

CORRESPONDENCE



Response to Expression of Concern Regarding VIGOR Study

TO THE EDITOR: We, the non-Merck authors of the VIGOR study,¹ welcome the opportunity to respond to your recent expression of concern² regarding the VIGOR study. No Merck employee or representative was involved in the drafting of this response. Our evaluation leads us to conclude that our original article followed appropriate clinical trial principles and does not require a correction. Three basic assertions were made in the expression of concern, and we would like to address these assertions point by point.

Point 1: Three additional myocardial infarctions were not included in the VIGOR paper and at least two of the authors knew of these events in ample time to add them to the paper during the review process.

Response: The cardiovascular analysis was performed according to a predefined plan developed prior to the close of the VIGOR study. In order for the results of clinical trials to be valid and unbiased, the plan must not be changed once the randomization code is broken and the study unblinded.

The VIGOR study was a double-blind, randomized outcomes study of upper gastrointestinal clinical events. We, as members of the steering committee, approved the study termination date of February 10, 2000, and the cutoff date of March 9, 2000, for reporting of gastrointestinal events to be included in the final analysis. Comparison of cardiovascular events was not a prespecified analysis for the VIGOR study.

At a time approaching the completion of the study, the data safety and monitoring board (the independent committee charged with overseeing any potential safety concerns) recommended to Merck that a data analysis plan be developed for serious cardiovascular events. The data safety and monitoring board stated that they did not feel it appropriate to bring this issue to members of the VIGOR steering committee since they were “not recommending a change to the trial conduct, simply that a prespecified plan be accomplished.”³ As a result, a cardiovascular data analysis plan was developed by Merck. Merck indicated that they chose the study termination date of February 10, 2000, as the cutoff date for reporting cardiovascular events to allow sufficient time to adjudicate these events.⁴ Per the data safety and monitoring board recommendation, we were unaware of the cutoff date for reporting of cardiovascular events.

Three additional myocardial infarctions in the rofecoxib group and one additional stroke in the naproxen group were reported between February 16 and February 22, 2000, after the prespecified February 10 cardiovascular cutoff date. These events were neither in the locked database used in the analysis for the VIGOR paper nor known to us during the review process. However, changing the analysis post hoc and after unblinding would not have been appropriate.

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Point 2: Not including these three myocardial infarctions made certain calculations and conclusions incorrect, resulting in an understatement of the difference in risk between rofecoxib and naproxen and the misleading conclusion that there was a difference in the risk of myocardial infarction between the aspirin indicated and aspirin not indicated groups.

Response: Tables 1 and 2 in the *Journal's* expression of concern show that the relative risks and 95 percent confidence intervals for myocardial infarction with rofecoxib versus naproxen were 4.25 (95 percent confidence interval, 1.39 to 17.37) without the three myocardial infarctions and 5.00 (95 percent confidence interval, 1.68 to 20.13) with the three myocardial infarctions. For patients without an indication for aspirin, an increase that is not statistically significant was seen without the three myocardial infarctions (relative risk, 2.25; 95 percent confidence interval, 0.63 to 10.02) and with the three myocardial infarctions (relative risk, 3.00; 95 percent confidence interval, 0.91 to 12.78). In patients with an indication for aspirin, there was a significant increase (relative risks, indeterminate [8/0]; 95 percent confidence intervals, 1.65 to indeterminate and 1.66 to indeterminate) in both analyses.

Assessment of the relative risks and widely overlapping 95 percent confidence intervals does not suggest a difference in the conclusions that can be drawn from the original data and the updated data. We do not accept, therefore, that the addition of three myocardial infarctions leads to qualitatively different conclusions. Furthermore, the analyses based on "aspirin indications" were post hoc subgroup analyses and therefore, wheth-

er or not the three myocardial infarctions are included, should be considered no more than hypothesis generating, requiring evaluation in other studies.

Point 3: Data on relevant cardiovascular adverse events were deleted from a presubmission draft of the manuscript two days prior to its initial submission.

Response: This statement incorrectly suggests that relevant cardiovascular events, including the three additional myocardial infarctions, were removed from the manuscript. Specifically, the editors indicate that a table of cardiovascular events was removed and that only percentages of events were provided without the actual numbers of cardiovascular events.⁵

Manuscripts commonly go through numerous iterations, and tables and figures are commonly deleted if the information can be captured in the text. The deleted table included information on death, cardiovascular death, myocardial infarctions, and ischemic stroke and is presented here in its original form (Table 1) to document that this information was presented in the text of the published manuscript. A composite that included these cardiovascular events plus one nonfatal hemorrhagic, nonthrombotic stroke (on rofecoxib) was in the table and not the text. The original table never included the three additional myocardial infarctions because they were not part of the locked database used for the analysis in the VIGOR paper.

In addition, providing percentages of events was an approach used for numerous end points throughout the article and not solely for cardiovascular events, and it was compliant with the Inter-

Table 1. Original Table of Cardiovascular Events from Presubmission Draft.

| Set of Events | Rofecoxib (N=4047) | Naproxen (N=4029) | Difference (95% CI) |
|--------------------------------------------|--------------------|-------------------|---------------------|
| All deaths | 22 (0.5%) | 15 (0.4%) | 0.1 (-0.15 to 0.49) |
| Cardiovascular deaths* | 7 (0.2%) | 7 (0.2%) | 0.0 (-0.21 to 0.21) |
| Cardiovascular death, nonfatal MI, or CVA† | 32 (0.8%) | 17 (0.4%) | 0.4 (0.01 to 0.73) |
| MI‡ | 17 (0.4%) | 4 (0.1%) | 0.3 (0.07 to 0.57) |
| Ischemic CVA§ | 9 (0.2%) | 7 (0.2%) | 0.0 (-0.17 to 0.27) |

* Includes sudden death, unknown cause of death, fatal myocardial infarction (MI), fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, and fatal gastrointestinal bleeding episode.

† Includes ischemic and hemorrhagic strokes.

‡ Includes serious adjudicated fatal and nonfatal myocardial infarction.

§ Includes serious adjudicated fatal and nonfatal ischemic cerebrovascular accidents (CVA).

national Committee of Medical Journal Editors requirements at the time of the VIGOR publication.

Thus, we stand by our original article, which was written in line with basic clinical trial principles, specifying that data must be analyzed according to plans that are determined before unblinding. Thrombotic cardiovascular events were not deleted from the manuscript, and there is no material difference in the conclusions that arise from the addition of the events reported after the predefined close-out date for cardiovascular events.

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1. 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.

2. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N Engl J Med* 2000;343:1520-8. *N Engl J Med* 2005;353:2813-4.

3. DSMB meeting minutes, December 1999.

4. Kim PS. An open letter from Merck. December 15, 2005. (Accessed February 23, 2006, at http://www.merck.com/newsroom/vioxx_withdrawal/Merck_Letter.swf.)

5. Winslow R, Westphal SP, Tesoriero HW. Medical journal says Merck study omitted key data. *Wall Street Journal*. December 9, 2005:A1.

TO THE EDITOR: We write in response to the expression of concern that was posted on the *Journal's* Web site on December 8, 2005, and appeared in the December 29, 2005, issue of the *Journal*.¹ We would like to address a few points.

First, the editorial states that three myocardial infarctions were not included in the 2000 *Journal* article² and suggests that this omission was inappropriate. In fact, these three myocardial infarctions on rofecoxib were not included simply because they were reported to Merck after the prespecified cutoff date for the primary analysis of cardiovascular events in the trial. Utilizing the prespecified cutoff date also resulted in an additional stroke on naproxen not being included in the article. Adherence to a prespecified plan is routine and appropriate when reporting scientific data precisely because this practice avoids later allegations that data were manipulated.

The editorial has also been misconstrued to be asserting that information obtained from a computer diskette shows that data (including the three myocardial infarctions in the rofecoxib group) "were deleted from the manuscript two days before it was initially submitted to the *Journal* on May 18, 2000." In fact, the draft manuscript submitted electronically to the *Journal* showed only the deletion of a header and footers for a table discussing cardiovascular events in the study. The table on the diskette did not include any data. (Indeed, no table containing post-cutoff cardiovascular events was ever included in any draft prior to submission of our paper. It is the case that an early draft of our manuscript included some pre-cutoff cardiovascular data in a table, and relevant data were moved from this table to text.) In fact, we did not know of the additional unblinded, adjudicated myocardial infarctions in the rofecoxib group at the time our manuscript was submitted to the *Journal* in May 2000.

Second, the editorial states that the omission of the post-cutoff date events rendered certain of the conclusions in the article incorrect. We disagree. The article clearly disclosed that there was

a significant difference in the rates of myocardial infarction in the Vioxx and naproxen arms of the study and reported those rates as 0.4 and 0.1, respectively, with a relative risk reported as 0.2. The inclusion of the post-cutoff date myocardial infarctions changes the Vioxx rate to 0.5 but does not meaningfully change the relative risk or the conclusion that there was a significant difference between the two arms of the study. Indeed, with such a small number of events (which were not a primary end point of the study) — and with such wide confidence intervals around them — it is difficult to imagine that this small numerical change could affect the interpretation of the data.

The editorial also notes that the rate among the non-aspirin indicated subgroup would have been changed from 0.2 to 0.3 by the inclusion of the post-cutoff date events. Nonetheless, as Table 2 of the editorial demonstrates, the disparity in this subgroup remains not statistically significant, as we reported in the article. The notable finding was in the subgroup of patients who were indicated for aspirin for secondary prophylaxis (but were not receiving aspirin), where there were eight myocardial infarctions on Vioxx and none on naproxen. The lack of events on naproxen was notable in this high-risk group, and these data did not change with the inclusion of the additional events.

We believe it is important to emphasize that Merck consistently made full and appropriate disclosures of the cardiovascular results from VIGOR. First, Merck voluntarily announced the difference in thromboembolic event rates in March 2000. Second, Merck asked the FDA for accelerated re-

view of labeling that would disclose the VIGOR results. Third, the three post-cutoff myocardial infarctions were promptly disclosed to the FDA and were discussed at the public February 2001 FDA advisory committee. Finally, the additional data were included in subsequent communications about VIGOR, including journal articles, the FDA-approved label, Merck press releases, and a transmittal letter to physicians that accompanied copies of the *Journal* VIGOR article provided by Merck. The authors of the *Journal* editorial acknowledge that they learned of the post-cutoff date events in 2001 as a result of Merck's disclosures.

We and our coauthors worked diligently to present the VIGOR data in what we believed to be a scientifically appropriate manner. In light of the view expressed by the authors of the editorial that they would like to have seen the post-cutoff date events prior to publication, we regret not providing them with those data. However, we stand firmly behind the propriety of the scientific analysis and presentation of data in the paper, as well as Merck's prompt disclosure of the post-cutoff date events to the FDA and the medical community.

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1. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis." *N Engl J Med* 2000;343:1520-8. *N Engl J Med* 2005;353:2813-4.

2. 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.

Epidemic *Clostridium difficile*

TO THE EDITOR: The two articles by McDonald et al.¹ and Loo et al.² (Dec. 8 issue) document the spread of NAP1 *Clostridium difficile* isolates of toxinotype III in North America. This emerging strain is thought to be more virulent than earlier strains, perhaps related to its increased capacity to produce toxins.³ However, NAP1 is not solely responsible for the increasing prevalence and severity of *C. difficile*-associated disease. At our hospital, the rate of *C. difficile*-associated disease has greatly increased, and we have documented substantial treatment failure and mortality.⁴ Only 18

percent of isolates have been of the epidemic NAP1, toxinotype III strain; most were NAP2, toxinotype 0. Whereas McDonald et al. found that NAP1 caused at least 50 percent of *C. difficile*-associated disease at five hospitals, non-NAP1 strains predominated at three others.

Thus, the overall burden of *C. difficile*-associated disease may be attributable, in part, not only to the spread of new, potentially more virulent NAP1 isolates but also to other factors, such as the presence in hospitals of older, debilitated adults with a greater severity or range of underlying dis-