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CLINICAL RESEARCH STUDY

NSAID Use and Progression of Chronic Kidney Disease

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ABSTRACT

PURPOSE: The effects of nonselective and selective cyclooxygenase-2 specific (COX-2) nonsteroidal anti-inflammatory drug (NSAID) use on the progression of chronic kidney disease (CKD) is uncertain. Due to the high prevalence of both CKD and NSAID use in older adults, we sought to determine the association between NSAID use and the progression of CKD in an elderly community-based cohort.

METHODS: All subjects ≥66 years of age who had at least one serum creatinine measurement in 2 time periods (July-December, 2001 and July-December, 2003) were included. Multiple logistic regression analyses, including covariates for age, sex, baseline estimated glomerular filtration rate (eGFR), diabetes, and comorbidity were used to explore the associations of NSAID use on the primary (decrease in eGFR of ≥15 mL/min/1.73^2) and secondary (mean change in eGFR) outcomes.

RESULTS: A total of 10,184 subjects (mean age 76 years; 57% female) were followed for a median of 2.75 years. High-dose NSAID users (upper decile of cumulative NSAID exposure) experienced a 26% increased risk for the primary outcome (odds ratio [OR] 1.26, 95% confidence interval [CI], 1.04-1.53). A linear association between cumulative NSAID dose and change in mean GFR also was seen. No risk differential was identified between selective and nonselective NSAID users.

CONCLUSIONS: High cumulative NSAID exposure is associated with an increased risk for rapid CKD progression in the setting of a community-based elderly population. For older adult patients with CKD, these results suggest that nonselective NSAIDs and selective COX-2 inhibitors should be used cautiously and chronic exposure to any NSAID should be avoided.

KEYWORDS: Chronic kidney disease; Progressive kidney disease; Non-steroidal anti-inflammatory drug; Cyclooxygenase-2 inhibitor; Elderly

Chronic kidney disease is a worldwide public health problem with an increasing incidence and prevalence, particularly in the elderly population.[1-7] Nonsteroidal anti-inflammatory drugs (NSAIDs) have been identified as nephrotoxic agents with both acute and chronic effects on kidney function. While the short-term biological effects of sodium retention, edema, and acute renal failure with NSAIDs are well documented, there are limited scientific data reporting the safety of these drugs on kidney function when NSAIDs are taken chronically or when they are taken by patients with pre-existing kidney disease. Existing data regarding long-term NSAID exposure is inconsistent, with earlier studies suggesting an increased risk for adverse kidney related outcomes,[8-12] though more recent reports have failed to confirm these risks.[13-15]

The frequency of NSAID use, including nonselective conventional NSAIDS and selective cyclooxygenase-2 (COX-2) inhibitors, has increased in the last several years. Potential factors responsible for this increase include over-the-counter availability, an aging population with concom-

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itant musculoskeletal disorders, and the perceived superior gastrointestinal safety profile associated with COX-2 inhibitors. In particular, COX-2 inhibitor use has increased substantially since their introduction in 1999. Of the more than 25% Albertan senior population who were prescribed at least 1 NSAID during a 1-year period, 68% received a COX-2 inhibitor.[16]

Given the high prevalence of both chronic kidney disease and NSAID use in the elderly, and the uncertainty of the chronic kidney disease risk associated with NSAIDs, this study sought to examine the association between NSAID use and progression of chronic kidney disease in a community-based cohort of elderly subjects. This study also sought to determine if this association differed for conventional nonselective NSAIDs versus selective COX-2 inhibitors.

CLINICAL SIGNIFICANCE

- High NSAID exposure is associated with a rapid decrease in kidney function.
- Traditional non-selective NSAIDs and cyclo-oxygenase-2 specific NSAIDs are associated with a similar risk of kidney function decline.
- Chronic exposure to any NSAID should be avoided in older adult patients with chronic kidney disease

METHODS

Study Population

The Conjoint Ethics Review Board at the University of Calgary approved this study. A cohort of elderly subjects aged ≥66 years were identified from the Calgary Laboratory Services database in Calgary, Alberta, Canada. This laboratory provides testing for the entire Calgary Health Region (catchment population 1.1 million) using a single regional laboratory and standardized methods that are recalibrated routinely against reference samples. To be eligible for inclusion in this study, participants required at least one serum creatinine measurement in 2 study periods: July 1, 2001 to December 31, 2001; and July 1, 2003 to December 31, 2003. To reduce the impact of episodes of acute renal failure, laboratory measurements associated with a hospital admission were not included. Subjects were also excluded from the cohort if they had more than 12 outpatient serum creatinine measurements in either of the 6-month observation periods, as they were likely to represent patients with acutely unstable kidney function. Subjects receiving dialysis at study entry were also excluded.

Measurement of Kidney Function and Definition of Outcomes

Glomerular filtration rate was used to estimate kidney function using the abbreviated Modification of Diet in Renal Disease (MDRD) equation, which includes variables for age, sex, race and serum creatinine.[17] Although data for race were not available for the cohort, less than 1% of the Alberta population is African American.[18] Therefore, the impact at the population level of eliminating race from the estimate of glomerular filtration rate was expected to be minimal. Furthermore, given the study's focus on change in glomerular filtration rate, information on race was not needed. Because of concerns about the validity of the MDRD equation for subjects with higher levels of kidney function,[19] subjects with baseline glomerular filtration rate values exceeding 90 mL/min/1.73^{2}were also excluded.

Serum creatinine measurements were analyzed in the same laboratory, thus eliminating the potential for inter-laboratory measurement variation. However, because of possible intra-laboratory variation in measurement resulting from changes in calibration of serum creatinine assays, measurements between the 2 time periods were assessed and calibrated in the following manner. First, a subset of healthy subjects (defined as subjects with no prescriptions for medications commonly used to treat cardiovascular disease, hypertension or diabetes mellitus in the year before the index glomerular filtration rate) younger than 80 years of age was identified. The median serum creatinine measurement for these subjects, by 1-year age increments, for the 2001 and the 2003 time periods was calculated. The difference between measurements for the 2 periods was calculated, and the average of the differences determined. To correct for the systematic differences in serum creatinine measurements evident from this analysis, 2.0 umol/L (0.02 mg/dL) was subtracted from the serum creatinine measurements in 2003.

The primary outcome was rapid progression of kidney disease, defined as a decrease in glomerular filtration rate ≥15 mL/min/1.73^2. Progression was calculated as the difference in the subject mean glomerular filtration rate for the 2 time periods: July 1, 2001 to December 31, 2001 and July 1, 2003 to December 31, 2003. A progression of ≥15 mL/min/1.73^{2}was approximately the 88th percentile for progression within the entire cohort. The change in mean glomerular filtration rate (as a continuous variable) over the study period was chosen a priori as a secondary outcome.

Measure of Exposure

Using the unique provincial health care number for each subject, laboratory data were linked to the provincial administrative Alberta Blue Cross database to obtain information on prescription drug use for the exposure period July 1, 2000 to March 31, 2003. All residents of Alberta aged 65 years and older receive insured health services including coverage for prescription drugs. NSAID exposure (for the period 1 year before the initial glomerular filtration rate measurement up to March 31, 2003) was defined using 2 approaches. The first was a broad approach based on the

presence or absence of exposure, while the second included a measure of the cumulative dose of NSAID received during the exposure period. For the broad categorization, there were 4 mutually exclusive categories: nonusers, which had no use of any NSAID; nonselective NSAIDs and COX-2 inhibitors combined, at least one prescription for a nonselective NSAID, as well as at least one prescription for a COX-2 inhibitor; nonselective NSAIDs only, at least one prescription for a nonselective NSAID, with no prescriptions for COX-2 inhibitors; COX-2 inhibitors only, at least one prescription for a COX-2 inhibitor with no prescription for a nonselective NSAID.

The second approach to the exposure definition took into account the cumulative NSAID dose, using the anatomical chemical therapeutic code and defined daily dose[20] to standardize NSAID exposure in the following manner:

Drug exposure = drug strength * drug quantity/defined daily dose

Total drug exposure was combined to obtain a cumulative dose of NSAID exposure for each subject and was categorized into nonusers (no use of any NSAID during the study period); low-dose users (cumulative dose $<90^{th}$ percentile); and high-dose users (cumulative dose $\geq 90^{th}$ percentile). Aspirin was excluded from the exposure classification as it is routinely available over the counter and, therefore, was not captured in the Alberta Blue Cross database.

Measure of Covariates

Other variables of interest included patient age and sex, diabetes, and overall co-morbidity status. Subjects were identified as having diabetes if they received at least 1 prescription for insulin or an oral hypoglycemic agent in the year before their first serum creatinine measurement. A measurement of comorbidity status, based on the use of prescription drugs, was calculated using the Chronic Disease Score (CDS) as described by Clark et al.[21] The CDS is a validated weighted index of prescription medications, whereby higher scores are a result of more classes of medications dispensed, especially medications used to treat serious diseases.

Statistical Methods

Baseline characteristics by type of NSAID user are presented as means and standard deviations for normally distributed continuous variables and percent prevalence for dichotomous variables. Given the skewed nature of the comorbidity score, these data are presented as median with interquartile range. The statistical significance of the differences in baseline characteristics across categories of NSAID use was determined by chi-squared test, analysis of variance, and Kruskal-Wallis analysis, where appropriate. The association between NSAID use and the risk of rapid progression was assessed using multivariate logistic regression, adjusting for age, sex, baseline glomerular filtration rate, diabetes and comorbidity score. Similar analyses were performed using cumulative NSAID dose as a categorical independent variable, using non-NSAID users as the reference group. Finally, multiple linear regression analyses were undertaken to assess the association of cumulative NSAID exposure (defined daily dose as a continuous variable) with decline in mean glomerular filtration rate. Given their clinical importance, age, sex, baseline glomerular filtration rate, diabetes, and comorbidity score were included in all adjusted models. Assumptions for the logistic and linear regression models were tested and met. All analyses were conducted using SAS (version 8.01, SAS Institute Inc., Cary, NC) or STATA (version 8, STATA Corp., College Station, Tex).

RESULTS

There were 12,641 subjects ≥66 years of age identified who had at least 1 outpatient measurement of serum creatinine in each of the 2 defined time periods. As outlined in Figure 1, a total of 2545 patients were excluded as they did not meet the inclusion criterion, for a final study cohort of 10,184.

Baseline subject characteristics by type of NSAID are shown in Table 1. Baseline subject characteristics varied by type of NSAID, with traditional NSAID users tending to be younger, male, and have a lower comorbidity score and mean glomerular filtration rate than COX-2 inhibitor users and the combined NSAID and COX-2 inhibitor users. NSAID use was inversely associated with the subject's age and comorbidity score and directly associated with a higher mean baseline glomerular filtration rate. Females were more likely than males to use any NSAID.

There were 1353 (13.3%) subjects who experienced the primary outcome of a decrease in glomerular filtration rate ≥15 mL/min/1.73 m^2 over a median of 2.75 years follow-up. In the multivariate logistic regression analysis with the NSAID type as a categorical variable, there was a significant interaction between mean glomerular filtration rate and NSAID type ($P = .03$). Results of this analysis are therefore presented stratified by patient mean glomerular filtration rate (Table 2). In this analysis, among subjects with a mean glomerular filtration rate of 60-89 mL/min/1.73m^2, COX-2 inhibitor users had a 25% increased risk of rapid progression of kidney disease (odds ratio [OR] 1.25, 95% confidence interval [CI], 1.05-1.47) and traditional NSAID users a 29% increased risk (OR 1.29, 95% CI, 1.02-1.63) compared with non-NSAID users. There was no association between NSAID use and rapid progression of chronic kidney disease for the other 2 categories of mean glomerular filtration rate.

NSAID Cumulative Dose and Chronic Kidney Disease Progression

Figure 2 illustrates the distribution of NSAID cumulative dose (defined daily dose) for study subjects that were exposed to at least one NSAID or COX-2 inhibitor. After adjusting for age, sex, mean glomerular filtration rate, diabetes, and comorbidity, high dose NSAID users (cumulative

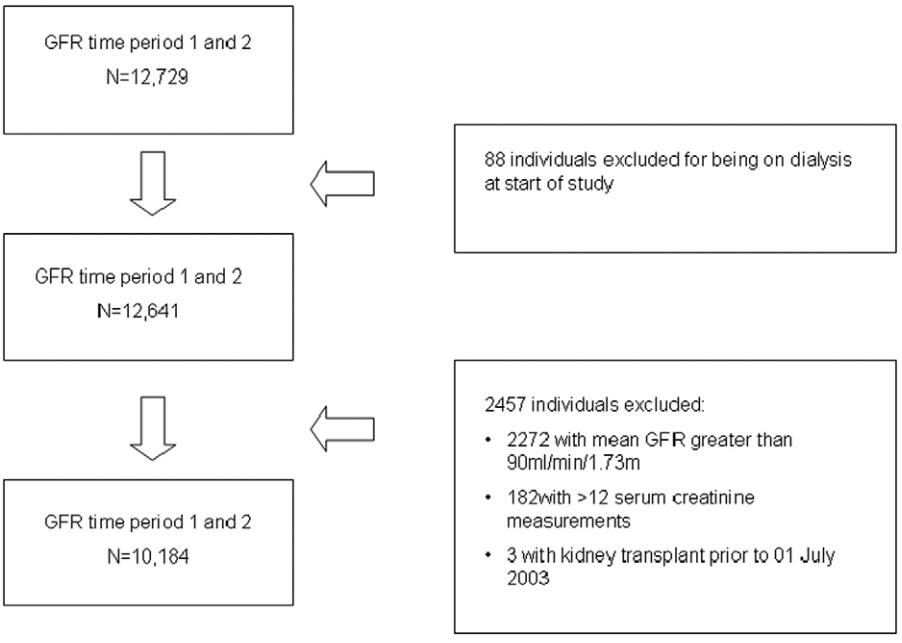

Figure 1 Formation of study cohort and reasons for exclusion (GFR = glomerular filtration rate).

dose ≥90th percentile for all subjects) were 26% more likely to develop the primary outcome than nonusers (OR 1.26, 95% CI, 1.04-1.53). The relationship between NSAID cumulative dose and progression of chronic kidney disease was further explored in multiple linear regression analysis with change in mean glomerular filtration rate as the dependent variable, adjusting for study mean glomerular filtration rate, age, sex, diabetes and comorbidity. For each 100-unit

Table 1 Baseline Subject Characteristics by NSAID Use

Characteristic	Non-NSAID Users (n = 5304)	Nonselective NSAID and COX-2 Inhibitor Users (n = 1167)	Nonselective NSAID Users Only (n = 1110)	COX-2 Inhibitor Users Only (n = 2603)	*P* Value
Age, years	76.3 ± 6.9	75.3 ± 6.2	74.9 ± 6.3	76.2 ± 6.5	<.0001
Females (%)	54.8	60.3	50.6	64.2	<.0001
Glomerular filtration rate, mL/min/1.73m^2	64.5 ± 16.9	63.3 ± 16.1	62.4 ± 17.5	64.5 ± 16.2	.0004
Chronic Disease Score	2011 (1432 – 2772)	2520 (1864 – 3468)	2283 (1590 – 3182)	2304 (1590 – 3262)	<.0001
Diabetes (%)	16.0	17.7	18.7	16.7	.13

Age and glomerular filtration rate expressed as mean ± standard deviation; Chronic Disease Score expressed as median and interquartile range.

Table 2 Multivariate Adjusted Odds Ratios for Rapid Progression of Kidney Disease and Type of NSAID Use, by Stage of Kidney Disease

	Stage of Chronic Kidney Disease (Glomerular Filtration Rate in mL/min/1.73m^2)					
	Glomerular filtration rate 60-89		Glomerular filtration rate 30-59		Glomerular filtration rate < 30	
Category of NSAID exposure	n	Odds ratio* (95% CI)	n	Odds ratio* (95% CI)	n	Odds ratio* (95% CI)
No NSAID se	3475	Ref	1590	Ref	239	Ref
Nonselective NSAID and COX-2 inhibitor use	722	1.10 (0.87-1.40)	411	0.82 (0.59-1.15)	34	2.03 (0.61-6.71)
Nonselective NSAID use only	671	1.29 (1.02-1.63)	374	0.75 (0.52-1.06)	65	1.53 (0.60-3.92)
COX-2 inhibitor use only	1705	1.25 (1.05-1.47)	816	0.85 (0.66-1.11)	82	1.17 (0.47-2.89)

*Adjusted for age, sex, diabetes, baseline glomerular filtration rate and comorbidity score.

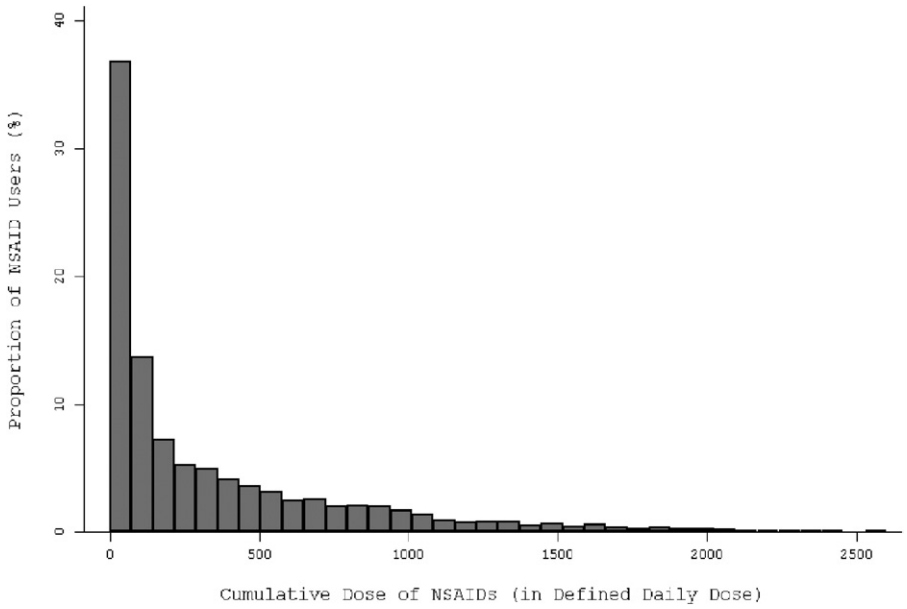

Figure 2 Distribution of NSAID cumulative dose (defined daily dose) for subjects exposed to at least one NSAID or COX-2 inhibitor.

increase in defined daily dose there was an associated decrease in glomerular filtration rate of 0.08 mL/min/1.73 m^2 (95% CI, 0.01 to 0.16; $P = .04$) over the study period. Figure 3 illustrates this linear relationship between NSAID cumulative dose and change in mean glomerular filtration rate.

DISCUSSION

In this prospective community-based study of over 10,000 elderly subjects a small, but statistically significant, increased risk of rapid progression of chronic kidney disease was found only among subjects with a baseline mean glomerular filtration rate between 60 and 89 mL/min/1.73 m^2 who were exposed to nonselective NSAIDs only or to COX-2 inhibitors only. NSAID use was not associated with an increased risk of rapid progression of chronic kidney disease for subjects with lower levels of kidney function, nor was any risk differential identified between the nonselective and selective NSAIDs. This data should be interpreted with caution given the conservative nature of the

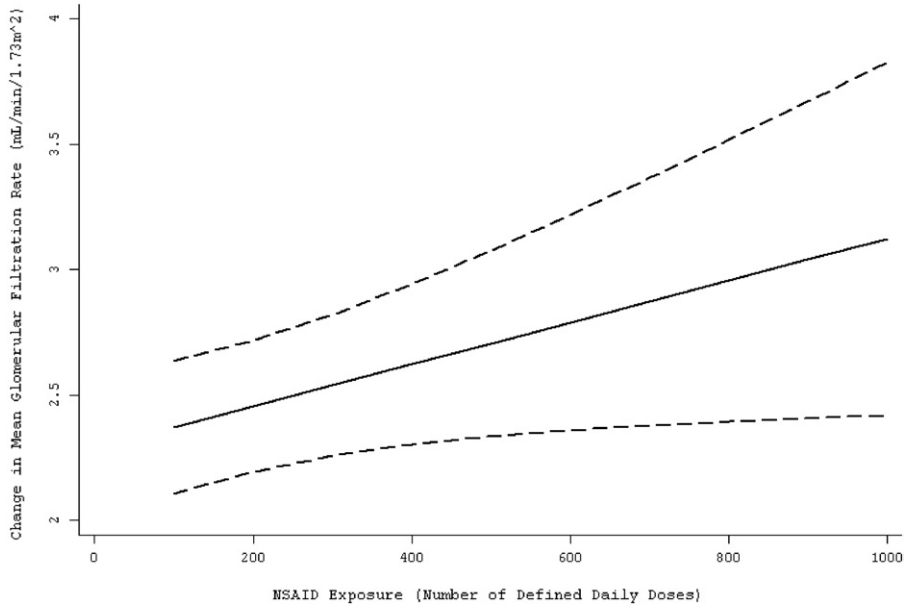

Figure 3 Relationship between NSAID exposure (defined daily dose) and change in mean glomerular filtration rate (mL/min/1.73m^2), adjusting for study mean glomerular filtration rate, age, sex, diabetes and comorbidity (solid continuous line represents predicted point estimates using linear regression, interrupted line represents 95% prediction intervals around these estimates).

Table 3 Quantification of High Daily Use (Upper Decile of Defined Daily Dose) for Several Common NSAIDs

NSAID	Dose per Tablet (mg)	Total Quantity for Study Duration (n tablets)	Mean Tablets per Day (n)	Mean Dose per Day (mg)
Celecoxib	100	1180	1.2	120
Celecoxib	200	590	0.6	120
Rofecoxib	12.5	1180	1.2	15
Rofecoxib	25	590	0.6	15
Naproxen	250	1180	1.2	300
Diclofenac	25	2360	2.3	60
Diclofenac	50	1180	1.2	60
Ibuprofen	200	3540	3.5	700

analysis. Many patients classified as NSAID users had very limited exposure to NSAIDs, thus increasing the probability of missing an important association between prolonged use of NSAIDs and deterioration in kidney function

Supporting this argument was the effect of NSAID cumulative dose on both rapid chronic kidney disease progression and change in mean glomerular filtration rate. In this analysis, high NSAID use, defined as the upper 90th percentile of defined daily dose, was associated with a 26% increase in risk of rapid progression, compared with non-NSAID use. To put this into context, Table 3 provides examples of several NSAID quantities that would be defined as "high NSAID use." These examples assume exposure to the NSAID for a duration of 2.75 years. For example, a patient consuming on average 120 mg of celecoxib per day for 1004 days would be defined as having high exposure. This finding was further supported by the linear regression analysis whereby each 100 increment in NSAID defined daily dose was associated with a decrease in mean glomerular filtration rate of 0.08 mL/min/1.73 m^2. A defined daily dose of 100 is equivalent to 100 tablets of celecoxib 200 mg, or 600 tablets of ibuprofen 200 mg.

The dose response effect seen in this study is consistent with the findings of Perneger et al (n = 1077), where the risk of end-stage renal disease was increased more than 8-fold with high lifetime NSAID use (>5000 tablets) compared with subjects using NSAIDs infrequently.[11] Sandler et al (n = 554) also found a 2-fold increased risk of end-stage renal disease in patients reporting daily NSAID use.[9] Several studies of NSAID use and incident acute renal failure have also reported a dose response effect.[22-24]

Despite the results from Perneger[11] and Sandler,[9] the effect of NSAID use on chronic kidney disease progression remains controversial, largely because of 2 recent publications. In analysis of data from the Nurses' Health Study (n = 1697), Curhan and colleagues found no association between NSAID exposure and the 11-year risk of kidney function decline.[14] Given that NSAID exposure was determined by questionnaire, it is possible that recall bias affected the study results. Furthermore, the study participants were all female, younger in age (mean age 56.5 years), and had better baseline kidney function (mean glomerular filtration rate 88 mL/min/1.73 m^2) than this study cohort, and were therefore at substantially less risk for kidney function decline. A 14-year follow-up study of 4494 male physicians within the United States also failed to show any association between NSAID use and kidney function loss.[15] Similar to the Nurses' Health Study, questionnaires were used to determine prior NSAID exposure, and study subjects were at a very low risk for progressive kidney disease (mean age 48.9 years and baseline percent diabetes 1.1%).

Although the current study provides important information on the relationship between NSAID exposure and decrease in kidney function, the results should be interpreted within the context of the study's limitations. Specifically, glomerular filtration rate was not measured directly but was estimated using a serum creatinine measurement. Also, there was no attempt to calibrate serum creatinine measurements with the Cleveland Clinic laboratory from which the MDRD equation was derived. Such calibration is critical to estimate prevalence of kidney disease. The primary interest, however, was in the *change* of kidney function, whereby such calibration was deemed unnecessary.

There are also limitations as a result of the study design. First, exposure assessment ceased on March 31, 2003, while the outcome assessment was undertaken after that (July 01, 2003 to December 31, 2003). As the study was interested in the chronic long-term effects of NSAID use, this is unlikely to adversely bias the study results. In fact, this difference in the timing of exposure and outcome assessment would likely reduce any impact of acute renal failure episodes on the study outcomes. Second, the use of laboratory data to define the study cohort limited the study to subjects who sought medical care and had a serum creatinine measurement obtained (bias by indication). As the study sample was based on the elderly, who are more likely to access the healthcare system and have laboratory testing performed, this is unlikely to substantially bias the study results. This is further supported by a similar age distribution in this study to that reported for the general population of the Calgary Health Region (data not shown). Data from a cohort identified by laboratory-based case finding is also easily generalized to primary care practice. Third, although the prescription drug database eliminates recall bias, exposure bias may still exist. This may occur if the dispensed NSAID is not consumed or if over-the-counter NSAIDs, such as ibupro-

fen, are used. This potential for exposure misclassification however, would be expected to bias the results towards the null. Finally, the possibility of residual confounding cannot be excluded. The results of the study were unable to be adjusted directly for blood pressure, although antihypertensive medication use contributes to the comorbidity score. Also, the possibility that NSAID use was triggered by a predisposing condition that directly impacts kidney function cannot be excluded.

Despite these limitations, the current study has several strengths. First, the study involved many NSAIDs used in today's clinical practice, unlike prior reports. The study was able to assess the effects of nonselective NSAID and COX-2 inhibitor exposure separately, an assessment not possible in previous studies. Second, recall bias was eliminated with the use of computerized drug prescription data. In contrast, several other large observational studies used questionnaires to determine exposure to NSAIDs.[9,11-14] Third, the size of the cohort (over 10,000 elderly subjects) and its community-based setting increases the generalizability of the study results to community-dwelling elderly individuals. This is particularly relevant given the prevalence of chronic kidney disease and musculoskeletal disorders in this population.

In conclusion, the results of this study show that high cumulative NSAID exposure is associated with an increased risk for rapid chronic kidney disease progression, as well as a decrease in mean glomerular filtration rate in the setting of a community-based elderly population. For older adult patients with chronic kidney disease, these results suggest that nonselective NSAIDs and selective COX-2 inhibitors should be used cautiously and chronic exposure to any NSAID should be avoided.

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