Do NSAIDs inhibit the cardioprotective effects of ASA?

Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003;108:1191-5.

Background: ASA is effective in primary and secondary prevention of coronary artery disease. The effects, if any, of other NSAIDs in this regard are less clear. Both ASA and NSAIDs affect platelet cyclo-oxygenase, but only ASA achieves consistent and sustained inhibition of platelet aggregation.[1] It is unclear if NSAIDs alone are useful for the primary prevention of myocardial infarction. Results of clinical studies of NSAID therapy plus ASA for the secondary prevention of coronary artery disease have been negative[2,3] or neutral.[4]

Design: In this study, 22 071 male physicians aged 40–84 years without a prior history of cardiovascular disease were randomly assigned to receive ASA (325 mg every other day), beta-carotene, both active agents or both placebos. Compliance, new diagnoses, health behaviours and medication use, including NSAIDs, were assessed by regular questionnaires. Participants were classified into 3 groups: no use of NSAIDs, intermittent use (1–59 days per year) or regular use (≥ 60 days per year). They were followed until the occurrence of a first myocardial infarction or completion of the study. Two multivariate regression models were constructed to determine the contribution of NSAIDs to the risk of myocardial infarction (Table 1).

Results: During the 5 years of follow-up, there were 378 myocardial infarctions: 139 in the ASA group and 239 in the placebo group (relative risk 0.56; 95% confidence interval [CI] 0.45–0.70). Intermittent use of NSAIDs was not associated with an increased risk of myocardial infarction in either the ASA or the placebo group. However, regular use of NSAIDs (≥ 60 days per year) was significantly associated with a risk of first myocardial infarction in those taking ASA in both of the multivariate models (Table 1).

Commentary: The post hoc subgroup analysis from this large randomized trial demonstrated a more than 2-fold increase in the risk of first myocardial infarction among participants receiving ASA who were also regularly taking an NSAID compared with those receiving ASA who did not take NSAIDs or used them intermittently. The results are strengthened by the large sample size and the prospectively collected data.

Limitations of this study include the inherent weakness of any post hoc subgroup analysis, the biases inherent in the data collection of NSAID use, the possibility of confounding factors linking chronic inflammatory states with coronary artery disease, and the homogeneity of the cohort (male physicians, 92% white). In addition, compared with the general population, the study groups had relatively few myocardial infarctions. Finally, no analysis of the effects of different NSAIDS or dose response could be determined, since this information was not collected.

Practice implications: The place of ASA in primary and secondary prevention of coronary artery disease is well established. The results of this study provide supportive evidence that the regular use of NSAIDs may negate the cardioprotective benefits of ASA for primary prevention. However, further research is required to confirm the results and to elucidate differences, if any, between NSAIDs.

Along with the well-established adverse effects of NSAIDs on other end-organ systems (e.g., renal and gastrointestinal), this study provides additional evidence to support the cautious use of chronic NSAID therapy.

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Table 1: Relative risks (RRs) of myocardial infarction (MI) according to time-varying NSAID use separately for ASA and placebo groups*

	ASA group			Placebo group		
NSAID use	MI, no. of patients	Model 1[†] RR (and 95% CI)	Model 2[‡] RR (and 95% CI)	MI, no. of patients	Model 1[†] RR (and 95% CI)	Model 2[‡] RR (and 95% CI)
None	107	1.00	1.00	193	1.00	1.00
1–59 d/yr	26	1.21 (0.78–1.87)	1.19 (0.77–1.85)	44	1.14 (0.81–1.60)	1.15 (0.82–1.63)
≥ 60 d/yr	6	2.86 (1.25–6.56)	2.84 (1.24–6.52)	1	0.21 (0.03–1.48)	0.20 (0.03–1.46)

*Adapted, with permission, from Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003;108:1191-5.
†Model 1: adjusted for baseline information on age, body mass index, exercise, history of arthritis, smoking status and randomized β-carotene assignment.
‡Model 2: adjusted for all variables in model 1 plus for baseline information on history of hypertension, history of diabetes and parental history of MI at < 60 years.

References
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