

## Cardiovascular Effects of NSAIDs

KAITYANN SHERVE, PharmD; CHRISTOPHER J. GERARD, MD; and JON O. NEHER, MD  
*Valley Family Medicine Residency, Renton, Washington*

LEILANI ST. ANNA, MLIS, AHIP, *University of Washington Health Sciences Library, Seattle, Washington*

Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (<http://www.cebm.net/?o=1025>).

The complete database of evidence-based questions and answers is copyrighted by FPIN. If interested in submitting questions or writing answers for this series, go to <http://www.fpin.org> or e-mail: [questions@fpin.org](mailto:questions@fpin.org).

A collection of FPIN's Clinical Inquiries published in *AFP* is available at <http://www.aafp.org/afp/fpin>.

### Clinical Question

Do nonsteroidal anti-inflammatory drugs (NSAIDs) cause a clinically significant increase in blood pressure?

### Evidence-Based Answer

Aspirin does not elevate blood pressure. Among nonselective NSAIDs, ibuprofen increases the risk of hypertension and stroke. Diclofenac does not increase the risk of hypertension, but does increase the risk of stroke. Naproxen (Naprosyn) does not increase the risk of hypertension or stroke. Celecoxib (Celebrex) does not increase the risk of hypertension or stroke.

### Evidence Summary

#### ASPIRIN AND NONSELECTIVE NSAIDS

Two meta-analyses (N = 158 studies) evaluated aspirin trials that included data on blood pressure.<sup>1,2</sup> Aspirin dosages were greater than 1.5 g per day. There was no statistically significant effect on blood pressure. In a trial of 18,700 patients with hypertension, participants were randomized to receive aspirin (75 mg daily) or placebo for a mean of 3.8 years.<sup>3</sup> There was no effect on blood pressure. There were significant reductions in rates of myocardial infarction among participants who were also receiving angiotensin-converting enzyme inhibitors (risk ratio [RR] = 0.39; 95% confidence interval [CI], 0.21 to 0.71).

A systematic review identified 32 randomized controlled trials (RCTs) that included 3,626 patients who were treated for at least four weeks with nonselective NSAIDs.<sup>4</sup> Patients were monitored for changes in blood pressure and rates of hypertension during treatment. Most studies enrolled patients with osteoarthritis or rheumatoid arthritis,

although some included patients with other conditions. Patients who received ibuprofen had a greater incidence of new hypertension compared with those in the control group (2.9% vs. 1%; RR = 2.9; 95% CI, 1.4 to 5.7; number needed to harm = 53).

#### CYCLOOXYGENASE-2 INHIBITORS

A meta-analysis of 19 RCTs that included 45,000 patients with arthritis evaluated blood pressure after more than four weeks of treatment with cyclooxygenase-2 inhibitors, nonselective NSAIDs, or placebo<sup>5</sup> (*Table 1<sup>1,5-7</sup>*). Another meta-analysis that included 49 RCTs with 130,000 patients—most of whom had arthritis—evaluated the effects of these agents on the diagnosis of hypertension after more than four weeks of treatment.<sup>6</sup> Celecoxib was not associated with an increased rate of hypertension. The study did not report absolute risk changes or provide numbers needed to treat or harm.

#### CARDIOVASCULAR OUTCOMES

A meta-analysis compared the cardiovascular safety of naproxen, ibuprofen, diclofenac, and celecoxib.<sup>7</sup> It included 31 RCTs (N = 120,000 patients) that had more than 100 patient-years of follow-up per treatment arm, and that reported on the cardiovascular end points of myocardial infarction, stroke, cardiovascular death, and death from any cause (*Table 1<sup>1,5-7</sup>*). None of the drugs significantly increased the risk of myocardial infarction. Compared with placebo, diclofenac increased the risk of stroke, the total cardiovascular death rate (rate ratio = 4.0; 95% CI, 1.5 to 13), and all-cause mortality (rate ratio = 2.3; 95% CI, 1.0 to 4.9). Ibuprofen, naproxen, and celecoxib had no significant effect on the total cardiovascular death rate or all-cause mortality.

**Table 1. Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs**

Medication	Change in systolic blood pressure (mm Hg; 95% CI) <sup>1,5</sup>	Change in diastolic blood pressure (mm Hg; 95% CI) <sup>1,5</sup>	Relative risk of hypertension vs. placebo (95% CI) <sup>1,6</sup>	Rate ratio of myocardial infarction vs. placebo (95% credibility interval*) <sup>7</sup>	Rate ratio of stroke vs. placebo (95% credibility interval*) <sup>7</sup>
Celecoxib (Celebrex)	2.6†	1.0†	1.2 (0.8 to 1.9)	1.4 (0.7 to 2.7)	1.1 (0.6 to 2.1)
Diclofenac	-0.5 (-1.5 to 0.6)	-0.56 (-1.2 to 0.07)	NA	0.8 (0.3 to 2.2)	2.9 (1.1 to 8.4)‡
Ibuprofen	3.5 (2.7 to 4.4)‡	1.2 (0.7 to 1.6)	2.8 (1.4 to 5.7)‡	1.6 (0.5 to 5.8)	3.4 (1.0 to 12)
Indomethacin	2.9 (-0.3 to 6.1)	1.6 (0.3 to 2.9)	NA	NA	NA
Nabumetone	1.7 (-0.02 to 3.4)	-0.1 (-1 to 0.86)	1.5 (0.5 to 4.5)	NA	NA
Naproxen (Naprosyn)	0.73 (-1 to 2.5)	-0.14 (-1.2 to 0.86)	2.1 (0.97 to 4.4)	0.8 (0.4 to 1.7)	1.8 (0.9 to 3.3)
Sulindac (Clinoril)	1.5 (-1.2 to 4.3)	0.17 (-1.3 to 1.7)	NA	NA	NA

CI = confidence interval; NA = not available.

\*—Bayesian credibility intervals may be interpreted as conventional CIs because the study authors assumed minimally informative prior distributions.

†—The meta-analysis did not give statistics for mean blood pressure changes resulting from treatment with celecoxib compared with baseline.

‡—Statistically significant.

Information from references 1, and 5 through 7.

**Recommendations from Others**

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure states that NSAIDs are associated with hypertension and resistant hypertension.<sup>8</sup>

Copyright Family Physicians Inquiries Network. Used with permission.

Address correspondence to KaityAnn Sherve, PharmD, at [KaitySherve@fhshealth.org](mailto:KaitySherve@fhshealth.org). Reprints are not available from the authors.

Author disclosure: No relevant financial affiliations.

**REFERENCES**

1. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of non-steroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med.* 1993;153(4):477-484.
2. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med.* 1994; 121(4):289-300.
3. Zanchetti A, Hansson L, Leonetti G, et al. Low-dose aspirin does not interfere with the blood pressure-lowering effects of antihypertensive therapy. *J Hypertens.* 2002;20(5):1015-1022.

4. Morrison A, Ramey DR, van Adelsberg J, Watson DJ. Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and hypertension. *Curr Med Res Opin.* 2007; 23(10):2395-2404.
5. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med.* 2005; 165(5):490-496.
6. Chan CC, Reid CM, Aw TJ, Liew D, Haas SJ, Krum H. Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis. *J Hypertens.* 2009;27(12):2332-2341.
7. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ.* 2011; 342:c7086.
8. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [published correction appears in *JAMA.* 2003;290(2):197]. *JAMA.* 2003;289(19):2560-2572. ■