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Nonsteroidal Antiinflammatory Drugs and Acute Renal Failure in Elderly Persons

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Renal prostaglandin inhibition by nonsteroidal antiinflammatory drugs (NSAIDs) may decrease renal function, especially under conditions of low effective circulating volume. To evaluate the risk of important deterioration of renal function due to this effect, the authors performed a nested case-control study using Tennessee Medicaid enrollees aged ≥65 years in 1987–1991. Cases were patients who had been hospitalized with community-acquired acute renal failure; they were selected on the basis of medical record review of Medicaid enrollees with selected discharge diagnoses. Information on the timing, duration, and dose of prescription NSAIDs used, demographic factors, and comorbidity was gathered from computerized Medicaid-Medicare data files. Of the 1,799 patients with acute renal failure (4.51 hospitalizations per 1,000 person-years), 18.1% were current users of prescription NSAIDs as compared with 11.3% of 9,899 randomly selected population controls. After control for demographic factors and comorbidity, use of NSAIDs increased the risk of acute renal failure 58% (adjusted odds ratio = 1.58; 95% confidence interval (CI): 1.34, 1.86). For ibuprofen, which accounted for 35% of NSAID use, odds ratios associated with dosages of ≤1,200 mg/day, >1,200–<2,400 mg/day, and ≥2,400 mg/day were 0.94 (95% CI: 0.58, 1.51), 1.89 (95% CI: 1.34, 2.67), and 2.32 (95% CI: 1.45, 3.71), respectively (test for linear trend: $p = 0.009$). Prescription NSAID use resulted in an estimated 25 excess hospitalizations associated with renal failure per 10,000 years of use. Thus, NSAIDs represent a relatively uncommon but avoidable cause of acute renal failure in frail elderly persons. *Am J Epidemiol* 2000;151:488–96.

aged; anti-inflammatory agents, non-steroidal; case-control studies; incidence; kidney failure, acute; risk factors

Nonsteroidal antiinflammatory drugs (NSAIDs) produce multiple undesirable renal effects. Most of these effects are attributable to inhibition of the synthesis of renal prostaglandins (1, 2), which influence cortical blood flow, glomerular filtration rate, and salt and water excretion (3). Virtually all NSAIDs can both decrease renal prostaglandin production and cause deterioration in renal function under conditions of decreased effective circulating volume (4–8), with a frequency of up to 13 percent in frail elderly nursing home patients (9).

Despite experimental studies documenting adverse renal effects of NSAIDs and case reports of dramatic NSAID-associated deterioration in renal function (10, 11), little is known about the contribution of NSAIDs to the burden of acute renal disease or the risks to individual NSAID users. Therefore, we studied a large population of elderly persons to determine the role of NSAIDs in acute deterioration of renal function. This report focuses on the development of pre-renal failure or renal failure for which inhibition of renal prostaglandins is likely to be important. Thus, the present analysis excludes interstitial nephritis, which has been associated with NSAID use through another mechanism (12), and other specific causes of renal failure (such as obstruction) for which NSAIDs are unlikely to play a major role.

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Abbreviations: CI, confidence interval; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.

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MATERIALS AND METHODS

Sources of data and population

Tennessee Medicaid is a joint federal-state program which insures approximately 15 percent of the state's population aged 65 years or older, with eligibility based on income and illness. Medicaid enrollment files identify dates of coverage, date of birth, gender, ethnicity, and county of residence for all enrollees. Linked Medicaid-Medicare-death certificate files (13) include hospital admission and discharge dates, diagnoses, and

underlying causes of death coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) (14). The pharmacy file contains records of all prescriptions for drugs on the Medicaid formulary that are filled for outpatients and nursing home residents, the date on which each drug is dispensed, the number of days' supply (maximum 30 days), and the number of pills dispensed. The nursing home file includes the beginning and ending dates of each nursing home stay.

The study population consisted of all Tennessee Medicaid enrollees aged ≥65 years in 1987–1991 who had been enrolled for at least 1 year (to assure a 1-year medical history). To reduce the costs of traveling to review medical records, we excluded residents of 19 remote counties (out of a total of 95 counties).

Identification of persons hospitalized with acute renal failure (cases)

To identify first hospital admissions for acute renal failure, we screened all hospital discharge codes and death certificates for acute renal failure (ICD-9-CM code 584), acute glomerulonephritis (code 580), nephrotic syndrome (code 581), chronic glomerulonephritis (code 582), other nephritis (code 583), chronic renal failure (code 585), renal failure, unspecified (code 586), hypertensive renal disease (codes 403, 404, and 587), diabetes mellitus with renal disease (code 250.4), pyelonephritis (codes 590.0 and 590.8), gouty nephropathy (code 274.1), cystic kidney disease (code 753.1), and other disorders of kidney function (codes 588, 589, and 593.9). Of the 7,364 persons with an eligible screening code, we excluded 127 persons identified by death certificate who had had no recent hospitalization and 92 people for whom the date of the initial hospitalization was uncertain (the screened hospitalization possibly represented a transfer). We sought the hospitalization records of the remaining 7,145 patients for review.

Case definition

Acute renal failure was defined by an admission creatinine level of ≥180 μmol/liter (2 mg/dl) and either a ≥20 percent increase in creatinine from a baseline value or a ≥20 percent decline in creatinine during hospitalization (representing recovery from renal failure), based on criteria used in prior studies (15, 16). Excluded were patients with end-stage renal disease (persons on dialysis or scheduled for access placement) and those with hospital-acquired acute renal failure. Trained nurses abstracted data from the charts of all potential cases using a structured instrument. Abstracts were independently reviewed by an internist (M. R. G.) and a nephrologist (A. Y.), masked as to exposure status, to classify persons with renal failure according to predetermined criteria. Disagreements were resolved by consensus.

Of the 7,145 persons screened on the basis of discharge codes indicating a renal condition, 2,314 (32 percent) met our definition of community-acquired acute renal failure. Reasons for exclusions included: an unavailable chart (11 percent), a lack of creatinine data or poor quality of other data (5 percent), an initial creatinine level of <180 μmol/liter (34 percent), end-stage renal disease (4 percent), stable chronic renal insufficiency (baseline creatinine level of >122 μmol/liter (1.4 mg/dl), without a 20 percent increase) (9 percent), and probable stable chronic renal insufficiency (no creatinine measurement in the past year but other evidence of chronic renal failure, such as bilateral small kidneys, and no change in creatinine level in the hospital) (6 percent).

Of the 2,314 patients with acute renal failure, we excluded from further analysis 515 patients (22 percent) with diagnoses of specific acute renal failure for whom inhibition of prostaglandins was unlikely to play a major role, including obstruction (12 percent); interstitial nephritis (4 percent); and other specific diagnoses, including glomerulonephritis, nephrotic syndrome, ischemic renal disease, rhabdomyolysis, and hepatorenal syndrome (3 percent), as well as those whose diagnoses were unclassifiable (3 percent).

The 1,799 remaining patients were classified as having pre-renal failure or renal failure using definitions similar to those used by Miller et al. (15). Pre-renal failure was defined by the development of acute renal failure associated with volume depletion, congestive heart failure, or transient hypotension, the return of creatinine levels toward normal values within 3 days after correction of the hemodynamic problems, and the absence of cellular casts. Intrinsic renal failure without another specific cause and including acute tubular necrosis was defined as progression of renal failure or a sustained increase in creatinine levels at day 3 after correction of hemodynamic causes, or development of anuria. The 122 (7 percent) cases with features of both pre-renal failure and intrinsic renal failure for which there was insufficient data to distinguish between the two were classified as indeterminate.

Of the 1,799 study patients, 761 (42 percent) were classified as having new renal disease. Of these, 34 percent had had a creatinine level of ≤122 μmol/liter within the previous 6 months; an additional 35 percent had a return to that value after hospital admission; and another 9 percent had had a creatinine level of ≤122 μmol/liter within the past 2 years. There was no other evidence in the medical record to indicate renal failure in these persons or in the remaining 22 percent who

did not have a documented prior creatinine value. There were 1,038 (58 percent) patients who were classified as having chronic renal failure with a superimposed acute deterioration based on a prior creatinine level of >122 μmol/liter, a physician-documented history of chronic renal failure, or imaging studies compatible with chronic renal disease.

Control selection

A date from 1987 through 1991 was randomly generated for all persons in the study population without a screening hospitalization. From those meeting eligibility requirements on their randomly selected date, 10,000 controls were randomly selected; the random date served as the index date for the control population. We excluded controls who were hospitalized on their index date ($n = 92$) or whose demographic data were incomplete ($n = 9$); this left 9,899 controls, who should have reflected the characteristics of the study base population (17).

Prescription NSAID exposure

To categorize exposure to nonaspirin prescription NSAIDs according to timing of use and specific drug and dosage, we identified all prescriptions filled for these drugs in the 365 days before the index date (date of initial hospitalization for cases). We defined four categories of exposure by timing of use: 1) current users' supply of NSAIDs included the index date; 2) recent and 3) past users' supply of NSAIDs ended 1–30 and 31–365 days prior to the index date, respectively; and 4) nonusers had filled no NSAID prescriptions in the 365 days prior to the index date. For each individual NSAID, low dosages were defined as those less than or equal to the minimum starting dose recommended for treatment of arthritis; high dosages were defined as those greater than or equal to the maximum starting dose; and medium dosages were defined as those between the above two levels (18). The dosage for current users was determined by dividing the total dose of the specific drug by the prescribed days' supply. Although nonprescription NSAIDs were available commercially during the study period, these drugs were available to the patients free of charge through the Medicaid program. Hospital medical records indicated NSAID use by 4 percent and 72 percent of patients classified as nonusers and current users, respectively.

Other variables

Age, gender, ethnicity, residence, nursing home status, index year, and use of other medical services and drugs were determined from the Medicaid files (table 1). We grouped users of a number of potentially nephrotoxic agents into a single category and included in this category those with a new prescription for cimetidine because of the ability of this agent to increase creatinine levels acutely ("other selected exposures" in table 1). Other factors (prevalence among controls) not listed in table 1 but controlled for in the analysis included prescriptions filled in the past year for the following: drugs associated with heart disease (35 percent), including digoxin, antiarrhythmic agents, nitrates, coumarin, or lipid-lowering agents; drugs associated with hypertension (32 percent), including beta blockers, calcium channel blockers, vasodilators, or sympatholytic agents; drugs associated with diabetes mellitus (13 percent), including insulin or oral hypoglycemic agents; drugs associated with lung disease (12 percent), including bronchodilators, inhaled steroids, ipratropium, or cromolyn; and drugs associated with immune suppression (2 percent), including chemotherapeutic agents or oral corticosteroids (at least 60 days' supply). Current use of prescription acetaminophen (2 percent) and aspirin (1 percent) was ascertained from Medicaid files; however, these measures underestimate use because of the absence of information on nonprescription drugs.

Analysis

The incidence of acute renal failure was calculated by dividing the number of persons with renal failure by the sum of the midyear populations for each study year, to estimate person-time. Relative risk of renal failure associated with NSAID use was estimated from odds ratios derived from a logistic regression model (19) in which nonuse of NSAIDs in the past year was the reference category, and which included age in years (continuous variable), all other variables listed in table 1, and the additional variables defined above. Variables not listed in table 1 were weak (odds ratios <1.25) independent predictors of acute renal failure (heart disease and hypertension) or were not associated with acute renal failure in our final model (diabetes mellitus, lung disease, immune suppression, and current use of aspirin or acetaminophen).

RESULTS

We identified 1,799 persons aged ≥65 years with community-acquired pre-renal failure or intrinsic renal failure, yielding an average annual incidence of 4.51 hospitalizations per 1,000 person-years. Patients had a median length of stay of 8 days (range, 1–100). In-hospital fatality was 29 percent, and another 7 percent of patients died within 30 days of admission. In-hospital

TABLE 1. Characteristics of patients hospitalized with acute renal failure (cases) and a random sample of Tennessee Medicaid enrollees aged ≥65 years (controls), 1987–1991

Characteristic	Cases		Controls	
	%	No.	%	No.
All subjects	100	1,799	100	9,899
Age (years)				
65–74	20	366	40	3,947
75–84	39	708	39	3,905
≥85	40	725	21	2,047
Gender				
Female	69	1,242	77	7,592
Male	31	557	23	2,307
Ethnicity*				
White	55	990	62	6,093
African-American	38	680	29	2,841
Nursing home resident				
Yes	46	831	20	1,934
No	54	968	80	7,965
Recent hospitalization				
Within 30 days	21	378	3	319
Within 31–365 days	33	601	22	2,168
None in the past year	46	820	75	7,412
Use of loop diuretic within the past 30 days				
Yes	35	638	13	1,330
No	65	1,161	87	8,569
Use of thiazide within the past 30 days				
Yes	26	476	22	2,160
No	74	1,323	78	7,739
Use of ACE† inhibitor within the past 30 days				
Yes	18	315	7	695
No	82	1,484	93	9,204
Use of antibiotics within the past 30 days				
Yes	32	582	13	1,254
No	68	1,217	87	8,645
Other selected exposures‡				
Yes	10	172	3	314
No	90	1,627	97	9,585

* Not included were 129 cases and 965 controls with other or unknown ethnicity.
† ACE, angiotensin-converting enzyme.
‡ Prescription for allopurinol, cyclosporin, gold, sulfinpyrazone, or penicillamine, first prescription for cimetidine in the past 60 days, or procedure code indicating intravenous radiocontrast within the past 30 days.

fatality was higher for those with intrinsic renal failure (59 percent) than for those with pre-renal failure (16 percent). Twenty-eight percent of patients underwent a diagnostic kidney ultrasonogram, scan, or biopsy during their hospital stay; 59 patients (3 percent) underwent acute dialysis, and 15 of them were subsequently dialyzed chronically. Presenting symptoms included nausea, vomiting and/or decreased appetite (57 percent), altered mental status (42 percent), new or increased fatigue (36 percent), shortness of breath (28 percent), and anuria or oliguria (9 percent). Diagnoses upon admission included dehydration (57 percent), suspected (18 percent) or confirmed (29 percent) urinary tract infection, suspected (21 percent) or confirmed (7 percent) bacteremia, congestive heart failure (17 percent), and pneumonia (15 percent).

Patients with acute renal failure differed from controls in several important ways (table 1). The most notable demographic differences were the proportions of patients with renal failure who were aged 85 years or older (40 percent vs. 21 percent) and were nursing home residents (46 percent vs. 20 percent). Patients admitted with acute renal failure also had greater comorbidity than population controls, with a greater

prevalence of recent hospitalization and greater use of diuretics, angiotensin-converting enzyme inhibitors, and antibiotics. Patients had had greater exposure to a number of agents known to be toxic to the kidney or to raise serum creatinine levels acutely.

Of the 1,799 patients with acute renal failure, 18.1 percent were current users of NSAIDs as compared with 11.3 percent of controls. Current NSAID use increased the risk of acute renal failure 58 percent (adjusted odds ratio (OR) = 1.58; 95 percent confidence interval (CI): 1.34, 1.86) (table 2). The prevalence of NSAID use in this population (controls) varied from a low of 8 percent among men and persons aged ≥85 years to a high of 17–18 percent among persons using diuretics. However, within each demographic and medical care stratum, the use of NSAIDs was associated with an increased risk of acute renal failure. Although, as expected, medications associated with cardiovascular disease, diabetes mellitus, and infection were associated with acute renal failure, there was no association between medications used to treat lung disease or cancer and acute renal failure (data not shown). In addition, persons who had stopped using NSAIDs within the previous 30 days and those with other use of NSAIDs in the past year did not have increased risks of renal failure (OR = 0.84 (95 percent CI: 0.55, 1.27) and OR = 0.87 (95 percent CI: 0.74, 1.01), respectively).

NSAIDs were associated with similar elevations of risk for pre-renal failure among those without underlying chronic renal insufficiency (OR = 1.65; 95 percent CI: 1.28, 2.12) and those with it (OR = 1.72; 95 percent CI: 1.37, 2.16) (table 3). NSAIDs significantly increased the risk of intrinsic renal failure only among persons with chronic renal insufficiency (OR = 1.83; 95 percent CI: 1.26, 2.64). The modest elevation in risk associated with new-onset intrinsic renal failure was not statistically significant (OR = 1.20; 95 percent CI: 0.74, 1.95).

We explored whether use of NSAIDs was a nonspecific marker of illness by examining the association of NSAIDs with two other categories of hospitalization that had one of the broad screening discharge codes (see "Materials and Methods") but did not meet our definition of community-acquired acute renal failure (table 3). The charts of patients with an initial creatinine level of <180 μmol/liter were not reviewed, but they probably represented patients with a broad range of acute and chronic renal conditions. The difference in current NSAID use between these patients and population controls was not statistically significant (OR = 1.16; 95 percent CI: 0.99, 1.34). Patients admitted to the hospital with a creatinine level of ≥180 μmol/liter who had no evidence of acute renal failure upon chart review were classified as having stable chronic renal failure (table 3). The prevalences of current NSAID use were similar in these patients and population controls (OR = 1.04; 95 percent CI: 0.79, 1.38).

In this population, 6 percent of current NSAID users had first begun using the drugs in the past 30 days (new users); an additional 33 percent had less than 180 days' use in the past year (short term users), and 61 percent had more than 180 days' use (long term users). Risk was highest among new users (OR = 2.83; 95 percent CI: 1.65, 4.85) but was similar among short term (OR = 1.68; 95 percent CI: 1.30, 2.18) and long term (OR = 1.55; 95 percent CI: 1.28, 1.89) users.

We examined the risk of acute renal failure among current users of individual NSAIDs (table 4). Ibuprofen accounted for 35 percent of NSAID use in this population, and it was associated with a 63 percent increase in risk compared with nonuse of any NSAID in the past year (OR = 1.63; 95 percent CI: 1.23, 2.08). Users of piroxicam, fenoprofen, and indomethacin and persons who had been prescribed more than one NSAID concurrently also had significantly elevated risks of acute renal failure. Use of naproxen and nonaspirin salicylates was relatively high in this population, but these drugs were not associated with renal failure; however, numbers of users were too small to rule out a 50 percent increase in risk. Use of other NSAIDs was relatively low, and confidence intervals around the estimates were wide.

We examined dose-response effects of the three individual NSAIDs which were significantly associated with acute renal failure and which had sufficient variability in dosage for assessment of three dose levels. Current use of ibuprofen at average daily doses of ≤1,200 mg (31 percent of current users), >1,200–<2,400 mg (45 percent), and ≥2,400 mg (24 percent) was associated with odds ratios of 0.94 (95 percent CI: 0.58, 1.51), 1.89 (95 percent CI: 1.34, 2.67), and 2.32 (95 percent CI: 1.45, 3.71), respectively (test for linear trend: $p = 0.009$). Current use of fenoprofen at daily doses of ≤900 mg (19 percent), >900–<2,400 mg (71 percent), and ≥2,400 mg (10 percent) was associated with odds ratios of 1.39 (95 percent CI: 0.41, 4.71), 1.81 (95 percent CI: 1.00, 3.27), and 2.38 (95 percent CI: 0.42, 13.54), respectively ($p = 0.557$). Current use of indomethacin at daily doses of ≤50 mg (13 percent), >50–<150 mg (61 percent), and ≥150 mg (25 percent) was associated with odds ratios of 2.98 (95 percent CI: 0.74, 11.94), 1.89 (95 percent CI: 0.97, 3.70), and 3.66 (95 percent CI: 1.34, 10.02), respectively ($p = 0.893$). In this population, 91 percent of piroxicam use was at a dose of 20 mg/day; prescription of a lower dose was not associated with a lower risk estimate. As table 4 shows, naproxen and nonaspirin salicylates were not

TABLE 2. Stratum-specific current use of NSAIDs* and associated adjusted odds ratios for hospitalization for acute renal failure among Tennessee Medicaid enrollees aged ≥65 years, 1987–1991

Characteristic	NSAID use				Odds ratio†	95% confidence interval
	Cases		Controls			
	%	No.	%	No.		
All subjects	18	326	11	1,119	1.58	1.34, 1.86
Age (years)						
65–74	19	70	12	462	1.49	1.07, 2.08
75–84	19	133	12	485	1.39	1.08, 1.79
≥85	17	123	8	172	2.14	1.60, 2.85
Gender						
Female	20	252	12	926	1.59	1.32, 1.91
Male	13	74	8	193	1.48	1.08, 2.11
Ethnicity‡						
White	17	173	11	691	1.49	1.22, 1.86
African-American	18	122	11	318	1.66	1.25, 2.19
Nursing home resident						
Yes	17	141	13	243	1.58	1.23, 2.05
No	19	185	11	876	1.46	1.19, 1.80
Recent hospitalization						
Within 30 days	15	57	12	38	1.55	0.93, 2.58
Within 31–365 days	13	79	11	244	1.21	0.88, 1.65
None in the past year	23	190	11	837	1.78	1.45, 2.19
Use of loop diuretic within the past 30 days						
Yes	20	127	17	225	1.64	1.22, 2.20
No	17	199	10	894	1.47	1.20, 1.79
Use of thiazide within the past 30 days						
Yes	28	131	18	392	1.94	1.46, 2.58
No	15	195	9	727	1.38	1.13, 1.69
Use of ACE* inhibitor within the past 30 days						
Yes	17	54	15	101	1.32	0.83, 1.96
No	18	272	11	1,018	1.65	1.38, 1.96
Use of antibiotics within the past 30 days						
Yes	19	109	15	190	1.61	1.17, 2.22
No	18	217	11	929	1.50	1.24, 1.81
Other selected exposures§						
Yes	27	46	21	66	2.38	1.29, 4.36
No	17	280	11	1,053	1.52	1.29, 1.81

* NSAIDs, nonsteroidal antiinflammatory drugs; ACE, angiotensin-converting enzyme.

† Odds ratios were adjusted for age (1-year intervals); for all other variables in the table; and as defined in "Materials and Methods": for year, residence, use of medications indicating heart disease, hypertension, diabetes, lung disease, or immune suppression, and current use of prescription aspirin and acetaminophen. Nonuse of NSAIDs in the past year was the reference category.

‡ Not included were 31 cases and 110 controls with other or unknown ethnicity.

§ Prescription for allopurinol, cyclosporin, gold, sulfinpyrazone, or penicillamine, first prescription for cimetidine in the past 60 days, or procedure code indicating intravenous radiocontrast within the past 30 days.

associated with development of acute renal failure; odds ratios associated with high dose naproxen (≥1,100 mg/day) and high dose salicylates (≥1,300 mg/day) were 1.25 (95 percent CI: 0.50, 3.13) and 0.78 (95 percent CI: 0.38, 1.60), respectively.

DISCUSSION

In this study, patients hospitalized with community-acquired acute renal failure were older and sicker than controls selected from the same population, with a

TABLE 3. Associations between current use of NSAIDs* and renal hospitalization among Tennessee Medicaid enrollees aged ≥65 years, 1987–1991

Hospitalization category	No.	% with use	Odds ratio†	95% confidence interval
None (controls)	9,899	11.3	1.00‡	
Acute renal failure (all cases)	1,799	18.1	1.58	1.34, 1.86
Pre-renal failure§				
New	539	19.9	1.65	1.28, 2.12
Chronic	736	18.8	1.72	1.37, 2.16
Renal failure§				
New	156	14.7	1.20	0.74, 1.95
Chronic	246	18.7	1.83	1.26, 2.64
No acute renal failure				
Creatinine level of <180 μmol/liter	2,384	13.9	1.16	0.99, 1.34
Stable chronic renal failure	624	12.7	1.04	0.79, 1.38

* NSAIDs, nonsteroidal antiinflammatory drugs.
† Nonuse of NSAIDs in the past year was the reference category. Each group of hospitalized patients was compared with population controls ("none" category). All odds ratios were adjusted for all of the variables listed in table 1.
‡ Referent.
§ Excludes 66 patients with new renal failure and 56 patients with chronic renal failure whose cases were classified as indeterminate.

TABLE 4. Associations between use of individual NSAIDs* and hospitalization for acute renal failure among Tennessee Medicaid enrollees aged ≥65 years, 1987–1991

NSAID	Current use (%)		Odds ratio†	95% confidence interval
	Cases	Controls		
Ibuprofen	6.34	3.97	1.63	1.23, 2.08
Naproxen	1.95	1.78	1.03	0.68, 1.56
Piroxicam	2.22	1.32	1.95	1.23, 2.93
Nonaspirin salicylates	0.83	0.83	0.90	0.48, 1.68
Fenoprofen	1.61	0.81	1.75	1.05, 2.92
Indomethacin	1.78	0.64	2.40	1.44, 4.00
Sulindac	0.78	0.60	1.40	0.74, 2.66
Diclofenac	0.28	0.24	1.47	0.49, 4.39
Tolmetin	0 22	0.24	0.77	0.24, 2.49
Ketoprofen	0.33	0.19	1.55	0.54, 4.45
Other single-use NSAID‡	1.00	0.43	2.24	1.19, 4.21
Two or more NSAIDs	0.78	0.25	3.35	1.54, 7.31

* NSAIDs, nonsteroidal antiinflammatory drugs.
† Nonuse of NSAIDs in the past year was the reference category. All odds ratios were adjusted for all variables listed in table 1.
‡ Includes flurbiprofen, meclofenamate, nabumetone, oxaprozin, and ketorolac.

high proportion of very old persons (>85 years), nursing home residents, and those with recent hospitalizations and other comorbidity. In analyses that controlled for these and other demographic and medical risk variables, current use of NSAIDs was associated with a 58 percent increased risk of acute renal failure. NSAIDs increased the risk of pre-renal failure among those with underlying chronic renal disease as well as those without it. NSAIDs were also associated with development of intrinsic renal failure, a much more serious outcome, but only among persons with chronic renal failure.

Our large number of cases and controls allowed for stratified analyses of subgroups of persons with and without selected important risk factors for acute renal failure (table 2). Within each stratum, persons with acute renal failure had a higher prevalence of NSAID use. In addition, stratified analyses that controlled for these variables demonstrated a consistent increase in risk associated with NSAID use.

NSAID-associated risk was highest among new users; however, most of the effect observed was associated with chronic use, the predominant pattern of use in this population. Of the six most commonly used NSAIDs, odds ratios were close to 2 for four—ibuprofen, piroxicam, fenoprofen, and indomethacin. For ibuprofen, fenoprofen, and indomethacin, where there was substantial variation in dose, risk was highest with the highest dose. Risk was also high for persons prescribed two or more NSAIDs simultaneously. For naproxen and nonaspirin salicylates, the odds ratio point estimates were close to 1, and there was no evidence for a dose-response effect. Additional studies will be needed to determine whether naproxen and salicylates are associated with a lower rate of renal effects. The numbers of users of other NSAIDs in our population were too small for us to obtain stable odd ratios.

A major strength of this study was the use of detailed pharmacy records to construct drug exposure histories that were not subject to incomplete recall or information bias. Noncompliance with filled prescriptions and use of over-the-counter NSAIDs may have caused

exposure misclassification. There are two lines of evidence suggesting that exposure misclassification was not a major problem. First, 72 percent of patients classified as current NSAID users had NSAID use recorded in their hospital charts, compared with 4 percent of those classified as nonusers. Second, among nursing home residents, compliance is excellent and use of medications not paid for by Medicaid is uncommon. The similarity of results seen in nursing home and community-dwelling residents suggests that exposure misclassification did not materially affect the validity of these findings.

Despite its relatively low strength, several lines of evidence support the causal nature of the association between NSAIDs and acute renal failure. First, the results were consistent for all age groups, for men and women, for Whites and African Americans, for community-dwelling participants and nursing home residents, and for persons with and without a variety of medical conditions. Second, the increase in risk was only present for current users of NSAIDs, not those with other patterns of NSAID use in the past year. Third, use of NSAIDs did not increase the risk of other hospitalizations with discharge diagnoses indicating renal disease that did not meet our case definition, including hospitalizations of patients with an initial creatinine level of <180 μmol/liter and of those with stable chronic renal failure. In addition, drugs used for treatment of other diseases not associated with renal failure (lung disease, cancer) were not more prevalent among persons hospitalized with acute renal failure. These findings suggest that the association with NSAIDs was not due to unmeasured factors associated with NSAIDs in particular or with prescription drug use in general. Fourth, there was a strong dose-response effect for ibuprofen, the only exposure with numbers of users sufficient to obtain precise dose estimates. Finally, the known actions of NSAIDs and the findings from three other population-based studies (16, 20, 21) support a causal association.

The higher relative risks observed in the two Saskatchewan population studies (20, 21) (table 5) probably reflect differences in case definitions of acute renal failure. These differences in case definition also explain the much lower incidence of study-defined renal failure and the resulting relatively low risk of disease attributable to NSAIDs. The case definition used by Evans et al. (16) was similar to ours, but the overall incidence of renal failure in Tayside, Scotland, was lower than that observed in the Medicaid population, which has proportionately more nursing home residents and other frail, elderly persons. Our study used a broad definition of renal failure and a population in which the incidence of such events was relatively high because of the high prevalence of comorbidity. Thus, in our population an increased risk of renal failure of

TABLE 5. Population-based studies of use of NSAIDs* and acute renal failure: case definitions and measures of association

Reference	Case definition	Population	Relative risk	95% confidence interval	Attributable incidence of hospitalization per 10,000 elder NSAID users per year
Guess et al., 1991 (20)	Specific codes: nephritis/nephropathy (n = 60)†, acute renal failure (n = 49)	All health care plan members in Saskatchewan, Canada	4.3 2.3	NA* NA	5‡
Perez Gutthann et al., 1996 (21)	Broad screening codes: confirmed idiopathic new symptomatic acute renal failure (n = 28)	All health care plan members in Saskatchewan, Canada with ≥1 filled NSAID prescription	4.1	1.5, 10.8	2
Evans et al., 1995 (16)	Specific screening codes: confirmed acute renal failure (n = 207)	All registered residents in Tayside, Scotland	2.20	1.49, 3.25	9‡
Griffin et al. (present study)	Broad screening codes: confirmed acute renal failure, other known causes excluded (n = 1,799)	Tennessee Medicaid recipients aged ≥65 years	1.58	1.34, 1.86	25

* NSAIDs, nonsteroidal antiinflammatory drugs; NA, not available.
† Numbers in parentheses, number of cases.
‡ Estimated from the authors' data.

58 percent would result in an estimated 25 excess hospitalizations per 10,000 years of NSAID use. In healthier populations, where the overall incidence of renal failure is low, attributable rates of disease would be correspondingly low.

In summary, this investigation and previous studies provide consistent evidence that NSAIDs increase the risk of acute renal failure. Renal failure of even a relatively minor degree has the potential to increase the risk of complications associated with hospitalization (22), and the development of renal failure has been shown to independently increase the odds of hospital-associated mortality nearly sixfold (23). Clinically important renal disease due to NSAID use is likely to be uncommon in healthy persons, in whom the baseline risk of acute renal failure is low. However, for patients with a higher baseline risk of new or worsening renal failure (low volume states, chronic renal failure), the 50–100 percent increase in risk associated with NSAID use may pose a substantial risk. Among such patients, NSAIDs should be avoided if possible, and should be initiated with caution at low doses and with monitoring of renal function.

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