

Cyclooxygenase-2-Specific Inhibitors and Cardiorenal Function: A Randomized, Controlled Trial of Celecoxib and Rofecoxib in Older Hypertensive Osteoarthritis Patients

Andrew Whelton,¹ John G. Fort,² Joseph A. Puma,³
Diane Normandin,⁴ Alfonso E. Bello,² and Kenneth M. Verburg,²
for the SUCCESS VI Study Group⁵

Background: Arthritis and hypertension are common comorbid conditions affecting elderly adults. Use of nonsteroidal anti-inflammatory drugs in patients treated with antihypertensive medication can lead to destabilization of blood pressure control and other cardiorenal events. The potential for similar interactions with cyclooxygenase-2-specific inhibitors has not been fully explored. The authors evaluated the cardiorenal safety of two new cyclooxygenase-2-specific inhibitors, celecoxib and rofecoxib.

Methods: This study was a 6-week, randomized, parallel-group, double-blind trial in patients with osteoarthritis who were ≥ 65 years of age and were taking antihypertensive agents. Patients received once-daily celecoxib 200 mg or rofecoxib 25 mg. The primary endpoints were the development of edema, changes in systolic blood pressure, and changes in diastolic blood pressure as measured at any time point in the study. Measurements occurred at baseline and after 1, 2, and 6 weeks of treatment.

Findings: Eight hundred ten patients received study medication (celecoxib, $n = 411$; rofecoxib, $n = 399$). Nearly twice as many rofecoxib- compared with celecoxib-treated patients experienced edema (9.5% vs. 4.9%, $P = 0.014$). Systolic blood pressure increased significantly in 17% of rofecoxib compared with 11% of celecoxib-treated patients ($P = 0.032$) at any study time point. Diastolic blood pressure increased in 2.3% of rofecoxib- compared with 1.5% of celecoxib-treated patients ($P = 0.44$). At week 6, the change from baseline in mean systolic blood pressure was +2.6 mmHg for rofecoxib compared with -0.5 mmHg for celecoxib ($P = 0.007$).

Conclusions: Patients taking antihypertensive therapy and receiving cyclooxygenase-2-specific inhibitors should be monitored for the development of cardiorenal events. Patients receiving

celecoxib experienced less edema and less destabilization of blood pressure control compared with those receiving rofecoxib.

Keywords: celecoxib, rofecoxib, osteoarthritis, cyclooxygenase-2-specific inhibitors, isolated systolic hypertension, cardiovascular risk, edema, NSAID.

...INTRODUCTION...

Arthritis is the most prevalent chronic condition affecting approximately 50% of adults aged 65 years or older. Hypertension is the second most common chronic condition affecting 40% of individuals 65 years of age and older.¹ Osteoarthritis is the most common form of arthritis and affects at least 20 million Americans.² Isolated systolic hypertension is the most

¹Universal Clinical Research Center, Inc. and The Johns Hopkins University School of Medicine, Baltimore, MD;

²Pharmacia, Peapack, NJ;

³The Heart and Vascular Center, Duke University Medical Center, Galax, VA;

⁴Clinical Research of West Florida, Clearwater, FL;

⁵Members listed in the Appendix.

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Address for correspondence: Pharmacia, 100 Route 206 North, Peapack, NJ 07977, USA; e-mail: john_g_fort@pharmacia.com

Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2-Specific Inhibitors and Cardiorenal Function: A Randomized, Controlled Trial of Celecoxib and Rofecoxib in Older Hypertensive Osteoarthritis Patients. *Am J Ther.* 2001;8(2):85-95.

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common form of hypertension and is present in nearly two thirds of hypertensive people aged 65 to 89 years.³ The Coordinating Committee of the National High Blood Pressure Education Program of the National Heart, Lung, and Blood Institute recommends that systolic blood pressure (BP) become the principal clinical endpoint for the detection, evaluation, and treatment of hypertension.⁴

In studies of patients with arthritis, hypertension is a common comorbidity. At least 12 million Americans are receiving concurrent therapy for the treatment of these two conditions.⁵ Therefore, management of these comorbidities raises important clinical concerns, especially with regard to potential drug–drug and drug–disease interactions. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs), which are used for the treatment of osteoarthritis, are well known to cause edema and hypertension.^{6–9} NSAIDs disrupt the effect of most antihypertensive medications, especially angiotensin-converting enzyme (ACE) inhibitors and β -blockers.^{8–11} Cyclooxygenase-2 (COX-2)-specific inhibitors, a new class of NSAIDs that includes celecoxib and rofecoxib, appear to have a significant safety advantage over conventional NSAIDs, which inhibit both COX-1 and COX-2. This safety advantage appears to be related to a lack of inhibition of COX-1, which is important in the maintenance of a number of physiologic processes. The safety advantage of COX-2-specific inhibitors is well established in terms of reduced adverse effects in the gastrointestinal tract and on platelet function.^{12–15} Furthermore, the gastrointestinal safety of celecoxib and rofecoxib recently has been confirmed in two separate large, gastrointestinal outcome trials.^{16,17}

The renal and cardiovascular effects of the COX-2-specific inhibitors are less well understood. It now appears that both COX-1 and COX-2 may play a role in both the healthy and the diseased kidney. However, the relative importance of each of these isoforms in the cardiovascular and renal systems is not fully understood.¹⁸ Current data suggest a renal adverse event profile with COX-2-specific

inhibitors that is similar to conventional NSAIDs. However, the effects of NSAIDs on cardiorenal function may vary depending on the particular NSAID. For example, indomethacin and naproxen appear to cause increases in mean arterial BP in patients treated for hypertension, but such changes are less apparent with sulindac, aspirin, and ibuprofen.⁶ Likewise, a potential difference with regard to COX-2-specific inhibitors has been suggested by available information derived from separate clinical trials. Rofecoxib has been shown to produce a decrease in glomerular filtration rate in salt-restricted elderly individuals that is similar to the conventional NSAID indomethacin.¹⁹ On the other hand, celecoxib decreased glomerular filtration rate significantly less than naproxen in nonsalt-restricted elderly individuals.²⁰ Furthermore, higher incidences of edema and hypertension have been observed in patients with osteoarthritis treated with rofecoxib 50 mg once daily compared with those treated with rofecoxib 12.5 and 25 mg once daily.²¹ With respect to celecoxib, no dose-related increases in these events have been observed.^{10,22} Beyond these observations, no direct comparative studies have been published that were designed to evaluate systematically the cardiorenal safety of these new COX-2-specific inhibitors.

The current study was designed to understand better the cardiorenal effects of the new and widely prescribed COX-2-specific inhibitors celecoxib and rofecoxib. Using a relevant setting, we tested whether celecoxib 200 mg once daily would be associated with less edema and hypertension destabilization than rofecoxib 25 mg once daily in an older hypertensive osteoarthritis population. The doses selected for investigation in this trial reflect the current, most frequently prescribed and approved daily regimens of each agent for the treatment of osteoarthritis.²³

...METHODS...

Study Design and Patients

The SUCCESS VI Study was a multicenter, parallel-group, double-blind, double-

dummy, randomized, controlled trial with a 6-week treatment period. Outpatients aged 65 years or older were eligible to participate in the study if they (1) had stable, controlled hypertension; (2) fulfilled American College of Rheumatology criteria for a diagnosis of osteoarthritis of the hip, knee, or hand; and (3) would benefit from chronic daily therapy with an NSAID to control arthritis symptoms.

Patients were required to have taken the same fixed dose of antihypertensive medication(s) on a regular basis for at least 3 consecutive months prior to screening. In addition, patients were required to have a seated diastolic BP of 95 mmHg or less and seated systolic BP of 160 mmHg or less at screening and at the baseline visit. Cuff BP, as opposed to ambulatory BP, was selected for BP measurements to reflect standard office-based clinical practice.

Patients were excluded from the study if they had active gastrointestinal tract disease; renal, hepatic, or coagulation disorders; history of New York Heart Association Class III or IV heart failure; or secondary hypertension, malignant hypertension, or renal artery stenosis. Patients also were excluded if they had any acute joint trauma, rheumatoid arthritis, active untreated crystal-induced arthropathies, or known hypersensitivity to celecoxib, rofecoxib, sulfonamides, NSAIDs, or related compounds. Patients with a history of esophageal, gastrointestinal, or duodenal ulceration within the 30 days prior to first dose of study medication, or who had used celecoxib or rofecoxib within the 30 days prior to first dose of study medication, were also ineligible. Other criteria for exclusion were a serum creatinine concentration of greater than 1.5 mg/dL (132.6 μ mol/L), a blood urea nitrogen level of at least 1.5 times the upper limit of normal, or a serum potassium concentration of less than 3.0 mmol/L or greater than 5.0 mmol/L.

This trial was conducted at 101 clinical outpatient sites across the United States and Canada in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was

approved by the institutional review board at each study site. Written informed consent was obtained from all patients prior to screening.

Prior to enrollment patients underwent a screening assessment, which included physical examination and clinical laboratory testing. Each participating study site was supplied with a new, calibrated, manual sphygmomanometer for measurement of BP. Conditions surrounding BP measurements were kept constant from visit to visit, including using the same patient arm, observer, and cuff size and maintaining similar office visit times, chair locations, temperatures, and noise levels. At the screening visit, three seated BP measurements were taken 5 minutes apart in one arm. The first reading was discarded, and the mean of the second and third measurements was calculated and used as the BP value. The same procedure was repeated in the opposite arm. The arm with the highest mean seated diastolic BP was used for all subsequent BP measurements taken during the study. The antihypertensive drugs and dosages taken by each patient were recorded.

After a minimum NSAID washout period of 4 days, a baseline clinical assessment was performed on all patients who met the inclusion criteria. BP was measured using the same equipment and under the same conditions as at the screening visit. Two BP measurements were taken in the arm designated at screening, and the mean of those two measurements was calculated. Prior to the first dose of study medication, body weight was measured, and patients were assessed for the presence of peripheral edema using a 5-point scale (0 to 4+) and a standardized, clinical detection method that was applied at comparable times and conditions for each patient.

Treatment and Randomization

Using a computer-generated 1:1 randomization schedule in block sizes of 4, patients were assigned to either oral celecoxib 200 mg once daily (Celebrex[®], Pharmacia, Peapack, NJ) or oral rofecoxib 25 mg once daily (Vioxx[®], Merck, Whitehouse Station, NJ). Both treatment regimens were

fully blinded such that all patients took the same number of identically appearing dosage units each morning with breakfast. The patients' treatment assignment was known only by the supplier's clinical packaging group and was kept in a sealed envelope by the statistician until the database was closed.

Aspirin use (≤ 325 mg/day) for cardio-protective reasons was permitted during the study if the patients had received a stable dose for at least 30 days before the first dose of study medication. Other antiplatelet agents, such as clopidogrel or ticlopidine, were also permitted. NSAIDs, oral or injectable corticosteroids, intra-articular hyaluronic acid, or prescription or over-the-counter antiulcer drugs were prohibited. Acetaminophen was permitted for occasional use for arthritic or nonarthritic pain at a dosage of up to 4 g per day. At the discretion of the investigator, the dose and/or type of diuretic or antihypertensive medication could be changed at any time during the study period.

Clinical Assessments

Clinical and laboratory assessments were performed at baseline and after 1, 2, and 6 weeks of treatment. Adverse events were also recorded at each post-baseline visit. Also, any change in antihypertensive therapy was recorded, as were reasons for therapy changes.

The primary endpoints of the study were significant edema and elevated hypertension events occurring at any time point during the study. Criteria for significant edema are defined in **Table 1**. Elevated hypertension was based on elevated systolic or diastolic BP, as defined in **Table 1**.

The following planned secondary endpoints were assessed at each post-baseline visit: elevated hypertension events, as previously defined; changes in diuretic and/or antihypertensive medications for the treatment of edema and/or hypertension; changes from baseline in the mean systolic BP and diastolic BP; new-onset or worsening congestive heart failure, as defined below; and clinically significant

Table 1. Criteria for Renal Events

<p>Significant edema Increase from baseline of at least 1 grade in peripheral edema and a 3% weight gain, or Increase from baseline of 2 or more grades in peripheral edema with or without weight gain, or Increase from baseline to 4+ peripheral edema, or Initiation or increase in medication for the management of edema</p>
<p>Elevated hypertension Elevated systolic blood pressure (BP): An increase >20 mmHg with an absolute value >140 mmHg Elevated diastolic BP: An increase >15 mmHg with an absolute value >90 mmHg</p>
<p>Clinically significant renal laboratory values Serum creatinine increase to 159 μmol/L or more, Blood urea nitrogen increase of at least 200% from baseline or absolute value of 17.9 mmol/L or more, Serum potassium increase to 5.5 mmol/L or more, Serum sodium decrease to less than 120 mmol/L</p>

laboratory renal events, as defined in **Table 1**. The diagnosis of congestive heart failure was based on standard clinical practice and on the investigator's judgment.

A post hoc analysis was conducted to evaluate systolic BP changes and weight gain changes in the subgroup of patients who experienced edema.

Statistical Analyses

All analyses were performed on the intent-to-treat cohort, defined as all patients who took at least one dose of study medication. The sample size for this study (405 patients per treatment arm) was designed to provide 90% power, with a two-sided significance level of 0.05 to detect a treatment difference if the true event rates for edema and hypertension for patients using rofecoxib and celecoxib were 10% and 4%, respectively.

Fisher exact test was used to compare the proportions of all incidences for primary and secondary endpoints. Baseline characteristics were analyzed using analysis of variance with site and treatment as

factors for continuous variables and Fisher exact test for categorical variables. The changes from baseline in mean systolic BP and diastolic BP were compared between treatment groups using a Student *t* test. The changes from baseline in mean systolic BP were analyzed using analysis of variance with baseline, race, and sex as factors. For primary and secondary endpoints, potential confounding variables were tested by using logistic regression analysis with race, sex, baseline antihypertensive medication, and treatment as factors.

Safety analysis comparing the incidence of adverse events between treatment groups was performed using Fisher exact test. A post hoc analysis of clinically significant elevations in systolic BP was performed on the subgroup of patients who experienced edema using Fisher exact test. All calculations were performed with SAS version 6.12 (SAS Institute, Inc., Cary, NC).

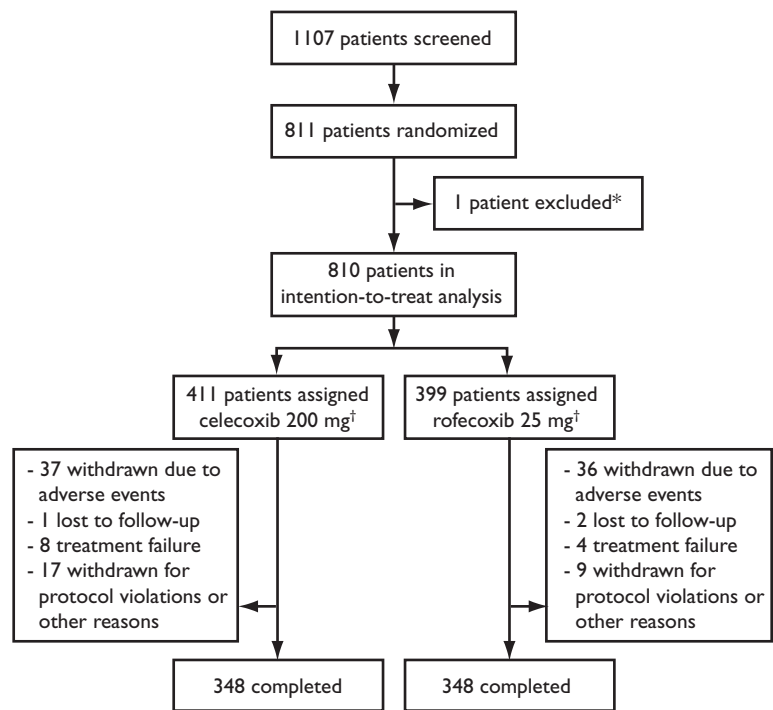
...RESULTS...

Demographic and Baseline Patient Characteristics

Patients were recruited for the study between October 1999 and April 2000. Investigators from the US and Canada included office-based rheumatologists, primary care physicians, cardiologists, and geriatricians. From 1107 screened patients, 811 patients were randomly assigned to receive celecoxib or rofecoxib: 412 received celecoxib and 399 received rofecoxib. The intent-to-treat population ($n = 810$) consisted of randomly assigned patients who took at least one dose of study drug (Fig. 1). A total of 696 patients (86%) completed the study, and the proportion of patients completing was similar in both treatment groups. Treatment failure occurred in 8 (1.9%) celecoxib- and 4 (1.0%) rofecoxib-treated patients ($P = 0.39$). Disposition of the study participants is shown in Figure 1.

The two treatment groups were similar with respect to most baseline characteristics, including cardiovascular disease history (Table 2). The mean duration of osteoarthritis was significantly longer for

Figure 1. Disposition of Patients Enrolled in Study



*One patient in the celecoxib group did not take the study medication.

†All patients were included in all intent-to-treat analyses.

the celecoxib- than for the rofecoxib-treated patients ($P = 0.012$). Most of the patients were female (66%) and white (91%). At the time of randomization, both treatment groups had similar mean baseline BP (celecoxib, 138/76 mmHg; rofecoxib, 137/76 mmHg).

Baseline antihypertensive therapies for both treatment groups are shown in Table 2. Most patients were receiving combination therapy. The most commonly used antihypertensive agent was a diuretic. Use of other antihypertensive drugs with or without diuretic treatment was similar across the treatment groups. However, more patients in the celecoxib group were treated with ACE inhibitors than in the rofecoxib group (40% vs. 29%, respectively; $P = 0.002$).

Cardiorenal Safety

Significant edema was observed in both treatment groups but occurred significant-

Table 2. Baseline Characteristics of All Randomized Patients

Characteristic*	Treatment Group	
	Celecoxib 200 mg Once Daily (n = 412)	Rofecoxib 25 mg Once Daily (n = 399)
Mean age (SD), y	74.0 (6.0)	74.1 (6.1)
<65 years	1	0
65–75 years	247	237
>75 years	164	162
Female	274 (66.5)	265 (66.4)
Ethnic origin		
White	378 (91.7)	358 (89.7)
Black	25 (6.1)	31 (7.8)
Other	9 (2.2)	10 (2.5)
Clinical characteristics, mean (SD)		
Hypertension duration, y	13.2 (10.2)	12.5 (10.3)
Osteoarthritis duration, y [†]	13.6 (10.9)	11.7 (10.4)
Systolic blood pressure, mmHg	138 (13.4)	137 (11.8)
Diastolic blood pressure, mmHg	76 (8.6)	76 (7.7)
Weight, kg	83.8 (18.2)	82.5 (17.5)
Cardiovascular history		
Angina	67 (16.3)	79 (19.8)
Coronary artery disease	74 (18.0)	68 (17.0)
Congestive heart failure	21 (5.1)	22 (5.5)
Myocardial infarction	33 (8.0)	37 (9.3)
Antihypertensive medications		
Diuretics	202 (49.0)	190 (47.6)
ACE inhibitors [†]	166 (40.3)	116 (29.1)
Calcium antagonists	147 (35.7)	150 (37.6)
β -blockers	133 (32.3)	120 (30.1)
Combination therapy	200 (48.5)	179 (44.9)
Other	20 (4.9)	30 (7.5)
Low-dose aspirin users	156 (37.9)	148 (37.1)

*Values are number (percentage) unless otherwise indicated.

Each patient may be included in more than one class of antihypertensive medication.

[†] $P < 0.05$.

ly more often in rofecoxib-treated (38 patients, 9.5%) than in celecoxib-treated patients (20 patients, 4.9%; $P = 0.014$). All celecoxib-treated patients with significant edema met the first two criteria for significant edema, including an increase of 2

grade points from baseline in peripheral edema or an increase from baseline of 1 grade point in peripheral edema with a 3% weight gain; 95% of rofecoxib-treated patients met these first two criteria.

As shown in **Figure 2**, significantly more rofecoxib- than celecoxib-treated patients (66 vs. 45 patients respectively $P = 0.032$) reached the systolic BP endpoint, which was an increase >20 mmHg together with an absolute value >140 mmHg at any time during the 6-week study. More rofecoxib- than celecoxib-treated patients (9 vs. 6 patients respectively; $P = 0.44$) reached the diastolic BP endpoint, which was an increase >15 mmHg with an absolute value >90 mmHg.

At each post-baseline assessment time point, more rofecoxib- than celecoxib-treated patients reached the systolic BP endpoint, with significantly more rofecoxib patients reaching the endpoint at weeks 2 and 6 (week 2: $P = 0.02$; week 6: $P = 0.05$) (**Fig. 3**).

Changes from baseline in mean systolic BP are shown in **Figure 4**. Mean changes decreased in the celecoxib-treated patients but increased in the rofecoxib-treated patients, with significant differences between the mean systolic BPs (differences from baseline: week 1, 2.4 mmHg, $P = 0.014$; week 2, 2.8 mmHg, $P = 0.006$; week 6, 3.1 mmHg, $P = 0.007$).

Investigators identified four patients, all from the rofecoxib group, who developed congestive heart failure during the conduct of the study. The difference between the rofecoxib and celecoxib groups in the incidence of congestive heart failure was not statistically significant ($P = 0.058$). However, using a log-rank analysis for cumulative event rates at week 6, the difference was found to be significant ($P = 0.043$).

Six patients in each group developed clinically significant serum renal laboratory values. In each instance, these abnormalities represented only minor increases in serum creatinine, blood urea nitrogen, or serum potassium.

In a post hoc subgroup analysis of all patients with and without edema, shown in **Figure 5**, a significantly higher change

from baseline in mean systolic BP in the rofecoxib group was observed at all time points compared with the celecoxib group. At week 6, for those individuals who manifested significant edema, the rofecoxib group had a +5.9 mmHg change from baseline versus a -1.1 mmHg change in the celecoxib group ($P = 0.003$).

In a post hoc subgroup analysis, relative weight gain changes (expressed as a percentage of baseline weight) were higher for rofecoxib- than for celecoxib-treated patients at weeks 1 (0.6% vs. 0.1%), 2 (0.7% vs. 0.2%), and 6 (0.6% vs. 0.2%). For all patients, the differences between the weight gain changes in the rofecoxib- and celecoxib-treated patients were significant at weeks 1, 2, and 6 ($P < 0.006$).

General Safety

The percentage of patients experiencing at least one adverse event was 58% in the celecoxib group and 61% in the rofecoxib group ($P = 0.28$). Adverse events constituting cardiorenal endpoints were excluded from this safety analysis. The most commonly reported ($\geq 5\%$) adverse events in the celecoxib group were upper respiratory tract infection (7.1%) and dyspepsia (5.1%). The most commonly reported adverse events in the rofecoxib group were headache (8.5%), dyspepsia (7.3%), diarrhea (5.5%), and abdominal pain (5.0%).

A total of 37 (9%) celecoxib- and 36 (9%) rofecoxib-treated patients withdrew from the study because of adverse events. The most common adverse event that contributed to patient withdrawal was abdominal pain, contributing to the withdrawal of 5 patients in the celecoxib and 7 patients in the rofecoxib group. In the rofecoxib group, aggravated hypertension contributed to the withdrawal of 6 (1.5%) patients in the rofecoxib and 2 (<1.0%) patients in the celecoxib group. Peripheral edema contributed to the withdrawal of 5 (1.3%) patients in the rofecoxib and 2 (<1.0%) patients in the celecoxib group. Serious adverse events were infrequent and occurred in 11 (2.7%) celecoxib- compared with 18 (4.0%) rofecoxib-treated patients.

Figure 2. Percentage of Patients Experiencing Clinically Important Changes in Systolic or Diastolic Blood Pressure at Any Visit

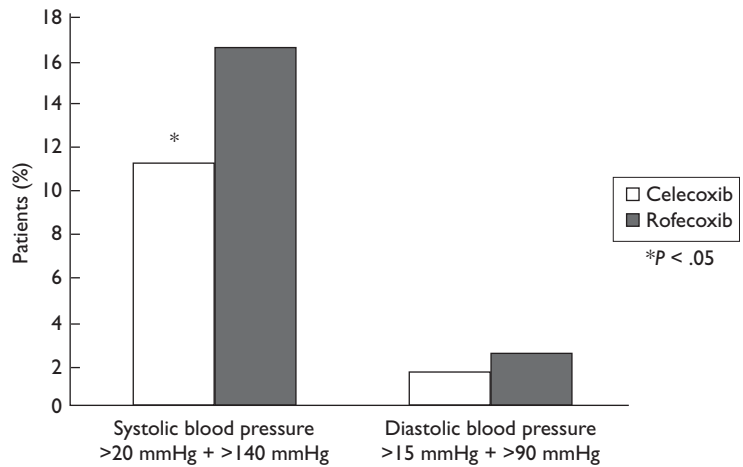
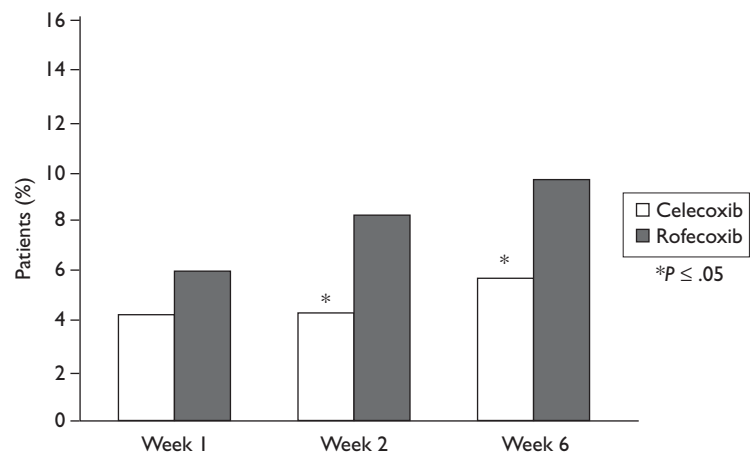
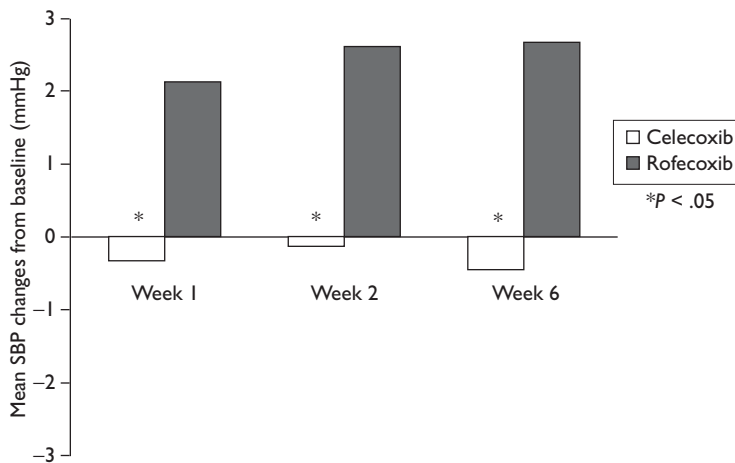
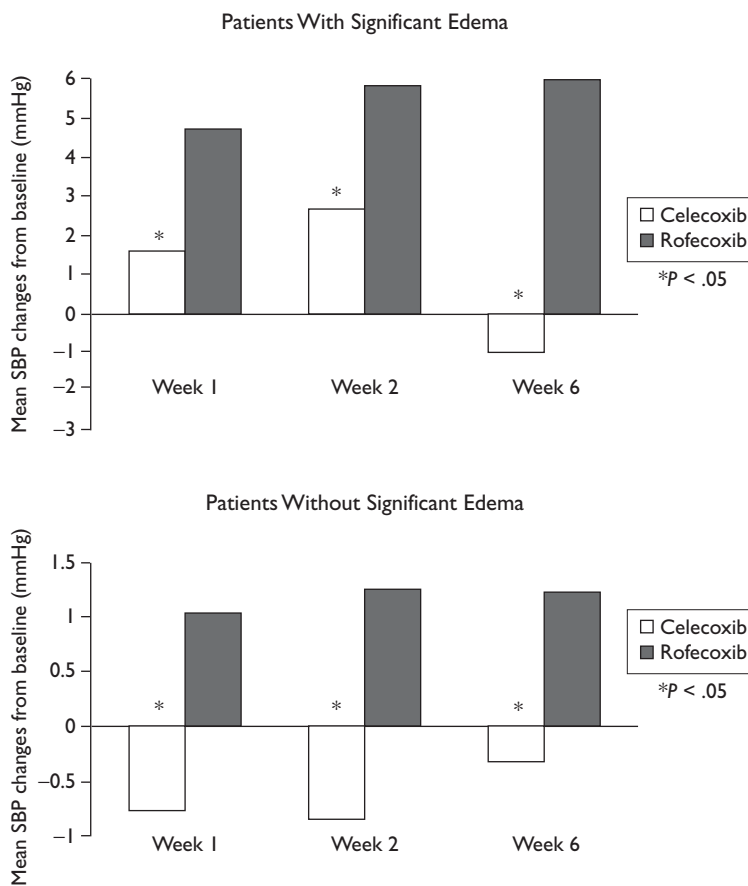


Figure 3. Percentage of Patients Experiencing Clinically Important Changes in Systolic Blood Pressure



...DISCUSSION...

In this study, use of COX-2-specific inhibitors was associated with cardiorenal events such as the development of edema and elevations in systolic BP. However, significantly fewer celecoxib-treated patients developed edema and elevations in systolic BP than did rofecoxib-treated patients. In addition, only patients in the rofecoxib group developed congestive

Figure 4. Mean Systolic Blood Pressure Changes From Baseline**Figure 5.** Mean Systolic Blood Pressure Changes From Baseline in Patients With and Without Significant Edema

heart failure. Rofecoxib also produced a significantly greater increase in mean systolic BP compared with celecoxib at each of the three time points during the study.

Treatment-emergent changes in serum creatinine, blood urea nitrogen, potassium, or sodium were infrequent and were not significantly different between the two study groups. Because patients were required to have normal serum creatinine at study entry, the latter finding was anticipated.

Previous outcome studies in large controlled trials, such as the Systolic Hypertension in Elderly Program²⁴ and the Systolic Hypertension in Europe Trial,²⁵ have established that elevated systolic BP is associated with cardiovascular endpoints such as heart failure, stroke, myocardial infarction, and death. These studies considered systolic BP reductions of at least 20 mmHg (and absolute values of less than 150–160 mmHg) to be clinically significant. Elevations of at least 20 mmHg would lead to changes in antihypertensive medication and, if persistent, would result in adverse cardiovascular outcomes.

The design of this study closely parallels actual clinical practice. The included population is particularly relevant because arthritis and hypertension occur as comorbid conditions in at least 40% of older patients. The selected dosages also are relevant because celecoxib 200 mg once daily was used 78% of the time and rofecoxib 25 mg once daily was used 86% of time for the management of osteoarthritis during the first half of 2000 (year-to-date, June 2000, Scott-Levin). Furthermore, assessments also used standard office-based clinical procedures, including cuff BP and peripheral edema measurement.

The 6-week duration was selected based on results of previous studies of conventional NSAID use in which most individuals who developed edema manifested this finding within the first 1 to 2 weeks of treatment. Results of the current study regarding onset of edema and BP destabilization reflect this temporal pattern.

Recent celecoxib and rofecoxib studies in elderly cohorts have evaluated the sta-

bility of renal function as measured by glomerular filtration rate.^{19,20} These studies have identified a pattern of modest systemic sodium retention (100 to 150 mmol) during the first few days of administration of the COX-2-specific agent. By approximately 5 to 7 days of treatment, the typical individual returned to a pre-treatment sodium balance state through renal elimination of the retained sodium, using homeostatic mechanisms that are independent of renal prostaglandin.^{20,26} Therefore, disordered or inadequately regulated sodium balance is the likely cause of clinical edema. Hence, the putative mechanism of edema formation would suggest the development of edema within 1 to 2 weeks of treatment with NSAIDs, as was observed in this study.

Despite the protocol-mandated freedom for the investigators to change diuretic or antihypertensive medication regimens, edema and BP changes were observed throughout the 6-week study. As shown in Figure 3, significant elevations in systolic BP accrued in the rofecoxib-treated group up to week 6. Additional long-term studies are necessary to define the time point of the plateau for this BP destabilization effect.

Older individuals have a tendency toward diminished renal function, which may be exacerbated by comorbid hypertension.²⁷ This impairment of renal function in elderly patients with hypertension may increase their sensitivity to the development of edema during the use of NSAID therapy. Nearly twice as many rofecoxib-compared with celecoxib-treated patients experienced edema in this study. In our post hoc subgroup analysis, a solid correlation emerged between the development of edema and the destabilization of hypertension control (Fig. 5). Specifically among patients with hypertension and edema there was a significantly higher change from baseline in mean systolic BP in the rofecoxib group compared with the change in the celecoxib group at week 6. For patients who developed a systolic BP increase endpoint, the pattern was already apparent by week 1, was slightly greater by week 2, and was sustained at week 6.

As indicated by these study results, when edema and hypertension develop during the use of a COX-2-specific inhibitor agent, the management of the edema is an important component in the restabilization of BP control.

The effect of NSAIDs on the risk of developing congestive heart failure has been examined in two previous studies.^{28,29} These studies demonstrated that recent use of NSAIDs by elderly patients at least doubled the odds of hospital admission for an episode of congestive heart failure. This was especially true for patients with a history of heart disease; in these patients, both high NSAID dose and long NSAID plasma half-life appeared to increase the risk of congestive heart failure.²⁸ In this study, only patients receiving rofecoxib developed congestive heart failure.

Several possible mechanisms may account for the observed differences between the two COX-2-specific inhibitors studied. The interactions between NSAIDs and antihypertensive regimens are complex and dependent on both the particular NSAID and the particular antihypertensive treatment.¹¹ Celecoxib and rofecoxib are different molecules with different pharmacokinetic profiles. Because renal function naturally deteriorates as part of the aging process, the potential for drug or metabolite accumulation exists in older populations.²⁰ The previously reported dose-related increases in hypertension and edema observed with rofecoxib, along with the findings of the current study, suggest that these events may be the result of direct renal effects of the rofecoxib molecule or its metabolites and not the result of a "class"-related COX-2 pharmacologic effect.¹⁰

The extensive analyses of the effects of NSAIDs on hypertension have focused on changes in mean BP in hypertensive populations.^{6,8} These changes, expressed as group averages, underestimate individual changes in BP. The importance of relatively small changes in mean BP has profound public health implications. In a number of large clinical trials, sustained increases in systolic BP of 3 mmHg could explain a 10% to 20% increase in congestive heart failure,³⁰ a 15% to 20% increase in stroke

risk,³¹ and a 12% increase in angina risk.³² These findings have meaningful clinical implications for the maintenance of adequate BP control among patients with arthritis and comorbid hypertension. A small but sustained loss of adequate BP control could lead to an increase in cardiovascular events.

There are several limitations to the current study. Not all patients enrolled in the study meet current guidelines for BP control. However, all patients were considered to have stable, controlled hypertension by the investigator. Specifically, current recommendations suggest that systolic BP should be less than 140 mmHg and that diastolic BP should be less than 90 mmHg.^{33,34} The slightly higher BP inclusion criteria used in the current study should help explore the effects of COX-2-specific inhibitors over a broader, clinically relevant range of systolic BP and diastolic BP. Although the mean systolic BP was 137 mmHg, the number of patients with systolic BP greater than 140 mmHg at baseline was actually higher in the celecoxib group (40%) than in the rofecoxib group (37%). Covariate analyses did not show a confounding effect of baseline systolic BP or diastolic BP on the primary endpoints.

The hypertensive effect of NSAIDs varies depending on the specific NSAID as well as the type of antihypertensive agent used, when taken concurrently.^{9,11} In the current study, significantly more patients in the celecoxib group than in the rofecoxib group were receiving baseline ACE inhibitor therapy. ACE inhibitors and β -blockers are the most common antihypertensive agents affected by NSAIDs.⁸⁻¹¹ Therefore, interactions between NSAIDs and ACE inhibitors are a common cause of destabilization of controlled hypertension in those patients managed with ACE inhibitors.¹⁰ In the current study, the use of baseline antihypertensives, including ACE inhibitors, was evaluated and was found not to influence the systolic BP changes.

The current study was conducted in an at-risk, older population (65 years and older). In addition, the population studied

was mostly female and white. Although covariate analyses did not support a confounding effect for race or age, data should be extrapolated with caution to a younger, nonhypertensive, or different racial population. The effect of celecoxib in a general population has been analyzed in other randomized, controlled trials in which celecoxib was not associated with dose-related increases in systolic BP or diastolic BP.¹⁰ The rates of hypertension and edema in this trial are higher than rates in other studies conducted in a more general population.^{21,22} These higher rates may be a consequence of a study design that uses ascertainment of cardiorenal events as primary or secondary study endpoints.

Conventional NSAIDs were not studied in this trial. Therefore, we do not know how either celecoxib or rofecoxib would compare directly with conventional NSAID therapy in terms of the incidence of hypertension or edema in such a high-risk population. However, in the Celecoxib Long-term Arthritis Safety Study (CLASS), more than 4,000 patients with osteoarthritis or rheumatoid arthritis (mean age of 60 years) were exposed to celecoxib for 6 months at supratherapeutic doses (800 mg per day). Patients receiving celecoxib experienced less hypertension and edema than those receiving conventional NSAIDs (diclofenac and ibuprofen).¹⁶

The effects of NSAIDs on cardiorenal function in general, and on systolic BP in particular, have important clinical implications because systolic BP is the primary modifiable factor in predicting cardiovascular risk in the elderly.³⁵ Careful BP monitoring is essential when treating patients with coexisting hypertension and osteoarthritis with NSAIDs. In appropriate individuals, alternative therapy to NSAIDs should be considered. The finding that celecoxib was associated with a lower incidence of cardiorenal events compared with rofecoxib, especially with regard to hypertension, should be considered when selecting a COX-2-specific inhibitor for the treatment of osteoarthritis. To further assess the implications of these observed differences on cardiorenal outcomes, future clinical trials with COX-2-specific

inhibitors should be conducted with the addition of conventional NSAIDs and possibly placebo groups.

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...APPENDIX...

SUCCESS VI Study Investigators: C. Arkin, M. Bageac, H. Baraf, S. Baumgartner, H. Bays, N. Bear, P. Blanchette, M. Block, B. Caciolo, J. Caldwell, J. Capezio, D. Cavanaugh, M. Chilvers, S. Cohen, W. Cox, T. Dzwonczyk, D. England, J. Fidelholtz, J. Fiechtner, D. Fried, S. Gaddam, J. Garcia, L. Gilderman, G. Gladstein, R. Goble, B. Gold, R. Gordon, S. Grainer, H. Graitzer, J. Green, D. Gremillion, C. Harmon, J. Harshbarger, R. Hart, S. Hellems, J. Herron, W. House, L. June, S. Karki, R. Kaufmann, A. Kivitz, G. Klipple, R. Kluge, M. Kohen, M. Layton, J. LeLevier, R. Lies, W. Makarowski, A. Mangione, F. Martin, P. Mayer, F. Mazzone, J. McKenny, K. Misik, B. Miskin, W. Mullican, J. Newman, W. O'Mahony, D. Owens, M. Patel, D. Paulson, K. Persaud, R. Pinner, B. Poque, J. Pooley, H. Prupas, B. Ramjattan, A. Razetti, S. Rosenblatt, J. Rubino, D. Ruff, D. Santram, K. Saul, M. Saul, J. Schmidt, A. Sebba, E. Sheldon, W. Shergy, W. Silverstone, D. Sinclair, W. Smith, T. Stevenson, J. Stokes, C. Stringer, M. Tonkon, M. Traeger, J. Voytas, C. Watt, M. Wheeler, K. Williams, L. Willis, G. Wolfley, A. Yashar, M. Ziter.

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