

ORIGINAL ARTICLE

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

Nancy A. Nussmeier, M.D., Andrew A. Whelton, M.D., Mark T. Brown, M.D., Richard M. Langford, F.R.C.A., Andreas Hoeft, M.D., Joel L. Parlow, M.D., Steven W. Boyce, M.D., and Kenneth M. Verburg, Ph.D.

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.

From the Texas Heart Institute at St. Luke's Episcopal Hospital, Houston (N.A.N.); Universal Clinical Research Center and Johns Hopkins University School of Medicine, Baltimore (A.A.W.); Pfizer, Global Research and Development, Ann Arbor, Mich. (M.T.B., K.M.V.); St. Bartholomew's Hospital, London (R.M.L.); the Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany (A.H.); Queen's University and Kingston General Hospital, Kingston, Ont., Canada (J.L.P.); and Washington Hospital Center, Washington, D.C. (S.W.B.). Address reprint requests to Dr. Nussmeier at the Texas Heart Institute at St. Luke's Episcopal Hospital, P.O. Box 20345, MC 1-226, Houston, TX 77225-0345, or at nnussmeier@heart.thi.tmc.edu.

This article was published at www.nejm.org on February 15, 2005.

N Engl J Med 2005;352:1081-91.

Copyright © 2005 Massachusetts Medical Society.

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

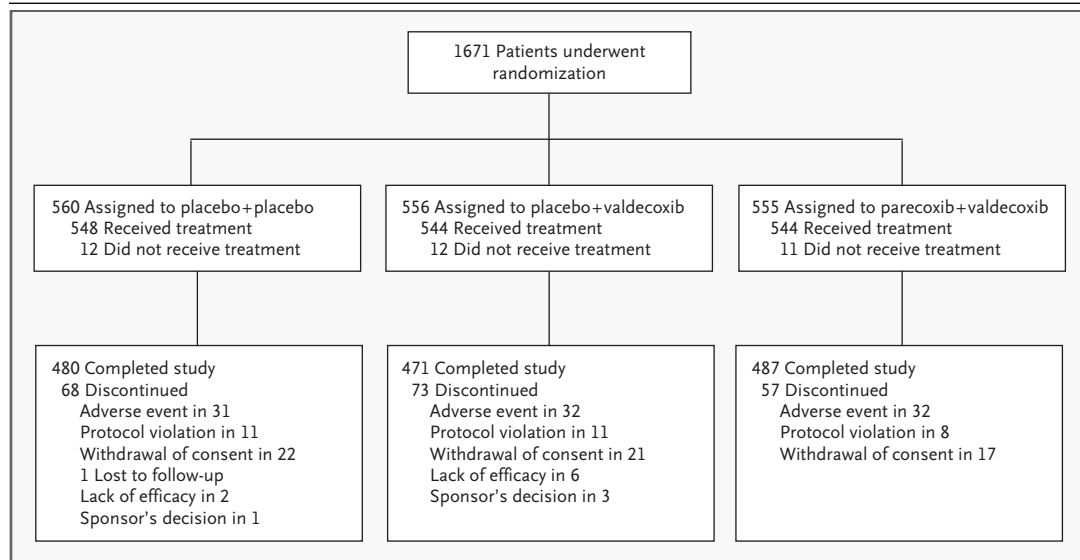


Figure 1. Enrollment and Outcome.

Patients who discontinued the study were included in all analyses. All decisions about discontinuation were made by the primary investigator, except for those noted as the sponsor's decision (made while study-group assignment was still blinded) in the case of four patients (e.g., because of failure to comply with the treatment regimen after discharge from the hospital).

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.*

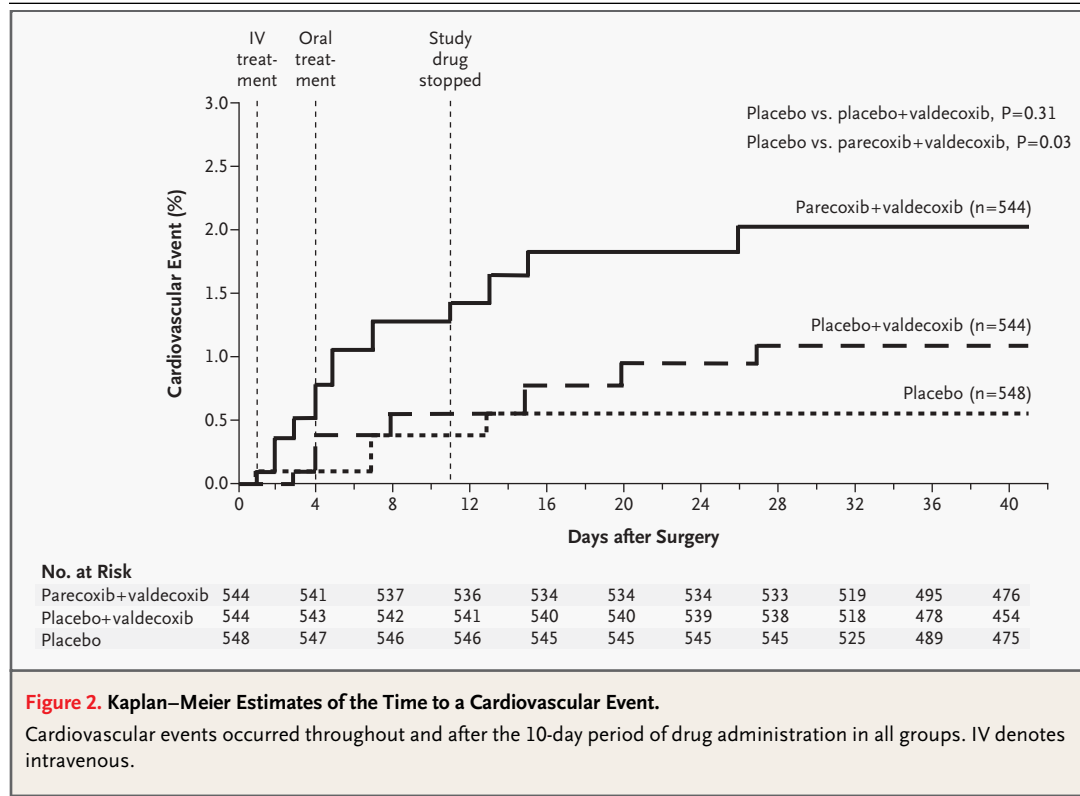
Adverse Event	Placebo (N=548)	Placebo + Valdecoxib (N=544)	Parecoxib + Valdecoxib (N=544)	Both COX-2- Inhibitor Groups (N=1088)	Placebo vs. Placebo + Valdecoxib		Placebo vs. Parecoxib + Valdecoxib		Placebo vs. Both COX-2- Inhibitor Groups	
					Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value	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.

Supported in part by Pharmacia and Pfizer.

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.

We are indebted to William K. Vaughn, Ph.D., for providing statistical support and to Stephen N. Palmer, Ph.D., E.L.S., for editorial assistance.

APPENDIX

The following persons and institutions participated in the CABG surgery study: Investigators: Academisch Ziekenhuis-Vrije Universiteit Brussel, Brussels — M. Diltor; Akademiska Sjukhuset, Uppsala, Sweden — H. Tyden; Allegheny General Hospital, Pittsburgh — T.A. Gasiar; Allegheny Pain Management, Altoona Hospital, Altoona, Pa. — M. Drass; Amarillo Heart Clinical Research Institute, Amarillo, Tex. — E. Rivera; Anaheim Memorial Medical Center, Anaheim, Calif. — H. Gogia; Arkansas Institute for Research and Education, Fayetteville — J. Weiss; Army's Center for Cardiovascular Diseases, Bucharest — I. Tintoiu; Av Diaz Velez, Buenos Aires — M. Litvak; Baylor College of Medicine, Houston — F. Masud; Baylor Medical Center at Irving, Irving, Tex. — J. Overbeck; Beth Israel Deaconess Medical Center, Boston — F. Sellke; Bikur Cholim Medical Center, Jerusalem — E. Deviri; Brevard Cardiothoracic Surgeons, Melbourne, Fla. — M. Malias; Cardiac Surgical Associates, Clearwater, Fla. — J. Pruitt; Cardiosurgery, Nemoenice Ceske Budejovice, Czech Republic — D. Cocek; Cardiosurgery, Nemoenice na Homolce, Prague — P. Krivacek; Cardiothoracic Centre, Liverpool, United Kingdom — J. Murphy; Cardiovascular Associates of Augusta, Augusta, Ga. — A. Chandler; Cardiovascular Surgery Clinic, Memphis, Tenn. — H. Garrett; Catharina Hospital, Eindhoven, the Netherlands — J. Schonberger; Centro Cardiologico Fondazione, Milan, Italy — A. Parolari; Centro Medico Nacional 20 de Noviembre, Mexico City — A. Castro; Christian-Albrechts-Universitaet, Kiel, Germany — J. Scholz; Centre Hospitalier Universitaire Liege, Liege, Belgium — M. Lamy; CHUS Hospital Fleurimont, Fleurimont, Que., Canada — M. Colas; Clinical Emergency Floreasca Hospital, Bucharest — S. Bradisteanu; Heart and Vascular Clinic of Northern Colorado, Fort Collins, Colo. — W. Miller; CMN SXXI IMSS-Hospital de Cardiología, Mexico City — G. Careaga; Col. Toriello Guerra C.P., Mexico City — E. Uruchurtu; Constituyentes, Buenos Aires — D. Nul; Crescent Clinical Research, Pensacola, Fla. — M. Mancao; CV Surgical Associates, Salisbury, Md. — J. Todd; Queens University and Kingston General Hospital, Kingston, Ont., Canada — J. Parlow; Bern University Hospital, Bern, Switzerland — F. Immer; Ospedale Cisanello-AOP-Pisana, Pisa, Italy — M. Mariani; Discovery Alliance, Charleston, S.C. — M. Edwards; Discovery Alliance, Hudson, Fla. — R. Sharma, R. Waters; Discovery Alliance, Mobile, Ala. — W. Higgs; Discovery Alliance, Pensacola, Fla. — S. Myers; Emory University Hospital, Atlanta — J. Ramsay; Feiringklinikken Feiring Heart Clinic, Feiring, Norway — T. Veel; FHS Research Center, Tacoma, Wash. — G. Johnston; Fundacion Cardio-Infantil, Bogota, Colombia — I. Franco; Fundacion Cardiovascular Del Oriente, Floridablanca, Colombia — O. Gomezese; Fundacion Clinica Shaio, Bogota, Colombia — R. Buitrago; Fundacion Valle de Lili, Cali, Colombia — M. Villegas; Amphia Hospital, Breda, the Netherlands — P. Rosseel; General University Hospital, Prague — J. Linder; Georg-August-Universitaet, Goettingen, Germany — D. Kettler; Hadassah Ein Kerem Medical Center, Jerusalem — A. Elami; Health Science Centre, Winnipeg, Man., Canada — P. Duke; Henry Ford Hospital, Detroit — R. Brewer; Hopital Erasme, Brussels — D. Schmartz; Hospital Alemán, Buenos Aires — J. Lopez; Hospital Clinico Universitario de Valencia, Valencia, Spain — J. Juste; Hospital de Bellvitge Ciudad Sanitaria L'Hospitalet de Llobregat, Barcelona, Spain — A. Matamala; Hospital Medica Sur, Mexico City — O. Gonzalez; Hospital Universitario La Paz, Madrid — A. Jimenez; ICCRS Policlinico, Pavia, Italy — M. Viganò; IKEM, Prague — J. Pirk; Indiana/Ohio Heart, Fort Wayne — J. Ladowski; Istituto di Clinica Medica Generale e Terapia Medica I, Florence, Italy — G. Gensini; Istituto Integral Denton Cooley, Buenos Aires — G. Bortman; Institutul de Boli Cardiovasculare Timisoara, Timisoara, Romania — S. Dragulescu; INTEGRIS Baptist Medical Center, Oklahoma City — J. Anderson; Jacksonville Cardiovascular Clinic, Jacksonville, Fla. — L. Lohrbauer; Jacksonville Center for Clinical Research, Jacksonville, Fla. — C. Cousar; Johannesburg, South Africa — A. Keene; John Radcliffe Hospital, Oxford, United Kingdom — R. Pillai; Juan Badiano No. 1 Col Seccion, Mexico City — P. Luna; Kaiser Permanente Medical Center, San Francisco — G. Roach; Kaplan Medical Center, Rehovot, Israel — G. Bregman; Karolinska Hospital, Stockholm — H. Jonsson; Katedra Anestezjologii i Intensywnej Terapii, Warsaw — R. Szulc; Keck School of Medicine of the University of Southern California, Los Angeles — P. Lumb; Klinika Kardiologii am w Warszawie, Warsaw — K. Suwalski; Klinika Kardiologii, Szczecin, Poland — S. Wiechowksi; Klinikum Kassel, Kassel, Germany — A. Fiehn; Kuopio University Hospital, Kuopio, Finland — P. Lahtinen; L'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain — H. Litvan; Legacy Clinical Research and Technology Center, Portland, Oreg. — J. Lemmer; London Health Services Centre, London, Ont., Canada — F. Ralley; Mater Misericordiae Hospital, Dublin — B. Marsh; Medical University of South Carolina, Charleston — F. Spinale; Mercy General Health Partners, Muskegon, Mich. — T. Boeve; Michael E. DeBakey Veterans Affairs Medical Center, Houston — S. Saleh-Shenaq; Mid-Atlantic Cardiovascular Associates, Towson, Md. — J. Laschinger; Monash Medical Centre, Clayton, Australia — A. Tucker; Montreal Heart Institute, Montreal — R. Martineau; Mount Auburn Hospital, Cambridge, Mass. — S. Tam; Mount Sinai Medical Center, New York — D. Bronheim; National Heart Centre, Singapore — Y. Chua; Nicolae Stanciu Heart Institute, Cluj-Napoca, Romania — R. Capalneau; North Ohio Heart Center, Sandusky — W. McGuinn; Northern California Medical Associates, Santa Rosa — P. Coleman; NuLife Clinical Research, Anaheim, Calif. — P. Wadhwa; Odense Universitetshospital, Odense, Denmark — L. Andersen; Oklahoma Heart Institute, Tulsa — W. Leimbach, Jr.; Orange County Heart Institute and Research Center, Orange, Calif. — D. Pan; Oulu University Hospital, Oulu, Finland — P. Laurila; Panorama Medi Clinic, Parow, Western Cape, South Africa — E. Vermaak; Pretoria Academic Hospital, Pretoria, Gauteng, South Africa — D. Du Plessis; Pretoria Heart Hospi-

tal, Pretoria, Gauteng, South Africa — J. Verster; Queen Elizabeth II Health Sciences Centre, Halifax, N.S., Canada — R. Hall; Queen's University, Kingston, Ont., Canada — B. Milne; Ramat Marpeh Medical Center, Petah Tikva, Israel — L. Priscu; Rambam Medical Center, Haifa, Israel — T. Adler; Regina General Hospital, Regina, Sask., Canada — S. Korkola; Research Institute of Transplantation and Artificial Organs of MoH, Moscow — I. Kozlov; Rigshospitalet, Copenhagen — P. Olsen; Royal University Hospital, Saskatoon, Sask., Canada — W. McKay; Royal Victoria Hospital, Montreal — B. De Varennes; Ruprecht-Karls-Universitaet, Universitaetsklinik fuer Anaesthesiologie, Heidelberg, Germany — E. Martin; Russian Research Center of Surgery, Moscow — A. Eremenko; RWTH Aachen Klinik fuer Anaesthesiologie, Aachen, Germany — W. Buhre; Rx Trials, Silver Spring, Md. — J. Armitage, S. Boyce, P. Cho, E. Lefrak, A. Qazi; Sacramento Heart and Vascular Medical Associates, Sacramento, Calif. — D. Roberts; Sarasota Memorial Health Care System Clinical Research Center, Sarasota, Fla. — C. Lewis; Sentara Norfolk General Hospital, Norfolk, Va. — G. Barnhart; Shaare Zedek Medical Center, Jerusalem — D. Bitran; Sheba Medical Center, Tel Hashomer, Israel — J. Lavee; Slovak Institute of Heart and Vascular Diseases, Bratislava, Slovakia — I. Olejarova; Hopitaux Universitaires de Geneve, Geneva — J. Romand; Soroka Medical Center, Beer Sheva, Israel — A. Appelbaum; Sourasky Tel-Aviv Medical Center, Tel Aviv — G. Uretzky; South Australian Cardiac Research, Ashford, Australia — J. Knight; St. Andrew's Place, Spring Hill, Australia — T. Mau; St. Augustine's Hospital, Berea, South Africa — S. Akoojee; St. Bartholomew's Hospital, London — R. Langford; St. James Hospital, Dublin — T. Ryan; St. Paul's Hospital, Vancouver, B.C., Canada — C. Cole; St. Thomas Hospital, London — R. Feneck; Stanford Medical Center, Stanford, Calif. — C. Mangano; Sterling Research Group, Cincinnati — E. Roth; Sunnybrook and Women's College Health Sciences Centre, Toronto — J. Kay; Szpital Kliniczny AM-Klinika Kardiologii, Bialystok, Poland — R. Jackowski; Texas Heart Institute/St. Luke's Episcopal Hospital, Houston — C. Collard; Dayton Heart Center, Dayton, Ohio — T. Markus; James Cook University Hospital, Middlesbrough, United Kingdom — J. Park; Lady Davis Carmel Medical Center, Haifa, Israel — J. Gurevitch; Lindner Clinical Trial Center, Cincinnati — S. Vester; Royal Infirmary of Edinburgh, Edinburgh — R. Alston; Toronto Hospital, Toronto — J. Karski; Western Pennsylvania Hospital, Pittsburgh — J. Grass; Thoraskliniken Universitetssjukhuset, Orebro, Sweden — M. Vidlund; Turku University Central Hospital, Turku, Finland — T. Savunen; UCLA Medical Center, Los Angeles — J. Jah; Jagiellonian University, Krakow, Poland — J. Sadowski; Unitas Hospital, Pretoria, South Africa — W. Mohr; Universitaet Bonn, Klinik und Poliklinik fuer Anaesthesiologie und spezielle Intensivmedizin, Bonn, Germany — A. Hoefl; Universitaetsklinik fuer Anaesthesiologie, Gefaesschirurgie, Graz, Austria — G. Rumpold-Seitlinger; Universitaetsklinikum Giessen, Giessen, Germany — G. Hempelmann; Universitaetsklinikum Grosshadern, Munich, Germany — E. Ott; Universitaetsklinikum Hamburg-Eppendorf Klinik und Poliklinik fuer Anaesthesiologie, Hamburg, Germany — J. Esch; Universitaetsklinikum Muenster Anaesthesiologie, Muenster, Germany — H. Van Aken; Universitaet Ziekenhuis Antwerpen, Edegem, Belgium — R. De Paep; University Community Hospital, Tampa, Fla. — M. Bloom; University Hospital Kralovske Vinohrady, Prague — Z. Straka; University Hospital Motol, Prague — J. Vojacek; University of Alberta Hospital, Edmonton, Canada — B. Finegan; University of Arizona, Tucson — P. Lichtenthal; University of California San Francisco, San Francisco — I. Russell; University of Iowa Hospitals and Clinics, Iowa City — J. Everett; University of Kansas Medical Center, Kansas City — P. Hild; University of North Texas Health Science Center at Fort Worth, Fort Worth — A. Olivencia-Yurvati; University of Texas Medical School, Houston — E. Pivalizza; University of the Free State, Bloemfontein, South Africa — A. Kachelhoffer; University of Vermont, Burlington — J. Rathmell; University of Wisconsin Medical School, Madison — R. Love; Vancouver General Hospital, Vancouver, B.C., Canada — H. Umedaly; Viahealth Rochester General Hospital, Rochester, N.Y. — R. Kirshner; Vychodoslovensky Ustav Srdcovych Chorob, Kosice, Slovakia — M. Hulman; Weezenlanden Hospital, Zolle, the Netherlands — A. Nierich; Wilgers Hospital, Pretoria, Gauteng, South Africa — M. Versace; William Beaumont Hospital, Royal Oak, Mich. — C. Hatrick; Wisconsin Center for Clinical Research, Milwaukee — C. Lanzarotti; Wolfson Medical Center, Holon, Israel — B. Medalion; Yale New Haven Hospital, New Haven, Conn. — S. Garwood; Ziekenhuis Oost-Limburg-Campus, Sint Jan, Belgium — R. Heylen; End-Point Committee: P. Barash, J. Brinker, G. Gerstenblith, J. Goldstein, P. Gorelick, M. Kelly, P. Waymack, A. Whelton (chair); Data and Safety Monitoring Board: G. Faich (chair), P. Hsu, M. Newman, W. White, D. Berry.

REFERENCES

- Gilron I, Milne B, Hong M. Cyclooxygenase-2 inhibitors in postoperative pain management: current evidence and future directions. *Anesthesiology* 2003;99:1198-208.
- Daniels SE, Grossman EH, Kuss ME, Talwalker S, Hubbard RC. A double-blind, randomized comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. *Clin Ther* 2001;23:1018-31.
- Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. *Br J Anaesth* 2003;90:746-9.
- Malan TP Jr, Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC. Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. *Anesthesiology* 2003;98:950-6.
- Joshi GP, Viscusi ER, Gan TJ, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral COX-2 specific inhibitor. *Anesth Analg* 2004;98:336-42.
- Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003;125:1481-92.
- Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
- Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001;104:2280-8.
- Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;360:1071-3.
- Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 2000;36:970-1062. [Erratum, *J Am Coll Cardiol* 2001;38:294-5.]
- Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. *Stroke* 1993;24:35-41.
- Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med* 1998;128:194-203.
- Konstantopoulos K, Grotta JC, Sills C, Wu KK, Hellums JD. Shear-induced platelet aggregation in normal subjects and stroke patients. *Thromb Haemost* 1995;74:1329-34.
- Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest* 1997;112:676-92.
- Davies GC, Sobel M, Salzman EW. Elevated plasma fibrinolytic activity and thromboxane B2 levels during cardiopulmonary bypass. *Circulation* 1980;61:808-14.

16. Park JL, Lucchesi BR. Mechanisms of myocardial reperfusion injury. *Ann Thorac Surg* 1999;68:1905-12.
17. FitzGerald GA. Coxibs and cardiovascular disease. *N Engl J Med* 2004;351:1709-11.
18. Faymonville ME, Deby-Dupont G, Larbuisson R, et al. Prostaglandin E2, prostacyclin, and thromboxane changes during nonpulsatile cardiopulmonary bypass in humans. *J Thorac Cardiovasc Surg* 1986;91:858-66.
19. Watkins WD, Peterson MB, Kong DL, et al. Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow. *J Thorac Cardiovasc Surg* 1982;84:250-6.
20. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
21. Mangano DT. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002;347:1309-17.
22. Zimmerman N, Kienzle P, Weber A-A, et al. Aspirin resistance after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2001;121:982-4.
23. Zimmerman N, Wenk A, Kim U, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation* 2003;108:542-7.
24. Möhnle P, Schwann NM, Vaughn WK, et al. Perturbations in laboratory values after coronary artery bypass graft surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2005;19:19-25.
25. Rocca B, Secchiero P, Ciabattini G, et al. Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed platelets. *Proc Natl Acad Sci U S A* 2002;99:7634-9.
26. Couzin J. Halt of Celebrex study threatens drug's future, other trials. *Science* 2004;306:2170.
27. Solomon SD, McMurray JVV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.
28. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.

Copyright © 2005 Massachusetts Medical Society.

CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.