What Price Pain Relief?

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C hronic pain affects more than 50 million Americans and results in more than 25 million physician visits a year for lower back pain alone. The burden is particularly great in the elderly, in whom associated cardiovascular disease is the leading cause of death. Nonselective, nonaspirin, nonsteroidal antiinflammatory agents (NSAIDs) are effective analgesic, antiinflammatory, and antipyretic agents, but associated gastrointestinal toxicity led to the development and widespread use of selective cyclooxygenase (COX)-2 inhibitors. Originally introduced for use in chronic conditions such as osteoarthritis, they are today used to mitigate acute pain in numerous conditions. Their benefit was presumed to be from their selective inhibition of COX 2, which along with COX-1 is responsible for the conversion of arachidonic acid to prostaglandin H2. Adverse events associated with NSAIDs were attributed to their inhibition of COX 1, which downstream would normally result in the production of prostaglandins responsible for maintenance of gastrointestinal integrity.2 More recent investigations, however, have identified that both COX-1 and COX-2 are involved in vascular hemostasis, and selective COX-2 inhibitors can have net prothrombotic effects. COX-2 inhibitors lower levels of prostacyclin, a platelet inhibitor and vasodilator, whereas uninhibited COX-1 action results in continued thromboxane A2 production, which promotes platelet aggregation.3 There is mounting evidence that nonselective NSAIDs, previously thought to be neutral or beneficial for risk of cardiovascular disease, may also confer harm because of each agent’s relative COX-1/COX-2 prothrombotic effects and potential to reduce glomerular filtration, exacerbate congestive heart failure, and raise blood pressure.4

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In this issue of Circulation, Gislason and colleagues5 report on the risk of death and reinfarction associated with the use of both nonselective, nonaspirin NSAIDs and selective COX-2 inhibitors in post–myocardial infarction (MI) patients in Denmark. The advanced database system in Denmark is remarkable; it enabled the investigators to use unique civil registration numbers to link the Danish National Patient Registry of all hospital admissions, the Danish Registry of Medicinal Product Statistics (a national prescription registry), and Statistics Denmark for vital status. The investigators identified patients hospitalized with their first MI between 1995 and 2002 and examined their risk of death or rehospitalization for MI. They identified prescriptions for rofecoxib, celecoxib, ibuprofen, diclofenac, and unspecified other NSAIDs and estimated daily dosages by calculating average dosage from up to 3 consecutive prescriptions. Ibuprofen is the only NSAID available without a prescription in Denmark and is dispensed in a low dosage and limited quantity, according to the authors. Understanding the limitations of analyses of observational data, the investigators used 2 methodologies to estimate the risk associated with the use of nonselective NSAIDs or COX-2 inhibitors after an MI. The first model assumed that patients were at risk only when they were taking the drug, and the risk was evaluated in an adjusted proportional hazards model with the drug as a time-dependent variable. The second method involved a case-crossover design in which each case subject with an event of interest served as his or her own control. The number having availability of a COX-2 inhibitor or NSAID in the period immediately (up to 30 days) before the event was compared with the number having medication available in 2 control periods, 60 to 90 or 90 to 120 days before the event.

More than 58 000 patients discharged alive after first MI were included, and a large proportion (36%) filled at least 1 prescription for an NSAID. As suggested in a previous report in Circulation, the authors reported the number needed to harm for low and high doses of these agents, which is the number of patients needed to treat for 1 year to cause 1 additional death. The number needed to harm is alarmingly low for rofecoxib (13) and celecoxib (14) and surprisingly low for diclofenac (24) and ibuprofen (45). The 2 methods used to assess the adjusted OR for death and rehospitalization for MI largely showed similar patterns. There was a >2-fold increase in the risk of death with any use of rofecoxib or celecoxib and a strong dose-response relationship for each. There was weaker excess risk for MI that was consistent for rofecoxib but less consistent for celecoxib between the 2 statistical methods. Importantly, there was no relationship between risk of reinfarction and dose.

In this study, the nonselective NSAIDs were also associated with substantial risk. Any use (ie, all doses grouped together) of ibuprofen or diclofenac was associated with a 1.5- to 2.4-fold increased risk of death. Furthermore, there was a strong dose-response relationship such that relatively lower daily doses of ibuprofen (≤1200 mg) and diclofenac (≤100 mg/d) were not associated with excess mortality risk, whereas higher doses were. Both ibuprofen and diclofenac were associated with excess risk of MI at both low and high dose, consistent with the data for COX-2 inhibitors. It is striking that the average duration of therapy was short (≈1 month), which supports a prothrombotic mechanism.
Although there were >7000 patients who received other NSAIDs, unfortunately, there was no information in this data set on naproxen use. Naproxen has generated great controversy because of conflicting evidence regarding excess risk versus protection from cardiovascular events, with the suspension of the ADAPT trial (Alzheimer’s Disease Antiinflammatory Prevention Trial) because of an elevated cardiovascular risk among patients taking naproxen. Despite the fact that a meta-analysis of observational studies did not suggest increased cardiovascular risk associated with naproxen, the weight of overall evidence justifies substantial concern, and a “black box” warning has been issued by the US Food and Drug Administration for all NSAIDs. Information regarding worsening of hypertension or heart failure, risk related to time since infarction, and risk in patients who had percutaneous coronary intervention or coronary artery bypass grafting after MI is also of interest but was not reported.

This carefully conducted and important report from Gislason et al. has a number of limitations. As in any observational study, unmeasured confounders cannot be adjusted for. In this particular case, important information on the use of aspirin is not available. The authors cite prior documentation regarding the common use of low-dose aspirin after MI, which is guideline-recommended care. Because aspirin may mitigate the excess risk of NSAIDs, the reported excess risk of death and recurrent MI for the use of NSAID alone may be substantially underestimated. However, it is possible that patients discontinued aspirin while they took NSAIDs to reduce the risk of gastrointestinal adverse effects or because they (or their doctor) thought the NSAID had similar cardioprotective effects. Cessation of aspirin after MI would increase the risk of recurrent cardiovascular events and lead to overestimation of the risk of NSAIDs in the present study. Conversely, the known interference of ibuprofen with the antithromboxane effect of aspirin is another confounder, because concomitant use is also associated with cardiovascular risk and increased risk of gastrointestinal bleeding.

The authors also recognize that the pain-eliciting condition that initially led to COX-2 or NSAID use may increase the risk of events and would inflate the apparent NSAID risk. The observation that acute infectious illnesses, including upper respiratory infections, are associated with increased risk of MI lends credence to this hypothesis, at least for a subset of patients.

The observational data described above will not be the last word on this topic. Pfizer will soon be initiating a noninferiority study, coordinated by the Cleveland Clinic, comparing naproxen, ibuprofen, and celecoxib in 21 000 patients with an Antiplaquelet Trialists’ Collaboration end point: nonfatal MI, nonfatal stroke, or vascular death (Steven Nissen, written communication, May 2006). Patient inclusion criteria include arthritis and either established cardiac disease or high cardiovascular risk; approximately two thirds of those enrolled will be taking aspirin.

There is a critical need for large, simple, clinical trials to test the safety, with reasonable certainty of the quantitative risk, and the real-world effectiveness of widely used available agents and those that are under development. Testing must include high-risk populations, including those with cardiovascular disease, and the study duration must be sufficient to reflect use in actual clinical practice. Independent head-to-head comparisons of multiple agents marketed by different pharmaceutical companies must be performed with oversight by the National Institutes of Health, in partnership with the Food and Drug Administration, to regain the public trust. To establish the absolute cardiovascular risk of these agents, a placebo or high-dose aspirin group should be included. The pharmaceutical companies that derive large profits from these agents must contribute substantially to support these studies. We need a new model for randomized clinical trials that streamlines the process and reduces costs. In addition, better surveillance data and standardization of diagnostic and adverse event codes are needed and should be facilitated by inpatient and outpatient electronic medical records, linked to over-the-counter and prescription medication information, as was accomplished to a degree by the Danish investigators.

We agree with the drug approval system change proposed by Strom; conditional drug approval, followed by full approval only after completion of mandatory large phase IV studies. This latest estimate of the cardiovascular risk of NSAIDs provides cause for concern. If even short-term (ie, <1 month) use is associated with relatively large risk for death and reinfarction in those with prior MI, then widespread use of such agents, especially in light of fewer treatment options with COX-2 withdrawals, may be resulting in substantial morbidity. Although these risks have not been as well-established for patients without prior evidence of cardiovascular disease, the use of NSAIDs must be viewed with caution among high-risk patients.

Despite time-tradeoff analyses that often reveal a wide range of patient preferences for quality versus quantity of life, the need for safe and effective treatment options is clear. Once considered virtually universally safe, even acetaminophen may be harmful. An analysis of data from the Nurses Health Study found a dose-response association between acetaminophen use and cardiovascular risk. The lack of acceptable alternatives (eg, acetaminophen, tricyclic antidepressants, or opioid agents) leaves us with even fewer options today than yesterday. Some promise has been shown by microsomal prostaglandin E1 synthase inhibitors, which may retain the antiinflammatory efficacy of COX-2 inhibitors by depressing prostaglandin E2 while avoiding the adverse cardiovascular consequences associated with prostaglandin H2 synthase–mediated prostaglandin I2 suppression. Our process for evaluation of these new agents must not reproduce past mistakes.

In his presidential address before the Royal Society of Medicine in 1965, Sir Bradford Hill noted the following 9 conditions that help strengthen causal inference for an observed association: strength of the association, consistency, specificity, temporality, dose response, plausibility, coherence, experiment, and analogy. With the body of evidence on the association between NSAIDs and cardiovascular disease, many of these criteria have been met. Although some uncertainty about the degree of risk of NSAIDs persists, the study by Gislason et al. contributes to the growing body of evidence that suggests that we temper...
our use of all NSAIDs, weighing risk versus benefit. This study was among the first that focused on post-MI patients, used a unique case-control method, and was designed to find that even a short duration of therapy was associated with risk. When pain demands treatment, a conversation that elicits patient preferences should help guide the first agents of choice. High-dose aspirin (up to 1500 mg/d) is associated with protection from cardiovascular events but also with gastrointestinal toxicity. Used with proton pump inhibitors, it is probably the safest choice for post-MI patients. When NSAIDs are used for patients at risk for or with established cardiovascular disease, they should be used at the lowest effective dose, for the shortest necessary duration, with concomitant low-dose aspirin and proton pump inhibitors as indicated.

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Disclosures
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References
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In the editorial by Hochman and Shah, “What Price Pain Relief?,” which appeared in the June 27, 2006, issue (Circulation. 2006;113:2868–2870), a reference was omitted. This caused a shift of several citations. The sentence, “Despite time-tradeoff analyses that often reveal a wide range of patient preferences for quality versus quantity of life, the need for safe and effective treatment options is clear” should cite reference 16. The sentence, “An analysis of data from the Nurses Health Study found a dose-response association between acetaminophen use and cardiovascular risk,” which originally cited reference 16, should cite the following reference: Cheng Y, Wang M, Yu Y, Lawson J, Funk CD, FitzGerald GA. Cyclooxygenases, microsomal prostaglandin E synthase-1, and cardiovascular function. J Clin Invest. 2006;116:1391–1399. This was added as reference 17 and subsequent references have been renumbered in the revised PDF available with this article (http://circ.ahajournals.org/reprint/113/25/2868). The authors apologize for the misattribution.

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