

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.<sup>1</sup> 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.<sup>2,3</sup> 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,<sup>4</sup> 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.<sup>5</sup> 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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## Cardiovascular Risk Associated with Celecoxib

**TO THE EDITOR:** Solomon et al., for the Adenoma Prevention with Celecoxib (APC) Study Investigators (March 17 issue),<sup>1</sup> reported an increase in cardiovascular events associated with the use of celecoxib, and two accompanying editorials<sup>2,3</sup> 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 studies<sup>4-8</sup> 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*.

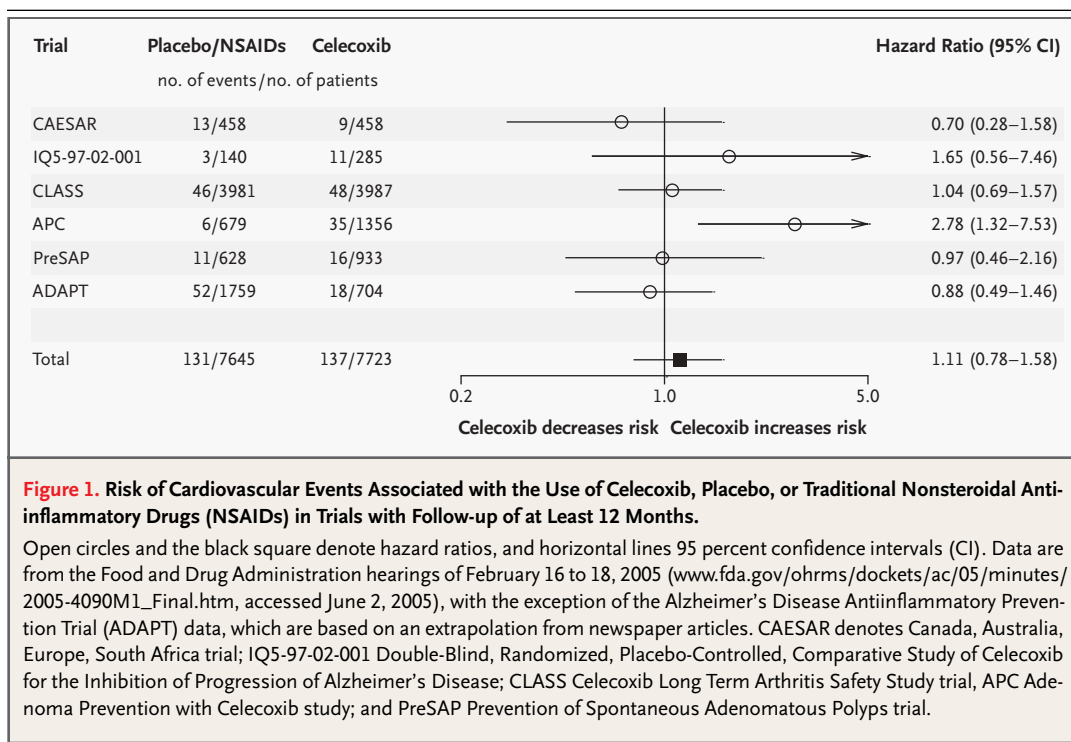
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**Figure 1. Risk of Cardiovascular Events Associated with the Use of Celecoxib, Placebo, or Traditional Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Trials with Follow-up of at Least 12 Months.**

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](http://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.

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**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 trials<sup>1-3</sup> 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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**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.<sup>1</sup> Brophy's figure lists 46 and 48 events for one year; but the report by White and colleagues lists 49 and 52 events.<sup>2</sup> 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."<sup>3</sup> 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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## 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)<sup>1</sup> 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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**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?<sup>1,2</sup> In elderly patients, decreased or absent ankle reflexes alone are not diagnostic of neuropathy.<sup>3</sup> 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.

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