Annals of Internal Medicine | ARTICLE

Gastrointestinal Tolerability and Effectiveness of Rofecoxib versus Naproxen in the Treatment of Osteoarthritis

A Randomized, Controlled Trial

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Background: **Gastrointestinal (GI) toxicity mediated by dual cyclooxygenase (COX)-1 and COX-2 inhibition of nonsteroidal anti-inflammatory drugs (NSAIDs) can cause serious alterations of mucosal integrity or, more commonly, intolerable GI symptoms that may necessitate discontinuation of therapy. Unlike NSAIDs, rofecoxib targets only the COX-2 isoform.**

Objective: **To assess the tolerability of rofecoxib compared with naproxen for treatment of osteoarthritis.**

Design: **Randomized, controlled trial.**

Setting: **600 office and clinical research sites.**

Patients: **5557 patients (mean age, 63 years) with a baseline diagnosis of osteoarthritis of the knee, hip, hand, or spine.**

Intervention: **Rofecoxib, 25 mg/d, or naproxen, 500 mg twice daily. Use of routine medications, including aspirin, was permitted.**

Measurements: **Discontinuation due to GI adverse events (primary end point) and use of concomitant medication to treat GI symptoms (secondary end point). Efficacy was determined by patient-reported global assessment of disease status and the Australian/Canadian Osteoarthritis Hand Index, as well as discontinuations due to lack of efficacy. Patients were evaluated at baseline and at weeks 6 and 12.**

Results: **Rates of cumulative discontinuation due to GI adverse events were statistically significantly lower in the rofecoxib group than in the naproxen group (5.9% vs. 8.1%; relative risk, 0.74 [95% CI, 0.60 to 0.92]; $P = 0.005$), as were rates of cumulative use of medication to treat GI symptoms (9.1% vs. 11.2%; relative risk, 0.79 [CI, 0.66 to 0.96]; $P = 0.014$]). Subgroup analysis of patients who used low-dose aspirin (13%) and those who previously discontinued using arthritis medication because of GI symptoms (15%) demonstrated a relative risk similar to the overall sample for discontinuation due to GI adverse events (relative risk, 0.56 [CI, 0.31 to 1.01] and 0.53 [CI, 0.34 to 0.84], respectively). No statistically significant difference was observed between treatments for efficacy in treating osteoarthritis or for occurrence of other adverse events.**

Conclusions: **In patients with osteoarthritis treated for 12 weeks, rofecoxib, 25 mg/d, was as effective as naproxen, 500 mg twice daily, but had statistically significantly superior GI tolerability and led to less use of concomitant GI medications. Benefits of rofecoxib in subgroup analyses were consistent with findings in the overall sample.**

Ann Intern Med. 2003;139:539-546. www.annals.org

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Osteoarthritis usually affects older persons who frequently take many medications for comorbid conditions (1–3). Patients with osteoarthritis often use nonsteroidal anti-inflammatory drugs (NSAIDs) to treat symptoms because of the analgesic and anti-inflammatory effects of these drugs; in addition, NSAIDs are preferred to simple analgesics such as acetaminophen or mild opiates (4). Gastrointestinal (GI) toxicity is a common side effect of dual cyclooxygenase (COX)-1– and COX-2–inhibiting NSAIDs. In older patients, GI toxicity is increased by concomitant aspirin use, previous GI intolerability, and other comorbid conditions. The 2 main forms of NSAID-induced GI toxicity manifest as serious alterations in mucosal integrity (leading to perforations, ulcers, and GI bleeding) and GI intolerability, which is more common. Gastrointestinal intolerability is exemplified by dyspepsia, constipation, and abdominal pain that in its most severe form prompts discontinuation of therapy or initiation of treatment with GI protective agents.

Nonsteroidal anti-inflammatory drugs affect prostaglandin synthesis through dual inhibition of COX isoforms COX-1 and COX-2 (5–8). Cyclooxygenase-1 is responsible for producing prostanoids involved in GI mucosal protection and normal platelet function, while COX-2 leads to the production of prostaglandins that mediate pain and inflammation (9–11). Gastrointestinal toxicity induced by NSAIDs is thought to be principally caused by inhibition of COX-1 (12, 13). Rofecoxib is a COX-2 selective inhibitor and spares COX-1 inhibition. A pooled analysis of 8 efficacy trials in osteoarthritis and a large prospective study of outcomes in rheumatoid arthritis showed that rofecoxib maintained efficacy and resulted in a significantly lower incidence of serious GI toxicity compared with nonspecific dual COX inhibitors (14, 15).

We prospectively compared rofecoxib and a dual COX-inhibiting NSAID (naproxen) in relatively unselected patients with characteristics typical of persons seen in clinical practice. Our study sample included elderly patients with comorbid conditions. Forty-nine percent had hypertension, 60% had a history of cardiovascular events, and 47% had a history of GI events, including previous discontinuation of therapy with arthritis medication because of GI symptoms (15%).

Context

Most trials that compare gastrointestinal effects of rofecoxib and nonsteroidal anti-inflammatory drugs examine highly selected patient samples.

Contribution

This randomized, double-blind, placebo-controlled trial of 5557 patients with osteoarthritis includes patients typical of community practice: older patients with comorbid conditions and patients using aspirin for cardiovascular prophylaxis. Rofecoxib and naproxen therapies were discontinued by 5.9% and 8.1% of patients, respectively, because of gastrointestinal side effects. Among low-dose aspirin users, 5.2% taking rofecoxib and 9.4% taking naproxen discontinued using the drugs.

Cautions

The trial tested daily doses of medicines for a short period (3 months) rather than long-term, intermittent dosing based on symptoms.

–The Editors

METHODS

Study Sample

Physicians predominantly at primary care practices associated with investigational sites recruited patients from their existing practices or recruited new patients presenting with osteoarthritis who were screened for study participation. Patients were at least 40 years of age and had osteoarthritis of the knee, hip, hand, or spine that had been symptomatic for more than 6 months and required regular treatment with an NSAID or acetaminophen. Osteoarthritis was classified as American College of Rheumatology functional class I, II, or III. Patients were excluded if, in the opinion of the investigator, they had a potentially confounding concurrent disease. Patients were not excluded because of a history of dyspepsia, ulcer, GI bleeding, or other GI symptoms besides history of malabsorption as long as they did not have a history of sustained use (>4 consecutive days) of GI protective medications such as H_2-blockers, antacids, and proton-pump inhibitors during the month before study entry. Low-dose aspirin (≤100 mg/d) was allowed if it had been taken for cardiovascular prophylaxis before randomization.

Study Design

We enrolled 5557 patients at 600 study sites, 581 in the United States and 19 in Sweden. At the baseline visit, written informed consent and medical history were obtained and eligible patients underwent physical examination. Baseline laboratory tests included complete blood count, serum chemistry studies, and urinalysis. In addition, at baseline, patients completed a Patient Global Assessment of Disease Status (PGADS) questionnaire, which is a 0- to 100-mm visual analogue scale, and the Medical Outcomes Study 36-item Short Form Health Survey, which measured quality of life. Patients who primarily had osteoarthritis of the hand completed the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index (16). Following an initial overview of the questionnaires with study staff, patients completed all efficacy questions without assistance from site personnel. A computer-generated randomization schedule was used to assign eligible patients in a 1:1 ratio to receive rofecoxib, 25 mg/d, or naproxen, 500 mg twice daily. Allocation was balanced by study site. To maintain blinding, patients took rofecoxib plus a naproxen placebo or naproxen plus a rofecoxib placebo in the morning and naproxen or naproxen placebo in the evening. Acetaminophen (≤2600 mg/d) was available to all patients as needed during the study as rescue medication for intolerable pain. Patients were also permitted to use concomitant GI protective medications during the trial (including proton-pump inhibitors, antacids, and H_2-blockers) if needed to treat GI symptoms.

Investigational site staff contacted patients by telephone for collection of safety data at weeks 3 and 9 of therapy. At week 6 and week 12 (or discontinuation), patients returned to the office and were questioned by a clinical investigator about adverse events and changes in medical therapy since the last visit. A physical examination was performed, vital signs were recorded, and patients completed the PGADS questionnaire. The investigator identified adverse events on the basis of physical examination of the patient and patient-reported adverse events; he or she also evaluated adverse events for severity and determined causality. Study medication, adherence, and rescue acetaminophen use were recorded. At week 12 (or discontinuation), a physical examination was performed; patients completed the Medical Outcomes Study 36-item Short Form Health Survey; and complete blood count, serum chemistry studies, and urinalysis were done. Patients with hand osteoarthritis completed the AUSCAN Osteoarthritis Hand Index. Adherence was assessed by measuring pill count (doses taken compared with doses scheduled) during study site visits at weeks 6 and 12. The investigators were instructed to report all laboratory and clinical adverse events that occurred during treatment and within 14 days of discontinuation of therapy with the study drug. Patients were instructed to contact an investigator if they wanted to discontinue treatment. An investigator could recommend that a patient discontinue treatment because of clinical or laboratory assessments.

Ethical Considerations

The study was conducted with consideration for the protection of patients, as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards or ethical review committees. All patients gave written informed consent before undergoing any examination or study procedure.

Statistical Analysis

All analyses were prespecified in the protocol and detailed in the data analysis plan. The primary end point, GI tolerability, was defined as discontinuation due to GI adverse events or abdominal pain during the 12-week treatment period. The primary time point or exposure period was defined as end of study, that is, from the time of the first dose up to 14 days after the 12-week visit (day 98) or discontinuation. For time-to-event data, the log-rank test was used to compare the cumulative incidence curves for discontinuation due to GI adverse events. The Cox proportional hazards model with treatment as a factor was used to estimate relative risk (RR) and corresponding 95% CIs for rofecoxib compared with naproxen. Similar analyses were conducted for any concomitant use of GI medications during the trial. Incidence of clinical and laboratory adverse events was tabulated by treatment group. Additional tabulations were prepared for serious adverse events, drug-related adverse events, and adverse events that resulted in study withdrawal. To determine the incidence of perforations, ulcers, bleeding, and cardiovascular events, two expert external committees (GI and cardiovascular) evaluated blinded data obtained from patients suspected of having an event that required adjudication, according to previously described criteria (17). A Cox proportional hazards model with treatment effect as a factor was used to estimate RRs and corresponding CIs for perforations, ulcers, bleeding, or cardiovascular events in the rofecoxib group compared with the naproxen group. The Fisher exact test was used to compare incidence of confirmed perforations, ulcers, bleeding, thrombotic events, and cardiovascular events according to Antiplatelet Trialists' Collaboration criteria (17). Summaries were prepared for all other safety variables.

The PGADS questionnaire was measured on a 0- to 100-mm visual analogue scale and was evaluated at baseline, week 6, and week 12. The analysis of PGADS applied a last-observation-carried-forward approach in which missing data at week 12 were imputed by data from week 6. Missing baseline and week 6 data were not imputed. For each efficacy evaluation, differences in treatment means and corresponding CIs were estimated from an analysis of covariance model with a factor for treatment and baseline PGADS value as a covariate. Summary statistics were also prepared for changes from baseline in vital signs, laboratory measurements, and adherence. We conducted subgroup analyses of patients who used low-dose aspirin (20 to 325 mg of aspirin, on average, per day), patients who previously discontinued therapy with arthritis medication because of GI symptoms, and patients with hypertension at baseline (those taking antihypertensive medications at randomization) to determine the consistency of results compared with the overall cohort.

For all analyses, we used a modified intention-to-treat approach: All patients who were randomly assigned and took at least 1 dose of study medication were included in the analysis. Data from 3 patients at 1 study site were excluded from all analyses because of questionable validity, but treatment blinding was maintained. A sample size of 2780 patients per treatment group was expected to provide 90% power to detect a difference of 2 percentage points between treatments for the primary safety variable. All statistical tests were two-sided and were performed at an α level of 0.05.

Role of the Funding Source

Funding for the study was provided by Merck & Co., Inc., which facilitated the collection and analysis of the study data. Merck authors and the clinical investigators jointly developed the manuscript content.

RESULTS

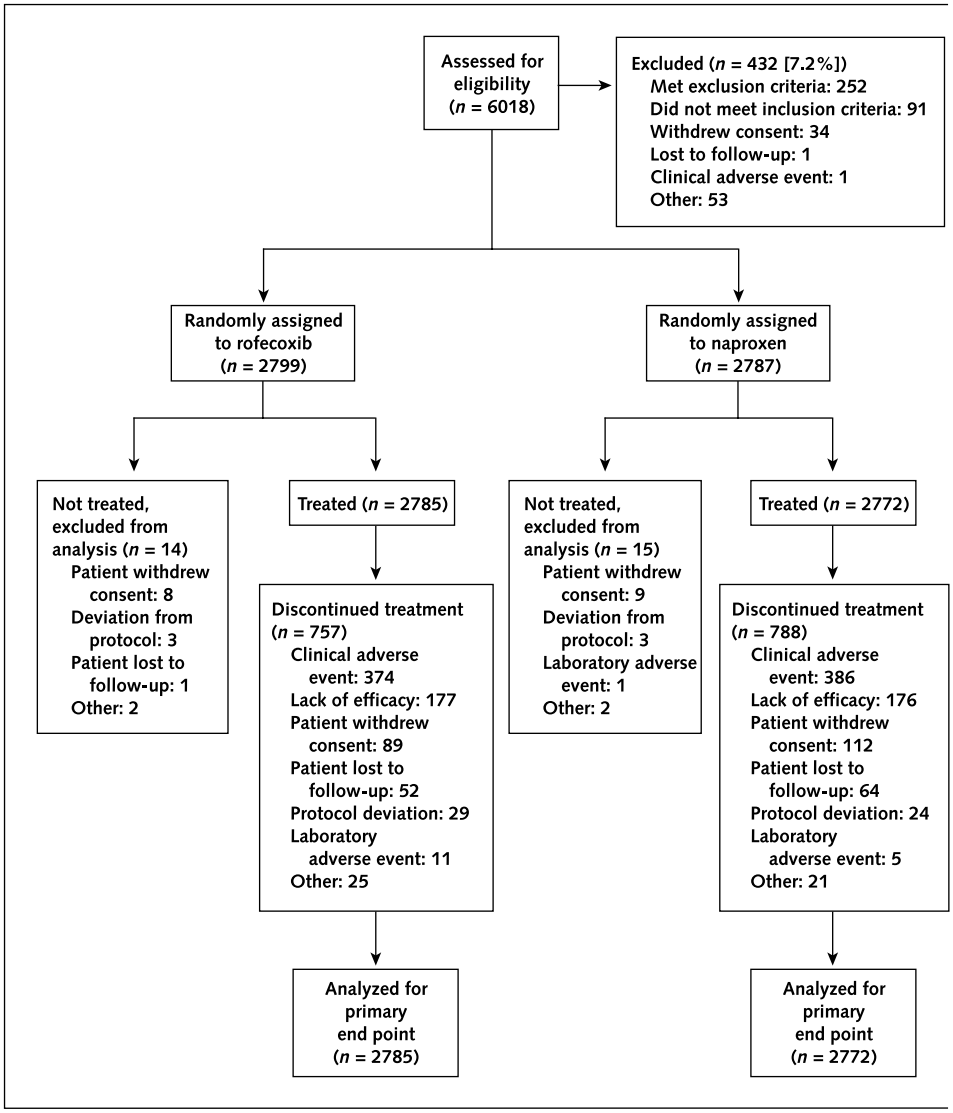
Patient Disposition and Baseline Characteristics

Of 6018 patients screened, 5557 received rofecoxib ($n = 2785$) or naproxen ($n = 2772$). Four hundred thirty-two did not meet entry criteria, and 29 were randomly assigned but never took the study drug (**Figure 1**). On average, more than 92% of scheduled doses were taken by patients in each group and nearly 90% of patients in both groups had greater than 80% adherence. Baseline demographic characteristics were similar between treatment groups (**Table 1**). Ninety percent of patients had osteoarthritis involving joints other than the primary study joint, and 92% had had osteoarthritis symptoms for more than 1 year. Most patients had previously used NSAIDs and, consistent with a previously published survey of medication use in osteoarthritis (4), 30% of patients had used NSAIDs with acetaminophen before randomization. The 2 treatment groups were similar in history of NSAID-associated GI symptoms. Overall, 29% of patients reported a history of GI events associated with NSAID use. In addition, 15% had stopped arthritis medication because of past stomach or abdominal symptoms and were considered to have previous GI intolerance of osteoarthritis treatment (that is, NSAIDs). The rofecoxib and naproxen groups had similar cardiovascular and GI system histories at baseline (previous cardiovascular events, 59% vs. 61% [hypertension, 44% vs. 46%]; previous GI events, 47% vs. 47%). At study entry, 13% of patients were receiving aspirin and 49% were taking antihypertensive medication; these patients were considered the low-dose aspirin subgroup and the hypertension subgroup, respectively, for additional analyses.

Primary and Secondary End Points

Rofecoxib compared with naproxen was associated with a significantly lower incidence of discontinuation due to GI adverse events (5.9% vs. 8.1%, respectively). Evaluation of the survival curve showed that treatment groups separated by week 3 and were statistically significantly different over the course of the entire study. The RR was 0.75 (CI, 0.59 to 0.96; $P = 0.020$) over 6 weeks and 0.74 (CI,

Figure 1. **Trial profile.**



0.60 to 0.92; $P = 0.005$) over the entire study (**Figure 2**, *top*). The GI adverse events that most often caused discontinuation of therapy with study medication (≥0.5%) were abdominal pain, epigastric discomfort, diarrhea, heartburn, nausea, and dyspepsia. The cumulative incidence of concomitant use of GI medication was also statistically significantly lower in patients taking rofecoxib than in patients taking naproxen: 6.0% versus 7.5% over 6 weeks and 9.1% versus 11.2% over the entire study. Corresponding RRs were 0.79 (CI, 0.64 to 0.98; $P = 0.033$) over 6 weeks and 0.79 (CI, 0.66 to 0.96; $P = 0.014$) over the entire study. There were 2 confirmed perforations, ulcers, or bleeding episodes in the rofecoxib group and 9 in the naproxen group (RR, 0.22; $P = 0.038$).

The reduction in discontinuation due to GI adverse events among patients in the low-dose aspirin subgroup assigned to rofecoxib compared with those assigned to naproxen (5.2% vs. 9.4%) (RR, 0.56 [CI, 0.31 to 1.01]) was similar to that in the overall sample (**Figure 2**). These findings were similar to those in the overall sample (**Figure 2**, *top*). Furthermore, analysis of interaction of treatment by low-dose aspirin showed no statistically significant modification of effect ($P > 0.2$), indicating a consistent risk reduction regardless of aspirin use. The reduction in concomitant use of GI medication among patients in the low-dose aspirin subgroup assigned to rofecoxib compared with those assigned to naproxen (12.5% vs. 15.3%) (RR, 0.76 [CI, 0.49 to 1.19]) was also similar to findings in the overall sample. Among patients who had stopped arthritis medication before the study because of stomach or abdominal problems (those who had previous GI intolerance), reduction in discontinuation due to GI adverse events in the rofecoxib group compared with the naproxen group was also consistent (7.6% vs. 14.4%) (RR, 0.53 [CI, 0.34 to 0.84]).

The most commonly reported adverse events in the 2

Table 1. **Summary of Baseline Characteristics**

Characteristic	Rofecoxib Group (*n* = 2785)	Naproxen Group (*n* = 2772)
Mean age ± SD, *y*	63 ± 11	63 ± 11
Sex, *n (%)*		
Male	815 (29)	794 (29)
Female	1970 (71)	1978 (71)
Ethnicity, *n (%)*		
White	2425 (87)	2396 (86)
Black	233 (8)	251 (9)
Hispanic	93 (3)	95 (3)
Asian	18 (0.7)	13 (0.5)
Native American	6 (0.2)	5 (0.2)
Other	10 (0.4)	12 (0.4)
Primary study joint, *n (%)*		
Knee	1431 (51)	1356 (49)
Hand	447 (16)	463 (17)
Hip	237 (9)	312 (11)
Spine	669 (24)	639 (23)
Previous osteoarthritis therapy, *n (%)*		
Nonsteroidal anti-inflammatory drugs only	1706 (61)	1741 (63)
Acetaminophen only	203 (7)	184 (7)
Both	851 (31)	816 (29)
Neither	25 (0.9)	31 (1.1)

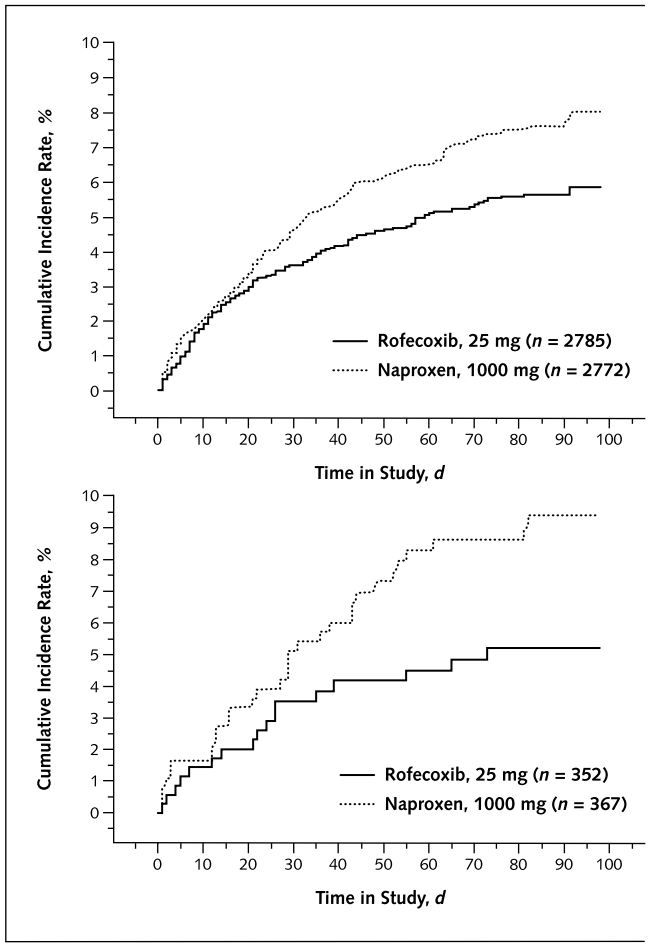
treatment groups were headache, upper respiratory tract infection, abdominal pain, nausea, diarrhea, and constipation. Approximately 30% of the patients in each group had at least 1 clinical adverse event that an investigator considered to be at least possibly related to the study drug. No statistically significant differences were seen in incidence of hypertension, predefined limits of change for systolic blood pressure or diastolic blood pressure, or lower-extremity edema (**Table 2**). Although incidence of these events was higher in hypertensive patients than in nonhypertensive patients, differences were not statistically significant between treatment groups (**Table 2**). The rofecoxib and naproxen groups did not differ significantly in the number of thrombotic cardiovascular events, as defined by the combined Antiplatelet Trialists' Collaboration end points (10 [0.4%] vs. 7 [0.3%]; $P > 0.2$) (17), or in adjudicated confirmed thrombotic events (9 [0.3%] vs. 12 [0.4%]; $P > 0.2$). Five myocardial infarctions occurred in the rofecoxib group, and 1 occurred in the naproxen group ($P > 0.2$). No strokes occurred in the rofecoxib group and 6, all thrombotic, occurred in the naproxen group ($P = 0.015$).

In terms of osteoarthritis efficacy, no statistically significant difference in PGADS scores was observed between the rofecoxib and naproxen groups over 12 weeks (−10.4 vs. −9.6; $P > 0.2$). Improvement from baseline between treatment groups was also not statistically significantly different when analyzed by primary study joint or history of arthritis treatment. Approximately 16% of patients identified the hand as their primary affected joint and were required to complete the AUSCAN Osteoarthritis Hand Index. This instrument uses a 5-point Likert scale (1 = no pain or difficulty; 5 = extreme pain or difficulty) to assess 3 domains of hand osteoarthritis (pain, stiffness, and physical function) (16). Improvement in AUSCAN scores was not statistically significantly different between the rofecoxib and naproxen groups (−0.28 vs. −0.31 for pain, −0.39 vs. −0.33 for stiffness, and −0.37 vs. −0.38 for function; $P > 0.2$ for comparisons of all domains). Overall, discontinuation due to lack of efficacy was also not statistically significantly different between the 2 groups (6.4% vs. 6.3%; $P > 0.2$).

DISCUSSION

Several previous clinical trials have shown that rofecoxib was as effective as high doses of NSAIDs for osteoarthritis treatment (18, 19). However, NSAIDs can lead to serious GI events, such as perforations, ulcers, and bleeding, as well as more common symptoms, such as dyspepsia and abdominal pain. These symptoms may lead patients to discontinue treatment or add gastroprotective medications to improve tolerability.

Figure 2. **Cumulative incidence of discontinuation due to gastrointestinal adverse events.**



Top. The incidence among the overall study sample. **Bottom.** The incidence among patients who used low-dose aspirin. For both parts, Kaplan–Meier curves display the time course of cumulative incidence of discontinuations due to gastrointestinal adverse events by treatment group.

Table 2. **Hypertension and Edema in the Overall Sample and in the Hypertensive Subgroup***

Event	Rofecoxib Group		Naproxen Group	
	Hypertensive Patients	Total Cohort	Hypertensive Patients	Total Cohort
Patients, *n*	1338	2785	1376	2772
Hypertension, *n (%)*	46 (3.4)	81 (2.9)	42 (3.1)	66 (2.4)
Discontinuations due to hypertension, *n (%)*	7 (0.5)	15 (0.5)	4 (0.3)	6 (0.2)
Lower-extremity edema, *n (%)*	58 (4.3)	97 (3.5)	62 (4.5)	104 (3.8)
Discontinuations due to lower-extremity edema, *n (%)*	8 (0.6)	13 (0.5)	7 (0.5)	8 (0.3)
Patients with blood pressure measurement, *n*†	1275	2654	1330	2654
Exceeding predefined limits of change for systolic blood pressure, *n (%)*‡	167 (13.1)	285 (10.7)	161 (12.1)	248 (9.3)
Exceeding predefined limits of change for diastolic blood pressure, *n (%)*§	58 (4.5)	91 (3.4)	47 (3.5)	81 (3.1)

* Hypertensive patients were defined as those who had taken any medication for hypertension as previous therapy.
† Patients with both baseline and at least one on-treatment blood pressure measurement.
‡ Defined as an increase > 20 mm Hg and a systolic blood pressure > 140 mm Hg.
§ Defined as an increase > 15 mm Hg and a diastolic blood pressure > 90 mm Hg.

Cyclooxygenase-2 selective inhibitors were developed to circumvent GI adverse events by sparing COX-1 inhibition. The GI safety of COX-2 inhibitors was first supported by endoscopy studies that examined the mucosal alterations associated with these agents compared with NSAIDs (20). Pooled analysis of several trials showed fewer perforations, ulcers, and bleeding episodes with COX-2 selective inhibitors (14), and these findings were confirmed in a large clinical trial in patients with rheumatoid arthritis (15). These studies did not allow concomitant aspirin use. In another study in which aspirin use was permitted, celecoxib did not provoke fewer GI adverse events (perforations, ulcers, and obstructions) than did combined NSAID therapy (diclofenac or ibuprofen) (21, 22).

To our knowledge, this trial is the first and the largest to compare GI symptoms prompting discontinuation of treatment with COX-2 inhibitors or a dual-inhibiting NSAID as the primary end point in a representative sample of patients with osteoarthritis that included regular users of low-dose aspirin and patients with a history of discontinuing NSAID use because of GI intolerability. The average age of participants (approximately 63 years), the predominance of women, and the high prevalence of comorbid conditions (for example, hypertension and cardiovascular disease) reflect typical characteristics of patients with osteoarthritis (2, 23). Many of our patients were treated for comorbid conditions with antihypertensive agents or low-dose aspirin for cardiovascular prophylaxis. Also, to our knowledge, our trial is also the first to compare the effect of a selective COX-2 inhibitor with that of an NSAID on the use of gastroprotective agents, as a key prespecified end point, in patients from this population.

Our trial showed that cumulative discontinuation due to GI adverse events was statistically significantly lower with rofecoxib than with naproxen. Subgroup analysis of patients who used low-dose aspirin yielded findings similar to those observed for the entire cohort. Although our study was not powered to be conclusive for this subgroup, the similarity of findings among low-dose aspirin users and the total study sample suggests that the advantages of selective COX-2 inhibition may extend to patients taking low-dose aspirin for cardiovascular prophylaxis (24, 25). In the subgroup of patients who stopped arthritis medication because of GI symptoms before study participation, rofecoxib led to a lower rate of discontinuation due to GI adverse events than naproxen.

Some researchers estimate that NSAID-related GI adverse events are associated with as many as 100 000 hospitalizations and 16 500 deaths yearly in the United States, including 41 000 hospitalizations and 3300 deaths among elderly persons (26–29). Patients who experience these events make up a relatively small percentage of all NSAID users in the United States but introduce a large financial burden at the population level (28, 30–32). While discontinuations due to GI adverse events and perforations, ulcers, and bleeding were decreased in the rofecoxib group in the present study, patients taking rofecoxib were not totally spared. Whether GI events in the rofecoxib group reflect the background rate or indicate that COX-1 sparing may not totally circumvent GI side effects could not be addressed in this study because our patients, who had symptomatic osteoarthritis, could not be treated with placebo. Of note, rofecoxib has previously been shown to reduce costs associated with GI-related side effects compared with NSAIDs (33, 34). These savings should be weighed against the higher cost of coxibs when assessing the potential for GI adverse events in individual patients.

An important additional finding in our trial, which encompassed nearly 1200 patient-years of experience, was the effect of rofecoxib on hypertension compared with that of naproxen. Both drugs had similar effects on all measures of blood pressure control, including the incidence of hypertension-related adverse events, mean change in blood pressure, increases in systolic and diastolic blood pressure exceeding predefined limits of change, and discontinuation rates due to hypertension. This is especially notable given the high proportion of patients who had a history of hypertension or were being treated with antihypertensive

agents. Examination of the hypertension subgroup showed no statistically significant differences in the relative incidence of alterations in blood pressure control and confirmed that such changes can be seen with both rofecoxib and NSAIDs, consistent with previous reports (35).

Although our study was not powered to make definitive conclusions, we used established Antiplatelet Trialists' Collaboration criteria and blinded adjudication of thrombotic events to assess the incidence of thromboembolic adverse events occurring during the trial. The results demonstrated no difference between rofecoxib and naproxen; however, there were too few end points to allow us to make authoritative conclusions about the relative effects of these agents on cardiovascular events (36, 37). Efficacy measured by global patient assessments showed that rofecoxib, 25 mg once daily, was comparable to naproxen, 500 mg twice daily. Discontinuations due to lack of efficacy were also similar between groups. Thus, these data provide clinical information needed to judge both the risks and benefits of rofecoxib and naproxen in the setting of equally efficacious doses of the two drugs.

Our study has limitations. Patients received regular daily doses of rofecoxib or naproxen. However, dosing with analgesic and anti-inflammatory medication for osteoarthritis is often less consistent since use of these agents is frequently prompted by flare-up of symptoms. In addition, our study lasted 3 months. Although benefit did not decrease over this time, our results may not apply to longer-term use of COX-2 inhibitors.

In summary, this large, randomized, double-blind, controlled trial of generally older patients with osteoarthritis showed that rofecoxib, 25 mg once daily, was as efficacious as naproxen, 500 mg twice daily, in controlling symptoms over a 3-month period and was associated with significantly better GI tolerability. The latter effect was confirmed by fewer discontinuations due to GI adverse events, reduced need for GI protective medications, and reduced incidence of serious GI events (perforations, ulcers, and bleeding). In addition, no significant differences were observed in general, cardiovascular, or hypertension-related adverse events. The GI advantages of rofecoxib appeared to apply also to patients receiving low-dose aspirin and patients who had a history of previously stopping arthritis treatment because of stomach or abdominal symptoms. Our study confirms that selective inhibition of COX-2 provided by rofecoxib was associated with important GI advantages compared with the dual-inhibiting conventional NSAID naproxen in a representative sample of patients with osteoarthritis and typical comorbid conditions.

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Acknowledgments: The authors thank Drs. John Yates, Thomas Dobbins, Desmond Thompson, Richard Petruschke, Douglas Watson, and Walter Straus for reviewing this manuscript and for providing helpful comments. They also thank Dr. Nicholas Bellamy for providing the AUSCAN Osteoarthritis Hand Index and Drs. Thomas Schnitzer, Marc Hochberg, Arthur Weaver, Walter Straus, and Glenn Gormley for their input into study design. In addition, they gratefully acknowledge the contribution of Kathy O'Brien for assistance with manuscript preparation and for comonitoring this trial and Dr. Martino Laurenzi for comonitoring sites outside the United States.

Grant Support: By Merck & Co., Inc.

Potential Financial Conflicts of Interest: *Employment:* C.S. Skalky (Merck and Co., Inc.), M.E. Dixon (Merck and Co., Inc.), A.B. Polis (Merck and Co., Inc.), G.P. Geba (Merck and Co., Inc.); *Consultancies:* J.R. Lisse (Merck and Co., Inc.); *Honoraria:* J.R. Lisse (Merck and Co., Inc.); *Stock ownership (other than mutual funds):* C.S. Skalky (Merck and Co., Inc.), M.E. Dixon (Merck and Co., Inc.), A.B. Polis (Merck and Co., Inc.), G.P. Geba (Merck and Co., Inc.).

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