

# Meta-analysis of Cyclooxygenase-2 Inhibitors and Their Effects on Blood Pressure

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**Background:** Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and are associated with blood pressure (BP) elevation. The development of selective cyclooxygenase-2 inhibitors (coxibs) raises the issue of the magnitude of BP response compared with nonselective NSAIDs. We therefore performed a meta-analysis comparing the effects of coxibs with placebo, nonselective NSAIDs, and each other on BP elevation and hypertension.

**Methods:** Nineteen randomized controlled trials involving coxibs were published before May 2004, with a total of 45 451 participants in which BP data were available. The Cohen method statistically combined weighted mean difference (WMD). The Der Simonian and Laird method pooled results concerning the relative risk (RR) of developing hypertension and the RR of clinically important BP elevations.

**Results:** Among the trials analyzed, coxibs caused a WMD point estimate increase in systolic and diastolic BP compared with placebo (3.85/1.06 mm Hg) and nonselective NSAIDs (2.83/1.34 mm Hg).

Cyclooxygenase-2 inhibitors were associated with a nonsignificantly higher RR of causing hypertension compared with placebo (RR, 1.61; 95% confidence interval [CI], 0.91-2.84;  $P=.10$ ) and nonselective NSAIDs (RR, 1.25; 95% CI, 0.87-1.78;  $P=.23$ ). Rofecoxib induced a WMD point estimate increase in systolic BP (2.83 mm Hg) and a nonsignificantly higher risk of developing clinically important systolic BP elevation (RR, 1.50; 95% CI, 1.00-2.26;  $P=.05$ ) compared with celecoxib.

**Conclusions:** Cyclooxygenase-2 inhibitors were associated with a point-estimate BP elevation compared with placebo and nonselective NSAIDs. There was a nonsignificantly higher incidence of developing hypertension compared with nonselective NSAIDs, as was observed with rofecoxib compared with celecoxib. These BP elevations may be clinically significant in relation to increased cardiovascular risk.

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**N**ONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) are among the most widely prescribed pharmacological agents.<sup>1</sup>

However, major limitations to their use have been associated with gastrointestinal toxic effects. This has resulted in a significant preference to prescribe cyclooxygenase-2 inhibitors (coxibs) over conventional NSAIDs because of their apparent lower toxicity profile,<sup>2,3</sup> despite most patients not meeting specified criteria for treatment.<sup>4,5</sup>

Additional toxic effects extending beyond the gastrointestinal tract have been identified. For example, rofecoxib has been associated with an increased risk of cardiovascular events.<sup>2</sup> Furthermore, coxibs may be associated with systemic hypertension,<sup>6-10</sup> as are nonselective NSAIDs.<sup>11,12</sup> However, it is unknown how the coxibs

compare with nonselective NSAIDs with respect to blood pressure (BP) effects and hypertension risk.

Available data on the potential association of coxibs with hypertension are conflicting because they are drawn from heterogeneous studies not specifically designed to address this issue.<sup>10,13</sup> Safety data from trials involving coxibs have alluded to an increased risk of BP elevation or development of hypertension.<sup>2,6,10,14-18</sup> However, the study population involved in previous trials was widely heterogeneous, the comorbidity of hypertension among participants remained elusive in trials involving arthritis patients, and the studies themselves varied in trial design. As such, it remains uncertain what magnitude of effect coxibs actually have on BP. To our knowledge, no long-term prospective study has attempted to specifically address this question to date.

Elevated systolic BP is closely associated with increased cardiovascular events including heart failure, myocardial infarction, and death.<sup>19,20</sup> The BP effects of coxibs are a question of major clinical and public health significance owing to widespread and increasing use of these agents. In the United States, at least 20 million people are affected by osteoarthritis,<sup>21</sup> many with comorbid hypertension.<sup>22,23</sup>

To determine if coxibs are associated with higher hypertension risk compared with nonselective NSAIDs, we performed a meta-analysis of available published data as of May 2004. We compared the effects of coxibs and nonselective NSAIDs on BP elevation and the risk of hypertension.

## METHODS

### OUTCOME MEASURES AND APPLIED DEFINITIONS

The outcome measures analyzed were (1) weighted mean difference (WMD) for systolic and diastolic BP, (2) relative risk (RR) of patients developing hypertension (for trials comparing coxibs and placebo and those comparing coxibs and nonselective NSAIDs), and (3) RR of patients developing a clinically important elevation in systolic or diastolic BP (for trials comparing rofecoxib and celecoxib).

For trials comparing coxibs with placebo or nonselective NSAIDs, hypertension was not directly defined and only assessed as part of the safety data obtained during trial observations.<sup>2,3,6,14,15,17,18,24-31</sup>

For the 3 trials comparing rofecoxib and celecoxib, a clinically important elevation in systolic BP was defined as an increase of 20 mm Hg with an absolute value higher than 140 mm Hg at any time during the trial, while a clinically important elevation in diastolic BP was defined as an increase of 15 mm Hg with an absolute value higher than 90 mm Hg at any time during the trial.<sup>8,9,32</sup>

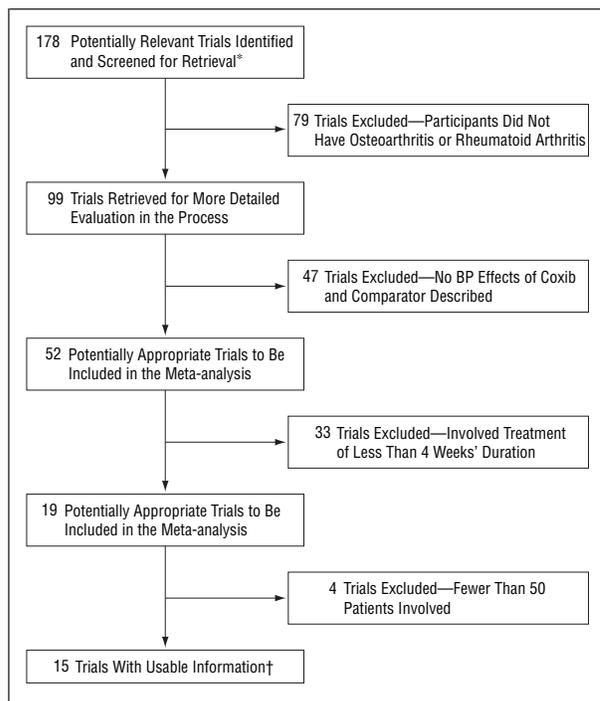
### CRITERIA FOR INCLUSION AND EXCLUSION OF STUDIES FOR META-ANALYSIS

Prospective randomized controlled trials of parallel design, published in English, were considered for inclusion in this meta-analysis. Studies were included if the BP effects of coxibs and comparator groups were described (available data were classified into appropriate treatment groups where necessary).

Studies with fewer than 50 patients or involving treatment of less than 4 weeks' duration were excluded. Trial participants with osteoarthritis and/or rheumatoid arthritis, with no restriction to age or sex, were considered for analysis. Studies with healthy volunteers were excluded. A flowchart detailing the reasons for exclusion of studies from consideration in this meta-analysis is provided, in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement<sup>33</sup> (**Figure 1**).

### SEARCH STRATEGY FOR STUDIES MEETING INCLUSION CRITERIA

We searched MEDLINE and the Cochrane Database of Systematic Reviews from date of inception through May 2004. Each search strategy included keywords related to trial design (meta-analysis, double blind, random allocation, randomized, clinical trial, placebo controlled) which were cross-linked with names of individual coxibs (celecoxib, rofecoxib, meloxicam, etori-



**Figure 1.** Flow diagram of exclusions for trials under meta-analytic consideration. Coxib indicates cyclooxygenase-2 inhibitor; asterisk, search for randomized controlled trials (RCTs) were conducted via MEDLINE and Cochrane Database of Systematic Reviews; and dagger, 4 RCTs<sup>16-18,32</sup> were also identified through searches of conference abstracts of major rheumatology, cardiology, and gastroenterology in North America and Europe.

coxib, and valdecoxib) and search terms of interest including NSAIDs, hypertension, blood pressure, and safety. Abstracts of major rheumatology, cardiology, and gastroenterology conferences from Europe and North America were reviewed, and bibliographies of all retrieved articles were consulted for additional publications. The Food and Drug Administration (FDA) Web site of currently licensed coxibs was reviewed for data concerning BP effects of coxibs.<sup>34,35</sup> Data extraction was undertaken independently by one investigator (T.-J.A.). Formal quantitative data synthesis was undertaken in a blinded manner by another investigator (S.J.H.), in accordance with the QUOROM statement.<sup>33</sup>

### TRIALS MEETING INCLUSION CRITERIA FOR ANALYSIS

Nineteen articles described random allocation of 1 or more coxibs and reported BP measurements.\* Ten studies were randomized but not placebo-controlled, in which 2 or more NSAIDs were compared.†

Most studies did not have BP measurements as the primary outcome, since these were mainly gastrointestinal safety or arthritis efficacy studies. Twelve articles provided data concerning quantitative change in systolic BP,‡ while 8 articles provided similar data regarding diastolic BP.<sup>2,10,14,17,24,25,31,32</sup> Only 1 article provided uncertainty data (in the form of SE of the mean) for BP measurements.<sup>10</sup> Sixteen articles provided actual numbers of patients who developed hypertension or experienced worsening of hypertension during the study.<sup>2,3,6,8-10,14,18,25-32</sup>

\*References 2, 3, 6, 8-10, 14, 15, 17, 18, 24-32.

†References 2, 3, 8, 9, 17, 18, 24, 25, 28, 32.

‡References 2, 8-10, 14, 15, 17, 24, 25, 28, 31, 32.

**Table. Characteristics of 19 Trials Meeting Inclusion Criteria for the Present Analysis**

Source	No. of Subjects (N = 45 451)	Mean Age, y	Sex, % Female	Patient Type	Design	Drug	Comparator	Study Duration, wk
Ehrich et al <sup>15</sup>	219	64	71	OA	R, C, B, D, MC, Par	Rofecoxib	Placebo	6
Hawkey et al <sup>6</sup>	660	51.7	82	RA	R, MC, DB, PC, Par	Rofecoxib	Placebo, naproxen	12
Schnitzer et al <sup>20</sup>	658	55	77	RA	R, PC	Rofecoxib, celecoxib	Placebo	8
Geba <sup>32</sup>	1082	62	F>M	OA	R, C	Rofecoxib, celecoxib	Placebo	6
White et al <sup>10</sup>	178	53	44	HT	R, DB, PC, Par	Celecoxib	Placebo	4
Simon et al <sup>31</sup>	1149	54	67	RA	R, MC, PC, DB	Celecoxib	Placebo	12
Collantes et al <sup>14</sup>	871	52	82	RA	R, C, MC, DB	Etoricoxib	Placebo, naproxen	12
Bombardier et al (VIGOR) <sup>2</sup>	8076	58	80	RA	R, C, MC, B, Par	Rofecoxib	Naproxen	36
Cannon et al <sup>24</sup>	784	64	68	OA	R, C, DB, Par	Rofecoxib	Diclofenac	52
Lisse et al (ADVANTAGE) <sup>28</sup>	5557	63	71	OA	R, C, B, MC	Rofecoxib	Naproxen	12
Sowers et al <sup>17</sup>	268	NA	NA	OA, DM	R, C, BD	Rofecoxib, celecoxib	Naproxen	6
Silverstein et al (CLASS) <sup>3</sup>	8059	60	68	OA, RA	R, C, DB, MC	Celecoxib	Ibuprofen, diclofenac	24
Emery et al <sup>25</sup>	655	55	73	RA	R, C, DB, DD, Par	Celecoxib	Diclofenac	24
Whelton (SUCCESS I) <sup>18</sup>	13274	62	67	OA	R, C, DB, MC	Celecoxib	Diclofenac, naproxen	NA
Whelton et al SUCCESS VI <sup>8</sup>	810	74	66	OA, HT	R, C, BD, Par, MC	Rofecoxib	Celecoxib	6
Whelton et al (SUCCESS VII) <sup>9</sup>	1092	73	62	OA, HT	R, C, BD	Rofecoxib	Celecoxib	6
Leung et al <sup>27</sup>	501	63	78	OA	R, DB, PC	Etoricoxib	Naproxen	12
Matsumoto et al <sup>29</sup>	816	56	77	RA	R, DB, PC	Etoricoxib	Placebo, naproxen	12
Hunt et al <sup>26</sup>	742	54	82	OA, RA	R, DB, PC	Etoricoxib	Placebo, naproxen	12

Abbreviations: B, blind; C, controlled; DB, double blind; DD, double dummy; DM, diabetes mellitus; MC, multicenter; NA, not available; OA, osteoarthritis; Par, parallel; PC, placebo controlled; R, randomized; RA, rheumatoid arthritis.

All trials were categorized into 3 groups: (1) trials comparing coxibs with placebo (10 trials),<sup>6,10,14,15,26,27,29-32</sup> (2) trials comparing coxibs with conventional NSAIDs (13 trials),<sup>2,3,6,14,17,18,24-29,31</sup> and (3) trials comparing coxibs with another coxib (3 trials).<sup>8,9,32</sup> Five studies involved arthritic patients with comorbid diabetes or hypertension.<sup>8-10,17,28</sup> Because there were no apparent systematic differences between trials, we considered it clinically appropriate to pool their results.

### STATISTICAL ANALYSIS

Available data were pooled using meta-analytical methods available in the STATA software program (version 7.0; Stata Corp, College Station, Tex). Weighted mean difference of both systolic and diastolic BP change was presented as a point estimate with no confidence interval of uncertainty (because uncertainty was not mentioned in most of the trials analyzed) using the Cohen method. Risk ratio estimates for the development of hypertension (the development of a clinically important elevation in either systolic or diastolic BP in the case of the rofecoxib vs celecoxib comparison) were presented as a point estimate, with 95% confidence intervals, using the Der Simonian and Laird (random effects) method.

STATA assigns relative weights to each individual study according to the contribution of each study to each meta-analysis performed.<sup>36,37</sup> In the case of the Cohen method for continuous data, this is based on a function concerning the treatment group size. For the Der Simonian and Laird method concerning dichotomous data, this is based on a function concerning the treatment group size and the number of events observed.

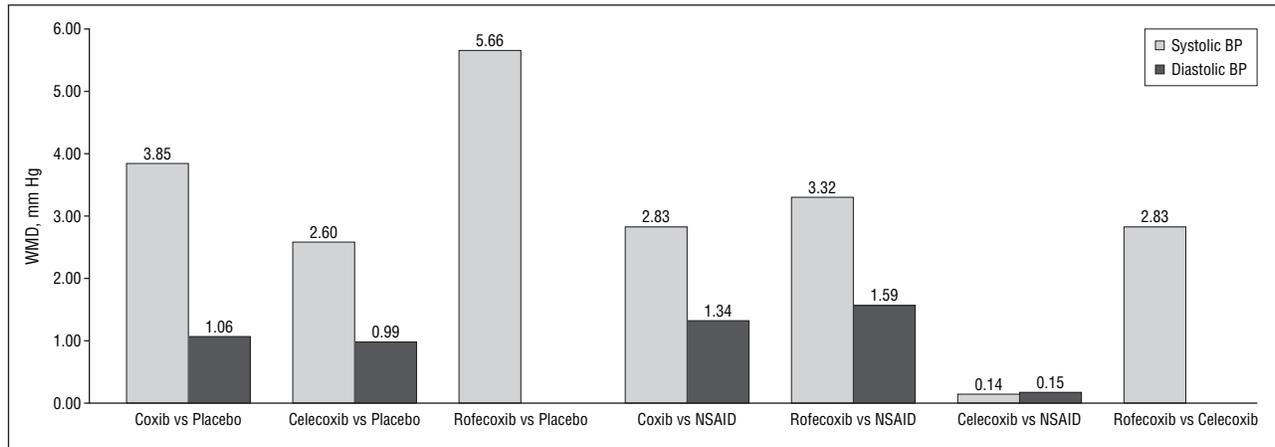
Statistical significance was set at the  $\alpha = .05$  level on the basis of 2-way z tests implicitly related to the Der Simonian and Laird method only. Statistical significance could not be calculated for WMD calculated via the Cohen method because these results are point estimates only.

## RESULTS

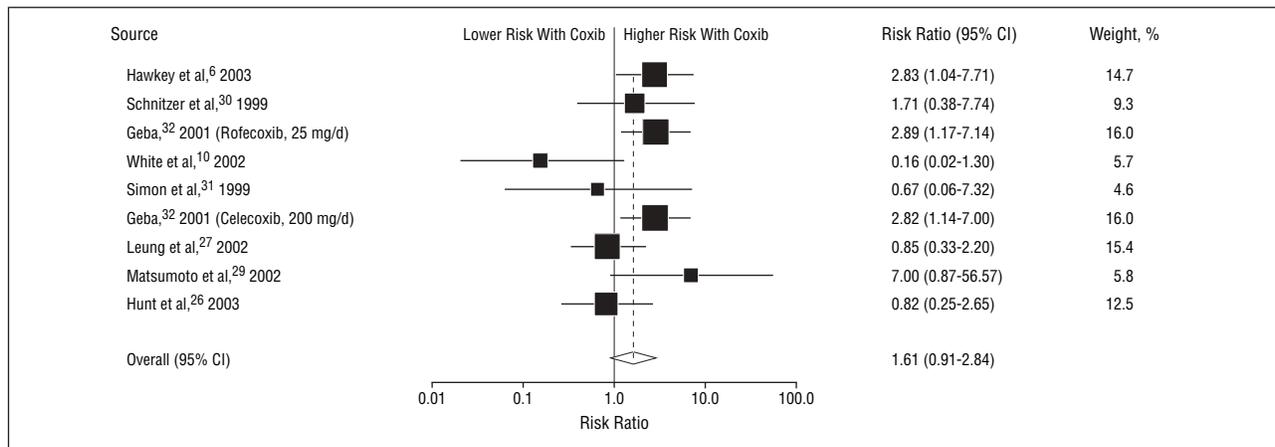
The meta-analysis included 45 451 patients from 19 trials (**Table**). In the trials providing sex stratification, there were overall more women studied, with a ratio of 2.5:1. Most patients had arthritis, of which 29 824 had osteoarthritis and 15 627 had rheumatoid arthritis. The number of patients in each category was (1) coxib vs placebo (n=5786), (2) coxib vs NSAID (n=40 888), and (3) rofecoxib vs celecoxib (n=2833). The coxibs used in the trials were celecoxib, rofecoxib, and etoricoxib. Placebo was a comparator in 10 trials,<sup>6,10,14,15,26,27,29-32</sup> and the most commonly used nonselective NSAID comparator was naproxen, which was used in 9 trials.<sup>2,6,14,17,18,26-29</sup>

The WMD increases for systolic BP comparing coxibs with placebo, coxibs with a nonselective NSAID, and rofecoxib with celecoxib were 3.85 mm Hg, 2.83 mm Hg, and 2.83 mm Hg, respectively (**Figure 2**). The WMD increases for systolic BP comparing rofecoxib with placebo, rofecoxib with a nonselective NSAID, celecoxib with placebo, and celecoxib with a nonselective NSAID were 5.66 mm Hg, 3.32 mm Hg, 2.60 mm Hg, and 0.14 mm Hg, respectively (Figure 2).

The WMD increases for diastolic BP comparing coxibs with placebo and coxibs with a nonselective NSAID were 1.06 mm Hg and 1.34 mm Hg, respectively (Figure 2). The WMD increases for diastolic BP comparing rofecoxib with a nonselective NSAID, celecoxib with a nonselective NSAID, and celecoxib with placebo were 1.59 mm Hg, 0.15 mm Hg, and 0.99 mm Hg, respectively (Figure 2). The WMD for diastolic BP comparing



**Figure 2.** Weighted mean difference (WMD) for systolic and diastolic blood pressure (BP). Coxib indicates cyclooxygenase-2 inhibitor; NSAID, nonsteroidal anti-inflammatory drug.



**Figure 3.** Der Simonian and Laird relative risks (random effects) plot of developing hypertension for cyclooxygenase-2 inhibitors (coxibs) vs placebo. CI indicates confidence interval.

rofecoxib vs celecoxib was not calculated because differences between the 2 agents have not been reported.<sup>8,9</sup>

The RR of developing hypertension for coxibs vs placebo (**Figure 3**) and coxibs vs nonselective NSAIDs (**Figure 4**) were 1.61 (95% confidence interval [CI], 0.91-2.84;  $P = .10$ ) and 1.25 (95% CI, 0.87-1.78;  $P = .23$ ), respectively. A breakdown of contribution for each individual coxib with respect to both of these RR calculations has also been provided (**Figure 5** and **Figure 6**). In the trials comparing rofecoxib vs celecoxib, the RR of developing a clinically important elevation in systolic BP was 1.50 (95% CI, 1.00-2.26;  $P = .05$ ), and the RR of developing a clinically important elevation in diastolic BP was 1.55 (95% CI, 0.91-2.63,  $P = .11$ ).

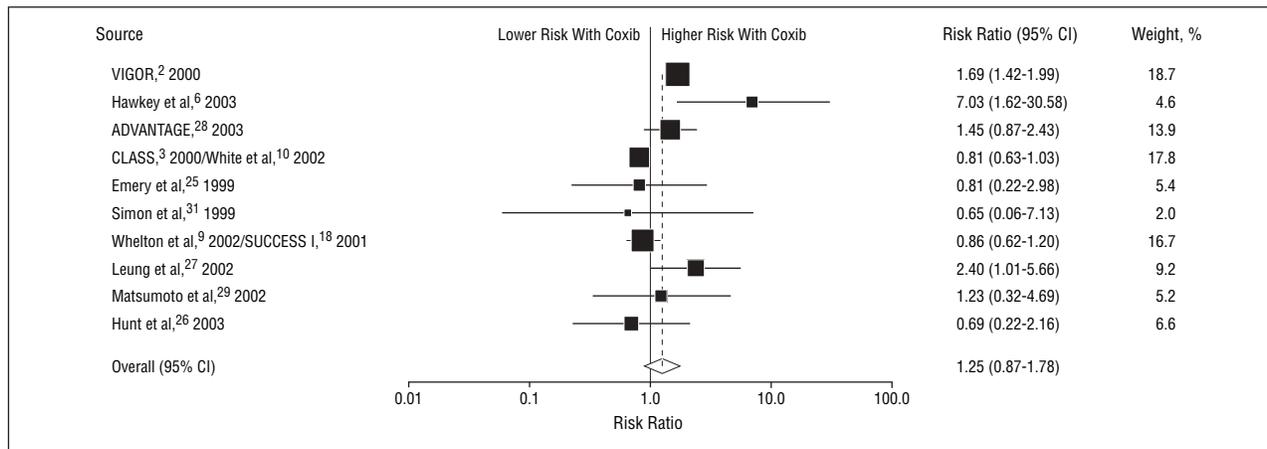
#### COMMENT

The development of coxibs, with their putative improved gastrointestinal safety profile, has led them to gain significant popularity as an alternative to nonselective NSAIDs for various musculoskeletal ailments.<sup>4,5,38</sup> Our results demonstrate that coxibs cause both systolic and diastolic BP elevation compared with placebo and nonselective NSAIDs. Whether this elevation is clinically significant remains uncertain.

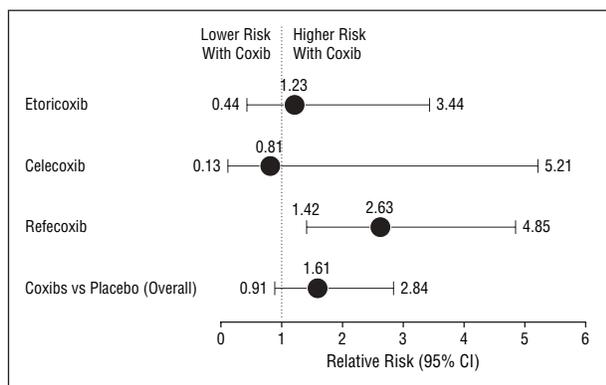
We note a disproportionate rise in systolic BP compared with diastolic BP, on average, with coxib use. This potential widened pulse pressure could have significant cardiovascular risk implications, as demonstrated in the Framingham study,<sup>39</sup> which observed a very steep relationship between systolic BP and cardiovascular risk. Interestingly, for each defined level of systolic BP, the lower the diastolic BP, the greater the cardiovascular risk.<sup>39,40</sup> The increase in systolic BP with a lesser change in diastolic BP observed, on average, among patients within these coxib studies over a relative short time may therefore be clinically significant in terms of potential cardiovascular risk.

Our analysis demonstrated a nonsignificantly increased risk of developing hypertension with coxib use compared with both placebo and nonselective NSAIDs. This risk was more pronounced when coxibs were compared with placebo (a 61% increase in RR) compared with nonselective NSAIDs (a 25% increase in RR). This is consistent with both coxibs and nonselective NSAIDs causing prostaglandin inhibition and possessing antinatriuretic and vasoconstrictor properties.<sup>12,41</sup>

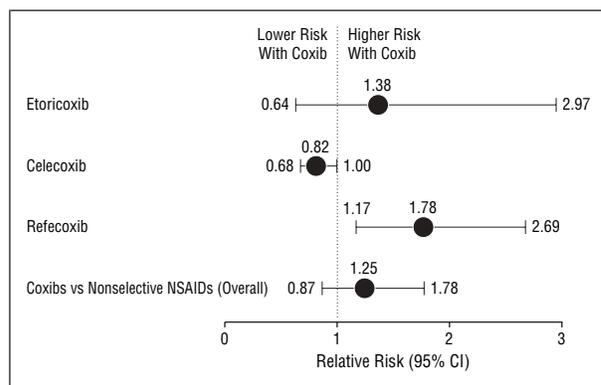
The question that arises is whether these demonstrated changes are of clinical significance. Cyclooxygenase-2 inhibitors are increasingly used<sup>4,5,38</sup> for muscu-



**Figure 4.** Der Simonian and Laird relative risks (random effects) plot of developing hypertension for cyclooxygenase-2 inhibitors (coxibs) vs nonselective nonsteroidal anti-inflammatory drugs.



**Figure 5.** Breakdown of contribution for each individual cyclooxygenase-2 inhibitor (coxib) with respect to the Der Simonian and Laird relative risks (random effects) plot of developing hypertension for coxibs vs placebo. CI indicates confidence interval.



**Figure 6.** Breakdown of contribution for each individual cyclooxygenase-2 inhibitor (coxib) with respect to the Der Simonian and Laird relative risks (random effects) plot of developing hypertension for coxibs vs nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). CI indicates confidence interval.

loskeletal ailments, most commonly arthritis.<sup>42</sup> The subgroup of patients most commonly afflicted are the elderly, often with cardiovascular comorbidities.<sup>23</sup> These agents can potentially cause or exacerbate hypertension in this patient group. Although the incremental change in BP is small, the potential widening of pulse pressure<sup>39</sup> and widespread use of these agents may have significant public health implications.

The other major observation of this investigation was that of a consistent increase in systolic and diastolic BP with rofecoxib in head-to-head trials vs celecoxib.<sup>8,9</sup> There also appears to be a differential effect when reviewing the individual contributions of each coxib with respect to the development of hypertension (Figure 5 and Figure 6). These differential effects on BP by seemingly similar agents may relate to differences in pharmacokinetic and pharmacodynamic properties. Celecoxib has a shorter half-life than rofecoxib, with differential effects on BP still evident during 24-hour ambulatory BP monitoring.<sup>10,35,43</sup> Rofecoxib is metabolized by cytosol reductase, which may (particularly at high doses) competitively inhibit the metabolism of aldosterone. This may further exacerbate fluid and sodium retention as well as vascular remodeling.<sup>44</sup> Alternatively, celecoxib may also inhibit carbonic anhydrase, leading to a diuretic action that would offset some

of the BP-elevating effect of cyclooxygenase-2 inhibition within the kidney.<sup>45</sup>

Analyses of this nature are subject to a variety of limitations. First, a number of studies have used a parallel study design, comparing 2 different NSAIDs (or doses) with a comparator. When combining the results, it was necessary to split the data into several classifications. For example, the study by Sower et al<sup>17</sup> investigated 3 patient groups treated with different NSAIDs (rofecoxib, celecoxib, and naproxen). To conform to meta-analytical methods, the data were split into the following 2 comparisons: rofecoxib (25 mg/d) vs naproxen (1000 mg/d) and celecoxib (200 mg/d) vs naproxen (1000 mg/d). This has resulted in “double counting” of comparator group patients (in this example, naproxen, 1000 mg/d). Considering that the relative weights attributed to both comparisons within the context of the analysis were low (eg, a total of 4.6% of the total weight for the above example), this limitation is unlikely to impact greatly on interpretation of the results.

Inconsistencies in reporting styles among the studies analyzed necessitated some assumptions to be imputed regarding the data. For example, the study by Collantes et al<sup>14</sup> reported a diastolic BP increase among their patients

of <1.1 mm Hg, while the study by Emery et al<sup>25</sup> reported a BP increase of 1-2 mm Hg. For the purposes of the present analysis, we used 1.1 mm Hg (worst case scenario) and 1.5 mm Hg (midpoint of the range), respectively, as the input data points for these particular studies.

The fact that BP was not a predetermined end point in the trials is another limitation of this analysis. Indeed, most outcomes concerning BP were ancillary considerations as part of the safety assessment for each compound and not part of the primary outcome measures. Most trials did not clearly define the term *hypertension*.<sup>\*</sup> As such, it was difficult to determine if the definitions used in this meta-analysis were universally applied throughout the trials analyzed, which has potential impact on the accuracy of the data available.

Apart from the trials that looked at BP effects as an outcome measure, there was no clear description of techniques (or calibration of instruments) used to measure BP, particularly among the multicenter trials. Two trials used 24-hour ambulatory BP,<sup>10,34</sup> whereas others presumably used clinic or office readings. There are limitations in regard to interpreting the analysis of such different methods of measuring BP.<sup>46</sup>

Similarly, some trials pooled for the analysis mention hypertension as an adverse event. Elevated BP could occur anywhere within each study and might not be related to NSAID effect. For example, a patient experiencing excessive pain during a study visit may have elevated BP and subsequently have been recorded as hypertensive. Given the generally similar analgesic efficacy of the active therapies, this would not be expected to make a significant difference to head-to-head comparisons.

Heterogeneity of the recruited study populations is another area of potential bias among the trials analyzed with respect to preexisting hypertension and use of antihypertensive medication. For instance, the proportion of patients in each study with hypertension at baseline was only noted in 5 of the studies analyzed.<sup>8-10,17,28</sup> It is therefore difficult to determine whether these BP effects occurred in trial participants with preexisting hypertension or in those without (or in both categories). There was also a lack of information about whether the proportion of patients using different antihypertensive medications was evenly distributed. Normotensive patients usually have no significant BP increase when using anti-inflammatory agents,<sup>1</sup> which may lead to an underestimate in our findings. Irrespective of the fact that these trials were randomized, the potential differences between hypertensive and normotensive patients increase the difficulty of establishing BP differences between treatment groups.

A further potential confounder to the individual trial data relates to the varying study designs used among trials, especially in regard to "wash-out" periods of previous NSAID therapy. Only 4 studies reported a "wash-out" period (mandatory in 3 studies<sup>9,14,30</sup> and not specifically required in another<sup>25</sup>). It is possible that baseline BP and early subsequent measurements could be influenced by prior NSAID use, thereby affecting the relative BP changes during the study.

<sup>\*</sup>References 2, 3, 6, 8-10, 14, 15, 17, 18, 24, 25, 28, 30-32.

The possibility of sponsorship bias exists among the data available. Among the Pfizer/Pharmacia-sponsored trials,<sup>3,8-10,18</sup> celecoxib was less likely to cause hypertension than rofecoxib, whereas in Merck Sharp Dohme-sponsored trials,<sup>2,6,15,24,28,30,32</sup> the BP effects of the 2 agents appeared to be similar.

Finally, a meta-analysis is no substitute for a double-blind, randomized, placebo-controlled clinical trial that is adequately powered. However, it is difficult to design a trial that considers the copious number of different combinations and permutations of commercially available NSAIDs. Because such data are not yet available, we are reliant on retrospective analysis to guide us.

Despite the aforementioned caveats, this meta-analysis conforms to recommendations regarding size and careful searching to reduce publication bias.<sup>36,47</sup> This enables these results to be, what we believe, the best possible summation of available information concerning the research question at hand.

## CONCLUSIONS

The results of this meta-analysis demonstrate that, among the trials analyzed, there appears to be a somewhat greater BP elevation with coxibs compared with placebo and non-selective NSAIDs. Rofecoxib appears to confer a greater risk of developing hypertension and clinically important elevations in both systolic and diastolic BP compared with celecoxib. The effects observed may have most clinical significance in the elderly, in whom the prevalence of arthritis and hypertension is high.

Cyclooxygenase-2 inhibitors are a welcome addition to the therapeutic options in the treatment of arthritis, which remains a chronic, debilitating, and painful condition. However, their potential (and differential) effect on BP elevation requires caution in their use and warrants further investigation. Clinicians need to weigh the risks of improved gastrointestinal safety vs potential hazards of developing elevated BP when considering the use of these agents, especially in the elderly population.

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