

ORIGINAL ARTICLE

Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery

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ABSTRACT

BACKGROUND

Valdecoxib and its intravenous prodrug parecoxib are used to treat postoperative pain but may involve risk after coronary-artery bypass grafting (CABG). We conducted a randomized trial to assess the safety of these drugs after CABG.

METHODS

In this randomized, double-blind study involving 10 days of treatment and 30 days of follow-up, 1671 patients were randomly assigned to receive intravenous parecoxib for at least 3 days, followed by oral valdecoxib through day 10; intravenous placebo followed by oral valdecoxib; or placebo for 10 days. All patients had access to standard opioid medications. The primary end point was the frequency of predefined adverse events, including cardiovascular events, renal failure or dysfunction, gastroduodenal ulceration, and wound-healing complications.

RESULTS

As compared with the group given placebo alone, both the group given parecoxib and valdecoxib and the group given placebo and valdecoxib had a higher proportion of patients with at least one confirmed adverse event (7.4 percent in each of these two groups vs. 4.0 percent in the placebo group; risk ratio for each comparison, 1.9; 95 percent confidence interval, 1.1 to 3.2; $P=0.02$ for each comparison with the placebo group). In particular, cardiovascular events (including myocardial infarction, cardiac arrest, stroke, and pulmonary embolism) were more frequent among the patients given parecoxib and valdecoxib than among those given placebo (2.0 percent vs. 0.5 percent; risk ratio, 3.7; 95 percent confidence interval, 1.0 to 13.5; $P=0.03$).

CONCLUSIONS

The use of parecoxib and valdecoxib after CABG was associated with an increased incidence of cardiovascular events, arousing serious concern about the use of these drugs in such circumstances.

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NONSTEROIDAL ANTIINFLAMMATORY drugs (NSAIDs) are established pharmacologic tools for treating postoperative pain. However, concern about the possibility of gastric ulceration, renal injury, and bleeding has limited the use of NSAIDs in some surgical and critical care settings.¹ The selective cyclooxygenase-2 (COX-2) inhibitor valdecoxib (Bextra, Pfizer) and its intravenous prodrug parecoxib (Dynastat, Pfizer) were found to exert significant opioid-sparing effects after dental, gynecologic, orthopedic, and other noncardiac surgical procedures, apparently without causing serious adverse effects.²⁻⁵ Similar efficacy was demonstrated in a study of parecoxib and valdecoxib in patients recovering from coronary-artery bypass grafting (CABG).⁶ In that study, however, these drugs were associated with a significantly higher overall incidence of serious adverse events, a significantly higher incidence of sternal-wound infections, and a higher incidence of postoperative cerebrovascular complications and myocardial infarction. In nonsurgical settings, studies of the long-term administration of COX-2 inhibitors have aroused concern regarding their potential to increase the risk of thromboembolic events.⁷⁻⁹ To clarify the safety of parecoxib and valdecoxib therapy in patients after CABG, we undertook a large randomized trial.

METHODS

STUDY DESIGN AND PROCEDURES

The CABG surgery study was conducted at 175 centers in 27 countries from January 2003 to January 2004 (see the Appendix). The study was a sponsor-initiated, randomized, double-blind, parallel-group, multiple-dose, placebo-controlled study involving 10 days of study-drug administration and 30 days of follow-up. All patients had access to standard opioid medications throughout the 10-day period. The protocol was approved by the institutional review board at each center. All patients gave written informed consent.

The study included three randomized groups. One group received an initial intravenous dose of 40 mg of parecoxib on the morning after surgery (day 1) and then 20 mg of parecoxib every 12 hours for 3 days, followed by 20 mg of oral valdecoxib every 12 hours through day 10. One group received placebo intravenously every 12 hours for 3 days, followed by 20 mg of oral valdecoxib every

12 hours through day 10. One group received placebo throughout the 10-day period. Patients who were unable to tolerate oral medications continued to receive the intravenous study drug. After CABG, all patients received aspirin in the allowed range of 75 to 325 mg daily through day 10. Other routinely administered postoperative medications, including prophylaxis against deep-vein thrombosis, were permitted, except for NSAIDs, sedating antihistamines, prophylactic antiemetic agents, intrathecal or epidural opioids, and local analgesics applied to the surgical incision.

END POINTS

The primary end point was the combined incidence of predefined adverse events in the following four clinically relevant categories: cardiovascular events, renal events, surgical-wound complications, and gastrointestinal complications. Cardiovascular events included cardiac, cerebrovascular, and peripheral vascular events. Cardiac events included myocardial infarction, severe myocardial ischemia (defined as typical ischemic chest discomfort lasting at least 10 minutes and associated with transient ST-segment changes of at least 1 mm on the electrocardiogram), sudden death from cardiac causes, or unexpected death without an identifiable noncardiac cause within 60 minutes after the onset of symptoms.

Myocardial infarction was diagnosed at autopsy or by the presence of two or more of the following: prolonged chest pain (lasting more than 20 minutes) that was not relieved by antianginal agents; a creatine kinase MB level of more than 25 ng per milliliter within 72 hours after CABG (or in excess of 10 ng per milliliter more than 72 hours after CABG) or a peak troponin I level of more than 3.7 μ g per liter; new wall-motion abnormalities that were consistent with the occurrence of a myocardial infarction (a two-grade change) detected during catheterization, echocardiography, or radionuclide scanning; and new Q waves on serial electrocardiography that were consistent with the occurrence of myocardial infarction.¹⁰ Cerebrovascular events included a new ischemic or hemorrhagic cerebrovascular accident lasting 24 hours or longer or a transient ischemic attack lasting less than 24 hours, diagnosed according to clinical criteria and confirmed by a diagnostic study (e.g., computed tomography or magnetic resonance imaging).¹¹ Peripheral vascular events included deep-vein thrombosis,

defined as increased unilateral or bilateral leg swelling, warmth, and edema, with a confirmatory diagnostic test, and pulmonary embolism, defined as chest pain, dyspnea, or hypoxemia, with a confirmatory imaging study.

Renal events included renal failure, defined as the need for hemodialysis or peritoneal dialysis after CABG, and severe renal dysfunction, defined by a postoperative serum creatinine level of at least 2.0 mg per deciliter (176.8 μ mol per liter), with an increase of at least 0.7 mg per deciliter (61.9 μ mol per liter) after randomization.¹²

Gastrointestinal complications were defined as a gastrointestinal ulcer resulting in bleeding (proven on the basis of endoscopy), perforation, or obstruction. Wound-healing complications included infection of the superficial incisional site, deep incisional site, or organ or space and noninfectious separation or dehiscence of the wound.

The primary investigator at each site was responsible for reporting all adverse events to the sponsor, including directly observed events and those spontaneously reported by the patients. Definitions of the predefined end points of interest were described in detail in the study protocol and reiterated in a newsletter regularly distributed to all investigational sites. An independent, external endpoint committee (see the Appendix) whose members were unaware of the patients' treatment assignments used these definitions to review the data on adverse events. Adjudicated, predefined adverse events in all four categories were combined for the primary safety analysis. A data and safety monitoring board (see the Appendix) independently monitored safety outcomes throughout the study.

PATIENT POPULATION

Men and women who were undergoing elective, primary CABG with cardiopulmonary bypass were eligible for the study. Inclusion criteria were an age of 18 to 80 years; New York Heart Association class I, II, or III or an ejection fraction of at least 35 percent; a body-mass index (the weight in kilograms divided by the square of the height in meters) of no more than 40; and a weight of more than 55 kg.

Exclusion criteria were a thromboembolic event (cerebrovascular accident, transient ischemic attack, deep-vein thrombosis, or pulmonary embolism) within 3 months before study entry, myocardial infarction within 7 days before entry, gastric or duodenal ulcer within 60 days before entry, receipt

of a radiographic contrast agent within 24 hours before entry, poorly controlled diabetes mellitus (defined by a blood glucose level of more than 350 mg per deciliter [19.4 mmol per liter] or a glycosylated hemoglobin value of more than 9.0 percent after an overnight fast), and any preoperative coagulopathy. Patients who were undergoing CABG without cardiopulmonary bypass were excluded, as were patients undergoing concomitant valvular or vascular surgery and those in whom cardiopulmonary bypass exceeded 3.5 hours.

Other prerandomization exclusion criteria were evidence of a new myocardial infarction (i.e., on the basis of creatine kinase MB or troponin levels, new Q waves, or a new elevation in the ST segment for more than 10 minutes), the use of an intraaortic balloon pump, a cardiac index of no more than 1.5 liters per minute per square meter of body-surface area, receipt of more than two pharmacologic infusions to support blood pressure, symptomatic dysrhythmia, a new neurologic deficit, clinically significant bleeding (defined by a total chest-tube output of more than 500 ml), a hemoglobin level of no more than 8 g per deciliter, urinary output of less than 50 ml per hour, a creatinine level of at least 1.8 mg per deciliter (159.1 μ mol per liter), or an increase in the creatinine level of more than 30 percent since the initial screening.

STATISTICAL ANALYSIS

We estimated that the enrollment of 500 patients per group would provide the study with a statistical power of at least 80 percent to detect an approximate doubling of the 4 percent estimated background incidence of all predefined adverse events combined. All eligible patients were stratified first according to risk (high versus low) and then according to geographic location (North America, Europe, or another location) before randomization. Patients were considered to be at high risk if they used aspirin daily for secondary cardiovascular prophylaxis, had a history of a cerebrovascular accident, or had two or more of the following: an age of more than 65 years, a body-mass index of more than 30, diabetes, hypertension, or a history of myocardial infarction, deep-vein thrombosis, or pulmonary embolism. (Only 4 percent of the patients in all groups combined did not meet the criteria for high risk.)

Each analysis included all patients who had taken at least one dose of study medication. For the primary safety analysis, Fisher's exact test was used

to examine the proportion of patients in each group with at least one predefined adverse event. Similar analyses were performed for individual events within each of the four end-point categories. For predefined cardiovascular events, analyses of the time to a first event were performed with the use of the log-rank test and presented by means of Kaplan–Meier curves. All statistical comparisons included treatment and country as factors, were two-tailed, and used an α value of 0.05; none of the comparisons were adjusted for interim analyses.

Pfizer held the data during the study. The authors had complete access to the data after unblinding. All final analyses were conducted by an independent statistician at the Texas Heart Institute in Houston. The data reported here were those available to the authors as of February 14, 2005.

RESULTS

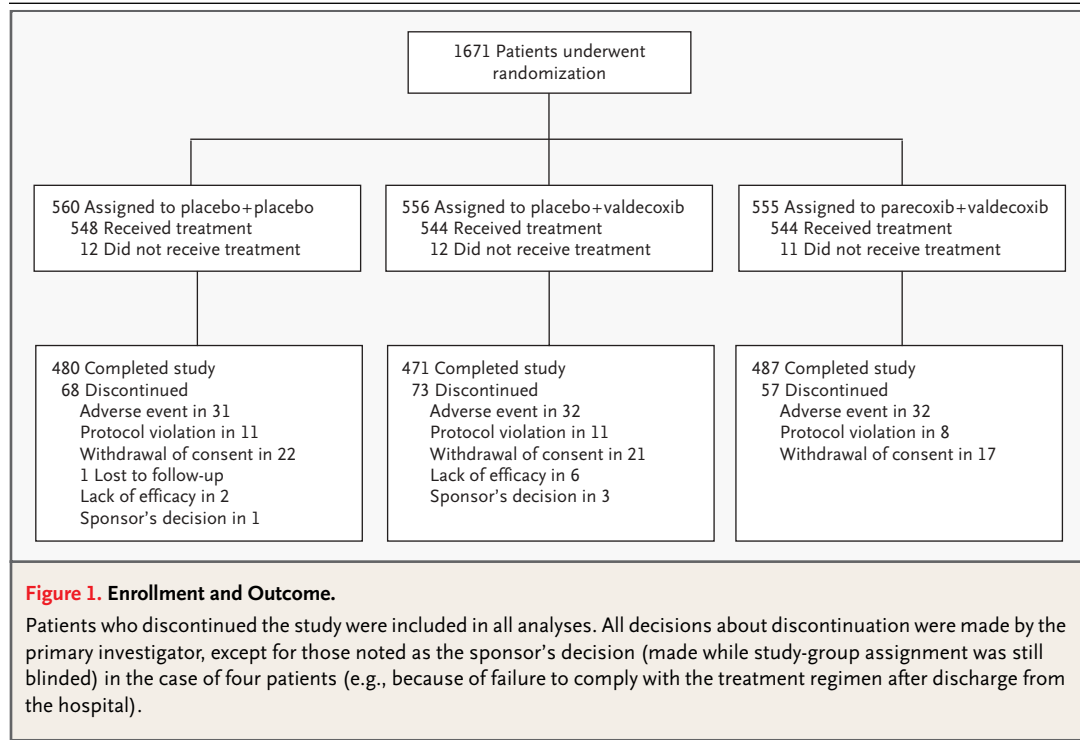
CHARACTERISTICS OF THE PATIENTS

A total of 1671 patients underwent randomization: 555 were assigned to the group given parecoxib and valdecoxib, 556 to the group given placebo and valdecoxib, and 560 to the placebo group. Enrollment and outcomes are outlined in Figure 1. There were no significant differences among the groups in pre-

operative characteristics (Table 1) or operative characteristics (Table 2).

PRIMARY END POINT

As compared with the placebo group, both the group given parecoxib and valdecoxib and the group given placebo and valdecoxib had significantly more patients with at least one confirmed predefined adverse event (7.4 percent in each of these two groups vs. 4.0 percent in the placebo group; risk ratio for each comparison with the placebo group, 1.9; 95 percent confidence interval, 1.1 to 3.2; $P=0.02$ for each comparison with the placebo group) (Table 3). Furthermore, the incidence of at least one predefined adverse event was also significantly higher in the pooled COX-2-inhibitor group than in the placebo group (7.4 percent vs. 4.0 percent; risk ratio, 1.9; 95 percent confidence interval, 1.1 to 3.1; $P=0.01$). Cardiovascular events were significantly more frequent in the group given parecoxib and valdecoxib than in the placebo group (2.0 percent vs. 0.5 percent; risk ratio, 3.7; 95 percent confidence interval, 1.0 to 13.5; $P=0.03$) (Table 3). The incidence of cardiovascular events in the group given placebo and valdecoxib (1.1 percent) did not differ significantly from that in either of the other two groups (Table 3). In fact, three of the six events in



the group given placebo and valdecoxib occurred in patients who had not yet begun treatment with valdecoxib. The time-to-event analysis revealed that cardiovascular events occurred throughout and after the 10-day period of drug administration in all groups (Fig. 2). Analyses of cardiovascular events in the pooled COX-2-inhibitor group and the control group did not reveal significant differences (1.6 percent and 0.5 percent, respectively; risk ratio, 2.9; 95 percent confidence interval, 0.8 to 9.9; P=0.08) (Table 3).

The incidence of noncardiovascular predefined adverse events (wound-healing complications, renal failure or dysfunction, and gastroduodenal ulcers) was higher in the two COX-2-inhibitor groups than in the placebo group, but not significantly so (Ta-

ble 3). The incidence of all adverse wound-related events did not differ significantly between the placebo group and the group given parecoxib and valdecoxib (P=0.48), but the difference between the placebo group and the group given placebo and valdecoxib approached significance (P=0.08). A comparison of surgical-wound events in the pooled COX-2-inhibitor group and the placebo group did not reveal significant differences (4.3 percent and 2.9 percent, respectively; risk ratio, 1.5; 95 percent confidence interval, 0.8 to 2.7; P=0.15). A post hoc analysis showed that sternal-wound infections or other complications of sternal-wound healing, such as instability or dehiscence, occurred in 18 of the 544 patients in the group given parecoxib and valdecoxib (3.3 percent; 12 infections and 6 other com-

Table 1. Preoperative Characteristics of All Randomized Patients.*

| Characteristic | Placebo (N=560) | Placebo + Valdecoxib (N=556) | Parecoxib + Valdecoxib (N=555) |
|---------------------------------|-----------------|------------------------------|--------------------------------|
| Age — yr | 62.1±8.6 | 61.6±9.1 | 62.0±9.1 |
| Age ≥65 yr — no. (%) | 219 (39.1) | 206 (37.1) | 228 (41.1) |
| Male sex — no. (%) | 477 (85.2) | 479 (86.2) | 475 (85.6) |
| Race or ethnic group — no. (%)† | | | |
| White | 514 (91.8) | 521 (93.7) | 524 (94.4) |
| Black | 14 (2.5) | 10 (1.8) | 6 (1.1) |
| Asian | 24 (4.3) | 15 (2.7) | 18 (3.2) |
| Not listed | 8 (1.4) | 10 (1.8) | 7 (1.3) |
| Height — cm | 172.0±8.9 | 171.6±9.8 | 172.2±8.7 |
| Weight — kg | 84.0±14.1 | 84.3±14.9 | 84.4±14.6 |
| Body-mass index | 28.3±3.9 | 28.7±6.2 | 28.4±4.0 |
| Body-mass index ≥30 — no. (%) | 164 (29.3) | 184 (33.1) | 167 (30.1) |
| Medical history — no. (%) | | | |
| Angina | 487 (87.0) | 483 (86.9) | 491 (88.5) |
| Hypertension | 406 (72.5) | 407 (73.2) | 411 (74.1) |
| Congestive heart failure | 43 (7.7) | 42 (7.6) | 32 (5.8) |
| Coronary-artery atherosclerosis | 517 (92.3) | 515 (92.6) | 524 (94.4) |
| Myocardial infarction | 221 (39.5) | 246 (44.2) | 242 (43.6) |
| Peripheral edema | 17 (3.0) | 24 (4.3) | 20 (3.6) |
| Hyperlipidemia | 418 (74.6) | 423 (76.1) | 438 (78.9) |
| Peripheral vascular disease | 47 (8.4) | 46 (8.3) | 49 (8.8) |
| Asthma | 20 (3.6) | 27 (4.9) | 18 (3.2) |
| Renal insufficiency | 11 (2.0) | 10 (1.8) | 12 (2.2) |
| Diabetes mellitus | 138 (24.6) | 157 (28.2) | 160 (28.8) |
| Anemia | 17 (3.0) | 22 (4.0) | 9 (1.6) |

* Plus-minus values are means ±SD.

† Patients chose one of these four options.

Table 2. Characteristics of the Surgical Procedures.*

| Characteristic | Placebo (N=560) | Placebo+Valdecoxib (N=556) | Parecoxib+Valdecoxib (N=555) |
|--|-----------------|----------------------------|------------------------------|
| Internal-thoracic-artery implants — no. of patients (%) | | | |
| 1 | 474 (84.9) | 470 (84.5) | 447 (80.8) |
| 2 | 50 (9.0) | 52 (9.4) | 68 (12.3) |
| 0 or none | 34 (6.1) | 34 (6.1) | 38 (6.9) |
| Data missing — no. of patients | 2 | 0 | 2 |
| Duration of surgery — min | 203.5±57.2 | 202.3±55.0 | 204.8±59.2 |
| Data missing — no. of patients | 31 | 25 | 28 |
| Duration of cardiopulmonary bypass — min | 81.9±32.3 | 80.6±29.5 | 80.5±30.7 |
| Data missing — no. of patients | 4 | 0 | 3 |
| Time from end of surgery to administration of study medication — min | 1243.8±169.9 | 1241.4±166.4 | 1231.3±159.6 |
| Data missing — no. of patients | 39 | 36 | 37 |

* Unless otherwise noted, the analysis includes all randomized patients. Plus-minus values are means ±SD.

plications of healing), 20 of the 544 patients in the group given placebo and valdecoxib (3.7 percent; 12 infections and 8 other complications of healing), and 11 of the 548 patients in the placebo group (2.0 percent; 9 infections and 2 other complications of healing). There were no significant differences among the groups. Analysis of the incidence of sternal-wound events in the pooled COX-2-inhibitor group and the placebo group revealed no significant differences (3.5 percent and 2.0 percent, respectively; $P=0.10$).

Eight deaths were reported during the study (Table 3): seven during the study period and one after the 30-day follow-up period. Of these deaths, four occurred in patients given parecoxib and valdecoxib, one each caused by cardiac arrest, ventricular fibrillation, myocardial infarction, and pulmonary embolism. Three deaths occurred among patients given placebo and valdecoxib, one each caused by cardiac arrest, cardiac failure, and pneumonia; all these deaths occurred in patients who had not yet begun treatment with valdecoxib. One patient in the placebo group died from intestinal perforation.

DISCUSSION

We found that short-term COX-2 inhibition is associated with a significant risk of thromboembolic events in patients at high risk for such events. Although a hint of this adverse effect was noted in an earlier trial of parecoxib and valdecoxib in patients

who had undergone CABG,⁶ there were only 311 patients in the group given parecoxib and valdecoxib and 151 patients in the control group. These numbers were sufficient only to detect a doubling in the total number of adverse events and an increase by a factor of seven in any single adverse event, such as myocardial infarction. In that study, the group given parecoxib and valdecoxib, as compared with the placebo group, had more perioperative myocardial infarctions (5 of 311 vs. 1 of 151) and cerebrovascular disorders (9 of 311 vs. 1 of 151) reported by investigators as serious adverse events, but these differences were not significant. Our study, which included more patients, showed a significantly higher incidence of combined thromboembolic events among patients receiving parecoxib and valdecoxib than among patients receiving placebo.

The increased risk of thromboembolic events among patients receiving parecoxib and valdecoxib after CABG may be due to preexisting generalized atherosclerotic disease, exposure to the additional risks of cardiopulmonary bypass, or both. Certainly, platelet activation resulting from shear stresses can occur in patients with atherosclerotic vessels.¹³ When such patients undergo cardiopulmonary bypass, contact between cellular and humoral blood components and the synthetic surfaces of the extracorporeal circuit results in the activation of platelets, leukocytes, and endothelial cells, possibly predisposing patients to thrombotic events.^{14,15} In addition, aortic cross-clamping, which is necessary

Table 3. Incidence of and Risk Ratios for Predefined Adverse Events and Death among Patients Who Received the Assigned Treatment.*

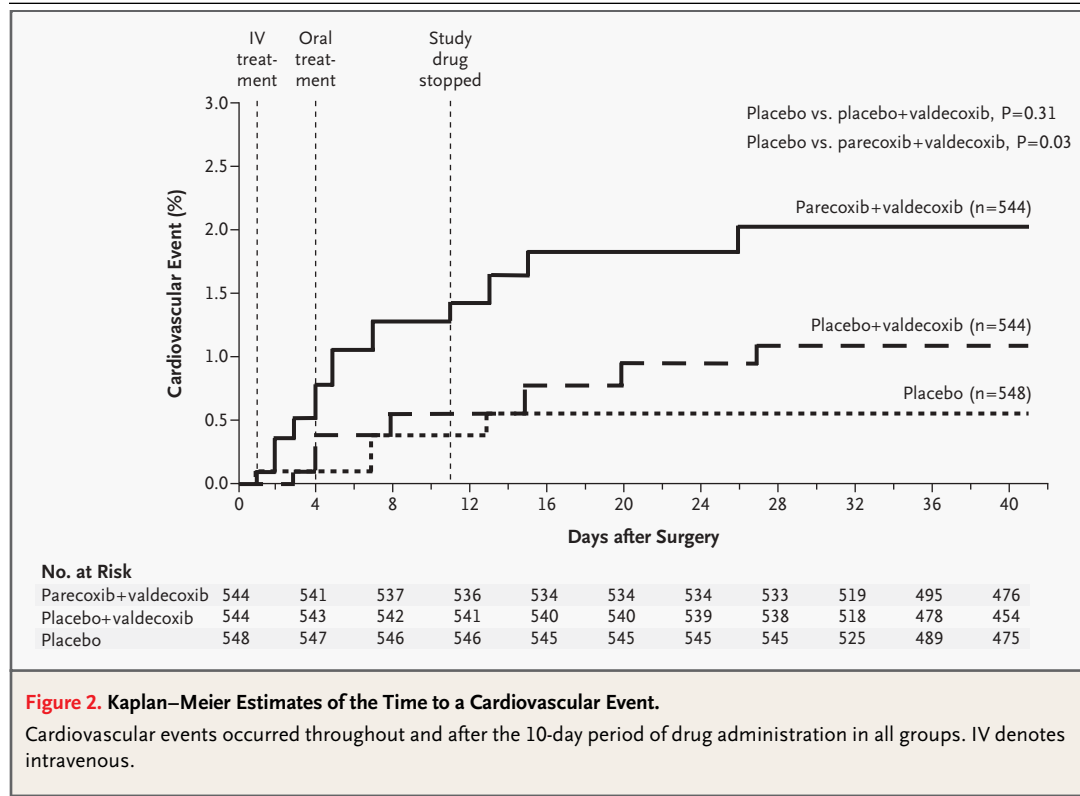
| Adverse Event | Placebo (N=548) | Placebo + Valdecoxib (N=544) | Parecoxib + Valdecoxib (N=544) | Both COX-2- Inhibitor Groups (N=1088) | Placebo vs. Placebo + Valdecoxib | | Placebo vs. Parecoxib + Valdecoxib | | Placebo vs. Both COX-2- Inhibitor Groups | |
|---|-------------------------------------|------------------------------------|--------------------------------------|--|--|------------|--|------------|--|------------|
| | | | | | Risk Ratio (95% CI) | P Value | Risk Ratio (95% CI) | P Value | Risk Ratio (95% CI) | P Value |
| | <i>number of patients (percent)</i> | | | | | | | | | |
| ≥1 Confirmed events | 22 (4.0) | 40 (7.4)† | 40 (7.4)† | 80 (7.4) | 1.9 (1.1–3.2) | 0.02 | 1.9 (1.1–3.2) | 0.02 | 1.9 (1.1–3.1) | 0.01 |
| Cardiovascular events | 3 (0.5) | 6 (1.1) | 11 (2.0)‡ | 17 (1.6) | 2.0 (0.5–8.1) | 0.31 | 3.7 (1.0–13.5) | 0.03 | 2.9 (0.8–9.9) | 0.08 |
| Myocardial infarction | 0 | 1 (0.2) | 1 (0.2) | 2 (0.2) | | | | | | |
| Cardiac arrest or sudden death from cardiac causes | 0 | 2 (0.4) | 3 (0.6) | 5 (0.5) | | | | | | |
| Probable or possible cardio- embolic stroke | 2 (0.4) | 1 (0.2) | 2 (0.4) | 3 (0.3) | | | | | | |
| Acute ischemic stroke | 0 | 1 (0.2) | 0 | 1 (0.1) | | | | | | |
| Transient ischemic attack | 0 | 0 | 3 (0.6) | 3 (0.3) | | | | | | |
| Vascular thrombosis or deep- vein thrombosis | 1 (0.2) | 0 | 0 | 0 | | | | | | |
| Pulmonary embolism | 1 (0.2) | 2 (0.4) | 2 (0.4) | 4 (0.4) | | | | | | |
| Renal failure or dysfunction§ | 3 (0.5) | 4 (0.7) | 7 (1.3) | 11 (1.0) | 1.3 (0.3–6.0) | 0.70 | 2.4(0.6–9.2) | 0.20 | 1.9 (0.5–6.7) | 0.34 |
| Upper gastrointestinal events | 2 (0.4) | 4 (0.7) | 6 (1.1) | 10 (0.9) | 2.0 (0.4–11.1) | 0.41 | 3.0 (0.6–15.2) | 0.15 | 2.5 (0.6–11.6) | 0.22 |
| Gastric or duodenal ulcer + hematemesis | 0 | 0 | 1 (0.2) | 1 (0.1) | | | | | | |
| Gastric or duodenal ulcer + melena | 0 | 0 | 2 (0.4) | 2 (0.2) | | | | | | |
| Documented gastric or duo- denal ulcer¶ | 2 (0.4) | 3 (0.6) | 3 (0.6) | 6 (0.6) | | | | | | |
| Perforation | 0 | 1 (0.2) | 0 | 1 (0.1) | | | | | | |
| Surgical-wound events | 16 (2.9) | 27 (5.0) | 20 (3.7) | 47 (4.3) | 1.7 (0.9–3.3) | 0.08 | 1.3 (0.7–2.5) | 0.48 | 1.5 (0.8–2.7) | 0.15 |
| Superficial incisional SSI | 12 (2.2) | 13 (2.4) | 8 (1.5) | 21 (1.9) | | | | | | |
| Deep incisional SSI | 1 (0.2) | 5 (0.9) | 5 (0.9) | 10 (0.9) | | | | | | |
| Organ or space SSI | 1 (0.2) | 1 (0.2) | 1 (0.2) | 2 (0.2) | | | | | | |
| Wound-healing complication | 2 (0.4) | 8 (1.5) | 6 (1.1) | 14 (1.3) | | | | | | |
| Death | 1 (0.2) | 3 (0.6) | 4 (0.7) | 7 (0.6) | 3.0 (0.3–29.3) | 0.31 | 4.1 (0.5–36.4) | 0.18 | 3.6 (0.4–29.1) | 0.20 |

* Some patients had more than one event. CI denotes confidence interval, and SSI surgical-site infection.
 † P=0.02 for the comparison with the placebo group.
 ‡ P=0.03 for the comparison with the placebo group.
 § Renal failure or dysfunction was the only type of renal event that occurred.
 ¶ Gastric or duodenal ulcer was documented by means of endoscopy.

during many cardiac surgical procedures involving cardiopulmonary bypass, results in ischemia-reperfusion injury of the myocardium.¹⁶ Myocardial tissue may be particularly susceptible to ischemia during and after CABG because of underlying coronary artery disease, perioperative hemodynamic insta-

bility, inadequate myocardial protection during bypass, coronary arterial embolization, or technical complications, such as spasm or kinking of the graft.

FitzGerald¹⁷ has suggested that an exaggerated thrombotic response in patients receiving selec-



tive COX-2 inhibitors may result from the ability of these drugs to inhibit the production of prostacyclin without affecting the production of thromboxane A₂, which is mediated by cyclooxygenase-1 (COX-1). Prostacyclin, the predominant cyclooxygenase product in endothelium, inhibits platelet aggregation, prevents the proliferation of vascular smooth-muscle cells in vitro, and causes vasodilatation. Thromboxane A₂, on the other hand, is the chief COX-1–mediated product of platelets and causes platelet aggregation, vasoconstriction, and vascular proliferation.

Cardiopulmonary bypass increases the levels of both prostacyclin and thromboxane A₂.^{18,19} However, administration of aspirin, as in our study, theoretically inhibits the formation of thromboxane by platelets. Low-dose aspirin prevents myocardial infarction and stroke,²⁰ and Mangano²¹ showed that postoperative administration of aspirin is associated with a reduced risk of death and cardiovascular and cerebrovascular ischemic complications after CABG requiring cardiopulmonary bypass. Although our study protocol required the administration of 75 to 325 mg of aspirin daily, resistance of platelets to aspirin is known to occur after CABG.²² These

aspirin doses, administered concurrently with a selective COX-2 inhibitor after CABG, may have been insufficient to block the formation of thromboxane by platelets in some patients.²³ Also, 7 of the 20 thromboembolic events (35.0 percent) occurred at least two days after all study medications had been discontinued. Another factor may be thrombocytosis, which is common within two weeks after surgery.²⁴ In clinical conditions of enhanced platelet regeneration, the prevalence of COX-2–dependent synthesis of thromboxane may be increased.²⁵

In the previous CABG study, sternal-wound infections and healing complications occurred more often among patients receiving parecoxib and valdecoxib than among those receiving placebo (3.2 percent vs. 0 percent, P=0.04).⁶ Although sternal-wound complications and all wound complications were more frequent among patients receiving parecoxib alone or with valdecoxib in our study, the difference fell short of statistical significance. Because the COX-2 enzyme mediates prostaglandin synthesis, inhibiting this enzyme might impede reparative inflammatory responses. Also, the analgesic and antipyretic effects of parecoxib and valdecoxib may have delayed the detection of an incipient ster-

nal-wound infection. Furthermore, in patients undergoing CABG with cardiopulmonary bypass, the increased incidence of serious adverse events, particularly thromboembolic events, clearly outweighs any analgesic benefit of these agents.

Recent data have shown that patients receiving other selective COX-2 inhibitors to prevent colorectal cancer have a higher incidence of serious arterial thromboembolic events than do patients receiving placebo.^{17,26} In view of all these findings, this study, and other current data,^{27,28} selective COX-2 inhibitors should be avoided in patients undergoing CABG. This caution should probably be extended to patients undergoing vascular pro-

cedures for atherosclerotic disease, although this population has not been studied.

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Dr. Nussmeier reports having served as a consultant for Pfizer and an advisory-board member for Pfizer and Novartis and having received lecture fees from Pfizer on two occasions. Dr. Whelton reports having received advisory fees from TAP Pharmaceuticals, Pfizer, GlaxoSmithKline, and Eyetech Pharmaceuticals; lecture fees from Pfizer; and consulting fees from Eyetech Pharmaceuticals. Drs. Brown and Verburg are employees of Pfizer and report owning equity and stock options in Pfizer. Dr. Langford reports having received grant support and lecture fees from Pfizer and having served on advisory boards for Pfizer and Novartis. Drs. Hoeft, Parlow, and Boyce report having received funds from Pfizer to carry out research related to this trial.

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APPENDIX

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