Cardiovascular issues of COX-2 inhibitors and NSAIDs

Melinda Wong, MBBS, FRACP, is Consultant Rheumatologist, Department of Rheumatology, St Vincent's Hospital, Melbourne, Victoria. melinda.wong@svhm.org.au

Phil Chowienczyk, FRCP, is Professor of Cardiovascular Pharmacology, Cardiovascular Division, King's College London, Department of Clinical Pharmacology, St Thomas' Hospital, London.

Bruce Kirkham, BA, MD, FRCP, FRACP, is Clinical Head, Rheumatology/Lupus, Department of Rheumatology, Guy's and St Thomas' Hospital, London.

BACKGROUND

Rofecoxib (Vioxx) was withdrawn from the market because of increased death from cardiovascular (CV) events. Other selective cyclooxygenase-2 (COX-2) inhibitors and traditional nonsteroidal anti-inflammatory drugs (NSAIDs) may share this risk, but to what extent is unclear.

OBJECTIVE

This article reviews the available evidence using a PubMed search for increased CV risk with COX-2 inhibitors and NSAIDs, explores possible mechanisms, and makes recommendations for their appropriate use in clinical practice.

DISCUSSION

Rofecoxib, celecoxib, and the combination of valdecoxib and parecoxib have been found in prospective trials to increase CV risk. NSAIDs have also been found to be associated with increased CV risk in observational studies, but large randomised controlled trials with adequate follow up are required to further investigate this. Recommendations are to use drugs at lowest dose and for shortest duration possible. In patients with or at high risk for CV disease, COX-2 inhibitors are contraindicated. A traditional NSAID plus proton pump inhibitor may be used, but with caution.

The selective cyclooxygenase-2 (COX-2) inhibitors gained widespread popularity, having equivalent analgesic and anti-inflammatory effect as the traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), yet with reduced gastrointestinal (GI) side effects.[1–5] However, rofecoxib (Vioxx) was shown to increase the risk of certain cardiovascular (CV) events: myocardial infarct (MI) and ischaemic stroke.[6] Cardiovascular safety of all COX-2 inhibitors, and indeed traditional NSAIDs, have since been under intense investigation. As these drugs are commonly used by patients with inflammatory arthritis, or older patients with osteoarthritis (OA) (groups already at an increased risk of vascular disease) this has caused major concern.[7]

Rofecoxib and CV disease risk

Rofecoxib was withdrawn from the market following the findings of the Adenomatous Polyp Prevention On Vioxx (APPROVe) study.[6] This was a multi-centre, randomised, placebo controlled, double blind study designed to determine whether or not rofecoxib prevented recurrence of colorectal polyps in patients with a history of colorectal adenomas. The study was terminated early due to the unexpected finding of a doubling of risk of CV events in the rofecoxib group compared with the placebo group (1.50 vs. 0.78 events per 100 patient years). This increased risk became apparent only after 18 months of treatment.[6] Previous studies may have missed this finding because outcomes were assessed at 1 year or less,[1,2,8,9] although a meta-analysis of randomised controlled trials and observational studies using rofecoxib found risk of MI to be increased after a few months of treatment.[10,11]

The APPROVe study also found congestive heart failure and pulmonary oedema to be increased in the rofecoxib group, but this became evident at around 5 months. Use of rofecoxib is associated with a higher incidence of hypertension, peripheral oedema, and congestive heart failure compared with celecoxib and NSAIDs.[1,12–14] This may contribute to the higher CV risk with chronic use of rofecoxib.

Debate regarding the CV safety of COX-2 inhibitors arose in 2000 from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study. This found a fourfold increase in risk of MI in patients taking rofecoxib (50 mg/day) compared to patients taking naproxen (incidence of MI, 0.4% vs. 0.1%).[1] In

contrast, the Celecoxib Long-term Arthritis Safety Study (CLASS) did not show a higher incidence of MI in patients taking celecoxib compared to patients taking diclofenac or ibuprofen. Differences in patient characteristics and concomitant use of aspirin were suggested to account for the differing findings between these studies.[2] Rheumatoid arthritis (RA) patients have a higher CV risk[7] and were included in the VIGOR study, while only patients with OA were enrolled in the CLASS study. Furthermore, 20% of patients in the CLASS study were using aspirin, while aspirin was not permitted in the VIGOR study. It was also suggested that naproxen, the comparator drug in the VIGOR study, may have a cardioprotective effect, but more recent studies suggest that this is not the case.[11,15,16]

Table 1. Therapeutic Goods Administration review on the use of COX-2 inhibitors (February 2005)

- Patients taking more than 200 mg per day of celecoxib or more than 15 mg per day of meloxicam should have treatment reviewed
- Celecoxib and meloxicam should not be prescribed for patients with increased CV risk
- Celecoxib and meloxicam should be prescribed only when other treatments cannot be tolerated or have caused serious adverse effects, and should be limited to the shortest time needed
- It is proposed that parecoxib and valdecoxib be withdrawn in Australia
- It is proposed that the approved uses for etoricoxib and lumiracoxib be greatly limited (these have not yet been marketed in Australia)

Is increased CV risk seen with other COX-2 inhibitors and NSAIDs?

There is mounting evidence that increased CV risk is seen with other COX-2 inhibitors and may indeed be seen with traditional NSAIDs. The Adenoma Prevention with Celecoxib (APC) study was similar to the APPROVe study both in design and the decision to terminate early because of increased risk of CV events. Death from CV causes, MI, stroke, or heart failure was higher in the groups taking celecoxib; 200 mg twice per day and 400 mg twice per day compared to the placebo group (7.8 and 11.4 vs. 3.4 events per 1000 patient years).[17] Like the APPROVe study, this increased CV risk became apparent only after at least 12 months of treatment. Furthermore, both studies found increased CV risk with increasing doses, which supports findings from previous studies.[1,6,10,17]

However, whether CV risk is increased with celecoxib is still debated; it has been suggested that rofecoxib has the higher risk.[10,14,18] A case controlled study with 1.4 million patients in Kaiser Permanente Health Insurance Scheme, California, found relative risk (95% confidence interval) from MI or sudden cardiac death for celecoxib 0.77 (0.60–0.99), naproxen 1.11 (0.96–1.30), rofecoxib 25 mg 1.02 (0.71–1.46), and rofecoxib >25 mg 5.04 (0.94–27.06).[18]

Evidence for CV risk with meloxicam is more limited. In a British cohort of patients, users of rofecoxib were found to have a higher incidence of cerebrovascular events compared to users of meloxicam (0.48% vs. 0.27%; relative risk 1.68), but not in CV events.[19] There were similar findings when comparing celecoxib with meloxicam (incidence of cerebrovascular events 0.39% vs. 0.27%; relative risk 1.66).[20] However, the cohort size was small, data on concomitant use of aspirin was incomplete, and there was no comparison made with patients using traditional NSAIDs or on no treatment.

Intravenous parecoxib and/or oral valdecoxib given postcoronary artery bypass graft surgery has been found to increase the risk of CV events. Myocardial infarct, cardiac arrest, stroke, and pulmonary embolism were more frequent among the patients given parecoxib and valdecoxib than among those given placebo (2.0% vs. 0.5%; relative risk 3.7). This study also highlights the risk of using COX-2 inhibitors in high CV risk patients, these patients being excluded from previous randomised controlled trials.[21]

As demonstrated by the APPROVe and APC studies, large long term trials are required in order to answer the CV question. However, pooled data from several smaller studies is all that is available for valdecoxib and etoricoxib, with no significant increase in CV events found.[8,9,22] More recently however, the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) was a large study designed to look at CV risk with lumiracoxib. Patients with OA were randomised to take lumiracoxib, naproxen or ibuprofen, with the primary endpoint being MI, stroke, and CV death. There was no difference in CV events when lumiracoxib was compared with naproxen and ibuprofen, irrespective of aspirin use.[8] Of clinical significance, the gastrointestinal benefits of lumiracoxib were lost when used together with aspirin, as has also been demonstrated with celecoxib in the CLASS study.[3]

Traditional NSAIDs have also been implicated. Recent case control studies suggested an increased risk of MI with the use of diclofenac, ibuprofen,[16,23] indomethacin, sulindac, piroxicam, and meloxicam.[23] The highest risk was associated with the use of indomethacin, with adjusted odds ratio (95% confidence interval) of 1.71, 1.35–2.17. Although these observational postmarketing cohorts are useful to investigate the use of medications in 'real life' practice, further prospective studies designed to answer the CV question for NSAIDs are required.

How might COX-2 inhibitors and NSAIDs increase CV events?

Pro-thrombotic vascular environment

Selective inhibition of COX-2 could theoretically predispose to a pro-thrombotic vascular environment. Cyclo-oxygenase-1 (COX-1) and COX-2 isoenzymes catalyse the conversion of arachidonic acid to prostaglandins. COX-1 is the main source of production of thromboxane A-2 (TXA-2) which mediates platelet aggregation

and vasoconstriction. COX-2 is the main source of prostacyclin (PGI-2) which has vasodilating, anti-aggregatory and antiproliferative effects. Therefore, selective inhibition of COX-2 causes suppression of PGI-2 without affecting TXA-2, and theoretically could predispose to hypertension and thromboembolic events.[24] Higher COX-2 selectivity and longer half life of rofecoxib compared to celecoxib has been proposed as the reason for higher CV risk associated with rofecoxib. However, this is probably less important given that etoricoxib and lumiracoxib have several fold higher COX-2 selectivity, and etoricoxib a longer half life than rofecoxib.

Renal impairment and hypertension

Both COX-2 inhibitors and NSAIDs predispose to renal impairment, hypertension and peripheral oedema, and it is possible that these may contribute to increase CV risk.[25,26] Rofecoxib is associated with a higher incidence of hypertension, peripheral oedema, and congestive heart failure compared with celecoxib and NSAIDs.[1,12–14] It has been suggested that the higher rates of hypertension seen with rofecoxib may be related to its metabolism by cytoplasmic reductases. The other four COX-2 inhibitors are metabolised via the cytochrome P450 enzymes. Vasoactive hormones, including aldosterone, are also metabolised by cytoplasmic reductases, so it is plausible that rofecoxib competitively inhibits metabolism of these hormones.[27]

Can COX-2 inhibitors improve CV risk?

There are theoretical mechanisms and some evidence that COX-2 inhibition may have a beneficial effect on vascular endothelial function. Inhibition of COX-2 may decrease vascular inflammation, mononuclear cell infiltration, improve nitric oxide availability, enhance plaque stability, and decrease atherosclerosis progression.[28]

Improvements in abnormal vascular endothelial function with celecoxib have been shown in patients with hypertension and with coronary artery disease already taking aspirin and statins.[29,30] Furthermore, in patients with coronary artery disease, high sensitivity C-reactive protein (HsCRP) and oxidised-LDL (Ox-LDL) decreased after treatment with celecoxib.[30] Improved vascular endothelial function has not been found in studies using rofecoxib[31–34] or parecoxib.[35] However, it is likely that mechanisms which increase thrombogenicity outweigh any beneficial effects on vascular endothelial function.

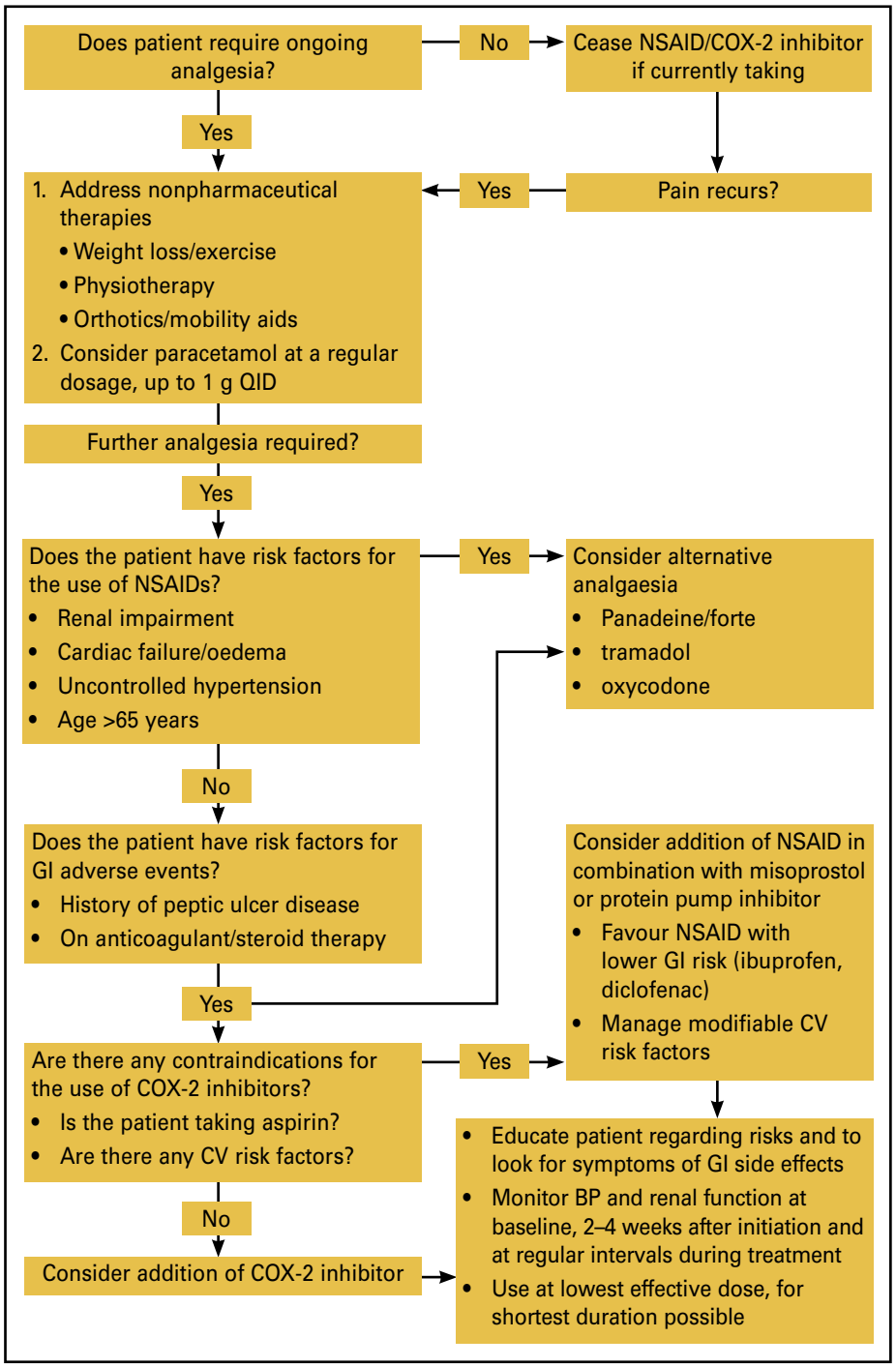

Figure 1. Decision making flowchart for the continuation or commencement of COX-2 inhibitors and NSAIDs

Conclusion

Rofecoxib is associated with increased CV risk. There is increasing evidence to suggest that this may indeed be a class effect, and that risk is associated with chronic use and higher doses. Recent studies have also

implicated traditional NSAIDs, possibly via similar mechanisms. *Table 1* summarises the review made by the Australian Therapeutic Goods Administration with regard to COX-2 inhibitors. A suggested decision making pathway for continuation or commencement of COX-2 inhibitors and NSAIDs is outlined in *Figure 1*.

Further reading

NPS Radar Review. Elevated cardiovascular risk with NSAIDs? Available at: www.npsradar.org.au/site.php?page=1&content=npsradar/content/nsaids.html

Conflict of interest: none declared.

References

1. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343:1520–8.
2. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomised controlled trial. Celecoxib Long term Arthritis Safety Study. JAMA 2000;284:1247–55.
3. Schnitzer TJ, Burmester GR, Mysler E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665–74.
4. Hunt RH, Harper S, Watson DJ, et al. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. Am J Gastroenterol 2003;98:1725–33.
5. Goldstein JL, Kivitz AJ, Verburg KM, Recker DP, Palmer RC, Kent JD. A comparison of the upper gastrointestinal mucosal effects of valdecoxib, naproxen and placebo in healthy elderly subjects. Aliment Pharmacol Ther 2003;18:125–32.
6. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092–102.
7. Wong M, Toh L, Wilson A, et al. Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation. Arthritis Rheum 2003;48:81–9.
8. Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675–84.
9. White WB, Strand V, Roberts R, Whelton A. Effects of the cyclooxygenase-2 specific inhibitor valdecoxib versus nonsteroidal antiinflammatory agents and placebo on cardiovascular thrombotic events in patients with arthritis. Am J Ther 2004;11:244–50.
10. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004;109:2068–73.
11. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004;364:2021–9.
12. Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. Hypertension 2004;44:140–5.
13. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2 specific inhibitors and cardiorenal function: a randomised, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther 2001;8:85–95.
14. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population based cohort study. Lancet 2004;363:1751–6.
15. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case control study. Lancet 2005;365:475–81.
16. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case control analysis. BMJ 2005;330:1366.
17. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.
18. Campen DH, Graham D, Cheetham C, et al. Risk of acute cardiac events among patients treated with cyclooxygenase-2 selective and nonselective nonsteroidal anti-inflammatory drugs. Arthritis Rheum 2004;50(9 Suppl):S657/1756.
19. Layton D, Heeley E, Hughes K, Shakir SA. Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription event monitoring (PEM) data. Rheumatology (Oxford) 2003;42:1342–53.
20. Layton D, Hughes K, Harris S, Shakir SA. Comparison of the incidence rates of thromboembolic events reported for patients prescribed celecoxib and meloxicam in general practice in England using Prescription-Event Monitoring (PEM) data. Rheumatology (Oxford) 2003;42:1354–64.
21. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352:1081–91.
22. Curtis SP, Mukhopadhyay S, Ramey D, Reicin A. Cardiovascular safety summary associated with the etoricoxib development program. Arthritis Rheum 2003;48(Suppl 9):S616.
23. Singh G, Mithal A, Triadafilopoulos G. Both selective COX-2 inhibitors and non-selective NSAIDs increase the risk of acute myocardial infarction in patients with arthritis: selectivity is with the patient, not the drug class. Ann Rheum Dis 2005;64(Suppl III):85. Abstract.
24. Fitzgerald GA. Coxibs and Cardiovascular Disease. N Engl J Med 2004;351:1709–11.
25. Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of COX-2-selective inhibitors. Am J Nephrol 2001;21:1–15.
26. Curtis SP, Ng J, Yu Q, et al. Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. Clin Ther 2004;26:70–83.
27. Krum H, Liew D, Aw J, Haas S. Cardiovascular effects of selective cyclooxygenase-2 inhibitors. Expert Rev Cardiovasc Ther 2004;2:265–70.
28. Baker CS, Hall RJ, Evans TJ, et al. Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalises with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages. Arterioscler Thromb Vasc Biol 1999;19:646–55.
29. Widlansky ME, Price DT, Gokce N, et al. Short and long term COX-2 inhibition reverses endothelial dysfunction in patients with hypertension. Hypertension 2003;42:310–5.
30. Chenevard R, Hurlimann D, Bechir M, et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. Circulation 2003;107:405–9.
31. Monakier D, Mates M, Klutstein MW, et al. Rofecoxib, a COX-2 inhibitor, lowers C-reactive protein and interleukin-6 levels in patients with acute coronary syndromes. Chest 2004;125:1610–5.
32. Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. J Am Coll Cardiol 2003;42:1747–53.
33. Verma S, Raj SR, Shewchuk L, Mather KJ, Anderson TJ. Cyclooxygenase-2 blockade does not impair endothelial vasodilator function in healthy volunteers: randomized evaluation of rofecoxib versus naproxen on endothelium dependent vasodilatation. Circulation 2001;104:2879–82.
34. Wong M, Kirkham B, Jiang B, McNeill K, Chowienczyk P. Effects of indometacin and rofecoxib on vascular function in patients with rheumatoid arthritis. Arthritis Rheum 2004;50(9 Suppl): S383/942.
35. Bulut D, Liaghat S, Hanefeld C, Koll R, Miebach T, Mugge A. Selective cyclo-oxygenase-2 inhibition with parecoxib acutely impairs endothelium dependent vasodilatation in patients with essential hypertension. J Hypertens 2003;21:1663–7.

AFP

Correspondence
Email: afp@racgp.org.au