Acute Ischemic Heart Disease

Under-reporting of cardiovascular events in the rofecoxib Alzheimer disease studies

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Background In September 2004, rofecoxib (Vioxx) was removed from the market after it was found to produce a nearly doubling of cardiovascular thrombotic (CVT) events in a placebo-controlled study. Its manufacturer stated that this was the first clear evidence of such risk and criticized previous analyses of earlier CVT risk for focusing on investigator-reported events. We studied contemporaneously adjudicated CVT events to assess the information on cardiovascular risk available while the drug was in widespread use.

Methods Using an intention-to-treat analysis of adjudicated CVT deaths, we analyzed detailed patient-level data collected during 3 randomized placebo-controlled trials of rofecoxib versus placebo that had been designed to define the drug’s possible role in the prevention or treatment of Alzheimer disease. All trials had been completed by April 2003.

Results In the 3 studies combined, the data indicated that rofecoxib more than tripled the risk of confirmed CVT death (risk ratio = 3.57 [1.48-9.72], P = .004). This finding reached the P < .05 level of significance by June 2001.

Conclusion Intention-to-treat analysis of placebo-controlled studies of rofecoxib for Alzheimer disease demonstrated that the drug produced a significant increase in confirmed CVT deaths nearly 40 months before it was removed from the market. By contrast, published analyses of these trials were restricted to on-treatment analyses (ending 14 days after cessation of treatment) that did not reveal this risk. Intention-to-treat analyses of clinical trial data can reveal important information about potential drug risks and should be performed routinely and reported in a timely manner. (Am Heart J 2012;164:186-93.)

On September 30, 2004, Merck & Company withdrew the COX-2 inhibitor rofecoxib (Vioxx) from the market after an interim safety analysis indicated that the drug produced a significant increase in the risk of cardiovascular thrombotic (CVT) events in the placebo-controlled Adenomatous Polyp Prevention on Vioxx (APPROVe) trial. This analysis prompted the trial’s Data Safety and Monitoring Board (DSMB) to recommend early termination of the study. The manufacturer’s chief executive officer assured Congress that it had not acted until September 2004 because all of its prior “clinical data… had shown no difference” in cardiovascular risk “between Vioxx and placebo.”

Even before the Food and Drug Administration (FDA) had approved the drug, the possibility of cardiovascular risk with selective COX-2 inhibition had been suggested by prior pharmacological hypotheses as well as evidence of a possible proatherogenic effect in a Merck-sponsored study. These findings, company scientists noted in 1998, “raised concern about the potential for VIOXX to predispose to thrombotic cardiovascular (CV) events.” Additional questions about the cardiovascular safety of rofecoxib arose in 2000 when the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, comparing rofecoxib with naproxen in patients with rheumatoid arthritis, found that rofecoxib caused a significantly increased risk of confirmed CVT events (risk ratio [RR] = 2.37, P = .002), including a 5-fold higher incidence of myocardial infarction. The lack of a placebo control in VIGOR complicated the interpretation of these findings. The drug’s manufacturer stated that the difference seen in VIGOR was likely the result of a cardioprotective effect of naproxen rather than a toxic effect of rofecoxib.

In March 2000, shortly after the preliminary results from the VIGOR trial became available to the company, it sought to evaluate the possible relation between...
rofecoxib and cardiovascular disease. According to its chief executive officer, “[B]ecause the VIGOR study compared two drugs—Vioxx and naproxen—and not Vioxx and placebo,” the company “took the step of looking into data” from ongoing placebo-controlled trials it “had already initiated.”2 Specifically, it unblinded safety data from 2 trials it had undertaken in which patients with early memory impairment or diagnosed Alzheimer disease (AD) were randomly assigned to receive rofecoxib or placebo. The studies had been based on the hypothesis that the anti-inflammatory effect of rofecoxib might slow or reverse the postulated inflammatory aspects of neurodegeneration in that condition.

One of the 2 trials—Protocol 091—investigated whether rofecoxib slowed the progression of AD, whereas the other—Protocol 078—studied whether it prevented the onset of AD in patients with mild cognitive impairment. Ultimately, the manufacturer undertook a third study—Protocol 126—which, like Protocol 091, investigated the efficacy of rofecoxib in retarding the progression of AD. We refer collectively to these as the “AD studies.” In late 2004, following the withdrawal of Vioxx, the company, referring to studies 078 and 091, reported that it had found “no difference in cardiovascular event rates in these two trials,”2 and the president of its research program concluded that “the most plausible explanation for the VIGOR results was that naproxen was exerting a cardioprotective effect” and not that rofecoxib increased CVT risk.9

In other statements, the manufacturer cited the benign safety data in its AD trials as evidence that the drug was not known to impose a risk of CVT events until the unanticipated data seen in the APPROVe trial that precipitated market withdrawal.10 “APPROVe was the first study,” the manufacturer declared, “to show a statistically increased increased risk of cardiovascular thrombotic events with rofecoxib 25 mg versus placebo,”11 the dose used in the AD studies.

As is customary in randomized clinical trials, the company had designed all 3 of the AD studies to be evaluated on an intention-to-treat (ITT) basis and had collected follow-up data regardless of whether the patient continued to take the study medication. The study protocols and data analysis plans had prespecified ITT as well as on-treatment safety analyses.12-14 However, the cardiovascular safety analyses that were ultimately presented to the scientific community from these trials focused on “confirmed” CVT events, that is, CVT events that were confirmed via an adjudication process. Other than for deaths, this process, however, discarded all events that occurred >14 days after discontinuation of drug therapy, thereby precluding an ITT analysis of confirmed events. Instead, the company presented “on-treatment” analysis only.

One published ITT analysis of investigator-reported CVT events in the AD and other placebo-controlled studies did show a statistically significant elevated CVT risk as early as June 2001,15 but the manufacturer dismissed this finding on the grounds that the investigator-reported outcome data used were “less reliable.”16 Because ITT represents the standard scientific and regulatory approach for analysis of clinical trial data,17,18 we set out to determine whether the planned ITT analysis of confirmed CVT events, necessarily restricted to deaths, in the AD studies would have revealed any evidence of CVT risks associated with rofecoxib before its withdrawal. We also set out to explore any lessons the rofecoxib experience holds for designing, conducting, analyzing, and reporting randomized controlled trials as well as for regulatory oversight and monitoring of drug safety.

**Methods**

**Data sources**

Protocol 078 was a placebo-controlled, parallel-group, 48-month, double-blind study that enrolled 1,457 patients >65 years old with mild cognitive impairment and randomized them to treatment with 25 mg rofecoxib daily or placebo. The primary end point was the development of AD, as determined by a battery of neuropsychological tests and referred to in study documents as “conversion.” The study began in April 1998, and data collection was completed on the last patient in April 2003. Protocol 091 was a placebo-controlled, parallel-group, 12-month, double-blind study that enrolled 691 patients >50 years old diagnosed with possible or probable AD and randomized them to treatment with 25 mg rofecoxib daily or placebo. The primary end point was a prespecified measure of cognitive decline, likewise measured by detailed neuropsychological testing. The study started in February 1999, with data collection on the last patient ending in November 2000. Protocol 126, which began in April 2000, was similar to Protocol 091 in its design, enrollment, and end points and enrolled 756 patients. It was terminated in March 2001 because of the lack of efficacy observed in Protocol 091. These studies were subjected to several interim and sometimes previously unscheduled unblindings and analyses.

We obtained from the manufacturer complete patient-level data for all 3 trials that it provided in litigation initiated by patients who had taken Vioxx.19 We then carried out an ITT analysis of data from each trial using “confirmed CVT” events as per the company’s protocol. Specifically, we carried out a “modified ITT” approach that included all patients who consumed at least one dose of study drug. In 1998, because of concern over the possible cardiotoxicity of rofecoxib, the manufacturer had initiated a standard operating procedure to adjudicate investigator-reported CVT events in all of its future randomized controlled trials of rofecoxib. This was in response to questions raised about the potential for selective COX-2 agents to cause a prothrombotic imbalance between thromboxane and prostacyclin production.3,20 In this process, during company-sponsored trials of rofecoxib, an independent panel of adjudicators blinded to treatment assignment considered all potential CVT events that were reported by site investigators to determine (via majority vote) whether the evidence furnished by the site investigator was sufficient to designate each as a “confirmed CVT event.”
All deaths were also adjudicated by the manufacturer as part of this process, including those occurring off-treatment, defined as >14 days after the last dose of the study drug, as well as on-treatment. By contrast, the company did not adjudicate nonfatal investigator-reported CVT events occurring off-treatment. Our own ITT analysis of confirmed CVT events, therefore, could be performed only for CVT deaths.

We used the computer language Perl and the statistical software R (version 2.9.1) to extract relevant data and conduct statistical analysis, respectively.

Main outcome measure

We prespecified one outcome measure for the present study: confirmed (ie, contemporaneously adjudicated by the manufacturer) CVT deaths.

Data analysis

All analyses presented below include all randomized patients who took at least one dose of study medication in any of the 3 AD trials. Following the manufacturer’s practice, we computed incidence rate ratios, stratified by study, with 2-sided P values and CIs derived from exact methods.21 Specifically, we present adjusted conditional maximum likelihood rate ratio estimates with mid-P exact CIs and P values. A Mantel-Haenszel analysis22 produces qualitatively similar results. The present analyses followed the ITT principle and considered each patient in the treatment group originally assigned, including all events regardless of whether the patient was taking the study medication at the time of the event. For comparative purposes, we also replicated the company’s on-treatment analyses; these are also reported.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

The ITT analyses revealed a highly significant tripling or quadrupling of the CVT mortality rate in patients who had been randomized to receive rofecoxib in these studies. Considering participants in all 3 Alzheimer studies combined, there were 20 confirmed CVT deaths in the rofecoxib arm versus 6 CVT deaths in the placebo arm (RR = 3.57 [1.48-9.72], P = .004). In many of its CVT analyses, including data it discussed in rofecoxib labeling approved in April 2002, the manufacturer pooled data from Protocols 078 and 091. In these 2 studies, our ITT analysis found 20 confirmed CVT deaths in the rofecoxib group versus 5 in the placebo group (RR = 4.29 [1.68-12.82], P = .001). In the ITT analysis of Protocol 078, which had nearly 3 times as many patient-years of rofecoxib and placebo (“placebo-controlled”) exposure than Protocols 091 and 126 combined, we found 17 confirmed CVT deaths in patients randomized to rofecoxib versus 4 for placebo (RR = 4.59 [1.63-15.89], P = .003).

For comparative purposes, we then conducted the on-treatment analytic approach used by the company and its consultants in the published reports of these studies. We applied this analytic approach to all 3 Alzheimer studies combined, considering only those deaths occurring within 14 days of the last study drug dose. This depicted a much smaller number of deaths in patients taking rofecoxib and a nonsignificant difference

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PYR, Patient years at risk; #, number of confirmed CVT deaths; n, number of patients.
compared with placebo: 11 confirmed CVT deaths on rofecoxib versus 6 on placebo (RR = 2.07 [0.77-6.06], P = .15). Similarly, in Protocols 078 and 091, the on-treatment analysis depicted 11 CVT deaths with rofecoxib versus 5 on placebo (RR = 2.50 [0.88-8.00], P = .09). In Protocol 078, 8 confirmed CVT deaths were reported on-treatment for rofecoxib versus 4 for placebo (RR = 2.31 [0.70-8.80], P = .18).

Table I displays the comparative numbers of confirmed CVT deaths using ITT analyses of the AD studies as of various significant dates. The manufacturer performed interim analyses of these trials with cutoff dates of September 15, 2000, and March 16, 2001. For all 3 Alzheimer studies combined, as early as September 15, 2000, ITT analysis would have revealed that there were 8 confirmed CVT deaths in the rofecoxib arm versus 2 for placebo (RR = 4.22 [0.98-29.1], P = .055). As of March 16, 2001, ITT analyses demonstrated 10 confirmed CVT deaths with rofecoxib versus 4 with placebo (RR = 2.64 [0.85-9.72], P = .097). By April 11, 2002, the date major new rofecoxib labeling was approved, ITT analyses showed 17 confirmed CVT deaths in patients randomized to rofecoxib versus 6 for placebo (RR = 3.03 [1.23-8.39], P = .015). This difference in mortality risk was not included in the new label information.

Table II displays data on confirmed CVT deaths as of these same dates that were counted by the manufacturer using its on-treatment analyses of these data. In contrast to the ITT analyses we performed, none of these results was statistically significant.

### Discussion

The manufacturer stated that it withdrew rofecoxib from the market in September 2004 because of new findings of increased cardiovascular risk first detected in the placebo-controlled APPROVe study, which it said were completely unanticipated. However, our analyses present evidence that the conventional ITT analyses of 3 placebo-controlled clinical trials that had been prespecified by the company would have revealed meaningful increases in CVT events with rofecoxib years earlier. These analyses are at odds with the manufacturer’s statements that APPROVe provided the first evidence of significantly greater CVT risk with rofecoxib versus placebo. The analyses performed by the manufacturer and its consultants and published in the literature reported only on-treatment safety events, truncating consideration of all adverse events that occurred N14 days after the last dose of a study drug.

Data from early 2000 had demonstrated its association with a significant increase in the rate of myocardial infarction with rofecoxib in the randomized VIGOR trial, which Merck dismissed because it was not placebo-controlled. Instead, the company reported “nonsignificant” differences in cardiovascular risks based on on-treatment analyses it had conducted of its large randomized controlled trials in Alzheimer patients comparing rofecoxib with placebo; but it did not report the planned ITT analyses of the drug’s safety in these studies.

A previous report calculated ITT rates of all-cause mortality but did not analyze the centrally important outcome of CVT toxicity, the drug’s most salient adverse
event. Another article using an ITT approach found a statistically significant increase in CVT events with rofecoxib derived from a pooled analysis of all randomized placebo-controlled trials of the drug sponsored by the manufacturer before September 2004 as well as the AD studies alone. However, that study was exclusively based on investigator-reported CVT events, an approach that was criticized by the manufacturer, which claimed it had subjected such events to a more “accurate” and “rigorous” procedure to identify events that “were confirmed by ... blinded external adjudicators as thrombotic.” A research letter reported an increase in investigator-reported CVT events during off-drug follow-up in 1 of the 3 Alzheimer trials, Protocol 078. The present study is the first to focus on cardiovascular events in all of the Alzheimer studies using an ITT analysis based on confirmed CVT events.

Need for ITT analysis

Our analysis reveals that the planned ITT analyses would have demonstrated that rofecoxib causes a statistically significant increase in confirmed CVT events in randomized, placebo-controlled trials as early as April 2002, >2 years before the drug was withdrawn from the market for this reason. We found that this increase in confirmed CVT deaths became statistically significant as early as June 2001, 39 months before market withdrawal. This contrasts with the reported on-treatment analyses, which consistently resulted in a smaller number of events and failed to show such an association at a level of statistical significance. This is all the more important because the ITT approach is generally seen as tending to dilute any such risk signals. Instances where ITT and on-treatment analyses differ in their implications have arisen in the past. More than 30 years ago, a clinical trial of sulfinpyrazone in the prevention of cardiac death after myocardial infarction provoked considerable controversy over conclusions that depended in part on the handling of off-drug deaths. The FDA in that instance weighed in on the side of the ITT approach. An ITT analysis of a placebo-controlled trial of diltiazem in myocardial infarction patients showed no significant effect of treatment. The literature is replete with examples of studies where analyses restricted to adherent patients disagree with ITT analyses.

These findings have important implications for the design, conduct, analysis, and reporting of randomized controlled trials. When safety is at issue, it is important to cast the widest possible net. Prospective protocols and data analysis plans prespecifying ITT analysis should not be disregarded or altered without good reason, especially if doing so decreases the amount of safety data to be analyzed. Moreover, whenever possible, ITT analysis should be undertaken and reported, particularly when, as here, patients have already been followed off-treatment, irrespective of whether ITT analysis was prespecified. Although this should be a universal practice, it is even more important when analyzing the cardiovascular risks of a drug that was already known to have a pathophysiological basis for predisposing to atherogenicity, hypertension, and congestive heart failure.

Similar analytic issues occurred with evaluating clinical outcomes of the APPROVe study, which the company initiated to determine the utility of rofecoxib in patients with colonic polyps. As the report on the Merck-sponsored 1-year ITT extension of the APPROVe study observed: “For chronic disease endpoints, such as myocardial infarction and stroke, we cannot assume that a high risk will dissipate within a few weeks of the end of treatment. If a drug has lingering effects or needs a latent period before an effect becomes evident, then an on-treatment analysis can provide only an incomplete picture of its toxicity.” In fact, subsequent follow-up ITT analysis of all randomized participants in the APPROVe study for at least 1 year off-treatment revealed that the risk of some rofecoxib-associated cardiovascular events persisted for at least 1 year after treatment cessation. Inclusion of off-treatment as well as on-treatment CVT events in the APPROVe analysis also demonstrated an important aspect of the onset of cardiovascular risk, which was found to increase very soon after the start of treatment. A recent as-yet unpublished study documenting an excess hypertension rate due to rofecoxib achieving statistical significance within 1 month of initiation of the VIGOR trial linked the appearance of this known precursor to serious cardiovascular events to the early emergence of serious CVT events in the ITT follow-up of the APPROVe population.

Regulatory implications

Five months after rofecoxib was withdrawn, but before any ITT analyses were made public, the FDA medical reviewer assigned to rofecoxib stated that the company’s AD trials presented “the most important” and “most relevant data” concerning the drug’s cardiovascular safety for the agency. Because they encompassed “at least 3 years” of “placebo-controlled” data, FDA “put a lot of weight on this information.” Based on the on-treatment results, the manufacturer and its consultants consistently reported that the AD trials did not indicate an excess of investigator-reported or confirmed CVT events with rofecoxib. In a December 18, 2001, submission to FDA, the manufacturer even stated that “if there is any trend in the data on cardiovascular events, it is in favor of Vioxx over placebo.” On February 16, 2005, members of and voting consultants to 2 FDA advisory committees meeting on rofecoxib expressed the need for ITT analysis. One FDA consultant stated that “if this is a pro-atherogenic therapy, it is going to persist quite a while after you stop the drug,
... we need to see [an] intent-to-treat analysis," adding that it was a “mistake” to censor events after 2 weeks. The FDA’s medical reviewer agreed with the committee chair that an ITT analysis would have been important. But when one FDA consultant inquired about off-treatment cardiovascular mortality data in the AD studies, he was told that they were not available. No ITT CVT data from the Alzheimer studies were presented or analyzed in any publicly available FDA reviews of these studies or of rofecoxib.

Consideration of ITT data could also have had important implications for how rofecoxib was labeled. The labeling FDA approved on April 11, 2002, stated that “mortality due to cardiovascular thrombotic events was 8 vs. 3 for VIOXX versus placebo, respectively” in “2 placebo-controlled studies” in “2,142 elderly patients,” namely, Protocols 078 and 091. This labeling was never updated as long as the drug was on the market. The “8 vs. 3” comparison was for confirmed CVT deaths occurring on-treatment in Protocols 078 and 091, a near tripling of the point estimate that was not statistically significant (RR = 2.97 [0.81-13.82], P = .10). This enabled the manufacturer to state that “[i]n April 2002, the FDA approved the revised Vioxx prescribing information, reflecting ... interim data from long-term placebo-controlled studies in elderly patients with Alzheimer’s disease which did not show an increased cardiovascular risk.”

However, the originally planned ITT analyses would have revealed substantially greater risks and statistically significant disparities. As of March 16, 2001, the cutoff used for the VIGOR-based labeling approved on April 11, 2002, the planned ITT analysis would have revealed that there were 10 confirmed CVT deaths in patients randomized to rofecoxib versus 3 in the placebo groups in Protocols 078 and 091 (RR = 3.53, P = .045). Subsequent ITT analysis found that, as of April 11, 2002, the date FDA approved this labeling, there had been 17 confirmed CVT deaths on rofecoxib versus 5 on placebo in these 2 trials (RR = 3.65, P = .007).

An external DSMB might have raised concerns about the AD trials as they progressed. The FDA assumed that a DSMB was providing oversight for Protocol 078; and indeed, the original protocol for 078 called for a DSMB. However, none of the AD trials had a DSMB.

To prevent recurrence of similar situations in the future, we recommend that regulatory agencies require trial designs that use ITT analyses and routinely undertake ITT safety analyses of randomized controlled trial data. We also recommend that regulators ensure the presence of a DSMB whenever appropriate—certainly for large clinical trials of medications with known potential for safety problems and particularly when the study population is by definition elderly.

Data on adverse events occurring within clinical trials are sometimes considered proprietary information owned by the company that sponsored the study and not made available by governmental regulatory bodies to the public or to researchers. This policy may require reassessment in the name of public health. The requirement that data from completed trials be presented on the federal Web site ClinicalTrials.gov, which is also more enforceably mandated by the FDA Amendments Act of 2007, will also be useful in this regard in that it will require the public depiction of all clinical outcomes, including adverse events, even if belatedly. However, presentation of such data will still depend on the study design chosen by the study sponsor. This will be influenced not only by analytic design, as demonstrated here, but also by the way adverse events are determined and adjudicated. Studies that assess safety-related events through specific inquiries find higher event rates than those that use only global questions about “side effects.” Finally, the current structure of adverse event listings in ClinicalTrials.gov makes it difficult to assess rates of adverse events at the patient level. Instead, counts are provided for specific diagnoses, rather than people. As a result, it is impossible to know whether cases involving, for example, one report each of angina, myocardial infarction, stroke, or cardiac death represent 1 participant, 4, or any number in between. Subsequent refinements to the rules governing this data repository may address this important problem.

All-cause mortality

In the AD trials, in addition to the CVT mortality discussed above, rofecoxib was also associated with a statistically significant near doubling of all-cause mortality: 61 deaths were reported on rofecoxib versus 34 deaths on placebo (RR = 1.91 [1.25-2.90], P = .003). However, the manufacturer disputed that there was any trend in the all-cause mortality data on the grounds that it found no statistically significant difference in confirmed CVT deaths between rofecoxib and placebo in its Alzheimer studies. This analysis, however, excluded confirmed CVT deaths that occurred >14 days after drug discontinuation.

In background information furnished to FDA advisory committees meeting on rofecoxib safety on February 16, 2005, the company noted “the difference between rofecoxib and placebo in overall mortality did not reflect any increases in particular types of events to suggest causality in the Alzheimer's studies.” In its publication on Protocol 078 in a peer-reviewed journal, Merck scientists and others similarly observed that “[p]atients died from a range of causes that were consistent with expectations for an elderly population, and there was no specific pattern as to the cause of death in either treatment group.” Although it discussed “off-treatment” as well as on-treatment fatal adverse events, such as myocardial infarctions and cardiac arrests, this publication did not provide comparative totals of confirmed CVT
decades earlier,52,53 rofecoxib has come to epitomize that, for patients in the VIGOR trial who were not data from Merck-conducted clinical trials, which demon-
strate that, for patients in the VIGOR trial who were not taking corticosteroids, the drug's widely reported gastro-
protective effect was not seen. Like thalidomide 4 decades earlier,52,53 rofecoxib has come to epitomize lessons that can be learned for the more appropriate management of drug risk.

Whereas the potential of rofecoxib to cause cardiovas-
cular toxicity may have been anticipated, for many other drugs, important adverse effects do not come with as much advance warning; examples include the valvu-
opathy caused by the anorexiant dexfenfluramine (Redux) or the drug-drug interactions of the antihistamine terfenadine (Seldane) or the calcium-channel blocker mibebradil (Posicor). These findings indicate that a proactive approach to adverse event analysis, including rigorous ITT analyses supervised by an independent DSMB, should be a routine aspect of all drug trials.

Disclosures

Conflict of interest: Drs. Avorn, Furberg, Madigan, and Mayer have served as consultants for plaintiffs in litigation against Merck & Co Inc related to rofecoxib. Dr. Avorn did this work pro bono and did not receive any compensation. Mr. Sigelman previously represented plaintiffs in litigation against Merck & Co Inc related to rofecoxib.

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