

## ORIGINAL ARTICLE

# Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

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## ABSTRACT

**BACKGROUND**

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Selective inhibition of cyclooxygenase-2 (COX-2) may be associated with an increased risk of thrombotic events, but only limited long-term data have been available for analysis. We report on the cardiovascular outcomes associated with the use of the selective COX-2 inhibitor rofecoxib in a long-term, multicenter, randomized, placebo-controlled, double-blind trial designed to determine the effect of three years of treatment with rofecoxib on the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas.

**METHODS**

A total of 2586 patients with a history of colorectal adenomas underwent randomization: 1287 were assigned to receive 25 mg of rofecoxib daily, and 1299 to receive placebo. All investigator-reported serious adverse events that represented potential thrombotic cardiovascular events were adjudicated in a blinded fashion by an external committee.

**RESULTS**

A total of 46 patients in the rofecoxib group had a confirmed thrombotic event during 3059 patient-years of follow-up (1.50 events per 100 patient-years), as compared with 26 patients in the placebo group during 3327 patient-years of follow-up (0.78 event per 100 patient-years); the corresponding relative risk was 1.92 (95 percent confidence interval, 1.19 to 3.11;  $P=0.008$ ). The increased relative risk became apparent after 18 months of treatment; during the first 18 months, the event rates were similar in the two groups. The results primarily reflect a greater number of myocardial infarctions and ischemic cerebrovascular events in the rofecoxib group. There was earlier separation (at approximately five months) between groups in the incidence of nonadjudicated investigator-reported congestive heart failure, pulmonary edema, or cardiac failure (hazard ratio for the comparison of the rofecoxib group with the placebo group, 4.61; 95 percent confidence interval, 1.50 to 18.83). Overall and cardiovascular mortality was similar in the two groups.

**CONCLUSIONS**

Among patients with a history of colorectal adenomas, the use of rofecoxib was associated with an increased cardiovascular risk.

\*The members of the APPROVe Trial are listed in the Appendix.

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**N**ONSTEROIDAL ANTIINFLAMMATORY drugs (NSAIDs) alleviate pain and inflammation but may cause gastrointestinal ulceration and bleeding, presumably by inhibiting cyclooxygenase (COX)-mediated production of prostaglandins. The discovery that there were two forms of cyclooxygenase, 1 (COX-1) and 2 (COX-2), provided the impetus for the development of selective inhibitors of COX-2 with a reduced risk of gastrointestinal complications whose analgesic and antiinflammatory efficacy was likely to be similar to that of nonselective COX inhibitors.

COX-2 is expressed at sites of inflammation, such as in atheromatous plaques, and in neoplasms, raising the possibility that COX-2 inhibition might also be useful in the treatment or prevention of atherosclerosis and various cancers.<sup>1,2</sup> However, predicting the consequences of COX-2 inhibition on cardiovascular disease is not a straightforward proposition. COX-2 inhibition has several effects that could increase the risk of cardiovascular disease, including reducing prostacyclin levels, increasing blood pressure, decreasing angiogenesis,<sup>3-11</sup> and destabilizing plaque.<sup>12</sup>

Rofecoxib is a selective COX-2 inhibitor that has been shown to be associated with significantly fewer gastrointestinal adverse events than NSAIDs.<sup>13</sup> In one trial,<sup>13</sup> there were more cardiovascular events among patients given a high dose of rofecoxib than among those given naproxen, an NSAID with platelet-inhibiting properties of unclear clinical relevance.<sup>4,5,14-16</sup> Pooled data from other randomized trials have not shown a significant difference in cardiovascular risk between rofecoxib and placebo or other nonselective NSAIDs.<sup>4,5,17</sup> Observational studies have provided conflicting data on the association of rofecoxib with cardiovascular risk: some studies suggested that there was no effect, some suggested that the risk was increased only at high doses, and others indicated a possible increase in the risk of cardiovascular events at standard or unspecified doses.<sup>6,9,11,18-21</sup>

The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial was designed to evaluate the hypothesis that three years of treatment with rofecoxib would reduce the risk of recurrent adenomatous polyps among patients with a history of colorectal adenomas. Potential thrombotic events were adjudicated by an independent committee, and all safety data were monitored by an external safety-monitoring committee. We report the cardiovascular findings from the study.

## METHODS

### DESIGN OF THE TRIAL

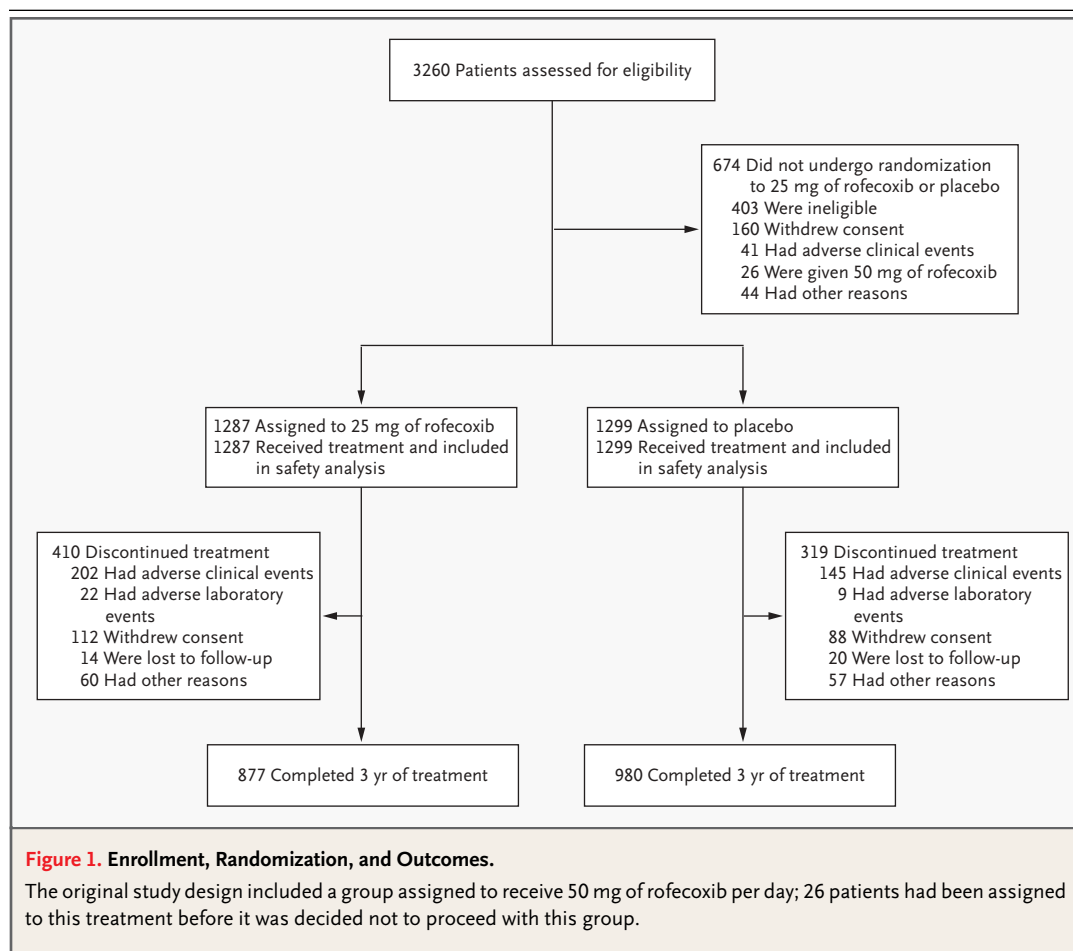
Enrollment occurred from February 2000 to November 2001 at 108 centers in 29 countries. Participating investigators are listed in the Appendix. Men and women who were at least 40 years old were eligible if they had had at least one histologically confirmed large-bowel adenoma removed within 12 weeks before study entry and were not anticipated to need long-term NSAID therapy (including high-dose aspirin) during the study. Initially, patients who were taking low-dose aspirin (no more than 100 mg daily) were excluded from the study. However, in May 2000, after the results of the Vioxx Gastrointestinal Research (VIGOR) trial<sup>13</sup> had become available, the protocol was amended to allow randomized subjects to take low-dose aspirin (no more than 100 mg daily) for cardiovascular protection. The proportion of subjects taking low-dose aspirin at enrollment was capped at 20 percent because of the possible chemopreventive effects of the drug.<sup>22</sup> Exclusion criteria were evidence of uncontrolled hypertension (defined by a blood pressure of more than 165/95 mm Hg); angina or congestive heart failure, with symptoms evoked by minimal activity; myocardial infarction, coronary angioplasty, or coronary-artery bypass grafting within the preceding year; or stroke or transient ischemic attack within two years before screening.

Written informed consent was obtained from all patients. The institutional review board at each center approved the study.

### TREATMENT

The randomized treatment period was preceded by a six-week, single-blind, placebo run-in period to assess patients' compliance. Patients who took at least 80 percent of their tablets during the placebo run-in period were randomly assigned to receive either one 25-mg tablet of rofecoxib per day (the maximal recommended long-term daily dose) or one identical-appearing placebo tablet per day for three years. The computer-derived randomization was stratified according to the clinical center and the use or nonuse of low-dose aspirin, with blocks of 2. Patients, investigators, and sponsor personnel who monitored the study, other than the unblinded study statistician, were unaware of the treatment assignments.

Patients were evaluated clinically at randomization and at weeks 4, 17, 35, 52, 69, 86, 104, 121,



138, 156, and 158 or after the discontinuation of treatment. Vital signs, including blood pressure obtained while the patient was seated, were measured at each clinic visit during the study according to the usual clinical practice. Adverse events occurring during the study were recorded and evaluated in a blinded fashion by the investigators. Follow-up of the patients for one year after the discontinuation of treatment is ongoing.

#### CARDIOVASCULAR EVENTS

Monitoring and analysis of the cardiovascular events in the trial were part of a planned assessment of the cardiovascular safety of rofecoxib. Data presented include events occurring during treatment and up to 14 days after the last dose of the study drug. Serious vascular events were reviewed in a blinded fashion by adjudication committees, which confirmed events that met prespecified case definitions for two sets of events. Thrombotic events included fatal and

nonfatal myocardial infarction, unstable angina, sudden death from cardiac causes, fatal and nonfatal ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism. The end point used in the Antiplatelet Trialists' Collaboration (APTC) study<sup>23</sup> was also analyzed: the combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; nonfatal myocardial infarction; and nonfatal ischemic and hemorrhagic stroke. Other relevant but not independently adjudicated events were also analyzed, including hypertension-related events, edema-related events, and the combined end point of congestive heart failure, pulmonary edema, or cardiac failure.

The procedure for confirming cardiovascular events was prespecified in the protocol. All serious adverse events were identified and recorded by the clinical investigators. Potential thromboembolic events, components of the APTC end point, and all

deaths (regardless of cause) were prespecified as eligible for adjudication according to standard procedures for rofecoxib studies initiated by the sponsor in 1998. For each eligible event, source documents were collected and sent to the cardiac, cerebrovascular, or peripheral vascular adjudication committee. Decisions were made on the basis of majority rule with the use of prespecified criteria.

#### STATISTICAL ANALYSIS

An independent, external safety-monitoring board met periodically to review safety data provided by a statistician who was aware of patients' study-group assignments. No formal stopping rule was specified for terminating the study.

Data were collected and held by the sponsor. The investigators had full and unfettered access to the data. A statistician who was aware of patients' study-group assignments but who was not otherwise involved in the study analyzed the data using SAS software (version 8.2). All patients who underwent randomization and took at least one dose of study medication were included in the analyses. For confirmed serious thrombotic events and the APTC end point, event rates were determined and relative risks (with 95 percent confidence intervals) were calculated with the use of Cox proportional-hazards models. However, if there were fewer than 11 events in either group, the rate ratio was computed with the use of the binomial distribution.<sup>24</sup> A test of the proportional-hazards assumption was specified in the cardiovascular-analysis plan. This was accomplished by evaluating the interaction between the logarithm of time and the assigned treatment in the Cox proportional-hazards model. Kaplan-Meier estimates of the cumulative event rates over time were also made.

Several exploratory analyses were performed to delineate the relation between mean arterial pressure and the study findings. One analysis summarized the relative risk of confirmed serious thrombotic adverse events according to the quartiles of change in mean arterial pressure at week 4. This time was chosen because treatment-based differences in mean arterial pressure occurred early and remained constant throughout the treatment period and because only two confirmed serious thrombotic events had occurred by week 4 (one in each group). The second analysis included changes from baseline in mean arterial pressure as a time-varying covariate in a Cox proportional-hazards model in which treatment was the main effect. This model

was used to investigate the association of the change in blood pressure over time with the occurrence of confirmed serious thrombotic events.

The data reported here are those available to the authors as of February 14, 2005.

## RESULTS

#### PARTICIPANTS

A total of 3260 patients were screened for the study, of whom 2586 were deemed to be eligible; 1287 of the eligible patients were randomly assigned to receive rofecoxib, and 1299 to receive placebo (Fig. 1). The two groups were generally similar with regard to baseline characteristics, including age, sex, use or nonuse of low-dose aspirin, and cardiovascular-risk status (Table 1). Concomitant medications used at some time during the study included low-dose aspirin (in 20 percent of the rofecoxib group and

**Table 1. Baseline Characteristics of the Patients.**

| Characteristic                                                    | Rofecoxib (N=1287) | Placebo (N=1299) |
|-------------------------------------------------------------------|--------------------|------------------|
| Age (yr)                                                          |                    |                  |
| Mean                                                              | 59                 | 59               |
| Range                                                             | 40–96              | 40–86            |
| Height (cm)                                                       |                    |                  |
| Mean                                                              | 170                | 170              |
| Range                                                             | 137–198            | 133–199          |
| Weight (kg)                                                       |                    |                  |
| Mean                                                              | 81                 | 81               |
| Range                                                             | 38–160             | 34–159           |
| Male sex (%)                                                      | 62                 | 62               |
| White race (%)*                                                   | 84                 | 84               |
| Use of low-dose aspirin (%)†                                      | 17                 | 16               |
| Use of antihypertensive medication (%)                            | 30                 | 29               |
| High cardiovascular risk (%)‡                                     | 30                 | 26               |
| History of symptomatic atherosclerotic cardiovascular disease (%) | 9                  | 8                |
| History of hypertension (%)                                       | 36                 | 34               |
| History of hypercholesterolemia (%)                               | 29                 | 26               |
| History of diabetes (%)                                           | 9                  | 9                |
| Current cigarette use (%)                                         | 22                 | 22               |

\* Race was self-reported.

† Low-dose aspirin was defined as 100 mg per day or less.

‡ A high cardiovascular risk was defined by a history of symptomatic atherosclerotic cardiovascular disease or the presence of at least two of the following risk factors for cardiovascular disease: history of hypertension, history of hypercholesterolemia, history of diabetes, or current cigarette use.

**Table 2. Incidence of Adjudicated Thrombotic Adverse Events.\***

| Adverse Event                     | Rofecoxib Group<br>(N=1287) |                        | Placebo Group<br>(N=1299) |                        | Hazard Ratio<br>(95% CI) |
|-----------------------------------|-----------------------------|------------------------|---------------------------|------------------------|--------------------------|
|                                   | No. of<br>Patients (%)      | Rate/100<br>Patient-yr | No. of<br>Patients (%)    | Rate/100<br>Patient-yr |                          |
| <b>Total</b>                      | 46 (3.6)                    | 1.50                   | 26 (2.0)                  | 0.78                   | 1.92 (1.19–3.11)         |
| <b>Cardiac events</b>             | 31 (2.4)                    | 1.01                   | 12 (0.9)                  | 0.36                   | 2.80 (1.44–5.45)         |
| Myocardial infarction             | 21                          |                        | 9                         |                        |                          |
| Fatal myocardial infarction       | 2                           |                        | 3                         |                        |                          |
| Sudden death from cardiac causes  | 3                           |                        | 1                         |                        |                          |
| Unstable angina pectoris          | 7                           |                        | 4                         |                        |                          |
| <b>Cerebrovascular events</b>     | 15 (1.2)                    | 0.49                   | 7 (0.5)                   | 0.21                   | 2.32 (0.89–6.74)         |
| Fatal ischemic stroke             | 1                           |                        | 0                         |                        |                          |
| Ischemic stroke                   | 11                          |                        | 6                         |                        |                          |
| Transient ischemic attack         | 5                           |                        | 2                         |                        |                          |
| <b>Peripheral vascular events</b> | 3 (0.2)                     | 0.10                   | 7 (0.5)                   | 0.21                   | 0.46 (0.08–2.03)         |
| Peripheral arterial thrombosis    | 1                           |                        | 1                         |                        |                          |
| Peripheral venous thrombosis      | 2                           |                        | 4                         |                        |                          |
| Pulmonary embolism                | 0                           |                        | 2                         |                        |                          |

\* The total duration of follow-up was 3059 patient-years in the rofecoxib group and 3327 patient-years in the placebo group. Although a patient may have had two or more clinical adverse events, the patient was counted once within a category. The same patient may appear in different categories. CI denotes confidence interval.

19 percent of the placebo group,  $P=0.52$ ), antihypertensive drugs (44 percent and 36 percent, respectively;  $P<0.001$ ), lipid-lowering agents (31 percent and 28 percent, respectively;  $P=0.09$ ), antiplatelet agents such as clopidogrel (4 percent and 2 percent, respectively;  $P=0.003$ ), insulin (3 percent and 2 percent, respectively;  $P=0.10$ ), and oral hypoglycemic agents (13 percent and 11 percent, respectively;  $P=0.12$ ).

The study was terminated on September 30, 2004, approximately two months ahead of the planned date of completion, at the recommendation of the external safety-monitoring board and the steering committee. At the time of termination, a total of 877 patients in the rofecoxib group and 980 patients in the placebo group had completed the scheduled three years of treatment. The mean duration of treatment was 2.4 years in the rofecoxib group and 2.6 years in the placebo group.

Before September 30, 2004, more patients discontinued rofecoxib treatment than placebo (32 percent vs. 25 percent) (Fig. 1). The main reason for discontinuation was an adverse clinical event. The three most common adverse events resulting in the discontinuation of treatment were hypertension (25 patients in the rofecoxib group and 7 patients in

the placebo group), increased blood pressure (6 in the rofecoxib group and 1 in the placebo group), and peripheral edema (7 in the rofecoxib group and 1 in the placebo group).

#### INCIDENCE OF THROMBOTIC EVENTS AND THE APTC END POINT

A total of 121 patients had investigator-reported serious thrombotic events (77 in the rofecoxib group and 44 in the placebo group). A total of 46 patients in the rofecoxib group had confirmed (i.e., adjudicated) thrombotic events during 3059 patient-years of follow-up (1.50 events per 100 patient-years), and 26 patients in the placebo group had such events during 3327 patient-years of follow-up (0.78 event per 100 patient-years). As compared with the placebo group, the rofecoxib group had an increased risk of confirmed thrombotic events (relative risk, 1.92; 95 percent confidence interval, 1.19 to 3.11). The types of confirmed serious thrombotic events are shown in Table 2. The difference between the two groups was mainly due to an increased number of myocardial infarctions and strokes in the rofecoxib group. There were 10 deaths in each group. Myocardial infarction was the cause of death in two patients in the rofecoxib group and three in the placebo

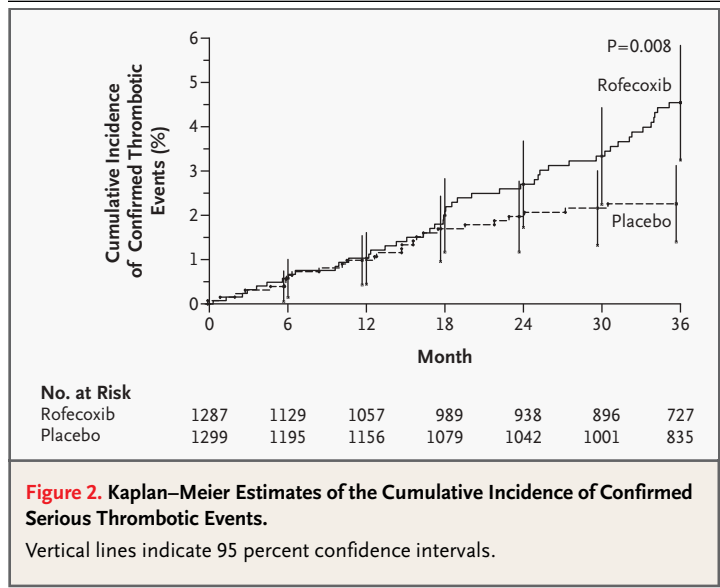
group, sudden death from cardiac causes occurred in three patients in the rofecoxib group and one in the placebo group, ischemic stroke was the cause of death in one patient in the rofecoxib group, and hemorrhagic stroke was the cause of death in one patient in the placebo group.

In a post hoc analysis, the difference between the two groups in the incidence of thrombotic events was evident in the second 18 months of the study, whereas the event rates were similar for the first 18 months (Fig. 2 and Table 3). The changing pattern of the treatment effect over time was confirmed by a failed test for proportionality of hazards ( $P=0.01$ ). Findings for the APTC end point were similar (Table 3).

There were no significant interactions between treatment group and subgroups ( $P>0.10$  for all comparisons) for confirmed serious thrombotic events in subgroup analyses based on country (United States vs. other); age; sex; use or nonuse of antihypertensive drugs at baseline, low-dose aspirin at baseline, or low-dose aspirin for more than 50 percent of follow-up; presence or absence of a history of hypertension, hypercholesterolemia, or ischemic heart disease; presence or absence of current cigarette use; or presence or absence of a high cardiovascular risk. A high cardiovascular risk was defined by a history of symptomatic atherosclerotic cardiovascular disease or the presence of at least two of the following risk factors for coronary artery disease: a history of hypertension, a history of hypercholesterolemia, a history of diabetes, or current cigarette use. However, point estimates for the relative risk in the rofecoxib group as compared with the placebo group were particularly high among patients with a history of symptomatic atherosclerotic cardiovascular disease (9.59; 95 percent confidence interval, 1.36 to 416) relative to those without such a clinical history (1.58; 95 percent confidence interval, 0.95 to 2.64;  $P$  for interaction=0.096). Also, the relative risk in the rofecoxib group as compared with the placebo group was 6.10 among patients with a history of diabetes (95 percent confidence interval, 1.36 to 56.1), in contrast to a relative risk of 1.55 among patients with no history of diabetes (95 percent confidence interval, 0.92 to 2.61;  $P$  for interaction=0.091).

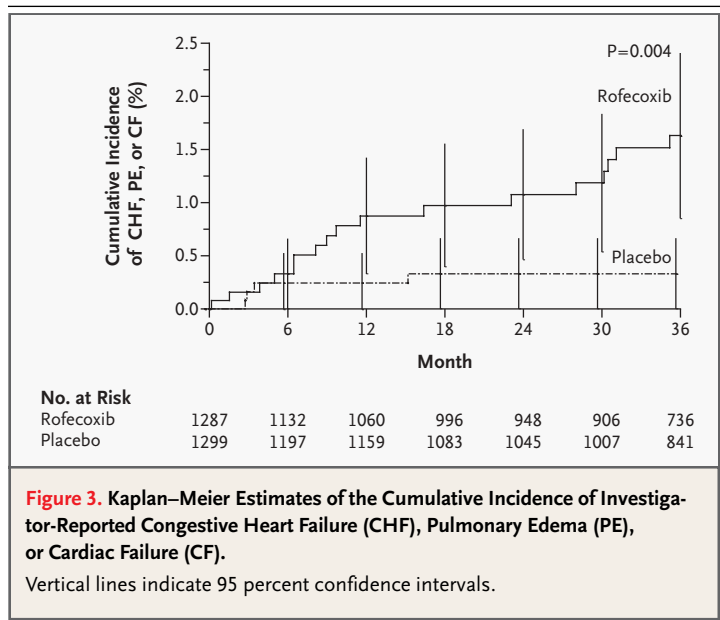
**NONADJUDICATED CARDIOVASCULAR EVENTS**

As compared with the placebo group, the rofecoxib group had higher percentages of patients with hypertension-related events and edema-related events.



**Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.**

Vertical lines indicate 95 percent confidence intervals.



**Figure 3. Kaplan–Meier Estimates of the Cumulative Incidence of Investigator-Reported Congestive Heart Failure (CHF), Pulmonary Edema (PE), or Cardiac Failure (CF).**

Vertical lines indicate 95 percent confidence intervals.

The Kaplan–Meier curves for the cumulative incidence of congestive heart failure, pulmonary edema, and cardiac failure (Fig. 3) showed early separation of the two groups (at approximately five months), with no significant departures from proportional hazards over time and a hazard ratio of 4.61 for the comparison of the rofecoxib group with the placebo group (95 percent confidence interval, 1.50 to 18.83). The hazard ratios for edema and hyperten-

**Table 3. Summary of Rates and Relative Risks of Confirmed Serious Thrombotic Events and the APTC End Point.\***

| Adverse Event          | Rofecoxib Group |               |                           |                     | Placebo Group |               |                           |                     | Difference in Rate (95% CI) | Relative Risk (95% CI)  |
|------------------------|-----------------|---------------|---------------------------|---------------------|---------------|---------------|---------------------------|---------------------|-----------------------------|-------------------------|
|                        | No. at Risk     | No. of Events | No. of Patient-yr at Risk | Rate/100 Patient-yr | No. at Risk   | No. of Events | No. of Patient-yr at Risk | Rate/100 Patient-yr |                             |                         |
| <b>Confirmed event</b> |                 |               |                           |                     |               |               |                           |                     |                             |                         |
| Overall                | 1287            | 46            | 3059                      | 1.50                | 1299          | 26            | 3327                      | 0.78                | 0.72<br>(0.19 to 1.25)      | 1.92<br>(1.19 to 3.11)  |
| Month 0–18             | 1287            | 22            | 1656                      | 1.33                | 1299          | 20            | 1765                      | 1.13                | 0.20<br>(–0.55 to 0.94)     | 1.18<br>(0.64 to 2.15)  |
| Month 19–36            | 989             | 24            | 1403                      | 1.71                | 1079          | 6             | 1561                      | 0.38                | 1.33<br>(0.58 to 2.08)      | 4.45<br>(1.77 to 13.32) |
| <b>APTC end point</b>  |                 |               |                           |                     |               |               |                           |                     |                             |                         |
| Overall                | 1287            | 34            | 3070                      | 1.11                | 1299          | 18            | 3334                      | 0.54                | 0.57<br>(0.12 to 1.02)      | 2.06<br>(1.16 to 3.64)  |
| Month 0–18             | 1287            | 14            | 1658                      | 0.84                | 1299          | 12            | 1769                      | 0.68                | 0.17<br>(–0.42 to 0.75)     | 1.25<br>(0.58 to 2.69)  |
| Month 19–36            | 994             | 20            | 1412                      | 1.42                | 1083          | 6             | 1565                      | 0.38                | 1.03<br>(0.34 to 1.73)      | 3.69<br>(1.43 to 11.24) |

\* CI denotes confidence interval, and APTC Antiplatelet Trialists' Collaboration.

sion were lower than those for the combined end point of congestive heart failure, pulmonary edema, or cardiac failure (Table 4), but the event curves showed an early separation similar to that for the combined end point (data not shown).

During the trial, the rofecoxib group had mean ( $\pm$ SE) increases of  $3.4\pm 0.4$  mm Hg in systolic blood pressure and  $0.9\pm 0.2$  mm Hg in diastolic blood pressure, as compared with respective changes of  $-0.5\pm 0.3$  mm Hg and  $-0.8\pm 0.2$  mm Hg in the placebo group ( $P<0.01$  for the comparison between the two groups). Blood-pressure effects were seen by four weeks and remained relatively constant throughout the study. To investigate the relation between changes in blood pressure and confirmed thrombotic events, we categorized patients according to the change from baseline in mean arterial pressure at four weeks. The relative risks of a confirmed thrombotic event in the rofecoxib group, as compared with the placebo group, were broadly similar across quartile categories of the change in blood pressure (data not shown). The mean arterial pressure throughout the study, included as a time-varying covariate, did not materially modify the treatment effect (relative risk for the comparison of the rofecoxib group with the placebo group, 1.87; 95 percent confidence interval, 1.14 to 3.06).

## DISCUSSION

COX-2 inhibitors have been widely used as anti-inflammatory and pain-relief agents and may hold promise as chemopreventive agents for a variety of epithelial cancers. In this randomized, placebo-controlled, double-blind trial, we found that long-term use of the COX-2 inhibitor rofecoxib was associated with an increased risk of cardiovascular events. In post hoc analyses, the increased relative risk of adjudicated thrombotic events was first observed after approximately 18 months of treatment. The overall risk did not appear to be significantly influenced by baseline or subsequent use of low-dose aspirin. In addition, there was an increased frequency of investigator-reported events, such as hypertension, edema, and congestive heart failure, which occurred much earlier in the study.

Thromboxane  $A_2$ , a major COX-1-mediated product of arachidonic acid metabolism, causes irreversible platelet aggregation, vasoconstriction, and smooth-muscle proliferation, whereas prostacyclin is an inhibitor of platelet aggregation, a vasodilator, and an inhibitor of smooth-muscle proliferation. COX-2 is the chief source of systemic prostacyclin synthesis,<sup>25</sup> and COX-2 inhibitors may increase the cardiovascular risk by shifting the functional bal-

**Table 4. Incidence of Nonadjudicated Cardiovascular Adverse Events.\***

| Adverse Event†                                                   | Rofecoxib Group<br>(N=1287) |                        | Placebo Group<br>(N=1299) |                        | Hazard Ratio<br>(95% CI) |
|------------------------------------------------------------------|-----------------------------|------------------------|---------------------------|------------------------|--------------------------|
|                                                                  | No. of<br>Patients (%)      | Rate/100<br>Patient-yr | No. of<br>Patients (%)    | Rate/100<br>Patient-yr |                          |
| Hypertension                                                     | 377 (29.3)                  | 14.9                   | 219 (16.9)                | 7.3                    | 2.02 (1.71–2.38)         |
| Serious event                                                    | 11                          |                        | 1                         |                        |                          |
| Edema                                                            | 111 (8.6)                   | 3.8                    | 76 (5.9)                  | 2.4                    | 1.57 (1.17–2.10)         |
| Serious event                                                    | 3                           |                        | 0                         |                        |                          |
| Congestive heart failure, pulmonary<br>edema, or cardiac failure | 17 (1.3)                    | 0.6                    | 4 (0.3)                   | 0.1                    | 4.61 (1.50–18.83)        |
| Serious event                                                    | 12                          |                        | 2                         |                        |                          |

\* The total duration of follow-up was 3059 patient-years in the rofecoxib group and 3327 patient-years in the placebo group. Although a patient may have had two or more clinical adverse events, the patient was counted once within a category. The same patient may appear in different categories. CI denotes confidence interval.

† A serious event was defined as one that was life-threatening, resulted in (or prolonged) hospitalization, or caused permanent disability.

ance of these vasoactive eicosanoids toward the promotion of thrombosis or atherogenesis. COX-2 inhibition combined with thromboxane-receptor antagonism may also lead to the destabilization of atheromatous plaque.<sup>12</sup> In addition, COX-2 plays a role in angiogenesis.<sup>1</sup> How these pharmacologic observations relate to the clinical cardiovascular findings with COX-2 inhibition is unknown. It is also not clear whether the partial inhibition of COX-1 by various nonselective NSAIDs offsets any adverse cardiovascular effects of COX-2 inhibition, since this possibility has not been evaluated explicitly in trials.

The VIGOR study<sup>13</sup> compared 50 mg of rofecoxib daily with 500 mg of naproxen twice daily in patients with rheumatoid arthritis and found rofecoxib to be associated with a higher incidence of myocardial infarction. It was unclear how much of the increase in risk was due to a deleterious effect of high-dose rofecoxib, a protective effect of naproxen, chance, or a combination of these factors.<sup>26</sup> A recent meta-analysis<sup>21</sup> suggested that the magnitude of any cardioprotective effect of naproxen is unlikely to account entirely for these findings.

In aggregate, previous randomized, controlled trials comparing rofecoxib with placebo or conventional NSAIDs other than naproxen have not demonstrated an increased cardiovascular risk associated with rofecoxib use. Analysis of a database including 5435 patients with osteoarthritis in eight double-blind, placebo-controlled, phase 2B or

phase 3 trials reported similar rates of thrombotic cardiovascular adverse events with rofecoxib, placebo, and various nonselective NSAIDs.<sup>5</sup> A pooled analysis of data from more than 28,000 patients with various diseases (representing more than 14,000 patient-years at risk) from 23 previous trials of rofecoxib (phase 2B through phase 5), including patients from the VIGOR trial, also did not demonstrate a significant increase in cardiovascular risk for rofecoxib as compared with placebo or NSAIDs other than naproxen.<sup>4</sup> This analysis used the APTC end point we evaluated. An updated analysis that included data from various placebo-controlled studies investigating rofecoxib for the treatment or prevention of Alzheimer's disease did not demonstrate an excess of cardiovascular events associated with rofecoxib therapy.<sup>5</sup> A recent meta-analysis comparing cardiovascular risk in trials that included various doses of rofecoxib suggested an increased relative risk among patients taking rofecoxib, as compared with those taking naproxen, but not placebo.<sup>22</sup> Differences between our results and these earlier clinical-trial data may be related to differences in defined end points or the duration of treatment, a possibility supported by the apparent absence of a difference in adjudicated thrombotic events during the first 18 months of our study.

Observational studies have provided conflicting data on the cardiovascular safety of rofecoxib. A Canadian retrospective cohort study did not demonstrate an increased risk of myocardial infarction

among new users of rofecoxib as compared with control subjects,<sup>18</sup> but a case-control study of patients 65 years of age or older suggested a dose-dependent elevation in the relative risk of acute myocardial infarction with rofecoxib therapy.<sup>7</sup> Unlike the findings in the current study, this risk was elevated during the first 90 days of use, but not thereafter. A retrospective cohort study that assessed the occurrence of serious coronary heart disease among NSAID users<sup>19</sup> showed an elevated cardiovascular risk associated with the use of high-dose rofecoxib, but no increased risk with the use of doses of 25 mg or less.

In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the long-term use of rofecoxib. The increase in adjudicated thrombotic events associated with rofecoxib therapy was not evident during the first 18 months of the trial. Other investigator-reported cardiovascular events known to be associated with NSAID use, such as congestive heart failure and pulmonary edema, although less well defined, occurred earlier (at approximately five months) and at a higher rate among patients taking rofecoxib than among those taking placebo.

Patients in the rofecoxib group had increases in systemic arterial pressure during the trial, a finding that is consistent with the previously reported renovascular effects of NSAIDs. These changes in blood pressure were observed early in the study, along with investigator-reported edema and congestive heart failure. Mean arterial pressure did not appear to have a significant association with confirmed thrombotic events, however, according to an assessment of changes from baseline to four weeks and an analysis that included mean arterial pressure as a time-varying covariate in a model of treatment effects. On the basis of these findings, it is unlikely that changes in blood pressure were the explana-

tion for the excess cardiovascular risk in our study. However, hemodynamic changes could have contributed to a degree that is difficult to determine from the available data.

It is unclear whether the results seen with rofecoxib represent a general effect of COX-2 inhibitors or a specific effect of rofecoxib. A recent case-control study<sup>27</sup> suggested that the odds of nonfatal myocardial infarction differ between patients who take rofecoxib and those who take celecoxib, and a nested case-control study<sup>20</sup> also suggested that there are differences in the risk of serious coronary heart disease between the two agents. Elsewhere in this issue of the *Journal*, Nussmeier et al. report that patients who received parecoxib and valdecoxib for pain in the first 10 days after coronary-artery bypass grafting had an increased risk of cardiovascular events during 30 days of follow-up.<sup>28</sup> Also in this issue, Solomon et al. report that an ongoing safety review of the Adenoma Prevention with Celecoxib Trial revealed that the risk of fatal or nonfatal cardiovascular events was increased by a factor of 2.3 among patients who were randomly assigned to receive celecoxib, as compared with those who were assigned to receive placebo,<sup>29</sup> leading the National Cancer Institute to suspend the trial. The possibility that conventional NSAIDs may have similar effects also has to be considered. Possible cardiovascular effects will need to be taken into account in an assessment of the potential ability of any of these drugs to prevent neoplasia in the large bowel and other organs.

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#### APPENDIX

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