



National Prescribing Service Limited

Fact sheet

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Diclofenac and cardiovascular risk

- Paracetamol is preferred first line to NSAIDs because it is an effective analgesic and has a much lower risk of adverse effects. Consider adding an NSAID when paracetamol (and non-drug therapy) does not provide adequate pain relief.
- When considering starting or switching NSAIDs, consider the individual patient's risk of *all* adverse effects, including cardiovascular, gastrointestinal and renal complications.
- People at high risk of the above adverse effects should avoid using an NSAID if possible.
- If an NSAID is used, it should be at the lowest effective dose for the shortest possible duration to minimise the risk of adverse effects.

Media reports of a study showing an increased risk of serious vascular events (such as myocardial infarction) associated with diclofenac have raised concerns that patients taking diclofenac should be switched to another NSAID.¹

What does this review mean for people taking diclofenac?

At present it is difficult to say with any certainty that one NSAID is associated with higher risk than another. It would be premature to recommend that all patients immediately stop taking diclofenac on the basis of this review alone. The review does not provide definitive evidence of elevated vascular risk with diclofenac. In addition, evidence of vascular risk associated with diclofenac should be considered alongside other known risks of NSAIDs.

The decision to use an NSAID and the choice of drug should take into account the individual patient's risk of *all* adverse effects. This includes the possibility of serious gastrointestinal complications such as perforations and bleeding. Diclofenac is associated with a lower risk of gastrointestinal complications than some other NSAIDs, so a switch from it to an alternative could lead to an increase in the risk of these adverse effects.

Further light will be shed on this issue as evidence continues to emerge. In particular, the results of the Therapeutic Goods Administration's assessment of the safety of NSAIDs are still to be released.

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What is the evidence for vascular risk associated with diclofenac and other NSAIDs?

The study is a systematic review of observational studies (that is, cohort and case–control studies). It found an elevated risk of serious vascular events — mainly myocardial infarction — associated with several COX-2 selective and conventional NSAIDs (Table 1).¹ In particular, it suggested that the relative risk of serious cardiovascular events was increased by 40% amongst people taking diclofenac compared with people not taking an NSAID.

The results of the review must be interpreted bearing in mind the limitations of observational studies. Observational studies reflect ‘real world’ use of medicines but they are much more susceptible to bias than randomised controlled trials. The studies included in the review took into account differences between the groups in some risk factors for vascular events, such as age, sex and use of other medicines. However, most were unable to adjust for other potential confounders such as body mass index, smoking and use of over-the-counter NSAIDs. Undetected differences between groups probably remained, which might have biased the results, so that the true effect size is unknown.

Other evidence for an association between use of diclofenac or other conventional NSAIDs and elevated cardiovascular risk is scarce and comes either from trials not designed to assess vascular event risk or from observational studies. Evidence about the vascular risk associated with COX-2 selective NSAIDs (such as celecoxib, lumiracoxib and rofecoxib) is more reliable, because large randomised controlled trials have been conducted to specifically address this question.

Consider the risk of *all* adverse effects when choosing an NSAID

The recent media reports focus on the potential vascular adverse effects of NSAIDs. NSAIDs can also cause serious gastrointestinal adverse effects. Carefully consider an individual’s risk of gastrointestinal, as well as vascular, adverse effects when choosing an NSAID. Patients judged to be at higher risk of adverse effects should avoid using an NSAID if possible.

On average 7 in 1000 people with osteoarthritis and 13 in 1000 with rheumatoid arthritis who take an NSAID for 1 year will experience a serious gastrointestinal adverse effect such as perforation, obstruction or bleeding.² Individuals vary in their risk of gastrointestinal adverse effects — the incidence of complications is higher in people with risk factors such as age > 65 years, a history of gastroduodenal ulcer and concomitant corticosteroids or anticoagulants. The choice and dose of NSAID also influences gastrointestinal risk. Diclofenac (in addition to celecoxib, ibuprofen ≤ 1200 mg and lumiracoxib) is associated with a low risk of gastrointestinal adverse effects. For people with risk factors for gastrointestinal complications, it is particularly important to choose an NSAID with a low risk of causing these adverse effects.

In clinical trials, approximately 12 in 1000 people taking a COX-2 selective NSAID for a year have experienced serious vascular events — 3 per 1000 more than with placebo treatment.³ This increased number of events would be higher amongst people at higher baseline cardiovascular risk. Evidence to distinguish between the NSAIDs in terms of cardiovascular risk is still emerging. At present it is difficult to say with any certainty that one NSAID is associated with higher risk than another.

NSAIDs can also cause acute renal failure and may exacerbate heart failure symptoms or cause them to develop in certain susceptible people. To date there is little evidence that NSAIDs differ in their propensity to cause these adverse effects.

Minimising the risk: lowest dose, shortest duration

If an NSAID is necessary, it should be used at the lowest effective dose and for the shortest time possible to minimise the risk of adverse effects. For persistent pain, adding short courses of an NSAID to regular paracetamol can help to control intermittent pain while minimising the risk of adverse effects.

Other NPS resources about NSAIDs

For more information, see also:

- NPS RADAR '[Elevated cardiovascular risk with NSAIDs?](#)' 1 August 2005
- NPS News 47: [Analgesic options for pain relief](#), August 2006
- Prescribing Practice Review 35: [Analgesic choices in persistent pain](#), September 2006

The NPS program, *Analgesic choices in persistent pain*, includes a range of educational resources and activities — including educational visiting, case studies and clinical audits — focusing on safe and effective use of analgesics in osteoarthritis and persistent back pain.

Table 1: Risk of serious vascular events associated with NSAIDs in a systematic review of observational studies

Drug	Relative risk of a serious vascular event* (95% confidence interval)
Celecoxib	1.06 (0.91 to 1.23)
Diclofenac	1.40 (1.16 to 1.70)
Ibuprofen	1.07 (0.97 to 1.18)
Meloxicam	1.25 (1.00 to 1.55)
Naproxen	0.97 (0.87 to 1.07)
Piroxicam	1.06 (0.70 to 1.59)
Rofecoxib (\leq 25 mg/day)	1.33 (1.00 to 1.79)
Rofecoxib ($>$ 25 mg/day)	2.19 (1.64 to 2.91)

*Serious vascular events evaluated in included studies were first or any fatal or non-fatal myocardial infarction, unstable angina pectoris, any thromboembolic cardiovascular event, ischaemic stroke and sudden cardiac death.

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.

References

1. McGettigan P & Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296:published online 13 September 2006.
2. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumat* 1999;26 Suppl 26:18-24.
3. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.