Potential Hazards of Adding Nonsteroidal Anti-inflammatory Drugs to Antithrombotic Therapy After Myocardial Infarction

Time for More Than a Gut Check

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Nonsteroidal anti-inflammatory drugs (NSAIDs) block prostaglandin and prostacyclin biosynthesis via their inhibition of cyclooxygenase (COX) enzymes. By inhibiting COX-1, aspirin reduces thromboxane production, and this leads to its antiplatelet effect. By more effectively inhibiting COX-2, other NSAIDs have relatively greater anti-inflammatory, antipyretic, and analgesic effects. The adverse effect profile of nonselective NSAIDs includes bleeding, particularly gastrointestinal bleeding, which is thought to result from gastric irritation, antiplatelet effects, and the loss of prostaglandin-mediated mucosal repair. Selective inhibitors of COX-2 were developed with the hope they would have fewer gastrointestinal adverse effects and would be highly effective against chronic inflammatory states, such as arthritis.

Evidence soon emerged, however, suggesting a link between some COX-2-selective inhibitors and increased rates of myocardial infarction. Subsequently, the question of cardiovascular toxicity of many NSAIDs, even those with less COX-2 selectivity, was raised. Observational studies demonstrated an association between ischemic cardiovascular events and the use of nonselective and more commonly available NSAIDs, such as ibuprofen and diclofenac, especially when taken at higher doses and by patients with known cardiovascular disease. Concern about the relationship between NSAIDs and higher rates of ischemic cardiovascular events prompted clinical guidelines to recommend against NSAID use in the setting of ischemic heart disease.

In this issue of JAMA, Schjerning Olsen and colleagues report a large observational study that examined the effect of adding NSAIDs to antithrombotic therapy among patients after myocardial infarction (MI). Danish administrative registries were surveyed to identify patients alive 30 days after their first MI. Prescription drug claims were used to classify patients into cohorts based on their secondary prevention treatment strategy: monotherapy with aspirin, clopidogrel, or a vitamin K antagonist; dual therapy with any of the drugs; or triple therapy. For a given patient, a change in antithrombotic treatment strategy could result in the movement from one cohort to another. The total exposure to concomitant NSAIDs was temporally determined, also using the drug claims database, because most NSAIDs are dispensed in Denmark by prescription only. The NSAIDs were categorized based on COX-2 selectivity as selective, nonselective, or other. Patients were followed up until an adverse event occurred (bleeding, death, recurrent MI, stroke, or arterial embolism) or until study completion.

The study population included nearly 62,000 patients, one-third of whom were prescribed an NSAID during an average follow-up of 3.5 years. Bleeding events were common, occurring in 5288 patients (8.5% of the study population); among these events, 799 (15%) were fatal. Ischemic cardiovascular events were frequent, occurring in 30% of the population. Multivariable analysis demonstrated an association between NSAID use and bleeding (hazard ratio [HR], 2.02 [95% CI, 1.81-2.26]) and between NSAID use and ischemic cardiovascular events (HR, 1.40 [95% CI, 1.30-1.49]). The associated bleeding risk with NSAID therapy was elevated regardless of the type or extent of concomitant antithrombotic therapy. Even among the rare cases in which patients received no antithrombotic therapy, NSAID therapy alone was associated with an increased risk of bleeding compared with patients not receiving an NSAID. Moreover, NSAIDs were linked to an increase in bleeding hazard, irrespective of their COX-2 selectivity. Perhaps most surprising, even very short-term therapy with NSAIDs was associated with a substantially increased bleeding risk. Specifically, the HR for bleeding was found to be markedly elevated within the first 3 days after the initiation of NSAID therapy (adjusted HR, 3.37 [95% CI, 2.57-4.41]) and was noted in each of the antithrombotic cohorts.

This finding is important because it is established that bleeding events are strongly related to subsequent adverse cardiovascular events among patients with acute coronary syndromes. In an evaluation of bleeding among patients with MI, a pooled analysis was performed with 34,146 patients enrolled in 3 large acute coronary syndrome trials. Patients with early bleeding complications were found to have a 1.5-fold higher risk of death between 30 days and 6 months from their index presentation. The mechanisms responsible for this increase in mortality are not clearly understood, but it has been suggested that bleeding results in a heightened inflammatory state as well as an interruption of antithrombotic therapies in some cases.

The findings of Schjerning Olsen and colleagues are consistent with prior reports and further support current guidelines that warn against the use of NSAIDs among patients with ischemic cardiovascular disease. It is concerning to note that roughly one-third of patients in the cohort were prescribed concomitant NSAIDs despite their recent MI. A counterargument might be that the assessed HRs with NSAIDs as reported in the study were not due to direct NSAID toxicity, but rather to the increased use of concomitant agents that were being prescribed in the setting of high bleeding risk.

The study by Schjerning Olsen and colleagues is a large observational study with important implications for the management of patients with acute coronary syndromes. It highlights the potential for NSAIDs to increase bleeding risk and suggests a need for further research to better understand the mechanisms behind these findings and to develop strategies to mitigate these risks.
present study are inaccurate because of the inherent limitations of observational studies and the potential for uncharacterized biases. It is true that several findings in the current dataset conflict with those from prospective controlled trials. First, no difference in cardiovascular outcomes was observed among patients treated with aspirin alone vs dual antiplatelet therapy (and clopidogrel monotherapy appeared worse). This is in contrast to prior reports from large randomized clinical trials testing antiplatelet therapy administered after MI. Second, the concomitant use of proton pump inhibitors (PPIs) in this study population was not associated with a lower bleeding risk. Use of PPIs is known to reduce endoscopic evidence of NSAID-induced gastric and duodenal ulceration, and other observational studies have identified a direct relationship between PPI use and a reduction in the risk of hospitalization for gastrointestinal bleeding. Furthermore, in a randomized placebo-controlled trial, the addition of a PPI to dual antiplatelet therapy reduced the rate of overt or occult gastrointestinal bleeding (HR, 0.34 [95% CI, 0.18-0.63]).

The cumulative evidence available is an important reminder that while NSAIDs can be helpful and at times necessary medications for satisfactory quality of life, use of these medications among patients with a history of a recent MI is likely to be associated with clinically meaningful bleeding and ischemic risks. Because the present study tracked only prescription NSAID use, it is plausible that an even greater health care effect might occur in many countries, such as the United States, where NSAIDs are widely available as over-the-counter medications and physicians may be unaware whether their patients are taking NSAIDs. Fortunately, a very large prospective randomized NSAID study will be reporting long-awaited cardiovascular safety results in the next year. The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen) trial has randomized approximately 24,000 patients with symptomatic rheumatoid arthritis or osteoarthritis and at high risk for or with established cardiovascular disease to 1 of 3 available NSAIDs. However, until the results from PRECISION are available, practitioners would do well to advise patients with cardiovascular disease against all NSAID use (except low-dose aspirin), especially patients with a recent acute coronary syndrome.

ARTICLE INFORMATION

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REFERENCES


