

ORIGINAL REPORT

Use of cyclo-oxygenase 2 inhibitors (COX-2) and prescription non-steroidal anti-inflammatory drugs (NSAIDs) in UK and USA populations. Implications for COX-2 cardiovascular profile[†]

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SUMMARY

Background COX-2 and NSAIDs differ in their gastrointestinal (GI) and cardiovascular (CV) toxicity from pharmacological, clinical and epidemiologic point of views.

Objective Describe the patterns of use of NSAIDs and COX-2 in The Health Improvement Network (THIN) database in UK and the PharMetrics database in USA.

Methods We examined the experience of 10 distinct cohorts of new users of diclofenac, naproxen, ibuprofen, piroxicam, other NSAIDs, meloxicam, celecoxib, etoricoxib, rofecoxib and valdecoxib. The study period was 1 January 1995 through 2004 (31 March in UK and 28 February in USA). We collected information on covariates including history of upper GI disease, CV disease, hepatic disease, dosage, concomitant medication, and visits to a rheumatologist.

Results We identified 486 076 unique patient-drug pairs in UK and 1 533 239 in USA. In UK population 78 201 (16%) were COX-2 users and in PharMetrics 324 206 (21%) were COX-2 users. Diclofenac and ibuprofen (NSAIDs), and celecoxib and rofecoxib (COX-2) were the agents prescribed most frequently. The duration of therapy was longer among celecoxib and rofecoxib users than among other users. More COX-2 users than NSAIDs users received concomitant gastroprotective agents (GPA), corticosteroids and anti-platelet therapy, and had a history of thromboembolic events and hypertension. PharMetrics patients were prescribed higher doses of NSAIDs and COX-2. The use of any single agent for more than 90 days was uncommon, but more frequent in PharMetrics. Switching was uncommon and was generally to a NSAID.

Discussion Our results confirm some previous findings from other authors such as the presence of both GI and CV channelling to COX-2 agents but refute others, such as the frequency of drug switching between these agents. The typical use

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of COX-2 agents in practice is for shorter duration, and at lower doses, than was employed in randomized clinical trials. This difference may help clarify the apparent discrepancy with respect to CV toxicity between the results from clinical trials, which showed a higher CV risk with these drugs, and non-experimental epidemiologic studies, which showed lower or no increase in risk. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS—COX-2; NSAID; drug utilization; cardiovascular profile

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis (PG) through the cyclo-oxygenase (COX-1 and COX-2) pathways.¹ COX-2 inhibition is responsible for anti-inflammatory effects and COX-1 inhibition is responsible for gastrointestinal (GI) toxicity.² Drug use varies from country to country depending on numerous factors, such as reimbursement policies, marketing practices and the presence of medication guidelines.

COX-2 inhibitors are supposed to achieve the same analgesic and anti-inflammatory properties as NSAIDs with less GI toxicity,^{3,4} although some disagree that this objective has been attained.⁵ NSAIDs vary in GI toxicity, with piroxicam generally found to have a greater GI risk than other NSAIDs,^{2,6} although some authors claim that this difference may be due to comparisons between non-equivalent doses.⁷ Rofecoxib, a COX-2 inhibitor, was first associated with an increased risk of acute myocardial infarction (MI) in the VIGOR study,⁸ which showed a five-fold increase in the risk of MI compared with naproxen. This finding was reinforced in several epidemiologic studies^{9–11} and later in the APPROVe trial,¹² which led to the voluntary withdrawal of rofecoxib from the market on 30 September 2004.¹³ Increased risk of cardiovascular (CV) toxicity reported in trials of parecoxib (the intravenous formulation of valdecoxib)¹⁴ and celecoxib¹⁵ have raised the possibility of a class effect for the COX-2 agents.

This paper compares NSAIDs and COX-2 drug utilization patterns among privately insured patients in a large USA claims database with patients covered by UK national health system. We present information on the use of NSAIDs and COX-2, including, dosage, duration of use and comorbidity. Our findings may help to reconcile the seemingly differing results regarding cardiotoxicity found in epidemiologic studies on one hand and clinical trials on the other.

METHODS

Study population and cohort definitions

Currently, The Health Improvement Network (THIN) dataset contains records for 308 medical practices covering more than 3.4 million UK patients of general practitioners, of whom more than 1.6 million patients are actively registered with the practices and can be followed.¹⁶ The remaining patients have historical data but have either left the practice or died. Most of these contributing practices have recorded several years of data on their system. For those practices that previously used VAMP systems, data entries extend as far back as 1985. THIN data are collected unobtrusively from the daily record keeping of general practices in UK. The data received from THIN are processed to provide full, coded demographic, medical and prescription details at the level of each individual patient. In addition, there is information on referral to specialists, diagnostics and laboratory results, some lifestyle characteristics and other measurements taken within the GP practice. The data are organized in files by individual practice and provide a longitudinal medical record for each patient.

PharMetrics data include 43 million US patients from 73 health care plans.¹⁷ In PharMetrics the computerized information available includes demographics, details from medical services, diagnoses from specialists' referrals and hospital admissions. Results of laboratory tests are available for a small subset of the patient population. The database includes both inpatient and outpatient diagnoses (ICD-9) and procedures (CPT-4, HCPCS), as well as both standard and mail order prescription records. Data on prescription records include the NDC code as well as days supplied and quantity dispensed. Both health plan-paid and charged amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables, plan type, payer type, provider specialty,

and plan enrollments dates. Records in the PharMetrics database are representative of the national managed care population, based on a variety of patient and health plan demographic measures that include geographic region, age, gender, and plan type with the exception of persons ≥ 65 (8% in PharMetrics vs. 13% in US census). Only health plans submitting data for all members are included in the database. Data contributions are also subjected to a series of quality checks to ensure a standardized format and low error rates.

We conducted essentially identical analyses in both databases, with some exceptions described below. These databases are generally thought to be representative of UK and USA populations. We identified all people 18 years of age or older in the populations who received at least one prescription for a NSAID or COX-2 from 1 January 1995 through 31 March 2004 in THIN and through 28 February 2004 in PharMetrics. We assigned an index date to each exposed person. This was defined as the date of the first prescription for each individual NSAIDS or COX-2, provided that it followed a period of at least 6 months with no evidence of exposure to any NSAIDS or COX-2. To ensure ample historical exposure data, we limited each cohort to people continuously enrolled in the database for at least 1 year before the index date. We identified 10 cohorts of new users of diclofenac, naproxen, ibuprofen, piroxicam, other NSAIDS, meloxicam, celecoxib, etoricoxib, rofecoxib, and valdecoxib. Etoricoxib is not available in USA; hence this cohort was compiled in UK only. Each patient was followed from the drug index date until the end of enrollment in the database, death, or the end of the study period. (31 March 2004 in THIN, 28 February 2004 in PharMetrics). Since patients were new to a drug in this analysis, they could only appear once as users of a particular drug. They could, however, appear as new users of multiple drugs for which the inclusion criteria were satisfied. If so, they would have separate index dates for each drug, which are the dates of the first prescription for each.

For the THIN cohorts, the duration of therapy for each drug was computed by dividing the total amount prescribed by the dose per day, yielding the days supplied. In PharMetrics we classified exposure using the prescription fill date and the days supplied recorded in the pharmacy database. Using this information, we created episodes of drug use and tallied person-time exposed to each agent. The computation of person-time (or 'current' drug exposure) was based on the continuation of drug therapy or expected refills. We added the days

supplied to the current prescriptions fill date to compute a therapy end date. If the same drug was filled again by the therapy end date, then the drug exposure episode was considered to continue until no more information on refills was found. When no prescriptions were found by the end date of the 'current' therapy period, the patient entered 'recent' drug therapy time. This period could last up to 30 days and then the patient entered 'past' drug therapy time. However, if a prescription was filled before the 'recent' time ends, a new 'current' therapy episode began. 'Past' time extended to the study end date unless a prescription was filled to start a 'current' therapy episode. We defined a chronic user as someone with 50% or more of follow-up time exposed to a study drug.

Drug switching and dosage

We defined switching as filling of a subsequent NSAIDS or COX-2 prescription during the day-supplied window of an existing NSAIDS or COX-2 prescription, plus a 7-day buffer period (e.g. for an initial prescription with a 30-day supply, a subsequent prescription filled for a different agent from day 3–37 after the initial prescription fill date was considered a switch). We calculated the prescribed daily dose for each drug by multiplying the number of pills dispensed times the strength per pill and dividing by the days supplied. We categorized daily dosages for each product into 'low', 'normal' and 'high' (Tables 2a and 2b). For each patient we looked at consecutive prescriptions for a particular drug and dosage changes were defined as any change in the categories defined (e.g. a change in a patient's diclofenac dosing from 25 mg/d to 50 mg/d would be classified as a dosage switch from 'low' to 'normal').

Covariates

We evaluated information on covariates as follows (presence for all covariates was assessed for a period of 6 months before the index date):

Gastrointestinal (GI) event history. We classified a patient to have a positive history for GI events if we found a diagnostic code consistent with upper GI bleeding, peptic ulcer disease, perforation or at least two of the following criteria: presence of an upper GI (UGI) procedure (gastroscopy, UGI radiologic examination); visit to a GI specialist; dispensing of a prescription gastro-protective agent (GPA) within 30 days before the index date.

Thromboembolic (TE) event history. We classified a patient to have positive history of TE events if we found a diagnostic code consistent with acute myocardial infarction (MI), angina, stroke, or receipt of a cardiovascular (CV) procedure (coronary artery bypass surgery, coronary angioplasty or coronary angiography). We also classified a patient with positive TE history if the database indicated a visit to a cardiologist and dispensing of low dose prescription aspirin or other antiplatelet therapy.

Cardio-renal event history. We classified a patient as having a positive history of cardio-renal events if we found a diagnostic code consistent with hypertension, congestive heart failure (CHF) or oedema, or if a patient met at least two of the following criteria: presence of a cardiac procedure (cardiac echography); visit to a cardiologist; dispensing of antihypertensive medication or agents for the treatment of CHF.

Hepatic disease history. We classified a patient as having a positive history of hepatic disease if he or she met one of the following criteria: presence of a diagnostic code compatible with hepatitis, non-infectious hepatitis, liver dysfunction, jaundice, hepatic necrosis; history of liver biopsy; or history of liver transplantation.

Other data

We created a chronic disease score (CDS) for each individual¹⁸ using criteria proposed by Von Korff and colleagues, by noting prescriptions filled within 6 months before the index date. We used the CDS as an indicator of chronic disease severity. We abstracted all concomitant medication history, defined as prescriptions filled within 30 days before the index date. We also recorded a history of visits to a rheumatologist.

Data analysis

We quantified drug utilization for each individual agent stratified by database (THIN and PharMetrics). These descriptive analyses included distribution by age, sex and covariates (gastrointestinal disease history, thromboembolic disease history, hypertension history, CHF, oedema or hepatic disease history, chronic NSAIDs or COX-2 use, chronic disease score, rheumatology visits, and concomitant use of corticosteroids, GPA, antiplatelets or anticoagulants). We

also report NSAIDs and COX-2 daily dosage and duration.

RESULTS

We identified 362 448 unique patients in THIN and 1 426 471 in PharMetrics. As mentioned above, a patient appears in the data for each drug definition he or she satisfies. Thus, in THIN, we identified 486 076 unique patient-drug pairs, of which 78 201 (16%) involved COX-2. In PharMetrics we identified 1 533 239 unique patient-drug pairs, of which 324 206 (21%) were COX-2. These patients received 1 337 114 prescriptions covering 35 642 251 therapy days in THIN and 3 241 881 prescriptions covering 68 579 829 therapy days in PharMetrics. In THIN the average number of prescriptions per patient was 4.1 (celecoxib), 4.4 (rofecoxib), 4.4 (meloxicam), 2.0 (valdecoxib), 2.8 (etoricoxib), 2.6 (diclofenac), 2.3 (ibuprofen), 2.4 (naproxen), 2.8 (piroxicam) and 2.6 (other). In PharMetrics the corresponding numbers were: 3.4 (celecoxib), 3.0 (rofecoxib), 2.3 (meloxicam), 2.0 (valdecoxib) 1.9 (diclofenac) 1.9 (ibuprofen) 1.8 (naproxen) 2.1 (piroxicam) 1.9 (other).

Diclofenac and ibuprofen accounted for 81% of all NSAIDs use in THIN, whereas ibuprofen and naproxen accounted for 80% of the NSAIDs use in PharMetrics. In both populations celecoxib and rofecoxib constituted most COX-2 use. Rofecoxib was used more frequently in US population than celecoxib (53% vs. 37%), whereas the use of celecoxib (38%) and rofecoxib (36%) was similar in THIN. The proportion of COX-2 use attributable to valdecoxib was low but 10 times higher in PharMetrics than in THIN (6% vs. 0.6%). In THIN, 6% of COX-2 use was attributable to etoricoxib (Tables 1a and 1b).

A larger proportion of COX-2 users were female, higher in THIN than in PharMetrics (65% vs. 60%). THIN users of both NSAIDs and COX-2 were older than PharMetrics users, but in both populations COX-2 users were older than NSAIDs users (Tables 1a and 1b). Celecoxib users were the oldest in both populations (median age 65.5 years in THIN and 51.0 years in PharMetrics).

Dosage & duration of use

Dosage and duration of first use differed between THIN and PharMetrics. Tables 2a and 2b show the percentage of patients exposed to each drug during continuous use, stratified by dosage. The duration of therapy was longer in THIN than PharMetrics,

Table 1a. Study cohorts and patient demographics (COX-2)

	Celecoxib		Rofecoxib		Meloxicam		Valdecoxib		Etoricoxib	
	THIN*	Pharm [†]	THIN	Pharm	THIN	Pharm	THIN	Pharm	THIN	Pharm
Total number of patients	29,363	119,454	28,274	170,739	14,962	13,956	721	20,057	4881	na
Males, N (%)	10,062 (34)	48,439 (41)	9,991 (35)	68,530 (40)	5,129 (34)	5,405 (39)	234 (33)	7,766 (39)	1,903 (39)	na
Age groups, N (%)										
18-34	1318 (4.5)	12,709 (10.6)	1596 (5.6)	23,738 (13.9)	1033 (6.9)	1,711 (12.3)	47 (6.5)	2,836 (14.1)	311 (6.4)	na
35-54	7260 (24.7)	59,079 (49.5)	7,622 (27.0)	89,194 (52.2)	4,417 (29.5)	7,277 (52.1)	219 (30.4)	10,605 (52.9)	1,481 (30.3)	na
55-74	13,447 (45.8)	41,441 (34.7)	12,526 (44.3)	51,545 (30.2)	6,368 (42.6)	4,571 (32.8)	318 (44.1)	6,166 (30.7)	2,101 (43.0)	na
75+	7,338 (25.0)	6,225 (5.2)	6,530 (23.1)	6,262 (3.7)	3,144 (21.0)	3,97 (2.8)	137 (19.0)	450 (2.2)	988 (20.2)	na
Median age	65.5	51	63	49	61	50	61	49	61	na
Total number of prescriptions	119,552	402,569	124,912	515,409	65,683	31,414	1,443	40,263	13,673	na
Mean prescriptions per patient	4.1	3.4	4.4	3.0	4.4	2.3	2.0	2.0	2.8	na
Total current therapy days	3,503,792	12,073,246	3,677,922	14,265,679	2,005,533	903,861	36,334	1,086,857	3,602,226	na
Mean therapy days per patient	119	101	130	84	134	65	50	54	74	na
Median therapy days per patient	41	31	41	31	31	31	31	31	29	na

*THIN, The Health Improvement Network Database (UK).

[†]Pharm, PharMetrics database (USA).

Table 1b. Study Cohorts and Patient Demographics (NSAID)

	Diclofenac		Ibuprofen		Naproxen		Piroxicam		Other	
	THIN	Pharm	THIN	Pharm	THIN	Pharm	THIN	Pharm	THIN	Pharm
Total number of patients	187,558	52,478	141,608	549,642	34,150	420,192	5,231	21,209	39,328	165,512
Males, N (%)	86,058 (46)	23,075 (44)	58,457 (41)	221,565 (40)	15,923 (47)	177,703 (42)	2,224 (43)	9,544 (45)	11,177 (28)	82,713 (50)
Age groups N (%)										
18-34	42,167 (22.5)	10,659 (20.3)	35,108 (24.8)	201,414 (36.6)	6,902 (20.2)	118,417 (28.2)	710 (13.6)	3,452 (16.3)	11,252 (28.6)	33,987 (20.5)
35-54	80,382 (42.9)	29,247 (55.7)	48,328 (34.1)	266,256 (48.4)	14,355 (42.0)	222,181 (52.9)	1,997 (38.2)	11,876 (56.0)	17,175 (43.7)	88,731 (53.6)
55-74	51,725 (27.6)	11,769 (22.4)	42,979 (30.4)	75,254 (13.7)	10,330 (30.2)	72,963 (17.4)	1,948 (37.2)	5,474 (25.8)	8,124 (20.7)	38,916 (23.5)
75+	13,284 (7.1)	803 (1.5)	15,193 (10.7)	67,118 (11.2)	2,563 (7.5)	66,631 (15.6)	576 (11.1)	407 (1.9)	2,777 (7.1)	3,878 (2.3)
Median age	48	46	50	40	49.5	43	54	48	43	46
Total number of prescriptions	490,611	102,069	321,959	1,045,498	83,365	749,419	14,522	44,222	101,394	311,018
Mean prescriptions per patient	2.6	1.9	2.3	1.9	2.4	1.8	2.8	2.1	2.6	1.9
Total current therapy days	12,760,092	2,508,423	7,738,619	15,125,841	2,285,500	15,659,899	431,404	1,241,271	2,842,829	5,714,752
Mean therapy days per patient	68	48	55	28	67	37	82	59	72	35
Median therapy days per patient	29	31	29	12	29	26	31	31	31	16

Table 2a. Duration of continuous first use per drug and strength. THIN. Percentage of patients

Drug	Strength (mg)	Duration (Days)					Total %	Total N 446 748
		≤30 %	31–60 %	61–90 %	91–180 %	≥181 %		
Celecoxib	100	26.0	52.0	15.0	5.0	2.0	9.0	2691
	200	16.5	71.0	8.0	3.5	1.0	88.0	25 740
	400	30.0	58.0	7.0	4.0	1.0	3.0	932
Diclofenac	50	63.0	34.5	2.0	0.5	0.0	16.0	30 045
	100	53.0	43.0	30.0	1.0	0	16.0	29 668
	150	86.5	12.0	1.5	0	0	68.0	127 845
Etoricoxib	60	70.0	18.0	7.0	4.0	1.0	53.0	2570
	90	71.0	19.0	5.5	3.5	1.0	29.5	1446
	120	86.0	11.0	2.0	1.0	0	17.5	865
Ibuprofen	<1000	82.0	14.0	2.5	1.5	0	12.0	17 613
	1000	100	0	0	0	0	0	21
	1200	84.0	15.0	1.0	0	0	76.0	107 507
	1600	88.0	11.0	1.0	0	0	12.0	16 467
Meloxicam	7.5	27.0	60.0	8.0	4.0	1.0	64.0	9577
	15	28.0	61.0	7.0	4.0	1.0	36.0	5385
Naproxen	<550	62.5	34.5	2.0	1.0	0	31.0	10 485
	550	86.0	12.5	1.0	0.5	0	14.0	4806
	1000	79.0	18.0	2.0	1.0	0	54.0	18 537
	1100	0	0	0	0	0	0	0
	>1100	84.0	14.0	2.0	0	0	1.0	322
Piroxicam	10	52.5	40.0	6.0	1.5	0	4.0	210
	20	55.0	40.0	4.0	1.0	0	93.0	4847
	40	65.0	33.0	1.0	0.5	0.5	3.0	174
Rofecoxib	12.5	66.0	20.0	6.5	6.0	1.5	57.0	16 193
	25	71.0	18.0	6.0	4.0	1.0	39.0	11 019
	50	87.0	10.0	2.0	1.0	0	4.0	1062
Valdecoxib	10	39.0	53.0	5.0	3.0	0	54.0	390
	20	46.5	43.0	7.0	3.5	0	39.0	278
	40	75.5	13.0	9.5	2.0	0	7.0	53

particularly among COX-2 and especially among users of celecoxib and rofecoxib. However, we found a higher prevalence of long-term users in PharMetrics than in THIN. The continuous use of any single agent was more frequent in PharMetrics than in THIN, regardless of the cut-off time used. (Tables 2a and 2b). In PharMetrics most celecoxib, valdecoxib and meloxicam users received these drugs for 31–60 days per year, while most patients on all other drugs received therapy for ≤30 days, with piroxicam positioned somewhere between these two groups. In THIN, duration of rofecoxib and etoricoxib differed little from that of NSAIDs. In PharMetrics, ibuprofen had a shorter duration of therapy than any other agent (12-day median duration). There was little difference in use among COX-2 agents with the majority of use being at 31–60 days.

In general, patients included in PharMetrics were prescribed higher dosages than those in THIN throughout the whole spectrum of NSAIDs and

COX-2 (Tables 2a and 2b). In PharMetrics, 71% of the celecoxib episodes used 200 mg/day and 26% 400 mg/day, whereas in THIN the proportion of 200 mg/day and 400 mg/day use was 88% and 3%, respectively. In UK population, most of the rofecoxib episodes involved 12.5 mg/day (57%), and only 4% involved 50 mg/day. In PharMetrics 71% of the episodes involved 25 mg/day and 23% received 50 mg/day. In THIN, 76% of the episodes for ibuprofen were for 1200 mg/day, whereas 94% in PharMetrics were for 1600 mg/day. In THIN 18% of the single-therapy episodes for etoricoxib were for 120 mg/day.

Covariates

Tables 3a and 3b summarize the covariate data. The use of GPA as concomitant medication was more frequent among COX-2 than among NSAIDs users in both populations (20% vs. 6% in THIN) and 12% vs. 5% in PharMetrics). Overall, COX-2 users were

Table 2b. Duration of continuous first use per drug and strength. PharMetrics. Percentage of patients

Drug	Strength (mg)	Duration (Days)					Total %	Total N 1 367 727
		≤30 %	31–60 %	61–90 %	91–180 %	≥181 %		
Celecoxib	100	28.5	42.0	9.0	11.0	9.5	3.0	4115
	200	20.0	49.5	10.0	11.0	9.5	71.0	84 491
	400	36.0	41.0	8.0	9.0	6.0	26.0	30 848
Diclofenac	50	44.0	41.0	6.0	5.0	4.0	4.0	2103
	100	43.0	42.0	7.0	5.0	3.0	22.0	11 566
	150	55.0	34.0	5.0	4.0	2.0	74.0	38 809
Ibuprofen	<1000	67.5	25.0	3.0	3.5	1.0	2.0	13 139
	1000	80.5	17.0	1.5	1.0	0	0	1140
	1200	66.0	28.0	3.0	2.0	1.0	4.0	19 398
	1600	81.0	16.0	2.0	1.0	0	94.0	515 965
Meloxicam	7.5	22.0	55.0	9.0	8.0	6.0	53.0	7396
	15	33.0	48.0	7.0	6.5	3.5	47.0	6560
Naproxen	<550	49.0	37.0	6.0	5.0	3.0	4.5	19 105
	550	60.0	33.0	4.0	2.0	1.0	8.0	33 009
	1000	52.0	40.0	4.0	2.0	1.0	62.0	262 269
	1100	66.5	29.5	2.5	1.0	0.5	14.0	57 384
	>1100	86.5	11.0	1.5	1.0	0	11.5	48 425
Piroxicam	10	51.0	33.0	7.5	5.5	3.0	4.5	979
	20	27.0	55.0	8.0	6.5	3.5	93.5	19 834
	40	67.0	25.0	4.0	3.0	1.0	2.0	396
Rofecoxib	12.5	22	47.5	9	11	10.5	6.0	9954
	25	22.0	51.0	9.5	9.5	8.0	71.0	120 777
	50	59.0	29.0	5.0	4.0	3.0	23.0	40 008
Valdecoxib	10	23.0	53.0	10.0	9.0	5.0	37.0	7414
	20	34.0	47.0	8.0	7.0	4.0	52.0	10 375
	40	73.0	20.5	3.0	2.5	1.0	11.0	2268

almost two times more likely to have a history of TE events compared with NSAIDS users in both populations, although the prevalence was higher in THIN (14% vs. 6%) than in PharMetrics (6% vs. 3%). Similarly, a positive cardio-renal history was more common among COX-2 users than NSAIDS users in both populations (37% vs. 20% in THIN; 33% vs. 21% in PharMetrics). Specifically, a previous history of hypertension was more prevalent in COX-2 users than in NSAIDS users (30% vs. 15% in THIN; 30.5% vs. 20% in PharMetrics), as was a history of congestive heart failure (CHF; 3.5% vs. 1% in THIN; 5% vs. 3% in PharMetrics). Overall, the CDS was lower for NSAIDS than COX-2 users in both databases.

Switching

In both databases most prescriptions were for single therapy (88–91% in PharMetrics and 59–84% in THIN). When switching occurred, most patients were switched to NSAIDS even if the original treatment was a COX-2. In THIN, 10% of COX-2 prescriptions

were switched to another COX-2 and 15% to an NSAIDS. Ten per cent of NSAIDS prescriptions were switched to a COX-2 and 20% to another NSAIDS. In PharMetrics, 2% of COX-2 prescriptions switched to another COX-2 and 6% to an NSAIDS. Six per cent of NSAIDS prescriptions switched to another NSAIDS and 3% to a COX-2.

DISCUSSION

The first COX-2 agent was introduced worldwide in 1999. There is a good correlation between the prevalence of chronic musculoskeletal disorders and the prevalence of NSAIDS use in a population,¹⁹ and the use of NSAIDS increases with age.^{20,21} The results of epidemiologic studies describing real-life use and clinical trials illustrating the experience of selected population using pre-defined regimens may be seen to be not only compatible but also complementary. The results from our study indicate that prescribing and utilization patterns in real-world clinical practice may account for the discrepancy seen between clinical trial

Table 3a. Covariates (THIN). Percentage of patients

	Celecoxib	Rofecoxib	Meloxicam	Valdecoxib	Etoricoxib	Diclofenac	Ibuprofen	Naproxen	Piroxicam	Other
Total number of patients	29 363	28 274	14 962	721	4881	187 558	141 608	34 150	5231	39 328
GI history	0.7	0.7	0.4	0.6	0.7	0.2	0.2	0.2	0.2	0.2
TE any prior history	14.1	13.9	12.3	13.0	12.9	6.0	7.0	6.5	9.2	6.0
Cardio-Renal history	38.0	36.5	34.1	36.9	37.1	18.7	21.0	20.8	25.2	19.2
Hypertension	30.0	28.2	26.8	28.3	29.6	15.3	17.1	16.7	19.4	15.2
CHF	3.6	3.6	3.1	3.7	3.4	1.2	1.5	1.4	2.4	1.6
Oedema	11.8	11.6	10.1	14.3	12.1	4.2	4.9	5.1	7.4	4.8
Hepatic history	0.6	0.6	0.5	0.4	0.6	0.4	0.3	0.3	0.3	0.4
Rheumatology specialty	1.1	1.3	1.4	0.3	0.9	1.0	0.8	1.3	1.1	1.0
Concomitant Corticosteroid	6.1	6.5	6.2	6.1	6.3	3.0	3.2	3.2	4.5	3.5
Concomitant GPA	20.8	21.1	17.1	23.4	20.5	6.1	5.8	6.8	11.0	7.7
Concomitant Antiplatelets	11.6	10.5	8.7	15.1	11.3	3.7	4.8	4.1	6.7	3.7
Concomitant Anticoagulants	0.9	0.8	0.5	0	0.8	0.2	0.3	0.2	0.3	0.3
Chronic user of drug	27.0	24.5	17.2	52.7	34.7	7.4	4.8	6.6	9.7	6.8
Chronic Disease Score ¹⁷										
0	35.8	37.4	43.9	32.6	35.3	65.8	63.0	62.7	52.2	61.6
1	16.4	16.9	15.5	18.7	16.0	10.2	9.9	11.0	13.4	12.3
2	11.1	11.0	11.3	10.4	11.5	9.9	10.9	10.3	11.2	10.4
3	8.6	8.4	7.5	7.8	7.3	3.9	4.5	4.5	5.8	4.5
4	4.7	5.0	4.2	4.2	4.7	2.0	2.3	2.0	3.4	2.2
5	6.5	5.8	5.5	6.7	6.1	2.9	3.4	3.2	4.4	2.9
6	5.5	5.1	4.5	6.7	5.9	1.9	2.1	2.2	3.2	2.2
7+	11.3	10.4	7.6	13.0	13.3	3.4	3.9	4.0	6.3	3.9

Table 3b. Covariates (PharMetrics). Percentage of patients

	Celecoxib	Rofecoxib	Meloxicam	Valdecoxib	Diclofenac	Ibuprofen	Naproxen	Piroxicam	Other
Total number of patients	119 454	170 739	13 956	20 057	52 478	549 642	420 192	21 209	165 512
GI history	3.4	4.8	2.9	3.0	1.6	1.5	1.6	1.8	2.0
TE any prior history	6.9	5.9	6.4	6.1	3.4	2.9	3.2	3.6	4.4
Cardio-renal history	35.2	30.8	35.7	33.9	23.6	19.2	21.5	25.9	27.2
Hypertension	32.8	28.7	33.4	31.4	21.8	17.8	20.0	23.9	25.4
CHF	5.9	5.0	5.4	4.9	2.8	2.4	2.6	3.1	4.1
Oedema	3.0	2.3	3.0	3.1	1.9	1.2	1.5	2.1	2.0
Hepatic history	4.5	4.4	4.2	4.6	3.2	3.1	3.1	3.3	3.6
Rheumatology specialty	7.3	6.1	8.8	6.1	5.7	2.2	3.3	6.2	5.2
Concomitant corticosteroids	4.2	4.0	4.1	3.7	3.4	2.6	2.7	3.5	4.0
Concomitant GPA	12.4	11.2	11.1	11.2	6.0	4.3	4.9	5.6	6.3
Concomitant anti-platelets	0.8	0.8	0.8	0.8	0.3	0.2	0.3	0.3	0.5
Concomitant anti-coagulants	1.5	1.1	0.5	0.9	0.2	0.2	0.2	0.2	0.5
Chronic user of drug	25.1	23.1	25.6	33.0	14.6	6.4	10.4	17.4	8.8
Chronic Disease Score ¹⁷									
0	19.7	22.3	20.9	24.8	29.6	36.4	32.9	27.9	27.5
1	15.50	16.0	16.5	17.6	18.0	17.1	17.7	17.5	16.9
2	13.1	13.4	12.9	13.4	14.4	14.4	14.4	14.4	13.5
3	10.0	10.1	9.6	9.4	9.6	9.0	9.5	10.3	9.6
4	8.1	7.8	7.6	7.2	7.3	6.6	7.0	7.7	7.6
5	7.4	7.0	7.4	7.0	5.9	4.9	5.3	6.1	6.3
6	7.0	6.3	6.9	6.0	4.9	3.7	4.1	5.1	5.3
7+	19.1	17.1	18.3	14.6	10.4	7.9	9.1	11.1	0.9

and epidemiological data with respect to the detection of a CV risk associated with COX-2 use.

Our results suggest that COX-2 users presented both GI and CV risk factors more frequently and stayed on the drugs longer than NSAID users. We found switching between NSAID and COX-2 to be an infrequent event. We found that approximately 25% of the users of either NSAID or COX-2 inhibitors in our study used COX-2 inhibitors rather than NSAID. This proportion was lower than the 60–65% found in some studies of US populations.^{22,23} Comparability among studies, however, may be affected by the different time windows used. Our findings support both GI^{22,24,25} and CV^{22,23} channelling towards COX-2 use (channelling may be defined as the preferential prescription to sicker patients of drugs perceived to be safer). In both US and UK populations, as in other studies, patients receiving COX-2 stayed on the drugs longer than patients prescribed NSAIDs, a finding described as longer persistency.²⁴ However, this effect was more marked in THIN. This finding may be due to better effectiveness or better GI tolerability of COX-2 agents, different indications between NSAID and COX-2 users, channelling (i.e. patients receiving COX-2 may be less prone to toxicities that may lead to discontinuation), or the fact that NSAIDs are available over-the-counter and some NSAIDs exposure is missed. Evidence of potential channelling is supported by the fact that patients on COX-2 were older (especially in THIN) and the duration of therapy increased with age, especially for COX-2. Likewise, the prevalence of chronic disease was more frequent among COX-2 users than NSAIDs users based both on the proportion of chronic users and the results of the CDS (Tables 3a and 3b). A higher CDS score correlates with the presence of chronic disease.¹⁸ Although the CDS score has been validated for a period of 12 months and we used it for a 6-month period we think this should not influence any inferences from the results. The indication for use of GPA (to prevent or treat GI events) could not be ascertained from either database.

Some literature indicates that switching is frequent among NSAIDs users. Ofman et al.²³ describe that 47% of COX-2 users in their study had previously used NSAIDs. We found switching to be infrequent in both databases and the majority of prescriptions for both NSAIDs and COX-2 users were for single therapy. In addition, when patients switched, most changed therapy to an NSAID even if they had initially been prescribed a COX-2 agent. This result was unexpected because whatever the initial indication for the COX-2

was, it would usually still be present at the time of the second prescription.

Our findings that the use of COX-2 tended to be shorter, more variable, and at lower doses in clinical practice than in some clinical trials^{11,15} provides a basis for reconciling the apparent discrepancies between these trials, which showed an increased risk of CV endpoints for both rofecoxib and celecoxib, and the findings from most non-experimental epidemiologic studies, which showed an increased risk with rofecoxib but not for celecoxib. In the non-experimental studies the increased risk with rofecoxib use was especially apparent at doses of 50 mg/day.^{9–11,26–30} Indeed, some of these studies did not find an increased risk with 25 mg/day⁹ or at all.^{27,31,32} In a recent trial, celecoxib use at 400–800 mg/day was reported to increase the risk of a combination of CV endpoints, including MI, compared to placebo, but only after approximately 12 months of continuous exposure.¹⁵ Given that celecoxib use rarely extended beyond 90 days in actual practice, it is not surprising that the overall epidemiologic evidence to date shows little or no increase in risk for celecoxib,³³ although some studies showed a small increase.^{29,30}

Drazen used the apparent discrepancy between the trial results and the non-experimental epidemiologic results for celecoxib to assert the superiority of trials, because they are subject to less 'inherent confounding'.³⁴ No details of the duration of therapy among rofecoxib users, who developed MI in VIGOR,⁷ where rofecoxib was used at 50 mg/day, are available. The use of ≥ 50 mg/day in our study was uncommon in THIN but not in PharMetrics (23% of single therapy episodes used 50 mg/day and 41% of these did so for more than 30 days). Assuming that rofecoxib at ≥ 50 mg/day increases the risk of MI by a factor of 2, our results indicate that unlike celecoxib, substantial numbers of rofecoxib users would receive a dose and duration of exposure that may be sufficient to increase their risk of MI enough to be detected in an epidemiologic study conducted among rofecoxib users treated in routine clinical practice with dosages > 25 mg/day.

Continuous use of NSAIDs or COX-2 for ≥ 1 year for pain indications is exceptional. For example, rofecoxib use for ≥ 1 year in our study was $\leq 2\%$ of all rofecoxib users). In APPROVe, rofecoxib was used at 25 mg/day and did not increase the risk of MI and other TE events over placebo until after approximately 18 months of continuous use.¹² Our results show that in clinical practice, patients are not treated continuously with any agent including rofecoxib for that long. Therefore, based on the results of APPROVe, most

patients treated continuously with rofecoxib at 25 mg/day would not be on the drug long enough to be at risk, which would not allow epidemiologic studies to detect an increased risk associated with rofecoxib used at this dosage. Some epidemiologic studies did detect a small increase in risk with 25 mg/day,^{10,11,26–30} suggesting that some patients included in these studies were at higher baseline CV risk status than the patients in APPROVe and could develop TE events earlier.

Continuous use of celecoxib for at least 12 months and use at dosages ≥ 400 mg/day (the dosage and exposure duration consistent with increased risk for CV events in the Adenoma Prevention with Celecoxib (APC) trial¹⁴) was uncommon in our study (3% of PharMetrics and 0.1% of THIN prescriptions for celecoxib were for durations ≥ 1 year). Thus, patients included in epidemiologic studies of celecoxib, using data derived from clinical practice, would not have been exposed to doses and duration sufficient to detect an increased risk of MI.

The results from our study indicate that prescribing and utilization patterns in real-world clinical practice may account for the discrepancy between clinical trial and epidemiological data with respect to the detection of a CV risk associated with COX-2 use. Therefore the results of epidemiologic studies and clinical trials may be seen to be not only compatible but also complementary.

CHF is considered the most important public health issue in CV medicine.³⁵ NSAIDs trigger CHF³⁶ and cause 19% of hospital admissions for CHF.³⁷ This effect is closely linked to the capacity of these drugs to induce hypertension³⁸ and increase SBP due to salt and water retention.³⁹ In our studies between 15% and 33% of patients had a history of hypertension and between 1% and 6% of CHF. Given the prevalence of both CHF and osteoarthritis among the elderly,⁴⁰ it is important to clarify the relative toxicity of NSAIDs and COX-2 in patients with CHF. In APPROVe, the hazard ratio of rofecoxib over placebo was 2.0 (95%CI 1.7–2.4) for hypertension and 4.6 (95%CI 1.5–18.8) for the combined endpoint CHF, pulmonary oedema and cardiac failure.¹² The Kaplan–Meier curves for the cumulative incidence of the combined endpoint separated at approximately 5 months as opposed to 18 months for TE events. In the APC trial,¹⁵ the incidence of heart failure was similar in placebo treated patients (0.3%) to that in celecoxib treated patients (0.4%), although it was higher in patients receiving 800 mg/day (0.6%) than in those receiving 400 mg/day (0.1%). Recently, an epidemiologic study showed a higher risk of hospital admission for CHF in users of rofecoxib and non-selective NSAIDs, but not celecoxib, relative

to non-NSAIDs controls.⁴¹ Celecoxib, however, as well as selective and non-selective NSAIDs, were associated with an increased use of antihypertensive or CHF treatment.⁴² Another study found that rofecoxib and celecoxib users had equivalent risk of initiating antihypertensive therapy.⁴³

The main advantage of our study is its size, involving almost 1.8 million patients and almost 4.6 million prescriptions. Although patient characteristics varied between databases, the methods used for the analyses in both populations were essentially identical. Some of the differences in patient characteristics between the databases affect comparisons across databases. In USA, many patients enroll in Medicare after their 65th birthday (and disenroll from health plans that contribute data to PharMetrics). This fact may partially explain the finding that US population contains younger patients than THIN. Since elderly patients account for a considerable proportion of the NSAIDs and COX-2 use, it is possible that the actual prevalence of use in USA is higher than we detected using PharMetrics, a database consisting of employment-based health care plans. We repeated the analyses standardizing to a common age–sex distribution, using the age and sex distribution of the PharMetrics population as the standard. The weights for the age categories 18–34, 35–54, 55–74 and 75+ respectively, were 10.3%, 22.1%, 8.9% and 0.8% for males, and 16.3%, 29.1%, 11.2% and 1.3% for females. Standardization introduced no important changes except for the proportion of COX-2 users in THIN, which went from 16% in the crude data to 12% after standardization.

Several EU countries suggested or imposed restrictions, such as those issued by the National Institute for Clinical Excellence (NICE) in UK,⁴⁴ on the use of COX-2 drugs. Elderly people are at higher risk of both CV and GI events, and COX-2 users are older than NSAIDs users. Therefore, following guidelines such as National Institute for Clinical Excellence (NICE), last released in 2001 restricting the use of COX-2 to patients at higher risk of GI events may have had the paradoxical effect of exposing patients at higher risk of CV events preferentially to COX-2 agents.⁴⁵

In summary, the patterns of utilization of NSAIDs and COX-2 agents in US and UK populations were relatively similar, except for higher dosages and longer, continuous duration of therapy in USA. Switching of drugs was uncommon. We found that the typical use of COX-2 agents in practice is for shorter duration, and at lower doses, than was employed in trials, a difference that may help clarify

KEY POINTS

- Use of NSAID and COX-2 is relatively similar in the UK and USA.
- Higher doses and longer continuous durations were observed in the USA.
- Switching was uncommon and generally to a NSAID even if the original drug taken was a COX-2.
- There was evidence of GI and CV channeling among users of COX-2.
- The shorter duration of therapy and lower doses used among COX-2 users observed may help to explain the differences in results between epidemiologic studies and clinical trials, such as APPROVE.

the apparent discrepancy between the results from clinical trials and non-experimental epidemiologic studies that examined the CV toxicity of COX-2 agents. Drug utilization studies provide real-life use data that may help answer some questions that remain elusive when clinical trial safety data are examined in isolation.

REFERENCES

1. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. *N Engl J Med* 1999; **340**: 1888–1899.
2. Hernández-Díaz S, García-Rodríguez LA. Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding/perforation. *Arch Intern Med* 2000; **160**: 2093–2099.
3. Bennett K, Teeling M, Feely J. 'Selective' switching from non-selective to selective non-steroidal anti-inflammatory drugs. *Eur J Clin Pharmacol* 2003; **59**: 645–649.
4. Chan FKL, Hung LCT, Suen BY, *et al.* Celecoxib versus diclofenac plus omeprazole in reducing the risk of recurrent ulcer bleeding in patients with rheumatoid arthritis. *N Engl J Med* 2002; **347**: 2104–2110.
5. Jüni P, Rutjes AWS, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? Adequate analysis of the CLASS trial indicates that this may not be the case. *BMJ* 2002; **324**: 1287–1288.
6. García-Rodríguez LA, Hernández-Díaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and non-steroidal anti-inflammatory drugs. *Epidemiology* 2001; **12**: 570–576.
7. Henry D, Lynn LLY, Garcia-Rodriguez LA, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312**: 1563–1566.
8. Bombardier C, Lain L, Reicin A, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; **343**: 1520–1528.
9. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin M. COX-2 selective non-steroidal anti-inflammatory drugs and the risk of coronary heart disease. *Lancet* 2002; **360**: 171–1073.
10. Solomon DH, Schneweis S, Glynn RJ, *et al.* Relationship between selective cyclo-oxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004; **109**: 2068–2073.
11. Graham DJ, Campen DH, Hui R, *et al.* Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005; **365**: 475–481.
12. Bresalier R, Sandler RS, Quan H, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352**: 1092–1102.
13. Merck Announces Voluntary Worldwide Withdrawal of VIOXX[®]. <http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp>. Last visited on October 2nd 2004.
14. Nussmeier NA, Whelton AA, Brown TA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2002; **352**: 1081–1091.
15. Solomon SD, McMurray JJV, Pfeffer MA, *et al.* Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352**: 1071–1080.
16. The Health Improvement Network (THIN). <http://www.epic-uk.org/thin.htm> Last visited March 5, 2005.
17. PharMetrics. http://www.pharmetrics.com/p_overview.html. Last visited March 5, 2005.
18. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1991; **45**: 197–203.
19. Helin-Salmivaara A, Klaukka T, Huupponen R. Heavy users of non-steroidal anti-inflammatory drugs: a nationwide prescription database study in Finland. *Eur J Clin Pharmacol* 2003; **59**: 477–482.
20. García-Rodríguez LA, Hernández-Díaz S. The risk of upper gastrointestinal complications associated with non-steroidal anti-inflammatory drugs, glucocorticoids, acetaminophen and combinations of these agents. *Arthritis Res* 2001; **3**: 98–101.
21. Dominick KL, Ahern FM, Gold CH, Heller DA. Gender difference in NSAID use among older adults with osteoarthritis. *Ann Pharmacother* 2003; **37**: 1566–1571.
22. Dai C, Stafford RS, Caleb AG. National trends in cyclooxygenase-2 inhibitor use since market release: nonselective diffusion of a selectively cost-effective innovation. *Arch Intern Med* 2005; **165**: 171–177.
23. Ofman JJ, Badamgarav E, Henning JM, Knight K, Laine L. Utilization of nonsteroidal anti-inflammatory drugs and anti-secretory agents: a managed care claims analysis. *Am J Med* 2004; **116**: 835–842.
24. Moride Y, Ducruet T, Rochon S, Lavoie F. Persistency of use of COX-2-specific inhibitors and non-specific non-steroidal anti-inflammatory drugs (NSAIDs) in Quebec. *Rheumatology* 2003; **42**: (Suppl. 3)iii17–iii22.
25. MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channeling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003; **52**: 1265–1270.
26. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005; **142**: 481–489.
27. Kimmel SE, Berlin JA, Reilly M, *et al.* Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med* 2005; **142**: 157–164.

28. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; **330**: 1366–1372.
29. Velentgas P, West W, Cannuscio C, Watson DJ, Walker AM. Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. PD Safe 2006 online. DOI: 10.1002/pds.1192
30. Johnsen SP, Larsson H, Tarone RE, et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAID. *Arch Intern Med* 2005; **165**: 978–984.
31. Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclo-oxygenase inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003; **163**: 481–486.
32. Shaya FT, Blume SW, Blanchette CM, Weir RW, Mullins CD. Selective cyclooxygenase-2 inhibition and cardiovascular effects. *Arch Intern Med* 2005; **165**: 181–186.
33. Hernández-Díaz S, Varas-Lorenzo C, García-Rodríguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; **98**: 266–274.
34. Drazen JM. COX-2 Inhibitors—A lesson in unexpected problems. *N Engl J Med* 2005; **352**: 1131–1132.
35. Congestive Heart Failure. http://www.chasemedical.com/hc_chf.htm. Last accessed on October 4th 2004.
36. García Rodríguez LA, Hernández-Díaz S. Non-steroidal anti-inflammatory drugs as a trigger of clinical heart failure. *Epidemiology* 2003; **14**: 240–246.
37. Page J, Henry D. Consumption of NSAID and the development of congestive heart failure in elderly patients. *Arch Intern Med* 2000; **160**: 777–784.
38. Krum H, Gilbert RE. Demographics and concomitant disorders in heart failure. *Lancet* 2003; **362**: 147–158.
39. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure JAM. 1996; **275**: 1557–1562.
40. Johansson S, Wallander MA, Ruigómez A, García Rodríguez LA. Incidence of newly diagnosed heart failure in UK general practice. *Eur J Heart Failure* 2001; **3**: 225–231.
41. Mamdani M, Juurlink DN, Lee DS, et al. 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**: 1751–1756.
42. Mamdani M, Juurlink D, Laupacis A. for the study research group. COX-2 inhibitors and risk of heart failure (letter). *Lancet* 2004; **364**: 1487.
43. Ulcickas Yood M, Watkins E, Wells K, et al. The impact of NSAID or COX-2 use on the initiation of antihypertensive therapy [abstract]. *Pharmacoepidemiol Drug Safety* 2004; **13**: S234.
44. National Institute for Clinical Excellence (NICE). Guidance on the use of cyclo-oxygenase (COX) II inhibitors, celecoxib, rofecoxib, meloxicam, and etodolac for osteoarthritis and rheumatoid arthritis. <http://www.nice.org.uk/pdf/coxiifullguidance.pdf>. Last accessed September 24th 2004.
45. Florentinus SR, Heerdink ER, de Boer A, van Dijk L, Leufkens HGM. The trade-off between cardiovascular and gastrointestinal effects of rofecoxib. *Pharmacoepidemiology and Drug Safety* 2005; **14**: 437–441.