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Cardiovascular Events Associated with Long-Term Use of Celecoxib, Rofecoxib and Meloxicam in Taiwan

An Observational Study

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Abstract

Background: Using national data (2001–2003), this study explored the risk of acute myocardial infarction (AMI), angina, stroke and transient ischaemic attack (TIA) in long-term users of rofecoxib and celecoxib in Taiwan and compared this data with that for those using meloxicam.

Methods: Patients included in the study had used celecoxib, rofecoxib or meloxicam for at least 180 days. Data were taken from National Health Insurance database for the period from 2001 to 2003. Main outcome measurements were the occurrence of AMI, angina, stroke or TIA after the initiation of long-term continuous use of these drugs. Person-time exposures and hazard ratios (HRs) were calculated based on data from 9602 eligible patients.

Results: In patients without a history of a cardiovascular event within the year before drug treatment began, the overall rates of AMI, angina, stroke and TIA were 1.1%, 0.6%, 2.0% and 0.6%, respectively. In those with cardiovascular events in the year before treatment began, the overall rates of AMI, angina, stroke and TIA were 5.0%, 4.8%, 6.6% and 5.8%, respectively. Compared with meloxicam users, celecoxib users had lower HRs for the development of AMI (HR 0.78, 95% CI 0.63, 0.96) and stroke (HR 0.81, 95% CI 0.70, 0.93). Rofecoxib users were at no higher risk of cardiovascular events than those receiving meloxicam. Regardless of treatment, having had a cardiovascular event in the year before treatment began played a significant role in the development of the same cardiovascular event during the prescription period; the HRs associated with having had the same cardiovascular event in the past year, versus not having had such an event, were 3.02 (95% CI 1.44, 6.32) for AMI, 5.82 (95% CI 3.19, 10.63) for

angina, 2.44 (95% CI 1.79, 3.33) for stroke and 7.16 (95% CI 3.70, 13.87) for TIA.

Conclusions: Patients taking celecoxib had a lower risk of cardiovascular events than those taking meloxicam. Patients taking rofecoxib were not found to be at higher cardiovascular risk than those taking meloxicam. The most significant determinant of cardiovascular risk was a history of such cardiovascular disease in the year preceding treatment initiation. Patients with a history of other medical conditions also appeared to be at higher risk of adverse cardiovascular events.

Background

Selective cyclo-oxygenase (COX)-2 inhibitors ('coxibs') form a new category of NSAIDs that reduce the occurrence of adverse gastrointestinal tract effects.[1,2] However, recent results from several large trials of coxibs have suggested a possible relationship between these drugs, particularly rofecoxib, and increased rates of myocardial infarction. The withdrawal of rofecoxib (Vioxx®)[1] was initiated because of the increased cardiovascular risk to long-term users of this drug in the APPROVe (Adenomatous Polyp Prevention on VIOXX) study.[3-5] Most significantly, the US National Cancer Institute halted its APC (Adenoma Prevention with Celebrex) trial after the data safety monitoring board reported a 2.5-fold greater risk of acute myocardial infarction (AMI) and stroke in patients treated with celecoxib 400 mg/day.[6] Similar concern has been raised about the cardiovascular toxicity of other coxibs, such as valdecoxib.[3,6-11] For example, patients treated with valdecoxib after coronary artery bypass surgery have been reported to have higher rates of AMI, stroke and death than those treated with opioids for postoperative pain.[3] It was strongly recommended that prescription of valdecoxib be halted for the sake of public safety.[11]

Since then, the US FDA has asked Pfizer, Inc. to voluntarily suspend direct-to-consumer advertising of celecoxib (Celebrex®). They have further requested that the company indicate on package inserts that the FDA recommends that physicians consider alternative therapies.[12,13] Current reports on adverse reactions associated with the selective COX-2 inhibitors are based on results from controlled clinical trials,[1,2,4,5,9,14] but limited information are available on adverse reactions associated with the actual use of these drugs.

On 6 April 2005, the FDA's Decision Memo on NSAIDs indicated that the available data did not permit a rank ordering of selective COX-2 NSAIDs with regard to cardiovascular events, and that data from large, long-term, controlled clinical trials that have included comparisons of COX-2 selective and non-selective NSAIDs did not clearly demonstrate that the COX-2 selective agents conferred a greater risk of serious adverse cardiovascular events than non-selective NSAIDs. In one cumulated meta-analysis of 18 randomised controlled trials and 11 observational studies, there was little evidence to clarify the cardiovascular risk difference between selective COX-2 inhibitors and NSAIDs. The relative risk differed depending on the control group (placebo, non-naproxen NSAID or naproxen; $p = 0.41$) and the trial duration ($p = 0.82$).[15] The FDA further stated that the available data would be best interpreted as being consistent with a class effect of an increased risk of serious adverse cardiovascular events for COX-2 selective and non-selective

1 The use of trade names is for product identification purposes only and does not imply endorsement.

NSAIDs.[1,3] Recent literature has provided some evidence to support such statements.[1,11,16-18]

In Taiwan, two coxibs, rofecoxib and celecoxib, were on the market and covered by the National Health Insurance (NIH) Reimbursement System at the time that Merck Sharp & Dohme Inc. withdrew rofecoxib from the market (September 2004). Because both the coxibs and NSAIDs are widely used by patients with rheumatoid arthritis or osteoarthritis, diseases that are associated with older ages, it is important to clarify the association between COX-2 selective or non-selective NSAIDs and cardiovascular events, such as AMI. Reviewing data from the Bureau of National Health Insurance (BNHI) for the years 2001–2003, we examined the risk of AMI, angina, stroke or transient ischaemic attack (TIA) in long-term users of rofecoxib and celecoxib in Taiwan using a less-selective NSAID, meloxicam, as the comparator.

Methods

An observational study was performed to examine the occurrence of cardiovascular events in long-term users (over 180 days of cumulative use) of celecoxib, rofecoxib and meloxicam; to discover whether long-term use (>180 days) of the coxibs, celecoxib or rofecoxib, increases the risk of AMI, angina, stroke or TIA more than long-term use of meloxicam; and to identify which factors might be related to the risk of cardiovascular events in long-term users of coxibs.

Study Population

We obtained our data on users of celecoxib, rofecoxib and meloxicam in Taiwan from the BNHI, which provided coverage to nearly 99% of Taiwan's population during the study period. The BNHI's computerised files allowed for cohort identification, classification of cardiovascular risk factor status and endpoint ascertainment. Potential eligible patients included all enrollees with records indicating continuous use of celecoxib, rofecoxib or meloxicam for >180 days between 1 January 2001 and 31 December 2003. We excluded any patient who had used a combination of these drugs or had used these drugs in combination with any other NSAIDs. We also excluded any patient who stopped taking the drug they were receiving for more than 14 days before receiving another prescription. We further excluded any patient whose accumulated prescription duration was <180 days.

We chose users receiving >180 days of treatment as our study subjects based on our pilot analysis for this study. We focused on long-term users, as our study population was based on the results of the APPROVe (Adenomatous Polyp Prevention on VIOXX®) trial. According to the APPROVe trial, patients had a higher risk of having a cardiovascular event after 18 months (540 days) of treatment. In addition, the data of patients receiving <180 days of treatment were more likely confounded by drug switching and dose adjustment, and so they were not included in our final analysis.

Data Collection

We used NHI pharmacy claim data for the period between 1 January 2001 and 31 December 2003 to collect information on celecoxib, rofecoxib and meloxicam use. For each medicine prescribed in an outpatient visit, a pharmacy record was made that included the starting date (the date the first prescription was dispensed [t_0]), quantity, dose and duration of prescription. We defined the end date of prescription duration (t_1) as the prescription dispensing date plus the prescription duration. We created a prescription profile for each patient taking any of the three medicines for further screening purposes. We also created a medical history profile for each patient to retrieve clinical conditions related to this study that had existed before the initiation of treatment and to identify the initial occurrence of (hos-

pitalisation for) the cardiovascular events analysed in our study.

In our study, we did not differentiate between dosages of celecoxib because initial analysis indicated that 92% of celecoxib users were prescribed a daily dosage of 200mg (78.9%) or less (13.5%). Users of higher dosage rofecoxib (50mg) were excluded in this study because of a relatively small sample size (n = 108).

The outcome variables of interest in this study were the occurrence of (i.e. hospitalisation for) serious cardiovascular events after starting on one of the medicines. We classified these hospitalised study subjects on the basis of International Classification of Diseases (9th Edition) [ICD-9-CM] codes for AMI (410.xx and 411.xx), angina (413.xx and 414.xx), stroke (433.xx and 444.xx) or TIA (435.xx and 437.1).

The covariate variables included age, sex, accumulated prescription duration and pre-existing (in the previous 1 year) medical conditions, as indicated by ICD-9-CM codes, of hypertension (401.xx–405.xx), hyperlipidaemia (272.4), diabetes mellitus (250.xx), heart failure (428.xx), and chronic kidney disease (580.xx-587.xx).

Statistical Analysis

We used descriptive statistics to compare the age, sex, prescription duration, occurrence of cardiovascular events in the year prior to treatment initiation, and the medical conditions of patients using the different drugs (celecoxib, rofecoxib and meloxicam).

A Cox proportional hazards model was used to evaluate the association of long-term use of selective COX-2 inhibitors with the subsequent risks of occurrence or recurrence of AMI, angina, stroke or TIA. A Cox proportional hazards model was used to compare the associations of the long-term use of selective COX-2 inhibitors and meloxicam with the subsequent risks of occurance or recurrence of AMI, angina, stroke or TIA. The entry day was the date of the first outpatient visit at which one of the three medications was prescribed. Follow-up time for each cardiovascular event extended until the earliest of the occurrence of hospitalisation for the specific cardiovascular event or until the end of the study period for those patients who did not have any cardiovascular events. The survival time of those patients did not have any cardiovascular event (outcome) and those who died during the study period were censored at the end of the study period and the day of death, respectively. Median time-to-onset among each subgroup is presented in table I.

A Cox proportional hazards model was performed using the package 'coxph' from S-plus Version 7.0.3. The assumption of the Cox proportional hazards model was checked and this check indicated that proportional hazards were a reasonable assumption (all p-values were >0.05). Residual analysis showed that the residuals were distributed around zero between −3 and 3 with no particular pattern, indicating that the model was a reasonable fit.

Results

Patient Characteristics

A total of 9602 patients were identified as receiving long-term treatment with celecoxib (n = 3762, 39.2%), rofecoxib (n = 1550, 16.1%) or meloxicam (n = 4290, 44.7%), with a total of 10 905 person-years of follow-up (table II). Nearly 75% of the patients were aged ≥64 years. The average accumulated duration of prescription over 3 years was 414.52 days (SD = 218.01). Meloxicam was taken for a longer duration than the other two drugs: 471.27 days (SD = 257.51) compared with 382.52 days (SD = 175.93) for celecoxib and 338.8 days (SD = 142.28) for rofecoxib ($p < 0.001$). Meloxicam was taken continuously for over 540 days by 33.64% of users.

Table I. Median time-to-onset (days) of cardiovascular events in continuous users of celecoxib, rofecoxib and meloxicam in Taiwan, 2001–2003

Subgroup	AMI	Angina	Stroke	TIA
Drug				
Meloxicam	392	393	394	393.5
Celecoxib	393	393.5	388.5	393
Rofecoxib	388	387	385	387
Age (y)				
≤44	380	402	393	413
45–54	385	392	385	399
55–64	392	405	382	385
>64	393	391	392	392
Sex				
Female	394	395	392	392
Male	388	388	389	392
Prescription duration (d)				
180–270	386	378	391	378
271–365	395.5	392	378	386.5
366–455	385	391	403.5	402.5
456–540	392	393	390	409
>540	403	418	395	406
Cardiovascular event in the year preceding treatment initiation				
Yes	358.5	392	392	379
No	392	402	402	392
Pre-existing medical condition				
Hypertension				
yes	389	391	391	385
no	394	394	392	399
Hyperlipidaemia				
yes	400	393	387	374
no	392	392	392	393
Diabetes mellitus				
yes	382	386	383	392
no	393	393	393	392
Heart failure				
yes	413	396	406	368
no	392	392	392	393
Chronic renal disease				
yes	372	375	381	392
no	393	393	392	399

AMI = acute myocardial infarction; **TIA** = transient ischaemic heart attack.

Of the 9602 patients, 180 (1.87%) had medical histories of AMI, 316 (3.29%) had a history of angina, 849 (8.84%) had a history of stroke and 191 (1.99%) had a history of TIA within the year preceding treatment initiation. Compared to meloxicam users, a higher proportion of COX-2 inhibitor users (particularly rofecoxib users) had medical histories of adverse cardiovascular events before they started taking these medications regularly ($p = 0.013$). Hypertension was present in 45.63% of the study popu-

Table II. Demographic information[a] of continuous users of celecoxib, rofecoxib and meloxicam in Taiwan, 2001–2003

Subgroup	Total (n = 9602)	Celecoxib (n = 3762)	Rofecoxib (n = 1550)	Meloxicam (n = 4290)	p-Value (Chi-squared)
Age (y)					0.348
≤44	619 (6.45)	241 (6.41)	88 (5.68)	290 (6.76)	
45–54	710 (7.39)	274 (7.28)	101 (6.52)	335 (7.81)	
55–64	1079 (11.24)	404 (10.74)	170 (10.97)	505 (11.77)	
>64	7194 (74.92)	2843 (75.57)	1191 (76.84)	3160 (73.66)	
Mean age in years (SD)	69.84 (14.42)	70.5 (14.15)	70.7 (13.96)	69.53 (14.66)	
Sex					0.191
Female	5644 (58.78)	2240 (59.54)	881 (56.84)	2523 (58.81)	
Male	3958 (41.22)	1522 (40.46)	669 (43.16)	1767 (41.19)	
Prescription duration (d)					<0.001
180–270	3223 (33.57)	1320 (35.09)	651 (42.00)	1252 (29.18)	
271–365	1996 (20.79)	824 (21.90)	387 (24.97)	785 (18.30)	
366–455	1187 (12.36)	498 (13.24)	211 (13.61)	478 (11.14)	
456–540	841 (8.76)	377 (10.02)	132 (8.52)	332 (7.74)	
>540	2355 (24.53)	743 (19.75)	169 (10.90)	1443 (33.64)	
Mean prescription duration in days (SD)	414.52 (218.01)	382.52 (175.93)	338.8 (142.28)	471.27 (257.51)	
Cardiovascular event within the year preceding treatment initiation					
Acute myocardial infarction	180 (1.87)	77 (2.05)	40 (2.58)	63 (1.47)	0.013
Angina	316 (3.29)	128 (3.40)	88 (5.68)	100 (2.33)	<0.001
Stroke	849 (8.84)	356 (9.46)	160 (10.32)	333 (7.76)	<0.001
Transient ischaemic attack	191 (1.99)	88 (2.34)	43 (2.77)	60 (1.40)	<0.001
Pre-existing medical condition					
Hypertension	4381 (45.63)	1774 (47.16)	828 (53.42)	1779 (41.47)	<0.001
Hyperlipidaemia	615 (6.40)	264 (7.02)	129 (8.32)	222 (5.17)	<0.001
Diabetes mellitus	1921 (20.01)	750 (19.94)	391 (25.23)	780 (18.18)	<0.001
Heart failure	511 (5.32)	231 (6.14)	92 (5.94)	188 (4.38)	<0.001
Chronic renal disease	635 (6.61)	266 (7.07)	99 (6.39)	270 (6.29)	0.348

a Data presented as number of patients (percentage) unless otherwise stated.

lation, 6.40% had hyperlipidaemia, 20.01% had diabetes mellitus, 5.32% had heart failure and 6.61% had chronic renal disease. Histories of hypertension, hyperlipidaemia and diabetes mellitus were all more frequent in rofecoxib users compared with the other two study groups (all $p < 0.001$).

Occurrence and Median Time-To-Onset of Cardiovascular Events During Prescription Duration

During the study period, 113 individuals had an AMI, 67 developed angina, 233 had a stroke and 68 experienced a TIA. Table III stratifies the occurrence of cardiovascular events with each drug according to the occurrence of each cardiovascular event in the year preceding treatment initiation. This shows that, during the study period, the prevalence of AMI for those with a medical history of the same disease was 5%, while only 1.10% of those without medical histories of AMI experienced this cardiovascular event. In those without medical histories of AMI, the rate of occurrence of AMI during the study period was highest among meloxicam users (1.37%), followed by celecoxib users (0.92%) and rofecoxib users (0.79%). The same trend was observed in meloxicam users for other cardiovascular events, however, rofecoxib users had higher rates of occurrence for angina, stroke and TIA than celecoxib users.

For patients with medical histories of AMI, recurrence of AMI occurred in 10% of rofecoxib users, followed by 3.90% of celecoxib recipients and 3.17% of meloxicam recipients. A similar trend was observed for angina. Concerning the cardiovascular event of stroke, meloxicam users had the highest recurrence rate (7.21%), followed by celecoxib users (6.46%) and rofecoxib users (5.63%). Rofecoxib users with prior medical histories of TIA had the highest rate of recurrence of TIA (6.98%), followed by meloxicam (6.67%) and celecoxib (4.55%) users (table III).

Table I shows the median time-to-onset of cardiovascular events according to sex, age, prescription duration, medical history of cardiovascular events, other pre-existing medical conditions and drug used. Time-to-onset of AMI, angina and TIA was longer in users of meloxicam and celecoxib than it was in users of rofecoxib. Time-to-onset of stroke was longer in users of meloxicam than it was for users of celecoxib and rofecoxib.

Survival Analysis on Cardiovascular Events

Table IV shows the results of the survival analysis for each cardiovascular event adjusted for sex, age, prescription duration, medical history of cardiovascular events and other pre-existing medical conditions. Compared to meloxicam users, celecoxib users had a lower risk of AMI (adjusted hazard ratio [HR] 0.78, 95% CI 0.63, 0.96). Having a medical history of AMI was significantly associated with AMI during the study period (HR 3.02, 95% CI 1.44, 6.32). Patients with medical histories of diabetes and chronic renal disease also had higher risks of developing AMI (HR 1.60, 95% CI 1.06, 2.41 and HR 1.81, 95% CI 1.05, 3.12, respectively).

The risk of angina during the prescription period is shown in table IV. Having a medical history of angina was significantly associated with the occurrence of angina during the study period (HR 5.82, 95% CI 3.19, 10.63). Patients with a medical history of heart failure had a higher risk of developing angina (HR 1.98, 95% CI 1.00, 3.91) than those who had not had heart failure.

As for the risk of stroke during prescription period, celecoxib users had a lower risk of stroke (HR 0.81, 95% CI 0.70, 0.93) than meloxicam users. Having a medical history of stroke was also significantly associated with the occurrence of stroke during the study period (HR 2.44, 95% CI 1.79, 3.33). Patients with a medical history of diabetes had a higher risk of developing stroke during prescription

Table III. Cardiovascular events during prescription period among users of celecoxib, rofecoxib and meloxicam users with/without such events in the year preceding treatment initiation; Taiwan, 2001–2003

Event	Celecoxib		Rofecoxib		Meloxicam		Total	
	with a history	without a history	with a history	without a history	with a history	without a history	with a history	without a history
AMI								
Prescription duration[a]	381.36 (173.65)	383.56 (176.00)	304.00 (130.88)	339.72 (142.50)	420.92 (237.89)	472.02 (257.74)	378.02 (194.97)	416.22 (218.90)
Occurrence during the prescription period[b]	3/77 (3.90)	34/3685 (0.92)	4/40 (10.00)	12/1510 (0.79)	2/63 (3.17)	58/4227 (1.37)	9/180 (5.00)	104/9422 (1.10)
Angina								
Prescription duration[a]	371.83 (158.22)	383.93 (176.53)	344.92 (143.26)	338.43 (142.27)	423.45 (240.33)	472.41 (257.82)	380.67 (186.77)	416.69 (219.44)
Occurrence during the prescription period[b]	6/128 (4.69)	16/3634 (0.44)	5/88 (5.68)	8/1462 (0.55)	4/100 (4.00)	28/4190 (0.67)	15/316 (4.75)	52/9286 (0.56)
Stroke								
Prescription duration[a]	346.39 (151.03)	387.40 (177.91)	324.09 (132.90)	340.49 (143.27)	418.49 (233.87)	475.71 (258.93)	370.47 (189.29)	419.87 (220.68)
Occurrence during the prescription period[b]	23/356 (6.46)	55/3406 (1.61)	9/160 (5.63)	26/1390 (1.87)	24/333 (7.21)	96/3957 (2.43)	56/849 (6.60)	177/8753 (2.02)
TIA								
Prescription duration[a]	351.91 (147.52)	384.27 (176.50)	347.33 (152.46)	338.56 (142.03)	321.25 (145.81)	473.40 (258.13)	341.25 (147.96)	417.01 (219.47)
Occurrence during the prescription period[b]	4/88 (4.55)	18/3674 (0.49)	3/43 (6.98)	9/1507 (0.60)	4/60 (6.67)	30/4230 (0.71)	11/191 (5.76)	57/9411 (0.61)

a Data in days [mean (SD)]

b Data in number of patients/total number of patients (%).

AMI = acute myocardial infarction; **TIA** = transient ischaemic attack.

Table IV. Risk of cardiovascular events in celecoxib, rofecoxib, and meloxicam users in Taiwan, 2001–2003

Covariate	Acute myocardial infarction		Angina		Stroke		Transient ischaemic attack	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex								
female	1.00		1.00		1.00		1.00	
male	1.16 (0.96, 1.39)	0.13	0.89 (0.69, 1.14)	0.36	1.06 (0.93, 1.21)	0.35	1.03 (0.81, 1.30)	0.84
Drug								
meloxicam	1.00		1.00		1.00		1.00	
celecoxib	0.78 (0.63, 0.96)	0.02	0.84 (0.63, 1.10)	0.20	0.81 (0.70, 0.93)	0.00	0.79 (0.60, 1.03)	0.08
rofecoxib	0.91 (0.76, 1.09)	0.30	1.01 (0.82, 1.24)	0.91	0.93 (0.83, 1.05)	0.27	0.98 (0.80, 1.21)	0.86
Age (y)	1.04 (1.02, 1.06)	0.00	1.03 (1.00, 1.05)	0.02	1.05 (1.04, 1.06)	0.00	1.04 (1.01, 1.06)	0.00
Prescription duration (d)	1.00 (1.00, 1.00)	0.26	1.00 (1.00, 1.00)	0.83	1.00 (1.00, 1.00)	0.05	1.00 (1.00, 1.00)	0.10
Cardiovascular event of same type in the year preceding treatment initiation								
no	1.00		1.00		1.00		1.00	
yes	3.02 (1.44, 6.32)	0.00	5.82 (3.19, 10.63)	0.00	2.44 (1.79, 3.33)	0.00	7.16 (3.70, 13.87)	0.00*
Prior medical condition								
Hypertension								
no	1.00		1.00		1.00		1.00	
yes	1.25 (0.85, 1.85)	0.26	1.59 (0.92, 2.73)	0.10	1.09 (0.82, 1.43)	0.56	1.76 (1.04, 2.96)	0.03
Hyperlipidaemia								
no	1.00		1.00		1.00			
yes	0.86 (0.39, 1.86)	0.69	1.55 (0.73, 3.31)	0.25	0.46 (0.22, 0.93)	0.03	NA	
Diabetes mellitus								
no	1.00		1.00		1.00		1.00	
yes	1.60 (1.06, 2.41)	0.02	1.17 (0.68, 2.02)	0.58	1.79 (1.35, 2.37)	0.00	1.23 (0.71, 2.11)	0.46
Heart failure								
no	1.00		1.00		1.00		1.00	
yes	1.69 (0.94, 3.02)	0.07	1.98 (1.00, 3.91)	0.04	1.37 (0.89, 2.11)	0.15	1.06 (0.42, 2.67)	0.90
Chronic renal disease								
no	1.00		1.00		1.00		1.00	
yes	1.81 (1.05, 3.12)	0.03	1.63 (0.79, 3.36)	0.19	1.37 (0.90, 2.08)	0.15	0.67 (0.24, 1.87)	0.45

HR = hazard ratio; **NA** = not applicable.

period (HR 1.79, 95% CI 1.35, 2.37) than those who had not had this disease.

Similarly, having a medical history of TIA was significantly associated with the occurrence of TIA during the study period (HR 7.16, 95% CI 3.70, 13.87). Patients with a medical history of hypertension had a higher risk of developing TIA during the prescription period than those who had no history of hypertension (HR 1.76, 95% CI 1.04, 2.96).

Discussion

The possible association of coxibs with cardiovascular adverse events has evolved into an important drug safety issue. When the pharmacology of the COX enzymes is considered it is not surprising to see that the thrombosis effect (COX-1 pharmacology), blocked by non-selective NSAIDs, is overexpressed in the selective COX-2 inhibitors model. The beneficial effect of both non-selective NSAIDs and selective COX-2 inhibitors on inflammation comes through inhibition of the COX-2 pathway. However, COX-1 is responsible for the thrombosis in the human body. Thus, non-selective NSAIDs, such as aspirin (which blocks COX-1 pathway), might provide an antiplatelet effect and help prevent cardiovascular disease. Without NSAID blockade of the COX-1 pathway, it would also be reasonable to suspect increased cardiovascular risk in users of COX-2 inhibitors compared with users of non-selective NSAIDs.[19] A question exists as to whether there is a significant 'class effect' produced by coxibs. Previous reports on the relationship between coxibs and cardiovascular disease were only obtained from controlled clinical trials. Clinical trials are considered to generate the most accurate results, yet they tend to be time-consuming to perform, with limitations provided by inclusion and exclusion criteria. The FDA's Decision Memo on 6 April 2005 provides an updated benchmarking of NSAID safety, both for coxibs and non-selective NSAIDs.[1,3]

Studies such as this, which are based on population-based data on the utilisation of coxibs, provide new information on selective COX-2 inhibitor safety to supplement the limitations in the data provided by clinical trials. As far as we know, no head-to-head comparisons of COX-2 inhibitors and NSAIDs in randomised trials are available to enable determination of the relative risks of cardiovascular events. Also, major trials have excluded patients with coronary heart disease and only a few such trials have been designed to measure cardiovascular events after patients have received selective COX-2 inhibitors and NSAIDs. We used 3 years of national data (2001–2003) as a resource to construct a large national cohort and provide longitudinal information on users of celecoxib, rofecoxib and meloxicam. In addition, since all information, including pharmacy records, was recorded on the computer, there was not the kind of recall bias that would occur with a survey-based study design. The most important risk factors for cardiovascular events in our study were the previous occurrence of a cardiovascular event or a pre-existing medical condition within the year before treatment with these drugs began.

This study has some design limitations. First, because we defined long-term users as those with >180 days of cumulative use of study medications, termination of drug prescription due to cardiovascular adverse events prior to this was not covered. Since it has been found that the time-to-onset of cardiovascular events varies from 6 weeks (42 days) to 56 weeks (392 days) from the initiation of treatment with coxibs,[15] future studies using a different definition of long-term users could be useful. Second, we selected users of meloxicam as our control group because the medication was widely prescribed in Taiwan and the BNHI was interested in it; cardiovascular risk comparisons between coxibs and other non-selective NSAIDs might also be clinically relevant. A truly non-selective NSAID, instead of a less selective COX-2 inhibitor like meloxicam,

might be a better comparator. Third, although we adjusted for a wide range of potential cardiovascular risk factors, it is difficult to control the potential confounding factor of patients taking non-prescribed NSAID medication or aspirin during the study period. Nor did we have any information on patient compliance. We also did not have information on the patients' smoking histories and family histories of cardiovascular disease. Fourth, because of data limitation (2001–2003, NHI database), only cardiovascular events that occurred within 1 year prior to treatment initiation were screened; therefore, some information bias could exist in our study. Finally, because we did not link to the National Mortality File databases, we did not know if fatal cardiovascular events occurred. Nonetheless, the results from our study offer unique insight into the real-life risks of the long-term usage of coxibs.

We found no significant difference in the rates of adverse cardiovascular events between the two coxibs, celecoxib and rofecoxib. Prior cardiovascular history was the most significant determinant of such risks. Patients with a history of other medical conditions were also found to be subject to a higher risk of cardiovascular events. Several controversies about the cardiovascular safety of celecoxib and other conventional NSAIDs still remain. The potential beneficial effects of celecoxib and its protective effects on endothelial function and coronary blood flow have been reported.[20]

Though package inserts for coxibs include a warning for patients with a cardiovascular event history, physicians may not have sufficient information to alert their patients with osteoarthritis or rheumatoid arthritis, who may consider taking coxibs, to the risks and benefits of their use. In addition, coxibs also present a costly lesson for regulatory agencies when they compare their possible benefits of reducing existing manageable adverse reactions with the possible risks of increasing unexpected adverse events.[21,22] Although an earlier FDA panel meeting raised concerns regarding coxib class effects, the same panel also voted to allow the return of rofecoxib to the market with a restrictive black box warning.[22] Recent reports tend to support the concept of class effects on cardiovascular events for both coxibs and non-selective NSAIDs, although the risks vary depending on study populations and the individual drugs.[17-19,21,23] The cardiovascular effects of non-selective NSAIDs pose similar cardiovascular concerns to those of coxibs. Our observational study seems to support, although not conclusively, a class-effect regarding the association of coxibs with adverse cardiovascular events. Our control group, who received the less-selective NSAID, meloxicam, had no less risk for adverse cardiovascular events than the groups using coxibs. Consequently, the potential risks from use of all coxibs and non-selective NSAIDs need continued exploration.

Conclusion

There is no significant difference between celecoxib and rofecoxib with regard to their association with adverse cardiovascular events. Celecoxib was associated with a lower risk of AMI and stroke than meloxicam. In contrast to previous reports, we found rofecoxib users to be at no higher risk of cardiovascular events than those receiving meloxicam. Instead, we found a close enough association between meloxicam and a higher risk of cardiovascular events to warrant caution regarding the safety of non-selective NSAIDs. A prior history of cardiovascular disease was the most significant determinant of such risks. Patients with a history of other medical conditions also appeared to have a higher risk of cardiovascular events when taking coxibs.

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