is metabolized to the prostanoids by different synthases expressed in a tissue-specific fashion (Figure 1).[6]

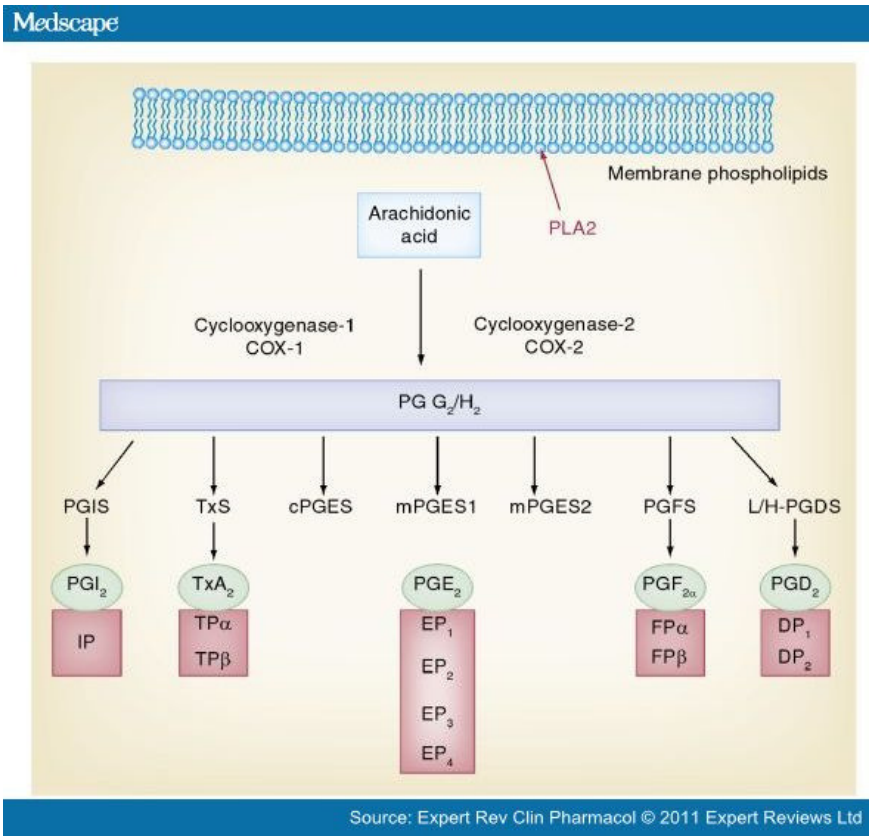

Figure 1. Cyclooxygenase pathways of arachidonic acid metabolism. Prostanoids are generated from arachidonic acid stored within the cell membrane and esterified to glycerol in phospholipids. A receptor-dependent event initiates phospholipid hydrolysis, mainly through the activity of phospholipase A2. Once released, intracellular free arachidonic acid is transformed to prostaglandin H2 by the activity of prostaglandin H synthases (named COX-1 and COX-2). Prostaglandin H2 is metabolized to the prostanoids by different synthases expressed in a tissue-specific manner.

COX: Cyclooxygenase; DP: Prostaglandin D receptor; EP: Prostaglandin E receptor; FP: Prostaglandin F receptor; IP: Prostacyclin receptor; PG: Prostaglandin; PGI_2: Prostacyclin; PLA2: Phospholipase A2; TP: Thromboxane A_2 receptor; TxA_2: Thromboxane A_2.

Cyclooxygenase isozymes are homodimers and each monomer is a heme-containing glycoprotein. COX-1 and COX-2 share the same catalytic activities[9] (i.e., the COX activity that oxidizes AA to PGG_2 and the peroxidase activity that reduces PGG_2 to the unstable endoperoxide, PGH_2). However, they are differently regulated catalytically, transcriptionally and post-transcriptionally.[10] The *COX-1* gene has the structural features of a 'housekeeping' gene and it is constitutively expressed in almost all tissues. By contrast, *COX-2* is an immediate early gene.[9,10] *COX-2* expression is controlled at various levels such as gene transcription and post-transcriptional events.[11,12] Transcriptional activation of *COX-2* occurs quickly and transiently in response to a wide range of stimuli including pathogens, cytokines, nitric oxide (NO), irradiation, growth factors and various extracellular ligands.[11]

In general, COX-1-dependent prostanoids play an essential homeostatic role in physiological functions (such as GI cytoprotection, platelet aggregation and vascular smooth muscle tone modulation),[13,14] while COX-2-dependent prostanoids play dominant roles in pathophysiologic processes such as inflammation and cancer, and physiological processes such as endothelial vasoprotection.[13,14]

Nonsteroidal anti-inflammatory drugs comprise traditional NSAIDs (tNSAIDs) and NSAIDs selective for COX-2 (coxibs).[15] They are indicated for pain and stiffness in inflammatory rheumatoid arthritis (RA) and for management of

pain in osteoarthritis (OA). They act as anti-inflammatory and analgesic agents by inhibiting COX-2-dependent prostanoids in the cells at an inflammatory site and in the spinal cord. In general, NSAIDs provide only symptomatic relief from the pain and inflammation associated with the disease and do not arrest the progression of pathological injury to tissue. Both nonselective NSAIDs and coxibs are widely prescribed because they are significantly more effective than acetaminophen in terms of managing pain and thus improving quality of life (QOL).[16] However, their concomitant inhibition of COX-1 and/or COX-2 in cells of the GI and CV systems translates into increased risk of upper GI bleeding (UGIB), atherothrombosis and hypertension.[3–5] Thus, the guidelines for OA recommend that where acetaminophen or topical NSAIDs are ineffective for pain relief, then substitution with an oral NSAID/COX-2 inhibitor should be considered, but they should be used at the lowest effective dose for the shortest possible period of time.[201] Similarly, guidelines for RA recommend the use of nonselective NSAIDs/COX-2 selective inhibitors for the treatment of arthritic pain.[17] Physicians prescribe NSAIDs in varying dosage levels dependent on the severity of the disease. They often prescribe higher doses of NSAIDs for patients with RA because the condition leads to a significant degree of swelling and stiffness in the joints. Lower NSAID doses are typically used in clinical practice for OA and muscle injuries, since there is less swelling and no warmth in the joints. Typically, several types of NSAIDs have to be administered before determining the most effective medication to relieve the discomfort.

Nonsteroidal anti-inflammatory drugs are grouped on the basis of their pharmacodynamic features – that is COX-1/COX-2 selectivity.[15] This is assessed *in vitro* and *ex vivo* (i.e., after drug administration) using human whole blood assays that evaluate the effects of drugs on platelet COX-1 and monocyte COX-2 levels.[18,19]

Nonsteroidal anti-inflammatory drugs are not specific drugs targeted at one COX isozyme but are selective drugs that affect only one or both isoforms depending on the dose administered.[15] The degree of COX selectivity of an NSAID, defined by its potency to inhibit COX-1 and COX-2 activities by 50% *in vitro*, is a chemical feature of the different drugs. We can group NSAIDs as being more selective *in vitro* for COX-1, such as naproxen and ibuprofen, and those more selective for COX-2, which are the majority of NSAIDs (Figure 2).[15,20] Among the NSAIDs more potent at inhibiting COX-2 than COX-1 *in vitro*, it has been shown that COX-2 selectivity is a continuous variable and some tNSAIDs show comparable experimental COX-2 selectivity to some coxibs (e.g., diclofenac and celecoxib).[15] However, it has to be noted that the degree of COX-isozyme selectivity found *in vivo* depends on the dose administered.[15,20] Finally, an important determinant of the clinical effects of drugs *in vivo* (both therapeutic and toxic effects) depends on the pharmacokinetic features of the different drugs such as half-life, and type of formulations such as slow-release or plain, which can influence the extent and duration of patient exposure to COX-isozyme inhibition. An intense area of research is to clarify the determinants of marked variability in how different people react to these drugs, based on their genetic background.

GI Toxicity of NSAIDs

Injury to the mucosa of the GI tract by NSAIDs is very common and ranges from minor lesions such as petechia or erosions to more serious (and also much less frequent) lesions such as ulcers, which can result in complications such as bleeding, perforation or obstruction. Patients may eventually die as a consequence of these complications.[21] Breaks in the epithelium of NSAID or aspirin users are usually rapidly repaired through a process called 'restitution'.[22] This process occurs rapidly without the need of cell division but it requires an undamaged basement membrane where healthy epithelial cells migrate. When damage does not penetrate the muscularis mucosa, the repair can be achieved within 1–3 days and involves cell proliferation and re-establishment of the glandular architecture. When an ulcer is formed (when the defect penetrates to the submucosa), repair can take from weeks to months involving re-establishment of the vasculature with new blood vessel growth. A number of growth factors including EGF and VEGF are involved in the process of ulcer repair.[23] Platelets seem to play an important role in ulcer healing outside their contribution to homeostasis.[24] Platelets contain a wide array or growth factors and can deliver those factors to the site of tissue damage. Drugs that affect the content of growth factors within the platelet may thereby affect rates of ulcer healing.

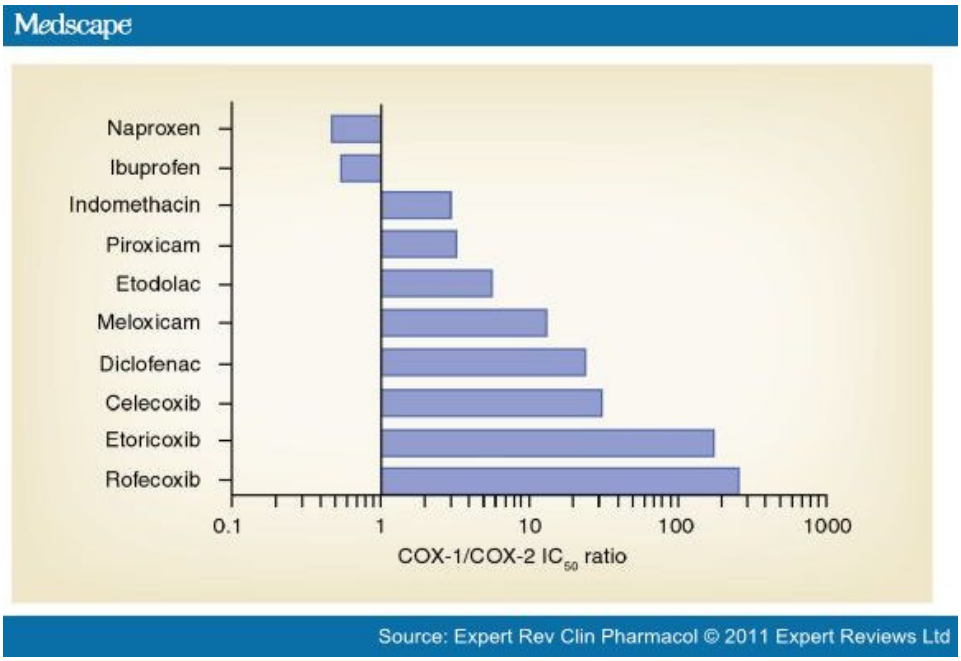

Figure 2. Degree of selectivity for COX-2 by the different NSAIDs *in vitro* expressed as ratio of IC_{50} values for COX-1 and COX-2. The degree of COX selectivity of NSAIDs, defined by their potency to inhibit by 50% COX-1 and COX-2 activities *in vitro*. Higher values of COX-1/COX-2 IC_{50} ratio (>1) mirror higher selectivity versus COX-2. Lower values (<1) mirror higher selectivity for COX-1. IC_{50} is the concentration of the drug required to inhibit the activity of COX-1 and COX-2 by 50%.
COX: Cyclooxygenase; IC_{50}: 50% inhibitory concentration.

The mechanisms responsible for NSAID-induced ulcerative lesions of the GI tract are not yet completely understood, particularly with respect to the lesions in the small and large intestine.[21,25] NSAIDs injure the gut by causing topical injury to the mucosa and by systemic effects associated with mucosal prostaglandin depletion derived from COX inhibition (Figure 3). Platelet inhibition has also been considered to be a key mechanism of bleeding of lesions of the GI tract. The systemic effects of NSAIDs appear to have a predominant role, since visible topical injury disappear with continuous use of NSAIDs in most cases, but ulcers and complications may continue to develop. This systemic effect may be the reason why the use of enteric-coated aspirin preparations and parenteral or rectal administration of NSAIDs, in order to prevent topical mucosal injury, has not been successful to prevent the development of gastroduodenal ulcers and their complications.

The widespread use of NSAIDs as analgesic, anti-inflammatory and antipyretic drugs converts the associated upper GI complications into a major public health concern. The most recent of these was in 1990 when some NSAIDs were introduced in the market claiming a better GI safety than tNSAIDs.[14,26] These new NSAIDs are coxibs. Indeed, reduced incidence of serious GI adverse effects compared with tNSAIDs has been demonstrated for these selective COX-2 inhibitors in large randomized clinical trials.[27,28] This was a proof-of-concept that sparing COX-1 in the GI tract and possibly in platelets translates into a safer GI profile.[26] In fact, COX-1 is constitutively expressed in the stomach and platelets,[29] whereas COX-2 does not appear to be expressed there or is expressed at very low levels. Experimental results using selective pharmacological inhibition or genetic deletion of *COX-1* and *COX-2* in mice have shown that COX-2 plays an important role in the healing of pre-existing ulcers.[30,31] In fact, COX-2 is rapidly upregulated in response to growth factors and cytokines and it was demonstrated that both *COX-2* mRNA and protein are strongly expressed in mouse stomachs in which ulcers had been induced.[32,33] Recent results may suggest that both COX isozymes are a source of cytoprotective prostanoids: thus, simultaneous inhibition translating into a profound suppression of prostanoids might

be a hazard for the GI system.[3] This is mechanistically plausible, with results obtained in the mouse showing that inhibition of both COX-1 and COX-2 is required for the formation of gastric lesions.[34]

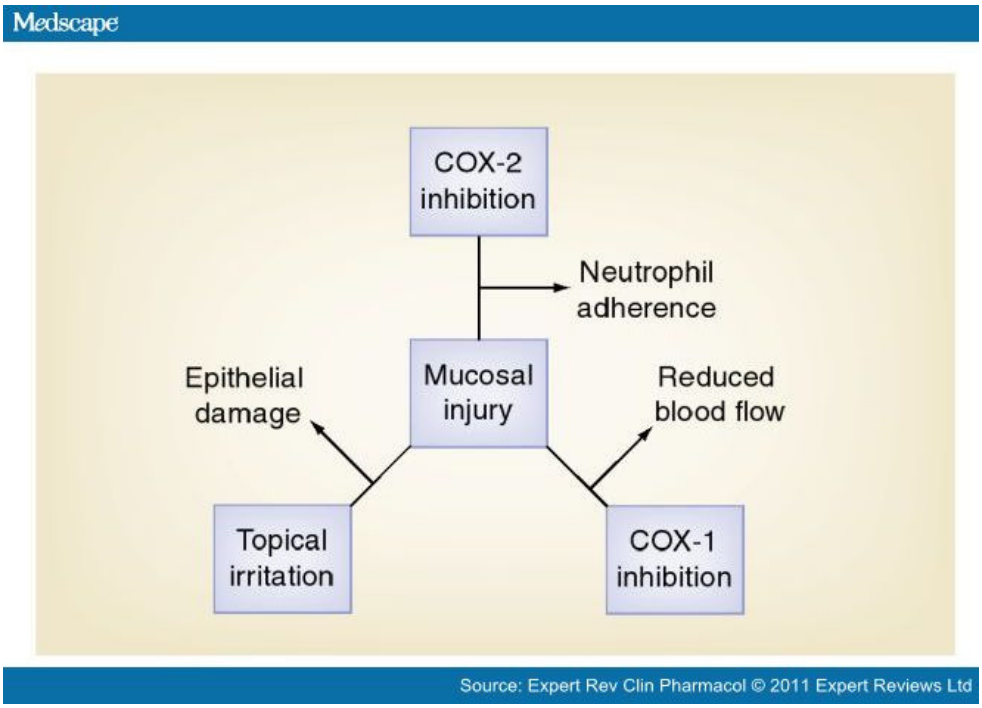

Figure 3. Mechanisms of NSAID-induced mucosal injury. NSAIDs injure the gut by causing topical injury to the mucosa and by systemic effects associated with mucosal prostaglandin depletion derived from COX inhibition.
COX: Cyclooxygenase

Prostanoids (mainly PGE_2 and PGI_2) have an important role protecting the gut by stimulating the synthesis and secretion of mucus and bicarbonate, increasing mucosal blood flow and promoting epithelial proliferation. The inhibition of prostanoids by NSAIDs creates an environment more susceptible to topical attack by endogenous and exogenous factors. Acid and *Helicobacter pylori* infection may play a key role in the pathogenesis of gastroduodenal mucosal damage but bile and bacteria seem the key intraluminal agents in the pathogenesis of intestinal mucosal damage. Inhibition of mucosal prostanoid synthesis also results in important changes in the GI microcirculation that appears to play a crucial role in the pathogenesis of ulceration.[21] Besides, the inhibition of platelet COX-1 blocks production of TXA_2, which increases bleeding when an active GI bleeding site is present.[35] On the other hand, the COX-2 isoform is induced in most tissues in response to inflammatory stimuli. Prostaglandins derived from COX-2 can be generated at the ulcer margin and appear to play an important role in ulcer healing through triggering the cell proliferation, promotion of angiogenesis and restoration of mucosal integrity.[36]

The rate of blood flow to the luminal surface of the stomach is essential for mucosal integrity. If the blood flow decreases, the mucosa becomes more susceptible to acid and pepsin-induced injury. This rate allows the mucosa to tolerate the acid back-diffusion so long as there is sufficient blood flow to reach buffering of the acid. NSAIDs decrease mucosal blood flow to the upper GI tract, but appear to do so in a 'patchy' way. That is, blood flow is only reduced in some parts in the stomach and they are the sites where NSAIDs cause injury.[37] NSAID-induced inhibition of the synthesis of PGE_2 and PGI_2, which are vasodilators, is likely to be underlying the cause of focal ischemia produced by these agents. Selective COX-2 NSAIDs do not reduce gastric mucosa blood flow.[38,39]

Nonsteroidal anti-inflammatory drugs can also stimulate leukocytes, particulary neutrophils, which adhere to the vascular endothelium within GI microcirculation.[40,41] Neutrophils play an important role in the pathogenesis of NSAID mucosal injury by initiating the vascular mucosal damage; this conclusion is supported by the results of a study that shows that such damage was absent in neutropenic rats[42] and can be prevented by treatment of animals with neutralizing antibodies directed against leukocyte or endothelial adhesion molecules.[43,44]

Some NSAIDs, particularly those that are weak acids, produce epithelial damage at the sites of contact with the GI mucosa.[45] In locations where the acid is in contact with the surface of the mucosa, these drugs behave in concordance with the pH partition hypothesis. The acidic properties of most NSAIDs (including aspirin) initiate mucosal damage. These weak acids remain in their nonionized lipophilic form in the highly acidic gastric environment. These conditions favor migration into surface epithelial cells, where NSAIDs are dissociated into the ionized form that trap hydrogen ions, thus inducing mucosal injury.[46] NSAIDs can also cause topical mucosal damage by diminishing the hydrophobicity of gastric mucus, thereby allowing endogenous gastric acid and pepsin to injure the surface epithelium.[47] In addition, topical mucosal injury may occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites.[48] These drugs may also uncouple mitochondrial respiration, leading to cell death.[25] Some studies have concluded that topical injury could be related to the time of contact of the drug with the GI mucosa.[49,50] However, in an experimental animal model of acid-and pepsin-induced esophagitis, both topical exposure to acidified aspirin and intravenous administration of aspirin increased mucosal injury and mucosal barrier dysfunction compared with controls.[51] In the stomach, the topical injury of NSAIDs may also be related to the ability of these drugs to decrease the hydrophobicitiy of the mucus gel layer in the stomach, which seems to be the first barrier to acid-induced damage.[52]

Topical side effects of NSAIDs appear to play an important role in the pathogenesis of small intestine damage, where the enterohepatic circulation of NSAIDs increases the exposure of intestinal epithelium to these drugs. Once the mucosal permeability is increased, bile, abdominal content and most importantly, bacteria, penetrate and increase the damage by inducing inflammation. Increased mucosal permeability and mucosal inflammation are often silent but occur with most NSAIDs.[53–57] Other findings include anemia, occult blood loss, malabsorption and protein loss. Video capsule endoscopy studies have shown that more than 50% of patients on NSAIDs or low-dose aspirin may have mucosal lesions or mucosal breaks in the small bowel.[58] As expected, antisecretory drugs do not offer protection to the distal gut.[59]

CV Effects of NSAIDs

The importance of prostanoids in maintaining CV homeostasis was primarily highlighted by the evidence that the NSAID, aspirin, at low-doses, reduces the secondary incidence of myocardial infarction and stroke by approximately one quarter.[60] Aspirin is the only NSAID that irreversibly inactivates platelet COX-1 activity through a selective acetylation of a specific serine residue (Ser529) of human COX-1, which translates into an almost complete suppression (>95%) of platelet capacity to produce TXA_2 at low doses throughout the 24-h dosing interval.[60] This complete and permanent suppression of platelet COX-1 activity by aspirin is necessary to translate into cardioprotection because even tiny concentrations of TXA_2 may cause platelet activation.[61] In contrast to aspirin, tNSAIDs and coxibs are associated with an increased CV risk.[4,62,63] Increased incidence of thrombotic events has been detected in placebo-controlled trials involving the COX-2 inhibitors celecoxib, rofecoxib and valdecoxib.[62–65] Importantly, results from observational studies and meta-analyses of data derived from randomized clinical trials with coxibs have shown that the CV hazard is also related to some tNSAIDs, such as diclofenac.[4,66,67] In a population-based retrospective cohort study with nested case–control analysis using data from The Health Improvement Network database in the UK, it was shown that patients taking NSAIDs, both COX-2 inhibitors and tNSAIDs, have a 35% increased risk of nonfatal myocardial infarction (MI; RR: 1.35; 95% CI: 1.23–1.48).[4] This elevation of risk increased with increasing treatment duration and daily dose. A network meta-analysis including 31 randomized controlled trials (116,429 patients) further supported evidences of the CV risk related to both COX-2 inhibitors and tNSAIDs, showing that:

- Rofecoxib and lumiracoxib were associated with the highest risk of MI (rate ratio: 2.12 and 2.00; 95% CI: 1.26–3.56 and 0.71–6.21, respectively);
- Ibuprofen and diclofenac were associated with the highest risk of stroke (rate ratio: 3.36 and 2.86; 95% CI: 1.00–11.6 and 1.09–8.36, respectively);
- Etoricoxib and diclofenac were associated with the highest risk of death due to CV causes (i.e., MI, fatal arrhythmia, pulmonary embolism and stroke [rate ratio: 4.07 and 3.98; 95% CI: 1.23–15.7 and 1.48–12.7, respectively]).[67]

The highest risk of death owing to CV causes for NSAIDs, such as diclofenac, observed in this meta-analysis, could be explained by the use of supratherapeutic doses of these drugs (>100 mg/day) in some of the analyzed randomized clinical trials.

The most plausible mechanism of the CV hazard associated with NSAIDs (both coxibs and tNSAIDs) is that they cause a profound inhibition of PGI_2[4,62,63] which is generated in the vasculature by COX-2.[68] PGI_2 is a protective mediator for the CV system and it acts mainly through the activation of its receptor (called IP) expressed in different cell types, such as platelets, and causing the increase in the intracellular levels of cAMP.[69] The increased risk of vascular events caused by the inhibition of COX-2-dependent PGI_2 might be mitigated by a concomitant suppression of platelet COX-1 activity and the generation of the pro-aggregatory mediator TXA_2. However, most tNSAIDs and coxibs do not affect platelet COX-1 activity at a degree (i.e., >95%) necessary to translate into inhibition of platelet function (Figure 4).[4,70] Naproxen is different among tNSAIDs because it shares a potent COX-1 inhibition and a long half-life,[1,4] thus profoundly and persistently affecting platelet COX-1 at therapeutic doses.[71,72] This has been proposed as one of the mechanisms by which naproxen could have a better CV safety profile than other tNSAIDs.[4] However, naproxen is not cardioprotective, plausibly because it profoundly inhibits PGI_2.[71,72]

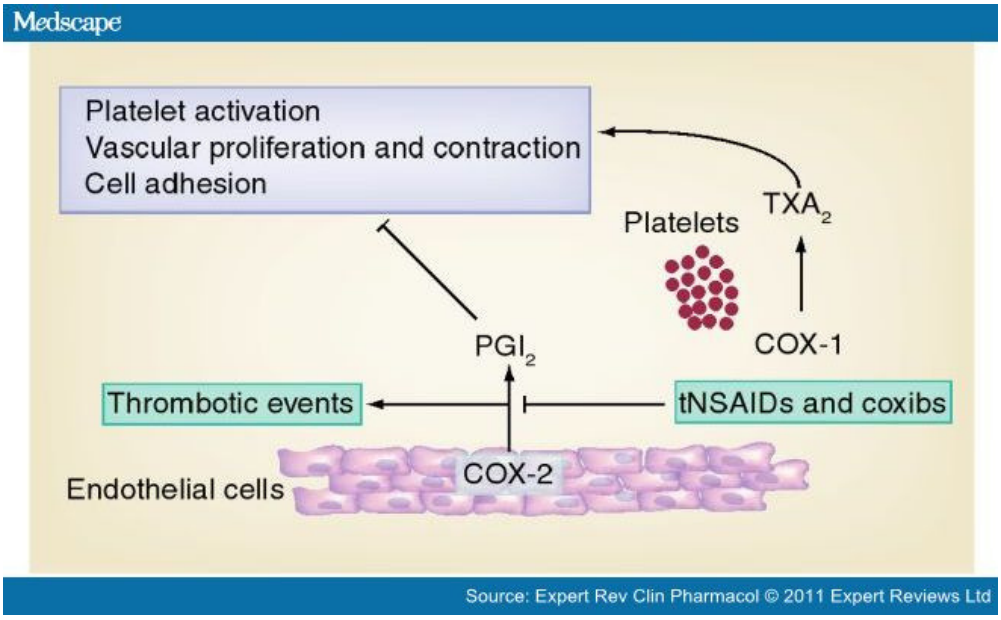

Figure 4. Mechanism of cardiovascular toxicity of NSAIDs**.** The cardiovascular toxicity associated with the administration of NSAID selective for COX-2 and some tNSAIDs occurs through a common mechanism involving the inhibition of COX-2-dependent prostacyclin, an atheroprotective prostanoid. Most tNSAIDs and coxibs are functionally selective for COX-2 – i.e., they cause a profound suppression of COX-2 associated with an inhibition of platelet COX-1 that is insufficient to translate into inhibition of platelet function. This

feature might explain the shared cardiovascular toxicity of some tNSAIDs and coxibs.
COX: Cyclooxygenase; PGI_2: Prostacyclin; tNSAID: Traditional NSAID; TXA_2: Thromboxane A_2.

COX-inhibiting NO Donators

To reduce GI and CV side effects, a new class of compounds named COX-inhibiting NO donators have been developed but they are still not commercially available. These compounds are derivative of NSAIDs to incorporate a NO-releasing moiety.[73] NO has important biologic effects on the CV system, including vasodilatory and platelet-inhibitory actions through activation of soluble guanylyl cyclase and consequent formation of cyclic guanosine monophosphate.[74] Moreover, NO is able to protect the gastric mucosa by a number of mechanisms, including promotion of mucous secretion, increased mucosal blood flow, and decreased adherence of neutrophils to the gastric vascular endothelium.[75]

Naproxcinod [(S)-2-(6-Methoxy-2-naphthyl)propanoic acid 4-nitrooxybutyl ester], that is, NO-naproxen, is the first of the class of cyclooxygenase-inhibiting NO donators, and is currently in Phase III clinical development for the treatment of OA. After absorption, it is cleaved to produce naproxen and an NO-donating moiety. Moreover, it has been demonstrated recently that it did not induce elevations of blood pressure) seen with naproxen, and it had similar effects on blood pressure to that of placebo in patients with OA.[76]

Managing GI Toxicity

From a clinical point of view, the main goal in the management of patients receiving NSAIDs is the prevention of GI complications rather than acute mucosal lesions, including erosions or even ulcers, since they are often asymptomatic and most do not complicate.[77] Other important clinical objective is the treatment and prevention of NSAID-induced dyspepsia. The correlation between dyspepsia and the presence of NSAID-induced lesions is poor, but dyspepsia is clinically relevant since up to 10% of patients stop taking NSAIDs because of that.[78]

Not all patients have the same risk of developing GI complications. Risk factors for ulcer complications in patients taking NSAIDs include: history of previous ulcer complications, history of previous noncomplicated ulcer, advanced age (>60 years), concomitant use of other NSAIDs, corticosteroids, antiplatelet or anticoagulant drugs, and significant CV disability.[79–83] Concomitant use of low-dose aspirin for the prevention of CV events is frequent in patients taking NSAIDs. In clinical trials, this proportion reaches at 20% of patients requiring NSAIDs. This aspect complicates the management of these patients, since it is unclear and unknown whether the use of NSAIDs/coxibs might interfere with the cardioprotective effect of low-dose aspirin. The addition of low-dose aspirin to tNSAIDs or coxibs increases the risk of GI events (estimated annual GI risk is 5.6–7.5% GI events/year). Because of that, patients who combine a NSAID with low dose-aspirin are a high-risk group for GI bleeding. Evidence from observational studies and randomized trials showed that the risk of coxib plus aspirin is lower than tNSAIDs plus aspirin, but both were increased by aspirin. Low-dose aspirin further increases the risk of upper GI bleeds in NSAID users and negates the GI benefits of coxibs over the nonselective NSAIDs.[28,84] Furthermore, owing to the association of tNSAID and coxib use with increased CV risk, the baseline CV risk should also be taken into account in the management of patients who need NSAIDs.

In Box 1, the prevention strategies to use in patients with GI risk factors who need NSAIDs are reported. Under a cost-effective perspective, patients with one or more risk factors should receive prevention strategies. In the following section, we describe the current approached for the management of patients who need NSAIDs.

Targeting Modifiable Risk Factors

There are some risk factors (e.g., age) than cannot be modified. However most risk factors associated with the development of GI complications in patients who need NSAIDs can be modified. In general, we should look for the

lowest effective NSAID dose and patients should take the medication for the lowest possible period of time. The risk of GI complications seems higher during the first month of therapy, but then it is constant over the entire period of treatment. Furthermore, the increased risk of CV events with the use of coxibs and probably tNSAIDs may be time-dependent.[64,65,85] Although many of the differences of GI risk observed among the different NSAIDs are driven by the dose used, there is agreement that ibuprofen, diclofenac, and aceclofenac are associated with the lowest relative risk (RR) of GI complications in clinical practice and, if possible, these tNSAIDs should be preferred to other NSAIDs. In this way, ketorolac and piroxicam are associated with the highest risk of GI complications.[86,87] In addition, if possible, the use of concomitant therapy with low-dose aspirin, corticosteroids, anticoagulants or even non-aspirin antiplatelet therapy should be avoided, since all they have been shown to further increase the risk of bleeding.[28,75,84] *H. pylori* infection eradication will reduce the incidence of peptic ulcers in, at least, a subset of NSAID users. This therapeutic approach will be discussed in another section.

The Addition of Gastroprotectants to NSAIDs

Patients with GI risk factors, who require nonselective NSAIDs, should receive a gastroprotectant. Misoprostol is a synthetic prostaglandin that stimulates mucus secretion in the upper GI tract. Several clinical trials have shown that the incidence of endoscopically diagnosed ulcers associated with NSAID use can be reduced by co-therapy with misoprostol.[88] A 6 month, randomized, double-blind, placebo-controlled trial involving 8843 rheumatoid arthritis patients receiving NSAIDs demonstrated that misoprostol reduced NSAID-associated upper GI complications (Misoprostol Ulcer Complications Outcomes Safety Assessment trial [MUCOSA]).[89] The study showed that misoprostol 200 µg four times a day significantly reduced symptomatic ulcers (adjusted RR: 0.36; 95% CI: 0.20–0.67) and serious GI complications (adjusted RR: 0.57; 95% CI: 0.36–0.91). However, misoprostol use in clinical practice is limited by its poor tolerability. In the MUCOSA trial, 27.5% of misoprostol-treated patients withdrew prematurely from the study due to adverse events, most of which were GI complaints.[90] The required dosing schedule of three-to-four-times daily may also be inconvenient for patients, thereby adversely affecting treatment outcomes. Besides GI symptoms, the major problem with using misoprostol is that it is contraindicated in women of child-bearing age because of abortion risk.

H2-receptor antagonists are gastroprotectans acting by a reversible interference and blockage of histamine receptors in the parietal cell which reduces acid secretion. When compared with placebo, different endoscopic studies have shown that ranitidine reduces the incidence of duodenal ulcers, but not gastric ulcers. High-dose famotidine has been shown to prevent both gastric and duodenal ulcers associated with NSAID use.[91] A meta-analysis showed that H2-receptor antagonists did not significantly reduce the risk of symptomatic ulcers among patients receiving NSAIDs (adjusted RR: 1.46; 95% CI: 0.06–35.3).[88,92]

Proton pump inhibitors (PPIs) block gastric acid secretion by inhibiting the H^+/K^+ ATPase and are significantly more effective than H2-receptor antagonists for treatment and prevention of acid-related diseases.[93] PPIs seem to be the best candidates to hinder the acidic mechanism of NSAID-induced gastroduodenal lesions. In fact, PPIs are largely used worldwide for the prevention of NSAID-induced gastropathy. PPIs inhibit gastric acid secretion and raise intragastric pH, decreasing the damaging potential of NSAIDs. PPIs inhibit the final step of acid secretion, the gastric acid pump. Epidemiological evidence has shown a parallel increase in the use of PPIs in the community with a decrease in the incidence of peptic ulcers and ulcer complications.[94] In one study misoprostol was compared with lansoprazole in patients on long-term NSAID use.[95] Each active treatment had an equivalent success rate of 69%. Other studies have confirmed that omeprazole 20 mg/day was more effective than ranitidine and low-dose misoprostol in the primary or secondary prevention of gastric and duodenal ulcers in NSAID users.[78,96,97] More recently, omeprazole 20 mg/day was shown to be more effective than *H. pylori* eradication in the prevention of ulcer bleeding recurrence in patients receiving naproxen for 6 months.[98] Different epidemiological studies have shown that PPIs reduce the risk of peptic ulcer bleeding in NSAID users.[99–101]

Proton pump inhibitor use has also been associated with adverse effects. Intestinal infection, including *Clostridium difficile* infection and pneumonia risk may be increased in patients taking these drugs.[102] *C. difficile* infection may become a clinical challenge and this side effect is currently being taken very seriously by several health authority bodies.[103–105] An increased risk of hip fracture has also been associated with PPI use although there are contradictory results.[106–109] A recent study by Ho *et al.*[110] found that concomitant use of clopidogrel and PPI after hospital discharge for acute coronary syndrome (ACS) was associated with an increased risk of CV adverse outcomes than use of clopidogrel without PPI, suggesting that use of PPI may be associated with attenuation of benefits of clopidogrel after ACS. Several other studies have been conducted in order to answer this question. The recently published Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) clinical trial has shown no differences in CV outcomes among patients taking a combined compound of clopidogrel–omeprazol plus aspirin, versus clopidogrel and aspirin alone. The primary GI end point was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction or perforation. The primary CV end point was a composite of death from CV causes, nonfatal MI, revascularization or stroke. A total of 3873 patients were randomly assigned and 3761 were included in analyses. A total of 109 patients had a CV event, with event rates of 4.9% with omeprazole and 5.7% with placebo (hazard ratio with omeprazole: 0.99; 95% CI: 0.68–1.44; p = 0.96).[111]

Prescribing Coxibs Instead of tNSAIDs

Coxibs were as effective as conventional agents in reducing pain and improving physical functioning in people with arthritis, and are associated with fewer GI events. A meta-analysis of 112 large-scale randomized clinical trials revealed that the risk of symptomatic ulcers and serious GI complications associated with coxibs (celecoxib, rofecoxib, etoricoxib and lumiracoxib) were lower than that of nonspecific NSAIDs (adjusted RR: 0.49; 95% CI: 0.38–0.62 and 0.55; 95% CI: 0.38–0.80, respectively).[92] Another meta-analysis of all available and published randomized clinical trials published by the Cochrane Collaboration concluded that compared with nonselective NSAIDs, coxibs (celecoxib, valdecoxib, etoricoxib, limiracoxib and rofecoxib) produced significantly fewer gastroduodenal ulcers (RR: 0.26; 95% CI: 0.23–0.30) and ulcer complications (RR: 0.39; 95% CI: 0.31–0.50), as well as fewer treatment withdrawals caused by GI symptoms. The coadministration of acetylsalicylic acid reduces the GI benefits of COX-2 over tNSAIDs in subgroup analyses.[112] Data from the newest coxibs (lumiracoxib, withdrawn from the market because of liver toxicity, and etoricoxib) confirm this safety profile in the GI tract,[28,113] although the Multinational Etoricoxib and Diclofenac Arthritis Long-term program did not show differences between diclofenac and etoricoxib in the incidence of upper GI complications. In the Celecoxib Long-Term Arthritis Safety Study study, patients treated with high-dose celecoxib 400 mg twice daily had significantly fewer upper GI ulcer complications than those treated with nonselective NSAIDs (0.44 vs 1.27%; p = 0.04)[80] in patients not taking aspirin. However, the GI benefits of celecoxib was lost with the addition of low dose-aspirin, as the annualized incidence rates of upper GI ulcer complications were 2.01 and 2.12%, respectively (p = 0.92) with aspirin use.

When prescribing all these agents, caution should be focused on patients with CV diseases. In Europe, coxibs are contraindicated in patients with previous CV events and etoricoxib in uncontrolled hypertension. Whether this population may benefit from the potential introduction of NO–naproxen into the market in the future remains to be seen. Nevertheless, this compound seems to have a favorable profile in patients with hypertension and to induce less gastroduodenal and intestinal mucosal damage than naproxen.[76,88,114]

Combining Gastroprotectants & Coxibs

Another strategy in order to prevent NSAID-induced GI complications is the combination of a PPI plus a COX-2 selective NSAID, especially in the high-risk patients. Available evidence indicates that patients with previous ulcer bleeding who take either a non-selective NSAID plus a PPI or a COX-2 selective NSAID alone still have a low but significant rate of ulcer rebleeding after 6 months of therapy.[115,116] In one of those studies, 287 patients with recent ulcer bleeding received *H. pylori* eradication.[115] After ulcer healing, patients were randomized to take celecoxib 200 mg twice daily versus co-therapy consisting of omeprazole 20 mg once daily plus diclofenac 75 mg twice daily. After 6 months, the celecoxib arm

had a 4.9% probability of recurrent ulcer bleeding, whereas patients on diclofenac plus omeprazole showed a 6.4% probability of recurrence (p = nonsignificant). As demonstrated recently, the combination of a PPI + COX-2 selective NSAID provides the safest option in patients at the highest risk of developing a GI complication. A recent small randomized controlled trial has evaluated the combination of celecoxib plus PPI to prevent GI events in high-risk patients with previous ulcer story. After 12 months of therapy, patients taking celecoxib 200 mg twice a day plus esomeprazole 20 mg/day had no recurrent ulcer bleeding events whereas 8.9% ($p < 0.001$) of patients taking the same of dose of celecoxib and placebo had a recurrence ulcer bleeding event.[117] This combination should be cost effective,[118] providing a 50% additional reduction in the incidence of upper GI complications already obtained with any of these strategies (tNSAIDs plus PPI vs coxib) alone. A recent study by Latimer *et al.* showed that prescribing a PPI for people with OA who are taking either a nonselective NSAID or coxibs is cost effective.[119]

Compliance with guidelines and prescription according to them are one problems we face in order to reduce the risk of GI complications in patients taking NSAIDs. A very recent cross-sectional study conducted in 1 day in over 17,000 patients suffering from OA showed that in over 50% of patients, the prescription of NSAIDs was not in accordance with current guidelines or recommendations made by regulatory agencies.[120] Adherence to the prescribed preventive therapy is an additional problem. A study by Sturkenboom *et al.*[121] showed that over 30% of patients were nonadherent and the lowest rate of nonadherence was associated with the first NSAID prescription (9%), increasing to 61% for patients with three or more prescriptions. Non-adherence patients had a higher risk of GI events compared with those who are fully adherent. Another study by Van Soest *et al.*[122] showed that the risk of GI complications in NSAID users increased 16% for every 10% decrease in adherence. Patients with proportion of NSAIDs treatment days covered by gastroprotective agents of 20–80% and <20% had higher risk of GI complications than patients with >80% of days covered: fourfold (95% CI: 1.2–13) and 2.5-fold (95% CI: 1.0–6.7), respectively.[119] Predictors of nonadherence include a high average daily dose of NSAIDs and long-term use of NSAIDs (>90 days). Predictors of adherence include use of low-dose aspirin, anticoagulant use and history of upper GI events, among others.[123]

Eradication of *H. pylori*

Eradication therapy is one of the mainstays of treatment in ulcer patients with *H. pylori* infection. However, the role of *H. pylori* eradication in patients receiving NSAIDs (including aspirin) has been controversial.[87,124] A meta-analysis of observational studies[125] showed synergism for the development of peptic ulcer and ulcer bleeding between *H. pylori* infection and NSAID use. Randomized controlled trials have shown that *H. pylori* eradication in naive NSAID users is associated with a significant reduction of the incidence of endoscopic ulcers in patients starting NSAIDs.[126,127] However, the benefit is less evident in patients already on long-term NSAIDs or in those who had an ulcer history or history of ulcer complications, where co-therapy with a PPI seems necessary.[98] Among patients with previous ulcer history, those treated with naproxen 500 mg twice daily plus omeprazole 20 mg/daily had recurrent rates of ulcer bleeding of 4.4 versus 18.8% ($p = 0.005$) in those who were treated with naproxen (same dose) and underwent *H. pylori* eradication after 6 months of follow-up. The results showed a clear advantage of PPIs over eradication therapy in this population. High-risk patients receiving low-dose aspirin may also use PPIs after eradication treatment to prevent ulcer recurrence.[128] Testing for and eradicating *H. pylori* in patients with a history of ulcer disease is recommended before starting chronic antiplatelet therapy. *Post hoc* analysis of the Vioxx GI Outcomes Research (VIGOR) study suggested that the GI benefits of coxib therapy are greater in patients without *H. pylori* infection than those with the infection.[78] It is unclear whether the strategy to eradicate *H. pylori* infection in all infected patients who start NSAID therapy will be cost effective.

Management of GI Risk With Asprin

Aspirin use is being recognized as one of the main reason for hospitalizations due to GI bleeding.[129] It is well known that low-dose aspirin increases the risk of UGIB. A meta-analysis of 14 randomized clinical trials, recently published,[130] has shown an absolute rate increase of major UGIB with aspirin above placebo of 0.12% per year (95% CI: 0.07–0.19%). Risk

factors for GI bleeding with asprin include age ≥70, ulcer history, co-therapy with NSAIDs, coxibs, anticoagulants or other antiplatelet agents.[35] Those at risk should be on GI prevention therapy.[131] Some key strategies have been proposed for minimizing the upper GI side effects of low-dose aspirin. These are the use of an alternative platelet inhibitor, such as clopidogrel, the use of co-therapy with a gastroprotective agent and eradicating *H. pylori*.

Cardiology guidelines recommend the antithrombotic agent clopidogrel for patients who are unable to take aspirin due to previous GI intolerance. However, in clinical practice two case–control studies, have found that clopidogrel is associated with a similar RR of ulcer bleeding to low-dose aspirin.[132,133] Two clinical trials have also found that high-risk patients on clopidogrel alone have an unacceptable rate of bleeding ulcers.[132,133]

Co-therapy with gastroprotective agents such as PPI, H2-receptor antagonists (H2-RAs) are currently the most widely used strategy to reduce this GI risk with aspirin.[99,100,134] A recent study showed that high-dose famotidine was effective in the prevention of gastric and duodenal ulcers in patients taking low-dose aspirin.[135] However, another study by Ng *et al.* concluded that in patients with aspirin-related peptic ulcers/erosions, high-dose famotidine therapy was inferior to pantoprazole standard doses in preventing recurrent dyspeptic symptoms or ulcer bleeding.[136] One study reported that the risk of recurrent ulcer bleeding in low-dose aspirin users treated with a PPI was similar to that of patients receiving eradication therapy composed of bismuth subcitrate, tetracycline and metronidazole (0.9 vs 1.9%; p = nonsignificant).[98] However, in another study with high-risk patients who underwent *H. pylori* eradication, lansoprazole was more effective than placebo in the prevention of ulcer bleeding recurrence in patients who receive low-dose aspirin for 12 months.[137] Esomeprazole associated with low-dose aspirin was also associated with a very low recurrence rate of ulcer rebleeding when compared with clopidogrel alone.[138] In a recent case–control study by Lanas *et al.*, PPIs reduced the risk of upper GI complications. PPI use was associated with risk reduction among both tNSAID and low-dose aspirin users and among patients taking NSAIDs and clopidogrel.[99]

Based on all these studies, the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association 2008 Expert Consensus Document[131] supports the use of PPIs instead of double-dose H2RAs in preventing recurrent low-dose aspirin-related injury.

Management of Patients With Peptic Ulcers or Dyspepsia Associated With NSAID Use

Nonsteroidal anti-inflammatory drugs and coxib therapy delay the healing of active peptic ulcers. In patients who develop a peptic ulcer during NSAID or coxib treatment, the drug should be stopped, patients treated with PPI therapy and *H. pylori* eradicated if the infection is present. If patients are unable to discontinue NSAID therapy, patients need to be treated with PPI twice a day co-therapy until the ulcer is healed, which must be confirmed by endoscopy.[139]

Nonsteroidal anti-inflammatory drug-associated dyspepsia is common, occurring in up to 25–50% of patients.[86,96,97] The presence of dyspepsia does not predict the presence of mucosal lesions in patients taking NSAIDs,[96,97,140] since up to 40% of persons with endoscopic evidence of erosive gastritis are asymptomatic, and conversely, as many as 50% of patients with dyspepsia have normal-appearing mucosa. COX-2-selective NSAIDs have a better GI tolerability and lower incidence of dyspepsia than non-selective NSAIDs.[141,142] Antisecretory drugs, especially PPIs, reduce the incidence of dyspepsia,[96,97] although up to 10% of patients with NSAID-induced dyspepsia will not obtain relief with antisecretory therapy.[78] In this clinical setting, two studies comparing omeprazole with ranitidine[97] or misoprostol[96] have shown that omeprazole provided greater relief of dyspeptic symptoms than ranitidine. Patients receiving the PPI reported a greater improvement in QOL than patients receiving misoprostol. The role of esomeprazole was evaluated in patients with upper GI symptoms taking NSAIDs, including COX-2 selective NSAID.[143] Esomeprazole was associated with highly significant symptom improvement compared with placebo. Esomeprazol improved symptoms in patients taking selective COX-2 NSAIDs, as well as those receiving nonselective NSAIDs. Esomeprazol was well tolerated and associated with

significant improvements in QOL. Similar data were observed in a *post hoc* analysis of other studies that aimed to evaluate the role of esomeprazole versus placebo and versus ranitidine.[144,145]

NSAIDs & Lower GI Damage

The clinical significance and frequency of adverse events with tNSAIDs in the lower GI tract have been increasingly reported, but are much more poorly characterized than those from the upper GI tract. Increased mucosal permeability and mucosal inflammation are often silent but occur with most tNSAIDs.[145,53–56] Other findings include anemia, occult blood loss, malabsorption and protein loss. Video capsule endoscopy studies have shown that more than 50% of patients on NSAIDs or low-dose aspirin may have mucosal lesions or mucosal breaks in the small bowel.[57] Clinically significant GI bleeding and perforation, diarrhoea, mucosal ulceration, symptomatic diverticular disease and strictures due to fibrous diaphragms may occur.[58] Two recent studies[146,147] have reported either similar or higher mortality frequency for complications from the lower GI tract when compared with those from the upper GI tract. NSAID use might damage the lower GI tract (small bowel, colon or anus), with a rate of bleeding events that is believed to be approximately a third of that of upper GI bleeding.

When comparing COX-2-selective NSAIDs with nonselective NSAIDs, the incidence of lower GI tract injury and clinical events with COX-2-selective NSAIDs is lower but less well characterized than those in the upper GI tract. Sigthorsson *et al.* demonstrated a significantly higher small intestinal permeability with indomethacin versus rofecoxib 25 and 50 mg.[55] Atherton *et al.* found that naproxen significantly increased small intestinal permeability when compared with lumiracoxib.[53] Small intestinal permeability was not significantly different when comparing COX-2-selective NSAID and placebo in these two studies. Two randomized clinical controlled trials in which healthy subjects receiving either celecoxib or a nonselective NSAID (naproxen or ibuprofen) or placebo underwent video capsule endoscopy, have shown that the percentage of subjects with intestinal mucosal breaks and the number of mucosal breaks per patient were significantly lower in the celecoxib groups versus naproxen or ibuprofen groups.[148,149] In terms of clinically relevant outcomes have shown less consistent results. *Post hoc* analysis of the VIGOR trial showed a lower incidence of serious lower GI clinical events (gross rectal bleeding other than melena, intestinal perforation, obstruction, diverticulitis) when compared rofecoxib versus naproxen;[27] however *post-hoc* analysis of the Multinational Etoricoxib and Diclofenac Arthritis Long-term program[150] have shown similar rates of lower GI events between etoricoxib and diclofenac. Chan *et al.* have recently published the first large, double-blind, randomized clinical trial to assess upper and lower GI events in patients needing chronic NSAID therapy.[151] In this study, diclofenac plus omeprazole was compared with celecoxib alone. The GI end point was the combination of gastroduodenal, small-bowel or large-bowel hemorrhage or perforation, gastric outlet obstruction or clinically significant anemia. They concluded that the risk of clinical outcomes throughout the GI tract was lower in patients treated with celecoxib 200 mg twice daily versus diclofenac SR 75 mg twice daily plus omeprazole 20 mg/day after 6 months of therapy.

At present, effective means to prevent NSAID-associated intestinal lesions in patients are not available. The efforts to generate safer NSAIDs, including aspirin, have followed different routes such as the development of enteric-coated or slow-release formulations or switch to a COX-2-selective agent, since these drugs have been found in some studies to be safer to the lower GI tract compared with tNSAIDs.[59,114,149,151–154] However, their long-term safety requires appropriate study.

If NSAID enteropathy is to be prevented, celecoxib seems a reasonable alternative based on the available data commented above. It may also be reasonable to coadminister misoprostol with the NSAID, as this reduces the permeability changes caused by NSAIDs. However, although misoprostol improves anemia in patients with proven NSAID enteropathy,[155] the evidence is poor and its ability to reverse intestinal permeability changes induced by indomethacin or naproxen for example is still controversial and needs further investigation.

Some attention is being focused on NO-donating NSAIDs. Preclinical studies with these compounds have demonstrated reduced intestinal adverse effects (i.e., ulceration and bleeding) compared with those of parent compounds.[75] Although NO–naproxen failed to increase intestinal permeability in healthy volunteers,[156] no clinical data regarding the lower GI tract are available in these patients. A good number of other potential approaches are being tested, but they are still in preclinical development.[157,158]

Pathologic similarities between NSAID enteropathy and inflammatory bowel disease have led to the suggestion that sulfasalazine may be a possible therapeutic option in NSAID enteropathy. Hayllar and colleagues assessed the use of disease-modifying antirheumatic drugs, including sulfasalazine, in patients taking NSAIDs. Sulphasalazine significantly reduced intestinal inflammation and blood loss, whereas other second-line antirheumatic drugs did not.[159]

Experimental and clinical investigations indicate that in the short term, antibacterial agents either reduce or abolish NSAID enteropathy.[160,161] The evidence from animal experiments has been confirmed in human studies, showing that metronidazole, an antimicrobial mainly targeted against anaerobic organisms, significantly prevented indomethacin-induced increase in intestinal permeability in healthy volunteers and reduced inflammation and blood loss in rheumatic patients taking NSAIDs.[162] Despite all the aforementioned evidence, no clinical trials have been formally performed in humans to evaluate the effect of antibiotics in the prevention of intestinal damage induced by NSAIDs.

Managing CV Toxicity

The CV toxicity associated with the use of NSAIDs is an important clinical issue which led to the withdrawal from the market of the coxibs, rofecoxib and valdecoxib. However, both observational studies and meta-analyses of data derived from randomized clinical trials showed that also some tNSAIDs, such as diclofenac, were associated with an increased CV risk.[4,63,120]

The most plausible mechanism underlying the CV risk of and NSAIDs (both coxibs and tNSAIDs) has been identified, that is, the profound inhibition of COX-2-dependent PGI_2 in the presence of incomplete and intermittent inhibition of platelet COX-1.[4,63] The use of a biomarker strategy of COX inhibition has allowed the understanding that the extent of patient exposure (magnitude and duration) is an important determinant of enhanced risk of nonfatal MI.[4] Since a linear relationship exists between the degree of inhibition of COX-2 and the degree of inhibition of PGI_2 *in vivo*,[4] reduction of the dose should translate into a reduction of the CV risk.

Importantly, it has been shown that it is necessary to block COX-2 by 80% in whole blood to translate into an analgesic effect *in vivo*.[163] However, we have found that NSAIDs are administered to patients at doses which are not bioequivalent. In particular, tNSAIDs with short half-lifes (such as diclofenac) are usually administered at supratherapeutic doses (almost completely suppressing whole blood COX-2 activity). This may represent an important determinant which explains the differences in CV toxicity among NSAIDs.[4] In fact, whole blood COX-2 inhibition by NSAIDs (tNSAIDs and coxibs) higher than that necessary for a therapeutic effect (i.e., >80%) seems associated with a CV risk.[4] Thus, a rational selection of the dose based on the use of a biomarker predictive of efficacy, such as whole blood COX-2, might be useful to reduce the CV risk of NSAIDs. The use of this biochemical marker together with genetic biomarkers (still to be identified) might allow the selection of patients uniquely susceptible to developing CV risk through inhibition of COX-2-dependent-PGI_2 when exposed to NSAIDs.

On the basis of evidences derived from the results of clinical studies, it is possible to suggest strategies for analgesic/anti-inflammatory treatment and CV prevention among patients with inflammatory disease and different levels of risk of vascular events (Table 1).[164] Patients with low CV risk (<1% per year) can be administered with a tNSAID or a coxib and the choice between the two classes of NSAIDs will be dependent on the GI risk of patients. In particular, the choice of NSAID for chronic and disabling inflammatory joint diseases like RA and OA is governed not only by GI risk but also by age, diagnosis, degree of severity, tolerability and relative efficacy in the given clinical situation. However, in

these patients, coxibs are not recommended for routine use. They should be used in preference to tNSAIDs only in patients who may be at 'high risk' of developing serious GI adverse effects. In conditions where inflammation of joints is minimal, as it occurs in OA patients, analgesics such as paracetamol should be preferred. In patients with and intermediate risk (1–3% per year), the choice will be to administer a tNSAID, such as low-dose ibuprofen or naproxen (+PPI) which have been shown to be associated with reduced incidence of vascular events.[4] If aspirin is indicated, ibuprofen should be avoided due to the demonstration of the capacity of ibuprofen to interfere with the antiplatelet effect of aspirin.[165,166] By contrast, we have recently shown that the sequential administration of aspirin 2 h before naproxen should minimize the interference of the tNSAID with aspirin effect on platelet COX-1.[167] In patients at high risk of a vascular event (>3%) with a low-dose aspirin indication, the choice is naproxen + PPI and aspirin, given 2 h before, or acetaminophen and aspirin.[4,168]

Table 1. Suggested strategies for analgesic/anti-inflammatory treatment and cardiovascular prevention among patients with inflammatory disease and different levels of risk of vascular events.

Risk of vascular event[†]	Pharmacological strategies
Low (<1% per year)	tNSAID or coxib depending on GI risk
Intermediate (1–3% per year)	tNSAID (low-dose ibuprofen or naproxen + PPI); if aspirin is indicated, naproxen + PPI and aspirin, given 2 h before[‡]
High (>3% per year)	Naproxen + PPI and aspirin, given 2 h before[‡]

[†]Vascular event is defined as the combined outcome of a nonfatal myocardial infarction, nonfatal stroke or vascular death [168].

[‡]Recent findings suggest that the possible interference of naproxen on the antiplatelet effect of aspirin can be minimized by the administration of aspirin 2 h before naproxen [167]. By contrast, ibuprofen should be avoided if aspirin is indicated [165,166].

GI: Gastrointestinal; PPI: Proton pump inhibitor; tNSAID: Traditional NSAID.

Expert Commentary

The beneficial therapeutic use of NSAIDs as anti-inflammatory and analgesic agents is associated with increased risk of GI and CV serious adverse events.[2–5] The integration of previously segregated fields of basic and clinical scientific research predicted and explained the efficacy and hazards from NSAIDs. Both beneficial and adverse effects are associated to the same mechanism of action – that is, the inhibition of COX activity.[1] The main clinically relevant GI side effects include GI bleeding, perforation and obstruction, while the major CV side effect is an increased risk of nonfatal MI.[2–5] The therapeutic effects of NSAIDs and coxibs are due to the inhibiton of COX-2 in inflammatory sites and spinal cord.[7,14] By contrast, the GI toxicity of tNSAIDs is dependent on the inhibition of COX-1 both in the GI mucosa and in platelets.[7,14,15] Interestingly, it has been shown that drugs which suppress profoundly both COX-isozymes are those at higher GI risk[3] and this finding supports the results obtained in animal models showing that also COX-2-dependent PGE2 may play a protective role by facilitating ulcer healing.[30–32] Recent studies of pharmacoepidemiology have shown that the administration of tNSAIDs and coxibs is associated with an increased risk of nonfatal MI.[4] Importantly, this study has shown that one determinant of the risk is the extent of inhibition of COX-2 and as a consequence the degree of reduction of vascular PGI_2.[4] Both the CV and GI risks are related to drug exposure thus supporting the recommendation that these drugs should be administered at lowest effective dose and for a short period of chronic administration.

The individual risk factors, both CV and GI, of patients have to be taken into consideration for the choice of NSAIDs. Patients with GI risk factors who require NSAIDs should receive the safest NSAIDs, such as coxibs, diclofenac, aceclofenac and ibuprofen, at the lowest possible dose for the shorter period of time. Moreover, the use of co-therapy with gastroprotectants is recommended. The co-therapy of NSAIDs with anticoagulants, antiplatelet agents or corticosteroids should be avoided.

Patients with low CV risk can be given a tNSAID or a coxib and, in particular, coxibs should be used in preference to tNSAIDs only in patients who may be at 'high risk' of developing serious GI adverse effects, in association with a PPI. In patients at high risk of CV events, coxibs should be avoided and if aspirin is indicated for CV prevention, the choice of the tNSAID should aim to minimize the possible interference of these drugs with the antiplatelet effect of aspirin.[165–167] Thus, ibuprofen should be avoided and naproxen should be given 2 h after low-dose aspirin (studies have been performed only with immediate-release aspirin).

Five-year View

The challenge of the next few years will be to learn how to use drugs at the individual level. This will lead to the development of a personalized medicine of NSAIDs. In order to realize this objective, it will be necessary to develop genetic and biochemical markers which might be useful to identify the responders to NSAIDs or who are uniquely susceptible at developing thrombotic or GI events by COX inhibition. This will lead to the development of individual responder approaches. In this context, the use of pharmacogenomics tools together with pharmacoepidemiological methods will open the way to a new era of pharmacovigilance. This will allow to put information out on drug hazard as quickly as possible and to make appropriate decision on risk management. However, the road is still very long and it is necessary for more work to be performed before this knowledge can be applied to daily practice.

Sidebar

Key Issues

- Conventional medical treatment for rheumatoid arthritis and osteoarthritis requires the use of NSAIDs because they provide unmistakable and significant health benefits in the treatment of pain and inflammation.
- NSAIDs share both beneficial and adverse effects due to the same mechanism of action, i.e. the inhibition of cyclooxygenase (COX) activity. Their beneficial therapeutic use as antiinflammatory and analgesic agents is associated with increased risk of gastrointestinal (GI) and cardiovascular (CV) serious adverse events (i.e., upper GI bleeding and nonfatal myocardial infarction [MI]).
- The risk of nonfatal MI was increased by 35% with current use of NSAIDs, but there was no increase in the risk of fatal MI. The excess risk increased with increasing treatment duration and daily dose.
- The increased incidence of thrombotic events associated with profound inhibition of COX-2-dependent prostacyclin (PGI2) can be mitigated, even if not obliterated, by a complete suppression of platelet COX-1 activity.
- Degree of inhibition of COX-2 for NSAIDs functionally selective for COX-2 is relevant to CV hazard and relates to drug potency (exposure). It has been proposed that the assessment of whole blood COX-2 *ex vivo*may represent a valid surrogate end point to predict CV risk for functionally selective COX-2 inhibitors.
- NSAIDs injure the GI tract by causing topical injury to the mucosa and by systemic effects associated with mucosal prostanoid depletion derived from COX inhibition. The main clinically relevant GI side effects include GI bleeding, perforation and obstruction.
- Management of patients with GI risk factors who require NSAIDs includes the use of the lowest possible dose for the shorter period of time, the use of the safest NSAIDs, the use of co-therapy with with gastroprotectants and the avoidance of co-therapy of NSAIDs with anticoagulants, antiplatelet agents or corticosteroids. Reduced

incidence of GI ulcers complications compared with traditional NSAIDs (tNSAIDs) has been demonstrated for COX-2 inhibitors. COX-2 plays an important role in the healing of pre-existing ulcers. This is supported by clinical data showing that coxibs are still associated with a small risk of upper GI bleeding, though smaller than that caused by tNSAIDs.

- Despite upper GI bleeding risk being multifactorial, drugs with a long half-life or slow-release formulation and/or associated with profound and coincident inhibition of both COX isozymes – which translates into deficiency of prostanoid generation in the GI tract – were associated with a greater risk of upper GI complications.
- The development of biomarkers predictive of the impact of NSAIDs on COX-1 and COX-2 activities *in vitro*, *ex vivo*and *in vivo*has been essential to read out the clinical consequences of selective and nonselective inhibition of COX isozymes in humans. Reduction of the dose is recommended and presumably will limit, but not delete, CV or GI risk by NSAIDs and coxibs.
- The use of pharmacogenomic tools to define the role of genetic factors in individual responses to drugs, in association with pharmacoepidemiological methods, represents a very promising approach to predict CV and GI risks for coxibs and tNSAIDs and to create personalized drugs with better efficacy and safety.

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Papers of special note have been highlighted as:
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