

# Arthritis Medicines and Cardiovascular Events—“House of Coxibs”

Eric J. Topol, MD

PHYSICIANS, PATIENTS, AND THE GENERAL PUBLIC ARE confronted with an acute confusional state regarding the cardiovascular safety of medicines for arthritis. Since September 30, 2004, the day that rofecoxib was precipitously withdrawn, there has hardly been a day without significant news on the general topic of cyclooxygenase 2 (COX-2) inhibitors. On December 9, 2004, the US Food and Drug Administration (FDA) issued a black box warning for valdecoxib for life-threatening skin reactions and cardiovascular risk.<sup>1</sup> Just over a week later, on December 17, 2004, the National Cancer Institute announced the premature cessation of a trial of celecoxib known as Adenoma Prevention with Celecoxib (APC) due to a significant excess of cardiovascular death, myocardial infarction (MI), and stroke.<sup>2</sup>

The principal cardiovascular event data for APC are summarized in the FIGURE. This was a trial of 2026 patients, with randomization to 1 of 3 groups: placebo; celecoxib, 200 mg twice daily; or celecoxib, 400 mg twice daily. The patients, each of whom had an adenomatous polyp removed before enrollment, were followed up for a mean of 33 months (of a planned 60 months) while taking the study drug, with the

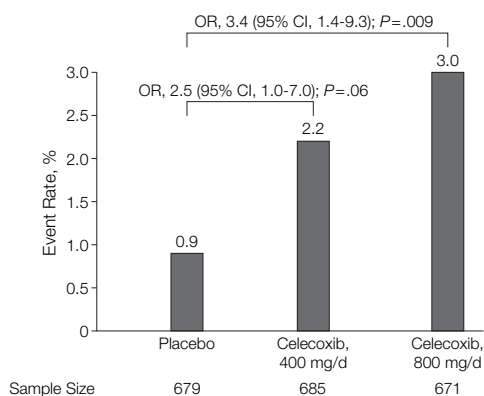
primary objective of limiting the development of colorectal cancer.

A significant excess of major cardiovascular events was demonstrated, with a dose-response effect (odds ratio, 2.5 for celecoxib 400-mg dose, and 3.4 at the 800-mg dose, vs placebo) (Figure). The absolute excess of major cardiovascular events of 13/1000 patients at the 400-mg dose and 21/1000 patients at the 800-mg dose is similar in magnitude to the results of trials with rofecoxib and valdecoxib.<sup>1,3</sup> However, it is not possible to meaningfully interpret interdrug differences because the patient populations in the various trials were different; the drug doses, strength, and duration of therapy were different; and each of the drugs in the coxib class are distinct molecules with specific biological properties. While celecoxib is the least COX-2 selective in the class of 5 agents that have gone through pivotal trials,<sup>4</sup> lumiracoxib is the most selective. A trial of 18325 patients, the largest in the field, demonstrated only modest (not statistically significant) excess of cardiovascular risk when lumiracoxib was compared with naproxen, but not when compared with ibuprofen.<sup>5</sup> Importantly, there have not been any direct comparative (head-to-head) trials of one of the agents vs another, which is the only way to definitively establish likeness or difference between the drugs.

Notwithstanding these concerns, several epidemiologic studies have considered large populations of patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors.<sup>6-10</sup> In general, these studies found an increased cardiovascular hazard for rofecoxib, especially at higher doses, but not for celecoxib. Some studies therefore concluded that celecoxib did not carry any risk for MI or stroke.

But in randomized trials, a signal for potential cardiovascular risk with celecoxib was present. As my colleagues and I described in a 2001 review<sup>11</sup> of the Celecoxib Long-term Arthritis Safety Study (CLASS),<sup>12</sup> the MI rate was 1.6% in the celecoxib group (at a dosage of 400 mg twice per day) and 1.2% in the diclofenac or ibuprofen group for the 1739 patients taking low-dose aspirin. This numerical excess, albeit not statistically significant, was also found in the 6229

**Figure.** Event Rates of Cardiovascular Death, Myocardial Infarction, and Stroke in the Adenoma Prevention With Celecoxib (APC) Trial



The difference for events between the 400-mg and 800-mg dose was not significant (OR, 0.7 [95% CI, 0.4-1.4];  $P=.30$ ). OR indicates odds ratio; CI, confidence interval. The dose response trend across all groups,  $P=.007$ .

**Author Affiliations:** Department of Cardiovascular Medicine, Cleveland Clinic Foundation; Office of the Provost, Cleveland Clinic Lerner College of Medicine; Case Western Reserve University, Cleveland, Ohio.

**Corresponding Author:** Eric J. Topol, MD, Desk F25, 9500 Euclid Ave, Cleveland Clinic Foundation, Cleveland, OH 44195 (topole@ccf.org).

patients not taking aspirin in the trial. Notably, the study drug duration was only 6 months. Underlying this finding were 2 other mechanistic issues. In experimental models of coronary artery occlusion, celecoxib had been found to be prothrombotic.<sup>13</sup> On the other hand, in patients with coronary artery disease, celecoxib has been associated with reduction of C-reactive protein and improvement of endothelial dysfunction.<sup>14</sup> Based on data available in 2001 for celecoxib and rofecoxib, my colleagues and I concluded: "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."<sup>11</sup> Unfortunately, no such trials were ever initiated and the official warnings for the coxib drugs took years to materialize.

In the wake of the high density of new data on coxibs, several important issues now need to be confronted. First, is there any continuing role for coxibs? Only rofecoxib has been shown to reduce gastrointestinal complications compared with naproxen, but valdecoxib and celecoxib have never been definitively confirmed to protect against gastrointestinal complications. While coxib superiority over NSAIDs for relief of arthritic pain has not been shown, many individual patients report pain relief with a coxib but not an NSAID. With the considerably higher cost, marginal efficacy, and known cardiovascular risks of the remaining agents on the market, valdecoxib and celecoxib, it would seem prudent, at the least, to avoid using these agents as first-line therapy. A contraindication is appropriate for patients with established coronary or cerebrovascular disease. Indeed, the only trials of patients with established coronary artery disease were performed with valdecoxib and parecoxib (an intravenous formulation) and the cardiovascular risk was quite apparent.<sup>15,16</sup> Ray and colleagues recently reasonably concluded: "We recommend that clinicians stop prescribing valdecoxib except in extraordinary circumstances."<sup>17</sup> Furthermore, Lester Crawford, the acting commissioner of the FDA, has declared "great concerns" about celecoxib and valdecoxib and is now considering forcing the withdrawal of celecoxib or placing a black box on its label.<sup>18</sup>

With celecoxib, only one trial has thus far shown cardiovascular hazard. While this clearly confirms a class effect, there has not yet been independent replication. Unlike rofecoxib, in which 3 independent randomized trials<sup>19</sup> and a cumulative meta-analysis<sup>20</sup> confirmed excess cardiovascular risk, a trial conducted in parallel to APC for the same indication has not shown any hazard for celecoxib. The celecoxib dose-response effect for cardiovascular events in APC is not shared by the data for rofecoxib.<sup>20</sup> It will be important to have a full analysis of the APC data, with timing of the event curve divergence, and careful examination of the cardiovascular risk profile of patients with events. Until more detailed information is available, it appears that celecoxib use should be restricted. A welcome new precedent was set

by the FDA and manufacturer with the agreement to stop marketing celecoxib to consumers while the review of all available data is ongoing.

Second, the NSAID benchmark safety has now been called into question. The pattern from multiple trials of coxibs, with different control NSAID comparators, has helped establish some useful findings. Naproxen appeared to be the only NSAID with some cardioprotective effect. Juni et al<sup>20</sup> reviewed all of the trials studying this agent and suggested that it is associated with a 14% reduction of MI, which is less than that of aspirin at 23%. On the other hand, ibuprofen appears to act in the opposite direction of naproxen, with an approximate 10% increase in MI as judged from the very large lumiracoxib trial that fortunately included these 2 different NSAIDs as controls.<sup>5</sup> From the body of data available, it appeared that naproxen may be the safest NSAID from a cardiovascular standpoint.

However, on December 20, 2004, the National Institutes of Health and FDA announced the premature cessation of the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT).<sup>21</sup> While the trial of approximately 2400 patients with an average of 3 years of follow-up (of a planned 5-7 years) was being reviewed for potential adverse cardiovascular events with celecoxib, an excess of cardiovascular events was found in the patients assigned to naproxen vs placebo. This was the first time in a placebo-controlled trial that naproxen has been associated with an excess of MI events. But the trial was interrupted and not designed to assess cardiovascular events for naproxen, and the events have not been adjudicated by cardiologists. Given the large body of evidence from multiple epidemiologic studies and randomized trials<sup>6,20</sup> supporting a modest degree of cardioprotection with naproxen, it seems premature to judge any possible untoward cardiovascular effect of naproxen until the final data from ADAPT become available.

Third, there are major concerns about how an entire drug class has gone awry with respect to unleashing significant cardiovascular hazard. A "house of cards" is defined as a flimsy situation that is in danger of collapsing or failing. From the outset, the coxib class of medicines seemed destined for potential collapse. These drugs were mass-marketed from the moment they were commercially available in the new world of direct-to-consumer advertising, with unrealistic expectations about pain relief, marked gastrointestinal protection, and safety. Rather than a sufficient waiting period after approval to firmly establish safety in the large, representative "real world" population, the unbridled promotion exacerbated the public health problem. This is so poignantly clear for an indication such as arthritis, which is one of the most common conditions requiring medication. Furthermore, one has to question the wisdom of allowing direct-to-consumer advertising for lifestyle medications that have no capability of preserving life or preventing major events such as MI or stroke. Here the paradox of actually promoting these events is all the more difficult to accept.

In recent weeks there has been considerable speculation on how the FDA authority and configuration can be bolstered to preempt a coxib-like problem in the future. There is ample evidence of the overemphasis and resource allocation for initial drug approval, with little priority for post-marketing surveillance.<sup>22</sup> An independent drug safety agency or center that compartmentalizes the vital functions of approval and surveillance seems to be gathering broad support.<sup>23</sup> Importantly, providing more authority to the FDA to shape and require the execution of vital trials is perhaps the most important lesson from the coxibs. Currently, for the FDA to mandate that a trial be performed in the post-approval phase of a drug, it has to confront the manufacturer that the drug in question may be withdrawn from the market. There is hardly a precedent for such a drastic step in the history of the FDA. Unfortunately, manufacturers of coxibs were not willing to initiate dedicated cardiovascular trials on their own accord. With early results of coxibs that brought out their prothrombotic potential, rapid initiation of follow-up randomized clinical trials was absolutely necessary. Furthermore, nearly half of "real world" patients with arthritis have coexisting cardiovascular disease,<sup>24</sup> and essentially no trials addressed this vacuum of knowledge. Accordingly, legislation is needed to empower the FDA to require industry to conduct trials that are deemed necessary to ensure the safety profile of a drug. Had coxib trials been conducted 5 years ago in patients with established cardiovascular disease, when the benefit and risk were indeterminate, clinicians would have quickly learned the risk and potentially avoided a major cardiovascular calamity.

The combination of mass promotion of a medicine with an unknown and suspect safety profile cannot be tolerated in the future. An aggressive position going forward is necessary not only for ensuring the safety of prescription medicines but also to restore a solid foundation of public trust.

**Financial Disclosure:** Dr Topol reports no conflict of interest/relationship with any manufacturer of COX-2 inhibitors or NSAIDs.

**Disclaimer:** The views expressed herein represent the author's and are not intended to represent the institutions with which he is affiliated.

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