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Do Some Inhibitors of COX-2 Increase the Risk of Thromboembolic Events?

Linking Pharmacology with Pharmacoepidemiology

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Abstract

Inhibitors of the cyclo-oxygenase (COX)-2 isoenzyme were developed with the expectation that their use would be accompanied by a reduction in adverse reactions thought to be mediated through COX-1 compared with conventional nonselective NSAIDs. However, the results of some clinical studies and other evidence have led to the hypothesis that use of COX-2 inhibitors may contribute to an increased risk of adverse thromboembolic (TE) events. In this review, we have evaluated the evidence from small-scale *in vitro* and *in vivo* pharmacological studies, clinical trials and large-scale pharmacoepidemiological studies and com-

mented on the relationship between the pharmacological characteristics related to thromboembolic events and the clinical effects in large-scale clinical trials and pharmacoepidemiological studies.

Overall, the pharmacological evidence suggests that a prothrombotic effect of COX-2 selective inhibitors is plausible. To date, despite the results from the Vioxx Gastrointestinal Outcome Research (VIGOR) study from which the clinical concern regarding cardiovascular TE risk arose, the published data from other randomised controlled trials (RCTs), retrospective observational studies and spontaneous reporting schemes provide a conflicting body of evidence on the TE risk with COX-2 inhibitors.

Concerns that COX-2 inhibitors may be associated with prothrombotic effects remain and these need to be addressed in large scale, RCTs designed specifically to investigate the possibility of an excess of adverse cardiovascular outcomes in users of some or all selective COX-2 inhibitors, both with and without concomitant low-dose aspirin (acetylsalicylic acid). Consideration must also be given to other pathophysiological mechanisms for potential cardiovascular risk linked with inhibition of COX-2.

In view of the evidence reviewed, it is recommended that selective COX-2 inhibitors should be prescribed with caution, only in patients with conditions for which these drugs have proven efficacy and with careful monitoring of outcomes and adverse events. This is particularly important in the elderly, in patients with cardiovascular/renal disease and in patients with other risk factors that might predispose them to adverse events.

Cyclo-oxygenase (COX)-2 isoenzyme inhibitors were developed with the aim of reducing the occurrence of gastrointestinal (GI) adverse reactions compared with non-selective NSAIDs. However, emerging information suggests that use of such drugs may contribute to an increased risk of adverse vascular events related to alteration in haemostasis.[1] It is not clear whether the higher risk applies to all cardiovascular events associated with thromboembolic (TE) events, whether it applies to all COX-2 inhibitors in all patients,[2] at all doses or only to some products at specific doses or dose ranges.[3] Published evidence relating to the hypothesis that selective COX-2 inhibitors are associated with a greater risk of TE events than nonselective COX inhibitors is reviewed.

This review aims to link the pharmacological evidence from small-scale *in vitro* and *in vivo* investigations with pharmacoepidemiological evidence from large-scale clinical trials, observational studies and spontaneous reporting schemes. The review will be structured according to the following:

1. The pharmacology of cyclo-oxygenase inhibition: this section discusses evidence from human and animal models regarding the pharmacological consequences of COX inhibition and relates this to the plausible pharmacological mechanism for TE events.

2. Clinical trials and pharmacoepidemiological studies of COX-2 specific inhibitors, celecoxib and rofecoxib: This section examines the published evidence from randomised controlled trials, retrospective analyses and meta-analyses of randomised controlled trials and observational studies relating to the hypothesis that selective COX-2 inhibitors are associated with a greater risk of TE events than non-selective COX-inhibitors.

3. Spontaneous reporting schemes of adverse drug reactions (ADRs): this section provides a summary of published information on suspected adverse reactions reported via post-marketing spontaneous reporting schemes worldwide.

1. Pharmacology of Cyclo-Oxygenase (COX) Inhibition

At least two COX isoforms, COX-1 and COX-2, metabolise arachidonic acid to prostaglandin (PG) H_2, the intermediate step in the synthesis of prostaglandins and related compounds (prostanoids), which include thromboxane (TX) A_2, prostacyclin (PGI_2) and PGE_2 synthesis. The traditional view is that COX-1 is a constitutive enzyme and is always present in high concentrations within tissues including platelets, vascular endothelial cells, gastric epithelial cells and the renal collective tubules, whilst COX-2 is predominantly an inducible enzyme with its expression induced within inflammatory and some other cells by inflammatory mediators such as bacterial lipopolysaccharides (LPS) and cytokines (e.g. interleukin [IL]-1β). Based on this traditional view, the products of COX-1 metabolism are involved in the normal regulation of physiological processes that include stimulation of the process of haemostasis through TXA_2 synthesis (which increases platelet adhesion and aggregation), inhibition of gastric acid secretion, stimulation of protective gastric mucus production and regulation of blood flow in various vascular beds through the synthesis of prostanoids such as PGI_2 and PGE_2. This was believed to be the dominant mechanism in a major homeostatic regulation of glomerular filtration in the kidney, via production of vasodilator prostanoids (e.g. PGI_2 and PGE_2) through COX-1 activity. Conversely, expression of COX-2 resulting in prostanoid synthesis at sites of inflammation was traditionally seen as producing the principle unwanted effects arising from the inflammatory process such as pain and excessive inflammation.[4]

Conventional NSAIDs (e.g. indomethacin, naproxen and diclofenac) are 'nonselective' in that they inhibit both COX-1 and COX-2, but with varying degrees of specificity for each enzyme.[5] These drugs thus show a wide spectrum of adverse effects, including adverse renal and gastric effects traditionally thought to be largely a result of inhibiting COX-1 and therefore the synthesis of prostanoids associated with normal physiological control.[4] Subsequently the development and marketing of NSAIDs, reported to be specific COX-2 inhibitors, was widely thought to herald a major breakthrough in NSAID therapy that would greatly reduce renal, gastric and other adverse effects without interference with physiological control.

However, in human and animal studies, evidence has accumulated to indicate that, whereas TXA_2 synthesis is primarily COX-1-dependant, synthesis of PGI_2 is contributed to by COX-2 activity.[6,7] Thus, inhibition of the COX-2 isoenzyme may produce effects other than the wanted reduction of pain and inflammation. One example, not covered in this review, is that COX-2 inhibition, through inhibition of PGI_2 synthesis and thus renal vasodilatation which helps maintain glomerular filtration, leads to sodium and fluid retention and a subsequent increase in hypertension, heart failure and other cardiovascular morbidity. Another important issue, which is the subject of much debate and is the focus of this review, is the potential increase in the risk of cardiovascular adverse events related to alteration in haemostasis, proposed as occurring through unopposed platelet-derived TXA_2 generation (figure 1).

1.1 Pharmacological Considerations of COX-2 Specific Inhibition and Haemostasis

Several *in vitro* and *in vivo* studies, have attempted to model the net effect of the interplay between the products of COX-1 and COX-2 isoenzymes. Similarities and differences between the structure and function of these isoenzymes have been reviewed.[8] Induction of COX-2 and formation of PGI_2 has now been demonstrated *in vitro* in cultured endothelial and vascular smooth muscle cells after exposure to many different chemical and

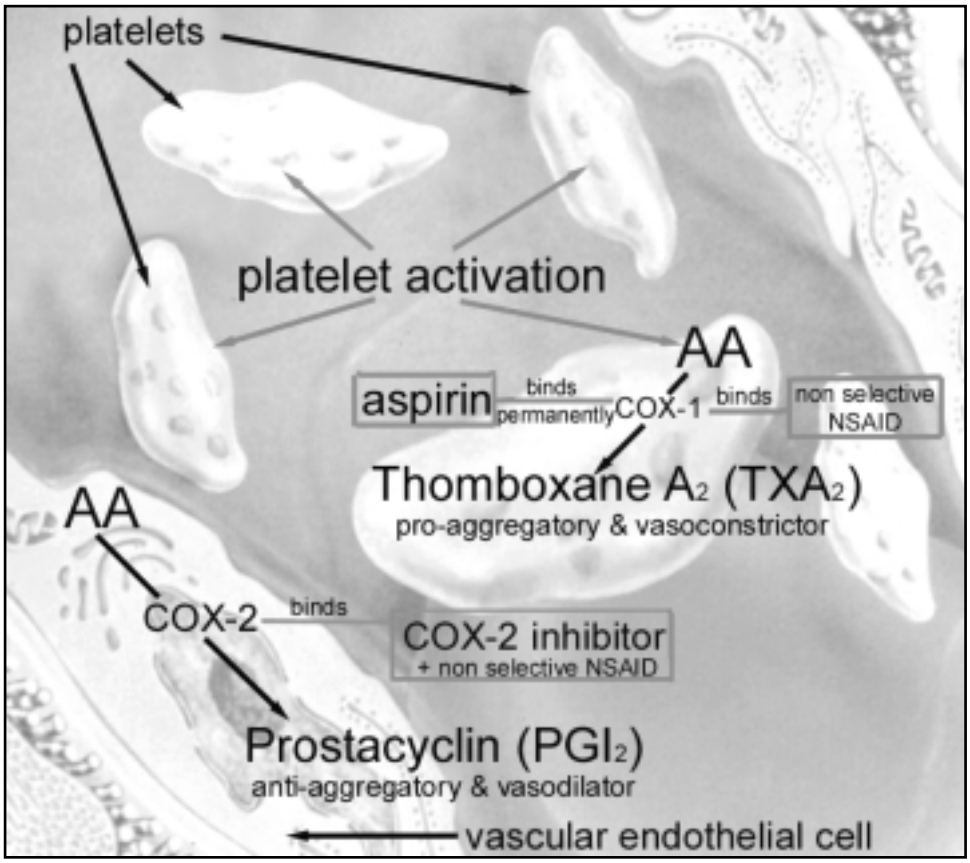

Fig. 1. This figure summarises the prostanoid synthetic pathways and sites of inhibition of synthesis against a stylised section of a blood vessel. Platelet activation results in initiation of the process of haemostasis with an initial step involving platelet aggregation. The pro-aggregatory prostanoid thromboxane A_2 (TXA_2) is synthesised from arachidonic acid (AA), which in turn is produced from membrane phospholipids. Synthesis of TXA_2, shown against an enlarged diagram of a platelet, is mediated by cyclo-oxygenase (COX)-1 and inhibited by NSAIDs including aspirin (acetylsalicylic acid; ASA) [which, in contrast to other NSAIDs, inhibits irreversibly]. Synthesis of the anti-aggregatory and vasodilator prostanoid, prostacyclin (PGI_2) also occurs in platelets and in vascular endothelial cells where its formation is catalysed by COX-2 which is induced in response to inflammatory and other stimuli. Thus, selective COX-2 inhibition may lead to suppression of PGI_2 formation without significant concomitant inhibition of TXA_2 biosynthesis and platelet aggregation and haemostasis may occur unopposed.

physical stimuli[6,7] and this supports a pathophysiological role of COX-2 in the modulation of vascular response to platelet activation and injury.

In vitro studies have shown that the COX-2 inhibitor, rofecoxib, does not inhibit platelet aggregation or prolong bleeding time (via COX-1 inhibition) when administered to healthy volunteers at a dosage of either 12.5 mg/day or 25 mg/day for 5 days.[9] Similarly, Leese et al., report that administration of celecoxib (600mg, twice daily for 10 days) does not lead to inhibition of platelet aggregation or prolong bleeding time in healthy volunteers.[10] In a study involving healthy human volunteers,[11] McAdam et al. compared the effects of celecoxib (100–800mg) with those of the nonselective inhibitor ibuprofen (800mg) on indices of COX-1 activity in platelets and on systemic biosynthesis of PGI_2. Both ibuprofen and celecoxib suppressed COX-2 activity and PGI_2 synthesis, but only ibuprofen significantly inhibited both COX-1 and COX-2 activity

and reduced platelet aggregation. No significant effect on models of platelet aggregation, serum TXA_2 (a marker of COX-1 activity) or urinary metabolites of TXA_2, was demonstrated following administration of celecoxib 800mg, but a modest reduction in serum TXB_2 (a metabolite of TXA_2) was observed. These findings support the idea that selective COX-2 inhibition alone may reduce the production of PGI_2, which normally inhibits platelet aggregation and dilates blood vessels, while still allowing COX-1-mediated synthesis of TXA_2 to induce platelet aggregation (figure 1).

The balance between TXA_2 (platelet aggregator) and PGI_2 (which counteracts platelet aggregation) is modulated by drugs such as aspirin (acetylsalicylic acid), where COX-1 is selectively inhibited by low-dose aspirin in activated platelets by acetylation of the hydroxyl group of a serine residue near the COX active site. The permanent inhibitory action by aspirin on COX-1 persists for the lifetime of the platelet and recovery is a function of platelet turnover. COX-2 activity is preserved and the balance is shifted to an antithrombotic state. In contrast, it is proposed that COX-2 inhibitors suppress PGI_2 formation within vascular endothelial cells and thus may shift the balance to a prothrombotic state. Induction of COX-2 and formation of PGI_2 has been demonstrated *in vitro* in cultured endothelial and vascular smooth muscle cells after exposure to many different chemical and physical stimuli[6,7] and this supports a pathophysiological role of COX-2 in the modulation of vascular response to platelet activation and injury.[8,11]

A number of studies have investigated the effects of inhibiting COX-2 in human endothelial cells. Caughey et al.,[12] demonstrated that such cells normally expressed only the constitutive enzyme, COX-1 resulting in synthesis of TXA_2. When a cytokine (IL-1β) was applied, induction of COX-2 occurred and there were large increases in the production of PGI_2 and PGE_2, but synthesis of TXA_2 was not changed significantly. Addition of a selective COX-2 inhibitor (NS-398) largely abolished PGI_2 and PGE_2 synthesis but had a minimal effect on TXA_2 synthesis. This further strengthens evidence that in the vascular endothelium, COX-2 inhibition reduces synthesis of prostanoids, such as PGE_2 and PGI_2. The authors conclude that their findings, involving the application of an inflammatory mediator, have particular importance with regard to the potential for cardiovascular consequences of COX-2 inhibition and support other investigations that demonstrate that the formation of both PGI_2 and TXA_2 is markedly enhanced in inflammatory conditions such as atherosclerosis where both COX-1 and COX-2 are expressed and contribute to an increase in PGI_2 as well as TXA_2.[13]

In animal studies, Hennan et al. specifically addressed the possibility that selective COX-2 inhibition suppresses the protective effects of PGI_2 derived from the vascular endothelium and that this results in an alteration of the haemostatic balance and vascular tone.[14] These investigators induced circumflex coronary artery thrombosis in dogs by vascular electrolytic injury. Administration of a selective COX-2 inhibitor (celecoxib) or high-dose aspirin did not alter time to occlusive thrombus formation compared with controls. However, high-dose aspirin produced a significant (and potentially beneficial) increase in time to vessel occlusion, which was abolished when celecoxib was administered. In addition, the vasodilator effect of PGI_2 derived from the endothelium of the coronary vessels was examined by monitoring coronary blood flow. In celecoxib-treated animals, vasodilation in response to application of arachidonic acid was reduced significantly compared with controls. Because of these results, the authors expressed concern regarding the possibility of an increased risk of acute vascular events in patients receiving COX-2 inhibitors, especially in individuals with underlying inflammatory disorders, including coronary artery disease.

Further evidence that PGI_2 may play a role in reducing the platelet aggregatory effects of TXA_2

came from the innovative approach of Cheng et al.[15] Using genetically modified mice, these investigators demonstrated an enhancement of the platelet aggregatory effects of TXA_2 in mice with reduced expression of PGI_2 receptors. In parallel experiments, involving mice with reduced expression of TXA_2 receptors, they demonstrated a reduction in platelet aggregation. Their experimental evidence is consistent with an increased risk of thromboembolism following selective inhibition of COX-2 mediated synthesis of PGI_2. The authors suggested that their work supports the explanation for the cardiovascular outcome in the Vioxx Gastrointestinal Outcome Research (VIGOR) trial (see section 2). The conclusions from these pharmacological studies and other experimental evidence support the view that selective COX-2 inhibition reduces synthesis of PGI_2 and may allow COX-1 mediated synthesis of pro-aggregatory and vasoconstrictor prostanoids to continue unchecked and increase the risk of thrombus formation and vascular occlusion.

In contrast, other investigators advocate that there is a large reserve of PGI_2 in endothelial cells and platelets, which prevents platelet aggregation *in vivo*, with a requirement of at least 90% inhibition of either system in order for clinical effects to be seen.[16] In studies of differing experimental designs, other investigators have reached the conclusion that therapeutic doses of the COX-2 inhibitor rofecoxib does not alter the haemostatic balance in healthy volunteers.[17,18] Little is known regarding the pharmacological functional consequences of COX-2 inhibition with regard to other 'protective' mediators involved in platelet-vessel wall interactions such as biological gases (nitric oxide and carbon monoxide).

In several of these studies, conducted in healthy human volunteers and animal models of vascular injury, neither rofecoxib nor celecoxib have been reported to have significant effects on haemostasis. Nevertheless, such an effect on platelet aggregation with possible clinical significance is suggested by observations of elevated prothrombin times and bleeding episodes with concomitant use of celecoxib and warfarin, in a patient with pre-existing cardiovascular disease,[19] and reports of patients with connective tissue disorder who developed arterial thrombosis after initiation of celecoxib therapy.[20] Inflammation appears to contribute to the atherosclerotic process, and upregulation of COX-2 has been demonstrated in atherosclerotic plaques.[13] However, it is unclear whether this upregulation plays a part in the pathogenesis of atherosclerosis, and whether COX-2 inhibition exerts beneficial[21]or detrimental effects[22] on this process. Elevated platelet synthesis of TXA_2 has been identified in patients with pre-existing cardiovascular disease (e.g. following acute myocardial infarction [MI] or in unstable angina) and in diabetes mellitus. This suggests that TXA_2 status is important.[2] Furthermore, an association between increasing urinary TXB_2 concentrations and risk of cardiovascular events (MI and cardiovascular death) has been reported.[23] While there are a number of possible explanations such observations, including the fact that there are a number of sources for TXA_2 other than platelets, serve to fuel the debate that patients with pre-existing cardiovascular disease may be more susceptible to alterations in haemostatic factors with subsequently alterations in cardiovascular risk. In a recent study in 60 patients with established coronary artery disease using low-dose aspirin (<325 mg/day) and randomised to received either rofecoxib (25 mg/day; n = 30) or placebo (n = 30), rofecoxib did not appear to have either favourable or adverse effects on endothelial dysfunction or vascular inflammation during the 8-week treatment period.[24]

1.2 Might Potency as a COX-2 Inhibitor Influence the Likelihood of Cardiovascular Events?

The relationship between COX isoenzyme activity, prostanoid formation and cell function *in vivo* is not necessarily linear.[25] There is a possible inverse relationship between daily doses of aspirin and a relative risk reduction in vascular events largely

Table I. Mean IC_{50} (with SE) for the inhibition of cyclo-oxygenase (COX)-1 and COX-2 in human whole blood assays. Values are ranked by the order of COX-2 selectivity as shown by the ratio of IC_{50} COX-1/COX-2 (from Riendeau et al.,[33] with permission from J Pharmacol Exp Ther)

	IC_{50} COX-1 (mmol/L)	N (donor)	IC_{50} COX-2 (mmol/L)	N (donor)	COX-2 selectivity ratio of IC_{50} COX-1/COX-2
Etoricoxib	116 ± 18	12	1.1 ± 0.1	26	106.0
Rofecoxib	18.8 ± 0.9	211	0.53 ± 0.02	614	35.0
Valdecoxib	26.1 ± 4.3	11	0.87 ± 0.11	14	30.0
Celecoxib	6.7 ± 0.9	13	0.87 ± 0.18	18	7.6
Nimesulide	4.1 ± 1.2	6	0.56 ± 0.12	6	7.3
Diclofenac	0.15 ± 0.04	10	0.05 ± 0.01	16	3.0
Etodolac	9.0 ± 2.5	3	3.7 ± 0.7	6	2.4
Meloxicam	1.4 ± 0.4	6	0.70 ± 0.28	5	2.0
Indomethacin	0.19 ± 0.02	36	0.44 ± 0.07	34	0.4
Ibuprofen	4.8 ± 3.5	5	24.3 ± 9.5	7	0.2
Piroxicam	0.76 ± 0.05	6	9.0 ± 1.3.3	16	<0.1

IC_{50} = concentration needed to produce 50% inhibition; **N (donor)** = the number of individuals donating blood for each IC value.

due to permanent irreversible inactivation of platelet COX-1, with higher aspirin doses also reversibly inactivating endothelial COX-2. However, the incomplete and reversible inhibition of COX-1 by non-aspirin NSAIDs does not lend itself to such a relationship, especially in view of the large interindividual variability in drug plasma levels with consequential differential inhibition of COX-1 and COX-2 isoenzymes.[26]

Structurally different COX-2 inhibitors vary in their potency as inhibitors of the COX-2 enzyme. Initial estimates of selectivity of drugs during their development are made using *in vitro* tests, but this may not necessarily reflect selectivity *in vivo*. Because of this, whole blood assays have been developed in order to standardise measurements and to provide estimates of selectivity that more closely approximate the clinical situation.[26,27] *In vitro* assays to more closely reflect selectivity *in vivo* involve a measure of COX-2 activity, such as induced PGE_2 production in whole blood or monocytes, and of COX-1 activity such as measurement of platelet TXB_2 production during blood clotting.[11,28,29] Selectivity for the COX-2 enzyme is often expressed as a ratio of COX-1 inhibitory concentration 50% (the concentration of COX-1 inhibitor needed to produce 50% inhibition [IC_{50}]) to COX-2 IC_{50} (i.e. the higher the ratio, the more selective the inhibitor). Selectivity and potency of COX-2 inhibitors, including rofecoxib and celecoxib, may differ in different tissues[27,30,31] and even in different types of cell from the same tissue.[32] This variation may be related to differences in tissue penetration, pharmacokinetic and other factors. However, in all tissues examined (both human and other animal) etoricoxib and rofecoxib appear more selective and more potent as COX-2 inhibitors than celecoxib.[27,30,31] Examples from a wide range of NSAIDs of the COX-1/COX-2 IC_{50}, as measured in human platelets, are given in table I.[33]

A possible limitation of the above comparative data, and those from similar studies, is that the IC_{50} values were derived by addition of drugs to human platelet preparations *in vitro*, and not by administering the drugs to humans to achieve therapeutic concentrations (*ex vivo* assays).[11,28] However, *ex vivo* IC_{50} values of rofecoxib and celecoxib from the same laboratory, enabling comparisons under similar experimental conditions, were not identified in the literature. The data presented (table I) demonstrate wide differences in IC_{50} values between several selective and nonselective COX inhibitors, including celecoxib and rofecoxib in human cells and provide a guide to their relative selectivity.

The COX-2 hypothesis proposed that at comparable COX-2 inhibiting doses, highly selective

COX-2 inhibitors would be as effective as traditional NSAIDs, but cause fewer GI adverse effects, as determined by clinical endpoints reflecting COX-1-dependent GI toxicity.[26] Evidence suggests that both minor symptoms (e.g. dyspepsia) and endoscopically detected lesions are not good predictors of future complicated GI disease. It is also unclear whether serious GI complications such as perforations and bleeding are a consequence of COX-1 inhibition in platelets or in gastric mucosa.[34] The large-scale prospective double-blind outcome studies of celecoxib and rofecoxib (see section 2) provided strong evidence that COX-2-specific inhibitors decrease both endoscopically detectable ulcers and clinically important GI events compared with active comparator drugs, thus supporting the COX-2 hypothesis.[35] However, insufficient appreciation has been given to the potentially negative effects of these drugs.

Although, on existing comparisons, rofecoxib appears more potent and more selective than celecoxib (table I), it is used in correspondingly lower doses. Two studies have been published that directly compare the efficacy of celecoxib with that of rofecoxib.[36,37] However, an assumption is often made that the two drugs are more or less therapeutically equivalent when comparing such data between studies. Whether this means that, when used in the different dosage regimes to achieve therapeutic equivalence, they are also equivalent *in vivo* in terms of blocking PGI_2 formation via COX-2 and not blocking possible COX-1-mediated prothrombotic events, requires further evaluation.

1.3 Do COX-2 Inhibitors Antagonise the Protective Effect of Aspirin?

As previously reported by McAdam et al. for celecoxib, COX-2 selective inhibitors, in addition to inhibiting COX-2, may also have varying degrees of inhibitory effect on COX-1 activity.[11] This has been investigated by Ouellet et al.,[38] who used an *in vitro* human platelet preparation to study the relative potential of the nonselective COX inhibitor, ibuprofen and of various selective COX-2 inhibitors (celecoxib, etoricoxib, rofecoxib, valdecoxib) to reduce the ability of aspirin to block the activity of COX-1

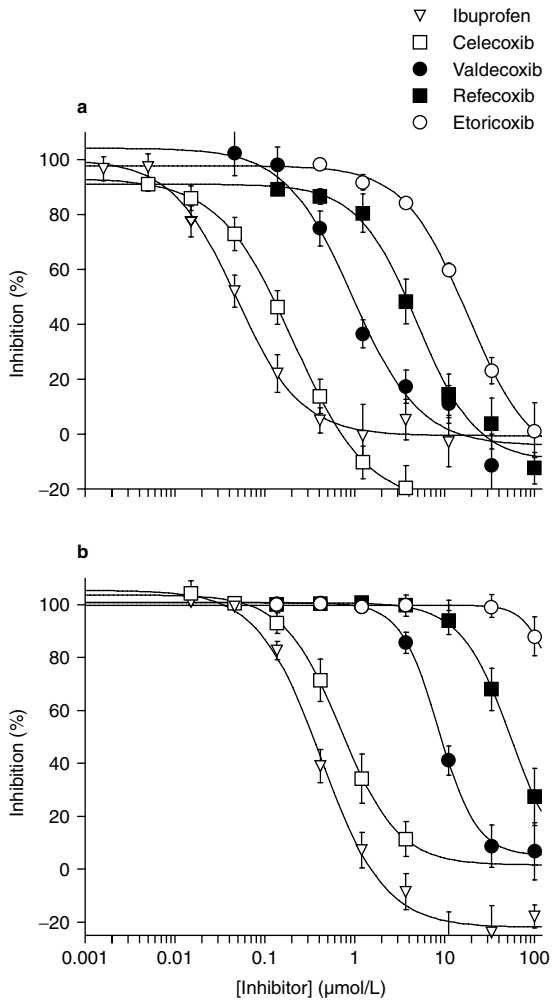

Fig. 2. Figure shows the antagonism of the aspirin (acetylsalicylic acid) inhibition of platelet cyclo-oxygenase (COX)-1 by ibuprofen and various coxibs. Platelets were treated with 0–100 μmol/L of ibuprofen, celecoxib, valdecoxib, rofecoxib and etoricoxib for 5 minutes before the addition of 10 μmol/L (**a**) or 100 μmol/L (**b**) aspirin. Data points represent the average of 6–11 titrations. After a 20-minute incubation, the platelets were washed twice and challenged with calcium ionophore. After 10 minutes, the reactions were quenched, and the amount of thromboxane B_2 produced was determined by enzyme immunoassay. For celecoxib, only data between 0.005–3.7 μmol/L are plotted, as higher concentrations showed inhibition from celecoxib alone (from Ouellet et al.,[38] with permission.

in the formation of pro-aggregatory prostanoids. The main aim of their investigation was to clarify the possible effect that various COX-2 inhibitors might have on the protection that aspirin provides against the possibility of thrombotic effects. They showed that blocking of COX-1 by aspirin is antagonised by ibuprofen and the COX-2 inhibitors, but with widely different potencies. The rank order of potencies for reducing the antagonism of COX-1 by aspirin was found to be ibuprofen > celecoxib > valdecoxib > rofecoxib, with the newer COX-2 inhibitor, etoricoxib requiring the highest concentration to inhibit aspirin's effect in blocking COX-1 (figure 2). This study supports that, amongst the COX-2 inhibitors, rofecoxib and etoricoxib are highly potent and selective COX-2 inhibitors with minimal effect on COX-1. In addition, the study provides evidence that celecoxib not only inhibits COX-1 itself over most of the concentration range used in this study, but also antagonises the COX-1 inhibition produced by aspirin (figure 2).

The results of this study suggest that less potent selective COX-2 inhibitors, in particular celecoxib, which also demonstrate some affinity for COX-1 in potentially therapeutic doses, may compete with aspirin's ability to block COX-1-mediated synthesis of prothrombotic prostanoids, as has been reported for the nonselective NSAID, ibuprofen.[39] On the other hand, therapeutic doses of rofecoxib, a highly potent COX-2 inhibitor, have been demonstrated not to interfere with the antiplatelet effect of aspirin in humans in therapeutic doses.[40]

In contrast to the *in vitro* findings of Ouellet et al.,[38] no significant difference was found in a small study of healthy human volunteers comparing celecoxib 400mg and placebo on the effect of aspirin on platelet aggregation.[41] Whether celecoxib, administered in lower therapeutic doses than 400mg, leads to clinically important inhibition of aspirin's effects on platelet aggregation needs to be determined in larger clinical studies.

The study by Title et al.[24] supports the assertion that rofecoxib in a therapeutic dose does not significantly alter the protective effects of aspirin in patients with established coronary artery disease and treated with aspirin 325 mg/day. Although this study makes an important contribution to the debate on the possible adverse cardiovascular effects of COX-2 inhibitors,[42] it does not address the question of whether celecoxib, which is claimed to antagonise aspirin's protective cardiovascular effect,[38] shows a similar lack of effect on endothelium function in aspirin-treated individuals. Furthermore, with the reports that rofecoxib does not antagonise the protective effects of aspirin,[39] it is important to investigate COX-2 inhibitor effects on endothelial function in patients not taking aspirin.

Overall, the pharmacological evidence supports the hypothesis that it is biologically plausible that COX-2 inhibition might lead to potentially serious cardiovascular problems in patients at high risk of cardiovascular adverse events. This is especially the case in clinical syndromes associated with elevated platelet activation where TXA_2 biosynthesis is increased (unstable angina, peripheral arterial obstructive disease and cerebral ischaemia) or in situations where the risk of peripheral venous thrombosis is high, such as immobilisation due to surgery.[43]

2. Clinical Trials and Pharmacoepidemiological Studies of COX-2-Specific Inhibitors

When considering the evidence to support or disprove a hypothesis, one must consider the quality of evidence available on the subject matter. Randomised controlled trials are accepted as the gold standard for assessing efficacy of medicines.[44] However, not all hazards can be identified or predicted from randomised controlled trials or pharmacological studies of a drug conducted prior to marketing approval, for reasons which have been described elsewhere.[45] The concern that increased cardiovascular risk may be associated with use of COX-2 inhibitors arose from two sources: (i) case reports of patients with connective tissue disease who developed arterial thrombosis after starting ce-

lecoxib;[20] and (ii) a large-scale randomised controlled trial which investigated the efficacy and tolerability of rofecoxib (the VIGOR trial).[46] Subsequent to this safety signal, it has become clear that there is a gap between experimental evidence regarding effects of COX inhibitors on haemostasis and the pharmacoepidemiological evidence of increased cardiovascular risk associated with these drugs.

In the first part of this review, we summarised the pharmacological evidence to support a biologically plausible mechanism for prothrombotic effects of celecoxib and rofecoxib. As mentioned previously, information on other COX-2 inhibitors (etoricoxib and valdecoxib) is limited and therefore these drugs have not been included in this review. In the following section we will present only the evidence from randomised controlled trials, retrospective re-analyses and meta-analyses of these randomised controlled trials, observational studies and summary data of suspected ADRs from spontaneous reporting schemes, which report specifically on this issue, as retrieved through literature searches on Medline and proceedings from scientific conferences.

2.1 Randomised Controlled Trials

Whilst data from randomised controlled trials have documented that aspirin is an effective antithrombotic agent for primary as well as secondary prevention of TE events,[47,48] trials of nonselective NSAIDs, which vary in their antithrombotic properties have been inconclusive.[9,10,49-51] In these trials of nonselective NSAIDs, the question of whether the degree of selectivity for COX-1 in non-aspirin NSAIDs is sufficient to translate into clinically detectable cardiovascular protection (as achieved by irreversible inhibition of COX-1 by aspirin) was not addressed.[52,53] For COX-2 inhibitors, as reported earlier, the pharmacological evidence suggests that the more selective the drug, the more likely the change in haemostatic balance in favour of platelet aggregation and occlusion.

2.1.1 Large-Scale Randomised Controlled Trials of Rofecoxib and Celecoxib Reporting on Cardiovascular Thromboembolic Outcomes

To date, the best clinically-based support for the experimental evidence discussed earlier of an increase in cardiovascular risk for the COX-2 inhibitors stems from the findings of the large randomised controlled trial conducted with rofecoxib: the VIGOR study (see table II).[46] A separate analysis of adjudicated cardiovascular events from the VIGOR study[3] provides overall serious adverse event data (death, hospitalisation or extension of hospitalisation and any life-threatening events or serious disability). The vascular events referred for adjudication included coronary events (MI, unstable angina, cardiac thrombus, resuscitated cardiac arrest and sudden or unexplained death), cerebrovascular events (ischaemic or haemorrhagic stroke, and transient ischaemic attack [TIA]), venous thrombosis and pulmonary embolism. The majority of the thrombotic cardiac events were MIs (rofecoxib 20 [0.5%] versus naproxen 4 [0.1%]). Of the serious vascular adverse events meeting criteria for adjudication, twice as many cases were reported for rofecoxib than for naproxen (n = 65 [1.6%] versus n = 33 [0.8%]). However, because of incomplete documentation for 33% of adverse events, the number of adjudicated events was much lower (n = 45 [1.1%] versus n = 19 [0.5%], respectively).

Stratification according to aspirin indicated or not indicated and use of the standard composite Antiplatelet Trialists' Collaboration (APTC) endpoints, revealed a lower risk of MI and stroke in the naproxen cohort compared with the rofecoxib cohort (aspirin-indicated relative risk [RR] for cardiovascular deaths, MI and stroke for naproxen versus rofecoxib was 0.26 [95% CI 0.07, 0.91]; and for aspirin not indicated RR 0.65 [95% CI 0.34, 1.12]). The risk of serious thrombotic events was significantly lower for naproxen than rofecoxib (RR 0.42 [95% CI 0.25, 0.72]), especially cardiac events (RR 0.36 [95% CI 0.17, 0.74]). Regarding time to event, there was clear divergence of the survival curves early after starting treatment (within 2 months)

which persisted during the remainder of the study period (log rank test result not reported). Of 37 adjudicated deaths of all causes, 22 (0.5%) were recorded within the rofecoxib cohort and 15 (0.4%) in the naproxen cohort. There was no difference in the incidence of adjudicated cardiovascular deaths (both 0.1%, n = 6) but acute MI was less common in the naproxen group (0.1%, n = 4) compared with the rofecoxib group (0.4%, n = 20) [RR 0.2 (95% CI 0.1, 0.7)]. Furthermore, a retrospective subgroup analysis based on patients meeting the criteria for aspirin use for cardioprotection revealed that there were significant lower rates of adjudicated events in the naproxen group compared with rofecoxib in both subgroups (aspirin indicated RR 0.20 [95% CI 0.06, 0.71] and aspirin not indicated RR 0.53 [95% CI 0.29, 0.97]).

The conclusion of the adjudication for the VIGOR study was that a significant difference was seen in the composite of stroke, MI and cardiac death that was unfavourable for rofecoxib compared with naproxen. Consistent with this result were the time to event tables and the adjudicated thrombotic serious cardiovascular events (MI and cardiovascular deaths). In the same document, similar adjudicated evaluations of two smaller efficacy randomised controlled trials of rofecoxib, named Study 085 (n = 1042) and Study 090 (n = 978) in which low-dose aspirin for cardioprotection was allowed, were undertaken.[3] The number of cardiovascular events reported in either trial was extremely small (three and nine, respectively). These two small-scale studies could not exclude such an association on the basis of smaller sample size and the event rate is similar to that in the VIGOR study. The overall conclusion from the report was that there was an increased risk of TE events, particularly MI, in patients exposed to rofecoxib compared with naproxen, accounting for some other cardiovascular risk factors. However, as there was no placebo group it was difficult to assess the risk compared with no therapy at all.

A large randomised controlled trial was also conducted with celecoxib. The Celecoxib Long-term Arthritis Safety Study (CLASS) was constructed to replicate clinical practice with non-restrictive inclusion and exclusion criteria (table II).[57] Noteworthy differences between the VIGOR compared with the CLASS study included: (i) the exclusion of patients using aspirin, anticoagulants or antiplatelet agents together with other cardiac-related exclusions for the VIGOR study while aspirin use for cardiovascular prophylaxis (≤325 mg/day) was permitted for the CLASS study; (ii) patients in the VIGOR study had rheumatoid arthritis (RA) while the CLASS trial studied a combination of patients with osteoarthritis (OA) [72%] and RA (28%); and (iii) the active comparator group for the 2-arm VIGOR study was naproxen, while two comparator drugs (diclofenac and ibuprofen) were chosen for the CLASS double protocol study. The possible effects of these differences on the estimates of cardiovascular risk are discussed in further detail later.

In order to further assess the overall safety profile of celecoxib, the US FDA requested an additional analysis of the CLASS trial, an open-label long-term post-marketing safety study (Study 024) and a summary of post-marketing surveillance data collected for celecoxib during 1999. This was undertaken primarily to re-examine and compare outcomes related to upper GI tract injury (complicated and endoscopically evaluated symptomatic ulcers) between celecoxib and comparator NSAIDs, as well as other potentially important drug-related toxicities, using the 12-month data from the completed arm of the CLASS trial.[61] Because of evidence for important differences among the treatment groups including presence of risk factors for cardiovascular disease, sub-group analyses were performed according to patients using aspirin and for those not taking aspirin. This was particularly important given that the published results of the CLASS trial revealed that the beneficial GI effect of celecoxib compared with the comparator NSAIDs was no longer so evident in aspirin users, and that the RR of ulcer

Table II. Summary of individual randomised controlled trials (RCTs), re-analyses of RCT data and meta-analyses reporting on cardiovascular thromboembolic (CV TE) events, for rofecoxib, celecoxib and both rofecoxib and celecoxib combined

Design (reference)	Setting, study population	Intervention and study size	Statistical analyses	Study endpoints
Rofecoxib studies				
MC, prosp, DB, stratified parallel-group RCT (VIGOR)[46]	301 centres/22 countries; projected 7000 pts (3500 from US). Pts aged 50+y, with RA requiring 1y NSAID treatment, or aged 40–49y on LT oral CS	Rof 50mg od (n = 4047) vs nap 500mg bid (n = 2039) Up to 6mo, or to 120+ confirmed PUBs and 40+ complicated PUBs	ITT. Cox PHM. Prespecified SG analysis (prior history of PUB, age, gender, race and region)	Primary: confirmed PUBs Secondary: complicated PUBs; discontinuation rates; efficacy measures. Other: CV events for future analysis
Retro safety analysis from OL, non-drug intervention 2×2 factorial design trial[54]	Outpatients of community rheumatologists in France Pts with OA of knee or hip, symptomatic > 6mo with joint pain >14d prior to screening	Four arms: tools, exercises, tools and exercises, no intervention (usual care) Rof 12.5mg od for 4 wk, to 25mg daily if needed (n = 2896). Mean duration of treatment 139d (62d)	Incidence of patient reported AE during treatment (+ 14d of stopping) at baseline, wk 4, 12 and 24	AE as defined by WHO and any untoward medical occurrence during treatment
Retro analysis of RCT safety data[55]	Studies reporting comparative data for rof vs NSAID and/or P. Median duration 3.5mo. Selected from OA safety database of 8 phase IIb to III rof trials for assessment of efficacy, 1995–1998	Rof 12.5+ mg, daily (n = 3357). Comparator NSAID cohort (ibu, dic and nab) [n = 1564] P cohort (n = 711)	Cox PHM of RR. KM estimate of cumulative event incidences. SG of risk factors of interest (NS)	Primary: investigator reported serious CV TE related events. Secondary: APTC endpoint
Retro re-analysis of RCTs[51,56]	Trials of rof vs comparator NSAID and/or P as selected from 23 phase IIb–V trials, ≥4wk duration, completed to 15 Sep 2000 Study update: 1033 additional pt-y follow-up added to rof vs non-nap NSAID studies, and 968 pts with 750 pt-y follow-up added to rof vs P studies	Rof (≥12.5mg) for treatment of RA, OA, AD and low back pain (n = 19 922) Non-nap comparator NSAID cohort (ibu, dic and nab) [n = 2755] Nap cohort (n = 78 700)	Modified ITT. Cox PHM of RR. Sensitivity analysis of effect of duration of study (≥6 mo) and dose	Combined endpoint used by the APTC Events adjudicated according to CV standard operating procedure
Celecoxib studies				
MC, prosp, DB, parallel-group RCT(CLASS)[57]	386 centres in US and Canada; projected total 800 pts, aged 18+y with RA or OA (>3mo) requiring NSAID for study duration	Cel 400mg bid (n = 3987) vs ibu 800mg tid (n = 1985) or dic 75mg bid (n = 1996), up to 6mo ASA use for CV prophylaxis (≤325 mg/day) permitted	ITT. KM plots of time to event of PUB. Pre-specified SG analysis according to potential risk factors. Incidence of AE	Primary: confirmed ulcer complications as per algorithm and independent committee adjudication process Secondary: symptomatic ulcers not meeting definition of ulcer complication (as above) Investigator defined treatment failure Other adverse experiences

Continued next page

Table II. Contd

Design (reference)	Setting, study population	Intervention and study size	Statistical analyses	Study endpoints
Retro analysis of RCT safety data[58]	Data for cel and NSAIDs from the CLASS trial (see above)	As for CLASS trial (see above)	ITT (both CLASS study protocols). Crude event rates and time to event analyses of all-cause CV events. Pre-specified SG analysis of all CV events in non-users of ASA. Analysis of incidence of MI in patients not taking ASA but ASA indicated	Primary: investigator reported serious CV TE events: (cardiac, cerebrovascular and peripheral vascular events)
Retro re-analysis of RCTs[59]	Cel vs comparator NSAID and/or P studies in pts ≥18y with RA or OA ≥3mo. Selected from 15 trials, ≥4wk duration: 13 new application studies and 2 postmarketing trials, CLASS and SUCCESS (a MC, prosp, DB, parallel group RCT) ASA (81–325 mg/day) use permitted in above trials	Cel 100–800 mg/day, (n = 18 942) P cohort (n = 1794) Comparator NSAID cohort: dic (n = 6542), ibu (n = 2330), nap (n = 2271)	ITT. Summary statistics. KM plots of time to APTC endpoint in entire cohort and SG not taking ASA. Cox PHM of RR (95% CI) for primary and secondary endpoints for all pts and ASA non-users (summary RR estimate assuming fixed effect approach). Heterogeneity among study categories tested for interaction	Primary: combined endpoint used by the APTC within 30d of last drug exposure, subject to independent adjudication Secondary: CV adverse events
	One LT OL dose escalation safety trial (Study 024)	Uncontrolled, OL cohort (n = 5209)	Analysis of event rates from OL study	
Rofecoxib and celecoxib combined studies				
Meta-analysis of RCTs[60]	Studies selected from MEDLINE search of published, English-language, RCT from Jan 1998–Feb 2001 (VIGOR, CLASS, Study 085 and Study 090) Search of AERS spontaneous reporting database in US	Cel and rof studies: VIGOR (n = 8076) CLASS (n = 7968) Study 085 (n = 1042) Study 090 (n = 978) Comparator cohort: P group from a meta-analysis of 4 studies (n = 48 540, P n = 23 407)	KM plots of event incidences Cox regression modelling of RR	Annualised MI rates KM survival estimates

AD = Alzheimer's disease; **AE** = adverse events; **AERS** = Adverse Event Reporting System; **APTC** = Anti-Platelet Trialists' Collaboration; **ASA** = aspirin (acetylsalicylic acid); **bid** = twice-daily; **cel** = celecoxib; **CLASS** = Celecoxib Long-Term Arthritis Safety Study; **COX** = cyclo-oxygenase; **CS** = corticosteroid; **DB** = double-blind; **dic** = diclofenac; **GI** = gastrointestinal; **ibu** = ibuprofen; **ITT** = intention to treat; **KM** = Kaplan-Meier; **LT** = long-term; **MC** = multicentre; **MI** = myocardial infarction; **nab** = nabumetone; **nap** = naproxen; **NS** = not specified; **OA** = osteoarthritis; **od** = once daily; **OL** = open-label; **P** = placebo; **PHM** = proportional hazards modelling; **prosp** = prospective; **pt(s)** = patient(s); **PUB** = Perforation, Ulceration and Bleed; **RA** = rheumatoid arthritis; **retro**. = retrospective; **rof** = rofecoxib; **RR** = relative risk; **SG** = subgroup; **SUCCESS** = Successive Celecoxib Efficacy and Safety Study; **tid** = three-times daily; **VIGOR** = Vioxx Gastrointestinal Outcome Research.

complications was significantly lower in non-aspirin users compared with aspirin users within the celecoxib cohort. In the FDA report, this stratification according to aspirin use was also applied to examination of selected cardiac and non-cardiac vascular adverse events. During the entire study period, the incidence of any TE event was 4-fold higher for aspirin users than non-aspirin users within either cohort (celecoxib RR 3.9; 95% CI 2.6, 5.7) and the comparator NSAIDs combined (RR 4.6; 95% CI 3.0, 7.0), but no difference between aspirin users between the two treatment cohorts (RR 1.1; 95% CI 0.7, 1.6) and non-aspirin users (RR 1.3; 95% CI 0.8, 2.0).

Study 024 examined exposure to celecoxib at doses of 100–400 mg/day for up to 2 years and involved 5157 patients with RA or OA.[61] The types of adverse events with an incidence of 3% or more were similar between the celecoxib arms of both the CLASS trial and Study 024. The types and incidence of the serious adverse events reported were also similar and considered representative of common causes of morbidity in populations with arthritis. There was no difference in the incidence of MI between these two cohorts (RR 1.4; 95% CI 0.9, 2.3). The post-marketing reporting rates of serious renal and cardiovascular adverse events were low (<3 per 100 000 patient-years of exposure).

The overall conclusions were that there was no difference in thromboembolic events seen between celecoxib and the conventional NSAIDs used in the CLASS trial and that the risk of cardiovascular events associated with celecoxib at supra-therapeutic dose is similar to that of conventional NSAIDs.

Clear concerns were voiced about the published summaries of both the VIGOR and the CLASS studies. Questions were raised as to why the VIGOR study was not stopped earlier because of the higher mortality rate and higher rate of serious cardiovascular events in the rofecoxib cohort compared with the naproxen cohort, and why information on MI only was provided in the published paper,[62] when the FDA report clearly showed a higher risk of serious thrombotic cardiovascular events for rofecoxib in both aspirin indicated and non-indicated patients compared with naproxen. Interestingly, another paper reports use of a cardiovascular adjudication standard operating procedure by the marketing authorisation holders before the VIGOR study, which was used to systematically collect data on all cases of CV serious adverse experiences.[51] Concerns raised regarding the CLASS trial included the statistical analysis of pooled data from both protocols; the selective and partial reporting of data only for 6 months when the follow-up was longer in the two separate protocols (12 months and 16 months) and the subgroup analysis.[63] While the authors acknowledge that an explanation was lacking in the published paper, they alluded to the differential survival of patients between the studies which would have confounded comparisons and that the statistical plan to analyse the combined data from both protocols was pre-specified.[64] Whether the methodological concerns of the CLASS trial had any effect on data collected on other adverse events including cardiovascular-related effects is uncertain.

2.2 Retrospective Analysis and Meta-Analysis of Randomised Controlled Trials of Rofecoxib and Celecoxib

Meta-analysis and re-analysis are techniques used to combine results from various studies. A meta-analysis is different to retrospective re-analysis in that there is no access to the raw data from each individual study; only the published estimates of exposure effect are available and are used to generate a pooled overall estimate. For both re-analyses and meta-analyses, it is essential to ensure that all studies (published and unpublished) are included since reliance on published studies tends to introduce a bias from over-representation of those which showed positive findings.

2.2.1 Retrospective Analyses of Randomised Controlled Trial Data of Rofecoxib

Three retrospective analyses of data collected from randomised controlled trials of rofecoxib have been published on this topic (table II). One study reported on the safety profile of patients included in an open-label study that was conducted to evaluate the influence of non-pharmacological interventions on the outcome of osteoarthritis in patients prescribed rofecoxib (table II).[54] However, the authors acknowledge the select nature of the cohort with its limited information on baseline cardiovascular risk, the absence of a control group and the danger of comparing incidence rates between studies of different design.

The second retrospective analysis examined the investigator-reported cardiovascular adverse event data held within the OA safety database collected for eight premarketing efficacy randomised controlled trials for rofecoxib (table II).[55] The authors acknowledged that the combined sample size of each treatment group together with the number of serious TE events and the numbers indicated for aspirin use was low, which may have contributed to the study findings of no difference.

The third re-analysis also investigated this topic but assessed TE events across 23 rofecoxib randomised controlled trials in over 28 000 patients with OA, RA, Alzheimer's disease or chronic back pain (table II).[51] The researchers concluded that the risk of a cardiovascular TE event was similar between rofecoxib and placebo cohorts and the non-naproxen NSAID group, but significantly higher relative to the naproxen cohorts and that these results supported the hypothesis of a cardioprotective effect of naproxen. This study was completed in September 2000. Since that time, additional adjudicated data for trials conducted up to May 2001 (number unknown) were published in a paper by Weir et al.,[56] where the pooled analysis was repeated. The overall results remained unchanged. In this same publication, Weir et al. described another pooled analysis of placebo-controlled cardiovascular safety data from the Alzheimer's Disease and Mild Cognitive Impairment programme, presented at a scientific meeting 2003.[65] Across two placebo-controlled trials and interim data from an ongoing placebo-controlled trial comprising 2899 elderly patients, predominantly male, similar rates of investigator-reported and -confirmed adjudicated cardiovascular events were observed in the rofecoxib and placebo groups. Weir et al.[56] reported that the rates in these populations were higher than that observed in the previous pooled analyses, given the Alzheimer studies were conducted in a higher risk population, but that the RR was still consistent with that reported previously. This publication stimulated much debate.[66,67]

2.2.2 Retrospective Analyses of Randomised Controlled Trial Data of Celecoxib

Two retrospective re-analyses of randomised controlled trial data for celecoxib have been published, both by White et al. (table II). The first examined cardiac events in almost 4000 patients within the CLASS trial,[58] while the second examined the incidence of cardiovascular events as reported across the entire controlled arthritis clinical trial database for celecoxib.[59] The results of the re-analysis of the CLASS study revealed no evidence for an increase in investigator-reported serious TE events, irrespective of whether patients were treated with concomitant aspirin. The authors also concluded that their findings further refuted the suggestion that COX-2 inhibitors, as a class, increased cardiovascular risk.[58] In the second study, the incidences of the primary and secondary events were not significantly different between celecoxib and placebo, for celecoxib compared with all NSAIDs, or for celecoxib compared with naproxen, regardless of aspirin use and NSAID type. Thus, the authors concluded that these comparative analyses demonstrated no evidence of increased risk of cardiovascular thrombotic events associated with celecoxib compared with conventional NSAIDs, naproxen or placebo. The authors also acknowledge that the event rates as reported differ from those reported elsewhere for celecoxib because of the use of the APTC endpoint and because of independent adjudication by clinical

experts rather than regulatory definitions and investigator coded diagnosis.[59]

2.2.3 Meta-Analysis of Randomised Controlled Trials Published for COX-2 Selective Inhibitors

One meta-analysis has been published with the aim of evaluating the totality of evidence on cardiovascular TE risk (table II).[60] This meta-analysis, conducted by Mukherjee et al., aimed to determine whether COX-2 inhibitors, as a class, were associated with a protective or hazardous effect on the risk of cardiovascular events by comparing the adjudicated cardiovascular outcomes from major trials COX-2 inhibitors with the annual MI rate as reported in the placebo group of a recent meta-analysis of four aspirin primary prevention trials.

The authors reported that their findings suggested a potential increase in cardiovascular event rates for users of COX-2 inhibitors as a 'class-effect', possibly due to a prothrombotic effect, despite examining data from trials of rofecoxib and celecoxib only. However, their conclusion was not adequately supported by their study: although the authors acknowledged some limitations in their study, there were also several methodological flaws. Our evaluation of this study revealed that the paper did not display each trial's finding in a consistent manner; it did not give an overall estimate of the magnitude of treatment difference nor did it investigate the heterogeneity between trials or explore the robustness of the main findings using sensitivity analysis. The randomised controlled trials were of different design; had different study endpoints; involved patient populations of dissimilar cardiovascular risk and they compared inequivalent therapeutic dosages of celecoxib and rofecoxib. In addition, the sample size of the different studies included in the meta-analysis varied and the crude estimate was likely to be heavily influenced by the size of the VIGOR study. Furthermore, a number of studies that were favourable to rofecoxib were excluded. There were no data comparing the cardiovascular event rates of the comparator NSAID cohort and placebo group and the crude incidence of MI only was compared across the different studies rather than the rate of thromboembolic events in totality. These fell within the range of rates reported for the four individual aspirin trials (0.36–1.33%) making it difficult to draw any conclusions. The authors also referred to data from spontaneous reporting schemes, but did not draw attention to the limitations of such systems or how this data supported their findings.

Despite accumulating published evidence on this topic, it is still difficult to draw any conclusions from the results of all these randomised controlled trials, retrospective re-analyses and the meta-analysis on differences of cardiovascular TE risk between celecoxib and rofecoxib. For the randomised controlled trials described earlier, the heterogeneity of study design (efficacy versus safety), the variability in the recording and the reporting of outcomes (based on both subjective and objective measures) especially adverse events, make comparisons of cardiovascular risk difficult. Furthermore, the sample size and primary outcomes of these randomised controlled trials were based on the assessment of upper GI risk, not cardiovascular risk. Thus, the randomised controlled trials were unlikely to have sufficient power to detect small clinically significant differences in rare cardiovascular outcomes, morbidity or mortality. In addition, with the exception of the VIGOR and CLASS trials, the length of follow-up of the trials was relatively short resulting in paucity of adverse effect data associated with long-term drug use.

In many of the studies reviewed, the choice of active comparator was either naproxen or a combination of nonselective NSAIDs, each with different COX-1/COX-2 selectivity. As mentioned earlier, the comparison with naproxen is important since three case-control studies support a potential cardioprotective effect of naproxen,[68-70] but not with other non-aspirin NSAIDs. What is clear is that there is still very little information on patients unexposed to NSAIDs, so that the excess risk to patients using COX-2 inhibitors still cannot be determined. To date, the second retrospective analysis by White

et al.[59] provides the best information on this subgroup, in that this study reports cardiovascular TE outcomes for a large pooled placebo cohort of over 1700 subjects.

Focusing on the characteristics of patients enrolled in these trials, as mentioned earlier, there was evidence of differential exclusion of patients with cardiac risk factors, i.e. a preferential selection of patients with low cardiovascular risk. In the VIGOR study, patients using aspirin were excluded, although 221 patients (4%) had a clear indication for aspirin, whereas aspirin use was permitted in the CLASS trial. Some authors advocate that a difference in TE rates in the CLASS trial was not revealed because of the use of aspirin by some patients.[26] As mentioned previously, it is possible that high-dose celecoxib competes with aspirin for COX-1 and thus abolishes any aspirin-mediated cardioprotective effect.[38] Modification by nonselective NSAIDs of the clinical benefits conferred by aspirin has been observed elsewhere.[71] The majority of serious TE events in the CLASS trial occurred in the population that were not receiving aspirin prophylaxis (78%, n = 3105). Strand and Hochberg[72] suggested that the best population to compare with the study population from the VIGOR study were those not taking aspirin in the CLASS study. The relative risk of serious TE events was 1.1 (95% CI 0.6, 1.9) for non-aspirin celecoxib users (0.8%, n = 25) versus non-aspirin users of NSAID-treated patients (0.7%, n = 23). The second retrospective analysis by White et al.,[59] also suggests that the findings of no difference in cardiovascular risk in users of celecoxib compared with NSAIDs is not attributable to the associated use of aspirin for cardioprotection in patients with cardiovascular risk factors.

Further complication in making comparisons between celecoxib and rofecoxib arise from differences in cardiovascular risk between patients who have RA compared with OA. Several investigations have reported that RA is associated with an increased risk for cardiovascular disease (MI, congestive heart failure and stroke), compared with those with OA, or no arthritis.[73,74] The indications of the study populations within each trial were clearly different. As yet, trials aimed to specifically compare the cardiovascular safety between the different COX-2 inhibitors in patients with equivalent cardiovascular risk, have not been undertaken.

Another important issue is that of the dose of each COX-2 inhibitor and active NSAID comparator used. In the VIGOR study, the dose of rofecoxib was intentionally high (50mg), whereas the dose for naproxen (1000mg) was within standard prescribing regimens. This prescribing bias (in favour of higher doses for the study drug of interest) is also reflected in the CLASS study, with supra-therapeutic daily doses of celecoxib (800mg) compared with standard daily doses of either ibuprofen (2400mg) or diclofenac (150mg). As discussed previously (figure 2), *in vitro* COX-1/COX-2 selectivity and potency differs between different nonselective NSAIDs and the COX-2 selectivity of celecoxib is lost at high doses (>800mg),[11] whereas the COX-2 selectivity of rofecoxib (25–1000mg) remains constant.[75] Such loss of selectivity of celecoxib at the dose used in the CLASS study, as well as the abolishment of the cardioprotective effect of aspirin, may have contribute to the observed overall lack of effect on cardiovascular risk compared with the nonselective NSAIDs. A more appropriate efficacy trial would be to compare therapeutically equivalent doses of each NSAID of interest. None of the aforementioned trials specifically addressed the issue of inequivalence of COX-2 inhibition. While we acknowledge that there is no consensus on methods for determining selectivity, one cannot yet draw conclusions regarding possible differences in cardiovascular risk between the COX-2 inhibitors being attributable to differences in COX-1/COX-2 selectivity. This hypothesis requires testing in large-scale randomised controlled trials.

In summary, only one meta-analysis has been published on this topic and, albeit methodologically flawed, this study was a comprehensive attempt to pool data between the COX-2 inhibitors. The retro-

spective re-analyses of randomised controlled trials were undertaken for each COX-2 inhibitor independently,[51,56,59] and examined patient derived data from all eligible randomised controlled trials for rofecoxib and celecoxib separately. They were well conducted and used endpoints accepted to be of world-wide clinical significance. While these re-analyses reported no evidence of increased risk of cardiovascular reactions according to these endpoints for either drug, these studies were still unable to answer the question of whether there is a difference between rofecoxib and celecoxib in terms of cardiovascular safety.

2.3 Observational Studies

Population-based pharmacoepidemiological studies aim to identify and quantify adverse events from the treatment experiences of the population from which the adverse events arose and examine that population for characteristic features in order to learn and inform from these experiences. Such studies usually include far more patients than randomised controlled trials, but suffer from likelihood of bias and confounding. Another important difference is that observational studies are often non-interventional in that they do not interfere in the prescribing decisions of the medical practitioners, nor do they require the strict inclusion criteria that are essential for randomised controlled trials. Therefore, findings in observational studies are more generalisable. Observational studies are often used to test a hypothesis at a population level and thus may contribute information on a possible relationship between any NSAID use and the risk of TE events in patients with concurrent medical problems and/or using concomitant medication.

As mentioned previously, one of the possible explanations for the observed difference in cardiovascular risk between rofecoxib and naproxen in the VIGOR study is that naproxen may be cardioprotective, yet the epidemiological evidence to support this assertion appears contradictory. A review of four epidemiological studies with different study designs and populations suggest no overall effect of traditional nonselective NSAIDs, including naproxen on the risk of coronary heart disease (CHD), regardless of chemical class or plasma half-life on the risk of CHD.[53] The results of this review included prepublication material from a large-scale observational study using a retrospective cohort design by Ray et al., which was later published in full.[76] The authors concluded that none of the NSAIDs included in this study should be used for cardioprotection, including naproxen, contrary to the VIGOR study, the retrospective analysis by Konstam et al.[51] and other observational studies.[68-70] However, the authors commented that consideration should be given to the higher cardiovascular risk in this study population compared with those patients involved in the VIGOR study.

There have been eight pharmacoepidemiological observational studies published that have reported on cardiovascular adverse events associated with either rofecoxib and/or celecoxib (table III). Of these, three studies were individual post-marketing studies (table III) while five studies were retrospective analyses of post-marketing data (table III).

2.3.1 Post-Marketing Surveillance Studies of Rofecoxib and Celecoxib

One prospective post-marketing cohort study assessed the efficacy and tolerability of rofecoxib in general practice conditions in Germany.[77] Two other post-marketing studies were conducted in England using the non-interventional observational cohort technique of prescription event monitoring (PEM) [table III],[78,79] where all events reported by patients to English National Health Service general practitioners (GPs) are collected prospectively in a systematic manner.[86] The authors' conclusions from these three post-marketing studies were that the tolerability of either drug was consistent with previous experience in controlled trials.

The issue regarding excess risk of cardiovascular TE events arose after the completion of the PEM study for rofecoxib[78] and during the PEM study for celecoxib.[79] In the two PEM studies, the incidence

of cardiovascular TE events was low (0.6%). The strengths and limitation of such observational studies have been discussed in detail elsewhere.[87] These post-marketing studies can provide information on the incidences and rates of common adverse events in cohorts, but the sample sizes (while large compared with most randomised controlled trials) are insufficient to detect rare adverse events with an incidence lower than 1 in 3000.[88]

2.3.2 Retrospective Analyses of Post-Marketing Databases

There have been four retrospective pharmacoepidemiological observational studies published that were specifically designed to investigate the issue regarding the risk of cardiovascular TE adverse events following the use of COX-2 inhibitors, with information for a fifth available in abstract form only (table III).[80-82,84]

The strongest evidence from observational studies to support the hypothesis to date regarding an increase in cardiovascular TE events between the COX-2 inhibitors, other NSAIDs and non-NSAID users comes from a second retrospective observational study by Ray et al., which was conducted using the multipurpose Medicaid database in the US (table III).[80] The authors concluded that high-dose rofecoxib (>25 mg/day) could be associated with a raised risk of serious CHD, whereas rofecoxib <25 mg/day, celecoxib, naproxen and ibuprofen were not. In contrast to the randomised controlled trials presented earlier, this study did not examine all serious cardiovascular TE events or report on the proportion of prescribed aspirin use, although this appears to have been adjusted for in the analysis. Unlike for the investigators' first retrospective study of CHD for nonselective NSAIDs described earlier,[76] it is not clear whether there was a difference in baseline risk of NSAID users compared with the controls, how information on other non-aspirin NSAIDs was analysed as for the other exposure categories and if the effect of recent use within 60 days was examined. In addition, it would have been useful to specifically examine the effect of concomitant low-dose aspirin in users of celecoxib and rofecoxib, especially by dose to determine whether the cardioprotective effect of aspirin persisted in rofecoxib users and/or was abolished in high-dose celecoxib users as suggested by the experimental study of Ouellet et al.[38]

A further retrospective observational study was conducted using administrative healthcare data from Ontario, Canada (table III).[81] The authors concluded that no significant difference was observed in acute MI risk for new users of celecoxib, rofecoxib, naproxen or non-naproxen NSAIDs (continuously for >30 days) compared with non-users. Notably patients who were reported to have taken one of the study drugs for 30 days or less were excluded, and the effect of this on the estimate of RR of MI in the short-term (≤30 days) is unclear.

In order to compare the safety profiles of these drugs as prescribed in general practice in the UK, two retrospective analyses of selected TE events were undertaken using patient event data collected during the large PEM studies for the individual COX-2 inhibitors: rofecoxib,[78] celecoxib[79] and meloxicam,[83] considered to be COX-2 selective but less so than celecoxib and rofecoxib (table I). For these two comparisons,[82,84] the TE events were categorised into three groups to mirror those endpoints as reported in randomised controlled trials, as presented earlier. After adjustment for age and sex, these two studies revealed a statistically significant higher rate of cerebrovascular TE events for both rofecoxib and celecoxib compared with meloxicam, a statistically significant lower rate of peripheral venous thrombotic events for the rofecoxib cohort compared with meloxicam, but neither revealed a difference in the rate of the cardiovascular TE event group.

A fifth analysis was presented at a scientific meeting in October 2003 (table III).[85] Information was available only from the abstract and has not yet been published in a peer review journal. This matched case-control study was also conducted using the Medicaid database in the US and directly

Table III. Summary of rofecoxib and celecoxib post-marketing observational studies and retrospective analyses of post-marketing databases, reporting on cardiovascular thromboembolic (CV TE) events

Design (reference)	Setting, study population	Drug exposure, follow-up duration, study size	Statistical analysis	Study endpoints
Post-marketing studies				
Retro PMS study[77]	GP in West Germany, May 2000–Jan 2001. 2-phase recruitment by 11 851 physicians Pts requiring 1st treatment for OA, or switch from existing medication, and no known contraindications to rof	Date of pres to (at least) 2nd follow-up minimum 28d after start of treatment. Mean duration of treatment NR 80 371 (1st wave, n = 42 140; 2nd wave, n = 38 231)	Descriptive stats and mean change in pain score, stratified by recruitment wave	Primary: efficacy (WOMAC score); change in quality of life (3-point scale) Secondary: all reported AE
PEM population based obs cohort study[78]	GP in England, UK All NHS patients prescribed and dispensed rof between Jul–Oct 1999	P-T from date of dispensing to stop date or end of survey date. Quest sent to prescribing physicians Feb–Nov 2000 (n = 15 268)	Descriptive statistics; unadjusted rates (ID) per 1000 pt-mo of treatment and ID difference (mo 1–mo 2 to 6); stratification of selected GI events according to potential risk factors using MH method	Health related events[a] reported by prescribing physicians during the study period
PEM population based obs cohort study[79]	GP in England, UK All NHS patients prescribed and dispensed cel between May–Dec 2000	P-T as above.[78] Quest sent to prescribing physicians Jan–Oct 2001 (n = 17 458)	As above[78]	As above[78]
Retrospective analyses of post marketing databases				
Retro obs cohort design[80]	Tennesse Medicaid programme, US. All pts enrolled in Medicaid between 1 Jan 1999 and 30 Jun 2001, aged 50–84y, eligible for benefits for past 365d, not in a nursing home and no history of non-CV life-threatening illness	Four exposure categories: NSAID user, new NSAID user, former NSAID user (n = 181 441), controls (no NSAID use) [n = 181 441] P-T: study start date to end of eligibility, 365d after last NSAID use, study end, or endpoint	PRM for adjusted incidence RR for NSAID exposure groups	Primary: serious CHD (defined as hospital admission for acute MI or death from CHD)
Retro obs cohort design[81]	Linked administrative healthcare databases, Ontario, Canada. All residents (1.44 million), aged 66+y, registered as receiving healthcare between Apr 1998 and Mar 2001	Three exposure categories: NSAID user, new NSAID user, (n = 66 964), controls (no NSAID use) [n = 100 000] P-T from index date to maximum 1y, to end eligibility, died, study end or endpoint	Crude and age/sex adjusted time to event analysis using Cox PHM with sensitivity analysis	Primary: hospital admission for acute MI (ICD9 diagnosis code 410)
Retro obs cohort design[82]	PEM database of events[a] reported in GP in England. Pt cohort from rof PEM study[78] and mel PEM study[83]	New users of rof (n = 15 268) vs new users of mel (n = 19 087, reference cohort) P-T from date of 1st pres dispensed to study end (270d) or endpoint	First event incidence rates; crude and adjusted RR calculated using PRM. KM time to event analysis	First reported TE associated event[a]: CV, CBV, peripheral venous thrombotic

Continued next page

Table III. Contd

Design (reference)	Setting, study population	Drug exposure, follow-up duration, study size	Statistical analysis	Study endpoints
Retro obs cohort design[84]	PEM database of events[a] reported in GP in England. Pt cohort from cel PEM study[79] and mel PEM study[83]	New users of cel (n = 17 458) vs new users of mel (n = 19 087, reference cohort) P-T as above[82]	As above[82]	As above[82]
Retro obs, matched case-control study[85]	State sponsored benefits programme in Pennsylvania and New Jersey, US. 54 475 patients, aged 65+y, receiving medication via benefit programme, 1999–2000	Case: primary outcome; either current study NSAID user (rof, cel, non-selective NSAIDs), or non-NSAID user (n = 10 895) Control: no hospitalisation, exposure as for case (n = 43 580, 1:4 cases to controls)	CLRM for adjusted RR for all doses and dose specific (high vs low equivalent doses)	Primary: hospitalisation for acute MI

a Any new diagnosis, any reason for referral to consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any other complaint which was considered of sufficient notice to enter into patients' notes.

cel = celecoxib; **CHD** = coronary heart disease; **CBV** = cerebrovascular; **CLRM** = conditional logistic regression modelling; **ICD** = International Classification of Diseases; **GP** = general practice; **MH** = Mantel-Haenszel; **ibu** = ibuprofen; **ID** = incidence density; **KM** = Kaplan-Meier; **mel** = meloxicam; **MI** = myocardial infarction; **NHS** = National Health Service; **NR** = not reported; **NSAID** = nonsteroidal anti-inflammatory drug; **OA** = osteoarthritis; **obs** = observational; **PEM** = prescription-event monitoring; **PHM** = proportional hazard modelling; **PRM** = poisson regression modelling; **PMS** = post-marketing surveillance; **pres** = prescription; **P-T** = person-time; **Quest** = questionnaire; **retro** = retrospective; **rof** = rofecoxib; **RR** = relative risk; **WOMAC** = Western Ontario and McMaster Universities OA Index.

compared the RR of acute MI between celecoxib and rofecoxib. The authors reported that current use of rofecoxib was associated with an increased adjusted RR of MI (of borderline significance) compared with celecoxib or non-NSAID users. Dose-specific comparisons suggested that the risk was highest for higher doses of rofecoxib (>25mg). Risk was also reported to be highest in the first 90 days.

Residual confounding, confounding by indication and bias are particularly important in observational studies that report a low RR estimate. Observational studies are vulnerable to various kinds of bias, which may have contributed to the failure to confirm the hypothesis of a consistent difference in cardiovascular TE risk between the COX-2 inhibitors. For example, for data retrieved from medical insurance data-bases, the longitudinal follow-up of an individual patient is dependent on their participation in the insurance programme, thus selection bias could be introduced by exclusion of patients with incomplete records of exposure. Another example is that inconsistent information on baseline cardiovascular risk of patients, no direct measure of adherence and the use of confounding variables such as use of aspirin, other concomitant drugs and past or present medical history of CHD could bias the summary effect estimate either towards or away from the null value. Furthermore, in observational studies, residual confounding by unknown risk factors should always be considered. Thus, the information from observational studies must be taken into consideration with other large-scale pharmacoepidemiological investigations on the same topic which examine these risk factors.

3. Spontaneous Reporting Schemes of Adverse Drug Reactions

A major source of information on suspected ADRs includes databases of post-marketing spontaneous reports held by pharmacovigilance centres, regulatory authorities or manufacturers. Such data give a different but complementary perspective on adverse reactions compared with randomised con-

trolled trials or observational studies, since they are derived from populations of national proportions, operate for the lifetime of the drug and include all drugs in both general practice and hospital settings. Spontaneous reporting schemes are effective for signal generation, particularly for very rare ADRs; however, a limitation of these databases is that the data in individual case reports is often incomplete. Comparisons between drugs based on spontaneous reports are inherently difficult given that reports of suspected ADRs are not homogenous with respect to the sources of the information, or time on the market between the drugs of interest. A variety of other factors may influence spontaneous reporting including the number of drugs on the market, drug prescribing policies, drug safety alerts, training of physicians and other healthcare professionals, reporting and publication bias between new entities versus other 'me-too' drugs, confounding by indication and confounding by unknown risk factors. It is also important to recognise that these are case reports based on suspicions of a causal relationship. The likelihood that the pharmaceutical product caused the suspected ADR requires further evaluation of the individual cases making up the safety signals by expert clinical reviewers. These factors and other strengths and limitations are discussed in detail elsewhere,[89] and should be considered when assessing the evidence regarding TE risk based on voluntary reporting schemes as presented below.

The WHO Uppsala Monitoring Centre (UMC) in Sweden maintains a database of spontaneous reports received from the national monitoring centres worldwide. Suspected adverse reactions are coded onto the WHO database according to the WHO Adverse Reaction Terminology (WHO-ART) hierarchical system. Signal scores are calculated for each drug-reaction (preferred term) combination for each pharmaceutical product recorded within the WHO database according to the Bayesian Confidence Propagation Neural Network (BCPNN),[90] and hypotheses created of associations between drugs and ADRs among the case reports on the WHO UMC database. An independent study of adverse reactions, primarily adverse renal effects, reported for rofecoxib (n = 2720) and celecoxib (n = 8434) reported to the WHO UMC up until the end of the second quarter of 2000, was conducted by Zhao et al.[91] Drug-reaction combination information component (IC) values and 95% CIs were calculated between both drugs and also compared with background expectation. In this study, TE events were also examined and compared (table IV). The IC values for MI and cerebrovascular events was significantly higher for rofecoxib compared with background expectations but not significantly different for celecoxib. IC values calculated for thrombotic reactions were not significantly different compared with the background expectation. The authors concluded that COX-2 specific inhibitors were not asso-

Table IV. Information component (IC)[a] and 95% CI[b] values for thromboembolic-related adverse drug reactions (ADRs) with rofecoxib and celecoxib, using ADR groups based on WHO adverse reaction (WHO-ART) preferred terms[91]

ADR group	Rofecoxib		Celecoxib		Celecoxib vs rofecoxib p-value
	IC value	95% CI	IC value	95% CI	
Myocardial infarction	1.44	0.92, 1.96	0.37	−0.07, 0.81	<0.05
Cerebrovascular events[c]	1.48	1.09, 1.87	0.03	−0.35, 0.41	<0.001
Thrombotic events[d]	0.46	−0.13, 1.05	−2.0	−0.64, 0.24	>0.05

a A positive IC value indicates that a drug-reaction combination has been reported more frequently than expected compared with the background of all reactions reported to the WHO database.

b If the lower level of the 95% CI is greater than zero, the IC value is significantly higher than background expectation.

c Category including cerebral infarction, cerebral ischaemia, cerebrovascular disorder, intracranial haemorrhage, transient ischaemic attack, cerebral haemorrhage and haemorrhagic stroke.

d Category including thromboembolism, deep thrombophlebitis, thrombophlebitis, thrombosis, pulmonary embolism, embolism-blood clot, arterial embolism, arterial thrombosis and arm or leg arterial thrombosis.

ciated with thrombotic reactions. Given that the primary outcome of the study revealed a difference in renal adverse reactions between the two drugs, the investigators suggested that the higher risk of cardiovascular events observed in patients treated with rofecoxib was likely to be associated with the higher risk of renal adverse reactions, particularly hypertension, rather than secondary to thrombotic episodes. However, it is important to recognise that such conclusions were based on analytical comparisons of IC values, and that the individual case reports were not clinically reviewed.

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA, formerly Medicines Control Agency, MCA) receives spontaneous reports submitted to the Committee on Safety of Medicines (CSM) via the Yellow Card Scheme and provides one of the major sources of data for pharmacovigilance. Statistical methods used in the quantitative analysis of anecdotal spontaneous ADRs at the MHRA include the use of Proportional Reporting Ratios (PRRs).[92] This technique tests the null hypothesis that the proportion of individual ADR reported for a drug of interest does not differ from the rest of the database. Signal generation using PRR within the MHRA Adverse Drug Reaction Online Information Tracking (ADROIT) database is automated and performed routinely on a weekly basis for monitoring purposes. Possible safety signals which fall above prespecified statistical criterion (PRR >2, χ^2 >4) are then highlighted for further examination by clinicians.

As discussed previously, one cannot make direct comparisons of reporting rates between drugs based on spontaneous reports and it is important to acknowledge that rofecoxib was the first of these two drugs to be marketed in the UK and thus the number of spontaneous reports will reflect this. Figure 3 and figure 4 represent graphically PRRs by systems order class (SOC) for rofecoxib and celecoxib. Clearly the ADR reports received for both drugs is dominated by the total number of reactions reported for the GI SOC, which is significantly different from the overall reporting profile for the database. The number of reports within the cardiovascular SOC is small (567 and 157, respectively) and the proportions of reports for each drug do not differ significantly from background expectation. However, one cannot draw any firm conclusions about differences between these drugs regarding cardiovascular risk, since ADR reporting rates are influenced by many factors, as highlighted earlier.

In Canada, spontaneous reports are submitted to the regulatory authority, Health Canada through the Canadian Adverse Drug Reaction Monitoring Program (CADRMP). By 12 October 2001, Health Canada had received 70 reports of suspected cardiovascular/cerebrovascular reactions for celecoxib (out of 528 in total) and 68 similar reports for rofecoxib (out of 348) since the date of marketing in Canada (April and November 1999, respectively).[93] The authors of the Canadian report commented that when interpreting whether the above cardiovascular effects are related to COX-2 inhibitor use, several factors must be considered such as preexisting medical conditions, the prevalence of cardiovascular disease in the population for whom the drugs are indicated and concomitant use of drugs that can cause cardiovascular reactions or drug interactions. Of the seven fatal cases reported in patients prescribed celecoxib, two were cases of cerebral haemorrhage in patients prescribed warfarin concomitantly.

In New Zealand, the New Zealand Pharmacovigilance Centre (NZ PhvC) receives spontaneous adverse reaction reports through the Centre for Adverse reactions Monitoring (CARM) which, through the Intensive Medicines Monitoring Programme (IMMP)[94] also undertakes PEM supplemented by spontaneous event reports. The IMMP prepares adverse event profiles for the monitored medicines, measures the incidence and is able to identify high-risk groups amongst the patients being treated. The total IMMP cohorts for celecoxib and rofecoxib are 32 630 and 52 874 patients, respectively. These cohorts are presently being followed up and analysed.

At a recent scientific meeting in October 2003,[95] an interim analysis reported that 1825 events for 971 patients had been processed for celecoxib with corresponding figures for rofecoxib reported as 1094 and 631, respectively. Of these, 17% (n = 315) of events for celecoxib and 20% (n = 214) of those for rofecoxib were cardiovascular related. Of 179 deaths reported for celecoxib, 68 were cardiovascular in origin of which 23 (12.9%) were causally related to treatment. The corresponding figures for rofecoxib were 293, 116 and 34 (11.6%). Concern was expressed at the high rate of cardiovascular reactions and the relatively high death rates. The authors also commented that there was substantial prescribing to patients at high risk such as the very elderly (80+ years), and those with a history of cardiovascular disease. Further information from the IMMP will be published in articles presently in preparation.

4. Conclusion

The pharmacological evidence suggests that highly selective COX-2 inhibitors such as rofecoxib, which have little or no affinity for COX-1, do not inhibit the synthesis of prothombotic prostanoids. Potent and highly selective COX-2 inhibitors thus appear to be more likely to contribute both to unwanted cardiovascular effects precipitating thrombotic events, such as MI and angina, than are the less selective COX-2 inhibitors. This is consistent with findings from some clinical observations. However, where aspirin is used concomitantly to protect against thrombotic events, less selective COX-2 inhibitors (celecoxib), but not highly selective COX-2

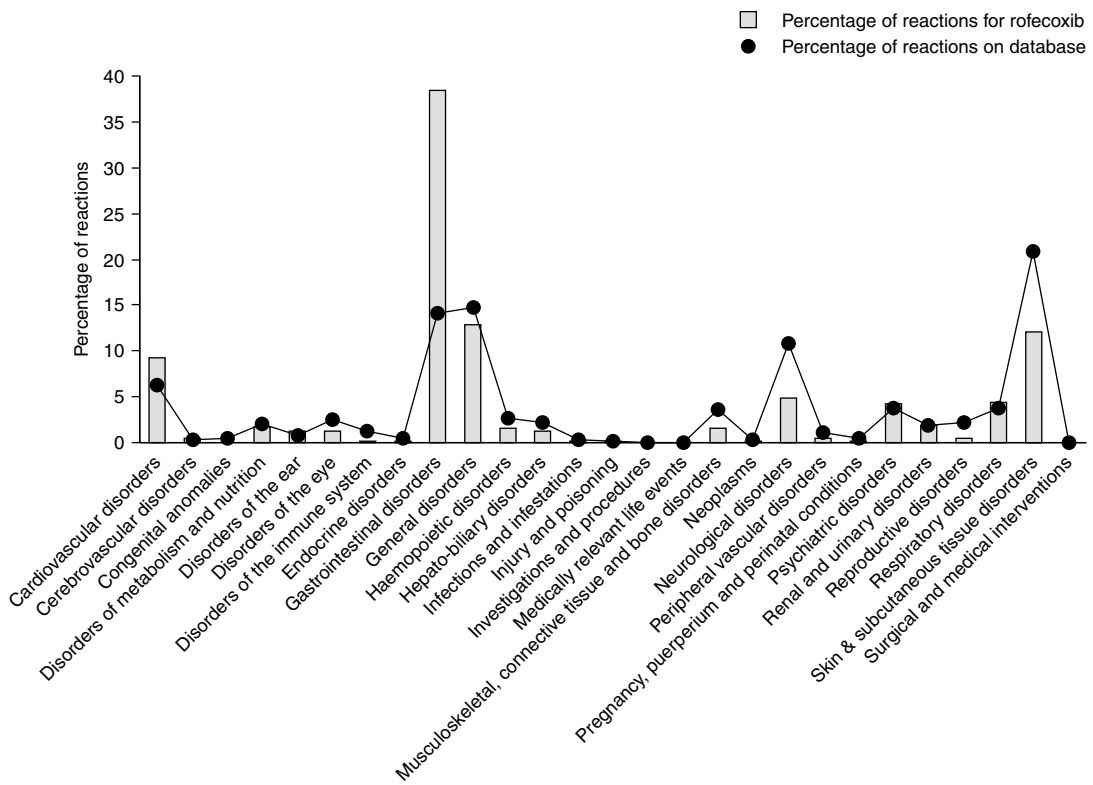

Fig. 3. The proportion of adverse drug reaction reports (percentages) for rofecoxib (total 6144 reports for rofecoxib on 3523 yellow cards) compared with the overall reporting profile for the Adverse Drug Reaction Online Information Tracking (ADROIT) database, by system order class up to 30 July 2003 (reproduced with permission from the UK Medicines and Healthcare products Regulatory Agency).

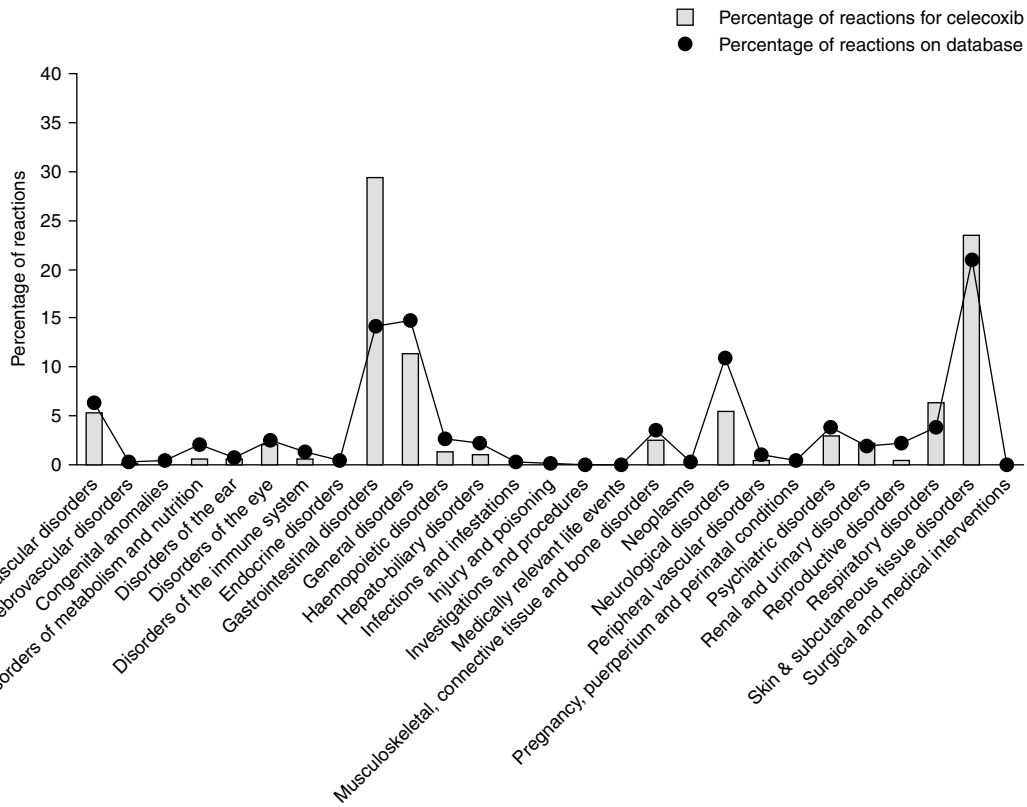

Fig. 4. The proportion of adverse drug reaction reports (percentages) for celecoxib (total 2943 reports for celecoxib on 1724 yellow cards) compared with the overall reporting profile for the Adverse Drug Reaction Online Information Tracking (ADROIT) database, by system order class up to 30 July 2003 (reproduced with permission from the UK Medicines and Healthcare products Regulatory Agency).

inhibitors (rofecoxib) may, at least partially, antagonise the protective effect of aspirin. Further studies are needed to evaluate the clinical use of COX-2 inhibitors in patients on low-dose aspirin.

In randomised controlled trials, the VIGOR study suggests that an excess risk of cardiovascular events may be associated with use of rofecoxib compared with naproxen. The reasons for this observation remain unclear, especially given the conflicting evidence in the literature regarding the cardioprotective effect of naproxen or the weak evidence to support a dose-response relationship of rofecoxib. To date, the data from other randomised controlled trials, retrospective observational studies and voluntary reporting schemes provide a conflicting body of evidence such that the hypothesis that proposes that use of COX-2 inhibitors as a class, or individually, may be associated with an excess thromboembolic risk can neither be supported nor refuted.

Explanatory or pragmatic randomised controlled trials aim to measure the effect of a particular intervention using the principle of randomisation to minimise bias and the study sample size is chosen with the aim of testing a specific hypothesis. However, randomised controlled trials suffer from selection bias in that the study participants may not be representative of the intended target treatment groups. Although considered as the gold standard for efficacy, the randomised controlled trials discussed in this paper provide insufficient evidence to support the conclusion that COX-2 inhibitors are associated with an increased risk of thromboembolic events;

the majority of randomised controlled trials were not designed to assess thromboembolic events and were statistically under-powered and of insufficient duration to detect differences in the occurrence of relatively rare and serious events such as MI, cerebrovascular accident or other thromboembolic events. Furthermore, the baseline cardiovascular risk profiles of the study populations involved in the CLASS and VIGOR study were clearly different, and given that RA may be an independent risk factor for such cardiovascular events, one cannot draw any conclusions regarding differences in risk between these two drugs from these trials.

The observational studies conducted with COX-2 inhibitors were retrospective analyses of systematically collected data on the health-related experiences of patients for whom the baseline cardiovascular risk factors were often unknown or inconsistently recorded and were not prospective studies specifically designed to investigate the cardiovascular risk of COX-2 inhibitors in patients with similar pre-existing cardiovascular risk factors. Spontaneous reports together with case reports and case series currently appear to be the cornerstone of post-marketing surveillance and regulatory decision making.[96] While these systems are effective in generating signals of rare events, they are not designed to compare adverse event frequency between drugs.

It is clear that all the information provided from the pharmacoepidemiological studies must be taken into consideration before attempting to quantify the risk. Small scale *in vitro* and *in vivo* studies must also be used to understand the pharmacological mechanisms of such hazards. We have described how the association between the use of COX-2 inhibitors and cardiovascular TE events may be related to pharmacological characteristics of these products such as the selectivity of COX inhibition, which vary between different products and is influenced by doses received. Furthermore, the concomitant use of aspirin with COX-2 inhibitors may influence the likelihood of the development of cardiovascular TE events. There is a need to control for differences in baseline cardiovascular risk between study populations, not only the prevalence of cardiovascular disease but also other risk factors associated with cardiovascular disease. Complications may also arise from the apparent preferential prescribing of COX-2 inhibitors to patients at higher risk of GI and cardiovascular events than nonspecific NSAIDs.[97] Therefore such factors should to be taken into account through adequate control of confounding when assessing the safety and risk/benefit of these drugs.

With the available data the concerns that COX-2 inhibitors may be associated with prothrombotic effects remain and these need to be addressed in large-scale randomised controlled trials and pharmacoepidemiological studies designed specifically to investigate the possibility of an excess of adverse cardiovascular outcomes in users of some or all selective COX-2 inhibitors, both with and without concomitant low-dose aspirin. Consideration must also be given to other pathophysiological mechanisms for potential cardiovascular risk linked to inhibition of COX-2, including imbalance of PGI_2 and TXA_2 and concomitant disease states. Altered renal perfusion leading to hypervolaemia and sodium retention both contribute to hypertension[98] and therefore modify cardiovascular risk. Given the association between COX-2 expression and states of intravascular inflammation arising from for example, atherosclerosis or intravascular laminar shear forces, the clinical importance of COX-2 expression in the vascular endothelium needs further investigation.

Although some of the evidence from large-scale clinical trials and pharmacoepidemiological studies is contradictory, the pharmacological evidence together with concerns arising from some clinical studies suggests that an increased cardiovascular risk associated with COX-2 inhibitor use remains a possibility. Selective COX-2 inhibitors should be prescribed with caution and with careful monitoring of outcomes and adverse events. This is particularly

important in the elderly, in patients with cardiovascular/renal disease and in patients with other risk factors that might predispose them to adverse events.

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