NSAIDS and the risk of myocardial infarction: do they help or harm?

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This editorial refers to ‘NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case–control study from Finland’ by A. Helin-Salmivaara et al., on page 1657

Non-steroidal anti-inflammatory drugs (NSAIDS) are commonly used for pain relief and appear to work primarily by inhibiting cyclooxygenase (COX) enzymes. Aspirin and other traditional NSAIDS non-selectively inhibit both COX-1 and COX-2 isoforms. In contradistinction, the various coxibs more selectively inhibit COX-2, with differing degrees of specificity. Aspirin has unequivocally been demonstrated to reduce myocardial infarction (MI) in patients with established coronary artery disease. The predominant mechanism by which aspirin provides cardiovascular protection is believed to be via irreversible inhibition of COX-1-mediated platelet aggregation. Prior reports in the literature regarding cardiovascular effects of NSAIDS have been conflicting, whereas the cardiovascular effect of COX-2 inhibitors has been nothing but controversial.

The important report by Helin-Salmivaara et al. in this issue of the European Heart Journal is the largest population-based matched case–control study of NSAIDS performed to date. A total of 33,309 patients with first MI were identified between 2000 and 2003 in Finland. The study found that NSAID use increased the risk of first MI by ~40%, with a similar increase in risk noted for conventional NSAIDS as well as for COX-2 inhibitors. The age of the user did not appear to modulate the risk. Concerningly, the signal of increased risk began with even short durations of therapy consisting of just a few weeks. The longer the duration from NSAID discontinuation, the more attenuated the association became—this finding is supportive of a causal relationship. In addition, heavy NSAID use in the prior year was a significant risk factor for MI, again supportive of a causal relationship. Although largely demonstrating a class effect for NSAIDS and COX-2 inhibitors, this analysis found that rofecoxib was associated with a significant risk of MI, but not celecoxib (at least at a dose of 200 mg daily). The effects of aspirin in this study cannot be ascertained, as over-the-counter drugs like aspirin (and NSAID use as well) were not captured in this analysis and this is a limitation. Fatal MI, of course, cannot be determined in this sort of analysis either. Despite these limitations, this article adds to a growing body of evidence that there may be cardiovascular risk with this class of agents.

A report from the Cleveland Clinic in 2001 first drew widespread attention to the issue of safety of COX-2 inhibitors. However, it appeared that the findings with respect to rofecoxib and celecoxib were divergent. Compared with naproxen, rofecoxib appeared to raise the risk of thrombotic ischaemic events. Whether this was due to an increased absolute risk of rofecoxib per se or a protective cardiovascular effect from naproxen was debated. However, rofecoxib is known to raise blood pressure and this can contribute to cardiovascular risk, though NSAIDS, including naproxen and ibuprofen, are known to have renovascular effects and can also raise blood pressure. This hypertensive property does not appear to be shared by celecoxib. However, a recent case–control study described a relationship between all COX-2 inhibitors and increased cardiovascular risk. COX-2 inhibitors could, in theory, raise thrombotic risk by altering the balance between COX-1 and COX-2. This pro-thrombotic potential may vary based on the relative degrees of COX-2 versus COX-1 inhibition as well as the dose of drug used. On the other hand, inflammation has been found to play a central role in the genesis of cardiovascular disease and, in particular, plaque rupture. Therefore, a COX-2 inhibitor by virtue of its anti-inflammatory effects could theoretically lower cardiovascular risk by this mechanism. Some studies have documented reductions in C-reactive protein levels and improvements in endothelial function with COX-2 inhibitors. A possible benefit of COX-2 inhibitors in cancer chemoprevention has also been demonstrated.

A potentially adverse interaction has been described between ibuprofen and aspirin. Via steric hindrance, ibuprofen binds reversibly to the site on the COX-1 enzyme where aspirin typically binds irreversibly to exert its anti-platelet effect. Theoretically, then, taking ibuprofen immediately before taking aspirin or taking ibuprofen around-the-clock may prevent aspirin from being able to provide cardiovascular protection. More recently, a pharmacodynamic interaction has been described for naproxen and aspirin. Conceivably, these sort of interactions may account for
some cases of aspirin resistance that have been reported in the medical literature. If these interactions are indeed clinically relevant, another layer of complexity is added to the possible effects of NSAIDS on cardiovascular risk.

A report by MacDonald and Wei described an increased risk of all-cause mortality and cardiovascular mortality among 7107 patients discharged after a first admission for cardiovascular disease who were taking aspirin and ibuprofen compared with taking aspirin alone. In a case–control study by Kimmel et al., both ibuprofen and naproxen use were associated with a significantly lower risk of MI in non-users of aspirin, whereas in users of aspirin, neither provided any incremental risk reduction. In this same analysis, aspirin use was also found to be associated with a lower risk of MI, but with increasing concomitant NSAID use, particularly ibuprofen, the benefit of aspirin in reducing risk of MI seemed to diminish.

Of course, there is also the potentiation of bleeding side effects, in particular gastrointestinal bleeding, when one combines aspirin with ibuprofen or naproxen. Though reversible anti-platelet agents, both do increase bleeding risks. Indeed, the risk of gastrointestinal haemorrhage with NSAIDS is not a trivial matter, accounting for a significant number of hospitalizations and even deaths every year. Proton pump inhibitors may partially offset some of the gastric side effects and bleeding hazard of NSAIDS.

Several of the non-randomized studies referenced earlier share certain limitations. Patients taking chronic NSAIDS often have osteoarthritis and are therefore older or have conditions such as rheumatoid arthritis, which is now known to be associated with increased cardiovascular risk, and which may confound any assessment of risk attributable to NSAID use, no matter how sophisticated the statistical modelling may be. This situation is further complicated by the fact that in many analyses, over-the-counter use of NSAIDS may occur and may not be fully captured and accounted for in an analysis, such as the case in the article by Helin-Salmivaara et al.

Thus, there are published data showing that NSAIDs and COX-2 inhibitors have a beneficial, harmful, or neutral effect on cardiovascular endpoints. In fact, it is very easy to construct a cogent argument, citing basic science mechanisms, animal data, and observational human data, that NSAIDS (and COX-2 inhibitors) are either cardioprotective or just the opposite. In this situation where there is clinical equipoise, a trial is ethical and indeed critical to determine which is the best treatment strategy for patients in need of pain relief. For precisely these reasons, the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) trial has been launched. This trial of approximately 20,000 patients with osteoarthritis or rheumatoid arthritis either with cardiovascular disease or at high risk of it will randomize patients to ibuprofen vs. celecoxib vs. naproxen and will examine the rate of cardiovascular death, MI, or stroke. Both concomitant aspirin users and non-users will be included. In addition, gastrointestinal and renal safety, as well as arthritis efficacy, will be evaluated. Importantly, the leadership of this trial is comprised of experts in cardiology, rheumatology, gastroenterology, and clinical trial science. Bringing all these different specialists to the same table is a distinguishing characteristic of this trial. Potentially, this well-powered trial will settle the question of what really is the most precise therapy for the patient in search of pain relief, weighing both cardiovascular and gastrointestinal risks, while factoring in adequacy of arthritic analgesia. The Multi-national Etoricoxib and Diclofenac Arthritis Long-term Study (MEDAL) program involves three trials of over 34,500 patients with osteoarthritis or rheumatoid arthritis, which compares the cardiovascular safety of the COX-2 inhibitor etoricoxib with diclofenac over an average of 20 months and results are expected soon.

In the meantime, the article by Helin-Salmivaara et al. gives us further reason to ponder the possible cardiovascular risks associated with the use of common drugs such as NSAIDS. Until further prospective, randomized data become available, the physician would be wise to remember that in a particular patient any drugs, including NSAIDS, have the potential to help or to harm.

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References