Cardiovascular and Gastrointestinal Toxicity of Selective Cyclo-oxygenase-2 Inhibitors in Man

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Abstract:

It is well established that the use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) increases the vulnerability of the gastrointestinal (GI) mucosa for the development of peptic lesions and serious ulcer complications. In addition, selective and traditional NSAIDs have also been associated with increased frequency of cardiovascular toxicity, especially in susceptible patients. The objective of this communication is to provide an overview of the salient GI and cardiovascular (CV) toxicity for these drugs. Traditional NSAIDs inhibit the constitutional cyclooxygenase-1 (COX-1) enzyme responsible for eicosanoids biosynthesis not only in joints, a beneficial effect, but also in the stomach, a detrimental effect. Selective NSAIDs were specifically designed to preferentially inhibit the cyclooxygenase-2 (COX-2), an inducible enzyme mediating the production of inflammatory eicosanoids in the joints but sparing the endogenous protective eicosanoids in the stomach. Selective COX-2 inhibitors (COXIBs) have been shown to possess much improved GI tolerability and reduced GI related adverse events when compared with nonselective COX-1inhibitors.

An unexpected CV toxicity had emerged during the COXIBs post marketing outcome studies. Many subsequent studies were carried out to

define the CV risks associated with COXIBs and NSAIDs. All COX inhibitors had shown this CV toxicity. In many clinical studies, rofecoxib use was associated with significantly more elevated CV risk when compared with celecoxib and non selective NSAIDs. The COX inhibitors associated CV toxicity has multiple manifestations, which include the induction of myocardial infarction (MI), edema, thrombosis, blood pressure destabilization and death. Patients at risk of CV disease or with a history of CV disease were the most significant determinants of CV events after receiving COX inhibitors. This CV toxicity not only led to the marketing withdrawal of rofecoxib and valdecoxib but also resulted in more restricted, but essentially identical, product labels in the United States for celecoxib and traditional NSAIDS. This CV toxicity is dose and treatment duration dependent and appears to be compound specific rather than COX specific. Additional comprehensive, long-term, prospective investigations comparing the CV and GI safety profile of marketed NSAIDs against each other and against selective inhibitors are needed to address the controversy of COX inhibitors.

Key Words: NSAIDs, Acetaminophen, Cyclooxygenases, COX-1, COX-2, Celecoxib, Diclofenac, Ibuprofen, Meloxicam, Naproxen, Rofecoxib, Valdecoxib.

Nonsteroidal anti-inflammatory drugs are one the most widely used class of drugs throughout the world. It is also well established that the use of NSAIDs increases the vulnerability of the GI mucosa for the development of peptic lesions (erosions, inflammation and ulceration) and serious ulcer complications (bleeding and perforation). In fact, in the United States alone, a total of 16,500 patients with rheumatoid arthritis or osteoarthritis died during 1997 from the GI toxicity of NSAIDs [1].

The efficacy and toxicity of NSAIDs is a consequence of the inhibition of the COX enzymes [2]. Recent research has disclosed at least two types of COX enzymes exits: COX-1 is a constitutive enzyme responsible for housekeeping functions in organs such as the stomach, kidney, intestine and platelets, while COX-2 is an inducible enzyme exerting its action at inflammatory sites of the joints and muscles [3,4]. Such important findings led to the development and subsequent introduction of the selective COX-2 inhibitors celecoxib, valdecoxib and rofecoxib, which have considerably reduced GI ulcerogenicity potential when compared with the older, non-selective NSAIDs [5]. Unexpectedly, during the post marketing studies, it was learned that COXIBs exhibited CV toxicity which was not found during their initial clinical development. The purpose of this communication is to review salient aspects of the GI and CV toxicity of

NSAIDs and COXIBs which are relevant to their use as anti-rheumatic and analgesic drugs.

Overview of Gastrointestinal Toxicity of NSAIDs

The mechanisms of GI injury by traditional NSAIDs include topical and systemic components [6-8]. Topical mucosal injury usually occurs after the ingestion of aspirin and other weakly acidic NSAIDs. Weak acids are not ionized in the acid environment of the stomach, freely penetrate the gastric barrier and increase the back diffusion of gastric acid across the mucosa causing further aggravation of the injury. The chronic administration of a prodrug, such as Sulindac, produces ulcers, even though its acute topical damaging action on the gastric mucosa is at minimum. Furthermore, enteric-coated preparations of aspirin and other NSAIDs are also ulcerogenic when administered chronically even though such preparations have minimum topical injury following acute administration. Such lines of evidence suggest that the topical injurious effect of NSAIDs is probably of limited pathophysiologic importance.

The inhibition of the COX-1 enzyme induced by traditional NSAIDs mediates their GI toxicity [6]. Traditional NSAIDs inhibit duodenal mucosal bicarbonate and gastric mucus secretion and reduce gastric mucosal

blood flow as a consequence of their inhibitory effects on the biosynthesis of protective endogenous prostaglandins [5,6]. Of interest is the observation that NSAIDs are associated with a higher frequency of injury to the stomach than the duodenum and this observation has major therapeutic implications [7,8]. NSAIDs also prevent the increase in cell replication at the ulcer margins, an action that has obvious effects on mucosal repair and ulcer healing [6]. The introduction of COXIBs with high selectively for the inhibition of COX-2 enzyme afforded drugs which are considerably less ulcerogenic than traditional NSAIDs possessing COX-1 inhibitory activity [5,9,10]. In the celecoxib and the rofecoxib major efficacy studies, the incidence of symptomatic ulcers and ulcer complications were significantly lower with these COXIBs than the comparative NSAIDs indicating that COXIBs have much less GI toxicity than traditional NSAIDs, while possessing similar anti-inflammatory and analgesic actions [9,10].

Historical Overview of COXIBs Cardiovascular Toxicity

The initial concern about potential CV toxicity of COXIBs was prompted by the disclosure of the rofecoxib outcome study referred to "Vioxx and Gastrointestinal Outcomes (VIGOR) trial" [10]. The study compared the safety of rofecoxib (Vioxx) with naproxen in patients with rheumatoid

arthritis who did not regularly take aspirin. In this trial, it was observed that there was a 5-fold increase in the risk of acute myocardial infarction (MI) with rofecoxib as compared with naproxen. In contrast, a similar outcome clinical study with another COXIB referred to as "Celecoxib Long-Term Arthritis Safety Study (CLASS)" compared celecoxib with ibuprofen and or diclofenac, but included the use of aspirin, did not show increased CV events between celecoxib and traditional NSAIDs, irrespective of aspirin use [9]. Although, the basis for the increased CV toxicity of rofecoxib over naproxen was not fully known at the completion of the VIGOR study, it was thought that it could have been a consequence of the absence of the use of aspirin, an antithrombotic agent in the trial design, since aspirin might induce ulcer and this could negate the rofecoxib benefits of decreased ulcerogenicity potential. However, given the absence of an increased CV toxicity noted with celecoxib in the CLASS trial when compared to the comparator drugs diclofenac and ibuprofen indicates that celecoxib does not exhibit more cardiovascular toxicity than the comparator NSAIDs ibuprofen and diclofenac. Additional independent reanalysis of the CLASS trial examining thromboembolic events found no increased MI risk associated with celecoxib over diclofenac and ibuprofen [11].

Subsequently, interim analyses of two large chemoprevention trials with rofecoxib [Polyp Prevention on Vioxx (APPROVEe)] and celecoxib [Adenoma Prevention with Celecoxib (APC)] showed increased cardiovascular risk among patients receiving the COXIBs in these studies and both trials had to be discontinued [12,13]. It is to be noted, however, that the dosages of the COXIBs used in these chemoprevention trials were much higher than the recommended anti-rheumatic/analgesic dosages used for treatment of osteoarthritis and rheumatoid arthritis.

Of more importance is the observation that naproxen (220 mg bid) also appeared to possess greater CV toxicity than celecoxib (200 mg bid) in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) and the study was therefore terminated because of this toxicity concern [14]. For celecoxib, the ADAPT data do not show the same level of risk as those of the APC trial, even though both studies used elderly patients. Nevertheless such observations derived from the COXIBs chemoprevention studies and the ADAPT trial clearly indicate that there is an inherent intrinsic risk for the induction of the CV toxicity not only in COXIBs but also for NSAIDs and this risk needs to be further assessed, especially with regards to other COX inhibitors, patient at risk, dosages, duration of treatment and other factors as discussed in this communication.

Retrospective and Prospective Controlled Clinical Studies Assessing Cardiovascular Risk for COXIBs and NSAIDS

Given the intrinsic CV toxicity shown for rofecoxib and celecoxib, there were several investigations and numerous review papers aimed at defining the CV risk for both COX-2 selective and COX-1 inhibitors. Several epidemiological studies assessing the CV risk of NSAIDs have been reported [15-21]. An analysis of retrospective observational studies, meta-analysis and systematic reviews found an increased CV risk of COX-2 inhibitors and NSAIDs [22-24]. It is important therefore to review some of the major clinical studies that were published with specific experimental design, with large patient population and well defined objectives in order to better define the CV risk associated with selective versus non-selective COX inhibitors. A brief narrative description of some of the trials and the main findings are detailed below:

(a) Solomon et al. [25] conducted a matched case-control study of 54,475 patients, aged 65 years or older, and studied the relative risk of acute MI among users of celecoxib, rofecoxib, and NSAIDs in Medicare beneficiaries with a comprehensive drug benefits over the course of 12 months period in the United States. The investigators constructed matched logistic regression models including indicators for patient demographics, healthcare use,

medications use and CV risk factors. As is evident from Table 1, current use of rofecoxib was associated with significantly elevated MI risk compared with celecoxib. In contrast, celecoxib was not associated with an increased relative risk of MI in any of the comparisons examined (Table 1). Dosages of rofecoxib >25 mg were associated with higher risk than dosage less than or equal to 25 mg. Furthermore, the risk was elevated in the first 90 days of use. Although not shown in Table 1, the MI risk was significantly elevated in patients with co-morbid conditions such as diabetes, hypertension, previous MI, angina, previous coronary revascularization, congestive heart failure, cerebrovascular attack, use of hormone replacement therapy and rheumatoid arthritis. This study clearly suggests that patients with a history of diabetes, CV disease and other comorbidity are at much increased risk for the induction of MI and CV adverse events.

(b) Johnsen et al. [26] conducted a population-based, case-control Danish study of 10,280 cases of first time hospitalization for MI and 102,797 sex- and age-matched non MI controls. Relative risk estimates for MI were adjusted for a history of CV disease, hypertension, diabetes, chronic bronchitis or emphysema, alcoholism, liver cirrhosis, upper GI bleeding, rheumatoid arthritis and systemic lupus erythematosis. The investigators found that COX-1 and COX-2 inhibitors (rofecoxib, celecoxib, etodolac,

meloxicam and nabumetone) were associated with increased risk of MI (Table 2). However, the MI risk estimate for celecoxib had the lowest value when compared with the other drugs studied in this report.

(c) Huang et al. [27] studied the risk of acute MI, angina, stroke and transient ischemic attack (TIA) in long-term users of rofecoxib and celecoxib in Taiwan and in comparison with meloxicam. The data were taken from National Health Insurance database for the period of 2001 to 2003. Patients included in this study had used one of these three drugs for at least 180 days. The main outcome measurements were the occurrence of MI, angina, stroke or TIA after the initiation of long-term continuous use of these drugs. Person-time exposures and hazard ratios (HRs) were calculated based on data obtained from 9602 patients. The investigators found that in patients without a history of CV events within the year before drug treatment was started; the overall rates for MI, angina, stroke and TIA were 1.1%, 0.6%, 2.0 % and 0.6%, respectively. In those with history of CV events in the year before treatment began, the overall rates for MI, angina, stroke, and TIA were 5.0%, 4.8%, 6.6% and 5.8%, respectively. Of major interest is the finding that celecoxib users had a statistically lower HRs for the development of acute MI (HR 0.78; $P = 0.02$) and stroke (HR 0.78; $P < 0.001$) when compared with meloxicam users (Table 3). In contrast,

rofecoxib users were at no higher risk of CV events than those receiving meloxicam, indicating that celecoxib has better CV tolerability than either rofecoxib or meloxicam. This result clearly indicates that rheumatic patients with positive history of CV disease will exhibit increased CV events by some 5 to 10 times than patients with no history of CV disease.

In a related study reported by the same investigators who conducted a follow-up, population-based, analysis using data from the Taiwanese Bureau of National Health Insurance (Taipei, Taiwan) database [Huang et al., 28]. Briefly, the study examined eligible patients, 18 years or older, had received etodolac, nabumetone, ibuprofen, naproxen or celecoxib for period equal to or greater than 180 days. The primary outcomes measure was the prevalence of serious CV events, MI, angina, cerebrovascular attack and/or TIA. Analyses were performed on data from all eligible patients and hazard ratios (HRs) were calculated to determine the risk for CV events with long-term use of the drugs. It was found that there were no significant differences in the risk of treatment-related CV events between groups prescribed 1 of 4 NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) or celecoxib. Furthermore, history of CV disease was the most significant determinant of CV events risk. Patients with preexisting medical conditions appeared to have a significantly higher risk of CV events associated with the use of

either NSAIDs or celecoxib compared with patients without these conditions.

(d) Rahme and Nedjar [29] conducted a retrospective cohort study using administrative healthcare records of patients aged 65 or greater and who filled a prescription for NSAID or acetaminophen during 1999-2000. The study compared the risks of hospitalization for acute MI and GI bleeding among these patients. Outcomes were compared using Cox regression models with time dependent exposures. Among non-users of aspirin, the adjusted hazard ratios (95% confidence interval) of hospitalization for the combined outcome for MI/GI vs. acetaminophen groups are shown in Table 4.

For non-aspirin users, naproxen had the highest risk of GI bleeding (Table 4) among all drugs tested. In contrast, the combined outcome MI/GI toxicity of celecoxib was the lowest among all drugs tested and was essentially similar to acetaminophen. Of interest is the observation that rofecoxib had a higher adjusted hazard ratio values for both MI and GI endpoints than celecoxib.

For patients who used aspirin, the adjusted hazard ratios for the combined MI/GI outcome are listed in Table 5. Rofecoxib had the highest MI/GI risk when compared to COX-1 NSAIDs and celecoxib. Although not

shown in the Table 5, naproxen had the highest GI risk, but the lowest MI risk. The drugs acetaminophen, celecoxib and naproxen had the lowest combined MI/GI hazard ratios of 1.29, 1.34 and 1.35, respectively.

It is to be noted that although acetaminophen is not a NSAID and has no anti-inflammatory value, GI toxicity or antiplatelet activity, it is very frequently used as an analgesic in arthritic patients due to its GI safety. However, it has recently been reported that acetaminophen increases the risk of hypertension in older women and such hypertension might increase the CV risk [29].

(e) McGettigan and Henry [22] conducted a large meta-analysis of observational studies which included 17 case-control analyses (N = 614,193) and 6 cohort studies involving very large number of patients (N = 1,045,859) and recorded CV events (thrombotic events, MI and stroke, which can be fetal) relative to nonuse/remote exposure. The relative risks (95 % confidence intervals) for COX-1 and COX-2 inhibitors are shown in Table 6. The results clearly indicate that the CV risk appears to be compound specific rather than being specific to the type COX being inhibited. The highest CV events risk was associated with diclofenac and rofecoxib. On the other hand, the lowest CV events risk was associated with naproxen and celecoxib. This analysis further indicate that there was no statistically

significant increase in CV events risk with the use of celecoxib compared with non use/remote NSAID exposure of any type.

Duration of Drug Treatment and Risk of CV Events

Many of the epidemiological studies concerning the CV risk with COXIBs and NSAIDs were not specifically designed to provide information on the duration of the treatment with the COX inhibitors and the occurrence of CV events. To address this issue, Motsko et al [31] conducted a retrospective analysis of the Veterans Integrated Service Network (VA) database. Medicare data and Texas Department of Health mortality data were incorporated to capture events occurring outside the VA healthcare network. The CV events included were MI, stroke, and MI-related death. Patients aged 35 or greater who received celecoxib, rofecoxib, ibuprofen, etodolac and naproxen for three years (1999-2001) were included. A short-term period was defined as 180 days or less, while long-term was defined to include exposure longer than 180 days. Multivariate Cox proportional hazard models and adjusted hazard ratio (95% CI) were determined. The investigators identified 12,188 exposure periods (11,930 persons) and 146 CV events over the entire study period. Compared with short-term ibuprofen, the short-term use of celecoxib (adjusted HR 0.75; 95% CI 0.42,

1.35) and rofecoxib (adjusted HR 0.85; 95% CI 0.39, 1.86) was not associated with any significant CV risk. However, compared with long-term ibuprofen use, long-term use of celecoxib (adjusted HR 3.64; 95% CI 1.36, 9.70) and rofecoxib (adjusted HR 6.64; 95% CI 2.17, 20.28) was associated with significant increase in CV risk. When restricted to patients aged 65 years or older, the CV risks associated with long-term celecoxib (adjusted HR 7.36; 95% CI 1,62, 33.48) and rofecoxib (adjusted HR 13.24; 95% CI 2.59, 67.68) use was increased. Neither long- nor short-term exposure to naproxen and etodolac was associated with cardionegative or cardioprotective effects when compared with ibuprofen. The findings of this VA observational study contradicted a similarly designed Taiwanese study with long-term (greater or equal to 180 days) exposure to NSAIDs and celecoxib as reported by Huang et al. [28]. The Huang et al study found no differences in CV risk between ibuprofen, etodolac, naproxen, nabumetone and celecoxib, when administered for a similar long-term period [28]. The basis for the different outcomes between these two studies is unknown.

Blood Pressure and Renal Effects

Hypertension and arthritis are among the most common chronic conditions in the United States and the prevalence of hypertension among arthritic

patients has been estimated to be 32% [32]. Concomitant use of NSAIDs or COX-2 inhibitors with antihypertensive drugs is therefore common among many rheumatic patients. The fact that COX inhibitors can inhibit the production of protective prostaglandins in vascular beds, endothelium and kidneys could influence not only the response of anti-hypertensive drugs and could also trigger a deleterious vassopressor response. Two meta-analysis clearly showed that NSAIDs increased blood pressure (BP) when used at effective anti-rheumatic dosages and the effect was most pronounced in patients with hypertension [33,34]. With the introduction of selective COX-2 inhibitors, it was important to know whether such drugs possess the same pharmacological action on BP as nonselective NSAIDs. Several prospective randomized studies examined the effect of COXIBs and NSAIDs on BP in rheumatic patients with the following conclusions [35-38]:

(a) All COX inhibitors have the potential of increasing BP to variable degrees.

(b) The use of rofecoxib, but not celecoxib or COX-1 inhibitors, was associated with an increased risk of edema and BP increases compared to nonusers of NSAIDs [38].

(c) Head-to-head trial showed significantly lower incidences of destabilized BP and edema with celecoxib compared with rofecoxib in persons aged 65 and older with osteoarthritis and hypertension [36].

(d) Rofecoxib treated patients were approximately 2 to 4 times more likely to report edema and BP increases as side effects compared with celecoxib treated patients [38].

(e) Rofecoxib caused the greatest increase in systolic BP in patients receiving angiotensin converting enzyme inhibitors or beta blockers, whereas those on calcium channel antagonists or diuretic monotherapy receiving either rofecoxib or celecoxib showed no significant increase in BP [35].

Clearly, given these observations, it appears that the vasopressors/edema response induced by NSAIDs or COXIBs, administered at ordinary anti-rheumatic dosages, is compound specific rather than class specific toxicity and the highest risk was shown for rofecoxib. None of the studies reviewed showed that celecoxib had higher vaspressor/edema inducing activity than traditional NSAIDs.

Mechanism of CV Adverse Effects

The mechanism of the apparent increased CV risk associated with COXIBs and NSAIDs is not only uncertain but it is also controversial. No hypothesis has yet been formally tested in relevant patient populations. The most frequently mentioned mechanism accounting for the COXIBs cardiovascular toxicity in the literature is the eicosanoids imbalance theory. Although NSAIDs inhibit both COX isoforms, the inhibition of COX-2 results in decreased prostacycline (PGI2), a vasodilator and modulator of platelet activation, without reducing COX-1 dependent thromboxanes (TXA2) contributing to platelet aggregation and vasoconstriction [38-40]. An excellent review by Joshi et al was written on the subject and critiqued the imbalance theory [24]. Recently, two relevant short-term (14 days of treatment) clinical pharmacology studies, performed in young healthy human subjects investigated this imbalance theory with conflicting result [42, 43] and the studies are briefly described. In the first study**,** Graff et al [42] compared the drugs naproxen (500 mg twice daily), rofecoxib (25 mg daily) and celecoxib (200 mg twice daily) on endogenous prostanoid biosynthesis and platelet functions. As would have been expected, naproxen suppressed the biosynthesis of PGEs, prostacycline and thromboxane. In contrast, both rofecoxib and celecoxib inhibited the biosynthesis of PGEs

and prostacycline without affecting the production of thromboxane. However, despite these biochemical alterations of eicosanoids biosynthesis, the platelet functions and expression of platelet aggregation markers were not affected by these COXIBs. Such observations do not support the eicosanoids imbalance theory in man as a basis of CV toxicity by COXIBs.

In the second study, Webber et al [43] also compared the effects of aspirin (300 mg/day) and rofecoxib (25 mg/day) on systemic prostacycline synthesis and on platelet function at rest and after exercise in healthy young volunteers using double, blind randomized, cross-over study design. Physical exercise resulted only in a minor platelet activation, as reflected by the expression of basal or adenosine diphosphate (ADP)-stimulated platelet activation markers or basal plasma concentrations of thromboxane B2. As expected, aspirin significantly reduced thromboxane B2, while rofecoxib significantly increased thromboxane B2. No increase in systemic prostacycline concentration was observed with any drug treatments. Despite such changes in thromboxane levels, the COX inhibitors did not induce exercise-related platelet activation. Clearly, both of these two clinical pharmacology studies [42,43] do not support the imbalance theory and have limitations, especially concerning the use of healthy, young subjects who are

not at risk of thrombosis and additional studies are needed to resolve the relationships between eicosanoids, platelet aggregation and thrombosis.

In addition, the imbalance hypothesis does not explain the differences in CV events between celecoxib and rofecoxib or the differences in CV events observed among COX-1 inhibitors. Furthermore, nonselective NSAIDs block COX-1 and COX-2 differentially, which indicate that the observed CV effects may not be a class effect of anti-inflammatory drugs but rather a compound specific toxicity. Diclofenac and nabumetone have also been shown to have a CV risk of a similar magnitude to COX-2 inhibitors, yet they do not affect the ratio of prostacycline to thromboxane A2 [44].

The differential effects of COX-1 and COX-2 inhibitors on coronary circulation have also been explored in dogs to explain possible differences in the physiological response COX receptors on coronary circulation. Hong et al [44] had shown that the arachadonic acid (AA)-induced vasodilation of the left circumflex coronary artery was suppressed to a similar extent with the COX-1 selective inhibitor SC-560, the COX-2 selective inhibitor nimesulide and the prostacycline receptor antagonist RO-3244794 indicating that the AA-induced vasodilation is not exclusively specific to COX-1 receptor but could also involve COX-2 and prostacycline receptors.

However, independent confirmatory studies by Gross and Moore [46] indicated that coronary circulation in dogs appears to be primarily COX-1 dependent. In addition, selective COX-2 inhibition does not affect either prostacycline or nitiric oxide mediated vasodilation in the canine coronary circulation indicating that compensatory mechanisms exist in the coronary circulation that are not exclusively COX mediated activities.

Furthermore, Hong et al [45] also investigated the effect of COX inhibition on thrombus formation in a model of carotid artery thrombosis secondary to electrolytic-induced vessel wall injury in dogs. The pretreatment with lipopolysaccharide (LPS 0.5 mg/kg i.v.) induced a systemic inflammatory response and prolonged the time to occlusive thrombus formation which was reduced in the LPS treated animals by the administration of COX-2 inhibitor nimesulide. In contrast, neither SC-560 nor naproxen influenced the time to thrombosis in animals pretreated with LPS. Such data suggest that both the endothelial constitutive COX-1 and the inducible vascular COX-2 serve important function in maintaining vascular homeostasis. However, given these observations, it is difficult to explain the basis of CV toxicity between rofecoxib and celecoxib or other COX-1 inhibitors. This needs further clarifications using additional investigations in dogs.

Finally, it should be mentioned that the protective antiplatelet effects of aspirin need to be maintained in selected patients given chronically either COX-1 or COX-2 inhibitors. For example, it has been shown that ibuprofen can interfere with the antiplatelet effect of low dose aspirin (81 mg/day) rendering aspirin to be less effective for cardioprotection and/or for stroke prevention [47]. In contrast, celecoxib has not been shown to interfere with the antiplatlet effects of low dose aspirin (equal to or less than 325 mg per day) [48]. However, no systematic investigations were conducted to examine available COX-1 inhibitors for potential interference with the cardioprotective effects of a low dose aspirin and this need to be considered in the assessment of the overall CV risk of NSAIDs and COXIBs.

Discussion

Considerable controversy existed concerning the CV safety COXIBs, especially following the withdrawal of the drug rofecoxib and valdecoxib from the market [49-52]. It was assumed that all COXIBs would share this CV toxicity and the COXIBs toxicity risk exceeded the toxicity of traditional nonselective NSAIDs. Many critics had advocated that the marketing of all COXIBs should be discontinued. However, much of the discussion about the CV safety of COXIBs was based on the theoretical considerations since we

did not have proper information needed to define the scope of the problem in order to promote public safety. In the United States, the FDA played a very positive and crucial rule by seeking the co-operation of academic scientists and the pharmaceutical industry towards the development of the best strategy towards protecting public health.

Many comparative prospective and retrospective epidemiological studies involving very large number of patients were carried out worldwide to define this CV risk, especially as to the issue of whether this CV risk is specific to all COX-2 inhibitors or only relevant to some of these inhibitors. Furthermore, the patients who are at risk need to be defined and finally the differences, if any, in the CV toxicity between COX-2 versus COX-1 inhibitors are need to be defined. The definition of patients who are at risk of this toxicity was one of the most the most important lesson learned from this toxicity debate [53, 54].

The clinical investigations carried out and summarized in this communication clearly established that the CV toxicity is not only restricted to COXIBs but it is also associated with COX-1 inhibitors suggesting that it is a class effect for anti-rheumatic drugs. Patients with cardiovascular disease or at risk of cardiovascular disease are at greater risk of this CV toxicity. Furthermore, the CV toxicity is dosage and duration-dependent.

When used for chemoprevention at dosages much higher than their effective anti-rheumatic dosages rofecoxib, celecoxib and naproxen showed CV toxicity suggesting a dose-dependent type of toxicity. From a pharmacological consideration, dose-dependency toxicity can be controlled by using the least effective dosage for the shortest treatment duration. On the other hand, drugs exhibiting all-or-none type of toxicity, such toxicity can not be controlled and such drugs should be totally avoided. With respect to the duration of treatment as a factor for the induction of CV toxicity, it appears that treatment with COX inhibitors for periods equal to or exceeding 6 months manifested this CV toxicity when compared with rheumatic patients receiving COX inhibitors for less than 6 months.

Within COX-2 inhibitors, many of studies directly compared celecoxib with rofecoxib, at equal anti-rheumatic dosages, and all such comparative studies showed that rofecoxib has statistically more CV toxicity than celecoxib clearly indicating that the CV toxicity is compound specific, rather than a class effect involving all COX-2 inhibitors. The compound specific toxicity is usually a function of the chemical structure, bioavailability and tissue distribution as a possible basis for this toxicity.

The studies summarized in this communication suggest that some COX inhibitors may possess less CV toxicity than other inhibitors. For

example, naproxen and celecoxib appear to have the least CV toxicity, while rofecoxib and diclofenac have the most CV toxicity. In one comparative study, patients taking celecoxib had a significantly lower risk of cardiovascular events than those taking meloxicam. In another study, the cardiovascular toxicity of celecoxib was similar to that of acetaminophen. In the ADAPT trial, celecoxib had less CV toxicity than naproxen. However, additional comprehensive, long-term, prospective investigations comparing the CV and GI safety profile of all marketed non selective NSAIDs against each other or against selective COXIBs are needed.

The fact that the CV toxicity for COXIBs and NSAIDs represents the same risk, the United States (FDA) requires that all prescription NSAIDs and celecoxib, to have the same medication guide with the same black box warnings. In addition, the FDA contraindicated the use of COX inhibitors in patients with perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. Likewise, the European Medicines Agency (EMEA) has a stricter product label (Physicians Prescribing Information) than the FDA and contraindicated the use of COXIBs in patients with established coronary heart disease, cerebrovascular disease and peripheral arterial disease and a number of warning statement concerning CV, GI and skin toxicity have been introduced in the products prescribing information [55].

In summary, we conclude that the CV toxicity is inherent with all COX inhibitors, especially in patients with history of or at risk of CV disease and other morbid illness. The toxicity is dose and treatment duration dependent. The toxicity is compound specific rather than a class specific affecting both COX-1 and COX-2. The COX-2 inhibitors have less GI toxicity than COX-1 inhibitors. Celecoxib appears to have significantly less CV toxicity than rofecoxib and meloxicam. Celecoxib has essentially similar CV toxicity to acetaminophen.

References:

1. Wolfe MM, Lichtenstein DR, Singh G: Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. New Engl J Med 1999; 340: 1888-1899.

2. Agrawal NM, Dajani EZ: Drug induced ulcerogenesis. In: *Gastrointestinal Pharmacology and Therapeutics*, Gerald Freeman et al., Eds. Philadelphia, Lippincott-Raven Publisher (1997) 55-63.

3. Riendeau D, Charleson S, Cromlish W *et al.*: Comparison of the cyclooxygenase-1 inhibitory properties of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, using sensitive microsomal and platelet assays. Can J Physiol Pharmacol 1997; 75: 1088-95.

4. Warner TD, Giuliano F, Vojnoavic I et al.: Nonsteroid drugs selective for cyclo-oxygenase-1 rather cyclo-oxygenase-2 is associated with human gastrointestinal toxicity: a full in-vitro analysis. Proc Natl Acad Sci U S A 1999; 96: 7563-8.

5. Dajani EZ, Agrawal NM: Selective COX-2 inhibitors and gastrointestinal mucosal injury: Pharmacological and therapeutic considerations. J Assoc Acad Min Physicians 2000; 11: 28-31.

6. Agrawal NM, Dajani EZ: Drug induced ulcerogenesis. In: *Gastrointestinal Pharmacology and Therapeutics,* Gerald Freeman et al., Eds. Philadelphia, Lippincott-Raven Publisher (1997) 55-63.

7. Dajani EZ, Agrawal NM: Prevention and treatment of ulcers induced by nonsteroidal anti-inflammatory drugs. J Assoc Acad Minor Physicians 1992; 3: 142-148.

8. Dajani EZ, Agrawal NM: NSAID-induced gastrointestinal damage in the elderly. Intern Med Specialist 1990; 11**:** 91-110.

9. Silverstein FE, Faich G, Goldstein JL et al: Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis; the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284 (10): 1247-55.

10. Bombadier C, Laine L, Reicin A et al: Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. The Vioxx and Gastrointestinal Outcomes (VIGOR) Trial. N Engl J Med 2000; 343: 1520-1528.

11. White WB, Faich G, Whelton A et al.: Comparison of thromboembolic events in patients treated with celecoxib, a cyclo-oxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. Am J Cardiol 2002; 89: 425-430.

12. Merck announces voluntary worldwide withdrawal of VIOXX. Press News Release. Whitehouse Station, NJ, 2004. Available at www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf.

13. FDA statement on the halting of a clinical trial of the Cox-2 inhibitor Celebrex. Rockville, Maryland: US Food and Drug Administration; December 17, 2004. Available at www.fda.gov/bbs/topics/news/2004/NEW01144.html.

14. ADAPT Research Group: Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). PLos Clin Trials 2006; 1(7): e33.

15. Solomon DH, Glynn RJ, Levin R, Avorn J: Non steroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002; 162: 1099-104.

16. Rahme E, Pilote L, LeLorier J: Association between naproxen use and protection against acute myocardial infarction. Arch Inter Med 2002; 162: 1111-5.

17. Mamdani M, Rochon P, Juurlink DN et al.: Effect of selective cyclo-oxygenase inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Inter Med 2003; 163: 481-6.

18. Graham DJ, Campen D, Hui R et al.: Risk of acute myocardial infarction and sudden death in patients treated with cyclo-oxygenase-2 selective and non selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005; 365: 475-81.

19. Hippisley-Cox, Coupland C: Risk of myocardial infarction in patient taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested-control analysis. Br Med J 2005; 330: 1366-9.

20. Garcia-Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A: Nonsteroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. Circulation 2004; 109: 3000-6.

21. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR: Current use of nonsteroidal anti-inflammatory drugs and the risk of acute myocardial infarction. Pharmacotherapy 2005; 25: 503-10.

22. McGettigan P, Henry D: Cardiovascular risk and inhibition of cyclooxygenases: a systematic review of observational studies of selective and non-selective inhibitors of cyclooxygenase-2. JAMA 2006; 296: 1633-44.

23. Kearney PM, Baigent C, Godwin J et al.: Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. Br Med J 2006; 322: 1302-8.

24. Joshi GP, Gertler R, Fricker R: Cardiovascular thromboembolic adverse effects associated with cyclooxygenase selective inhibitors and non selective anti-inflammatory drugs. Anesthesia and Analgesia 2007; 105: 1793-1804.

25. Solomon DH, Schneeweiss S, Glynn RJ et al.: Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; 109 (17): 2068-73.

26. Johnsen SP, Larsson H, Tarone RE et al.: Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs. A population-based, case-controlled study. Arch Intern Med 2005; 165: 978-984.

27. Huang WF, Hsiao FY, Tsai YW et al.: Cardiovascular events associated with long-term use of celecoxib, rofecoxib and meloxicam in Taiwan. An observational study. Drug Safety 2006; 29: 261-272.

28. Huang WF, Hsiao FY, Wen YW, Tsai YW: Cardiovascular events associated with the use of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen or naproxen) versus a cyclooxygenase-2 inhibitor (celecoxib): A population-based analysis in Taiwanese adults. Clin Therap 2006; 28(11): 1827-36.

29. Rahme E, Nedjar H: Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefits? A retrospective cohort study. Rheumatology 2007; 46: 435-438.

30. Forman JP, Stampler MJ, Curhan GC: Non narcotic analgesic dose and risk of incident hypertension in US women. Hypertension 2005; 46: 500-07.

31. Motsko SP, Rascati KL, Busti AJ et al.: Temporal relationship between use of NSAIDs including selective COX-2 inhibitors, and cardiovascular risk. Drug Safety 2006; 29(7): 621-32.

32. Burt VL, Whelton P, Rocella EJ et al.: Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995; 25: 305-13.

33. Johnson AJ, Nguyen TV, Day RO: Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994; 121: 289-300.

34. Pope JE, Anderson JJ, Felson DT: A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993; 153: 477-84.

35. Whelton A. Fort JG, Puma JA et al.: Cyclo-oxygenase-2 specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients (SUCCESS VI Study Group). Am J Therap 2001; 8: 85-95.

36. Whelton A, White WB, Bello AE et al.: Effect of celecoxib and rofecoxib on blood pressure and edema in patients older or equal to 65 years of age with systemic hypertension and osteoarthritis (SUCCESS-VII Study Group). Am J Cardiol 2002; 90(9): 959-63.

37. Sowers JR, White WB, Pitt B et al.: Celecoxib Rofecoxib Efficacy and Safety in comorbidties Evaluation Trial (CRESCENT). The effects of cyclo-oxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hours blood pressure, and type-2 diabetes mellitus. Arch Intern Med 2005; 165(2): 161-8.

38. Wolfe F, Zhao S, Reynolds M, Pettit D: Blood pressure destabilization among 8538 users of celecoxib, rofecoxib and nonselective nonsteroidal anti-inflammatory drugs (NSAID) and nonusers of NSAID receiving ordinary clinical care. J Rheumatol 2004; 31:1143-51.

39. Lipsky PE, Brooks P, Crofford IJ et al.: Unresolved issues in the role of cyclo-oxygenase-2 in normal physiologic process and disease. Arch Intern Med 2000: 160: 913-920.

40. FitzGerald GA, Patrono C: The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med2001; 345: 433-442.

41. Krotz EF, Schiele TM, Klauss V, Sohn HY: Selective COX-2 inhibitors and risk of myocardial infarction. J Vasc Res 2005; 42: 312-24.

42. Graff J, Skarke C, Klinkhardt U et al.: Effects of selective COX-2 inhibition on prostanoids and platelet physiology in young healthy volunteers. J Thromb Haemos 2007; 5(12): 2376-85.

43. Weber AA, Heim HK, Schumacher M, Schror K, Hohlfeld T: Effects of selective cyclo-oxygenase isoform inhibition on systemic prostacycline synthesis and on platelet function at rest and after exercise in healthy volunteers. Platelets 2007; 18(5): 379-385.

44. Stichtenoth DO, Marhauer V, Tsikas D, Gutzki FM, Frolich JC: Effects of specific COX-2 inhibition on rennin release and renal and systemic prostanoid synthesis in healthy volunteers. Kidney Int 2005; 68: 2197-207.

45. Hong TT, Huang J, Barrett TD, Lucchesi BR: Effects of cyclo-oxygenase inhibition on canine coronary blood flow. Am J Physiol Circ Physiol 2008; 294 (1): H145-55.

46. Gross GJ, Moore J: Effect of COX-1/Cox-2 inhibition versus selective COX-2 inhibition on coronary vasodilator responses to arachidonic acid and acetycholine. Pharmacology 2004; 71(3): 135-42.

47. Food and Drug Administration. New information for healthcare professionals: concomitant use of ibuprofen and aspirin. September 2006. Available at: http://www.fda.gov.CDER/drug/InfoSheets/HCP/ibuprofen_aspirinHCP.htm.

48. Wilner KD, Rushing M, Walden C et al: Celecoxib does not affect the antiplatelet activity on aspirin in healthy volunteers. J Clin Pharmacol 2002; 42: 1027-1030.

49. Topol EJ, Falk GW: A coxib a day won't keep the doctor away. Lancet 2004; 364: 639-640.

50. Topol EJ: Failing the public health-rofecoxib, Merck and the FDA. N Engl J Med 2004; 351:1707-1709.

51. Ray WA, Griffin MR, Stein CM: Cardiovascular toxicity of valdecoxib. N Engl J Med 2004; 351: 2767.

52. Topol EJ: Arthritis medicines and cardiovascular events-"house of coxibs". JAMA 2005; 293: 366-368.

53. Hampton T: Experts point to lessons learned from controversy over rofecoxib safety. JAMA 2005; 293: 413-414.

54. Drazen JM: COX-2 inhibitors-a lesson in unexpected problems. N Engl J Med 2005; 352: 1131-1132.

55. Heim HK, Broich K: Selective COX-2 inhibitors and risk of thromboembolic events-regulatory aspects. Thromb Haemost 2006; 96(4): 423-32

Table 1: Adjusted Association between COXIBs Use and Acute Myocardial Infarction in Older Patients. Adapted from Solomon et al Study [25] [(a)]

Groups	Adjusted Odds Ratio (95% Confidence Interval)	P
Exposure (reference group)		
Rofecoxib (celecoxib)	1.24 (1.05-1.46)	0.011
Celecoxib (no current NSAIDs use)	0.93 (0.84-1.02)	0.13
Rofecoxib (no current NSAIDs use)	1.14 (1.00-1.31)	0.054
Celecoxib (naproxen)	0.95 (0.74-1.21)	0.7
Rofecoxib (naproxen)	1.17 (0.90-1.52)	0.2
Celecoxib (ibuprofen)	0.98 (0.76-1.26)	0.9
Rofecoxib (ibuprofen)	1.21 (.92-1.58)	0.2
Celecoxib (other NSAID)	0.95 (0.82-1.10)	0.4
Rofecoxib (other NSAID)	1.17 (.99-1.38)	0.073

[(a)] The authors conducted a matched, case control study in 54,475 older patients (65 years or older) and examined the relative risk of acute myocardial infarction among users of celecoxib, rofecoxib and NSAIDs in Medicare beneficiaries with a comprehensive drug benefit.

Table 2: Adjusted Relative Risk Estimates for Myocardial Infarction Receiving Coxes or NSAIDs. Adapted from Johnsen et al Study [26] [(a)]

Groups (Current Users)	Adjusted Relative Risk (95% Confidence Interval)
Nonusers	1.0 (reference)
Rofecoxib	1.80 (1.47-2.21)
Celecoxib	1.25 (0.84-1.02)
Other COX-2 Inhibitors [(b)]	1.45 (1.09-1.93)
Naproxen	1.50 (0.99-2.29)
Conventional NSAIDs	1.68 (1.52-1.85)

[(a)] The authors conducted a case control study in 10,280 cases of first time hospitalization for myocardial infarction and examined the relative risk among users of celecoxib, rofecoxib and NSAIDs. The RR risk was adjusted for discharge diagnoses of cardiovascular disease, hypertension, diabetes, chronic bronchitis or emphysema, alcoholism, liver cirrhosis, upper GI bleeding, rheumatoid arthritis and systemic lupus erythematosis.

[(b)] The other COX-2 inhibitors used by the investigators were etodolac, meloxicam and nabumetone.

Table 3: Risk of Myocardial Infarction and Stroke in Chronic Celecoxib, Rofecoxib and Meloxicam Users in Taiwan. Adapted from Huang et al Study [27] [(a)]

Covariate	HRs for MI (95% CI)	P for MI	HRs for Stroke (95% CI)	P for Stroke
Meloxicam	1.0 (reference Drug)			
Celecoxib	0.78 (0.63-0.96)	0.02	0.81 (0.70-0.93)	< 0.001
Rofecoxib	0.91 (0.76-1.09)	0.03	0.93 (0.83-1.05)	0.27

(a) The investigators conducted an observational study in 9602 eligible patients to explore the cardiovascular events associated with long term use (at least 180 days) of celecoxib, rofecoxib and meloxicam. The main study outcome measurements were the occurrence of MI, angina, stroke, or TIA. Pearson-time exposures and hazard ratios (HRs) were calculated. The table shows only the MI and stroke results since there were no statistical differences in the HRs noted with the other parameters angina or TIA.

Table 4: Results of the Cox Regression Models to Determine Association between COXIBs/NSAIDS Exposure, Myocardial Infarction (MI) and Gastrointestinal (GI) Hospitalization among All Patients and Among Patients with Osteoarthritis Who Did Not Use Aspirin. Adapted from Rahme and Nedjar Study [29] [(a)]

Test Drug	HRs (95% CI) MI	GI	MI/GI	OA Patients MI/GI
Acetaminophen	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Rofecoxib	1.14 (1.00-1.31)	1.60 (1.31-1.95)	1.27 (1.13-1.42)	1.36 (1.07-1.72)
Celecoxib	0.97 (0.86-1.10)	0.82 (0.66-1.01)	0.93 (083-1.03)	1.13 (0.92-1.40)
Ibuprofen	1.04 (0.68-1.59)	1.11 (0.56-2.16)	1.05 (0.74-1.51)	0.61 (0.19-1.91)
Diclofenac	1.17 (0.96-1.43)	1.18 (0.86-1.62)	1.17 (0.99-1.38)	1.54 (1.12-2.11)
Naproxen	1.16 (0.89-1.51)	2.75 (2.05-3.69)	1.59 (1.31-1.93)	1.86 (1.23-2.80)

(a) The investigators conducted a retrospective cohort study in patients who filled a prescription for NSAID or acetaminophen. Outcomes were compared using Cox regression models and the Hazard Ratios (HRs) and 95 % confidence interval were determined. The data are adjusted for age; sex diagnosis in the prior year of ischemic heart disease, heart failure, renal failure, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, anemia or blood disease, alcohol or drug abuse and gastric ulcers.

Table 5: Results of the Cox Regression Models to Determine Association between COXIBs/NSAIDS Exposure, Combined Myocardial Infarction (MI) and Gastrointestinal (GI) Hospitalization among All Patients Who Used Aspirin. Adapted from Rahme and Nedjar Study [29] [(a)]

Test Drug	HRs (95% CI) MI/GI
Acetaminophen and aspirin	1.29 (1.17-1.42)
Rofecoxib and aspirin	1.73 (1.52-1.98)
Celecoxib and aspirin	1.34 (1.19-1.52)
Ibuprofen and aspirin	1.51 (0.95-2.41)
Diclofenac and aspirin	1.69 (1.35-2.10)
Naproxen and aspirin	1.35 (0.97-1.88)

(a) The investigators conducted a retrospective cohort study in patients who filled a prescription for NSAID or acetaminophen. Outcomes were compared using Cox regression models and the Hazard Ratios (HRs) and 95 % confidence interval were determined. The data were adjusted for age; sex diagnosis in the prior year of ischemic heart disease, heart failure, renal failure, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, anemia or blood disease, alcohol or drug abuse and gastric ulcers.

Table 6: Adverse Cardiovascular Events Data from Meta Analysis of 23 Observational Studies for Selected COX-1 and COX-2 Inhibitors. Adapted from McGettigan & Henry Study [22] [(a)]

Test Drugs	Cardiovascular Events Relative Risk (95% CI)
Naproxen	0.97 (0.87-1.07)
Celecoxib	1.06 (0.91-1.23)
Ibuprofen	1.07 (0.97-1.18)
Melcoxicam	1.25 (1.00-1.55)
Rofecoxib	1.35 (1.35-1.59)
Diclofenac	1.40 (1.16-1.70)

(a) The investigators conducted a large comprehensive meta-analysis of observational studies, which included 17 case-control (N = 614,193) and 6 cohort analysis (N = 1,045,859). Risk was measured relative to non use/remote exposure. The relative risk for the test drugs is presented in the order of increased CV toxicity.