Perspective

New, Long-term Insights from the Adenoma Prevention with Celecoxib Trial on a Promising but Troubled Class of Drugs

Perspective on Bertagnolli et al., p. 310

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Conclusive findings of cardiovascular (CV) toxicity associated with nonsteroidal anti-inflammatory drugs (NSAID) in two major colorectal-adenoma prevention trials (1, 2) shocked the world of biomedical research in 2005. Sometimes called coxibs, the NSAIDs used in these trials specifically inhibit cyclooxygenase-2 (COX-2) and were widely prescribed for relief of pain and inflammation related to arthritis. In response to reports of this CV toxicity, one major COX-2–specific NSAID (rofecoxib) was removed from the market; the use of other COX-2 inhibitors for standard pain relief was reduced; and investigations of the role of COX-2 in cancer and other disease prevention were scaled back. Despite their adverse CV effects, these drugs still have major beneficial effects that potentially could be very important for public health. Fortunately, clinical evaluations of COX-2–specific inhibitors and other NSAIDs have continued and are shedding new light on the effects of this important class of drugs. Two major areas of investigation involve the prevention of colorectal adenomas and cancer and CV toxicity (3), which include investigations into the poorly understood biological mechanisms of this toxic effect.

Originally reported in 2005 and 2006 in two articles in *The New England Journal of Medicine*, the Adenoma Prevention with Celecoxib (APC) trial randomized 2,035 high-risk patients (following colorectal adenoma resection) to receive celecoxib at either 200 mg twice daily (low dose) or 400 mg twice daily (high dose) or placebo for 3 years (2, 4). With a 3-year adenoma risk of >60% in the placebo arm, the APC trial population was a very high-risk group. Significant overall reductions in adenoma risk (versus placebo) were 33% for low-dose celecoxib and 45% for high-dose celecoxib; celecoxib also reduced adenoma size, number, and burden (versus placebo). Greater reductions occurred in advanced adenoma risk, and patients at the highest colorectal cancer risk had the greatest benefit. The adenoma risk reduction at 1 year was highly significant and similar in magnitude to that at 3 years. APC adenoma results are similar to those of another large randomized trial of celecoxib for colorectal adenoma prevention (5). The two-part history of adverse CV events in the APC will be discussed later in this article. In this issue of *Cancer Prevention*

Research, Bertagnolli and colleagues (6) report the planned follow-up analysis of adenomas and CV events in the APC trial at 5 years.

The original design for this APC follow-up study included the option for patients to stay on celecoxib for the full 5 years. The drug was discontinued, however, when adverse CV effects were discovered in December 2004, and 933 of the original 2,035 study patients agreed to participate in the long-term follow-up after discontinuing treatment. Therefore, treatment of the long-term APC patients comprised a median of ~3 years of intervention, a median of ~2 years of follow-up surveillance off intervention, and a preplanned endoscopy at 5 years. Six hundred thirty-nine follow-up patients received the 5-year endoscopy, more than 90% of whom had been off treatment for ≥1 year. A key long-term finding is that the chemopreventive efficacy of celecoxib against adenomas, including advanced adenomas, persisted at a significant level, albeit somewhat reduced, as follows: 29% on low dose (versus 33% at 3 years) and 38% on high dose (versus 45% at 3 years) for overall adenoma reductions; 52% on low dose (versus 57% at 3 years) and 51% on high dose (versus 66% at 3 years) for advanced adenoma reductions (6). An encouraging possibility emerging from these comparisons is that low-dose celecoxib may be as or more effective than high-dose celecoxib in reducing advanced adenoma risk over time; the low dose also was associated with fewer adverse CV events (versus high dose). The advanced-adenoma comparison favoring the low dose must be interpreted with caution, however, because of greatly reduced numbers in the subset of advanced adenomas in the follow-up subgroup of the original trial.

The only other long-term data on a COX-2–selective NSAID in the setting of colorectal adenoma chemoprevention or adjuvant therapy involve rofecoxib (or Vioxx; refs. 7, 8). The plan for the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial included a 3-year treatment period and a colonoscopy at 4 years, or 1 year after treatment stopped. Rofecoxib (25 mg/d) reduced overall adenoma risk by 24% ($P < 0.0001$) and advanced adenoma risk by 28% ($P < 0.01$) at 3 years, but the protective effect declined during the 1 year off drug, when the overall adenoma risk ratio for rofecoxib (versus placebo) was 1.21 ($P = 0.04$; ref. 7). The overall patterns of adenoma reductions in the APPROVe and APC trials were similar, and celecoxib seemed to be more effective than was rofecoxib at the tested doses.

The APC trial also found that celecoxib reduced adenoma risk in patients who were resistant to the established protective effect of aspirin against adenomas. Patients taking or not taking chronic low-dose aspirin for CV protection had similar celecoxib-associated adenoma risk reductions. It seems reasonable to infer that many patients used low-dose aspirin for years before entering the APC trial and so became eligible

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through adenoma development and resection while on the aspirin regimen. The aspirin-related findings are consistent with the hypothesis that the protective effects of celecoxib and low-dose aspirin involve different mechanisms. Whereas clinical and basic researches indicate that high-dose aspirin may work via COX-2 inhibition (9, 10), data on low-dose aspirin indicate that it is a rather poor inhibitor of COX-2 and may prevent adenomas through COX-1 inhibition (10, 11). Therefore, COX-2–selective celecoxib may be effective in aspirin users at risk of COX-2–expressing adenomas, which constitute about 50% of all adenomas (12). It must be stated, however, that aspirin and celecoxib have non-COX targets (9, 13, 14) that could be involved in the celecoxib effect among patients resistant to low-dose aspirin.

Although not originally planned, the other major analysis of the long-term APC follow-up study became adverse CV events because of their statistically significantly increased risk in the APC trial and their tremendous public health implications. The long-term analysis in this issue of the journal is the third and final formal analysis of CV toxicity reported for the APC trial. Although different in certain respects, all three reported analyses came to similar conclusions. The first analysis involved CV end points adjudicated by a panel of CV experts, who devised a combined end point of myocardial infarction, stroke, congestive heart failure, and death of CV disease (2). Published while the trial and drug treatment were ongoing, this analysis was motivated by CV findings of rofecoxib in APPROVe; the celecoxib-associated increased relative risk was 2.6 (low dose) and 3.4 (high dose) versus a placebo risk of 1%. The combined CV end point of this analysis not only was not prespecified but also was complex. The second published CV analysis came out with the 3-year adenoma prevention efficacy results and after drug had been stopped (4). The CV end point of this analysis differed from that in the first report by including nonadjudicated, investigator-reported adverse events in an intention-to-treat analysis. It also, however, was a combined end point (although slightly different from that of the first study). In the third and final APC analysis of CV events (6), the CV end point was investigator reported (nonadjudicated), and the primary analysis was not based on intent-to-treat but on treatment-emergent events. Although different from each other, all three well-designed analyses came to the similar conclusion that there was a dose-response relationship between celecoxib and adverse CV events during treatment. The expanded data set of the last study has allowed assessments of potential interactions between baseline CV risk factors (including age, smoking, diabetes, hypertension, and atherosclerosis) and celecoxib. The study captured CV events that occurred during 2 years off therapy. The two major new findings of this analysis are that increased celecoxib-related adverse CV effects wore off (relative to placebo) in the 2-year period off drug and that a history of atherosclerotic disease was the *only* risk factor that interacted statistically with drug in producing adverse CV events ($P < 0.004$). The recent extended analysis of CV events in the APPROVe trial (15) produced long-term overall findings similar to those of the APC trial and found nonsignificant trends of increased risk associated with baseline CV risk factors, although no clear reported data address the role of a history of atherosclerosis. Other safety end points included upper gastrointestinal tract disease, which was not significantly increased by cele-

coxib in the APC trial but was increased by rofecoxib in APPROVe (16).

The long-term CV analysis of the APC is consistent with an important pooled analysis by Solomon and colleagues (17), where adverse CV events associated with celecoxib did not increase in patients with a low baseline CV risk (defined by no known risk factors including a history of atherosclerosis). The large numbers of the pooled analysis coupled with the prospective, longitudinal data from the long-term APC follow-up provide compelling evidence in support of further study of the CV effects of COX-2 inhibitors. Although it had big numbers and was useful in general, the pooled analysis could not assess potential specific risk factor interactions because, in part, it had only the 3-year CV data of the APC trial (2) and high interstudy variation with respect to CV risk factor definitions and data collection. Pinpointing the dependence of this adverse drug effect on preexisting atherosclerosis in the APC trial allows the inference that plaque formation is necessary before COX-2 inhibitors pose a threat of CV events, which is consistent with suggestive animal data.

Fitzgerald and colleagues suggested that the prothrombotic mechanism of COX-2–selective inhibitors involves blocking the production of cardioprotective prostacylin by vascular endothelium and not inhibiting the COX-1–dependent synthesis of thromboxane A_2 in platelets (18). This line of study suggests that a combination of cardioprotective low-dose aspirin (which selects for COX-1 inhibition) and celecoxib may reduce the cardiotoxicity of celecoxib alone. Although CV risk was not reduced among low-dose aspirin users (versus nonusers) on celecoxib in the APC trial, this trial was not a good test of the hypothesis because the subset sample size was small and cardioprotective aspirin users in the APC already had a higher CV risk at baseline.

Another provocative hypothesis for the prothrombotic effects of COX-2–selective NSAIDs is provided by Duffield-Lillico and colleagues (19) in this issue of the journal; they found that inhibiting elevated COX-2 shunts substrate (arachidonic acid) into the 5-lipooxygenase pathway in humans, which has implications for adverse CV effects (20). These results are consistent with the APC long-term follow-up finding of an increased celecoxib-related CV risk in patients with a history of atherosclerotic disease and add to the data of Fitzgerald and colleagues and other investigators (18, 21) in elucidating potential mechanisms of the prothrombotic effects of COX-2–selective NSAIDs. Furthermore, COX-2 (and 5-lipooxygenase) expression is increased in atherosclerotic plaques (20, 22).

Nonrandomized observational studies have suggested that nonselective NSAIDs cause adverse CV effects similar to those associated with the COX-2–selective NSAIDs (3). Published recently, the only relevant randomized clinical data (from a colorectal adenoma prevention trial) indicated that a combination involving the nonselective NSAID sulindac may increase CV risk overall and less so in patients with a lower baseline CV risk (23).

In the final analysis, COX-2–selective and other NSAIDs are tremendously important to public health as treatment options for pain relief, and they could be equally efficacious for cancer prevention. For example, several large randomized controlled trials have shown that various NSAIDs, alone or in combination (24), significantly reduced colorectal adenoma development; long-term data from large randomized controlled trials of the NSAID aspirin for CV protection indicated that

a reduction in the risk of colorectal cancer (25), presumably through adenoma reduction (26). Furthermore, colonoscopy with polypectomy reduces colorectal cancer incidence (27) and mortality (28), further supporting adenoma risk reduction for reducing the risk of colorectal cancer. COX-2 is progressively increased in the adenoma-carcinoma sequence (12), and NSAIDs are more active in preventing advanced adenomas (versus all adenomas) and COX-2–dependent (versus non-COX-2–dependent) colorectal cancer (9). Recent data also suggest that people with certain germ-line genetic changes may be especially sensitive to NSAIDs for colorectal adenoma prevention (29–31). The once gently curving path of NSAIDs from bench to bedside has become convoluted with the discovery of the adverse CV effects of NSAIDs. Rather than letting these effects derail this tremendously important class of drugs altogether, investigators should take NSAIDs back to the bench for mechanistic studies to develop new, safer classes of NSAIDs and more careful patient selection that will not be encumbered by an unacceptable risk of adverse CV events.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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