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Perspective

Prostaglandin Inhibition and Cardiovascular Risk: Maybe Timing Really Is Everything

Perspective on Zell et al., p. 209

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Nonsteroidal anti-inflammatory drugs (NSAID) are among the oldest known medicines. White willow bark, which contains salicin, has been used to combat fevers and pain for thousands of years (1). The term "nonsteroidal anti-inflammatory drug" was coined by rheumatologists in 1949 to distinguish the activity of phenylbutazone from that of glucocorticoids, whose anti-inflammatory properties in the treatment of arthritis had recently been identified. This term came to apply to all aspirin-like drugs that were used clinically as antipyretics, analgesics, and anti-inflammatory agents. NSAIDs include three distinct types: nonselective NSAIDs (e.g., ibuprofen), selective cyclooxygenase (Cox)-2 inhibitors (coxibs), and nonacetylated NSAIDs (e.g., salsalate). NSAIDs are consistently among the most frequently prescribed drugs, and prescription use accounts for only a minor contribution given their wide over-the-counter availability.

Prostaglandins are responsible for pain and inflammation and mediate all stages of tumorigenesis. NSAIDs block prostaglandin production by inhibiting Cox enzymes, which exist in two isoforms: Cox-1 and Cox-2. NSAIDs vary in their relative ability to block Cox-1 and Cox-2. Even among the selective Cox-2 inhibitors, there is a range of Cox-2 selectivity (rofecoxib > valdecoxib > celecoxib). The biological effects of NSAIDs are governed by the tissue distribution of both Cox enzymes and prostanoid receptors and the selectivity of the drug for Cox-1 versus Cox-2. Because Cox-1 mediates gastric mucosal protection, nonselective NSAIDs (i.e., NSAIDs that inhibit both Cox-1 and Cox-2) can produce damage to the mucosa of the stomach and duodenum and increase the complication rate of preexisting peptic ulcers (2). Endoscopic surveillance of patients using NSAIDs regularly shows a 20% prevalence of gastric ulceration, often not associated with dyspepsia. Older patients and those with a prior history of gastroduodenal ulcers are at particular risk for serious complications, including upper gastrointestinal hemorrhage and perforation. Because of their specificity for the inducible isoenzyme that is not responsible for gastric protection, selective Cox-2 inhibitors (coxibs) have a significantly reduced incidence of both minor and severe gastrointestinal side effects (2). Both selective and nonselective NSAIDs, however, have been associated with renal toxicity and also with development of hypertension or exacerbation of existing hypertension (3, 4).

Unfortunately, it is now clear that Cox-2 inhibition increases the risk of cardiovascular thrombotic events, particularly in individuals with a preexisting history of cardiovascular disease (3, 5). Equally worrisome is the growing suspicion that nonaspirin nonselective NSAIDs also increase the risk for cardiovascular complications (6). A Food and Drug Administration–sponsored nested case-control study from Kaiser Permanente examined the relationship between NSAID use and cardiovascular risk using detailed medication prescribing data from the post-coxib era (7). The study end point measured was the occurrence of acute myocardial infarction or sudden cardiac death, and included 8,143 events in 2.3 million person-years of follow-up. Compared with remote users of NSAIDs, the adjusted odds ratio for cardiovascular events was 1.18 for naproxen ($P = 0.01$), 1.69 for diclofenac ($P = 0.06$), 1.33 for indomethacin ($P = 0.005$), 1.29 for rofecoxib ≤25 mg/d ($P < 0.01$), and 3.15 for rofecoxib >25 mg/d ($P < 0.01$; ref. 7). In an October 2006 review of the cardiovascular safety of both Cox-2–selective and nonselective NSAIDs, the U.K. Commission of Human Medicines found evidence indicating that the increased cardiovascular thrombotic risk associated with the nonselective NSAID diclofenac is equal to that of the Cox-2–selective NSAID etoricoxib.[4] High-dose ibuprofen (2,400 mg/d) was also associated with increased thrombotic risk.[4,5] Observational data must be interpreted with caution because it is extremely difficult to account for all confounders and to address intrinsic biases. In support of these data, however, randomized, placebo-controlled data from the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) found an increased risk of cardiovascular toxicity for those treated with the nonselective NSAID naproxen (8). Another placebo-controlled trial, conducted by Meyskens et al. (9), examined the combination of sulindac with difluoromethylornithine in patients at high risk for colorectal adenomas. This study also observed significantly more cardiovascular adverse events among NSAID users.

Chronic inflammation, which is mediated by prostaglandins, is a characteristic of the development and progression of atherosclerosis (10). Why, then, should prostaglandin inhibition be hazardous rather than protective when it comes to acute cardiovascular events? One hypothesis is that prostaglandin inhibition is effective and safe for atherosclerosis prevention, but once a vascular lesion is present, NSAID treatment causes an imbalance in eisocanoid production that

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[4] www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con2025036&RevisionSelectionMethod=Latest
[5] www.npc.co.uk/MeReC_Extra/2008/no30_2007.html

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promotes thrombosis. Data concerning the nature of NSAID-associated thrombosis is provided by the work of Fitzgerald and colleagues (11, 12). They showed that administration of NSAIDs to normal volunteers lowered urinary excretion of prostacyclin, the eicosanoid responsible for vasodilation and inhibition of platelet activation. Animal studies found that genotypic or pharmacologic removal of prostacyclin induced thrombosis and destabilized existing atherosclerotic plaques (13, 14). Importantly, prostacyclin deficiency in these models did not produce spontaneous thrombosis but required the coexistence of endothelial damage.

Data from human clinical trials also support the hypothesis that NSAID cardiovascular toxicity requires preexisting atherosclerosis. An extended safety analysis of the APC Trial, done with a median treatment duration of 2.95 years, found that a baseline history of atherosclerotic heart disease was strongly associated with risk for cardiovascular toxicity in patients treated with celecoxib (15). The NIH-sponsored Cross Trials Safety Analysis pooled data from six placebo-controlled celecoxib studies. The resulting adjudicated analysis showed that patients with the lowest baseline cardiovascular risk have a lower absolute risk for cardiovascular events and also a lower relative risk for celecoxib-related cardiovascular events (16). Finally, the report in this issue by Zell et al. (17) extends this observation to the nonselective NSAID sulindac. Like the larger studies testing coxibs against placebo, a subgroup analysis of this trial found that the excess risk for cardiovascular events observed in NSAID users were more common in patients with a pretreatment history of cardiovascular disease.

NSAIDs are highly beneficial drugs whose use in both chronic arthritis and cancer prevention is currently restricted because of real but poorly understood cardiovascular side effects. Despite significant antitumor activity in patients at high risk for developing colorectal cancer, NSAIDs cannot currently be recommended for routine chemoprevention of sporadic tumors. For patients with severe arthritis, the American Heart Association recommends a "stepped care" strategy, advocating the use of agents with lowest theoretical risk for cardiovascular events (6). The specific recommendation is for short-term use of aspirin and a proton pump inhibitor, followed by acetaminophen, nonacetylated salicylates (e.g., salsalate), tramadol, and opioid analgesics. Both selective Cox-2 inhibitors and nonselective NSAIDs are excluded. Finally, although the degree of harm caused by over-the-counter use of NSAIDs in patients with cardiovascular disease cannot be quantified, this public safety risk should not be ignored.

Before the emergence of cardiovascular toxicity data from cancer prevention trials, NSAIDs were viewed as potentially beneficial with respect to cardiovascular disease. What if this is still the case, as long as patients are treated with NSAIDs before and not after they develop vascular damage that can precipitate thrombosis? For several reasons, cancer chemoprevention trials are able to uncover biological phenomena that are important to understanding overall health and the nature of chronic disease. First, they involve relatively large studies of asymptomatic individuals. Second, they involve study populations with high cancer risk, a condition that is associated with other chronic inflammatory conditions. Finally, cancer risk also increases with age, and older individuals are more sensitive to treatment-associated toxicity. Given the widespread use of NSAIDs for pain and inflammation and their significant potential for disease prevention, it is imperative that we understand the real nature of NSAID-associated cardiovascular side effects. A reasonable, well-supported first step would be a three-arm trial of placebo versus a nonselective NSAID, versus a coxib, conducted in patients at high risk for colorectal cancer but at low risk for cardiovascular complications. This study should include a treatment population and study end points that adequately address both adenoma prevention and cardiovascular safety.

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