Predicting the Risk of Gastrointestinal Bleeding Due to Nonsteroidal Antiinflammatory Drugs: NSAID Electronic Assessment of Risk

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ABSTRACT. ***Objective.*** To validate that, using patient demographics and other risk factors readily obtained from computerized databases, one can predict a priori the risk for developing a nonsteroidal antiinflammatory drug (NSAID) associated gastrointestinal (GI) bleed prior to exposing patients to therapy.

Methods. We conducted a retrospective cohort analysis using computer-stored information from a large group-model health maintenance organization. All patients who received one or more prescriptions for a single NSAID over a 9 month period were eligible. Historical and risk factor data was obtained for age, sex, prior GI bleeds, use of GI medications, prednisone use, and use of disease modifying antirheumatic drugs (DMARD). We tested a model (*e*SCORE) that is based on a previous risk stratification method. The primary outcome was a hospital admission for a GI bleed (GI event).

Results. A total of 303,211 NSAID patient-users met eligibility requirements. Serious GI events occurred in 302 patients, for a rate of 0.68% (0.68 events per 100 patient-years' exposure). All the risk factors except DMARD use were associated with a significant increase in the GI event rate. Higher *e*SCORE points were associated with increased GI event rates.

Conclusion. The study supports the concept that the rate of GI events can be predicted by a defined set of easily assessed patient criteria using the *e*SCORE. Stratification of patients by risk score can guide the physician to appropriate therapeutic options, with the potential of protecting patients at greatest risk for a GI event. (J Rheumatol 2003;30:2241–4)

Key Indexing Terms:
ANTIINFLAMMATORY AGENTS, NONSTEROIDAL
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The risk of developing a serious gastrointestinal (GI) bleeding event (perforation, obstruction, or bleed) secondary to nonsteroidal antiinflammatory drug (NSAID) administration is low, 0.1% to 2% per year[1-3]. However, millions of patients take NSAID each year, resulting in a significant number of GI bleeds related to these drugs. If the risk for developing an NSAID associated GI bleed could be estimated prior to initiating therapy, appropriate strategies could be developed to help lower that risk, such as using an NSAID with a lower risk for GI events or adding a GI-protecting drug (misoprostol, H_2 blocker, or proton-pump inhibitor) to the patient's therapy.

Several epidemiologic studies have identified patient factors associated with an increased risk for developing a GI bleed[4-11]. In 1991, Fries, *et al* published a GI bleeding risk model using the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database[12]. A refinement of the original risk model was presented in abstract form by Singh, *et al* in 1998[13]. This updated model (the SCORE© tool) features a 6 question survey that estimates risk for a serious NSAID induced GI event based on a point system[14] [for information on the SCORE© tool, contact Dr. G. Singh, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, USA]. Points were determined for each question using a Cox proportional hazards model, with low total points associated with low GI risk and high points associated with progressively higher risk for a GI event. The SCORE© tool questions include the patient's age, diagnosis of rheumatoid arthritis (RA), use of corticosteroids, history of a prior GI bleed, health status, and history of dyspepsia.

At Kaiser Permanente Southern California (KPSC) we revised the SCORE© model slightly, allowing us to estimate a patient's risk using computer-stored medical and demographic information. We report preliminary results on the ability of our revised SCORE© tool model to estimate risk for a serious GI event.

MATERIALS AND METHODS

This is a retrospective cohort analysis using computer-stored information from a large integrated healthcare delivery system (KPSC). All patients who received one or more prescriptions for a single NSAID during a 9 month period (July 1, 1999 to March 31, 2000) were identified. The date of

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the first prescription was the index date (t_0). Historical data for each patient were collected in a manner to replicate the original SCORE© tool: prior GI bleed with hospitalization (up to 10 years prior to t_0), history of dyspepsia (defined as recent use of GI medications), steroid use for 12 months prior to t_0, age, and presence of RA (defined by prescriptions for disease modifying antirheumatic drugs, DMARD). Points were awarded for each risk factor consistent with the original SCORE© tool model[13,14]. Outcome data on hospital admissions for GI events were collected for as long as the patient continued using NSAID therapy from t_0 through December 31, 2000. Serious GI events were defined as a hospitalization with DRG codes (174-178, 180, 181) plus an *International Classification of Disease-9* discharge diagnosis of GI hemorrhage, ulcer, or perforation (codes 531, 532, 533, 535, 569, or 578). Exposure was defined as the total prescription days' supply plus 4 weeks. Hospitalizations occurring more than 4 weeks after the exposure were not counted as GI events. Patients were excluded if they did not have at least 12 months of enrollment prior to t_0, changed drugs, or received a prescription NSAID in the 6 months prior to the index prescription (prescription NSAID-naive).

The original SCORE© tool questionnaire is administered by asking patients the 6 questions. The KPSC modification (*e*SCORE) allows stored computer data to estimate the total points for each patient without patient interviews. Table 1 lists the risk factors, the SCORE© tool questions, the administrative database modifications used to determine the *e*SCORE, and the points awarded. The general health question is not included in the *e*SCORE at this time because the current method does not allow an automated assessment of health status.

The primary outcome was comparison of the rate of GI events (hospitalizations per 100 patient-years of exposure) versus the *e*SCORE points. An analysis of the GI event rate associated with each of the risk factors included in the *e*SCORE assumed a Poisson distribution when estimating the 95% confidence intervals. Odds ratios were estimated using a multivariate logistic regression model controlling for SCORE© tool risk factors, sex, and days of therapy.

RESULTS

A total of 303,211 NSAID users met eligibility requirements. Women accounted for 58.8% of the patients. The average age for the group was 45.2 ± 15.5 (SD) years. The mean duration of NSAID therapy was 54 ± 72 days. The total NSAID exposure was 44,685 person-years.

Hospitalizations for a GI event occurred in 302 patients while they were exposed to an NSAID. The rate of GI bleeds for the entire population was 0.68 events per 100 patient-years. Figure 1 depicts the rate of GI bleeds compared to the *e*SCORE, higher *e*SCORE values being associated with increased GI event rates. Event rates remained relatively flat with lower risk scores, beginning to rise at 16 to 18 points and then increasing dramatically as the point values increase. All risk factors were associated with a significant increase in the GI event rate, except DMARD use (Table 2). The odds ratios derived from our multivariate logistic model were consistent with the GI event rate analysis (Table 2). Both the GI event rates and the odds ratios indicate that the risk of developing a GI event is most highly associated with a history of a GI bleed and the patient's age.

DISCUSSION

The ARAMIS researchers developed a scoring system (the SCORE© tool) to predict the risk of a serious GI event in patients treated with traditional NSAID. This study confirms that the rate of GI events can be predicted by a defined set of easily assessed patient criteria.

Our study differs from the original report by Singh, *et al*[13]: we modified the original SCORE© criteria to an electronic, automated format (*e*SCORE). The KPSC Health Plan provides integrated health care for over 3 million members and the population is fundamentally different from the ARAMIS population, which is limited to patients with RA and osteoarthritis.

Overall, our findings are consistent with previous results, but limitations do exist with the data and how we define the various risk factors. To be included, all patients were required to have 12 months of historical data; however, we collected data going back 10 years when looking at previous GI bleeding events. A bias exists if a patient had a GI event in the past 10 years but was not a KPSC member at the time because information about the event would not be recorded in our database. So although a previous GI event was highly associated with a future event, our results may actually underestimate this risk. The use of DMARD (a proxy for RA) may introduce data for patients with other severe chronic diseases, and the use of GI medications may not indicate dyspepsia but other significant GI pathology instead. However, with the exception of DMARD use, all of the individual risk factors were associated with an increased rate of serious GI events. There are several potential reasons that RA was not associated with an increased risk of GI

Table 1. Risk factors and scoring for SCORE© tool versus *e*SCORE.

Risk Factor	SCORE© Tool Question	*e*SCORE Database Modification**	Points Awarded*
1. Age	How old are you?	Demographic (membership database)	0 to 18
2. Health status	How do you rate your current health status?	Not captured electronically	0 to 4
3. Rheumatoid arthritis	Do you have rheumatoid arthritis?	DMARD use (automated pharmacy data)	0 or 2
4. Corticosteroid use	Have you taken prednisone or other corticosteroids in the past year and if so for how many months?	Corticosteroid use (automated pharmacy data)	0 to 5
5. Prior GI bleed	Have you been hospitalized for a GI bleed or an ulcer?	Hospital records (based on DRG and ICD-9 codes)	0 or 8
6. NSAID dyspepsia	Have you ever had GI side effects when taking NSAIDs?	Automated pharmacy data (GI medication use in past 12 mo)	0 or 2

* See references 13 and 14. ** Adapted from the SCORE© Tool for electronic use within Kaiser Permanente.

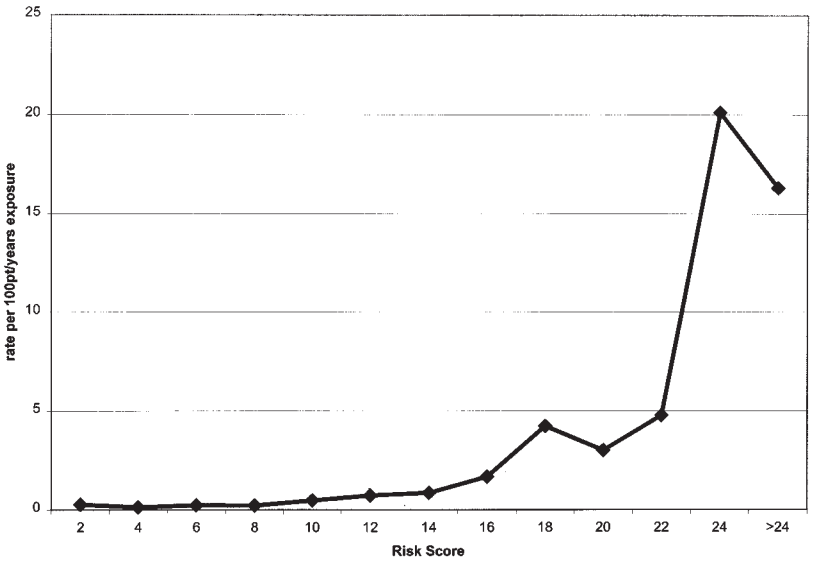

Figure 1. GI hospitalization rate versus *e*SCORE.

Table 2. GI admission rates by individual *e*SCORE risk factor.

*e*SCORE Risk Factor	Rate*	95% CI		OR**	95% CI		
		Lower	Upper		Lower	Upper	p
Total Population (n = 303,211)	0.68	0.62	0.77				
Age Group, yrs				2.02	1.85	2.19	< 0.001
≤ 44 (n = 152,516)	0.32	0.24	0.42				
45–54 (n = 67,705)	0.4	0.3	0.54				
55–64 (n = 40,068)	0.55	0.41	0.72				
65–74 (n = 26,717)	1.09	0.86	1.38				
≥ 75 (n = 13,205)	3.15	2.58	3.84				
DMARD use				1.25	0.39	4.00	0.71
No (n = 302,035)	0.68	0.6	0.76				
Yes (n = 1,176)	0.63	0.2	1.73				
Corticosteroid use				2.03	1.46	2.81	< 0.001
No (n = 285,297)	0.63	0.55	0.71				
Yes (n = 17,914)	1.25	0.94	1.67				
Prior GI bleed				7.15	4.23	12.10	< 0.001
No (n = 302,420)	0.64	0.57	0.72				
Yes (n = 791)	10.1	6.198	16.1				
GI medication use				1.42	1.08	1.87	0.012
No (n = 269,787)	0.6	0.53	0.68				
Yes (n = 33,424)	1.11	0.88	1.39				

* Rate per 100 patient-years of NSAID exposure, by risk factor. ** Odds ratios based on multivariate logistic regression, controlling for *e*SCORE risk factors, sex, and days of therapy.

events: our population is different than that of Singh, *et al*; the definition we used for RA (DMARD use); or the small number of RA patients compared to the total population. Overall, age and a prior hospitalization for a GI bleed were the best predictors of a future GI event.

The modified *e*SCORE can easily be applied to estimate the risk of a GI event in large populations of patients requiring treatment with an NSAID. Using our system, the pharmacy staff is able to identify patients at high risk for a GI event (high *e*SCORE) and to contact the prescribing physician to consider other forms of therapy with better GI safety profiles, to suggest adding concomitant therapy (i.e.,

H_2 blockers, proton-pump inhibitors), or to use alternative types of drugs. Future studies, using these risk models, are needed to define which alternative therapies provide the most benefit for high risk patients. Use of the SCORE© tool and *e*SCORE represents a potential method for predicting NSAID risk before the patient takes the medication.

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