ORIGINAL RESEARCH ARTICLE

Drug Safety 2006; 29 (7): 621-632
0114-5916/06/0007-0621/$39.95/0

Temporal Relationship between Use of NSAIDs, Including Selective COX-2 Inhibitors, and Cardiovascular Risk

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Abstract

Background and Objective: The search for NSAIDs with less gastrointestinal toxicity led to the introduction of the selective cyclo-oxygenase-2 (COX-2) inhibitors. However, following their introduction into the market, concerns have developed regarding their safety, particularly their cardiovascular safety. The purpose of this study was to assess the cardiovascular risk (events included were myocardial infarction, stroke and myocardial infarction-related deaths) associated with long-term (>180 days of exposure) and short-term (≤180 days of exposure) use of non-selective NSAIDs, including 'preferential COX-2 inhibitors' (i.e. etodolac, nabumetone and salsalate), and selective COX-2 inhibitors.

Methods: A retrospective analysis of the Veterans Integrated Service Network 17 Veterans Affairs (VA) database was conducted. Medicare data and Texas Department of Health mortality data were incorporated to capture events occurring outside the VA healthcare network. Patients ≥35 years of age who received celecoxib, rofecoxib, ibuprofen, etodolac and naproxen from 1 January 1999 through 31 December 2001, were included. Multivariate Cox proportional hazard models were used to analyse the relationship between cardiovascular risk and NSAID use, including selective COX-2 inhibitor use, while adjusting for various risk factors.

Results: We identified 12 188 exposure periods (11 930 persons) and 146 cardiovascular events over the entire study period. Compared with long-term ibuprofen use, long-term use of celecoxib (adjusted hazard ratio [HR] 3.64; 95% CI 1.36, 9.70) and rofecoxib (adjusted HR 6.64; 95% CI 2.17, 20.28) was associated with a significant increase in cardiovascular risk. When restricted to patients ≥65 years of age, the cardiovascular risks associated with long-term celecoxib (adjusted HR 7.36; 95% CI 1.62, 33.48) and rofecoxib (adjusted HR 13.24; 95% CI 2.59, 67.68) use increased. Short-term use of celecoxib (adjusted HR 0.75; 95% CI 0.42, 1.35) and rofecoxib (adjusted HR 0.85; 95% CI 0.39, 1.86) was not associated with any significant change in cardiovascular risk when compared with short-term ibuprofen use. Neither long- nor short-term exposure to naproxen and etodolac

was associated with cardionegative or cardioprotective effects when compared with ibuprofen use.
Conclusions: The findings of this observational study, along with recent clinical trial results, suggest that prolonged exposure to selective COX-2 inhibitors may be associated with an increased risk of adverse cardiovascular outcomes.

Background

The gastrointestinal (GI) toxicity associated with NSAIDs led to the search for and development of the selective cyclo-oxygenase-2 (COX-2) inhibitors. This new generation of pain medication held the promise of effective pain relief without the concern of serious adverse effects. However, this perception changed when a large prospective clinical trial found a link between an increased risk of serious cardiovascular events and rofecoxib use.[1] A 5-fold increased risk of an acute myocardial infarction (AMI) was found with the use of rofecoxib 50 mg/day compared with naproxen 1000 mg/day in the VIGOR (Vioxx® Gastrointestinal Outcomes Research) study.[1] Subsequently, clinical, epidemiological and other studies have provided supporting evidence that the use of selective COX-2 inhibitors may be associated with an increased risk of cardiovascular events.[2-15] In contrast, results from several other clinical and epidemiological studies do not support the hypothesis that selective COX-2 inhibitors increase cardiovascular risk.[16-23] These contrasting results may be due to different study populations, use of concomitant aspirin (acetylsalicylic acid), COX-2 selectivity/agent-specific differences, dose, comparator group and/or study duration. Several biological mechanisms of actions have been reported, ranging from changes in blood pressure, effects on low-density lipoprotein (LDL) oxidation, and effects on the prostanoid synthetic pathways.[24-26]

The purpose of this study was to investigate the association between use of NSAIDs, including selective COX-2 inhibitors, and cardiovascular risk among the Texas, US, Veterans Affairs (VA) population.

Methods

Data Source

The study encompasses patients receiving healthcare services from the VA Heart of Texas Health Care Network, termed the Veterans Integrated Service Network (VISN) 17. This VISN services a population of 1 million veterans living across central Texas. Most of this population are aged, disabled and lack additional healthcare insurance. In addition to the VA, Medicare provides medical coverage to roughly 25% of veterans, with only 0.1% of veterans having additional prescription coverage.[27] Computerised medical files from the VA allowed for identification of drug exposure, cardiovascular risk factors and study endpoint events amongst patients. Rofecoxib and celecoxib were both on a restricted formulary, requiring many patients to receive prior treatment with non-selective NSAIDs, including 'preferential COX-2 inhibitors' (i.e. etodolac, nabumetone and salsalate).[28]

In order to minimise missing information due to the use of outside healthcare coverage, Medicare data were obtained and analysed. A sensitivity analysis was conducted restricting the population to those ≥65 years of age. This analysis was done to address the potential influence of missing information resulting from the use of outside healthcare coverage and to assess an older and sicker population. Furthermore, to capture fatal cardiovascular events occurring outside the Medicare and VA healthcare systems, mortality data from the Texas Department of Health were collected and analysed. This project was approved by all participating investigational review boards.

Study Population

Patients ≥35 years of age who received a non-selective NSAID or selective COX-2 inhibitor between 1 January 1999 and 31 December 2001 were

included in the study. Data from 1 January 1998 to 31 December 1998 were used to evaluate prior cardiovascular conditions, NSAID exposure, and confounding factors. Patients were stratified into five different study groups determined by non-selective NSAID or selective COX-2 inhibitor exposure. The study groups included patients who had received naproxen, ibuprofen, etodolac, celecoxib and rofecoxib, respectively. Ibuprofen served as the control for the other four study groups. Additionally, naproxen and etodolac served as control groups in several sensitivity analyses. Etodolac was chosen as a study group due to the high number of patients using this drug and because several pharmacological studies have found etodolac to have some COX-2 selectivity.[29] To date, no study has specifically examined the cardiovascular risk of etodolac.

Because of the limited number of patients receiving high-dose rofecoxib (>25mg) and celecoxib (≥300mg), a dose-response relationship was not evaluated. The date of the initial prescription during the study period was used as the index date. Patients who received a prescription for any selective COX-2 inhibitor or non-selective NSAID within the 6 months prior to their index date were excluded from the study. Additionally, patients were excluded if they were exposed to the cohort-defining drug in the year prior to the index date. The duration of cohort involvement started on the index date and lasted until the individual experienced a censorship point: a study endpoint event, exposure to other NSAIDs, including selective COX-2 inhibitors, death, discontinuation of study medication or the end of the study. Patients were allowed to re-enter the cohort or join a new cohort if the patient met the inclusion criteria. Additionally, patients who experienced a study endpoint were not allowed to re-enter the study. A sensitivity analysis was conducted assessing only the first non-selective NSAID or selective COX-2 inhibitor exposure.

Study Periods

In order to assess the cardiovascular effect of long-term exposure versus short-term exposure to NSAIDs (including selective COX-2 inhibitors), the study evaluated events occurring before and after 180 days of exposure to study medications. Patients who experienced a study endpoint (i.e. acute myocardial infarction [AMI], stroke, and/or AMI-related death) during the first 180 days of exposure were excluded from the long-term analysis. The *a priori* decision to evaluate risk after 180 days of exposure was due to the limited availability of long-term data from clinical trials.

To evaluate short-term cardiovascular risk, the evaluation period was limited to ≤180 days of therapy. The association between overall use (risk after first day of use) of NSAIDs, including selective COX-2 inhibitors, and cardiovascular risk was also assessed.

A series of *post hoc* analyses with the exposure time changed to 60 days, 90 days, 120 days, 150 days, 210 days and 240 days, was conducted. The purpose of these *post hoc* analyses was to further explore the relationship between exposure time and cardiovascular events.

Patients who received <30 days of study medication were excluded from the study. Furthermore, only observation periods with two or more prescriptions were considered. Patients who were dispensed more than one study drug on the index date were excluded. Patients were allowed a grace period that was 20% of the previous prescribed duration of supply to refill the next prescription. Inpatient pharmacy data were available for a portion of the population; patients receiving a study drug while admitted to the hospital were allowed a 10-day grace period in which to experience a subsequent exposure. To ensure an adequate baseline assessment, patient observations without at least 1 year of prior healthcare use within the VA healthcare system were excluded.

Study Variables

The primary study endpoint was the combination of either a diagnosis for an AMI, death from an AMI or a cerebrovascular event. Specifically, a study endpoint required an International Classification of Diseases – 9th edition (ICD-9) discharge diagnosis code of 410 (AMI), an ICD-10 AMI cause of death code of I21–I22, or an ICD-9 discharge diagnosis for cerebrovascular events using a high-specificity model.[30] A study within the VA healthcare system assessing code veracity of stroke-related ICD-9 codes has been conducted. The high-specificity algorithm yielded 59% sensitivity and 84% specifici-

ty; the high-sensitivity model yielded 89% sensitivity and 57% specificity.[30] Research conducted within the VA healthcare system found a 96.9% positive predictive value for AMIs coded in the primary position.[31] Patients discharged alive were required to have a length of stay of no less than 3 days and no greater than 180 days. Of note, the duration of stay and position of the ICD-9 code were not available for this study, thus possibly decreasing the positive predictive value of the AMI diagnosis.

A recent study in Medicare recipients evaluated the validity of AMI ICD-9 codes. This study found a 92.3% positive predictive value for an AMI coded in the primary or secondary position without a length of stay restriction, providing some flexibility with regards to field position and length-of-stay requirements.[32] Diagnostic coding for cardiovascular-related deaths is believed to be less accurate; however, it is necessary for capturing fatal myocardial infarctions that occur outside the hospital.

To address concerns regarding the choice of endpoint events, several sensitivity analyses were conducted that varied this parameter. These included assessing only AMI and AMI-related deaths, evaluating a high-sensitivity stroke model in place of the high-specificity model[30] and expanding the mortality definition to death from ischaemic heart disease (ICD-10 codes I20–I25) and death from any major cardiovascular disease (ICD-10 codes I00–I78).

Baseline Covariates

A 1-year baseline period prior to the index date was used to evaluate and control for potential confounding factors. These factors include life threatening conditions (neoplasms, HIV, renal failure, respiratory failure, insufficiency and arrest); cardiovascular conditions (heart failure, prior myocardial infarction, cerebrovascular disease, peripheral vascular disease [ICD-9 code or prescription for cilostazol, cyclandelate or pentoxifylline], angina [ICD-9 code or prescription for a nitrate] and atrial fibrillation); diabetes mellitus (ICD-9 code or use of a antidiabetic medication); inflammatory conditions (osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus and connective tissue disorders); and chronic obstructive pulmonary disease (COPD).

Baseline medications included β-adrenoceptor antagonists (β-blockers), calcium channel antagonists, digoxin, other hypertensive medications, loop diuretics, methotrexate, warfarin, ACE inhibitors/angiotensin II receptor antagonists, antiplatelet drugs, antirheumatic drugs, corticosteroids, cholesterol-lowering drugs, other diuretics and other anticoagulants.

A separate analysis was conducted to evaluate baseline differences in body mass index (BMI), blood pressure readings, and cholesterol levels. Patient vital signs and laboratory readings occurring in the year prior to the index date were averaged into a single value. Because of the limited availability of readings for all patients, these variables were not factored into the model.

Statistical Analyses

An historical cohort study design was used to analyse the cardiovascular effects of the specified NSAIDs and selective COX-2 inhibitors. An alpha level of 0.05 was used to test for statistical significance. Analyses and data management were conducted with SPSS 12.0 (SPSS, Chicago, IL, USA) and SAS 8.2 (SAS, Cary, NC, USA). Analysis of events in relation to person-time was analysed via the Cox proportional hazard model. The Wald test was used to determine statistical differences between individual nonselective NSAIDs and selective COX-2 inhibitors.

Results

During the study period, 84 677 individuals (122 683 observations) were exposed to NSAIDs, including selective COX-2 inhibitors, with 11 930 individuals (12 188 observations) meeting the study criteria. Of note, the majority of the censored observations resulted from sporadic use (receiving <30 days and/or receiving only one prescription of the study medications). Of the 12 188 eligible observations, 4481 (36.8%) were of ibuprofen use, 3240 (26.6%) were of naproxen use, 1530 (12.6%) were of celecoxib use, 2371 (19.5%) were of etodolac use and 566 (4.6%) were of rofecoxib use. The majority of the observations were for short-term use (≤180 days), comprising roughly 60% of the celecoxib and rofecoxib observations and roughly 75% of

ibuprofen, etodolac and naproxen observations. More than 90% of the population consisted of men, with similar proportions in each of the cohorts. Patients taking celecoxib or rofecoxib were, on average, 7 years older than patients taking ibuprofen, etodolac or naproxen. Furthermore, a higher percentage of patients taking celecoxib or rofecoxib had cancer, diabetes, arthritis and cardiovascular conditions (table I). Baseline laboratory data and other patient measurements were assessed using available readings. When comparing values across the study groups, blood pressure, cholesterol level and BMI values varied slightly between the categories (table II). However, lower total cholesterol and LDL-cholesterol levels were found in the celecoxib and rofecoxib cohorts than in the other study cohorts. No relevant differences with regards to baseline vital signs and laboratory parameters were found between overall users, short-term or long-term users of the study medications.

When adjusting for the covariates listed in table I, the results did not reveal a statistically significant association between overall use (long-term and short-term use combined) of any of the study medications and cardiovascular risk (table III). Specifically, when compared with ibuprofen, the results yielded an adjusted hazard ratio (HR) of 1.13 (95% CI 0.70, 1.83) for celecoxib users; 1.59 (95% CI 0.87, 2.90) for rofecoxib users, 0.82 (95% CI 0.48, 1.40) for etodolac users, and 0.86 (95% CI 0.53, 1.40) for naproxen users.

Several covariates in the model were associated with a statistically significant increased cardiovascular risk. These included COPD, osteoarthritis, prior AMI and stroke, age and use of β-blockers, loop diuretics, methotrexate or antiplatelets. Other covariates did not show statistically significant associations, but may have contributed to the model.

After partitioning patients into short-term and long-term users, long-term use of celecoxib and rofecoxib was associated with a significant increase in cardiovascular risk when compared with long-term ibuprofen use (adjusted HR 3.64; 95% CI 1.36, 9.70 and adjusted HR 6.64; 95% CI 2.17, 20.28, respectively). In contrast, a statistically significant increase in cardiovascular risk was not found in patients who received long-term etodolac (adjusted HR 1.26; 95% CI 0.35, 4.56) or naproxen (adjusted HR 1.15; 95% CI 0.35, 3.77) when compared with long-term ibuprofen users. Short-term use of any non-selective NSAID or selective COX-2 inhibitor was not associated with an increased or decreased cardiovascular risk when compared with short-term ibuprofen use (table III). The *post hoc* temporal assessments further demonstrate the increasing cardiovascular risk over time with celecoxib and rofecoxib use (table IV). No significant change in risk over time was found in the *post hoc* temporal assessment of etodolac and naproxen.

Several sensitivity analyses were conducted. These included using only the first non-selective NSAID or selective COX-2 inhibitor exposure; modification of the primary endpoint; using different comparator NSAIDs; and restricting the population to those patients who were ≥65 years of age. The sensitivity analyses using only the first non-selective NSAID or selective COX-2 inhibitor exposure resulted in findings similar to those reported previously. Regarding the primary endpoint definition (AMI, death from an AMI, or a cerebrovascular event), comparable results were found when restricting the primary endpoint to serious coronary events (AMI or death from an AMI). When expanding the mortality definition of the primary endpoint to include deaths from ischaemic heart disease, comparable results were also found. However, two of the sensitivity analyses varying the primary end-point yielded different results; these included changing the mortality definition from an AMI-related death to death from a major cardiovascular disease and replacing the high-specificity stroke model with the high-sensitivity stroke model. After modifying the mortality definition to capture death from any major cardiovascular disease, the long-term use of celecoxib was no longer statistically associated with an increased cardiovascular risk when compared with long-term ibuprofen use (adjusted HR, 2.17, 95% CI 0.94, 5.03). All other results were comparable. Regarding the high-sensitivity stroke model, all results were found to be statistically non-significant.

The following sensitivity analyses evaluated the use of different comparator groups, i.e. naproxen and etodolac. Compared with ibuprofen, naproxen yielded similar adjusted HRs in all categories. Long-term users of celecoxib and rofecoxib users were significantly more likely to experience a primary

Table I. Percentages of subjects with a baseline medical diagnosis or exposure to a medication in the year prior to the index date by study drug

Parameter	Celecoxib n = 1530[a]	Rofecoxib n = 566[a]	Etodolac n = 2371[a]	Naproxen n = 3240[a]	Ibuprofen n = 4481[a]
Age (mean; y)	67.5	66.7	61.6	60.3	58.8
Male sex	94.4	92.6	93.5	93.3	93.7
Medical conditions					
atrial fibrillation	6.7	5.6	2.1	1.4	1.0
angina	8.0	8.5	5.2	4.0	2.8
cancer	19.5	20.5	13.8	11.2	10.2
COPD	9.9	13.2	7.1	5.4	5.1
diabetes mellitus	15.6	17.5	11.3	10.2	8.9
heart failure	8.3	9.0	4.1	3.1	3.0
HIV/AIDS	0.0	0.4	0.0	0.1	0.2
lupus[b]	0.5	1.1	0.1	0.1	0.1
osteoarthritis	24.7	24.0	13.8	11.0	8.5
PVD	5.2	5.3	2.4	2.6	2.1
renal failure	1.1	2.5	0.7	0.3	0.3
respiratory failure	1.0	1.2	0.6	0.3	0.4
RA	3.1	2.6	1.6	0.8	0.7
prior AMI	1.6	1.9	1.1	0.8	0.8
prior stroke[c]	0.6	0.5	0.3	0.2	0.3
Medications					
antiarrhythmic drugs	3.7	3.2	1.2	1.3	0.8
aspirin (acetylsalicyclic acid)	31.8	31.6	27.6	28.5	26.5
β-adrenoceptor antagonists	23.9	28.0	20.7	18.4	16.9
calcium channel antagonists	32.4	29.8	25.6	24.4	21.9
antidiabetic drugs	20.0	22.6	18.3	19.0	16.8
digoxin	12.2	9.5	5.3	4.1	3.5
estrogen	2.6	3.7	2.8	3.0	2.8
other antihypertensives	24.2	22.9	20.9	16.9	15.0
loop diuretics	18.1	16.8	11.6	8.8	8.9
methotrexate	1.3	0.9	0.5	0.4	0.3
nitrate	22.4	22.6	16.8	14.4	14.1
PVD drugs	1.2	1.6	0.7	0.8	0.6
warfarin	14.1	13.1	3.6	2.4	1.9
ACE inhibitors/ARBs	33.7	33.3	31.2	29.7	26.3
antiplatelet drugs	5.9	6.5	3.0	2.9	2.7
antirheumatic drugs	0.7	0.2	0.3	0.2	0.2
corticosteroids	9.3	8.1	5.9	5.0	5.6
cholesterol-lowering drugs	37.6	37.9	33.3	31.6	25.9
other diuretics	17.5	16.8	18.6	15.5	14.3
other anticoagulants	1.4	2.3	0.5	0.6	0.9

a Observations.

b Systemic lupus erythematosus and connective tissue disorders diagnoses.

c Using the high specificity model.

AMI = acute myocardial infarction; **ARBs** = angiotensin II receptor antagonists; **COPD** = chronic obstructive pulmonary disease; **PVD** = peripheral vascular disease; **RA** = rheumatoid arthritis.

Table II. Baseline patient vital signs and laboratory parameters (mean [SD]) by study drug

Parameters	Celecoxib	Rofecoxib	Etodolac	Naproxen	Ibuprofen
BMI (kg/m^2)	29.2 (5.5)	29.0 (5.9)	29.5 (6.0)	29.3 (5.7)	28.9 (6.0)
SBP (mm Hg)	139.6 (18.3)	139.9 (18.0)	139.0 (17.8)	139.2 (17.2)	138.5 (18.1)
DBP (mm Hg)	73.7 (9.8)	73.5 (10.3)	75.6 (10.5)	76.1 (10.2)	76.6 (10.4)
TC (mg/dL)	187.3 (36.9)	187.4 (44.7)	192.3 (39.6)	193.8 (40.6)	192.3 (40.0)
HDL-C (mg/dL)	45.5 (13.2)	45.4 (12.5)	43.7 (12.8)	45.2 (13.2)	45.2 (13.4)
LDL-C (mg/dL)	106.5 (31.8)	108.1 (32.4)	112.4 (32.4)	114.2 (33.5)	113.6 (33.3)
Triglyceride (mg/dL)	190.0 (130.9)	188.3 (197.0)	193.9 (143.7)	189.2 (140.2)	189.9 (151.2)

BMI = body mass index; **DBP** = diastolic blood pressure; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TG** = triglyceride; **SD** = standard deviation; **SBP** = systolic blood pressure; **TC** = total cholesterol.

endpoint event than long-term naproxen users (adjusted HR 3.16; 95% CI 1.16, 8.57 and adjusted HR 5.76; 95% CI 1.82, 18.21, respectively). Long-term exposure to etodolac yielded non-significant results when compared with naproxen. Additionally, overall use and short-term use of all study medications were not associated with an increase in cardiovascular risk. With regards to using etodolac as a comparator group, two of the results differed from the models using ibuprofen as a comparator. Long-term users of celecoxib were not found to be statistically different from long-term users of etodolac in terms of cardiovascular risk (adjusted HR 2.89, 95% CI 0.95, 8.80). However, the overall use of rofecoxib was associated with a statistically significant increase in cardiovascular risk when compared with

Table III. Adjusted association between non-selective NSAIDs/selective cyclo-oxygenase-2 (COX-2) inhibitors and serious cardiovascular events[a] – comparison with ibuprofen

Drug	Person years	Events[b]	Rate per 100 person years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]	p-Value
Overall use						
Celecoxib	964	39	4.05	2.04 (1.30, 3.20)	1.13 (0.70, 1.83)	0.61
Rofecoxib	286	17	5.94	2.88 (1.62, 5.11)	1.59 (0.87, 2.90)	0.13
Etodolac	1021	23	2.25	1.08 (0.64, 1.81)	0.82 (0.48, 1.40)	0.47
Naproxen	1439	29	2.02	0.99 (0.61, 1.60)	0.86 (0.53, 1.40)	0.54
Ibuprofen[d]	1851	38	2.05	1.0	1.0	
>180 days[e]						
Celecoxib	416	18	4.33	3.72 (1.47, 9.39)	3.64 (1.36, 9.70)	0.01
Rofecoxib	87	8	9.24	7.46 (2.59, 21.54)	6.64 (2.17, 20.28)	<0.01
Etodolac	257	4	1.56	1.25 (0.35, 4.44)	1.26 (0.35, 4.56)	0.73
Naproxen	442	6	1.36	1.18 (0.38, 3.66)	1.15 (0.35, 3.77)	0.81
Ibuprofen[d]	526	6	1.14	1.0	1.0	
≤180 days						
Celecoxib	548	21	3.83	1.61 (0.93, 2.79)	0.75 (0.42, 1.35)	0.34
Rofecoxib	199	9	4.53	1.90 (0.91, 3.98)	0.85 (0.39, 1.86)	0.69
Etodolac	764	19	2.49	1.04 (0.59, 1.83)	0.73 (0.41, 1.30)	0.28
Naproxen	997	23	2.31	0.96 (0.56, 1.64)	0.83 (0.48, 1.42)	0.50
Ibuprofen[d]	1325	32	2.42	1.0	1.0	

a Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event.

b 40 of the 146 events were attributed to cerebrovascular events.

c Controlling for variables listed in table I.

d Control group with comparable duration of exposure.

e Person years and rates for long-term use were calculated after 180 days of exposure.

HR = hazard ratio.

Table IV. *Post hoc* temporal assessment of the adjusted association[a] between non-selective NSAIDs/selective cyclo-oxygenase-2 (COX-2) inhibitors and serious cardiovascular events when compared with ibuprofen users

Exposure time[b] (days)	Celecoxib; adjusted HR (95% CI)	Rofecoxib; adjusted HR (95% CI)	Etodolac; adjusted HR (95% CI)	Naproxen; adjusted HR (95% CI)
>60	1.64 (0.89, 3.00)	2.49 (1.18, 5.24)	0.98 (0.48, 2.00)	0.82 (0.42, 1.63)
>90	1.43 (0.73, 2.80)	2.29 (0.99, 5.31)	1.04 (0.48, 2.24)	0.60 (0.27, 1.35)
>120	1.72 (0.84, 3.49)	2.54 (1.03, 6.26)	0.81 (0.32, 2.03)	0.72 (0.31, 1.68)
>150	1.85 (0.81, 4.22)	3.46 (1.31, 9.11)	0.94 (0.34, 2.64)	0.79 (0.30, 2.08)
>180	3.64 (1.36, 9.70)	6.64 (2.17, 20.28)	1.26 (0.35, 4.56)	1.15 (0.35, 3.77)
>210	3.49 (1.30, 9.37)	6.64 (2.12, 20.84)	0.99 (0.24, 4.07)	1.18 (0.36, 3.84)
>240	4.56 (1.44, 14.42)	7.42 (1.88, 29.25)	1.05 (0.19, 5.91)	0.88 (0.19, 4.09)

a Controlling for variables listed in table I.

b Rates calculated after the designated exposure time.

HR = hazard ratio.

etodolac (adjusted HR 1.93; 95% CI 1.02, 3.67). All other results were comparable to results obtained with models using ibuprofen as the control group.

The patients included in the analysis were restricted to those aged ≥65 years to assess an older population who more at risk for cardiovascular disease. When evaluating the primary study endpoint and restricting included patients to those ≥65 years of age, long-term celecoxib use yielded an adjusted HR of 7.36 (95% CI 1.62, 33.48) and long-term rofecoxib use yielded an adjusted HR of 13.24 (95% CI 2.59, 67.68) when compared with long-term ibuprofen use. A statistically significant association between overall rofecoxib use and cardiovascular risk was found in this age group when compared with ibuprofen use (adjusted HR 2.14; 95% CI 1.09, 4.19). For all other comparisons, no statistically significant differences were found.

Discussion

The results of this study suggest a temporal relationship between cardiovascular risk and the use of celecoxib and rofecoxib. After long-term exposure to celecoxib and rofecoxib, an increased risk of a cardiovascular event (defined as AMI, death from an AMI or a cerebrovascular event) was found. Long-term exposure to celecoxib and rofecoxib significantly increased the risk for a cardiovascular event. When the long-term use of non-selective NSAIDs and selective COX-2 inhibitors was restricted to patients ≥65 years of age, the adjusted HRs associated with celecoxib and rofecoxib use nearly doubled, defining a population at greater cardiovascular risk. This study failed to find an increased risk associated with short-term use of either celecoxib or rofecoxib. Although etodolac has been found to possess some affinity for the COX-2 enzyme over the COX-1 enzyme, an elevated cardiovascular risk was not found with this drug. In contrast to some studies, our study did not find a cardioprotective effect associated with naproxen use.[3]

A wide range of results from observational studies have been reported regarding the cardiovascular safety of rofecoxib and celecoxib.[2,4-6,10-14,16,17,22,33,34] One study even found a cardioprotective effect among celecoxib users when compared with patients who were not receiving NSAIDs.[6] However, the study had several limitations (i.e. possibility of recall bias and low-response rate) and when compared with other NSAID users, the protective effect was not found. Our study similarly found no increase in cardiovascular risk for the overall exposure (combination of short-term and long-term users) to celecoxib.

However, unlike previous studies, our study segmented the population into two time periods to evaluate the cardiovascular risk after long-term exposure (>180 days) and short-term exposure (≤180 days). The long-term use of celecoxib was found to be associated with an increased cardiovascular risk, whereas short-term exposure to celecoxib was not associated with an increased risk. Studies may have failed to detect a cardiovascular risk with overall celecoxib use because of the higher proportion of patients taking celecoxib in the short term, as op-

posed to long term, thereby diluting the hazard. Specifically, by assuming a proportional hazard rate when duration of exposure is related to an increased cardiovascular risk, the early hazard is overestimated and the later hazard is underestimated. Therefore, if a population primarily consists of short-term and sporadic users, the cardiovascular risk of long-term users may be nullified.

In addition, each non-selective NSAID and selective COX-2 inhibitor has unique properties that may detract from or contribute to cardiovascular risk. Ibuprofen was chosen as the baseline comparator because it has not been associated with an increase or decrease in cardiovascular risk. However, ibuprofen has been found to have a greater inhibitory effect on the antiplatelet effects of aspirin than celecoxib and rofecoxib, resulting in a possible increased number of cardiovascular events among ibuprofen users.[35,36] With regards to the sensitivity analyses using different comparator NSAIDs, similar results in all models were found with naproxen as the comparator NSAID. Additionally, etodolac yielded similar results; however, the increased risk associated with long-term celecoxib use was no longer statistically significant. This could be attributed to the COX-2 selectivity of etodolac and/or the smaller sample size (~25% fewer observations than naproxen and ~60% fewer observations than ibuprofen).

To evaluate the full range of possibilities, the primary endpoint was changed to capture additional stroke cases (high-sensitivity model). This alteration resulted in non-significant results in all analyses. Of note, previous research has found a high percentage of false-positive cerebrovascular events when using this model of nearly 40%.[30] Due to the difficulty in evaluating stroke cases from ICD-9 codes, only AMI and AMI-related deaths were evaluated. This sensitivity analysis yielded similar results to the primary endpoint analyses. When expanding the definition of the primary model to include death from ischaemic heart disease, no significant changes in any of the models were found. When any major cardiovascular disease-related death was assessed, similar results were found; however, the increased risk associated with the long-term use of celecoxib was no longer statistically significant. The statistically non-significant result may be explained by the broad scope of conditions found in the 'any major cardiovascular disease' category, ranging from hypertensive diseases through rheumatic fever.

Many of the observational studies have revealed no statistically significant increase in cardiovascular risk when exposed to low doses of rofecoxib (≤25mg).[2,4,5] Additionally, studies combining high-dose (>25mg) and low-dose rofecoxib use failed to find a statistically significant increase in cardiovascular risk.[16,17] As with previous studies, our study did not find an increased risk associated with short-term and overall use of rofecoxib. However, an increased risk was found with long-term use of rofecoxib. Similar to the reason for not finding a cardiovascular risk with celecoxib in previous observational studies, the cardiovascular risk associated with rofecoxib may have been diluted by the disproportionate number of short-term and sporadic users. Based on the findings from epidemiological studies and the VIGOR study, the cardiovascular signal for high-dose (>25mg) rofecoxib seems to be much stronger than for low-dose rofecoxib use.[1,2,5] However, due to the low number of high-dose rofecoxib users in our study population, a dose-response relationship could not be examined.

The temporal findings in our study contrast with those from a study conducted by Solomon et al.[4] That study evaluated the association between duration of rofecoxib and celecoxib exposure (≤30 days; 31–90 days; and >90 days) and AMI events. Compared with celecoxib, short-term exposure (≤90 days) to rofecoxib was associated with an increased cardiovascular risk. The increased cardiovascular risk dissipated in patients with more than days of rofecoxib use. The study failed to show an increased risk in any time period for celecoxib when compared with rofecoxib. A follow-up study conducted by Solomon et al.[13] in the same population found similar results to their previous study, with the exception of a persistent cardiovascular risk over a 3-year period for rofecoxib users versus non-NSAID users. A possible reason for the discrepancy between the studies by Solomon et al.[4,13] and our study is the different definitions of long-term use, exclusion of patients with ≤30 days of exposure, different comparator groups and study design. Furthermore, our study comprised a different patient population with different characteristics (e.g. prima-

rily consisting of men). Additionally, a study conducted by Huang and colleagues[33] evaluated the long-term (≥180 days exposure) cardiovascular safety of celecoxib and rofecoxib compared with meloxicam. This study found a lower cardiovascular risk with celecoxib and no difference in cardiovascular risk with rofecoxib compared with meloxicam. The use of meloxicam as a comparator group and/or other study parameters may explain the differing results.

There are several limitations when evaluating the cardiovascular safety in clinical trials. Although clinical trials are considered the gold standard for determining safety and efficacy, they usually involve a small number of patients and may not be powered to detect unexpected adverse effects (such as cardiovascular disease). Furthermore, many of the clinical trials involved short durations of therapy and were unable to show the ramifications of long-term exposure. In attempts to obtain 'clean' results, many of these studies exclude individuals with various risk factors (i.e. cardiovascular risk factors). Therefore, many of the studies evaluating selective COX-2 inhibitors may not be representative of the population actually receiving the drug.

Two clinical trials supporting our results (in addition to the VIGOR study) are the APPROVe (Adenomatous Polyp Prevention On Vioxx) trial and the APC (Adenoma Prevention with Celecoxib) trial.[7,9] In both of these trials, a significant cardiovascular risk was found with rofecoxib and celecoxib after long-term use when compared with a placebo group. In the APPROVe trial, the first 18 months of therapy were not associated with an increase in cardiovascular risk (relative risk [RR] 1.18; 95% CI 0.64, 2.15); however, after 18 months of therapy, a significant increased risk was found (RR 4.45; 95% CI 1.77, 13.32).[7] This result lends support to a relationship between prolonged exposure to COX-2 inhibitors and cardiovascular risk. Regarding the APC trial, patients taking celecoxib in this long-term cancer prevention trial had a higher risk of experiencing a cardiovascular event as compared with those taking a placebo. Specifically, patients taking celecoxib 400mg daily were 2.5 times (95% CI 1.0, 6.4) more likely to have a cardiovascular event than placebo recipients, and patients taking celecoxib 800mg were 3.4 times (95% CI 1.4, 8.5) more likely to have an event.[9] Of note, our study primarily consisted of low dose (<300mg) celecoxib users. In contrast, another long-term study, the PreSAP (Prevention of Spontaneous Adenomatopus Polyps) trial, did not reveal an increased risk of cardiovascular events for patients taking celecoxib 400mg daily compared with those taking placebo.[23]

To further elaborate on the cardiovascular risk associated with COX-2 inhibitors, a randomised, placebo-controlled study performed in patients receiving valdecoxib and its intravenous prodrug paracoxib immediately after coronary-artery bypass grafting showed an increased cardiovascular risk compared with placebo (RR 3.7; 95% CI 1.0, 13.5; p = 0.03).[8] This adds to the hypothesis that individuals already at an increased risk of cardiovascular events are more susceptible to the negative cardiovascular effects of COX-2 inhibitors.[37-41]

With any observational study several limitations exist. With regards to hospital proximity, VA patients not living near a VA hospital may have limited ability to receive healthcare services from a VA facility in the event of a major cardiovascular event. To control for this factor, Medicare data were obtained to capture events occurring outside the VA healthcare system. A previous study was conducted evaluating point of care for AMI among elderly veterans (≥65 years).[42] This study found that more than half (54%) of elderly veterans with prior use of the VA medical system were initially hospitalised in a Medicare hospital when they suffered an AMI. Although the Medicare data will help capture events occurring outside the VA medical system in patients enrolled in Medicare, data for individuals not enrolled who experience an event may not be captured. In our study, individuals receiving celecoxib and rofecoxib were found to have higher percentages of baseline risk factors than those receiving ibuprofen, etodolac and naproxen. This could be explained by the larger percentage of individuals aged >65 years who had received celecoxib (63.3%) and rofecoxib (59.3%) than ibuprofen (33.2%), etodolac (38.4%) and naproxen (36.9%). Additionally, the adjusted model helps to control for these factors. Regarding prescription coverage, even though automated pharmacy claims are one of the best sources of information on drug use,[43] information concerning compliance and the use of drugs from outside sources may

be lacking. Concurrent use of aspirin was allowed in this study; however, very few patients were found to have overlapping use. Therefore, many patients may have been taking over-the-counter aspirin. This parameter would only be a problem if use differed across the study groups. Comparable percentages of baseline aspirin use were found between all five study groups (~30%). Furthermore, other studies evaluating this issue have not shown a difference in aspirin use between patients who took non-selective NSAIDs and those who took selective COX-2 inhibitors.[4,5] Only select medications and ICD-9 codes were available for analysis, thereby limiting the ability to determine overall disease burden or the frequency of medical care. It is unknown if these variables would significantly contribute to this study. Because of the population studied and specific inclusion and exclusion criteria, the results from this study may not be generalisable to individuals not reflective of the study population. One of the primary differences is the disproportionate number of men compared with women. However, this difference may be advantageous because most (if not all) of the previous observational studies evaluating selective COX-2 inhibitor-related cardiovascular risk consisted primarily of women.[2,4,5,16] A large proportion of this population was estimated to be at risk for cardiovascular disease and results may not be reflective of healthier populations. Because of the small number of observations and endpoint events, caution is advised when interpreting these results.

Conclusion

NSAIDs, including selective COX-2 inhibitors, are some of the most widely prescribed medications in the world. Due to this factor, the findings of this study have wide reaching implications. Two long-term prospective clinical trials now support the findings of this study.[7,9] However, additional studies are needed to examine this issue with regards to celecoxib and other COX-2 inhibitors currently on the market or under evaluation, especially in a population at risk for cardiovascular disease. However, some may question if it is even ethical to conduct such a study. Because of the findings of this study and two prospective clinical trials,[7,9] caution is advised in the prolonged use of celecoxib or rofecoxib (rofecoxib was voluntarily withdrawn in September 2004).

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest directly relevant to the content of this study.

This study was undertaken and first presented at the University of Texas prior to Dr Motsko commencing employment with the Degge group; this manuscript was written after he assumed his current position.

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