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## Expression of Concern Reaffirmed

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On December 8, 2005, we published an expression of concern<sup>1</sup> regarding an article by Bombardier et al. on the Vioxx Gastrointestinal Outcomes Research (VIGOR) study that was published in the *Journal* on November 23, 2000.<sup>2</sup> Our expression of concern was prompted by evidence that the VIGOR article did not accurately represent the safety data available to the authors when the article was being reviewed for publication.

More than four months before the article was published, at least two of its authors were aware of critical data on an array of adverse cardiovascular events that were not included in the VIGOR article. These data, which should have raised concern about potential cardiovascular toxicity of rofecoxib, are part of an internal Merck memorandum.<sup>3</sup> Two tables and a figure that are representative of the data in that document are shown in Supplementary Appendix 1 (available with the full text of this article at [www.nejm.org](http://www.nejm.org)). The data indicate that there were 47 confirmed serious thromboembolic events in the rofecoxib (Vioxx) group and 20 in the naproxen group. The VIGOR article reported 56 upper gastrointestinal events in the rofecoxib group and 121 in the naproxen group. Thus, the prevention of 65 upper gastrointestinal events (of which 21 were complicated — i.e., perforation, obstruction, or severe upper gastrointestinal bleeding) came at the cost of 27 additional serious thromboembolic events in the rofecoxib group (see Supplementary Appendix 2). Prevention of one complicated gastrointestinal event was offset by the occurrence of about one serious thromboembolic event.

Although the information in the internal Merck memorandum<sup>3</sup> was reported to the FDA and posted on its Web site<sup>4</sup> three months after publication of the VIGOR article, it was not made available to the *Journal* editors during the manuscript review process. Because these data were not included in the published article, conclusions regarding the safety of rofecoxib were misleading.

We wrote to the authors explaining the reasons for our concern and requested a written response. The authors' responses appear unedited elsewhere in this issue of the *Journal*.<sup>5,6</sup>

As part of our expression of concern, we also pointed out that three myocardial infarctions in the rofecoxib group were not included in the data submitted to the *Journal*. The authors state that these events did occur during the trial but did not qualify for inclusion in the article because they were reported after a "prespecified cutoff date" for the reporting of cardiovascular events. This date, which the sponsor selected shortly before the trial ended, was one month earlier than the cutoff date for the reporting of adverse gastrointestinal events. This untenable feature of trial design, which inevitably skewed the results, was not disclosed to the editors or the academic authors<sup>5</sup> of the study.

The information we have indicates that the VIGOR article, because it did not contain relevant safety data available to the authors more than four months before publication, did not accurately reflect the potential for serious cardiovascular toxicity with rofecoxib. We therefore reaffirm our expression of concern.

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4. Memorandum from Shari L. Targum, M.D., on the cardiovascular safety of rofecoxib. (Accessed February 23, 2006, at [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2\\_06\\_cardio.pdf](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf).)

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