

CARDIOVASCULAR RISK and NSAIDs

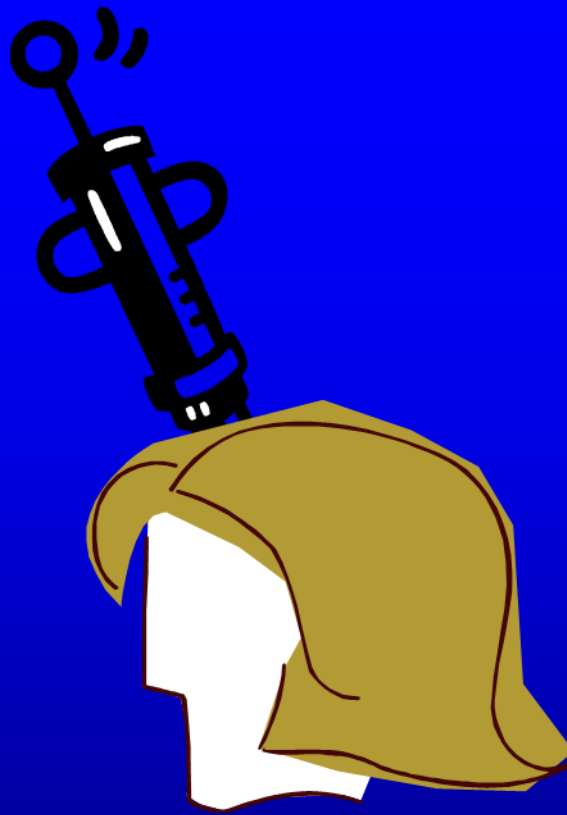
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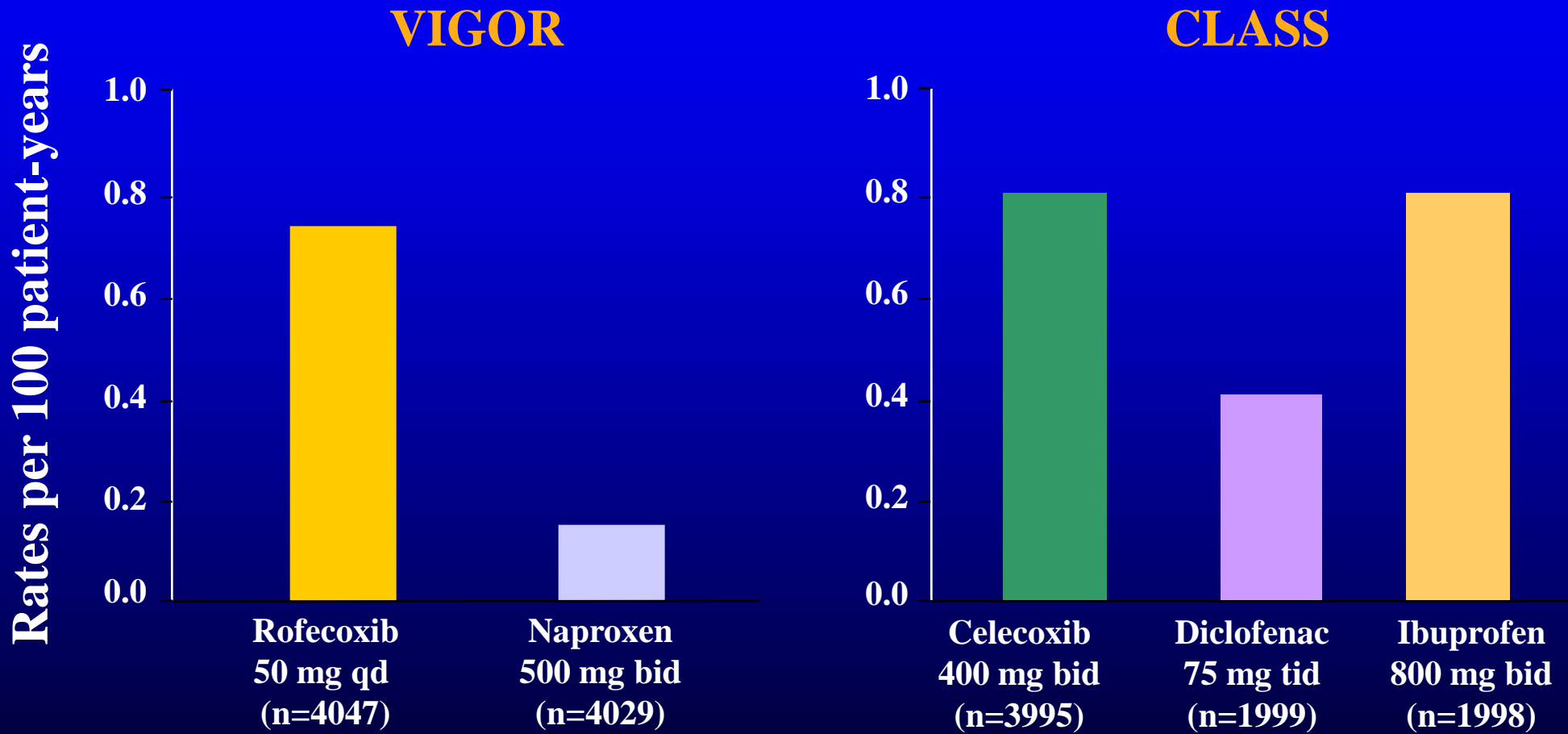
INTRODUCTION

- ❖ NSAIDs are most commonly prescribed drugs
- ❖ Recent evidence that cardiovascular mortality is increased by NSAIDs has raised much concern
- ❖ Debate surrounds the cardiovascular safety of selective cyclo-oxygenase-2 (COX-2) inhibitors
- ❖ Similar concerns about traditional NSAIDs
- ❖ The original rationale of NSAIDs is still valid
- ❖ Controversy and confusion prevail among clinicians about the optimum use of NSAIDs



**WHAT STARTED THE
CONTROVERSIES?**

Rates of MI in Original Randomized Trials of Vioxx and Celecoxib

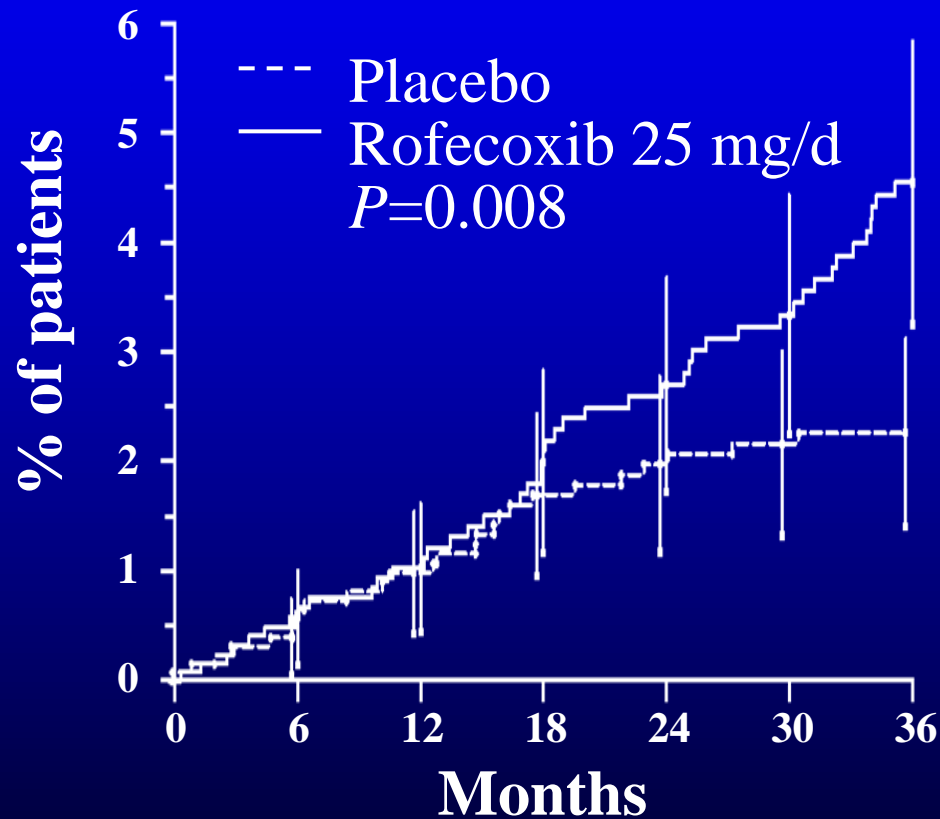


Bombardier C NEJM. 2000;343:1520-8 *Silverstein FE, JAMA. 2000;284:1247-55.*

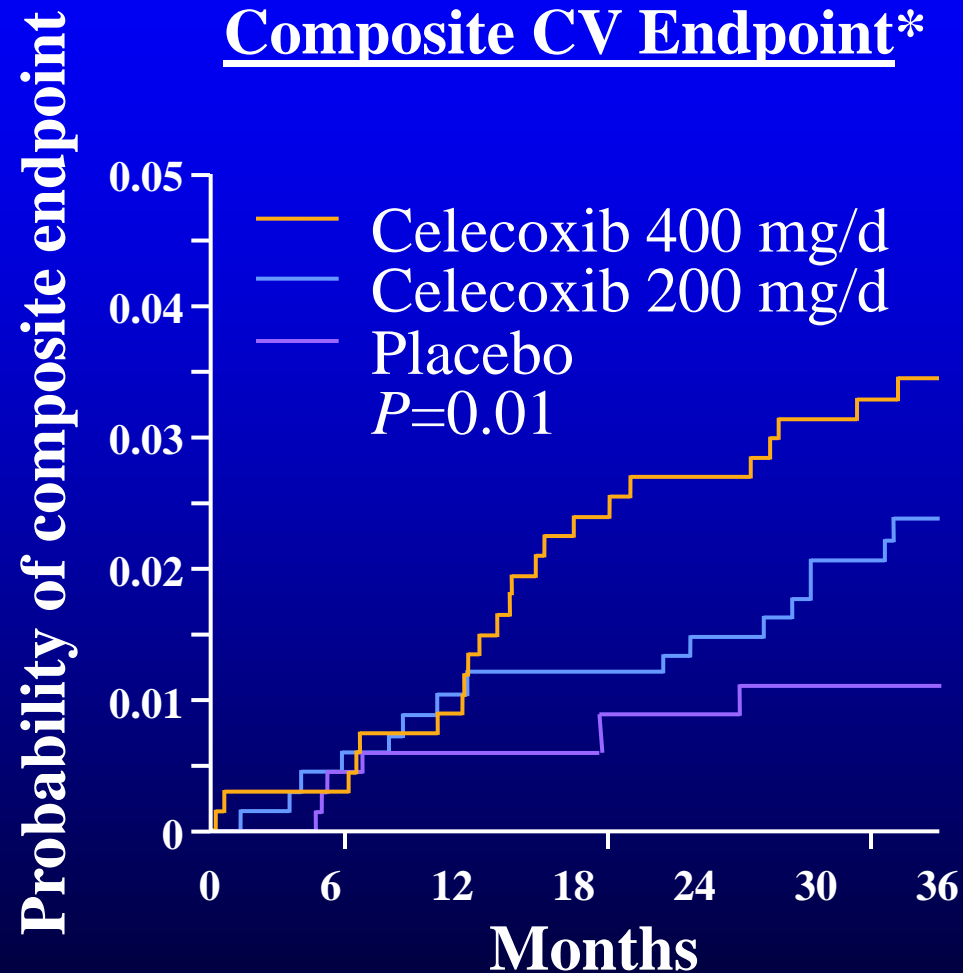
Mukherjee D, Nissen SE, Topol EJ JAMA 2001;286(8):954-959

Cardiovascular Results From Chemo-prevention Trials of Rofecoxib and Celecoxib

Confirmed Thrombotic Events



Composite CV Endpoint*



*Includes death from cardiovascular causes, myocardial infarction, stroke, or heart failure.

Bresalier et al. *N Engl J Med.* 2005;352:1092.

Solomon et al. *N Engl J Med.* 2005;352:1071.

FDA Class Warning

2005-6 FDA and European regulatory agencies added a warning of an increased thrombotic CV risk for all NSAIDs (both COX-2 selective and traditional)

Cardiovascular Risk

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS).

Questions arising with COX-2 selective and traditional NSAID therapies



1. Whether CV risk of NSAIDs varies with
 - a) clinical outcome?
 - b) individual drugs?
 - c) dose and duration?
 - d) according to patient characteristics?
2. Does greater COX-2 selectivity increase CV risk vs traditional NSAIDs?
3. How far are the OTC NSAIDs safe?
4. How to act in response to the latest evidences?

Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta analysis.

BMJ. 2011 Jan 11;342:c7086

Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. (2011)

- ❖ 31 trials in 116 429 patients with more than 115 000 patient years of follow-up were included.
- ❖ Naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo were allocated.
- ❖ The pre-specified primary outcome was fatal or non-fatal myocardial infarction.
- ❖ Secondary outcomes were fatal or non-fatal stroke; CV death, and death from any cause

Cardiovascular Risk with NSAIDs: Systematic Review of Population-Based Controlled Observational Studies

McGettigan P, Henry D (2011). PLoS Med 8(9): e1001098.

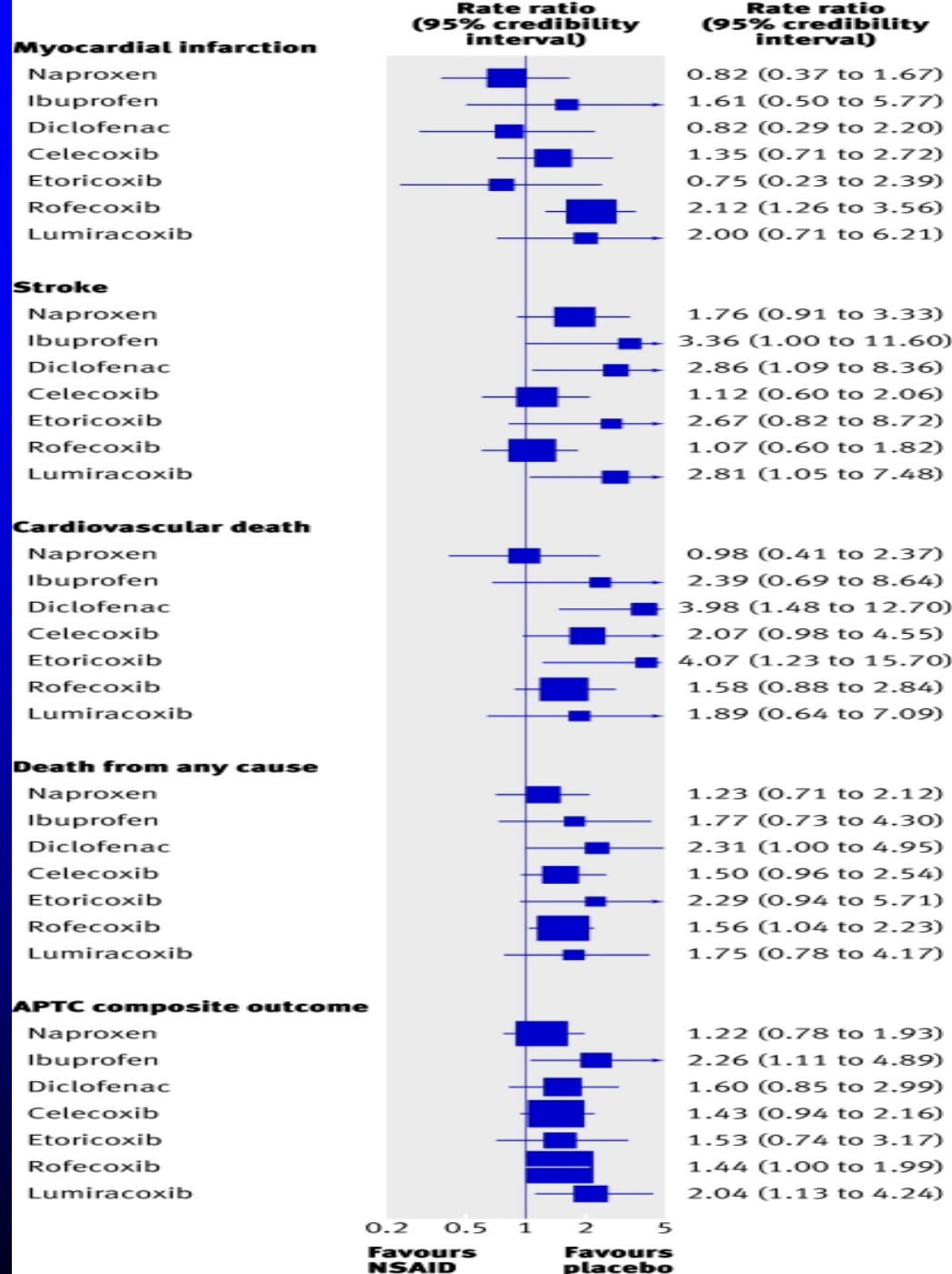
- ❖ 30 case-control studies included 184,946 CV events**
- ❖ 21 cohort studies described outcomes in >2.7 million exposed individuals**
- ❖ As both RCTs and observational studies have their strength and limitations, these meta-analyses together quite fulfil each other.**



Does risk vary with clinical outcome?

Fig:
Estimates of
rate ratios
for NSAIDs
compared
with placebo.

APTC=Antiplatelet
Trialists'
Collaboration



Safety profiles of individual drugs varied considerably depending on the outcome

Clinical outcome	Drugs with high rate ratio > 1.3	Drugs with low rate ratio
Myocardial Infarction	Rofecoxib(2.12, credibility interval 1.26 to 3.56), Ibuprofen (1.61, 95% 0.50 to 5.77), celecoxib (1.35, 0.71 to 2.72),	Naproxen, diclofenac, etoricoxib
Stroke	Ibuprofen(3.36, 1.00 to 11.60), Diclofenac(2.86, 1.09 to 8.36), Etoricoxib(2.67, 0.82 to 8.72)	
CV death	Etoricoxib(4.07, 1.23 to 15.70), Diclofenac(3.98, 1.48 to 12.70), Celecoxib(2.07, 0.98 to 4.55)	Naproxen
Death from any cause	Diclofenac(2.31, 1.00 to 4.95), Etoricoxib (2.29, 0.94 to 5.71),	

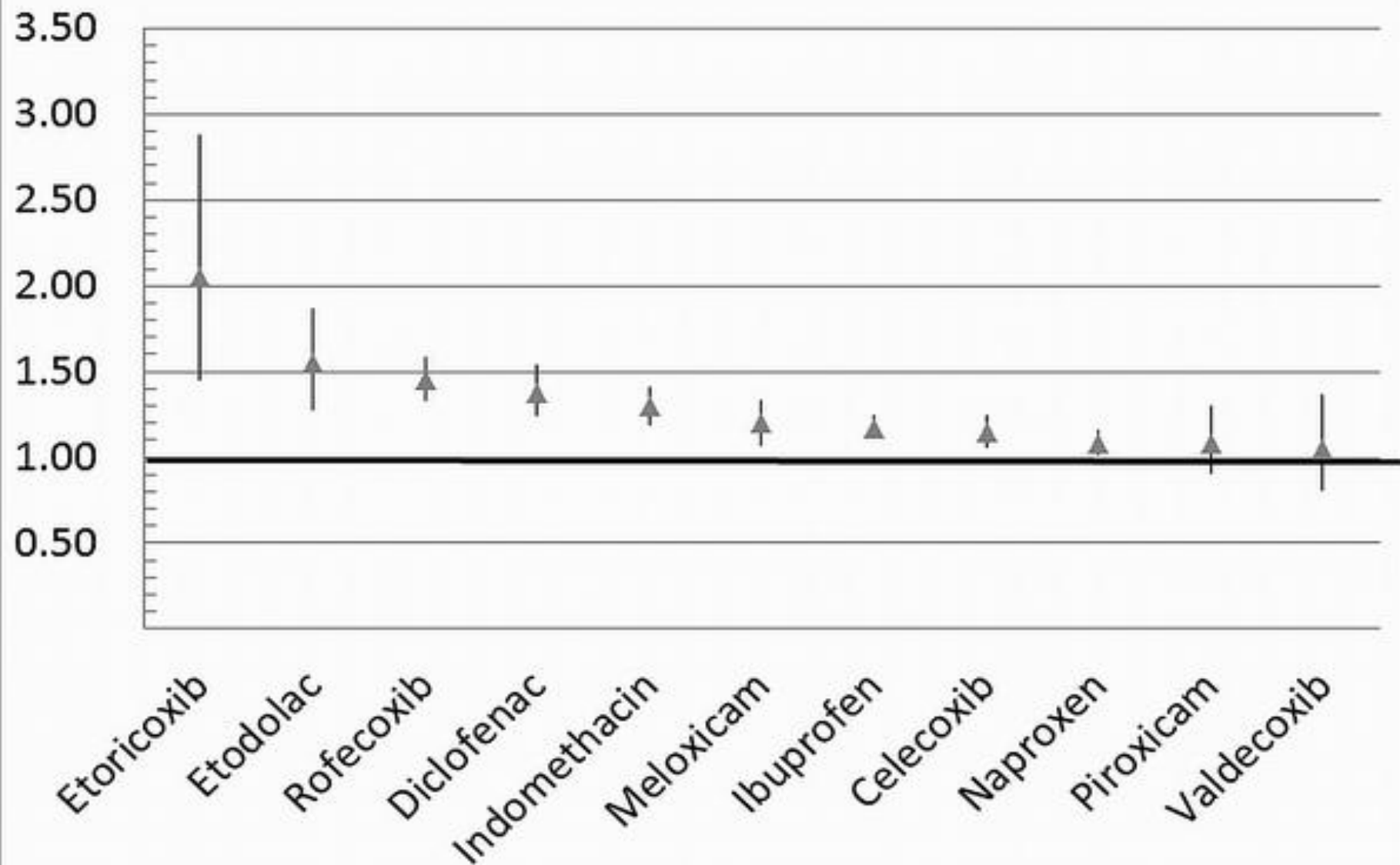


Does risk vary with individual drugs?

Relative risks for individual NSAIDs

- ❖ Rofecoxib, 1.45 (95% CI 1.33, 1.59), and Diclofenac 1.40 (1.27, 1.55) had the highest overall risks
- ❖ Naproxen, 1.09 (1.02, 1.16) and Ibuprofen, 1.18 (1.11, 1.25) had the lowest overall risks
- ❖ Celecoxib, in the pair-wise analyses, was similar to naproxen. But, in the overall analyses, and in the investigations of dose, it had risk increases.
- ❖ Indomethacin was quite close to diclofenac
- ❖ Among less extensively studied drugs:
 - ✓ Etoricoxib had high risks
 - ✓ Meloxicam and piroxicams' risks were low

Summary Data 2000 - 2010





Does risk vary with dose?

RESULTS: THE DOSE ANALYSES

- ❖ An apparent increase in risk with dose was seen for all drugs except naproxen
- ❖ Risk was elevated with low doses of
 - ✓ Rofecoxib
 - ✓ Celecoxib
 - ✓ Diclofenac
- ❖ Ibuprofen risk was only evident with higher doses
- ❖ Naproxen had no additional risks at any dose.



Does risk vary with duration?

RESULTS: Timing of Risk Increase

- ❖ Most of the NSAIDs show increases in risk within the first month of treatment
- ❖ Diclofenac increased risk from the beginning of treatment and had the highest risk, with a hazard ratio of 3.26 (95% CI 2.57, 3.86)
- ❖ Ibuprofen after 7 d
- ❖ Celecoxib after 14–30 d
- ❖ Rofecoxib was increased after 7–14 d



Does greater COX-2 selectivity increase cardiovascular risk?

- ❖ **No clear relation between specificity of COX-2 inhibitors and risk of cardiovascular events.**
- ❖ **Other mechanisms need to be considered.**
- ❖ **Multi-factorial: differential effects on-**
 - ✓ **prostacyclin and thromboxane A₂ synthesis**
 - ✓ **endothelial function and nitric oxide production**
 - ✓ **blood pressure**
 - ✓ **volume retention and other renal effects**
 - ✓ **pharmacokinetics**



**Does CV events increase with
previous cardiovascular risk?**

Estimated RRs of cardiovascular events according to risk of cardiovascular disease.

Information Reported	Drug				
	Rofecoxib	Celecoxib	Ibuprofen	Naproxen	Diclofenac
Low risk population	1.49 (1.28, 1.75)	1.16 (1.02, 1.31)	1.15 (0.99, 1.33)	1.29 (1.09, 1.46)	1.19 (1.07, 1.32)
High risk population	1.54 (1.28, 1.84)	1.17 (1.04, 1.31)	1.32 (1.10, 1.57)	1.23 (1.00, 1.50)	1.14 (0.99, 1.30)
<i>p</i> -Value for difference between RR estimates	0.787	0.921	0.242	0.709	0.625
Number of studies contributing data	11	11	6	9	6

Data are given as pooled RR (95% CI). Analyses are from studies that made paired comparisons of cardiovascular risk with individual drugs in low and high risk populations; the definitions of these populations are given in the text, and individual studies are described in Table S1. The RR values in this table differ from those in Table 1 because only a sub-set of all available studies provided data to assess the relationship between RR and background risk of cardiovascular events.

doi:10.1371/journal.pmed.1001098.t003

Importance of Background Risk

- ❖ **Background risk of cardiovascular events did not modify the RR in users of these drugs**
- ❖ **“Low risk” individuals are exposed to the same proportional increase risk as those at high background risk**
- ❖ **These findings are at odds with the results of an individual patient meta-analysis of randomised placebo-controlled trials of celecoxib**



How far are the OTC NSAIDs safe?

- ❖ **Observation that cardiovascular risk is not clearly associated with specificity of cyclo-oxygenase-2 inhibitors, implies that no NSAIDs are safe**
- ❖ **The review supports the calls for regulatory action on diclofenac, particularly as it is available without prescription in several countries**
- ❖ **In the case of ibuprofen, labelling warnings should be strengthened to avoid dosage above 1200 mg/d**



How do we respond?

Clinician's Note

- ❖ Chronic treatment **low CV** and **low GI risk**
 - Naproxen (2b, 2a)
 - Ibuprofen (2b, 2a)

- ❖ Chronic treatment **low CV** and **high GI risk**
 - Naproxen + proton pump inhibitor (2b, 2a)
 - Ibuprofen + proton pump inhibitor (2b, 2a)
 - Possibly celecoxib

Clinician's Note...

❖ Chronic treatment **high CV** and **low GI risk**

- ✓ Naproxen + Clopidogrel
- ✓ Ibuprofen + clopidogrel

❖ Chronic treatment **high CV** and **high GI risk**

- ✓ Naproxen + proton pump inhibitor + clopidogrel
- ✓ Ibuprofen + proton pump inhibitor + clopidogrel

THE CENTRAL DICTUM IN NSAID TREATMENT IS:

**Always prescribe the lowest effective
dose for the shortest possible time**

SUMMARY OF THE ANALYSES

- ❖ Among the NSAIDs analysed, naproxen seemed least harmful for cardiovascular safety
- ❖ Low dose Ibuprofen comes next, though may attenuate the antiplatelet effects of aspirin
- ❖ Benefits weighed against the drugs' GI risks
- ❖ While Celecoxib may be used with caution in low CV risk group, Etericoxib raise serious concerns
- ❖ Safety profiles of individual drugs varied considerably depending on the outcome, dose and duration but not absolutely on enzyme selectivity

LIMITATIONS

- ❖ **The number of events for most outcomes was low and estimates of ratios imprecise**
- ❖ **Observational studies are subjected to a range of biases**
- ❖ **Data derived from large linked administrative databases or electronic health records**
- ❖ **In the absence of large scale comparative trials we cannot determine which best serves patients**

CONCLUSION

- ❖ **Drugs for symptomatic relief must be evaluated with regard to the target symptoms as well as less frequent yet serious adverse effects**
- ❖ **Assessment of absolute risks regarding cardiovascular and kidney disease need to take into account in use of medications such as NSAIDs.**
- ❖ **The potential to make a substantial impact on chronic disease burden via improved use of NSAIDs is considerable**

THANK YOU