Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors

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Atherosclerosis is a process with inflammatory features and selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. To define the cardiovascular effects of COX-2 inhibitors when used for arthritis and musculoskeletal pain in patients without coronary artery disease, we performed a MEDLINE search to identify all English-language articles on use of COX-2 inhibitors published between 1998 and February 2001. We also reviewed relevant submissions to the US Food and Drug Administration by pharmaceutical companies.

Our search yielded 2 major randomized trials, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR; 8076 patients) and the Celecoxib Long-term Arthritis Safety Study (CLASS; 8059 patients), as well as 2 smaller trials with approximately 1000 patients each. The results from VIGOR showed that the relative risk of developing a confirmed adjudicated thrombotic cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks) with rofecoxib treatment compared with naproxen was 2.38 (95% confidence interval, 1.39-4.00; *P*=.002). There was no significant difference in cardiovascular event (myocardial infarction, stroke, and death) rates between celecoxib and nonsteroidal anti-inflammatory agents in CLASS. The annualized myocardial infarction rates for COX-2 inhibitors in both VIGOR and CLASS were significantly higher than that in the placebo group of a recent meta-analysis of 23 407 patients in primary prevention trials (0.52%): 0.74% with rofecoxib (*P*=.04 compared with the placebo group of the meta-analysis) and 0.80% with celecoxib (*P*=.02 compared with the placebo group of the meta-analysis).

The available data raise a cautionary flag about the risk of cardiovascular events with COX-2 inhibitors. Further prospective trial evaluation may characterize and determine the magnitude of the risk.

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ASPIRIN AND NONSTEROIDAL anti-inflammatory agents (NSAIDs) have proven analgesic, anti-inflammatory, and antithrombotic properties but also have significant gastric toxicity. The gastrointestinal toxicity appears to be related to cyclooxygenase 1 (COX-1) inhibition.[1] In 1990, Fu et al[2] detected a novel COX protein in monocytes stimulated by interleukin, and a year later Kujubu et al[3] identified a gene with considerable homology to COX-1.

Identification of this COX-2 protein rekindled the efforts of the pharmaceutical industry to produce a safer analgesic and anti-inflammatory drug via selective inhibition of COX-2, and this class of agents was introduced in 1999. By October 2000, celecoxib and rofecoxib had sales exceeding $3 billion in the United States, and a prescription volume in excess of 100 million for the 12-month period ending in July 2000.[4]

The development of COX-2 inhibitors as anti-inflammatory agents without gastric toxicity is based on the premise that COX-1 predominates in the gastric mucosa and yields protective prostaglandins, whereas COX-2 is induced in inflammation and leads to pain, swelling, and discomfort. However, selective COX-2 inhibitors decrease vascular prostacyclin (PGI_2) production and may affect the balance between prothrombotic and antithrombotic eicosanoids.[5] Unlike the platelet inhibition afforded by COX-1 inhibitors, COX-2 inhibitors do not share this salutary antithrombotic property. In contrast, by decreasing vasodilatory and antiaggregatory PGI_2 production, COX-2 antagonists may tip the balance in favor of prothrombotic eicosanoids (eg, thromboxane A_2) and may

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lead to increased cardiovascular thrombotic events.[6] However, atherosclerosis is a process with inflammatory features[7] and selective COX-2 inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. Herein,we analyze the randomized trials that have been performed to determine whether COX-2 inhibitors are associated with a protective or hazardous effect on the risk of cardiovascular events.

METHODS

We used MEDLINE to identify all published, English-language, randomized, double-blind trials of COX-2 inhibitors from January 1998 to February 2001. Keywords used for our search included *COX-2*, *cyclooxygenase*, *rofecoxib*, and *celecoxib*. We also searched the World Wide Web using the same keywords. A number of studies[8-17] focused only on the gastrointestinal effects of COX-2 inhibitors and did not assess cardiovascular events, most likely because investigators were unaware of any cardiovascular adverse effects at that time. These studies were not included in our analysis because there was no reporting of cardiovascular adverse effects.

COX-2 inhibitors were approved in 1998 and there have been 2 major postmarketing multicenter trials with these agents. These include the Vioxx Gastrointestinal Outcomes Research study (VIGOR)[18] and the Celecoxib Arthritis Safety Study (CLASS).[19] We also reviewed cardiovascular event rates from Study 085 and Study 090, both submitted to the US Food and Drug Administration (FDA).[20] TABLE 1 summarizes the design of these trials. We also compared the annualized myocardial infarction (MI) rates in the placebo group of a recent meta-analysis of 4 aspirin primary prevention trials with MI rates in the VIGOR and CLASS trials.

An October 12, 2000, Adverse Events Reporting System search limited to the United States was conducted for rofecoxib and celecoxib using the following MedDRA terms: *central nervous system hemorrhages and cerebral accidents*, *coronary artery occlusion*, *coronary artery embolism*, *myocardial infarction*, *gastrointestinal arterial occlusion and infarction*, and *embolism, thrombosis, and stenosis*.[21]

Time-to-event analysis of cardiovascular events was performed based on Kaplan-Meier estimates of cumulative event incidences. The relative risk (RR) of rofecoxib with respect to naproxen was derived from an unstratified Cox model in which the number of events was at least 11; otherwise, RR is the ratio of rates and the *P* value was calculated from a discrete log-rank distribution. Event rates in the CLASS trial were expressed as percentages of patients, with end points. Frequency of MIs across the trials was compared using the Fisher exact test. Statistical analysis was performed using Statistica version 5.5 (StatSoft Inc, Tulsa, Okla).

Table 1. Trials of Cyclooxygenase Inhibitors*

Study, y	No.	Treatment Groups		
VIGOR,[18] 2000	8076	Rofecoxib 50 mg/d (n = 4047)	Naproxen 1000 mg/d (n = 4029)	NA
CLASS,[19] 2000	7968	Celecoxib 800 mg/d (n = 3987)	Ibuprofen 2400 mg/d (n = 1996)	Diclofenac 150 mg/d (n = 1985)
Study 085,[20] 2001	1042	Rofecoxib 12.5 mg/d (n = 424)	Nabumetone 1000 mg/d (n = 410)	Placebo (n = 208)
Study 090,[20] 2001	978	Rofecoxib 12.5 mg/d (n = 390)	Nabumetone 1000 mg/d (n = 392)	Placebo (n = 196)

*VIGOR indicates Vioxx Gastrointestinal Outcomes Research; CLASS, Celecoxib Arthritis Safety Study; and NA, not applicable.

RESULTS

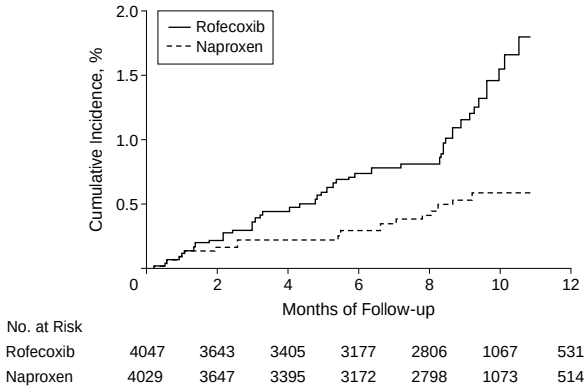
VIGOR Trial

The VIGOR trial[18] was a double-blind, randomized, stratified, parallel group trial of 8076 patients comparing the occurrence of gastrointestinal toxicity with rofecoxib (50 mg/d) or naproxen (1000 mg/d) during long-term treatment for patients with rheumatoid arthritis. Aspirin use was not permitted in the study. Although not fully published, cardiovascular event data from the VIGOR trial sponsor was recently submitted to the FDA.[22] The baseline characteristics between the treatment groups in the VIGOR trial demonstrated no meaningful or significant differences. Patients requiring aspirin for cardiac reasons were excluded from this trial.

Based on excessive cardiovascular adverse effects in one group in an interim analysis, the data and safety monitoring board recommended blinded adjudication of cardiovascular events.[22] Ninety-eight cases (65/4047 from the rofecoxib group, 33/4029 from the naproxen group) were sent for adjudication of vascular events. Of these, 45 patients (46 events) in the rofecoxib group and 20 patients (20 events) in the naproxen group were adjudicated to have serious thrombotic cardiovascular adverse events (MI, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks). Event-free survival analysis of these 66 patients showed that the RR (95% confidence interval [CI]) of developing a cardiovascular event in the rofecoxib treatment group was 2.38 (1.39-4.00), $P<.001$[22] (FIGURE 1).

A subgroup analysis was performed for patients classified as either "aspirin indicated" or "aspirin not indicated." In the VIGOR trial, aspirin-indicated patients were defined as those with past medical history of stroke, transient ischemic attack, MI, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions. Only 321 (3.9%) patients were aspirin-indicated patients (170 in the rofecoxib group; 151 in the naproxen group), because the need for aspirin was an exclusion criterion. The RR of developing serious cardiovascular events among aspirin-indicated patients between the rofecoxib group and the naproxen group was 4.89 (95% CI, 1.41-16.88), $P=.01$, and the RR for as-

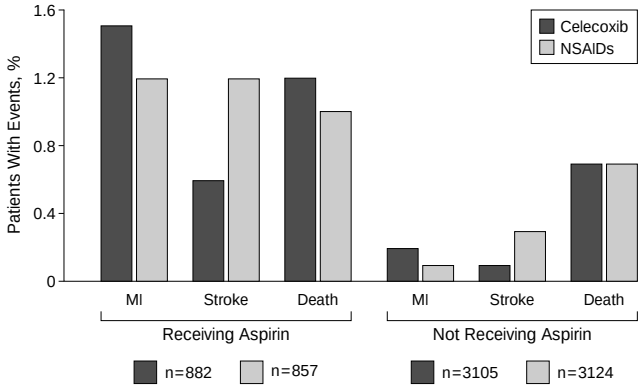
Figure 1. Time to Cardiovascular Adverse Event in the VIGOR Trial



No. at Risk							
Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514

Relative risk (95% confidence interval)=2.38 (1.39-4.00); $P<.001$. VIGOR indicates Vioxx Gastrointestinal Outcomes Research.

Figure 2. Incidence of MI, Stroke, and Death in the CLASS Trial, Stratified by Aspirin Use



MI indicates myocardial infarction; CLASS, Celecoxib Arthritis Safety Study; and NSAIDs, nonsteroidal anti-inflammatory drugs.

pirin not indicated patients was 1.89 (95% CI, 1.03-3.45), $P=.04$.[22] Of note, no patient in the aspirin indicated group sustained an MI.

If all cardiovascular events from the adverse event data sets that were termed "serious" in the FDA medical reviewer's opinion were compared, there were 111 patients in the rofecoxib group and 50 patients in the naproxen group with serious cardiovascular events. Event-free survival analysis showed the risk of serious cardiovascular events in the rofecoxib group was 2.2 times higher (95% CI, 1.62-3.21; $P<.001$) than in the naproxen group.[22]

CLASS Trial

CLASS was a double-blind, randomized controlled trial in which 8059 patients were randomized to receive 400 mg of celecoxib twice per day, 800 mg of ibuprofen 3 times per day, or 75 mg of diclofenac twice per day.[19] Aspirin use (<325 mg/d) was permitted in this study. Although not published, cardiovascular event data from the CLASS study submitted to the FDA were included in our review.[23] The CLASS trial with celecoxib demonstrated no significant difference in cardiovascular events compared with the NSAIDs. FIGURE 2 shows the thrombotic event rates in the CLASS trial. The event rates are stratified by patients receiving aspirin and those not receiving aspirin.

Study 085 and Study 090

Study 085 (N=1042) was a randomized, double-blind, parallel-group, placebo-controlled trial of the efficacy and safety of rofecoxib (12.5 mg/d) vs nabumetone (1000 mg/d) vs placebo after 6 weeks of treatment for osteoarthritis of the knee. Patients were allowed to take low-dose aspirin for cardioprotection.[20] There were 3 total cardiovascular events in this trial: 1 event (0.2%) in the rofecoxib group, 2 events (0.4%) in the nabumetone group, and no events in the placebo group.

Study 090 (N=978) was a randomized, placebo-controlled, parallel-group, double-blind trial of the efficacy and safety of rofecoxib (12.5 mg/d) vs nabumetone (1000 mg/d) vs placebo in patients with osteoarthritis of the knee. Low-dose aspirin for cardioprotection was also allowed in this study. Study 090 reported a total of 9 serious cardiovascular events: 6 (1.5%) events in the rofecoxib group, 2 (0.5 %) in the nabumetone group, and 1 (0.5%) in the placebo group.

Adverse Event Reporting System

An Adverse Event Reporting System search revealed 144 unduplicated thrombotic or embolic cases for celecoxib and 159 cases for rofecoxib.[21] Forty-two celecoxib cases and 60 rofecoxib cases were excluded for a lack of documented event or for hemorrhagic stroke in which the prothrombin time, partial thromboplastin time, or international normalized ratio was above the normal range; also excluded were secondhand reports with no confirmed diagnosis. Ninety-nine thrombotic or embolic events were attributed to rofecoxib and 102 cases to celecoxib. TABLE 2 summarizes the thrombotic events reported with each agent.

Comparison With Contemporary Meta-analysis

The meta-analysis of the US Physicians' Health Study, the UK Doctors Study, the Thrombosis Prevention Trial, and the Hypertension Optimal Treatment trials included 48 540 patients, of whom 25 133 were treated with aspirin and 23 407 were given placebo.[24] The annualized MI rate in the placebo group in this meta-analysis was 0.52%. The annualized MI rates for both the VIGOR and the CLASS trials were higher: 0.74% with rofecoxib ($P=.04$, compared with the placebo group of the meta-analysis) and 0.80% with celecoxib ($P=.02$, compared with the placebo group of the meta-analysis) (FIGURE 3).

COMMENT

Aspirin and NSAIDs inhibit prostaglandin synthesis via a cyclooxygenase enzyme. This action is the key to both their therapeutic and toxic effects. The COX-1 isoform is constitutively expressed in most cells, which results in the production of homeostatic prostaglandins that maintain gastrointestinal mucosal integrity and renal blood flow. The COX-1 isoform is also expressed in platelets and mediates production of thromboxane A_2, a potent platelet activator and aggregator. The COX-2 isoform produces prostaglandins at inflammatory sites as well as PGI_2, which is a vasodilator and inhibitor of platelet aggregation. Nonselective NSAIDs inhibit the production of both thromboxane and PGI_2. Selective COX-2 inhibitors have no effect on thromboxane A_2 production, but by decreasing PGI_2 production may tip the natural balance between prothrombotic thromboxane A_2 and antithrombotic PGI_2, potentially leading to an increase in thrombotic cardiovascular events.[25,26]

We reviewed the cardiovascular event rates in the 2 major trials with selective COX-2 inhibitors and in 2 smaller trials. The VIGOR trial demonstrated significantly increased risk of cardiovascular event rates with use of rofecoxib although the study enrolled patients who did not require aspirin for protection from ischemic events. Patients with angina, congestive heart failure, MI, coronary artery bypass graft surgery within 1 year, stroke or transient ischemic attacks within 2 years, and uncontrolled hypertension were excluded from this trial. However, these criteria can be viewed as too stringent, given data from trials that support more liberal use of aspirin for primary prevention.

The results of the VIGOR study can be explained by either a significant prothrombotic effect from rofecoxib or an antithrombotic effect from naproxen (or conceivably both). There are differential effects of NSAIDs and COX-2 inhibitors on ex vivo platelet aggregation to 1 mM arachidonic acid. Naproxen has significant antiplatelet effects, with mean platelet aggregation inhibition of 93% compared with platelet aggregation inhibition of 92% for those taking aspirin (81 mg).[22] Thus naproxen, but not ibuprofen (platelet aggregation of approximately 80%) or diclofenac (platelet aggregation of approximately 40%), resulted in a high level of platelet aggregation inhibition similar to that achieved with aspirin.[22] There is clinical evidence that flurbiprofen, 50 mg twice daily for 6 months, reduced the incidence of MI by 70% compared with placebo.[27] Indobufen, another NSAID, was as effective as aspirin in preventing saphenous vein graft occlusion after coronary artery bypass graft surgery.[28]

Because of the evidence for an antiplatelet effect of naproxen, it is difficult to assess whether the difference in cardiovascular event rates in VIGOR was due to a benefit from naproxen or to a prothrombotic effect from rofecoxib. Therefore, we examined results from a meta-analysis of 4 aspirin primary prevention trials[24] to evaluate whether the cardiovascular event rates observed with rofecoxib were similar in VIGOR to a placebo-treated population with similar cardiac risk factors. While acknowledging that comparison of patient populations in 2 different trials is always problematic, the results of this meta-analysis may further demonstrate the prothrombotic potential of rofecoxib and celecoxib and suggest that increased event rates with COX-2 inhibitors are possibly due to a prothrombotic effect, not merely a failure to offer the protection of aspirin-like NSAIDs. However, it is important to point out that rheumatoid arthritis increases risk of MI, making intertrial comparisons difficult.[29]

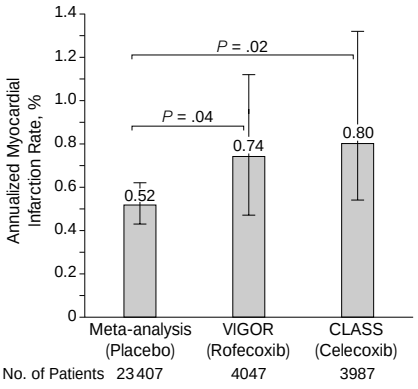
In contrast to the VIGOR study, the CLASS study with celecoxib did not show a significant increase in cardiovascular event rates compared with NSAIDs, possibly due to the use of low-dose aspirin in the CLASS trial or to pharmacological differences in the NSAID agents used as controls in the 2 studies. Diclofenac and ibuprofen have significantly less antiplatelet effects compared with naproxen.[22] To have a vascular protective effect, near-complete inhibition of thromboxane over time is needed[30] and the degree of thromboxane inhibition with diclofenac and ibuprofen may not afford cardioprotection. Furthermore, diclofenac exhibits more effect on PGI_2 inhibition than does naproxen. Van Hecken et al[31] demonstrated that diclofenac causes 94% inhibition of COX-2 compared with 71% inhibition of COX-2 for naproxen. Thus, diclofenac not only has less antiplatelet effect, but may have some intrinsic prothrombotic effect among NSAIDs due

Table 2. Thrombotic Adverse Events With COX-2 Inhibitors Reported in the United States*

Events	Rofecoxib (n = 99)†	Celecoxib (n = 102)†
Myocardial infarction	26	37
Pulmonary embolism/ venous thrombosis	19	27
Stroke	43	31
Miscellaneous‡	14	10

*COX-2 indicates cyclooxygenase 2.
†With both agents, the number of events slightly exceeded the number of cases (parentheses). For rofecoxib, 1 case reported both myocardial infarction (MI) and pulmonary embolus (PE) and 2 cases reported PE and stroke; for celecoxib, 2 cases reported both MI and stroke and 1 case reported both PE and stroke.
‡Miscellaneous thrombotic events in the rofecoxib group included arterial thrombosis (n = 1), portal vein thrombosis (n = 1), ocular vascular occlusion (n = 4), and mesenteric arterial thrombosis (n = 8). Miscellaneous thrombotic events in the celecoxib group included ocular vascular occlusion (n = 3), digital ischemia/limb embolism (n = 5), and ischemic colitis (n = 2).

Figure 3. Comparison of MI Rates Among Subjects Receiving Placebo vs Rofecoxib or Celecoxib



MI indicates myocardial infarction. Error bars indicate 95% confidence intervals.

to inhibition of vasodilatory PGI_2 and this may have masked the increase in event rates with celecoxib. Furthermore, the MI rate with celecoxib (0.80%) was similar to that reported with rofecoxib (0.74%) when rates were recalculated as an annualized percentage rate to enable direct comparison.

Shinmura et al[32] recently demonstrated that up-regulation of COX-2 plays an essential role in the cardioprotection afforded by the late phase of ischemic preconditioning. Administration of selective COX-2 inhibitors 24 hours after ischemic preconditioning abolished the cardioprotective effect of late ischemic preconditioning against myocardial stunning and MI.[32] These data would further suggest potential deleterious cardiac effects of COX-2 inhibitors.

The availability of selective COX-2 inhibitors has raised several important clinical questions. These concern the prothrombotic potential of COX-2 inhibitors, differences in the antithrombotic effect of various NSAIDs, the mandatory use of aspirin with selective COX-2 inhibitors, and whether simultaneous use of aspirin negates the gastrointestinal protective effect of selective COX-2 inhibitors.

Current data would suggest that use of selective COX-2 inhibitors might lead to increased cardiovascular events. Two smaller studies (Study 085 and Study 090) of rofecoxib that both allowed the use of low-dose aspirin did not demonstrate the significant increase in cardiovascular event rate noted in VIGOR. However, these studies had smaller sample sizes, used only 25% of the dose of rofecoxib used in VIGOR, and had few events for meaningful comparison. Thus the prothrombotic effect seen with rofecoxib may potentially be dose dependent. Also, the use of low-dose aspirin in these protocols may negate some of the gastrointestinal benefits of selective COX-2 inhibition. There is evidence that gastrointestinal bleeding from aspirin is not dose related.[33]

COX-2 inhibitors also have been shown to increase blood pressure,[34] and more patients in the VIGOR trial developed hypertension in the rofecoxib group compared with the naproxen group. For rofecoxib, the mean increase in systolic blood pressure in the VIGOR trial was 4.6 mm Hg and the mean increase in diastolic blood pressure was 1.7 mm Hg, compared with a 1.0-mm Hg increase in systolic blood pressure and a 0.1-mm Hg increase in diastolic blood pressure with naproxen. Changes in blood pressure in the CLASS trial were not reported. Previous work has shown that a 2-mm Hg reduction in diastolic blood pressure results in about a 40% reduction in the rate of stroke and a 25% reduction in the rate of MI.[35] The Heart Outcomes Prevention Evaluation study demonstrated significant reduction in cardiovascular events with a 3- to 4-mm Hg reduction in blood pressure.[36] Moreover, a recent reanalysis of 20 years of blood pressure data from the Framingham Heart Study[37] suggests that the degree of benefit expected from a decrease in blood pressure may have been underestimated. Thus, the elevation in blood pressure reported with use of COX-2 inhibitors may also play an important role in adverse cardiovascular outcomes.

Based on this review, it is useful to consider nonselective and selective COX inhibitors as possessing a spectrum of biological effects, both favorable and unfavorable. At one end of the spectrum, COX-2 inhibitors show less propensity for gastrointestinal toxicity but greater prothrombotic potential. At the other end of the spectrum, aspirin and naproxen show greater potential for gastrointestinal toxicity but have a cardioprotective effect. Other agents fall along intermediate points in this spectrum. Clinicians may want to consider these patterns of risk and benefit in selecting the most appropriate agent for individual patients.

Our analysis has several significant limitations. The increase in cardiovascular events in these trials was unexpected and evaluation of these end points was not prespecified. There remains considerable uncertainty in any post hoc analysis. The patient populations in these trials were heterogeneous, and it has been established that patients with rheumatoid arthritis have a higher risk of MI.[29] This leads to difficulty in assessing risk in a more representative sampling of patients. Also, the trials we examined only addressed continuous use of COX-2 inhibitors. Currently, no data exist on cardiovascular safety for the sporadic, intermittent use of these agents by individuals for musculoskeletal pain, which appears to be the most frequent pattern of use.

Our findings suggest a potential increase in cardiovascular event rates for the presently available COX-2 inhibitors. It is possible that concomitant use of aspirin may not fully offset the risk of selective COX-2 inhibitors. However, definitive evidence of such an adverse effect will require a prospective randomized clinical trial. On the other hand, the inflammatory component of atherosclerosis has recently been emphasized[7,38,39] and may be suppressible by COX-2 inhibitors. Given the remarkable exposure and popularity of this new class of medications, we believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents. Until then, we urge caution in prescribing these agents to patients at risk for cardiovascular morbidity.

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Critical revision of the manuscript for important intellectual content, study supervision: Nissen, Topol.
Statistical expertise: Mukherjee, Topol.
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The whole of science is nothing more than a refinement of everyday thinking.
—Albert Einstein (1879-1955)