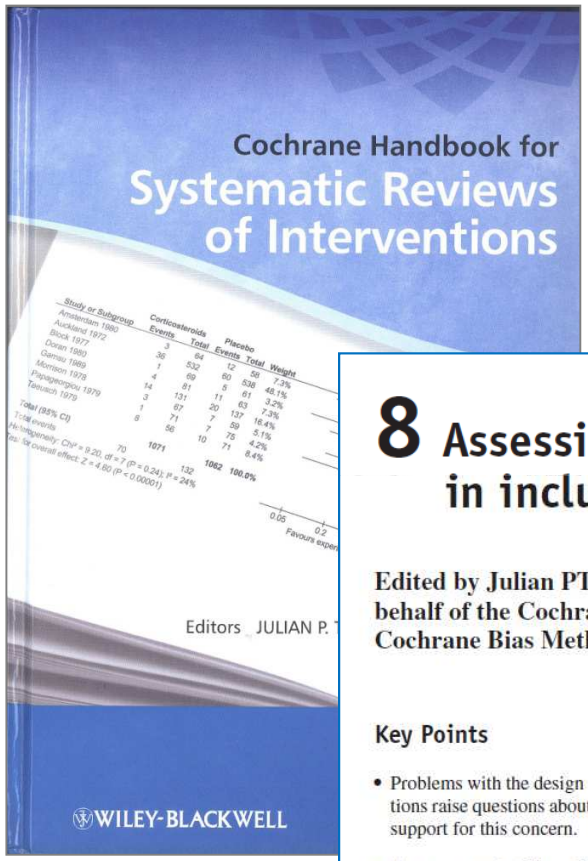
Why the Cochrane risk of bias tool should not include funding source as a standard item

Jonathan Sterne

Cochrane Methods Symposium, Quebec City

September 2013



8 Assessing risk of bias in included studies

Edited by Julian PT Higgins and Douglas G Altman on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group

Key Points

- Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings; empirical evidence provides support for this concern.
- An assessment of the validity of studies included in a Cochrane review should emphasize the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect.
- Numerous tools are available for assessing methodological quality of clinical trials. We recommend against the use of scales yielding a summary score.
- The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a description and a judgement for each entry in a 'Risk of bias' table, where each entry addresses a specific feature of the study. The judgement for each entry involves answering a question, with answers 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating either lack of information or uncertainty over the potential for bias.

BMJ 2011; 343: d5928

RESEARCH METHODS & REPORTING

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials

Julian P T Higgins,[1] Douglas G Altman,[2] Peter C Gøtzsche,[3] Peter Jüni,[4] David Moher,[5 6] Andrew D Oxman,[7] Jelena Savović,[8] Kenneth F Schulz,[9] Laura Weeks,[5] Jonathan A C Sterne,[8] Cochrane Bias Methods Group Cochrane Statistical Methods Group

Flaws in the design, conduct, analysis, and reporting of randomised trials can cause the effect of an intervention to be underestimated or overestimated. The Cochrane Collaboration's tool for assessing risk of bias aims to make the process clearer and more accurate

Randomised trials, and systematic reviews of such trials, provide the most reliable evidence about the effects of healthcare interventions. Provided that there are enough participants, randomisation should ensure that participants in the intervention and comparison groups are similar with respect to both known and unknown prognostic factors. Differences in outcomes of interest between the different groups can then in principle be ascribed to the causal effect of the intervention.[1]

Causal inferences from randomised trials can, however, be undermined by flaws in design, conduct, analyses, and reporting, leading to underestimation or overestimation of the true intervention effect (bias).[2] However, it is usually impossible to know the extent to which biases have affected the results of a particular trial.

Systematic reviews aim to collate and synthesise all studies that meet prespecified eligibility criteria[3] using methods that attempt to minimise bias. To obtain reliable conclusions, review authors must carefully consider the potential limitations of the included studies. The notion of study "quality" is not well defined but relates to the extent to which its design, conduct, analysis, and presentation were appropriate to answer its research question. Many tools for assessing the quality of randomised trials are available, including scales (which score the trials) and checklists (which assess trials without producing a score).[4-7] Until recently, Cochrane reviews used a variety of these tools, mainly checklists.[8] In 2005 the Cochrane Collaboration's methods groups embarked on a new strategy for assessing the quality of randomised trials. In this paper we describe the collaboration's new risk of bias assessment tool, and the process by which it was developed and evaluated.

SUMMARY POINTS

Systematic reviews should carefully consider the potential limitations of the studies included

The Cochrane Collaboration has developed a new tool for assessing risk of bias in randomised trials

The tool separates a judgment about risk of bias from a description of the support for that judgment, for a series of items covering different domains of bias

Development of risk assessment tool

In May 2005, 16 statisticians, epidemiologists, and review authors attended a three day meeting to develop the new tool. Before the meeting, JPTH and DGA compiled an extensive list of potential sources of bias in clinical trials. The items on the list were divided into seven areas: generation of the allocation sequence; concealment of the allocation sequence; blinding; attrition and exclusions; other generic sources of bias; biases specific to the trial design (such as crossover or cluster randomised trials); and biases that might be specific to a clinical specialty. For each of the seven areas, a nominated meeting participant prepared a review of the empirical evidence, a discussion of specific issues and uncertainties, and a proposed set of criteria for assessing protection from bias as adequate, inadequate, or unclear, supported by examples.

During the meeting decisions were made by informal consensus regarding items that were truly potential biases rather than sources of heterogeneity or imprecision. Potential biases were then divided into domains, and strategies for their assessment were agreed, again by informal consensus, leading to the creation of a new tool for assessing potential for bias. Meeting participants also discussed how to summarise assessments across domains, how to illustrate assessments, and how to incorporate assessments into analyses and conclusions. Minutes of the meeting were transcribed from an audio recording in conjunction with written notes.

After the meeting, pairs of authors developed detailed criteria for each included item in the tool and guidance for assessing the potential for bias. Documents were shared and feedback requested from the whole working group (including six who could not attend the meeting). Several email iterations took place, which also incorporated feedback from presentations of the proposed guidance at various meetings and workshops within the Cochrane Collaboration and from

Current Cochrane tool for risk of bias in randomized trials

- Six sources of bias (with optional 'Other')
- For each source,
  - Free text to describe what happened
  - Judgement: Low risk / Unclear risk / High risk of bias
- Some sources can be repeated for different endpoints

- **So should we add "source of funding" and classify industry-funded studies as at high risk of bias?**

Pharmaceutical industry trials

- Tend to be done by highly skilled and experienced professionals
- Tend to be based on detailed and extensively documented standardized operating procedures
- Little evidence that:
  - Trial methods are more likely to be flawed if a trial is industry-funded
  - Fraud is more likely if a trial is industry-funded
- **The problems are (mainly) with selective reporting of outcomes, non-reporting of whole studies, and choice of comparator**

NSAIDs

- A seminal study showed that in rheumatoid arthritis salicylates were more effective in relieving pain than pethidine
- But aspirin, like steroids, is not well tolerated, so it seemed that we needed some non-aspirin, non-steroidal anti-inflammatory agents (NSAIDs)
- A plethora of new NSAIDs were invented – indomethacin, ibuprofen, naproxen …. now = c. 30
- But toxicity of NSAIDs received increasing coverage (gut, renal, other)
  - Some people suggested that NSAIDs have no advantage over simple analgesics for painful disorders that are not inflammatory in origin

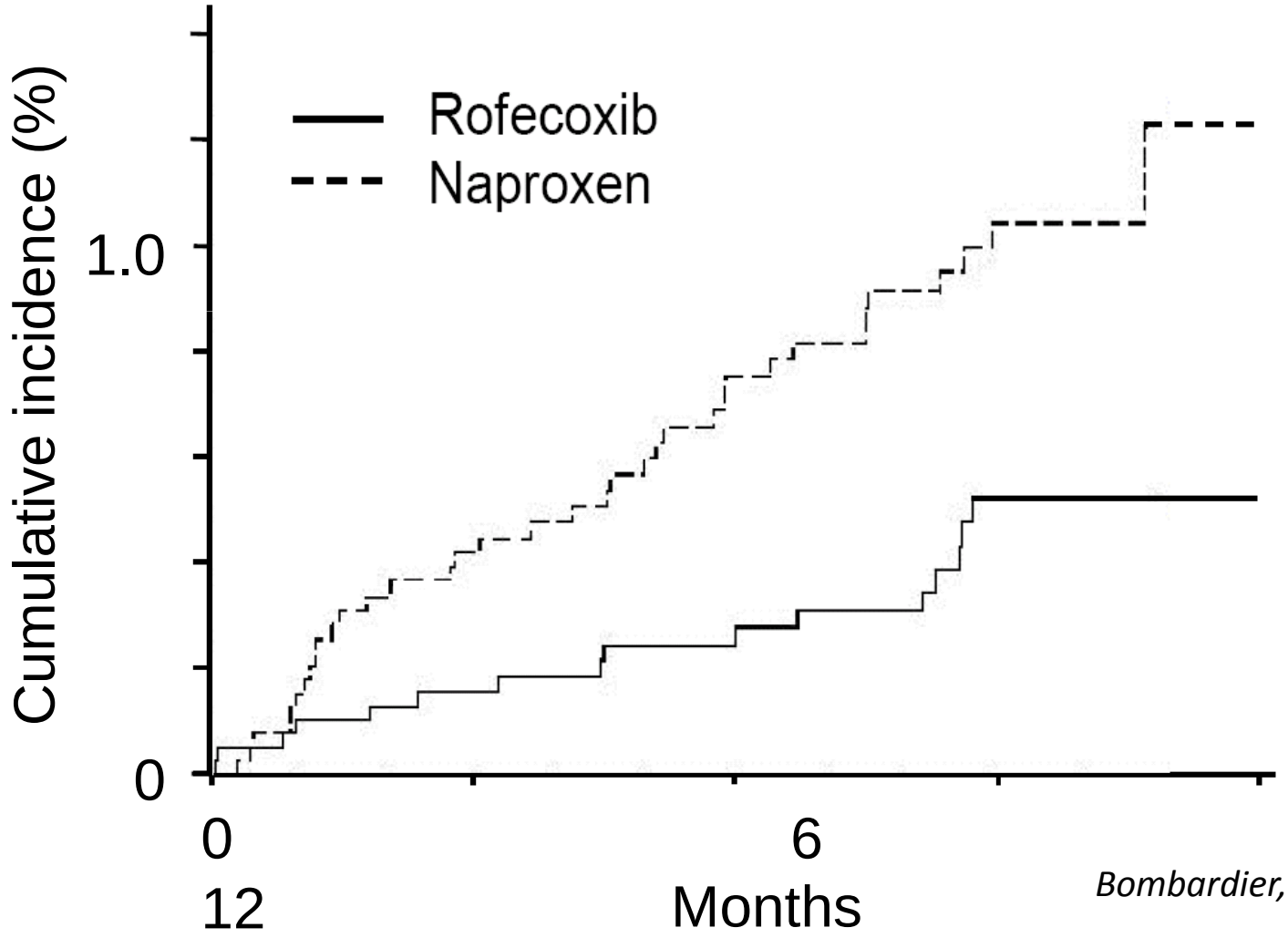
A new era……

- “There can be a bit of toxicity, but now we have these brilliant new COX-2 inhibitors that will do all the good things (anti-inflammatory and analgesic) and none of the bad things (GI toxicity)”
- COX-2 inhibitors were launched with aggressive marketing tactics
- They soon took over a large proportion of the existing $3 billion market, as well as expanding it

VIGOR

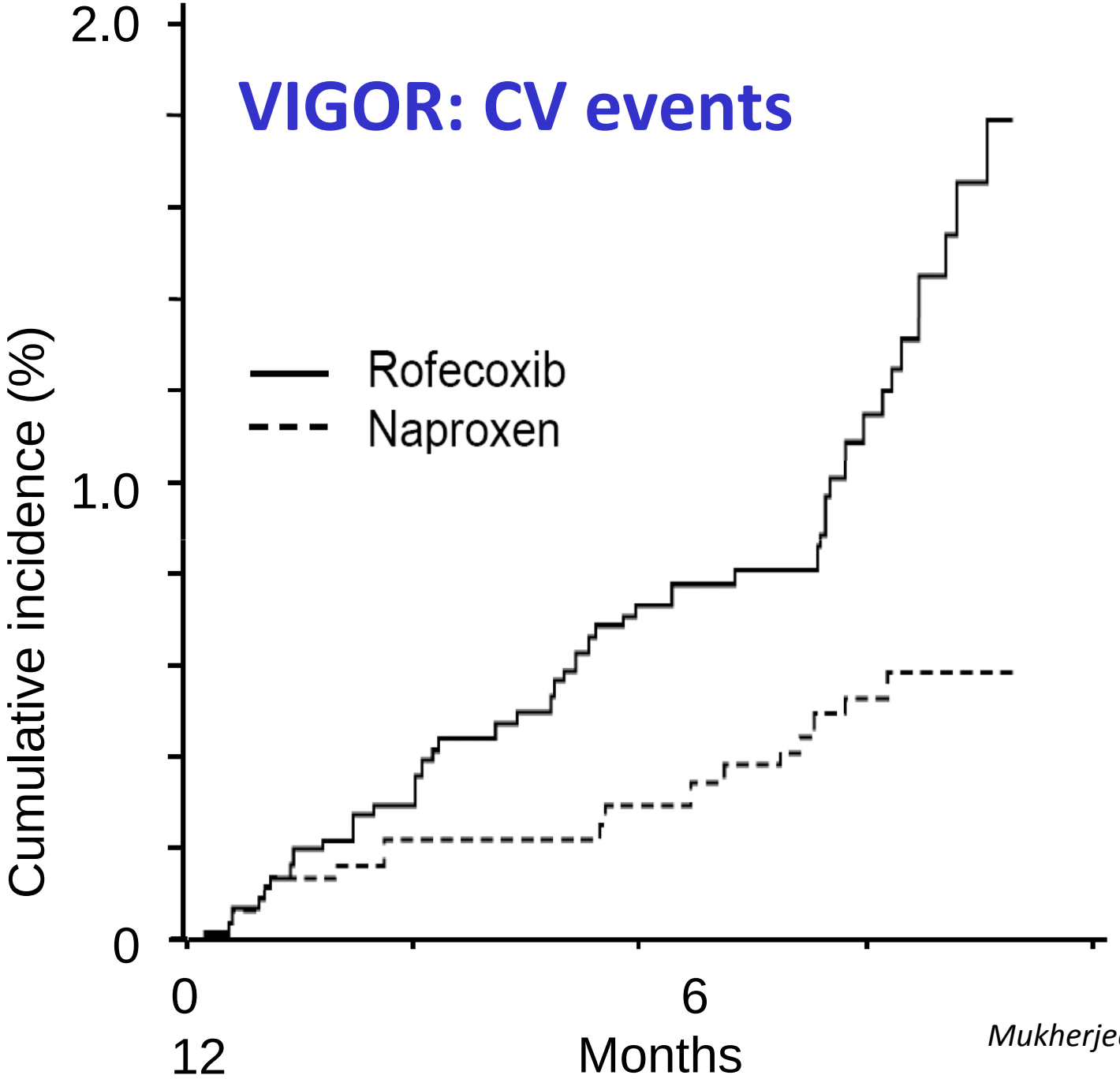
- Shows unequivocal evidence of less GI toxicity
- Shows a large increase in CV toxicity

VIGOR: Ulcer complications



Bombardier, Am J Cardiol 2002

VIGOR: CV events



Mukherjee et al, JAMA 2002

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D.,

Our results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection owing to its selective inhibition of cyclooxygenase-2 at its therapeutic dose and at higher doses.

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From the abstract

Results Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.6; $P<0.001$). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; $P=0.005$). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.

Conclusions In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. (N Engl J Med 2000;343:1520-8.)

Conflict of interest statement

Supported by a grant from Merck.

Editor's note: Our policy requires authors of Original Articles to disclose all financial ties with companies that make the products under study or competing products. In this case, the large number of authors and their varied and extensive financial associations with relevant companies make a detailed listing here impractical. Readers should know, however, that 11 of the 13 principal authors (C.B., L.L., R.B.-V., B.D., R.D., M.B.F., C.J.H., M.C.H., T.K.K., T.J.S., A.W.) have had financial associations with Merck — which sponsored the study — and, in most cases, with many other companies. The associations include consultancies, receipt of research grants and honorariums, and participation on advisory boards. The other two principal authors (A.R., D.S.) are employees of Merck. Details are included as part of the article on the *Journal 's* Web site (http://www.nejm.org).

Supported by a grant from Merck.

Dr. Bombardier has received clinical research support from Aventis Pharma, Merck Research Laboratories, and Merck Frosst Canada. She has served as a consultant to Knoll Pharmaceutical, Aventis Canada, Schering Canada, Merck Research Laboratories, and Wyeth–Ayerst.

Dr. Laine has received clinical research support from Merck, Wyeth– Ayerst, and AstraZeneca. He has served as a consultant to Merck, Searle, Johnson & Johnson, AstraZeneca, Wyeth–Ayerst, and Tap Pharmaceuticals.

Dr. Burgos-Vargas has received clinical research support from Merck Sharp & Dohme, Pfizer, and Boehringer Ingelheim. He has served as a consultant to Merck and has been a member of a speakers' bureau sponsored by Merck Sharp & Dohme.

Dr. Davis has served as a consultant to Mirvant, Merck Research Laboratories, Parke-Davis, and SmithKline Beecham.

Dr. Day has received clinical research support from Merck, Searle, Pfizer, Roche, and Amgen. He has served as a consultant to Merck, Searle, and Pfizer. He has been a member of speakers' bureaus sponsored by Merck Sharp & Dohme, Searle, Pfizer, and SmithKline Beecham.

Dr. Ferraz has received clinical research support from Bristol-Myers Squibb, Merck Sharp & Dohme, and Aventis Pharma. He has served as a consultant to Aventis Pharma.

Dr. Hawkey has received clinical research support from AstraZeneca, Asta Medica, Boehringer Ingelheim, Boots Healthcare International, Cell Tech, Eisai, Elan, Merck Research Laboratories, NicOx, and Novartis. He has served as a consultant to AstraZeneca, Abbott, Cell Tech, Eisai, Merck Research Laboratories, NicOx, Novartis, Parke-Davis, and Synthelabo Pharmacie. He has been a member of speakers' bureaus sponsored by AstraZeneca, Boehringer Ingelheim, Boots Healthcare International, Takeda, Wyeth Lederle, and Merck Research Laboratories.

Dr. Hochberg has received clinical research support from Merck and Quintiles (Aventis Pharma). He has served as a consultant to Aventis Pharma, Biomatrix, Merck, Negma Laboratories, Procter & Gamble, Roche, and Wyeth–Ayerst. He owns stock in Johnson & Johnson, Eli Lilly, Merck, Procter & Gamble, and Schering-Plough.

Dr. Kvien has received clinical research support from Merck, Searle, Aventis Pharma, and Schering-Plough. He has served as a consultant to Merck, Searle, Aventis Pharma, and Schering-Plough. He has been a member of a speakers' bureau sponsored by Merck and Aventis Pharma.

Dr. Schnitzer has received clinical research support from Abbott, Boehringer Ingelheim, Johnson & Johnson, McNeil Consumer Products, Merck, Novartis, Ortho-McNeil, Parke-Davis, Searle, and Wyeth–Ayerst. He has served as a consultant to Boehringer Ingelheim, Merck, Novartis, Ortho-McNeil, Searle, and SmithKline Beecham. He has been a member of speakers' bureaus sponsored by Boehringer Ingelheim, Merck, Ortho- McNeil, Wyeth–Ayerst, and Searle.

Dr. Weaver has received clinical research support from Merck, Searle, Immunex, Wyeth–Ayerst, Aventis Pharma, Pharmacia–Upjohn, Eli Lilly, Connetics, Parke-Davis, Procter & Gamble, Pfizer, Hoffmann–LaRoche, Centocor, Amgen, Cyprus Bioscience, Helsinn, Novartis, and Boehringer Ingelheim. He has served as a consultant to Merck, Searle, Immunex, Wyeth –Ayerst, Aventis Pharma, Pharmacia–Upjohn, Eli Lilly, Connetics, Parke-Davis, Procter & Gamble, Pfizer, Hoffmann–LaRoche, Centocor, Amgen, Cyprus Bioscience, Helsinn, Novartis, and Boehringer Ingelheim. He has been a member of speakers' bureaus sponsored by Merck, Searle, Immunex, Wyeth–Ayerst, Aventis Pharma, Pharmacia–Upjohn, Eli Lilly, Connetics, Parke-Davis, Procter & Gamble, Pfizer, Hoffmann–LaRoche, Centocor, Amgen,

Press release in May 2001 – “Merck reconfirms favourable cardiovascular safety of Vioxx ….numerous publications by Merck’s consultants and employees supported this notion”

MERCK

ONCE DAILY VIOXX® (rofecoxib)

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Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004—Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Peter Jüni, Linda Nartey, Stephan Reichenbach, Rebekka Sterchi, Paul A Dieppe, Matthias Egger

Lancet 2004; 364: 2021–29

Published online
November 5, 2004
http://image.thelancet.com/extras/04art10237web.pdf

See Comment page 1995

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 Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of
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Interpretation Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

On Sept 30, 2004, a press release from Merck announced the withdrawal of rofecoxib (Vioxx) because of an increased cardiovascular risk ... The decision was based on the 3-year results of the unpublished Adenomatous Polyp Prevention on Vioxx (APPROVe) study... By the time it was withdrawn, rofecoxib had been taken by an estimated 80 million people and sales had reached US$2·5 billion in 2003

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Lancet Cover

August 21st 2004

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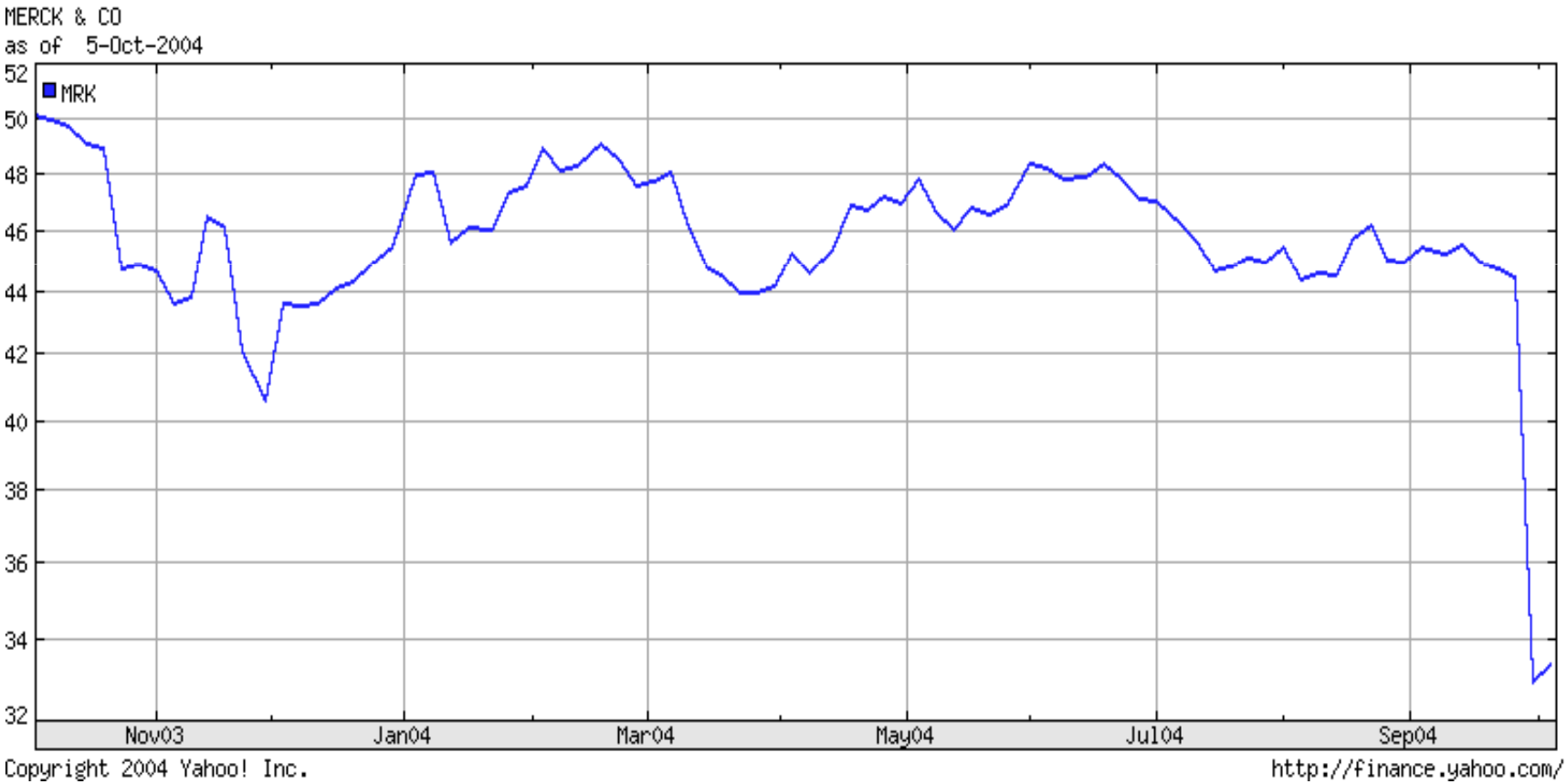

Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials

Patricia M Kearney, Colin Baigent, Jon Godwin, Heather Halls, Jonathan R Emberson, Carlo Patrono

BMJ 3 June 2006;332:1302–5

Conclusions Selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but high dose naproxen is not associated with such an excess.

Lessons from the Vioxx debacle

- Although unpublished data were accessed in subsequent meta-analyses, the results were staring the scientific community in the face
- The choice of comparator is likely to have been influenced by the interests of the trial sponsor
- **The important question is the best choice from among the wide range of possible NSAIDS, balancing benefits and harms (and costs)**

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Last Updated: Thursday, 22 November 2007, 12:18 GMT

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Pandemic flu drug order doubles

Britain is doubling its stockpile of antiviral medicines in preparation for any future flu pandemic, health secretary Alan Johnson has announced.

Some scientists believe a global flu pandemic could be imminent

This will be enough to treat about half the British population - the proportion scientists now believe could be hit by a pandemic.

Mr Johnson said the updated plan makes the country one of the most prepared in the world against pandemic flu.

Some scientists believe a global flu pandemic could be imminent.

Worse case scenario

Mr Johnson described the move as "defence in depth" based on a worst case scenario that up to 2.5% of people who fell ill with the flu would die.

He said the use of the anti-viral drug Tamiflu would be a key defence against pandemic flu in the weeks it would take to develop a vaccine against the culprit virus, but did not say what the financial cost would be.

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Tamiflu drug bill 'shocking waste of taxpayers' money'

The government spent £424m stockpiling a drug to treat flu despite there being question marks over the effectiveness of the medicine called Tamiflu, a public spending watchdog has found.

The **National Audit Office (NAO) report** reveals how much taxpayers' money was wasted.

Of the 40 million units of Tamiflu bought, a quarter were written off.

The antiviral drug is designed to ease flu symptoms

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Tamiflu Efficacy, Safety in Doubt, Says BMJ

Troy Brown
Nov 14, 2012

Print

EDITORS' RECOMMENDATIONS

- Adverse Drug Events Reporting News & Perspectives
- Influenza News & Perspectives
- Clinical Trials News & Perspectives

The *British Medical Journal* (*BMJ*) has alleged that pharmaceutical giant Roche is deliberately hiding clinical trial data about the efficacy of oseltamivir (*Tamiflu*) in patients with influenza. The journal says global stockpiling and routine use of the drug are not supported by solid evidence and alleges that Roche concealed neurological and psychiatric adverse events associated with the neuraminidase inhibitor drug.

In an open letter from Fiona Godlee, MD, editor-in-chief of [illegible] Professor John Bell, FRS, HonFREng, PMedSci,

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From: Maclean, Donald [mailto:donald.maclean@roche.com]
Sent: Thursday, 22 November 2012 8:38 PM
To: Chris Del Mar
Subject: Tamiflu Data

Dear Prof Del Mar

I am writing to you as the Coordinating Editor of the Cochrane Acute Respiratory Infections Group, concerning our debate on Tamiflu data. Over the last few years we have been corresponding concerning the requests of the Cochrane group for access to further Tamiflu data. Unfortunately, we have not been able to agree due to a combination of many factors including disagreement on the type of analyses you wish to do, the type of data you need to do them and constraints on making patient level data available.

We have been looking at how we may come to some mutually agreeable solution to the debate that focuses on the scientific and clinical aspects. Consequently, in order to reach an amicable resolution, Roche plans to set up a multi-party advisory board comprising experts from academia and private institutions, including the Cochrane Collaboration, to review the totality of Tamiflu data with the objective to agree on a statistical analysis plan outlining the types of analyses that would be useful in a public health discussion on Tamiflu. Once an analysis plan has been agreed the board would decide how best to execute the work.

We believe this proposal is a sensible, fair and transparent way of addressing this public debate and look forward to your consideration of this proposal.

Don MacLean
Life Cycle Leader - Tamiflu
phone 41 61 6882331

26 February 2013 Last updated at 13:00 ET

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Fergus Walsh
Medical correspondent
More from Fergus

Drug firm Roche pledges greater access to trials data

COMMENTS (16)

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The Tamiflu scandal

- It makes little sense (to me) to classify the published trial results as at high risk of bias
- **It is the meta-analysis that is biased, because it (almost certainly) omits the negative studies**

BMJ, 18 Sept 2004

Compulsory registration of clinical trials

Will be a requirement before submission to the BMJ from July 2005

"The case for registering all clinical trials - first advanced a decade ago - is now unanswerable." Editors of the *BMJ* and *Lancet* made this statement in 1999. Five years of industry resistance, government impotence, and public confusion followed. Medical journals persisted with noble intentions and wise words but were themselves in part resistant, impotent, and confused about how to enforce registration. Some journals, including the *BMJ*, tried an amnesty for unpublished trials, with little success.[3] The *BMJ* also considered asking for compulsory registration, but it seemed to us that trial registries were too diverse, disorganised, and easily disregarded to insist on registration before submission.

BMJ 2004;329:637–8

- **In September 2004 a number of major general medical journals announced that they will no longer publish trials that were not registered at inception**
  - "By suppressing negative findings and exaggerating positive ones, by downplaying harms and talking up benefits, healthcare decisions are based on incomplete data and ultimately harm the patients"


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Foam dressings for venous leg ulcers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomised in blocks of six to one of the two treatment groups using sequentially numbered, sealed opaque envelopes." Comment: sequence generation not reported.
Allocation concealment (selection bias)	Low risk	Quote: "Subjects were randomised in blocks of six to one of the two treatment groups using sequentially numbered, sealed, opaque envelopes." Comment: allocation process adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because the study was not blinded, secondary absorbent dressing and peri ulcer treatments used were at the discretion of the investigator." Comment: stated as not being blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Because the study was not blinded, secondary absorbent dressing and peri ulcer treatments used were at the discretion of the investigator." Comment: stated as not being blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: numbers withdrawing and reasons reported by group (Group 1: 14/60 (23%); Group 2: 5/58 (9%)) but a higher proportion of participants withdrew from Group 2 and analysis not undertaken as ITT.
Selective reporting (reporting bias)	Unclear risk	Comment: although all trial outcomes described in the published report are in the supplied RCT protocol, it was unclear from the published report what the primary outcomes were (maceration in the protocol). A secondary outcome of 'ability to adapt' in the protocol (translated from Danish) is not identifiable in the published report.

The current RoB tool does not work well for assessment of selective reporting

- Many authors classify this item as “unclear”
- Reliability is low
- More importantly:
  - It makes little sense to classify a reported result as biased because it comes from a study that failed to report a further result (eg relating to an adverse effect)
  - **The risk of bias is elsewhere** (in the meta-analysis examining the adverse effect)

New RoB NRS tool: bias in selection of the reported result

Signalling questions	*Rationale / Remark*
6.1 Is it unlikely that the reported effect estimate is available primarily because it was a notable finding among numerous exploratory analyses?	Exploratory studies may be entirely justifiable at an early stage of knowledge about associations between an intervention and outcomes, but In an exploratory NRS there is a serious risk of selective reporting if the researchers have tested many associations and reported only the ones that were statistically significant (or selected in some other way).
6.2. Is the reported effect estimate unlikely to be prone to selective reporting from among multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset are reported, there is a risk of selective reporting on the basis of results.
6.3 Is the reported effect estimate unlikely to be prone to selective reporting from among multiple *analyses* of the outcome measurements?	Analysts may implement different analytic methods to address the limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; different sets of covariates used for adjustment; different analytic strategies for dealing with missing data. If multiple estimates are generated but only one or a subset are reported, there is a risk of selective reporting.
6.4 Is the reported effect estimate unlikely to be prone to selective reporting from among different *subgroups*?	It is possible to generate multiple effect estimates for different subgroups. If multiple estimates are generated but only one or a subset are reported, there is a risk of selective reporting.

A new tool to assess reporting biases

- Should focus on searching for, identifying and accessing unpublished information
  - Much more important than funnel plots....
- Should include guidance from experts on how to access and use:
  - Trial protocols
  - Trial registries
  - Information available to regulators
- Assessments should be at the level of the meta-analysis (for an outcome), **not** at the level of an individual study

Addressing COI

- Should be a routine component of Cochrane reviews
- Relates mainly to the **context** in which the review results should be interpreted
  - If most of the information comes from a company with a commercial interest in the intervention of interest, that is vital contextual information
  - It is not in itself a reason to dismiss the accumulated evidence, but it may be a reason to search particularly hard for unreported or selectively reported evidence, and for careful scrutiny of the chosen comparator(s)

Dealing with inappropriate comparators

- Should be through
  - Intelligent and informed interpretation of pairwise meta-analyses
  - Routine use of network meta-analysis, so that we focus on the question of major interest, which is the best intervention from among all the candidates
  - Increased use of methods that integrate effects on benefits and harms, in order to facilitate informed treatment choices

Summary

- Conflict of interest in reporting of medical research is a huge problem, and we do not currently deal with it well
- There are particular problems associated with pharmaceutical-industry funded research
- These problems should be dealt with by:
  - Display of and comments on conflicts of interest as a standard component of Cochrane systematic reviews
  - Much better procedures, and a much improved tool, to assess reporting biases
  - More extensive use of mixed treatment comparisons
- These problems should not be dealt with by adding source of funding in systematic reviews

Conclusion

The fight to access all trial data is of fundamental importance to the Collaboration and to evidence-based health care

but

The Cochrane risk of bias tool should not include funding source as a standard item