Clinical Appraisal on Risk & Harm Study
Section for Clinical Epidemiology and Biostatistics

Definition of Risk Study

Most often used to express the probability that a particular outcome will occur following a particular exposure is "RISK STUDY"
Principles

• Are the results valid? (Need to assessment!!)
• What are the results?
• Application or How can I apply this result to our patient care?

• Are the results valid? (Need to assessment!!)
  • Cohort study
    – Similar prognosis factors?
    – Method to detect outcome similar?
    – Sufficient of follow up?
  • Case-control study
    – Case vs. Control have circumstances that would lead to exposure
    – Same circumstances and methods to determine the exposure
  • Cross-sectional study

• What are the results?
  • Strong association between exposure and outcome
  • How precise was the estimate of risk

• Application?
  • Study patients similar to patients in my practices
  • Long sufficient follow up?
  • Similar exposure with my patients
  • What is magnitude of risk?
  • Are there any benefits that are know to be associated with exposure?
Example

- Does Soy milk increase the risk of developing peanut allergy in children?

Validity

- Similar prognosis
  - RCT: Limitation or unethical
  - Observational Studies
    - Cohort study
      - Similar prognosis factors?
      - Method to detect outcome similar?
      - Sufficient of follow up?
    - Case-control study
      - Case vs. Control have circumstances that would lead to exposure
      - Same circumstances and methods to determine the exposure
  - Adjusted analysis
Validity

• Ascertainment of exposure
  – How to measure the exposure
  – Recall bias?

Validity

• Outcome measurement
  – The same way
Validity

– Follow Up
  • Drop-out ?
  • Follow up complete ?

What is the range of validity ?
(Scoring in your mind)

• Similar prognosis
• Exposure ascertainment
• Outcome measurement
• Complete FU

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Result

- Magnitude of association

Exposure → Outcome

Relative risk
Odds ratio

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Results

- How precise of the association

Relative risk
Odds ratio

95% CI

P-value 0.001  0.09  0.103

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Application

• Our patients = Patients in this review
• Is FU long enough?
• Magnitude of risk: BIG?? vs. SMALL
• Should I stop the exposure?

Number needed to harm

• NNH: number of patients you need to treat to harm one of them for any odds ratio (OR)
• your patient's expected event rate for this adverse event if they were not exposed to this treatment (PEER):
  • \[ \text{NNH} = \frac{\text{PEER} (\text{OR}-1)+1}{\text{PEER} (\text{OR}-1) \times (1-\text{PEER})} \]
**NNH table**

<table>
<thead>
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<th>CER</th>
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<th>0.85</th>
<th>0.9</th>
<th><strong>Odds Ratios</strong></th>
<th><strong>NNTs for efficacy</strong></th>
<th><strong>NNTs for harm</strong></th>
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<td>0.05</td>
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<td>18</td>
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<td>0.7</td>
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<tr>
<td>0.9</td>
<td>12</td>
<td>15</td>
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<td>22</td>
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<td>34</td>
<td>46</td>
<td>64</td>
<td>101</td>
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</tr>
</tbody>
</table>

**Should I stop the exposure?**

- NNH = 1
- NNH = 50
- NNH = 100
- NNH = 500

- Itching
- Skin infection
- Limping
- Pain
- CVA
- Death
Application

- Patients’ preference
- Alternative treatment?

Example of Clinical Appraisal of Risk Study
Risk Drugs (Risk vs Harm)

- Glucosamine in OA
- High efficacy of ATB to treatment tonsillitis (Zithromax, Cephalosporin vs. S.pyrogenis)
- ASA/Anticoagulant in CVH
- Bromhexine in Asthma
- Nifedipine vs. Hypertensive crisis
- Cimetidine Rx PU compared with Ranitidine (More drug interaction metformin, Chloroquin)
- Clopidogrel vs low dose ASA rx noncardioembolic TIA with stroke

Lessons & Learnt form the withdrawal of Rofecoxib
Question

- 65 years old
- Female
- OA knee
- Received Vioxx (Rofecoxib) for 2 years
- Worry about CVS side-effect

Would you change analgesic drug?

3 skills for handling evidence:

- Forming answerable clinical questions
- Searching for the best evidence answer
- Critical appraisal
Categories of Clinical Questions

4 parts of clinical question

- Patient or Problem  \( P \)
- Intervention or exposure  \( I \)
- Comparison  \( C \)
- Outcome  \( O \)
Converting a clinical problem into a clinical question

1. Patient
   Among OA female patients…
2. Intervention
   Would treating with Vioxx
3. Comparison intervention
   compared with other NSAIDs…
4. Outcome : increased CV events

What EBM?

“Expertise in integrating
1. Best research evidence
2. Clinical Circumstance
3. Patient values
in clinical decisions”

Haynes, Devereaux, & Guyatt, 2002
Monitor change
Critical Appraisal of the Evidence

Cardiovascular events associated with Rofecoxib in a colorectal adenoma chemoprevention trial

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The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators

Funded by Merck Research Laboratories.


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Harm

Users’ Guides for an article about harm

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Are the results valid?

- Did experimental and control groups begin the study with a similar prognosis?
- Did the investigators demonstrate similarity in all known determinants of outcome; did they adjust for differences in the analysis?

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Are the results valid?

- Were exposed patients equally likely to be identified in the two groups?
- Did experimental and control groups retain a similar prognosis after the study started?
Are the results valid?

- Were the outcomes measured in the same way in the groups being compared?
Are the results valid?

- Was follow-up sufficiently complete?
  - Loss to follow-up?
What is the range of validity? (in your mind)

0 50 100

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What are the results?

• How strong in the association between exposure and outcome?

- Hazard Ratio
- Relative risk

• How precise is the estimated of the risk?

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rosflxib Group (N=1287)</th>
<th>Placebo Group (N=1299)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>46 (3.6)</td>
<td>26 (2.0)</td>
<td>1.92 (1.33–3.11)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21 (2.4)</td>
<td>12 (0.9)</td>
<td>2.80 (1.44–5.45)</td>
</tr>
<tr>
<td>Sudden death from cardiac causes</td>
<td>3 (3.0)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Laminar and proteinuria</td>
<td>7 (1.3)</td>
<td>4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>11 (1.7)</td>
<td>7 (0.5)</td>
<td>2.32 (0.88–6.74)</td>
</tr>
<tr>
<td>Fatal ischemic stroke</td>
<td>1 (0.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>5 (0.4)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular events</td>
<td>3 (0.2)</td>
<td>7 (0.5)</td>
<td>0.46 (0.04–2.03)</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis</td>
<td>2 (1.8)</td>
<td>1 (0.8)</td>
<td></td>
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<tr>
<td>Peripheral venous thrombosis</td>
<td>2 (1.6)</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>
How can I apply the results to patient care?

- Were the study patients similar to the patient under consideration in my practice?
- Was the duration of follow-up adequate?
- What was the magnitude of the risk?
- Should I attempt to stop the exposure?
Rofecoxib story

Biosynthesis of eicosanoids

Stimulus
Phospholipase A_2

Lipoxynogenases

12-HETE, 15-HETE, LTA_4

LTB_4, LTC_4, LTD_4, LTE_4

Anandamide Acid
Lycoxxygenases

COX-1 and COX-2

PGD_2, PGE_2, PGF_2 alpha, PGI_2, TXA_2
The COX-2 Hypothesis

Arachidonic acid

COX-1 constitutive

PGs
- GI cytoprotection
- Platelet aggregation
- Renal function (blood flow)

COX-2 inducible

PGs
- Inflammation
  - Fever
  - Pain
  - Headache
- Carcinogenesis

Rofecoxib development

- 1987 Two enzymes-cyclooxygenase COX-1 and COX-2
- 1999 First two drugs were approved by FDA (Food and Drug Administration)
  celebrex: CLASS
  rofecoxib: VIGOR
- 2004 Merck withdrew rofecoxib
  APPROVe trial
Drug development

- Conceptual work
- Preclinical toxicology testing on animals
- Investigational new drug application
- FDA acceptance of IND

Clinical trials

- Phase I
  - Include < 100 people, to establish safety
- Phase II
  - Include 100-1000 people, to establish efficacy
- Phase III
  - Include >1000 people, to confirm short and long term efficacy

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Clinical trial

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Clinical pharmacology / toxicology, safety, dose fining</td>
</tr>
<tr>
<td>Phase II</td>
<td>Initial clinical investigation for treatment effect, <strong>pilot study</strong></td>
</tr>
<tr>
<td>Phase III</td>
<td>Full-scale evaluation of treatment effect (<strong>efficacy</strong>)</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Post-market surveillance (<strong>effectiveness</strong>)</td>
</tr>
</tbody>
</table>
Efficacy study

• Efficacy trial: Does receiving treatment work under ideal conditions?
• Efficacy is established by restricting patients in a study to those who will cooperate fully with medical advice.

Effectiveness study

• Effectiveness trial: Does offering treatment help under ordinary circumstances?
• The extent to which a specific intervention, procedure, regimen, or service, when deployed in the field.
Efficiency

- The effects or end results achieved in relation to the effort expended in terms of money, resources and time
- The measure of the economy (or cost in resources) with which a procedure of known efficacy and effectiveness is carried out

Duration (years) | Chance of reaching the market (%)
--- | ---
2.5 | 10
1.5 | 20
2.5 | 50
3 | 80

- Preclinical development: 1,000 chemicals
- Phase I: 100 chemicals
- Phase II: 10 drugs
- Phase III: 1 drug
- Market approval: 80%
Evaluation of drug safety
Type of Adverse Drug Reaction

Type A
Expected/known mechanism, often dose-related
Eg. bradycardia from beta-blocker

Type B
Unexpected/ unclear mechanism, unclear causation
Eg. allergic reactions
Evaluation of drug safety
Type of Adverse Drug Reaction

Type A
Expected/known mechanism, often dose-related
Eg. bradycardia from beta-blocker

Type B
Unexpected/ unclear mechanism, unclear causation
Eg. allergic reactions

Type C
Unexpected/relation detected statistically
Eg. coronary deaths from rofecoxib

Hierarchy of Evidence

- Systematic reviews and meta-analysis
- Randomized controlled trial
- Cohort study
- Case-control study
- Cross-sectional study
- Case series
- Case report
22/04/57

Experimental

RCT
Quasi-experimental

Assign exposure

Natural exposure

Observational

Descriptive
No comparison gr.

Comparison gr.
Analytic

Case series
Cross-sectional

Cross-sectional
Cohort
Case-control

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Randomized controlled trials

Sample

Population of patients
With the Condition

Random sampling

Outcomes

Experimental
Improved
Not improved

Comparison
Improved
Not improved
Loopholes in ADR evaluation

<table>
<thead>
<tr>
<th>Phase</th>
<th>ADR type</th>
<th>Hierarchy of usefulness</th>
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<tbody>
<tr>
<td>Pre-clinic</td>
<td>A</td>
<td>Animal studies</td>
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<tr>
<td>Phase I</td>
<td>A, B</td>
<td>Cohort (before-after)</td>
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<tr>
<td></td>
<td></td>
<td>CS</td>
</tr>
<tr>
<td>Phase II</td>
<td>A, B</td>
<td>RCT (Cohort&gt;CC&gt;CS)</td>
</tr>
<tr>
<td>Phase III</td>
<td>A, B, C</td>
<td>RCT/Meta (Cohort&gt;CC&gt;CS)</td>
</tr>
<tr>
<td>Phase IV</td>
<td>A, B, C</td>
<td>CS&gt;Cohort&gt;CC&gt;RCT/Meta</td>
</tr>
</tbody>
</table>

CC=case-control, CS=case series

Sample size consideration

<table>
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<tr>
<th>ADR incidence</th>
<th>Background incidence</th>
<th>n</th>
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<td>1/100</td>
<td>0</td>
<td>360</td>
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<tr>
<td>1/10,000</td>
<td>520</td>
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</tr>
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<td>1/1,000</td>
<td>730</td>
<td></td>
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<tr>
<td>1/100</td>
<td>2,000</td>
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<td>1/1,000</td>
<td>3,600</td>
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<td>1/10,000</td>
<td>7,300</td>
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<td>1/1,000</td>
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<td>1/100</td>
<td>136,400</td>
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<td>1/5,000</td>
<td>0</td>
<td>18,200</td>
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<td>67,400</td>
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<td>1/1,000</td>
<td>363,000</td>
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</tr>
<tr>
<td>1/100</td>
<td>3,255,000</td>
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</table>
Rofecoxib development

- 1987 Two enzymes-cyclooxygenase COX-1 and COX-2
- 1999 First two drugs were approved by FDA (Food and Drug Administration)
  celebrex: CLASS
  rofecoxib: VIGOR
- 2004 Merck withdrew rofecoxib
  APPOVe trial

September 30, 2004

Dr Peter Kim, president of Merck Research Laboratories, said that the company was considering withdraw rofecoxib (Vioxx) from the market.
FDA Public Health Advisory: Safety of Vioxx

Merck & Co., Inc. today announced a voluntary withdrawal of Vioxx from the U.S. market due to safety concerns. Vioxx is a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms. It is also approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children.

The Agency was informed by Merck & Co., Inc. on September 27, 2004, that the Data Safety Monitoring Board for an ongoing long-term study of Vioxx (APPROVE) had recommended that the study be stopped early for safety reasons. The study was being conducted in patients at risk for developing recurrent colon polyps. The study showed an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx compared to placebo, particularly those who had been taking the drug for longer than 18...
VIGOR study
Vioxx Gastrointestinal Outcomes Research

- 8076 patients (over 40 yrs) with RA
- Rofecoxib vs. Naproxen
- Median F/U: 9 months
- Exclude pts with stroke in the last 2 years or MI/CABG in the last year or those who required ASA

Critical appraisal

- Short-term trial
- The exclusion of high-risk patients
- Methodologic inattention to CVS events

Minimized the possibility of evidence of CVS harm
Results

VIGOR study

- Primary endpoint: complicated GI endpoints (perforation, obstruction, or severe bleeding)
  0.6/100 pt-yr (ROf) vs. 1.4/100 pt-yr (Nap)

- MI
  0.53/100 pt-yr (ROf) vs. 0.13/100 pt-yr (Nap)

---

VIGOR study

NEJM 2000;343:1520-28

<table>
<thead>
<tr>
<th>Event</th>
<th>ROf</th>
<th>Nap</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI perforation</td>
<td>0.6/100 pt-yr</td>
<td>1.4/100 pt-yr</td>
</tr>
<tr>
<td>MI</td>
<td>0.53/100 pt-yr</td>
<td>0.13/100 pt-yr</td>
</tr>
</tbody>
</table>

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. Hemorrhagic cerebral 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 to 0.9 percent confidence interval, 0.2 to 0.7). Four percent of the study advance the evidence that the Food and Drug Administration (FDA) for the use of aspirin for secondary cardiovascular prophylaxis in patients with a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty, or coronary bypass has been made not taking low-dose aspirin therapy. These patients accounted for 18 percent of the patients in the subgroup who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group). When the data showing a reduction in the rate of myocardial infarction in the naproxen group became available after the completion of this trial, March, the manufacturer of rofecoxib, received more frequent reporting in ongoing studies of a change in the epidemic curve with a diminution in the rate of myocardial infarction.
Treatment effect

• Attributable risk reduction (ARR)
  \( I_c - I_{Rx} \)

• Number needed to treat (NNT)
  \( 1/\text{ARR} \)

• Number needed to harm (NNH)
  \( 1/I_{Rx} - I_c \)

The power of EBM

• NNT = \( 1/0.014-0.006 = 125 \)
• NNH = \( 1/0.053-0.0013 = 250 \)
The power of EBM

- NNT = 1/0.014-0.006 = 125
- NNH = 1/0.053-0.0013 = 250

For every 250 pts treated, 2 severe GI events are avoided but 1 MI is caused

The power of EBM

- Lacked of placebo group
- An increased cardiovascular risk with rofecoxib?
- A protective effect of naproxen?
Why?

• 11 of the 13 principal authors have had financial associations with Merck.

What they do next?

• Should be the study that address primary question of cardiovascular toxicity

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What they do next?

- Should be the study that address primary question of cardiovascular toxicity
- Instead, the efficacy trials designed to investigate the prevention of recurrent colonic polyps was launched, with monitoring of CVS events of safety

Observational study

- What if, a large case-control study conducted to test hypothesis whether or not the increase was from rofecoxib rather than waiting the results of RCT not designed to find the adverse effect.
- Sooner
- Less cost
- Not need large sample as in RCT
Can we trust meta-analysis?

Fallacy perpetuated
Meta-analysis

Konstam MA et al. Circ 2001;104:2280
Fallacy perpetuated
Meta-analysis

- **Conclusions**— This analysis provides no evidence for an excess of CV events for rofecoxib relative to either placebo or the non-naproxen NSAIDs that were studied. Differences observed between rofecoxib and naproxen are likely the result of the antiplatelet effects of the latter agent.

Konstam MA et al. Circ 2001;104:2280

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Fallacy perpetuated
Meta-analysis

- 5 of 7 authors were Merck employees
- Pooled composite endpoint of all-cause mortality, non-fatal MI, and non-fatal stroke
- Trials included were all Merck sponsored studies and were weighted with unpublished in-house phase II/III studies
Independent meta-analysis

- Lancet 2004;364:2021
- Cumulative meta-analysis
- Data from
  - Cochrane
  - MEDLINE
  - EMBASE
  - CINAHL

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Pete Jovic, Lin de Nooy, Stephan Reichenbach, Robbeka Bavinck, Paul A Deppe, Matthias Egger

Summary
Background The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the VIGOR trial, but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2001.

Methods We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint.

Findings We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20 742 patients) the relative risk from randomised controlled trials was 2.30 (95% CI 1.22–4.33, p<0.019), and 1 year later (144 events, 21 431 patients) it was 2.34 (1.14–4.42, p=0.007). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAIDs, or naproxen: p=0.41) or trial duration (p=0.42). In observational studies, the cardioselective effect of naproxen was small (combined estimate 0.16 [95% CI 0.05–0.28]) and could not have explained the findings of the VIGOR trial.
Meta-analysis of RCT comparing rofecoxib with control

Cumulative meta-analysis of RCT comparing rofecoxib with control
Mechanism

- COX-2 inhibitor
  - Lack of antiplatelet effect (inhibiting production of prostacyclin)
  - Without changing the production of the prothrombotic product, thromboxane.

Government ineptitude

- FDA approves drugs on the proviso that companies collect, and report all ADRs.
- Companies often promise post-marketing clinical trials but in practice, more than half are never undertaken.
- FDA under pressure to speed up approvals but no money for surveillance or analysis.
Lessons

1. Pharmaceutical companies cannot be trusted
2. Earlier critical appraisal might have helped
3. No substitute for independent external review
4. RCTs are not the best way to detect harm
5. Observational studies should not be forgotten
6. Healthy skepticism is good

Dr. Graham, associate director in the FDA's Office of Drug Safety, said an estimated 88,000 to 139,000 Americans had heart attacks and strokes as a result of taking rofecoxib.

The number, he said, far exceeds earlier disasters such as the 5000 to 10,000 children born in the 1960s with birth defects related to thalidomide.
Do no harm

Why Evidence-Based Medicine Practice?
EBM AS A CYCLE

Decision
Clinical circumstance and patient values
Assessment of applicability

Clinical Question
Systematic search for best evidence
Assessment of validity

What EBM is not:
• Cookbook medicine
• Overrules experience/expertise
• Always about RCT’s
• Always cost-minimizing

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Thank you