**NSAIDs May Block the Cardioprotective Effect of Aspirin**


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**Study Overview**

**Objective.** To examine the association between nonsteroidal antiinflammatory drug (NSAID) use and first myocardial infarction (MI) in men taking aspirin and those not taking aspirin.

**Design.** Posthoc subgroup analysis of NSAID users and non-NSAID users in a 5-year placebo-controlled trial of aspirin. Participants responded to surveys about NSAID use.

**Setting and participants.** Male physicians aged 40 to 84 years at entry entered in a randomized trial of aspirin (325 mg every other day) and beta-carotene.

**Main outcome measures.** First fatal or nonfatal MI.

**Main results.** As previously reported, aspirin reduced the rate of first MI by 44% [1]. Among those in the aspirin group, NSAID use for 1 to 59 days per year was not associated with a change in the risk of MI (relative risk [RR], 1.21 [95% confidence interval {CI}, 0.78–1.87], but NSAID use for 60 or more days per year was associated with an increased risk of MI (RR, 2.86 [95% CI, 1.25–6.56]) compared with no NSAID use. NSAIDs were not associated with an increase in MI in the placebo group for 1 to 59 days of use (RR, 1.14 [95% CI, 0.81–1.60]) or for 60 or more days of use (RR, 0.21 [95% CI, 0.03–1.48]). Adjustment for potential confounders did not reduce the increased risk of regular NSAID use among participants taking aspirin.

**Conclusion.** The beneficial effects of aspirin in preventing first MI appear to be inhibited by regular NSAID use.

**Commentary**

Regular aspirin use greatly lowers the risk of initial and recurrent cardiovascular events and is thought to act by irreversibly inhibiting platelet cyclooxygenase-1. Whether other drugs that act on cyclooxygenase isoenzymes increase or decrease the risk of cardiovascular events is an area of active debate. Ibuprofen, a nonselective reversible cyclooxygenase inhibitor, has been shown to interfere with aspirin’s inhibition of platelets when taken before aspirin or when used 3 times daily [2]. The article by Kurth et al is consistent with these findings and suggests that the antagonism of aspirin-induced platelet inhibition has important clinical consequences. In this randomized controlled trial of aspirin, regular NSAID use (≥ 60 days per year) did not appear to increase the risk of first MI in the placebo group, but regular NSAID users in the aspirin group showed a statistically robust increase in first MI compared with those who did not use NSAIDs.

While the record of NSAID use was self-reported and observational in nature, the fact that aspirin was assigned randomly strengthens the results of these findings. Unlike purely observational studies, unmeasured confounding factors should be evenly divided between the aspirin and placebo groups, and the NSAID users were evenly divided between the 2 treatment groups. When the authors adjusted for possible confounding factors, their results were essentially unchanged. Therefore, it seems likely that the effects they observed are truly due to the interaction between NSAIDs and aspirin. The authors point out that ibuprofen was widely used during the time of their study. Experimental work has shown that not all NSAID regimens block aspirin’s effect on platelets to the same degree. Regular use of delayed-release diclofenac (another nonspecific NSAID) did not appear to block aspirin’s effect, nor did the selective cyclooxygenase-2 inhibitor rofecoxib [1]. It is possible that differences in inhibition of aspirin’s effects on platelets may lead to differences in clinical outcomes; however, this is not yet proven.

**Applications for Clinical Practice**

Regular NSAID use may block the cardioprotective effect of aspirin. Patients who depend on aspirin to reduce their risk of MI should consider avoiding regular NSAID use. There is some evidence to suggest that for intermittent
NSAID users, aspirin’s benefit may be preserved if it is taken at least 2 hours before an NSAID [2]. Whether all NSAIDs interfere with aspirin’s benefit to an equal degree is not known.

—Review by Stephen D. Persell, MD, MPH

References