

## HEALTH CARE REFORM

# Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data

## Lessons for Postmarket Pharmaceutical Safety Surveillance

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**Background:** In September 2004, rofecoxib was voluntarily withdrawn from the worldwide market. Our objective was to determine whether and when analysis of published and unpublished placebo-controlled trials could have revealed cardiovascular risk associated with rofecoxib before its withdrawal as an example to inform future post-market pharmaceutical safety surveillance efforts.

**Methods:** We conducted a cumulative subject-level pooled analysis of data from all randomized, placebo-controlled trials of rofecoxib conducted by the manufacturer before September 2004. Our main outcome measurement was incidence of any investigator-reported death from any cause or cardiovascular thromboembolic (CVT) adverse event.

**Results:** We identified 30 randomized, placebo-controlled trials of rofecoxib that enrolled a combined 20 152 subjects. Trial duration ranged from 4 weeks to 4 years; enrollment ranged from 17 to 2586 subjects prescribed either rofecoxib or placebo; and rofecoxib dose ranged from 12.5 mg to 50 mg. As of December 2000, 21 of these trials had been com-

pleted (70%), and the risk of a CVT adverse event or death was greater among subjects assigned to the rofecoxib group (rate ratio [RR], 2.18; 95% confidence interval [CI], 0.93-5.81) ( $P = .07$ ), raising concerns from a safety standpoint. Subsequently collected data through June 2001 showed that rofecoxib was associated with a 35% increased risk of a CVT adverse event or death (RR, 1.35; 95% CI, 1.00-1.96) ( $P = .05$ ). Analyzing data available as of April 2002, we found a 39% increased risk (RR, 1.39; 95% CI, 1.07-1.80) ( $P = .02$ ), and using data available as of September 2004, we found a 43% increased risk (RR, 1.43; 95% CI, 1.16-1.76) ( $P < .001$ ).

**Conclusion:** Cumulative pooled analysis of all randomized, placebo-controlled trials demonstrates a trend toward increased cardiovascular risk associated with rofecoxib compared with placebo as early as December 2000, the comparison reaching a  $P$  value of .05 by June 2001, nearly 3½ years before the manufacturer's voluntary market withdrawal.

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**D**URING ITS BRIEF AVAILABILITY on the worldwide market, rofecoxib, a selective cyclooxygenase 2-selective agent, was a striking commercial success, its sales reaching \$2 billion annually soon after its introduction in

*See also pages 1969  
and 2024*

May 1999. Merck & Co Inc, Whitehouse Station, New Jersey (hereinafter, "Company"), the maker of rofecoxib under the brand name Vioxx, promoted it as a safer alternative to traditional nonsteroidal anti-inflammatory drugs (NSAIDs), although there were concerns about its cardiovascular adverse effects early in its development, years before its launch.<sup>1,2</sup> In Septem-

ber 2004, the manufacturer voluntarily withdrew rofecoxib from the market after an interim safety analysis indicated that the drug was associated with increased risk of cardiovascular events within the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.<sup>3</sup> The APPROVe trial, which tested the hypothesis that rofecoxib reduced the risk of colon polyp recurrence

*See Invited Commentary  
at end of article*

(and thus colorectal cancer), was terminated early by its data safety and monitoring board (DSMB). In November 2004, the manufacturer's chief executive officer testified to the United States Senate Committee that "Until data from [APPROVe] . . . , the combined data from randomized con-

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trolled clinical trials showed no difference in confirmed cardiovascular event rates between Vioxx and placebo.”<sup>4</sup>

Today, the medical community acknowledges the cardiovascular risks associated with rofecoxib.<sup>5-7</sup> A “scientific statement by the American Heart Association”<sup>8</sup> affirmed that selective cyclooxygenase 2 inhibitors have adverse cardiovascular effects, including increased risk for myocardial infarction, stroke, heart failure, and hypertension. A pertinent question is whether the US Food and Drug Administration (FDA) and the manufacturer could have known before the time of its withdrawal that rofecoxib increased the risk of cardiovascular events compared with placebo through the analysis of the manufacturer’s published and unpublished clinical trial data. Three Company-sponsored and -conducted meta-analyses reported no increased cardiovascular risk associated with the drug while it remained on the market in 2001,<sup>9</sup> 2002,<sup>10</sup> and 2003,<sup>11</sup> although none of the 3 focused specifically on placebo-controlled studies or used all available data.

This question is particularly relevant as we consider current and future challenges in drug safety monitoring. Can the example of the rofecoxib experience inform and improve the approach used by industry and regulators to conduct postmarket pharmaceutical safety surveillance? If all available data, both published and unpublished, had been independently and iteratively analyzed, could the increased cardiovascular risk compared with placebo have been known earlier? Understanding whether this approach may be informative is of even greater importance after the September 2007 enactment of the FDA Amendments Act (FDAAA) in the United States, which requires the sponsors of all drug, biological, and device trials not only to register their studies at inception in the publicly available ClinicalTrials.gov database (with the exception of phase I clinical trials) but also to update the registry for approved drugs and devices within 12 months of study completion (24 months if the studied drug is under review at the FDA) to include primary and principal secondary outcomes as well as safety outcomes from the trial results. Therefore, our objective was to determine whether and when analysis of published and unpublished placebo-controlled trials could have revealed cardiovascular risk associated with rofecoxib before its withdrawal, using the manufacturer’s trial data made available through the rofecoxib litigation, as an example to inform future postmarket pharmaceutical safety surveillance efforts.

## METHODS

### DATA SOURCE

We included in our analyses all randomized clinical trials that compared rofecoxib with placebo and were completed as of termination of the APPROVe trial.<sup>3</sup> Consistent with the manufacturer’s protocol for earlier meta-analyses of rofecoxib, we included only trials that examined adults using rofecoxib at daily doses of 12.5 mg or more for 4 weeks or longer and excluded data from trial arms using rofecoxib in other doses or for shorter time periods.<sup>9-11</sup> In addition, we included only data from subjects enrolled in the clinical trials who took at least 1 dose of the study drug (rofecoxib or placebo). We excluded data from

6 trials that did not include a placebo arm (eFigure, <http://www.archinternmed.com>). In addition, we excluded data from 2 large ongoing trials that were terminated shortly after the APPROVe trial and the market withdrawal of the drug: “Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer”<sup>12</sup> (hereinafter, “the VICTOR trial”) and the “Vioxx in Prostate Cancer Prevention study”<sup>13</sup> (hereinafter, “the ViP trial”). At the time of termination, both of these trials had enrolled 25% to 33% of the planned number of subjects for a median treatment duration of 7.4 and 4.1 months, respectively.<sup>12,13</sup> However, data from these trials were not pooled with APPROVe data at its termination to evaluate rofecoxib’s safety. A complete list of the randomized clinical trials included in this analysis is provided in **Table 1**.

### DATA SOURCE VALIDATION

To confirm that the data made available by the manufacturer were accurate, we compared the following characteristics of the data made available through the rofecoxib litigation with the data published within trial manuscripts or data reported to the FDA as part of each trial’s clinical study report: number of study subjects, mean age, and proportion of women in each trial arm (eTable 1).

### MAIN OUTCOME MEASURE

Our prespecified outcome measure for the present study was incidence of any investigator-reported death or cardiovascular thromboembolic (CVT) adverse event that occurred in an enrolled clinical trial subject. As prespecified by the Company, all trials collected adverse event data on subjects either while they were using the study medication (rofecoxib or placebo) or within 14 days after they stopped using it. In addition, studies 078, 091, and 122 collected adverse event data on subjects beyond 14 days after they stopped using the study drug until study termination. For these trials, all available data were used in an intention-to-treat fashion, the gold standard approach for analysis of clinical trial data.<sup>35</sup>

The randomized controlled trials conducted by the Company used either Clinical and Regulatory Information Strategic Program (CRISP) or Medical Dictionary for Regulatory Activities (MedDRA) terms for the reporting of trial adverse events; approximately 50% of trials used each set of terms. The CRISP is the Company’s clinical data system medical terminology, and MedDRA is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. We identified CVT events from lists of terms used by both the CRISP and MedDRA systems. Two of us (J.S.R. and H.M.K.) independently reviewed all adverse event terms used by the medical terminology systems and categorized those terms that represented CVT events without knowledge of the effect on the results. Disagreements were resolved by consensus. Examples of selected terms include *acute myocardial infarction*, *embolic stroke*, and *unstable angina*. The complete list of included CVT event terms is provided in eTable 2.

### DATA ANALYSIS

All statistical analyses used subject-level data and did not pool summary information. We first calculated event rates and relative risks using Cox proportional hazards models stratified by study with treatment as the sole covariate. To replicate the manufacturer’s analytical practice,<sup>3</sup> if there were fewer than 11 events in either study arm, we computed the rate ratio by using exact meth-

**Table 1. Randomized, Placebo-Controlled Rofecoxib Trials of 4 Weeks' Duration or Longer Conducted by Merck & Co Inc Included in Analyses**

Source	Trial No.	Indication Studied	Intervention		Planned Duration, wk	LPO
			Rofecoxib Dose, mg	Control		
Ehrich et al, <sup>14</sup> 1999	010	Osteoarthritis	25 and 125	Placebo	6	February 8, 1996
Ehrich et al, <sup>15</sup> 2001	029	Osteoarthritis	12.5, 25, and 50	Placebo	6	February 5, 1997
Saag et al, <sup>16</sup> 2000	033	Osteoarthritis	12.5 and 25	Placebo	6	November 18, 1997
Day et al, <sup>17</sup> 2000	040	Osteoarthritis	12.5 and 25	Placebo	6	January 1, 1998
Laine et al, <sup>18</sup> 1999	044	Osteoarthritis	25 and 50	Placebo	24	February 18, 1998
Hawkey et al, <sup>19</sup> 2000	045	Osteoarthritis	25 and 50	Placebo	24	February 18, 1998
Truitt et al, <sup>20</sup> 2001	058	Osteoarthritis	12.5 and 25	Placebo	6	April 1, 1998
Unpublished	083	Osteoarthritis	25	Placebo	64	February 9, 2000
Kivitz et al, <sup>21</sup> 2004	085	Osteoarthritis	12.5	Placebo	6	March 3, 1999
Weaver et al, <sup>22</sup> 2006	090	Osteoarthritis	12.5	Placebo	6	May 17, 1999
Smugar et al, <sup>23</sup> 2006	112	Osteoarthritis	12.5 and 25	Placebo	6	September 8, 2000
Smugar et al, <sup>23</sup> 2006	116	Osteoarthritis	25	Placebo	6	June 22, 2000
Laine et al, <sup>24</sup> 2004	136	Osteoarthritis	25	Placebo	12	February 5, 2002
Birbara et al, <sup>25</sup> 2006	219	Osteoarthritis	12.5	Placebo	6	November 28, 2003
Birbara et al, <sup>25</sup> 2006	220	Osteoarthritis	12.5	Placebo	6	November 24, 2003
Unpublished	017	Rheumatoid arthritis	125 and 175	Placebo	6	May 21, 1997
Schnitzer et al, <sup>26</sup> 1999	068	Rheumatoid arthritis	25 and 50	Placebo	8	September 10, 1998
Truitt et al, <sup>27</sup> 2001 (abstract only)	096	Rheumatoid arthritis	12.5 and 25	Placebo	12	July 21, 2000
Geusens et al, <sup>28</sup> 2002	097	Rheumatoid arthritis	25 and 50	Placebo	12	June 6, 2000
Hawkey et al, <sup>29</sup> 2003	098 and 103	Rheumatoid arthritis	50	Placebo	12	July 6, 2000
Thal et al, <sup>30</sup> 2005	078	Alzheimer disease	25	Placebo	208	April 23, 2003
Reines et al, <sup>31</sup> 2004	091	Alzheimer disease	25	Placebo	52	November 30, 2000
Unpublished	126	Alzheimer disease	25	Placebo	52	May 30, 2001
Nickel et al, <sup>32</sup> 2003	118	Chronic nonbacterial prostatitis	25 and 50	Placebo	6	July 26, 2000
Katz et al, <sup>33</sup> 2003	120 and 121	Low back pain	25 and 50	Placebo	4	June 27, 2000
Bresalier et al, <sup>3</sup> 2005, and Baron et al, <sup>34</sup> 2008	122	Colorectal adenomas	25	Placebo	156	September 30, 2004
Unpublished	125	Migraine prophylaxis	25	Placebo	12	June 29, 2001
Unpublished	129	Familial adenomatous polyposis	25	Placebo	24	May 14, 2002

Abbreviation: LPO, last patient out (clinical trial completion date).

ods. We then cumulatively calculated event rates and relative risks using Cox proportional hazards models (or exact methods), pooling new data as clinical trials were completed and became available for analysis. To account for the time necessary in practice to prepare and organize a final clinical trial data set for analysis, with 3 exceptions, we made certain that data were eligible for pooling only 3 months after the last-person-out date of each randomized clinical trial or the trial termination date (trial 126 [unpublished] was terminated early after the researchers of trial 091<sup>31</sup> found rofecoxib to not be effective).

Exceptions to this rule were made for trials 078<sup>30</sup> and 122.<sup>3,34</sup> Because data from trial 078 were included in 2 pooled analyses of cardiovascular events by the Company within safety update reports required by the FDA while the study was ongoing, we likewise included data from trial 078 in our pooled analysis as of the same dates.<sup>36</sup> The first safety update report included all clinical trial data available as of March 16, 2001, and the second as of January 31, 2002. As of these report dates, trial 078 was the only sizable placebo-controlled trial for which data were included while collection was ongoing. Similarly, data from trial 122, the APPROVe trial,<sup>3</sup> were initially analyzed by the trial's data and safety monitoring board while the study was ongoing; these interim results were subsequently published<sup>3</sup> before completion of the long-term postdrug follow-up of participants.<sup>34</sup> We likewise included data from trial 122 as of the date of the interim analysis, September 30, 2004.

For every fitted Cox model on complete data sets, we checked the proportionality assumption using a standard test based on

the scaled Schoenfeld residuals. No failures of proportionality were noted. We did not include drug dose as a covariate in our analyses because more than 90% of the patient-years of observation were of patients using 25 mg of rofecoxib. All statistical tests were 2 tailed, and analyses were performed using the R statistical software environment, version 2.8.0 (<http://www.r-project.org>).

## RESULTS

### DATA SOURCES

We identified 30 randomized placebo-controlled trials including a total of 17 256 subjects that met our inclusion criteria. Fifteen of these trials examined the efficacy of rofecoxib for treating osteoarthritis; 6 for treating rheumatoid arthritis; 3 for preventing or delaying the progression of Alzheimer disease; and 6, including the APPROVe trial,<sup>3</sup> for other indications, (Table 1). To our knowledge, reports of 24 of these 30 trials were published as articles, although 6 (excluding APPROVe) were published after Merck withdrew rofecoxib from the worldwide market; therefore, data representing 36% of patients studied in placebo-controlled clinical trials prior to APPROVe had not

been published prior to market withdrawal. Trial duration ranged from 4 weeks to 4 years; enrollment ranged from 17 to 2586 subjects assigned either rofecoxib or placebo; and rofecoxib dose ranged from 12.5 to 50 mg, although more than 90% of the patient-years of observation were of patients using 25 mg of rofecoxib.

#### CARDIOVASCULAR RISK IDENTIFIED FROM PLACEBO-CONTROLLED TRIALS

Through September 2004, there were 301 CVT adverse events reported by investigators during these 30 randomized placebo-controlled trials, 182 among 7034 patient-years of rofecoxib use and 119 among 6695 patient-years of placebo use (rate ratio [RR], 1.48; 95% confidence interval [CI], 1.17-1.87) ( $P < .001$ ) (**Table 2**).

#### MORTALITY RISK IDENTIFIED FROM PLACEBO-CONTROLLED TRIALS

Through September 2004, there were 130 deaths from any cause reported by investigators during the 30 randomized placebo-controlled trials, 81 among 7158 patient-years of rofecoxib use and 49 among 6805 patient-years of placebo use (RR, 1.71; 95% CI, 1.20-2.45) ( $P = .003$ ) (Table 2).

#### CARDIOVASCULAR AND MORTALITY RISK IDENTIFIED FROM PLACEBO-CONTROLLED TRIALS

Through September 2004, there were 372 subjects for whom an investigator reported either a CVT adverse event or death from any cause during these 30 randomized placebo-controlled trials, 221 among 6357 patient-years of rofecoxib use and 151 among 5723 patient-years of placebo use (RR, 1.43; 95% CI, 1.16-1.76) ( $P < .001$ ) (Table 2).

#### TIME COURSE OF THE IDENTIFICATION OF CARDIOVASCULAR AND MORTALITY RISK

Results of the cumulative pooled analysis of the 30 identified randomized placebo-controlled trials are displayed in the **Figure**. As of December 2000, 21 of these trials had been completed (70%), having enrolled 9884 subjects for 1749 patient-years of observation to either the rofecoxib or placebo arm, during which time 36 subjects experienced either a CVT adverse event or death from any cause. At that time, risk of either of these events was greater among subjects assigned to rofecoxib (RR, 2.18; 95% CI, 0.93-5.81) ( $P = .07$ ), raising concerns from a safety standpoint (**Table 3**).

With the analysis of additional data available through June 2001, 12 207 subjects had been observed for 4946 patient-years. At that time, rofecoxib was associated with a 35% increased risk of a CVT adverse event or death (RR, 1.35; 95% CI, 1.00-1.96) ( $P = .05$ ).

The association between rofecoxib and risk of CVT adverse event or death strengthened with the addition of subsequently collected data. As of January 2002, 14 406

subjects had been observed for 7806 patient-years, and rofecoxib was associated with a 39% increased risk of a CVT adverse event or death (RR, 1.39; 95% CI, 1.07-1.80) ( $P = .02$ ).

Finally, after the addition of all data available as of the date of interim analysis of data from trial 122 (APPROVe),<sup>3,34</sup> September 2004, 20 152 subjects had been observed for 17 310 patient-years, and rofecoxib was associated with a 43% increased risk of a CVT adverse event or death (RR, 1.43; 95% CI, 1.16-1.76) ( $P < .001$ ).

#### COMMENT

Our cumulative pooled subject-level analysis of the data from all published and unpublished randomized placebo-controlled trials of rofecoxib demonstrates a trend toward increased cardiovascular risk associated with the medication compared with placebo as early as December 2000, the association reaching a  $P$  value of .05 by June 2001, nearly 3-1/2 years before the manufacturer voluntarily withdrew rofecoxib from the worldwide market. These findings are particularly compelling because as early as the late 1990s there were concerns about cardiovascular risk that emerged in the drug development process.<sup>1,2</sup>

The present analyses provide a roadmap for how drug safety can and should be assessed, particularly after a drug has been introduced into the market. Because the recently enacted FDAAA requires the public disclosure of trial results within the ClinicalTrials.gov database within 12 to 24 months of study completion, including both efficacy and safety outcomes, clinical trial data will be available to conduct comprehensive iterative meta-analyses independent of the FDA and manufacturers. Substantial amounts of clinical trial data that have rarely been fully used to understand drug efficacy or safety will now be available and can be used by independent investigators to complement and corroborate surveillance done by the FDA and the manufacturers.

The data used in our study were not publicly available for analysis by independent investigators at the time rofecoxib was being marketed and have only now become available through litigation. One critical advantage of our approach was the use of subject-level data, which allows far more flexibility with respect to pre-specifying and defining the outcome of interest, using statistical methods to manage heterogeneity, and investigating specific subgroups of subjects as well as rare outcome events, a critical issue in pharmaceutical post-market safety surveillance. Currently, the data that will be available through the ClinicalTrials.gov database will be summary-level data, which may lack information necessary to investigate specific subgroups or outcomes, particularly rare safety outcomes.

In 2006, the Institute of Medicine (IOM)<sup>37</sup> released a report commissioned by the FDA to examine drug safety. Until recently, the centerpiece of the FDA's pharmaceutical postmarket surveillance has been the adverse event reporting system (AERS),<sup>37</sup> which combines voluntary reporting of adverse events by patients and clinicians and mandatory reporting of adverse events by manufacturers. The FDA traditionally relied on AERS because

**Table 2. Incidence and Relative Risk of Investigator-Reported CVT Adverse Events and All-Cause Mortality in Merck-Conducted Randomized Placebo-Controlled Rofecoxib Trials<sup>a</sup>**

Study Block	Trial No. <sup>b</sup>	Rofecoxib	Placebo	Relative Risk (95% CI)	P Value
<b>CVT Adverse Events</b>					
Rheumatoid arthritis	017	1 (8)	0 (7)	4.11 (0.60-96.2)	.18
	068	1 (49)	0 (24)		
	096	4 (97)	0 (58)		
	097	0 (137)	0 (62)		
	098	0 (11)	1 (12)		
	103	0 (44)	0 (45)		
	Total	6 (345)	1 (208)		
Osteoarthritis	010	2 (16)	0 (7)	1.42 (0.60-3.67)	.45
	029	3 (46)	0 (16)		
	033	1 (66)	1 (9)		
	040	2 (72)	0 (11)		
	044	3 (154)	0 (52)		
	045	3 (157)	3 (61)		
	058	1 (21)	0 (6)		
	083	0 (21)	1 (21)		
	085	1 (61)	0 (28)		
	090	5 (56)	0 (27)		
	112	0 (104)	0 (15)		
	116	1 (54)	0 (15)		
	136	1 (95)	1 (201)		
	219	0 (18)	1 (8)		
220	0 (18)	0 (8)			
	Total	23 (959)	7 (485)		
Rheumatoid arthritis and osteoarthritis	Total	29 (1309)	8 (689)	1.74 (0.79-4.16)	.18
Alzheimer disease	078	73 (1628)	56 (1758)	1.35 (1.00-1.82)	.049
	091	13 (369)	14 (381)		
	126	11 (193)	7 (197)		
	Total	97 (2190)	77 (2337)		
Other	118	0 (15)	0 (8)	Not reported	Not reported
	120	1 (28)	0 (14)		
	121	0 (23)	0 (11)		
	125	0 (23)	0 (22)		
	129	0 (3)	0 (4)		
	Total	1 (92)	0 (59)		
APPROVe trial <sup>3</sup>	122	55 (3448)	34 (3606)	1.69 (1.10-2.59)	.02
Total	NA	182 (7034)	119 (6695)	1.48 (1.17-1.87)	<.001
<b>Mortality</b>					
Rheumatoid arthritis	017	0 (8)	0 (7)	Not reported	Not reported
	068	1 (49)	0 (24)		
	096	1 (97)	0 (58)		
	097	0 (137)	0 (62)		
	098	0 (11)	0 (12)		
	103	0 (44)	0 (45)		
	Total	2 (345)	0 (208)		
Osteoarthritis	010	0 (16)	0 (7)	Not reported	Not reported
	029	0 (46)	0 (16)		
	033	0 (66)	0 (10)		
	040	1 (72)	0 (11)		
	044	0 (154)	0 (52)		
	045	0 (157)	0 (61)		
	058	0 (21)	0 (6)		
	083	0 (21)	0 (21)		
	085	0 (61)	0 (28)		
	090	0 (56)	0 (27)		
	112	0 (104)	0 (15)		
	116	0 (54)	0 (15)		
	136	0 (95)	0 (201)		
	219	0 (18)	0 (8)		
220	0 (18)	0 (8)			
	Total	1 (960)	0 (485)		
Rheumatoid arthritis and osteoarthritis	Total	3 (1305)	0 (693)	Not reported	Not reported

(continued)

**Table 2. Incidence and Relative Risk of Investigator-Reported CVT Adverse Events and All-Cause Mortality in Merck-Conducted Randomized Placebo-Controlled Rofecoxib Trials (continued)<sup>a</sup>**

Study Block	Trial No. <sup>b</sup>	Rofecoxib	Placebo	Relative Risk (95% CI)	P Value
<b>Mortality (continued)</b>					
Alzheimer disease	078	41 (1688)	20 (1822)	1.91 (1.25-2.90)	.003
	091	16 (373)	9 (387)		
	126	4 (195)	5 (198)		
	Total	61 (2256)	34 (2408)		
Other	118	0 (15)	0 (8)	Not reported	Not reported
	120	0 (28)	0 (14)		
	121	0 (23)	0 (11)		
	125	0 (23)	0 (22)		
	129	0 (3)	0 (4)		
	Total	0 (92)	0 (59)		
APPROVe trial <sup>3</sup>	122	17 (3504)	15 (3645)	1.18 (0.59-2.36)	.64
Total	NA	81 (7158)	49 (6805)	1.71 (1.20-2.45)	.003
<b>CVT Adverse Event or Mortality</b>					
Rheumatoid arthritis	017	1 (8)	0 (7)	4.72 (0.72-108.1)	.12
	068	1 (49)	0 (24)		
	096	5 (97)	0 (58)		
	097	0 (137)	0 (62)		
	098	0 (11)	1 (12)		
	103	0 (44)	0 (45)		
	Total	7 (345)	1 (208)		
Osteoarthritis	010	2 (16)	0 (7)	1.42 (0.60-3.68)	.45
	029	3 (46)	0 (16)		
	033	1 (66)	1 (9)		
	040	2 (72)	0 (11)		
	044	3 (154)	0 (52)		
	045	3 (157)	3 (61)		
	058	1 (21)	0 (6)		
	083	0 (21)	1 (21)		
	085	1 (61)	0 (28)		
	090	5 (56)	0 (27)		
	112	0 (104)	0 (15)		
	116	1 (54)	0 (15)		
	136	1 (95)	1 (201)		
	219	0 (18)	1 (8)		
220	0 (18)	0 (8)			
Total	23 (959)	7 (485)			
Rheumatoid arthritis and osteoarthritis	Total	30 (1304)	8 (692)	1.81 (0.83-4.32)	.14
Alzheimer disease	078	91 (1047)	70 (1075)	1.32 (1.01-1.71)	.04
	091	23 (273)	20 (189)		
	126	12 (193)	11 (100)		
	Total	126 (1514)	101 (1365)		
Other	118	0 (15)	0 (8)	Not reported	Not reported
	120	1 (28)	0 (14)		
	121	0 (23)	0 (11)		
	125	0 (23)	0 (22)		
	129	0 (3)	0 (4)		
	Total	1 (92)	0 (59)		
APPROVe trial <sup>3</sup>	122	64 (3447)	42 (3607)	1.59 (1.08-2.35)	.02
Total	NA	221 (6357)	151 (5723)	1.43 (1.16-1.76)	<.001

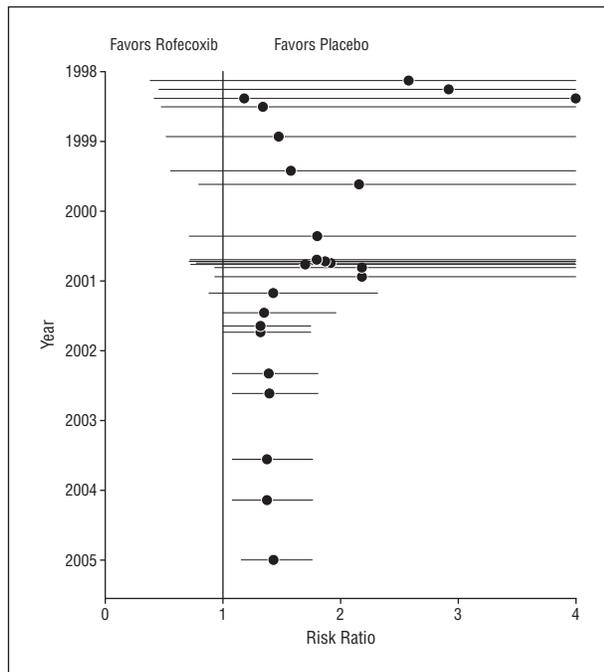
Abbreviations: APPROVe, Adenomatous Polyp Prevention on Vioxx<sup>3</sup>; CI, confidence interval; CVT, cardiovascular thromboembolic; NA, not applicable.

<sup>a</sup>Unless otherwise indicated, data are reported as number of events (number of person-years of observation); totals do not sum exactly because of rounding of patient years.

<sup>b</sup>See Table 1 for correspondences between trial numbers and reference numbers when references are available.

clinical trials conducted by industry as part of the new drug approval or indication application are often not large or long enough to evaluate safety outcomes. In addition, many of the large phase IV randomized trials requested by the FDA at the time of drug approval to further investigate potential drug safety issues are not conducted for a wide variety of reasons, including feasibility, recruitment barriers, and cost.

The IOM report<sup>37</sup> included 25 recommendations that together suggested that the FDA needed to better prioritize ongoing, systematic efforts to monitor drug safety during the product's entire market life, such as the approach we have modeled. Nevertheless, identifying those safety outcomes that should be monitored prospectively through an iterative and timely meta-analysis will be challenging and should be driven by biological plau-



**Figure.** Cumulative pooled analysis of investigator-reported cardiovascular thrombotic events and all-cause deaths among all randomized, placebo-controlled rofecoxib trials of 4 weeks' duration or longer conducted by Merck & Co Inc (Whitehouse Station, New Jersey).

sibility; safety signals that arise during the drug development process; during preapproval studies; and by systematic monitoring of surveillance systems such as AERS and other health care data sources through the FDA's Sentinel Initiative (<http://www.fda.gov/Safety/FDASentinelInitiative/default.htm>), including Medicare Part D claims, the Department of Veteran Affairs, the HMO Research Network, and others.

Our analysis builds on the prior work of Jüni et al,<sup>7</sup> published shortly after rofecoxib was withdrawn from the market, which concluded that rofecoxib was associated with more than twice the risk of myocardial infarction by the end of 2000, although it differs in several ways. First, our analysis used all published and unpublished data at the patient level, whereas Jüni et al were restricted to published data at the summary level. Moreover, the cumulative meta-analysis of Jüni et al examined the risk of myocardial infarction, whereas ours examines the risk of CVT event or death, a more comprehensive assessment of drug safety. In addition, the meta-analysis of Jüni et al included all randomized clinical trials, including trials that used NSAIDs as a comparator. The largest trial with the largest effect size was the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) trial,<sup>38</sup> which compared rofecoxib to naproxen. In fact, the stratified analysis of Jüni et al<sup>7</sup> estimated a tripling of the risk associated with rofecoxib compared with naproxen and a nonsignificant increase in risk associated with rofecoxib compared with placebo, although a test of interaction by comparator was not significant. Our analysis extends and strengthens these findings, demonstrating an increased cardiovascular risk associated with rofecoxib compared with placebo.

Our analysis differs in several ways from those conducted by the manufacturer and published before rofecoxib's withdrawal from the market.<sup>9-11</sup> First, each of the earlier pooled analyses focused on the Antiplatelet Trialists' Collaboration (APTC)<sup>39,40</sup> and Antithrombotic Trialists' Collaboration (ATTC)<sup>41</sup> end point, which accounts only for cardiovascular, hemorrhagic, and unknown deaths, including hemorrhagic gastrointestinal deaths, as well as non-fatal myocardial infarctions and strokes (ischemic and hemorrhagic). The APTC/ATTC end point is a composite outcome developed for the purpose of testing the net efficacy and safety of antiplatelet therapeutics that may prevent ischemic events but simultaneously may cause hemorrhagic events. Specifically, the APTC/ATTC end point captures overall benefits and risks of antiplatelet medications, but it is not appropriate for evaluating the CVT risk of cyclooxygenase-2 inhibitors. In contrast, we accounted for all ischemic-related CVT adverse events as well as deaths from any cause. Accounting for all deaths is important for studies of cardiovascular risk (particularly among clinical trials not designed to examine cardiovascular outcomes) because cardiovascular deaths are not always apparent as such. In addition, nearly three-quarters of deaths in the present analysis occurred within the 3 Alzheimer trials. Studying all-cause death is particularly important among patients with Alzheimer disease or cognitive impairment who may not report symptoms accurately and may not always be as thoroughly evaluated when brought for medical attention.

Second, we examined all available data from all 30 trials with a placebo-controlled arm, including data not used in company-conducted analyses<sup>9-11</sup> (eTable 3), although we did exclude data from the VICTOR<sup>12</sup> and ViP<sup>13</sup> trials, 2 large ongoing trials that were terminated shortly after APPROVe and the decision to withdraw the drug from the market. Finally, we accounted for all investigator-reported adverse events among all trials and included outcomes observed beyond the 14-day window after the subjects stopped taking the study drugs in an intention-to-treat fashion, the gold standard approach for analysis of clinical trial data<sup>35</sup> and the approach prespecified within these trials' data analysis plans.

Our analysis raises the issue of how investigators should interpret data relevant to drug safety. Although we want to avoid false-positive interpretations, conventional standards of statistical significance may be too strict for issues of safety.<sup>42,43</sup> The importance of a safety finding depends on many factors, including plausibility of harm, effect size, number of people exposed, and alternatives to treatment. Understanding the range in the estimation of the risk may be more important than focusing on hypothesis testing using a *P* value threshold for significance of .05.<sup>42</sup> For instance, when the VIGOR trial<sup>38</sup> findings were published in November 2000, 4 years before rofecoxib was withdrawn from the market, concern about rofecoxib's cardiovascular risk was already heightened, and clear alternatives for treatment of osteoarthritis and rheumatoid arthritis were available. Our analyses suggest that rofecoxib was associated at that time with more than a doubling of the cardiovascular risk that nonetheless did not reach statistical significance (95% CI, 0.93-5.81) (*P*=.07). Notwithstanding the lack of statistical significance, this indication of risk should have been interpreted along with the 5-fold

**Table 3. Cumulative Relative Risk of Investigator-Reported CVT Events and All-Cause Deaths Among All Randomized, Placebo-Controlled Rofecoxib Trials of 4 Weeks' Duration or Longer Conducted by Merck**

Trial No. <sup>a</sup>	Date Available <sup>b</sup>	Rofecoxib		Placebo		Cumulative Relative Risk (95% CI)	P Value
		Events (PYR)	Sample Size, No.	Events (PYR)	Sample Size, No.		
10	May 1996	2 (16)	147	0 (7)	72		
29	May 1997	3 (46)	378	0 (16)	145		
17	August 1997	1 (8)	69	0 (7)	68		
33	February 1998	1 (66)	446	1 (9)	69	2.58 (0.38-60.8)	.41
40	April 1998	2 (72)	486	0 (11)	74	2.92 (0.45-67.0)	.33
44	May 1998	3 (154)	381	0 (52)	177	3.96 (0.66-87.2)	.16
45	May 1998	3 (157)	388	3 (61)	194	1.18 (0.41-4.13)	.71
58	June 1998	1 (21)	174	0 (6)	52	1.35 (0.47-4.77)	.63
68	December 1998	1 (49)	332	0 (24)	168	1.47 (0.51-5.15)	.52
85	June 1999	1 (61)	424	0 (28)	208	1.58 (0.56-5.50)	.43
90	August 1999	5 (56)	390	0 (27)	196	2.16 (0.79-7.37)	.15
83	May 2000	0 (21)	98	1 (21)	100	1.80 (0.71-5.40)	.24
97	September 2000	0 (137)	612	0 (62)	299	1.80 (0.71-5.40)	.24
121	September 2000	0 (23)	210	0 (11)	100	1.80 (0.71-5.40)	.24
116	September 2000	1 (54)	471	0 (15)	151	1.86 (0.74-5.56)	.21
120	September 2000	1 (28)	252	0 (14)	128	1.91 (0.77-5.62)	.17
98	October 2000	0 (11)	45	1 (12)	48	1.70 (0.71-4.61)	.25
103	October 2000	0 (44)	174	0 (45)	173	1.70 (0.71-4.61)	.25
96	October 2000	5 (97)	459	0 (58)	301	2.18 (0.93-5.81)	.07
118	October 2000	0 (15)	102	0 (8)	58	2.18 (0.93-5.81)	.07
112	December 2000	0 (104)	915	0 (15)	150	2.18 (0.93-5.81)	.07
91	February 2001	23 (273)	346	20 (189)	346	1.43 (0.88-2.31)	.15
78	June 2001 <sup>c</sup>	57 (1257)	723	46 (1478)	728	1.35 (1.00-1.96)	.051
126	August 2001	12 (193)	380	11 (100)	376	1.32 (1.00-1.75)	.054
125	September 2001	0 (23)	89	0 (22)	83	1.32 (1.00-1.75)	.054
78	April 2002 <sup>d</sup>	78 (1148)	723	59 (1374)	728	1.39 (1.07-1.80)	.02
136	May 2002	1 (95)	399	1 (201)	816	1.39 (1.07-1.81)	.01
129	August 2002	0 (3)	8	0 (4)	9	1.39 (1.07-1.81)	.01
78	July 2003	91 (1047)	723	70 (1075)	728	1.38 (1.08-1.77)	.01
220	February 2004	0 (18)	159	0 (8)	85	1.38 (1.08-1.77)	.01
219	February 2004	0 (18)	157	1 (8)	76	1.37 (1.07-1.75)	.01
122	September 2004 <sup>e</sup>	64 (3429)	1287	42 (3598)	1299	1.43 (1.16-1.76)	<.001

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration; PYR, person-years of observation.

<sup>a</sup>See Table 1 for correspondences between trial numbers and reference numbers when references are available.

<sup>b</sup>Date available is the date of the last patient out plus 3 months.

<sup>c</sup>Trial data were included in the first safety update report, which pooled all clinical trial data available as of March 16, 2001, and was submitted to the FDA in June 2001.

<sup>d</sup>Trial data were included in the second safety update report, which pooled all clinical trial data available as of January 31, 2002, and was submitted to the FDA in May 2002.

<sup>e</sup>Trial data through September 8, 2004, were examined by the data safety and monitoring board on September 30, 2004.

increased risk of myocardial infarction among rofecoxib users<sup>44</sup> found in the VIGOR trial as well as with the concerns about cardiovascular risk that emerged in the drug development process.<sup>1,2</sup>

Physicians and the public deserve to be in a position to make informed choices about risks and benefits, and the disclosure and dissemination of information about potential risk immediately after its recognition is absolutely essential. Our study provides insight into what should have been known about the risks of rofecoxib. The signal of cardiovascular risk appeared soon after the drug was FDA-approved and made available in May 1999. But more importantly, our study suggests that such analyses should be ongoing for all drugs for which trials are being conducted, with attention to the rapid addition of new data about potential harm to any cumulative pooled analyses. Ideally, subject-level data should be made available to the public to allow for independent assessments.

If we are to detect harms early and protect the public's health, while ensuring the availability of new, clinically effective therapeutics, a system must be established that makes full use of all existing evidence.

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**Additional Information:** An eFigure and 3 eTables are available at <http://www.archinternmed.com>.

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## INVITED COMMENTARY

### HEALTH CARE REFORM

# Bringing the FDA's Information to Market

**H**ere is a challenge: Imagine you are asked to turn a new prescription drug into a blockbuster. The drug is approved by the US Food and Drug Administration (FDA) to treat arthritis pain. That is good news because the arthritis market is huge. But you face some big challenges. First, there are several over-the-counter drugs available that treat pain equally well and at one-fiftieth of the cost. Your only comparative advantage is that your drug causes less gastrointestinal tract (GI) bleeding than other arthritis pain medicines. But this reduction is not very big and only applies to a very small slice (probably <5%) of the market—people at high risk for GI bleeding. And, oh yes, your drug may triple the chance of myocardial infarction.

*See also pages 1969,  
1976 and 2024*

Do you think you could get physicians to prescribe your drug to over 20 million Americans? Could you achieve over \$2 billion in annual sales? Well, the makers of Vioxx (Merck & Co Inc, Whitehouse Station, New Jersey) did just that—until the drug was pulled from the market.

Ross et al show how a cumulative meta-analysis might have led the FDA to halt sales of Vioxx in 2001, 3 years before Merck voluntarily stopped selling it. Doing so might have prevented thousands of myocardial infarctions. We applaud this study and hope that independent investigators will apply the same methods to other drugs to help answer important safety questions. But the article left us wondering, just how did Vioxx get so big and stay so big for so long?

The Vioxx story really highlights the difference between marketing and informing. If physicians and patients had had the facts, it would have taken an alchemist, not a marketing department, to turn this lemon into gold.

The problem is that when it comes to prescription drugs, a lot more effort goes into marketing than informing. It has been estimated that drug companies spend \$30 billion to \$50 billion a year on drug promotion (advertising, detailing visits, free samples, and other promotion techniques).<sup>1</sup> That means that the industry can really get its message out.

And marketing works.<sup>2</sup> Physicians and patients are influenced by the enormous volume of commercial information that they receive. In this issue of the *Archives*, Weppner et al<sup>3</sup> document that the familiar marketing tactics, long used in direct-to-consumer advertisements in maga-