

Relationship Between COX-2 Specific Inhibitors and Hypertension

Daniel H. Solomon, Sebastian Schneeweiss, Raisa Levin, Jerry Avorn

Abstract—There is controversy whether cyclooxygenase-2 (COX-2) specific inhibitors are associated with elevations in blood pressure requiring treatment in typical clinical practice. We examined the risk of new onset hypertension in a retrospective case-control study involving 17 844 subjects aged ≥ 65 years from 2 US states. Multivariable logistic models were examined to assess the relative risk of new onset hypertension requiring treatment in patients who used celecoxib or rofecoxib compared with patients taking either the other COX-2 specific inhibitor, a nonspecific NSAID, or no NSAID. During the 1999 to 2000 study period, 3915 patients were diagnosed and began treatment for hypertension; 4 controls were selected for every case. In no model was celecoxib significantly associated with the development of hypertension. Rofecoxib users were at a significantly increased relative risk of new onset hypertension compared with patients taking celecoxib (odds ratio [OR] 1.6; 95% confidence interval [CI], 1.2 to 2.1), taking a nonspecific NSAID (OR 1.4; 95% CI, 1.1 to 1.9), or taking no NSAID (OR 1.6; 95% CI, 1.3 to 2.0). There were no clear dosage or duration effects. In patients with a history of chronic renal disease, liver disease, or congestive heart failure, the relative risk of new onset hypertension was twice as high in those taking rofecoxib compared with celecoxib (OR 2.1; 95% CI, 1.0 to 4.3). In this retrospective case-control study of patients aged ≥ 65 years, rofecoxib use was associated with an increased relative risk of new onset hypertension; this was not seen in patients taking celecoxib. (*Hypertension*. 2004;44:140-145.)

Key Words: cyclooxygenase ■ drug therapy ■ hypertension, detection and control ■ epidemiology

In addition to the well recognized gastrointestinal toxicity caused by nonspecific NSAIDs, these agents have also been found to produce a mean increase in blood pressure of 5.0 mm Hg.¹ An observational study found that NSAID users had an increased risk of starting antihypertensive medications.² The increase in blood pressure associated with non-specific NSAIDs is likely caused by an inhibition of prostaglandin-dependent counter-regulatory mechanisms in the renal vasculature and seems to occur early during the use of these agents.³ Such mechanisms may be especially important in patients with reduced intravascular blood volume. Currently, there are conflicting data as to whether selective inhibition of cyclooxygenase-2 (COX-2) by agents such as celecoxib, rofecoxib, or valdecoxib can also result in blood pressure elevations.^{4,5,6}

The pivotal randomized controlled trials of celecoxib and rofecoxib did not establish hypertension as a major adverse effect of these agents,^{7,8} but subsequent review of data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial raised concerns in this regard⁹; secondary analyses of data collected from this randomized trial found that patients taking rofecoxib were twice as likely as patients taking naproxen to have elevations in blood pressure. Another controlled trial

involving more than 1000 patients with osteoarthritis also found that those randomized to rofecoxib were found to more frequently have clinically significant elevations in blood pressure compared with celecoxib.¹⁰ Although both of these randomized trials establish that elevations in blood pressure may occur in subjects taking COX-2 specific inhibitors, it is not clear whether these elevations in blood pressure are large enough to prompt treatment or whether they are observed in typical clinical practice. As well, hypertension does not appear to be a widely known side effect of COX-2 specific inhibitors and is not a prominent part of product labeling.

We sought to determine whether celecoxib or rofecoxib, the 2 available COX-2 specific inhibitors during the study period, were associated with new onset hypertension in patients seen in typical community practice.

Methods

Participants

All patients studied were Medicare beneficiaries receiving prescription medications through either the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled (PAAD) from 1998 to 2000. These 2 programs cover medication

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From the Division of Pharmacoepidemiology and Pharmacoeconomics (D.H.S., S.S., R.L., J.A.), Division of Rheumatology, Immunology, and Allergy (D.H.S.), Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

Correspondence to Daniel H. Solomon, MD, MPH, Division of Pharmacoepidemiology, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120. E-mail dhsolomon@partners.org

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expenses for low-to-moderate income elderly with annual household incomes of between \$10 000 and \$20 000. Reimbursement for COX-2 specific inhibitors and non-specific NSAIDs were without restrictions for both of these state programs.

To be included in this study, participants had to be enrolled, active users of Medicare and the respective prescription drug benefit program for 2 consecutive years out of the 3-year study period, 1998 to 2000. Active use was demonstrated by presence in the program eligibility files, filling a prescription, and any health care claim in each 6-month period of the 2 consecutive years. We further required that during the first 2 consecutive study years study subjects have no prior diagnosis of hypertension (ICD-9-CM 401 to 405) and no use of any medications that are typically used to lower blood pressure. This included all antihypertensive agents from the following categories: nonloop diuretics, β blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, α blockers, direct vasodilators, and combination products from the above categories.

In this pool of eligible patients, new onset hypertension (case-defining event) was defined as a new diagnosis of hypertension and the filling of at least 1 prescription for 1 of the aforementioned antihypertensive agents. Four controls were randomly selected for each case using a random number generator. They were selected from all eligible patients who had not yet become cases. The date of diagnosis of hypertension was considered the index date for cases, and a randomly selected date of filling another medication was considered the index date for controls. The index dates of controls were frequency-matched to those of cases.

All patient identifiers were deleted from the study database after data sources were linked. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

COX-2 Specific Inhibitor and Nonspecific NSAID Use

The study database contained information on all prescription drugs filled by eligible beneficiaries, including drug name, dosage, frequency, and days supply. Based on the hypothesis that the impact of specific and nonspecific NSAIDs on blood pressure was relatively rapid, we examined an exposure period from 1 to 90 days before the index date for use of celecoxib, rofecoxib, or non-specific NSAIDs. Patients were considered exposed to these medications if they had an active prescription on the day before the index date. Patients with prescriptions for >1 of the drug categories during this time were excluded from the analyses.

Low and high dosage of the 2 available COX-2 specific inhibitors were defined a priori based on their modal dosage. For celecoxib, prescriptions were considered to be low dosage if the daily use was ≤ 200 mg and high dosage if daily dose was >200 mg. For rofecoxib, low dosage was defined as daily dose ≤ 25 mg and high dosage as >25 mg per day. We also considered 2 duration categories: 1 to 30 days ("short") and 31 to 90 days ("long").

Covariates

Covariates were defined based on data from the 12 months before the index date. Although information for most of these patients and covariates is available for longer than 12 months, we restricted the ascertainment to this period to reduce any potential for bias that might arise because of varying lengths of covariate assessment. The covariates included age, gender, race, prior hospitalization, number of visits for ambulatory care, number of comorbid medical conditions,¹¹ use of oral glucocorticoids, coronary artery disease, diabetes, rheumatoid arthritis, and osteoarthritis. The count of comorbid condition excluded congestive heart failure, renal disease, coronary artery disease, liver disease, and diabetes because these were included as separate covariates. Coronary artery disease was defined based on diagnoses or procedures indicating the presence of a myocardial infarction, angina, or coronary revascularization.

Several variables of interest were not available within the study database, including body mass index, tobacco use, and socioeconomic status. In theory, these variables could be differentially related

to COX-2 specific inhibitor exposure, non-specific NSAID exposure, and hypertension.^{12,13,14} We, therefore, analyzed data from the Medicare Current Beneficiary Survey,¹⁵ a representative in-home survey with a 97% response rate conducted among 10 479 beneficiaries in 1999.¹⁶ Beneficiaries' body mass index, tobacco use, and socioeconomic status were compared between those reporting use of celecoxib ($n=659$), rofecoxib ($n=283$), or a non-specific NSAID ($n=1,655$). These analyses showed that body mass index was almost identical in both groups of COX-2 specific inhibitor users (celecoxib 27.5 kg/m² versus rofecoxib 27.2 kg/m², $P=0.4$) and similar to non-specific NSAID users (27.7 kg/m², $P=0.4$ versus COX-2 specific inhibitor users). Current tobacco use was similar in users of each COX-2 specific inhibitor (celecoxib 11.1% versus rofecoxib 10.3%, $P=0.9$) and was lower than non-specific NSAID users (15.9%, $P<0.0001$ versus COX-2 specific inhibitor users). There were no differences in educational attainment ($P=0.11$) or income status ($P=0.8$) between celecoxib and rofecoxib users. Based on these findings, it is not likely that a comparison of rofecoxib versus celecoxib with regard to the incidence of hypertension is significantly biased away from the null by body mass index, current tobacco use, or socioeconomic status.

Analyses

We first examined the unadjusted relationships between each drug exposure category and new onset hypertension using contingency tables with χ^2 tests. Each exposure group was sequentially compared with every other category of exposure as the reference group. For example, patients taking rofecoxib were compared with 3 distinct reference groups: unexposed to any NSAID, users of non-specific NSAIDs, and patients taking celecoxib. We then built multivariable logistic regression models by placing all potential covariates in separate models for each exposure and using backward selection with a threshold for removal of $P>0.2$. The only variables that did not remain in at least 1 model were the use of oral glucocorticoids and rheumatoid arthritis. All other variables were therefore used in constructing the final multivariable logistic regression models. Dosage and duration were explored in similar models where celecoxib and rofecoxib were compared with the relevant dosage or duration of the reference exposures.

Finally, we studied several subgroups of patients hypothesized a priori to be at an increased risk of COX-2 specific inhibitor-induced hypertension. COX-2 specific inhibitors are metabolized within the liver¹⁷ and, thus, we were interested whether patients with known cirrhosis would be at a higher risk of hypertension. Non-specific NSAID hypertension is thought to be mediated by the inhibition of prostaglandin-dependent counter-regulatory mechanisms in patients with low intrarenal blood flow.³ We therefore determined whether the use of these drugs in patients with chronic renal disease or congestive heart failure, 2 conditions associated with low intravascular blood volume, increased the risk of hypertension. To test for this, we stratified the population based on chronic renal disease,¹⁸ liver disease, or congestive heart failure and then assessed exposure states in multivariable logistic regression models. All analyses were performed using SAS (SAS Institute, version 8.0).

Results

During the 1999 to 2000 study period, 3915 patients were diagnosed and began treatment for hypertension; 4 controls were selected for every case. We assessed the characteristics of patients in each drug exposure category (Table 1). Patients were similar across all groups with respect to age. Users of non-specific NSAIDs or COX-2 specific inhibitors were more likely to be women; the gender distribution was similar for celecoxib and rofecoxib users. The majority of patients in all exposure categories were white, and few patients had recently spent time in nursing homes. About a quarter of all patients had been hospitalized in the prior year; this was slightly more common in rofecoxib users. Coronary artery disease was

TABLE 1. Characteristics of Study Population by Drug Exposure Status at Index Date

Baseline Characteristic	Nonspecific			
	NSAID	Celecoxib	Rofecoxib	Unexposed
No. (%)	869 (100)	878 (100)	386 (100)	15711 (100)
Age, mean±SD	78±7	80±7	79±7	79±7
Gender, female	726 (84)	756 (86)	332 (86)	12551 (80)
Race, white	827 (95)	845 (96)	377 (98)	14823 (94)
Nursing home resident	37 (4)	55 (6)	23 (6)	917 (6)
Recently hospitalized	167 (19)	212 (24)	113 (29)	3890 (25)
Diabetes mellitus	198 (23)	187 (21)	73 (19)	3541 (23)
Coronary artery disease	49 (6)	57 (6)	42 (11)	1242 (8)
Loop diuretic use	52 (6)	71 (8)	27 (7)	948 (6)
Rheumatoid arthritis	123 (14)	131 (15)	45 (12)	676 (4)
Osteoarthritis	479 (55)	595 (68)	267 (69)	4937 (31)
Oral glucocorticoid use	53 (6)	74 (8)	44 (11)	1070 (7)
Comorbid conditions, mean±SD	1.7±1.8	1.9±1.7	1.9±2.0	1.9±1.9
No. of medications, mean±SD	8±5	8±5	9±5	7±5
No. of physician visits, mean±SD	9±7	10±7	11±8	8±7
No. of patients with new onset hypertension	203 (23)	181 (21)	106 (27)	3425 (22)

N (%) unless noted.

slightly more common in patients taking rofecoxib (11%) than celecoxib (6%) or nonspecific NSAIDs (6%). As expected, rheumatoid arthritis and osteoarthritis were much more common in patients taking a nonspecific NSAID or COX-2 specific inhibitor than in the unexposed group. Users of rofecoxib were slightly more likely to take oral glucocorticoids than the other exposure groups. Comorbid conditions, medication use, and number of physician visits were similar across all groups. Cases were more likely to be nonwhite, have diabetes and coronary artery disease, and be nonusers of loop diuretics than controls. Otherwise, cases and controls were similar.

The results of the multivariable logistic regression models are presented in Table 2. Rofecoxib use was associated with

a significantly increased relative risk of new onset hypertension compared with patients taking celecoxib (odds ratio [OR] 1.6; 95% confidence interval [CI], 1.2 to 2.1), taking a nonspecific NSAID (OR 1.4; 95% CI, 1.1 to 1.9), or taking no NSAID (OR 1.6; 95% CI, 1.3 to 2.0). Celecoxib was not associated with an increased relative risk of new onset hypertension in any of these models.

There did not appear to be a clear dose or duration relationship between either COX-2 specific inhibitor and new onset hypertension (Table 3). There was no difference in relative risk between low- and high-dosage celecoxib or rofecoxib compared with the low- and high-dosage reference groups, or between short and long duration use of celecoxib and the respective reference groups. Long duration rofecoxib

TABLE 2. Multivariable Adjusted Associations Between COX-2 Specific Inhibitors and Hypertension, 1999–2000

Variable of Interest	Reference Group			
	Unexposed	Nonspecific NSAID	Celecoxib	
Exposure				
Celecoxib	...	1.0 (0.9–1.2)	...	0.9 (0.7–1.1)
Rofecoxib	1.6 (1.3–2.0)	...	1.4 (1.1–1.9)	...
Covariates				
Age≥75 years	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.4 (1.0–1.8)	1.4 (1.1–1.8)
Male gender	0.9 (0.9–1.0)	0.9 (0.9–1.0)	1.2 (0.8–1.7)	1.1 (0.8–1.5)
White race	0.6 (0.6–0.7)	0.6 (0.5–0.7)	0.8 (0.4–1.6)	0.5 (0.3–0.8)
Hospitalization in prior year	1.1 (1.0–1.2)	1.1 (0.9–1.2)	1.0 (0.7–1.5)	0.8 (0.6–1.1)
Nursing home resident in prior year	0.8 (0.6–0.9)	0.7 (0.6–0.9)	0.8 (0.4–1.7)	0.3 (0.1–0.7)
Diabetes mellitus	1.0 (0.9–1.1)	1.3 (1.2–1.5)	1.1 (0.7–1.5)	1.1 (0.8–1.4)
Coronary artery disease	1.8 (1.5–2.0)	1.8 (1.6–2.1)	1.2 (0.7–2.1)	1.8 (1.1–2.8)
Osteoarthritis	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.8–1.3)	0.9 (0.7–1.2)

Adjusted odds ratio (95% CI). All variables were adjusted for all others listed as well as physician visits in prior year, number of different medications, and comorbid illnesses (described in text).

TABLE 3. Multivariable Adjusted Associations Between COX-2 Specific Inhibitor Dosage and Duration and Hypertension, 1999–2000

Variable of Interest	No.	Reference Group*		
		Unexposed	Nonspecific NSAID	Celecoxib
Celecoxib				
≤200 milligrams	692	1.0 (0.8–1.2)	0.9 (0.6–1.1)	...
>200 milligrams	186	1.2 (0.8–1.7)	1.1 (0.6–1.7)	...
Rofecoxib				
≤25 milligrams	359	1.6 (1.2–2.0)	1.4 (1.0–1.9)	1.6 (1.2–2.2)
>25 milligrams	27	1.6 (0.6–4.2)	1.2 (0.4–4.5)	1.6 (0.5–5.7)
Celecoxib				
1–30 days	762	1.4 (1.0–1.9)	0.8 (0.5–1.3)	...
>30 days	116	0.9 (0.7–1.1)	0.9 (0.7–1.2)	...
Rofecoxib				
1–30 days	347	1.9 (1.2–2.8)	1.1 (0.7–2.0)	1.3 (0.8–2.3)
>30 days	39	1.5 (1.1–2.0)	1.5 (1.0–2.1)	1.6 (1.1–2.2)

Adjusted odds ratio (95% CI). All exposures were adjusted for age, gender, race, recent hospitalizations, recent nursing home stays, number of physician visits and medications in prior year, number of comorbid conditions, and the presence of diabetes mellitus, coronary artery disease, and osteoarthritis.

*The reference group is always similar in dosage and duration to the exposure group, for example use of low-dosage celecoxib is compared with use of low-dosage nonspecific NSAID.

was associated with a slightly higher risk (OR 1.5; 95% CI, 1.0 to 2.1) than short duration rofecoxib (OR 1.1; 95% CI, 0.7 to 2.0) when compared with nonspecific NSAIDs. Similar trends were seen when rofecoxib use of long duration (OR 1.6; 95% CI, 1.1 to 2.2) and short duration (OR 1.3; 95% CI, 0.8 to 2.3) were compared with celecoxib.

In the clinical subgroups shown in Table 4, patients with chronic renal disease who took rofecoxib appeared to be at a higher relative risk for developing new onset hypertension than patients taking celecoxib (OR 5.3; 95% CI, 0.6 to 43.7), although with a wide CI because of the relatively small number of patients. The presence of congestive heart failure did not appear to identify a subgroup at significantly increased risk for COX-2 specific inhibitor-associated hypertension. There were too few patients with liver disease to estimate the relative risks of hypertension. When all strata were combined (renal disease, liver disease, or congestive heart failure), patients taking rofecoxib had a relative risk of

new onset hypertension that was more than 2-fold higher than that seen in comparable patients taking celecoxib (OR 2.1; 95% CI, 1.0 to 4.3).

Discussion

We conducted a case-control study to examine the potential relationship between the 2 COX-2 specific inhibitors available during the study period, celecoxib and rofecoxib, and new-onset hypertension. The possibility of a relationship between these agents and hypertension had been raised in prior reports, particularly for rofecoxib.¹⁰ When compared with celecoxib users, patients who used rofecoxib were significantly more likely to develop new onset of hypertension. These relationships were seen when either COX-2 specific inhibitor was compared with nonspecific NSAID users or when compared to patients unexposed to either type of agent.

TABLE 4. Association Between COX-2 Specific Inhibitors and Hypertension in High Risk Subgroups, 1999–2000

Exposure (Reference)	Renal Disease (n=648)		Congestive Heart Failure (n=1972)		Renal, CHF, or Liver Disease (n=2539)	
	Yes	No	Yes	No	Yes	No
Rofecoxib (unexposed)	1.5 (0.6–3.9)	1.6 (1.2–2.0)	1.3 (0.7–2.4)	1.7 (1.3–2.2)	1.5 (0.9–2.5)	1.6 (1.3–2.1)
Celecoxib (unexposed)	0.5 (0.2–1.5)	1.1 (0.9–1.3)	0.8 (0.4–1.3)	1.1 (0.9–1.3)	0.7 (0.4–1.1)	1.1 (0.9–1.3)
Rofecoxib (NSAID)	2.9 (0.1–68.9)	1.4 (1.0–1.8)	0.9 (0.4–2.1)	1.5 (1.1–2.1)	1.2 (0.6–2.5)	1.4 (1.0–2.0)
Celecoxib (NSAID)	...	0.9 (0.7–1.1)	0.6 (0.3–1.3)	0.9 (0.7–1.2)	0.7 (0.3–1.3)	0.9 (0.7–1.2)
Rofecoxib (celecoxib)	5.3 (0.6–43.7)	1.5 (1.1–2.1)	1.8 (0.8–4.3)	1.6 (1.1–2.1)	2.1 (1.0–4.3)	1.5 (1.1–2.0)

Adjusted odds ratio (95% CI). CHF indicates congestive heart failure; ellipses, there were too few people in this exposure category to produce an interpretable estimate.

The stratified analysis for liver disease is not shown because there were too few patients with liver disease to make meaningful comparisons. All exposures were adjusted for age, gender, race, recent hospitalizations, recent nursing home stays, number of physician visits and medications in prior year, number of comorbid conditions, the presence of diabetes mellitus, coronary artery disease, and osteoarthritis.

These findings are consistent with the findings from randomized trials in smaller groups of patients receiving protocolized care. Data from the VIGOR trial comparing rofecoxib to naproxen suggested the possibility that rofecoxib may be associated with an increased frequency of clinically significant hypertension. In secondary analyses available from the Food and Drug Administration,⁹ subjects taking rofecoxib had a 3.6 mm increase in systolic blood pressure compared with naproxen users. This translated into a 9.7% rate of hypertension as an adverse event in subjects randomized to rofecoxib compared with 5.5% in those randomized to naproxen. Data from the Celecoxib Long-term Arthritis Safety Study (CLASS) trial suggest that the rates of hypertension in celecoxib users were about equal to patients using nonspecific NSAIDs, 2.7% versus 3.4%.⁷ Comparison of these data are limited by diverse study populations and slightly different definitions of hypertension. However, another study compared the blood pressure effects of celecoxib to rofecoxib in a head-to-head randomized controlled trial.¹⁰ More than 1000 patients with osteoarthritis and stable hypertension were recruited and followed for 6 weeks with blood pressure measurements at baseline and at weeks 1, 2, and 6. Subjects were randomized to receive celecoxib 200 mg per day or rofecoxib 25 mg per day, the most common dosages used of these medicines. During the study, 14.9% of subjects using rofecoxib reached the criteria for worsening systolic hypertension with at least a 20 mm increase in blood pressure. This compared with 6.9% of subjects taking celecoxib ($P < 0.001$). Diastolic blood pressure changes were not significantly different.

These findings must be interpreted in light of the study's limitations, many of which are common to studies that use health care claims databases. It is possible that doctors diagnosed hypertension and prescribed antihypertensive medications differentially to patients taking different NSAIDs and COX-2 specific inhibitors. Because this study used data from 1999 to 2000, a time before published data regarding possible differences in these agents, we think this is very unlikely. Medications used for hypertension are used for many other indications, including congestive heart failure and angina, so that we may have misclassified some patients as having hypertension who did not. We applied conservative definitions requiring a diagnosis of hypertension as well as use of medications that lower the blood pressure. These definitions were applied equally across all relevant exposures. Hence, if there was substantial nondifferential misclassification, it would have biased all findings toward the null. The study database does not include use of over-the-counter medications, such as several nonspecific NSAIDs. However, use of these agents is less common than prescription agents in a lower income population with full drug coverage, such as the one studied. As well, it would be unlikely that use of over-the-counter nonspecific NSAIDs occurred differentially across the two COX-2 specific inhibitor groups. Other unmeasured factors may confound these results. We did examine several potential confounders in a different Medicare cohort (such as body mass index, tobacco use, and socioeconomic status) and found that the bias would have been toward the null in comparisons between COX-2 specific inhibitors

and nonspecific NSAIDs. However, there is the possibility for residual confounding. Finally, the study cohorts included only patients enrolled in a drug benefit program for low-to-moderate income elderly. It will be important for hypertension to be studied in other populations taking these agents.

It is not clear why there may be differences in the effect on blood pressure between rofecoxib and celecoxib. These effects may be specific to the individual molecular structure of the 2 different molecules,¹⁹ but this issue needs further examination so that the safety of these agents can be improved. Data from rat models of hypertension suggest that celecoxib but not rofecoxib may be associated with improvements in endothelial function and reductions in oxidative stress, but this finding has not been reported in all studies.^{5,6} There are other examples of specific agents in a medication class with distinct side effect risks, such as bromfenac, a nonspecific NSAID, with a higher than typical risk of hepatotoxicity²⁰ and cerivastatin, a lipid-lowering agent that is associated with rhabdomyolysis at increased rates compared with other statins.²¹

Perspectives

We found that rofecoxib was associated with an increased relative risk of new onset hypertension requiring treatment compared with celecoxib, nonspecific NSAIDs, and no NSAID. This relative risk appeared to be increased for patients taking rofecoxib who also had renal disease, liver disease, or congestive heart failure. Although this study cannot prove causality, it adds significant new information about the risk of hypertension requiring treatment for patients taking rofecoxib seen in typical practice.

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