

# Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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## **Treating Osteoarthritis With Cyclooxygenase-2–Specific Inhibitors: What Are the Benefits of Avoiding Blood Pressure Destabilization?**

Steven A. Grover, Louis Coupal and Hanna Zowall

*Hypertension* 2005;45:92-97; originally published online Nov 15, 2004;

DOI: 10.1161/01.HYP.0000149684.01903.b8

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

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# Treating Osteoarthritis With Cyclooxygenase-2-Specific Inhibitors

## What Are the Benefits of Avoiding Blood Pressure Destabilization?

Steven A. Grover, Louis Coupal, Hanna Zowall

**Abstract**—Osteoarthritis and hypertension are highly prevalent among older Americans. Anti-inflammatory medications can destabilize blood pressure control. We estimated the decreased cardiovascular risk, premature mortality, and direct health care costs that could be avoided if blood pressure control is not destabilized among hypertensive Americans taking cyclooxygenase-2 (COX-2)-specific inhibitors for osteoarthritis. Data from the Third National Health and Nutrition Examination Survey (NHANES III) provided the distribution of cardiovascular risk factors among American adults with osteoarthritis and hypertension. The Cardiovascular Disease Life Expectancy Model was used to estimate the impact of a 2.26% increase in systolic blood pressure on the basis of results of a randomized trial comparing COX-2-specific inhibitors. A similar analysis was completed for American adults with osteoarthritis and untreated hypertension ( $\geq 140/90$  mm Hg). Among 7.3 million Americans with treated hypertension, maintaining blood pressure control would avoid >30 000 stroke deaths and 25 000 coronary deaths resulting in >449 000 person years of life saved and \$1.4 billion in direct health care cost savings. When an additional 3.8 million Americans with untreated hypertension are considered, maintaining blood pressure control could prevent >47 000 stroke deaths, 39 000 coronary deaths, and result in 668 000 person years of life saved and >\$2.4 billion in direct health care cost savings. We conclude that even a small increase in systolic blood pressure among hypertensive Americans with osteoarthritis may substantially increase the clinical and economic burden of cardiovascular disease. Maintaining blood pressure control may be associated with substantial benefits. (*Hypertension*. 2005;45:92-97.)

**Key Words:** blood pressure ■ cardiovascular disease

Osteoarthritis is highly prevalent in the United States. Among nearly 116 million US adults  $\geq 35$  years of age,  $\approx 24$  million (21%) have osteoarthritis.<sup>1</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for osteoarthritis. NSAIDs inhibit the cyclooxygenase-1 (COX-1) and COX-2 enzymes.<sup>2</sup> One of the most serious side effects of nonspecific NSAIDs is upper gastrointestinal ulceration and bleeding resulting from a reduction in the prostaglandins produced by COX-1.

Recent clinical trials suggest that COX-2-selective NSAIDs are associated with a reduced incidence of gastrointestinal bleeding compared with nonselective NSAIDs.<sup>3,4</sup> This reduced gastric toxicity has been primarily responsible for the growing popularity of these drugs in the United States and Canada. With this increased use, other issues surrounding COX-2-specific inhibitor toxicity are now receiving additional attention. For instance, in the Vloxx Gastrointestinal Outcome Research (VIGOR) study, whereas rofecoxib was associated with a lower risk of gastrointestinal events compared with naproxen, myocardial infarctions were more

frequent with this COX-2-specific inhibitor.<sup>3</sup> Controversy continues as to whether rofecoxib is associated with an increased risk of myocardial infarction or whether naproxen offers protection against cardiovascular disease.<sup>5-10</sup>

It has been well recognized that nonspecific NSAIDs may interfere with hypertension management. A number of meta-analyses have concluded that this appears to be a class effect, whereby systolic and diastolic pressure are increased among previously controlled patients.<sup>11,12</sup> Data surrounding the effects of COX-2-specific inhibitors on hypertension have only recently become available. Among hypertensive patients with osteoarthritis, recent head-to-head, double-blind, clinical trials have evaluated the blood pressure changes associated with COX-2-specific inhibitors. In the SUCcessive Celecoxib Efficacy and Safety Study (SUCCESS) VI, 810 patients were randomized to receive 200 mg of celecoxib or 25 mg of rofecoxib once daily. After 6 weeks of treatment, there was a significant increase in systolic blood pressure (+2.6 mm Hg) for rofecoxib compared with -0.5 mm Hg for celecoxib.<sup>13</sup> Clinically important hypertension also developed in both

Received September 2, 2004; first decision September 28, 2004; revision accepted October 25, 2004.

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*Hypertension* is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000149684.01903.b8

treatment arms but was more common among rofecoxib patients. A similar result was observed in a second but larger study, SUCCESS VII.<sup>14</sup>

The prevalence of osteoarthritis increases with age, as does the risk of cardiovascular disease. The prevalence of high blood pressure also increases with age. Accordingly, a substantial number of patients with osteoarthritis are likely to be receiving concurrent therapy for hypertension. We used the Cardiovascular Life Expectancy Model,<sup>14</sup> a validated Markov model, and data from the Third National Health And Nutrition Examination Survey (NHANES III)<sup>15</sup> to estimate the impact of small changes in blood pressure. These analyses focus on American adults with osteoarthritis and hypertension, treated and untreated, to estimate the potential clinical and economic impact of blood pressure destabilization after COX-2-specific inhibitor prescription.

## Methods

Using blood pressure data provided by the SUCCESS VI study, we estimated the impact of blood pressure destabilization among hypertensive patients receiving COX-2-specific inhibitor therapy for the treatment of osteoarthritis.<sup>13</sup> The impact of blood pressure changes on cardiovascular risk was modeled using the Cardiovascular Life Expectancy Model.<sup>14</sup> This validated Markov model was used to estimate the increased risk of coronary events, cerebrovascular events, and premature mortality after blood pressure changes. The incremental risk observed in the SUCCESS VI study was then extrapolated to the American adults diagnosed with osteoarthritis and receiving treatment for hypertension. These analyses were based on the distribution of risk factors among adults in the NHANES III survey.<sup>15</sup> Finally, we also estimated the impact of blood pressure destabilization on adults with osteoarthritis and untreated hypertension.

### Blood Pressure Changes Observed in SUCCESS VI

SUCCESS VI was a 6-week randomized parallel group, double-blind trial in patients with osteoarthritis who were  $\geq 65$  years of age and were taking antihypertensive agents.<sup>13</sup> Patients received 200 mg of celecoxib or 25 mg rofecoxib once daily. Primary end points included changes in blood pressure and development of edema.

Approximately 400 patients were entered into each arm of the study. Baseline characteristics were balanced between the 2 treatment groups, including an average of 74 years of age, female gender in 66% of participants, baseline systolic blood pressure of 137 to 138 mm Hg, and diastolic blood pressure of 76 mm Hg. During 6 weeks of therapy, mean systolic blood pressure decreased in the celecoxib-treated patients but increased among those receiving rofecoxib. The net difference between the 2 treatment arms increased from 2.4 mm Hg ( $P=0.014$ ) at week 1, to 2.8 mm Hg ( $P=0.006$ ) at week 2, to 3.1 mm Hg ( $P=0.007$ ) at week 6. Clinically important elevated hypertension (prespecified as an increase of  $>20$  mm Hg with an absolute value  $>140$  mm Hg) developed among 66 rofecoxib patients compared with 45 patients receiving celecoxib ( $P=0.03$ ). In summary, systolic blood pressure decreased by 0.36% among those receiving celecoxib and rose 1.9% among those receiving rofecoxib. These net changes in blood pressure (2.26%) were used to estimate the associated change in cardiovascular risk.

### Estimating Cardiovascular Events and Life Expectancy

The Cardiovascular Disease Life Expectancy Model was used to estimate the impact of the differential blood pressure effect of celecoxib versus rofecoxib.<sup>15</sup> This Markov model estimates the annual probability of fatal and nonfatal cardiovascular events on the basis of multivariate logistic regression models developed using the Lipid Research Clinics Prevalence Study.<sup>16</sup> Independent risk factors in-

clude age, gender, blood pressure, LDL cholesterol, HDL cholesterol, mean arterial pressure, the presence of cigarette smoking, diabetes, and diagnosed cardiovascular disease at baseline. The clinical criteria for cardiovascular events and the odds ratios (ORs) for the independent risk factors have been reported previously.<sup>15</sup>

A cohort of patients is entered into the model with specified levels of risk factors. Each year, subjects can die of coronary heart disease or of cerebrovascular disease or other noncardiovascular causes. Surviving subjects age 1 year and re-enter the model for the following year. Mean life expectancy can be calculated by summing across the total person years of life experienced by the cohort and dividing by the subjects at risk at entry into the model. The model has been described in detail previously and shown to reasonably estimate events in 9 clinical trials of dyslipidemia or hypertension.<sup>15</sup>

### Estimating Risk of Cardiovascular Events Among American Adults

The Third National Health and Nutrition Survey (NHANES III) was used to provide a representative sample of Americans with osteoarthritis and hypertension (treated or untreated).<sup>17</sup> This study was conducted in 2 phases between 1988 and 1994.

Cigarette smokers included self-reported current smokers who had smoked  $>100$  cigarettes in their lifetime or subjects with serum cotinine levels  $>13$  mg/mL. The presence of cardiovascular disease was defined as a subject's self-report of a previous physician diagnosis of heart attack, stroke, congestive heart failure, or symptoms consistent with angina (Rose questionnaire) or intermittent claudication. Presence of diabetes was based on a patient's self-report of previous physician diagnosis of diabetes or the American Diabetes Association criteria of a fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L).

Specific weights were assigned to each sampled subject to estimate the total number of Americans represented by that subject after adjustment for selection probabilities and nonresponse.

### Primary Analyses

Using NHANES III data, the presence of osteoarthritis among adults  $\geq 50$  years of age was based on a positive response to the question: "Has a physician ever told you that you had arthritis?" They were then asked whether it was osteoarthritis or rheumatoid arthritis. We excluded all patients with rheumatoid arthritis. Individuals were classified as having treated hypertension if they had been told by their physician that they had hypertension and were taking prescribed medication for it. Untreated hypertension was defined as a measured systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg among individuals who were not taking prescribed medication.

The Cardiovascular Disease Life Expectancy Model was then used to estimate the impact of a 2.26% net increase in systolic blood pressure on the lifetime risk of cardiovascular events. Initially, the analysis focused only on individuals with treated hypertension. The analysis was then repeated for individuals with untreated hypertension.

Initially, we calculated the fatal strokes and coronary events (undiscounted) that would be avoided if blood pressure is not destabilized. We then calculated the person years of life saved because of premature mortality associated with an increased risk of cardiovascular disease. Finally, we calculated the direct health care cost savings associated with preventing cardiovascular disease. Person years of life saved and cost savings were discounted 3% annually.

### Estimating Direct Health Care Costs of Cardiovascular Disease

The economic perspective adopted in the present analysis is that of a third-party payer providing comprehensive coverage of all health care services. Cardiovascular disease treatment costs included the costs of hospitalizations, physician fees, outpatient care, and emergency services where applicable. Physician fees, outpatient care,

**TABLE 1. Cardiovascular Risk Factors Among Americans  $\geq 50$  Years of Age With Osteoarthritis and Hypertension**

Risk Factors	Taking Medication for Hypertension	No Medication but Blood Pressure $>140/90$ mm Hg
Sample size	440	246
Population estimate	7 296 893	3 826 010
Male	28%	35%
Mean age	69	72
Cigarette smokers	19%	21%
Diagnosed angina	12%	6%
Previous heart attack	15%	11%
Diagnosed congestive heart failure	12%	8%
Previous cerebrovascular accident	11%	7%
Diagnosed coronary heart disease	26%	17%
Diabetes	28%	14%
Systolic blood pressure (mm Hg)	144	155
Diastolic blood pressure (mm Hg)	76	77
Total cholesterol (mg/dL)	227	226
LDL cholesterol (mg/dL)	139	141
HDL cholesterol (mg/dL)	50	54
Triglycerides (mg/dL)	188	153
Total cholesterol/HDL ratio	5	4.6

emergency services, and drug prescriptions also included in the model have been reported previously in detail.<sup>18</sup>

American health care costs were derived from published reports. Hospital costs were based on the National Medicare Provider Analysis and Review data and the National Sample of the Health Care Costs and Utilization Project.<sup>19,20</sup> Laboratory tests and physician fees were based on the Medicare Resource-Based Relative Value Scale.<sup>21</sup> Annual medication costs were derived from the 1998 *Drug Topics Red Book*.<sup>22</sup>

### Role of the Study Sponsor

This investigator-initiated study was supported by a grant-in-aid from Pfizer Canada, Inc, which manufactures celecoxib. The sponsor of the study had no role in data analysis, data interpretation, or writing of the report. Before submission, the study sponsor made nonbinding suggestions to the study authors.

### Results

Using survey data from NHANES III,  $\approx 26$  million individuals were estimated to have physician-diagnosed osteoarthritis. The prevalence of osteoarthritis grew with increasing age for men and women. The use of antihypertensive medications also grew with increasing age. A total of 440 adults  $\geq 50$  years of age reported a diagnosis of osteoarthritis and were taking antihypertensive medication. This represents a population of  $\approx 7.3$  million American adults. The prevalence of cardiovascular disease and associated cardiovascular risk factors are summarized in Table 1. The average age of this population was 69 and 28% were male. Coronary heart disease had been diagnosed previously in 26% of respondents, and 11% had experienced a cerebrovascular accident. Congestive heart failure was also present in 12% of respondents, and diabetes was reported in 28%. Blood pressure

**TABLE 2. Fatal Strokes and Coronary Events Avoided if Blood Pressure Is Not Increased With COX-2-Specific Inhibitors Among Americans With Osteoarthritis Taking Antihypertensive Medication**

Gender	Age Group (years)	Americans Affected	Stroke Deaths Avoided	CHD Deaths Avoided
Men	50 to 59	280 783	994	1258
	60 to 74	1 292 201	4413	4560
	$\geq 75$	460 770	4656	1211
	All	2 033 753	7064	7030
Women	50 to 59	970 850	4398	3782
	60 to 74	2 959 448	13 599	10 920
	$\geq 75$	1 332 842	5325	3611
	All	5 263 140	23 321	18 313
All		7 296 893	30 385	25 343

CHD indicates coronary heart disease.

averaged 144/76 mm Hg among those who were receiving treatment for hypertension.

Compared with the baseline characteristics of patients enrolled in the SUCCESS VI study, the NHANES III population appears to be at somewhat higher risk of future cardiovascular events. In SUCCESS VI, the mean age was 74, and 33.5% of participants were male. Coronary artery disease was diagnosed in  $\approx 18\%$  of participants and congestive heart failure in 5%. Baseline blood pressure was also lower than in the NHANES III population, averaging  $\approx 138/76$  mm Hg. These data reflect the study exclusion criteria whereby patients had to have a diastolic blood pressure of  $\leq 95$  mm Hg and a systolic blood pressure of  $\leq 160$  mm Hg to enter the study. Those with New York Heart Association Class III or IV heart failure were also excluded. Presence of cigarette smoking, diabetes, and blood lipid levels were not reported.

In SUCCESS VI, rofecoxib was associated with a 2.26% net increase in systolic blood pressure compared with celecoxib. We therefore estimated the cardiovascular events that could be avoided if this increase in systolic blood pressure did not occur (Table 2). Among American men and women  $\geq 50$  years of age,  $\approx 30$  000 stroke deaths and 25 000 coronary deaths would be avoided among 7.3 million individuals with osteoarthritis who are also taking antihypertensive medication. The majority of these events would be prevented in women among whom osteoarthritis and hypertension are more than twice as prevalent compared with men. After discounting future events 3% annually, this would translate into 449 000 person years of life saved, including 123 000 among men and 326 000 among women (Table 3). When the direct health care costs associated with treating cardiovascular disease are also considered, the cost savings of maintaining blood pressure control exceed \$1.43 billion, including \$227 million among men and \$1.2 billion among women.

The potential benefits of not raising systolic blood pressure were also considered for 3.8 million Americans with osteoarthritis who are not taking antihypertensives but had a blood pressure of  $\geq 140/90$  mm Hg. The baseline characteristics of this population are also summarized in Table 1. Compared

**TABLE 3. Estimated Benefits and Cost Savings if Blood Pressure Is Not Increased With COX-2-Specific Inhibitors Among Americans With Osteoarthritis Taking Antihypertensive Medication**

Gender	Age Group (years)	Discounted Person Years of Life Saved	Discounted Cost Savings (millions)
Men	50 to 59	26 279	\$ 27
	60 to 74	77 133	\$ 121
	≥75	19 272	\$ 78
	All	122 684	\$ 227
Women	50 to 59	74 598	\$ 233
	60 to 74	196 798	\$ 710
	≥75	55 072	\$ 256
	All	326 468	\$1198
All		449 152	\$1425

with adults receiving antihypertensives, they tend to be older, are more likely to be male but less likely to have cardiovascular disease or diabetes, and have higher mean systolic blood pressure. Among these untreated hypertensive adults, ≈17 000 stroke deaths and 14 000 coronary deaths would be avoided (Table 4). An additional 219 000 person years of life saved would be associated with better blood pressure control as well as \$945 million in direct health care cost savings (Table 5).

Overall, the potential benefits of maintaining blood pressure control in these 2 populations could exceed 47 000 stroke deaths and 39 000 coronary deaths prevented, >668 000 person years of life saved, and >\$2.4 billion in direct health care cost savings.

**Discussion**

These analyses suggest that a small but significant net increase in the average systolic blood pressure among individuals receiving COX-2-specific inhibitors could translate into a substantial increase in cardiovascular risk and premature mortality. Direct health care costs associated with treating cardiovascular disease would also increase. One must acknowledge these results are based on estimates derived

**TABLE 4. Fatal Strokes and Coronary Events Avoided if Blood Pressure Is Not Increased With COX-2-Specific Inhibitors Among Americans With Osteoarthritis and Elevated Blood Pressure**

Gender	Age Group (years)	Americans Affected	Stroke Deaths Avoided	CHD Deaths Avoided
Men	50 to 59	277 437	1080	1038
	60 to 74	675 620	2552	2566
	≥75	389 937	1562	1382
	All	1 342 993	5194	4986
Women	50 to 59	229 675	1045	1044
	60 to 74	1 101 073	5292	4430
	≥75	1 152 269	5083	3624
	All	2 483 017	11 420	9098
All		3 826 010	16 614	14 084

CHD indicates coronary heart disease.

**TABLE 5. Estimated Benefits and Cost Savings if Blood Pressure Is Not Increased With COX-2-Specific Inhibitors Among Americans With Osteoarthritis and Untreated Hypertension**

Gender	Age Group (years)	Discounted Person-Years of Life Saved	Discounted Cost Savings (millions)
Men	50 to 59	25 511	\$ 10
	60 to 74	42 928	\$ 69
	≥75	17 940	\$ 85
	All	86 380	\$164
Women	50 to 59	10 723	\$ 82
	60 to 74	70 732	\$355
	≥75	51 123	\$344
	All	132 578	\$781
All		218 958	\$945

from the Markov model simulation and not a large head-to-head clinical trial. Nonetheless, there is a substantial body of evidence to support the conclusion that small changes in blood pressure among individuals with osteoarthritis and hypertension will prove to be clinically important and costly as well.

The benefits of treating systolic hypertension have been confirmed in such studies as the Systolic Hypertension in the Elderly Program (SHEP).<sup>23</sup> During 4.5 years of follow-up, active treatment was associated with a 12-mm drop in systolic blood pressure and a 4-mm drop in diastolic blood pressure. For individuals ≥60 years of age, this resulted in a significant 36% reduction in stroke and 27% reduction in clinical nonfatal myocardial infarction plus coronary death. However, one must recognize that the blood pressure changes observed in SHEP were 4-fold greater than those observed in the SUCCESS VI study.

In the Heart Outcomes Prevention Evaluation (HOPE) study, an angiotensin-converting enzyme inhibitor (ramipril) was compared with placebo among patients who were at high risk for a cardiovascular event.<sup>24</sup> Approximately 50% of the patients had documented hypertension, and the average blood pressure at entry into the study was 139/79 (nearly identical to the baseline blood pressure of SUCCESS VI patients). At the end of the study, systolic blood pressure among the ramipril-treated group was 3 mm Hg lower than the placebo group. In spite of this small change in blood pressure, ramipril significantly reduced the rates of death, myocardial infarction, and stroke by 20% to 32%. The HOPE investigators have used epidemiological data to suggest that the blood pressure benefits observed with treatment could not fully account for the entire observed reduction in stroke or myocardial infarction.<sup>25</sup> However, recent re-analyses of blood pressure data from the Framingham Heart Study suggest that the benefits of reducing blood pressure may have been underestimated previously in observational studies.<sup>26</sup>

In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), the doxazosin arm of the study was terminated prematurely after 3.3 years of follow-up because of a significantly increased risk of stroke, combined cardiovascular events, and congestive heart failure

compared with patients receiving the diuretic chlorthalidone.<sup>27</sup> Once again, the difference in blood pressure between the 2 groups ranged from 2 to 3 mm of systolic blood pressure during the 3-year follow-up of the study. The recently published final report of ALLHAT also demonstrated that the angiotensin-converting enzyme inhibitor lisinopril versus the diuretic chlorthalidone was associated with a higher combined rate of cardiovascular disease, stroke, and heart failure.<sup>28</sup> Once again, chlorthalidone was associated with a greater reduction in systolic pressure of 2- to 3-mm difference in systolic blood pressure in favor of chlorthalidone.

The results presented herein are also consistent with an earlier analysis by Cook et al in which the impact of a 2-mm reduction in diastolic blood pressure was estimated to result in a 6% reduction in coronary heart disease events and a 15% reduction in stroke.<sup>29</sup> This analysis was based on Framingham Heart Study data and population survey data from the NHANES II. A 2-mm reduction in diastolic blood pressure approximates a 4-mm drop in systolic blood pressure based on an overview analysis of 14 randomized trials of antihypertensive drugs published by Collins et al.<sup>25</sup>

In the absence of long-term clinical trial data, the estimates presented in these analyses have been necessarily conservative. Only adults  $\geq 50$  years of age are included in these analyses. NHANES III participants representing  $>1$  million adults were also excluded from the analyses because of missing data on cardiovascular risk factors. We also recognize that the diagnosis of osteoarthritis used in NHANES III was based only on patient self-report. However, this data set provided the complete assessment of cardiovascular risk factors necessary for our analyses. Nonetheless, one would expect that the absolute prevalence of osteoarthritis presented herein may be somewhat inflated. It should be recognized that in SUCCESS VI, clinically important blood pressure increases were observed despite the fact that a patient's antihypertensive medication could be titrated upward as required by the treating physician.<sup>13</sup> Blood pressure changes were also more likely to be noticed in this clinical trial setting in which blood pressure was a primary outcome and measured  $3\times$  over 6 weeks. Recent analyses of the NHANES III data demonstrate that the diagnosis and treatment of hypertension on a national basis is probably less optimal. It is estimated that 31% of Americans were unaware that they had hypertension, and only 23% were taking medications that control their hypertension adequately.<sup>30,31</sup> Accordingly, it is reasonable to expect that blood pressure destabilization is more likely to go unnoticed in routine clinical practice than that observed in the SUCCESS VI study. Finally, although these analyses focused only on COX-2 inhibitors, blood pressure destabilization has also been observed with many nonspecific NSAIDs.<sup>11,12</sup>

SUCCESS VI was not large enough or long enough in duration to demonstrate a significant difference in coronary events or stroke. Nonetheless, the significant increase in peripheral edema among rofecoxib-treated patients (9.5%) versus celecoxib-treated patients (4.9%;  $P=0.01$ ) and the 4 cases of congestive heart failure all among the rofecoxib group ( $P=0.058$ ) support the conclusion that small average changes in blood pressure among a patient cohort are not

benign because they may represent large changes among a few susceptible patients.<sup>13</sup> Whereas a 3-mm increase is the average change observed in the study, 17% of patients were significantly ( $P<0.05$ ) more likely to have a clinically important increase of  $\geq 20$  mm in their blood pressure in the rofecoxib group compared with 11% in the celecoxib group. It appears that neither treatment is without any risk whatsoever.

Additional data from a similar but larger study (SUCCESS VII) confirms an increased risk of edema and an increase in systolic blood pressure among patients receiving rofecoxib versus celecoxib.<sup>14</sup> In SUCCESS VII, additional analyses also suggest that calcium channel blockers or diuretic model therapy may protect against the blood pressure increases noted with rofecoxib, suggesting that hypertension is avoidable with appropriate detection and treatment.

The results of the 2 large COX-2-specific inhibitor gastric toxicity trials and 2 observational studies also support the conclusion that rofecoxib may increase the risk of coronary events. Cardiovascular outcomes were measured in 2 large, recently published long-term studies. In the VIGOR trial, myocardial infarction was observed in 0.4% of the rofecoxib-treated patients versus 0.1% of the naproxen-treated patients (relative risk, 0.2; 95% confidence interval [CI], 0.1 to 0.7).<sup>3</sup> A similar comparison between 400 mg of celecoxib twice daily versus 800 mg of ibuprofen  $3\times$  per day or 75 mg of diclofenac twice daily demonstrated no significant increase in cardiovascular events in the celecoxib group (0.9) versus the combined NSAID group (1.0).<sup>4</sup> In a large cohort study conducted by Ray et al, the users of high doses of rofecoxib ( $>25$  mg) were found to be at increased risk of experiencing serious coronary heart disease compared with nonusers (incidence rate ratio of 1.7 with 95% CI of 0.98 to 2.95).<sup>10</sup> Another large cohort study by Mamdani et al found hospitalizations for congestive heart failure were more frequent in rofecoxib users relative to controls not exposed to NSAIDs (adjusted rate ratio, 1.8; 95% CI, 1.5 to 2.2).<sup>32</sup> In this study, celecoxib users had a risk of congestive heart failure comparable to that of the NSAID-naïve controls (adjusted rate ratio, 1.0; 95% CI, 0.8 to 1.3). There was also a significantly higher risk associated with rofecoxib versus celecoxib (adjusted rate ratio, 1.8; 95% CI, 1.0 to 1.9). Finally, a case-control study of Medicare beneficiaries by Solomon et al compared the cardiovascular safety of COX-2-specific inhibitors to untreated controls or those receiving nonspecific NSAIDs. In 1 analysis, rofecoxib use was associated with a significantly increased risk of new onset hypertension relative to NSAIDs (OR, 1.4), celecoxib (OR, 1.6), or not taking any NSAID (OR, 1.6).<sup>33</sup> In a second analysis of the same data set, rofecoxib was also associated with an increased risk of acute myocardial infarction compared with celecoxib (OR, 1.24) and with not taking NSAIDs.<sup>34</sup> Case-control studies cannot be used to prove causality, but these results and the others presented herein do suggest that rofecoxib is associated with blood pressure destabilization, which may result in increased cardiovascular complications.<sup>35</sup>

## Perspectives

Hypertension and osteoarthritis are common conditions among middle-aged and elderly Americans. The prescription

of COX-2-specific inhibitors is likely to increase given the concerns regarding NSAID-associated gastrointestinal toxicity. Increases in systolic blood pressure have been observed among hypertensive patients receiving NSAIDs and COX-2-specific inhibitors, and clinically important hypertension may also occur. These changes may represent clinically important events among specific patients. They should not be ignored because they could result in a substantial increase in cardiovascular events and associated premature mortality. The estimated health care costs associated with treating these cardiovascular events appear to be substantial. Individuals with hypertension who are also treated with an NSAID are at increased risk of blood pressure destabilization. This may lead to an increased risk of cardiovascular events.

## References

- Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *Am J Manag Care*. 2002;8:S383-S391.
- Fitzgerald GA, Patrono C. The Coxibx, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2001;345:433-442.
- Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowitz JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS Study: a randomized controlled trial. *J Am Med Assoc*. 2000;284:1247-1255.
- Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MS, Kvien TK, Schnitzer TJ; 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.
- Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *J Am Med Assoc*. 2001;286:954-959.
- Dalen JE. Selective COX-2 inhibitors, NSAIDs, aspirin, and myocardial infarction. *Arch Intern Med*. 2002;162:1091-1092.
- Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Intern Med*. 2002;162:1099-1104.
- Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med*. 2002;162:1105-1110.
- Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Arch Intern Med*. 2002;162:1111-1115.
- Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast prostaglandin (PG), Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet*. 2002;360:1071-1073.
- 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.
- Johnson AG, Nguyen TV, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med*. 1994;121:289-300.
- Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM; SUCCESS VI Study Group. Cyclooxygenase-2-specific inhibitors and cardiorenal function: A randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther*. 2001;8:85-95.
- Whelton A, White WB, Bello AE, Puma JA, Fort JG; SUCCESS VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients >65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol*. 2002;90:959-963.
- Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease. A comparison of primary vs secondary prevention. *Arch Intern Med*. 1998;158:655-662.
- Central Patient Registry and Coordinating Centre for the Lipid Research Clinics. *Reference Manual for the Lipid Research Clinics Prevalence Study*. Volumes 1 and 2. Chapel Hill, NC: Department of Biostatistics, University of North Carolina; 1974.
- National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988-1994, Reference Manuals and Reports (CD-ROM). NHANES III. 1996. Hyattsville, Md: Centers for Disease Control and Prevention.
- Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med*. 1999;159:593-600.
- Department of Health and Human Services. Medicare Provider Analysis and Review Database. Washington, DC: US Department of Health and Human Services, Health Care Financing Administration; 1998.
- Agency for Health Care Policy and Research. Healthcare Costs and Utilization Project, HCUP-3. Rockville, Md: US Department of Health and Human Services; 1998.
- American Medical Association. *Medicare RBRVS: The Physicians' Guide 1999*. Chicago, Ill: American Medical Association; 1999.
- Medical Economics Company. *Drug Topics Red Book*. Montvale, NJ: Medical Economics Company; 1998.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *J Am Med Assoc*. 1991;265:3255-3264.
- Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-153.
- Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Peto R, MacMahon S. Blood pressure, stroke, and coronary heart disease. Part II. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827-838.
- Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;150:341-353.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to Doxazosin vs Chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc*. 2000;283:1967-1975.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc*. 2002;288:335:2981-2997.
- Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med*. 1995;155:701-709.
- Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995;25:305-313.
- Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. *N Engl J Med*. 2001;345:479-486.
- Mamdani M, Juurlink D, Lee D, Rochon P, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet*. 2004;363:1751-1756.
- Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension*. 2004;44:140-145.
- Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, Avorn J. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation*. 2004;109:2068-2073.
- White WB. Hypertension associated with therapies to treat arthritis and pain. *Hypertension*. 2004;44:123-124.