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REVIEW

# Nonsteroidal anti-inflammatory drugs in chronic pain: implications of new data for clinical practice

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**Abstract:** COX2-selective and nonselective (ns) nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for chronic pain management. There are marked differences in the risk of adverse gastrointestinal (GI) and cardiovascular (CV) events among different NSAIDs. In 2017, publication of two randomized controlled trials and an individual patient-data meta-analysis provided robust data on the relative GI and CV tolerability profiles of currently available NSAIDs. The PRECISION study showed similar CV-event rates with celecoxib vs naproxen and ibuprofen, but GI tolerability was better for celecoxib. In the CONCERN study of high-GI-risk patients, celecoxib was associated with fewer adverse GI-tract events than naproxen. The meta-analysis showed no significant difference between celecoxib and ns-NSAIDs in the rate of acute myocardial infarction, and celecoxib was the only COX2-selective NSAID with a lower risk of adverse CV and GI events vs ns-NSAIDs. These data add to the body of knowledge about the relative tolerability of different NSAIDs and were used to propose an updated treatment algorithm. The decision about whether to use an NSAID and which one should be based on a patient's risk of developing adverse GI and CV events. Lower- and upper-GI-tract events need to be considered. Celecoxib has a better lower-GI-tract tolerability profile than ns-NSAIDs plus a proton-pump inhibitor. In addition, the latest data suggest that long-term use of celecoxib 200 mg/day may be appropriate for patients at increased CV risk.

**Keywords:** nonsteroidal anti-inflammatory drugs, chronic pain, COX2 inhibitors, cardiovascular risk, gastrointestinal risk

## Introduction

Chronic pain is defined by the International Association for the Study of Pain as "pain that persists beyond normal tissue healing time, which is assumed to be 3 months".[1] Chronic pain is one of the most prominent causes of disability worldwide and represents a major challenge for public health.[2] Patients with chronic pain report that this has a significant impact on their work and daily function.[3] The presence of inflammation is a common underlying mechanism of chronic pain.[4] Inflammation can occur in the affected organ and/or nerves.[5] Low-grade inflammation, both local and systemic, is also the hallmark of many chronic, progressing, and painful conditions, such as osteoarthritis (OA) and rheumatoid arthritis (RA).[6,7]

Existing guidelines recommend paracetamol (acetaminophen) as the first-line analgesic agent.[8–10] However, this is not an ideal choice for chronic inflammatory pain, because paracetamol lacks anti-inflammatory activity and has been shown to be less effective than alternative nonopioid options in chronic conditions involving connective tissue.[11–14] In addition, although traditionally seen as a better-tolerated analgesic

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option, there are safety concerns with the use of paracetamol, particularly at dosages >3 g/day, for extended periods (eg, several years).[15–20]

COX2-selective (c2s) and nonselective (ns) nonsteroidal anti-inflammatory drugs (NSAIDs), which display both analgesic and anti-inflammatory properties, are useful options for the management of chronic pain. However, use of these agents is limited by side effects, specifically adverse gastrointestinal (GI) and cardiovascular (CV) events.[6] Nevertheless, it is increasingly being recognized that adverse NSAID-related events, including those associated with c2s agents, are not a class effect and vary substantially among different drugs. One example of this is etodolac, which has been shown in vitro to be more c2s than celecoxib,[21] but like indomethacin, ketorolac, sulindac, and tolmetin is classified as a carbo- or heterocyclic acid based on chemical structure.[22]

All NSAIDs are inherently acidic, but there is wide interagent variation. The acid-dissociation constant (pKa) for celecoxib is 9.7 compared with 5.2, 4.2, and 4.0 for ibuprofen, naproxen and diclofenac, respectively[23,24] (lower pKa values indicate higher acidity). As weak acids, ns-NSAIDs are invariably lipophilic, providing them with detergent properties. Detergent properties allow these agents to interact with phospholipids, which are essential constituents of the brush border. This causes direct damage to the surface epithelium.[25] Another way that the acidity of different NSAIDs could contribute to between-agent differences in activity and toxicity is the intracellular accumulation of an NSAID being proportional to its acidity. At micromolar concentrations, NSAIDs are able to uncouple oxidative phosphorylation, which reduces intracellular ATP production. This results in the loss of intercellular integrity, because intercellular junctions are under the control of ATP-dependent actin–myosin complexes, leading to increased intestinal permeability and inflammatory enteropathy.[25] On this basis, less acidic drugs would be expected to have fewer adverse GI effects.

Different NSAIDs also have different molecular structures and chemical properties. Diclofenac is a benzeneacetic derivative, ibuprofen and naproxen are propionic acid derivatives, celecoxib and valdecoxib have a sulfonamide group, and etoricoxib and rofecoxib have a sulfonyl group.[26] c2s-NSAIDs with a sulfonyl group increase the susceptibility of biological lipids (eg, low-density-lipoprotein cholesterol) to oxidative modification via a nonenzymatic process independently of COX2 inhibition, an effect not seen for c2s-NSAIDs with a sulfonamide group or ns-NSAIDs.[27] Oxidation of LDL is an important factor contributing to the development of atherosclerotic CV disease.

This consensus document provides an overview of the latest published data on the long-term use of NSAIDs commonly used for the management of chronic pain of musculoskeletal origin, with a focus on GI and CV risk and safety. The aim was to discuss the latest clinical trial data and use these to provide an evidence-based consensus on the most appropriate NSAID options for different groups of patients with chronic pain and propose an updated treatment algorithm.

## Latest clinical trial data

Relevant studies that have been published since the last consensus document in this field are the PRECISION[28] and CONCERN[29] clinical trials and a meta-analysis of individual patient data authored by Bally et al.[30] The PRECISION trial was the first study of NSAIDs in high-CV-risk patients and the first to compare a c2s agent with naproxen and ibuprofen.[28] All three NSAIDs provided effective pain relief in patients with OA or RA (with no clinically significant differences between groups). Celecoxib was noninferior to naproxen and ibuprofen for the primary CV-event end point and was associated with significantly fewer GI and serious renal events compared with the ns-NSAIDs.[28]

The focus of the CONCERN study was adverse GI events.[29] The trial included patients with arthritis who also had cardiothrombotic diseases requiring low-dose aspirin and a history of upper-GI-tract bleeding. Subjects were randomized to celecoxib 100 mg twice daily or naproxen 500 mg twice daily, both in combination with a prophylactic proton-pump inhibitor (PPI). The primary end point was recurrent upper-GI-tract bleeding within 18 months. The cumulative incidence of primary end-point events with celecoxib was less than half that with naproxen. The rate of serious CV events (a secondary end point of the trial) did not differ significantly between the two treatment groups.[31] The key features and results of the PRECISION and CONCERN studies, along with the earlier MEDAL program that looked at long-term use of etoricoxib, are summarized in Table 1.

The individual patient-data meta-analysis published by Bally et al included clinical trials of ns- and c2s-NSAIDs that had acute myocardial infarction (MI) as a specific outcome, and compared the rate of this adverse event in NSAID users vs nonusers.[30] All the NSAIDs studied (celecoxib, diclofenac, naproxen, ibuprofen, and rofecoxib) increased the risk of acute MI compared with no NSAID use, but there were no significant differences in the risk of acute MI between celecoxib (adjusted OR 1.24, 95% CI 0.91–1.82) and ns-NSAIDs (OR 1.50 [95% CI 1.06–2.04] for diclofenac, OR 1.48 [95% CI 1.00–2.26] for ibuprofen, and OR 1.53 [95% CI

**Table 1** Overview of recent key clinical trials of COX2 inhibitors vs nonselective NSAIDs

| | PRECISION[28] | MEDAL[51] | CONCERN[29] |
|---|---|---|---|
| Investigational agent | Celecoxib 100 mg BID (n=8,072) | Etoricoxib 90 mg once daily (n=11,787) | Celecoxib 100 mg BID (n=257) |
| Comparator | Naproxen 375 mg BID (n=7,969) or ibuprofen 600 mg TID (n=8,040) | Diclofenac 75 mg BID (n=11,717) | Naproxen 500 mg BID (n=257) |
| Design | Randomized, double-blind, parallel | Randomized, double-blind, parallel | Randomized, double-blind, parallel |
| Key inclusion criteria | Age ≥18 years RA or OA requiring daily NSAIDs High CV risk/established CV disease | Age ≥50 years RA or OA requiring chronic NSAIDs | Arthritis pain not relieved by basic analgesics Previous upper-GI bleeding during NSAID use Requirement for low-dose aspirin, or multiple CV risk factors |
| Aspirin use | Allowed (46% of patients) | Recommended | Recommended for all patients (used by 72%) |
| PPI use | Esomeprazole 20–40 mg once daily | Recommended | Esomeprazole 20 mg once daily |
| Primary end point | First occurrence of APTC event composite (noninferiority) | Thrombotic CV-event composite (noninferiority) | Recurrent GI bleeding within 6 months |
| Duration of therapy | Mean 20.3±16.0 months | Mean 19.4–20.8 months | Median 18 months |
| CV events | Primary-outcome event rates: 2.3%, 2.5%, and 2.7% for celecoxib, naproxen, and ibuprofen, respectively. HR (95% CI) 0.93 (0.76–1.12) for celecoxib vs naproxen, 0.85 (0.70–1.04) for celecoxib vs ibuprofen, and 1.08 (0.90–1.31) for ibuprofen vs naproxen (noninferiority $P$-values <0.001, <0.001, and<0.02, respectively) Results were consistent across subgroups based on low-dose aspirin use, indication for treatment, and in patients with or without existing CV disease | The HR for thrombotic events with etoricoxib vs diclofenac was 0.96 (95% CI 0.81–1.15). The upper bound of the 95% CI was well below the prespecified noninferiority bound of 1.30 Results for the subgroup of patients on low-dose aspirin were consistent with those for the overall population (HR 0.89, 95% CI 0.69–1.14) for etoricoxib vs diclofenac, although there was a slightly greater numerical risk reduction for etoricoxib vs diclofenac in the subgroup of patients on low-dose aspirin compared with the overall study population | The cumulative rate of serious CV events at 6 months was 4.4% (85% CI 2.4%–7.7%) in the celecoxib group and 5.5% (95% CI 3.3%–9.2%) in the naproxen group ($P$=0.543; crude HR 0.78, 95% CI 0.36–1.73; $P$=0.544) |
| GI events | CSGIE event rates were 0.5%, 0.7%, and 0.9% in the celecoxib, naproxen and ibuprofen groups, respectively HR (95% CI) for CSGIE end point 0.97 (0.67–1.40, $P$=0.86) for celecoxib vs naproxen and 0.76 (0.53–1.08, $P$=0.12) for celecoxib vs ibuprofen Composite CSGIE and iron-deficiency anemia of GI origin event rates were 1.1%, 1.5%, and 1.6% in the celecoxib, naproxen, and ibuprofen groups, respectively; HR for composite GI adverse-event end point 0.71 for celecoxib vs naproxen ($P$=0.01) and 0.65 for celecoxib vs ibuprofen ($P$=0.002) | Discontinuations due to GI adverse events were significantly less frequent with etoricoxib than diclofenac Rates of lower-GI clinical events were similar for the two drugs: 0.32 (95% CI 0.25–0.39) per 100 patient-years for etoricoxib and 0.38 (95% CI 0.31–0.46) per 100 patient-years for diclofenac (HR 0.84, 95% CI 0.63–1.13) | Cumulative incidence of recurrent bleeding was 5.6% (95% CI 3.3%–9.2%) in the celecoxib group and 12.3% (8.8%–17.1%) in the naproxen group ($P$=0.008; crude HR 0.44, 95% CI 0.23–0.82; $P$=0.010) |

**Abbreviations:** APTC, Antiplatelet Trialists' Collaboration; BID, bis in die (twice daily); CSGIE, clinically significant GI event; CV, cardiovascular; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PPI, proton-pump inhibitor; RA, rheumatoid arthritis; TID, ter in die (thrice daily).

1.07–2.33] for naproxen; the rate was highest with rofecoxib [OR 1.58 [95% CI 1.07–2.17]). The acute MI risk appeared to be dependent on the NSAID dosage, but not the duration of therapy, with usage for longer than 1 month associated with risk similar to shorter therapy durations.[30]

# Cardiovascular side effects of NSAIDs

Concerns about the CV safety of c2s-NSAIDs first appeared when the VIGOR trial demonstrated a significantly increased risk of thromboembolic CV events with rofecoxib vs naproxen (relative risk 2.38, 95% CI 1.39–4.00; $P<0.05$).[32,33] Rofecoxib was also shown to increase the number of Antiplatelet Trialists' Collaboration events compared with placebo in the APPROVE trial (HR 4.61, 95% CI 1.50–18.83; $P=0.008$).[34] Results from these studies led to the worldwide withdrawal of rofecoxib in 2004.

The Fitzgerald hypothesis suggested that increased platelet activation and aggregation occurring via selective blockade of prostacyclin formation with little inhibition of prothrombotic platelet-derived thromboxane $A_2$ ($TXA_2$) was the primary mechanism for increased CV risk with c2s-NSAIDs.[35,36] However, COX2 selectivity varies among c2s-NSAIDs, being greater for lumiracoxib, rofecoxib, etoricoxib, and valdecoxib and comparatively lower for celecoxib.[37] In addition, other potential mechanisms might influence the CV risk of an NSAID. For example, rofecoxib has prooxidant activity (potentially proatherosclerotic) and celecoxib reduces endothelial tissue-factor expression, a key initiator of the coagulation cascade (potentially protective against thrombosis).[38,39]

The CLASS[40] trial showed a similar risk of adverse thromboembolic CV events with celecoxib 400 mg twice daily (a dose twice that recommended in RA and four times that recommended in OA) compared with diclofenac.[41] Of note, 22% of the CLASS population were taking low-dose aspirin and 40% had a history of CV disease, and thus, a reasonable proportion were at risk of having a CV event during the 1-year trial.[41] Around the same time, the results of the VIGOR study reported lower rates of MI with naproxen vs rofecoxib (RR 0.2, 95% CI 0.1–0.7), although the CV death rate was similar in the two groups.[32] However, there were concerns that some MI events in rofecoxib recipients were not included in the published paper, leading to an underestimation of the between-group difference in the rate of this adverse event.[42] Note that patients included in the CLASS study had OA, whereas the VIGOR study included patients with RA, a population that is at higher theoretical risk of

thromboembolic disease, due to the association between chronic inflammatory mediators and prothrombotic factors and endothelial dysfunction.[43] Furthermore, the comparator agent in VIGOR was naproxen, which may protect against thromboembolic disease.[44] In contrast, it has been suggested that diclofenac (the comparator in the CLASS study) may have some intrinsic prothrombotic effects, limiting the ability to detect a difference between celecoxib and diclofenac with respect to the rate of thrombotic events.[33] Data from the CLASS trial have been presented to show the incidence of MI in patients who were vs were not receiving low-dose aspirin because of the thromboembolic protection provided by aspirin and the fact that those not taking aspirin were presumably at lower risk of thromboembolic events when enrolled in the trial.[33] In patients not receiving concomitant aspirin, rates of fatal and nonfatal MI were 0.2% and 0.1%, respectively, in the celecoxib and diclofenac groups (compared with 0.5% and 0.2%, respectively, in the overall population). It is also important to note that the latest analysis of PRECISION trial data showed that celecoxib had a more favorable overall safety profile than naproxen or ibuprofen when not taken with aspirin.[45] The safety advantage of celecoxib over the ns-NSAIDs was attenuated by the addition of aspirin, although celecoxib was still associated with fewer GI events than ibuprofen or naproxen and fewer renal events than ibuprofen.[45]

In contrast, a review of all potentially serious CV events among 2,035 patients with a history of colorectal neoplasia who were enrolled in a trial comparing two doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal adenomas showed a dose-dependent increase in the composite end point of CV death, MI, stroke, or heart failure in celecoxib recipients, resulting in early trial termination.[46] The celecoxib doses used in this study were high compared to those used for chronic pain management (eg, in RA or OA). Another study with a similar indication (prevention of colorectal adenomatous polyps) failed to find any significant difference in the serious CV-event rate with celecoxib 400 mg once daily vs placebo (RR 1.3, 95% CI 0.65–2.62). In the ADAPT study, use of naproxen 220 mg twice daily was associated with a 60% increase in the risk of MI, congestive heart failure, cerebrovascular accident or transient ischemic attack compared with placebo (HR 1.40, 95% CI 1.12–1.75; $P<0.05$), but the higher rate of CV events in the celecoxib group (200 mg twice daily) did not reach statistical significance (HR 1.10, 95% CI 0.67–1.79).[47] However, it should be noted that safety was not a prespecified end point in this trial.

On April 7, 2005, the US Food and Drug Administration (FDA) added a black-box warning for all NSAIDs (both c2ns and c2s) highlighting the risk of adverse CV events. In the CNT collaboration study, the only NSAID that did not increase vascular risk was naproxen,[48] but the FDA maintained the black-box warning for all NSAIDs. There are several differences between rofecoxib and celecoxib that might account for the different trial outcomes[26,39] and suggest that increased risk of CV events might not be a class effect of c2s-NSAIDs (Table 2).

Data from an FDA nested case–control study using a US managed-care organization database showed that the risk of acute MI and sudden death was by far the highest with rofecoxib at doses >25 mg.[49] The only other NSAIDs associated with a significant increase in CV risk compared with control were indomethacin and diclofenac.[49] In a meta-analysis, celecoxib and valdecoxib were the only two c2s-NSAIDs that were associated with lower CV- and GI-event rates than ns-NSAIDs.[50] Based on the data analyzed,

treatment of 1,000 patients for a year with celecoxib rather than with an ns-NSAID would be associated with 12 fewer upper-GI-tract complications and two fewer fatal or non-fatal MIs or strokes.[50] The MEDAL program was the first CV-outcome analysis prospectively designed to evaluate the relative thrombotic CV risk of a c2s inhibitor and a traditional NSAID.[51] The results showed no difference in risk of thrombotic CV events in arthritis patients on long-term therapy with etoricoxib or diclofenac. However, both drugs increased blood pressure, and the rate of discontinuation due to hypertension was higher in the etoricoxib group.[51] As already described, the PRECISION trial did not show any increased CV risk with celecoxib compared with naproxen or ibuprofen.[28]

There were a number of differences between the MEDAL and PRECISION studies (Table 1), including lower overall CV risk, less aspirin use, and less use of gastroprotective therapy in patients in the MEDAL trial. In addition, and perhaps most importantly, the ns-NSAID comparator in

**Table 2** Differential features of celecoxib, etoricoxib, and rofecoxib

| Celecoxib | | Etoricoxib | | Rofecoxib | |
|---|---|---|---|---|---|
| **Characteristics** | **Clinical implications** | **Characteristics** | **Clinical implications** | **Characteristics** | **Clinical implications** |
| Sulfonamide structure | No effect on lipid-oxidation susceptibility | Methylsulfone structure | Increased lipid-oxidation susceptibility → increased risk of atherosclerosis | Methylsulfone structure | Increased lipid-oxidation susceptibility → increased risk of atherosclerosis |
| Lower COX2 selectivity | Lower levels of COX2 inhibition associated with lower thrombotic risk | ~14 times greater COX2 selectivity vs celecoxib | Thrombotic risk higher with higher levels of COX2 inhibition and lower levels of COX1 inhibition | Fivefold-greater COX2 selectivity vs celecoxib | Thrombotic risk higher with higher levels of COX2 inhibition and lower levels of COX1 inhibition |
| Lower acidity (pKa 9.7) | Low intestinal permeability and less GI damage | Moderate acidity (pKa 4.5) | Greater intestinal permeability and risk of GI damage | Intermediate acidity (pKa 8.6) | Intermediate intestinal permeability and risk of GI damage |
| Shorter elimination half-life | Lesser impact on CV and renal function due to short-acting COX2-inhibitory activity | Elimination half-life twice as long vs celecoxib | Greater impact on CV and renal function due to persistent inhibition of COX2 | Elimination half-life ~1.5 times to twice as long vs celecoxib | Greater impact on CV and renal function due to persistent inhibition of COX2 |
| Less relative inhibition of prostaglandin synthesis | Risk of elevated blood pressure or development of hypertension similar to ns-NSAIDs | Moderate inhibition of prostaglandin synthesis | Increased risk of elevated blood pressure or development of hypertension vs celecoxib | Greater relative inhibition of prostaglandin synthesis | Greatest risk of elevated blood pressure or development of hypertension of all NSAIDs |
| No effect on endothelial nitric oxide expression | Endothelial function improved or maintained | NA | NA | Significantly reduces endothelial nitric oxide expression | Impaired endothelial function |

**Note:** Data from these studies.[16,23,26,48,61,87,92–101]
**Abbreviations:** CV, cardiovascular; GI, gastrointestinal; NA, not available; ns, nonselective; NSAIDs, nonsteroidal anti-inflammatory drugs.

MEDAL was diclofenac, whereas naproxen and ibuprofen were used in PRECISION. This choice of comparator for PRECISION was made because naproxen had been shown to be the ns-NSAID associated with the lowest vascular risk (followed by ibuprofen).[13,48,52] In addition, the Arthritis and Drug Safety and Risk Management Advisory Committee of the US FDA recommended in 2005 that naproxen be the preferred comparator for large trials of c2s-NSAIDs. The FDA voted against approval of etoricoxib, based on the fact that CV-safety studies were conducted using diclofenac as the comparator.[53] In a recently published trial, SCOT,[54] there was no difference in the incidence of adverse CV events between celecoxib and ns-NSAIDs; similar results were seen in an observational Japanese study of patients with RA or OA.[55]

Assessment of a patient's CV risk is mandatory before initiation of NSAID therapy. Patients with New York Heart Association class I or II heart failure were included in the PRECISION study,[28] and the results demonstrated acceptable long-term CV tolerability with the use of NSAIDs in this patient group. The results of a meta-analysis based on pooled individual patient data (n=446,763) supported the main conclusions of the PRECISION study in terms of noninferiority of CV risk with celecoxib compared with ibuprofen or naproxen.[30] Other important findings of the meta-analysis were that NSAID-related CV risk was greater when daily doses were higher, CV risk did not appear to increase as duration of NSAID therapy increased, and the risk of MI during the use of rofecoxib (especially at >25 mg/day) was greater than that associated with use of any other NSAID, including celecoxib.[30] It is suggested that physicians should use adequate, but not high, doses of c2s-NSAIDs, to obtain analgesic and anti-inflammatory benefit without markedly increasing CV risk.

## Gastrointestinal side effects of NSAIDs

Potential GI side effects of NSAID therapy are a concern for physicians. Traditionally, adverse upper-GI-tract effects have been the focus, but there is increasing recognition that lower-GI complications are also an important issue.[56–58] Infection with *Helicobacter pylori* is also relevant and may be more common in some populations.[59–61] *H. pylori* infection increases the risk of GI complications during NSAID therapy,[62] and eradication of *H. pylori* prior to commencing long-term antiplatelet therapy is recommended to reduce GI risk.[63]

Other risk factors for upper-GI-tract complications during NSAID therapy include older age (≥60 years), history of dyspepsia, concomitant use of corticosteroids and/or oral anticoagulants, and a history of peptic ulcer bleeding.[64] In the last few decades, mortality rates in patients with NSAID-associated upper-GI bleed or perforation have increased.[65] Serious GI complications necessitating emergency surgery or hospitalization can occur without prior symptoms. Approximately 60%–80% of arthritis patients hospitalized or requiring surgery for serious GI complications during NSAID therapy report no previous GI symptoms.[66,67] This highlights the need for a proactive approach to risk management, given that lack of symptoms makes it difficult to intervene before GI events become life-threatening.

NSAIDs are associated with different GI risks, and it is important that this is taken into account in clinical practice. Data from a nested case–control study showed that celecoxib was the only NSAID that did not have a significantly higher rate of upper-GI-tract events compared with placebo.[68] In contrast, the risk of adverse upper-GI-tract events with rofecoxib, ibuprofen, diclofenac, naproxen, and aspirin was significantly higher than in controls.[68] Celecoxib has also been shown to be associated with a significantly lower rate of GI intolerability than naproxen, ibuprofen, or diclofenac in elderly patients (age ≥65 years).[69]

The addition of a PPI for ulcer prophylaxis significantly decreases the proportion of NSAID recipients who will develop a gastric or duodenal ulcer during chronic NSAID therapy.[6,58,70,71] In very high-risk subjects (defined as those who had previous NSAID-induced ulcer bleeding and continued need for anti-inflammatory analgesics), combining celecoxib with PPI provides even greater gastroprotection (cumulative incidence of recurrent ulcer bleeding over 13 months' follow-up: 0% for celecoxib+ esomeprazole vs 8.9% for celecoxib alone; $P$=0.0004).[31] However, PPIs do not have any protective effects in the lower GI tract.[58,72,73] It is also important to note that PPIs are not a risk-free therapy, and thus, care needs to be taken in the setting of long-term PPI use.[58] Adverse events associated with a PPI include increased risk of *Clostridium difficile* infection and hospital-acquired pneumonia, hypersensitivity with resulting organ damage (eg, interstitial nephritis), increased fractures in postmenopausal women, altered absorption of vitamins and minerals, increased risk of CV complications, and potential for drug interactions.[74–78] In addition, PPI treatment has been shown to increase the incidence of small-intestine bacterial overgrowth.[79]

Epidemiological data from Spain showed that although the number of NSAID-related GI events decreased over the period 1996–2005 (probably due to the addition of PPI

therapy), there was a corresponding increase in the number of lower-GI-tract events associated with NSAID use.[80] NSAID-induced enteropathy and bleeding may occur more often than NSAID-induced gastropathy.[81,82] One study estimated that approximately 70% of chronic NSAID users have significant small-intestine damage and bleeding.[56,57] In addition, lower-GI-tract events are more severe than upper-GI-tract events in terms of higher mortality rate, prolonged length of hospital stay, and more diagnostic tests required.[80]

The most likely mechanism for lower-GI-tract damage with ns-NSAIDs is increased lower-GI-tract mucosal permeability and inflammation.[83] ns-NSAIDs cause direct damage to the surface epithelium, increasing intestinal permeability, which results in a tissue reaction known as inflammatory enteropathy.[25] Anemia, occult blood loss, malabsorption, and protein loss are common.[83] Clinically significant GI bleeding, perforation, diarrhea, mucosal ulceration, diverticular disease, and strictures may also occur.[83] Capsule-endoscopy studies have increased understanding of the adverse lower-GI-tract effects of NSAIDs, with one showing biochemical and direct evidence of macroscopic injury to the small intestine in 68%–75% of volunteers after 2 weeks' treatment with slow-release diclofenac.[84] Such changes appear to develop even after the addition of a PPI.[72,73,85]

Lower-GI-tract injury has been shown to be significantly lower with celecoxib 200 mg twice daily compared with either naproxen 500 mg twice daily or ibuprofen 800 mg three times daily, both given in combination with omeprazole.[72,73] The CONDOR study was a randomized, double-blind trial comparing *H. pylori*-negative OA or RA patients with high GI and low CV risk treated with celecoxib 200 mg twice daily or diclofenac SR 75 mg twice daily with omeprazole 20 mg once daily for 6 months.[86] A composite of clinically significant adverse upper- and lower-GI-tract events was the primary end point. The cumulative proportion of primary end-point events was significantly lower in patients receiving celecoxib compared with the diclofenac and omeprazole group (0.9% vs 3.8%, *P*<0.0001). The lower rate of adverse GI events with celecoxib was evident from 1 month of therapy onward.[86] The same clinically significant upper- and lower-GI-tract event end point was used in the GI-REASONS study, in which approximately 8,000 patients in the US were randomized to celecoxib 200 mg once daily or ns-NSAIDs for 6 months (dosages could be adjusted based on US prescribing information).[87] The rate of primary end-point events was significantly lower in the celecoxib group (1.3%) than in patients treated with ns-NSAIDs (2.4%, *P*=0.0003).[87] In the MEDAL study, upper-GI-tract tolerability of etoricoxib was significantly better than that of diclofenac, but there was no significant difference between the two groups with respect to the cumulative incidence of lower-GI-tract clinical events (bleeding, perforation, or obstruction).[88]

GI safety was investigated in the PRECISION trial, which had clinically significant GI events as a secondary outcome and iron-deficiency anemia of GI origin as a tertiary outcome.[28] GI outcomes for the on-treatment population showed that among the three agents studied (celecoxib, naproxen, and ibuprofen), significantly fewer clinically significant GI events occurred in the celecoxib group. Similarly, there was a lower incidence of anemia in celecoxib recipients compared with those receiving ns-NSAIDs.[28]

In the CONCERN study on arthritis patients with both high GI and high CV risk, the cumulative incidence of recurrent upper-GI-tract bleeding (the primary end point) was 5.6% in the celecoxib group compared with 12.3% in the naproxen group (HR 0.44, 95% CI 0.23–0.82; *P*=0.01), and no treatment-related deaths occurred. On the basis of their findings, the authors suggested that naproxen be avoided in high-GI/high-CV-risk patients, "despite its perceived cardiovascular safety".[29]

## Treatment recommendations – an update

Prior to publication of the PRECISION trial, the most recent consensus document on NSAID use and the balance between GI and CV risks was by Scarpignato et al.[6] Key treatment-related recommendations and levels of evidence from that paper are summarized in Table 3, and quality grading for levels of evidence is defined in Table 4. The risk of adverse events throughout the GI tract not being prevented by PPIs, better GI-tolerability profile of celecoxib, and the similarity of celecoxib to ns-NSAIDs in terms of CV risk were statements made in that document. This is consistent with the results of a systematic review of data from and meta-analyses of randomized controlled trials that showed that celecoxib and valdecoxib were the only NSAIDs associated with lower rates of both GI and CV adverse events compared with ns-NSAIDs.[50] In contrast, although the rate of GI events was lower with other c2s-NSAIDs (including etoricoxib and rofecoxib), the rate of CV events was higher than with ns-NSAIDs.[50]

Given the new findings from PRECISION,[28] CONCERN,[29] and the most recent meta-analysis by Bally et al,[30] an updated and simplified treatment algorithm has been proposed (Figure 1). The decision on whether to use an NSAID and the choice of NSAID should be based on a patient's risk of developing adverse GI and CV events. However, the new

**Table 3** Summary of NSAID treatment-related statements from consensus guidelines by Scarpignato et al[6]

| Statement | Level of evidence[a] |
|---|---|
| Analgesic efficacy of ns-NSAIDs and c2s inhibitors in pain is comparable in patients with OA or RA | A |
| NSAID use associated with increased risk of adverse events throughout the entire GI tract; this is associated with substantial mortality | A |
| NSAID-induced adverse events in the lower-GI tract not prevented by PPIs | B |
| Celecoxib associated with fewer adverse events throughout the entire GI tract compared to ns-NSAIDs | A |
| Combination of celecoxib plus low-dose aspirin associated with lower risk of adverse events in upper-GI tract compared with ns-NSAIDs plus low-dose aspirin | B |
| Risk of CV events associated with celecoxib use is similar to that associated with the use of most ns-NSAIDs | A[b] |
| c2s inhibitors do not interfere with the antiplatelet effect of low-dose aspirin | A |

**Notes:** [a]Levels of evidence defined in Table 4; [b]PRECISION results consistent with this statement, and thus the study contributes to the high level of evidence for this statement.
**Abbreviations:** CV, cardiovascular; GI, gastrointestinal; ns, nonselective; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PPIs, proton-pump inhibitors; RA, rheumatoid arthritis; c2s, COX2-selective.

**Table 4** Evidence-quality grading based on the GRADE system

| Evidence level | Study design | Study execution | Consistency | Evidence directness |
|---|---|---|---|---|
| A | Pairwise meta-analysis of comparative RCTs (interventions) RCTs (interventions) Non-randomized studies (diagnosis and prognosis) | No important flaws | Consistent | Direct or strong indirect |
| B | Meta-analysis of RCTs or RCTs (interventions) Non-randomized studies (diagnosis and prognosis) | Important flaw OR inconsistent OR weak indirect | | |
| | Non-randomized controlled studies (interventions) | No important flaws | Consistent direct OR strong indirect | |
| C | Non-randomized controlled studies (interventions) | Important flaw OR inconsistent OR weak indirect | | |
| D | Meta-analyses or RCTs with a combination of important flaws AND inconsistency AND/OR indirect evidence Other evidence (not expert opinion) | | | |
| E | Expert opinion | | | |

**Abbreviation:** RCTs, randomized controlled trials.

algorithm takes into consideration data showing that adverse lower-GI-tract events need to be considered during NSAID therapy, that the risk of adverse CV events is similar with celecoxib and naproxen/ibuprofen at the dosages used in the PRECISION trial,[28] the lack of any significant difference in the rate of acute MI between celecoxib and ns-NSAIDs,[30] and the suggestion that naproxen should be avoided in high-GI/high-CV-risk patients.[29] Based on these data, celecoxib appears to be the c2s-NSAID with the best tolerability profile. However, direct comparisons between celecoxib and etoricoxib are lacking. Nevertheless, the facts that etoricoxib contains a sulfonyl group (like rofecoxib) and the NSAID comparator in the MEDAL program was diclofenac (rather than the better-tolerated agents naproxen and ibuprofen) need

to be taken into account when assessing the available evidence and applying it in clinical practice. Based on the latest data, long-term use of celecoxib 200 mg/day may be appropriate for patients at increased CV risk. However, the 2007 scientific statement from the American Heart Association stating that COX2 inhibitors should be used at the lowest possible dose and for the shortest possible time to minimize the risk of CV events remains valid.[89]

The consideration of both upper- and lower-GI risk is also very important. Given the increased risk of lower-GI-tract side effects with all ns-NSAIDs and the inability of PPIs to protect against these adverse effects, the algorithm considered ns-NSAIDs inappropriate for use in a patient with high GI risk (Figure 1). Of the c2s agents, celecoxib has consistently
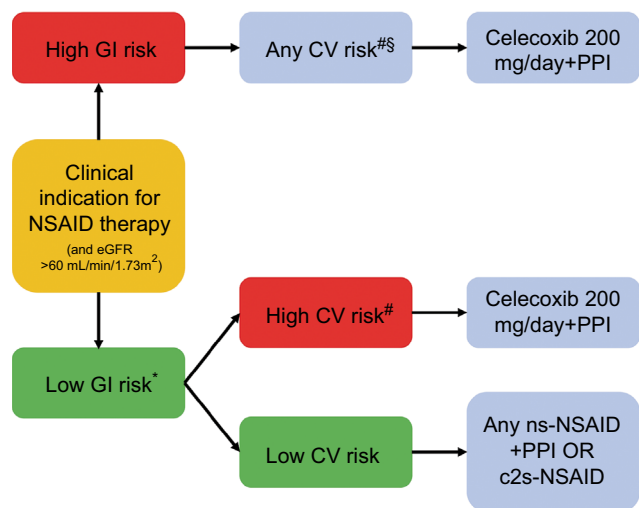
**Figure 1** Updated simplified treatment algorithm for the use of NSAIDs in different patient groups.
**Notes:** *Assess upper- and lower-GI risk and note that PPIs do not prevent lower GI-tract NSAID-related side effects; #celecoxib currently contraindicated in patients with existing CVD, and all NSAIDs should be avoided in these patients; §recommendations the same, irrespective of CV-risk status.
**Abbreviations:** CV, cardiovascular; CVD, CV disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; ns, nonselective; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

been shown to have a better lower-GI-tract tolerability profile than ns-NSAIDs ± PPI,[86,90,91] but etoricoxib is not superior to ns-NSAIDs with respect to lower-GI-tract tolerability.[88]

## Conclusion

The choice of NSAID for an individual patient should be based on their risk of developing both GI and CV adverse events. Based on the latest published evidence, both lower- and upper-GI adverse events need to be considered when evaluating the tolerability profile of NSAIDs. The latest published evidence suggests that celecoxib is associated with a lower risk of both upper- and lower-GI-tract side effects than ns-NSAIDs. In addition to the choice of NSAID, use of prophylactic PPIs and eradication of *H. pylori* can help improve GI tolerability, particularly for preventing adverse upper-GI-tract events. Data from the most recent studies on long-term use of moderate doses of celecoxib showed that it also has a favorable CV-risk profile that is not worse than ns-NSAIDs.

## Acknowledgments

## Author contributions

## Disclosure

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