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Selective Cyclo-Oxygenase-2 Inhibitors and Myocardial Infarction

How Strong is the Link?

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Abstract

There are concerns that selective cyclo-oxygenase (COX)-2 inhibitors may be prothrombotic and increase the risk of myocardial infarction. This has largely arisen because of an unexpected finding of a higher rate of myocardial infarction in patients receiving rofecoxib compared with patients receiving naproxen in a study of gastrointestinal toxicity. The results of this study, a similar study of celecoxib versus ibuprofen or diclofenac, and data obtained from a meta-analysis of aspirin (acetylsalicylic acid) primary prevention trials suggest that differences in the rates of myocardial infarction between rofecoxib and naproxen may have been due to an unexpectedly low rate of myocardial infarction in patients receiving naproxen. However, population surveillance data also suggest that rofecoxib may be associated with a greater risk of myocardial infarction than celecoxib and certain nonselective nonsteroidal anti-inflammatory drugs. The magnitude of this increase in risk, if real, is uncertain but it is likely to be relatively small in patients for whom cardiovascular prophylaxis with aspirin is not indicated. Patients who require nonsteroidal anti-inflammatory therapy for arthritis and who are at high risk of cardiovascular disease should receive aspirin, probably in conjunction with selective COX-2 inhibitor therapy, as the risk of gastrointestinal ulceration may be lower than for aspirin plus a nonselective nonsteroidal anti-inflammatory drug. In patients who do not require aspirin for the prevention of cardiovascular events, the lower risk of gastrointestinal ulceration associated with COX-2 inhibitor compared with non-selective nonsteroidal anti-inflammatory drugs would be expected to outweigh any increase in the risk of myocardial infarction, if one exists.

Recent publications[1,2] have raised concerns that cyclo-oxygenase (COX)-2 inhibitors (celecoxib and rofecoxib) may be prothrombotic and increase the risk of myocardial infarction. This has arisen because of theoretical concerns that COX-2 inhibitors may affect the balance between prothrombotic and antithrombotic prostaglandins.[1,2] Furthermore, of two studies comparing COX-2 inhibitors with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs),[3,4] one found a significantly higher rate of myocardial infarction in patients receiving rofecoxib compared with the NSAID naproxen.[4]

Selective COX-2 inhibitors reduce the forma-

tion of prostacyclin while having little or no significant impact on thromboxane production.[1,2] COX-2 plays a role in the cardio-protection afforded by the late phase of ischaemic preconditioning.[5] COX-2 is expressed in atherosclerotic plaques and may play a role in either the inflammatory atherosclerotic process or in plaque stabilisation.[6] NSAIDs have been shown to have inhibitory effects on platelet aggregation due to inhibition of thromboxane formation in humans, while selective COX-2 inhibitors have no significant effect.[7] However, unlike aspirin (acetylsalicylic acid), NSAIDs do not appear to significantly reduce the risk of myocardial infarction in humans[8,9] – with the possible exception of naproxen.[10-12] Selective COX-2 inhibition has been shown to increase infarct size in animals following coronary artery ligation,[13] but to paradoxically improve cardiac function following myocardial infarction.[14] Mice genetically deficient in the IP (prostacyclin) receptor (which mediates the vascular effects of prostacyclin) demonstrate enhanced injury-induced vascular smooth muscle cell proliferation and platelet activation, suggesting that the removal of the effects of prostacyclin would have adverse vascular effects.[15] In addition, addition of celecoxib therapy to dogs pre-treated with high-dose aspirin abolished the delay in electrolytically-induced occlusion of coronary arteries afforded by aspirin.[16] Thus, selective COX-2 inhibitors could theoretically have both adverse or beneficial effects in patients at risk of experiencing myocardial infarction.

1. Myocardial Infarction in Randomised, Controlled Clinical Trials of Selective Cyclo-Oxygenase (COX)-2 Inhibitors Versus Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Celecoxib Long-Term Arthritis Safety Study (CLASS)[3] and Vioxx Gastrointestinal Outcomes Research (VIGOR) study[4] were two large comparative trials designed to assess differences in the risk of gastrointestinal ulceration and its complications between COX-2 inhibitors and NSAIDs when used for the treatment of arthritis. CLASS failed to demonstrate a significant benefit of celecoxib on the primary endpoint of complicated upper gastrointestinal ulcers. In contrast, VIGOR demonstrated a significant benefit in favour of rofecoxib on the primary endpoint of complicated plus confirmed, symptomatic uncomplicated ulcers. It should be noted that the primary endpoint for VIGOR was more liberal than for CLASS, and the comparable (secondary) endpoint for CLASS was statistically significant in favour of celecoxib. The effects of these drugs on cardiovascular thrombotic events were not pre-specified nor adjudicated end points, and much larger studies would have been needed to adequately study these outcomes. The two studies were of a similar size and duration. CLASS included patients with osteoarthritis or rheumatoid arthritis, while VIGOR included only patients with rheumatoid arthritis.

A potentially important difference in the entry criteria of these two trials related to the use of aspirin. Twenty-two percent of the patients in the CLASS study were taking aspirin while aspirin use was prohibited in the VIGOR trial. Four percent of the VIGOR study population were retrospectively deemed to be deserving of aspirin therapy for cardiovascular prophylaxis as they had a history of myocardial infarction, unstable or chronic stable angina, previous coronary revascularisation, stroke or transient ischaemic attack. These patients almost certainly were at significantly higher risk of myocardial infarction than the patients who took aspirin in the CLASS study, partly because they were not taking aspirin and because the patients taking aspirin in the CLASS study were probably more representative of the general, and less clearly indicated, use of aspirin in the community.

The main features of these two studies are presented in table I. Myocardial ischaemic events in these two studies have been analysed in reports published by the US Food and Drug Administration (FDA).[17,18] The FDA reports include some differences in the number of events described compared with the results reported in the primary publications of the CLASS trial.[3] This difference is due to the inclusion of additional data collected subsequent to the publication of the 6-month data for the CLASS trial, which was designed to run until 45 primary endpoints were obtained.

Table I. Characteristics of the Celecoxib Long-Term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research (VIGOR) study populations

	CLASS[a]	VIGOR[a]
Number of patients	8059	8076
Duration	12 months (6-month data initially published)	0.5-13 months (median 9)
Age (y)	60 (18-90)	58 ± 10
Women	70%	80%
Cardiovascular exclusions	None	Myocardial infarction in last year
Smokers	15%	20%
Cardiovascular risk factors other than smoking	Not stated	50% (one or more)
Aspirin (acetylsalicylic acid) use	20%	Aspirin users excluded
Arthritis aetiology	27.3% rheumatoid arthritis. Remainder osteoarthritis	All rheumatoid arthritis
Drug therapy	Celecoxib 400mg twice daily or ibuprofen 800mg three times daily or diclofenac 75mg three times (this is twice the usual dose of celecoxib compared with the usual doses of ibuprofen and diclofenac)	Rofecoxib 50 mg/day or naproxen 500mg twice daily (this is twice the usual dose of rofecoxib compared with the usual dose of naproxen)

a Number of withdrawals similar in both treatment arms of both studies.

The estimated rates of myocardial infarction, expressed as percent per patient per year at risk (PPY) were 0.82 (95% confidence interval [CI] 0.55 to 1.09) for celecoxib compared with 0.60 (95% CI 0.36 to 0.84) for the NSAIDs ibuprofen or diclofenac in the CLASS study and 0.74 (95% CI 0.48 to 1.00) for rofecoxib and 0.15 (95% CI 0.03 to 0.27) for naproxen in the VIGOR study. It is clear that among the four groups studied the result at variance from the rest is the low rate of myocardial infarction in the naproxen arm of the VIGOR study. It should be noted that these estimates of the rate of myocardial infarction are based on a very small number of events. Only four myocardial infarctions occurred in the naproxen arm of the VIGOR study compared with 20 in the rofecoxib arm of the VIGOR trial, which studied 8076 patients for a median of 9 months. Thirty-seven percent of the myocardial infarctions in the VIGOR study occurred in the 4% of patients who were retrospectively considered to have indications for aspirin therapy. Nonetheless, the difference in myocardial infarction between rofecoxib and naproxen arms of the VIGOR trial was statistically significant, and much has been made of it.

The potential impact of the use of aspirin can be assessed by comparing the rates of myocardial infarction in patients from the CLASS study who did not receive aspirin with the majority of patients in the VIGOR study in whom aspirin was, in retrospect, not considered to be indicated. The rates for myocardial infarction in these groups were 0.28 (95% CI 0.04 to 0.52) for celecoxib, 0.23 (95% CI 0.00 to 0.52) for ibuprofen/diclofenac, 0.46 (95% CI 0.20 to 0.72) for rofecoxib and 0.15 (95% CI 0.00 to 0.30) for naproxen. While the rate for rofecoxib remained significantly higher than that of naproxen, the apparently higher incidence for rofecoxib compared with celecoxib and ibuprofen/diclofenac was not statistically significant.

2. Meta-Analysis of Trials Reporting Myocardial Infarction During COX-2, NSAID or Aspirin (Acetylsalicylic Acid) Therapy

A paper by Mukherjee et al.[1] argues that the rates of myocardial infarction observed during selective COX-2 inhibitor therapy in the CLASS and VIGOR study are significantly higher than that found for patients receiving placebo in a meta-analyses of studies evaluating the use of aspirin for the primary prevention of cardiovascular disease.[19] The authors argue that these observations support a prothrombotic effect of selective COX-2 inhibitor therapy in increasing the risk of myocardial infarction. They cite a myocardial infarction rate of 0.52% (95% CI 0.43 to 0.61) per patient year at risk in patients not receiving aspirin in the meta-analysis of primary prevention studies of as-

pirin. The paper by Mukherjee et al.[1] had some major limitations, the main one being the inappropriate comparison of rates of myocardial infarction across studies performed in different populations. Other limitations included the fact that cardiovascular endpoints were not prespecified in the CLASS and VIGOR studies, and a lack of homogeneity in the variance of the meta-analysis of aspirin primary prevention trials.[19]

Comparisons between the rates of myocardial infarction during celecoxib, ibuprofen or diclofenac, rofecoxib or naproxen therapy with the rate of myocardial infarction in patients receiving and not receiving aspirin in the meta-analyses of aspirin trials is presented in figure 1.

The individual rates of myocardial infarction from the four studies used in this meta-analyses are presented in table II. Myocardial infarction rates varied from 0.36 to 1.13, a range which encompasses the incidence observed in the celecoxib and the NSAID arms of the CLASS and the rofecoxib arm of VIGOR, but not the naproxen arm of VIGOR.

It is of interest that the lowest rate of myocardial infarction was found in the Hypertension Optimal Treatment (HOT) study despite this population consisting entirely of patients with hypertension, 20% of whom had established cardiovascular disease.[20] The populations studied varied considerably between these trials, raising concerns about the appropriateness of including them in a meta-analysis. Furthermore, an important point was not conceded in the article by Mukherjee et al.[1] The rate of myocardial infarction in the naproxen arm of the VIGOR study was significantly lower than the rates observed in both the control group ($p = 0.02$) and the aspirin treated group ($p = 0.02$) of the meta-analyses of aspirin primary prevention studies (figure 1).

Table II. Rates of myocardial infarction (percentage of patients per year exposed) observed in the placebo arms of the four trials included in a meta-analysis of the effects of aspirin (acetylsalicylic acid) for the primary prevention of cardiovascular disease[19]

US Doctors Study	0.44
UK Doctors Study	0.93
Thrombosis Prevention Trial	1.30
Hypertension Optimal Treatment Study	0.36
All	**0.52 (aspirin = 0.37)**

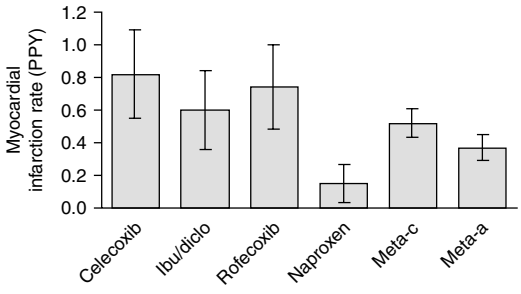

Fig. 1. Myocardial rates expressed as the percentage of patients per year exposed (PPY) to celecoxib and ibuprofen/diclofenac (ibu/diclo) from the Celecoxib Long-Term Arthritis Safety Study (CLASS) study, rofecoxib and naproxen from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study and patients receiving placebo (meta-c) or aspirin (acetylsalicylic acid) [meta-a] from a meta-analysis of trials that evaluated the use of aspirin as primary prevention for cardiovascular disease. The rate of myocardial infarction for naproxen in the VIGOR study was significantly ($p < 0.05$) lower than in all the other groups, including the patients who received aspirin in the meta-analysis of aspirin therapy.[3,4,19]

A meta-analyses of trials comparing rofecoxib with NSAIDs concluded that the rate of cardiovascular thrombotic events was significantly lower in patients who received naproxen therapy than in those who received other NSAIDs or rofecoxib (the rate of myocardial infarction did not differ between patients receiving rofecoxib, non-naproxen NSAIDs or placebo).[21] The authors suggested that the lower incidence of thrombotic vascular events in patients receiving naproxen may have been due to a greater inhibition of platelet aggregation by naproxen than other NSAIDs. Differences in the rate of thrombotic vascular events between naproxen and other NSAIDs in the meta-analysis of prospective randomised rofecoxib trials[22] may have been significantly influenced by the VIGOR study, which accounted for approximately 55% of the patient years of follow up. However, three case control studies have supported a reduced risk of myocardial infarction in patients receiving naproxen compared with other NSAIDS or placebo,[10-12] while another large cohort study found no difference.[9] The relative risk for myocardial infarction in patients receiving naproxen

therapy in these trials ranged from 0.61 to 0.95. It therefore seems unlikely that a beneficial effect of naproxen on myocardial infarction alone accounted for the 80% difference in the rate of myocardial infarction between naproxen and rofecoxib in the VIGOR study.

3. Selective COX-2 Inhibitors and Myocardial Infarction in Postmarketing Surveillance Data

The relative rates of reporting of suspected adverse drug reactions involving celecoxib and rofecoxib has been reported from data collected by the World Health Organization/Uppsala Monitoring Centre (WHO/UMC).[22] The extent to which an adverse event appeared to be reported more frequently than expected was expressed using a statistical parameter designated the information component (IC), which was calculated from the number of reports of a specific adverse event attributable to a particular drug divided by the product of the total number of reports of the specific adverse event and the total number of all adverse event reports involving the drug. An IC value of 1.0 indicated a reporting rate equivalent to that expected if the drug was not specifically associated with the adverse event. This study had the usual, potentially major, limitations of adverse drug reaction reports, including reporting that is influenced by publicity surrounding the release of a drug or the publicising of a new adverse event, a potential lack of homogeneity between the populations using different drugs, and differences in the patterns of use of drugs. Nonetheless, the data are of some interest. The analysis was based on a total of 8434 reports of adverse events for celecoxib and 2720 reports for rofecoxib.

Reports of myocardial infarction during rofecoxib therapy were significantly higher than expected (IC = 1.44, 95% CI 0.92 to 1.96), while reports for celecoxib were lower than the number expected. (IC = 0.37, 95% CI 0.07 to 0.81). Reports of cerebrovascular events were also significantly higher than expected for rofecoxib (IC = 1.48, 95% CI 1.09 to 1.87) but were lower than expected for celecoxib (IC = 0.03, 95% CI 0.35 to 0.41).

Reporting of other thrombotic events did not differ from the number expected for either rofecoxib or celecoxib, although it should be noted that this category included venous as well as arterial thromboses. Reports of treatment emergent hypertension or increases in blood pressure were significantly more frequent than expected for rofecoxib, but not for celecoxib. Similar results were found for oedema and worsening renal function. Reports of myocardial infarction, stroke, hypertension and renal dysfunction during celecoxib were similar to the rates observed for NSAIDs. In support of these findings, significantly more patients receiving rofecoxib discontinued therapy in the VIGOR study[18] because of hypertension-related adverse events than those receiving naproxen while adverse events related to blood pressure elevation in the CLASS study appeared to be very low and similar for celecoxib and ibuprofen/diclofenac.[17] Rofecoxib 25 mg/day has been shown to increase blood pressure to a greater extent than celecoxib 200 mg/day in a 6 week study in 810 patients with hypertension in one study.[23]

If a greater risk of myocardial infarction exists in patients receiving rofecoxib than celecoxib or NSAIDs, it is possible that this is due to a greater effect of rofecoxib in increasing blood pressure rather than a prothrombotic effect. It is unclear why rofecoxib may be more likely to increase blood pressure than celecoxib at the commonly used clinical doses. Possible explanations include inherent pharmacological differences between the two drugs or differences in the extent of COX-2 inhibition at doses considered to be clinically equivalent. Previous studies have suggested equivalent analgesic and anti-inflammatory effects of celecoxib 200 mg/day and rofecoxib 25 mg/day.[24] However, clinical estimates of analgesic and anti-inflammatory effects may be less precise indices of COX-2 inhibition than blood pressure.

In conclusion, while differences in the rates of myocardial between celecoxib, rofecoxib, ibuprofen, diclofenac and naproxen in the CLASS and VIGOR trials may have been due to an unexpectedly low rate of myocardial infarction in the naproxen arm of the VIGOR study, rofecoxib therapy may be associated with a greater risk of myo-

cardial infarction than celecoxib and certain NSAIDs, perhaps because of a greater tendency to increase blood pressure. However, the issue of whether selective COX-2 inhibitors, and in particular rofecoxib, have a prothrombotic effect remains uncertain. It also remains uncertain whether the use of selective COX-2 inhibitors may negate the beneficial effects of aspirin in patients at high risk of cardiovascular disease. Animal studies support this possibility,[16] while the analysis of data from patients receiving aspirin in the CLASS study provide some reassurance. Very large trials would be needed to resolve this issue, a fact which places into perspective the relatively low risk of a putative increase of the risk of myocardial infarction in patients with arthritis in whom aspirin prophylaxis is not indicated compared with the risk of gastrointestinal ulceration, which occurs in 15 to 44% of patients receiving NSAIDs for up to 6 months.[25] At least one such study is planned comparing the selective COX-2 inhibitor lumiracoxib with NSAIDS in 18 000 patients over a 1-year period (the Therapeutic Arthritis Research and Gastrointestinal Event Trial).

4. Implications for the Use of COX-2 Inhibitors and Nonselective NSAIDs in Patients at High Risk of Cardiovascular Disease

It is now well established that patients at high risk of cardiovascular disease should receive aspirin. Aspirin appears to be of definite value if the risk of myocardial infarction is greater than 1.5% per patient per year of risk and of possible value in patients with risks of 1.0 to 1.5%.[14] Patients with a lower risk of myocardial infarction should not receive aspirin (and certainly not NSAIDs) as prophylactic treatment for the prevention of thrombotic vascular disease as the risks of treatment (principally gastrointestinal haemorrhage and other bleeding complications) negate or out-weigh the potential cardiovascular benefits. Patients with arthritic problems in whom aspirin is not indicated for the prevention of cardiovascular events (myocardial infarction rate of <1% per year per patient at risk) would be expected to be better off receiving COX-2 inhibitors rather than NSAIDs because the lower risk of gastrointestinal bleeding and ulceration is likely to far outweigh any increased risk of myocardial infarction or other thrombotic events, if such a risk actually exists.

Of greater concern than a theoretical increase in the risk of thrombotic events during selective COX-2 inhibitor therapy are adverse effects on renal function and blood pressure, particularly in elderly patients. Adverse effects of selective COX-2 inhibitors on blood pressure and renal function are at least as common as NSAIDs, and may be more frequent for rofecoxib than celecoxib or for the NSAIDs with which rofecoxib has been compared so far.[23] Blood pressure and renal function should therefore be carefully monitored in patients receiving both selective COX inhibitors and nonselective NSAIDs, particularly if they are elderly or have abnormal renal function.

5. Conclusions

There is no conclusive evidence whether or not selective COX-2 inhibitors significantly increase the risk myocardial infarction because of an increased thrombotic tendency. There are indirect data suggesting that rofecoxib therapy may be associated with a greater risk of myocardial infarction than celecoxib and some NSAIDs. However, this risk is likely to be small in patients with a low risk of myocardial infarction compared with differences in the risk of gastrointestinal ulceration between selective COX-2 inhibitors and NSAIDs. Patients with a high risk of myocardial infarction who require nonsteroidal anti-inflammatory therapy should receive low dose aspirin therapy, irrespective of the anti-inflammatory drug that is chosen for their treatment. Selective COX-2 inhibitor therapy may be expected to be associated with a lower risk of gastrointestinal ulceration and bleeding than NSAIDS in patients in whom aspirin therapy is indicated in cardiovascular prophylaxis.

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