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Evaluation of Risk Profiles for Gastrointestinal and Cardiovascular Adverse Effects in Nonselective NSAID and COX-2 Inhibitor Users

A Cohort Study Using Pharmacy Dispensing Data in The Netherlands

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Abstract

Background: Newly approved drugs, in comparison with older drugs, are more often prescribed to patients who have not responded satisfactorily to established related drugs or as first-line therapy to patients with a high baseline risk for adverse outcomes (i.e. channelling). However, these patients are less likely to benefit from the prescribed drug and/or are more prone to adverse drug reactions. Therefore, it is difficult to unravel whether observed risks or increases in risk of new drugs are real, i.e. related to the pharmacology, or whether these are related to selective prescribing to patients who are more susceptible to adverse events because of some underlying risk factor(s). The channelling paradox may exist for cyclo-oxygenase (COX)-2 selective inhibitors ('coxibs') instead of traditional nonselective NSAIDs in relation to both gastrointestinal (GI) and cardiovascular (CV) safety.

Objective: To evaluate the risk profiles for GI and CV adverse effects in nonselective NSAID and coxib new-user populations over time, in terms of a quantitative measure since the introduction of coxibs.

Methods: This was a population-based cohort study using the Dutch pharmaceutical claims database (Foundation for Pharmaceutical Statistics). Eligible patients (≥18 years) were those where the date of their first prescription (index date) of an NSAID (first-line [e.g. ibuprofen] or second-line [e.g. piroxicam] nonselective NSAID, COX-2 preferential NSAID or coxib) was between January 1999 and December 2003. For each patient, GI and CV risk profiles at index date were defined by a cumulative score derived from dispensing data (patient age, sex and history of medication use within 6 months of index date). Risk scores were categorized as low (score = 0), medium (1) or high (2+). Patients were recorded as switchers based on other NSAID use prior to the index date. Other information collected included the Chronic Disease Score (CDS). Crude odds ratios (ORs) were calculated for risk factors for each NSAID group versus first-line nonselec-

tive NSAID users as the reference cohort. The effect of calendar time was examined by plotting mean CV or GI risk score by quarter-year. Correlation between GI and CV scores was examined using the Pearson correlation coefficient (R). Data were stratified by patients' history of switching.

Results: The four cohorts comprised patients using: first-line nonselective NSAIDs (n = 42 750); second-line nonselective NSAIDs (n = 1771); COX-2 preferential NSAIDs (n = 3661) and coxibs (n = 4861) patients. New coxib users were most likely to have high GI and CV risk scores (OR 5.3 [95% CI 5.0, 5.6] and OR 2.2 [95% CI 2.1, 2.4], respectively). At the individual patient level, GI and CV risk profiles were moderately well correlated for all NSAID cohorts (R range 0.48 to 0.62). There was no remarkable change in mean GI or CV risk profile of patients over calendar time since the market introduction of coxibs.

Discussion: Of the four NSAID cohorts, new coxib users tended to have the highest numbers of GI and CV risk factors, with no obvious change over calendar time. There was also evidence of correlation between GI and CV risk scores. Thus, selective prescribing of coxibs applies to people with co-existing CV as well as GI risk factors. This is important when comparing the safety and/or efficacy of new therapies to existing therapies, and emphasizes the difficulties encountered by prescribers in assessing levels of risk when initiating coxib treatment.

Background

Newly approved drugs are, in comparison with older drugs, often prescribed to patients who have not responded satisfactorily to therapy with established related drugs, or as first-line therapy to patients with a high baseline risk for adverse outcomes.[1] Marketing strategies have been shown to contribute to the latter phenomenon.[2] Thus, new drugs may be selectively prescribed or 'channelled' to patients who are *a priori* less likely to benefit from the new drug and/or are more prone to adverse drug reactions. In clinical practice, these new drugs may then paradoxically be associated with less favourable outcomes than conventional treatments. Therefore, it is difficult to unravel whether observed risks or increases in risk of new drugs are real, i.e. related to the pharmacology, or whether these are related to selective prescribing to patients who are more susceptible to adverse events because of some underlying risk factor(s).

This phenomenon, known as 'channelling' has been described for a number of therapeutic drug classes, including newly marketed NSAIDS.[3-7] Since the 1980s, there have been several examples of NSAIDs marketed with a claimed gastrointestinal (GI) safety advantage but for which the potential benefits, at that time, had not been demonstrated in clinical practice. Examples include the slow-release formulation of indometacin,[8] the controlled release formulation of ketoprofen,[3] meloxicam[4,5] and, more recently, the cyclo-oxygenase (COX)-2 selective inhibitors (hereafter termed collectively as 'coxibs').[9-13]

The channelling paradox may also exist for coxibs in relation to cardiovascular (CV) safety. The unexpected CV safety signal, which appeared shortly after marketing of rofecoxib,[14] has biologically plausible pharmacological mechanisms explaining such risks.[15,16] On the other hand, collective evidence from observational studies has also shown that coxibs have been channelled to patients with existing GI and CV morbidity in the first few years following launch (post-marketing).[10]

Channelling can introduce important bias in the assessment of a relative safety profile if relevant differences between the baseline characteristics of patients initially prescribed new drugs and patients prescribed existing treatments are not recognized or accounted for. This is of particular concern if those events of interest such as serious upper GI complications (e.g. perforations or bleeding) or myocardial infarctions[17,18] occur rarely in the general popula-

tion, when a limited number of risk factors can be reliably examined.

There are a number of studies that have examined changes in prescribing patterns of coxibs over time, in several countries.[11,19-25] This study will contribute to these data by evaluating the risk profiles for GI and CV adverse effects of new users of coxibs and other NSAIDs over time, in terms of a quantitative measure utilizing pharmacy dispensing data. Thus, the aims of this study are were to examine differences in GI and CV risk profiles between these cohorts, to evaluate the correlation of GI and CV risk profiles and to describe patterns of these profiles over time since the introduction of the coxibs.

Methods

Study Design and Setting

This was a population-based cohort study, conducted using data from the Stichting Farmaceutische Kengetallen (Foundation for Pharmaceutical Statistics) [SFK] pharmaceutical claims database. The SFK collects data on the dispensing of pharmaceuticals through community pharmacies in The Netherlands. Data are derived from approximately 1600 (out of a total of 1734) community pharmacies, which serve about 13.5 million people.[26] In this study, a pre-existing subset of these data (previously utilized to conduct a linkage study between the Dutch National Survey of General Practitioners and the SFK), representing a total population of 200 000 individuals was used.[26]

Study Population

Eligible patients were those aged ≥18 years who had received at least one prescription for a relevant NSAID study drug between 1 January 1999 and 31 December 2003. NSAIDs were grouped as follows: coxibs (rofecoxib, celecoxib and valdecoxib), preferential COX-2 inhibitors (meloxicam and nabumetone), first-line nonselective NSAIDs (diclofenac, naproxen and ibuprofen) and second-line nonselective NSAIDs (piroxicam and ketoprofen). First-line refers to those NSAIDs most frequently prescribed as first choice therapy and associated with low or intermediate gastropathy. Second-line refers to those NSAIDs prescribed to patients in whom first-line treatment has proved ineffective but who are considered to be at higher risk of gastropathy.[27,28]

For each NSAID group, the index date was defined as the date of the first prescription of any one of the individual study drugs within each NSAID group, as appropriate. Patients subsequently excluded were those with less than 6 months registration within the SFK prior to and after the time of entry ('index date'). Patients could appear as new users within one or more of the NSAID groups for which the eligibility criteria were satisfied. If so, they would have separate index dates for each cohort as appropriate.

Prescribed starting dose was categorized into low, standard or high according to recommended anti-inflammatory dosages as per the WHO defined daily dose (DDD) for each study drug (table I). Information on any drug use, defined by anatomical

Table I. Dosage categories (mg/day) for each NSAID

Generic name	Low dosage	Standard dosage	High dosage	SPC dosage range[a]	WHO DDD
Celecoxib	<200	200	>200	200–400	200
Rofecoxib	<25	25	>25	12.5–25	25
Valdecoxib	<10	10	>10	10–20	10
Meloxicam	<15	15	>15	7.5–15	15
Nabumetone	<1000	1000	>1000	1000–2000	1000
Diclofenac	<100	100	>100	75–150	100
Naproxen	<500	500	>500	500–1000	500
Ibuprofen	<1200	1200	>1200	600–1800	1200
Piroxicam	<20	20	>20	10–30	20
Ketoprofen	<150	150	>150	100–200	150

a Anti-inflammatory dose range in The Netherlands from the summary of product characteristics (SPC); the thresholds for each dose category correspond to the WHO defined daily dose (DDD).

therapeutic-chemical classification (ATC) during the 6 months prior to index use was also collected.

Patient Characteristics: Cardiovascular (CV) and Gastrointestinal (GI) Risk Profiles

The primary patient characteristics of interest in this study were CV and GI risk profiles. Each score profile was independently assembled from a set of known risk factors for serious GI complications (perforations and bleeding) and thrombotic vascular CV complications respectively, data for which were derived from selected co-prescribed medicines used as markers of co-morbidity and also from demographic characteristics (age and sex) [table II].

Risk factor variables were dichotomized; a score of 1 was allocated if one or more of the drugs within each group had been issued to eligible patients within the 6 months prior to the index date (drugs initiated at or post NSAID index date were not included); a score of zero was allocated otherwise. Age at index date was dichotomized into two groups (aged ≤64 years or ≥65 years). The risk factors were aggregated accordingly, with no weighting applied (table II).

The GI risk score comprised: age (≥65 years), history of drugs for the treatment of gastropathy,[29] antithrombotic agents (including low-dose aspirin [acetylsalicylic acid] 30–80 mg/day),[30] the use of selective serotonin reuptake inhibitors (SSRIs) and related antidepressants,[31] systemic corticosteroids, analgesic dose (>300 mg/day) aspirin and any NSAID.[29]

The CV risk score comprised: age (≥65 years), male sex, the indication rheumatoid arthritis (RA) and history of the use of antithrombotic agents (including low-dose aspirin 30–80 mg/day), antihypertensives, antidiabetic agents, cardiac therapies and serum lipid-lowering agents.[18]

Specific information on diagnosis (osteoarthritis, RA or other indications) is not collected within the

Table II. Risk factors included in gastrointestinal (GI) and cardiovascular (CV) risk scores. Co-morbidities defined according to drug anatomical therapeutic class (ATC)

Risk factor	Category	GI risk score	CV risk score
Age	≥65 years	1	1
Sex	Male	0	1
Indication RA	One or more of the following drug ATC codes: L04 (immunosuppressive agents); L01BA01 (methotrexate); M01C (specific antirheumatic agents)	0	1
Drugs for gastropathy	One or more of the following drug ATC codes: A02A (antacids); A02B (drugs for the treatment of peptic ulcer); A02E (antiregurgitants); A02X (other antacids, drugs for treatment of peptic ulcers and flatulence)	1	0
Antithrombotic agents	One or more of the following drug ATC codes: B01A (antithrombotic agents); BO1B (heparins); BO1AC (platelet aggregation inhibitors excluding heparin); BO1AD (enzymes); BO1AX (other antithrombotics)	1	1
Antihypertensives	One or more of the following drug ATC codes: C02 (antihypertensives); C03 (diuretics); C04 (peripheral vasodilators); C07 (β-blocking agents); C08 (calcium channel blockers); C09 (agents acting on the renin-angiotensin system)	0	1
SSRI and related antidepressants	One or more of the following drug ATC codes: N06AB (SSRIs); N06AX16 (venlafaxine); N06AX11 (mirtazapine)	1	0
Antidiabetic agents	One or more of the following drug ATC codes: A10A (insulins and analogues); A10B (oral blood glucose-lowering drugs); A10X (other drugs used in diabetes mellitus)	0	1
Cardiac therapy	One or more of the following drug ATC codes: C01A (cardiac glycosides); C01B (antiarrhythmics, class I and III); CO1C (cardiac stimulants excluding glucosides); CO1D (vasodilators in cardiac disease); CO1E (other cardiac preparations)	0	1
Lipid-lowering agents	One or more of the following drug ATC codes: C10A (serum lipid-reducing agents)	0	1
Corticosteroids	One or more of the following drug ATC codes: H02a, H02b	1	0
NSAIDs	One or more of the following drug ATC codes: M01a	1	0
High-dose aspirin (>300 mg/day)	One or more of the following drug ATC codes: N02ba01	1	0

RA = rheumatoid arthritis; **SSRI** = selective serotonin reuptake inhibitor.

SFK database. However, prescriptions of medicines (other than NSAIDs) used for the treatment of rheumatic disease (table II; immunosuppressive agents, methotrexate, specific antirheumatic agents), as well as other drugs used in the treatment of inflammatory conditions were used as markers of co-morbidity related to the indication of RA. Patients for whom such drugs were not prescribed were assumed to have other non-RA inflammatory conditions (table III).

In addition, patients were categorized as 'switchers' based on records of prescriptions for NSAIDs in the previous 6 months prior to index date, given that switchers are known to have different levels of risk in relation to initiating therapy.

Other information collected for eligible patients included the Chronic Disease Score (CDS) at index date.[32] The CDS is a validated measure of the chronic disease status among prescription drug users.[33] It can be considered as an indicator of an individual's morbidity and overall health status and was used in this study as an additional variable to describe general disease morbidity. Exposure to various prescription medicines (utilizing pharmacy dispensing databases) has been shown to be a valid measure of certain chronic somatic diseases and the score ranges increase with the complexity of the drug regimen and the number and severity of chronic diseases.

Data Analysis

Descriptive statistics were used to characterize patients in each NSAID cohort and to examine drug utilization according to patients' individual risk factors. Univariate analysis was used to calculate crude odds ratios (OR) and 95% CI to estimate the strength of association of different covariate factors and type of NSAID prescribed. Strengths of correlations between GI and CV risk scores were examined using Pearson correlation coefficients (R).

For cross-tabulation purposes to look at simple associations, each score was categorized into tertiles based on the distribution of the relevant score for the first-line nonselective NSAIDs (group of lowest risk): low (score 0); medium (score 1); and high (score 2+), accounting for the categorical nature of these two variables. These categories (and cut-off levels) were then applied to the scores of the other three cohorts.

To examine changes over time since coxib introduction, the pattern of relationships between the mean cumulative GI or CV risk profile scores (mean GI or CV risk score) at index dates, when categorized into 3-month intervals, were explored for each NSAID group. Data were stratified by selected patient characteristics (i.e. recent or past history of switching) and CDS score. A sensitivity analysis was conducted to determine the effect of excluding patients identified to be of low and medium risk when examining patterns in time. All analyses were conducted in STATA 8.2 (Stata Corp., Texas, USA).

Results

Patient Characteristics

Table III shows the utilization of NSAIDs according to subjects' demographic and risk profiles, with crude ORs (and 95% CI) presented in table IV. No eligible patients were prescribed valdecoxib. Between mid 1999 and mid 2003, the first-line nonselective NSAIDs were the most commonly prescribed NSAID (80.6%), followed by the coxibs (9.2%).

Regarding individual patient characteristics, patients starting coxibs were significantly more likely to be ≥65 years of age, be female, have RA[1] (although the frequency was very low: 2.1% vs 0.4%) and have a higher CDS (≥4). For each of the above-mentioned risk factors, there was suggestion of a relationship such that the relative effect was strongest with coxib use, followed by use of COX-2 preferential inhibitors, second-line nonselective NSAIDs and then first-line nonselective NSAIDs. Compared with first-line nonselective NSAIDs, patients initiated on coxibs were significantly (30 times) more likely to be issued treatment at standard doses, as were the other two drug categories, with suggestion of the same relationship described above. The inverse was observed for high and low doses.

1 The licence was extended for rofecoxib to include treatment of rheumatoid arthritis in December 2001.

Table III. Summary characteristics of NSAID users receiving at least one prescription for first-line nonselective NSAIDs, second-line nonselective NSAIDs, cyclo-oxygenase (COX)-2 preferential inhibitors or COX-2 selective inhibitors (coxibs) for the first time between 1999 and 2003, by NSAID group

NSAID group [n (%)]	First-line nonselective NSAID n = 42 750	Second-line nonselective NSAID n = 1771	COX-2 preferential inhibitor n = 3661	Coxib n = 4861	Chi-squared test[a]
Age at index date					
≤64 years	32 273 (80.14)	1 386 (80.72)	2478 (68.91)	2836 (58.79)	df (3)[b]
≥65 years	7 997 (19.86)	331 (19.28)	1118 (31.09)	1988 (41.21)	p < 0.0001
Mean age in years (SD)	48.58 (16.93)	49.47 (15.91)	54.90 (16.69)	59.70 (16.22)	
Not known (% of total cohort)	2 480 (5.80)	54 (3.05)	65 (1.78)	37 (0.76)	
Sex					
Males	15 632 (36.58)	656 (37.08)	1 098 (30.01)	1359 (27.99)	df (3)[b]
Females	27 099 (63.42)	1 113 (62.92)	2 561 (69.99)	3496 (72.01)	p < 0.0001
Not known (% of total cohort)	19 (0.04)	2 (0.11)	2 (0.05)	6 (0.12)	
Indication					
RA	155 (0.36)	17 (0.96)	72 (1.97)	102 (2.10)	df (3)
Non-RA[c]	42 595 (99.64)	1 754 (99.04)	3589 (98.03)	4759 (97.90)	p < 0.0001
Dose category					
Low	4 615 (10.99)	22 (1.27)	760 (20.87)	202 (4.20)	df (6)[b]
Standard	10 143 (24.16)	981 (56.71)	2675 (73.45)	4353 (90.56)	p < 0.0001
High	27 218 (64.84)	727 (42.02)	207 (5.68)	252 (5.24)	
Not known (% of total cohort)	774 (1.81)	41 (2.32)	19 (0.52)	54 (1.11)	
CDS					
Low (score 0)	15 125 (35.38)	465 (26.26)	717 (19.58)	721 (14.83)	df (6)
Medium (score 1–3)	14 497 (33.91)	621 (35.06)	1053 (28.24)	1362 (28.02)	p < 0.0001
High (score 4+)	13 128 (30.71)	685 (38.68)	1891 (51.65)	2778 (57.15)	
NSAID use history					
New user (no NSAID use in previous 6 mo)	38 820 (90.81)	992 (56.01)	1886 (51.52)	2493 (51.29)	df (3) p < 0.0001
Switcher (NSAID use in previous 6 mo)	3 930 (9.19)	779 (43.99)	1775 (48.48)	2368 (48.71)	
Risk factors					
Past history of:					

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Table III. Contd

NSAID group [n (%)]	First-line nonselective NSAID n = 42 750	Second-line nonselective NSAID n = 1771	COX-2 preferential inhibitor n = 3661	Coxib n = 4861	Chi-squared test[a]
gastropathy	4 256 (9.96)	266 (15.02)	811 (22.15)	1358 (27.94)	All
thrombosis treatment	3 918 (9.16)	150 (8.47)	537 (14.67)	873 (17.96)	df (3)[d]
hypertension	8 348 (19.53)	372 (21.01)	1069 (29.20)	1710 (35.18)	p <0.001
antidepressant use	2 037 (4.76)	106 (5.99)	207 (5.65)	361 (7.43)	
diabetes mellitus	1 992 (4.66)	79 (4.46)	253 (6.91)	419 (8.62)	
cardiac disorders	1 598 (3.74)	64 (3.61)	236 (6.45)	378 (7.78)	
hyperlipidaemia	2 766 (6.47)	103 (5.82)	324 (8.85)	570 (11.73)	
corticosteroids	1 434 (3.35)	113 (6.38)	335 (9.15)	456 (9.38)	
high-dose aspirin (>300 mg/day)	18 (0.04)	3 (0.17)	1 (0.03)	5 (0.10)	
Risk score					
GI risk category[e]					
low (score 0)	24 423 (60.65)	626 (36.46)	903 (25.11)	930 (19.28)	df (6)[f]
medium (score 1)	10 133 (25.16)	637 (37.10)	1323 (36.79)	1642 (34.04)	p < 0.0001
high (score 2–7)	5 714 (14.19)	454 (26.44)	1370 (38.10)	2252 (46.68)	
mean (SD)	0.58 (0.85)	1.00 (0.99)	1.32 (1.09)	1.52 (1.14)	
CV risk category[g]					
low (score 0)	17 359 (43.11)	695 (40.48)	1289 (35.85)	1383 (28.67)	df (6)
medium (score 1)	13 281 (32.98)	624 (36.34)	1131 (31.45)	1454 (30.14)	p < 0.0001
high (score 2–8)	9 626 (23.91)	398 (23.18)	1176 (32.70)	1987 (41.19)	
mean (SD)	1.03 (1.28)	1.02 (1.2)	1.30 (1.43)	1.53 (1.46)	
no score[h] (% of total cohort)	2 484 (5.81)	54 (3.04)	65 (1.78)	37 (0.76)	

a n (%) compared across all four cohorts.

b Excludes values not known.

c Non-RA inflammatory conditions: one or more of the following drug ATC codes: N02A (opioids); N02B (other analgesics and antipyretics); H02A (corticosteroids for systemic use, plain); H02B, (corticosteroids for systemic use, systemic); M01A (anti-inflammatory and antirheumatic products, non-steroids); M01B (anti-inflammatory/antirheumatic agents in combination); M04 (anti-gout preparations).

d n (%) with risk factor compared with those n (%) without.

e GI risk score: cumulative score of: age (≥65 years), past history of drugs for the treatment of gastropathy, use of antithrombotic agents (including low-dose aspirin 30–80 mg/day), selective serotonin reuptake inhibitors and related antidepressants, corticosteroids, high-dose aspirin (>300 mg/day) and NSAIDs.

f n (%) for each category vs other categories combined.

g CV risk score: cumulative score of: age (≥65 years), male sex, indication RA, past history of antithrombotic agents (including low-dose aspirin 30–80mg/day), antihypertensive agents, cardiac therapy, antidiabetic agents and serum lipid-lowering agents.

h No score calculated where information on risk factors (age at index date, sex) was missing.

ATC = anatomical therapeutic class; **CDS** = Chronic Disease Score; **CV** = cardiovascular; **df** = degrees of freedom; **GI** = gastrointestinal; **RA** = rheumatoid arthritis.

Table IV. Crude odds ratios (OR) and 95% confidence intervals for characteristics of NSAID users receiving at least one prescription for second-line nonselective NSAIDs, cyclooxygenase (COX)-2 preferential inhibitors or COX-2 selective inhibitors (coxibs) for the first time between 1999 and 2003, compared with first-line NSAIDs. Significant OR values are highlighted in italics

NSAID group	First-line nonselective NSAID n = 42 750	Second-line nonselective NSAID n = 1771	COX-2 preferential inhibitor n = 3661	Coxib n = 4861
Age ≥65 years at index date	Reference	0.96 (0.85, 1.09)	*1.82 (1.69, 1.96)*	*2.83 (2.66, 3.01)*
Female sex	Reference	0.98 (0.89, 1.08)	*1.35 (1.25, 1.45)*	*1.48 (1.39, 1.59)*
RA as indication[a]	Reference	*2.66 (1.51, 4.42)*	*5.51 (4.10, 7.35)*	*5.89 (4.53, 7.63)*
Dose category				
Low	Reference	*0.10 (0.07, 0.16)*	*2.13 (1.96, 2.33)*	*0.36 (0.31, 0.41)*
Standard	Reference	*4.11 (3.72, 4.54)*	*8.68 (8.03, 9.38)*	*30.09 (27.22, 33.27)*
High	Reference	*0.39 (0.36, 0.43)*	*0.03 (0.03, 0.04)*	*0.03 (0.03, 0.03)*
CDS				
Low (score 0)	Reference	*0.65 (0.58, 0.73)*	*0.44 (0.41, 0.48)*	*0.32 (0.29, 0.35)*
Medium (score 1–3)	Reference	1.05 (0.95, 1.16)	*0.79 (0.73, 0.85)*	*0.76 (0.71, 0.81)*
High (score 4+)	Reference	*1.42 (1.29, 1.57)*	*2.41 (2.25, 2.58)*	*3.01 (2.83, 3.20)*
Switcher (NSAID use in previous 6 mo)	Reference	*7.76 (7.01, 8.58)*	*9.30 (8.63, 10.00)*	*9.38 (8.79, 10.01)*
Risk factors				
Past history of:				
gastropathy	Reference	*1.60 (1.39, 1.83)*	*2.57 (2.36, 2.80)*	*3.51 (3.27, 3.76)*
thrombosis treatment	Reference	0.92 (0.77, 1.09)	*1.70 (1.54, 1.88)*	*2.17 (2.00, 2.35)*
hypertension	Reference	1.10 (0.97, 1.23)	*1.70 (1.58, 1.83)*	*2.24 (2.10, 2.38)*
antidepressant use	Reference	*1.27 (1.03, 1.56)*	*1.20 (1.03, 1.39)*	*1.60 (1.43, 1.80)*
diabetes mellitus	Reference	0.96 (0.75, 1.20)	*1.52 (1.32, 1.74)*	*1.93 (1.73, 2.16)*
cardiac disorders	Reference	0.97 (0.74, 1.25)	*1.77 (1.54, 2.05)*	*2.17 (1.93, 2.44)*
hyperlipidaemia	Reference	0.89 (0.72, 1.10)	*1.40 (1.24, 1.59)*	*1.92 (1.74, 2.12)*
corticosteroids	Reference	*1.96 (1.60, 2.40)*	*2.90 (2.56, 3.29)*	*2.98 (2.67, 3.33)*
high-dose aspirin (>300 mg/day)	Reference	4.47 (0.85, 15.39)	0.72 (0.02, 4.58)	2.72 (0.79, 7.61)
Risk score				
GI risk category[b]				
low (score 0)	Reference	*0.37 (0.34, 0.41)*	*0.22 (0.20, 0.24)*	*0.15 (0.14, 0.17)*
medium (score 1)	Reference	*1.75 (1.58, 1.94)*	*1.73 (1.61, 1.86)*	*1.53 (1.44, 1.64)*
high (score 2–7)	Reference	*2.17 (1.94, 2.43)*	*3.72 (3.46, 4.01)*	*5.30 (4.97, 5.64)*

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Table IV. Contd

NSAID group	First-line nonselective NSAID n = 42 750	Second-line nonselective NSAID n = 1771	COX-2 preferential inhibitor n = 3661	Coxib n = 4861
CV risk category[c]				
low (score 0)	Reference	*0.90 (0.81, 0.99)*	*0.74 (0.69, 0.79)*	*0.53 (0.50, 0.57)*
medium (score 1)	Reference	*1.16 (1.05, 1.29)*	0.93 (0.87, 1.00)	*0.88 (0.82, 0.94)*
high (score 2–8)	Reference	0.97 (0.86, 1.08)	*1.55 (1.44, 1.67)*	*2.23 (2.09, 2.37)*

a Non-RA inflammatory conditions: one or more of the following drug ATC codes: N02A (opioids); N02B (other analgesics and antipyretics); H02A (corticosteroids for systemic use, plain); H02B, (corticosteroids for systemic use, systemic); M01A (anti-inflammatory and antirheumatic products, non-steroids); M01B (anti-inflammatory/antirheumatic agents in combination); M04 (anti-gout preparations).

b GI risk score: cumulative score of: age (≥65 years), past history of drugs for the treatment of gastropathy, use of antithrombotic agents (including low-dose aspirin 30–80 mg/day), SSRI and related antidepressants, corticosteroids, high-dose aspirin (>300 mg/day) and NSAIDs.

c CV risk score: cumulative score of: age (≥65 years), male sex, indication RA, past history of antithrombotic agents (including low-dose aspirin 30–80 mg/day), antihypertensive agents, cardiac therapy, antidiabetic agents and serum lipid-lowering agents.

ATC = anatomical therapeutic class; **CDS** = Chronic Disease Score; **CV** = cardiovascular; **GI** = gastrointestinal; **RA** = rheumatoid arthritis; **SSRI** = selective serotonin reuptake inhibitor.

Coxib users were also the most likely of the four cohorts to be identified as switchers (table IV).

Patient GI and CV Risk Profiles

Of the individual risk factors, coxib users were significantly more likely than first-line nonselective NSAID users to have indicators of a history of drugs for the treatment of gastropathy, antithrombotic agents, antihypertensives, SSRIs and related antidepressants, antidiabetic agents, cardiac agents, serum lipid-lowering agents, corticosteroid use and high-dose aspirin use (although numbers were very low) [table IV]. Of these, the strongest measures of effect were related to drugs for the treatment of gastropathy (OR 3.51; 95% CI 3.27, 3.76; 27.9% vs 10.0% in the reference group) and corticosteroid use (OR 2.98; 95% CI 2.67, 3.33; 9.4% vs 3.4%).

Overall, patients prescribed coxibs were most likely to have high (+2) GI and CV risk scores (OR 5.30; 95% CI 4.97, 5.64 and 2.23; 95% CI 2.09, 2.37, respectively) versus first-line nonselective NSAIDs. For first-line nonselective NSAIDs the inverse was observed for low and medium GI and CV risk scores (table IV).

There was evidence of a significant, positive linear correlation between GI and CV risk when scores were plotted at individual patient level for each cohort (table V). The slopes for each model show that for a unit increase in GI risk score, CV risk score increases by approximately 0.40 units in each cohort. This means that as the number of GI risk factors increases, so does the number of CV risk factors. As expected, CDS was less well correlated with the GI or CV score for each NSAID group, but still significantly so (R range 0.48–0.54).

Calendar Time

There was no remarkable change in the mean GI or CV risk scores of patients initiated on treatment within each cohort during the study period (figure 1 and figure 2), or in subgroups of patients defined by history of previous NSAID use (data not shown). Similarly, no temporal changes were observed in the sensitivity analysis which examined mean scores for high GI or CV risk patients only (data not shown). Note also that the plots for patients initiated on coxibs start 30 June 2000. This reflects the date

Table V. Linear regression analyses of relationship between cardiovascular (CV) risk score and gastrointestinal risk score, by NSAID cohort

CV risk score	Pearson correlation coefficient (R)	Intercept	Slope[a] (95% CI)	No. observations in model
First-line nonselective NSAID	0.62	0.15	0.41 (0.41, 0.42)	40 266
Second-line nonselective NSAID	0.48	0.60	0.40 (0.36, 0.43)	1 717
COX-2 preferential NSAID	0.57	0.75	0.43 (0.41, 0.45)	3 596
Coxib	0.54	0.88	0.42 (0.41, 0.44)	4 824

a All p-values for slope (β) significant (<0.0001); linear assumptions checked.

COX = cyclo-oxygenase.

when rofecoxib first became available for reimbursement by medical insurance companies in The Netherlands (April 2000).

Examination of plots of mean CDS score by quarter-year for each NSAID cohort, showed some evidence of a decreasing trend over time (figure 3). In light of this, we conducted a *post hoc* analysis and fitted a simple linear regression model to examine this relationship further. For each model, there was a significant negative linear relationship indicating a change in the baseline characteristics of these patients, as defined by CDS: coxibs (β = −0.06; 95% CI −0.09, −0.03); COX-2 preferential inhibitors (β = −0.05; 95% CI −0.08, −0.02); second-line nonselective NSAIDs (β = −0.08; 95% CI −0.12, −0.04) and first-line nonselective NSAIDs (β = −0.05; 95% CI −0.06, −0.05) [all p < 0.0001].

Discussion

Main Findings

This drug utilization study shows that coxibs are channelled towards the patients at higher risk for GI and CV complications. Whilst the GI and CV risk profiles of patients differed between the first-line nonselective NSAIDs and the coxibs, there was no suggestion of any change in this pattern over time. In addition, at the individual patient level, the risk profile for GI adverse events was moderately well correlated with the risk profile for CV adverse events.

Patient Characteristics

The demographic characteristics of patients in these cohorts appeared to be representative of NSAID users, including coxibs, in other populations.[22,25,34-36] The prevalence of switching was high. This is as expected, given that a significant proportion of patients (at least 25% of new users) do

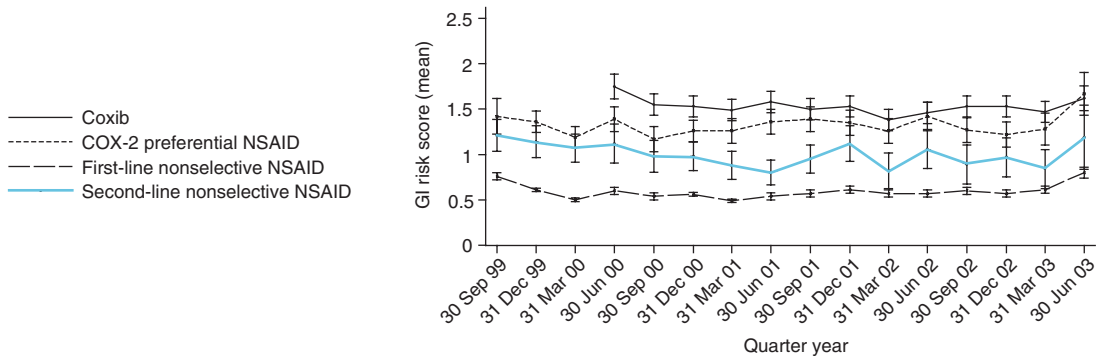

Fig. 1. Mean gastrointestinal (GI) risk score per quarter-year, by NSAID cohort. T-bars represent upper and lower 95% CI. **COX-2** = cyclo-oxygenase 2; **coxib** = COX-2 selective inhibitor.

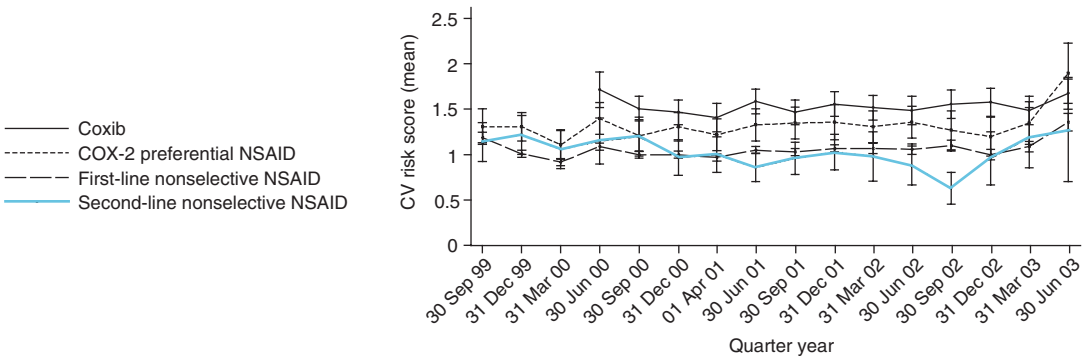

Fig. 2. Mean cardiovascular (CV) risk score per quarter-year, by NSAID cohort. T-bars represent upper and lower 95% CI. **COX-2** = cyclooxygenase 2; **coxib** = COX-2 selective inhibitor.

not respond to or tolerate the first NSAID treatment prescribed.[37] That the alternative NSAID groups (including coxibs) were being used as first-line agents supports findings from other published studies.[22,24,38]

Reassuringly, coxibs were more likely to be initiated at standard anti-inflammatory doses than the first-line nonselective NSAIDs. This supports other findings reported elsewhere.[34] The finding that high anti-inflammatory doses were frequently prescribed for first-line nonselective NSAIDs is of concern, given that prescribing recommendations suggest use of the lowest dose at the start of treatment to minimize the risk of adverse effects. The implications are that such prescribing can contribute to potentially avoidable morbidity, as well as to elevated costs.[39]

Patient GI and CV Risk Profiles

The majority of patients in all four cohorts had few, if any risk factors at the start of treatment. This also supports findings reported elsewhere.[20,40] The finding that new coxib users were more likely to have a history of drug administration for the treatment of gastropathy was expected. We acknowledge that such drugs may be used for prevention of NSAID-induced gastropathy; however, utilization is still an indicator for patients considered to be at risk of GI adverse events.

The significant positive correlation between GI and CV risk, regardless of NSAID type, suggests that patients with an increasing number of GI risk factors are also likely to have an accompanying increase in CV morbidity. This is of particular relevance in light of recent reports regarding a possible class effect of increased CV risk for all NSAIDs.[41] Such selective prescribing of coxibs towards the

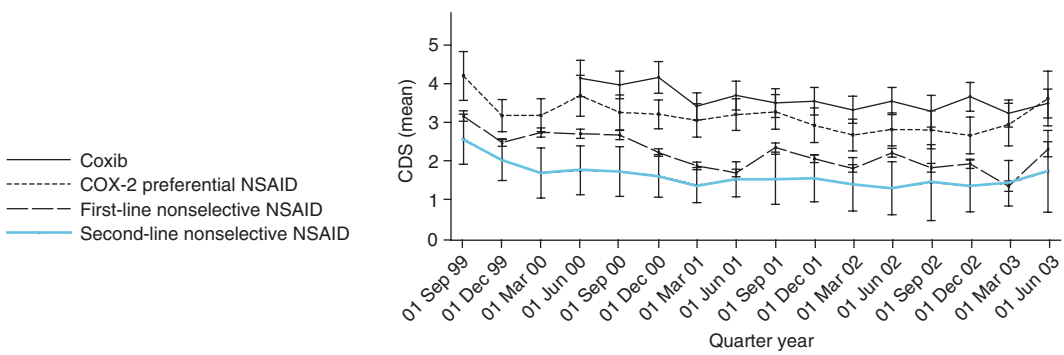

Fig. 3. Mean Chronic Disease Score (CDS) per quarter-year, by NSAID cohort. T-bars represent upper and lower 95% CI. **COX-2** = cyclooxygenase 2; **coxib** = COX-2 selective inhibitor.

patients with most co-morbidity supports findings from another study conducted in The Netherlands, which reported that NSAIDs were widely prescribed to elderly patients with established risk factors.[42] That a higher proportion of new users of coxibs received antithrombotic treatment (of which low-dose aspirin 30–80 mg/day accounted for at least 50% in all four cohorts) is of interest because of the debate regarding the possible confounding effect of aspirin on studies evaluating the CV risk of coxibs.[43]

Also of interest is the marked difference in prevalence of the use of antihypertensive agents, with the highest proportion reported for the coxib cohort. This is important for two reasons. First, hypertension is a risk factor for thrombotic vascular events.[44] Second, the influence of COX-2 function on the cardio-renal system in susceptible patients was still being elucidated during the time period being examined in this study, and clinicians may have prescribed these drugs to patients with hypertension whilst uncertain of the sequelae of COX-2 antagonism. Further evidence of channelling of coxibs to patients with more underlying morbidity is supported by the high prevalence of chronic disease amongst coxib users in this study. This has also been reported elsewhere.[45]

Strengths and Limitations

The risk scores used in this study were intended to be simple and easily derived from the SFK data in a standardized, identical manner for each NSAID cohort.[46] Age, sex and other selected GI or CV risk factors were not adjusted for, but profiles were assembled from a set of known risk factors for NSAID-related GI and CV complications. Analysis was conducted by means of stratification of selected patient characteristics and restriction to selected sub-groups, so that baseline risk profiles of different sub-groups of patients could be examined, overall and by calendar time.

Exposure duration, changes in dose and adherence for each NSAID after starting treatment were not measured, nor were subsequent CV or GI outcomes. Approximately 8% of patients contributed data to more than one cohort and thus initiated treatment with different NSAID classes within the study period. These patients were not excluded from the analysis since this reflects real-life use, but were categorized as switchers where relevant and data analysed as appropriate. The results pertain to pooled combinations of NSAIDs; within-group comparisons between individual drugs are not reported here. The proportion of new celecoxib users within the coxib cohort was very small (<4%, n = 186); therefore, the GI and CV risk profiles were dominated by new rofecoxib users, for whom a higher proportion have been reported as having pre-existing CV risk factors than for other NSAIDs in a similar setting.[10] However, in this study, no differences were found between patients in terms of their GI and CV risk profile for celecoxib compared with rofecoxib (data not shown, all ORs non-significant).

Drug-dispensing data as surrogate measures of concurrent morbidity have been utilized in other studies.[3,47,48] Compliance for these treatments was unknown and diagnoses were not validated. Nevertheless, since data are required for pharmacist reimbursement and remuneration, it is unlikely that the data are of poor quality.

RA was the only indication that could be confirmed (see table II); therefore, associations between different indications and NSAID use could not be examined. Information on other risk factors such as smoking and alcohol use is also not available within the SFK database; therefore, their impact on baseline risk could not be examined. All three of the first-line nonselective NSAIDs are available over the counter (OTC) in The Netherlands; however, the potential impact of these and other OTC drugs (e.g. aspirin and gastroprotective agents) could not be examined using SFK data. Reports in the published literature indicate that OTC medication use is likely to be common,[49,50] and there is no reason to believe that use would systematically differ across the four groups.

Calendar Time

No remarkable temporal changes were observed when the mean GI or CV risk scores were plotted by quarter-year period up to 30 June 2003. One explanation may be that the scores are not sensitive enough to show changes over time. Examination of individual score category by quarter-year time period does show a small variation in the proportion of patients within each category. Thus, the absence

of any trend does not appear to be related to the derivation of the score itself, but to some other factor. The observed temporal effect in CDS warrants further investigation, since patient GI and CV risk profiles changed little over the study period examined.

One explanation for these differing observations over time may be related to how these scores were derived. In this study, the GI and CV risk scores are derived from pharmacy utilization data from the 6 months preceding initiation of treatment. Similarly, the CDS is based on such data, but measures comorbidity in the previous 12 months and it does not utilize information regarding medicines used in the management of symptomatic conditions, such as analgesics or NSAIDs. Thus, the GI and CV scores described in this study provide a different measure of baseline risk factors (although some factors are common to both). In common to all three scores is a lack of information on severity of disease. The risk factors chosen for inclusion within the GI risk score were chosen to reflect those with a well known, strong association with GI bleeding. Some may disagree with our choices. However, there does appear to be a lack of consensus with regard to which risk factors are important, between both scientific publications[13,17,29,51,52] and national prescribing guidelines on this topic.[53,54]

For all NSAID cohorts, the GI and CV risk scores were moderately correlated. This does not appear to be entirely related to commonality in risk factors (age ≥65 years and use of antithrombotic agents). A *post hoc* sensitivity analysis by cross-tabulation of restricted scores (excluding those two common risk factors) showed that correlation between scores also exists for a subset of patients (18.8% [n = 914] for the coxib cohort; 18.2% [n = 666] for the preferential COX-2 inhibitors; 17.47% [n = 309] for the second-line nonselective NSAIDs and 7.5% [n = 3311] for the first-line nonselective NSAIDs) despite the remaining factors being unrelated. Given the limited number of variables included within each score, further refinement is needed to improve discrimination and identify specifically which risk factors correlate, but keeping the emphasis on simplicity. These results show that GI and CV risk should not be considered independently and that selective prescribing of coxibs applies to people with underlying GI and CV morbidity.

Findings from Other Studies

A similar study has been conducted using a general practice research database in The Netherlands.[25] Patient characteristics were similar to those reported in our study, as were important determinants for prescription of a coxib, for example, prevalence of GI comorbidity (adjusted OR 1.82; 95% CI 1.72, 1.92) and past use of an NSAID (adjusted OR 3.23; 95% CI 3.07, 3.41). Most coxib users had very few GI risk factors (age >65 years, previous use of systemic corticosteroids, anticoagulants, aspirin, history of peptic ulcer or GI bleeding) or CV risk factors (history of stroke, heart failure, ischaemic heart disease) [76% and 65%, respectively]. The authors also reported that an increasing number of GI risk factors increased the probability of the patient being prescribed a coxib (adjusted OR 1.31; 95% CI 1.19, 1.44) and the prevalence of CV disease was higher in coxib users than in users of nonselective NSAIDs (adjusted OR 1.35; 95% CI 1.28, 1.42). Contrary to our study, channelling of coxibs to patients with at least one GI risk factor decreased over time, whilst no such trend was observed for patients with at least one CV risk factor. The authors also reported that first-time coxib prescribing was also dependent on physicians' preferences.

Implications for Prescribing and Future Research

Prescribers need to revise therapeutic options for treating patients who require NSAIDs, especially those with multiple co-morbidities. Selection bias in clinical trials means that there is discrepancy between experimental and real-life clinical situations. The initiation of coxibs in patients at high GI and CV risk during the immediate post-marketing period, may have been a consequence of restricted treatment options for such patients, and/or a reflection of the uncertainty of prescribers in treating these types of patients, and/or variation in perception of the importance of reported risks, such as concomitant aspirin use.[55] Regardless of the scenario, the findings of our study emphasize the difficul-

ties experienced by clinicians in assessing various levels of risk when initiating treatment with coxibs or any other NSAID.

Observational studies suggest that the uptake of newly approved drugs is associated with a minor subset of prescribers.[56] Further research is required to investigate whether the channelling effect is observed for all prescribers or only sub-sets. Research is now also needed to determine the characteristics of patients who continue to be treated with coxibs and also monitor subsequent health outcomes. The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen) study is an example of a study investigating the use of drug combinations in high-risk groups.[57] Results of that study are expected in 2010.

In 2005, regulatory agencies worldwide concluded that in estimating the benefit-risk ratio of new NSAIDs such as the coxibs, CV adverse events have to be balanced against perceived GI safety benefits in individual patients.[58] In some circumstances, the GI benefits may offset the risk of CV harm. In this regard, physicians, particularly frequent prescribers, need to examine patients' baseline risk profiles prior to initiating treatment and use this information to optimize individual patient management.

Conclusion

Our study shows how drug utilization studies can provide important information on the characteristics of patients using newly approved drugs since their introduction into clinical practice, as well as new users of existing treatments. Of the four NSAID cohorts, new users of coxibs tended to have the highest numbers of GI and CV risk factors, with no obvious change over calendar time. There was also evidence of a correlation between GI and CV risk scores. Thus, selective prescribing of coxibs applies to people with co-existing CV as well as GI risk factors. This is important when comparing the safety and/or efficacy of new therapies with existing therapies, and emphasizes the difficulties encountered by prescribers in assessing levels of risk when initiating coxib treatment.

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