

# Cox-2's

## Hype vs. Reality



Institute of Medicine

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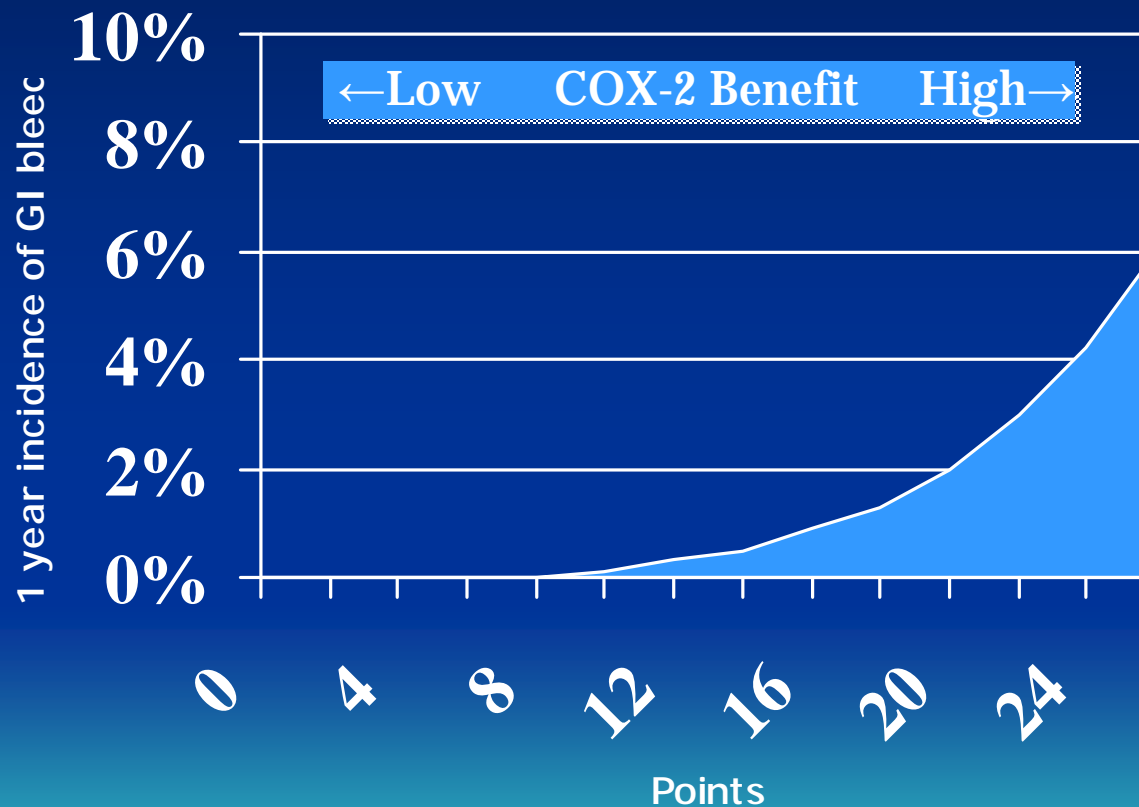
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# Overview

- Introduction of Coxibs – The Hope
- Usefulness in Practice - The Reality
- Potential Risks – Dangers - early signs
- Investigation of Risk - The Answers
- Recommendations

# GI Risk Prediction SCORE<sup>®</sup> Tool

(Predicts Risk of NSAID caused GI Bleed)



# CLASS

## Data Suppression?

- 6 month data showed GI benefit for Celebrex and was presented to JAMA with a resulting favorable editorial (Dr. M. Michael Wolfe- Gastroenterologist BU)
- 1 year data showing no benefit was available at the time of publication. "I am furious. . . . I wrote the editorial. I looked like a fool," said Wolfe Wash Post 9/17/01

# VIGOR

## Data Misleading?

NEJM Nov 2000

“The rate of death from cardiovascular causes was 0.2% in both groups. Ischemic cerebrovascular events occurred in 0.2% of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1% vs. 0.4%; 95 CI= 0.1-0.6; RR 0.2 CI=0.1-0.7)”

**”Our results are consistent with the theory naproxen has a (4x) coronary protective effect...” (Aspirin only .30 risk reduction)**

Bombardier, Laine, Reicin et.al NEJM Nov 23, 2000 1520-1527

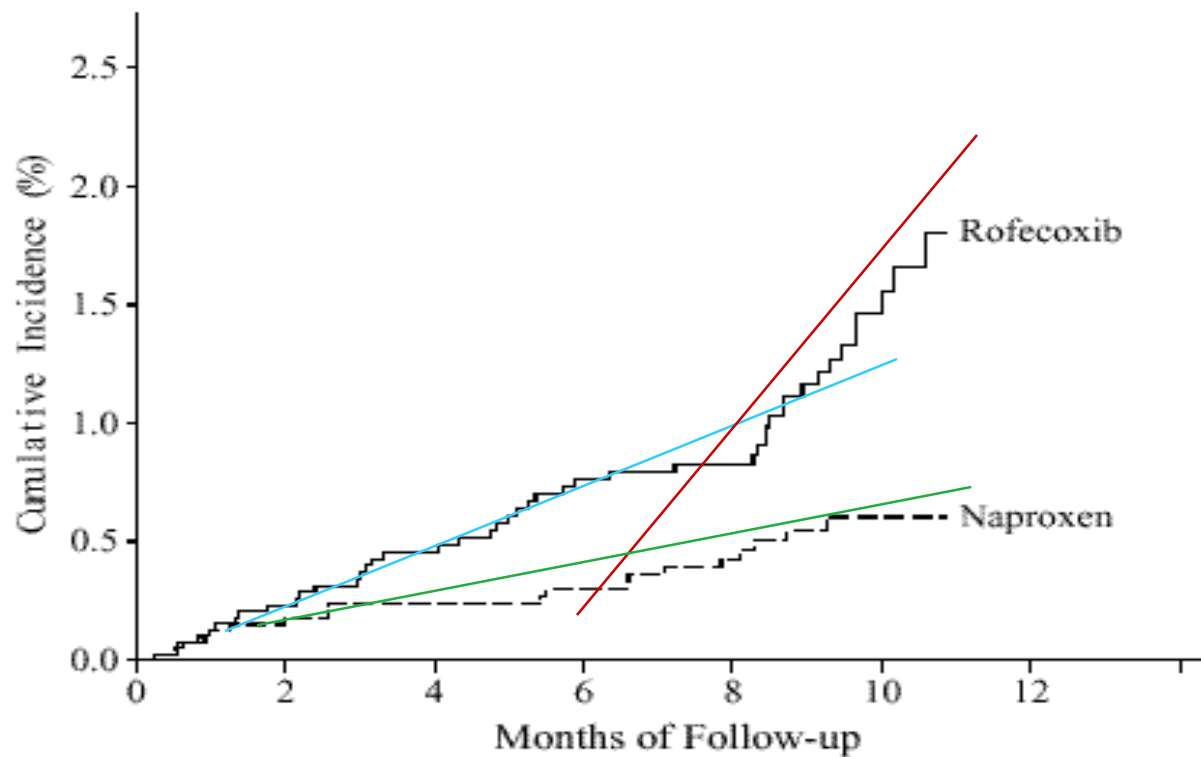
# Drug Trials

## Need for Transparency

“The Editor in Chief of the New England Journal of Medicine accused three of the largest drug companies of "making a mockery" of efforts to create transparency in clinical trials” WSJ 5-24-05

# COX-2 Cardiovascular Safety Concerns

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences  
in Rheumatoid Arthritis Patients in the VIGOR Study  
Time-to-Event Plot (All Patients Randomized)  
Updated Application Data



# at Risk	0	2	4	6	8	10	12
Rofecoxib	n=4047	3643	3405	3177	2806	1067	531
Naproxen	n=4029	3647	3395	3172	2798	1073	514

# **Risk of Acute Myocardial Infarction and Sudden Cardiac Death with Use of COX-2 Selective and Non-Selective NSAIDs**

**Lancet 1-25-2005**

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C Cheetham,<sup>2</sup> S Shoor,<sup>2</sup> G Levy,<sup>2</sup> and WA Ray<sup>3</sup>

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# Conclusions

- Rofecoxib use at a dose  $> 25$  mg/d increased the risk of AMI and SCD.
- Current use of several other NSAIDs appears to increase the risk of AMI and SCD.
- Naproxen is NOT protective
- 47% of Rofecoxib pts were  $>65$ .

# Direct-to-Consumer Advertising of COX-2 Inhibitors: Effect on Appropriateness of Treatment

Michele Spence, Craig Cheetham, Mirta Millares  
Kaiser Permanente  
Stephanie Teleki, RAND  
Stuart Schweitzer, UCLA School of Public Health

Medical Care Research and Review, Vol. 62 No. 5,  
(October 2005)

Funding: California HealthCare Foundation



# Results

- Patients who saw COX-2 ads and asked their doctor were 4 times more likely to be prescribed a COX-2 instead of a traditional NSAID according to guidelines (Adjusted OR=4.03, 95% CI=2.77-5.87, p=.001).
  - This finding was consistent across three different guidelines.
  - Suggests that DTC advertising leads to inappropriate prescribing.

# FDA Advisory Committee

## Feb 16-18, 2005

- 10 of the 32 Committee Members had recent consulting relations with Drug Manufacturers (NYT 2-25-05)
- HHS Secretary acknowledged conflicts but stated they were “mitigated”.
- The 17 to 15 vote allowing Vioxx to return to the market would have been 8 to 14 against it’s return had panelists with conflicts of interest been excluded
- Conservatively – The appearance of Conflict of Interest undermined the Advisory Committee’s review and credibility of FDA

10 Voters on Panel Backing Pain Pills Had Industry Ties  
NYT Feb 25, 2005

# Recommendations

- Drug Trial Transparency
- Advertising Limits/Oversight
- Address FDA post marketing surveillance  
Funding Constraints
- Implement Strong Conflict of Interest  
Policy re Advisory Committees