Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib

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Background—In comparing aspirin, nonselective nonsteroidal antiinflammatory agents (NSAIDs), and cyclooxygenase (COX)-2 inhibitors, variation in platelet inhibitory effects exists that may be associated with differential risks of cardiovascular (CV) thrombotic events. Among the randomized, controlled trials with the COX-2 inhibitor rofecoxib, one study demonstrated a significant difference between rofecoxib and its NSAID comparator (naproxen) in the risk of CV thrombotic events. A combined analysis of individual patient data was undertaken to determine whether there was an excess of CV thrombotic events in patients treated with rofecoxib compared with those treated with placebo or nonselective NSAIDs.

Methods and Results—CV thrombotic events were assessed across 23 phase IIb to V rofecoxib studies. Comparisons were made between patients taking rofecoxib and those taking either placebo, naproxen (an NSAID with near-complete inhibition of platelet function throughout its dosing interval), or another nonselective NSAIDs used in the development program (diclofenac, ibuprofen, and nabumetone). The major outcome measure was the combined end point used by the Antiplatelet Trialists’ Collaboration, which includes CV, hemorrhagic, and unknown deaths; nonfatal myocardial infarctions; and nonfatal strokes. More than 28,000 patients, representing >14,000 patient-years at risk, were analyzed. The relative risk for an end point was 0.84 (95% CI: 0.51, 1.38) when comparing rofecoxib with placebo; 0.79 (95% CI: 0.40, 1.55) when comparing rofecoxib with non-naproxen NSAIDs; and 1.69 (95% CI: 1.07, 2.69) when comparing rofecoxib with naproxen.

Conclusions—This analysis provides no evidence for an excess of CV events for rofecoxib relative to either placebo or the non-naproxen NSAIDs that were studied. Differences observed between rofecoxib and naproxen are likely the result of the antiplatelet effects of the latter agent. (Circulation. 2001;104:2280-2288.)

Key Words: rofecoxib ■ anti-inflammatory agents, nonsteroidal ■ cardiovascular diseases ■ thrombosis

Nonselective, nonsteroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, diclofenac, nabumetone, naproxen, indomethacin, and aspirin inhibit both cyclooxygenase isomers (COX-1 and COX-2) over their clinical dose range.1 In contrast, rofecoxib is highly selective for only the COX-2 isomer over its clinical dose range.2,3 In the gastrointestinal system, nonselective NSAIDs have been associated with gastroduodenal mucosal injury, whereas selective COX-2 inhibitors have demonstrated improved gastrointestinal safety and tolerability.4–10 COX-1 inhibition has been associated with decreased synthesis of platelet-derived thromboxane, a vasoconstrictor and potent inducer of platelet aggregation.11

In comparing aspirin, nonselective NSAIDs, and COX-2 inhibitors, variation in platelet inhibitory effects may result in different influences on the rates of cardiovascular (CV) thrombotic events.11 Sustained inhibition of COX-1–mediated thromboxane synthesis underlies the efficacy of aspirin in significantly reducing the incidence of CV death, myocardial infarction (MI), and stroke in high-risk patients.11–14 Aspirin produces irreversible inhibition of platelet COX-1: this inhibition is near-complete and is sustained for at least 48 hours after a single dose.14 In contrast to aspirin, nonselective NSAIDs are reversible inhibitors of COX-1: the extent and duration of inhibition closely follows their potency and systemic plasma drug concentrations, and the effect is reversible as a function of drug elimination.14 Some evidence suggests that nonselective NSAIDs that mediate near-complete inhibition of platelet function throughout their entire dosing interval may be similar to aspirin and also
reduce the risk of CV events.\textsuperscript{10,15–17} NSAIDs with less substantial platelet inhibition are unlikely to have as great an impact on the incidence of CV thrombotic events.\textsuperscript{11} Given their lack of clinically recognized effects on platelet-derived thromboxane and platelet aggregation,\textsuperscript{18} selective COX-2 inhibitors would not be expected to be cardioprotective on the basis of platelet inhibition. Some authors have speculated that selective COX-2 inhibitors might adversely affect hemostatic balance, and even favor thrombosis, by selectively inhibiting COX-2–derived endothelial prostacyclin (a vasodilator and inhibitor of platelet activation) without affecting platelet-derived thromboxane.\textsuperscript{11,19–21}

As a result of an evolving understanding of the interplay between COX-1 and COX-2 expression and the inhibition of vasoactive eicosanoids,\textsuperscript{10,20} in 1999, Merck introduced a standard operating procedure to evaluate and adjudicate CV events in all ongoing and all future rofecoxib clinical trials. In addition, a retrospective analysis of the CV events in the already completed rofecoxib osteoarthritis phase IIb/III program was conducted.\textsuperscript{22} This analysis (in 5435 patients) detected no difference between rofecoxib, comparator nonselective NSAIDs, and placebo in CV thrombotic risks.\textsuperscript{22}

A significant difference between rofecoxib and naproxen, its active NSAID comparator, in the risk of CV thrombotic events.\textsuperscript{10} In VIGOR, patients with rheumatoid arthritis were randomized to rofecoxib 50 mg daily or naproxen 500 mg twice daily; the protocol prohibited the use of aspirin or other antplatelet and anticoagulant medications. The primary objective of the study was to assess rigorously the gastrointestinal safety of the drug relative to a common, nonselective NSAID comparator; hence, the 50 mg dose of rofecoxib (twice the 25 mg maximum recommended does for long-term administration) was used. The study demonstrated that a supratherapeutic dose of rofecoxib was associated with a significantly reduced risk of clinical upper gastrointestinal events (54\% reduction). However, naproxen was associated with a significantly lower risk of thrombotic CV serious adverse experiences compared with rofecoxib.\textsuperscript{10} This difference in thrombotic events was mostly due to a difference in the incidence of MIs between treatment groups.\textsuperscript{10} However, the differences in peripheral vascular events and cerebrovascular events trended in the same direction.

Because of the possibility, raised by the results of VIGOR, that there might be an increased risk of CV adverse experiences associated with the use of rofecoxib, a pooled CV safety analysis was conducted using all relevant data as of September 2000. Patient level data were com-

\begin{table}
\begin{center}
\caption{Studies Included in Cardiovascular Events Pooled Analysis}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Indication for Therapy & Abbreviated Study Description & Total Sample Size & Planned Duration of Patient Follow-Up & Rofecoxib Doses, mg & NSAID Comparator & Placebo Group & Aspirin Allowed at Study Start \\
\hline
Rheumatoid arthritis & Phase IIb dose finding & 634 & 2 years & 25/50 & Naproxen & Yes & No \\
& Phase III: domestic US & 909 & 1 year & 12.5/25/50 & Naproxen & Yes & Yes \\
& Phase III: international & 1058 & 1 year & 25/50 & Naproxen & Yes & No \\
& Phase III: endoscopy & 660 & 13 weeks & 50 & Naproxen & Yes & No \\
& VIGOR: GI outcome trial & 8076 & 9 months* & 50 & Naproxen & No & No \\
Osteoarthritis & Phase IIb/III OA studies† & 5505 & 86 weeks & 12.5/25/50 & Diclofenac & Yes & No \\
& Bone metabolism study & 305 & 15 months & 25 & Ibuprofen & Yes & No \\
& Nabumetone study 1 & 1042 & 6 weeks & 12.5 & Nabumetone & Yes & Yes \\
& Nabumetone study 2 & 978 & 6 weeks & 12.5 & Nabumetone & Yes & Yes \\
& Naproxen study & 481 & 6 weeks & 12.5 & Naproxen & No & Yes \\
& Arthrotoe study & 483 & 6 weeks & 12.5 & Diclofenac & No & No \\
& ADVANTAGE & 5556 & 12 weeks & 25 & Naproxen & No & Yes \\
Other & Alzheimer’s prevention & 1406 & 4 years‡ & 25 & NA & Yes & No \\
& Alzheimer’s treatment & 682 & 15 months§ & 25 & NA & Yes & No \\
& Phase III chronic low back pain & 380 & 4 weeks & 25/50 & NA & Yes & Yes \\
& Phase III chronic low back pain & 310 & 4 weeks & 25/50 & NA & Yes & Yes \\
\hline
\end{tabular}
\end{center}
\footnotesize
\textsuperscript{*Duration was event-based; median duration is reported; maximum duration was 13 months.}
\textsuperscript{†}Combined data from 8 trials: 1 phase IIb dose ranging, 2 phase III US, 2 phase III international, 1 phase III endoscopy US, 1 phase III endoscopy international, and 1 limited study in patients $>$ 80 years of age.
\textsuperscript{‡}Interim look $\sim$ 28 months after first patient enrolled.
\textsuperscript{§}Interim look $\sim$ 12 months after first patient enrolled.
\end{table}
bined across rofecoxib phase IIb through V trials to assess the relative risk of CV thrombotic events among patients randomized to rofecoxib compared with those randomized to placebo, the nonselective NSAIDs studied that lacked potent or sustained inhibition of platelet function (diclofenac, ibuprofen, and nabumetone), or naproxen, an NSAID with near-complete inhibition of platelet function throughout its dosing interval.

### Methods

#### Selection of Trials

The data for this pooled analysis were derived from all rofecoxib Phase IIb through V trials conducted by Merck that lasted at least 4 weeks. All such trials included comparative data between rofecoxib and nonselective NSAIDs, rofecoxib and placebo, or both. Studies performed in healthy volunteers or in which rofecoxib was compared with celecoxib were excluded. Data from treatment periods using doses of rofecoxib <12.5 mg (subtherapeutic doses) were excluded.

### Table 2: Summary of Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Rofecoxib Relative to Placebo, n (%)</th>
<th>Rofecoxib Relative to Non-Naproxen NSAIDs, n (%)</th>
<th>Rofecoxib Relative to Naproxen, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>368 (22.7)</td>
<td>220 (22.2)</td>
<td>1455 (24.0)</td>
</tr>
<tr>
<td>Age, y (median)</td>
<td>54</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Female sex</td>
<td>1296 (79.9)</td>
<td>783 (79.2)</td>
<td>4826 (79.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>327 (20.2)</td>
<td>197 (19.9)</td>
<td>1182 (19.5)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>401 (24.7)</td>
<td>250 (25.3)</td>
<td>1733 (28.6)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>87 (5.4)</td>
<td>65 (6.6)</td>
<td>357 (5.9)</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>188 (11.6)</td>
<td>81 (8.2)</td>
<td>584 (9.6)</td>
</tr>
<tr>
<td>History of at least one risk factor for coronary disease</td>
<td>784 (48.3)</td>
<td>471 (47.6)</td>
<td>3033 (50.1)</td>
</tr>
<tr>
<td>History of a CV event*</td>
<td>58 (3.6)</td>
<td>38 (3.8)</td>
<td>245 (4.0)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>1433 (45.3)</td>
<td>534 (44.0)</td>
<td>1414 (46.7)</td>
</tr>
<tr>
<td>Age, y (median)</td>
<td>63</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female sex</td>
<td>2257 (71.3)</td>
<td>832 (68.5)</td>
<td>2158 (71.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>332 (10.5)</td>
<td>136 (11.2)</td>
<td>2151 (71.4)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1268 (40.1)</td>
<td>435 (35.8)</td>
<td>1284 (45.7)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>262 (8.3)</td>
<td>106 (8.7)</td>
<td>334 (11.0)</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>592 (18.7)</td>
<td>223 (18.4)</td>
<td>821 (27.1)</td>
</tr>
<tr>
<td>History of at least one risk factor for coronary disease</td>
<td>1812 (57.3)</td>
<td>661 (54.4)</td>
<td>1801 (59.5)</td>
</tr>
<tr>
<td>History of a CV event*</td>
<td>250 (7.9)</td>
<td>92 (7.6)</td>
<td>254 (8.4)</td>
</tr>
<tr>
<td>Alzheimer’s/Low Back Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>1093 (72.7)</td>
<td>1052 (82.3)</td>
<td>215 (7.8)</td>
</tr>
<tr>
<td>Age, y (median)</td>
<td>72</td>
<td>73</td>
<td>254 (8.4)</td>
</tr>
<tr>
<td>Female sex</td>
<td>705 (46.9)</td>
<td>542 (42.4)</td>
<td>264 (8.8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>148 (9.8)</td>
<td>124 (9.7)</td>
<td>215 (7.8)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>513 (34.1)</td>
<td>413 (32.3)</td>
<td>215 (7.8)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>142 (9.4)</td>
<td>137 (10.7)</td>
<td>254 (8.4)</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>324 (21.6)</td>
<td>288 (22.5)</td>
<td>162 (12.7)</td>
</tr>
<tr>
<td>History of at least one risk factor for coronary disease</td>
<td>824 (54.8)</td>
<td>696 (54.5)</td>
<td></td>
</tr>
<tr>
<td>History of a CV event*</td>
<td>182 (12.1)</td>
<td>162 (12.7)</td>
<td>162 (12.7)</td>
</tr>
</tbody>
</table>

*Patients with a past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention.
Antiplatelet Trialists’ Collaboration End Point

The outcome measure used was the combined end point defined by the Antiplatelet Trialists’ Collaboration (APTC).12,21 This end point consists of the combined incidence of (1) CV, hemorrhagic, and unknown death; (2) nonfatal MI; and (3) nonfatal stroke. This end point was chosen for this analysis because it is the most common and widely accepted end point used in quantifying the overall CV impact of antithrombotic compounds in clinical trials. All APTC end points were confirmed after a review of case information in a blinded fashion.

After the phase IIb/III osteoarthritis program but before VIGOR, Merck Research Laboratories implemented a CV adjudication standard operating procedure to collect CV data in a uniform manner and to systematically review, in a blinded fashion, all case reports of CV serious adverse experiences. This process was created to improve the diagnostic accuracy of investigator-reported events. Adjudicated data were used for all studies except the phase IIb/III osteoarthritis studies and the phase IIb rheumatoid arthritis dose-finding studies that were implemented before the initiation of the CV standard operating procedure. For those studies in which adjudicated data were unavailable, investigator-reported data were used.

Statistical Methods

This pooled analysis used individual patient data. All analyses were conducted according to a modified intention-to-treat approach, and adverse experiences were followed until 14 days after either study completion or patient discontinuation. There was no other data censorship. Patients were included in the treatment group to which they were randomized, and patients were included in the analysis if and only if they received at least one dose of study drug. The duration of follow-up for adverse experiences was 14 days after time of study drug discontinuation.

Patient cohorts randomized to receive rofecoxib doses of 12.5, 25, or 50 mg were combined into the rofecoxib treatment group. The patients who were randomized to receive non-naproxen comparator NSAIDs (which included ibuprofen, diclofenac, and nabumetone) were combined into the non-naproxen NSAID treatment group, whereas patients randomized to receive naproxen were analyzed separately.

The comparisons of primary interest were rofecoxib relative to placebo, rofecoxib relative to other non-naproxen nonselective NSAIDs, and rofecoxib relative to naproxen. Data from patients in a study were included in a comparison if the study included both of the treatments being compared. For example, the analysis comparing rofecoxib with placebo was restricted to studies including both rofecoxib and placebo. Some studies in osteoarthritis and rheumatoid arthritis patients consisted of 2 parts. In part I, patients were randomized to receive rofecoxib, placebo, or nonselective NSAIDs. In part II extensions, treatment assignments remained double-blinded, but placebo patients were reassigned to active treatments (either rofecoxib or a nonselective NSAID) while other patients continued their previous therapy. The rofecoxib relative to placebo pooled analysis included only data from part I. Comparisons of rofecoxib with naproxen and with other nonselective NSAIDs included data from parts I and II from patients who did not switch treatments and included only part II data from placebo patients who switched to blinded active treatment. For the latter patients, time to an APTC event or censoring was measured from the date of the switch to the part II therapy.

Cox proportional hazards models were used to evaluate the effect of rofecoxib relative to the various comparators for the APTC end point. Heterogeneity among the blocks formed by indications for therapies was examined. If no significant heterogeneity was found ( \( P > 0.05 \) ), then a Cox model using treatment as the explanatory variable and therapy indications (block) as a stratification variable provided estimates of relative risk and 95% confidence intervals (CIs) for APTC events for the comparisons.

To evaluate the difference in relative risk between comparisons to naproxen and comparisons to other nonselective NSAIDs, the

| Table 3 | Pooled Analysis of APTC End Point: Rofecoxib Relative to Placebo |
|---|---|---|---|---|
| Indication for Treatment | Rofecoxib | Placebo | Relative Risk (95% CI) |
| | No. of Patients | Patient-Years at Risk | APTC Events | No. of Patients | Patient-Years at Risk | APTC Events |
| Rheumatoid arthritis | 1622 | 3/337 (0.89) | 989 | 1/201 (0.50) | 1.78 (0.14, 9.37) |
| Osteoarthritis | 3165 | 12/655 (1.83) | 1215 | 3/232 (1.30) | 1.53 (0.43, 5.44) |
| Alzheimer’s/low back pain | 1503 | 18/1197 (1.50) | 1278 | 28/1246 (2.25) | 0.68 (0.37, 1.23) |
| Total | 6290 | 33/2189 (1.51) | 3482 | 32/1678 (1.91) | 0.84 (0.51, 1.38) |

*Rate=APTC events per 100 patient-years at risk.

| Table 4 | Pooled Analysis of APTC End Point: Rofecoxib Relative to Non-Naproxen NSAIDs |
|---|---|---|---|
| Indication for Treatment | Rofecoxib | Non-Naproxen NSAIDs | Relative Risk (95% CI) |
| | No. of Patients | Patient-Years at Risk | APTC Events | No. of Patients | Patient-Years at Risk | APTC Events |
| Rheumatoid arthritis | 0 | ... | 0 | ... | ... |
| Osteoarthritis | 4549 | 21/1934 (1.09) | 2755 | 14/984 (1.42) | 0.79 (0.40, 1.55) |
| Alzheimer’s/low back pain | 0 | ... | 0 | ... | ... |
| Total | 4549 | 21/1934 (1.09) | 2755 | 14/984 (1.42) | 0.79 (0.40, 1.55) |

*Rate=APTC events per 100 patient-years at risk.
interaction between treatment effect and naproxen/other nonselective NSAID trial effect was examined.

Relative risk estimates within blocks were obtained from a Cox model with treatment as the explanatory variable when the total number of patients with events was at least 11. When there were <11 cases, relative risk and the 95% CI were based on the ratio of event rates. Blocks instead of studies were used as strata for the estimated relative risks because many studies had few or no events.

The proportional hazards assumptions for each comparison (rofecoxib versus naproxen, rofecoxib versus non-naproxen NSAIDs, and rofecoxib versus placebo) were tested by including the factor treatment×log(time) in the individual models; non-significance (P>0.05) of this factor implies proportionality, i.e., constancy of treatment effect over time. In each of the 3 models, the proportional hazard assumption was met, implying that the relative risk was constant over time. Event rates were summarized by number of events per 100 person-years (equivalent to percent per year). The relative risk ratio was used to estimate the comparative effects between treatment groups.

### Results

#### Primary Analysis

More than 28,000 patients in 23 studies (osteoarthritis, rheumatoid arthritis, Alzheimer’s, and chronic low back pain trials) representing >14,000 patient-years at risk were included in the analysis. Table 1 summarizes the individual studies/groups of studies, and Table 2 shows the baseline characteristics of population included in the pooled analysis. Groups being compared were balanced with respect to the characteristics in Table 2.

As shown in Table 3, the relative risk for an APTC end point was 0.84 (95% CI: 0.51, 1.38) when comparing rofecoxib (n=6290 patients) relative to placebo (n=3482 patients). No significant heterogeneity was seen across indications (P=0.381). Placebo was given for a limited duration in osteoarthritis, rheumatoid arthritis, and chronic low back pain studies, so the majority of the patient years at risk were attributable to Alzheimer’s patients. The Alzheimer’s patients were older (95% were ≥65 years, and 55% were ≥75 years), and the majority were male.

As shown in Table 4, the relative risk for an APTC end point was 0.79 (95% CI: 0.40, 1.55) when comparing rofecoxib (n=4549 patients) relative to non-naproxen NSAIDs (n=2755 patients). However, non-naproxen NSAIDs were studied only in osteoarthritis patients; no trials with non-naproxen NSAID comparators were conducted in patients with rheumatoid arthritis, Alzheimer’s disease, or chronic lower back pain. Among the various osteoarthritis studies, the data all trended in the same direction. Given the low event rates and the limited patient-years of therapy, comparisons among the different individual NSAIDs were not possible.

As shown in Table 5, the relative risk for an APTC end point was 1.69 (95% CI: 1.07, 2.69) when comparing rofecoxib (n=9083 patients) relative to naproxen (n=7870). Rheumatoid arthritis patients (n=10,916 patients), especially from VIGOR (n=8076 patients), provided the vast majority of patient years for this comparison. Although the overall results are driven by VIGOR, the osteoarthritis data trended in the same direction. Test of homogeneity across indications showed no evidence of difference in relative risk (P=0.834).

The difference in treatment effects between the comparisons of rofecoxib relative to non-naproxen NSAIDs and rofecoxib relative to naproxen approached statistical significance (P=0.057).

Table 6 summarizes the APTC events by type of event. The incidence of hemorrhagic deaths and hemorrhagic strokes was quite low (5 total events). Exclusion of these events did not change the conclusions of the primary analysis. The overall rates of APTC events were markedly lower in the naproxen group compared with any other treatment group. In comparison with the overall population, those with APTC events were more likely to be ≥65 years of age, male, and have a history of at least one risk factor for coronary artery disease. Approximately one third of the patients who had an APTC event had a prior history of a CV event (defined as a past medical history of cerebrovascular accident, transient ischemic attack, MI, unstable angina, stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention).

### Additional Analyses

After the pooled analysis combined studies of varying duration and rofecoxib dosages, a series of additional analyses were undertaken.

To ensure that studies of short duration did not unduly influence the results, the pooled analysis was repeated using studies ≥6 month in duration. The results are consistent with the primary analyses (Figures 1 and 2).

We attempted to examine APTC events by dose of rofecoxib across all studies. Because only one small trial compared all 3 doses, we separately examined those studies in which patients were randomized to either 12.5 or 25 mg (analysis 1) and those studies in which patients were random-
ized to either 25 or 50 mg (analysis 2). Table 7 summarizes these 2 analyses. Consistent with the small number of events, the individual point estimates of risk associated with each dose vary widely and do so in an inconsistent way. The relative risk for 25 mg of rofecoxib varied from 0.30 to 1.16.

The pooled analysis was repeated in the subgroup of patients at high risk for CV thrombotic events. This group was defined as those with either coronary artery disease (current smoker, history of diabetes, history of hypertension, and/or history of hypercholesterolemia) or with a prior history of a CV thrombotic event. The relative risk for an APTC end point was 1.04 (95% CI: 0.51, 2.12) when comparing rofecoxib (n = 1306 patients) relative to placebo (n = 728 patients), 0.96 (95% CI: 0.40, 2.29) when comparing rofecoxib (n = 1021 patients) relative to non-naproxen NSAIDs (n = 631 patients), and 1.88 (95% CI: 0.93, 3.81) when comparing rofecoxib (n = 1700 patients) relative to naproxen (n = 1460 patients). Although limited by a small number of events, the results are consistent with the primary analysis.

**Discussion**

The primary objective of this analysis was to assess whether rofecoxib was associated with an excess of CV events. There was no evidence that rofecoxib was associated with excess CV events compared with either placebo or non-naproxen NSAIDs. Specifically, >28 000 patients in 23 studies (osteoarthritis, rheumatoid arthritis, Alzheimer’s, and chronic low back pain trials) representing >14 000 patient-years at risk were analyzed for differences in CV thrombotic event rates using the APTC combined end point. The relative risk for an APTC end point was 0.84 (95% CI: 0.51, 1.38) when comparing rofecoxib with placebo, 0.79 (95% CI: 0.40, 1.55) when comparing rofecoxib with the studied non-naproxen NSAIDs, and 1.69 (95% CI: 1.07, 2.69) when comparing rofecoxib with naproxen. The results were essentially unchanged when the analysis was limited to studies with a duration ≥6 months.

Most importantly, the results of the rofecoxib relative to placebo comparison demonstrated a comparable risk of APTC events in both groups. Because placebo was given for a limited duration in the osteoarthritis, rheumatoid arthritis, and chronic low back pain studies, the majority of patient-years came from the Alzheimer’s trials, whose populations included predominantly elderly, male patients. These data, which were obtained from studies directly comparing rofecoxib and placebo, are most reassuring that there is no evidence for any increased risk of CV thrombotic events with rofecoxib. The results of the rofecoxib relative to non-naproxen NSAID comparison also demonstrated comparable risks of APTC events in both groups. However, non-naproxen NSAIDs were only studied in osteoarthritis patients, and there were insufficient data to differentiate the effects of the individual NSAIDs studied.

The available data indicate that naproxen was different than other NSAIDs and was associated with a decreased risk of CV events relative to rofecoxib. Overall, the results of the rofecoxib relative to naproxen comparison was driven primarily by the VIGOR trial because of the trial’s size and long duration of follow-up. However, the limited osteoarthritis naproxen comparator data also trended in the same direction as the VIGOR results. Among the trials in the rofecoxib

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**TABLE 6. Summary of APTC End Points by Type of Event**

<table>
<thead>
<tr>
<th>APTC Events</th>
<th>Rofecoxib Relative to Placebo</th>
<th>Rofecoxib Relative to Non-Naproxen NSAIDs</th>
<th>Rofecoxib Relative to Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 6290)</td>
<td>(n = 4549)</td>
<td>(n = 9083)*</td>
</tr>
<tr>
<td>Patients with events</td>
<td>33 (0.52)</td>
<td>21 (0.46)</td>
<td>57 (0.63)</td>
</tr>
<tr>
<td>Total CV, hemorrhagic, and unknown deaths</td>
<td>9 (0.14)</td>
<td>1 (0.02)</td>
<td>12 (0.13)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>3 (0.05)</td>
<td>0 (0.00)</td>
<td>8 (0.09)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>2 (0.02)§</td>
</tr>
<tr>
<td>Non-central nervous system hemorrhagic deaths</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>1 (0.01)†</td>
</tr>
<tr>
<td>Sudden/unknown cause of death</td>
<td>6 (0.09)</td>
<td>3 (0.09)</td>
<td>1 (0.01)</td>
</tr>
<tr>
<td>Nonfatal cardiac events¶</td>
<td>16 (0.25)</td>
<td>13 (0.37)</td>
<td>29 (0.32)</td>
</tr>
<tr>
<td>Nonfatal cerebrovascular events¶</td>
<td>8 (0.13)</td>
<td>15 (0.43)</td>
<td>17 (0.19)†</td>
</tr>
</tbody>
</table>

Values are n (%).

*One patient in this group had 2 events: an MI and a stroke.
†One confirmed hemorrhagic stroke occurred in both the rofecoxib and naproxen groups.
‡One patient had a ruptured aortic aneurysm.
§One patient had arterial rupture, and one patient had an unspecified hemorrhage (suspected upper GI bleed).
||This category includes patients with the following diagnoses: MI and resuscitated cardiac arrest.
¶This category includes patients with the following diagnoses: carotid artery obstruction, cerebrovascular accident, ischemic cerebrovascular stroke, lacunar infarct, and hemorrhagic stroke.
#Two confirmed nonfatal hemorrhagic strokes occurred in the rofecoxib group.
development program, only VIGOR found a significant difference between rofecoxib and a comparator NSAID in the risk for the development of CV thrombotic events. In VIGOR, the rate of CV thrombotic events in the naproxen and rofecoxib groups diverged significantly (0.70 versus 1.67 patients with events per 100 patient-years, respectively). Although the magnitude of this difference was not anticipated, it was recognized that naproxen, when used as doses of 500 mg twice daily, would have antiplatelet effects similar to those reported for aspirin (that is, near-maximal inhibition of platelet aggregation sustained throughout its dosing interval) and, therefore, might confer some cardioprotective benefit. Although the data are suggestive, neither the VIGOR results nor the current analysis provide sufficient evidence to establish the potential cardioprotective benefits of naproxen. Therefore, patients at risk for CV thrombotic events who are prescribed a COX-2 inhibitor or an NSAID should receive appropriate antiplatelet therapy as clinically indicated.

Despite the lack of definitive, prospective studies designed to assess the cardioprotective effects of NSAIDs, there is evidence from several small clinical trials that strongly suggests that flurbiprofen and indobufen, both potent inhibitors of platelet-derived thromboxane, may be cardioprotective. Flurbiprofen produced a 70% reduction in the rate of reinfarction, compared with placebo, among patients in whom an acute MI was successfully treated with thrombolysis, angioplasty, or both. In ex vivo studies, indobufen has been associated with 90% inhibition of platelet thromboxane generation throughout its dosing interval. Clinical trials have demonstrated the efficacy of oral indobufen in the secondary prevention of thromboembolic complications in patients with atrial fibrillation, in the prevention of graft occlusion after coronary artery bypass graft surgery and in the treatment of intermittent claudication. In contrast to naproxen and indobufen, the NSAID comparators used in the rofecoxib osteoarthritis phase IIb/III clinical trials program (ibuprofen, diclofenac, and nabumetone) all have less pronounced and/or less sustained antiplatelet effects through their dosing interval.

We chose the APTC end point as our outcome measure because it is a widely accepted indicator of the overall CV impact of antithrombotic compounds evaluated in clinical trials. This end point summarizes the morbid and fatal CV sequelae of atherosclerosis, as well as the fatal hemorrhagic sequelae that may accompany therapy with antiplatelet agents. The use of this combined end point helped ensure...
consistency between trials that used adjudicated data and those that used investigator-reported data. In the rofecoxib clinical trials program, investigator-reported events and adjudicated data were consistent for certain diagnoses (e.g., MI and stroke) but were less consistent for other diagnoses (e.g., unstable angina and transient ischemic attacks). The use of the APTC end point, which included all fatal hemorrhagic sequelae, could have introduced a potential bias favoring rofecoxib relative to the nonselective NSAIDs, because rofecoxib has been shown to reduce gastrointestinal bleeds. However, this bias would have been against rofecoxib in the comparison with placebo, because despite a reduced risk of gastrointestinal toxicity relative to that of nonselective NSAIDs, this risk is not completely eliminated.6,10 However, the incidence of bleeding deaths and hemorrhagic strokes was quite low (5 total events). Exclusion of these events did not change the conclusions of the primary analysis.

Both nonselective NSAIDs and selective COX-2 inhibitors have dose-dependent renal-based side effects that include mild elevations in blood pressure.26 The absence of an excess risk of rofecoxib relative to placebo argues against blood pressure elevation as an important factor in the current analysis. Within VIGOR, CV event rates and relative risks were analyzed within groups stratified by change from baseline blood pressure. An association between CV events and blood pressure changes was not observed.

As noted, our analysis provides no evidence that rofecoxib was associated with excess CV events compared with placebo, nor was there evidence of an increased risk of such events relative to the non-naproxen NSAIDs that were studied. However, the rofecoxib development program did not study all possible NSAID comparators and all possible doses in all disease states. Additional analyses were conducted to assess the influence of study duration and dose on APTC event rates. Comparison of relative risks across individual doses failed to demonstrate a consistent dose effect. Although no dose relationship was found, these analyses suffered from limited patient-years of exposure, few APTC events, and point estimates associated with extremely wide confidence intervals for some of the comparisons.

The placebo comparison data provided the strongest evidence available to date that the partial inhibition of systemic prostacyclin synthesis observed with COX-2 inhibitors11,19–21 does not seem to result in an increased risk of CV thrombotic events. However, it is possible that a shift in the prostacyclin/thromboxane balance might have physiological importance in some patients at high risk for CV thrombotic events, such as those predisposed to thrombotic events or those with accelerated atherosclerotic disease.11,21 In a subgroup analysis restricted to those with either ≥2 major risk factors for coronary artery disease or a history of a prior CV event, the results were consistent with those of the primary analysis.

The strength of the present analyses was the pooling of individual patient level data from randomized trials that included both rofecoxib and the respective comparators in the same trial. This type of combined analysis with pooled individual patient data is preferable to comparing absolute rates across different studies. The latter method was used by Mukherjee and colleagues27 in a recently published article that raised concerns about the CV safety profile of COX-2 inhibitors. Specifically, they compared rates of CV thrombotic events in 4 rofecoxib and celecoxib trials to a “placebo group” from a meta-analysis of patients who had participated in aspirin primary prevention trials.28 Comparing absolute event rates across different studies in this manner is hazardous and considerably less reliable than a prospective, randomized comparison and assumes similar CV risks in the underlying populations, as well as similarity in ascertainment of study end points. The large variability in MI event rates seen within the trials comprising the aspirin primary prevention meta-analysis26 raises statistical concerns about using this type of calculated MI event rate as a placebo group outside the original meta-analysis. Furthermore, the annualized event rates reported for rofecoxib (0.74%) and for celecoxib (0.80%) fall well within the range of event rates for the trials comprising the aspirin meta-analysis referenced by Mukherjee et al27 (0.36% to 1.33%). It is thus difficult to draw any conclusions from that article.

Conclusions
Data from >28 000 patients in 23 studies representing >14 000 patient-years at risk demonstrated that rofecoxib was not associated with excess CV thrombotic events compared with either placebo or non-naproxen NSAIDs. The data suggest, but are insufficient to ascertain, the cardioprotective benefits of naproxen.

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References


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