COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs

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Compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs), COX-2-selective drugs such as rofecoxib, celecoxib, and lumiracoxib reduce the risk of gastrointestinal side-effects. However, the recent 20-to-1 vote of the FDA advisory panel against etoricoxib highlights the concern that they also increase the risk of thrombotic events.[1–5] This idea has been represented by the American Heart Association and others in illustrations that associate drugs with increased COX-2 selectivity with increased thrombotic risk, and drugs with increased COX-1 selectivity with increased gastrointestinal risk (figure 1).[1–3]

However, the idea that NSAIDs and COX-2-selective drugs inherently cause different cardiovascular side-effects is fundamentally flawed, since it relies on the incorrect premise that at standard doses traditional NSAIDs inhibit COX-2 less than COX-2 selective drugs do. Figure 1 is also therapeutically misleading because it implies that, irrespective of dose, traditional NSAIDs pose less cardiovascular risk than do COX-2-selective drugs. Clinical evidence firmly shows otherwise, since any changes in cardiovascular risk factors linked to inhibition of COX-2 are dose-driven effects shown by both NSAIDs and COX-2-selective drugs.[1–6]

COX-2 selectivity has generally been defined by measuring the potencies of drugs as inhibitors of COX-1 and COX-2 in isolated cells or enzymes.[3,4] Thus, concepts such as COX-2 selective, COX-1 selective, and COX-2 preferential have evolved, although these concepts often mean different things to different researchers. These terms can also hide the true activities of the different drugs.

For example, in direct in-vitro comparisons ketorolac is highly COX-1 selective, but is also a more potent inhibitor of COX-2 than many COX-2 selective inhibitors.[7] Such understanding of the assays and calculations underlying the production of data for COX selectivity suggests that great care needs to be taken in using in-vitro data to inform clinical use.

When used therapeutically, which drugs will more strongly inhibit COX-2? It would be wrong to suppose, as figure 1 implies, that drugs that are highly COX-2 selective in vitro will inhibit COX-2 as strongly in therapeutic use. In fact, whatever their selectivities in vitro,[4,6] in clinical use all NSAIDs and COX-2-selective drugs are used at doses that substantially inhibit COX-2, because it is inhibition of COX-2 that causes their anti-pyretic, anti-inflammatory and analgesic effects (figure 1, table 1).[1–6,10,11]

Thus, extrapolating ratios of selectivity to levels of COX-2 inhibition in vivo is of little benefit—irrespective of their in-vitro selectivities, all these drugs are used at COX-2-inhibiting doses. The most notable difference between COX-2-selective drugs and traditional NSAIDs is that when used at therapeutic doses the COX-2-selective drugs have little effect on COX-1 whereas traditional NSAIDS inhibit COX-1. Using data from in-vitro tests we have calculated how much a range of NSAIDs and COX-2-selective drugs would inhibit COX-1 when producing a standard 80% inhibition of COX-2 (which occurs at the typical range of circulating NSAID concentrations following standard oral dosing) (figure 1).[12] This analysis shows that COX-1 inhibition ranges from less than 10% for highly COX-2-selective inhibitors to more than 95% for some traditional NSAIDs. This modelling is supported by direct comparisons of NSAIDs in humans. For example, administration of high clinical doses of rofecoxib, diclofenac, ibuprofen, naproxen, or meloxicam produce COX-2 inhibitions between 70% and 95% (ie, around the 80% level suggested in figure 1) but COX-1 inhibitions between 7% and 95%.[11] Thus, in clinical use, drugs that have become known as COX-2 selective drugs are COX-1 sparing drugs, by comparison with NSAIDs.[12]

Which COX-dependent mechanisms underlie gastrointestinal side-effects? Broadly, the gastrointestinal side-effects of NSAIDs are largely dependent on inhibition of COX-1 within the gastrointestinal tract and, in direct clinical trials, COX-2-selective drugs produce less severe gastrointestinal adverse events than

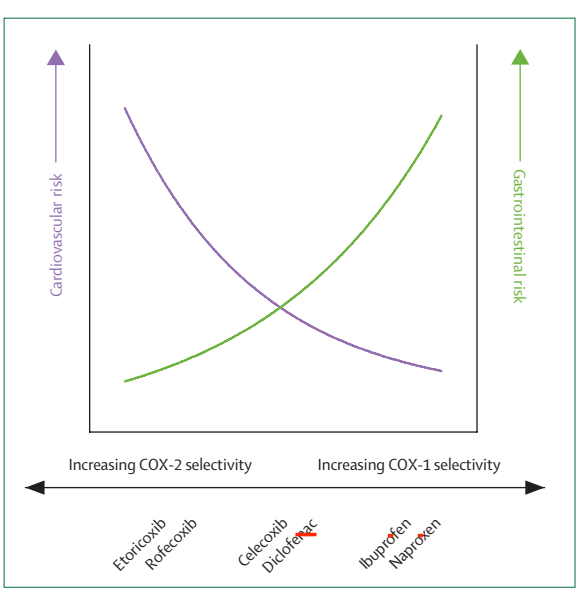

Figure 1: **Currently suggested, but misleading, graphic of relation between COX-1 and COX-2 selectivity and cardiovascular and gastrointestinal side-effects[1–3]**

do comparator NSAIDs (table 1).[1–4,6,7] This is simply explained by the fact that at clinical doses COX-2-selective drugs inhibit COX-1 very much less than do traditional NSAIDs.[1–6,8,7]

The mechanisms responsible for cardiovascular side-effects are less well understood. High doses of COX-2-selective drugs could increase the risk of thrombotic events, but in direct comparisons with traditional NSAIDs at standard doses few differences have been identified.[4,5,10,13] For example, an analysis of data from the TARGET clinical trial showed that in patients with high risk for thrombotic events lumiracoxib, which has high COX-2-selectivity in vitro, produced no more cardiovascular mortality, non-fatal myocardial infarctions or strokes than did ibuprofen.[14]

Several mechanisms could underlie any increases in thrombotic risk caused by NSAIDs and COX-2-selective drugs. First, both NSAIDs and COX-2-selective drugs dose-dependently reduce the urinary content of prostaglandin I$_2$ (PGI$_2$) metabolites (table 1).[1–5] Since PGI$_2$ is an anti-thrombotic and antiplatelet hormone, reductions in its formation could increase platelet reactivity. The origins of these urinary PGI$_2$ metabolites are still unknown. Surprisingly, it is often remarked, as in a recent statement from the American Heart Association, that "it is accepted that endothelial cells make PGI$_2$ through COX-2".[1] Actually, there is almost no direct physical evidence that COX-2 is normally expressed to any extent in human or animal blood vessels, outside of some specialised circulations such as the kidney or the vasa vasora, despite evidence for the abundant expression of COX-1.[4,8,9] Similarly endothelial cells isolated in culture rarely express COX-2, whereas they do express COX-1.

Some researchers argue that this is because endothelial cells in culture do not get the physical shear stress of blood flow, as shown more than 10 years ago by Topper and colleagues.[15] However, although some studies show that shear upregulates COX-2, others show COX-2 downregulation and even COX-1 upregulation.[4,8] Furthermore, studies of shearing for periods of 2 days or longer do not show upregulation of COX-2 expression, and endothelial cells within the body are constantly exposed to shear.[4,8]

Second, NSAIDs, but not COX-2-selective drugs, reduce the urinary levels of metabolites of thromboxane A$_2$ (TXA$_2$).[1–5] TXA$_2$ is produced by COX-1 within platelets, and so the urinary reductions could indicate reduced platelet activation. Indeed, NSAIDs given to people at standard oral or intravenous doses inhibit platelet activity and increase bleeding time[1–5,16–18] in accordance with their circulating half-lives, and this could contribute to NSAID-induced gastrointestinal bleeding.[7,10,11] For example, single doses of piroxicam (half-life 40–50 h) inhibit platelets for more than 2 days, while inhibition caused by ibuprofen (half-life 4–6 h) lasts just a few hours.[5,16,17,18] The important difference between aspirin and other NSAIDs is that aspirin irreversibly inhibits platelet COX-1 and thus TXA$_2$ production, and unlike the other NSAIDs is not at the mercy of pharmacokinetics.

	Traditional NSAIDs	COX-2-selective drugs	COX enzyme target*
Anti-inflammatory	Yes	Yes	COX-2
Analgesic	Yes	Yes	COX-2
Antipyretic	Yes	Yes	COX-2
Increase blood pressure	Yes	Yes	COX-2
Reduce urinary PGI$_2$ metabolites	Yes	Yes	COX-2
Reduce urinary TXA$_2$ metabolites	Yes	No	COX-1
Inhibit platelets	Yes	No	COX-1
Increase bleeding time	Yes	No	COX-1
Gastrointestinal toxicity	Yes	No	COX-1 (and possibly COX-2)

PGI$_2$=prostaglandin I$_2$. TXA$_2$=thromboxane A$_2$. NSAIDs=non-steroidal anti-inflammatory drugs. *Evidence from basic science studies, knockout animal experiments, and clinical studies.[1–9]

Table 1: **Properties of NSAIDs and COX-2-selective drugs**

So in judging in-vitro activity data (figure 2) we must also take into account the plasma half-lives of NSAIDs and COX-2-selective drugs which will dictate the duration of any antiplatelet effects.[5] This could explain why, unlike aspirin, NSAIDs do not seem to have a general ability to reduce the occurrence of thrombotic events because episodic use would not confer antiplatelet protection. Naproxen could be a notable exception to this, since at standard twice-daily doses it is one of the few NSAIDs to provide sustained inhibition of platelet COX-1.[1–5,19,20]

Third, both NSAIDs (including naproxen, ibuprofen, and diclofenac) and COX-2-selective drugs can increase blood pressure in normotensive individuals and in those who have existing hypertension (table 1).[1–5] Mechanistically this seems to be linked to inhibition of COX-2, causing reduced sodium excretion and thus increased active fluid retention.[5] Data from the TARGET study show that at clinically relevant doses, lumiracoxib precipitates the same development of congestive heart failure as naproxen but to a lesser extent than ibuprofen.[14] This similarity in clinical outcomes between a COX-2-selective drug and traditional NSAIDs is explained by the fact that both

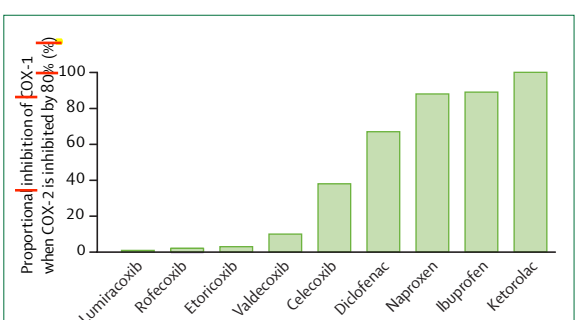

Figure 2: **Representation of the COX-1-sparing actions of COX-2-selective drugs**
Data from an in-vitro blood-based assay to show the varying inhibitions of COX-1 coupled to concentrations of drugs that inhibit COX-2 by 80% (adapted from reference 12).

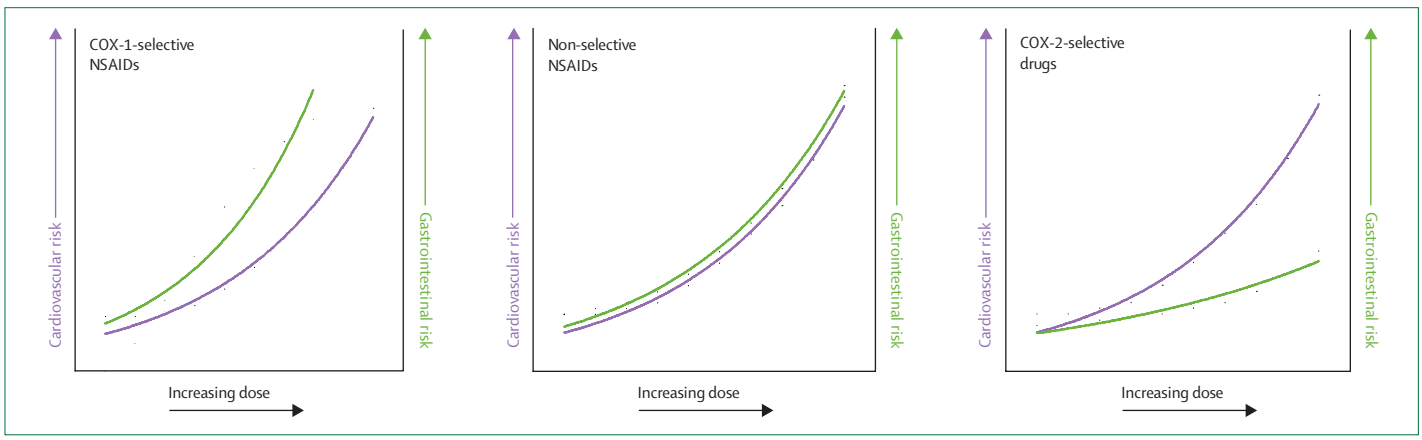

Figure 3: **Proposed figure to show association between dose, cardiovascular risk, and gastrointestinal risk for COX-1-selective NSAIDs, non-selective NSAIDs, and COX-2-selective drugs**

types of drug inhibit COX-2 in clinical use and so both types of drugs have the potential to drive COX-2-dependent increases in fluid retention and blood pressure.

The following conclusions are clear: (1) in therapeutic use both NSAIDs and COX-2-selective drugs inhibit COX-2 whereas only NSAIDs inhibit COX-1; (2) NSAIDs and COX-2-selective drugs dose-dependently reduce the levels of urinary PGI_2 metabolites, which could be associated with an increase in thrombotic risk; (3) NSAIDs and COX-2-selective drugs dose-dependently increase blood pressure, which could increase thrombotic risk; (4) inhibition of platelet COX-1 by NSAIDs dose-dependently reduces platelet reactivity, which could reduce thrombotic risk; and (5) COX-2-selective drugs cause fewer severe gastrointestinal side-effects than do NSAIDs (table 1).

These conclusions do not fit within the concept shown in figure 1 that side effects simply vary with selectivity. Rather, we must consider that in therapeutic use NSAIDs are COX-2 inhibitors (table 1) and so we need to represent the associations between the use of these drugs and their side-effects differently (figure 3). For COX-1-selective drugs, gastrointestinal side-effects arise rapidly with increasing doses, since at anti-inflammatory doses (ie, when COX-2 is inhibited) these drugs produce substantial inhibition of COX-1 in the gut (figure 3). Such a drug is ketorolac, which cannot be used at clinical doses for longer than a few days because of the high risk of gastrointestinal and renal side-effects.[21] For non-selective NSAIDs both gastrointestinal risks and cardiovascular risks increase with dose (figure 3). Drugs within this group, which generally show less than ten-fold selectivity in vitro towards COX-1 or COX-2, include ibuprofen, diclofenac, and naproxen. For these drugs there is clear evidence of dose-dependent cardiovascular risk.[1–5,19] However, these risks could be functionally limited because in clinical use sustained high doses are constrained by gastrointestinal side-effects. High doses of some of these drugs might also produce antiplatelet effects through inhibition of COX-1, although these vary widely in extent and duration.[4,5,16,17,18]

This provides a rational explanation of why, although producing similar maximum levels of inhibition of COX-1 and COX-2, the short-acting[5] traditional NSAIDs ibuprofen and diclofenac could increase thrombotic risk at high dose while the longer-acting[5] traditional NSAID naproxen does not.[5,19] For COX-2-selective drugs, increasing doses increase cardiovascular risk as for the other NSAIDs. This explains that although lumiracoxib and celecoxib are more COX-2-selective than ibuprofen, no differences in thrombotic risk have been shown in direct comparisons in either the TARGET or CLASS trials.[1–5,12,19,20] Similarly, in real-world use neither celecoxib nor rofecoxib (at doses less than 25 mg) show any indications of thrombotic risk greater than traditional NSAIDs, including ibuprofen, diclofenac, and even naproxen (table 2).[13]

In the absence of gastrointestinal side-effects, however, doses of COX-2-selective drugs can be used that produce higher and more sustained levels of COX-2 inhibition than can be achieved with traditional NSAIDs (figure 3). An example of this is the 50 mg per day dose of rofecoxib used for 12 months in the VIGOR study, a dose of the COX-2-selective drug that is 2–4 times greater than that generally used in clinical practice. So, as is readily accepted for gastrointestinal side-effects of NSAIDs, we

	Adjusted odds ratio (95% CI)	p
Control	1	
Celecoxib	0·84 (0·67–1·04)	0·12
Ibuprofen	1·06 (0·96–1·17)	0·27
Naproxen	1·14 (1·00–1·30)	0·05
Rofecoxib ≤25mg	1·23 (0·89–1·71)	0·21
Rofecoxib >25mg	3·00 (1·09–8·31)	0·03
Other NSAIDs	1·13 (1·01–1·27)	0·03

Results are from a 2-year observational study in 1·4 million people given various NSAIDs in a closed formulary health-maintenance organisation in California.[13]

Table 2: **The relative risk of acute myocardial infarction with use of selected NSAIDs compared with remote use of an NSAID (control group)**

should understand that cardiovascular side-effects are dose-dependent (table 2). For example, more than 10 years ago, meta-analysis showed that ibuprofen produced fewer gastrointestinal adverse events than did comparator NSAIDs but this was explained by ibuprofen being largely used at low dose (<1200 mg per day).[22] At high dose (>1200 mg per day) ibuprofen was no safer than comparators.

Thus, it is important to understand that NSAIDs and COX-2 selective drugs do not differ by their ability to inhibit COX-2—in fact, this is one of their few common properties. NSAIDs are COX-2 inhibitors; if inhibition of COX-2 by COX-2-selective drugs precipitates thrombotic events then we must accept the same to be true for traditional NSAIDs. If there is a difference in thrombotic risk, this could only be explained by differential effects on COX-1 or by mismatched, high doses of COX-2-selective drugs (table 1 and table 2). This understanding should inform therapeutic decisionmaking in the use of NSAIDs and COX-2-selective drugs. In particular, we must guard against the increasingly prevalent idea that traditional NSAIDs have inherently lower cardiovascular risks than do COX-2-selective drugs.

Conflict of interest statement

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Role of the funding source

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COX-2 inhibition is key to NSAID-related cardiotoxicity
J Am Coll Cardiol 2008; 52: 1628–1636

18 November 2008

MedWire News: The increased cardiovascular (CV) risk associated with different nonsteroidal anti-inflammatory drugs (NSAIDs) is largely related to the extent to which they inhibit cyclo-oxygenase (COX)-2, researchers have shown.

The finding could help resolve the ongoing debate over the cardiotoxicity of NSAIDs and suggests that separating these drugs into selective and nonselective COX-2 inhibitors is not relevant to predicting their CV risk.

The study, by Luis Garcia Rodriguez (Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain) and colleagues, was a retrospective case–control analysis nested within a British population database, the Health Improvement Network.

Garcia Rodriguez and team identified 8852 cases of nonfatal myocardial infarction (MI) in patients aged 50–84 years and matched them for gender and age with 20,000 MI-free controls. All patients and controls were classified according to exposure to NSAIDs, and current users of a single NSAID agent were evaluated for drug duration, dose, and plasma half-life/formulation.

The team also used in vitro human whole-blood assays to determine the inhibitory effects of average therapeutic concentrations of 10 different NSAIDs toward platelet COX-1 and monocyte COX-2.

Reporting their study in the Journal of the American College of Cardiology, Garcia Rodriguezet al reveal that risk for MI was increased with current use of NSAIDs, at a relative risk (RR) of 1.35. The risk increased with treatment duration and daily dose.

Most importantly, the in vitro degree of inhibition of whole-blood COX-2 explained 75% of the variance in the risk for MI associated with individual NSAIDs that lacked complete suppression of platelet COX-1 activity ($p=0.0027$).

Individual NSAIDs with a degree of COX-2 inhibition <90% at therapeutic concentrations, such as naproxen and ibuprofen, were associated with a RR of 1.18 for MI, whereas those with ≥90% inhibition, such as diclofenac and rofecoxib, had an RR of 1.60.

The authors conclude: “We propose that the extent of inhibition of COX-2–dependent prostacyclin may represent an independent key determinant of the increased risk for MI among NSAIDs with nonfunctional suppression of platelet COX-1, a property shared by most NSAIDs and coxibs.”

They add: “The assessment of whole-blood COX-2 may represent a surrogate endpoint to predict the CV risk of these drugs.”