

Elevated cardiovascular risk with NSAIDs?

Summary

- Elevated cardiovascular risk has been associated with COX-2 selective NSAIDs in some studies. Evidence for the long-term cardiovascular safety of conventional NSAIDs is limited and does not provide strong evidence of a lower risk than for COX-2 selective NSAIDs. Until information is available that distinguishes between them, the most cautious approach is to assume that all NSAIDs carry a similar risk of cardiovascular events.
- All NSAIDs should be used at the lowest effective dose for the shortest possible duration.
- When assessing the need for new or continuing NSAID therapy, carefully weigh the risk of cardiovascular, renal and gastro-intestinal effects against the potential benefits of treatment for each patient.
- All NSAIDs have equivalent efficacy, although there may be interindividual variation in response.
- All NSAIDs have a similar capacity to cause renal impairment, congestive heart failure, hypertension and oedema.
- All NSAIDs can cause serious ulcer complications. Celecoxib appears to have a lower risk of serious ulcer complications than conventional NSAIDs, at least in the short term; the evidence for meloxicam is more limited.

What action have regulatory authorities taken?

In February 2005, after reviewing the cardiovascular safety of COX-2 selective NSAIDs, the Therapeutic Goods Administration (TGA) advised that their use be restricted (Box 1).¹

The TGA requested that manufacturers include prominent warnings in the product information for COX-2 selective NSAIDs and proposed to cancel or limit the registration of some of these agents. Overseas regulatory authorities have also warned about the potential for an increased risk of cardiovascular events with COX-2 selective NSAIDs.²⁻⁵ Celecoxib and meloxicam are the only oral COX-2 selective NSAIDs available in Australia.

Further advice is likely

The TGA is likely to issue further advice on the use of NSAIDs after its review of the cardiovascular and gastro-intestinal safety of conventional NSAIDs is completed,

Box 1: TGA advice on use of COX-2 selective NSAIDs (14 February 2005)¹

- COX-2 selective NSAIDs should be prescribed only when other treatments cannot be tolerated or have caused serious adverse effects.
- Celecoxib and meloxicam should not be prescribed for patients at increased risk of cardiovascular events.
- Treatment with celecoxib or meloxicam should be limited to the shortest time needed.
- People taking daily doses greater than celecoxib 200 mg or meloxicam 15 mg should have their treatment reviewed and dose reduced.

which is likely to be by mid-2006.⁶ There may also be further changes to the product information for the COX-2 selective NSAIDs. The sponsors of meloxicam have lodged appeals against the TGA's action and have

obtained a Federal Court order to prevent warnings having to appear in the product information for the time being. They have also agreed to provide prescribers and pharmacists with additional precautionary information about the limited cardiovascular safety data available whenever the product information for meloxicam is provided.^{7,8} A warning currently appears in the product information for celecoxib, but Pfizer has lodged an appeal with the aim of having it removed.⁹

What is the evidence of increased cardiovascular risk?

An increased risk of serious cardiovascular events (such as myocardial infarction and stroke) relative to the risk with placebo has been seen in some trials of the COX-2 selective NSAIDs celecoxib, rofecoxib and the combination of valdecoxib and parecoxib. It is not known whether other COX-2 selective NSAIDs (meloxicam, lumiracoxib and etoricoxib) are associated with a similar risk because long-term placebo-controlled trials evaluating their cardiovascular safety are not available.

Evidence for the long-term cardiovascular safety of conventional NSAIDs is limited and does not provide strong evidence for a lower risk than with COX-2 selective NSAIDs. Until there is evidence to distinguish between them, the most cautious approach is to assume that all NSAIDs are associated with a similar risk of cardiovascular events.

COX-2 selective NSAIDs may elevate cardiovascular risk

Elevated cardiovascular risk was first noted in the VIGOR study in rheumatoid arthritis, in which the incidence of myocardial infarction was four times higher in the rofecoxib 50 mg group than the naproxen group (0.4% vs 0.1%, respectively).¹⁰ There was debate over whether the difference was attributable to a cardioprotective effect of naproxen. When a later trial, APPROVe, found an elevated risk of thrombotic events with rofecoxib 25 mg compared with placebo (1.50 vs 0.78 events per 100 patient-years)¹¹, the manufacturer withdrew the drug from the market.

Subsequently, the APC trial of celecoxib for prevention of colon polyps found a significantly elevated risk of cardiovascular events and death in people taking celecoxib 400 mg twice daily compared with placebo

(11.4 vs 3.4 events per 1000 patient-years).¹² People taking celecoxib 200 mg twice daily also had a higher rate of cardiovascular events and death than those on placebo (7.8 vs 3.4 events per 1000 patient-years), but this did not reach statistical significance. Evidence for elevated cardiovascular risk with celecoxib is inconsistent, with two other studies showing no significant difference in the rate of cardiovascular events between subjects taking placebo or celecoxib 400 mg daily.¹³ The celecoxib dose most commonly used in Australia, 200 mg/day, has not been used in long-term placebo-controlled trials, so there is currently no evidence to support or refute elevated cardiovascular risk at this dose.

Using parecoxib followed by valdecoxib for post-operative pain after coronary artery bypass surgery has also been found to elevate the risk of cardiovascular events.^{14,15} However, a study in general surgery patients failed to find an increased risk of cardiovascular events relative to placebo.¹⁶

Several observational studies have also indicated an elevated risk of myocardial infarction associated with some COX-2 selective NSAIDs^{17–20} although others have found no evidence of significantly elevated risk.^{21–23}

Evidence for the effect of dose on the elevated cardiovascular risk possibly associated with COX-2 selective NSAIDs is extremely limited. In the APC trial, the relative risk of cardiovascular death, non-fatal myocardial infarction, stroke or heart failure compared with placebo appeared to increase with dose. Relative risk compared with placebo was 2.3 (95% confidence interval, 0.9 to 5.5) in patients taking celecoxib 400 mg/day and 3.4 (95% CI, 1.4 to 8.5) at a daily dose of 800 mg.¹² Other trials have not evaluated the effects of varying doses but observational studies have found a higher risk with rofecoxib doses above 25 mg than with doses of 25 mg or less.^{19–21}

Evidence for conventional NSAIDs is limited

Studies of the size and duration of those that detected the potential increase in risk relative to placebo for the COX-2 selective NSAIDs have not been conducted for conventional NSAIDs. The highest-quality evidence for the long-term safety of conventional NSAIDs probably comes from the studies in which these were compared with COX-2 selective NSAIDs. VIGOR was the only randomised controlled trial to find a significantly raised risk of myocardial infarction with a COX-2 selective NSAID compared with a conventional NSAID.¹⁰ Other trials do not provide strong evidence of a difference in

cardiovascular risk between COX-2 selective and conventional NSAIDs.^{13,24}

A recent trial comparing celecoxib, naproxen and placebo for prevention of Alzheimer's disease found some evidence of an increased risk of cardiovascular events with naproxen.²⁵ Several observational studies have also indicated a possibly elevated risk of cardiovascular events for people taking conventional NSAIDs compared with people not taking NSAIDs.^{17–19}

The United States Food and Drug Administration (FDA) concluded that until further information is available, current data 'are best interpreted as being consistent with a class effect of an increased risk of serious adverse [cardiovascular] events for COX-2 selective and non-selective NSAIDs'.¹³ The FDA has requested that US labelling of all prescription NSAIDs include a warning about the potential for increased risk of cardiovascular events and gastro-intestinal adverse effects.²⁶ The TGA intends to review the cardiovascular safety of conventional NSAIDs before providing further advice.⁶

Weigh potential benefits against risk of harm for each patient

Carefully compare the risk of harm from using an NSAID with the potential benefits when deciding whether to initiate or continue treatment. This should include considering the value that the patient places on the potential benefits and the risk of harms (Figure 1). When an NSAID is prescribed, ensure that the risks of gastro-intestinal, cardiovascular and renal adverse effects are minimised and that patients understand what to do if they suspect they are experiencing an adverse effect.

Choosing an NSAID

COX-2 selective NSAIDs have equivalent efficacy and a similar range of adverse effects to those of conventional NSAIDs, so they are not preferred routinely to conventional NSAIDs.

There can be variation in individual response to NSAIDs. If one NSAID is ineffective, it is reasonable to try others, including COX-2 selective NSAIDs.

The most clinically significant difference between COX-2 selective and conventional NSAIDs is likely to be in their propensity to cause serious gastro-intestinal adverse events. However, evidence for a safety advantage for celecoxib or meloxicam over conventional NSAIDs is limited, particularly in the long term. Celecoxib appears to be associated with a reduced risk of ulcer complications,

at least during short-term use; evidence for meloxicam is more limited (see *Risk of serious gastro-intestinal events with available COX-2 selective NSAIDs*).

Using a COX-2 selective NSAID is most justified in people at higher risk of gastro-intestinal adverse effects (Box 3), in whom the absolute reduction in risk of adverse effects will be largest. In the general NSAID-using population, the incidence of serious ulcer complications is low, so the absolute reduction in the risk of complications when using a COX-2 selective NSAID rather than a conventional NSAID is small for most people.

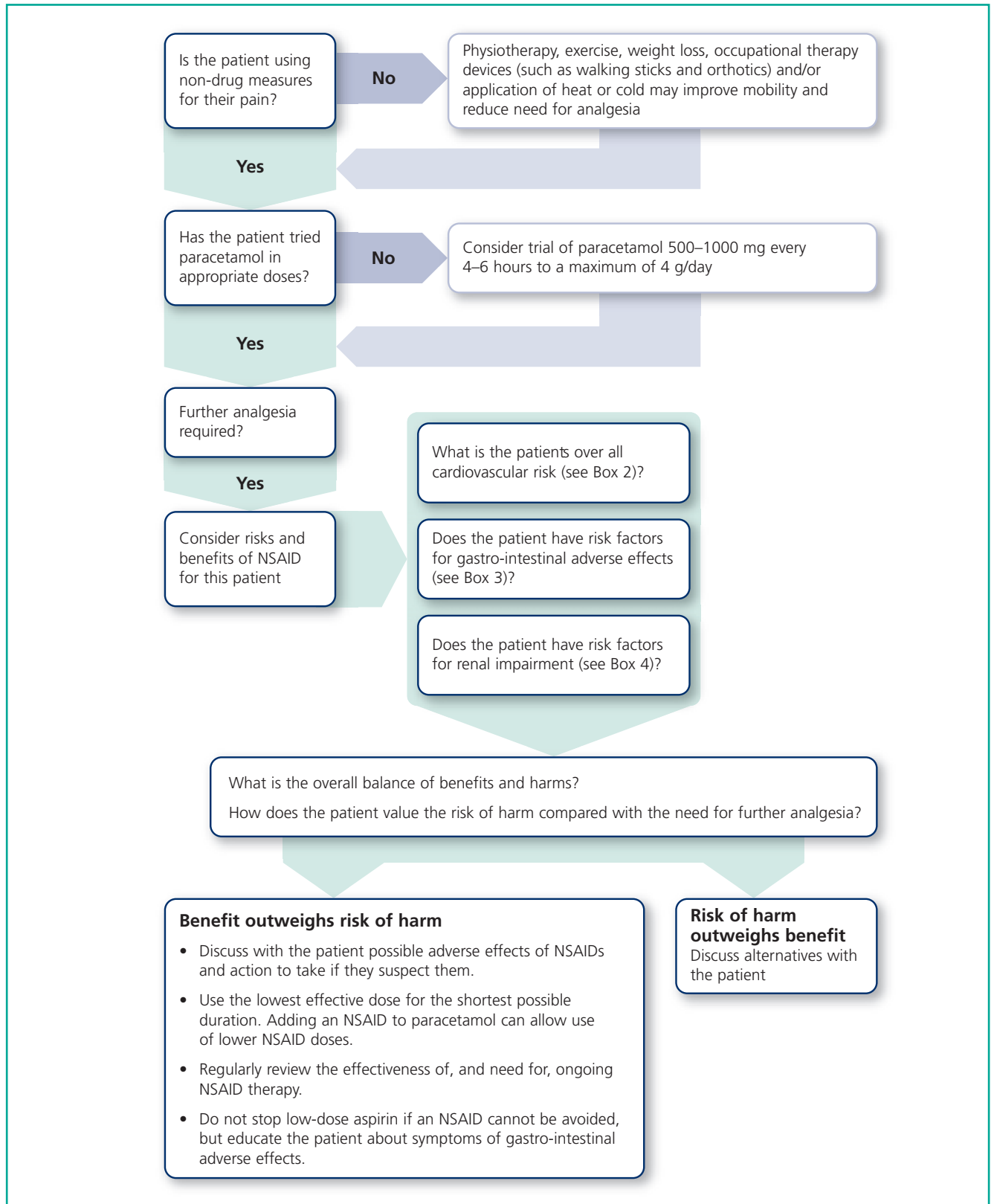
Risk of serious gastro-intestinal events with available COX-2 selective NSAIDs

Ulcer complications (perforation, outlet obstruction and significant ulcer bleeding) are the most clinically important outcomes on which to assess the gastro-intestinal safety of NSAIDs because these events usually lead to hospitalisation and may be fatal. Some trials use the combined incidence of ulcer complications and symptomatic ulcers (usually defined as uncomplicated gastroduodenal ulcers detected on endoscopy for dyspepsia) as a basis for comparison of gastro-intestinal safety of NSAIDs. However, this is a less clinically important endpoint because many complications occur without a symptomatic ulcer as a precursor, and symptomatic ulcers may not progress to serious complications.²⁷

The Pharmaceutical Benefits Advisory Committee has accepted that celecoxib is associated with a lower rate of ulcer complications than conventional NSAIDs for at least the first 3 months of therapy. This conclusion was based on an unpublished pooled analysis of 3-month data from randomised controlled trials.^{28,29} It is not clear whether the gastro-intestinal toxicity advantage persists beyond 3 months because reliable long-term data are lacking. A pooled analysis of the only two arthritis trials of at least 6 months' duration found only a marginally statistically significant result in favour of celecoxib. The CLASS study, which was designed to compare the long-term gastro-intestinal toxicity of celecoxib and conventional NSAIDs, failed to find a significantly lower risk of ulcer complications with celecoxib, although definitive conclusions cannot be drawn from this study because it was underpowered to detect a difference between treatment arms and was potentially confounded by a high drop-out rate.³⁰

There is no reliable evidence that meloxicam is associated with a lower risk of ulcer complications than other NSAIDs.

Figure 1: Pathway for assessing risk of new or continuing NSAID use



Box 2: Cardiovascular risk

There is insufficient evidence to establish whether different NSAIDs are associated with varying degrees of cardiovascular risk. Until such information is available, the most cautious approach is to assume that all are associated with the same level of risk. Uncertainty about the relationship of risk to dose or duration of NSAID use underlines the importance of using the lowest effective dose for the shortest possible duration.

Evaluating the risk

- Estimate overall cardiovascular risk using a tool such as the New Zealand Guideline Group's Cardiovascular Risk Calculator (www.nps.org.au/healthpro, then choose 'Cardiovascular risk calculator' from the 'Topics and Resources' menu).

Minimising the risk

- Use NSAIDs with greater caution in people at higher cardiovascular risk because they are likely to have larger absolute increases in risk of thrombotic events than those at lower cardiovascular risk. For example, if use of an NSAID were to double the risk of cardiovascular events, the absolute risk for a person with a 5-year risk of cardiovascular events of 2.5% would increase to 5%, whereas for a person with a 5-year risk of 15%, it would increase to 30%.
- Monitor and manage modifiable cardiovascular risk factors.

Box 3: Gastro-intestinal risk

COX-2 selective and conventional NSAIDs can cause serious ulcer complications (perforation, obstruction, bleeding)^{10,30,34,35} and should be avoided in people at high risk if possible. Celecoxib appears to be associated with a reduced risk of ulcer complications, at least during short-term use; evidence for meloxicam is more limited.

Evaluating the risk

Risk factors for gastro-intestinal adverse effects of NSAIDs include³⁶:

- age \geq 65 years
- history of ulcer
- concomitant use of anticoagulants or corticosteroids
- presence of serious comorbidity
- use of NSAIDs with higher gastro-intestinal risk
- prolonged use of high NSAID doses (which includes the combination of aspirin and another NSAID or of two non-aspirin NSAIDs).

Minimising the risk

- Prefer NSAIDs with a lower risk of serious gastro-intestinal adverse effects (celecoxib, ibuprofen, diclofenac).
- Do not use more than one non-aspirin NSAID concurrently.
- Consider misoprostol or a proton pump inhibitor in combination with a conventional NSAID for people at high risk of gastro-intestinal adverse effects. Misoprostol is the only drug shown to reduce the risk of NSAID-induced ulcer complications. Proton pump inhibitors reduce the risk of gastroduodenal ulcers detected by endoscopy but their effect on the risk of ulcer complications has not been assessed.³⁷

Box 4: Renal risk

COX-2 selective and conventional NSAIDs have similar risks of renal impairment, congestive heart failure, hypertension and oedema and should be used with caution in people at risk.

Evaluating the risk

Risk factors for renal impairment include³⁸:

- congestive heart failure
- cirrhosis
- glomerular filtration rate \leq 60 mL/min
- age $>$ 60 years
- use of diuretics, ACE inhibitors, angiotensin II receptor antagonists, cyclosporin or aspirin
- salt-restricted diet

Minimising the risk

- If an NSAID is prescribed, assess for symptoms and signs of heart failure, measure weight and blood pressure and assess renal function at baseline, 2–4 weeks after initiation and at regular intervals during treatment.³⁹

Box 5: What about aspirin?

Gastro-intestinal adverse effects

Aspirin use increases the risk of gastro-intestinal adverse effects in people taking other NSAIDs. The relative safety of combining a COX-2 selective or conventional NSAID with aspirin is not well evaluated. There is no reliable evidence that, when combined with aspirin, a COX-2 selective NSAID causes fewer ulcer complications than a conventional NSAID. Subgroup analyses in people taking aspirin in trials have found no statistically significant differences in ulcer complication rates between COX-2 selective and conventional NSAIDs.^{30,34} Combining any NSAID with aspirin should therefore be done with caution and patients educated about the risks and symptoms of gastro-intestinal adverse effects.

Cardiovascular risk

There is little evidence that concomitant aspirin removes the potential excess cardiovascular risk associated with NSAIDs. Cardiovascular risk was elevated to a similar degree in people taking low-dose aspirin at baseline as in the entire trial population in the APPROVe and APC studies.^{11,12} In the VIGOR trial, in which aspirin use was not permitted, many of the excess myocardial infarctions that occurred in the rofecoxib group were in patients with an indication for low-dose aspirin therapy¹⁰, underlining the importance of continuing aspirin therapy when it is indicated.

A meta-analysis conducted by the UK National Institute for Clinical Excellence showed a lower rate of symptomatic ulcers plus ulcer complications with meloxicam than comparator NSAIDs³¹; however, this analysis relied almost entirely on studies using a daily meloxicam dose of 7.5 mg whereas meloxicam 15 mg tablets are more commonly prescribed in Australia.³²

Furthermore, the comparator used in many studies in the analysis was piroxicam, which is accepted as having a higher risk of gastro-intestinal adverse effects than ibuprofen, diclofenac or naproxen, which were used as comparators in gastro-intestinal safety studies of other COX-2 selective NSAIDs.³³

Information for patients

Discuss with patients of the possible adverse effects of NSAIDs and direct them to seek prompt medical attention if they experience possible gastro-intestinal, cardiovascular or renal adverse effects, such as:

- black stools or dark, coffee-coloured vomit
- swollen ankles or feet
- chest pain, irregular heart beat, collapse or fainting, or swollen or sore leg veins.

Suggest or provide the appropriate consumer medicine information (CMI) leaflet.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.