



Review

Role of coxibs in the strategies for gastrointestinal protection in patients requiring chronic non-steroidal anti-inflammatory therapy

Corrado Blandizzi*, Marco Tuccori, Rocchina Colucci, Matteo Fornai, Luca Antonioli, Narcisa Ghisu, Mario Del Tacca

Division of Pharmacology and Chemotherapy, Department of Internal Medicine, University of Pisa, Via Roma 55, Pisa 56126, Italy

ARTICLE INFO

Article history:

Accepted 18 November 2008

Keywords:

Coxibs
Gastrointestinal safety
NSAIDs
Ulcer healing

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs due to their high efficacy in the treatment of pain, fever, inflammation and rheumatic disorders. However, their use is associated with the occurrence of adverse effects at the level of digestive tract, ranging from dyspeptic symptoms, gastrointestinal erosions and peptic ulcers to more serious complications, such as overt bleeding or perforation. To overcome problems related to NSAID-induced digestive toxicity, different therapeutic strategies can presently be considered, including the co-administration of drugs endowed with protective activity on the upper gastrointestinal tract, such as the proton pump inhibitors, or the prescription of coxibs, which have been clinically developed as anti-inflammatory/analgesic drugs characterized by reduced damaging activity on gastrointestinal mucosa. The availability of different treatment options, to reduce the risk of NSAID-induced adverse digestive effects, has fostered intensive preclinical and clinical research aimed at addressing a number of unresolved issues and to establish rational criteria for an appropriate use of coxibs in the medical practice. Particular attention is being paid to the management of patients with high degrees of digestive risk, resulting by concomitant treatment with low-dose aspirin for anti-thrombotic prophylaxis or ongoing symptomatic gastroduodenal ulcers. The present review discusses the most relevant lines of evidence concerning the position of coxibs in the therapeutic strategies for gastrointestinal protection in patients who require NSAID therapy and hold different levels of risk of developing adverse effects at the level of digestive tract.

© 2008 Elsevier Ltd. All rights reserved.

Contents

1. Introduction.....	91
2. Classification and COX selectivity of NSAIDs and coxibs.....	91
3. Preclinical studies.....	91
3.1. Effects of tNSAIDs and coxibs on gastric mucosa.....	91
3.2. Combined effects of coxibs and aspirin on gastric mucosa.....	92
3.3. Effects of tNSAIDs and coxibs on gastric ulcer healing.....	92
3.4. Effects of tNSAIDs and coxibs on intestinal mucosa.....	93
4. Clinical studies.....	93
4.1. Effects of tNSAIDs and coxibs on upper GI tract.....	93
4.1.1. Coxibs versus tNSAIDs.....	93
4.1.2. Coxibs versus tNSAIDs plus gastroprotective cotherapy.....	94
4.2. Combined effects of coxibs and aspirin on upper GI tract.....	95
4.3. Effects of tNSAIDs or coxibs on upper GI tract in high-risk patients.....	95
4.4. Effects of tNSAIDs and coxib on lower intestinal tract.....	96
5. Role of coxibs in the strategies for gastrointestinal protection.....	96

* Corresponding author. Tel.: +39 050 830148; fax: +39 050 562020.
E-mail address: c.blandizzi@virgilio.it (C. Blandizzi).

6. Novel options for gastrointestinal protection against NSAIDs	97
7. Conclusion	97
Conflicts of interest	97
References	97

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs due to their high efficacy in the treatment of pain, fever, inflammation and rheumatic disorders. However, their use is associated with the occurrence of adverse effects at the level of digestive tract, ranging from dyspeptic symptoms, gastrointestinal (GI) erosions and peptic ulcers to more serious complications, such as overt bleeding or perforation. For example, a recent review of prospective outcome studies on arthritis patients, treated with NSAIDs for at least 6 months, has reported an annualized incidence of overall upper GI adverse events ranging from 2.7 to 4.5% [1]. A number of factors can expose patients to an increased risk of NSAID-induced GI damage, and the most relevant include a prior history of GI ulcer or bleeding, age of 65 years or older, long-term therapy with NSAIDs, aspirin use for cardioprotection, concomitant use of different NSAIDs, concomitant use of glucocorticoids or anticoagulants, and severe medical conditions, such as cardiovascular disease, renal or hepatic failure and diabetes [2].

To overcome problems related to NSAID-induced GI toxicity, different therapeutic strategies have been evaluated, including the co-administration of drugs endowed with protective activity on the upper GI tract, and evidence has been obtained that the prostaglandin analogue misoprostol [3] or proton pump inhibitors (PPIs, including omeprazole, lansoprazole, pantoprazole and esomeprazole) can prevent the occurrence of ulcerations associated with NSAID therapy [4,5]. In addition, following the discovery of two cyclooxygenase isoforms (COX-1, COX-2), and based on the assumption that COX-2 was an inducible enzyme responsible for inflammation but devoid of gastroprotective functions [6], selective COX-2 inhibitors (coxibs, including celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib and lumiracoxib) were clinically developed as novel anti-inflammatory/analgesic drugs characterized by reduced GI toxicity [7]. These advances have fostered intensive preclinical and clinical research supporting the view that coxibs may confer some advantages over conventional non-selective NSAIDs in terms of GI risk reduction. Nevertheless, there are still a number of unresolved issues in this field, and the criteria for an appropriate use of coxibs in patients with various degrees of GI risk remain matter of debate. The present review discusses the most relevant lines of evidence concerning the position of coxibs in the therapeutic strategies for GI protection in patients who require chronic NSAID therapy and hold different levels of risk to develop adverse GI effects.

2. Classification and COX selectivity of NSAIDs and coxibs

Differences in chemical structure and selectivity for COX isoforms are regarded as important determinants, which may account for the differential capability of COX inhibitors to impair the integrity of gastrointestinal mucosa. Most NSAIDs are endowed with acidic structure, which is known to contribute to the direct damaging actions of these drugs on digestive mucosa. Among coxibs, only lumiracoxib has maintained an acidic structure, while celecoxib (sulphonamide derivative) and etoricoxib (methylsulphone derivative) are devoid of acid moieties, and therefore they are expected to not exert direct detrimental actions on the digestive tract [8].

The ability of NSAIDs and coxibs to differentially inhibit COX-1 and COX-2 can be determined by *in vitro* assays on human whole blood. In these tests, COX-2 is induced through stimulation of monocytes by lipopolysaccharide and its activity is measured in terms of PGE₂ production, while activation of constitutive COX-1 in platelets is triggered by induction of blood clotting and can be estimated in terms of TXB₂ production [9,10]. Based on this methodology, three main groups of COX inhibitors have been identified: (1) non-selective NSAIDs with inhibitory actions on both COX-1 and COX-2, such as ibuprofen, ketoprofen, naproxen; (2) NSAIDs with preferential COX-2 inhibitory activity, such as meloxicam, nimesulide and diclofenac, which display from 18- to 29-fold higher *in vitro* potency for COX-2 over COX-1; (3) coxibs, which inhibit COX-2 with a degree of selectivity ranging from 30 to over 400 [11,12]. A similar classification has been proposed by means of a modified human whole blood assay and calculation of COX-2/COX-1 IC₈₀ ratios: (1) compounds able to exert a full inhibition of COX-1 and COX-2 with poor degree of selectivity (up to 5-fold COX-2 selective); this group includes most NSAIDs, such as ketoprofen, naproxen, ibuprofen, piroxicam and diclofenac; (2) compounds with preference toward COX-2, such as nimesulide, celecoxib, meloxicam and etodolac, which are characterized by 5- to 50-fold *in vitro* COX-2 selectivity; (3) compounds which selectively inhibit COX-2 with weak activity against COX-1, including coxibs with over 50-fold COX-2 selectivity [10,13]. Of note, in both classifications diclofenac and celecoxib display comparable levels of *in vitro* COX-2 selectivity and might be classified as COX inhibitors endowed with preferential COX-2 blocking activity.

COX-2 selectivity, as assessed by *in vitro* testing, may not necessarily reflect the ability to discriminate between COX-1 and COX-2 *in vivo* when drugs are administered to patients at anti-inflammatory doses. To address this issue, Capone et al. [14] have compared plasma concentrations, achieved by COX inhibitors in patients after dosing, with IC₈₀ values estimated for the *in vitro* activity of these drugs against COX-1 and COX-2. The results can be summarized as follows: (a) plasma levels achieved by non-selective NSAIDs, such as ibuprofen and naproxen, are higher than those required to inhibit both COX-1 and COX-2 by 80% *in vitro*; (b) therapeutic concentrations of etoricoxib and lumiracoxib are adequate to inhibit more than 80% of *in vitro* COX-2 activity, while being insufficient to block COX-1; (c) diclofenac (150–200 mg) achieves plasma levels which can fully inhibit COX-2 and are 2-fold lower than those required to block COX-1; (d) plasma concentrations of celecoxib (100–200 mg) do not block COX-1 and are 2-fold lower than those needed to obtain 80% COX-2 inhibition (although an 80% COX-2 inhibition can be expected at the dose of 400 mg/day). Thus, celecoxib and diclofenac display similar degrees of COX-2 selectivity in *in vitro* assays, but they are likely to exert differential inhibitory effects against COX-1 in clinical settings. Based on current classifications, in the subsequent sections of this review the designation “traditional NSAIDs” (tNSAIDs) has been used to refer to non-aspirin non-selective NSAIDs (including diclofenac).

3. Preclinical studies

3.1. Effects of tNSAIDs and coxibs on gastric mucosa

The pathogenesis of tNSAID-induced gastric damage depends partly on COX inhibition and partly on COX-independent mech-

anisms, which may result from systemic or local tNSAID actions [1]. COX inhibition can increase the susceptibility of gastric mucosa to tNSAID-induced injury by suppression of a number of prostaglandin-mediated protective functions. For example, prostaglandins inhibit the activation of neutrophils and the local release of reactive oxygen species (ROS). The formation of prostacyclin by the endothelium of mucosal microcirculation is highly relevant in ensuring a tonic inhibition of neutrophil adherence. Therefore, by blocking prostaglandin biosynthesis, tNSAIDs can shift the mucosal balance toward the recruitment and endothelial adhesion of circulating neutrophils [15,16]. Once adhered, neutrophils clog the microvasculature causing a local decrease in mucosal blood flow and release of tissue damaging factors, including proteolytic enzymes and leukotrienes, which enhance the vascular tone, exacerbate tissue ischaemia, stimulate the production of ROS, and promote the destruction of intestinal matrix, leading to a severe degree of focal tissue necrosis, particularly in the presence of a low luminal pH [16,17]. COX-dependent inhibition of bicarbonate secretion contributes also to gastric mucosal injury elicited by tNSAIDs. Indeed, the secretion of bicarbonate ions in the mucus gel layer generates a pH gradient on the gastroduodenal mucosal surface, thus providing a first line defense against luminal acid [18]. A number of studies have demonstrated the expression of bicarbonate/chloride ion exchanger in the apical membranes of gastric surface epithelial cells, and shown that COX-derived prostaglandins stimulate bicarbonate secretion via activation of EP₁ receptors [19,20].

Most tNSAIDs are weakly acidic and this property accounts for local COX-independent injury of gastric mucosa. In the presence of gastric acidity, the undissociated form of acidic tNSAIDs can attenuate the hydrophobic surface barrier of the stomach. This transformation of the gastric mucosal surface from a non-wettable to a wettable state appears to be linked to the ability of acidic tNSAIDs to interact with and destabilize an extracellular lining of zwitterionic phospholipids, and particularly phosphatidylcholine, which are present within and on the surface of the mucus gel layer [21,22]. Lichtenberger has shown that such an effect contributes significantly to tNSAID-induced gastric injury in experimental models, and that it can persist for prolonged periods after discontinuation of tNSAID administration [23]. There is also consistent evidence that the protonophore actions of aspirin and other acidic tNSAIDs take a significant part in the topical damage to gastric mucosa. In particular, upon exposure to an acidic environment, the undissociated lipid-soluble form of aspirin is able to penetrate cell membranes and accumulate into epithelial cells, where the inner pH is at a physiological level of 7.4. At this pH value, aspirin dissociates and remains segregated within cells. This accumulation enhances the inhibition of prostaglandin biosynthesis, and it brings also into play other properties of aspirin, such as the uncoupling of mitochondrial oxidative phosphorylation. The consequence of this mitochondrial dysfunction is a decrease in ATP production and an increase in AMP and ADP levels, which are responsible for increments of intracellular calcium concentration. These changes are followed by mitochondrial injury, increased generation of ROS and alterations in the Na⁺/K⁺ balance, which lead to weakening of mucosal barrier and cellular necrosis [24,25]. An additional mechanism, involved in the injurious effects of tNSAIDs on GI mucosa, is related to the detrimental action of these drugs on the integrity of epithelial tight junctions, which are known to separate the apical from basolateral cell surface domains to establish cell polarity and to provide a barrier function against the back diffusion of acid and other solutes through the paracellular space [26]. It has been suggested that COX inhibition may be implicated in tNSAID-induced alterations of intercellular epithelial permeability [27]. However, recent evidence indicates that aspirin can elicit gastric epithelial barrier dysfunction through down-regulation of claudin-7, a member of the claudin

protein family, which play important roles in the formation of tight junctions [28].

Coxibs do not alter the integrity of normal gastric mucosa in preclinical models, and their clinical development has been based on the concept that COX-2 is not expressed in the gastric mucosa [1]. However, this initial hypothesis has not been supported by subsequent observations, demonstrating the constitutive presence of both COX-1 and COX-2 in human and rodent gastric mucosa [29]. In addition, studies on COX-1-knockout mice showed no evidence of spontaneous gastric injury and demonstrated the ability of tNSAIDs to damage the gastric mucosa via COX-2-dependent mechanisms [30]. Wallace et al. investigated the functional roles of COX isoforms in the gastric mucosa, showing that COX-1-dependent prostaglandins are involved in the maintenance of mucus/bicarbonate secretion and blood flow, while COX-2 protects the mucosa from leucocyte endothelial adhesion and supports epithelial renewal. In addition, they observed that selective COX-1 or COX-2 inhibitors did not damage the stomach when tested alone, while tNSAIDs or the combined administration of COX-1 plus COX-2 inhibitors resulted in gastric erosions [31]. Overall, it is currently acknowledged that tNSAIDs can impair the gastric protection via concomitant blockade of COX-1 and COX-2, while coxibs lack damaging actions on gastric mucosa by preserving COX-1-dependent prostaglandin production [32].

3.2. Combined effects of coxibs and aspirin on gastric mucosa

Concomitant administration of aspirin and selective COX-2 inhibitors is expected to increase the risk of gastric ulceration as a consequence of the combined blockade of mucosal COX-1 and COX-2. Studies performed on preclinical models, while confirming the occurrence of such adverse interaction, have proposed an alternative pathogenic explanation [33]. Indeed, aspirin inhibits the biosynthesis of prostaglandins via acetylation of a serine residue located in proximity of the active site of both COX-1 and COX-2. This reaction leads to different functional consequences, since COX-1 undergoes a full enzymatic blockade, while acetylated-COX-2 acquires the ability to convert arachidonic acid into 15-R-hydroxyeicosatetraenoic acid (15-R-HETE), which can be converted to 15-R-epilipoxin A4 (LXA4, designated also as aspirin-triggered lipoxin, ATL) by the 5-lipoxygenase pathway. Of note, ATL can exert protective actions on gastric mucosa via inhibition of neutrophil chemotaxis and reduction of neutrophil-dependent tissue injury [34]. Accordingly, the suppression of COX-2-dependent ATL production has been suggested as a predominant mechanism whereby the combined administration of aspirin and COX-2 inhibitors may increase the risk of gastric mucosal ulceration. In support of this proposal, co-administration of a selective COX-2 inhibitor with aspirin in rats was found to block the elevated formation of ATL in the stomach, thus confirming that COX-2 activity is required for ATL biosynthesis, and this effect was associated with an increase in the severity of gastric mucosal damage [33].

3.3. Effects of tNSAIDs and coxibs on gastric ulcer healing

Gastric erosions can progress towards the formation of chronic ulcers, where the damage penetrates deeper into the mucosa and affects the layers of submucosa and muscularis mucosa. The repair of ulcers is complex and requires the formation of granulation tissue together with reconstruction of epithelial structures and regeneration of the microvascular network [35]. tNSAIDs are known not only to alter the integrity of gastric mucosa, but also to impair the healing of pre-existing ulcers through mechanisms which have ascribed mainly to COX inhibition [36].

Preclinical studies have shown that the impairing action of tNSAIDs on ulcer healing is shared by selective COX-2 inhibitors,

suggesting a role for COX-2 in the process of ulcer repair (for review see [36]). Mizuno et al. [37] provided the first demonstration that COX-2 expression was increased in experimental ulcers of mouse stomach and, more recently, Hatazawa et al. [38] confirmed the importance of COX-2-dependent PGE₂ production in the healing of gastric ulcer. Despite this supportive evidence, a number of observations argue against an exclusive role of COX-2 in ulcer repair: (a) data on cellular COX-2 expression at the level of gastric ulcer are conflicting; indeed, immunohistochemistry assays in humans have identified COX-2 induction in the regenerating epithelium of ulcer margin or, by contrast, in macrophages, myofibroblasts and endothelial cells at the ulcer base [39,40]; (b) different patterns of time- and dose-dependence have been reported when comparing the effects of COX-2 inhibitors on PGE₂ production and ulcer healing [41]; (c) COX-1 may also contribute to ulcer healing; Schmassmann et al. [42] have observed that ulcer healing was unaffected in COX-1-deficient mice or wild-type animals treated with COX-1 inhibitors; however, in the same study the combined inhibition of COX-1 and COX-2 delayed ulcer repair to a higher degree than COX-2 inhibition alone, suggesting that COX-1-dependent prostaglandins are important in the healing mechanism when COX-2-dependent prostaglandins are deficient; (d) upon combined administration of aspirin and coxib, the delaying action of aspirin on ulcer healing is likely to result from its ability to destabilize extracellular zwitterionic phospholipids, and not from COX-1-dependent mechanisms. In support of this mechanism, Lichtenberger et al. [22] have shown that phosphatidylcholine-associated aspirin in combination with celecoxib did not affect gastric ulcer healing in rats, despite a significant reduction in tissue prostaglandin biosynthesis; (e) COX-independent mechanisms contribute to the gastric injurious effects of tNSAIDs, but the involvement of these mechanisms in the delaying action of tNSAIDs or COX-2 inhibitors on ulcer healing remains unclear; in this respect, we have obtained preliminary evidence that ulcer healing in rats was impaired by indomethacin and DFU (selective COX-2 inhibitor), but not significantly affected by celecoxib, and that the detrimental actions of indomethacin and DFU could depend on their ability to enhance the expression of NSAID-activated gene-1 (NAG-1), a factor which promotes apoptotic cell death [43].

3.4. Effects of tNSAIDs and coxibs on intestinal mucosa

The pathogenic mechanisms accounting for intestinal injury associated with tNSAID treatment remain unresolved. Current information suggests a complex network of damaging mechanisms, which partly coincide with those known to act at gastric level and include local epithelial injury, barrier dysfunction, mucosal invasion by bacteria, microcirculatory alterations, inflammatory cell infiltration and ROS generation, with a reinforcing action maintained by enterohepatic recirculation (for review see [8,44]). Enteral bacteria and enterohepatic drug recirculation are regarded as important mechanisms contributing to intestinal injury by tNSAIDs. There is evidence that some tNSAIDs can promote the translocation of bacteria from gut lumen to the intestinal wall. For example, tNSAIDs were found to enhance the growth of Gram-negative bacteria [45], and tNSAID-induced bowel damage was reduced in germ-free rats [46], or following pretreatment with antibiotics [47]. It is currently postulated that lipopolysaccharides, released from translocated bacteria, stimulate a local production of inflammatory cytokines, which then trigger a cascade of events supporting the intestinal injury [44]. A number of tNSAIDs, including indomethacin, diclofenac and piroxicam, undergo enterohepatic recirculation, and this process has been implicated in intestinal damage, as also suggested by the evidence that bile-duct ligation in rats can attenuate the indomethacin-induced mucosal damage [48,49]. Thus, the recirculation and excretion of tNSAIDs into the

gut lumen through the bile produces a prolonged exposure of jejunal mucosa to high concentrations of both tNSAIDs and their active metabolites. Moreover, the secreted bile can concur with tNSAIDs in promoting the local damage to the intestinal mucosa, as indicated by studies indicating that bile acids may exacerbate the injurious actions of tNSAIDs on the small bowel [50].

Whether, and to what extent, COX pathways play a role in tNSAID-induced intestinal damage remains a debated issue. At variance with gastric mucosa, COX-2 does not appear to be constitutively expressed in intestinal mucosa, as shown by our group in an immunohistochemical study on normal human colon [51]. Pharmacological studies in rodents have demonstrated that COX-1 or COX-2 inhibitors lack injurious actions on small intestine when given alone, since COX-2 undergoes induction following COX-1 blockade, and that a combined inhibition of both COX isoforms is required to elicit enteric mucosal lesions [52]. Consistently with these observations, treatment of COX-1- or COX-2-knockout mice with indomethacin, as well as administration of COX-1 inhibitor to COX-2-knockout mice or administration of COX-2 inhibitor to COX-1-knockout mice, caused similar degrees of intestinal damage [53]. Subsequent investigations have argued against the significance of COX isoforms in the pathogenesis of intestinal damage evoked by tNSAIDs. For example, Menozzi et al. [54] found that indomethacin evoked small intestinal lesions which were associated with increments of bacterial translocation into mucosa, myeloperoxidase activity and lipid peroxidation. By contrast, ibuprofen, SC-560 (COX-1 inhibitor), celecoxib or the combination of SC-560 plus celecoxib did not cause any intestinal injury.

4. Clinical studies

4.1. Effects of tNSAIDs and coxibs on upper GI tract

4.1.1. Coxibs versus tNSAIDs

In the general populations of tNSAID users, major adverse effects on upper GI tract can result in uncomplicated (i.e., symptomatic ulcer confirmed by endoscopy) or complicated events, including bleeding, perforation and obstruction. These adverse effects have been taken as endpoints in the following outcome trials, designed to assess the risk of upper GI events associated with coxibs in comparison with tNSAIDs: CLASS (celecoxib versus ibuprofen or diclofenac; 8059 osteoarthritis or rheumatoid arthritis patients) [55]; VIGOR (rofecoxib versus naproxen; 8076 rheumatoid arthritis patients) [56]; ADVANTAGE (rofecoxib versus naproxen; 5557 osteoarthritis patients) [57]; TARGET (lumiracoxib versus ibuprofen or naproxen; 18,325 osteoarthritis patients) [58]; SUCCESS-1 (celecoxib versus naproxen or diclofenac; 13,274 osteoarthritis patients) [59]; MEDAL (etoricoxib versus diclofenac; 34,701 osteoarthritis and rheumatoid arthritis patients) [60].

In the above trials, the relative risk (RR) of upper GI complications for coxibs over comparator tNSAIDs ranged from 0.14 (SUCCESS-1) to 0.91 (MEDAL), while RR values ranged from 0.46 (VIGOR, TARGET) to 0.69 (MEDAL) when considering the overall upper GI clinical events (for review see [1,61]), indicating a large variability in the results, which likely depends on differences in coxibs, comparator tNSAIDs, doses of test drugs, inclusion criteria or methodology for evaluation of upper GI outcomes. For example, in the CLASS study patients taking ibuprofen or diclofenac developed higher rates of symptomatic ulcers or ulcer complications than patients receiving celecoxib, but the rate of ulcer complications did not differ significantly. However, a number of biases may account for these unfavourable results of the CLASS trial. In particular, the study population included a high proportion of patients receiving chronic low-dose aspirin as a co-medication (over 20%), celecoxib was used at a high-dose (800 mg/day, 2–4 folds the max-

imum dosage recommended in clinical practice), and ibuprofen is less likely than other tNSAIDs to cause upper GI ulcer complications, as demonstrated by previous studies [62]. Consistently with these arguments, the SUCCESS-1 trial, where osteoarthritis patients were randomized to treatment with celecoxib (200 or 400 mg/day) or tNSAIDs (diclofenac 100 mg/day or naproxen 1000 mg/day) and 7% of the study population was allowed concomitant aspirin medication, showed that significantly more upper GI events occurred within the tNSAID group compared with the celecoxib group, in terms of both ulcer complications and overall clinical events [59]. In the MEDAL study, a pre-specified pooled analysis was carried out on data from three clinical trials in which patients were randomly assigned to treatment with etoricoxib (60 or 90 mg/day) or diclofenac (150 mg/day), and the results showed the occurrence of significantly fewer uncomplicated upper GI events with etoricoxib compared to diclofenac, while no significant difference was detected when examining complicated events [60]. However, these findings have been questioned, since the MEDAL study was primarily designed to assess the influence of COX inhibition on thrombotic cardiovascular events, and therefore patients were allocated in accordance with cardiovascular risk factors rather than upper GI risk factors, thus introducing a potential source of bias. In addition, patients included in the MEDAL study were allowed to take PPIs or low-dose aspirin, a condition that on one hand reflected the real-world clinical practice but, on the other hand, was likely to act as a confounding factor because of the lack of random allocation of patients within subgroups [63].

Endoscopic studies have been also performed to assess whether coxibs can significantly decrease the development of upper GI ulcerations as compared with tNSAIDs, although the use of endoscopic endpoints as surrogate markers for clinical adverse events is currently debated [25]. Despite these limitations, initial trials indicated that administration of celecoxib or rofecoxib to rheumatic patients for 12–24 weeks was associated with lower rates of gastroduodenal ulcers in comparison with tNSAIDs [64,65]. Accordingly, recent analyses of pooled endoscopic studies have shown that ulcer rates were significantly decreased when all five coxibs (celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib) were tested against any of the most commonly employed tNSAIDs (ibuprofen, naproxen, diclofenac) [1,66].

Randomized trials, evaluating endoscopic ulcers, ulcer complications or adverse GI symptoms associated with coxib use, have been subjected to systematic review and meta-analysis by Rostom et al. [66]. In this overview, when compared with tNSAIDs, coxibs were found to produce 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), suggesting that coxibs offer greater upper GI safety and tolerability than tNSAIDs. This conclusion agrees with findings of case-control studies. In particular, Hippisley-Cox et al. [67] evaluated a large population of patients, to determine the comparative risk of adverse upper GI events in patients taking different coxibs and tNSAIDs in primary care (9407 cases versus 88,867 matched controls). After adjustments for potential confounding variables, these authors found that the highest odds ratio (OR) was associated with naproxen (2.12), followed by diclofenac (1.96), aspirin (1.60), ibuprofen (1.42), and celecoxib (1.11). More recently, Garcia-Rodriguez and Barreales Tolosa [68] evaluated the occurrence of upper GI complications in patients treated with coxibs (celecoxib, etoricoxib, rofecoxib, valdecoxib) or tNSAIDs (1561 cases versus 10,000 matched controls). They found that the adjusted RR of adverse events was 3.7 for tNSAIDs and 2.6 for coxibs, and the overall RR associated with coxib use was 0.8 (95%CI 0.6–1.1) in comparison with current intake of tNSAIDs. Thus, despite some uncertainties resulting from methodological issues, clinical outcome and endoscopic studies, taken together with the findings of meta-analyses and case-control studies, support the contention

that coxibs are associated with a reduced risk of upper GI adverse events when compared to tNSAIDs.

4.1.2. Coxibs versus tNSAIDs plus gastroprotective cotherapy

Two primary therapeutic strategies are currently suggested to reduce the risk of serious upper GI adverse effects of tNSAIDs: use of coxib or administration of tNSAIDs with concomitant protective medications (i.e., PPIs, histamine H₂-antagonists, misoprostol) [7,69]. Misoprostol was developed to replace endogenous GI prostaglandins, the formation of which is reduced by tNSAIDs, and it has been the first drug with demonstrated efficacy for both prevention and treatment of tNSAID-induced ulcers. In the MUCOSA trial, the administration of 200 µg misoprostol four times a day for 6 months to elderly patients under treatment with tNSAIDs was found to reduce the overall rate of serious GI complications by about 40% (OR versus placebo: 0.598, *P* = 0.049) [3]. Unfortunately, while confirming the ability of misoprostol to prevent tNSAID-induced gastroduodenal damage, subsequent studies highlighted an unfavourable tolerability profile, related mainly to the occurrence of diarrhoea [70,71], which has limited the use of this drug in current clinical practice.

Subsequent trials, designed to test the gastroprotective activity of PPIs or H₂-antagonists in tNSAID-treated patients, had endoscopic lesions as an endpoint [72,73]. It is unlikely that large outcome studies of cotherapy with these drugs in tNSAID users will be conducted, mainly because of ethical arguments against the randomization of patients into control groups receiving tNSAIDs without protective cotherapy. Therefore, it remains uncertain whether or not PPIs or H₂-blockers can prevent upper GI adverse events associated with tNSAIDs. There is also a lack of adequately powered outcome trials comparing coxibs with tNSAIDs plus gastroprotective cotherapy. However, such a comparison is being addressed by the ongoing CONDOR trial, the results of which are expected to appear in 2009. As anticipated by Peura et al. [74], CONDOR is a large, randomized, double-blind trial, designed to compare the global GI safety of celecoxib with that of diclofenac, and all patients assigned to the diclofenac arm will receive also omeprazole, since the study population includes patients at high GI risk, for whom treatment with a tNSAID alone would not be an ethical option. Of note, in the CONDOR trial the primary endpoint is based on the combination of adverse events occurring both in the upper and lower GI tract.

For the above reasons, observational studies on large cohorts of patients have been performed to obtain data suitable for guiding therapeutic choices in the clinical practice. In a retrospective analysis, Ray et al. [62] studied cases of peptic ulcer hospitalizations in a cohort of patients. To decrease potential channelling bias, this study included only cases of new tNSAID or coxib use and controlled for multiple baseline GI risk factors. Ray et al. [62] examined 234,010 and 48,710 cases of new tNSAID and coxib use, respectively, with 363,037 person-years of follow-up and 1223 peptic ulcer hospitalizations. Their results showed that tNSAID use without gastroprotective cotherapy was associated with an adjusted incidence of peptic ulcer hospitalizations of 5.65 per 1000 person-years, which was 2.76 times greater than that estimated for persons not using either tNSAIDs or coxibs. This risk was reduced by 39% (95%CI: 16–56%) in patients receiving tNSAIDs with gastroprotective cotherapy and 40% (95%CI: 23–54%) in patients under coxib treatment without concomitant gastroprotection. When the analysis was restricted to patients under PPI protection, tNSAIDs plus PPIs were found to confer a safety advantage comparable to that of coxibs, with respective risk reductions of 54 and 40%. In addition, the best gastroprotection was associated with concurrent use of celecoxib and a PPI, which was significantly safer than either naproxen alone or in combination with a PPI. A recent case-control study was carried out by Targownik et al. [75], who analyzed 1382

users of tNSAIDs or coxibs with upper GI complications, to determine the relative efficacy of different gastroprotective strategies. In this analysis, the cases consisted of all subjects who were using a tNSAID or a coxib and were hospitalized with an admitting diagnosis of upper GI complication. The results indicated that combined treatments with coxib plus PPI were associated with the highest risk reduction for upper GI events (OR 0.36, 95%CI 0.28–0.47), followed by coxib alone (OR 0.51, 95%CI 0.43–0.60) and tNSAID plus PPI (OR 0.67, 95%CI 0.48–0.95). In this study, the risk reduction promoted by coxib alone did not differ from that afforded by PPIs in combination with tNSAIDs ($P=0.110$). However, when celecoxib-treated patients were analyzed separately, the use of celecoxib was associated with a reduced risk of upper GI complications versus the strategy based on tNSAID plus PPI administration ($P=0.002$) [75]. Overall, retrospective observational studies suggest that coxibs or tNSAIDs plus protective medications may offer similar levels of protections against upper GI complications, but this proposal needs to be corroborated by direct comparative outcome trials.

4.2. Combined effects of coxibs and aspirin on upper GI tract

A large number of patients are subjected to combined treatments with low-dose aspirin and tNSAIDs or coxibs owing to the concomitance of thrombotic risk and rheumatic disorders. Several lines of evidence suggest that upper GI injury and complications with aspirin plus a tNSAID exceed those of either drug alone [76], while the possibility of a lower GI risk with aspirin plus a coxib remains an open issue. As discussed above, most outcome trials have not been able to identify a significant reduction in adverse GI events with coxibs compared to tNSAIDs in aspirin users, but data of the MEDAL study suggest that etoricoxib reduces the risk of uncomplicated upper GI events in patients receiving low-dose aspirin [60]. In the case-control study by Garcia-Rodriguez and Barreales Tolosa [68], aspirin was found to abolish the GI safety advantage conferred by coxibs over tNSAIDs, thus confirming the data reported by Lanas et al. [77], who concluded that the lower risk of upper GI bleeding estimated for coxibs over tNSAIDs tends to disappear upon administration in combination with low-dose aspirin.

The issue of upper GI adverse effects associated with coxibs plus aspirin has been addressed by clinical studies based on endoscopic endpoints, which have yielded heterogeneous results. In a 12-week endoscopic study on osteoarthritis patients, Laine et al. [78] reported that the ulcer incidence was significantly higher (16%) in the group receiving aspirin (81 mg/day) plus rofecoxib (25 mg/day) than in subjects allocated to aspirin alone (7%), but it did not differ significantly from that estimated in the aspirin plus ibuprofen (2400 mg/day) group (17%). By contrast, in a 1-week placebo-controlled study, comparing celecoxib (200 mg/day) with naproxen (1000 mg/day) in healthy subjects taking aspirin (325 mg/day), Goldstein et al. [79] observed that aspirin alone was associated with a significantly lower ulcer rate than aspirin plus celecoxib (8% versus 19%, respectively). However, the celecoxib plus aspirin ulcer incidence was significantly lower than the 27% incidence found in subjects receiving naproxen plus aspirin. Similar results were obtained in a 1-week study on healthy volunteers, where celecoxib and naproxen were tested in combination with aspirin at the daily dose of 81 mg [80]. Of note, in this trial the incidence of upper GI ulcers was considerably lower with celecoxib plus aspirin 81 mg (7%) than with celecoxib plus aspirin 325 mg (19%), as previously reported by Goldstein et al. [79].

Since the combinations of aspirin with coxibs or tNSAIDs are associated with different degrees of upper GI risk, and considering that different guidelines recommend the prescription of a coxib or a tNSAID plus a PPI to aspirin-treated patients requiring NSAID therapy [81,82], Goldstein et al. [83] have compared these two strategies in osteoarthritis patients under treatment with low-

dose aspirin (81 or 325 mg/day). For this purpose, aspirin-treated patients ($n=1045$) were randomized to celecoxib (200 mg/day) or naproxen (1000 mg/day) plus lansoprazole (30 mg/day) for 12 weeks, and endoscopic examinations were carried out both at baseline and at the end of study period. Although the authors hypothesized a lower gastroduodenal ulcer rate in the naproxen plus lansoprazole arm, on the basis of previous findings [71], the results showed a lack of significant difference (9.9% celecoxib versus 8.9% naproxen plus lansoprazole), thus leaving this important issue open to future investigations. For the purpose of current clinical practice, it should be considered that similar levels of upper GI risk decrease are likely to be obtained when aspirin-treated patients receive coxibs or tNSAIDs in combination with PPIs.

4.3. Effects of tNSAIDs or coxibs on upper GI tract in high-risk patients

There is currently a need for randomized trials to compare the ability of coxibs and tNSAIDs plus gastroprotective drugs to reduce the incidence of GI complications in patients with low-to-moderate levels of digestive risk. However, this issue has been addressed in studies on patients with high risk for ulcer complications, since they are often allowed to continue NSAID use despite a previous history of ulcer bleeding and/or the concomitance of predisposing risk factors, such as aging and medical diseases (for example, heart failure, diabetes or cirrhosis). Chan et al. [84] evaluated 287 arthritis patients who used tNSAIDs and developed upper GI ulcer bleeding. After having ensured ulcer healing and *Helicobacter pylori* (HP) negativity, these patients were randomly assigned to receive either celecoxib (400 mg/day; twice the maximal dose approved by FDA for osteoarthritis) plus placebo or diclofenac (150 mg/day) plus omeprazole (20 mg/day) for 6 months. At the end of observation, the incidence of recurrent ulcer bleeding was similar in patients treated with celecoxib or diclofenac plus omeprazole. However, the risk of recurrent ulcer bleeding with both treatments was quite high (4.9 celecoxib versus 6.4 diclofenac plus omeprazole), suggesting that neither regimen can completely protect high-risk patients from bleeding recurrence [84]. Chan et al. have performed a subsequent study where 287 tNSAID users with recent episodes of ulcer bleeding and HP negativity were randomly assigned to receive celecoxib (400 mg/day) plus placebo or diclofenac (150 mg/day) plus omeprazole (20 mg/day) for 6 months. In this trial, patients were subjected to endoscopy if they developed recurrent bleeding, while those without bleeding recurrence underwent endoscopy only at the last follow-up visit. Among patients without episodes of recurrent bleeding within the study period, the incidence of recurrent upper GI ulcers was unexpectedly high (19% celecoxib versus 26% diclofenac plus omeprazole). In addition, when combining bleeding ulcers and endoscopic ulcers, the 6-month incidence of recurrent ulcers was 24% for celecoxib and 32% for diclofenac plus omeprazole, thus indicating that neither treatment can adequately protect high-risk patients from ulcer recurrence (even if there was a non-significant difference of about 8% in favour of celecoxib) [85]. Similar findings have been obtained in an open-label study, with recurrent ulcer complications as a primary endpoint, where 224 high-risk patients were randomly assigned to treatment with celecoxib (200 mg/day) or naproxen (750 mg/day) plus lansoprazole (30 mg/day) for 24 weeks. At end of the study period, 3.7% of patients in the celecoxib group and 6.3% of patients in the naproxen plus lansoprazole group developed recurrent ulcer complications, indicating that celecoxib was as effective as gastroprotective cotherapy with lansoprazole in the prevention of upper GI adverse events [86]. In this study, the occurrence of dyspepsia was also assessed as a secondary endpoint, and it was found that a higher proportion of celecoxib-treated patients developed dyspeptic symptoms when compared with naproxen–lansoprazole combination [86].

The lower prevalence of dyspepsia in the latter group of patients was likely to result from treatment with lansoprazole, since coxibs and tNSAIDs seem to induce dyspeptic symptoms to similar extents [56], and PPIs can exert relieving effects on dyspepsia associated with tNSAID administration [87].

Results of comparative studies on celecoxib versus tNSAIDs plus PPIs suggest that neither of these treatments can offer adequate protection to patients with high GI risk, thus raising the question of whether a combined treatment with a coxib plus a PPI might represent a better option to protect this category of patients. In this respect, a 6-month endoscopic study has shown that esomeprazole reduced the ulcer rate in high-risk patients on long-term treatment with NSAIDs, including a subgroup of patients receiving coxibs [88]. However, this study was not specifically powered to assess whether a combination of coxib plus PPI would provide greater GI protection than a tNSAID plus PPI. Therefore, in an attempt to clarify this point, Chan et al. [89] enrolled 441 high-risk patients in a trial designed to evaluate recurrent ulcer bleeding up to 1 month after the end of a 12-month treatment with celecoxib (400 mg/day) in combination with placebo or esomeprazole (40 mg/day). In this study, the combined treatment with celecoxib plus esomeprazole was more effective than celecoxib alone for prevention of ulcer bleeding recurrence, since the 13-month cumulative incidence of the primary endpoint was 0% in the celecoxib plus esomeprazole group and 8.9% in controls assigned to celecoxib alone. These findings are of high clinical interest and should foster the performance of trials specifically designed to further verify that the administration of a coxib with a PPI can be the most convenient option in high-risk patients requiring anti-inflammatory therapy.

4.4. Effects of tNSAIDs and coxib on lower intestinal tract

In the clinical setting, damaging effects of tNSAIDs may occur throughout the GI tract, including the small bowel and colon, and long-term complications arising from intestinal injury include protein-losing enteropathy, bleeding and development of strictures or perforations [90,91]. Through the years, the occurrence of tNSAID-induced intestinal lesions has been documented mainly by indirect techniques, such as scintigraphy, faecal calprotectin assay and intestinal excretion of ¹¹¹In-labelled leucocytes. More recently, the development of video capsule endoscopy (VCE) has allowed a direct observation of intestinal damage (for review see [92]). Laine et al. [91] have performed a systematic review of 47 functional, endoscopic and outcome studies on the lower GI effects of tNSAIDs: 17 of 22 studies on enteric permeability reported an increase compared with no tNSAID or placebo; although eight case-control studies found higher rates of intestinal bleeding for tNSAIDs over placebo, the OR ranged from 1.9 to 18.4, reflecting the wide heterogeneity of these investigations and the difficulty in controlling for confounding factors.

Endoscopic studies have demonstrated the ability of tNSAIDs to induce intestinal injury. Lengeling et al. [93] reported that 83% of patients with ulcerative ileitis, identified during routine ileoscopy, were taking tNSAIDs (including aspirin, naproxen, diclofenac and ibuprofen). In an open-label study in patients with arthritis, VCE demonstrated the presence of small bowel injury in 71% of tNSAID users [94]. Another VCE trial demonstrated the ex-novo occurrence of small bowel lesions in 68% of 40 healthy volunteers taking diclofenac plus omeprazole for 14 days [95].

Endoscopic investigations support the notion that coxibs are associated with significant lower risk of intestinal ulceration than tNSAIDs. Goldstein et al. [96], using VCE in a placebo-controlled study, showed that healthy subjects treated with placebo developed less small bowel damage (7% of 118) than those receiving naproxen plus omeprazole (55% of 118), and that celecoxib was associated with an approximate 9-fold lower rate of enteric mucosal injury

(16% of 120) versus naproxen plus omeprazole. In a subsequent trial, healthy volunteers with normal VCE were randomly assigned to receive celecoxib (400 mg/day), ibuprofen (2400 mg/day) plus omeprazole (20 mg/day), or placebo for 14 days. Healthy subjects treated with celecoxib or placebo developed significantly less small bowel damage compared with volunteers exposed to ibuprofen plus omeprazole. In particular, the mean number of mucosal breaks per subject was 3.5 times higher in the ibuprofen plus omeprazole group compared with the celecoxib group (0.7 versus 0.2, $P < 0.001$) [97].

Despite evidence provided by endoscopic studies, the exact prevalence of intestinal complications associated with tNSAID or coxib in the clinical practice remains unknown. The results of large-scale outcome trials have suggested, but not conclusively demonstrated, that intestinal complications contribute substantially to tNSAID lower GI toxicity. For example, in the CLASS study, significantly more patients treated with ibuprofen or diclofenac had reductions of haematocrit and/or haemoglobin compared with celecoxib-treated patients, which may have resulted from occult blood loss in the lower GI tract [55]. Laine et al. [98] carried out a post-hoc analysis of serious lower GI clinical events in over 8000 patients with rheumatoid arthritis treated with rofecoxib or naproxen, and they found that the event rate per 100 patient/years was 0.41 for rofecoxib and 0.89 for naproxen. More recently, results from the MEDAL study showed also the contribution of lower GI events (bleeding, perforation and obstruction) to the overall GI toxicity, and etoricoxib and diclofenac were associated with lower GI event rates of 0.32 and 0.38 per 100 patient/years, respectively [99]. Overall, NSAID-induced injury to the lower GI tract appears to be a relevant clinical problem, but outcome data on the relative risk associated with tNSAIDs or coxibs are conflicting. Therefore, intensive research efforts are needed to identify specific risk factors and, above all, to assess whether coxibs may offer significant advantages over therapies based on tNSAIDs plus PPIs.

5. Role of coxibs in the strategies for gastrointestinal protection

Coxibs were developed and introduced into the clinical practice with the purpose to treat patients with anti-inflammatory/analgesic drugs as effective as tNSAIDs, but endowed with reduced toxic activity on the GI tract. Subsequent evidence, from controlled trials, that coxibs are associated with an increased risk of adverse cardiovascular events led to withdrawn of some coxibs from clinical use and has generated a debate about the best choice of drug to prescribe to patients requiring long-term anti-inflammatory/analgesic therapy [100,101].

From the cardiovascular standpoint, uncertainties have been generated by emerging evidence suggesting that most tNSAIDs tend also to increase the risk of adverse events in the long-term. For example, a database analysis of patients with first-ever diagnosis of myocardial infarction suggested an increased risk of this event with current use of rofecoxib, diclofenac and ibuprofen, but not naproxen [67]. Moreover, both tNSAIDs and coxibs can increase blood pressure in normotensive subjects as well as in patients with pre-existing hypertension [102]. Thus, any comparison of the cardiovascular risk-benefit ratio of coxibs versus tNSAIDs remains undetermined and, recognizing that conclusive data in this field are lacking, several authors cautiously recommend the avoidance of both coxibs and most tNSAIDs in patients with ischaemic heart or cerebrovascular and peripheral vascular disease [100,101].

With regard for GI adverse events, it is currently recognized that routine use of coxibs or PPI addition to tNSAIDs in unselected patient populations is not justified, and that the decision to adopt protective strategies must be weighed against a careful assessment

of the GI risk in individual patients. There is a general consensus that in patients without evident risk factors tNSAIDs can be prescribed without any need of protective co-therapy. However, in patients with low to moderate GI risk (i.e., one or more risk factors without history of peptic ulcer complications) it appears appropriate to use coxibs or tNSAIDs plus PPIs [7,100]. These strategies are supported by both preclinical and clinical evidence, with the caveat that coxibs have been tested against tNSAIDs alone in comparative clinical outcome trials, while studies on the use of PPIs in tNSAID-treated patients had endoscopic lesions as primary endpoint.

Patients with high degrees of GI risk may need to continue the use of NSAID therapy. These patients require protection with drugs able to prevent ulcer complications despite ongoing NSAID administration [7,103]. Clinical experiences in this setting have shown that coxibs or tNSAIDs plus PPI, while offering equivalent levels of protection, are not able to completely abate the risk of upper GI bleeding recurrence, and that combined treatments regimens, consisting of a coxib plus a PPI, may be required to achieve adequate levels of GI protection.

Another source of concern is represented by elderly patients who are frequently prescribed low-dose aspirin as anti-thrombotic prophylaxis. These patients can be at increased risk for development of NSAID-induced GI lesions, and most of them are often under long-term treatment with NSAIDs for concurrent rheumatic complaints [76,103]. Clear indications on the management of the digestive risk in this particular population are lacking, and it is presently being discussed whether to offer them a PPI-based protection or switching to a coxib. As discussed above, most of clinical outcome trials have not been able to identify a significant reduction in adverse GI events with coxibs compared to tNSAIDs in aspirin users. However, endoscopic studies have shown that the ulcer incidence was lower in patients treated with aspirin plus celecoxib than those receiving aspirin plus a tNSAID, and that in aspirin-treated patients similar degrees of upper GI risk reduction can be achieved by administration of a coxib or a tNSAID plus PPI [83].

Both preclinical and clinical evidence support the contention that lower intestinal injuries can contribute to the overall GI toxicity of several tNSAIDs. Endoscopic studies have shown a reduced risk of intestinal ulceration with coxibs in comparison with tNSAIDs plus PPIs. However, the prevalence of intestinal complications associated with tNSAIDs or coxibs in the clinical practice remains undermined, and there are no clear indications on how to manage this type of digestive risk in patients requiring chronic courses of anti-inflammatory/analgesic therapy. Accordingly, clinical research efforts are required in this field, in order to unravel specific risk factors and to identify adequate therapeutic strategies.

6. Novel options for gastrointestinal protection against NSAIDs

Novel pharmacological strategies are being investigated to counteract the detrimental actions of tNSAIDs on the GI tract. The most prominent options currently under evaluation are: (a) dual inhibitors of COX and 5-lipoxygenase (5-LOX), to prevent the injury of GI mucosa which results from the enhanced biosynthesis of leukotrienes, due to shunting of arachidonic acid metabolism towards the leukotriene pathway as a consequence of COX blockade; (b) tNSAIDs associated with phosphatidylcholine, to attenuate the destabilizing action of tNSAIDs on extracellular lining of zwitterionic phospholipids; (c) nitric oxide (NO) donating tNSAIDs, designated as COX inhibitor NO donors (CINODs) and designed to prevent the injurious actions of tNSAIDs with the gastroprotective activity of exogenous NO; (d) tNSAIDs able to release hydrogen sulfide, a new gaseous mediator which, like NO, is involved in the maintenance of GI mucosal integrity and blood flow (for

detailed review of the pharmacology of these compounds see [8,23,104,105]).

Some of the above mentioned drugs have reached the level of clinical development. The dual COX/5-LOX inhibitor licofelone (ML 3000) has been shown to spare the human gastric mucosa (endoscopic endpoint) when administered for 4–12 weeks to healthy volunteers or osteoarthritic patients in phase II or phase III trials controlled with placebo or naproxen [106,107]. Anand et al. [108], in a 4-day study in healthy volunteers, observed that the aspirin ability to induce gastric erosions, as assessed by endoscopy, was significantly reduced if the drug was associated with soy phosphatidylcholine, although prostaglandin levels in gastric biopsies were decreased by over 80% with both treatments. Studies in healthy volunteers have displayed also favourable GI safety profiles of CINODs. For example, a proof of concept endoscopic study showed that the NO donating aspirin NCX-4016 was virtually devoid of gastroduodenal toxicity when tested on healthy subjects ($n = 40$) allocated to receive NCX-4016, aspirin or placebo for 7 days [109]. Likewise, in a trial on 31 healthy volunteers, the upper GI endoscopic events following oral administration of AZD 3582, a NO donating naproxen, for 12 days were significantly decreased in comparison with naproxen [110]. These findings were confirmed by Wilder-Smith et al. [111], who evaluated the effects of equimolar doses of AZD 3582 and naproxen in 25 healthy volunteers treated for 12 days and found that this CINOD displayed an improved gastroduodenal safety profile in comparison with naproxen. Lohmander et al. [112] have investigated the GI tolerability profile of AZD 3582 750 mg twice daily compared with naproxen 500 mg twice daily or placebo in 970 patients with hip or knee osteoarthritis. Their results showed no significant differences between AZD 3582 and naproxen for the primary endpoint (incidence of gastroduodenal ulcers with diameter ≥ 3 mm), whereas the assessment of secondary endpoints (Lanza and erosion scores) favoured the CINOD. Clearly, further clinical studies are needed to establish whether CINODs confer actual advantages over tNSAIDs in terms of GI safety.

Additional strategies for the prevention of tNSAIDs-induced GI damage include the ongoing clinical development of pharmaceutical products containing fixed combinations of a tNSAID with a gastroprotective drug, such as naproxen/omeprazole, naproxen/lansoprazole, naproxen/esomeprazole and ibuprofen/famotidine (information available at: www.pozen.com; www.horizontherapeutics.com).

7. Conclusion

Current evidence suggests that coxibs may have a role in the strategies for both upper and lower GI protection in patients requiring chronic NSAID therapy, and that subjects with high levels of upper GI risk may benefit from combined administration of coxibs plus PPIs. However, the correct management of single patients depends on a careful and balanced assessment of both GI and cardiovascular risk. In this respect, additional clinical research is needed to establish more solid criteria for guiding rational therapeutic choices. Novel therapeutic approaches to GI protection against tNSAIDs are currently under investigation and appear to be far from entering clinical practice.

Conflicts of interest

The authors Corrado Blandizzi, Marco Tuccori, Rocchina Colucci, Matteo Fornai, Luca Antonioli, Narcisa Ghisu, and Mario Del Tacca state that they have no conflict of interest to declare.

References

- [1] Laine L, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology* 2008;135:41–60.

- [2] Laine L, Bombardier C, Hawkey CJ, Davis B, Shapiro D, Brett C, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcome study in patients with rheumatoid arthritis. *Gastroenterology* 2002;123:1006–12.
- [3] Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;123:241–9.
- [4] Naesdal J, Brown K. NSAID-associated adverse effects and acid control aids to prevent them. *Drug Safety* 2006;29:119–32.
- [5] Blandizzi C, Tuccori M, Colucci R, Gori G, Fornai M, Antonioli L, et al. Clinical efficacy of esomeprazole in the prevention and healing of digestive toxicity associated with non-steroidal anti-inflammatory drugs in elderly patients. *Drugs Aging* 2008;25:197–208.
- [6] Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol* 1998;38:97–120.
- [7] Dubois RW, Melmed GY, Henning JM, Laine L. Guidelines for the appropriate use of non-steroidal anti-inflammatory drugs, cyclooxygenase-2-specific inhibitors and proton pump inhibitors in patients requiring chronic anti-inflammatory therapy. *Aliment Pharmacol Ther* 2004;19:197–208.
- [8] Coruzzi G, Venturi N, Spaggiari S. Gastrointestinal safety of novel nonsteroidal anti-inflammatory drugs: selective COX-2 inhibitors and beyond. *Acta Biomed* 2007;78:96–110.
- [9] Patrignani P, Panara MR, Greco A, Fusco O, Natoli C, Iacobelli S, et al. Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. *J Pharmacol Exp Ther* 1994;271:1705–12.
- [10] Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci USA* 1999;96:7563–8.
- [11] Patrono C, Patrignani P, Garcia-Rodriguez LA. Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. *J Clin Invest* 2001;108:7–13.
- [12] Tacconelli S, Capone ML, Sciulli MG, Ricciotti E, Patrignani P. The selectivity of novel COX-2 inhibitors in human whole blood assays of COX-isozyme activity. *Curr Med Res Opin* 2002;18:503–11.
- [13] Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB J* 2004;18:790–804.
- [14] Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins other Lipid Mediat* 2007;82:85–94.
- [15] Rodriguez-Tellez M, Arguelles F, Herrerias Jr JM, Ledro D, Esteban J, Herrerias JM. Antiinflammatory agents less dangerous for gastrointestinal tract. *Curr Pharm Des* 2001;7:951–76.
- [16] Whittle BJ. Gastrointestinal effects of nonsteroidal anti-inflammatory drugs. *Fundam Clin Pharmacol* 2002;17:301–13.
- [17] Jiménez MD, Martín MJ, Alarcón De La Lastra C, Bruseghini L, Esteras A, Herrerias JM, et al. Role of L-arginine in ibuprofen-induced oxidative stress and neutrophil infiltration in gastric mucosa. *Free Radic Res* 2004;38:903–11.
- [18] Allen A, Flemström G. Gastroduodenal mucus bicarbonate barrier: protection against acid and pepsin. *Am J Physiol Cell Physiol* 2005;288:C1–19.
- [19] Takeuchi K, Yagi K, Kato S, Ukawa H. Roles of prostaglandin E-receptor subtypes in gastric and duodenal bicarbonate secretion in rats. *Gastroenterology* 1997;113:1553–9.
- [20] Rossmann H, Bachmann O, Vieillard-Baron D, Gregor M, Seidler U. Na⁺/HCO₃⁻ cotransport and expression of NBC1 and NBC2 in rabbit gastric parietal and mucous cells. *Gastroenterology* 1999;116:1389–98.
- [21] Darling RL, Romero JJ, Dial EJ, Akunda JK, Langenbach R, Lichtenberger LM. The effects of aspirin on gastric mucosal integrity, surface hydrophobicity, and prostaglandin metabolism in cyclooxygenase knockout mice. *Gastroenterology* 2004;127:94–104.
- [22] Lichtenberger LM, Romero JJ, Dial EJ. Surface phospholipids in gastric injury and protection when a selective cyclooxygenase-2 inhibitor (Coxib) is used in combination with aspirin. *Br J Pharmacol* 2007;150:913–9.
- [23] Lichtenberger LM. Where is the evidence that cyclooxygenase inhibition is the primary cause of nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal injury? Topical injury revisited. *Biochem Pharmacol* 2001;61:631–7.
- [24] Wallace JL. Pathogenesis of NSAID-induced gastroduodenal mucosal injury. *Best Pract Res Clin Gastroenterol* 2001;15:691–703.
- [25] Bjarnason I, Scarpignato C, Takeuchi K, Rainsford KD. Determinants of the short-term gastric damage caused by NSAIDs in man. *Aliment Pharmacol Ther* 2007;26:95–106.
- [26] Schneeberger EE, Lynch RD. The tight junction: a multifunctional complex. *Am J Physiol Cell Physiol* 2004;286:C1213–28.
- [27] Joh T, Takezono Y, Oshima T, Sasaki M, Seno K, Yokoyama Y, et al. The protective effect of rebamipide on paracellular permeability of rat gastric epithelial cells. *Aliment Pharmacol Ther* 2003;18(Suppl 1):133–8.
- [28] Oshima T, Miwa H, Joh T. Aspirin induces gastric epithelial barrier dysfunction by activating p38 MAPK via claudin-7. *Am J Physiol Cell Physiol* 2008;295:C800–6.
- [29] Zimmermann KC, Sarbia M, Schror K, Weber AA. Constitutive cyclooxygenase-2 expression in healthy human and rabbit gastric mucosa. *Mol Pharmacol* 1998;54:536–40.
- [30] Langenbach R, Morham SG, Tiano HF, Loftin CD, Ghanayem BI, Chulada PC, et al. Prostaglandin synthase 1 gene disruption in mice reduces arachidonic acid-induced inflammation and indomethacin-induced gastric ulceration. *Cell* 1995;83:483–92.
- [31] Wallace JL, McKnight W, Reuter BK, Vergnolle N. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. *Gastroenterology* 2000;119:706–14.
- [32] Wallace JL. COX-2: a pivotal enzyme in mucosal protection and resolution of inflammation. *Scientific World J* 2006;6:577–88.
- [33] Wallace JL, Devchand PR. Emerging roles for cyclooxygenase-2 in gastrointestinal mucosal defense. *Br J Pharmacol* 2005;145:275–82.
- [34] Devchand PR, Arita M, Hong S, Bannenberg G, Moussignac RL, Gronert K, et al. Human ALX receptor regulates neutrophil recruitment in transgenic mice: roles in inflammation and host defense. *FASEB J* 2003;17:652–9.
- [35] Tarnawski AS. Cellular and molecular mechanisms of gastrointestinal ulcer healing. *Dig Dis Sci* 2005;50(Suppl. 1):S24–33.
- [36] Halter F, Tarnawski AS, Schmassmann A, Peskar BM. Cyclooxygenase 2—implications on maintenance of gastric mucosal integrity and ulcer healing: controversial issues and perspectives. *Gut* 2001;49:443–53.
- [37] Mizuno H, Sakamoto C, Matsuda K, Wada K, Uchida T, Noguchi H, et al. Induction of cyclooxygenase 2 in gastric mucosal lesions and its inhibition by the specific antagonist delays healing in mice. *Gastroenterology* 1997;112:387–97.
- [38] Hatazawa R, Tanaka A, Tanigami M, Amagase K, Kato S, Ashida Y, et al. Cyclooxygenase-2/prostaglandin E₂ accelerates the healing of gastric ulcers via EP₄ receptors. *Am J Physiol Gastrointest Liver Physiol* 2007;293:G788–97.
- [39] Jackson LM, Wu KC, Mahida YR, Jenkins D, Hawkey CJ. Cyclooxygenase (COX) 1 and 2 in normal, inflamed, and ulcerated human gastric mucosa. *Gut* 2000;47:762–70.
- [40] To KF, Chan FKL, Cheng ASL, Lee TL, Ng YP, Sung JY. Up-regulation of cyclooxygenase-1 and -2 in human gastric ulcer. *Aliment Pharmacol Ther* 2001;15:25–34.
- [41] Shigeta J, Takahashi S, Okabe S. Role of cyclooxygenase-2 in the healing of gastric ulcers in rats. *J Pharmacol Exp Ther* 1998;286:1383–90.
- [42] Schmassmann A, Zoidl G, Peskar BM, Waser B, Schmassmann-Suhijar D, Gebbers JO, et al. Role of the different isoforms of cyclooxygenase and nitric oxide synthase during gastric ulcer healing in cyclooxygenase-1 and -2 knockout mice. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G747–56.
- [43] Colucci R, Ghisu N, Antonioli L, Fornai M, Bernardini N, Ippolito C, et al. NSAID activated gene (NAG-1) plays a role in the impairing effects of cyclooxygenase inhibitors on gastric ulcer repair. *Gastroenterology* 2008;134(Suppl 1):A738.
- [44] Whittle BJR. Mechanisms underlying intestinal injury induced by anti-inflammatory COX inhibitors. *Eur J Pharmacol* 2004;500:427–39.
- [45] Yamada T, Deitch E, Specian RB, Perry MA, Sartor RB, Grisham MB. Mechanisms of acute and chronic intestinal inflammation induced by indomethacin. *Inflammation* 1993;17:641–62.
- [46] Robert A, Asano T. Resistance of germfree rats to indomethacin-induced intestinal lesions. *Prostaglandins* 1977;14:333–41.
- [47] Evans SM, Whittle BJ. Interactive roles of superoxide and inducible nitric oxide synthase in rat intestinal injury provoked by non-steroidal anti-inflammatory drugs. *Eur J Pharmacol* 2001;429:287–96.
- [48] Duggan DE, Hooke KF, Noll RM, Kwan KC. Enterohepatic circulation of indomethacin and its role in intestinal irritation. *Biochem Pharmacol* 1975;24:1749–54.
- [49] Reuter BK, Davies NM, Wallace JL. Nonsteroidal anti-inflammatory drug enteropathy in rats: role of permeability, bacteria, and enterohepatic circulation. *Gastroenterology* 1997;112:109–17.
- [50] Petruzelli M, Vacca M, Moschetta A, Cinzia Sasso R, Palasciano G, van Erpecum KJ, et al. Intestinal mucosal damage caused by non-steroidal anti-inflammatory drugs: role of bile salts. *Clin Biochem* 2007;40:503–10.
- [51] Bernardini N, Colucci R, Mattii L, Segnani C, Fornai M, De Giorgio R, et al. Constitutive expression of cyclooxygenase-2 in the neuromuscular compartment of normal human colon. *Neurogastroenterol Motil* 2006;18:654–62.
- [52] Tanaka A, Hase S, Miyazawa T, Ohno R, Takeuchi K. Role of cyclooxygenase (COX)-1 and COX-2 inhibition in nonsteroidal anti-inflammatory drug-induced intestinal damage in rats: relation to various pathogenic events. *J Pharmacol Exp Ther* 2002;303:1248–54.
- [53] Sigthorsson G, Simpson RJ, Walley M, Anthony A, Foster R, Hotz-Behoftsitz C, et al. COX-1 and 2, intestinal integrity, and pathogenesis of nonsteroidal anti-inflammatory drug enteropathy in mice. *Gastroenterology* 2002;122:1913–23.
- [54] Menozzi A, Pozzoli C, Giovannini E, Solenghi E, Grandi D, Bonardi S, et al. Intestinal effects of nonselective and selective cyclooxygenase inhibitors in the rat. *Eur J Pharmacol* 2006;552:143–50.
- [55] Silverstein F, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *J Am Med Assoc* 2000;284:1247–55.
- [56] Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520–8.
- [57] Lisse JR, Perlman M, Johansson G, Shoemaker JR, Schechtman J, Skalky CS, et al. Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial. *Ann Intern Med* 2003;139:539–46.
- [58] Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction

- in ulcer complications: randomized controlled trial. *Lancet* 2004;364:665–74.
- [59] Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-1 study. *Am J Med* 2006;119:255–66.
- [60] Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP, the MEDAL Steering Committee. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomized comparison. *Lancet* 2007;369:465–73.
- [61] Lazzaroni M, Battocchia A, Bianchi Porro G. COXIBs and non-selective NSAIDs in the gastroenterological setting: what should patients and physicians do? *Dig Liv Dis* 2007;39:589–96.
- [62] Ray WA, Chung CP, Stein CM, Smalley WE, Hall K, Arbogast PG, et al. Risk of peptic ulcer hospitalizations in users of NSAIDs with gastroprotective cotherapy versus coxib. *Gastroenterology* 2007;133:790–8.
- [63] Drenth JPH, Verheugt FWA. Do COX-2 inhibitors give enough gastrointestinal protection? *Lancet* 2007;369:439–40.
- [64] Emery P, Zeidler H, Kvien TK, Gulslandi M, Naudin R, Stead H, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison. *Lancet* 1999;354:2106–11.
- [65] Laine L, Harper S, Simon T, Bath R, Johanson J, Schwartz H, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterology* 1999;117:776–83.
- [66] Rostom A, Muir K, Dubé C, Jolicoeur E, Boucher M, Joyce J, et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. *Clin Gastroenterol Hepatol* 2007;5:818–28.
- [67] Hipsley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *Br Med J* 2005;331:1310–6.
- [68] Garcia-Rodriguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. *Gastroenterology* 2007;132:498–506.
- [69] Goldstein JL, Howard KB, Walton SM, MacLaughlin TP, Kruzikas DT. Impact of adherence to concomitant gastroprotective therapy on nonsteroidal-related gastroduodenal ulcer complications. *Clin Gastroenterol Hepatol* 2006;4:1337–45.
- [70] Koch M. Non-steroidal anti-inflammatory drug gastropathy: clinical results with misoprostol. *Ital J Gastroenterol Hepatol* 1999;31(Suppl 1):S54–62.
- [71] Graham DY, Agrawal NM, Campbell DR, Haber MM, Collis C, Lukasik NL, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med* 2002;162:169–75.
- [72] Hawkey CJ, Karrasch JA, Szczepański L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus misoprostol for NSAID-induced ulcer management. *N Engl J Med* 1998;338:727–34.
- [73] Yeomans ND, Tulassay Z, Juhász L, Rácz I, Howard JM, van Rensburg CJ, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. *N Engl J Med* 1998;338:719–26.
- [74] Peura D, Chan FKL, Wilcox CM, Niculescu L, Berger M. The called-for large clinical trial is already ongoing. *Gastroenterology* 2007;134:370–1.
- [75] Targownik LE, Metge CJ, Leung S, Chateau DG. The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. *Gastroenterology* 2008;134:937–44.
- [76] Lanás A, Ferrández A. Inappropriate prevention of NSAID-induced gastrointestinal events among long-term users in the elderly. *Drugs Aging* 2007;24:121–31.
- [77] Lanás A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez-Perez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006;55:1731–8.
- [78] Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. *Gastroenterology* 2004;127:395–402.
- [79] Goldstein JL, Lowry SC, Lanza FL, Schwartz HI, Dodge WE. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor. *Aliment Pharmacol Ther* 2006;23:1489–98.
- [80] Goldstein JL, Aisenberg J, Zakko SF, Berger MF, Dodge WE. Endoscopic ulcer rates in healthy subjects associated with use of aspirin (81 mg q.d.) alone or coadministered with celecoxib or naproxen: a randomised, 1-week trial. *Dig Dis Sci* 2008;53:647–56.
- [81] Chan FK, Graham DY. Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications—review and recommendations based on risk assessment. *Aliment Pharmacol Ther* 2004;19:1051–61.
- [82] Laine L. Proton pump inhibitor co-therapy with nonsteroidal anti-inflammatory drugs: nice or necessary? *Rev Gastroenterol Disord* 2004;4(Suppl 4):S33–41.
- [83] Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib plus aspirin versus naproxen and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. *Clin Gastroenterol Hepatol* 2007;5:1167–74.
- [84] Chan FKL, Hung LCT, Suen BY, Wu JCY, Lee KC, Leung VKS, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002;347:2104–10.
- [85] Chan FKL, Hung LCT, Suen BY, Wong VWS, Hui AJ, Wu JCY, et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. *Gastroenterology* 2004;127:1038–43.
- [86] Lai KC, Chu KM, Hui WM, Wong BCY, Hu WHC, Wong WM, et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *Am J Med* 2005;118:1271–8.
- [87] Hawkey C, Talley NJ, Yeomans ND, Jones R, Sung JJ, Långström G, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors. *Am J Gastroenterol* 2005;100:1028–36.
- [88] Scheiman JM, Yeomans ND, Talley NJ, Vakili N, Chan FK, Tulassay Z, et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006;101:701–10.
- [89] Chan FKL, Wong VWS, Suen BY, Wu JCY, Ching JYL, Hung LCT, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomized trial. *Lancet* 2007;369:1621–6.
- [90] Adebayo D, Bjarnason I. Is nonsteroidal anti-inflammatory drug (NSAID) enteropathy clinically more important than NSAID gastropathy? *Postgrad Med J* 2006;82:186–91.
- [91] Laine L, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2006;24:751–67.
- [92] Fortun PJ, Hawkey CJ. Nonsteroidal anti-inflammatory drugs and the small intestine. *Curr Opin Gastroenterol* 2007;23:134–41.
- [93] Lengeling RW, Mitros FA, Brennan JA, Schulze KS. Ulcerative ileitis encountered at ileo-colonoscopy: likely role of nonsteroidal agents. *Clin Gastroenterol Hepatol* 2003;1:160–9.
- [94] Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005;3:55–9.
- [95] Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. *Gastroenterology* 2005;128:1172–8.
- [96] Goldstein JL, Elsen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin Gastroenterol Hepatol* 2005;3:133–41.
- [97] Goldstein JL, Elsen GM, Lewis B, Gralnek IM, Aisenberg J, Bhadra P, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. *Aliment Pharmacol Ther* 2007;25:1211–22.
- [98] Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology* 2003;124:288–92.
- [99] Cannon CP, Curtis SP, FitzGerald G, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomized comparison. *Lancet* 2006;368:1771–81.
- [100] Nielsen OH, Ainsworth M, Csillag C, Rask-Madsen J. Systematic review: coxibs, non-steroidal anti-inflammatory drugs or no cyclooxygenase inhibitors in gastroenterological high-risk patients? *Aliment Pharmacol Ther* 2006;23:27–33.
- [101] Jones R, Rubin G, Berenbaum F, Scheiman J. Gastrointestinal and cardiovascular risks of nonsteroidal anti-inflammatory drugs. *Am J Med* 2008;121:464–74.
- [102] Warner TD, Mitchell JA. COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. *Lancet* 2008;371:270–3.
- [103] Singh G, Triadafilopoulos G. Appropriate choice of proton pump inhibitor therapy in the prevention and management of NSAID-related gastrointestinal damage. *Int J Clin Pract* 2005;59:1210–7.
- [104] Whittle BJ. Cyclooxygenase and nitric oxide systems in the gut as therapeutic targets for safer anti-inflammatory drugs. *Curr Opin Pharmacol* 2004;4:538–45.
- [105] Fiorucci F, Distrutti E. Cyclo-oxygenase (COX) inhibiting nitric oxide donating (CINODs) drugs: a review of their current status. *Curr Top Med Chem* 2007;7:277–82.
- [106] Bias P, Buchner A, Klesser B, Laufer S. The gastrointestinal tolerability of the LOX/COX inhibitor, licofelone, is similar to placebo and superior to naproxen therapy in healthy volunteers: results from a randomized, controlled trial. *Am J Gastroenterol* 2004;99:611–8.
- [107] Becker JC, Domschke W, Pohle T. Current approaches to prevent NSAID-induced gastropathy—COX selectivity and beyond. *Br J Clin Pharmacol* 2004;58:587–600.
- [108] Anand BS, Romero JJ, Sanduja SK, Lichtenberger LM. Phospholipid association reduces the gastric mucosal toxicity of aspirin in human subjects. *Am J Gastroenterol* 1999;94:1818–22.
- [109] Fiorucci S, Santucci L, Gresele P, Faccino RM, Del Soldato P, Morelli A. Gastrointestinal safety of NO-aspirin (NCX-4016) in healthy human volunteers: a proof of concept endoscopic study. *Gastroenterology* 2003;124:600–7.

- [110] Hawkey CJ, Jones JI, Atherton CT, Skelly MM, Bebb JR, Fagerholm U, et al. Gastrointestinal safety of AZD3582, a cyclooxygenase inhibiting nitric oxide donator: proof of concept study in humans. *Gut* 2003;52:1537–42.
- [111] Wilder-Smith CH, Jonzon B, Fornstedt-Wallin B, Hedman A, Karlsson P. Dose-effect comparisons of the CINOD AZD3582 and naproxen on upper gastrointestinal tract mucosal injury in healthy subjects. *Scand J Gastroenterol* 2006;41:264–73.
- [112] Lohmander LS, McKeith D, Svensson O, Malmenäs M, Bolin L, Kalla A, et al. A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. *Ann Rheum Dis* 2005;64:449–56.