Cancer Prevention Research

Perspective
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Cardiovascular Risk Markers and Mechanisms in Targeting the COX Pathway for Colorectal Cancer Prevention

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Abstract

COX-2 inhibition reduces the incidence of colorectal neoplasia. The increased risk of thrombotic cardiovascular events produced by selective or nonselective COX-2 inhibitors, however, has confounded the consideration of employing them in cancer prevention. Developing a strategy for preventing colorectal cancer by inhibiting COX-2 depends on research advances in several key areas, including predictive biomarkers to identify people at the lowest risk for cardiovascular events, the molecular mechanisms whereby interdicting the COX-2 pathway produces thrombotic events, and the pharmacology of the widely divergent agents that act on COX-2 and its downstream pathway. *Cancer Prev Res; 4(8); 1145–8. ©2011 AACR.*

From the moment that the randomized controlled trial (RCT) called Adenomatous Polyp Prevention on Vioxx (APPROVe; ref. 1) showed that the COX-2–selective inhibitor rofecoxib (Vioxx) increased the risk of thrombotic cardiovascular (CV) events (versus placebo) in patients, investigators have appreciated the potential value of identifying predictors of this increased CV risk. Myocardial infarction was the most prominent of the thrombotic CV outcomes. Later, results of the Adenoma Prevention with Celecoxib (APC) trial (2) made it apparent that these events were a class effect of the COX-2 inhibitors and raised concern (which was substantiated) that they were an effect of most nonselective COX inhibitors as well, intensifying the need for defining the subgroup of individuals on whom COX inhibitors produce this toxic effect. Unfortunately, the indisputable evidence for serious CV consequences of COX inhibitors, or nonsteroidal anti-inflammatory drugs (NSAID), has stymied their use for colorectal cancer prevention, even though compelling evidence supports their efficacy for this use.

Subsequent to the initial APC report of celecoxib-associated CV toxicity, Solomon and colleagues clearly showed in their analysis of 6 randomized placebo-controlled trials that this adverse effect is related to a high, and not a low, baseline CV risk determined by the Framingham model (3). In the APC trial itself, baseline atherosclerotic heart disease predicted increased CV risk (4). In this issue of the journal, Chan and colleagues (5) present important new evidence on CV risk stratification using high-sensitivity C-reactive protein (hsCRP) in the APC trial cohort. hsCRP is a circulating inflammatory biomarker of chronic conditions including CV disease. These investigators found that an elevated level ($\geq$3.0 mg/L) of hsCRP was associated with an increased relative risk of CV events in patients who received high-dose celecoxib (400 mg bid). On the contrary, the average relative risk of CV events was a low 1.11 (95% CI: 0.61–2.02) in patients on high-dose celecoxib and with an hsCRP level less than 3.0 mg/L. These data indicate that individuals with low hsCRP have a lower risk of celecoxib-associated CV toxicity; with the CI showing a relative risk as high as 2.02, however, the data do not yet support a firm clinical inference that a COX-2 inhibitor is safe in patients within the entire range of hsCRP less than 3 mg/L. These findings compel consideration of similar analyses of hsCRP within the other relevant long-term (placebo-controlled) RCTs including APPROVe (1), the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT; ref. 6), and the Prevention of Colorectal Sporadic Adenomatous Polyps trial (7) to provide data for possible meta-analysis that could strengthen the inference of relative safety from CV events in patients with low hsCRP. Such additional data also could enable a more informative analysis of the relative CV event risk as a continuous variable across the range of hsCRP levels.

The concerted findings from RCTs and observational studies of COX inhibitors provide strong evidence that COX inhibition prevents colorectal cancer (1, 4, 8–10). Research designed to translate this valuable insight into a safer approach for cancer prevention should have a high priority. In considering scientific efforts to achieve this goal, one is struck by how little is understood about the CV consequences of inhibiting COX-2. Research is needed to address the following major voids (or near voids) in this area of knowledge: (i) the robust identification of an individual's CV risk when taking a COX-2 inhibitor; (ii) mechanism(s) whereby COX-2 inhibition causes thrombotic vascular disease; (iii) pharmacologic differences that might affect the risk/benefit ratios of different

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COX-2 inhibitors; and (iv) molecular targets downstream of COX-2 that contribute to neoplastic progression.

The demonstration that both celecoxib and rofecoxib inhibit prostacyclin biosynthesis (11, 12) led to the hypothesis that the mechanism whereby COX-2 inhibitors promote thrombosis is by removing prostacyclin's restraint of platelet aggregation, doing so without blocking the production of proaggregatory thromboxane A_2 by platelets. This mechanism is consistent with the early occurrence of CV toxicity after the initiation of COX-2 inhibitors (13) and with the large, early increase in CV events when valdecoxib and parecoxib were given to patients with a high inherent risk of thrombosis following coronary artery bypass grafting (14). The importance of prostacyclin as a restraint on thrombosis is supported by the demonstration of an increased thrombotic propensity in mice lacking the prostacyclin receptor (15). Indeed, a recently reported RCT of a prostacyclin analogue, which should not increase thrombotic CV risks, has produced promising results in lung cancer prevention (16).

Emerging evidence, however, suggests an additional mechanism for COX-2 inhibitor–induced thrombotic CV events. In follow-up of patients in the APPROVe trial, the elevated risk in rofecoxib patients persisted during the year after discontinuation of therapy, suggesting an increased proclivity for thrombotic events independent of the loss of prostacyclin's effect on platelets (13). And there is no published evidence to date that aspirin use countered the increased CV risk of COX-2 inhibitors in the long-term RCTs of these agents. During the treatment phase of the APPROVe study, there was a suggestion that the HR for thrombotic events increased over time, with a *P* value for time × treatment (linear HR change over time) of 0.014 and for logarithmic time × treatment (exponential HR change over time) of 0.071. Taken together, these findings suggest the hypothesis that a long-term effect on the vessel wall adds to the immediate effect of blocking prostacyclin's restraint of platelets in increasing thrombotic risk. Important support for (or the rejection of) this mechanistic hypothesis could be obtained by a meta-analysis of change in HR over time in the multiyear placebo-controlled trials, thus, further illuminating the mechanism of the CV risk from COX-2 inhibitors and other NSAIDs. Because the rupture or fissure of an unstable plaque initiates most coronary thromboses, these findings suggest a mechanism whereby COX inhibition could lead to myocardial infarction by promoting the development of unstable plaques. Such a mechanism, independent of the prostacyclin–platelet interaction, could provide a basis for considering that inhibition of COX catalysis would alter the inflammatory biology that is central to the instability of coronary plaques, thereby, producing a persisting risk for coronary thrombosis. The link between CV risk and CRP, an acute phase response protein, also suggests that COX-2 inhibition interacts with the inflammatory nature of coronary artery plaques.

Prostacyclin inhibits certain inflammatory responses (17, 18) and blocks proinflammatory cytokine production by and T-cell stimulatory function of dendritic cells in mice (19). Deletion of the prostacyclin receptor in mice produces intimal hyperplasia in response to vascular injury (20); this type of vascular response is associated with the release of growth factors from platelets but is not, characteristic of labile plaques. In mice lacking the low-density lipoprotein receptor, absence of the prostacyclin receptor increased aortic atherosclerosis in females but not in males, a gender effect not seen in the human studies showing adverse CV events associated with COX-2 inhibition (21).

The regulation of many cells involved in the immune response and inflammation by prostaglandin E_2 (PGE_2) has been characterized in investigations too extensive for reviewing here (22–24). The multiplicity of PGE_2 effects does not permit the designation of PGE_2 as either a general inhibitor or stimulator of inflammation or of the immune response. For example, PGE_2 inhibits the release of TNFα (25) and INFγ, but stimulates the release of interleukin 6 (26) and matrix metalloproteinase 9 (27) from macrophages. This panoply of effects of PGE_2 on inflammatory and immune cells results in part from the actions of this ligand on the following 4 different G-protein–coupled receptors: prostaglandin E receptor 1 (EP1), EP2, EP3, and EP4. A deficiency of EP4 in mouse macrophages suppresses early atherogenesis (28), indicating that EP4 is a key receptor mediating an athero-protective effect associated with the deletion of microsomal PGE (m-PGE) synthase (29). EP4 deficiency also increases apoptosis of lesion cells in early atherogenesis, although the implications of this effect for plaque stability in advanced lesions are unknown.

These findings in mice, where aortic atherogenesis is not a proven surrogate for the pathophysiology of human coronary disease, only provide the basis for the hypothesis that EP4 antagonists would pose less human risk of CV events than do COX-2 inhibitors. Therefore, investigations of EP4 inhibitors in humans should proceed, with prospective adjudicated assessments of thrombotic vascular endpoints. Because signaling via EP4 is associated with colorectal carcinogenesis (30–33), targeting the EP4 receptor is a consideration for colorectal cancer prevention with the potential for action that is more selective than is that of either COX-2 inhibitors or m-PGE–synthase inhibitors, which are in preclinical development. The greater specificity of inhibitors of EP4 and of m-PGE synthase encourages future investigation of these drugs as safer ways to prevent COX-2–dependent colon cancer.

Current options for colorectal cancer prevention are limited to agents that inhibit COX-2, whether selective or nonselective. Relevant differences in the pharmacology of COX inhibitors go beyond isoform selectivity. Aspirin (acetyl salicylic acid) irreversibly inhibits both COX isoforms by covalently acetylating a serine residue in the active site. It is not isoform selective, but rather exhibits a cellular selectivity (34). Aspirin's effect on the COXs is inhibited in cellular environments with a high hydroperoxide concentration that induces redox cycling of the enzyme, such as in

activated inflammatory cells. Accordingly, the anti-inflammatory effect of aspirin is less than that of COX-2 and other COX inhibitors.

The collective data from RCTs of daily aspirin for a mean of 6 years show a reduction in the 20-year risk of colon cancer (HR = 0.76) and colon cancer mortality (HR = 0.65; ref. 8). The reduction in risk was limited to cancer of the proximal colon (incidence HR = 0.45; mortality HR = 0.34), with no reduction of cancer in the distal colon or rectum. Benefit increased in proportion to duration of treatment. Doses of aspirin in the range of 75 to 300 mg daily were as effective as larger doses. Consistent with the efficacy of low-dose aspirin, the 81-mg dose reduces PGE_2 in rectal biopsy samples (35). Unlike the COX-2 inhibitors and the non-naproxen NSAIDs, aspirin reduces CV risk. Therefore, consideration of the risk/benefit ratio for long term daily aspirin aligns the benefits of preventing both cancer and thrombotic vascular events against the risk of serious hemorrhagic complications.

Naproxen is associated with reduced CV complications when compared with COX-2 inhibitors in some studies (36), putatively because of its protracted "aspirin-like" inhibition of COX-1 in platelets. Naproxen appeared to increase CV risk in the placebo-controlled ADAPT trial (6), however, raising concerns about naproxen as a preventive agent. Interpretation of the ADAPT CV data is limited, however, because they did not pertain to a prespecified endpoint, and the trial was stopped early. At the time of the premature discontinuation of ADAPT, the CV HR of naproxen was 1.63 (95% CI: 1.04–2.55; $P = 0.03$). Certainly, this adverse finding makes it extremely unlikely that naproxen would have shown a CV benefit compared with placebo in ADAPT if the trial had been completed. The data might reflect the use of a lower dose of naproxen (220 mg bid) compared with the higher doses employed in the trials showing a CV advantage of naproxen over COX-2 inhibitors. The inhibitory effect of this lower dose of naproxen on platelet COX-1 is less than that of aspirin at the end of the interval between one and the next dose (dosage interval; ref. 37), possibly contributing to the unfavorable result. A further possibility is that the favorable CV outcomes for naproxen in comparison with COX-2 inhibitors occurred predominantly in trials of a short duration, whereas the longer exposure to naproxen in the ADAPT trial was a median of 14 months with data collection extending to 24 months. This consideration of whether naproxen is safe for long-term administration further emphasizes the need to know whether there is a time-dependent increase in HR that is independent of prostacyclin's restraint of platelet aggregation.

The nonselective COX inhibitor ibuprofen prevents the antiplatelet action of aspirin when the 2 are administered together. This disadvantage of ibuprofen results from its blocking of the acetylation of the COXs by aspirin, but its aspirin-like effect on platelet COX-1 does not extend throughout the dosage interval, as naproxen does, thus, allowing unimpeded thromboxane A_2 biosynthesis. At the doses likely to be required for cancer prevention, there is sufficient ibuprofen present to antagonize the effect of aspirin given at any point during the dosage interval (38, 39).

Sulindac was the first COX inhibitor to be shown to cause regression of colorectal polyps in patients with familial adenomatous polyposis (40, 41), and an RCT of a sulindac combination produced striking results in preventing sporadic colorectal polyps (42). It is a prodrug, the active metabolite of which, sulindac sulfide, is the COX inhibitor. The mechanism whereby sulindac sulfide inhibits COX is unclear, as it does not antagonize the effect of aspirin (43). Intestinal microflora metabolize sulindac to sulindac sulfide (44, 45), which then undergoes enterohepatic recirculation. The potential for turning this unique property of sulindac to advantage in colorectal cancer prevention deserves investigation.

Salicylic acid, which lacks the acetyl moiety of aspirin, does not inhibit the COXs irreversibly, but is a competitive inhibitor that also exhibits cellular selectivity (46). It does not inhibit platelet function. Studies in humans and tumor bearing experimental animals could ascertain whether salicylic acid can inhibit COX-2 in tumors at clinically relevant doses.

In conclusion, the Chan and colleagues (5) finding that low concentrations of hsCRP are associated with a lower incidence of celecoxib-induced CV events provides a novel approach to risk stratification, and suggests that hsCRP may be a useful biomarker for selecting patients for cancer prevention trials and for determining the risk of COX inhibitors in clinical practice. This observation encourages evaluation of the relation of hsCRP to CV outcomes in the other long-term placebo-controlled trials of COX inhibitors to strengthen the estimate of risk in the low hsCRP group and to permit analysis of risk as a continuous variable. On a broader front, consideration of targeting the COX-2 pathway for colorectal cancer prevention requires further research into the mechanisms of its CV effects, into the diverse pharmacology of the current crop of COX inhibitors, including aspirin, and particularly into the greater selectivity afforded by targets downstream of the COXs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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