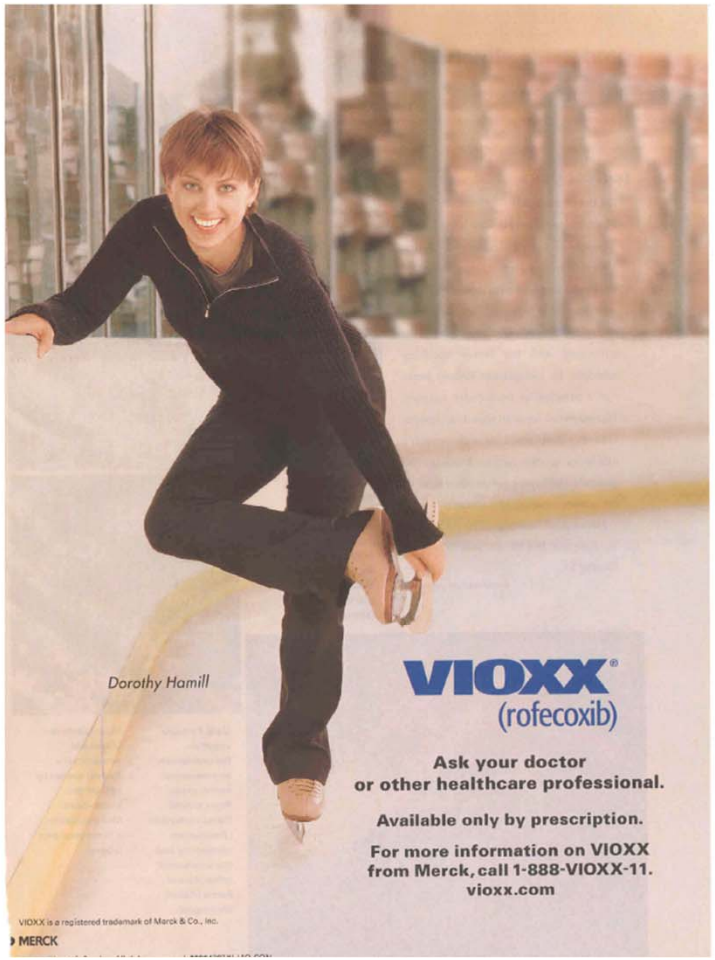
Lying with Statistics – the Vioxx Scandal

- Definition of Lying
  - To present false information with the intention of deceiving.
  - To convey a false image or impression: *Appearances often lie.*
  - to evade or depart from the truth

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

- NSAIDs are used to treat osteoarthritis, rheumatoid arthritis and certain other types of inflammatory disorders and for pain relief. Some NSAID's reduce fever and decrease clotting.
- The NSAIDS work by inhibiting the action of two enzymes, Cox-1 and Cox-2.
- There are two types of NSAIDS, 'non-selective' and 'selective'.
- Aspirin, ibuprofen and naproxen are non-selective inhibitors of both the Cox-1 and Cox-2 enzyme. Cox-1 inhibition is associated with a small increased risk of gastrointestinal bleeding (ulcers).
- Vioxx is one of a class of drugs that are selective Cox-2 inhibitors e.g. they only inhibit the Cox-2 enzyme that is involved in inflammation and pain and thus they have reduced risk for GI bleeds.

Vioxx Advertising on TV and in Popular Press

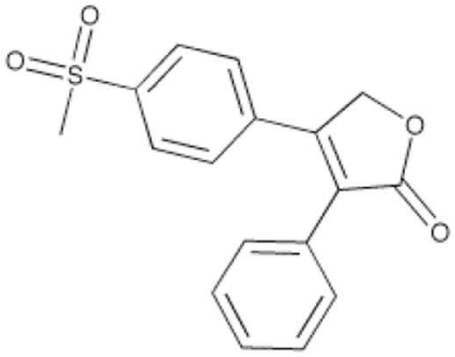


In 2000 Vioxx was the drug with the largest direct-to-consumer advertising campaign in the U.S. at ~$160m.

More than Budweiser ($146m)
or Pepsi ($125m).

Vioxx Key Events

1991	1999	2004
Discovery	**Approval**	**Withdrawal**



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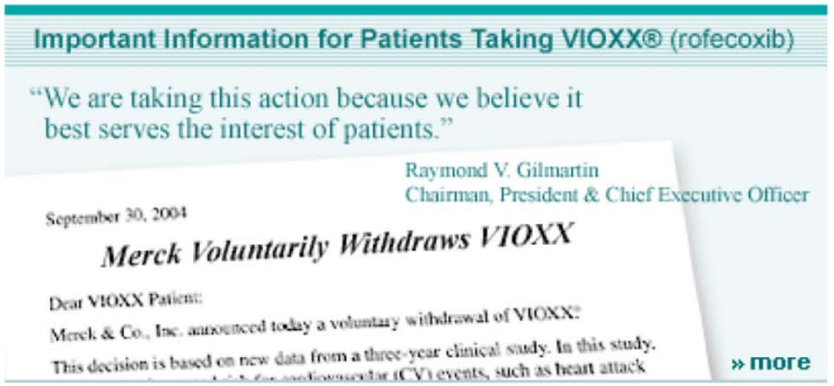


What Led to the Withdrawal of Vioxx in 2004?

- Legal suits claiming that Vioxx caused cardiovascular events.
  - 23,800 cases for 41,750 plaintiffs
  - 275 class action suits either for personal injury or economic damages (including consumer fraud suits, seeking reimbursement for patients' costs of buying a drug that was allegedly misrepresented as being safer than it really was)
- The termination of a study (APPROVe) in 2004 because of a statistically significant excess of cardiovascular events in Vioxx compared to placebo patients.

Settlement of most of the legal cases in 2007

$5 Billion Vioxx Settlement a Victory for Merck, Could Inspire Other Wrongdoers

By Brandon Keim ✉ November 13, 2007 | 11:28:34 AM Categories: Drugs & Alcohol, Medical Ethics, Medicine & Medical Procedures

VIOXX Gastrointestinal Outcomes Research Study (VIGOR)

- A total of 8076 patients were randomized to either rofecoxib 50 mg daily or naproxen 1000 mg daily.
- The median follow-up time for the trial was 9 months (maximum = 13 months).
- The primary endpoint of the trial was confirmed upper gastrointestinal events adjudicated by a blinded panel.
- Patient visits were at 6 weeks, 4 months, and every 4 months until study termination. The last patient exited the trial in early 2000, and the data was unblinded shortly thereafter, on or about March 9, 2000.

VIGOR Study Safety Results

- **General Safety**

  The safety of both rofecoxib and naproxen was similar to that reported in previous studies. The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group. The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7).

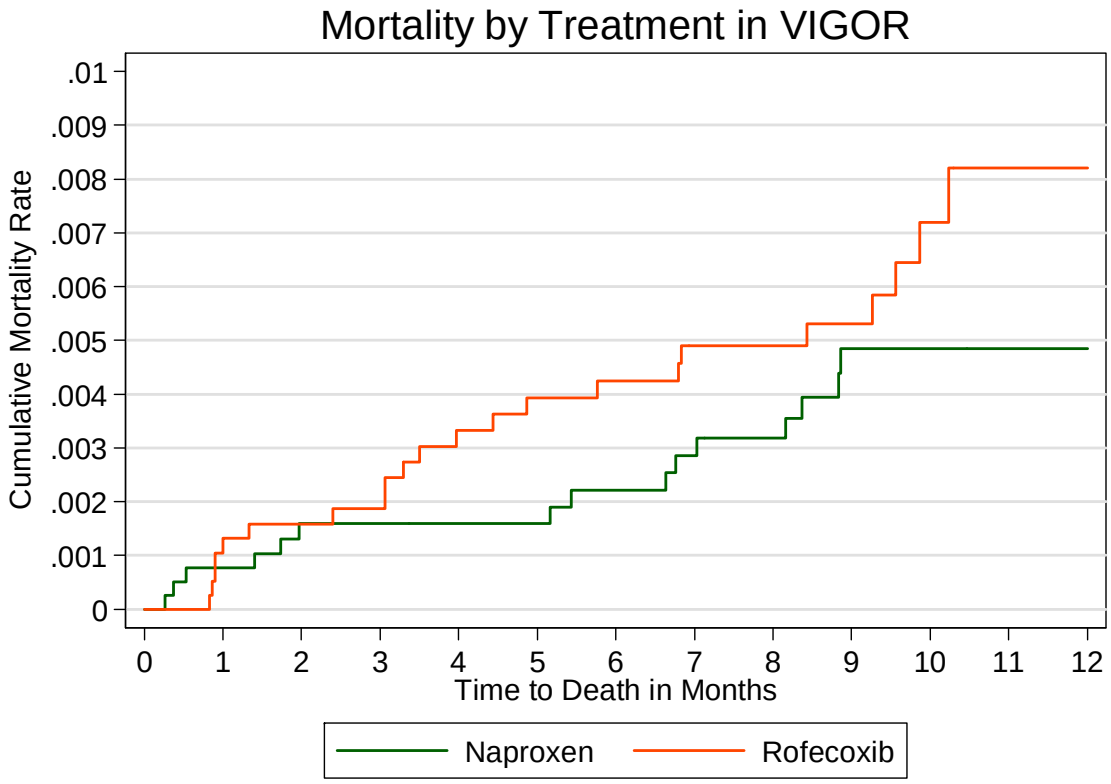
VIGOR Study Safety Results

- General Safety

  The incidence of adverse effects related to renal function was low and was similar in the two groups (1.2 percent in the rofecoxib group and 0.9 percent in the naproxen group);

VIGOR Study Safety Results – the Truth

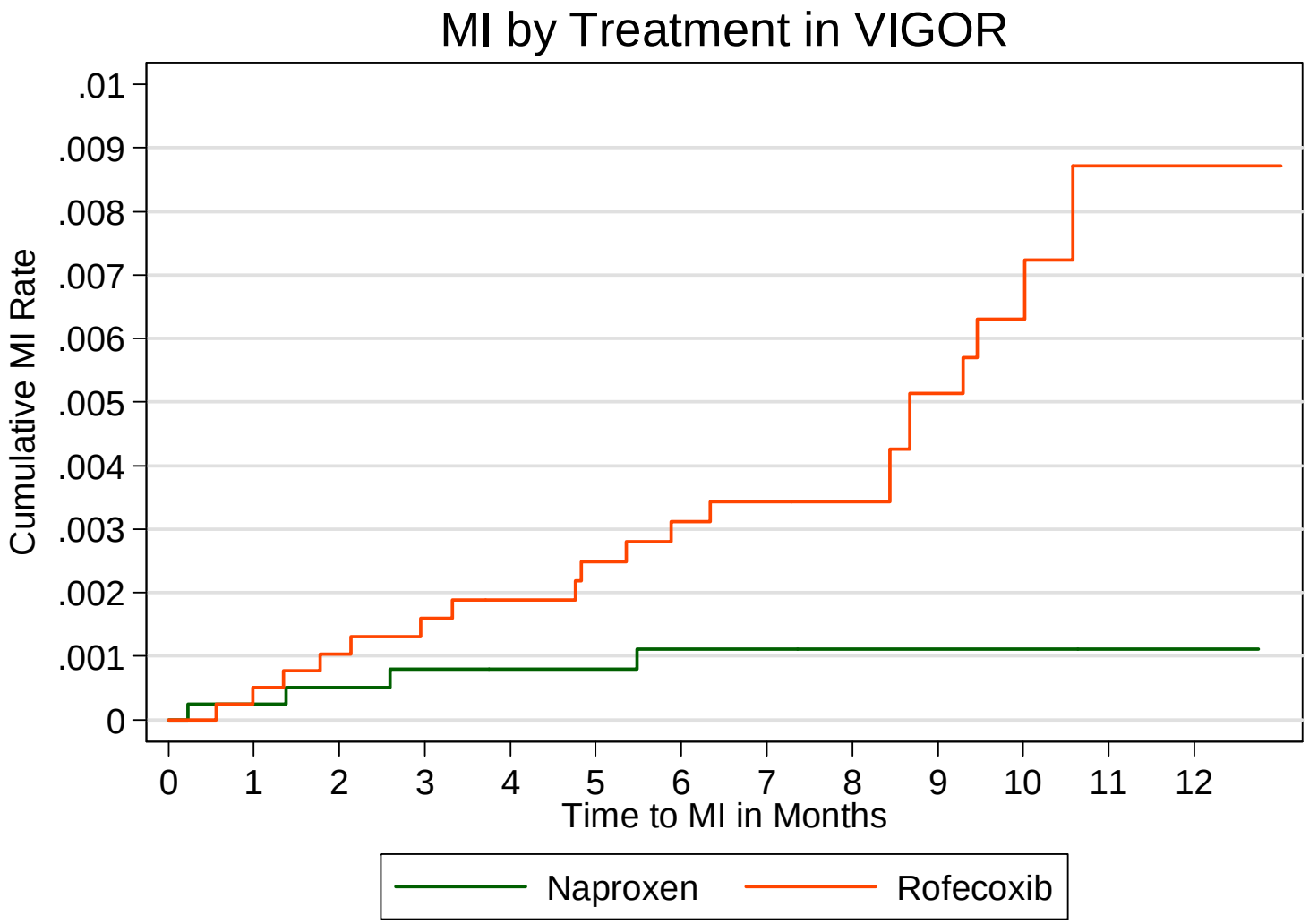
- Reported in NEJM - The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group.
- The Truth - The incidence of death in VIGOR was 22/4047 (0.54%) (for Rofecoxib) and 15/4209 (0.37%) (for Naproxen).



VIGOR Study Safety Results – the Truth

- Reported in NEJM - Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7).
- The Truth - there were 20 MIs (0.494%) in the Rofecoxib group and only 4 (0.099%) in the Naproxen group ($p<0.005$), a hazard ratio of 5.0 ($p<0.005$, 95% CI=1.7 – 14.6) for the comparison of Rofecoxib to Naproxen. The data presented in the NEJM excluded 3 MI's in the Rofecoxib group that several of the Merck authors were aware of prior to the final revision of the paper but chose not to include in the paper. Note that the number of events was not given in the paper.

VIGOR Study Safety Results – the Truth

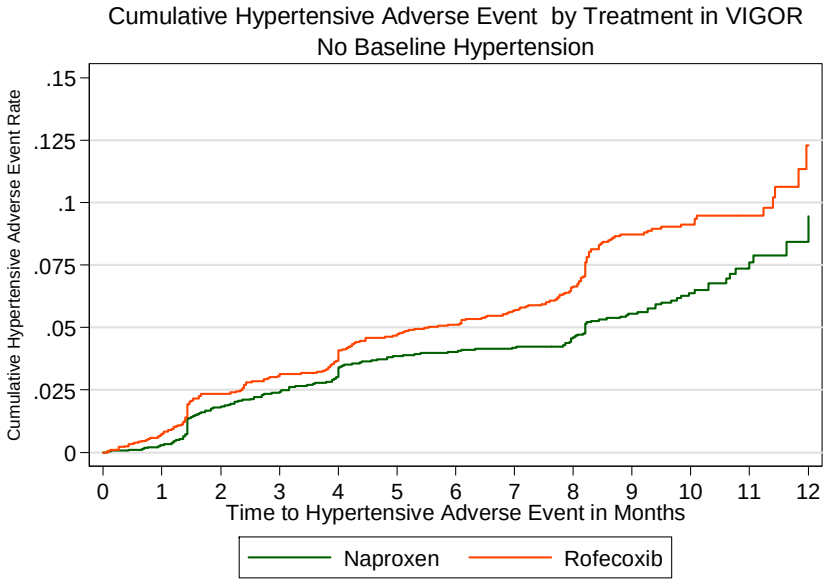


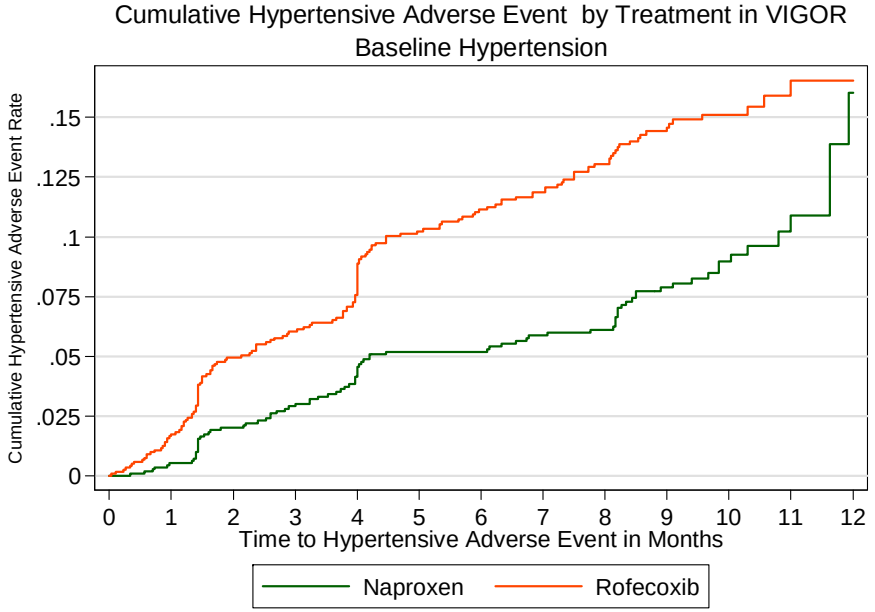
VIGOR Study Safety Results – the Truth

- Reported in NEJM - The incidence of adverse effects related to renal function was low and was similar in the two groups (1.2 percent in the rofecoxib group and 0.9 percent in the naproxen group);
- The Truth – The statement above comes close to being a lie, because they didn't include in renal adverse events, hypertension, congestive heart failure and edema, which are related to renal dysfunction.

VIGOR Study Safety Results – the Truth
Renal Adverse Events

- Hypertension
  - the rate of hypertension adverse events is 35/1000 person years greater in the Rofecoxib treatment patients *without* hypertension at baseline (p<0.0003) and 92/1000 greater in those *with* hypertension at baseline (p< 0.00001) than for patients taking Naproxen.



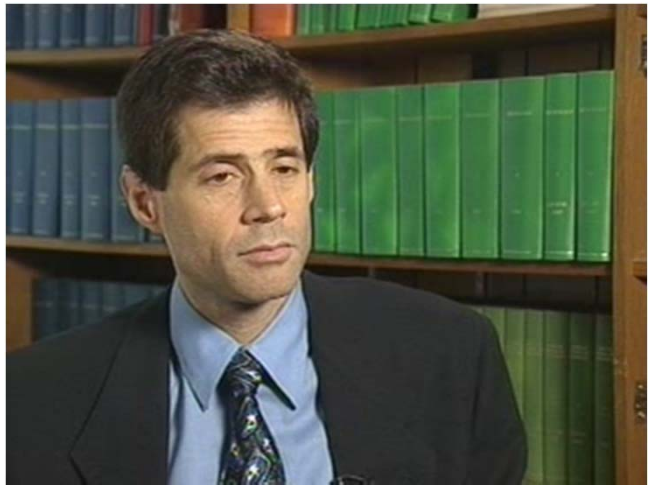


VIGOR Study Safety Results – the Truth
Renal Adverse Events

- Edema and Congestive Heart Failure
  - The 1 year rate of edema was about 10% in the Rofecoxib group compared to about 5% in the Naproxen group.
  - There were 19 cases of CHF in the Rofecoxib group compared to 9 in the Naproxen group. In addition, 15 of the 28 reported CHF cases were judged to be serious adverse events. Of these, 12 events were in the Rofecoxib group and 3 in the Naproxen group ($p<0.025$)

VIGOR Study Safety Results – Renal Adverse Events

- Did Merck know that there were renal safety issues?



The Alzheimer's Studies

- Theory: Vioxx would slow the progression and/or onset of Alzheimer's disease.
- Three studies (known as protocol 078, protocol 091, and protocol 126), 3,000 patients, 48 months therapy, average age = 75.
- Data analysis plan (submitted to the FDA) called for intent-to-treat analysis for safety and efficacy.
- No DSMB.

Alzheimer's Studies

- Protocol 078
  - enrolled 1457 patients older than 65 years with mild cognitive impairment and randomly assigned them to blinded treatment with rofecoxib, 25 mg, or placebo.
  - Patients were recruited at 46 US study sites between April 1998 and March 2000.
  - The planned duration of the study was 24 months, but because the event rate was lower than anticipated, the study was extended to 48 months.
  - The primary end point was the development of Alzheimer disease.
  - In 2002, the study participants were reconsented for the extension of study 078.
  - The Study ended in April 2003

Alzheimer's Studies

- Study 091
  - Randomly assigned 692 patients older than 50 years and diagnosed with possible or probable Alzheimer disease to blinded treatment with rofecoxib, 25 mg, or placebo.
  - Patients recruited at 31 US study sites from February to September 1999.
  - The planned duration of the study was 12 months.
  - The primary end point was reduction in cognitive decline.
  - At the conclusion of the study, there was no difference in risk of progression of Alzheimer's disease between treatment groups.

Study 091 – Reported Mortality Results

- “There were no drug-related deaths during the study. Non-drug related deaths occurred in 11 patients (9 in the rofecoxib group and 2 in the placebo group) while taking study treatment or within 14 days of the last dose.”
- “Rofecoxib was generally well tolerated by the elderly patients in our study”

Alzheimer's Studies - 078

Neuropsychopharmacology (2005), 1–12

www.neuropsychopharmacology.org

A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment

Leon J Thal[1], Steven H Ferris[2], Louis Kirby[3], Gilbert A Block[4], Christopher R Lines*[,4], Eric Yuen[4], Christopher Assaid[4], Michael L Nessly[4], Barbara A Norman[4], Christine C Baranak[4] and Scott A Reines[4], on behalf of the Rofecoxib Protocol 078 study group[5]

[1]University of California, San Diego, CA, USA; [2]New York University School of Medicine, New York, NY, USA; [3]Pivotal Research Centers, Peoria, AZ, USA; [4]Merck Research Laboratories, West Point, PA, USA

Protocol 078 –Abstract

- “The primary end point was the percentage of patients with a clinical diagnosis of AD. The estimated annual AD diagnosis rate was lower than the anticipated 10- 15%: 6.4% in the rofecoxib group vs 4.5% in the placebo group (rofecoxib: placebo hazard ratio = 1.46 (95% CI: 1.09, 1.94), p = 0.011).”
- “The results from this MCI study did not support the hypothesis that rofecoxib would delay a diagnosis of AD.”

Protocol 078 - Reported Safety Results

- In addition to evaluating efficacy, the present study provided important placebo-controlled data on the safety of rofecoxib 25 mg over periods of up to 4 years in an elderly population. The median duration of exposure to study medication was approximately 2 years. The mean age of patients was 75 years and approximately 50% were at least 75 years old.

Protocol 078 - Reported Mortality Results

- “The total number of deaths and causes of death on-drug were consistent with expectations for an elderly population, and there was no specific pattern as to the cause of death in either treatment group. The off-drug mortality data are difficult to assess since follow-up information was available for less than half the patients, there was an imbalance in the extent of follow-up data between the two groups, and the majority of deaths occurred more than 48 weeks after treatment had been discontinued.”

Protocol 078 – Reported Mortality Results

- A total of 39 deaths occurred in patients who were taking study treatment or from fatal adverse events that started within 14 days of the last dose (24 or 3.3% for rofecoxib and 15 or 2.1% for placebo). Patients 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. The only specific fatal adverse events with more than one patient per treatment group were myocardial infarction (four patients on rofecoxib and three on placebo), cardiac arrest (two patients on rofecoxib and none on placebo), pneumonia (two patients on rofecoxib and none on placebo), and renal failure (one patient on rofecoxib and two on placebo). (An individual patient may have had more than one adverse event associated with death.) Off-drug follow-up mortality data were available for less than half of the patients (N= 356 for rofecoxib, N= 307 for placebo); the median duration of off-drug follow-up in these patients was 29 weeks in the rofecoxib group and 20 weeks in the placebo group. There were an additional 22 deaths in the off-drug period (17 in patients assigned to rofecoxib and five in patients assigned to placebo); 12 of these (11 in the rofecoxib group and one in the placebo group) occurred more than 48 weeks after treatment discontinuation. Compared with the on-drug period, there were an additional five patients with off-drug myocardial infarction fatal adverse events (five rofecoxib, none placebo), and an additional two patients with each of cardiac arrest (two rofecoxib, none placebo), pneumonia (two rofecoxib, none placebo), and renal failure (two rofecoxib, none placebo) off-drug fatal adverse events.

Merck's Internal Mortality Analyses and Reporting to the FDA

- In 2000, Merck scientists decided that the Alzheimer's study might be informative concerning the CHD risks seen in Vigor. However, the only data available was for mortality. A Merck statistician, Chen was charged with doing the analyses.
- In a report, to Merck management in April 2001, he reported the following:

Chen's Mortality Report

Table 1.2.2 Mortality Frequency (Combined ITT Analysis)

Number of Deaths (%)	MK-0966 (N=1069)	Placebo (N=1078)
Total *	34 (3.2)	12 (1.1)
Protocol 091 (AD) **	13 (38.2%)	3 (25%)
Protocol 078 **	21 (61.8%)	9 (75%)

* total number of deaths in each treatment arm (% number of patients in the treatment arm)
** number of deaths from individual protocol (% total deaths in the treatment arm)

Table 2. Relative Risks of Death for Rofecoxib compared to Placebo from Chen's Analysis

Study	Relative Risk	Confidence Interval		p-value
Protocol 091	4.43	1.26	15.53	<0.01
Protocol 078	2.55	1.17	5.56	<0.02
Combined 091 + 078	2.99	1.55	5.77	<0.001

Merck's Internal Mortality Analyses and Reporting to the FDA

- Merck's Response to these findings.
  - Called several emergency meetings to discuss what action to take.
  - Discussed whether they should appoint a DSMB for study 078 which was ongoing.
  - Decided that a DSMB wasn't necessary and that an internal (Merck) monitoring was sufficient.
  - Apparently decided that it wasn't necessary to report these findings to the FDA in their July 2001 Safety Update Report.
  - No one connected with the study (investigators or IRB's) were notified about these results.

Merck's Internal Mortality Analyses Compared to that Reported to the FDA

- In July 2001 Safety Update Report (SUR) Merck included some (but not all results) for mortality in the Alzheimer's studies.

Table. Deaths in Studies of Patients With Alzheimer Disease or Impaired Cognitive Function

Protocol No.	No./Total: Rofecoxib, 25 mg	No./Total: Placebo	Counting Method
Sponsor's Data Submitted to the FDA July 2001[11,a]			
091	14/346	8/346	12 Months of study plus 3 months after trial completion
078	15/721	9/729	On treatment plus 14 days after the end of treatment
Sponsor's Intention-to-Treat Analyses in April 2001[14,b]			
			HR (95% CI)
091	13/346	3/346	4.43 (1.26-15.53)
078	21/723	9/732	2.55 (1.17-5.56)
Combined[9]	34	12	2.99 (1.55-5.77)

- Merck states in the SUR that: "Therefore, review of the deaths does not identify a specific increased risk with rofecoxib."

FDA Letter to Merck (Dec. 2001)

- On Dec. 5, 2001, the FDA sent a letter to Merck asking for the answer to a question they had about the ethics of continuing study 078 based on the excess mortality seen in study 091. The question posed to Merck was:
  - *"Please clarify whether the safety monitoring board and the IRB overseeing these studies are aware of the excess in total cause mortality in the Vioxx 25 mg group as compared to placebo (p=0.026) and the trend against Vioxx 25 mg on CV mortality compared to placebo. Have these oversight groups commented on the ethics of continuing study 078 in light of the mortality data …"*

Merck's Response to the FDA Letter

- In its response to the FDA, Merck reiterated the mortality data and characterized the rofecoxib/placebo findings as "small numeric differences. . . most consistent with chance fluctuations."
- Merck also stated: "With regard to dissemination of these data, individual study site IRBs, rather than a single, central IRB are providing oversight for the 078 study. There is no data safety monitoring board. MRL[Merck Research Laboratories] has not provided these data to the individual IRBs because MRL does not believe that a safety issue has been identified. Moreover, the 078 study is still under blind both to personnel at study sites and to personnel at MRL monitoring these studies. In the absence of a compelling and clear safety issue, MRL has not broken study blind to individuals involved in these studies."
- Study 078 continued for an additional two years!

If there had been a DSMB?

- What would a DSMB have done had they reviewed the data from 078?
- Review of risk/benefit of rofecoxib.

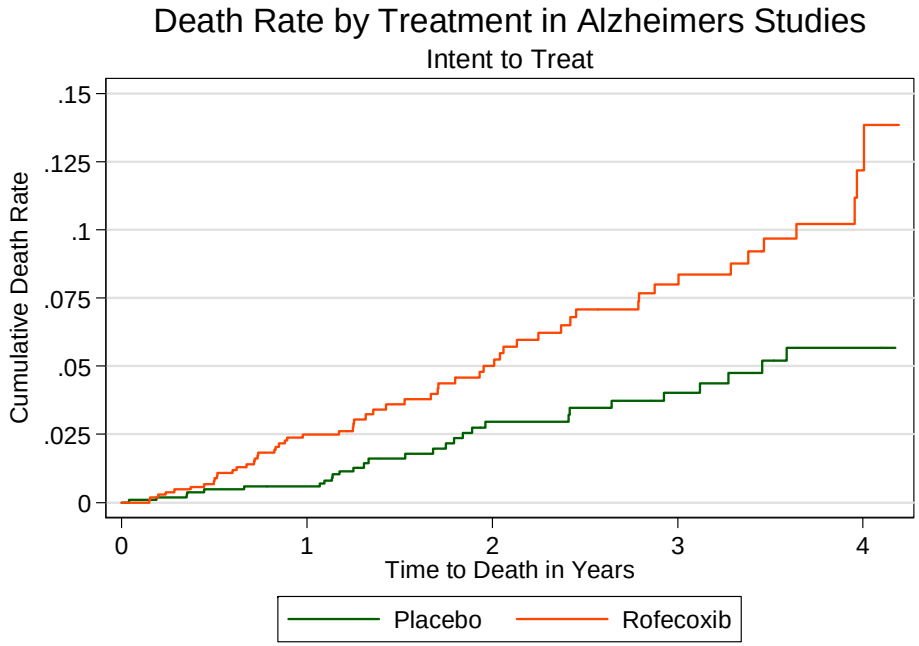
Relative Risks for Alzheimer's Study 078 for the Mortality and Alzheimer's Endpoints.

For Follow-up Through Sept. 15, 2000	Relative Risk	95% Confidence Interval		p-value
Alzheimer's	1.58	1.04	2.39	0.03
Mortality	3.22	1.17	8.87	0.02
For Follow-up Through March 23, 2001				
Alzheimer's	1.64	1.12	2.39	0.01
Mortality	2.41	1.14	5.10	0.02

Final Mortality Results from Alzheimer's Studies

Independent Intention-to-Treat Analyses, Including All Data From Studies 078 and 091 [c]

Cause of Death	n=1069 (2060 Person-Years)	n=1074 (2209 Person-Years)	HR (95% CI)	*P* Value
Cancer	12	11	1.19 (0.78-2.94)	.41
Noncancer	45	18	2.71 (1.57-4.68)	<.001
Heart disease	21	6	3.84 (1.54-9.51)	<.005
Other	24	12	2.15 (1.07-4.29)	<.05
Total mortality	57	29	2.13 (1.36-3.33)	<.001



Ethical Violations by Merck in Study 078

- Ethical Violations:
  - Study was continued when there was evidence that the risk/benefit ratio was high.
  - In 2002 patients in 078 were reconsented to continue in the study. They were not informed of the mortality findings from 091 and 078 or the Vigor findings. This violates the informed consent provisions of the Declaration of Helsinki.
  - The IRB's and investigators were not informed of the mortality data.
  - The company persisted in marketing Vioxx until 2004 resulting in many MI's and deaths.

Lessons Learned and Remedies

- Pharmaceutical firms shouldn't run their own studies.
- Statistical analysis should be done by independent statisticians.
- The FDA should require independent DSMB's for all phase III studies and most other studies.
- When pharmaceutical firms want to do a study they should contract the study out to independent investigators and not be involved until reporting to the FDA of the findings are required.

The World Medical Association Declaration of Helsinki – as shown on the FDA Website

- **World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects**
- **Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989.**

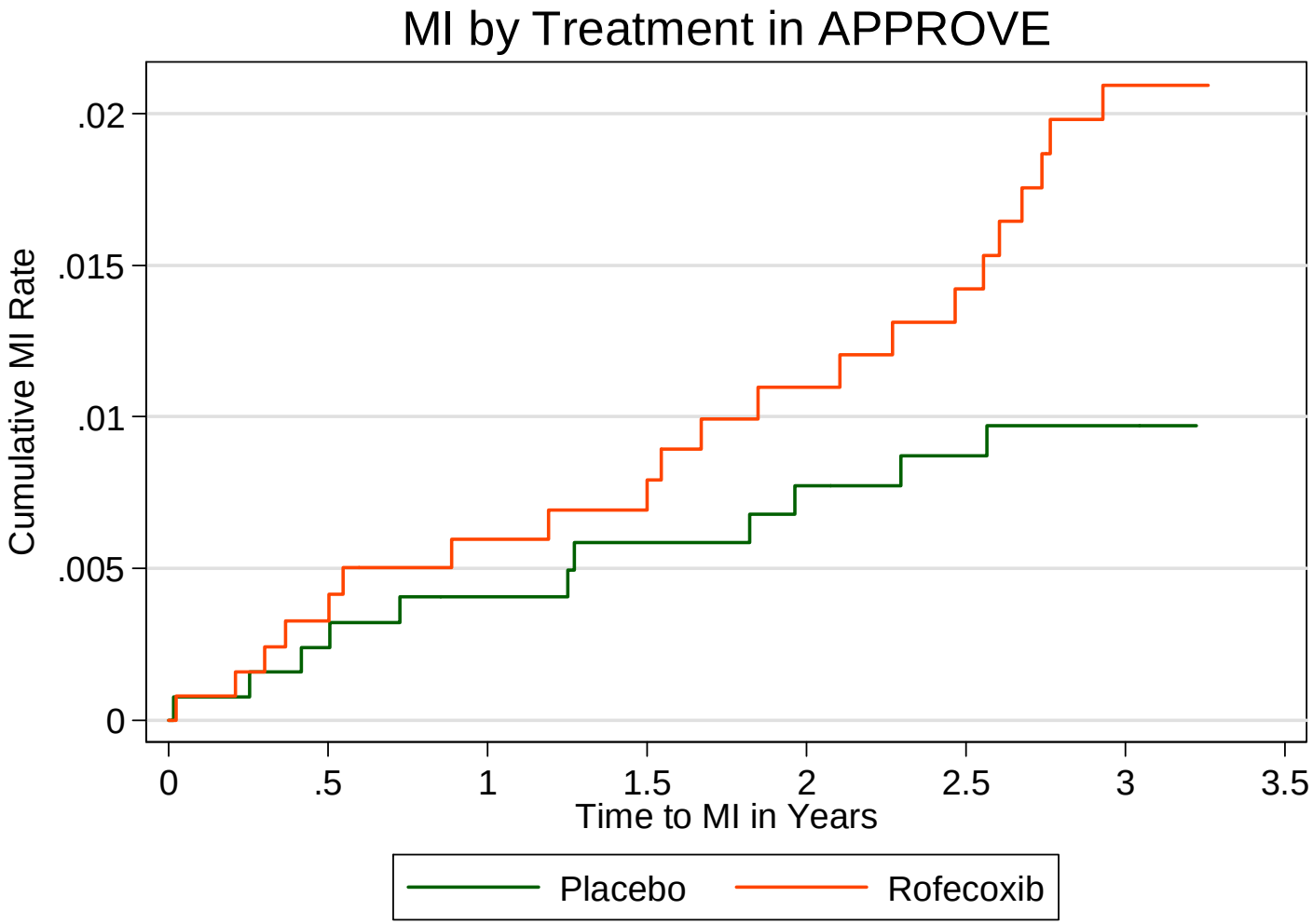
The World Medical Association Declaration of Helsinki – as shown on the FDA Website

- **Basic Principles** (Excerpts)
  - Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
  - Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
  - Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

The World Medical Association Declaration of Helsinki – as shown on the FDA Website

- **Basic Principles** (Excerpts)
  - In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

APPROVe MI Results (on Treatment)



All Merck Studies of Vioxx – MI Results

Relative Risk of MI by Study Population

Study Population	Relative Risk	95% Confidence Interval		p-value
Arthritis	2.24	1.31	3.84	0.003
Non-Arthritis	1.99	1.39	3.05	0.003
Overall Estimate (stratified)	2.09	1.48	2.95	0.00002

Cumulative MI Rates for All Merck Studies