

Renal effects of nonselective NSAIDs and coxibs

MATTHEW R. WEIR, MD

■ ABSTRACT

Despite the ubiquitous use of both over-the-counter and prescription nonsteroidal anti-inflammatory drugs (NSAIDs), clinical syndromes—NSAID-related hypertension, salt and water retention, edema, and hyperkalemia—are highly infrequent. Nevertheless, they remain a concern, and patient populations at risk for renal adverse effects from NSAIDs can be prospectively identified. Patients at risk include those with age-related declines in glomerular filtration rate; those with hypovolemia, particularly patients taking loop diuretics; and those with congestive heart failure, cirrhosis, or nephrosis. The following patient populations are at higher risk for increases in blood pressure with concomitant use of an NSAID and an antihypertensive: those with congestive heart failure, liver disease, or kidney disease, and those taking angiotensin-converting enzyme inhibitors or diuretics. Nonselective NSAIDs and COX (cyclooxygenase)-2–selective inhibitors (coxibs) appear to have similar effects on renal function

if dosed equivalently, and standard precautions to avoid renal toxicity with use of nonselective NSAIDs apply to coxibs.

Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used. These agents share anti-inflammatory, analgesic, and antiplatelet properties and also have many side effects in common. The most frequent is ulcerogenesis; by inhibiting cyclooxygenase (COX)-1, the nonselective NSAIDs can alter protective mechanisms in the gastric mucosa and increase acid secretion.¹ By selectively inhibiting only the COX-2 isoform, the COX-2–selective inhibitors (coxibs) are less likely to cause ulcerogenesis and have shown improved gastrointestinal safety and tolerability.²⁻⁷ Nevertheless, there are renal syndromes and toxicities common to both the nonselective NSAIDs and the coxibs.

This article will summarize current knowledge regarding nonsteroidal renal syndromes associated with nonselective NSAIDs and COX-2–selective inhibitors. It will identify patients at risk for developing renal toxicity with the use of these drugs, and provide strategies to primary care physicians to minimize these risks.

■ PHYSIOLOGIC AND PATHOPHYSIOLOGIC ROLES OF PROSTAGLANDINS IN THE KIDNEY

COX-1–related prostaglandins are largely constitutive and responsible for maintaining the integrity of the gastrointestinal mucosa, platelet adhesion, and acid secretion. Though constitutive in some physio-

From the Division of Nephrology, University of Maryland School of Medicine, Baltimore.

Address correspondence to M.R.W., Professor of Medicine and Director, Division of Nephrology, University of Maryland School of Medicine, 22 South Greene St., Baltimore, MD 21201; e-mail: mweir@medicine.umaryland.edu.

Disclosure. The author has indicated that he has received grant or research support from Pharmacia, has been a consultant for Merck and Pharmacia, and is on the speaker's bureau of Merck.

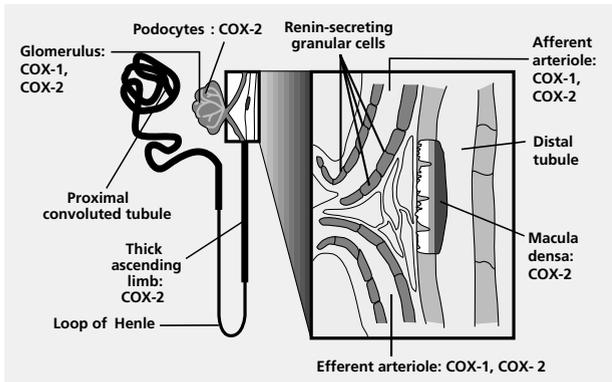


FIGURE 1. The role of prostaglandins in the kidney.^{8,9}

logical systems, COX-2–related prostaglandins are largely inducible and mediate pain and inflammation. NSAIDs alter renal function through their effects on renal prostaglandins.

In general, COX-1 functions in the control of renal hemodynamics and the glomerular filtration rate (GFR); COX-2 functions affect salt and water excretion, although there is some overlap. This separation of COX-mediated functions in the kidney is based in part on the physiologic/anatomic distribution of COX-1 compared to COX-2 (Figure 1); blockade of either or both of these enzymes can have, therefore, different effects on renal function.^{8,9} However, renal syndromes associated with the use of nonselective NSAIDs and COX-2–selective inhibitors can be either prostaglandin-dependent (ie, functional) or prostaglandin-independent (ie, anatomic).

As shown in Figure 2,¹⁰ the renal syndromes caused by nonselective NSAIDs and coxibs can be grouped according to their effects on prostaglandin (PG)E₂ and PGI₂. So whereas PGI₂, or prostacyclin, mostly affects renal homeostatic mechanisms, PGE₂ and PGD₂ dilate the renal vascular bed, lower renal vascular resistance, and increase renal perfusion.¹ In a person with normal renal hemodynamic parameters, prostaglandins do not play a dominant physiologic role in maintaining renal blood flow; PGE₂ and PGI₂ also normally play minor roles in maintaining the GFR.¹ However, in a person with compromised renal hemodynamics (for example, decreased circulating volume), the kidney synthesizes vasodilating prostaglandins to offset vasoconstricting autocooids and to maintain renal perfusion.¹¹ These prostaglandins become critically involved in maintaining the GFR. When production of PGI₂ is

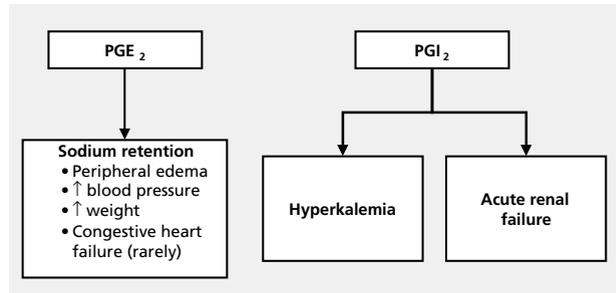


FIGURE 2. Renal syndromes caused by NSAID effects on prostaglandins.¹⁰

blocked, hyperkalemia and acute renal failure can result. The effects of blocking production of PGE₂ may include peripheral edema, increased blood pressure, weight gain, and, though rare, congestive heart failure.¹⁰

■ CLINICAL CONSIDERATIONS

Overall, the different nonselective NSAIDs produce similar renal effects. And, despite the ubiquitous use of both over-the-counter and prescription NSAIDs, the most frequent clinical syndromes related to their use—hypertension, salt and water retention, edema, and hyperkalemia—are relatively infrequent. Nevertheless, they remain a concern. But patient groups who are at risk for renal adverse effects from NSAIDs can be prospectively identified. Especially at risk are those with extreme liver dysfunction, or nephrotic patients with high-level proteinuria, or those with very low renal function.¹⁰ Furthermore, the increased risk for ARF and subsequent hospitalization due to NSAID use has been known for some time. Because of the role of COX-2 in regulating salt and water excretion, the COX-2–selective inhibitors, rofecoxib, celecoxib, and, most recently, valdecoxib, would be expected to have similar effects. Therefore, the standard renal precautions that apply to use of nonselective NSAIDs also apply to use of coxibs.

When effective arterial blood volume is diminished, greater susceptibility to renal prostaglandin inhibition and changes in renal function can occur. In patients with preexisting decreased renal blood flow, the inhibition of vasodilating prostaglandins contributes to a further decrease in glomerular blood flow and overall renal perfusion.

COX-2–derived PGE₂ is found primarily on the thick ascending limb of the loop of Henle; it pro-

motes diuresis and natriuresis by inhibiting reabsorption of sodium and water. NSAID-induced decreases in PGE₂ can increase sodium and water reabsorption and can produce some weight gain and occasionally edema. As noted, in persons with decreased circulating volume, vasodilating prostaglandins are produced by the kidneys to offset other vasoconstricting autocooids. In clinical settings in which renal blood flow depends on prostaglandin synthesis, NSAIDs can significantly decrease renal blood flow, with resultant acute renal failure.^{12,13} Patients at risk include those with age-related declines in GFR; those with hypovolemia, particularly patients taking loop diuretics; and those with congestive heart failure, cirrhosis, or nephrosis. Similarly to use of a nonselective NSAID, use of a COX-2-selective inhibitor should be carefully assessed in patients with any of these risk factors.

Some drug therapies, eg, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, also cause functional, but reversible, renal insufficiency that may worsen with NSAIDs. NSAIDs can lessen response to diuretics, especially the loop-acting diuretics (eg, furosemide), by as much as 20%. This effect may be more pronounced in patients likely to retain sodium, such as in those with congestive heart failure or cirrhosis.¹⁰

Concomitant use of NSAIDs and antihypertensives

Another concern is the 20 million people in the United States who currently take both an antihypertensive drug and an NSAID. Nonselective NSAIDs can induce dose-related fluid retention and raise blood pressure (BP) in some patients. Age-related declines in renal blood flow are more prominent in hypertensive persons and, as noted, NSAIDs can reduce renal blood flow and also cause a dose-dependent form of BP salt sensitivity. This can be clinically significant in susceptible persons.

In different studies of selective and nonselective NSAIDs, a 3- to 5-mm Hg increase in BP is seen across populations. In a meta-analysis by Pope and colleagues of 54 clinical trials involving 123 NSAID treatment arms and 1,324 participants, the effects of NSAIDs on BP, after adjusting for dietary salt intake, were noted only in hypertensive subjects. Indomethacin and naproxen raised mean arterial pressure by 3.59 and 3.74 mm Hg, respectively, while placebo, ibuprofen, and aspirin each lowered

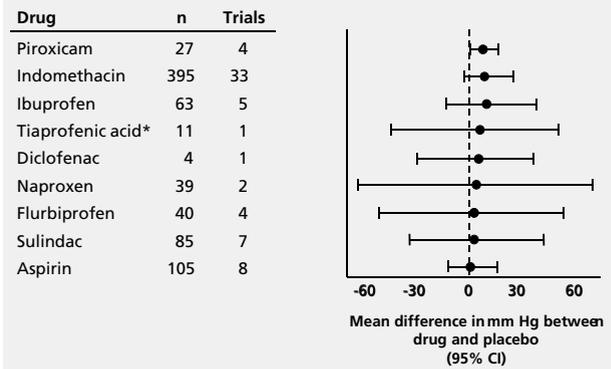


FIGURE 3. Hypertension with traditional NSAIDs. Adapted with permission from Johnson et al. *Ann Intern Med* 1994; 121:289–300.¹⁵ *Not available in the United States.

mean arterial pressure. The investigators concluded that, in short-term use, NSAIDs vary considerably in their effects on BP.¹⁴

In their meta-analysis of pooled data from 50 trials and 771 patients, Johnson and colleagues showed that NSAIDs increased supine mean arterial BP by 5 mm Hg (Figure 3). Mean weight gain was 0.3 kg; mean decrease in urinary sodium was 0.1 mmol/day, and urinary PGE₂ decreased by 162.7 ng/day.¹⁵

The effect of coxibs on BP is less well studied. A 6-week analysis by Geba and colleagues compared rofecoxib (25 mg QD), celecoxib (200 mg QD), and placebo in 1,082 patients with osteoarthritis of the knee or hip after withdrawal of previous osteoarthritis therapy. More than 40% of patients had a history of hypertension. Predefined changes in systolic blood pressure (>140 mm Hg and increase of >20 mm Hg) occurred in 9.6%, 9.4%, and 3.3% of patients taking rofecoxib, celecoxib, and placebo, respectively. This difference was significant in coxibs vs placebo ($P = .015$), but not between rofecoxib and celecoxib. Mean changes in systolic blood pressure were 1.9 mm Hg, 0.2 mm Hg, and -4.3 mm Hg for rofecoxib, celecoxib, and placebo, respectively.¹⁶

In the VIGOR trial, rofecoxib increased mean systolic and diastolic BP by 4.6 and 1.7 mm Hg vs increases of 1.0 and 0.1 mm Hg, respectively, with naproxen.¹⁷ In the same trial, the incidence of renal-related adverse events was low and similar in the two treatment groups: 1.2% in the rofecoxib group and 0.9% in the naproxen group.⁶ (The cardiovascular effects noted in the VIGOR trial are detailed elsewhere in this issue.)

Renal effects of NSAIDs and coxibs

The standard renal precautions that apply to use of nonselective NSAIDs also apply to coxibs. They should be used carefully in patients with hypertension, particularly those taking ACE inhibitors and/or potassium-sparing diuretics; patients taking salt substitutes; in patients with diabetes, particularly those with type IV renal tubular acidosis and possibly renal insufficiency; and in patients who are volume-depleted or who have cirrhosis or congestive heart failure.

If dosed in therapeutically equivalent ways, nonselective NSAIDs and coxibs show no evidence of major differences in renal effect.

Clinicians should be aware of the 3- to 5-mm Hg increase in BP seen across populations in different studies of COX-2-selective and nonselective NSAIDs. This BP-raising effect must be weighed against the therapeutic impact.

When a patient's BP increases, the following strategies are recommended: use a lower dose of nonselective NSAID or coxib; try to restrict dietary salt; inquire about patients' home remedies and over-the-counter drug use, including NSAIDs; review all medications being taken, including over-the-counter NSAIDs; and adjust the antihypertensive as appropriate.

NSAID-related renal syndromes include hypertension, salt and water retention, edema, and hyperkalemia. Despite the ubiquitous use of NSAIDs, these clinical syndromes occur infrequently. Nevertheless, they remain a concern, given the large number of patients at risk.

The clinical significance of an increase of as much as 5 mm Hg in mean arterial BP is unclear. Increases of this size in systolic and diastolic BPs have been shown to increase the risk for stroke and heart failure.¹⁸ For the vast majority of patients, the BP increase seen with concurrent use of an NSAID and an antihypertensive is probably clinically insignificant and can be treated with a reduction in dietary salt or an adjustment of medication.

Still, there are patient populations that are at higher risk for an increase in BP with concomitant use of an NSAID and an antihypertensive—those with congestive heart failure, liver disease, or kidney disease, and those taking ACE inhibitors or diuretics. In such patients, more careful management is mandated. It may be necessary to use additional diuretics to maintain a patient with congestive heart failure in an edema-free state. Frequent monitoring of BP, weight, and serum creatinine and potassium levels is appropriate.¹

The following strategies are recommended to clinicians when treating hypertension in a patient

taking an NSAID: lower the dose of the nonselective NSAID or coxib as much as possible, without compromising efficacy; lower salt intake; retitrate the antihypertensive; and inquire about the patient's use of over-the-counter NSAIDs. Another strategy is to use aspirin or the atypical opioid-like agent, tramadol. Use of a non-NSAID or aspirin is preferable to use of those NSAIDs that have been described as "renal-sparing" (nabumetone), since the renal-sparing effects have never been convincingly demonstrated.¹⁰

RENAL EFFECTS OF COX-2-SELECTIVE INHIBITORS

Before discussing the renal-effects profile of COX-2-selective inhibitors, NSAID-related renal syndromes will be briefly summarized. Several distinct syndromes of disturbed renal function—including fluid and electrolyte disorders, acute renal dysfunction, nephrotic syndrome/interstitial nephritis, and renal papillary necrosis—are associated with the use of nonselective NSAIDs. In addition, by blunting the homeostatic renal effects of prostaglandins, NSAIDs can hinder BP control, particularly with concomitant use of ACE inhibitors, diuretics, and beta-blockers. The risk of congestive heart failure is also significantly increased when NSAIDs are given to patients receiving diuretic therapy who have cardiovascular risk factors.¹⁹

Rossat and colleagues studied the renal effects of celecoxib vs naproxen in 40 healthy young men (age range 18 to 35 years) who were randomized to one of four treatment groups: celecoxib 200 or 400 mg twice daily, naproxen 500 mg twice daily, or placebo for 7 days. Subjects were salt-depleted by a low-sodium diet that began 5 days before drug administration and continued through the 7-day study. (Prostanoid-dependent renal function may become more pronounced in the setting of sodium depletion.) On days 1 and 7, GFR, renal blood flow, urine output, and urinary sodium were measured before and for 3 hours after drug administration.²⁰

Selective inhibition of COX-2 with celecoxib resulted in as much sodium and potassium retention as that seen with naproxen. At 400 mg twice daily, celecoxib transiently lowered the GFR and effective renal plasma flow; these effects were not seen with naproxen. Rossat and colleagues concluded that selective inhibition of COX-2 with celecoxib caus-

es as much sodium and potassium retention as with a nonselective coxib in salt-restricted persons. Unlike the nonselective NSAID, high-dose celecoxib transiently but significantly lowered GFR and effective renal plasma flow.²⁰

The effect of celecoxib on GFR in the elderly has also been studied. Whelton and colleagues administered celecoxib and naproxen to 29 healthy elderly subjects (age range, 65 to 80 years) using a single-blind, randomized, crossover format. Participants received celecoxib 200 mg twice daily for 5 days followed by 400 mg twice daily for 5 days, or the alternate schedule of naproxen 500 mg twice daily for 10 days. After a 7-day washout, subjects were crossed over to the other regimen. GFR was measured with radiolabeled sodium 2 days before drug administration and then 3 to 5 hours after drug administration on days 1 and 6 of treatment. Sodium intake was not controlled.²¹

Naproxen lowered the GFR with the first dose; the difference between naproxen and celecoxib in lowering GFR was statistically significant on day 6 (change from baseline on day 6, naproxen vs celecoxib, -7.5 ± 2.4 vs -1.1 ± 1.9 mL/min/1.73 m², respectively, $P = .004$). Small, transient decreases in sodium excretion, which returned to baseline by study end, were seen with both drugs.²¹ None of these changes are likely to be clinically significant.

Catella-Lawson and colleagues administered rofecoxib under double-blind conditions to 36 healthy older adults who were sodium restricted.²² Participants received rofecoxib 50 mg once daily, or indomethacin 50 mg three times daily, or placebo for 2 weeks. As seen in **Figure 4**, in the first 72 hours of treatment, both rofecoxib and indomethacin decreased urinary sodium excretion significantly. The change seen in the rofecoxib arm, however, was transient; only indomethacin lowered the GFR significantly vs rofecoxib and placebo. Neither agent produced any significant change in BP or weight.

Swan and colleagues also gave rofecoxib to 60 elderly subjects (age range, 65 to 80 years) on a low-salt diet using a randomized, multidose, parallel-group design. On day 6, peak effect on GFR was measured after the first dose. Both rofecoxib and indomethacin significantly lowered the GFR compared to placebo. On day 6, however, neither urinary sodium nor potassium was significantly lowered. The investigators note that the study subjects were generally healthy. Predisposed per-

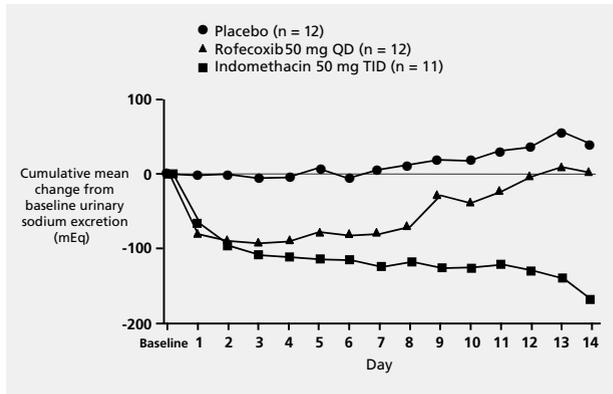


FIGURE 4. Renal effects of rofecoxib: mean change from baseline in urinary sodium excretion. Adapted with permission from Catella-Lawson et al. *J Pharmacol Exp Ther* 1999; 289:735–741.

sons who have lower effective circulating fluid volume (eg, those with congestive heart failure, with cirrhosis, or taking diuretics) may have clinically significant renal insufficiency with use of coxibs, similar to NSAID-induced alterations. Renal precautions that are observed for nonselective NSAIDs should also be observed for COX-2-selective inhibitors.²³

In a direct comparison study, Schwartz and colleagues administered rofecoxib (25 mg QD), celecoxib (200 mg BID), naproxen (500 mg BID), or placebo to 67 healthy elderly subjects for 2 weeks (age range, 60 to 80 years), and measured urinary sodium excretion. There were no significant differences among the three active treatments in daily average sodium excretion over the first 3 days or over 2 weeks of treatment. Peripheral edema did not occur. One subject each given rofecoxib and celecoxib experienced an increase in systolic BP. The investigators concluded that rofecoxib and celecoxib have similar effects on urinary sodium excretion, and that these effects are similar to those of nonselective NSAIDs.²⁴

These clinical trials comparing changes in renal function between nonselective NSAIDs and coxibs indicate only subtle changes in renal hemodynamics and BP. Thus, the renal effects of celecoxib and rofecoxib appear to be similar to nonselective NSAIDs and class specific. However, how to use these drugs in patients at higher risk for nonsteroidal renal syndromes has not been fully elucidated, as these studies have not been conducted in patients with renal disease.

■ CONCLUSIONS

Nonselective NSAIDs and COX-2-selective inhibitors are widely used drugs that appear to be similar in terms of their effects on renal function if they are dosed in therapeutic equivalents. Although the prevalence of renal toxicity in patients treated with NSAIDs is relatively low, the extensive use of both prescription and over-the-counter agents places many persons at risk. The mechanisms whereby these agents affect the kidney are understood, which allows at-risk patients—eg, the elderly and the hypovolemic, or patients with diabetes, hypertension, or congestive heart failure—to be

identified prospectively. Standard precautions to avoid renal toxicity with use of nonselective NSAIDs also apply to COX-2-selective inhibitors.

An increase in BP is often seen with concomitant use of an NSAID and an antihypertensive. Although this increase is probably clinically insignificant, the following strategies are recommended if BP increases in a patient taking a nonselective NSAID or a COX-2-selective inhibitor with an antihypertensive: lower the dose of the nonselective NSAID or coxib; lower salt intake; retitrate the antihypertensive; and inquire about the patient's use of over-the-counter NSAIDs. Another strategy is to use a non-NSAID, eg, tramadol or aspirin.

■ REFERENCES

1. Weir MR, Froch L. Weighing the renal effects of NSAIDs and COX-2 inhibitors. *Clinical Dilemmas* 2000; 1:3–12.
2. Lanza FL, Rack MF, Simon TJ, et al. Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. *Aliment Pharmacol Ther* 1999; 13:761–767.
3. Laine L, Harper S, Simon T, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999; 117:776–783.
4. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999; 282:1929–1933.
5. Hawkey C, Laine L, Simon T, et al, for the Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, controlled, double-blind, placebo-controlled trial. *Arthritis Rheum* 2000; 43:370–377.
6. Bombardier C, Laine L, Reicin A, et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343:1520–1528.
7. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; 284:1247–1255.
8. Nantel F, Meadows E, Denis D, Connolly B, Metters KM, Giaid A. Immunolocalization of cyclooxygenase-2 in the macula densa of human elderly. *FEBS Lett* 1999; 457:475–477.
9. Schnermann J, Briggs JP. The macula densa is worth its salt. *J Clin Invest* 1999; 104:1007–1009.
10. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. *Am J Med* 1999; 107(suppl 6A):65S–71S.
11. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. *Kidney Int* 1987; 32:1–12.
12. Brater DC, Anderson S, Baird B, Campbell WB. Effects of ibuprofen, naproxen, and sulindac on prostaglandins in men. *Kidney Int* 1985; 27:66–73.
13. Toto RD, Anderson SA, Brown-Cartwright D, Kokko JP, Brater DC. Effects of acute and chronic dosing of NSAIDs in patients with renal insufficiency. *Kidney Int* 1986; 30:760–768.
14. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; 153:477–484.
15. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994; 121:289–300.
16. Geba GP, Polis AB, Dixon ME, Dobbins TW, Rush JE, Weir MR. Comparative blood pressure effects of rofecoxib, celecoxib and placebo in patients with osteoarthritis (OA): a randomized controlled trial. Presented at: The Congress of the European League Against Rheumatism (EULAR), Prague, Czech Republic, June 13–16, 2001.
17. Data on file, Merck and Co.
18. Ruoff GE. The impact of nonsteroidal anti-inflammatory drugs on hypertension: alternative analgesics for patients at risk. *Clin Ther* 1998; 20:376–387.
19. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med* 1999; 106(suppl B):13S–24S.
20. Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. *Clin Pharmacol Ther* 1999; 66:76–84.
21. Whelton A, Schulman G, Wallemark C, et al. Effects of celecoxib and naproxen on renal function in the elderly. *Arch Intern Med* 2000; 160:1465–1470.
22. Catella-Lawson F, McAdam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther* 1999; 289:735–741.
23. Swan SK, Rudy DW, Lasseter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. *Ann Intern Med* 2000; 133:1–9.
24. Schwartz JL, Malice MP, Lasseter KC, Holmes GB, Gottesdiener KM, Brune K. Effects of rofecoxib, celecoxib, and naproxen on urinary sodium excretion in elderly volunteers. Presented at: The Congress of the European League Against Rheumatism (EULAR), Prague, Czech Republic, June 13–16, 2001.