

CORRESPONDENCE



Rofecoxib, Merck, and the FDA

TO THE EDITOR: Merck has been proactive and conscientious in evaluating the cardiovascular profile of rofecoxib (Vioxx); Dr. Topol's remarks to the contrary in his Perspective article (Oct. 21 issue)¹ are false. First, his description of the time line obfuscates the facts. The Food and Drug Administration (FDA) approved Vioxx in May 1999. The clinical data then existing on 5435 patients who had been treated for up to 22 months did not suggest an adverse cardiovascular effect.² Nevertheless, because the literature suggested a hypothetical possibility of both cardioprotective and prothrombotic effects of cyclooxygenase-2 (COX-2) inhibitors,¹ Merck initiated adjudication of cardiovascular events by an external expert panel at the end of 1998 (i.e., before the Vioxx Gastrointestinal Outcomes Research [VIGOR] trial began) for future studies of Merck's COX-2 inhibitors.

Merck learned the preliminary VIGOR results in March 2000, with more cardiovascular events over a period of one year in patients receiving Vioxx than in those receiving naproxen, and promptly disclosed this finding to the FDA, other regulators, and the media, beginning that month. Two months later, the VIGOR manuscript was submitted to the *Journal*, and it was published in November 2000. An application to include the results in the prescribing information was submitted to the FDA in June 2000, followed by a public Advisory Committee meeting in February 2001. In April 2002, the FDA approved the revised Vioxx prescribing information, reflecting the cardiovascular data from VIGOR (which lacked a placebo group) and interim data from long-term, placebo-controlled studies in elderly patients with Alzheimer's disease, which did not show an increased cardiovascular risk.³

Second, Dr. Topol neglects to mention that beginning in 2000, Merck undertook three prospective, randomized, placebo-controlled trials of Vioxx in more than 24,000 patients with or without known cardiovascular disease. After deliberations with numerous consultants, Merck finalized a protocol

in 2002, which prespecified the analysis of adjudicated cardiovascular-event data from these studies as a hypothesis-testing end point. Two of these studies, Adenomatous Polyp Prevention on Vioxx (APPROVe), with approximately 2600 patients, and Vioxx in Colorectal Therapy, Definition of Optimal Regimen (VICTOR), a study of 7000 patients with a history of colon cancer, had already begun, and the third, a study of 15,000 patients at risk for prostate cancer, was initiated after consultation with regulatory agencies.

Third, before the results of the APPROVe study were available, completed and ongoing randomized trials involving more than 28,000 patients with more than 14,000 patient-years of exposure showed an incidence of cardiovascular events among patients taking Vioxx that was similar to the incidence among those taking placebo and those taking nonsteroidal antiinflammatory drugs (NSAIDs) other than naproxen.^{2,4} Because naproxen inhibits platelet aggregation in similar fashion to low-dose aspirin, we concluded that the VIGOR results were most likely due to the effects of naproxen.⁵ Even Topol and colleagues stated that "aspirin and naproxen . . . have a cardioprotective effect."⁶

Fourth, Dr. Topol argues that observational studies "confirmed" cardiovascular risks with rofecoxib. However, one observational study reported in the peer-reviewed literature and another such study re-

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ported in abstract form, neither funded by Merck, did not.^{7,8}

The APPROVe study began nine months after the FDA approved Vioxx and one month before the results of the VIGOR study were known. Analysis of cardiovascular events was prespecified for the reason cited above. Because the study was designed to examine the effects of long-term use of rofecoxib on gastric polyps, we were able to detect an increase in cardiovascular risk that began after 18 months of continuous Vioxx therapy. At that time, September 2004, Merck moved promptly and voluntarily to remove Vioxx from the market. The record, in short, is one of careful analysis at every stage, a continued commitment to research, and prompt and decisive action in response to clinical-study results.

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3. Prescribing information for Vioxx. Whitehouse Station, N.J.: Merck. (Accessed December 8, 2004, at http://www.vioxx.com/rofecoxib/vioxx/consumer/prescribing_information.jsp.)
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6. Mukherjee DM, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
7. Mamdani M, Rochon P, Juurlink DM, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;163:481-6.
8. Shaya FT, Blume SW, Blanchette CM, Mullins CD, Weir MR. Cardiovascular risk of selective cyclooxygenase-2 inhibitors compared to other nonsteroidal anti-inflammatory agents: an observational study of a Medicaid population. *Pharmacoepidemiol Drug Saf* 2004;13:S234. abstract.

TO THE EDITOR: Dr. Topol shows a lack of understanding of the FDA's regulatory authority. The FDA cannot "mandate" post-marketing clinical trials. Dr. Topol also fails to appreciate the successful efforts by the FDA to negotiate ongoing evaluation of cardiovascular safety in several multiyear clinical trials, one of which helped to resolve the cardiovascular questions first noted in the post-marketing VIGOR study.

The FDA convened an advisory committee (on February 8, 2001) to review the data from VIGOR in order to ensure a full public airing and assessment by additional scientific experts. The study showed a 50 percent decreased risk of gastroduodenal perforations, symptomatic ulcers, and bleeding with Vioxx (50 mg daily) but twice the risk of cardiovascular thrombotic events (mostly myocardial infarctions, with no differences in strokes or cardiovascular deaths), as compared with naproxen. The study had several limitations that hampered the generalization of these findings. After careful review, the expert panel (which included cardiologists) recommended that the label for Vioxx should include the unquestionable gastrointestinal advantage as well as the negative cardiovascular safety information in order to provide doctors and patients with the available data on the potential risks and benefits of Vioxx as compared with naproxen.¹ Subsequently, the FDA approved changes in the labeling to reflect the risk of cardiovascular thrombotic events as reported in the VIGOR study. Specifically, the new labeling advised doctors to use caution in prescribing Vioxx for patients with ischemic heart disease and stated that Vioxx at 50 mg per day is not recommended for long-term use.

The finding of an increased risk of myocardial infarctions and strokes in Merck's study of colon-polyp prevention (APPROVe) with the 25-mg dose was unexpected but not an accident. The extensive safety monitoring in this and other studies was intended in part to address the fact that, as noted in the precautions section of the Vioxx label, "Prospective studies specifically designed to compare the incidence of serious cardiovascular events in patients taking Vioxx as compared with those taking NSAIDs or placebo have not been performed."

The FDA worked vigorously with Merck to inform the public of the potential cardiovascular risks associated with Vioxx and to ensure adequate ascertainment and analyses of these cardiovascular events in Merck's prevention trials. The FDA will continue to work within its regulatory authority to protect the public health while balancing the available evidence in a rapidly changing scientific and clinical landscape.

(The views presented in this article do not necessarily reflect those of the Food and Drug Administration.)

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1. Food and Drug Administration. Transcripts, briefing documents and slide presentations. February 2001. (Accessed December 8, 2004, at <http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Arthritis>.)

TO THE EDITOR: Both Topol and FitzGerald,¹ in his Perspective article in the same issue, comment that ample warning was issued regarding the thrombogenic potential of rofecoxib before its withdrawal, including our review of the gastrointestinal toxicity of NSAIDs in the *Journal* in 1999.² However, celecoxib and rofecoxib were specifically approved for — and numerous reports attested to their utility in — the treatment of arthritis. The Celecoxib Long-Term Arthritis Safety Study (CLASS) and VIGOR,^{3,4} which I helped review in February 2001 as a member of the FDA Advisory Board, were performed to assess gastrointestinal safety. At this meeting, the members of the board discussed extensively both the improved gastrointestinal safety and the increased incidence of myocardial infarction observed with rofecoxib, but not with celecoxib.

Although the reasons for these differences cannot be ascertained without a direct prospective comparison, the study design may have contributed. Because aspirin use was not permitted in VIGOR, despite the inclusion of patients with prior myocardial infarction, the thrombogenic potential of rofecoxib may have been not only unmasked but actually potentiated. The possibility that naproxen might be protective was discussed but dismissed because no studies had examined this specific question. Nevertheless, three subsequent retrospective analyses suggested that naproxen may indeed be cardioprotective.

In contrast, 21 percent of the participants took aspirin in CLASS, which, as suggested by FitzGerald, may have concealed the deleterious properties of celecoxib. My one voiced criticism of the FDA was its role in these two studies, which although seemingly similar, included at least three major differences that precluded any meaningful direct comparison — most important, the use of aspirin. Thus, I fully agree with Topol and FitzGerald that on the basis of pharmacologic principles, all precautions should be extended to the use of every coxib. Moreover, FitzGerald's group has reported that nonselective NSAIDs that inhibit thromboxane A₂ to a lesser extent than aspirin may not effectively inhibit platelet aggregation.⁵ In theory, the effective inhibition of prostaglandin I₂ by NSAIDs, without sufficient suppression of thromboxane, may promote thrombosis. Thus, in addition to coxibs, I

would recommend, that all NSAIDs be reexamined to determine their thrombogenic potential.

Finally, it must be emphasized that the VIGOR study and, to some extent, CLASS did show a decrease in serious gastrointestinal adverse events. The obvious lesson learned from the development of coxibs is that the potential for serious adverse events appears to have outweighed any conferred benefit. As additional information is accrued, pharmaceutical companies, the FDA, and the National Institutes of Health need to work together to prevent future debacles by mandating a thorough investigation of all new and old drugs for which there is even the theoretical possibility of serious effects.

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2. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340:1888-99. [Erratum, *N Engl J Med* 1999;341:548.]
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4. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
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DR. TOPOL REPLIES: In response to Drs. Kim and Reicin, I believe that many vital steps were not taken to evaluate the cardiovascular safety of rofecoxib properly. They assert that the clinical data for the initial FDA approval “did not suggest an adverse cardiovascular effect.” In contrast, at the time of approval in May 1999, the FDA reviewer, Dr. Villalba, wrote, “The data seem to suggest thromboembolic events are more frequent in patients receiving rofecoxib than placebo.”¹ In 2000, along with the VIGOR trial,² a second trial conducted by Merck, known as Study 090, also showed a significant excess of heart attacks and strokes among patients taking rofecoxib, as compared with controls (Table 1).³ Together with the results of the VIGOR trial, there was indeed replication in an independent, randomized, controlled trial of an excess of the cardinal cardiovascular end point of death, heart attack, and stroke. The excess of these events occurred within six weeks in Study 090, and the event curves were divergent by 30 days in the VIGOR trial. Not only was Study 090 never published and available

Table 1. Deaths and Cardiovascular Events in Two Trials of Rofecoxib.*

Trial	Rofecoxib Group	Control Group	Odds Ratio (95% CI)	P Value
VIGOR				
No. of patients	4047	4029		
Death — no.	22	15		
Heart attack — no.	20	4		
Stroke — no.	11	9		
Total — no. (%)	53 (1.3)	28 (0.7)	1.9 (1.2–3.0)	0.006
Study 090				
No. of patients	390	588		
Death — no.	0	0		
Heart attack — no.	3	1		
Stroke — no.	2	0		
Total — no. (%)	5 (1.3)	1 (0.2)	7.6 (1.2–146.3)	0.03
Death, heart attack, and stroke in the 2 trials — no./total no. (%)	58/4437 (1.3)	29/4617 (0.6)	2.1 (1.4–3.3)	0.001

* The data for the VIGOR trial are from Bombardier et al.,² and the data for Study 090 are from the FDA.³ The VIGOR trial, conducted from 1999 to 2000, compared rofecoxib (50 mg, given for nine months) with naproxen. Study 090, conducted from 1998 to 1999, compared rofecoxib (12.5 mg, given for six weeks) with nabumetone or placebo. CI denotes confidence interval.

solely through a subsequent FDA memorandum,³ but the data presented in the VIGOR article also suffered from errors of omission, along with erroneous information and lack of completeness.² In Table 1, the data from the FDA report³ for VIGOR are presented. In the VIGOR article, the actual deaths were not reported, but it is stated in the article in three places that the overall mortality rate was similar in the two groups. The heart-attack rate for rofecoxib was erroneous. More than half of the thrombotic events are not presented in the VIGOR article but appear in the FDA report.³ (The updated cardiovascular-event data from VIGOR were submitted to the FDA on October 13, 2000, six weeks before the VIGOR study was published.)²

Unfortunately, although my colleagues and I called for dedicated cardiovascular trials in 2001,⁴ Merck never initiated one and maintains that its trials conducted to seek new medical indications were determining cardiovascular risk. There was ample evidence that COX-2 inhibitors improve endothelial function and lower inflammatory proteins, such as C-reactive protein,⁵ justifying the benefit-and-risk assessment of these drugs directly in patients with established cardiovascular disease.

We indeed acknowledged that naproxen may have a cardioprotective effect,⁵ but the magnitude of the effect would be unlikely to exceed that of aspirin, at a 25 percent reduction of heart attacks. Instead, in the VIGOR trial, there was a 500 percent increase in heart attacks. This makes any “naproxen hypothesis” of cardioprotection mathematically indefensible.

Drs. Villalba and Witter are incorrect in suggesting that the FDA cannot influence post-marketing clinical trials that a sponsor performs. Their claim that the “50 percent decreased risk of gastroduodenal perforations” outweighed the cardiovascular risk in the VIGOR trial is not substantiated by the data. There were no differences in the rate of perforation (0.1 percent in both the rofecoxib and naproxen groups).² It is hard to imagine that the small protection from gastric or duodenal ulcers in the VIGOR trial is an acceptable trade-off as compared with twice the incidence of death, heart attacks, and strokes. Indeed, Dr. Targum, the FDA reviewer of the VIGOR, wrote in her report, in reference to the cardiovascular findings, “This analysis could lead one to conclude that naproxen, with a 51 percent reduction compared to rofecoxib, would be the preferred drug.”³ It took 14 months after the expert FDA panel convened, from February 2001 to April 2002, to change minimally the cardiovascular safety information for rofecoxib in the package insert. After their cumulative meta-analysis, Juni et al. correctly stated, “Our findings indicate that rofecoxib should have been withdrawn several years earlier.”⁶

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Dr. Topol reports having served as a paid advisor to Great Point Partners, an investment fund that has traded in Merck stock. He reports that he did not invest in the fund, was not compensated on the basis of the fund's performance, and was not aware of its investment in Merck.

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CORRECTION

Rofecoxib, Merck, and the FDA

Rofecoxib, Merck, and the FDA . In the letter by Topol, in Table 1 on page 2878, the 95 percent confidence interval for the number of total deaths and cardiovascular events in study group 090 should have been "1.2–46.3," rather than "1.2–146.3," as printed.