

Nonsteroidal Anti-Inflammatory Drug-Associated Gastropathy: Incidence and Risk Factor Models

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PURPOSE: The most prevalent serious drug toxicity in the United States is increasingly recognized as gastrointestinal (GI) pathology associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The incidence of serious GI events (hospitalization or death) associated with NSAID use was therefore prospectively analyzed in patients with rheumatoid arthritis (RA) and patients with osteoarthritis.

PATIENTS, METHODS, AND RESULTS: The study consisted of 2,747 patients with RA and 1,091 patients with osteoarthritis. The yearly hospitalization incidence during NSAID treatment was 1.58% in RA patients and was similar in all five populations studied. The hazard ratio of patients taking NSAIDs to those not taking NSAIDs was 5.2. The incidence in osteoarthritis may be less. The risk of GI-related death in RA patients was 0.19% per year with NSAIDs. Multivariate analyses assessing risk factors for serious GI events were performed in the 1,694 (98 with an event) RA patients taking NSAIDs at the predictive visit. The main risk factors were higher age, use of prednisone, previous NSAID GI side effects, prior GI hospitalization, level of disability, and NSAID dose. A rule is presented that allows estimation of the risk for the individual patient with RA.

CONCLUSION: Knowledge of the risk factors for NSAID-associated gastropathy and their interrelationships provides a tool for identification of the patient at high risk and for initiation of appropriate therapeutic action.

Gastrointestinal (GI) pathology associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is increasingly recognized as the most prevalent serious drug toxicity in the United States, resulting in an estimated 2,600 deaths and 24,000 hospitalizations annually in patients with rheumatoid arthritis (RA) alone [1,2]. The predominant syndrome consists of antral prepyloric ulcers, which may eventuate in GI hemorrhage or perforation, although events in the duodenum, small bowel, and the large bowel are also seen. Ulcerations visible on endoscopy have a point prevalence of 10% to 25%, and severe erosions are seen in additional patients [3-5]. The risk of GI hospitalization has been estimated at 1% to 1.5% per year in persons taking NSAIDs [1], and the risk of death is approximately 0.13% per year in individuals treated with NSAIDs [1,6,7]. The importance of the syndrome has been emphasized by gastroenterologists [3,8,9], rheumatologists [2,5,10], and the Food and Drug Administration (FDA) [11].

Important information required for estimation of the magnitude of the problem and for development of strategies for resolution, however, has been lacking. For example, the prevalence of complications in conditions other than RA, such as osteoarthritis, has not been established. Generalizability of the observations to different practice sites has not been presented. Quantitation of likely risk factors such as prior bleeding has not been reported, and the frequency of deaths has not been confirmed by prospective study. Most importantly, while individual risk factors have been suggested by a number of investigators [1,12,13], no multivariate risk factor model that permits estimation of risk in the individual patient has been presented.

This report addresses these issues in two steps: (1) with descriptive analyses of 2,747 patients with RA followed prospectively for an average of 4 years at five ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) data bank centers [14,15] and 1,091 patients with osteoarthritis, and (2) with risk factor analyses based on the 1,694 of these RA patients taking NSAIDs at the predictive visit.

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TABLE I
Rheumatoid Arthritis Gastrointestinal (GI) Hospitalization by Center

	Center					
	All Centers	Santa Clara	Saskatoon	Phoenix	Stanford	Wichita
Number of patients	2,747	302	679	307	379	1,080
Person-years of observation	9,525	1,632	2,468	1,016	1,318	3,091
Person-years taking NSAIDs	6,741	1,122	1,712	720	903	2,284
GI hospitalizations						
Number of patients	116	13	34	14	16	39
Rate per person-year (%)	1.22	0.80	1.38	1.38	1.21	1.26
Number taking NSAIDs	107	13	30	13	15	36
Rate per year while taking NSAIDs (%)	1.58	1.16	1.75	1.81	1.66	1.58
Number of years of observation after 1st hospitalization	201	24	73	22	27.5	54.5
Number of additional GI hospitalizations while taking NSAIDs	10	2	4	0	2	2
Rate for at least one more GI hospitalization per year while taking NSAIDs (%)	4.98	8.33	5.48	0.00	7.27	3.66
Number of patients with upper GI hospitalizations	95	13	27	11	13	31
Rate of upper GI hospitalizations per year while taking NSAIDs (%)	1.41	1.16	1.58	1.53	1.44	1.36
Number of patients with lower GI hospitalizations	12	0	3	2	2	5
Rate of lower GI hospitalizations per year while taking NSAIDs (%)	0.18	0	0.18	0.30	0.22	0.22

PATIENTS AND METHODS

Two thousand seven hundred and forty-seven patients with RA consecutively enrolled and followed at five ARAMIS centers, for a total of 9,525 years of observation, were available for study (Table I). The Santa Clara County population of 302 patients represents a community population recruited by advertisement. The other populations were formed by consecutive patient accrual at the site. The 679 Saskatoon patients are believed to make up the great majority of patients in Northern Saskatchewan province, the 307 Phoenix patients were drawn from a rheumatology private practice, as were the 1,080 Wichita patients, and the 379 Stanford patients were enrolled from a tertiary care referral center. Data are collected in two modes. First, all routine clinical data including diagnosis, symptoms, signs, demographics, past history, laboratory tests, and treatment are entered for each patient encounter and hospitalization. Second, patients complete the Health Assessment Questionnaire (HAQ) [1,16–18] at 6-month intervals, providing validated self-report of disability, discomfort, drug toxicity, and economic impact. All hospitalizations and deaths are audited by abstraction of discharge summaries and NSAID usage at time of event confirmed. Deaths are reviewed by death certificate discharge summary and recent clinical notes. The system, procedures, and validation techniques have been previously described [2,14–18].

The dependent variable in this study was "GI event," consisting of an event sufficiently serious as

to result in hospitalization or death. Events are counted only when they are the primary basis for hospitalization or death, not if they occurred during a hospitalization or as part of a terminal illness sequence. Patients are considered to be taking NSAIDs if they report on the HAQ immediately prior to the event that they are taking any one of the following drugs: aspirin, naproxen, ibuprofen, piroxicam, indomethacin, sulindac, meclofenamate, tolmetin, fenoprofen, ketoprofen, nonacetylated salicylates, salsalate, diflunisal, or diclofenac.

For risk factor delineation, items considered were those available at the HAQ prior to the event—the predictive visit. Patients had had from one to 13 6-month periods of observation. Obviously, patients analyzed for risk factors for NSAID gastropathy were required to be taking an NSAID at the predictive visit. Among the 130 patients with GI events, 32 patients were not included in the analysis because they were not taking NSAIDs at the predictive visit, or did not have HAQ data within 9 months prior to the event. Therefore, 98 patients with GI events were available for comparison with patients without GI events (controls). Similarly, of the 2,617 (2,747 minus 130) patients eligible as controls, 1,021 were excluded because they did not meet one or more of the above criteria. By definition, the non-event group could not have a GI event; however, control patients' records were randomly truncated to match the number of 6-month periods in which events occurred in patients with GI events. For example, 5% of the GI events occurred at the seventh

TABLE II
Variables Associated with Gastrointestinal (GI) Hospitalization or Death at Predictive Visit

	GI Events (n = 98)		No GI Events (n = 1,596)		p Value
	Number Defined	Mean (SE)	Number Defined	Mean (SE)	
Continuous variables					
Age (years)	98	65.47 (1.05)	1,596	58.65 (0.33)	<0.001
Education level (years)	95	11.94 (0.25)	1,525	12.50 (0.07)	0.06
Disease duration (years)	98	18.75 (1.20)	1,583	16.86 (0.28)	0.11
Disability index (0-3)	98	1.69 (0.08)	1,596	1.38 (0.02)	<0.001
Smoking (packs/day)	75	0.10 (0.04)	1,287	0.17 (0.01)	0.08
Alcohol (drinks/day)	92	0.20 (0.08)	1,529	0.44 (0.12)	0.09
Specialty care	98	0.53 (0.04)	1,558	0.59 (0.01)	0.15
NSAID dose (see text)	93	1.03 (0.06)	1,582	0.91 (0.01)	<0.05
Number of DMARDs	93	0.45 (0.06)	1,583	0.56 (0.01)	0.07
Number of H ₂ -antagonists	74	0.28 (0.05)	1,314	0.09 (0.01)	<0.001
Number of antacids or H ₂ -antagonists	93	0.53 (0.07)	1,583	0.22 (0.01)	<0.001
Categorical variables (% positive)					
Female sex	98	76.5	1,596	76.7	0.97
White race	95	98.9	1,545	94.5	0.06
Smoker	75	10.7	1,287	17.2	0.14
Alcohol	92	13.0	1,529	18.2	0.21
NSAID GI side effect ever	93	32.3	1,583	18.5	<0.001
Prednisone	93	51.6	1,583	31.0	<0.001
Antacids	74	20.3	1,312	10.1	<0.01
H ₂ -antagonists	74	28.4	1,314	9.1	<0.001
Antacids or H ₂ -antagonists	93	40.9	1,583	19.2	<0.001

6-month observation period and, therefore, prediction was made using information at the sixth observation period; similarly, a random 5% of the control subjects were analyzed at the sixth observation period as predictive of an "event" at the seventh observation period. This method was applied to each of the 13 possible 6-month observation periods to adjust for differences that would otherwise have been present in the amount of data available for prediction in cases and controls. The mean time interval between the predictive data at the HAQ prior to the event and the HAQ associated with the event was 6.1 months.

Univariate analyses were performed using a t-test for 11 continuous variables and by using a chi-square test on 2 × 2 tables for nine binary variables. The p values are those computed for each individual comparison and may be adjusted for multiple comparisons by the Bonferroni adjustment. All variables statistically significant as predictors at the 0.05 level (two-tailed) and several additional variables considered as potentially important were further analyzed by multivariate analyses. Stepwise multiple logistic regression and recursive partitioning (classification and regression tree) analyses were employed [19].

RESULTS

Incidence

Of the 2,747 RA patients available for study, 130 had GI events sufficiently serious to result in hospitalization or death. When hospitalizations were tabulated in these 130 patients, 116 patients had

128 hospitalizations (10 patients had two hospitalizations and one patient had three) and 17 had GI-related deaths. Among the 17 GI deaths, three patients had had prior GI hospitalizations. Data presented in Table I describe the 116 hospitalization events (the last event among patients with multiple hospitalizations). Data subsequently presented in Tables II through VI result from analysis of the last GI event (death or hospitalization). Fourteen patients had previous GI events (three pa-

TABLE III

Odds Ratios for Selected Variables with Respect to Gastrointestinal (GI) Hospitalization or Death

Variable	Odds Ratio	95% Confidence Interval
Female sex	1.0	0.61-1.60
White race	5.5	0.75-39.73
Smoker	0.6	0.27-1.22
Alcohol	0.7	0.36-1.25
Prior GI complaint	2.1	1.32-3.27
Prednisone	2.4	1.56-3.62
Antacid	2.3	1.25-4.12
H ₂ -antagonist	3.9	2.30-6.76
Antacid or H ₂ -antagonist	2.9	1.89-4.48
NSAID dose > 1.0 (see text)	1.4	0.87-2.11
Age		
> 45 years	7.0	2.21-22.35
> 50 years	4.4	2.01-9.52
> 60 years	2.7	1.70-4.30
> 65 years	2.4	1.56-3.55
> 70 years	2.0	1.30-3.08
> 75 years	2.2	1.28-3.85
Disability index (0-3)		
> 1	1.8	1.13-2.95
> 2	1.9	1.23-2.91

TABLE IV
Risk Factors for Gastrointestinal (GI) Complications Related to Hospitalization or Death: Stepwise Logistic Regression

Step Number	Variable	Coefficient (SE)	Improvement p Value	Odds Ratio	95% Confidence Interval for Odds Ratios
1	Age (years)	0.047 (0.01)	<0.0001	1.05:1 per year	1.03–1.07
2	Prednisone	0.35 (0.11)	<0.0001	1.42:1 yes/no	1.15–1.76
3	Previous NSAID GI side effect	0.39 (0.12)	0.001	1.48:1 yes/no	1.18–1.86
4	NSAID dose	0.29 (0.18)	0.07	1.34:1 per unit	0.95–1.90
5	Disability index (0–3)	0.19 (0.14)	0.18	1.21:1 per unit	0.92–1.59

tients with GI-related deaths who had previous GI hospitalizations, and 11 patients with multiple GI hospitalizations).

Of the 116 last hospitalizations, 107 occurred while patients were taking NSAIDs. Ninety-five of these were noted as upper GI problems on discharge summaries, and 82 of these were gastric in location. Twelve were localized to the lower GI tract. The overall rate of GI hospitalizations per year of observation was 1.2%. During periods when NSAIDs were

being taken, the overall frequency was 1.58% per year. When the analysis was limited to upper GI hospitalizations, the rate during treatment with NSAIDs was 1.4% per year.

Table I breaks down these hospitalizations by data bank center to evaluate the generalizability of the observations. The percentage of GI hospitalizations per year during NSAID treatment ranged from 1.2% in Santa Clara County to 1.8% in Saskatoon and in Phoenix. Upper GI hospitalizations

TABLE V
Characteristics of Classification Tree Subgroups with Respect to Gastrointestinal (GI) Hospitalization or Death

Subgroup Number	Characteristics	Number of Patients GI/No GI Event	Percent of Patients with GI Event	GI Event Rate per Year Taking NSAIDs (%)
1	Age 76 years or older, no prednisone	12/79	13.2	4.2
2	Age 48 years or older, taking prednisone, disease duration > 3.7 years, disability index > 1.7	33/199	14.2	3.9
3	Age 48 to 63 years, previous NSAID side effects, disability index > 1.3	7/36	16.3	3.8
4	GI event group: 10 second events out of 98 (10.2%)			3.1
5	Age 48 years or older, taking prednisone, disease duration > 3.7 years, disability index 0.3 to 1.7	13/148	8.1	2.2
6	Age 63 to 76 years, no prednisone	27/369	6.8	1.9
7	Age < 47 years	3/342	0.9	0.3
8	Age 47 to 63 years, no prednisone, never NSAID side effects	3/340	0.9	0.3
9	Age 47 to 63 years, previous NSAID side effects, disability index ≤ 1.3, no prednisone	0/37	0	0
10	Age 47 years or older, taking prednisone, disease duration ≤ 3.7 years	0/24	0	0
11	Age 47 years or older, taking prednisone, disease duration > 3.7 years, disability index ≤ 0.3	0/22	0	0

TABLE VI
Description of Selected Variables Within Subgroups of Tree (Figure 1)^a

	Subgroup Number (GI Event Group)										
	All	1	2	3	4	5	6	7	8	9	10
Number of patients	1,694	91	232	43	98	161	396	345	343	37	24
Variables											
Age (years)	59 (0.3)	79 (0.3)	65 (0.6)	57 (0.7)	65 (1.1)	63 (0.6)	69 (0.2)	39 (0.3)	56 (0.2)	57 (0.6)	66 (1.8)
Disease duration (years)	17 (0.3)	18 (1.2)	21 (0.7)	16 (1.5)	19 (1.2)	19 (0.9)	20 (0.7)	12 (0.4)	17 (0.5)	15 (0.1)	2 (0.2)
Disability index (0-3)	1.4 (0.02)	1.7 (0.1)	2.3 (0.02)	1.9 (0.07)	1.7 (0.1)	1.2 (0.03)	1.5 (0.04)	1.1 (0.04)	1.2 (0.04)	0.7 (0.1)	1.5 (0.2)
Previous NSAID-related GI side effects (%)	20	13	20	100	32	14	20	24	0	100	8
NSAID dose (see text)	0.9 (0.01)	0.8 (0.1)	1.0 (0.03)	1.0 (0.1)	1.0 (0.1)	0.9 (0.04)	0.9 (0.03)	0.9 (0.03)	1.0 (0.03)	1.0 (0.1)	1.3 (0.2)
Use of prednisone	30	0	100	0	52	100	0	29	0	0	100
Use of antacids or H ₂ -antagonists (%)	20	20	35	26	41	28	21	15	11	24	21
Time taking NSAIDs (months)	41 (0.5)	38 (2.2)	43 (1.3)	51 (3.3)	40 (2.1)	43 (1.6)	43 (1.1)	38 (1.1)	41 (1.2)	45 (3.2)	16 (1.2)

^aValues are means (SE).

ranged from 1.2% per year with NSAID treatment in Santa Clara County patients to 1.6% in Saskatoon. Results at all centers were similar, without statistically significant differences.

Table I also lists patients taking NSAIDs who were hospitalized more than once. One subject was hospitalized three times. After the first hospitalization, the 10 additional hospitalizations occurred in only 201 years of observation, for a rate of 5% for at least one more GI hospitalization per year during treatment with NSAIDs. This rate varied from 0% in Phoenix to 8.3% in Santa Clara County. This overall rate of rehospitalization is approximately four times the rate of first hospitalization.

There were 17 GI-related deaths occurring during these 9,525 years of observation. Thirteen of these deaths occurred in patients who were reliably known to be taking NSAIDs at the time of death; each of the others might have been. This gives an overall GI death rate of 0.18% per year and a GI death rate during known treatment with NSAIDs of 0.19% per year.

Risk Factor Analyses

Table II lists continuous variables analyzed univariately for their association with serious GI events (hospitalization or death) for patients having taken NSAIDs at the predictive visit. The number of subjects reflects the inclusion criteria previously described. The most significant differences were obtained for age, HAQ disability index, NSAID dose, and use of antacids or H₂-antagonists. The difference in HAQ disability scores of 0.31 is clinically significant, representing the equivalent of 4 years of disease progression in RA. NSAID dose was calcu-

lated by setting a value of 1.00 for the manufacturer's highest recommended dose on the package insert and normalizing the dose of each patient to this standard. Thus, the value 1.03 means that patients with events, on average, were taking 103% of the manufacturer's highest recommended dose. "DMARDs" refers to prior use of "disease-modifying antirheumatic drugs." The variable "specialty care" refers to the proportion of all doctor visits that were made to rheumatologists.

The second part of Table II presents univariate comparisons of potentially predictive categorical variables dichotomized as present or absent (presented as percent positive). The statistically most significant differences were seen for having previously reported GI symptoms attributed to use of an NSAID (nausea, heartburn, loss of appetite, vomiting, or upper abdominal pain), use of prednisone (average dosage 7 mg/day) in the previous 6 months, and use of antacids or H₂-antagonists within 9 months of the event. Female sex was not predictive. Race was not predictive, nor was cigarette smoking or alcohol use, although these analyses were limited in power because of small numbers of nonwhites, smokers, and heavy drinkers. Eight of the 10 statistically significant ($p < 0.05$) differences remain significant after adjustment for the 20 multiple comparisons of Table II.

Odds ratios for selected variables with respect to GI events along with 95% confidence intervals are shown in Table III. For example, the odds ratio for females was obtained as follows: the proportion of females with GI events was 75 of 98 = 76.5%; thus, the odds are $76.5/(100 - 76.5) = 3.26$. Similarly, the proportion of females without GI events was 1,224

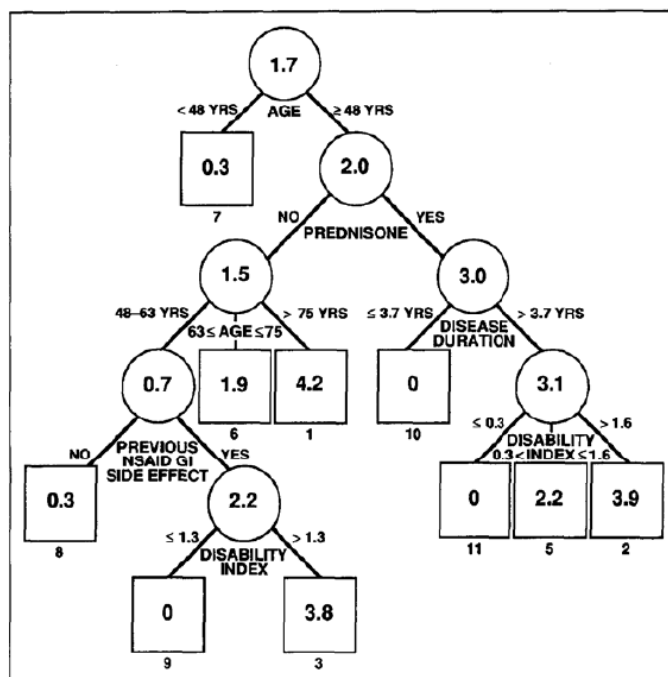


Figure 1. Classification tree for GI hospitalization or death (GI event). The value within the circles and boxes is the percentage of patients with GI events per year during treatment with NSAIDs. Numbers below the boxes are subgroup identification numbers of final subgroups. NSAID dose = 1.0 corresponds to the manufacturer's highest recommended dose.

of 1,596 = 76.7%; thus, the odds are $76.7/(100 - 76.7) = 3.29$. Therefore, the odds ratio for females with GI events to females without GI events is $3.26/3.29 = 1.0$. For the values considered, age showed the highest odds ratio when dichotomized at age 45 (only two events occurred below that age). Odds ratios are significant at $p < 0.05$ if 95% confidence limits do not include the value of 1.

Table IV summarizes the results of stepwise logistic regression analysis using most of the variables of Table II. Three variables had improvement p values less than 0.05: age, use of prednisone, and previous NSAID GI side effects. NSAID dose and disability index were the next two variables stepped into the model. The odds ratio is the estimated multiplicative effect of a 1-unit increase in that variable on the odds of having a GI event, holding all other covariates constant.

Figure 1 summarizes the results of the classification tree analysis (recursive partitioning). Each node of the tree (represented by round and square boxes) contains the risk per year during NSAID treatment for patients in that node, in percent. With this method, each node of the tree is recursively partitioned into two subgroups, one containing cases with variable values less than some cutoff point and the other containing cases with values greater than this cutoff.

The "best" variable along with its splitting value (cutoff point) is selected with the use of a "goodness-of-split" criterion. The program (CART) cross-validates the results to present a stable tree structure [19]. The same variable may appear twice in succession in the tree at different cutpoints; this occurred with both age and disability.

The tree split first on age, yielding a very-low-risk group (0.3% events per year during NSAID therapy) below age 47. The tree split next on prednisone use, and then on age and disease duration. Disability index and previous NSAID GI side effects appeared at lower levels of the tree. The tree displayed in Figure 1 contains 10 classifying subgroups (represented by square boxes). Eleven groups are numbered and ranked in order of risk, from a high of 4.2% per year while taking NSAIDs in individuals over the age of 75 and not taking prednisone at the predictive visit to near zero: for example, in the groups with young individuals and with individuals between 48 and 63 years of age not taking prednisone at the predictive visit and without previously having had an NSAID GI side effect.

Table V provides descriptive data for Figure 1, and Table VI describes the average values of the major risk variables in each group of Figure 1; the

very different patient characteristics are apparent.

COMMENTS

Results reported here confirm prospectively the high relative risk of hospitalization or death in RA patients taking NSAIDs. The rate of GI hospitalizations per year in patients taking NSAIDs is 1.58%, compared with a hospitalization rate of 0.3% (nine of 2,784) in patients not treated with NSAIDs, for a hazard ratio of 5.2. As previously reported [1], use of NSAIDs in RA does not appear to represent a severity marker for RA, and mean HAQ disability scores, pain scores, age, disease duration, and use of prednisone are closely similar in patients taking NSAIDs and in those not taking NSAIDs. Without a randomized controlled trial of NSAID versus no NSAID use, one cannot absolutely attribute causality to the use of NSAIDs, but this use does not appear likely to be a marker of disease severity.

Our results were consistent across all five populations studied. It appears likely from preliminary data that the rate of hospitalizations in patients with osteoarthritis may be half or less of that observed in patients with RA. Previous GI hospitalization is identified as a major risk factor.

We performed a preliminary evaluation of patients with osteoarthritis, with a smaller number of years of observation available. Patients with osteoarthritis were drawn from the Wichita population (590 patients, 893 years of observation) and from a national pool of osteoarthritis patients who had taken the Arthritis Self-Management Course [20,21] offered by the Arthritis Foundation (501 patients, 251 patient-years of observation). Only three GI hospitalizations occurred in these patients with osteoarthritis. All of these cases were gastric in location and all were in patients taking NSAIDs. Thus, the rate of upper GI hospitalizations per year during NSAID treatment was 1.4% in RA and only 0.4% in osteoarthritis. There were no GI-related deaths during this period of observation. This suggests the possibility of a higher hospitalization rate for RA patients, but the numbers of patients with osteoarthritis were too small to achieve statistical significance.

Other studies have addressed the question of incidence of serious GI events, and generally yield estimates consistent with those here. Thus, Carson *et al* [22,23] found hospitalization rates of 0.5% per year for bleeding ulcer in NSAID users for all indications, and FDA estimates of "serious" problems are from 2% to 4% per year [24]. Other estimates are somewhat lower [25–27], but underascertainment appears to be present in some of these studies. Our

data by study protocol do not allow for overascertainment. Indeed, even the data presented here are subject to some underascertainment, since if our patients did not report a hospitalization, we did not routinely seek discharge summaries, and additionally we failed to obtain discharge summaries about 5% of the time. In general, the literature data are consistent with the highest incidences in RA patients, who have the highest levels of NSAID intake, and lower incidences for more occasional NSAID users [1,12,22–27].

Two recent major publications further reinforce the results reported here. In a nested case-control study of Tennessee Medicaid GI hospitalizations, Griffin *et al* [28] found a relative risk of 4.1 for NSAID users versus nonusers regardless of disease indication, rising to a relative risk of 8.0 for current users at high NSAID dosage. Excess risk was found to be 17.4 events per 1,000 patient-years, as compared with 15.8 per 1,000 patient-years as reported here. Dosage was found important, and no role for confounding by current smoking or current heavy alcohol use could be identified. Soll *et al* [29] provide a careful review of published data on NSAID-associated ulcers, with a full discussion of relative risk, mechanisms, and approaches to prevention.

Previous studies have suggested that one half to two thirds of GI deaths in RA patients taking NSAIDs are "excess," while the remainder represent "background" events [6,7]. Thus, these data are similar to the 0.13% per year excess GI death rate previously estimated [1].

The individual clinical variables appearing to be predictive of serious GI events included age, disability, NSAID dose, previous GI hospitalization, prior GI complaints with NSAIDs, and use of prednisone, antacids, or H₂-antagonists. Inadequate data were available for analysis of prior sucralfate use. Female sex was not predictive, in contrast to the preponderance of female admissions reported in a series of GI hospitalizations [9]. These findings are not contradictory, since the prevalence of NSAID use is much higher in females than in males [13]. A variable termed "specialty care" was not predictive, suggesting that hospitalization and death rates are not related to the experience or expertise of the particular provider.

The stepwise logistic regression model identified five variables that appear predictive (improvement *p* value <0.20), and these are, in the main, intuitive. The univariate finding that prior use of GI protective agents (antacids or H₂-antagonists) was a strong predictive factor (*p* <0.001) was somewhat surprising. Most NSAID GI ulcers are "silent" [3,8], but a substantial number of patients had prior

GI-EVENT SCORE TABLE FOR RA	
AGE (years)	x 2 =
HISTORY OF PREVIOUS NSAID GI SIDE EFFECT	50 =
DISABILITY INDEX (0-3) OR (ARA CLASS - 1)	x 10 =
NSAID DOSE (fraction of maximum recommended)	x 15 =
CURRENT PREDNISONE USE	40 =
TOTAL SCORE	_____

GI-EVENT RISK PER YEAR ON NSAIDS IN RA	
$\text{RISK} = (\text{SCORE} - 100) / 40$	

Figure 2. GI event score table for RA. Derived from logistic regression results, a simplified scheme is presented here: the sum of (1) patient age $\times 2$, (2) 50 points if there is a prior history of NSAID dyspepsia, (3) 0 points for American Rheumatism Association (ARA) functional class 1 (normal), 10 for class 2 (adequate), 20 for class 3 (limited), or 30 for class 4 (unable), (4) 15 times the fraction patient NSAID dose/manufacturer's highest recommended dose, and (5) 40 points for current prednisone use. When 100 is subtracted from this sum and the result divided by 40, the risk of GI hospitalization or death over the next 12 months, in percent, is obtained.

symptomatology that might have led to the use of "protective" agents. These agents are not believed to be effective in prevention of NSAID ulcers [4,5,10,30-33], and this is supported by the experience reported here. There are two possible mechanisms by which these agents might prove harmful in

practice: first, by treating dyspeptic symptoms and removing premonitory warning signs, and second, by reassuring the physician that preventive measures had been taken. However, "protective" agents are probably given to patients already considered to be at higher risk, thus expressing the higher risk

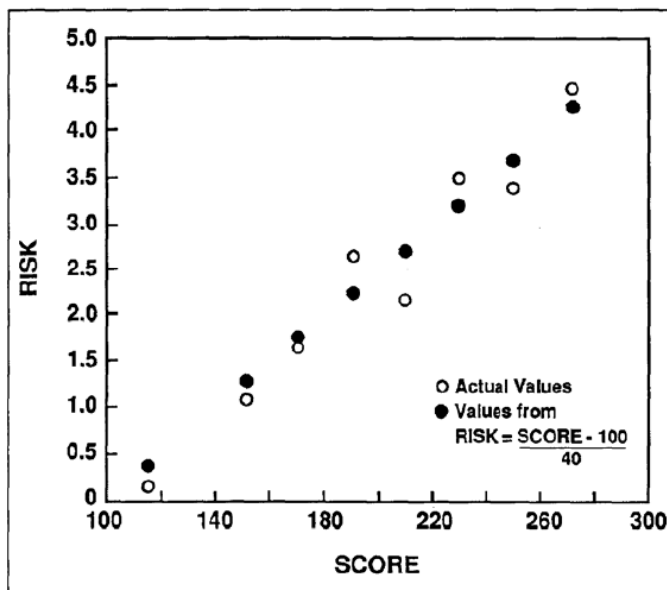


Figure 3. Risk for GI hospitalization or death per year during treatment with NSAIDs. Comparison of risk scores for individual patients (Figure 2) with actual measured risk (GI events/years at risk) for patients grouped by 20-unit score categories, demonstrating a strong correlation between results predicted by the simplified scoring rule and actual experience.

level of those patients, without representing a direct risk factor per se; hence, use of GI protective agents was not included as a predictor in the multivariate analyses. Additionally, it is our perception that the use of H_2 -antagonists and antacids is declining and, therefore, this association would have minimal predictive value in the future.

The classification tree identifies subgroups of individuals at higher or lower risk in terms of their variable values. Using this technique (Figure 1), it is possible to predict 92 of 98 GI events with only a few variables required to establish membership in the five subgroups numbered 1, 2, 3, 5, and 6. History of a prior serious GI event identifies a separate high-risk subgroup. On the other hand, age below 47 identifies subjects at low risk. Several important implications for patient management emerge from these results: the risk for GI events is highly concentrated in older individuals, use of prednisone is independently associated with risk, and disability and disease duration are important. Prior history of NSAID GI intolerance cannot be neglected. The two multivariate methods, logistic regression and the classification tree, allow risk in the individual to be estimated quantitatively.

Age has proven to be a major risk factor in previous studies, as here [1,5,9,12,13]. The effect is presumably related to a decreased ability of the host to protect the mucosa and to heal mucosal lesions, and possibly related to impaired clearance of drugs. Disability is another complex factor, related to frailty, comorbidity, and polypharmacy. The history of prior GI side effects serves to remind us that not all NSAID ulcers are silent; 32% of cases, but only 19% of the controls, reported prior side effects.

We did not expect to find that prednisone use, at an average dose of only 7 mg/day, would remain predictive after adjustments for age, disability, and NSAID dose were made, but the association persisted after statistical adjustment; this finding suggests that in RA patients, especially of older age, even low-dose prednisone may impede the healing process for NSAID ulcers. These data do not suggest that low-dose prednisone, in the absence of NSAIDs, is necessarily a risk factor for serious GI events.

With use of a linear discriminant function, we have developed a scoring system for estimating risk (percent per year while being treated with NSAIDs) in the individual patient with RA, using the five variables that appeared in the logistic regression model. Disability is estimated by the HAQ disability index; for convenience, the American Rheumatism Association functional class may be used instead, since an HAQ of 0, 1, 2, or 3 corresponds roughly to functional class 1, 2, 3, or 4. NSAID dose is the fraction of the manufacturer's highest recom-

mended dose, and contributes relatively little for most patients. Other factors are readily ascertained by history. Figure 2 presents a simple scoring table.

In these data sets, the estimated risk for serious GI events over the next year is well approximated by subtracting 100 from the score and dividing by 40. Figure 3 displays the relationship between risk as estimated by the scoring rule and actual incidence of events per year during NSAID therapy in subjects grouped into 20-unit score categories. It is apparent that the scoring rule accurately models actual experience of events per year during NSAID therapy in these RA patients.

These major risk factors are modifiable in part, since prednisone use and NSAID dose may be changed. It is likely, but not yet proven, that substantial differences between NSAIDs, not analyzed here, may allow choice of less hazardous agents for some patients. Prophylaxis with exogenous prostaglandins greatly reduces the rate of endoscopic ulcerations in similar patients, and current evidence suggests consideration of use of these agents in high-risk groups [1,8,13,25,28,29]. Increased understanding of the role of clinical and demographic factors in determining the risk of NSAID gastropathy will provide an important means to reduce the magnitude of this serious national problem.

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