

## Theme Issue Article

# Does a coxib-associated thrombotic risk limit the clinical use of the compounds as analgesic, antiinflammatory drugs?

## Arguments against

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### Summary

The issue of the risk-benefit assessment of cyclooxygenase-2 (COX-2) inhibitors, as compared to traditional non-steroidal anti-inflammatory drugs (tNSAIDs), is far from being resolved. These compounds need to be carefully re-evaluated in order to

avoid hasty conclusions, as it happened when COX-2 inhibitors were introduced into clinical practice. Several arguments support the concept, that COX-2 inhibitors remain a valuable therapeutic option at least for selected patients.

### Keywords

Arterial thrombosis, lipid mediators, inflammation, haemostasis, clinical studies

**Thromb Haemost 2006; 96: 413–6**

## Introduction

Selective cyclooxygenase (COX)-2 inhibitors were designed to minimize gastrointestinal toxicity of traditional non-steroidal anti-inflammatory drugs (tNSAIDs). In fact, the hazard related to tNSAIDs of inducing GI damage was reduced in patients, treated with selective COX-2 inhibitors. Thus, there is an advantage of COX-2 inhibitors, as compared to tNSAIDs, with regard to gastrointestinal toxicity.

However, serious concerns about the safety of COX-2 inhibitors have been raised. In particular, adverse renal effects, hypertension, edema, and, importantly, an increased risk of myocardial infarction, have been described. Although some controversial issues remain open (1), the biological basis for these effects has been extensively discussed ([2] and other papers in this theme issue of *Thrombosis and Haemostasis*).

Interestingly, much of the noise was precipitated by the initial way in which COX-2 inhibitors were marketed. The aggressive strategy, including direct-to-consumer marketing, as well as the enthusiastic reception in the scientific community (“super aspirins” [3]), rendered the COX-2 inhibitors “blockbuster drugs”. Although the rationale for the development of these compounds only supported a niche concept, namely to treat patients who had gastrointestinal intolerance for tNSAIDs, it has been estimated that only about 5% of the patients treated with COX-2 inhibitors

had been at risk of gastrointestinal toxicity from tNSAIDs (4). Thus, many patients at risk for cardiovascular events have been unnecessarily exposed to these compounds.

On the other hand, the intensive discussion about the adverse effects of COX-2 inhibitors carries some risk that hasty conclusions will be made about the future use of these compounds. Thus, a balanced reflection of these controversial issues appears to be necessary. This paper critically discusses some favourable arguments on the future of this class of drugs.

## Gastrointestinal tolerability

The major advantage of COX-2 inhibitors is their improved gastrointestinal tolerability compared to tNSAIDs. Principally, a similar gastrointestinal tolerability as with COX-2 inhibitors can be achieved by the combination of proton-pump inhibitors (PPIs) with tNSAID (5). However, in patients with a previous history of gastrointestinal bleeding, PPI plus tNSAID or a COX-2 specific inhibitor alone may not be sufficient to prevent gastrointestinal complications (6). Recently, the efficacy of omeprazole in the prevention of gastrointestinal ulcers was compared in high-risk patients using tNSAIDs and COX-2 inhibitors, respectively (7). In this study, an effectivity of the PPI in preventing ulcers was demonstrated for both tNSAIDs and COX-2 inhibitors. However, since more higher-risk patients

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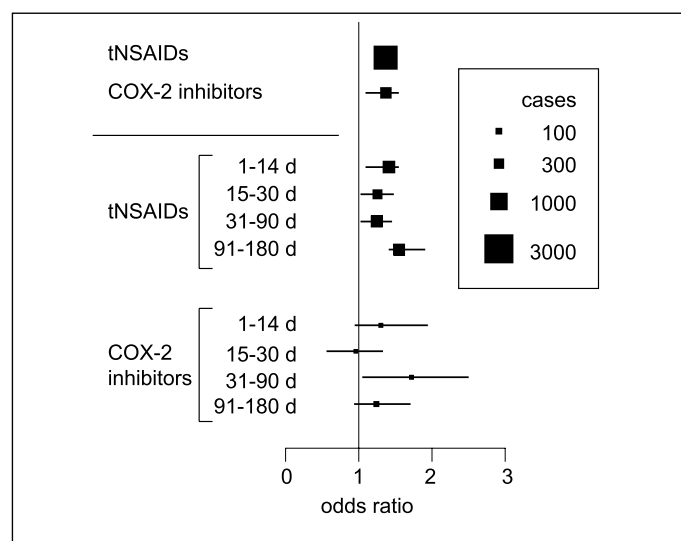
Received August 14, 2006  
Accepted after resubmission August 28, 2006

Prepublished online September 13, 2006 doi:10.1160/TH06-08-0445

were treated with COX-2 inhibitors, this study could not establish whether, in patients taking a PPI, the use of a COX-2 inhibitor was associated with a lower risk of gastrointestinal complications as compared to tNSAIDs. However, for selected patients with the highest risk of tNSAID-induced ulceration, COX-2 inhibitors in combination with a PPI might well represent a very valuable therapeutic alternative. This is an important issue which warrants further investigation.

## Cardiovascular risk of COX-2 inhibitors

The increased cardiovascular risk of COX-2 inhibitors has been extensively discussed ([2] and other papers in this theme issue of *Thrombosis and Haemostasis*). The possibility of an increased cardiovascular risk under COX-2 inhibitors has drawn much attention, although the validity of the available database used remains a matter of debate. The source of information derives from different types of studies with different comparators and from different trial populations with different cardiovascular risk profiles. Notably, there are only two controlled trials (APC and APPROVe) comparing against placebo which ensure an increased cardiovascular risk, predominantly due to an excess in myocardial infarction (8, 9). Both trials investigated possible protective effects of COX-2 inhibitors in polyposis coli. Thus, an interesting question might be whether patients with polyposis coli are at a higher risk for adverse cardiovascular events. However, only the APPROVe trial had a pre-specified cardiovascular endpoint, and assessment of any cardiovascular event – although in most trials independently adjudicated – was done retrospectively in all other trials.



**Figure 1: Adjusted risk of first time myocardial infarction among current users of tNSAIDs as compared to COX-2 inhibitors (upper panel).** Adjusted risk of first time myocardial infarction among current users of tNSAIDs as compared to COX-2 inhibitors stratified by the duration of continuous therapy (days) (lower panel). Odds ratios and 95% confidence intervals are shown. The numbers of cases are indicated by the size of the square (see calibrator). Data from Helin-Salmivaara et al. (17).

Most other data from randomised controlled trials were generated in a population of patients with rheumatoid arthritis and had tNSAIDs comparators. A recent meta-analysis of all controlled trials showed that cardiovascular event rates were larger in patients treated with COX-2 inhibitors, when naproxen was the comparator, but similar to other NSAR in all trials with non-naproxen comparators (10). The unadjusted cardiovascular event rate under placebo was 0.9% compared to 1.2% under COX-2 inhibitors, 1.1% under all non-naproxen tNSAIDs, whereas the cardiovascular event rate was 0.7% under naproxen.

Observational studies (11) and case-controlled studies (12–15) are the source for all other evidence on the adverse cardiovascular profile of COX inhibitors after short- or long-term use. The results are heterogeneous, and only some studies indicate an increased cardiovascular risk for coxibs only. In several studies all tNSAID treatments were associated with higher cardiovascular event rates, and in other studies even no risk was detectable.

An analysis of a large database (13) showed that for 2302,029 person-years of follow-up, 8,143 cases of serious coronary heart disease occurred. Multivariate adjusted odds ratios (OR) for rofecoxib versus celecoxib were 1.59 [95% confidence interval (CI) 1.10–2.32,  $p=0.015$ ]. Thus, these observational data might allow the conclusion to be drawn that current and new users of all classes of non-aspirin tNSAIDs had elevated relative risk estimates for myocardial infarction (MI).

Taken together, COX inhibitors are a heterogeneous group of drugs with a heterogeneous risk profile. However, the absolute risk for cardiovascular complications for both COX-2 inhibitors and tNSAIDs is low and needs to be balanced against the risk for gastrointestinal damage.

One more argument is worth being reflected here. A moderate (about 2-fold) increase in the risk of MI upon treatment with COX-2 inhibitors has been observed in some, but not all studies. For example, in the TARGET trial, no increase was seen in the rate of MIs in patients using lumiracoxib compared to patients using tNSAIDs (ibuprofen or naproxen) (16). This was true for both aspirin users and non-users. It has been argued that the TARGET study not only included patients with a lower cardiovascular risk (osteoarthritis) as compared to patients with rheumatoid arthritis but also excluded most patients with a prior history of cardiovascular disease. These are valid points. However, these arguments can also be regarded as a “proof of concept” for the hypothesis that the risk of COX-2 inhibitor-induced MI may be limited to high-risk patients only and that, in turn, many patients without risk factors (e.g. coronary atherosclerosis, hypertension etc.) would not have an increased cardiovascular risk upon treatment with a COX-2 inhibitor. Importantly, in the TARGET study trial, patients treated with lumiracoxib had a significantly smaller mean change from baseline for blood pressure, as compared to tNSAIDs (16).

## Cardiovascular risk of tNSAIDs?

An important problem arises when tNSAIDs (with or without aPPI) are used as an anti-inflammatory and analgesic therapy. Most of the studies designed to measure the efficacy and safety of these compounds focused on gastrointestinal adverse effects

but were generally underpowered to detect possible cardiovascular hazards. However, as mentioned in the previous section, observational studies have indicated that tNSAIDs may also be associated with an increased cardiovascular risk (14, 15). Interestingly, in a very recent population-based case-control study (more than 30,000 cases with first time MI; more than 130,000 matched controls), both tNSAIDs and COX-2 inhibitors have been shown to be associated with a modest risk of MI (OR 1.34 vs. 1.31) of MI (Fig. 1) (17). These findings were recently supported by another, smaller case-control study (18), where the risk of MI was increased in users of non-naproxen tNSAID with an OR of 1.77 (1.03 to 3.03). Another important problem that may occur with tNSAIDs is the increased risk of MI (OR 1.52) upon discontinuation of treatment (19). Thus, the possibility of an increased cardiovascular risk of tNSAIDs must not be ignored in the discussion about the safety of COX-2 inhibitors, in particular if tNSAIDs are regarded as a therapeutic alternative.

### Drug interactions with aspirin

One theoretical advantage of COX-2 inhibitors is the lack of interference with aspirin. Traditional NSAIDs are widely used to treat inflammatory disease (Roberts and Morrow, 2001) (20). Many patients treated with NSAID also require aspirin for secondary prevention of MI or stroke. Because both the aspirin- and the NSAID-binding sites are located within a narrow hydrophobic channel within the COX, a potential competitive interaction between NSAID and aspirin is a matter of concern. Administration of ibuprofen before aspirin to healthy volunteers significantly antagonized the irreversible COX inhibition by aspirin (21). Thus, commonly used NSAID may limit the cardioprotective effects of aspirin. Importantly, administration of rofecoxib did not antagonize the effects of aspirin. Thus, COX-2 inhibitors probably do not interfere with the antithrombotic actions of aspirin. However, a combination therapy with aspirin and a COX-2 inhibitor will probably offset the gastroprotective advantage of COX-2 inhibitors (22).

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### COX-2 inhibitors in combination with thienopyridines?

Since it is assumed that the cardiovascular risk of COX-2 inhibitors is due to a suppression of COX-2-dependent prostacyclin formation resulting in an augmentation of pro-thrombotic and hypertensive stimuli (2), an antithrombotic therapy is important in patients using COX-2 inhibitors who are at risk of atherothrombotic complications. As outlined before, a combination of COX-2 inhibitors with aspirin would be disadvantageous in terms of gastrointestinal tolerability. However, it is well known that clopidogrel is at least as effective as aspirin in the prevention of atherothrombosis in patients with atherosclerosis (23). Thus, it might well be that thienopyridines, such as clopidogrel or prasugrel (not yet approved) may allow anti-inflammatory and analgesic therapy with COX-2 inhibitors without an increased cardiovascular risk. This important issue also warrants further investigation.

### Individual susceptibility to the analgesic effects of COX-2 inhibitors?

There is anecdotal evidence for a unique action of COX-2 inhibitors in some patients who do not adequately respond to tNSAIDs. It is clear that this phenomenon needs to be evaluated by clinical studies and may be restricted to a very limited number of patients. However, if correct, COX-2 inhibitors may represent a very valuable pharmacological treatment for selected patients.

### Conclusions

In conclusion, the issue of the risk-benefit assessment of COX-2 inhibitors, as compared to tNSAIDs, is far from being resolved. These compounds need to be carefully re-evaluated in order to avoid hasty conclusions, as it happened when COX-2 inhibitors were introduced into clinical practice. Several arguments support the concept that COX-2 inhibitors may represent a valuable therapeutic option for selected patients.

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