

Panel discussion: treatment approaches to control gastrointestinal risk and balance cardiovascular risks and benefits: proposals and recommendations

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INTRODUCTION

Having heard the evidence presented at this meeting by rheumatologists, cardiologists and gastroenterologists, the objective of this Session was for Panel Members to propose recommendations guiding prescribing clinicians on the optimal approach to reduce the gastrointestinal (GI) risks associated with non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 (COX-2) inhibitors and low-dose aspirin.

There are many factors that the clinician needs to consider when treating patients with NSAIDs – which agent to use, whether the patient is also taking aspirin and the individual patient's GI and cardiovascular (CV) risks. These recommendations take into account not only the GI and CV perspectives, but also the practicalities of implementing them in everyday practice for the physician. Whether the concomitant use of a gastro-protective agent (GPA), such as a proton-pump inhibitor (PPI), can solve the problem of GI damage in high-risk patients was discussed. Guidelines issued by the regulatory agencies in the USA, France and Europe were reviewed, with the objective of subsequently discussing and agreeing on CV and GI risk category definitions, because these differ between countries and regions, and then proposing prescribing recommendations to assist clinicians worldwide.

RECOMMENDATIONS OF THE US FOOD AND DRUG ADMINISTRATION

In the light of recent evidence regarding the potential CV safety issues for COX-2 inhibitors, the United States Food and Drug Administration (FDA) Arthritis Advisory Committee met in February 2005 to review prescribing guidelines for these agents.¹ The panel comprised rheumatologists, cardiologists and gastroenterologists and other scientists who advised on risk across drug categories. The CV effects of the three COX-2 inhibitors, celecoxib, valdecoxib and rofecoxib, were recognized; however, one of the unanswered questions was whether potential CV risks exist with the whole class of NSAIDs, including the non-selective agents. These effects have not been well studied to date but the limited data that do exist, mostly from observational studies, point to the consistent conclusion that among the non-selective agents, the one that appears to be associated with the least CV risk is naproxen. The recommendation of the Advisory Committee for an alternative strategy in patients with GI risk factors to a COX-2 inhibitor and a PPI was therefore naproxen and a PPI. However, some studies have suggested that some non-selective NSAIDs, but not COX-2 inhibitors, could interfere with the antiplatelet effect of low-dose aspirin and thus could decrease its cardioprotective effect.²

ADAPT was a prospective trial conducted by the National Cancer Institute comparing naproxen, celecoxib and placebo in patients with Alzheimer's disease (Martin BK and the ADAPT Research Group, unpublished data). The trial was halted prematurely in December 2004, and one of the reasons given was CV concerns about naproxen on the basis of unadjudicated events. However, the results have not yet been published and these concerns were not confirmed by the FDA panel; the reason the trial was stopped was that they had difficulty in enrolling patients because of concerns about the CV risks of celecoxib, which had recently been announced. Juni *et al.*³ have published a meta-analysis of the relative CV risk of various NSAIDs. Overall, the NSAID class had a relative risk (RR) of 1.0, while naproxen had a RR of 0.86, suggesting a slight cardioprotective effect with naproxen. The Advisory Committee also expressed concern that the use of concomitant aspirin would offset the GI benefits of selective COX-2 agents and recommended physicians choose a non-selective NSAID and a PPI in aspirin users. Although there were CV concerns indicated for all COX-2 inhibitors, evidence suggested that celecoxib was the COX-2 inhibitor associated with the fewest CV adverse events and appeared safest at low doses (200 mg/day).

Following the withdrawal of rofecoxib from the market and after consideration of the accumulated evidence including the Arthritis Advisory Committee discussions, in April 2005 the FDA recommended that the package insert for celecoxib should be revised to include a black-box warning including specific clinical trial data reporting an increase in CV events and a Medication Guide.⁴ In addition, clinicians were encouraged to use the lowest effective dose of 200 mg/day for the shortest duration of treatment. In the case of valdecoxib, the FDA considered that the overall risk-benefit ratio was unfavourable and asked the manufacturer to voluntarily withdraw the product from the market.⁴

RECOMMENDATIONS OF THE FRENCH SOCIETY OF RHEUMATOLOGY

The recommendations of the French Society of Rheumatology (FSR) were presented in detail earlier in the meeting. To summarize briefly, they recognize that NSAIDs have proven efficacy to act on pain in bone and joint diseases. In high-risk patients, co-prescription of

GPIIs or the use of COX-2 inhibitors is known to decrease GI toxicity significantly. Despite the potential CV risks, they agreed that treatment with conventional NSAIDs or COX-2 agents could be maintained if the prescription was in accordance with the marketing authorization and limited to the flare, the CV risk had been correctly assessed by the general practitioner, the lowest effective dose was used in elderly, and antiplatelet drugs, such as aspirin, were continued if needed. The FSR recommended that the risk-benefit ratio of the chosen NSAID treatment should be evaluated by the physician in agreement with the individual patient.

RECOMMENDATIONS OF THE EUROPEAN MEDICINES EVALUATION AGENCY

The European Medicines Evaluation Agency (EMA) also met in February 2005 to discuss prescribing recommendations for the COX-2 inhibitor class. They recommended switching to alternative treatments, such as paracetamol (acetaminophen), for patients with established ischaemic heart disease (IHD) or CV disease (including those with both moderate and severe heart failure). They also stated that the physician should balance the GI and CV risks when prescribing, particularly in those patients with risk factors for heart disease and those taking low-dose aspirin. The physician should also consider a GPA, such as a PPI, for patients switched to non-selective NSAIDs. The EMA also recommended that all COX-2 inhibitors are contraindicated in patients with IHD or stroke, and introduced a warning for prescribing COX-2 inhibitors in patients with CV risk factors, such as hypertension, hyperlipidaemia, diabetes, smoking and peripheral arterial disease. In common with the recommendations of the other national regulatory agencies they also advised using the lowest effective dose for the shortest duration of treatment.

Panel comments

Some concerns have been expressed in the literature regarding the GI safety of paracetamol (acetaminophen) at high dose. It was noted that observational studies of paracetamol likely reflected channelling bias, as the patients receiving paracetamol probably were high risk for GI problems because they were being treated with this agent rather than a traditional NSAID. There

are currently no published data to suggest that aspirin and paracetamol cause any greater GI risk than aspirin alone.

The FDA's recommendation that low-dose aspirin should not be used with COX-2 agents because the loss of the GI-sparing effect was challenged; it was considered that this combination might benefit patients taking aspirin who have minimal GI risk. However, it was noted that most studies comparing NSAIDs and aspirin had been undertaken in high-risk groups, and considering the available evidence, to date there are limited data to support a difference between NSAIDs or COX-2 agents in combination with aspirin. The use of COX-2 agents in patients taking aspirin was questioned – if the patient is taking aspirin implies some existing CV risk why add a COX-2 inhibitor? It was commented that addition of aspirin to a NSAID substantially increases the GI risk, and then adding a gastroprotective PPI, while very effective, might create a compliance issue in a patient taking three different drugs. It was considered that some of the FDA and EMEA recommendations were not evidence based because the studies they considered when assessing the CV risk of COX-2 inhibitors were undertaken in patients who in most cases were without known pre-existing CV risk, for example the APPROVe trial.⁵ It is also important to note that there are currently no data to suggest that aspirin has any protective effect against CV events in high-risk CV patients taking COX-2 agents.⁶ Although results of the APPROVe (rofecoxib vs. placebo for the prevention of colorectal polyps)⁵ and APC (celecoxib vs. placebo for the prevention of colorectal adenomas)⁷ trials demonstrated that aspirin does not prevent the CV risks of COX-2 inhibitors, to date no randomized, controlled trial has addressed this issue specifically.

RISK CATEGORY DEFINITIONS FOR GI RISK PATIENTS

The risk factors for NSAID-induced ulcer complications have been well described and include prior complicated ulcer, multiple NSAID use, age and *Helicobacter pylori* infection.^{8–11} How to evaluate the risk, and the importance of each of these risk factors, for individual patients needed to be defined. Chan and Graham¹² described low, moderate, high and very high GI risk categories. At the time this proposal was developed, the CV risks of COX-2 agents had not been described. Not all risk factors have equal importance, for example some-

one with a previous ulcer bleed would be considered as very high risk.

- Low: no risk factors
- Moderate: 1 to 2 risk factors – high-dose or multiple NSAIDs; CV disease; concomitant use of low-dose aspirin and other antiplatelet drugs, steroids or warfarin; age >70
- High: ≥ 3 risk factors; or NSAID and aspirin, steroids or warfarin
- Very high: a history of recent ulcer complications

Many physicians may be confused about where the boundaries between these categories lay and require some guidance. The Panel agreed it was important to develop clear and simple recommendations that the physician can follow easily and will therefore be encouraged to use. It was suggested that from a practical point of view, two categories of GI risk might be preferable – high and low – because it was sometimes difficult to define 'moderate' risk. However, some considered that the definitions within each category needed simplification rather than the categories themselves. It was also suggested that patients with a history of recent ulcer complications should be removed from the high-risk category altogether to form a special category in which NSAIDs should be avoided, although it was recognized that this type of patient would not be encountered frequently. This would give three categories: low risk, increased risk and a special, highest risk category (if no CV risk, they would not be treated with either aspirin or NSAIDs and if they do have CV risks, they would be treated with aspirin and a PPI). The overall number of GI risk categories depends on how similar the treatment recommendations are – for example between moderate and high – and whether they can therefore be combined. Also, it was important that there was sufficient data to support the recommendations for each separate category. GI risk category definitions are presented in Table 1.

Most risk factors can be considered relatively comparable apart from 'previous ulcer event', which carries a high risk, and age, whose significance may vary. There is a subgroup of older patients (age > 65 years) who may not need GI protection if there are no other risk factors involved; this point warrants a footnote to Table 1. Epidemiological studies have shown that age increases the RR by 2.5. Risks are greater, however, in patients aged over 70 years. If the

Table 1. Gastrointestinal risk categories and definitions

Low	Increased	High
No risk factors	≥1 risk factor: past uncomplicated ulcer (given <i>Helicobacter pylori</i> eradication therapy); high-dose* or multiple NSAIDs† (including OTC treatments); CV disease; concomitant use of low-dose aspirin or other antiplatelet drugs, steroids or warfarin; advanced age‡	History of ulcer complication (specifically a previous bleed, obstruction or perforation)

NSAIDs, non-steroidal anti-inflammatory drugs; OTC, over-the-counter; CV, cardiovascular.

*High-dose NSAIDs – see recommended doses in Table 4.

†Not recommended but commonly occurs because of patient misunderstanding, see supplementary table of commonly used OTC NSAIDs (Table 5).

‡Age alone may not be a risk factor; treatment should be individualized over the age of 65–70 years.

only risk factor is age, the GI risk is similar to taking aspirin alone and the beneficial effect of a PPI may not be cost effective because the GI risk is low. There was some discussion as to whether the term ‘high-dose NSAIDs’ would be well understood and it was suggested that to have a supplementary table (Table 4) of the usual anti-inflammatory and analgesic doses of NSAIDs; this should be noted as a footnote in Table 4. It was also noted that the term ‘multiple NSAIDs’ was intended to describe patients taking a prescribed NSAID and an over-the-counter (OTC) remedy; this was recognized as a huge problem in the USA – around 40% of patients taking a prescribed NSAID also took an OTC NSAID. Physicians would not prescribe two NSAIDs, however, patients needed to be educated that OTC NSAIDs were associated with the same GI risks as prescribed treatments and that the risk increased further if the two were combined. A supplementary table of commonly used OTC NSAIDs might also be useful (Table 5).

Helicobacter pylori is an important risk factor for GI risk and while it was recognized that it was not practical to test and treat all patients for *H. pylori* infection, in patients with a previous ulcer history, whether uncomplicated or complicated, *H. pylori* infection should ideally be eliminated. However, the practicing rheumatologist or cardiologist may be unlikely to recognize this as a risk factor and treat accordingly.

In terms of NSAID treatment of patients in these GI risk categories, the panel recommended the following:

- low risk: a non-selective NSAID;
- increased risk: a non-selective NSAID and GPA, such as a PPI, or COX-2 inhibitor (where there is no CV risk or aspirin use);

- high risk: if a NSAID is required, COX-2 inhibitor and GPA, such as a PPI.

It is important to note that ‘GPA’ refers to PPIs or misoprostol only; there is only limited evidence for the efficacy of H₂-receptor blockers for this indication. High-dose famotidine has been suggested in some cases as an alternative for GPA.¹³ However, there are no direct comparisons of high-dose H₂-receptor blockers vs. PPIs, and the current balance of evidence is in favour of PPIs being the most effective agent.¹⁴ It should be stressed that throughout these treatment recommendations, the lowest effective dose of NSAID or COX-2 agents and the shortest duration of treatment should be used in all categories.

RISK CATEGORY DEFINITIONS FOR CV RISK PATIENTS

The panel then considered CV risk category definitions for patients taking low-dose aspirin for CV risk. According to the US Preventive Services Task Force Guidelines, the definition of who should be receiving low-dose aspirin is that it should be considered for all apparently healthy men and women whose 10-year risk of a CV event is ≥6%.¹⁵ However, the American Heart Association (AHA) Guidelines state that it should be considered for all apparently healthy men and women whose 10-year risk of a CV event is ≥10%.¹⁶

As described previously during the meeting, various guidelines exist on the definition of CV risk – the US ATP Guidelines, European Guidelines and French Guidelines. It was suggested that the USA guidelines, which have low, intermediate and high risk categories, were preferable to the others. One of the key differences

Table 2. Cardiovascular risk categories and definitions

Low	Intermediate	High
1 risk factor; absolute risk <10% in 10 years	2 risk factors, see risk factors below; absolute risk between >10% and <20% in 10 years Risk factors: Two main risk factors of coronary artery disease: causal risk or family history of premature CHD	>2 risk factors; absolute risk >20% (asymptomatic patients) see risk factors below Risk factors: Coronary artery disease (acute coronary syndrome, stable angina, revascularization procedures) Peripheral arterial disease, acute aneurysm of the aorta Stroke Multiple risk factors with an absolute risk >20% in 10 years Type 2 diabetes

between the US and European recommendations is that in the US asymptomatic, young diabetic patients are considered high risk, whereas in Europe they are not, unless there are complications. In cases of intermediate CV risk, where there are only two risk factors, there is an argument that rather than giving aspirin immediately, the underlying risk factors, such as smoking, should be tackled first, although this is not currently stated in guidelines.

Cardiovascular risk category definitions are presented in Table 2. It was agreed that in the 'intermediate risk category' an 'absolute risk >10%' would be used, which follows the AHA Guidelines. Studies have suggested range between 6 and 10% for the absolute risk cut-off in this category, and this varies depending on the population examined.

OVERALL TREATMENT RECOMMENDATIONS FOR NSAID USE ACCORDING TO A PATIENT'S GI OR CV RISK FACTORS

Having considered both GI and CV risk category definitions, the Panel then debated recommendations for NSAID treatment of patients with consideration of their GI and CV risk factors. As recent placebo-controlled studies of COX-2 inhibitors indicate increased incidences of myocardial infarction in patients with and without baseline CV risks,⁵ the panel felt that NSAID management from the CV perspective would be better assessed based on whether the patient currently takes aspirin or not. The results of these discussions are summarized in Table 3. GI risks were categorized as no risk, increased risk or high risk; aspirin exposure was categorized as

Table 3. Overall treatment recommendations for non-steroidal anti-inflammatory drug (NSAID) use according to a patient's gastrointestinal (GI) risk factors and aspirin exposure

	GI risk		
	No risk	Increased risk	High risk (history of ulcer complications)
Aspirin exposure			
NSAID, no aspirin	Non-selective NSAID	Non-selective NSAID + PPI* or COX-2 inhibitor (no CV risk or aspirin treatment)	COX-2 inhibitor + PPI*
NSAID + aspirin	Lack of data†	PPI* + non-selective NSAID (one with the lowest GI risk)	No NSAID recommended; continue aspirin + PPI*
Aspirin alone	Low-dose aspirin	Low-dose aspirin and PPI*,‡	Low-dose aspirin and PPI*,‡

PPI, proton-pump inhibitor; COX-2, cyclo-oxygenase-2; CV, cardiovascular.

*Gastroprotective agent may be PPIs or misoprostol only; the lowest effective dose of NSAID or COX-2 agents and the shortest duration of treatment should be used in each case.

†Consider low-dose COX-2 inhibitor (the CV risks for celecoxib 200 mg appear low) or move to next higher GI risk category.

‡Recommend to test and treat for *Helicobacter pylori*.

NSAID but no aspirin, NSAID and aspirin, or aspirin alone.

For patients with a low GI risk who take aspirin to reduce CV risk and also require an anti-inflammatory drug, although data are limited, a low-dose COX-2 inhibitor, such as celecoxib 200 mg, could be considered, although direct comparative data are not available. For increased and high GI risk patients who require low-dose aspirin for reducing the CV risk and who also require an anti-inflammatory drug, it is recommended to prescribe GPA, such as a PPI, for reducing the GI risk, irrespective of NSAID or COX-2 inhibitor use.

It should be noted that all these recommendations are based on currently available data and may change when further data become available, for example on the use of low-dose COX-2 inhibitors. It was suggested that these recommendations could be further developed to distinguish between long- and short-term NSAID treatments.

SUPPLEMENTARY MATERIAL

Table 4 and Table 5.

Table 4. Commonly used NSAIDs and adult dosage ranges for primary therapeutic indications¹⁷

Generic drug name	Brand name (US)	Dose range (mg)
Diclofenac	Cataflam, Voltaren Voltaren SR	50 mg PO BID to TID; 75 mg PO BID 100 mg PO QD-BID
Etodolac	Lodine Lodine XL	300–1000 mg PO QD-TID 400–1000 mg PO daily*
Fenoprofen	Nalfon	300–600 mg PO TID-QID
Ibuprofen	Motrin	1200–3200 mg PO daily*
Indomethacin	Indocin	75–200 mg QD*
Ketoprofen	Orudis	100 to 300 mg QD*
Ketoprofen SR	Oruvai	200 mg PO QD
Nabumetome	Relafan	2 grams PO QD-BID
Naproxen	Naprosyn	250–500 mg PO BID
Oxaprozin	Daypro	600 mg PO QD-BID
Sulindac	Clinoril	150–200 mg PO BID
Tolmetin	Tolectin	200–600 mg PO TID

Key: * = doses may be divided BID-QID; BID = twice daily; TID = three times daily; QID = four times daily; PO = orally; QD = daily.

Table 5. Commonly used over-the-counter NSAIDs available in the USA containing aspirin, aspirin-like compounds, ibuprofen, naproxen or ketoprofen

Products containing aspirin or aspirin-like compounds	Alka-Seltzer Antacid/Pain Reliever Effervescent Tablets, Alka-Seltzer Plus Cold Medicine Tablets, Anacin Caplets/Tablets, Arthritis Pain Formula Tablets, Arthritis Strength Bufferin Tablets, Ascriptin Caplets/Tablets, Ascriptin A/D Caplets, Aspergum, Bayer Aspirin Caplets/Tablets, Bayer Children's Chewable Tablets, Bayer Plus Tablets, Maximum Bayer Caplets/Tablets, 8-Hour Bayer Extended-Release Tablets, BC Powder, BC Cold Powder, Buffaprin Caplets/Tablets, Bufferin Arthritis Strength Caplets, Bufferin Caplets/Tablets, Cama, Doan's Pills Caplets, Ecotrin Caplets/Tablets, Empirin Tablets, Excedrin Extra-Strength Caplets/Tablets, Midol Caplets, Mobigesic Analgesic Tablets, Norwich Tablets, P-A-C Analgesic Tablets, Pepto-Bismol Liquid/Tablets, Sine-Off Tablets: Aspirin Formula, St. Joseph Adult Chewable Aspirin, Therapy Bayer Caplets, Ursinus Inlay-Tabs, Buffaprin Caplets/Tablets, Vanquish Analgesic Caplets
Products containing ibuprofen	Advil Caplets/Tablets, Advil Cold/Sinus Caplets, Bayer Select Ibuprofen Pain Relief Formula Caplets, Dristan Sinus Caplets, Haltran Tablets, Ibuprofen Caplets/Tablets, Midol IB Tablets, Motrin IB Caplets/Tablets, Nuprin Ibuprofen Caplets/Tablets, Sine-Aid IB
Products containing naproxen	Aleve Caplets/Tablets
Products containing ketoprofen	Orudis Tablets

Note: Compiled May 2005. In the future, OTC manufacturers may add new products which contain aspirin or NSAIDs or may reformulate some of the current products.

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