

Comparison of the Baseline Cardiovascular Risk Profile Between Hypertensive Patients Prescribed COX-2-Specific Inhibitors or Nonspecific NSAIDs: Data From Real-Life Practice

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Abstract

Objective: To evaluate the baseline cardiovascular (CV) risk of hypertensive patients newly starting cyclooxygenase (COX)-2-specific inhibitors (celecoxib or rofecoxib) or nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods: Cross-sectional analysis was performed based on real-life practice data contained in the LifeLink™ Integrated Claims Solutions employer claims database. Patients who newly received treatment of celecoxib, rofecoxib, ibuprofen, naproxen, or diclofenac between January 1, 1999, and September 30, 2000, were identified from the database. Among them, only those who had a stable hypertensive condition for at least 3 consecutive months before the index prescription were included. Baseline characteristics were determined from claims data at the time of the index prescription.

Results: A total of 55 396 index prescriptions were identified, which consisted of 20 915 (37.8%) prescriptions for celecoxib, 12 952 (23.4%) for rofecoxib, 10 789 (19.5%) for ibuprofen, 8840 (16.0%) for naproxen, and 1900 (3.4%) for diclofenac. Both univariate and multivariate analyses showed that the patients prescribed COX-2-specific inhibitors were older and more likely to be female than those given nonspecific NSAIDs. Patients prescribed COX-2-specific inhibitors had a significantly higher baseline history of and/or current CV conditions, including ischemic heart disease, heart failure, other forms of heart disease, and cerebrovascular diseases or disorders, than patients prescribed nonspecific NSAIDs. The baseline proportion of patients with rheumatoid arthritis was also higher among COX-2-specific

inhibitor users. In addition, COX-2-specific inhibitor users at baseline had higher prescription rates for medications that influence blood pressure, including estrogens, certain types of antidepressants, and corticosteroids.

Conclusion: COX-2-specific inhibitors were prescribed preferentially to patients who, at the time of their index COX-2-specific inhibitor prescription, were at an increased baseline risk of CV events compared with patients prescribed nonspecific NSAIDs. Researchers aiming to compare the incidence of CV events between COX-2-specific inhibitors and nonspecific NSAIDs using observational study designs should take into account the underlying baseline CV risk of the populations being compared.

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The cyclooxygenase (COX)-2-specific inhibitors celecoxib and rofecoxib have been shown to provide efficacy comparable to nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of osteoarthritis and rheumatoid arthritis (RA).¹⁻⁶ Unlike the nonspecific NSAIDs, however, the COX-2-specific inhibitors have very little effect on the COX-1 isozyme, and, accordingly, they are associated with a significantly lower risk of symptomatic ulcers and ulcer complications ($P < .001$).^{4,7,8}

Physicians in the United States are well aware of published data relating to the

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improved upper gastrointestinal (GI) safety of the COX-2-specific inhibitors. As a result, physicians may be preferentially prescribing COX-2-specific inhibitors to patients who, at the time of prescription, are already at an increased risk of upper GI events relative to patients prescribed non-specific NSAIDs. Recent data indicate that patients who switched from non-specific NSAIDs to COX-2-specific inhibitors were significantly older, had a higher baseline history of any upper GI adverse drug reactions, and had a higher baseline history of GI medication use than patients remaining on non-specific NSAIDs.⁹ The factors mentioned above, particularly advanced age and GI history, are some of the important risk factors for patients to develop upper GI events while taking non-specific NSAIDs.¹⁰

Cardiovascular disease (CVD) and upper GI complications share several common risk factors, including advanced age, anticoagulant use, smoking, and low-dose aspirin use. If COX-2-specific inhibitor users have reported a higher prevalence of upper GI risk factors than non-specific NSAID users, and CVD shares many of these risk factors with upper GI complications, COX-2-specific inhibitor users may, by default, also have a higher prevalence of cardiovascular (CV) risk factors than non-specific NSAID users.

An evaluation of the baseline risks of CV disorders has taken on increasing importance, based on recent empirical evidence demonstrating an increased risk for CV events with rofecoxib use versus a non-specific NSAID.^{4,11} This has led some researchers to theorize that all COX-2-specific inhibitors may pose an increased CV risk.¹¹ However, before any observational studies can be undertaken to characterize CV outcomes of the various COX-2-specific inhibitors and non-specific NSAIDs, it is important to thoroughly characterize the baseline CV risk of patients who are prescribed COX-2-specific inhibitors and non-specific NSAIDs to guard against channeling bias.

We are unaware of previously published studies that empirically evaluate the CV risk profile of multiple COX-2-specific

inhibitors and non-specific NSAID users. The present study used the LifeLink™ insurance claims database (LifeLink Corp., Park City, UT), which contains real-life clinical practice data, to describe the demographics and clinical characteristics of 2 COX-2-specific inhibitors, celecoxib and rofecoxib, and 3 commonly used non-specific NSAIDs (ibuprofen, naproxen, and diclofenac) in a hypertensive population.

...PATIENTS AND METHODS...

Databases

LifeLink Integrated Claims Solutions is an employer claims database covering approximately 1.8 million employees, dependents, and retirees. These claims are captured from more than 40 indemnity and preferred provider organization (PPO) plans, representing all specialties from all sites of care, including outpatient and inpatient facilities, nursing homes, rehabilitation centers, ambulatory surgical centers, psychiatric care facilities, clinical laboratories, and retail and mail-order pharmacies. Accordingly, the database allows patients to be tracked longitudinally across multiple sites of care.

Patients

Patients who newly started treatment with celecoxib, rofecoxib, ibuprofen, naproxen, or diclofenac between January 1, 1999, and September 30, 2000, were identified from the LifeLink database. To qualify as newly treated, patients must not have filled a prescription for any non-specific NSAID or COX-2-specific inhibitor therapy during the 180-day period before their index prescription.¹² Patients were included only once for each possible drug of interest.

Eligible patients had been receiving stable antihypertensive drug therapy for at least 3 consecutive months at the time of their new COX-2-specific inhibitor or non-specific NSAID index prescription. Stable antihypertensive therapy consisted of the regular use of a fixed dose of an antihypertensive drug or diuretic, alone or in combination. For the purposes of this analysis, 3 months was determined from

the days-supply field of the claim; it was defined as at least 90 days of therapy over the 120-day period before the index prescription. Eligible patients were to be enrolled continuously in the database for at least 12 months before the COX-2-specific inhibitor or nonspecific NSAID index prescription. These patients were to remain enrolled until March 31, 2001—the cutoff date in the LifeLink database through which both pharmacy and medical claims were paid at the time of study initiation—or until they disenrolled, whichever occurred first. Patients with a prescription for more than 1 COX-2-specific inhibitor or nonspecific NSAID therapy of interest on the same day during the study period were excluded from the analysis.

The daily drug dose was computed from the units dispensed, multiplied by the strength, and divided by the number of days supplied. If multiple prescriptions were filled on the same date for the same drug, the doses were added together based on the assumption that the patient was using the different strengths concomitantly.

Patient demographics and baseline clinical risk factors were defined at the time of the COX-2-specific inhibitor or nonspecific NSAID index prescription. The primary provider specialty represents the specialty of the provider who wrote the index prescription. Medical history conditions were identified by *International Classifications of Diseases, Ninth revision, Clinical Modification* (ICD-9-CM) diagnosis codes that were recorded during the 12-month period prior to the COX-2-specific inhibitor or nonspecific NSAID index prescription. Antihypertensive drug use during the 12-month period before the index prescription was classified broadly as antihypertensives, diuretics, or combination products, and then segmented according to drug class. Medications that influence hypertension, including estrogens, corticosteroids, sympathomimetics, appetite suppressants, cyclosporine, and erythropoietin, were also determined during the 12-month period prior to the index prescription. Demographics and medical histories were compared across study groups using χ^2

tests for categorical measures and Student *t* tests for continuous measures. A multivariate analysis was performed to compare patients' baseline risk profile between COX-2-specific inhibitors and nonspecific NSAIDs. All statistical comparisons were conducted in Statistical Analysis System (SAS) Release 8.02 (SAS Institute, Cary, NC).

...RESULTS...

A total of 374 129 prescriptions for celecoxib, rofecoxib, ibuprofen, naproxen, and diclofenac were started between January 1, 1999, and September 30, 2000. After excluding new-drug starts from patients with previous COX-2-specific inhibitor or nonspecific NSAID therapy in the prior 6 months, 55 396 index prescriptions were identified in patients with less than 12 months of continuous enrollment in the database, those filling prescriptions for multiple drugs of interest on the same date, and those who were not receiving stable antihypertensive therapy. These prescriptions consisted of 20 915 (37.8%) for celecoxib, 12 952 (23.4%) for rofecoxib, 10 789 (19.5%) for ibuprofen, 8840 (16.0%) for naproxen, and 1900 (3.4%) for diclofenac.

Patients in the 5 drug groups differed significantly in terms of age and gender ($P < .001$). The average age of patients receiving the COX-2-specific inhibitors celecoxib (68.2 years) or rofecoxib (67.6 years) was higher than that of patients receiving the nonspecific NSAIDs ibuprofen (61.8 years), naproxen (62.4 years), or diclofenac (63.6 years) (**Table 1**). Moreover, about 75% of patients receiving the COX-2-specific inhibitors were aged 60 years or older, as compared with 55% to 62% of those receiving nonspecific NSAIDs. Women accounted for a larger percentage of patients taking COX-2-specific inhibitors (63%) than those taking nonspecific NSAIDs (53%-55%). During the year before the index prescription, the average baseline cost per patient differed significantly across the 5 study groups ($P < .001$), with baseline costs being higher in the groups subsequently given cele-

Table 1. Demographics of Study Groups

Characteristic	Celecoxib (n = 20 915)	Rofecoxib (n = 12 952)	Ibuprofen (n = 10 789)	Naproxen (n = 8840)	Diclofenac (n = 1900)	χ^2 or F Statistic	P
Patient Age Categories							
Mean Age	68.2	67.6	61.8	62.4	63.6	840.60	<.001
Distribution (%)							
60+	75.6	73.3	54.7	56.8	62.4	2337.60	<.001
50-59	19.0	20.9	31.1	29.8	26.6		
<50	5.3	5.8	14.2	13.4	11.0		
Gender (%)							
Female	63.2	62.8	53.0	54.9	54.7	459.70	<.001
Male	36.8	37.2	47.0	45.1	45.3		
Primary Provider Specialty (%)							
Family practice	31.9	33.4	28.0	35.9	37.9	3764.66	<.001
Internal medicine	29.3	32.8	19.7	24.2	24.8		
Orthopedic surgery	9.8	8.0	3.6	6.2	10.3		
Rheumatology	3.9	3.2	0.3	0.5	1.5		
Cardiology	2.4	2.4	1.6	1.2	1.3		
Neurology	1.6	1.8	1.0	1.5	1.3		
Other	13.3	10.8	30.2	20.5	15.6		
Unknown	7.8	7.6	15.6	10.1	7.2		
Average Prior Year Cost Per Patient	\$6091	\$6196	\$4915	\$4513	\$4593	79.33	<.001

coxib (\$6091) or rofecoxib (\$6196) than in the groups subsequently given nonspecific NSAIDs (\$4513-\$4915).

The distribution of index prescriptions according to primary provider specialty also differed significantly across study groups ($P < .001$). Primary care physicians (family practice and internal medicine) accounted for the largest percentage of index prescriptions in each group except ibuprofen, where the category “other” was responsible for the largest percentage (Table 1). Physicians in orthopedic surgery accounted for a variable percentage of index prescriptions, ranging from 3.6% of those in the ibuprofen group to 10.3% of those in the diclofenac group. Physicians in rheumatology and cardiology wrote a larger percentage of index prescriptions in the COX-2-specific inhibitor study groups than in the nonspecific NSAID groups, whereas the percentage of index prescriptions written by physicians in neurology was generally comparable across groups.

As shown in Table 2, a larger percentage of patients in the celecoxib and rofe-

coxib groups had ischemic heart disease or other forms of heart disease as compared with the nonspecific NSAID groups ($P < .001$). Moreover, the rates of heart failure ($P < .001$), cerebrovascular disease ($P < .001$), and diseases of the pulmonary circulation ($P = .003$) were higher in the COX-2-specific inhibitor groups. Hyperlipidemia was significantly more common in the nonspecific NSAID groups ($P < .001$), whereas the rates of diabetes ($P = .029$), acute renal failure ($P = .023$), nephritis ($P = .053$), and myocardial infarction ($P = .077$) differed among the groups to a lesser extent. Overall, 2.5% of patients in the celecoxib group had RA, which was higher than the rates in the rofecoxib (1.8%), ibuprofen (0.7%), naproxen (0.7%), or diclofenac (1.4%) groups ($P < .001$).

Differences among the study groups were seen in the use of diuretics ($P < .001$) and fixed-dose combination antihypertensives ($P = .027$), but not in the use of non-fixed-dose combination antihypertensive medications alone ($P = .069$) (Table 3). The most commonly used

Table 2. Medical History of Study Groups

Medical History of:	Celecoxib (n = 20 915) (% of Patients)	Rofecoxib (n = 12 952) (% of Patients)	Ibuprofen (n = 10 789) (% of Patients)	Naproxen (n = 8840) (% of Patients)	Diclofenac (n = 1900) (% of Patients)	χ^2 Statistic	P
Ischemic heart disease	23.1	22.9	20.4	17.6	17.4	154.86	<.001
Other forms of heart disease	21.7	21.1	16.2	14.7	14.7	322.42	<.001
Hyperlipidemia	21.2	23.7	26.3	24.8	25.3	120.80	<.001
Diabetes	14.5	14.9	15.4	14.0	13.5	10.78	.029
Cerebrovascular disease	8.9	9.0	6.1	6.0	5.8	151.16	<.001
Heart failure	6.0	5.7	3.3	3.1	3.2	203.91	<.001
Rheumatoid arthritis	2.5	1.8	0.7	0.7	1.4	207.30	<.001
Myocardial infarction	1.6	1.5	1.5	1.2	1.3	8.44	.077
Diseases of pulmonary circulation	1.1	1.1	0.8	0.8	0.6	16.25	.003
Nephritis/nephrotic syndrome	1.0	0.8	0.7	0.8	0.6	9.37	.053
Acute renal failure	0.3	0.3	0.2	0.2	0.1	11.30	.023

Table 3. Concomitant Drug Use in Study Groups

Characteristic	Celecoxib (n = 20 915) (% of Patients)	Rofecoxib (n = 12 952) (% of Patients)	Ibuprofen (n = 10 789) (% of Patients)	Naproxen (n = 8840) (% of Patients)	Diclofenac (n = 1900) (% of Patients)	χ^2 Statistic	P
Blood Pressure Medication Type							
Antihypertensive	85.1	85.0	84.5	84.4	82.9	8.70	.069
Diuretic	39.5	37.3	32.5	32.9	33.4	216.86	<.001
Combination	11.5	12.6	12.3	11.7	12.0	10.93	.027
Antihypertensive Medications							
Calcium channel blocker	38.7	37.5	36.0	36.6	35.2	29.90	<.001
ACE inhibitor	30.0	30.0	30.8	30.4	29.8	2.85	.582
β -blocker	28.2	28.5	26.7	26.7	24.5	26.64	<.001
Alpha blocker	9.1	9.2	9.1	8.8	8.9	1.14	.888
Angiotensin II blocker	7.8	8.9	6.2	6.2	7.2	89.51	<.001
Central alpha agonist	2.1	2.3	2.4	2.2	1.9	3.79	.435
Peripheral antiadrenergic	1.6	1.8	1.4	1.2	1.3	15.23	.004
Vasodilator	0.4	0.3	0.4	0.3	0.1	7.03	.134
Diuretics							
Thiazides	24.6	23.7	23.4	24.0	24.2	7.11	.130
Loop diuretics	16.2	14.5	9.5	9.2	9.4	463.26	<.001
Potassium-sparing diuretics	1.1	1.2	0.9	0.8	0.9	10.58	.032
Medications Influencing Hypertension							
Sympathomimetics	24.4	24.1	24.1	25.1	25.4	4.39	.356
Estrogens	23.9	24.2	21.2	22.3	23.6	40.07	<.001
Corticosteroids	15.6	15.1	10.3	10.9	12.5	250.52	<.001
Appetite suppressants	2.2	2.7	2.4	2.3	1.8	9.75	.045
Cyclosporine	0.1	0.1	0.1	0.0	0.1	3.65	.456
Erythropoietin	0.1	0.2	0.1	0.2	0.1	6.28	.179
Antidepressants	23.4	23.9	17.4	18.2	17.7	269.87	<.001
Anticoagulants	7.3	6.7	2.9	2.6	3.1	479.06	<.001

ACE indicates angiotensin-converting enzyme.

antihypertensives were calcium channel blockers (37.4%), angiotensin-converting enzyme inhibitors (30.2%), and β -blockers (27.6%). Significant differences across study groups were seen in the rates of calcium channel blocker and β -blocker use (both $P < .001$) but not ACE inhibitors ($P = .582$). The other antihypertensive classes were used less frequently. Thiazide diuretics were used at similar rates in each group, whereas the rate of loop diuretics was highest in the celecoxib group.

Among drugs that affect blood pressure, the rate of corticosteroid use differed significantly across groups, with the highest rate seen in the COX-2-specific inhibitor groups ($P < .001$) (Table 3). Antidepressant, anticoagulant, and estrogen use also differed significantly, with rates being higher in the COX-2-specific inhibitor groups than in the nonspecific NSAID groups ($P < .001$). The rates of sympathomimetics ($P = .356$), appetite suppressants ($P = .045$), cyclosporine ($P = .456$), and erythropoietin ($P = .179$) did not differ significantly.

To test the hypothesis that significant differences in the omnibus χ^2 were due to differences between COX-2-specific inhibitors and nonspecific NSAIDs, celecoxib and rofecoxib were combined into 1 "COX-2-specific inhibitor" group. Similarly, the 3 nonspecific NSAIDs were combined into 1 "NSAID" group. The baseline CVD risk profiles between these 2 classes of drugs were compared using both univariate and multivariate analyses (Table 4). The multivariate analysis, comparing COX-2-specific inhibitor users versus nonspecific NSAID users, controlled for all baseline factors in Table 4. The multivariate logistic regression analysis indicated that factors that differed significantly between these 2 drug classes included age of patients; gender; primary provider specialty; blood pressure (BP) medication type; ischemic heart disease; heart failure; other forms of heart disease; cerebrovascular disease; concomitant corticosteroids, anticoagulants, appetite suppressants; antidepressants; and average cost in the prior year. Specifically, patients prescribed COX-2-specific inhibitors were

older and more likely to be female than those given nonspecific NSAIDs. Users of COX-2-specific inhibitors had higher baseline rates of a history of and/or current disorders, including ischemic heart disease (23.0% vs 19.0%), heart failure (5.9% vs 3.2%), other forms of heart disease (21.5% vs 15.4%), cerebrovascular disease (8.9% vs 6.1%), and RA (2.3% vs 0.8%). They were also likely to have higher baseline prescription rates of antidepressants (23.6% vs 17.7%) and medications that influence hypertension, including corticosteroids (15.4% vs 10.7%).

Baseline differences between these 2 classes of drugs in antihypertensive medication usage, although statistically significant in some cases, were generally small. Patients receiving COX-2-specific inhibitors were more likely to be receiving diuretics (38.7% vs 32.7%; $P < .001$) at baseline. This difference was largely attributed to the rate of prescriptions for loop diuretics (15.6% vs 9.4%; $P < .001$) rather than the more commonly prescribed thiazides (24.3% vs 23.7%; $P > .05$).

...DISCUSSION...

In this analysis of real-life practice data from approximately 1.8 million employees, dependents, and retirees from indemnity and PPO plans across multiple sites of care, hypertensive patients with a recent diagnosis of CVD were significantly more likely to be prescribed a COX-2-specific inhibitor than a nonspecific NSAID ($P < .001$). COX-2-specific inhibitor users were, therefore, at increased risk of having a CV event before receipt of a COX-2-specific inhibitor in comparison with nonspecific NSAID users. In addition to having a higher baseline prevalence of CVD, patients prescribed COX-2-specific inhibitors were older and more likely to use certain types of medications that influence BP control, all of which serve to increase baseline CV risk. Researchers who aim to compare the incidence of CV events between COX-2-specific inhibitors and nonspecific NSAIDs using observational study designs must take into account the underlying baseline CV risk when comparing

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Table 4. Comparison of Demographics and Clinical Factors Between Patients Prescribed COX-2–Specific Inhibitors and Nonspecific NSAIDs

Variable	COX-2–Specific Inhibitors		Nonspecific NSAIDs		P	
	n	%	n	%	Univariate Analysis	Multivariate Analysis
Patients	33 867	100	21 529	100		
Average Patient Age (years, 95% CI)	67.95 (67.83-68.07)		62.19 (62.03-62.35)		<.001	N/A
Patient Age Categories						
60+	25 316	74.8	12 106	56.2	<.001	<.001
50-59	6685	19.7	6489	30.1		N/A
<50	1866	5.5	2934	13.6		N/A
Patient Gender						
Female	21 357	63.1	11 620	54.0	<.001	<.001
Male	12 510	36.9	9909	46.0		
Primary Provider Specialty						
Family practice	11 004	32.5	6913	32.1	<.001	<.001
Internal medicine	10 370	30.6	4728	22.0		
Orthopedic surgery	3091	9.1	1134	5.3		
Rheumatology	1218	3.6	110	0.5		
Cardiology	811	2.4	297	1.4		
Neurology	581	1.7	267	1.2		
Other	4185	12.4	5374	25.0		
Unknown	2607	7.7	2706	12.6		
Medical History of:						
Ischemic heart disease	7798	23.0	4085	19.0	<.001	.026
Hyperlipidemia	7501	22.1	5510	25.6	<.001	.756
Other forms of heart disease	7280	21.5	3323	15.4	<.001	<.001
Diabetes	4963	14.7	3159	14.7	.951	.926
Cerebrovascular disease	3022	8.9	1303	6.1	<.001	.015
Heart failure	1986	5.9	691	3.2	<.001	.005
Rheumatoid arthritis	767	2.3	165	0.8	<.001	<.001
Myocardial infarction	540	1.6	290	1.3	.019	.185
Diseases of pulmonary circulation	379	1.1	168	0.8	<.001	.215
Nephritis, nephrotic syndrome	316	0.9	159	0.7	.016	.419
Acute renal failure	103	0.3	36	0.2	.002	.464
Blood Pressure Medication Type						
Antihypertensive	28 813	85.1	18 160	84.4	.020	<.001
Diuretic	13 093	38.7	7050	32.7	<.001	<.001
Combination	4035	11.9	2588	12.0	.706	<.001
Antihypertensive Medications						
Calcium channel blocker	12 948	38.2	7793	36.2	<.001	N/A
ACE inhibitor	10 151	30.0	6576	30.5	.153	N/A
β-blocker	9595	28.3	5702	26.5	<.001	N/A
Alpha blocker	3091	9.1	1935	9.0	.579	N/A
Angiotensin-II inhibitor	2785	8.2	1354	6.3	<.001	N/A
Central alpha agonist	751	2.2	492	2.3	.600	N/A
Antiadrenergic, periph. acting	572	1.7	284	1.3	<.001	N/A
Vasodilator	124	0.4	68	0.3	.326	N/A
Diuretics						
Thiazide diuretic	8220	24.3	5111	23.7	.154	N/A
Loop diuretic	5267	15.6	2017	9.4	<.001	N/A
Potassium-sparing diuretic	381	1.1	186	0.9	.003	N/A
Other	115	0.3	60	0.3	.213	N/A
Medications Influencing Hypertension						
Sympathomimetics	8239	24.3	5308	24.7	.382	.525
Estrogens	8129	24.0	4713	21.9	<.001	.966
Corticosteroids	5212	15.4	2314	10.7	<.001	<.001
Appetite suppressants	817	2.4	492	2.3	.337	<.001
Erythropoietin	46	0.1	22	0.1	.270	.244
Cyclosporine	33	0.1	13	0.1	.140	.146
Antidepressants	7984	23.6	3820	17.7	<.001	<.001
Anticoagulants	2391	7.1	599	2.8	<.001	<.001
Average Prior Year Costs	\$6131.60 (\$6029.69-\$6233.50)		\$4722.30 (\$4606.35-\$4838.25)		<.001	<.001

N/A indicates the variables are not included in multivariate analysis; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme.

COX-2-specific inhibitors and nonspecific NSAIDs in terms of CV outcomes. The most valid information on the CV safety of COX-2-specific inhibitors, however, comes from clinical trials in which CV risk factors are randomly distributed among treatments.

One explanation for the observed differences between COX-2-specific inhibitors and nonspecific NSAIDs may be channeling bias.^{9,13} As new drugs are introduced into the market, they are forced to compete with existing treatments for the same condition, which can result in selective prescribing. Patients often receive newer drugs because of a poor response or adverse events with older drugs. This was also observed and has been reported for COX-2-specific inhibitors. Patients with more severe disability, pain, and stiffness were prescribed COX-2-specific inhibitors more often than nonspecific NSAIDs.⁹

The study found that the baseline CVD risk profiles were generally similar between celecoxib and rofecoxib users, possibly because of the study period, which was between January 1999 and September 2000. This study occurred before the publication (November 2000) and Food and Drug Administration review (February 2001) of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (February 2001), in which a higher risk of thromboembolic events was reported with rofecoxib than naproxen.^{14,15} This may be one reason why there were no significant differences in the CVD risk profiles of patients receiving rofecoxib or celecoxib during the study period. Therefore, it will be important to conduct additional analyses based on the most recent data to compare the baseline CVD risk profiles between celecoxib and rofecoxib.

The results of this study have important implications for evaluating CVD safety issues related to use of COX-2-specific inhibitors. As previously described, patients prescribed COX-2-specific inhibitors had a higher baseline CV risk profile than those prescribed nonspecific NSAIDs. Consequently, in observational studies, patients who receive COX-2-specific inhibitors would be expected to have

higher incidences of CV events than nonspecific NSAID users due to channeling bias and differences in baseline disease.

Channeling bias should be considered when an economic evaluation is conducted using observational data. For example, this study showed that the total health-care utilization cost for patients taking COX-2-specific inhibitors was nearly \$1500 higher than that for nonspecific NSAIDs in the year prior to the index prescription date. Much of this difference is due to greater baseline disease severity and more comorbidities (ie, CVD) in patients prescribed COX-2-specific inhibitors compared to nonspecific NSAIDs.

Background information was based on a 12-month history period, which may have missed a significant number of baseline CV risk factors that were manifest prior to this time period. Additionally, prescription plans used in this analysis provided equal access to nonspecific NSAIDs and COX-2-specific inhibitors. Therefore, the generalizability of our results may be limited to only those plans providing equal access to these 2 classes of medication. We would anticipate that differences in baseline CV risk between patients using nonspecific NSAIDs and those using COX-2-specific inhibitors would be greater than those observed here in plans where COX-2-specific inhibitors are restricted to patients with upper GI risk factors.

... CONCLUSION ...

In summary, the results from this observational study indicate that patients prescribed COX-2-specific inhibitors have a significantly higher baseline CV risk than patients prescribed nonspecific NSAIDs. Future safety and economic studies of COX-2-specific inhibitors and nonspecific NSAIDs will need to carefully measure and adjust for these baseline differences in risk factors. Additional studies are needed to fully characterize and differentiate the safety profiles among COX-2-specific inhibitors based on newly available data in the year 2002.

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