PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2005; **14**: 437–441
Published online 2 June 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.1123

ORIGINAL REPORT

The trade-off between cardiovascular and gastrointestinal effects of rofecoxib†

Stefan R. Florentinus PharmD[1], Eibert R. Heerdink PhD[1]*, Antonius de Boer MD, PhD[1], Liset van Dijk PhD[2] and Hubert G. M. Leufkens PharmD, PhD[1]

[1]*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Faculty of Pharmaceutical Sciences, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, The Netherlands*
[2]*NIVEL (Netherlands Institute for Health Services Research), Utrecht, The Netherlands*

SUMMARY

Background The cyclooxygenase-2 (COX-2) inhibitor rofecoxib was registered in 1999. By 2000, the first reports were published indicating that the agent was possibly associated with an increased risk of myocardial infarction. Since then a surge of data supporting this association has become available. To interpret these data it is essential to ascertain the cardiovascular risk profile of users of rofecoxib relative to other non-steroidal anti-inflammatory drug (NSAID) recipients.
Objective To assess differences in cardiovascular risk between starters of rofecoxib versus starters of any other NSAID.
Setting Data sampled from a representative research network of Dutch general practitioners (GPs) in 2001.
Design New users (starters) of rofecoxib were compared to starters of any other NSAID, unmatched and matched on age, gender, and indication nested in the cohort of the second Dutch National Survey of General Practice.
Results A total of 40.4% of patients starting on rofecoxib had cardiovascular co-morbidity. Patients starting on rofecoxib were twice more likely to have a history of gastrointestinal (GI) morbidity, compared to patients starting on other NSAIDs ($OR_{adj} = 2.09$; 95%CI = 1.65–2.66). These patients were also more likely to have cardiovascular co-morbidity (OR = 1.90; 95%CI = 1.60–2.24) compared to recipients of rofecoxib with no GI co-morbidity. Cardiovascular morbidity was present at the time of rofecoxib exposure in over 61% of carriers of a composite risk profile including age 60 years or older, GI co-morbidity and diagnosis of rheumatoid arthritis and osteoarthritis.
Conclusions In general, a typical recipient of an NSAID is aged and carrier of a serious cardiovascular risk profile. Selective prescribing of rofecoxib to provide claimed gastroprotection, indirectly and unintentionally resulted in prescribing rofecoxib in a population with high frequencies of cardiovascular morbidities. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — rofecoxib; new drugs; prescribing; family practice; diffusion of innovation

INTRODUCTION

The risk-benefit balance of new drugs is of great importance to ensure public health. To safeguard this, new drugs are subjected to licensing procedures by drug regulatory agencies. These organizations evaluate the scientific evidence for new products handed over by the manufacturer and can subsequently authorize market approval. However, the postmarketing clinical application of the drug is shaped by several factors, such as the dissemination of new scientific evidence about safety and efficacy and the subsequent reaction of doctors and patients. In 1999, rofecoxib, a non-steroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclooxygenase-2 (COX-2) was introduced as the first representative of the COX-2 inhibitors. The idea that the COX-2 causes the anti-

* Correspondence to: Dr E. R. Heerdink, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, P.O. Box 80082, 3508 TB Utrecht, The Netherlands. E-mail: E.R.Heerdink@pharm.uu.nl
† No conflict of interest was declared.

Received 10 March 2005
Revised 29 March 2005
Accepted 25 April 2005

inflammatory effects and COX-1 the gastrointestinal (GI) side effects led to the development of drugs selectively blocking COX-2.[1,2] Since the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study were published on 23rd November 2000, the cardiovascular safety profile of rofecoxib has been questioned.[3] The VIGOR-study showed a gastroprotective effect of rofecoxib over naproxen, but also a fivefold higher incidence of myocardial infarction in the rofecoxib group. This finding fuelled the ongoing discussion about the trade-off between the cardiovascular risk and GI protective effects of COX-2 inhibitors.[3–6] Meanwhile, the GI safety was the spearhead of the marketing campaigns, resulting in an estimated 80 million users worldwide and US $2.5 billion in sales in 2003.[7] On 30 September 2004, rofecoxib was withdrawn from the market after the APPROVe-study had shown a twofold increased risk of myocardial infarctions and strokes in rofecoxib patients compared to placebo.[8] In the aftermath of the withdrawal of rofecoxib, a passionate debate has been held about the regulatory and clinical consequences.[7,8]

A fundamental question underlying the full understanding of this safety issue is the *a priori* cardiovascular risk of patients starting with the drug, particularly in the context of a trade-off between GI and cardiovascular risk factors.[5]

METHODS

Data sources

We used prescribing data of general practitioners (GPs) who participated in the second Dutch national survey of general practice (DNSGP-2).[9] NIVEL (The Netherlands Institute for Health Services Research) conducted the DNSGP-2 among 195 GPs, practicing in 104 practices, and 385 461 patients in 2001. The GPs were considered representative for all Dutch GPs ($n = 7217$). No statistically significant differences for age, gender, region of residence and urbanization were found. The patients captured by the 104 practices are a good representation of the Dutch population on age, gender, and type of health insurance.[9] All eligible patients were approached to co-operate in a census to determine among other things their socio-demographic characteristics, including their self-reported health. Computerized clinical and prescribing data, including ICPC-coded (International Classification of Primary Care) diagnoses,[10] were obtained. The DNSGP-2 was conducted 9 months after the introduction of rofecoxib in The Netherlands.

Study design

We compared patients starting on rofecoxib with patients starting on any other NSAID. The date of the first prescription in the study period for either rofecoxib or another NSAID was defined as the index date. Starting was defined as a prescription for rofecoxib or another NSAID and no prescription for the same type of drug the 6 months before the index date. In The Netherlands, medicines are dispensed for a maximum of 3 months. Due to differences in age, gender, and diagnosis between the group of patients starting on rofecoxib or any other NSAID, the comparison was conducted unmatched as well as matched on age, gender, and indication. Rofecoxib initial licensed indication was the treatment of osteoarthritis. In December 2001, a label extension for the treatment of rheumatoid arthritis was granted, followed by the approval for the treatment of acute pain and primary dysmenorhea in January 2002.

In order to assess the patient's cardiovascular and GI co-morbidity, a time window of 6 months around the index date was used. Cardiovascular co-morbidity was defined as receiving a prescription with a diagnosis from ICPC chapter 'K' (Circulatory), except 'K95' (hemorrhoids) and 'K96' (varicose veins of leg) or a drug with an ATC-code starting with 'C' (Cardiovascular system). GI co-morbidity was estimated by using ICPC-codes 'D02' (Abdominal pain epigastric), 'D03' (Heartburn), 'D84' (Oesophagus disease), 'D85' (Duodenal ulcer), 'D86' (Peptic ulcer other), 'D87' (Stomach function disorder), and 'D90' (Hiatus hernia) and the ATC-code 'A02' (Drugs for acid related disorders).

RESULTS

A total of 2770 patients received rofecoxib during the study period, of whom 1655 (59.7%) patients could be defined as newly starting on rofecoxib. Of these patients 1505 (90.9%) started on a daily dose of 25 mg, 120 patients started on 12.5 mg (7.3%), and 30 patients (1.8%) started on a daily dose of 50 mg or more. Only 15.3% of the patients starting on rofecoxib received it for the in 2001 licensed indications osteoarthritis and rheumatoid arthritis. A total of 31 403 patients were defined as new starters on any other NSAID. Most patients started on diclofenac (44.1%), ibuprofen (24.5%), or naproxen (20.2%), which are the three most frequently prescribed NSAIDs in The Netherlands.

The characteristics of all patients newly starting on rofecoxib or any other NSAID are shown in Table 1.

Table 1. Characteristics of patients newly starting on rofecoxib or any other NSAID

	Starters on rofecoxib	Starters on any other NSAID	Odds ratio (95%CI)	Adjusted odds ratio (95%CI)
No. of patients	1655	31 403		
Gender				
Male	506 (30.5%)	13 644 (43.4%)	Reference	Reference
Female	1149 (69.4%)	17 759 (56.6%)	1.7 (1.6–1.9)	1.43 (1.26–1.62)
Age (SD) (increase per 10 years)	60.9 (16.4)	46.6 (17.5)	1.0 (1.0–1.0)	1.04 (1.03–1.04)
Indication				
Other	1401 (84.7%)	30 709 (97.8)	Reference	Reference
RA and OA	254 (15.3%)	694 (2.2%)	8.0 (6.9-9.4)	4.39 (3.64–5.27)
Self-reported health				
Good	658 (51.5%)	13 262 (42.2%)	Reference	Reference
Average	512 (30.9%)	5034 (16.0%)	2.5 (2.2–2.8)	1.46 (1.28–1.66)
Bad	108 (6.5%)	773 (2.5%)	3.5 (2.8–4.3)	1.93 (1.52–2.44)
Cardiovascular co-morbidity				
No	986 (59.6%)	25 312 (80.6%)	Reference	Reference
Yes	669 (40.4%)	6091 (19.4%)	2.8 (2.5–3.1)	1.19 (1.04–1.36)
Gastrointestinal co-morbidity				
No	1211 (73.2%)	28 295 (90.1%)	Reference	Reference
Yes	444 (26.8%)	3108 (9.9%)	3.3 (3.0–3.7)	2.00 (1.73–2.30)

Clear differences were noted between starters on rofecoxib and all other starters on any other NSAID. GI ($OR_{adj} = 2.00$; 95%CI = 1.73–2.30) and cardiovascular co-morbidity ($OR_{adj} = 1.19$; 95%CI = 1.04–1.36) were more common among patients starting on rofecoxib. Furthermore, rofecoxib was more often prescribed to older (mean age 60.9 vs. 46.6 years) and female ($OR_{adj} = 1.43$; 95%CI = 1.26–1.62) patients, who reported their own health as bad (OR_{adj} compared to good = 1.93; 95%CI = 1.52–2.44). Osteoarthritis and rheumatoid arthritis were diagnosed more frequently in patients starting on rofecoxib ($OR_{adj} = 4.39$; 95%CI = 3.64–5.27) than in starters on any other NSAID.

The discrepancies in GI and cardiovascular co-morbidity between starters on rofecoxib and any other NSAID might be caused due to differences in age, gender, and indications. However, pairwise comparison using a conditional logistic regression model revealed significant differences in GI co-morbidity and self-reported health. Table 2 shows the characteristics of starters on rofecoxib or other

Table 2. Characteristics of patients newly starting on rofecoxib or any other NSAID—matched on age, sex, and indication

	Starters on rofecoxib	Starters on any other NSAID	Odds ratio (95%CI)	Adjusted odds ratio (95%CI)
No. of patients	1640	1640		
Gender				
Male	497 (30.3%)	497 (30.3%)	Matched on	
Female	1143 (69.7%)	1143 (69.7%)		
Age (SD)	60.8 (16.3)	60.8 (16.3)	Matched on	
Indication				
Other	1399 (85.3%)	1399 (85.3%)	Matched on	
RA and OA	241 (14.7%)	241 (14.7%)		
Self-reported health*				
Good	652 (39.8%)	763 (46.5%)	Reference	Reference
Average	506 (30.9%)	408 (24.9%)	1.35 (1.11–1.64)	1.25 (1.02–1.52)
Bad	108 (6.6%)	56 (3.4%)	2.09 (1.44–3.04)	1.82 (1.24–2.67)
Cardiovascular co-morbidity				
No	979 (59.7%)	1074 (65.5%)	Reference	Reference
Yes	661 (40.3%)	566 (34.5%)	1.34 (1.15–1.56)	1.22 (0.99–1.49)
Gastrointestinal co-morbidity				
No	1198 (73.0%)	1399 (85.3%)	Reference	Reference
Yes	442 (27.0%)	241 (14.7%)	2.27 (1.88–2.74)	2.09 (1.65–2.66)

*Numbers do not add up due to missing values.

Table 3. Association between cardiovascular co-morbidity and risk factors for NSAID or rofecoxib prescribing

	No. of patients	% Cardiovascular co-morbidity
No risk factors	22 523	9.9% (2235)
Age ≥60	8197	48.6% (3986)
Age ≥60 + GI co-morbidity	1587	61.0% (968)

NSAIDs, matched on age, gender, and indication. Patients starting on rofecoxib were twice as likely to have GI complaints, compared to patients starting on other NSAIDs ($OR_{adj} = 2.09$; 95%CI = 1.65–2.66). Cardiovascular co-morbidity was univariately associated with starting on rofecoxib (OR = 1.34; 95%CI = 1.15–1.56), but after adjusting for the other covariates the association became weaker ($OR_{adj} = 1.22$; 95%CI = 0.99–1.49). Still 40.3% of the patients starting on rofecoxib had cardiovascular co-morbidity.

Among all matched patients, cardiovascular co-morbidity was higher among those with GI co-morbidity, compared to patients with no GI co-morbidity (OR = 1.90; 95%CI = 1.60–2.24). The clinical profile of a typical rofecoxib user (with GI co-morbidity and age >60) results in prescribing these drugs to patients with cardiovascular co-morbidity. The percentage of patients with cardiovascular co-morbidity increased to 61.0% when rofecoxib or any other NSAID is prescribed to patients older than 60 years with GI morbidity (Table 3).

DISCUSSION

The primary objective of this study was to assess differences in cardiovascular and GI co-morbidity between patients starting on rofecoxib versus starters on any other NSAID. Our findings show that Dutch GPs prescribed rofecoxib in 2001 more often to patients with GI co-morbidity, as expected based on the claimed differential GI risk of the COX-2 inhibitors, also leading to a surplus of cardiovascular morbidity in this patients.

For new drugs entering crowded markets, such as the market for anti-inflammatory and pain medication, it is essential to display a real or at least a perceived advantage over its direct competitors to gain a viable market share.[11] The higher percentage of GI co-morbidity among starters on rofecoxib was expected and in line with other studies.[12–14] Cutts *et al*. found in a study among 72 Australian GPs that in 30.6% of the patient's GI side effects from conventional NSAIDs were a reason for prescribing rofecoxib. In 23.8% of the cases, GPs had the perception of rofecoxib as a safer alternative for conventional NSAIDs.[12]

The legitimate reasons for prescribing rofecoxib to patients susceptible to GI adverse effects, namely older patients with GI co-morbidity, and morbidities like osteoarthritis and rheumatoid arthritis, consequently fuelled prescribing of rofecoxib to patients with cardiovascular co-morbidity. Therefore, the trade-off between GI and cardiovascular safety is affected even when only considering gastroprotection.

In a recent meta-analysis, Jüni *et al*.[4] argued that already at the end of 2000 enough evidence was available to conclude that rofecoxib caused an increased risk of myocardial infarction. Some of the studies used by Jüni *et al*. in the meta-analysis were never published so it is unlikely that GPs in 2001 had a complete picture of the risk-benefit ratio of rofecoxib. However, in 2000 the results of the VIGOR study noted a fivefold higher incidence of myocardial infarction for rofecoxib compared to naproxen.[3] The differences in cardiovascular risk were attributed to the cardioprotective effects of naproxen rather than to cardiotoxic properties of rofecoxib. The discussion about the trade-off between gastroprotection and cardiotoxicity was further encouraged by other studies[15] iterating the protective effect of naproxen, while others advocated the opposite.[16] Our findings show that the percentage of patients with cardiovascular co-morbidity among those starting on rofecoxib was higher than in patients starting on any other NSAID. Perhaps due to conflicting reports about the cardiovascular safety of rofecoxib, and therefore the absence of unequivocal evidence in 2001, cardiovascular safety was not reflected in the decision to prescribe rofecoxib. The finding that only 15.3% of the patients received rofecoxib for approved and licensed indications strengthens this notion.

Several studies have shown that rofecoxib is channeled towards patients with high-risk of GI hemorrhage[17,18] and congestive heart failure.[19] What this study shows is that the channeling of rofecoxib into patients with cardiovascular co-morbidity is partly the result of a focus on GI safety and the clustering of cardiovascular co-morbidity in patients with GI co-morbidity.

The results of this study need to be interpreted in light of its limitations. For this study, we used prescribing data of GPs. Although representative for all Dutch GPs and the patient population, prescriptions of hospital specialists were not captured in the data. Some of the patients starting on rofecoxib or another NSAID may have received a prescription of a hospital specialist before the index date. This may have led to

KEY POINTS

- Aiming to provide GI safety resulted in prescribing of rofecoxib to patient with high cardiovascular risk.
- GPs should be aware of indirect effects of selective prescribing of new drugs.
- Unintentional channelling is an important mechanism by which new drugs are prescribed to high risk patients.

misclassification by defining patients as starters. However, GPs adopted rofecoxib instantly and by 2001 rofecoxib alone contributed for 14.5% to the total volume of for NSAIDs prescribed in The Netherlands.[20]

In conclusion, as expected GI co-morbidity was more common among patients starting on rofecoxib. Selective prescribing of rofecoxib to provide gastroprotection, indirectly and unintentionally resulted in the channeling of rofecoxib in more severely ill patients with cardiovascular risk factors relevant to take into account when weighing the pros and contras of COX-2 inhibitors against other NSAIDs.

REFERENCES

1. Weir MR, Sperling RS, Reicin A, Gertz BJ. Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. *American Heart Journal* 2003; **146**(4): 591–604.
2. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353**(9149): 307–314.
3. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; **343**(21): 1520–1528, 2 p following 1528.
4. Topol EJ. Failing the public health—rofecoxib, Merck, and the FDA. *N Engl J Med* 2004; **351**(17): 1707–1709.
5. Merk, Merk announces voluntary worldwide withdrawal of VIOXX®. Available at:. http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf (accessed Sep 30, 2004).
6. Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der Zee J. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. *Eur J Public Health* 2005; **15**(1): 59–65.
7. Lamberts H, Woods M, Hofmans-Okkes I. The international classification of primary care in the European Community. Oxford University Press: Oxford, 1993.
8. Rodgers E. Diffusion of Innovations. Free Press: New York, 1995.
9. Cutts C, LaCaze A, Tett S. A clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice. *Br J Clin Pharmacol* 2002; **54**(5): 522–527.
10. Layton D, Riley J, Wilton LV, Shakir SA. Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study. *Br J Clin Pharmacol* 2003; **55**(2): 166–174.
11. Kerr SJ, Mant A, Horn FE, McGeechan K, Sayer GP. Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. *Med J Aust* 2003; **179**(8): 403–407.
12. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; **364**(9450): 2021–2029.
13. Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, Gertz BJ. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001; **104**(19): 2280–2288.
14. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *Jama* 2001; **286**(8): 954–959.
15. MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003; **52**(9): 1265–1270.
16. Mamdani M, Rochon PA, Juurlink DN, Kopp A, Anderson GM, Naglie G, Austin PC, Laupacis A. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *BMJ* 2002; **325**(7365): 624.
17. Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel PTA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet* 2004; **363**(9423): 1751–1756.
18. The Dutch Health Care Insurance Board. GIP databank at. www.cvz.nl (accessed on 14 January, 2005).

