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SPECIAL ARTICLE

# Unbalanced reporting of benefits and harms in abstracts on rofecoxib

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**Abstract**
*Purpose* It was predicted from the mechanism of action that, compared to older non-steroidal anti-inflammatory drugs, rofecoxib (Vioxx) would reduce gastrointestinal bleeding, but also that it would increase the occurrence of cardiovascular thrombosis. From the patient's point of view, both effects are important and should be investigated and reported similarly. We studied how they have been reported over time.
*Methods* We searched PubMed for abstracts on rofecoxib that commented on gastrointestinal bleeding or cardiovascular thrombosis or both. Two researchers, blinded to date of publication and authors, assessed the abstracts independently. We judged the authors' view on rofecoxib and comments on gastrointestinal bleeding and thrombosis as being favourable, neutral or unfavourable towards rofecoxib.
*Results* We included 393 abstracts commenting on gastrointestinal bleeding (72%) and cardiovascular thrombosis (54%) or both. Before October 2000, all abstracts ($n$=27) mentioned only gastrointestinal bleeding and 89% were positive towards rofecoxib. The year before the withdrawal of rofecoxib (October 2003 to September 2004) ($n$=46), 59% of abstracts commented on gastrointestinal bleeding only, 17% on thrombosis only, 24% on both and 67% were still positive. From October 2006 to September 2007 ($n$=54), 13% mentioned gastrointestinal bleeding, 54% thrombosis, 33% mentioned both and only 11% were positive.
*Conclusions* The reporting of benefits and harms was not balanced and changed markedly over time. Knowledge of increased risk of thrombosis existed early on, but the harms came into focus too late, when the drug was already withdrawn, and when tens of thousands of patients had been harmed unnecessarily.

**Keywords** Rofecoxib · Cyclooxygenase-2 inhibitors · Abstracts · Bias · Thrombosis · Gastrointestinal bleeding

## Introduction

Rofecoxib was marketed in 1999 as first-line treatment of osteoarthritis with the claim that it reduced pain as effectively as conventional non-steroidal anti-inflammatory drugs (NSAIDs), but with less gastrointestinal bleeding. However, the drug also caused serious thrombotic cardiovascular events [1, 2]. On 30 September 2004, Merck, the manufacturer, withdrew it from the market. Rofecoxib has been estimated to have caused the death of tens of thousands of patients because of thromboses [3].

The part of a paper that is most often read is the abstract and sometimes clinical decisions are based solely on abstracts [4, 5]. The recently published CONSORT guideline for abstracts states that any important adverse (or unexpected) effects of an intervention should be described in the abstract [5]. We quantified how often benefits and harms in terms of gastrointestinal bleeding and cardiovascular thrombosis, respectively, were reported in abstracts on rofecoxib, how often the drug was described favourably, and how this pattern changed over time.

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## Methods

### Search strategy and data extraction

One author searched PubMed (24 September 2007) using the search terms "Vioxx OR rofecoxib". All records with an abstract were assessed for inclusion by two observers independently. At the same time, they extracted the data using a pilot-tested data sheet. Any disagreements were settled by discussion. The observers were blinded to any information about authors and institutions and to the date of publication, and assessed only the title and the text of the abstract. The blinding was obtained by exporting the relevant parts of the PubMed records into Microsoft Excel.

### Inclusion and exclusion criteria

We included abstracts that commented on the effect of rofecoxib on gastrointestinal bleeding or cardiovascular thrombosis or both, and contained a comment reflecting the authors' view on rofecoxib. We accepted abstracts that implicitly referred to these harms by using phrases such as "gastrointestinal adverse effect" and "cardiovascular risk". We also included abstracts that commented on the effect of cyclooxygenase 2 (COX-2) inhibitors and other NSAIDs in general when these included rofecoxib, albeit indirectly, e.g. "celecoxib had no tangible advantage in terms of serious gastrointestinal complications … overall mortality was higher with celecoxib than in the placebo group. The difference was similar to that observed in placebo-controlled trials of rofecoxib in Alzheimer's disease."

We excluded abstracts that only commented on harms that did not involve gastrointestinal bleeding or cardiovascular thrombosis, such as nausea or hypertension. We also excluded abstracts that did not have a comment reflecting the authors view on rofecoxib, e.g. "The manufacturer claims that in clinical studies rofecoxib inhibits COX-2 but not COX-1, has the power of high-dose NSAIDs—diclofenac and ibuprofen—and superior GI [gastrointestinal] safety profile compared to conventional NSAIDs." Abstracts of in vitro studies, animal studies, medical devices and pharmacokinetics were also excluded.

### Evaluation of the authors' view on rofecoxib

We categorised the authors' view on rofecoxib as either favourable, neutral or unfavourable. If an active comparator was not used as a reference, we accepted placebo or statements that did not involve a comparator. The judgement was preferentially made using the conclusion of the abstract. If this was not possible, we used statements in the results section or elsewhere, e.g. "Because of its more favorable gastrointestinal toxicity profile compared with non-selective NSAIDs, rofecoxib is safer in patients …". We also judged the individual comments on gastrointestinal bleeding and cardiovascular thrombosis in the same way.

### Analysis

We used graphs and descriptive statistics to assess how the reporting in abstracts changed over time. Because rofecoxib was withdrawn on 30 September 2004, our 1-year intervals are from October to September, e.g. year 2000 was defined as October 1999 to September 2000, both months included. For abstracts that only contained information about the year of publication, we used the date the citation was added to the PubMed database [EDAT].

## Results

Our PubMed search identified 2,047 records and we included 393 abstracts. Most records were excluded because there was no abstract in PubMed or because the abstract did not contain a comment on gastrointestinal bleeding or cardiovascular thrombosis (Fig. 1). Twenty-nine of the excluded abstracts mentioned hypertension, but did not comment on cardiovascular thrombosis.

### Reporting of harms over time

During the whole observation period, 181 of the included abstracts (46%) commented on gastrointestinal bleeding only, 110 (28%) on cardiovascular thrombosis only and 102 (26%) commented on both. Of the 283 (181+102) abstracts commenting on gastrointestinal bleeding, 141 (50%) used the explicit terms "ulcer", "gastrointestinal bleeding" or "perforation", or "serious gastrointestinal adverse effect". The remaining 142 abstracts (50%) used the less explicit terms "gastrointestinal risk", "gastrointestinal safety", or "gastrointestinal adverse effect". Of the 212 (110+102) abstracts commenting on cardiovascular thrombosis, 137 (65%) used the explicit terms "thrombosis", "thromboembolic" or "thrombotic effect", "myocardial infarction" or "stroke". The remaining 75 abstracts (35%) used the less explicit terms "cardiovascular risk", "cardiovascular safety" or "cardiovascular adverse effect".

Until and including September 2000, no abstracts commented on cardiovascular thrombosis (the first was published in November 2000), i.e. 100% ($n$=27) of the abstracts commented only on gastrointestinal bleeding (Fig. 2). The percentage of abstracts that only commented on gastrointestinal bleeding decreased to 59% in 2004 ($n$=46), before rofecoxib was withdrawn, and to 13% in 2007 ($n$=54). The percentage of abstracts that commented only on cardiovascular thrombosis increased from 0 to 17% in

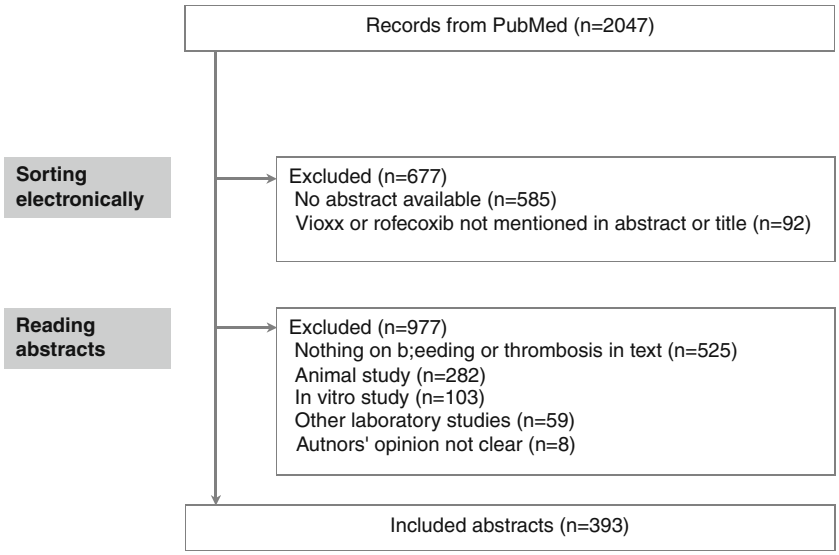


**Fig. 1** Search for relevant abstracts

2004 and to 54% in 2007. The percentage commenting on both gastrointestinal bleeding and cardiovascular thrombosis increased from 0 to 24% in 2004, and to 33% in 2007. The greatest change in reporting was seen immediately after the withdrawal of rofecoxib in 2004 (Fig. 2).

Authors' general view on rofecoxib over time

Until and including September 2000 ($n$=27), the proportion of abstracts favouring rofecoxib was 89%. In 2004 ($n$=46), it was 67%. The greatest change was seen after the withdrawal of rofecoxib and in 2007 ($n$=54) where only 11% of the abstracts were positive (Fig. 3). We investigated the robustness of this result by including only those abstracts where our judgement was based on the conclusion section of the abstracts. This graph had a similar slope (dotted line in Fig. 3).

Authors' views on harms before and after the withdrawal of rofecoxib

Two hundred and eleven abstracts (54%) were published before the withdrawal of rofecoxib in 2004 and 182 (46%) were published after.

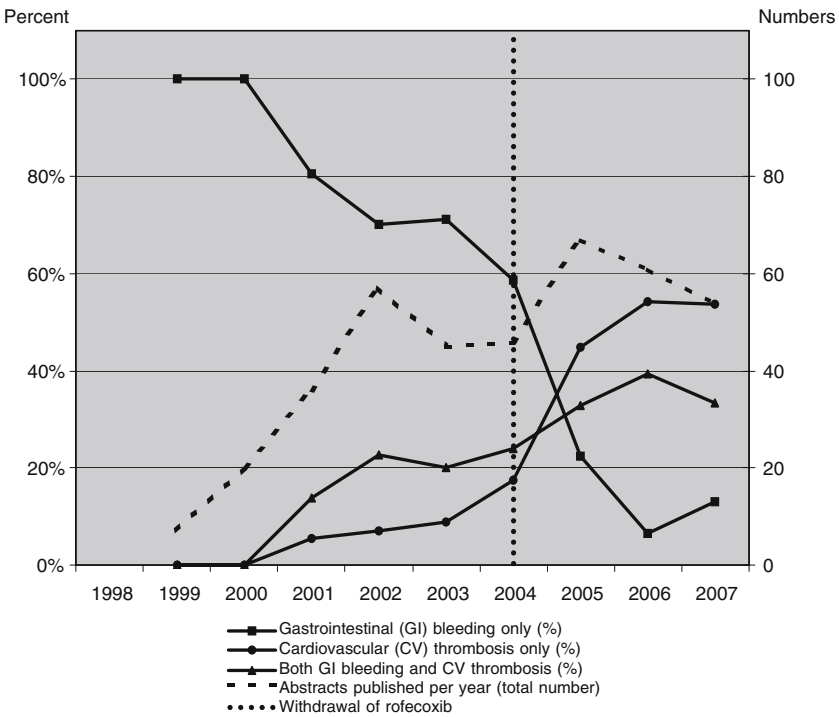


**Fig. 2** Abstracts published per year. Total number of abstracts published per year and percentage commenting on gastrointestinal bleeding, cardiovascular thrombosis or both. The three proportions add up to 100%

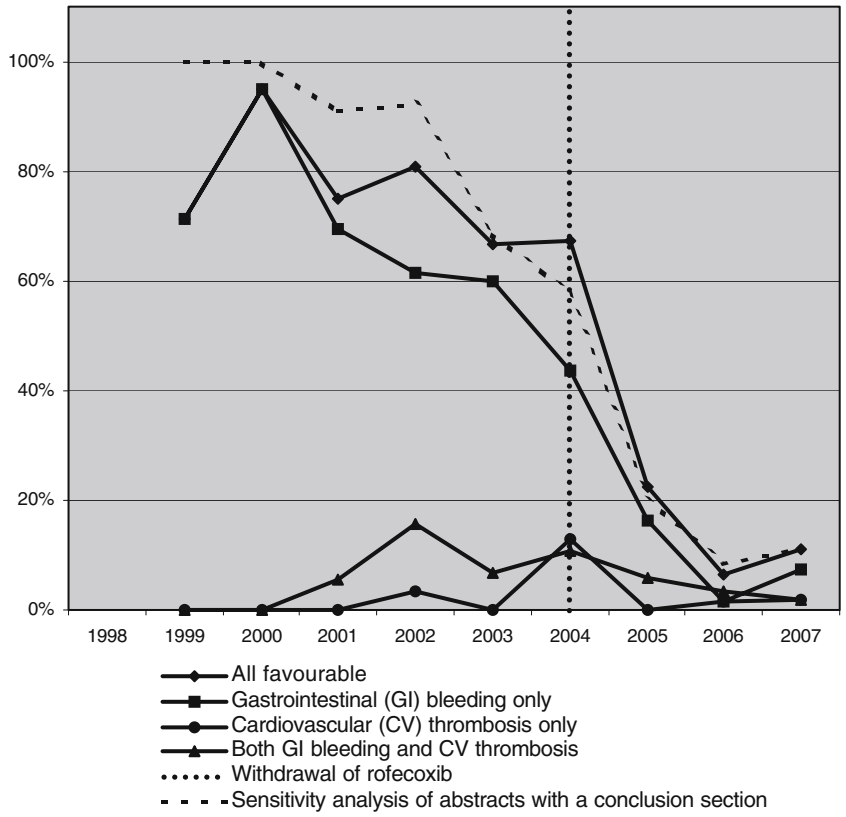


**Fig. 3** Abstracts favouring rofecoxib. Percentage of abstracts favouring rofecoxib among those commenting on gastrointestinal bleeding, cardiovascular thrombosis or both

Before the withdrawal, 193 (91%) abstracts commented on gastrointestinal bleeding, and 168 (87%) of them were favourable towards rofecoxib, 19 (10%) were neutral and 6 (3%) unfavourable. Fifty-six (27%) abstracts commented on cardiovascular thrombosis, and 5 (9%) of those were favourable towards rofecoxib, 31 (55%) neutral and 20 (36%) unfavourable.

After the withdrawal, the effect on gastrointestinal bleeding was mentioned in 89 (49%) abstracts, and 67 (75%) of those were favourable towards rofecoxib, 14 (16%) neutral and 8 (9%) unfavourable. The thrombotic effect was mentioned in 156 (86%) abstracts and, none of them were favourable towards rofecoxib, 26 (17%) neutral and 130 (83%) unfavourable.

## Discussion

We found that most abstracts on rofecoxib reported only on the beneficial effect regarding less gastrointestinal bleeding, and that they were generally in favour of rofecoxib, from the introduction of the drug in 1999 to its withdrawal in 2004. After the withdrawal, most abstracts reported on the harmful effects, cardiovascular thrombosis, and few were in favour of rofecoxib.

Such findings might be expected for drugs with important but rare harms that are unknown when the drugs are introduced on the market and only discovered later. However, this is not the only explanation for our findings. It has been documented that the company suppressed cardiovascular harms in the scientific literature [6] and intimidated researchers and speakers who were critical of rofecoxib [6–8].

Before its introduction, it was predicted from the mechanism of action that the drug should reduce the incidence of gastrointestinal bleeding [9] but also increase the incidence of thrombosis, compared with non-selective NSAIDs [10–12]. Two trials conducted by Merck, 090 [3, 13, 14] and VIGOR [15], both showed that rofecoxib increased the risk of cardiovascular events significantly. However, the first trial, which ended in 1999, was not published in a scientific journal until 2006 [14]. The second trial was published in the *New England Journal of Medicine*, but the increased risk of myocardial infarction was interpreted as a beneficial aspirin-like prophylactic effect of the control NSAID [15]. This interpretation was speculative and was later refuted. Furthermore, three cases of myocardial infarction in the rofecoxib arm had been omitted from the paper [16].

In 2001, it was documented in a systematic review that COX-2 inhibitors increased the risk of cardiovascular events [17], and a cumulative meta-analysis of trials from 2004 showed that a clear relationship between rofecoxib and increased risk of myocardial infarction existed already

**Neurological disorders**
Hemicrania continua
Schizophrenia
Sclerosis
Alzheimers dementia
Migraine
Premenstrual migraine

**Surgery**
Prevention of urethral strictures after TURP
Pre-medication for tonsilectomy
Pre-medication for uterine curettage
Hernia operations
Post CABG
Pre-medication for ear-nose-throat surgery in general
Minor dental surgery (e.g. removal of molars)
Minor orthopaedic surgery

**Cancer**
Treatment for glioblastoma multiforme
Protection against colorectal neoplasia in familiar polyposis
Treatment of malignant melanoma and sarcomas
Treatment of prostate cancer
Treatment of bone cancer
Treatment of breast cancer
Treatment of lung cancer

**Other**
Reduction of atherosclerosis among ACS-patients post-infarction
Congenial nephrogenous diabetes insipidus
Menstrual pain
Endometriosis
Non-bacterial prostatitis
Haemophilic arthropathy
Premenstrual acne
Prevention of ectopic ossification in arthroplasty

**Fig. 4** Conditions for which the effect of rofecoxib was mentioned

by the end of 2000 [18]. Two other meta-analyses did not find evidence of an increase in cardiovascular risk with rofecoxib, but they were conducted by employees of Merck [19, 20].

Over the studied time period, there has been an increased focus on harms [21–23] and the quality of reporting trial results in abstracts [5], which may have had an impact on our results. However, our sample of abstracts did not exclusively consist of trial abstracts, and the increased attention to harms does not explain the dramatic change in focus from beneficial to harmful effect when rofecoxib was withdrawn.

The safety data from trials on rofecoxib were far too positive compared to a real-world setting. None of the trials in the application for marketing approval were designed to evaluate the cardiovascular risk [6]. In fact, they included patients that had an unusually *low* cardiovascular risk. Medicare patients in Tennessee, who were treated with rofecoxib in clinical practice, had a baseline risk of getting a myocardial infarction that was eight times higher than that for the patients in the trials [18]. Patients at high risk of developing peptic ulcers were also often left out of trials on rofecoxib. In 2002, an analysis of cardiovascular adverse events was added to the protocols of three studies [23] including the one [2] that led to the withdrawal of rofecoxib [1]. This was considered breaking news and is likely to have initiated the change in focus from beneficial effects to harms.

Publishing and disseminating scientific papers on medical interventions is an important marketing strategy for the pharmaceutical industry [24], and Merck's active role in the writing of journal articles is likely to have influenced how rofecoxib was portrayed and perceived by the clinicians. It is difficult to explore Merck's role in more detail in relation to our results. Merck's information control could have been clarified by looking at reporting in relation to type of financial support. We did not attempt to do this, as ghost authorship and other forms of support from drug companies are often not revealed in scientific papers [25], and Merck used guest and ghost authors for many of the papers on rofecoxib [26]. Merck also conducted a seeding trial [27], the ADVANTAGE trial, published in *Annals of Internal Medicine* [28], and sponsored the *Australasian Journal of Bone and Joint Medicine*, which looked like a peer-reviewed medical journal but was only a marketing tool. Most of the articles in the journal presented data favourable to Merck products, including rofecoxib, without disclosing sponsorship [29].

A strategy to increase drug sales that has been used by Merck [30] and many other drug companies is to stimulate off-label use [24, 31]. This may also be the case for rofecoxib [32] and could explain why many abstracts mentioned or evaluated the effect of rofecoxib in relation to other conditions than arthritis (Fig. 4). After having assessed one-third of the abstracts ($n$=1,370), one observer decided to register the conditions (apart from arthritis) that rofecoxib was proposed for. These were mainly neurological disorders, cancer and pain related to minor surgery. The U.S. Food and Drug Administration approved rofecoxib for osteoarthritis, acute pain, primary dysmenorrhea and rheumatoid arthritis.

We searched for abstracts in PubMed only, as PubMed is the most widely used database for medical research. It is likely that more abstracts would have been included if we had searched additional databases, but we would not expect it to have led to any important changes in our results.

It has been suggested that increases in blood pressure related to rofecoxib are a mechanism for the increase in the risk of cardiovascular events [33]. We excluded 26 abstracts for the reason that they only commented on hypertension, but they would not have changed the results much as they were scattered over the years 2001 to 2007.

We believe that if the reporting of benefits and harms in abstracts is unbalanced, doctors will get a false perception of the drug's value. In particular, readers need information

on deaths, and on harms that can be lethal, such as thromboses causes by COX-2 inhibitors. In the drug literature, there is plenty of evidence of flawed research [34–43], ghost-written articles [24, 25, 44–47], intimidation of researchers [44, 45, 48–56] and misleading and false statements in research papers and marketing [24, 44–47, 57–65].

We suggest that studies like ours should be done on other drugs than rofecoxib, preferably with newly marketed drugs associated with high expectations.

## Conclusions

The basic principle of balanced reporting of benefits and harms seems to have been seriously distorted in abstracts on rofecoxib, although the harms were equally predictable as the benefits from the mechanism of action of the drug. Before the withdrawal of rofecoxib, abstracts mostly reported on gastrointestinal bleeding and were in favour of rofecoxib. The harms came in focus too late, when the drug had already been withdrawn, and when tens of thousands of patients had been harmed unnecessarily [3, 66, 67].

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