

LAW AND JUSTICE

Vioxx Mock Trial

The Plaintiffs' Perspective on the Scientific Literature:
The Risks Outweigh the Benefits



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VIGOR Findings, Patient Perspective

	Naproxen, 1g	Rofecoxib, 50mg
Person-years	2714	2694
Ulcer complications	37	16
Rate/1000	13.7	5.9
Rate difference	0	-7.8
Cardiovascular events	20	45
Rate/1000	7.5	16.8
Rate difference	0	9.4

Sources: Bombardier et al, *N Engl J Med*, Weir et al, *Am Heart J* 2003;146:591; Mukherjee et al, *JAMA* 2001;286:954

VIGOR study
PUBLISHED 2001

“From the day the VIGOR trial was published, we should have known that naproxen was a safer alternative for patients.”

“There are 9.4 more serious cardiovascular events in the rofecoxib arm than in the naproxen arm.”

Rofecoxib, Serious Cardiovascular Disease^a

	Comparator		Rofecoxib		RR (p)
	Persons	Events	Persons	Events	
Development, Placebo	1678 ^b	32	2189 ^b	33	0.79(.33)
091 (25mg), AD, Placebo	346	11	346	4	0.36 (.07)
VIGOR (50mg), Naproxen 1g	4029	20	4027	45	2.27(.001)
APPROVe (25mg), Placebo	3315 ^b	25	3041 ^b	45	1.96(.007)

^a Sources: Weitz et al, *Am Heart J* 2003;146:591; Mukherjee et al, *JAMA* 2001;286:954; Bresler et al ACR abstract, 2004
^b Person-years

Development Program with pooled results

“These pooled analyses of many, many small trials, particularly in this field, have serious limitations.”

“Most are of very short duration. They may have different periods of follow-up for the NSAID and the comparator, and the events that they are studying are typically not events that they set out to study. Rather, they are adverse reactions reported in the course of the trial.”

“The effect of all these limitations will be misclassification, which would tend to obscure true differences. I think here we see an object lesson of just how much false assurance these kinds of analyses can give us.”

Rofecoxib, Serious Cardiovascular Disease^a

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a. Sources: Weir et al, *Am Heart J* 2003;146:591; Mukherjee et al, *JAMA* 2001;286:954; Bresalier et al ACR abstract, 2004

b. Person-years

The 091 Alzheimer's study

“Trial 091 in Alzheimer's disease trial was conducted in elderly patients at high risk of cardiovascular disease, presumably, and yet no evidence of increased risk. If anything, it looks like the trend is going the other way.”

“But look at how small the numbers of patients and the numbers of events are, which looks like a classic underpowered trial. Sometimes there's a tendency when we only have small amounts of data to put great faith in them, but when we are betting patients' safety on this, we should ask for adequately powered studies before we proceed.”

Epidemiologic Studies: Results

	Naproxen	Celecoxib	Rofecoxib, ≤25mg	Rofecoxib, >25mg
<i>Relative Risk</i>				
Ray ^a	0.92	0.88	1.02	1.93*
Mamdani	1.0	0.9	1.0	
Solomon ^b	0.97	0.93	1.21*	1.70*
Graham	1.18	0.86	1.29	3.15*
Kimmel	0.48	0.4	1.2	
* p<.05				

a. Results for New Users. b. Reference groups for rofecoxib are celecoxib ≤200mg and >200mg

Epidemiologic Studies

“Here are the findings of those studies with regard to naproxen. Until recently, here was a very active community promoting the hypothesis that naproxen was strongly cardioprotective. That was the explanation of the VIGOR finding.”

“The epidemiologic studies actually spoke to that issue. So what I'm going to show you for each of these NSAIDs is the relative risk.”

Epidemiologic Studies: Results

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a. Results for New Users. b. Reference groups for rofecoxib are celecoxib ≤200mg and >200mg

Epidemiologic Studies

“1.0 means no difference.”

“Less than 1.0 means cardioprotective.”

“Greater than 1.0 means cardiotoxic.”

Epidemiologic Studies: Results

	Naproxen	Celecoxib	Rofecoxib, ≤25mg	Rofecoxib, >25mg
<i>Relative Risk</i>				
Ray ^a	0.92	0.88	1.02	1.93*
Marndani	1.0	0.9	1.0	
Solomon ^b	0.97	0.93	1.21*	1.70*
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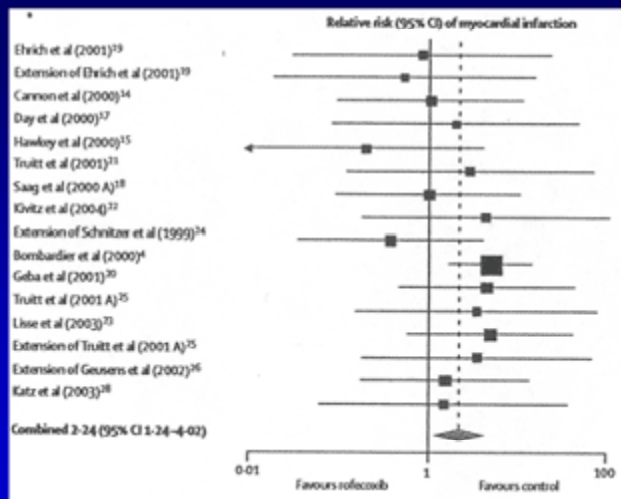
a. Results for New Users. b. Reference groups for rofecoxib are celecoxib ≤200mg and >200mg

Epidemiologic Studies

“Rofecoxib is different.”

“In each of the studies the relative risks are greater than those for either naproxen or celecoxib, and in three of the studies there was a dose-response, with a greater risk for the 50-mg dose.”

Meta-analysis of 18 Randomized Rofecoxib Trials (Juni et al, Lancet 2004)



Meta-analysis of randomized trials comparing rofecoxib with control

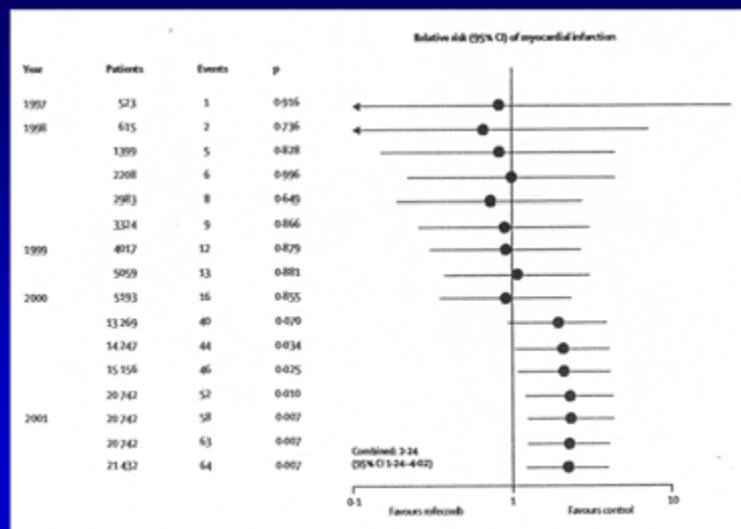
Meta-analysis

“No.”

“These are the data that appeared recently in *The Lancet*.”

“This is a meta-analysis of a large number of trials of rofecoxib vs. a variety of comparators. Many trials that were of far shorter duration than 18 months showed a difference between rofecoxib and the control agent in favor of the control agent. So I think it probably is not true that we have some unusual pathophysiology here.”

Meta-analysis of 18 Randomized Rofecoxib Trials (Juni et al, Lancet 2004)



Cumulative meta-analysis of randomized trials

Meta-analysis

“Our usual statistical standard is that the outcome was due to chance alone is no more than 1 in 20, *P* less than .05.”

“Conclusions from a meta-analysis, because of the issues of nonhomogeneity, etc., should be less than 1 in 100, *P* less than .01.”

“That bar would have been passed somewhere in 2001, when the value dropped below .01.”

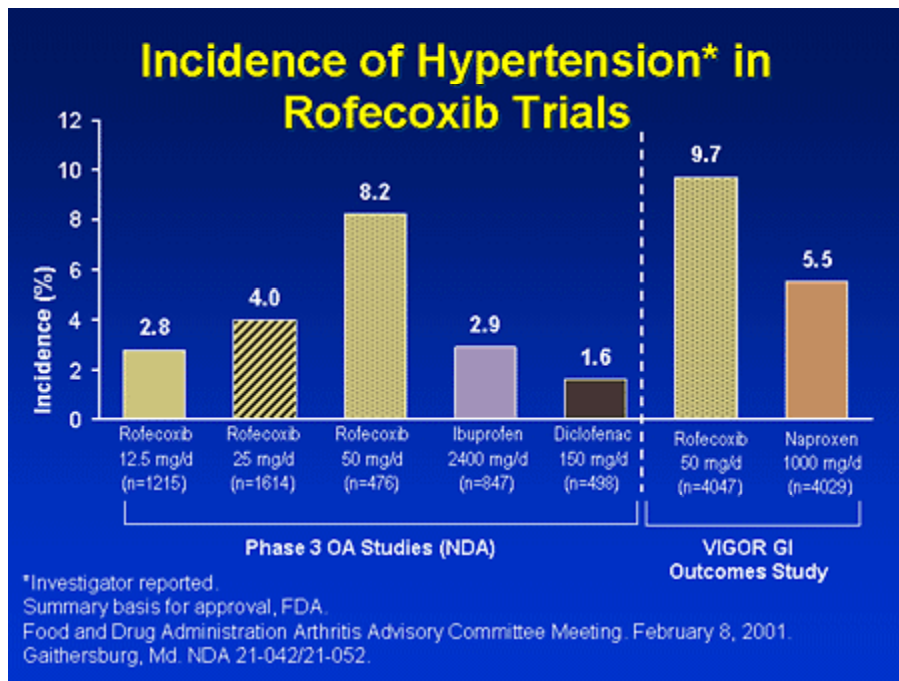
The plaintiff's second expert witness

Lee S. Simon, M.D.

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Boston, Massachusetts

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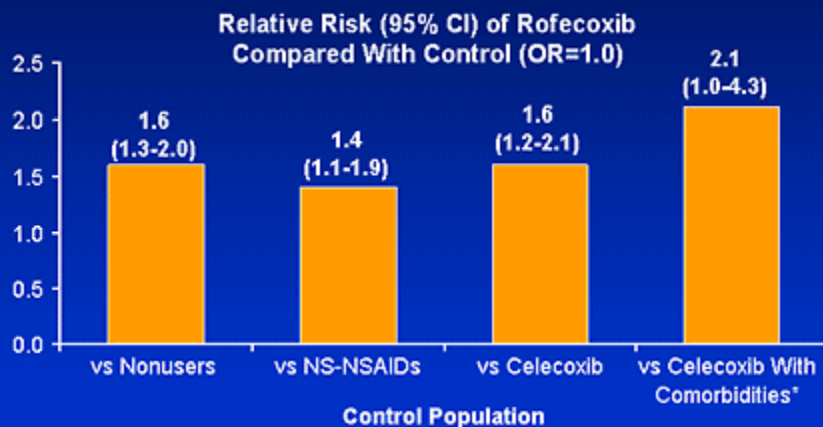




Hypertension

“We discovered early on that rofecoxib was quite unique. There was clear evidence that there was a statistically significant dose-response relationship for hypertension, particularly seen at the 50-mg dose in all of the OA studies. In addition, it was corroborated in the VIGOR trial and was statistically very similar compared with the active comparators.”

Risk for New Onset Hypertension With Rofecoxib and Other NSAID and Coxib Users Aged ≥ 65 Years

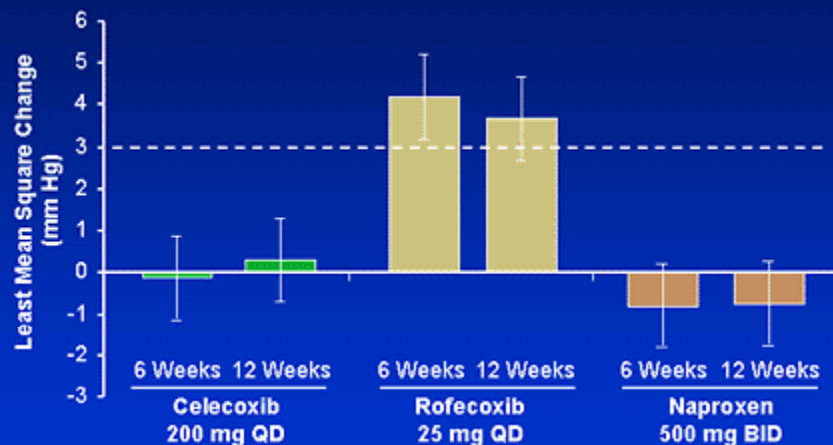


*Users w/history of chronic renal disease, liver disease, or congestive heart failure.
Solomon et al. *Hypertension*. 2004;44: 140-145.

Hypertension

“If you look at rofecoxib in the same data set compared with celecoxib, nonusers, and NSAIDs there is a significant risk of hypertension with rofecoxib that was unique to that particular therapy.”

CRESCENT: 24-Hour Mean BP Change, 6 and 12 Weeks



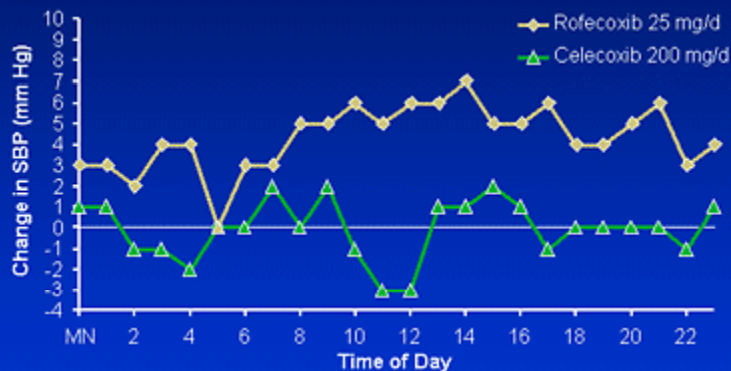
White et al. *Arch Intern Med.* 2004. In press.

Hypertension

CRESCENT study

“This patient population was quite unique. it was particularly at risk. All patients were being treated with antihypertensives, they were diabetic, and they had OA. At 6 weeks, there was an increased incidence of hypertension with rofecoxib compared with celecoxib and naproxen.”

CRESCENT: Ambulatory SBP Changes From Baseline After 6 Weeks of COX-2 Inhibitor Treatment



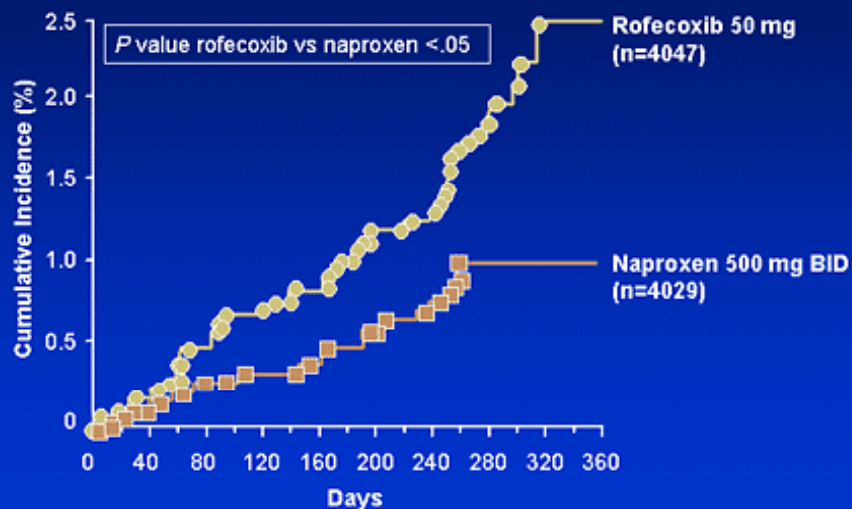
Overall $P = .039$.
White et al. *Arch Intern Med.* 2004. In press.

Hypertension

CRESCENT study

“The other interesting thing about this trial is that hypertension was determined as ambulatory blood-pressure monitoring, not just by cuff monitoring. Under these circumstances, looking at time of day, there was an interesting sustained continued effect after dosing with rofecoxib, a 4.2-mm rise in blood pressure compared with celecoxib, which has no sustained change over time, and this continued each day that was measured over the 6-week period.”

VIGOR: Serious Thromboembolic CV AEs



VIGOR study

“At about 80 days, there was a statistically significant difference that was carried out through the rest of the trial.”

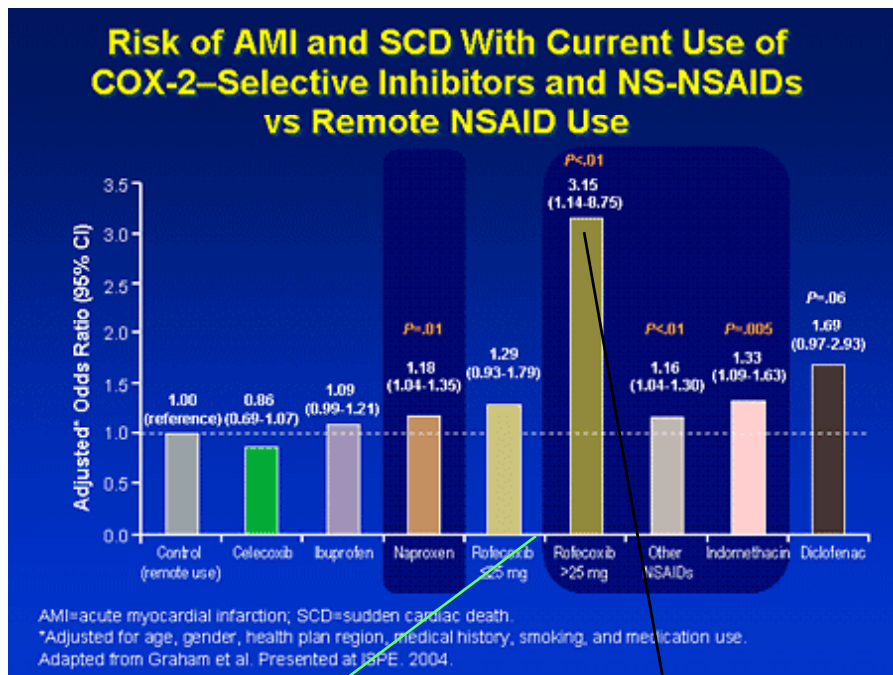
Adjusted Relative Risk of AMI With Rofecoxib Compared With Celecoxib

Time	Odds Ratio	95% CI	P Value
Days 1-30	1.43	1.12-1.83	0.005
Days 31-90	1.46	1.14-1.861	0.003
Days >90	1.04	0.223-1.38	0.8

Solomon et al. *Circulation*. 2004;109:2068-2073.

Heart attack in the first 90 days

“In data taken by Solomon *et al.* from Pennsylvania and New Jersey Medicare databases, comparing rofecoxib with celecoxib, you see in the first 30 days of exposure a clear and significant increased risk of AMI with rofecoxib.”



Vioxx ≤ 25 mg

Vioxx > 25 mg

FDA/Kaiser Permanente collaboration

“Rofecoxib at greater than 25 mg/day had a statistically significant increased relative risk of AMI and sudden cardiac death at 3.15. The relative risk for the 25-mg dose is 1.29.”

“Naproxen had a lower but nonetheless increased risk. I remind you of the argument that VIGOR did not show an increased event rate because naproxen was possibly protective.”

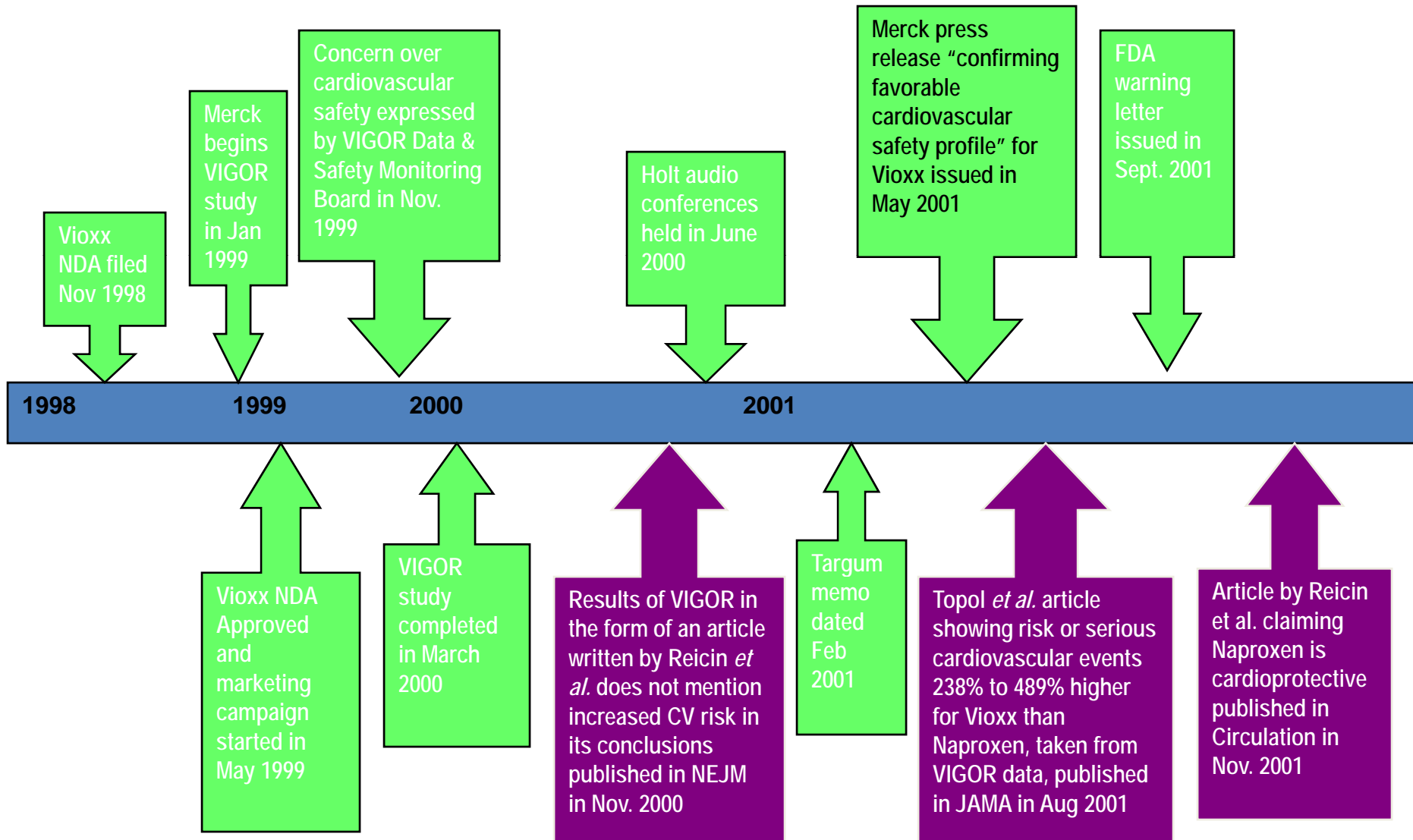
“In fact, these data, the most robust data we have had, would suggest that naproxen may actually cause this event.”

Merck's current naproxen position

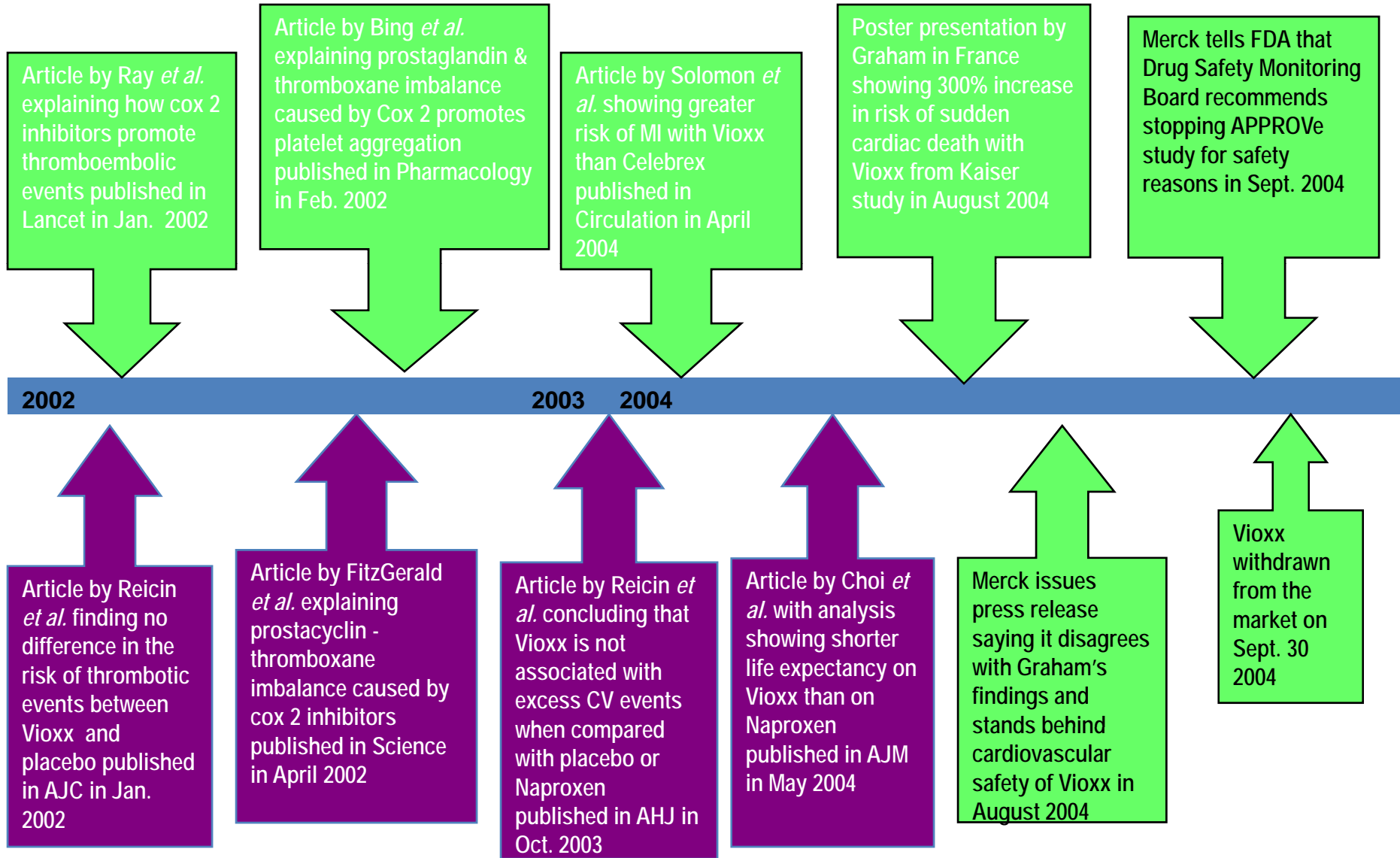
“No, no. I am not.”

Marvin A. Konstam, M.D., Tufts University, Merck consultant, lead author of pooled analysis published in *Circulation* in October 2001, speaking at the FDA Advisory Committee meeting on Feb. 16, 2005.

Vioxx scientific literature



Vioxx scientific literature



Plaintiff's third expert witness

FitzGerald Topol Singh, M.D

Professor of Medicine, St. Zydeco University

Edwin W. Edwards Center for Medicine and Ethics

Sinking Causeway, Louisiana



Edwards Medical Center Emergency Department entrance



General causation questions tailored to individual causation circumstances.

Q. Does reliable, published scientific literature show that Vioxx at 25 mg per day or higher increases the risk of having a heart attack?

A. Yes

Q. Does reliable, published scientific literature show that this increased risk can materialize by contributing to causing a heart attack within five months of starting on 25 mg per day of Vioxx?

A. Yes