COX-2 Inhibitors and Cardiovascular Risk

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INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) have provided comfort to patients with pain, fever and inflammation for thousands of years and patients with coronary artery disease for many years. The enthusiasm for NSAIDs has been overshadowed at times by life threatening side effects involving several organ systems such as the gastrointestinal track. The severity of these side effects, especially gastrointestinal hemorrhage, led to the search for NSAIDs that possess the beneficial antiinflammatory, antipyretic and analgesic effects with fewer serious adverse effects. The discovery of the class of drugs that selectively inhibits cyclooxygenase-2 (COX-2 inhibitors) resulted from this search. The makers of these COX-2 inhibitors promised the analgesic and antiinflammatory properties of other NSAIDs with a significantly lower incidence of serious gastrointestinal bleeding[1]. While this promise seemed plausible based on the mechanistic explanations discussed below, reports of increased risk for heart attack and stroke in patients taking rofecoxib (Vioxx®) lead to the voluntary withdrawal of the drug from the market by its manufacturer. This withdrawal was accompanied by tremendous indignation in the lay and medical press regarding the ethics of the manufacturer of Vioxx® as well as the effectiveness of the FDA as a protector of the public from drugs that have unexpected side effects. Some have attacked physicians who provide consultative and marketing functions for pharmaceutical companies. Others have recommended the establishment of a separate Food and Drug Administration to deal with post-marketing surveillance and safety of approved drugs. Some respected clinical researchers in the cardiovascular field even suggested that the inaction of the FDA in removing Vioxx® from the market led to tens of thousands of heart attacks and cerebrovascular accidents[2]. This concept was embraced by many personal injury attorneys across the nation.

On the other hand, an expert advisory panel for the FDA recently recommended that celecoxib (Celebrex®) and valdecoxib (Bextra®) remain on the market, and that rofecoxib (Vioxx®) be returned to the market for use by certain patients with pain and/or certain inflammatory diseases[3]. The panel also recommended that each drug have a black box warning for increased cardiovascular risk added to the package insert.

It is not surprising that much confusion exists in the lay and medical community as well as the lay press regarding the use of COX-2 inhibitors. Given the above series of events, it is also not surprising that many physician offices are being bombarded with phone calls from patients with questions, confusion and anxiety regarding the use of COX-2 inhibitors. This review will attempt to examine the reasons for the withdrawal of Vioxx® from the market and examine the chances that other drugs of this class will also possess the similar side effect of increased cardiovascular risk.

COX-1 AND COX-2: THE EARLY YEARS

Cyclooxygenase (prostaglandin H synthase) catalyzes the first step of the synthesis of prostanoids by converting arachidonic acid into prostaglandin H_2 which is the common substrate for other prostaglandin synthetases. The general pathway is illustrated in Figure 1.

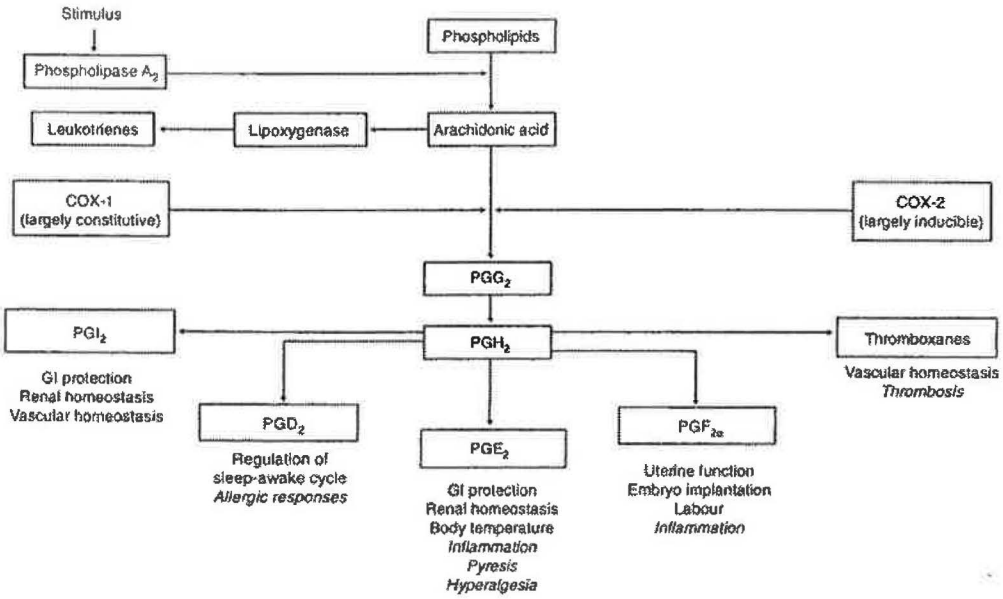


Figure 1[4]. COX-1 and COX-2 in the production of prostaglandins

The enzyme works in two parts[5] with fatty acid cyclooxygenase (COX) activity catalyzing the conversion of arachidonic acid to prostaglandin G_2 and prostaglandin hydroperoxidase catalyzing the conversation of prostaglandin G_2 to prostaglandin H_2. Subsequent activity by a variety of other enzymes in various tissues produces several arachidonic acid metabolites involved in various homeostatic and inflammatory processes which are tissue and functionally specific, often with functions opposed to the metabolites of other tissues. For example, the platelet-derived arachidonic metabolite TxA_2 (thromboxane) favors platelet aggregation, vasoconstriction, smooth muscle proliferation and thrombosis while an endothelial derived metabolite PGI_2 (prostacyclin) produces vasodilation, inhibits platelet aggregation, and inhibits vascular smooth muscle proliferation. Various arachidonic acid metabolites and their functions can be found in Table 1.

Table 1. Functions of Various Prostaglandin H_2 Metabolites

Prostaglandin	Function
PGE_2, PGI_2	GI protection, renal homeostasis
PGI_2, TXA_2	Vascular homeostasis
$PGF_{2\alpha}$	Uterine function, embryo implantation, labor
PGD_2	Regulation of sleep-wake cycle
PGE_2	Body temperature

Thirty years ago, it was discovered that aspirin-like drugs produce their desired antiinflammatory effect by blocking the action of cyclooxygenase and thereby decrease the synthesis of proinflammatory prostaglandins such as PGE_2[6]. Prostaglandin E_2 is an important mediator of

inflammation, potentiates the effects of agents that cause pain by lowering nociceptor threshold, and causes fever. Blocking the effects of this prostaglandin was thought to have important therapeutic implications in patients with inflammatory processes and pain so other compounds with similar characteristics were sought. This search for inhibitors of the synthesis of prostaglandin E_2 yielded more than 30 NSAIDs since the 1070's.

A decade ago, cyclooxygenase was demonstrated to exist in two isoforms, COX-1 and COX-2. The existence of two different enzymes was suggested by the fact that dexamethasone, a glucocorticoid, inhibited the increase in cyclooxygenase activity induced by lipopolysaccharide (LPS) in macrophages but had no effect on basal prostaglandin production[7]. In addition, *in vivo* administration of dexamethasone inhibited COX induction following *in vivo* administration of lipopolysaccharide. These effects are illustrated in Table 2.

Addition to whole blood	PGE_2	
	4 hr	24 hr
	ng/ml	
None	<0.05	<0.10
LPS (10 μg/ml)	0.87 ± 0.8	9.30 ± 4.46
LPS + dexamethasone (2 μM)	0.08 ± 0.07*	0.56 ± 0.15*

Values are mean ± S.D., n=3; LPS + dexamethasone vs. LPS; *P < .05.

Table 2[7]. Effects of LPS and dexamethasone on PGE_2 production in human whole blood

Both of these observations suggested that the dexamethasone effect on prostaglandin synthesis was due to inhibition of *de novo* (LPS inducible) and not basal COX synthesis. It was thought that the basal cyclooxygenase activity was due to COX-1 and the inducible activity due to COX-2. Evidence indicated that COX-1 was constitutively expressed in almost all tissues and mediated many homeostatic (housekeeping) responses such as platelet aggregation and cytoprotection of the gastric mucosa. Inhibition of this enzyme inhibited platelet function and explained the usefulness of aspirin in treating diseases that resulted from platelet activation such as unstable angina pectoris, peripheral vascular disease exacerbations, myocardial infarction, sudden death in coronary artery disease, stroke, and following angioplasty[8,9]. Inhibition of COX-1 also removes the gastric cytoprotective of certain prostaglandins and explained the higher incidence of gastric ulceration and upper gastrointestinal bleeding in patients using NSAIDs when compared to placebo. On the other hand, prostacyclin (PGI_2) produced in vascular endothelium by a COX-2 function was found to inhibit platelet aggregation, induce vasodilatation and inhibit vascular smooth muscle proliferation. Studies also suggested that COX-2 was expressed in an inducible fashion primarily in tissues that are in involved in inflammatory processes, such as macrophages and synovial cells, as illustrated below in Table 3 and Table 4.

Table 3. Inducible COX-2 Expression

Synoviocytes
Chondrocytes
Macrophages
Polymorphonuclear leukocytes
Endothelial cells
Vascular smooth muscle

Table 4. Stimuli for Inducible COX-2 Expression

Lipopolysaccharides
Serum Grow Factors
Tyrosine Kinases
Hormones
Cytokines/interleukins
Tumor Necrosis /factor

The induction of COX-2 expression in these tissues was thought to be responsible for the prostanoids involved in pathologic processes that involve inflammation. Many of the side effects of NSAIDs such as gastrointestinal bleeding and inhibited platelet function could be ascribed to COX-1 functions. On the other hand, the therapeutic effects of NSAIDs on pain, fever and inflammation were felt to be due to the inhibition of the COX-2[10] derived prostaglandins which were thought to be pathologic. This fact lies behind the hypothesis that inhibition of COX-2 would exhibit the therapeutic actions of nonselective NSAIDs, and not cause the unwanted side effects such as gastrointestinal bleeding (Figure 2).

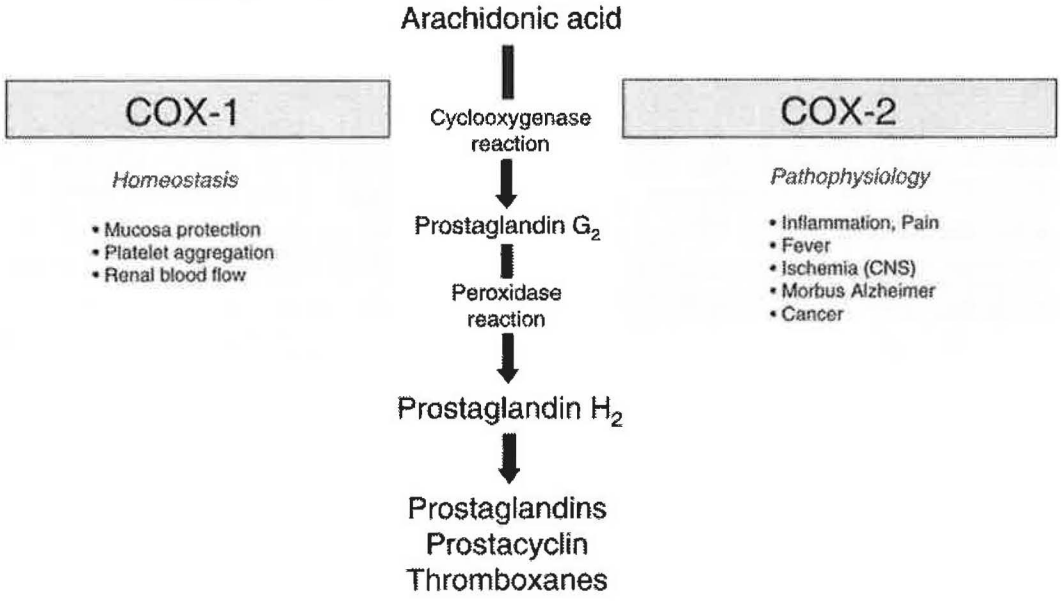


Figure 2. Bifunctional role of the COX enzyme in the biosynthesis of prostaglandins and thromboxanes, and the physiologic and pathophysiological effect of the COX isoenzyme (Adapted from Hinz[11]).

COX-2 can be induced by several transcription factors such as the nuclear factor for interleukin-6 expression and the cyclic AMP response element binding protein. The expression of the COX-2 gene is regulated by many mediators involved in inflammation such as lipopolysaccharide, proinflammatory cytokines (interleukin-1ß, and tumor necrosis factor) and growth factors. Other substances such as glucocorticoids, interleukin-3 and interleukin-10 inhibit the expression of the gene. In addition, there is evidence that suggests that products of the COX-2 pathway may also exert regulatory feedback actions on the expression of the enzyme by up-regulating COX-2 at sites

of inflammation. COX-2 has also been shown to have been regulated at the post-transcriptional levels by various effects on messenger RNA. Loss of this post-transcriptional regulation of COX-2 through mutations of proteins that interact with various post-transcriptional COX-2 elements may lead to COX-2 over-expression. It has been suggested that this mechanism is involved in colon carcinogenesis.

The structure of COX proteins consists of three domains: an N-terminal epidermal growth factor domain, a membrane-binding motif, and a C-terminal catalytic domain that contains the COX and peroxidase active sites. The active site of COX is at the end of a hydrophobic channel that runs from the membrane-binding surface of the enzyme into the interior of the molecule. NSAIDs act at the COX active site in various ways. Aspirin irreversibly inactives both COX-1 and COX-2 by acetylating the active-site serine. This covalent modification interferes with the binding of arachidonic acid at the active site. Other nonselective NSAIDs reversibly inhibit COX-2. Some of those drugs, such as ibuprofen, compete with arachidonic acid for the COX-2 active site. The action of other drugs, such as indomethacin, depend on a slow time-dependent reversible inhibition which results from a salt bridge between the drug and the active site. Inhibition of prostaglandin biosynthesis probably does not account for all the pharmacological action of NSAIDs. This has been suggested by the fact that salicylate is an effective inhibitor of prostaglandin formation *in vivo* at sites of inflammation, but does not inhibit COX activity *in vitro*. Some have suggested that inhibition of the transcription factor NF-κB could be a mechanism by which salicylates exert their antiinflammatory action.

The ability to inhibit COX-2 specifically by certain drugs seems to rely in an amino acid difference in position 523 of the COX enzyme. A valine amino acid in that position in COX-2 appears to account for the binding site of COX-2 selective substances. Celecoxib and rofecoxib are referred to as slow, time-dependent, irreversible inhibitors of COX-2. Other inhibitors that acetylate and irreversibly activate COX-2 inhibitors are being developed.

As expected from the specificity of the enzymes, inhibition of COX-2 with selective drugs can be accomplished without effect on COX-1 function as illustrated in Figure 3 where per cent change in thromboxane B_2 was measured while taking rofecoxib compared to placebo and Figure 4 where platelet aggregation was measure under the same conditions[12].

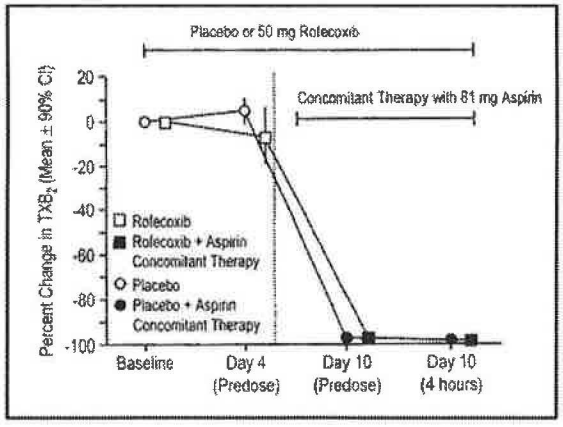


Figure 3. Percent change from baseline TXB_2 production for each day by time point. The offset of symbols on the x-axis was added to clarify the data and does not represent a time difference in samples[12]

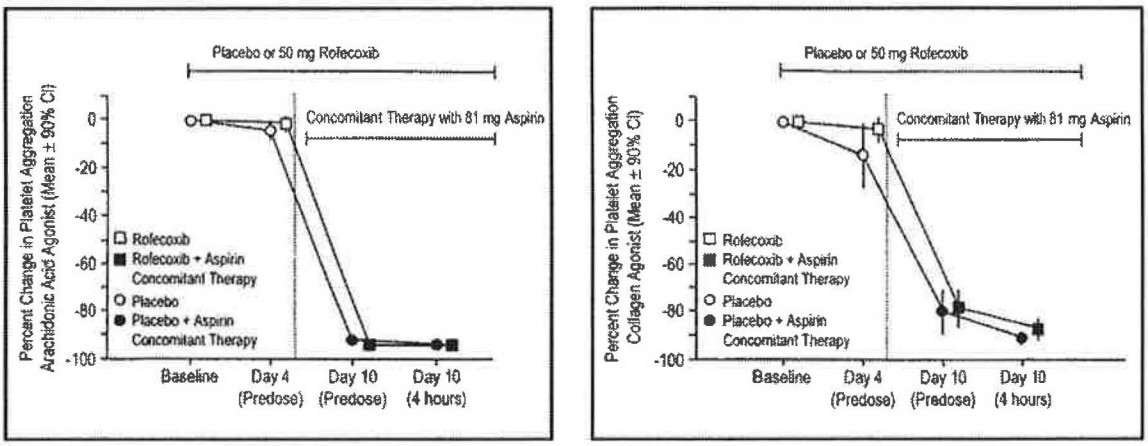


Figure 4. Percent changes from baseline platelet aggregation[12]

In summary, the data at the time the selective COX-2 inhibitors were release on the market suggested that the main effect of COX-2 mediated prostaglandins was to mediate inflammation in various cells and tissues while COX-1 derived metabolites were responsible for tissue protective roles to maintain vascular and tissue (such as gastric) integrity. Nonselective NSAIDs effectively inhibited both COX-1 and COX-2 which resulted in effective modulation of the inflammatory effect but also produced side effects by inhibiting the protective effect of various COX-1 prostaglandins. It made good sense to develop drugs that selectively inhibited COX-2. This was accomplished quickly by various pharmaceutical companies and soon three drugs were released for use in the United States. These were rofecoxib (Vioxx®), celecoxib (Celebrex®) and valdecoxib (Bextra®). The strong selectivity of these drugs is illustrated in Figures 5, 6, and 7 where celecoxib was compared to placebo and ibuprofen in its ability to inhibit COX-1 by inhibiting thromboxane production and platelet aggregation and COX-2 by inhibition of PGE_2[13].

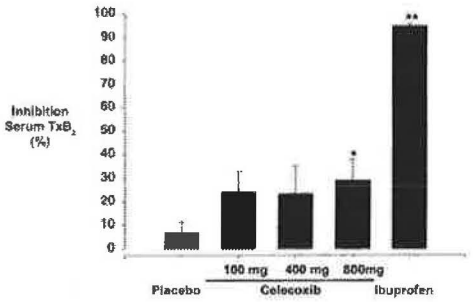


Figure 5. Inhibition of serum TXB_2, an index of COX-1 activity *ex vivo* in volunteers 4 hr after receiving placebo, 800 mg ibuprofen, or various doses of celecoxib[13]

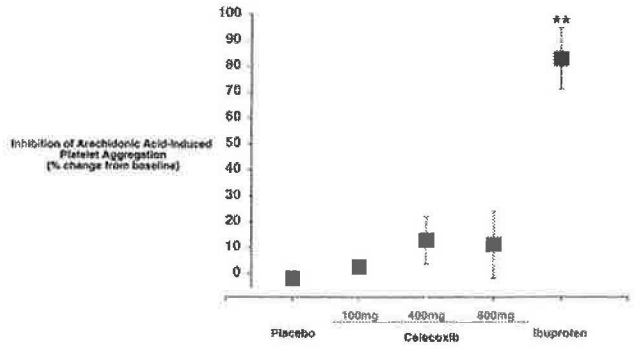


Figure 6. Inhibition of arachidonic acid-induced platelet aggregation *ex vivo* in volunteers 3 hr after dosing with placebo, 800 mg ibuprofen, and various doses of celecoxib[13]

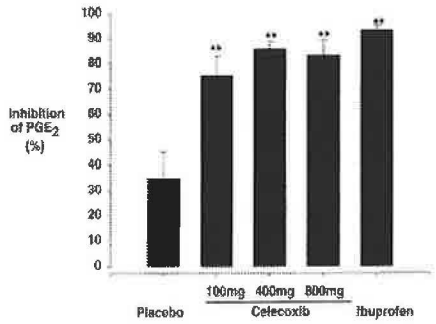


Figure 7. Inhibition of LPS-stimulated plasma PGE2, an index of COX-2 activity, ex vivo in volunteers receiving placebo, 800 mg ibuprofen, and various doses of celecoxib[13]

III. RISK OF CARDIOVASCULAR SIDE EFFECTS IN EARLY STUDIES WITH COX-2 INHIBITORS

Early studies examining the cardiovascular risks of COX-2 inhibitors revealed conflicting results. Konstam, *et al*[14], reviewed 23 Phase IIb/IV rofecoxib studies. Cardiovascular risk was not a primary end point in these studies. However, an analysis of the 28,000 studied patients involving more than 14,000 years of exposure to one of the treatment modalities allowed the authors to have some confidence in assessing the cardiovascular risk in a retrospective manner. The major outcome measure in this retrospective analysis was the combined end point used by the Anti-platelet Trialist Collaboration which included cardiovascular, hemorrhagic, and unknown deaths; non-fatal myocardial infarction and non-fatal stroke. In these studies rofecoxib was compared to various nonselective, nonsteroidal antiinflammatory medications. The patients in these 23 studies suffered from osteoarthritis, rheumatoid arthritis, Alzheimer's disease and low back pain. The authors concluded that the risk of a cardiovascular event in patients taking rofecoxib was no different than the risk in patients taking placebo or nonselective NSAIDs (excluding naproxen) as shown in Figure 8. However, the relative risk when compared to naproxen was 1.69 (95% CI: 0.40,1.55). Length of

exposure to the NSAID did not seem to influence cardiovascular risk as assessed by the APTC end point for rofecoxib compared to placebo, non-naproxen NSAIDs and naproxen in studies that were ≥6 months duration as illustrated in Figure 9.

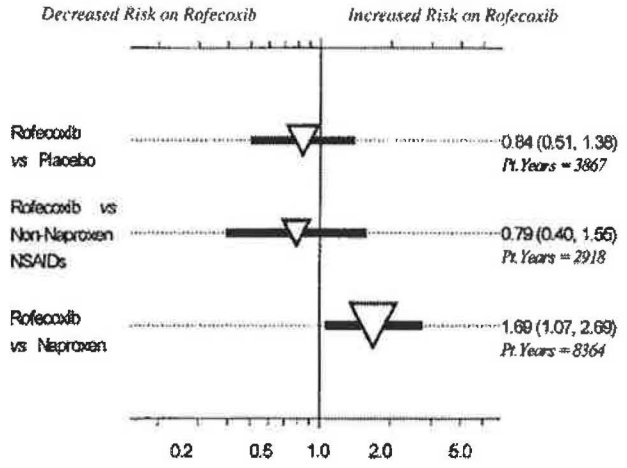


Figure 8. Relative risk (95% CI) of the APTC end point for rofecoxib relative to placebo, non-naproxen NSAIDs, and naproxen in the entire population studied. Triangles represent relative risk, and size of triangles represents patient-years of exposure. Bars indicate 95% CI.

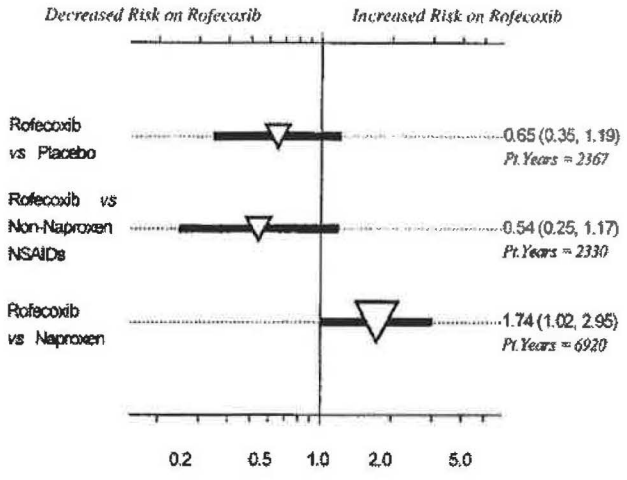


Figure 9. Relative risk (95% CI) of the APTC end point for rofecoxib relative to placebo, non-naproxen NSAIDs, and naproxen in studies ≥6 months in duration. Triangles represent relative risk, and size of triangles represents patient-years of exposure. Bars indicate 95% CI.

In the same analysis, data included in Table 5 examined the relative risk of cardiovascular events comparing rofecoxib with all NSAIDs. Although there is a trend for increased relative risk with increasing doses, the risk was not statistically significant. Although these authors did not feel the risk was dose dependent, others have found that patients taking a dose of rofecoxib greater than 25

mg per day have a higher risk of cardiovascular events than those taking 25 mg per day or less[15].

TABLE 5. Rofecoxib Dose Comparisons

	Rofecoxib			Comparator—All NSAIDs		
	Dose	No. of Patients	APTC Events/ Patient-Years at Risk (Rate)*	No. of Patients	APTC Events/ Patient-Years at Risk (Rate)*	Relative Risk (95% CI)
Analysis 1: 12.5 mg and 25 mg	12.5 mg	638	6/503 (1.19)	590	9/484 (1.86)	0.65 (0.23, 1.82)
	25 mg	673	3/537 (0.56)	590	9/484 (1.86)	0.30 (0.08, 1.12)
Analysis 2: 25 mg and 50 mg	25 mg	1513	6/928 (0.65)	1079	3/538 (0.56)	1.16 (0.25, 7.18)
	50 mg	1378	11/846 (1.30)	1079	3/538 (0.56)	2.08 (0.57, 7.51)

*Rate=APTC events per 100 patient-years at risk.

In an analysis of a sub-group of these patients, the Merck Research Laboratories reported the cardiovascular risk associated with the use of rofecoxib in their arthritis safety database[16]. A summary of investigator-reported thrombotic cardiovascular adverse events can be seen in Figure 10 in which the cumulative incidence of thrombotic events is plotted against months of followup. As can be seen, the incidence of thrombotic events by this method was not significantly different when rofecoxib was compared to other NSAIDs used in the studies.

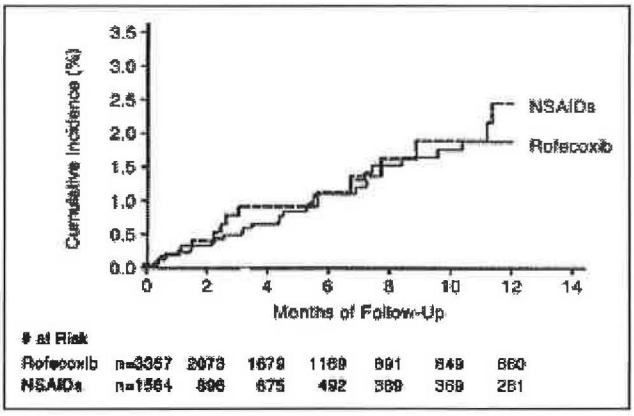


Figure 10[16]. Investigator-reported thrombotic cardiovascular adverse experiences in the phase IIb/III clinical program for rofecoxib in osteoarthritis time-to-event plot

All patients who were receiving aspirin and other anti-platelet drugs were excluded from participation in the osteoarthritis trials reported above. A sub-group analysis of the rate of thrombotic cardiovascular events by treatment group in patients with a history of symptomatic atherosclerotic cardiovascular disease who met conventional criteria for aspirin therapy is summarized in Table 6[16]. Although these patients accounted for only about 8% of the study population, they suffered 30% of the thrombotic cardiovascular events. As can be seen, the small number of patients with these events did not allow for significant statistical analysis, but a trend toward increased incidence of rofecoxib-associated cardiovascular events was noted in patients who were at high risk at baseline for developing those events.

TABLE 6. Incidence and Relative Risk of Investigator-Reported Cardiovascular Thrombotic Events

Treatment	No.	Patients With Events	Patient-Yrs*	Rates†	Relative Risk‡ Estimate	95% CI
A. Comparison of Rofecoxib With Nonselective NSAIDS						
Overall population						
Rofecoxib	3,357	32	1,657	1.93	1.15	(0.63, 2.09)
Nonselective NSAID	1,564	16	706	2.27		
Subgroup Analysis Based on History of Symptomatic Atherosclerotic Cardiovascular Disease§						
Aspirin indicated						
Rofecoxib	285	10	121	8.27	1.45	(0.53, 4.00)
Nonselective NSAID	127	6	48	12.47		
Aspirin not indicated						
Rofecoxib	3,072	22	1,536	1.43	1.04	(0.49, 2.21)
Nonselective NSAID	1,437	10	658	1.52		
B. Comparison of Rofecoxib With Placebo						
Overall population						
Rofecoxib	2,253	14	516	2.71	0.94	(0.31, 2.92)
Placebo	711	4	156	2.57		
Subgroup Analysis Based on History of Symptomatic Atherosclerotic Cardiovascular Disease§						
Aspirin indicated						
Rofecoxib	190	3	38	7.99	1.24	(0.02, 15.47)
Placebo	55	1	10	9.92		
Aspirin not indicated						
Rofecoxib	2,063	11	478	2.3	0.89	(0.24, 3.26)
Placebo	656	3	146	2.06		

*Patient-years at risk.
†Per 100 patient-years.
‡Relative risk of comparator (nonselective NSAID or placebo) with respect to rofecoxib.
§The "Aspirin indicated" cohort represents patients with a past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention.
CI = confidence interval.

The VIGOR trial (Vioxx Gastrointestinal Outcomes Research) trial[40] was designed to investigate the safety of rofecoxib compared to naproxen in patients with rheumatoid arthritis. The mean patient exposure to the drug was about 9 months in this study. Aspirin use was not allowed. After about 80 days of treatment, more thromboembolic events occurred in those receiving 50 mg of rofecoxib when compared to 500 mg of naproxen per day. For example, the incidence of MI was 0.2% in the rofecoxib group and 0.1% in the naproxen group. A post hoc analysis identified 321 patients who had a history of a prior cardiovascular event. All 8 of the myocardial infarctions that occurred in this group occurred in the patients taking rofecoxib. In fact, the relative risk of all serious cardiovascular events was 4.89 when rofecoxib was compared to naproxen in aspirin indicated patients. Unfortunately, no placebo group was available to be sure the difference was not due to a protective effect of Naprosyn rather than a detrimental effect of rofecoxib. An analysis of the time to the serious thrombotic events in this study is found in Figure 11[18].

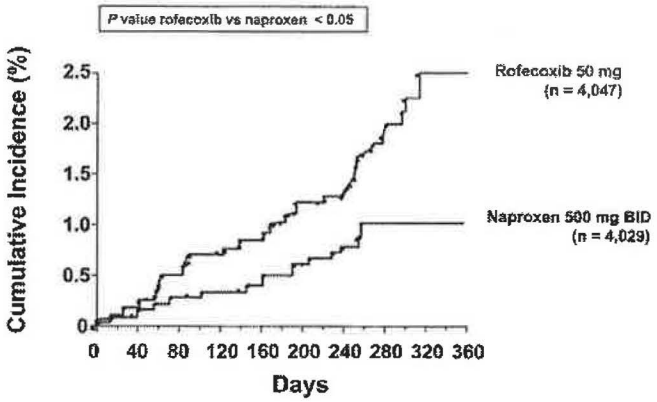


Figure 11. Kaplan-Meyer analysis of time to serious thromboembolic cardiovascular adverse event in Vioxx Gastrointestinal outcome Research trial[18]

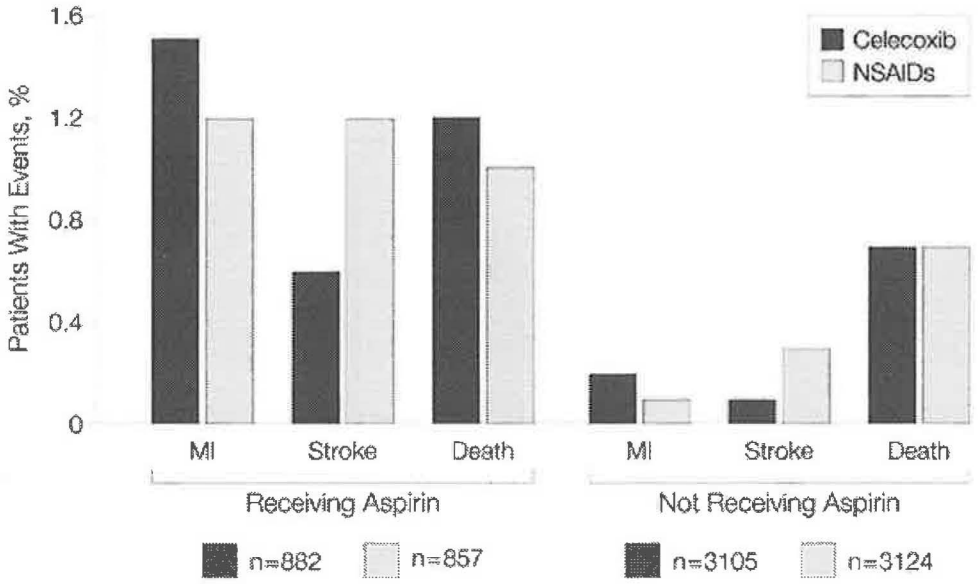
Some have argued that the odds were stacked against rofecoxib since the patients had an inflammatory disease (rheumatoid arthritis) that may predispose to cardiovascular events and that naproxen actually has a protective effect with respect to cardiovascular risk. The later is supported by other investigations which suggest naproxen has a protective effect against acute myocardial infarction[19,20] although it is not as protective as aspirin. However, other studies have not found a cardiovascular protective effect from naproxen[21,22].

Another data analysis of patient taking rofecoxib was undertaken by Ray, *et al*, using the data base of the Tennessee Medicaid program[23]. Participants analyzed were 50-84 years of age and had no life-threatening noncardiac disease. Users of high dose (>25 mg per day) rofecoxib were 1.70 times more likely than non-users to have a cardiac event while patients using low dose (≤25 mg per day) had no increased risk.

The final study for rofecoxib was the Adenomatous Polyp Prevention on Vioxx (APPROVe)[42] trial which was designed to evaluate the effect of rofecoxib on colon adenomas. Patients with prior polyps were enrolled to receive 25 mf rofecoxib per day. Patients with history of cardiovascular disease were excluded. In this study the incidence of the combined end point of stroke or myocardial infarction was 3.5% vs 1.9% and the difference was statistically significant. When this data was analyzed, Vioxx was withdrawn from the market.

The CLASS study[41] was a double-blind randomized control trial in which >8,000 patients were randomized to receive 400 mg celecoxib twice a day, 800 mg. ibuprofen 3 times per day or 75 mg diclofenac twice per day. Aspirin use was permitted in this study unlike those described above. Although the incidence of myocardial infarction was slightly higher in the celecoxib group in both aspirin users and nonusers, the difference was not significantly different when compared to other NSAIDs. Figure 12 shows the thrombotic event rates in the CLASS trial stratified by those patients receiving aspirin and those patients not receiving aspirin.

Figure 12



Another analysis of the celecoxib data in the entire controlled, arthritis clinical trial database (including CLASS) also concluded that relative risk for ATC endpoints of Celebrex compared to other NSAIDs was 1.06 for all patients and 0.86 for the subgroup not taking aspirin[17]. These studies as well as some smaller comparisons in which the number of total cardiovascular events was very small gave little concern for cardiovascular events early in the use of COX-2 inhibitors.

However in December, 2004, the National Cancer Institute announced that the APC trail (Adenoma Prevention with Celecoxib would be stopped due to an excess of cardiovascular death, myocardial infarction and stroke in the patients taking celecoxib. In this study, celecoxib at 400 and 800 mg per day was compared to placebo to determine the effect on polyp formation in patients who had a previous adenomatous polyp. After a mean of 33 months (half of the planned study), the odds ration for major cardiac events compared to placebo was a significant 2.5 and 3.4 for the 400 mg and 800 mg doses, respectively[42].

The possible increase in myocardial infarction rate with celecoxib and rofecoxib when compared to meta-analysis placebo expected rate is shown in Figure 13 for both the VIGOR and CLASS studies. This analysis certainly questioned the finding of the author of CLASS who concluded that Celebrex did not increase risk[24].

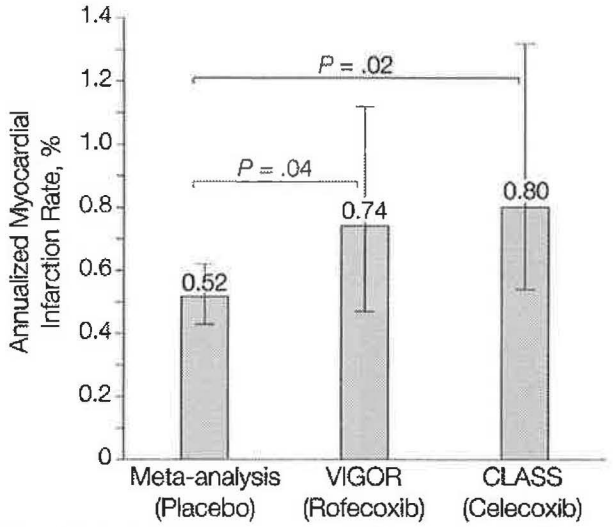


Figure 13.

The cardiovascular safety of valdecoxib has been questioned also by Ott, et al[25], who conducted a multi-center, placebo-controlled, double bind comparison of parecoxib/valdecoxib. Parecoxib was given intravenously early, then oral valdecoxib given later in patients undergoing coronary artery bypass surgery to assess pain control. They found that adverse events were statistically more frequent in the active drug group, primarily due to more sternal wound infection. Although statistical significance was not reached, there was a suggestion that cardiovascular events may have been more frequent in the active drug group. The adverse events and p-values for each are listed in Table 7.

	Standard care, N = 151 (%)	Current study parecoxib/valdecoxib, N = 311 (%)	*P* value*
Any SAE	15 (9.9)	59 (19.0)	.015
Death	0	4 (1.3)	.309
Cerebrovascular disorder	1 (0.7)	9 (2.9)	.177
Myocardial infarction	1 (0.7)	5 (1.6)	.669
Cardiac failure	2 (1.3)	3 (1.0)	.664
Abnormal renal function or increased creatinine level	0	6 (1.9)	.184
Gastrointestinal hemorrhage	0	3 (1.0)	.554
Pleural effusion	1 (0.7)	7 (2.3)	.283
Pneumonia	3 (2.0)	4 (1.3)	.688
Sternal wound infection	0	10 (3.2)†	.035
Thrombophlebitis	0	3 (1.0)	.554

Table 7. SAEs occurring in more than 2 patients in either group.

Several others also have questioned the safety of valdecoxib[26], but other studies have shown valdecoxib does not increase the risk of cardiovascular events in ambulatory arthritis patients[27].

In summary, the risk of cardiovascular events in patients taking COX-2 inhibitors seems to be increased in general, especially in those at high risk for having coronary or cerebral vascular disease at baseline. The evidence is most convincing for rofecoxib, but data suggests a similar effect for other drugs in this class although this has not been proven.

WHY WAS THE RISK OF CARDIOVASCULAR DISEASE NOT ANTICIPATED FROM THE START?

The increased risk of cardiovascular events with the use of at least one of the COX-2 inhibitors was not fully realized when the drugs were first released. This probably occurred because the development of the drugs proceeded faster than the science of COX-2 inhibition. As the risks of these drugs with respect to the heart and cerebrovascular system were becoming apparent to investigators, new functions for COX-2 were being discovered. As noted above, early investigators thought COX-2 expression was only in response to pathologic conditions and was responsible for many of the pathologic responses to various diseases, especially those with a significant inflammatory component. This is the reason selective COX-2 inhibitors were predicted to revolutionize our treatment of inflammatory conditions without as many side effects as nonselective inhibitors.

However, new data suggested COX-2 was expressed constitutively in some tissues and inducible COX-2 could play an important role in protection from some pathologic processes[28,29,30]. Constitutive COX-2 has been demonstrated in the central nervous system involved in pain regulation, vascular endothelium and smooth muscle, and the eye.

Vascular endothelium function obviously plays an important role in cardiovascular health and disease because of its critical action in the local control of blood flow and protection from arterial thrombosis[39]. Much of the attention on endothelial function has focused on two endothelial derived substances, nitric oxide (NO) and prostaglandin I_2 (prostacyclin). It has been suggested that endothelial COX-2 confers a vasoprotective and anti-atherogenic action by virtue of prostacyclin, its major product which inhibits platelet aggregation, deactivation of leukocytes and accumulation of cholesterol in vascular walls[31]. Up-regulation of endothelial COX-2 has been induced by various responses to stress in the vascular endothelium. This suggests that COX-2 may provide an adaptive vascular protective role in conditions that induce endothelial stress and injury such as inflammation[32]. Blocking this protective role of COX-2 may be involved in the unfavorable balance induced by COX-2 inhibitors with respect to thrombosis when the endothelium is injured[33]. Patients taking rofecoxib may especially be at risk since it uniquely inhibits COX-2 with little or no effect on COX-1[34]. The regulation of peripheral vascular homeostasis by prostacyclin and thromboxane A_2 is illustrated in the following Figure 14[11].

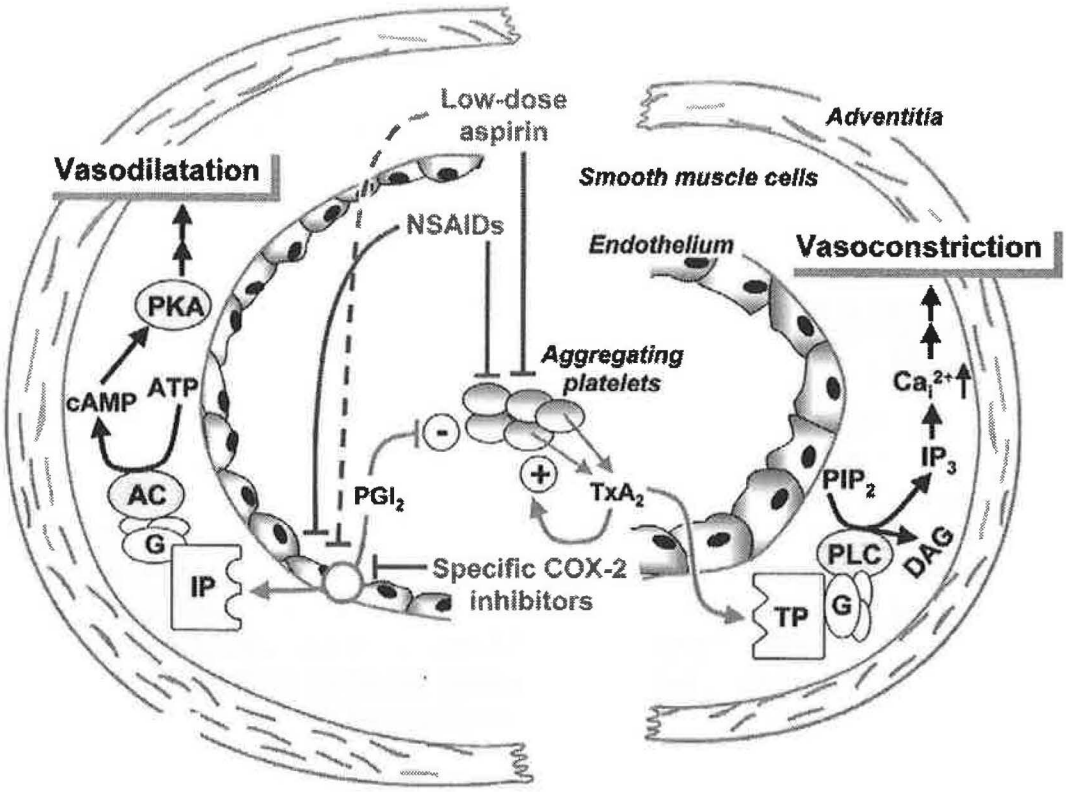


Figure 14. Regulation of peripheral vascular tone by prostacyclin (PGI_2) and thromboxane A_2 (TxA_2). Thromboxane release from aggregating platelets stimulates thromboxane receptors (TP) thereby activating phospholipase C (PLP), which in turn mediates platelet aggregation and vasoconstriction (G, G protein; PIP_2, phosphatidylinositol-4,5-bisphosphate; DAG, diacylglycerol:IP_3, inositol-1,4,5-triphosphate; Ca_i^{2+}, intracellular calcium). PGI_2 , the physiological antagonist of the system is generated in the vessel wall and confers inhibition of platelets aggregation and vasodilatation by virtue of its cAMP-releasing capacity (IP, PGI_2, receptor; AC, adenyl cyclase; PKA,protein kinase A). Whereas aspirin more potently inhibits COX-1-dependent TxA_2 synthesis than COX-2-derived PGI_2 formation (dotted arrow), nonselective NSAIDs suppress both eicosanoids with varying degrees. By contrast, specific COX-2 inhibitors inhibit prostacyclin production without a concomitant suppression of thromboxane formation.

The clinical implications of selective versus nonselective inhibition of cyclooxygenase on thrombosis may explain the increased risk of cardiac complications with COX-2 inhibitors. Low dose aspirin inhibition of COX-1 is more complete than its inhibition of COX-2[37]. Consequently, low doses of aspirin inhibits thromboxane synthesis without much effect on basal prostacyclin production. Both of these actions favorably affect aspirins protective effect with respect to cardiovascular disease. On the other hand, other nonselective NSAIDs inhibit both COX-1-induced thromboxane A and COX-2-induced prostacyclin. This activity reduces their cardioprotective action.

COX-2 specific inhibitors selectively inhibit prostacyclin synthesis. In patients at high risk for the development of cardiovascular disease, this inhibition may be detrimental even if basal synthesis of

prostacyclin is not increased. In patients who have high levels of inducible COX-2 as a protective response to endothelial inflammation or injury, the effect may be devastating and allow a shift in the homeostatic mechanisms toward thrombosis. The effect of COX-2 inhibition in various situations is illustrated in Table 8[36].

	PGI_2	TxA_2	Thrombotic Risk
Low-Dose Aspirin	=	⇩⇩	⇩
Conventional NSAIDs	⇩	⇩	Unclear
COX-2 Specific Inhibitors	⇩	=	Unclear

Table 8. Aspirin, conventional NSAIDs, and COX-2-specific inhibitors exhibit a different pattern of inhibition of COX-1-mediated thromboxane (TxA_2) biosynthesis and COX-2-mediated prostacyclin (PGI_2) biosynthesis[36]

Bulut et al[38], studied the effects of COX inhibition on endothelial blood flow regulation in hypertensive patients without other cardiovascular risks. They compared forearm vasodilator responses to intra-arterial acetylcholine (endothelial dependent) and sodium nitroprusside (endothelial independent) and the effects of an intravenous COX-inhibiting drugs. It was found that selective COX-2 inhibition with parecoxib impairs endothelial function, whereas, nonselective COX inhibition with acetylsalicylate improved endothelial mediated vasodilatation indicating that acetylcholine-induced vasodilation is partially mediated by prostacyclin in hypertensive patients.

In contrast to the above studies and discussion which implies that COX-2 activity in vascular pathologic processes is beneficial, some studies have suggested that COX-2 may contribute to the atherosclerotic process through its mediation of inflammation. COX-2 has been found to promote early atherosclerotic lesion formation in LDL receptor mice[35]. In addition, treatment of the mice with rofecoxib and Indocin both resulted in significant reductions in the atherosclerotic lesions. Since rofecoxib did not affect platelet thromboxane production, it was assumed this beneficial effect was a function of the COX-2 inhibition by both rofecoxib and indomethacin. In humans, a similar beneficial effect of COX-2 inhibition was found by Chenevard, et al[43] in 2003 by studying the effect of celecoxib on endothelial function assessed by flow-mediated dilatation of the brachial artery. All of their patients were on low dose aspirin. They found that celecoxib, but not placebo, improved endothelial-mediated vasodilatation and both had no effect on endothelial-independent vasodilatation. In another study by Title, et al[44], rofecoxib was found to have no effect on endothelial function in patients with known coronary artery disease while on aspirin.

Even more confusing is the fact that different COX-2 inhibitors seem to have different effects on endothelial function. In hypertensive rats, for example, celecoxib but not rofecoxib or diclofenac improved the endothelial dysfunction that is present in hypertension Dahl rats[45].

Independent of its endothelial function, COX-2 inhibition may affect cardiovascular risk by its effect on blood pressure and renal salt handling. While nonselective NSAIDs have a similar salt and blood pressure effect, their protective effects by inhibiting COX-1 may counteract some of the long term risks of the drug-induced hypertension. Rofecoxib seems to induce hypertension approximately

twice as often as celecoxib[46,48]. The elevation of blood pressure affects systolic pressure more than diastolic and is most pronounced in patients taking ACE inhibitors and β-blockers. Blood pressure in patients taking calcium channel blockers was not changed in patients taking either drug. Although not as frequent as with rofecoxib, elevated blood pressure is also seen with celecoxib[46,47]. The effects of cyclooxygenase inhibition on renal hemodynamics are complex but it appears that salt retention is probably mediated through COX-2 inhibition and the decrease in GFR is mediated through COX-1 inhibition[36].

COX-2 INHIBITORS AND CARDIOVASCULAR RISK: 2005

In summary, it is likely that all selective COX-2 inhibitors possess the capability of increasing the risk of thrombosis with subsequent myocardial infarction and stroke. This side effect was not widely anticipated when Vioxx®, Celebrex® and Bextra® were approved because the complexity of the balance among the cyclooxygenase functions was incompletely understood. That complexity is more apparent now but is still not fully developed. Not only is there a delicate balance between COX-1 and COX-2 function but the interaction between inflammatory (atherogenic) and protective (prostacyclin) functions of COX-2 must be considered. To make matters even more complicated, a COX-3 function recently has been suggested[49].

However, we do have a better understanding of COX-2 inhibition in 2005 than we did before. The following are important points to remember when making the decision regarding whether or not to prescribe a COX-2 inhibitor for a given patient:

1. Atherosclerosis is associated with upregulation of COX-2 activity in the vascular endothelium.
2. Upregulated vascular endothelial activity of COX-2 is associated with harmful (inflammatory) and beneficial (prostacyclin) effects.
3. Aspirin, especially low dose, exerts its cardioprotective effect by near complete inhibition of COX-1-mediated thromboxane production with little effect on COX-2-mediated prostacyclin production.
4. With nonselective NSAIDs, the potentially harmful effects of COX-2 inhibition of prostacyclin synthesis are counteracted by suppression of COX-1 thromboxane production.
5. COX-2 inhibitors offer the possibility of fewer serious side effects (gastrointestinal) when compared to nonselective COX inhibitors. However, the pain and inflammation relieving effects are the same as nonselective inhibitors.
6. Rofecoxib may have more cardiovascular risk than the other available COX-2 inhibitors, but the magnitude of the difference in risk is not known. Since the risk may be related to the strength of COX-2 inhibition, equivalent pain relieving doses may confer equivalent risk
7. The cardiovascular risk of COX-2 inhibitors is probably dose related. The highest risk is for patients taking rofecoxib >25 mg per day and celecoxib > 200 mg per day.
8. The cardiovascular risk of COX-2 inhibitors may be lessened with concomitant use of low dose aspirin. However this combination eliminates the beneficial gastrointestinal side effect profile of COX-2 inhibitors.
9. Patients who are at high risk for cardiovascular disease at baseline are the most at risk for developing a cardiovascular complication of COX-2 inhibition.

10. As of today, the safest NSAID for patients high baseline risk for cardiovascular disease is probably a nonselective NSAID (perhaps naproxen) with a gastric mucosal protective agent such as a proton pump inhibitor (PPI).

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