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Management of Patients on Nonsteroidal Anti-inflammatory Drugs: A Clinical Practice Recommendation From the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents

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BACKGROUND: Prescribing nonsteroidal antiinflammatory drugs (NSAIDs) is challenging because physicians have to consider gastrointestinal (GI) and cardiovascular (CV) safety issues.

OBJECTIVE: The purpose of the study was to determine appropriate NSAID treatment strategies based on different combinations of GI and CV risks.

METHODS: The working party comprised a multidisciplinary international panel of 19 experts. Two hundred eighty-eight vignettes were evaluated for the appropriateness of each of six options: naproxen, non-naproxen nonselective NSAIDs, naproxen plus proton pump inhibitor (PPI)/misoprostol, non-naproxen nonselective NSAID plus PPI/misoprostol, cyclooxygenase-2 selective NSAID (coxib), or coxib plus PPI/misoprostol. Using a two-stage modified Delphi process, the panel anonymously ranked the appropriateness of each option from 1 (extremely inappropriate) to 9 (extremely appropriate). Vignettes were considered appropriate if $\geq$80% of all panelists' scores were 7–9 and inappropriate if $\geq$80% of all panelists' scores were 1–3.

RESULTS: The panel rated nonselective NSAIDs as appropriate when the patient had average GI risk ($<$70 yr of age; no prior upper GI event; no corticosteroids, antithrombotic agents, anticoagulants). In patients with GI risk factors, cotherapy with a PPI/misoprostol was appropriate. Either a nonselective NSAID or a coxib was rated appropriate in patients with average CV risk; naproxen was preferred in patients with high CV risk. None of the options was considered appropriate in patients with multiple GI risk factors and high CV risk.

CONCLUSIONS: The initial choice of an NSAID (naproxen *vs.* others) relates to a patient's CV risk, and the need for therapy to decrease GI complications (PPI/misoprostol or coxibs) is determined by severity and number of GI risk factors.

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INTRODUCTION

Prescribing nonsteroidal antiinflammatory drugs (NSAIDs) has become increasingly complex in recent years. NSAIDs have been recognized as a major cause of gastrointestinal (GI) complications, such as bleeding, perforation, and obstruction, for decades. In the United States, the direct costs of treating ulcer complications associated with NSAID use exceed $4 billion a year (1). Despite the availability of gastroprotective agents, the mortality of NSAID-associated ulcer

*See list of panel members in the Appendix.

complications has remained high during the past decade (2). The introduction of cyclooxygenase-2 selective inhibitors (coxibs) had led to the hope that the antiinflammatory action of nonselective NSAIDs could be dissociated from their GI toxicity. However, enthusiasm for coxibs has waned because of an increase in serious cardiovascular (CV) events with coxibs (3, 4). Emerging evidence suggests that nonselective NSAIDs, with the possible exception of naproxen, also increase CV risk (5–9). In April 2005, the US Food and Drug Administration (FDA) mandated that all NSAIDs should include a "black box" warning to highlight the potential increase in the risk of serious CV thrombotic events, along with the warning about potentially life-threatening GI events (10). Thus, physicians now have to consider a multitude of GI and CV risk factors before prescribing NSAIDs. Furthermore, the large amount of new data on CV and GI risks of NSAIDs can be difficult for physicians to access and integrate into a practical tool for patient care.

Current recommendations on the use of NSAIDs have been developed from different perspectives including rheumatology (11, 12), gastroenterology (13), and cardiology (14). Previous attempts to integrate viewpoints of different specialists lacked a global representation (15). In an effort to develop practical recommendations for physicians, a multidisciplinary international working party was convened to review the latest clinical evidence regarding NSAID-associated GI toxicity and CV risk and to promote multidisciplinary discussion regarding the most appropriate use of NSAIDs for different clinical scenarios. The aim of the working party was to generate clinical recommendations for safer NSAID prescribing among patients with different levels of GI and CV risks. A modified Delphi approach for consensus development was used to derive final recommendations, following a review of the literature and consideration of expert opinion.

METHODS

Convening Authority and Funding Sources

The Institute of Digestive Disease, Chinese University of Hong Kong, convened a multidisciplinary international working party to propose clinical recommendations for safer use of NSAIDs. The meeting was funded by an educational grant from the Institute of Digestive Disease, Chinese University of Hong Kong, supplemented by unrestricted educational grant funding from the Asia Pacific offices of AstraZeneca, Pfizer, Eisai, Altana Pharma, and Takeda (Japan). The working party was held in Miami, Florida, on November 18 and 19, 2006. The supporting pharmaceutical sponsors did not attend the consensus conference. No honoraria were provided to panel members.

Panel Selection

The panel was led by a steering committee (Francis Chan, Neena Abraham, Loren Laine), which developed clinical vignettes and selected a multidisciplinary group of international experts. We convened a panel of 19 members using the following criteria: (1) expertise in NSAID- and aspirin-related issues; (2) representation from different regions of the world; and (3) representation of a variety of specialties including primary care, gastroenterology, cardiology, rheumatology, clinical pharmacology (two members with CV expertise), epidemiology and biostatistics (two members with CV expertise), and health services research. Members were from eight countries representing North America, Asia, and Europe.

Development of Clinical Vignettes

The steering committee constructed a comprehensive series of possible case scenarios (clinical vignettes) to reflect common clinical prescribing scenarios among patients with different combinations of GI and CV risk factors. We predefined high GI risk as age $\geq$70 yr (16, 17); prior upper GI event (18, 19); and concomitant use of aspirin, corticosteroids, anticoagulants, or other antiplatelet drugs (20–23) that are considered common pharmacological risk factors for GI bleeding. High CV risk was predefined as the presence of established CV disease (*e.g.*, prior myocardial infarction, prior stroke, angina) or an estimated 10-yr CV risk of greater than 20% in patients without established CV disease (24, 25). The base-case patient was an arthritis patient who required prolonged (>1 month) NSAID treatment. The clinical vignettes categorized patients on the basis of permutations of several clinical factors, including (i) no prior upper GI clinical event *versus* prior upper GI clinical event (defined as a bleeding or symptomatic ulcer), (ii) age (<70 *vs.* $\geq$70), (iii) risk of developing CV disease over the next 10 yr ($\leq$20% *vs.* >20%), (iv) concomitant use of corticosteroids (none *vs.* corticosteroids), and (v) other pharmacological risk factors for GI bleeding (none *vs*. aspirin *vs.* anticoagulants *vs.* aspirin plus other antiplatelet agent/anticoagulants). The permutation of these five factors created 64 ($2 \times 2 \times 2 \times 2 \times 4 = 64$) different clinical vignettes. These vignettes were then evaluated for each of six treatment options (naproxen, a non-naproxen nonselective NSAID [*e.g.*, ibuprofen, diclofenac], naproxen plus a PPI or misoprostol, a non-naproxen nonselective NSAID plus PPI or misoprostol, a coxib, or a coxib plus PPI or misoprostol), creating 384 ($64 \times 6 = 384$) base vignettes. Ninety-six vignettes on concomitant use of aspirin or aspirin plus other antiplatelet agent/anticoagulant in patients with average CV risk were excluded because the panelists considered these vignettes to be inappropriate clinical practice and discouraged such behavior.

We chose the above six treatment options to evaluate the vignettes based on collective, but not conclusive data, in the literature. Naproxen was differentiated from other nonselective or COX-2 selective NSAIDs because current evidence suggests that the CV risk is lower for high-dose naproxen (500 mg b.i.d.) than other full-dose NSAIDs or coxibs (6). In a meta-analysis of 21 randomized controlled trials, naproxen was associated with a significant reduction in the risk of myocardial infarction by 50% (95% CI 29%, 66%) when compared with coxibs. There was no significant difference in the risk of myocardial infarction or other CV events

between coxibs and non-naproxen nonselective NSAIDs (6). Another meta-analysis of observational studies also found a lower risk of myocardial infarction with naproxen compared with non-naproxen nonselective NSAIDs (R.R. 0.86, 95% CI 0.75, 0.99) (9). Comparing to placebo or no NSAID therapy, a meta-analysis of 23 observational studies showed that the risk of CV events was not increased with naproxen (R.R. 0.97, 95% CI, 0.87, 1.07) (7). The panel decided not to add additional treatment options related to dose, frequency, and duration of therapy in their deliberations because of insufficient evidence and the impracticality of including multiple dosing schedules for each vignette. We differentiated coxibs from other nonselective NSAIDs because systematic reviews of endoscopic and GI clinical outcome trials have shown that coxibs are superior to nonselective NSAIDs in GI safety (26–28).

We used both PPIs and misoprostol interchangeably as both agents have been shown to decrease the rate of endoscopic gastroduodenal ulcers in NSAID users (29–31). Only misoprostol co-therapy has been shown to reduce the risk of NSAID-associated ulcer complications in a large-scale, placebo-controlled outcome study in an arthritis population (32), although co-therapy with a PPI was documented to be effective in preventing recurrent ulcer bleeding in randomized trials among high-risk NSAID users (33, 34). Data from observational studies and secondary analysis of a large-scale randomized trial also indicate that PPIs reduce the risk of NSAID-associated ulcer bleeding (35, 36).

Literature Review

Comprehensive reviews were commissioned by the steering committee to address the GI risk of NSAIDs and coxibs (by James Scheiman and Byron Cryer), the CV risk of NSAIDs and coxibs (by Colin Baigent), the risk *versus* benefits of aspirin and other antiplatelet drugs (by Carlo Patrono), and the efficacy of co-therapies (by James Scheiman and Byron Cryer). No formal review was commissioned to address pharmacoeconomic or health-related quality-of-life considerations. Using MEDLINE searches, we identified relevant articles published in English between 1980 and September 2006. Search terms included upper gastrointestinal bleeding, peptic ulcer bleeding, gastric ulcer, duodenal ulcer, gastroduodenal ulcer, osteoarthritis, rheumatoid arthritis, musculoskeletal pain, NSAIDs, COX-2-selective inhibitors, proton-pump inhibitors (PPIs), misoprostol, histamine-2 receptor antagonists, aspirin, clopidogrel, anti-platelet drugs, corticosteroids, anti-coagulants, *Helicobacter pylori*, clinical trials, observational studies, systematic reviews, and meta-analyses.

Each member of the working party received the literature reviews and a series of clinical vignettes. Members were asked to read the comprehensive reviews and then to rank the appropriateness of different therapeutic options for each of the clinical vignettes. Summaries of the reviews were also presented at the consensus meeting. Although panelists were provided with doses of gastroprotective drugs from studies of the prevention of NSAID-induced GI injury, no statements regarding a specific dose were provided for the medications assessed in each vignette.

The Modified Delphi Process

The Delphi method is based on anonymity, controlled feedback, and statistical group response and is well validated for systematically assessing and organizing expert opinion (37, 38). After reading the evidence-based reviews, panelists anonymously responded to a survey representing a series of clinical vignettes as described above, forwarding their responses to the conference organizer. Each panel member was asked to rank the appropriateness of each of the six therapies on a Likert scale anchored by 1 and 9, where 1 indicated extremely inappropriate and 9 extremely appropriate. The modified Delphi method included a face-to-face meeting of panelists during the working party session, as previously described (39, 40). At this group meeting, the authors of the commissioned reviews presented their data and the group participated in a discussion. In a feedback round, panelists were shown the distribution of the group's response regarding each clinical vignette (*i.e.*, controlled feedback) and discussion was promoted to provide context for the observed results and for vignettes for which a divergence of opinion was observed. During this feedback round, panelists were encouraged to explain extreme positions prior to a call for reassessment of clinical vignettes that did not meet a level of 80% agreement on the first iteration. A second anonymous iteration of the survey was administered during the working party meeting, including only vignettes from the first iteration that failed to meet a level of 80% agreement. Panelists were asked to reconsider their initial response in light of the first round's overall results and the preceding group discussion of the evidence. The consensus method did not force agreement. The group's responses were summarized and results collated for publication. Vignettes were considered appropriate if $\geq$80% of all panelists' scores were 7–9, inappropriate if $\geq$80% of all panelists' scores were 1–3, and uncertain if 80% agreement was not reached for scores 7–9 or 1–3.

Preparation of the Report

The steering committee drafted the manuscript, which was then reviewed and approved by all panel members prior to submission for peer review.

RESULTS

The panel rated therapy as appropriate in 23% of the 288 clinical scenarios, inappropriate in 41%, and uncertain in 36%. A summary of the results is shown in Tables 1–4.

Patients Without Prior GI Event and With Average CV Risk (Table 1)

In patients aged <70, with no prior upper GI event, with average CV risk, and no concomitant pharmacological risk factors for GI bleeding, the panel rated the use of nonselective NSAIDs (naproxen or non-naproxen nonselective NSAIDs) as appropriate, the use of a coxib alone

Table 1. Treatment Strategy for Patients With No Prior Upper GI Event and Average CV Risk (10-yr Risk <20%)

	No Aspirin or Anticoagulant	Low-Dose Aspirin Alone	Anticoagulant (*e.g.*, Warfarin) Alone	Low-Dose Aspirin + Other Antiplatelet (*e.g.*, Clopidogrel) or Anticoagulant
No Corticosteroids				
Naproxen	Appropriate if <70 Uncertain if ≥70	Not applicable	Inappropriate	Not applicable
Non-naproxen NSAID	Appropriate if <70 Uncertain if ≥70		Inappropriate	
Naproxen + PPI/misoprostol	Inappropriate if <70 Appropriate if ≥70		Appropriate	
Non-naproxen NSAID + PPI/misoprostol	Inappropriate if <70 Appropriate if ≥70		Appropriate	
Coxib	Uncertain		Uncertain	
Coxib + PPI/misoprostol	Inappropriate if <70 Uncertain if ≥70		Uncertain	
Taking Corticosteroids				
Naproxen	Uncertain if <70 Inappropriate if ≥70	Not applicable	Inappropriate	Not applicable
Non-naproxen NSAID	Uncertain if <70 Inappropriate if ≥70		Inappropriate	
Naproxen + PPI/misoprostol	Appropriate		Appropriate	
Non-naproxen NSAID + PPI/misoprostol	Appropriate		Appropriate if <70 Uncertain if ≥70	
Coxib	Uncertain		Uncertain	
Coxib + PPI/misoprostol	Uncertain		Uncertain	

Results applied to both patients aged <70 and ≥70, with the exception of those results as shown.
GI = gastrointestinal; CV = cardiovascular; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; coxib = cyclooxygenase-2 selective inhibitor.

Table 2. Treatment Strategies for Patients with No Prior Upper GI Event and High CV Risk (10-yr Risk >20%)

	No Aspirin or Anticoagulant	Low-Dose Aspirin Alone	Anticoagulant (*e.g.*, Warfarin) Alone	Low-Dose Aspirin + Other Antiplatelet (*e.g.*, Clopidogrel) or Anticoagulant
No Corticosteroids				
Naproxen	Appropriate if <70 Uncertain if ≥70	Uncertain	Inappropriate	Inappropriate
Non-naproxen NSAID	Uncertain if <70 Inappropriate if ≥70	Inappropriate	Inappropriate	Inappropriate
Naproxen + PPI/misoprostol	Inappropriate if <70 Appropriate if ≥70	Appropriate	Appropriate	Appropriate
Non-naproxen NSAID + PPI/misoprostol	Inappropriate	Uncertain	Uncertain	Uncertain
Coxib	Inappropriate	Inappropriate	Inappropriate if <70 Uncertain if ≥70	Inappropriate
Coxib + PPI/misoprostol	Inappropriate	Inappropriate if <70 Uncertain if ≥70	Inappropriate if <70 Uncertain if ≥70	Uncertain
Taking Corticosteroids				
Naproxen	Uncertain if <70 Inappropriate if ≥70	Inappropriate	Inappropriate	Inappropriate
Non-naproxen NSAID	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Naproxen + PPI/misoprostol	Uncertain if <70 Appropriate if ≥70	Appropriate	Appropriate	Appropriate
Non-naproxen NSAID + PPI/misoprostol	Uncertain	Uncertain	Uncertain	Uncertain
Coxib	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Coxib + PPI/misoprostol	Inappropriate	Uncertain	Inappropriate if <70 Uncertain if ≥70	Uncertain

Results applied to both patients aged <70 and ≥70, with the exception of those results as shown.
GI = gastrointestinal; CV = cardiovascular; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; coxib = cyclooxygenase-2 selective inhibitor.

Table 3. Treatment Strategies for Patients with Prior Upper GI Event and Average CV Risk (10-yr Risk <20%)

	No Aspirin or Anticoagulant	Low-Dose Aspirin Alone	Anticoagulant (*e.g.*, Warfarin) Alone	Low-Dose Aspirin + Other Antiplatelet (*e.g.*, Clopidogrel) or Anticoagulant
No Corticosteroids				
Naproxen	Inappropriate	Not applicable	Inappropriate	Not applicable
Non-naproxen NSAID	Inappropriate		Inappropriate	
Naproxen + PPI/misoprostol	Appropriate		Appropriate	
Non-naproxen NSAID + PPI/misoprostol	Appropriate		Appropriate	
Coxib	Uncertain		Uncertain	
Coxib + PPI/misoprostol	Appropriate		Appropriate	
Taking Corticosteroids				
Naproxen	Inappropriate	Not applicable	Inappropriate	Not applicable
Non-naproxen NSAID	Inappropriate		Inappropriate	
Naproxen + PPI/misoprostol	Appropriate		Appropriate	
Non-naproxen NSAID + PPI/misoprostol	Appropriate if <70 Uncertain if age >70		Appropriate if <70 Uncertain if age >70	
Coxib	Uncertain		Uncertain	
Coxib + PPI/misoprostol	Appropriate		Appropriate	

Results applied to both patients aged <70 and ≥70, with the exception of those results as shown.
GI = gastrointestinal; CV = cardiovascular; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; coxib = cyclooxygenase-2 selective inhibitor.

as uncertain, and the use of a nonselective NSAID or a coxib plus a PPI/misoprostol as inappropriate. In contrast, if the same patient was receiving concomitant corticosteroids and/or anticoagulants, a nonselective NSAID plus a PPI/misoprostol was rated as appropriate. A coxib with or without a PPI/misoprostol was still rated as uncertain, and a nonselective NSAID alone was rated as uncertain or inappropriate.

If the patient was at or above the age of 70, the panel rated the use of naproxen plus a PPI/misoprostol as appropriate irrespective of concomitant use of anticoagulants or corticosteroids. Non-naproxen nonselective NSAIDs received similar ratings as naproxen in the elderly except that naproxen was preferred in patients receiving concomitant corticosteroids and anticoagulants. The use of a nonselective NSAID alone was rated as inappropriate if the patient used concomitant corticosteroids whereas a coxib with or without co-therapy with a PPI/misoprostol was rated as uncertain.

Patients Without Prior GI Event and With High CV Risk (Table 2)

Table 2 addresses the patient with high CV risk who does not have prior upper GI event. If the patient was below the

Table 4. Treatment Strategies for Patients with Prior Upper GI Event and High CV Risk (10-yr Risk >20%)

	No Aspirin or Anticoagulant	Low-Dose Aspirin Alone	Anticoagulant (*e.g.*, Warfarin) Alone	Low-Dose Aspirin + Other Antiplatelet (*e.g.*, Clopidogrel) or Anticoagulant
No Corticosteroids				
Naproxen	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Non-naproxen NSAID	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Naproxen + PPI/misoprostol	Appropriate	Appropriate	Appropriate	Appropriate
Non-naproxen NSAID + PPI/misoprostol	Uncertain	Uncertain	Uncertain	Uncertain
Coxib	Inappropriate if <70 Uncertain if >70	Inappropriate	Uncertain	Inappropriate
Coxib + PPI/misoprostol	Uncertain	Uncertain	Uncertain	Uncertain
Taking Corticosteroids				
Naproxen	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Non-naproxen NSAID	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Naproxen + PPI/misoprostol	Appropriate	Appropriate	Appropriate	Appropriate if <70 Uncertain if >70
Non-naproxen NSAID + PPI/misoprostol	Uncertain	Uncertain	Uncertain	Uncertain
Coxib	Uncertain	Inappropriate	Uncertain	Uncertain if <70 Inappropriate if >70
Coxib + PPI/misoprostol	Inappropriate if <70 Uncertain if >70	Uncertain	Uncertain	Uncertain

Results applied to both patients aged <70 and ≥70, with the exception of those results as shown.
GI = gastrointestinal; CV = cardiovascular; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; coxib = cyclooxygenase-2 selective inhibitor.

Table 5. Summary of Recommendations based on GI and CV risks

	Average GI Risk	High GI Risk*
Average CV risk	Nonselective NSAID alone†	Nonselective NSAID + PPI/misoprostol or Coxib + PPI/misoprostol‡
High CV risk§	Naproxen (if not on aspirin)**	Avoid NSAIDs if possible
	Naproxen + PPI/misoprostol (if on aspirin)	Naproxen + PPI/misoprostol (irrespective of concomitant use of aspirin)

GI = gastrointestinal; CV = cardiovascular; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; Coxib = cyclooxygenase-2 selective inhibitor.
*High GI risk was defined as age ≥ 70 yr, prior upper GI event, and concomitant use of concomitant aspirin, corticosteroids, or anticoagulants.
†A nonselective NSAID includes both naproxen and a nonselective NSAID.
‡Coxib + PPI/misoprostol was recommended for patients with prior complicated upper GI event or multiple GI risk factors.
§High CV risk was defined as established coronary artery disease, any CV disease that required prophylactic low-dose aspirin, or an estimated 10-year CV risk of greater than 20%.
**In clinical practice, patients may not take aspirin though it is clinically indicated.

age of 70 and did not have concomitant pharmacological risk factors for GI bleeding, the panel rated the use of naproxen as appropriate, the use of a non-naproxen nonselective NSAID as uncertain, and the use of a coxib as inappropriate. Co-therapy with a PPI/misoprostol was mostly rated as inappropriate. If the same patient was receiving combinations of corticosteroids and low-dose aspirin, anticoagulants, or multiple antiplatelet agents/anticoagulants, the use of naproxen plus a PPI/misoprostol was rated as appropriate.

In contrast, if the same patient with no prior GI event but high CV risk was at or above the age of 70, naproxen plus a PPI/misoprostol was rated as appropriate, irrespective of concomitant use of low-dose aspirin, anticoagulants, corticosteroids, or combinations of low-dose aspirin and other antiplatelet agents or anticoagulants. A coxib with or without a PPI/misoprostol was rated as either uncertain or inappropriate.

Patients With Prior GI Event and Average CV Risk (Table 3)

Table 3 addresses the patient with a prior upper GI event and average CV risk. The panel's ratings were virtually identical whether the patient was <70 or ≥70 yr. With or without any concomitant pharmacological risk factors for GI bleeding, the panel rated the use of either a nonselective NSAID plus a PPI/misoprostol or a coxib plus a PPI/misoprostol as appropriate, the use of a nonselective NSAID as inappropriate, and the use of a coxib as uncertain. One exception was that non-naproxen nonselective NSAIDs plus a PPI/misoprostol was rated uncertain for patients aged ≥70 yr who received concomitant corticosteroids.

Patients With Prior GI Event and High CV Risk (Table 4)

Table 4 addresses the patient with a prior upper GI event and high CV risk. If the patient is below the age of 70, and with or without concomitant pharmacological risk factors for GI bleeding, the panel rated the use of naproxen plus a PPI/misoprostol as appropriate, a nonselective NSAID alone as inappropriate, either a non-naproxen NSAID or a coxib plus a PPI/misoprostol as uncertain, and a coxib with or without co-therapy with a PPI/misoprostol as either uncertain or inappropriate. If the same patient was at or above the age of 70, the panel's ratings were virtually identical. One notable exception was the scenario in which the older patient was also receiving concomitant corticosteroids, low-dose aspirin, and other antiplatelet agents or anticoagulants. In this scenario, the panel could not identify any treatment strategy as appropriate.

Summary of Appropriate Management Strategies

Table 5 summarizes the appropriate treatment strategies according to the patient's GI and CV risk, using a 2 × 2 table. For patients with average GI risk and average CV risk, the panel rated the use of a nonselective NSAID alone as appropriate. In patients with high GI risk but average CV risk, either a nonselective NSAID plus a PPI/misoprostol or a coxib plus a PPI/misoprostol was rated as appropriate. Coxib plus a PPI/misoprostol was preferred in patients with prior complicated upper GI event or multiple GI risk factors. In patients with high CV risk but average GI risk, the panel rated the use of naproxen alone as appropriate for those who did not use aspirin. If the patient was receiving prophylactic aspirin, naproxen plus a PPI/misoprostol was rated as appropriate. In patients with high CV and high GI risk, the panel rated the use of naproxen plus a PPI/misoprostol as appropriate irrespective of whether the patient was receiving concomitant aspirin. Although corticosteroid co-therapy increases the risk of GI events in NSAID users, the presence or absence of corticosteroid use in the vignettes had little effect on the panelists' votes. Therefore, corticosteroid use was not included in our final summary recommendations.

DISCUSSION

For the first time, a multidisciplinary international expert panel used a validated, systematic approach to the development of consensus clinical recommendations based on current best evidence for the appropriate use of nonselective NSAIDs, coxibs, and prophylactic PPI or misoprostol among patients with different combinations of GI and CV risk factors. The panel rated 288 separate clinical scenarios, which reflects the complexity and controversy surrounding the use of these agents. Despite the large number of scenarios, we were able to identify common themes that allowed the development of practical recommendations for clinicians.

The recommendations can be used to focus on patient characteristics (GI and CV risk factors) and identify which therapeutic options are appropriate for specific combinations of patient characteristics.

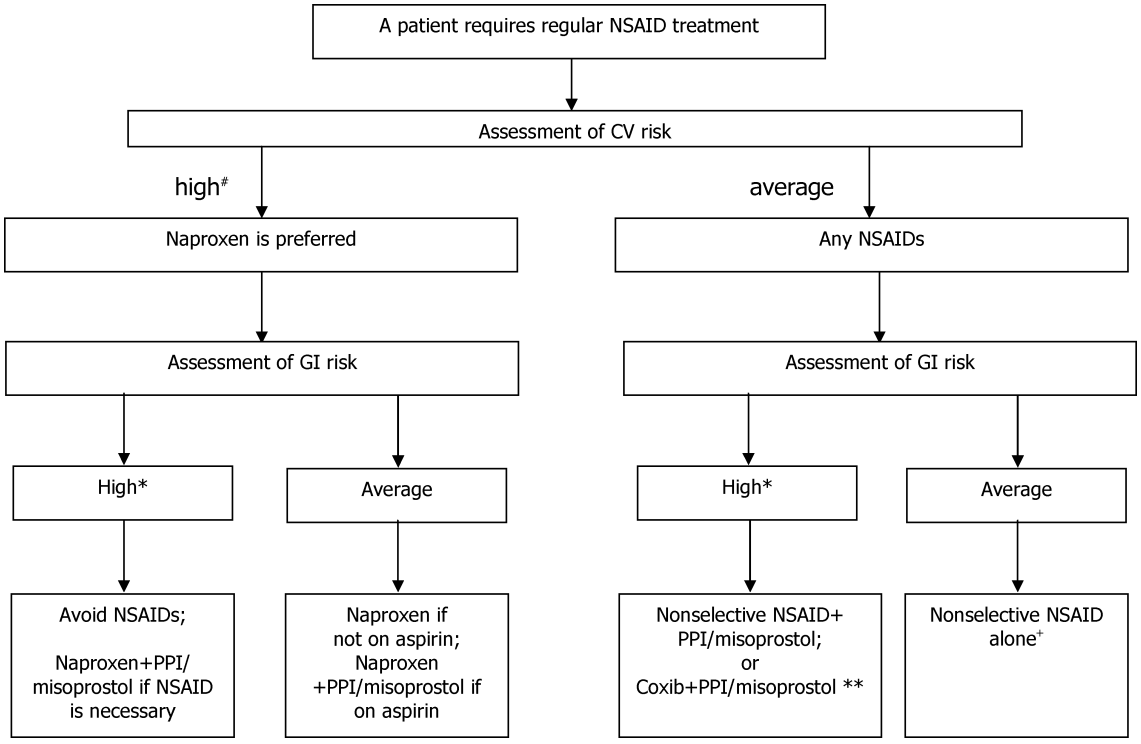

Figure 1. Management algorithm of patients on NSAIDs and aspirin. GI = gastrointestinal; CV = cardiovascular; NSAID = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; coxib = cyclooxygenase-2 selective inhibitor. *High GI risk was defined as age ≥70 yr, prior upper GI event, and concomitant use of concomitant aspirin, corticosteroids, or anticoagulants. **Coxib + PPI/misoprostol was recommended for patients with prior complicated upper GI event or multiple GI risk factors. #High CV risk was defined as established coronary artery disease, any CV disease that required prophylactic low-dose aspirin, or an estimated 10-yr CV risk of greater than 20%. +A nonselective NSAID includes both naproxen and a nonselective NSAID.

The panel rated the use of naproxen or non-naproxen nonselective NSAIDs as appropriate when the patient had average GI risk (*i.e.*, <70 yr of age; no prior upper GI event; no corticosteroids, antithrombotic agents, anticoagulants). Any absolute benefit was too small to justify using a coxib or co-therapy with a PPI or misoprostol in these patients.

The only factor in choosing between naproxen and non-naproxen nonselective NSAIDs was the patient's CV risk: naproxen was preferred if the patient had high CV risk. The latter recommendation was based on systematic reviews of randomized trials and observational studies that naproxen is associated with fewer CV events than coxibs and non-naproxen NSAIDs (6, 9). However, one should be cautioned that these systematic reviews were largely derived from patients with low CV risk. For example, the annual rate of CV events in the placebo arm in the meta-analysis of coxib trials was <1% and the vast majority of study subjects were not on low-dose aspirin (6). The most plausible explanation for the apparent heterogeneity between naproxen and non-naproxen NSAIDs in terms of their comparative CV safety is probably the fact that many patients on naproxen achieved adequate inhibition of platelet COX-1 throughout the dosing interval of the drug. In clinical practice, however, patients with high CV risk should be on low-dose aspirin. The latter will abolish platelet COX-1 activity, theoretically rendering all NSAIDs different only in terms of their extent (as a function of dose) and duration (as a function of half-life and dosing regimen) of COX-2 inhibition on the vessel wall. From this mechanistic perspective, naproxen given to aspirin-treated patients may behave like all other non-naproxen NSAIDs and coxibs. Unfortunately, clinical data assessing the CV risk of different NSAIDs with low-dose aspirin therapy are not available. Thus, good evidence does not exist to allow clear-cut, "evidence-based" recommendations regarding choice of NSAIDs in low-dose aspirin users.

In a patient with high GI risk, cotherapy with a PPI/misoprostol co-therapy was appropriate. The choice of NSAIDs among patients requiring a gastroprotective agent largely depended on the estimated CV risk. Non-naproxen NSAIDs were not regarded as appropriate in any vignette with high CV risk. The panel rated naproxen plus a PPI/misoprostol as appropriate when the patient had high CV risk and other GI risk factors, such as age ≥70, a prior upper GI event, and/or concomitant pharmacological risk factors for GI bleeding. A combination of PPI/misoprostol plus a nonselective NSAID (naproxen or non-naproxen NSAIDs) or a PPI/misoprostol plus a coxib was rated appropriate in patients with high GI risk but average CV risk. Arguably, these last recommendations are not entirely consistent with the current evidence in the literature. Previous studies indicated that

neither a nonselective NSAID plus a PPI nor a coxib alone was sufficient to prevent recurrent ulcer bleeding among patients with a recent ulcer complication (41–43), and recent data showed that a coxib plus a PPI was superior to a coxib alone in patients with high GI risk (34, 44). Our category of upper GI clinical event included both prior bleeding ulcer as well as symptomatic ulcer. One may consider stratifying by GI risk when choosing between coxib plus PPI/misoprostol or nonselective NSAID plus PPI/misoprostol. The "safer" but more expensive regimen (*i.e.*, a coxib plus a PPI) may not be recommended in every circumstance. The combination of a coxib plus PPI/misoprostol is recommended for patients at very high risk (*e.g.*, recently hospitalized for ulcer bleeding) but PPI/misoprostol plus nonselective NSAID may be acceptable for patients with less serious GI risk factors (*e.g.*, concomitant corticosteroid therapy). No trial specifically designed to determine whether a coxib plus a PPI/misoprostol is superior to a nonselective NSAID plus a PPI/misoprostol has been carried out in patients with high GI risk.

Finally, the panel felt that no form of NSAID therapy could be considered appropriate in patients with high CV risk and very high GI risk (*e.g.*, multiple GI risk factors). In this population, non-NSAID analgesia would be recommended. If antiinflammatory therapy is required, the choice of therapy will be a trade-off between individual patient's CV and GI risk. The panel chose naproxen plus a PPI or misoprostol among patients whose CV risk outweighed their GI risk (*e.g.*, recent myocardial infarction). If a coxib plus a PPI or misoprostol is required to maximize gastric protection in patients with very high GI risk as well as increased CV risk, use of the lowest possible dose of coxibs seems prudent because the CV toxicity of coxibs may be dose related (4, 6). A systematic review of randomized trials found that the relative risk with celecoxib 200 mg daily was approximately 1 (although the confidence interval was wide) with a significant increase in risk as the dose increased to 400 mg and 800 mg daily (6). However, it must be emphasized that there have been no studies addressing the safety of low-dose coxibs (*e.g.*, celecoxib 200 mg once daily) in patients with or at risk for coronary artery disease.

Our process of developing clinical recommendations had limitations despite the rigorous methodology used. First, dichotomizing nonselective NSAIDs as naproxen and nonnaproxen NSAIDs could restrict the panel in their choice for appropriate therapy. Whether naproxen has a lower CV hazard than other NSAIDs needs to be confirmed by randomized trials as previously mentioned. In addition, not all nonselective NSAIDs are equivalent with respect to GI safety. For example, naproxen may have a better CV safety profile but a higher GI risk compared with other NSAIDs. In contrast, diclofenac has one of the lowest odds ratios for upper GI bleeding but it is associated with a significant increase in CV risk (7). Although stratifying NSAIDs according to different combinations of CV and GI safety profiles may offer more treatment options, the number of vignettes needed would be exponentially increased and render the final recommendations too complex and impractical. Second, we did not perform a comprehensive review of the benefits of NSAIDs. It is clear that that there are competing risks and benefits of NSAIDs. Whilst the benefits of symptomatic relief are less easy to quantify than the risks, for many patients they are of immense importance. Thus, the decision to prescribe must be set in light of individual patient benefits. Third, many ratings on patients with high CV risk largely reflect expert opinion rather than evidence because we do not have the data from randomized trials of the CV safety of different NSAIDs and coxibs in patients receiving aspirin.

In conclusion, we used an evidence-based methodology to develop a management algorithm to assist physicians in choosing an appropriate NSAID treatment strategy in patients with different combinations of GI and CV risks (Fig. 1). The patient's CV risk determines the initial choice of an NSAID (naproxen *vs.* others), while the severity and number of GI risk factors determine the need for therapy to decrease GI complications (PPI/misoprostol, coxibs).

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CONFLICT OF INTEREST

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