COMMENTARY

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The sad story of Vioxx, and what we should learn from it

ON SEPTEMBER 30, 2004, Merck & Co. withdrew its blockbuster arthritis medication rofecoxib (Vioxx) from the market after the drug was found to increase the risk of myocardial infarction (MI) and stroke. This event, the largest prescription drug withdrawal in history, has important implications both for the millions of patients with arthritis and for the pharmaceutical field in general.

THE ROAD TO WITHDRAWAL

Rofecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that is specific for cyclo-oxygenase-2 (COX-2); it is therefore termed a COX-2 inhibitor, or coxib.

To tell the story of how it came to be withdrawn, we must start in 1999 when the Food and Drug Administration (FDA) approved it for the relief of arthritis symptoms. The approval was based on data from trials lasting 3 to 6 months and involving patients at low risk for cardiovascular illness.

VIGOR suggests a problem

Strong evidence that rofecoxib increases the risk of MI came from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study,[1] published in 2000.

In that study, 8,076 patients with rheumatoid arthritis were randomized to receive either rofecoxib 50 mg daily or naproxen 500 mg twice a day. The median follow-up was 9 months. Patients with prior stroke, MI, or coronary artery bypass graft (CABG) surgery were excluded, as were patients who had been taking aspirin or a gastroprotective agent.

Unexpectedly, the incidence of MI was higher in the rofecoxib group than in the naproxen group (0.5% vs 0.1%, $P < .05$).

These published figures were actually too low, because adverse cardiovascular events had not been anticipated and were incompletely reported. Such events had not been prospectively defined, and the trial did not have a prespecified adjudication process. The FDA subsequently reviewed the raw data and found a much higher incidence of major cardiovascular events than originally reported, with an absolute difference of approximately 1.5% between the rofecoxib and naproxen groups (a difference remarkably similar to what was later found in the APPROVe trial—see below). The divergence between the treatment groups began by 30 days (FIGURE 1)[2]— not after a lag or "incubation" phase as in the APPROVe trial.

Our group called attention to the substantial excess of MIs in the VIGOR trial, and we noted that, in patients for whom aspirin was indicated because they had risk factors for coronary artery disease, the risk ratio with rofecoxib use was 4.9.

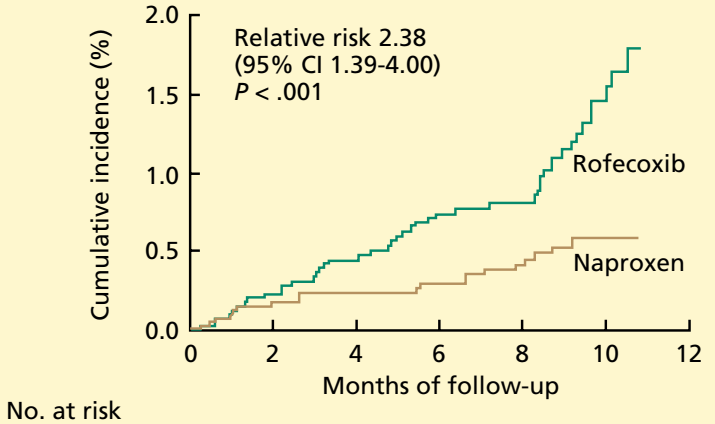
We also discovered that the annual incidence of MI was higher in rofecoxib recipients than with placebo in several primary prevention trials (0.74% vs 0.52%, $P = .04$).[2] Of note, these warning signs of the cardiovascular risk of rofecoxib came from study populations at low cardiovascular risk. In concluding, we called for a trial specifically assessing cardiovascular risk and benefit of these agents.[2–4]

Merck proposes an alternative explanation

Faced with this evidence that rofecoxib may increase the risk of MI, what was the reaction of Merck & Co.? Did it in fact undertake a trial to ensure that rofecoxib was safe in

The Vioxx withdrawal has important implications for arthritis patients and the pharmaceutical field in general

VIGOR data: Higher cardiovascular risk with rofecoxib than with naproxen



No. at risk							
Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514

FIGURE 1. Time to cardiovascular adverse event in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial.

REPRODUCED WITH PERMISSION FROM MUKHERJEE D, NISSEN SE, TOPOL EJ. RISK OF CARDIOVASCULAR EVENTS ASSOCIATED WITH SELECTIVE COX-2 INHIBITORS. JAMA 2001; 286:954–959.

The safety of other coxibs should be readdressed

patients with established coronary disease?

It did not. Instead, it asserted that the evidence was flawed and no thorough evaluation of rofecoxib's cardiovascular safety was necessary—both of which were highly questionable.

Merck and its consultants claimed that the excess in MIs observed in the VIGOR trial, a number higher than would have been anticipated from previous studies, was due to a cardioprotective effect of naproxen. But whether naproxen is cardioprotective had never been proven or quantified.

Epidemiologic evidence accumulates

Meanwhile, several well-conducted epidemiologic studies[5–8] showed that rofecoxib use was associated with a substantial risk of MI, which was greater than that with other coxibs or the over-the-counter NSAIDs (TABLE 1).

Graham et al[5] examined the California Kaiser Permanente population (about 1.4 million patients) and demonstrated in a case-control study that current use of rofecoxib at doses greater than 25 mg daily was associated with increased risk of MI or sudden cardiac death compared with no use of NSAIDs (odds ratio 3.15, $P < .05$).

Solomon et al[6] conducted a case-control study of more than 54,000 patients 65 years of age or older and demonstrated that current use of rofecoxib was associated with an increased risk of MI compared with celecoxib or with no use of an NSAID.

Ray et al[7,8] studied the Tennessee Medicaid population (N = 378,776) and showed that the relative risk of cardiovascular death or MI among new users of rofecoxib 50 mg daily was 1.93 ($P = .024$) compared with patients not using any NSAID. Further, these investigators could confirm only a mild cardioprotective effect of naproxen.

Each time that these data were presented, Merck claimed that the epidemiologic studies were flawed. As we now know, during the whole time that Merck opted to ignore the warning signs and market Vioxx to consumers,[9] including those with cardiovascular disease, patients taking this popular medication likely continued to suffer heart attacks, in part due to this drug.

The FDA fails to act

Particularly disconcerting is that the FDA, entrusted with protecting the public health, went along with this passive approach and did not require Merck to prove that rofecoxib was safe in the face of evidence suggesting otherwise.

We strongly feel that the FDA's reaction of waiting for further data to emerge was too little too late. Given the large number of patients treated with rofecoxib, this strategy has very likely contributed to tens of thousands of heart attacks and strokes.[10,11]

Another notable issue is that the benefit of relieving arthritic pain in this situation got pitted against promoting heart attacks, the number-one killer of Americans.

APPROVe confirms the danger

The final blow for rofecoxib came from the Adenomatous Polyp Prevention on VIOXX (APPROVe) trial, which was designed to evaluate the possible effect of rofecoxib on colonic adenomas. It enrolled 2,600 patients with prior colon polyps to receive rofecoxib 25 mg daily or placebo for 3 years. Patients with any history of cardiovascular disease were excluded.

An unanticipated finding (although it shouldn't have been) was a higher incidence

TABLE 1

Epidemiologic studies of rofecoxib and cardiovascular risk

STUDY	N (TOTAL)	N (ROFECOXIB)*	RELATIVE RISK†	P-VALUE
Solomon et al[6]	54,475	941	1.40	.005
Ray et al[7]	378,776	24,132	1.93	.024
Mamdani et al[24]	166,964	12,156	1.0	NS
Mamdani et al[25]	138,882	14,583	1.8	< .05
Graham et al[5]	1,394,764	26,748	3.15	< .05

*Rofecoxib use of 1–30 days (Solomon et al[6]), new use of rofecoxib > 25 mg (Ray et al[7]), any use of rofecoxib (both of the Mamdani et al studies[24,25]), and current use of rofecoxib > 25 mg (Graham et al[5]).

†End points were myocardial infarction (Solomon et al,[6] Mamdani et al[24]), a composite of myocardial infarction and cardiovascular death (Ray et al[7]), admission for congestive heart failure (Mamdani et al[25]), and a composite of myocardial infarction and sudden cardiac death (Graham et al[5]). Comparator groups were celecoxib users (Solomon et al,[6] Mamdani et al[25]) and nonusers of nonsteroidal anti-inflammatory drugs (Ray et al,[7] Mamdani et al,[24] Graham et al[5]).

The FDA's inaction led to tens of thousands of heart attacks and strokes

of the combined end point of MI or stroke among the patients on rofecoxib: 3.5% vs 1.9% ($P < .001$). The increased risk was noted after 18 months of therapy.

DO ALL COX-2 DRUGS CAUSE THROMBOSIS?

It is not entirely clear at this point whether the increased thrombotic risk noted with rofecoxib is a class effect of all COX-2 inhibitors or specific to this drug only. Two other coxibs are marketed in the United States: celecoxib (Celebrex) and valdecoxib (Bextra). Other coxibs, not currently approved for use in the United States, include lumiracoxib (Prexige) and etoricoxib (Arcoxia).

Mechanism of a possible class effect

In theory, all COX-2 inhibitors have the potential to induce or facilitate thrombosis.

There are two COX isozymes: COX-1 and COX-2. COX-1 is present in platelets and the gastric mucosa. In platelets, COX-1 mediates thromboxane A_2 generation, leading to platelet aggregation, vasoconstriction, and vascular proliferation. In the gastric mucosa, COX-1 activation leads to prostacyclin production and thus, gastric cytoprotection.

COX-2 mediates prostaglandin I_2 (prostacyclin) production, which inhibits platelet aggregation, causes vasodilatation, and prevents vascular smooth muscle cell proliferation.

Compared with nonselective NSAIDs, the COX-2 inhibitors inhibit COX-2 more than COX-1. In this situation, therefore, thromboxane A_2 is unopposed by prostacyclin. The net effect is to upset eicosanoid homeostasis, favoring platelet aggregation.

CLASS: Equivocal evidence with celecoxib

The Celecoxib Long-term Arthritis Safety Study (CLASS) randomized 8,059 patients with osteoarthritis or rheumatoid arthritis to receive either celecoxib 400 mg twice daily, ibuprofen 800 mg three times a day, or diclofenac 75 mg twice a day.[12] The aim was to determine whether celecoxib is associated with a lower incidence of significant upper gastrointestinal toxic effects.

Celecoxib was not associated with any gastrointestinal benefit among the patients concomitantly receiving aspirin. Furthermore, at 12 months of therapy (the published data were truncated at 6 months), celecoxib did not have any gastrointestinal benefit over ibuprofen or diclofenac regardless of aspirin use.

In light of these findings, it is worth noting a study by Chan et al[13] in 287 patients with arthritis who presented with ulcer bleeding. Those receiving a regimen of diclofenac plus omeprazole for 6 months had a rate of recurrent bleeding similar to that in patients receiving celecoxib 200 mg twice daily (6.4% vs 4.9%, respectively, P = NS).

The risk of MI in the CLASS trial was slightly higher in the celecoxib group among both aspirin users and nonusers, but the difference was not statistically significant. Any possible prothrombic effect of celecoxib may have been masked because the comparator drugs, ibuprofen and diclofenac, have less platelet-inhibiting effect than naproxen does. As we did with rofecoxib, our group analyzed available trials of celecoxib[2] and found that patients receiving it had a higher annual incidence of MI than did patients on placebo: 0.80% vs 0.52%, respectively, P = .02.[2]

Conclusions. Celecoxib is less COX-2-selective than rofecoxib, and also appears to be less thrombogenic and less gastroprotective. It does not appear to offer appreciable gastric protection in patients who take aspirin, but if aspirin is withheld from patients who should take it for cardioprotection, the more modest thrombogenic potential of celecoxib may become clinically apparent. Therefore, more data are needed in patients with cardiovascular disease before asserting celecoxib's safety.

It is important to point out that coxibs, including celecoxib, have been found to improve endothelial function and lower levels of high-sensitivity C-reactive protein in patients with arterial inflammation.[14,15] This is an ideal foundation for a trial to examine whether celecoxib is beneficial in patients who have coronary disease, osteoarthritis requiring medication, and evidence of arterial inflammation reflected by an increased C-reactive protein level.

Inadequate data for lumiracoxib and valdecoxib

The lessons from the rofecoxib debacle need to be used to preempt such a travesty in the future

The TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial)[16,17] trial randomized 18,325 patients with osteoarthritis to receive either lumiracoxib 400 mg once a day, naproxen 500 mg twice a day, or ibuprofen 800 mg three times a day for 12 months. Patients taking gastroprotective drugs were excluded. Also excluded were patients with prior MI or stroke and patients with certain anginal symptoms, electrocardiographic findings, or heart failure.

In the patients not taking low-dose aspirin, the hazard ratio for an adverse gastrointestinal event in the lumiracoxib group was 0.21 (0.20% vs 0.92%, $P < .0001$). However, there was no benefit among patients taking low-dose aspirin (similar to the celecoxib data). More patients had adverse cardiovascular events in the lumiracoxib group (hazard ratio 1.14); the difference was not statistically significant ($P = .51$), but the trial lacked power to detect a difference in the incidence of MI, as the patients were at low cardiovascular risk.

In other developments that raised questions about the cardiovascular safety of the coxibs, Pfizer, the maker of valdecoxib (Bextra), announced on October 15, 2004 that in a trial of patients undergoing CABG, valdecoxib was associated with an increased risk of MI and stroke.[18] Earlier, the valdecoxib prodrug parecoxib (Dynastat), used in conjunction with valdecoxib, was associated with a cluster of adverse cardiovascular events in a study of patients undergoing CABG.[19] Prompted by these very worrisome data, Pfizer finally announced that it would study the safety of valdecoxib among patients at increased cardiovascular risk.[20]

Conclusions. The safety data for coxibs are inadequate among patients at low cardiovascular risk and altogether absent among patients at moderate to high risk or with frank cardiovascular disease. It is also unclear what the interactions are with aspirin and coxibs with respect to offsetting cardiovascular risk.

LESSONS LEARNED

The discovery of rofecoxib's harm, although a sad story in US medicine, offers many lessons.

Clearly, both the drug companies and the FDA should have a higher burden of proof in the future as they evaluate the cardiovascular safety of medications that affect platelet physiology. The safety studies must be of sufficient size and include patients with cardiovascular risk factors. Patients with frank cardiovascular disease on proven therapies such as aspirin should also participate.

If evidence of potential harm emerges after a medication is approved, it should be addressed aggressively. If not already performed, additional clinical trials should be immediately started (sponsored by the manufacturer) with the premise that continued approval of the drug will need to be justified in the face of the new data suggesting harm. In the case of rofecoxib, the drug is now off the market. Patients in the APPROVe trial should continue to be monitored.

In addition, the safety of the other coxibs celecoxib and valdecoxib should be readdressed, especially in patients with established cardiovascular disease or at high risk of developing it. Physicians would do well to switch patients at high risk who are taking these medications to other NSAIDs such as naproxen, ibuprofen, or acetaminophen while

coxib safety is being studied. Naproxen in particular may possess some antithrombotic effect compared with ibuprofen, based on data from the TARGET trial and a large analysis of the Tennessee Medicaid population.[8,17,21]

Consideration should be given to the use of gastroprotective medications such as proton pump inhibitors, especially since they do not interfere with NSAID actions. Patients at cardiovascular risk should take low-dose aspirin (81 mg daily).

The lessons learned from the rofecoxib debacle need to be comprehensive and used to strengthen the FDA and preempt such a travesty in the future. The only institution that the FDA is accountable to is the Congress of the United States. At this time, senators and congressmen are pursuing an investigation that will ultimately provide all the behind-the-scenes information. We have already learned how one FDA investigator, David Graham, had his study that demonstrated rofecoxib's harm harshly criticized by his colleagues and was obligated to share the data with Merck before it became public information.[22,23]

In parallel to learning the full chain of events with rofecoxib, it will be critical to learn more about the other coxibs and provide assurance that there is no clinically significant cardiovascular risk.

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