

TITLE: RCT reports will always have
"randomized controlled trial" in the title

Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

The CLASS Study: A Randomized Controlled Trial

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FOR PATIENTS WITH MUSCULOSKELETAL disorders, conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of clinical care.¹⁻³ Well-established limitations of NSAID therapy, however, include the risk of developing significant injury to the upper gastrointestinal (GI) tract.⁴⁻¹⁰ The annualized incidence rate of symptomatic GI ulcers and ulcer complications in NSAID users ranges from 2% to 4% (1%-2% for ulcer complications alone).¹¹⁻¹⁵ NSAID-related ulcer complications are estimated to lead to

Context Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a spectrum of toxic effects, notably gastrointestinal (GI) effects, because of inhibition of cyclooxygenase (COX)-1. Whether COX-2-specific inhibitors are associated with fewer clinical GI toxic effects is unknown.

Objective To determine whether celecoxib, a COX-2-specific inhibitor, is associated with a lower incidence of significant upper GI toxic effects and other adverse effects compared with conventional NSAIDs.

Design The Celecoxib Long-term Arthritis Safety Study (CLASS), a double-blind, randomized controlled trial conducted from September 1998 to March 2000.

Setting Three hundred eighty-six clinical sites in the United States and Canada.

Participants A total of 8059 patients (≥ 18 years old) with osteoarthritis (OA) or rheumatoid arthritis (RA) were enrolled in the study, and 7968 received at least 1 dose of study drug. A total of 4573 patients (57%) received treatment for 6 months.

Interventions Patients were randomly assigned to receive celecoxib, 400 mg twice per day (2 and 4 times the maximum RA and OA dosages, respectively; $n=3987$); ibuprofen, 800 mg 3 times per day ($n=1985$); or diclofenac, 75 mg twice per day ($n=1996$). Aspirin use for cardiovascular prophylaxis (≤ 325 mg/d) was permitted.

Main Outcome Measures Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period.

Results For all patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% ($P=.09$) and 2.08% vs 3.54% ($P=.02$), respectively. For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% ($P=.04$) and 1.40% vs 2.91% ($P=.02$). For patients taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 2.01% vs 2.12% ($P=.92$) and 4.70% vs 6.00% ($P=.49$). Fewer celecoxib-treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. No difference was noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use.

Conclusions In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.

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107 000 hospitalizations and 16 500 deaths yearly in the United States.¹⁰

NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for conversion of arachidonic acid to prostaglandins.¹⁶ COX exists in 2 isoforms.¹⁷ COX-1 is a ubiquitous constitutive isozyme producing prostaglandins responsible for homeostatic functions such as maintenance of GI mucosal integrity.¹⁷ COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.¹⁷ NSAIDs inhibit both COX-1 and COX-2 to varying degrees.^{18,19} Thus, the therapeutic effects of conventional NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents, particularly in the upper GI tract, arise from inhibition of COX-1 activity.

Celecoxib, a COX-2-specific inhibitor, recently was approved by the US Food and Drug Administration (FDA) for symptomatic treatment of rheumatoid arthritis (RA) and osteoarthritis (OA). To determine whether the COX-2 specificity of celecoxib is associated with lower COX-1-related adverse effects, we compared celecoxib administered at 2 and 4 times the maximum FDA-approved effective dosages for RA and OA, respectively, with commonly used therapeutic dosages of ibuprofen and diclofenac. The dosage of celecoxib exceeded the maximum dosage approved by the FDA for OA and RA to permit a safety assessment of the higher dosages. However, based on previous studies,^{20,21} exceeding the dosages approved by the FDA would not improve patients' symptom relief. The dosages of ibuprofen and diclofenac were based on prescription data; 48% and 60% of OA and RA patients, respectively, who received ibuprofen were prescribed a dosage of at least 2400 mg/d, and 36% and 57% of OA and RA patients, respectively, who received diclofenac were prescribed a dosage of at least 150 mg/d.²²

METHODS

Study Population

Outpatients aged 18 years or older were eligible to participate in the study if, on screening, they were diagnosed as hav-

ing RA or OA evident for at least 3 months and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from study participation if at screening they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; history of gastric or duodenal surgery other than an oversew; or known immediate-type hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might have become pregnant, or were lactating.

Study Protocol

This prospective, randomized double-blind trial was conducted at 386 centers in the United States and Canada from September 1998 to March 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site, and all patients provided written informed consent. Prior to enrollment, patients completed a physical examination and clinical laboratory testing. After a baseline visit, follow-up clinic visits took place at weeks 4, 13, and 26 after the initial dose of medication, and every 13 weeks thereafter. All patients were provided an opportunity to complete a minimum of 6 months of treatment.

Patients withdrawing from study participation prior to 6 months were classified as follows: preexisting violation of entry criteria, protocol noncompliance (investigator-defined failure to comply with the requirements of the protocol, eg, failure to take at least 70% of the study medication in any 13-week interval), treatment failure (investigator-defined failure of study medication to control arthritis signs and symptoms), or adverse effect (investigator-defined signs or symptoms unrelated to arthritis; see "Clinical Assessments" herein). These patients nonetheless were followed up for end-

point evaluation for 2 months or until study termination.

Treatment

Patients were randomly assigned to receive treatments (celecoxib, 400 mg twice per day; ibuprofen, 800 mg 3 times per day; or diclofenac, 75 mg twice per day) on a 2:1:1 basis by an interactive voice response system (ClinPhone, Nottingham, England) according to a computer-generated randomization schedule. All treatment regimens were blinded and double dummy. Treatment assignment for 3 patients was unblinded by study site personnel during trial conduct (1 at the investigation site, 2 via the interactive voice response system). None of these patients experienced a study outcome event. One celecoxib patient experienced diverticular bleeding; 2 patients (1 celecoxib and 1 diclofenac) experienced non-GI-related adverse events; and in no instance was the treatment assignment made known to personnel of the drug company (Pharmacia, Skokie, Ill) or to members of the oversight committees prior to final review of all end points by a GI events committee.

Concomitant Medications

NSAIDs (except for stable dosages of aspirin up to 325 mg/d); antiulcer drugs (except for occasional antacid use); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *Helicobacter pylori* infection; and antineoplastics (except methotrexate or azathioprine for RA) were prohibited during the study. Use of oral, intramuscular, and intra-articular glucocorticoids and disease-modifying antirheumatic drugs was permitted.

Clinical Assessments

Investigators were instructed to identify and report all potential upper GI ulcer complications. Evaluation of such events was outlined in a prespecified algorithm structured to reproduce clinical practice norms. Evaluation was required for any of the following presentations: hematemesis; melena; acute

METHODS: Trial design, participant information, interventions, outcomes, sample size, randomization information, blinding information, and more.

hypovolemia/hypotension; development of postural dizziness, lightheadedness, or syncope; history of dark stool, hematochezia, or anal or rectal bleeding; development of new anemia (defined as a hematocrit level outside of the reference range) or a decrease in hematocrit of at least 5 percentage points; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of occult blood-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator's clinical judgment.

All documentation relating to potential ulcer complications was forwarded to a GI events committee (J.L.G., G.E., N.M.A., and W.F.S). The committee collectively reviewed each case in a treatment-blinded fashion and assigned it by unanimous consensus as either meeting or not meeting the definition of an upper GI ulcer complication (TABLE 1). Symptomatic ulcers consisted of cases that did not meet the definition of an ulcer complication but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study and included in the analysis as having had a study end point.

Adverse effect data were collected at each visit (and as reported spontaneously) using the following question: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?" All affirmative responses were recorded regardless of severity or relationship to study drug. Laboratory data were also collected at each visit and as indicated according to the investigators' discretion. Clinically significant changes in hematocrit and hemoglobin were predefined as decreases of at least 10 percentage points and 20 g/L, respectively. Clinically significant changes in serum urea nitrogen and creatinine were predefined as values at 6-month follow-up of at least 40 mg/dL (14.3 mmol/L) and 1.8 mg/dL (159 μ mol/L),

Table 1. Protocol-Specified Definitions and Adjudication Criteria for Ulcer Complications

Event	Criteria for Confirmed Event
Gastric or duodenal perforation	Perforated lesion requiring surgery. Could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible on radiograph or peritoneal signs on physical examination.
Gastric outlet obstruction	Gastric outlet obstruction requiring diagnosis by investigator; diagnosis was required to be supported by endoscopy (eg, ulcer with a tight edematous pyloric channel) or by radiographic results (eg, dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, severe outlet narrowing and edema)
Upper gastrointestinal bleeding	Hematemesis with a lesion (ulcer or large erosion) on endoscopy or radiograph Lesion (ulcer or large erosion) on endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer) Melena with a lesion (ulcer or large erosion) on endoscopy or radiograph Occult blood-positive stool with a lesion (ulcer or large erosion) on endoscopy or radiograph and with evidence of serious bleeding, including at least 1 of the following: Decrease from baseline in hematocrit of ≥ 5 percentage points or in hemoglobin of > 15 g/L Postural vital sign changes (increase in heart rate of ≥ 20 /min and/or decrease in systolic blood pressure of ≥ 20 mm Hg and/or in diastolic blood pressure of ≥ 10 mm Hg) Transfusion of ≥ 2 units of blood Blood in stomach on endoscopy or nasogastric aspiration

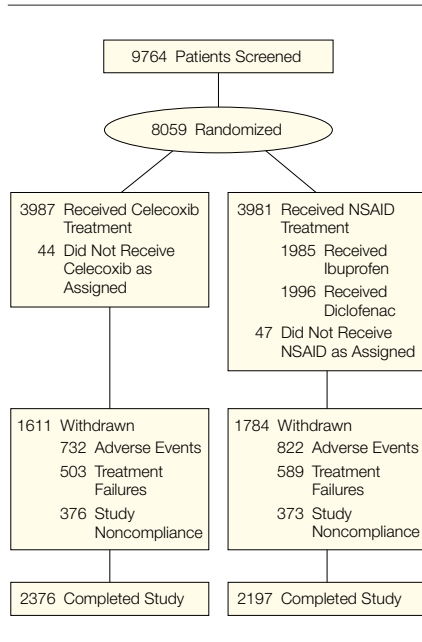
respectively. Clinically significant changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were predefined as increases to at least 3 times the upper limit of normal. Trial safety (eg, serious adverse effects) was monitored in a treatment-blinded fashion during the study by the data safety monitoring board (G.F., T.P., A.W., and R.M.).

Statistical Analysis

Sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect this difference with a 2-sided .05 significance level with statistical power of 85% and assuming a 35% withdrawal rate, a sample size of approximately 4000 patients was required for the celecoxib group and 2000 patients were needed for each of the 2 NSAID groups.

Homogeneity of the treatment groups at baseline was analyzed using the χ^2 test for categorical data and 2-way analysis of variance with treatment and center effects for continuous-valued data. Statistical analyses were conducted on the intent-to-treat population, defined a priori

in the protocol as consisting of all patients who received at least 1 dose of assigned study medication. An additional prespecified analysis was performed on the population of patients not taking aspirin (since aspirin use was a predefined risk factor for GI events). Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on cumulative event rates (symptomatic ulcers and/or ulcer complications) for the 6-month study period and are expressed as annualized incidence rates (number of events per 100 patient-years of exposure or percentage). The log-rank test was used to compare time-to-event curves among treatment groups. Based on the recommendation of the GI events committee and as specified by the protocol a priori, upper GI ulcer complications were defined as a study end point (ie, an uncensored event) if they occurred within the 6-month treatment period and occurred 48 hours after the first dose day or before 14 days after the last known dose of study drug (to avoid confounding due to prestudy or poststudy NSAID use). Patients who had upper GI ulcer complications outside of the specified

Figure 1. Flowchart of Patient Disposition at 6 Months

time frame were censored for purposes of time-to-event analysis. This recommendation was based on the pharmacologic washout period for most common NSAIDs and evidence in the literature of carryover effects of NSAIDs in terms of GI toxic effects.^{8,23} Analyses were conducted with and without these censored patients. The effects of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were analyzed by Cox proportional hazards models. The incidences of treatment-emergent adverse effects or clinical laboratory changes in the different treatment groups during the 6 months were compared using the Fisher exact test. All *P* values and 95% confidence intervals (CIs) are 2-sided. No significant differences in adverse events were noted by sex, so results are presented with women and men combined. Adverse events for diclofenac and ibuprofen were similar

except for liver enzyme elevations, for which results are presented separately.

RESULTS

A total of 8059 patients were randomized (FIGURE 1). Ninety-one patients did not receive study drug (32 were randomized and found to be ineligible prior to administration of study drug; 59 withdrew consent prior to taking study drug). Of these 91 patients, 44 were randomized to celecoxib and 47 were randomized to NSAIDs.

A total of 7968 patients received at least 1 dose of medication. Of these, 3987 patients were treated with celecoxib, 400 mg twice per day, and 3981 patients were treated with NSAIDs (1985 received ibuprofen, 800 mg 3 times per day, and 1996 received diclofenac, 75 mg twice per day). The celecoxib and NSAID groups had 1441 and 1384 total patient-years of exposure, respectively. Baseline characteristics did not differ significantly between groups (TABLE 2). More than 20% of the patients were taking low-dosage aspirin (≤ 325 mg/d). Approximately 57% of the patients ($n=4573$) completed 6 months of treatment (Figure 1). More patients in the NSAID treatment group withdrew from the study for either adverse effects ($n=822$ [20.6%]) or lack of therapeutic efficacy ($n=589$ [14.8%]) than did celecoxib-treated patients ($n=732$ [18.4%] and $n=503$ [12.6%], respectively; $P=.01$ and $P=.005$; Figure 1). No patients were lost to follow-up (ie, a cause of withdrawal was determined for all patients who withdrew).

GI Toxicity

A total of 260 cases were selected by the GI events committee for adjudication. The committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic but uncomplicated gastroduodenal ulcers (TABLE 3). Four upper GI ulcer complications (2 in celecoxib-treated patients and 2 in NSAID-treated patients) were censored according to predetermined criteria (see "Methods" section). The remaining 177 cases not meeting the definition of gastroduodenal ulcer or ulcer

Table 2. Baseline Patient Characteristics*

Characteristics	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)
Age, mean (range), y	60.6 (20-89)	59.8 (18-90)
>65 y, %	39.1	37.3
>75 y, %	12.2	11.4
Women, %	68.5	69.1
Race/ethnicity, %		
White	88.5	87.9
Black	7.5	8.2
Hispanic	2.7	2.8
Asian	0.7	0.8
Other	0.6	0.6
Primary rheumatoid arthritis, %	27.3	27.5
Duration of disease, mean (SD), y		
Osteoarthritis	10.3 (9.7)	10.1 (9.9)
Rheumatoid arthritis	11.3 (9.9)	10.7 (9.6)
NSAID therapy at study entry, %	81.4	81.6
Ibuprofen	21.7	20.9
Diclofenac	13.6	14.0
Potential risk factor, %		
History of gastrointestinal bleeding	1.7	1.5
History of gastrointestinal ulcer	8.4	8.1
<i>Helicobacter pylori</i> infection, %	38.5	38.2
Tobacco use, %	15.8	14.9
Alcohol use, %	30.9	30.1
Concurrent medications, %		
Aspirin (≤ 325 mg/d)	20.9	20.4
Corticosteroids	30.6	29.5
Anticoagulants	1.1	1.1

*NSAID indicates nonsteroidal anti-inflammatory drug.

complication were assigned a diagnosis from the categories listed in Table 3.

The annualized incidence of upper GI ulcer complications in celecoxib-treated patients was 0.76% (11 events/1441 patient-years) vs an incidence of 1.45% (20 events/1384 patient-years) for patients taking NSAIDs ($P = .09$; FIGURE 2A). The relative risk (RR) for celecoxib compared with NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was 2.08% (30 events/1441 patient-years) vs 3.54% (49 events/1384 patient-years) for patients taking NSAIDs ($P = .02$; Figure 2A). The RR for celecoxib compared with NSAIDs was 0.59 (95% CI, 0.38-0.94).

Inclusion of the 2 censored events in each group did not alter the interpretation of results. For upper GI ulcer complications, the rates without censoring were 0.90% (13 events/1441 patient-years) and 1.59% (22 events/1384 patient-years) for celecoxib and NSAIDs, respectively ($P = .11$). For upper GI ulcer complications plus symptomatic ulcers, the rates were 2.22% (32 events/

1441 patient-years) and 3.68% (51 events/1384 patient-years) for celecoxib and NSAIDs, respectively ($P = .03$). Corticosteroid use was not significantly associated with the incidence of upper GI ulcer complications in either treatment group (RR, 0.2 and 0.6 for patients treated with celecoxib and NSAIDs, respectively; $P = .13$ and $P = .27$).

GI Toxicity With Aspirin Use

Based on time-to-event analyses using a Cox proportional hazard model, low-dosage aspirin use was found to have a significant effect on the incidence of upper GI ulcer complications in celecoxib-treated patients. Within the celecoxib treatment group, the RR of an upper GI ulcer complication was 4.5 with low-dosage aspirin use: 6 events in 833 patients taking low-dosage aspirin vs 5 events in 3154 non-aspirin users ($P = .01$). Low-dosage aspirin use did not have a significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (RR, 1.7; $P = .29$).

When the non-aspirin-using cohort was examined, 2 upper GI ulcer complications were censored (1 in each

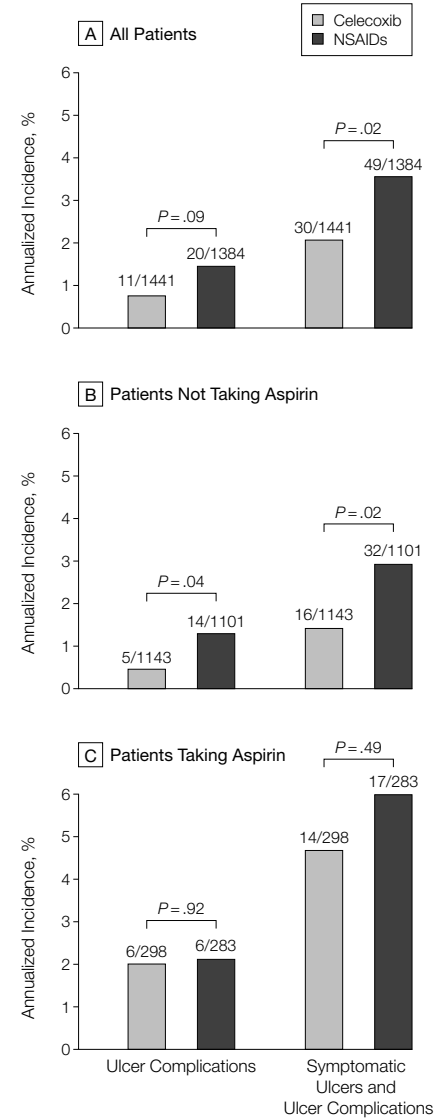
group). The annualized incidence of upper GI ulcer complications in non-aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% [5 events/1143 patient-years] vs 1.27% [14 events/1101 patient-years]; $P = .04$; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence

Table 3. Adjudicated Cases Meeting and Not Meeting Prespecialized Definitions of Gastroduodenal Ulcers and Ulcer Complications*

	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)
Total No. of cases adjudicated	111	149†
No. of adjudicated cases not meeting the definition of a gastroduodenal ulcer or ulcer complication		
Esophageal disease	23	21
Gastroduodenitis	12	21
Colonic or small bowel disease	10	7
Nonulcer bleeding	10	17
Miscellaneous GI symptoms	18	20
Anemia	5	12
Cholelithiasis	1	0
Total	79	98
No. of adjudicated cases meeting the definition of a gastroduodenal ulcer or ulcer complication		
Gastroduodenal ulcers	19	29
Ulcer complications‡	13	22
Upper GI bleeding	10	20
Perforation	0	0
Gastric outlet obstruction	1	0
Total	32	51

*NSAID indicates nonsteroidal anti-inflammatory drug; GI, gastrointestinal.
 † $P < .001$ vs celecoxib group.
 ‡Four ulcer complications (2 in the celecoxib group and 2 in the NSAID group) were censored from the analysis because of the timing of the event based on a priori-specified definitions.

Figure 2. Annualized Incidence of Upper Gastrointestinal Tract Ulcer Complications Alone and With Symptomatic Gastroduodenal Ulcers



Numbers above bars indicate events per patient-years of exposure. NSAIDs indicates nonsteroidal anti-inflammatory drugs.

of upper GI ulcer complications plus symptomatic ulcers in patients not taking aspirin was also significantly lower with celecoxib than with NSAIDs (1.40% [16 events/1143 patient-years] vs 2.91% [32 events/1101 patient-years]; $P=.02$; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.48 (95% CI, 0.28-0.89).

Inclusion of the 1 censored event in each group did not alter the interpreta-

tion of results. For upper GI ulcer complications, the rates without censoring were 0.52% (6 events/1143 patient-years) and 1.36% (15 events/1101 patient-years) for celecoxib and NSAIDs, respectively ($P=.05$). For upper GI ulcer complications plus symptomatic ulcers, the rates were 1.49% (17 events/1143 patient-years) and 3.00% (33 events/1101 patient-years) for celecoxib and NSAIDs, respectively ($P=.02$).

For patients taking aspirin (Figure 2C), the annualized incidences of symptomatic ulcers and/or upper GI complications were not significantly different in patients taking celecoxib vs NSAIDs. For upper GI complications, the observed rates were 2.01% for patients taking celecoxib vs 2.12% for patients taking NSAIDs (6 events/298 patient-years vs 6 events/283 patient-years, respectively; $P=.92$). For upper GI ulcer complications plus symptomatic ulcers, the observed rates were 4.70% for patients taking celecoxib vs 6.00% for patients taking NSAIDs (14 events/298 patient-years vs 17 events/283 patient-years, respectively; $P=.49$). Including the 2 censored events (1 in each group), the rates were 2.35% and 2.47%, respectively, for upper GI ulcer complications and 5.03% and 6.36%, respectively, for upper GI ulcer complications plus symptomatic ulcers.

Other Adverse Effects

Adverse effects with an incidence of at least 5% in either treatment group during the 6-month treatment period were GI symptoms, upper respiratory tract infection or related symptoms, headache, and rash. Adverse effects causing withdrawal with an incidence of at least 1% in either treatment group were GI symptoms, rash, and elevated transaminase levels. For these categories, celecoxib was associated with equivalent or lower incidences of adverse effects and withdrawals compared with NSAID therapy, with the exceptions of rash and pruritus (TABLE 4).

Serious adverse effects (representing hospitalizations or malignancies detected during the 6-month treatment period) were reported for 4.3% of celecoxib patients (172 events/3987 patients) and 4.2% of NSAID patients (168 events/3981 patients). The most common serious adverse effects in patients taking celecoxib and NSAIDs were accidental fractures (7 and 8 events, respectively), back pain (8 and 8 events, respectively), pneumonia (9 and 9 events, respectively), cardiac failure (9 and 10 events, respectively), myocardial infarction (10 and 10 events, re-

Table 4. Adverse Effects During the 6-Month Treatment Period*

Adverse Effects	All Patients		Patients Not Taking Aspirin	
	Celecoxib Group (n = 3987)	NSAID Group (n = 3981)	Celecoxib Group (n = 3154)	NSAID Group (n = 3169)
Gastrointestinal				
Dyspepsia	575 (14.4)	640 (16.1)†	427 (13.5)	496 (15.7)†
Abdominal pain	387 (9.7)	522 (13.1)†	286 (9.1)	395 (12.5)†
Diarrhea	373 (9.4)	392 (9.8)	288 (9.1)	293 (9.2)
Nausea	277 (6.9)	370 (9.3)†	213 (6.8)	277 (8.7)†
Constipation	68 (1.7)	234 (5.9)†	48 (1.5)	172 (5.4)†
Total	1250 (31.4)	1465 (36.8)†	942 (29.9)	1127 (35.6)†
Withdrawals	345 (8.7)	427 (10.7)†	252 (8.0)	321 (10.1)†
Hepatic				
Elevated serum ALT	23 (0.6)	88 (2.2)†	18 (0.6)	68 (2.1)†
Elevated serum AST	18 (0.5)	73 (1.8)†	13 (0.4)	60 (1.9)†
Total	24 (0.6)	93 (2.3)†	18 (0.6)	72 (2.3)†
Withdrawals	2 (<0.1)	46 (1.2)†	2 (<0.1)	36 (1.1)†
Bleeding-related				
Anemia	81 (2.0)	175 (4.4)†	59 (1.9)	123 (3.9)†
Ecchymosis	28 (0.7)	32 (0.8)	22 (0.7)	26 (0.8)
Hematochezia	17 (0.4)	40 (1.0)†	11 (0.3)	29 (0.9)†
Total	123 (3.1)	238 (6.0)†	90 (2.9)	171 (5.4)†
Withdrawals	16 (0.4)	26 (0.7)	13 (0.4)	19 (0.6)
Renal				
Peripheral edema	113 (2.8)	138 (3.5)	90 (2.9)	108 (3.4)
Hypertension	66 (1.7)	90 (2.3)†	50 (1.6)	65 (2.1)
Increased creatinine level	28 (0.7)	48 (1.2)†	20 (0.6)	33 (1.0)
Total	200 (5.0)	263 (6.6)†	155 (4.9)	198 (6.2)†
Withdrawals	44 (1.1)	41 (1.0)	37 (1.2)	32 (1.0)
Cardiovascular				
Cerebrovascular accident	5 (0.1)	10 (0.3)	3 (<0.1)	5 (0.2)
Myocardial infarction	10 (0.3)	11 (0.3)	3 (<0.1)	4 (0.1)
Angina	24 (0.6)	22 (0.6)	10 (0.3)	7 (0.2)
Total	37 (0.9)	39 (1.0)	16 (0.5)	14 (0.4)
Withdrawals	12 (0.3)	13 (0.3)	9 (0.3)	5 (0.2)
Cutaneous				
Rash	218 (5.5)	103 (2.6)†	180 (5.7)	91 (2.9)†
Pruritus	91 (2.3)	59 (1.5)†	72 (2.3)	44 (1.4)†
Urticaria	22 (0.6)	14 (0.4)	18 (0.6)	13 (0.4)
Total	298 (7.5)	163 (4.1)†	241 (7.6)	136 (4.3)†
Withdrawals	109 (2.7)	49 (1.2)†	92 (2.9)	43 (1.4)†

*Data are given as No. (%) of patients. Categories are nonadditive; patients may have experienced more than 1 adverse event in each category. NSAID indicates nonsteroidal anti-inflammatory drug; ALT, alanine aminotransferase; and AST, aspartate aminotransferase.
† $P\leq .05$ vs celecoxib group.

spectively), and coronary artery disease (9 and 7 events, respectively). No serious rashes or unexpected serious adverse events were observed in patients taking celecoxib.

The overall incidence of GI symptoms experienced by patients taking celecoxib was significantly lower than by those taking NSAIDs, as was the rate of withdrawal due to GI intolerance (Table 4). Of the most commonly reported GI adverse effects, dyspepsia, abdominal pain, nausea, and constipation were significantly less common with celecoxib than with NSAIDs, although there was no difference in the incidence of diarrhea (Table 4).

The overall incidence of bleeding-related adverse events, and specifically, anemia and hematochezia, experienced by patients taking celecoxib was significantly lower than that among patients taking NSAIDs for all patients and for those not taking aspirin (Table 4). Similar results were noted for patients taking aspirin; the incidences of all bleeding-related adverse events were 4.0% and 8.3% for patients taking celecoxib and NSAIDs, respectively, and for anemia were 2.6% and 6.4%, respectively ($P < .001$ for both comparisons). Celecoxib was also associated with a lower incidence ($P < .001$) of clinically meaningful reductions in hematocrit and/or hemoglobin for the entire patient cohort than NSAIDs (Figure 3). A lower incidence was noted both in patients not taking aspirin (1.3% vs 3.4% in patients taking celecoxib and NSAIDs, respectively; $P < .001$) and patients taking aspirin (2.6% vs 4.9% in the 2 groups, respectively; $P = .02$). This difference persisted when all cases selected by the GI events committee for adjudication were excluded from the analysis, thus removing all patients with ulcer complications, symptomatic ulcers, or other diagnosed GI disease (Figure 3). Mean serum iron-iron binding capacity ratios increased in patients taking celecoxib and decreased in patients taking NSAIDs (1.4% vs -2.3%; $P = .007$).

As shown in Figure 4, the incidence of serum ALT or AST elevations that exceeded 3 times the upper limit

of normal was several-fold and statistically significantly higher in patients receiving NSAIDs than those receiving celecoxib. The incidence of ALT elevation for diclofenac was 3.2% vs 0.3% for ibuprofen; for AST, it was 1.8% vs 0.1%, respectively. Similarly, investigators reported a significantly higher incidence of adverse effects related to elevated ALT and AST with NSAID treatment (Table 4). Study withdrawals due to such elevations were also higher in patients receiving NSAIDs (Table 4). Overall, 97% of ALT and AST abnormalities occurred in patients receiving diclofenac.

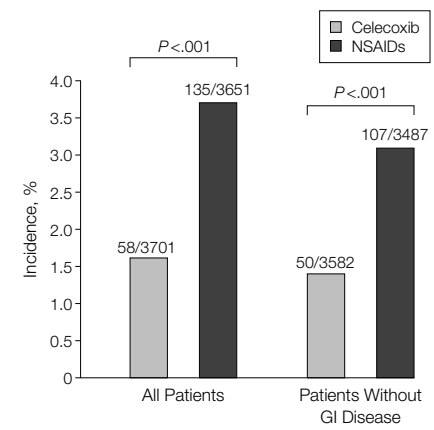
The overall incidence of renal adverse effects, and the incidence of increased creatinine and hypertension in particular, were significantly lower in patients receiving celecoxib than in those receiving NSAIDs (Table 4). Also, significantly more patients receiving NSAIDs exhibited clinically significant elevations in serum creatinine and/or serum urea nitrogen levels than with celecoxib (Figure 4).

The overall incidence of cardiovascular events, and the incidences of cerebrovascular events and myocardial infarction in particular, were similar in the 2 treatment groups (Table 4). No treatment-related differences in such events were apparent in the cohort of patients not taking aspirin for cardiovascular prophylaxis (Table 4). Incidence of myocardial infarction in patients taking either celecoxib or NSAIDs was 0.3%, with 95% CIs of 0.12% to 0.46% and 0.14% to 0.49%, respectively. For patients not taking aspirin, incidence of myocardial infarction in patients taking celecoxib was less than 0.10% (95% CI, 0.02%-0.28%) and was also 0.10% (95% CI, 0.03%-0.32%) in patients taking NSAIDs.

COMMENT

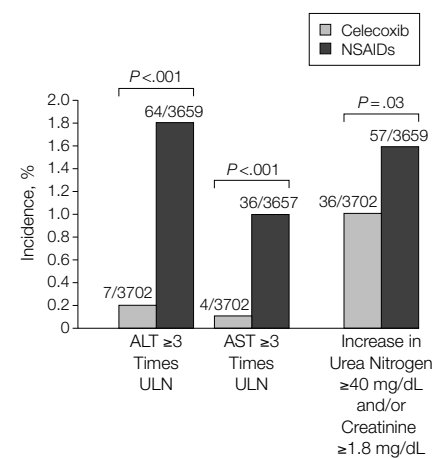
This study determined that celecoxib, a COX-2-specific inhibitor, when used for 6 months in a dosage 2 to 4 times the maximum therapeutic dosage, is associated with a lower incidence of combined clinical upper GI events than comparator NSAIDs (ibuprofen and di-

Figure 3. Patients With Decreases in Hematocrit and/or Hemoglobin at 6 Months



Data are shown for patients with decreases from pretreatment levels in hematocrit of 10 percentage points or more, in hemoglobin of 20 g/L or more, or both. Results for the entire study population are shown on the left. On the right, results for all patients excluding those with an upper gastrointestinal (GI) ulcer complication, symptomatic ulcer, or other diagnosed GI disease are shown. NSAIDs indicates nonsteroidal anti-inflammatory drugs. Numbers above bars indicate the number of patients with the event per total number of patients in the treatment group.

Figure 4. Patients With Increases in Serum Creatinine and/or Serum Urea Nitrogen and With Elevations in ALT and AST at 6 Months



Data are shown for patients with increases from pretreatment levels in serum creatinine to 1.8 mg/dL (159 μmol/L) or more, in serum urea nitrogen to 40 mg/dL (14.3 mmol/L) or more, or both; and for patients with elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to a level of at least 3 times the upper limit of normal (ULN). In the nonsteroidal anti-inflammatory drug (NSAID) group, 97% of ALT and AST abnormalities occurred in patients taking diclofenac. Numbers above bars indicate the number of patients with the event per total number of patients in the treatment group.

clofenac) used at standard therapeutic dosages.

In this study, patients taking NSAIDs had significantly higher rates of symptomatic ulcers or ulcer complications than did patients taking celecoxib, but the rate for ulcer complications did not differ. The statistically indistinguishable rate of ulcer complications associated with celecoxib and NSAIDs appears to be a function of the higher-than-expected event rate observed in the celecoxib group. The previously reported annualized incidence rate for ulcer complications in patients taking celecoxib (used for the sample size determination) was 0.2%, obtained from pooled analyses of 14 randomized controlled trials.¹⁵

This increased ulcer complication rate was likely attributable to higher-than-anticipated concurrent low-dosage aspirin use. The percentage of patients using low-dosage aspirin for cardiovascular prophylaxis was nearly double that seen in other clinical trials that we have conducted recently, albeit within the range reported for the general population.²⁴ Low-dosage aspirin therapy has clearly been associated with serious GI ulcer complications.²⁵⁻²⁹

In contrast, analysis of non-aspirin users alone demonstrated that celecoxib was associated with a significantly lower incidence of symptomatic ulcers and/or ulcer complications compared with NSAIDs. The rate of ulcer complications in non-aspirin users taking celecoxib (0.44%) is similar to the background rate of ulcer complications observed in patients not taking NSAIDs or aspirin in the general population (0.1%-0.4%).^{8,9,11,12,30-33}

The observed incidences of symptomatic ulcers and/or ulcer complications were not significantly different in patients taking celecoxib vs NSAIDs who were also taking concomitant low-dosage aspirin. Data from endoscopic trials suggest that there may be a significant but smaller risk reduction in patients taking low-dosage aspirin, but this remains to be proven in terms of clinical outcomes.³⁴

In addition to the assessment of GI effects, the present study determined that the increased dosage of celecoxib used in this study did not change the adverse effect profile observed at lower dosages.^{20,21,35}

Of note, celecoxib-treated patients had a significantly lower incidence of clinically significant decreases in hemoglobin and/or hematocrit compared with NSAID-treated patients, even when patients with upper GI ulcer complications, symptomatic ulcers, and other GI diseases were excluded. Celecoxib was also better tolerated than NSAIDs, as evidenced by the decreased incidence of GI symptoms and withdrawals for such symptoms.

The clinical consequences of NSAIDs on kidneys are heterogeneous, and, at present, the relative importance of COX-1 and COX-2 in the human kidney is not well defined.³⁶ Regardless, celecoxib appeared to be associated with significantly less renal toxicity compared with NSAID therapy in this study.

Although it has been hypothesized that COX-2-specific inhibitors might increase the risk of cardiovascular thromboembolic events via inhibition of vascular prostacyclin synthesis without a corresponding inhibition of platelet thromboxane, no such increase was evident in the current study.³⁷ In both the entire study population and the cohort not taking aspirin (who would conjecturally be at greatest risk of such an effect), the incidence of cardiovascular events, particularly myocardial infarction, was comparable between the celecoxib and NSAID groups.

Despite the size and duration of this trial, the populations of patients with OA and RA are much larger and therapy continues for substantially longer than 6 months.³⁸ Moreover, many patients with OA and RA have comorbid illnesses (eg, active GI disease) that would have excluded them from the current study. Consequently, the results of this study do not address the occurrence of rare adverse events, nor can they be extrapolated to all patients seen in general clinical practice.

Despite these caveats, however, our results demonstrate that celecoxib, at a dosage 2- to 4-fold greater than the maximum therapeutic dosages and those approved for labeling for RA and OA, is associated with a lower rate of upper GI toxic effects compared with standard therapeutic dosages of NSAIDs. This finding supports the COX-2 hypothesis that COX-2-specific agents exhibit decreased GI toxic effects.^{17,39} Despite the high dosage used, other adverse effects did not emerge. Our findings thus have significant implications with respect to drug therapy for the symptomatic treatment of RA and OA.

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REFERENCES

1. *The American College of Rheumatology Clinical Guidelines*. Atlanta, Ga: American College of Rheumatology; 1997.
2. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal anti-inflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum*. 2000;43:378-385.
3. Pincus T, Swearingen C, Cummins P, Callahan LF. Preference for nonsteroidal anti-inflammatory drugs versus acetaminophen and concomitant use of both types of drugs in patients with osteoarthritis. *J Rheumatol*. 2000;27:1020-1027.
4. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med*. 1991;115:787-796.
5. Henry D, Lim LL, Garcia RL, et al. Variability in risk of gastrointestinal complications with individual nonsteroidal anti-inflammatory drugs: results of a col-

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- laborative meta-analysis. *BMJ*. 1996;312:1563-1566.
6. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med*. 1991;114:257-263.
 7. Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual nonsteroidal anti-inflammatory drugs. *Lancet*. 1994;343:1075-1078.
 8. Macdonald TM, Morant SV, Robinson GC, et al. Association of upper gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ*. 1997;315:1333-1337.
 9. Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am J Epidemiol*. 1995;141:539-545.
 10. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med*. 1999;340:1888-1899.
 11. Gutthann SP, Garcia RL, Raiford DS. Individual nonsteroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology*. 1997;8:18-24.
 12. Singh G, Rosen Ramey D. NSAID-induced gastrointestinal complications: the ARAMIS perspective—1997: Arthritis, Rheumatism, and Aging Medical Information System. *J Rheumatol Suppl*. 1998;51:8-16.
 13. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1995;123:241-249.
 14. Paulus HE. FDA arthritis advisory committee meeting: serious gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs; drug-containing renal and biliary stones; diclofenac and carprofen approved. *Arthritis Rheum*. 1988;31:1450-1451.
 15. Goldstein JL, Silverstein FE, Agrawal NM, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol*. 2000;95:1681-1690.
 16. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. *Nature*. 1971;231:235-239.
 17. Crofford LJ, Lipsky PE, Brooks P, Abramson SB, Simon LS, Van de Putte LBA. Basic biology and clinical application of specific cyclooxygenase-2 inhibitors. *Arthritis Rheum*. 2000;43:4-13.
 18. Gierse JK, Koboldt CM, Walker MC, Seibert K, Isakson PC. Kinetic basis for selective inhibition of cyclooxygenases. *Biochem J*. 1999;339:607-614.
 19. Gierse JK, Hauser SD, Creely DP, et al. Expression and selective inhibition of the constitutive and inducible forms of human cyclooxygenase. *Biochem J*. 1995;305:479-484.
 20. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA*. 1999;282:1921-1928.
 21. Bensen WG, Fiechtner JJ, McMillen JJ, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc*. 1999;74:1095-1105.
 22. *Scott-Levin Physician Drug and Diagnosis Audit* [database]. Newtown, Pa: Scott-Levin; 1997.
 23. Paulus HE, Bulpitt KJ. Nonsteroidal anti-inflammatory drugs. In: Weyand CM, Wortmann RL, eds. *Primer on the Rheumatic Diseases*. Atlanta, Ga: Arthritis Foundation; 1997:422-426.
 24. Physician advice and individual behaviors about cardiovascular disease risk reduction—seven states and Puerto Rico, 1997. *MMWR Morb Mortal Wkly Rep*. 1999;48:74-77.
 25. Stalnikowicz DR. Gastrointestinal bleeding during low-dose aspirin administration for prevention of arterial occlusive events: a critical analysis. *J Clin Gastroenterol*. 1995;21:13-16.
 26. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. *Am J Ther*. 2000;7:121.
 27. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol*. 1993;35:219-226.
 28. Weil J, Colin JD, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ*. 1995;310:827-830.
 29. Kelly JP, Kaufman DW, Jurgelson JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet*. 1996;348:1413-1416.
 30. Garcia RL, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual nonsteroidal anti-inflammatory drugs. *Lancet*. 1994;343:769-772.
 31. Lanza LL, Walker AM, Bortnichak EA, Dreyer NA. Peptic ulcer and gastrointestinal hemorrhage associated with nonsteroidal anti-inflammatory drug use in patients younger than 65 years: a large health maintenance organization cohort study. *Arch Intern Med*. 1995;155:1371-1377.
 32. Hallas J, Lauritsen J, Villadsen HD, Gram LF. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding: identifying high-risk groups by excess risk estimates. *Scand J Gastroenterol*. 1995;30:438-444.
 33. Rodriguez LAG, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med*. 1998;158:33-39.
 34. Goldstein JL, Agrawal NM, Silverstein FE, et al. Influence of *H pylori* (Hp) infection and/or low dose aspirin (ASA) on gastroduodenal ulceration in patients treated with placebo, celecoxib or NSAIDs. *Gastroenterology*. 1999;116(suppl 4):G0759
 35. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet*. 1999;354:2106-2111.
 36. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med*. 1999;106:135-245.
 37. McAdam BF, Catella LF, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci U S A*. 1999;96:272-277.
 38. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41:778-799.
 39. Verburg KM, Maziasz TJ, Weiner E, Loose L, Geis GS, Isakson PC. COX-2 specific inhibitors: definition of a new therapeutic concept. *Am J Ther*. In press.