Searching for a Safe Analgesic in Patients With Cardiovascular Disease

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Painful musculoskeletal conditions commonly coexist with cardiovascular disease. Older persons with elevated body mass index are at risk of degenerative arthritis, and low back pain as well as cardiovascular disease. Inflammatory arthritis, including rheumatoid arthritis, lupus, and psoriatic arthritis, are associated with an elevated risk of cardiovascular events. The overlapping epidemiology of arthritis and cardiovascular disease ensures that analgesics will always be widely prescribed to patients at risk for future cardiac events. Thus, even though the selective and some nonselective nonsteroidal antiinflammatory drugs (NSAIDs) are known to be associated with cardiac events, they are widely used even in patients with known cardiovascular disease.

Several randomized controlled trials comparing COX-2 selective NSAIDs (e.g., celecoxib, rofecoxib, and valdecoxib) with nonselective agents or placebo found an elevated risk of cardiac events with the selectives agents.1–3 The cardiac risk observed with the COX-2 selective agents appears to differ by agent and by dosage. However, a number of nonselective NSAIDs also may be associated with cardiovascular risk, such as diclofenac.4 Information about nonselective NSAID risk has primarily been derived from observational data, as few randomized controlled trials of adequate duration have examined cardiovascular risk with these agents. What can be learned from observational data regarding the cardiovascular risk of NSAIDs?

Although randomized controlled trials serve as the standard for judging a drug’s efficacy, there are many reasons why trials may not be as useful for assessing toxicity. First, efficacy for arthritis is typically judged at 12 weeks of follow-up and does not require more than several hundred subjects, resulting in too little person-time to accrue adequate numbers of cardiac events. The cardiovascular risk of selective COX-2 NSAIDs was best observed in the longer-term gastrointestinal safety studies that enrolled thousands of subjects. Second, subjects at high risk for toxicity, such as cardiac events, are often excluded from randomized controlled trials. Finally, subgroup analyses in trials is disfavored by some journals. Subgroup analyses in randomized trials are frequently underpowered, and the risk of type II error is high.

The cardiovascular risk of NSAIDs is best determined in observational data. Such analyses suffer from many problems, including selection bias, confounding, and the misclassification of outcomes. However, observational data are critical for determining the cardiovascular risk of NSAIDs. The cardiovascular risk associated with rofecoxib was the subject of recent analyses of two randomized controlled trials, the VIGOR trial and the Heart Protection Study (HPS). Although the HPS was the first randomized controlled trial of a COX-2 selective agent, its data were not thoughtfully adjudicated, resulting in too few cardiovascular events. The VIGOR trial was longer and had more subjects, but the numbers of cardiac events were still too low to establish reliable risk estimates. The VIGOR study also did not use an appropriate comparator group. The use of celecoxib as the comparator of rofecoxib was inappropriate because celecoxib was not approved for cardiovascular indications.

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In this issue of Circulation, Ray and colleagues present a careful analysis of the safety of NSAIDs in persons with known cardiovascular disease. This study demonstrates many of the hallmarks of a well-done pharmacoepidemiologic analysis. The outcomes were defined using algorithms with high positive predictive values. Similar to the use of end point adjudication criteria, this means that there is little misclassification of outcomes. The exposures were thoughtfully characterized and their time-varying nature is accounted for. The authors considered potential confounders and included them wherever available. A variety of sensitivity analyses were consistent with the primary findings, suggesting that the results are robust. These sensitivity analyses included a new-user analysis and the use of naproxen as an active comparator.

This study breaks new ground in focusing on patients with known cardiovascular disease. As noted above, arthritis and cardiovascular disease commonly coexist. Thus, studying the cardiovascular safety of NSAIDs in this subgroup is of great public health value. Several important results emerge from their analyses. Diclofenac was associated with a statistically significant elevation in risk of serious cardiovascular disease or death compared with nonusers (relative risk 1.38, 95% confidence interval 1.18 to 1.61) or naproxen (RR 1.52, 95% CI 1.22 to 1.89). Neither naproxen nor celecoxib were associated with statistically significant elevations in risk of cardiovascular events or death in any analysis. Whereas the confidence intervals all overlapped unity, the relative risks with ibuprofen and rofecoxib were numerically elevated in several analyses. Rofecoxib at dosages above 25 mg was associated with an elevated relative risk of serious coronary heart disease compared with nonusers and naproxen.

Several aspects of the findings should give us pause about their appropriate interpretation. There appeared to be some heterogeneity in results across the three databases used in the analysis (see Table 5). Although the confidence intervals for the Canadian and UK data were very wide, limiting interpretation of the comparison across cohorts, the lack of consistency is notable. One might have anticipated a dosage effect for diclofenac, with higher relative risks observed in the group using 150 mg or more. However, this was not the case. Finally, the relative risks for rofecoxib were consistently lower when death from any cause was also included in the end point.

The suggestion of a reduced risk from rofecoxib when all-cause mortality is included in the outcome raises the interesting possibility that death from gastrointestinal bleeds...
were reduced in persons using rofecoxib. The authors do not provide information or conjecture about this possibility, but data from Table 1 demonstrate that 54% to 66% of subjects were prescribed low dose aspirin and 31% to 44% other platelet inhibitors. Concomitant use of nonselective NSAIDs and antiplatelet therapy is associated with a substantial risk of gastrointestinal bleeding. Although the relative reduction in gastrointestinal toxicity for COX-2 selective agents is not clear across agents, the preponderance of data suggest that these agents are safer than nonselective agents. An important unknown, however, is whether COX-2 selective agents are safer on the gastrointestinal tract in the setting of antiplatelet therapy.

Although a full accounting of overall safety was clearly not the goal of the presented analyses, the apparent reduction in toxicity with rofecoxib when death is considered raises questions about how to measure the overall safety of the drug. Cardiovascular safety in patients with known cardiovascular disease is tremendously important, but clinicians and patients should focus on “net” safety. The net safety of a drug is a difficult concept to understand and even harder to measure. Because no drug is absolutely safe, one must consider the relative safety of a drug (or a treatment strategy) compared to others used for arthritis pain. Of course, nonpharmacologic strategies (eg, physical therapy) or topical therapies with little systemic absorption should be considered, but these will not be adequate for many patients. Intraarticular injections, acetaminophen, or opioids may be safe options in some patients. Such strategies carry possible cardiovascular and other risks as well. Thus, many patients with cardiovascular disease will need an NSAID to achieve adequate analgesia. Because the risk of gastrointestinal toxicity in the setting of concomitant antiplatelet therapy is substantial, measuring net safety requires a more precise understanding of the cardiovascular risk versus the gastrointestinal risk across different analgesic strategies.

Decision analytic modeling that explicitly defines the probabilities of a given event and the decrement in quality of life associated with such events is one method for attempting to define net safety. Another method, a global index of risks and benefits, was used by the Women’s Health Initiative study of estrogen and progestin. This index attempted to account for risks and benefits across many different types of outcomes, including cardiovascular, cancer, and fractures. Because mortality is the ultimate toxicity outcome across both cardiovascular and gastrointestinal system, one could focus on death. However, this does not account for the substantial morbidity associated with other events, such as a gastrointestinal bleed, a stroke, or myocardial infarction. Serious adverse events, such as those requiring hospitalization, might be another possible common toxicity outcome across body systems. Questions of comparative safety and effectiveness are paramount for patients and an emphasis of the American Recovery and Reinvestment Act of 2009.

Already, the Agency for Healthcare Research and Quality has published several monographs in this area.

The use of NSAIDs in patients with cardiovascular disease is concerning because of the cardiovascular and gastrointestinal toxicities associated with these agents. Until newer analgesics are developed, these agents will continue to be used in this patient group. A very large randomized trial among moderate risk cardiovascular patients is comparing the cardiovascular safety of celecoxib, naproxen, and ibuprofen. Results from this trial will not be available until 2011 or later. Thus, we will continue to rely on well-done pharmacoepidemiology to help answer questions about the relative safety of various analgesic strategies in important subgroups of patients. The study by Ray and colleagues gives us new and useful information from an observational study focusing on an important subgroup with known cardiovascular disease. Diclofenac use should be limited in this group and naproxen appears relatively safe, but non-NSAID analgesic strategies might also be considered.

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References
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