

cebo groups in the rate of the primary end point was driven primarily by differences in the patency of the infarct-related artery. This should not be surprising, since our trial was designed to test whether clopidogrel would improve patency.¹ As we stated, death or myocardial infarction before angiography was included as a necessary surrogate for failed reperfusion or reocclusion. Multiple studies have validated the association between the TIMI flow grade and clinical outcomes.^{2,3} To that end, in CLARITY-TIMI 28 we demonstrated that clopidogrel not only improved patency, but also significantly reduced the odds of death from cardiovascular causes, recurrent myocardial infarction, or urgent revascularization through 30 days. Furthermore, we direct the attention of Chua and colleagues to the results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study 2,⁴ which were presented alongside those of CLARITY-TIMI 28 findings and which showed that in nearly 46,000 patients with acute myocardial infarction, the addition of clopidogrel resulted in a significant, 7 percent reduction in mortality.⁵ Thus, the angiographic and clinical data are quite consistent in in-

dicating that clopidogrel improves the rate of patency of the infarct-related artery and reduces the rate of adverse clinical events, including death.

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1. Sabatine MS, McCabe CH, Gibson CM, Cannon CP. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial. *Am Heart J* 2005;149:227-33.
2. Dalen JE, Gore JM, Braunwald E, et al. Six- and twelve-month follow-up of the phase I Thrombolysis in Myocardial Infarction (TIMI) trial. *Am J Cardiol* 1988;62:179-85.
3. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-22.
4. Second Chinese Cardiac Study (CCS-2) Collaborative Group. Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. *J Cardiovasc Risk* 2000;7:435-41.
5. Chen Z. COMMIT/CCS-2, 54th Scientific Session of the American College of Cardiology, Orlando, Fla., March 9, 2005.

Cardiovascular Risk Associated with Celecoxib

TO THE EDITOR: Solomon et al., for the Adenoma Prevention with Celecoxib (APC) Study Investigators (March 17 issue),¹ reported an increase in cardiovascular events associated with the use of celecoxib, and two accompanying editorials^{2,3} supported the conclusion of a class effect for cyclooxygenase-2 (COX-2) inhibitors. Although abundant and concordant data from both randomized trials and observational studies show that the use of rofecoxib is associated with cardiovascular risk, the literature concerning the risk with the use of celecoxib is more heterogeneous. Numerous observational studies⁴⁻⁸ have failed to identify an increased risk with celecoxib. Moreover, among randomized trials of celecoxib with a minimum of 12 months of follow-up, the totality of the evidence of an increased cardiovascular risk is again far from conclusive (Fig. 1, facing page). Caution in prescribing any COX-2 inhibitor, including celecoxib, is mandatory, but publication of the results of the APC trial without insistence on a more thorough discussion of other, similar trials may present a biased picture. Although an increased cardiovascular risk associated

with the use of celecoxib is certainly possible, particularly in the incompletely studied high-risk population, this risk has not been established with the conviction implied in the *Journal*.

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1. Solomon DS, McMurray JJV, 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.
2. Drazen JM. COX-2 inhibitors — a lesson in unexpected problems. *N Engl J Med* 2005;352:1131-2.
3. Psaty BM, Furberg CD. COX-2 inhibitors — lessons in drug safety. *N Engl J Med* 2005;352:1133-5.
4. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclooxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365:475-81.
5. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005;142:481-9.
6. Shaya FT, Blume SW, Blanchette CM, Weir MR, Mullins CD. Selective cyclooxygenase-2 inhibition and cardiovascular effects: an observational study of a Medicaid population. *Arch Intern Med* 2005;165:181-6.
7. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship be-

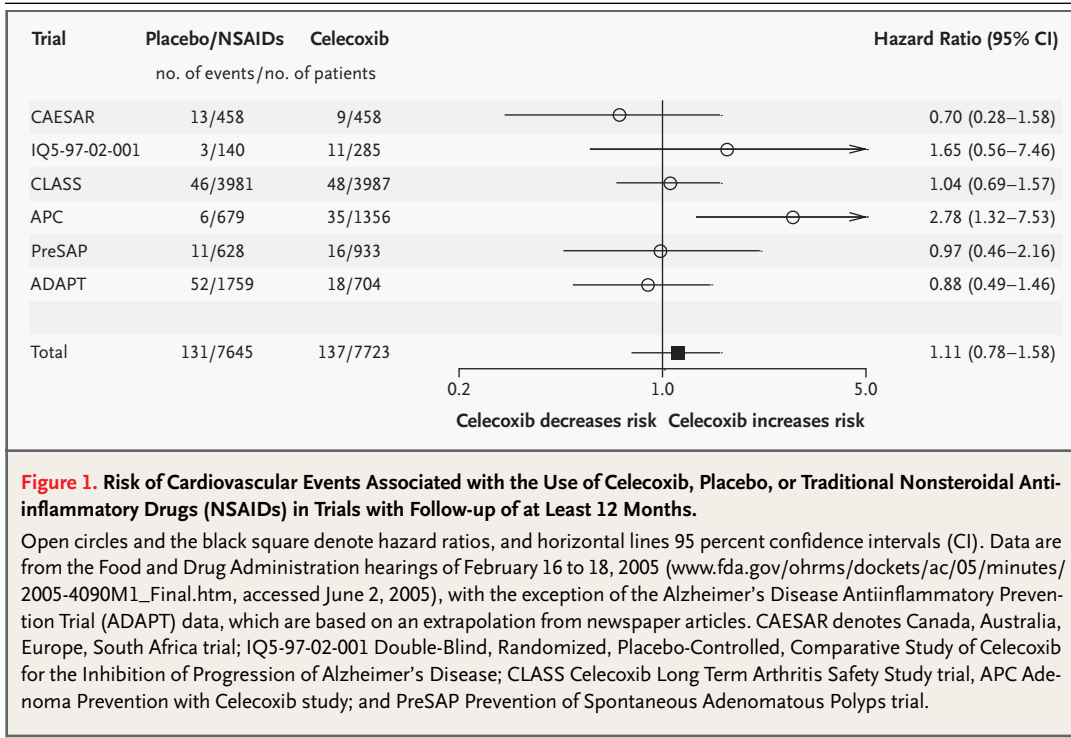


Figure 1. Risk of Cardiovascular Events Associated with the Use of Celecoxib, Placebo, or Traditional Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Trials with Follow-up of at Least 12 Months.

Open circles and the black square denote hazard ratios, and horizontal lines 95 percent confidence intervals (CI). Data are from the Food and Drug Administration hearings of February 16 to 18, 2005 (www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4090M1_Final.htm, accessed June 2, 2005), with the exception of the Alzheimer's Disease Antiinflammatory Prevention Trial (ADAPT) data, which are based on an extrapolation from newspaper articles. CAESAR denotes Canada, Australia, Europe, South Africa trial; IQ5-97-02-001 Double-Blind, Randomized, Placebo-Controlled, Comparative Study of Celecoxib for the Inhibition of Progression of Alzheimer's Disease; CLASS Celecoxib Long Term Arthritis Safety Study trial, APC Adenoma Prevention with Celecoxib study; and PreSAP Prevention of Spontaneous Adenomatous Polyps trial.

tween selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004;109:2068-73.

8. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *Lancet* 2002;359:118-23.

THE AUTHORS REPLY: Most data on the cardiovascular risk associated with celecoxib have come from observational studies or short-term randomized trials. Discrepant findings between observational studies and randomized trials¹⁻³ underscore the potential limitations of observational data. A modest "signal" of harm may also be obscured by misclassification of end points that are not carefully adjudicated. The heterogeneity of the trials analyzed by Dr. Brophy—including differences in study design, populations, length of follow-up, dosing, and ascertainment of outcomes—makes interpretation of these results challenging. Only three studies cited by Dr. Brophy were placebo-controlled—APC, PreSAP, and IQ5-97-02-001—and all showed hazard ratios above 1 (the data presented for PreSAP were preliminary). The conclusions of our study were tempered by the small number of events and wide confidence intervals; however, the internal consistency of the data—increased hazards for all cardiovascular end points and a dose-response relationship—along with similar findings from trials

of other drugs in this class support our conclusions. Moreover, a consistent safety concern should not require the same degree of statistical conviction as a proof of benefit.

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1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
2. Smigel K. Beta carotene fails to prevent cancer in two major studies; CARET intervention stopped. *J Natl Cancer Inst* 1996;88:145.
3. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005;293:1338-47.

THE EDITORIALISTS REPLY: We agree that the literature concerning celecoxib is heterogeneous. One

source of the heterogeneity is discrepancies in the numbers of events reported for celecoxib across various versions of the same trial. For instance, the original CLASS trial publication included only the first six months of events.¹ Brophy's figure lists 46 and 48 events for one year; but the report by White and colleagues lists 49 and 52 events.² In the Alzheimer's study (IQ5-97-02-001), celecoxib is weakly associated with an increase in cardiovascular risk (odds ratio, 1.65; 95 percent confidence interval, 0.56 to 7.46), but the unpublished report indicates that "a statistically significant difference favoring placebo in adverse events was observed for certain cardiovascular-risk-related body system terms."³ Events in some but not all of the trials were adjudicated by independent committees. Brophy's analysis pools two different comparison groups, users of nonsteroidal antiinflammatory drugs and placebo groups. Timely publication and full reporting of

events would have enabled physicians and scientists to adequately assess the risks associated with celecoxib.

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1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* 2000;284:1247-55.
2. White WB, Faich G, Whelton A, et al. Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002;89:425-30.
3. Pfizer. A double-blind, randomized, placebo-controlled, comparative study of celecoxib (SC-58635) for the inhibition of progression of Alzheimer's disease: protocol IQ5-97-02-001. (Accessed June 2, 2005, at http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf.)

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

TO THE EDITOR: The cleverly designed and carefully conducted crossover trial reported by Gilron et al. (March 31 issue)¹ shows better control of neuropathic pain with the combination of morphine and gabapentin than with single agents or placebo. Although we admire the meticulousness of the investigators, we also marvel at the unusually rigid adherence of the majority of the patients to a demanding and complex drug regimen. We must conclude that this was a very select group of highly motivated and fastidious patients. It is likely that they had many more personality traits in common with one another than with the general population.

Given that an improvement in mood is associated with a reduction in the perception of pain severity, a finding again replicated in this study, it is likely that the response to any drug therapy is highly dependent on personality. This leads us to question whether this result can be applied to the rest of patients who have neuropathic pain. Further studies are needed to determine the effectiveness of this combination in clinical practice.

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1. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005;352:1324-34.

TO THE EDITOR: Gilron et al. report the superior efficacy of gabapentin and morphine combined in relieving neuropathic pain. Additional information might further elucidate their important findings.

First, was the neurologic assessment scored to fulfill minimal criteria for the diagnosis of diabetic peripheral neuropathy?^{1,2} In elderly patients, decreased or absent ankle reflexes alone are not diagnostic of neuropathy.³ Were peripheral pulses assessed, since peripheral vascular disease, which is common in diabetes, is associated with pain? Also, since glycemic control influences the intensity of pain, were additional measurements of glycosylated hemoglobin performed over the five months of the study?

Second, we were surprised that 40 percent of the patients with diabetes had not had any pain-relieving drugs prescribed previously. If these patients had milder pain, could this have influenced the results? Is first-line use of combination treatment in such cases necessary?

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Dr. Tesfaye reports having received consulting fees from Pfizer.

1. Scott LA, Tesfaye S. Measurement of somatic neuropathy for clinical practice and clinical trials. *Curr Diab Rep* 2001;1:208-15.
2. Report and recommendations of the San Antonio conference on diabetic neuropathy. *Diabetes Care* 1992;15:Suppl 3:1080-107.