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# Inhibition of Clinical Benefits of Aspirin on First Myocardial Infarction by Nonsteroidal Antiinflammatory Drugs

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**Background**—There is clear evidence from numerous randomized trials and their meta-analyses that aspirin reduces risks of first myocardial infarction (MI). Recent data also suggest that other nonsteroidal anti-inflammatory drugs (NSAIDs) may interfere with this benefit of aspirin.

**Methods and Results**—We performed subgroup analysis from a 5-year randomized, double-blind, placebo-controlled trial of 325 mg aspirin on alternate days among 22 071 apparently healthy US male physicians with prospective observational data on use of NSAIDs. A total of 378 MIs were confirmed, 139 in the aspirin group and 239 in the placebo group. Aspirin conferred a statistical extreme ( $P < 0.00001$ ) 44% reduction in risk of first MI. Among participants randomized to aspirin, use of NSAIDs on 1 to 59 d/y was not associated with MI (multivariable adjusted relative risk [RR], 1.21; 95% confidence interval [CI], 0.78 to 1.87), whereas the use of NSAIDs on  $\geq 60$  d/y was associated with MI (RR, 2.86; 95% CI, 1.25 to 6.56) compared with no use of NSAIDs. In the placebo group, the RRs for MI across the same categories of NSAID use were 1.14 (95% CI, 0.81 to 1.60) and 0.21 (95% CI, 0.03 to 1.48).

**Conclusions**—These data suggest that regular but not intermittent use of NSAIDs inhibits the clinical benefits of aspirin. Chance, bias, and confounding remain plausible alternative explanations, despite the prospective design and adjustment for covariates. Nonetheless, we believe the most plausible interpretation of the data to be that regular but not intermittent use of NSAIDs inhibits the clinical benefit of aspirin on first MI. (*Circulation*. 2003;108:1191-1195.)

**Key Words:** myocardial infarction ■ aspirin ■ prevention ■ epidemiology

The clinical benefits of aspirin in secondary prevention of cardiovascular disease and primary prevention of myocardial infarction (MI) have been shown in numerous studies.<sup>1-4</sup> The most plausible mechanism by which aspirin prevents ischemic events is by irreversible inhibition of the isoenzyme cyclooxygenase-1 (COX-1).<sup>5</sup> In the United States, nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used<sup>6</sup> for their analgesic, anti-inflammatory, and antipyretic effects. These effects result primarily from inhibition of COX-2<sup>7</sup> and reduced prostaglandin production. Nonselective NSAIDs also inhibit COX-1.<sup>8</sup> Unlike aspirin, NSAIDs bind reversibly at

the active site of the isoenzyme, leading to impaired platelet function for only a portion of the dosing interval.<sup>9</sup> Aspirin and NSAIDs share a common docking site on COX-1,<sup>10,11</sup> raising the potential for a competitive interaction between the two. A recent crossover study in healthy subjects<sup>12</sup> and an observational study of concomitant administration of aspirin and ibuprofen on cardiovascular mortality<sup>13</sup> in secondary prevention support this hypothesis.

In this article, we investigate whether NSAIDs inhibit the clinical benefit of aspirin on first MI among 22 071 apparently healthy male US physicians.

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Dr Glynn received consulting fees from AstraZeneca and grant support from Bristol-Myers Squibb. Dr Walker is employed by Ingenix, Auburndale, Mass. United Health Group owns both Ingenix and UnitedHealthcare, which as an insurer has a financial interest in cost-effective reduction of myocardial infarction risk. At various times, he has conducted research sponsored by most manufacturers of NSAIDs. Dr Hennekens receives research grant support from the National Institutes of Health, Bayer, and PharMed. He serves as a consultant, including Chair or membership on Data and Safety Monitoring Boards, to AstraZeneca, Bayer, Bristol-Myers Squibb, Chattem, Delaco, Food and Drug Administration, Glaxo-Smith Kline, McNeil, National Institutes of Health, Novartis, Pfizer, and Reliant. Dr Gaziano received research funds from BASF, McNeil, Roche, and Wyeth. During 2002 and 2003, he also served as a consultant to McNeil and Wyeth.

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## Methods

Study subjects were participants in the Physicians' Health Study (PHS), a completed randomized trial of aspirin and  $\beta$ -carotene in the primary prevention of cardiovascular disease and cancer. The methods and results of the PHS have been described in detail previously.<sup>1,14</sup> In brief, 22 071 apparently healthy male physicians, 40 to 84 years old at entry, without a previous history of cardiovascular disease, cancer, or other major illnesses were randomized to either aspirin (325 mg every other day as Bufferin, supplied by Bristol-Myers Products),  $\beta$ -carotene (50 mg every other day as Lurotin, supplied by BASF AG), both active agents, or both placebos.

Baseline information was collected by mailed questionnaires that asked about many demographic, medical history, and lifestyle variables. Follow-up questionnaires were sent to participants at 6, 12, 24, 36, 48, and 60 months after randomization asking about newly diagnosed medical conditions, including MI, study compliance, medication use, and health behaviors during the study period.

This study includes randomized data on aspirin from the beginning of the trial in 1982 to January 25, 1988, the date the blinded aspirin component was terminated early, primarily because of the emergence of a statistically extreme ( $P < 0.00001$ ) 44% reduction in risk of first MI.<sup>1</sup> At that time, participants had been followed for an average of 60.2 months; 99.7% were still providing information on morbidity, and mortality follow-up was 100% complete.

### Information on Aspirin and NSAID Use

We classified participants into aspirin (325 mg every other day) and placebo users according to the original randomized aspirin treatment assignment. Compliance with randomized treatment was identical for the aspirin and placebo groups.<sup>15</sup> Observational data on NSAIDs were collected on baseline and follow-up questionnaires. Participants were asked, "On how many of the past 30 days did you take nonsteroidal anti-inflammatory agents other than aspirin?" From this information, we calculated the number of days per year on which nonaspirin NSAIDs were ingested. We categorized participants who reported use of NSAIDs into 3 groups: no use, intermittent use (1 to 59 d/y), and regular use ( $\geq 60$  d/y) for each follow-up questionnaire. To reduce confounding by indication, information about NSAID use was obtained before MI occurrence. In a sensitivity analysis, we also evaluated NSAID intake categories of none, 1 to 29, and  $\geq 30$  d/y. If information on NSAID use on a follow-up questionnaire was missing, we used the most recent information.

### Documentation of MI

We included only first nonfatal or fatal MI, defined according to the criteria of the World Health Organization.<sup>16</sup> When a participant or next of kin reported an MI, written consent for the review of his medical record was obtained. Self-reported MI was confirmed only after review of the appropriate medical record by an end-points committee blinded to aspirin treatment assignment and unaware of the NSAID hypothesis.

### Statistical Analysis

We used the general linear models procedure (SAS version 8.2, SAS Institute) to compare continuous measurements adjusted for age. We compared categorical variables adjusted for age using direct standardization. We used time-varying Cox proportional hazards models<sup>17</sup> to analyze the association between aspirin, placebo, and NSAID use and MI. Person-time was calculated from the return of the baseline questionnaire until the date of the MI, date of death, or the study's end, whichever occurred first. We ran separate models in the aspirin and placebo groups. In addition, we evaluated the effect of aspirin, placebo, and NSAIDs in the entire PHS cohort using indicator variables for use of aspirin or placebo according to NSAID categories. We calculated age- and multivariable-adjusted hazard ratios as a measure for the relative risk (RR) and the corresponding 95% confidence intervals (CIs).

We built 2 multivariable regression models. The first controlled for variables considered to be potential confounders of the association between NSAID use and MI. This model controlled for age (in 5-year

increments), history of arthritis at baseline, exercise ( $< 1$  time/mo, 1 time/mo to 4 times/wk,  $\geq 5$  times/wk), body mass index (continuous), history of smoking (never, past, current), and randomized  $\beta$ -carotene assignment. The second multivariable model also controlled for other major risk factors for MI, including baseline information on history of hypertension (defined as self-reported systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or antihypertensive medication regardless of blood pressure), history of diabetes, and parental history of MI before age 60 years.

To evaluate whether NSAID use inhibited the clinical benefit of aspirin on first MI, we compared the likelihood of the regression model containing only the main effects of aspirin and NSAIDs with the likelihood of the regression model that also included the interaction of aspirin and NSAIDs using the likelihood-ratio test.

## Results

During a mean follow-up of 5 years, a total of 378 MIs were confirmed: 139 in the aspirin group and 239 in the placebo group (RR, 0.56; 95% CI, 0.45 to 0.70).<sup>1</sup> The age-adjusted baseline characteristics with respect to NSAID use categories are summarized in Table 1. Participants who used NSAIDs on  $\geq 60$  d/y in any of the follow-up years had greater body mass index; reported more history of arthritis, diabetes, and hypertension; and were more likely to be current smokers. Participants in the intermittent-use group tended to be younger.

Table 2 presents the number of participants according to aspirin and NSAID use and the number of MIs in each exposure group and follow-up period. Relatively few MIs were confirmed in the intermittent and regular NSAID-use categories. Among participants randomized to placebo who took NSAIDs on  $\geq 60$  d/y, only 1 MI occurred. For 13 MIs, information on NSAID use was not available in the follow-up year before the events occurred. Using the most recent NSAID information for the preceding year, 7 of these MIs occurred in the placebo-only group, 1 occurred in the placebo and intermittent NSAID use group, and 4 occurred in the aspirin-only group. For 1 MI event, no NSAID information was available. In the last interval set, a total of 8 MIs occurred before the aspirin arm of the PHS was stopped.

The results of the age- and multivariable-adjusted models that adjusted for potential confounders of the association between aspirin and NSAID intake and MI as well as other risk factors for MI are summarized in Table 3. Intermittent use of NSAIDs (1 to 59 d/y) was not associated with an increased risk of MI in either the aspirin or placebo group. The combined use of aspirin and other NSAIDs on  $\geq 60$  d/y was significantly associated with MI, whereas the use of placebo and other NSAIDs on  $\geq 60$  d/y was not. Among participants randomized to aspirin, the multivariable-adjusted RRs of MI were 1.21 (95% CI, 0.78 to 1.87) for NSAID use on 1 to 59 d/y and 2.86 (95% CI, 1.25 to 6.56) for NSAID use on  $\geq 60$  d/y compared with no NSAID use. Among participants randomized to placebo, the RRs of MI were 1.14 (95% CI, 0.81 to 1.60) for NSAID use on 1 to 59 d/y and 0.21 (0.03 to 1.48) for NSAID use on  $\geq 60$  d/y compared with never use. Additional adjustment for risk factors for MI did not attenuate the RR associated with aspirin and regular NSAID use (model 2).

When we used a different cutoff for NSAID use (none, 1 to 29, and  $\geq 30$  d/y), similar trends were observed. Among participants randomized to aspirin and placebo, use of NSAIDs on 1 to 29 d/y was not associated with increased risk

**TABLE 1. Age-Adjusted\* Baseline Characteristic of Participants According to NSAID Use in the PHS**

Baseline Characteristics	Never (n=10 589)	NSAID 1–59† (n=10 232)	NSAID ≥60‡ (n=1248)
Age, (SD)	55.2 (10.0)	52.1 (8.8)	54.9 (9.9)
Systolic blood pressure, mm Hg (SEM)	126.0 (0.12)	126.1 (0.12)	126.8 (0.34)
Diastolic blood pressure, mm Hg (SEM)	78.8 (0.08)	78.8 (0.08)	79.3 (0.22)
Body mass index, kg/m <sup>2</sup> , mean (SEM)	24.8 (0.03)	25.0 (0.03)	25.4 (0.09)
Arthritis, %	0.8	1.8	6.9
Hypertension, %	23.7	23.9	26.6
Diabetes, %	2.6	3.0	3.6
Parental history of MI, %	9.1	9.2	9.8
Smoking, %			
Never	52.0	47.5	45.0
Past	37.0	41.4	43.2
Current	11.0	11.0	12.0
Physical activity, %			
<1 time/mo	15.0	12.4	12.8
1 time/mo to 4 times/wk	69.1	71.3	70.1
≥5 times/wk	16.0	16.3	17.1
Randomized to aspirin	49.8	50.3	47.9

\*Adjusted for age at baseline (5 year increments).  
 †1–59 NSAIDs in at least 1 year of the study but never ≥60 NSAIDs.  
 ‡≥60 NSAIDs in at least 1 year of the study.

of MI. Compared with never use of NSAIDs, the multivariable-adjusted RRs were 1.20 (95% CI, 0.76 to 1.89) in the aspirin group and 1.15 (95% CI, 0.81 to 1.63) for the placebo group. Different risks associated with use of NSAIDs for 30 days or more, however, were observed in the aspirin group (RR, 2.20; 95% CI, 1.06 to 4.54) and the placebo groups (RR, 0.52; 95% CI, 0.19 to 1.41) compared with never use.

We created indicator variables for each of the possible aspirin, placebo, and NSAID category combinations and calculated the RRs of MI (Table 4). Compared with the use of placebo alone, the use of aspirin alone and the use of aspirin plus an intermittent concomitant level of NSAID use (between 1 and 59 d/y) were associated with a reduced risk of MI. In contrast, no protective effect of aspirin was apparent among participants who used NSAIDs ≥60 d/y.

The likelihood ratio test contrasting the age-adjusted main effects of aspirin and NSAIDs with a model that included also the interaction between aspirin and NSAID use yielded a  $\chi^2$  value of 8.39 (2 degrees of freedom [df],  $P=0.015$ ). The same contrast in multivariable model 1 yielded a  $\chi^2$  value of 8.68 (2 df,  $P=0.013$ ), and for multivariable model 2, a  $\chi^2$  value of 8.84 (3 df,  $P=0.012$ ).

In a sensitivity analysis, we included 7 additional confirmed MI cases that occurred before the randomized aspirin arm was terminated but that were not confirmed by the end-points committee before the data set was closed for the final report of the aspirin arm.<sup>1</sup> Six of these cases occurred in the aspirin arm and 1 in the placebo arm. The results were quite similar to the primary analysis. Among participants randomized to aspirin, the multivariable-adjusted RRs of MI

**TABLE 2. NSAID Use in the Aspirin and Placebo Groups and Subsequent Myocardial Infarction Separately for Each Questionnaire**

	Baseline		6 Mo		12 Mo		24 Mo		36 Mo		48 Mo		60 Mo	
	n	MI*	n	MI*	n	MI*	n	MI*	n	MI*	n	MI*	n	MI*
Placebo	10 795	26	8520	18	8185	36	8044	28	7176	47	7436	26	7354	5
Placebo+1–59 NSAID	175	1	2161	4	2402	12	1451	4	1987	10	2590	12	2573	0
Placebo+≥60 NSAID	29	0	133	0	196	0	192	0	210	0	248	1	244	0
Aspirin	10 780	14	8517	11	8172	22	8104	17	7299	15	7492	22	7398	2
Aspirin+1–59 NSAID	195	0	2203	4	2420	8	1432	5	2038	3	2578	5	2561	1
Aspirin+≥60 NSAID	25	0	110	0	188	3	179	3	159	0	230	0	225	0
Missing NSAID info	72	1	404	1	450	1	2535	5	2969	2	1169	3	1298	0
Cumulative died	0	...	23	...	58	...	134	...	233	...	328	...	418	...
Total	22 071	42	22 071	38	22 071	82	22 071	62	22 071	77	22 071	69	22 071	8

\*MI indicates MI in the subsequent time interval.

**TABLE 3. RRs and Their 95% CIs of MI According to Time-Varying NSAID Use Separately for Aspirin and Placebo Groups**

	Randomized to Aspirin			Randomized to Placebo				
	MI, n	Age-Adjusted* RR (95% CI)	Model 1† RR (95% CI)	Model 2‡ RR (95% CI)	MI, n	Age-Adjusted* RR (95% CI)	Model 1† RR (95% CI)	Model 2‡ RR (95% CI)
None	107	1.00	1.00	1.00	193	1.00	1.00	1.00
1–59 d/y	26	1.18 (0.76–1.83)	1.21 (0.78–1.87)	1.19 (0.77–1.85)	44	1.17 (0.84–1.63)	1.14 (0.81–1.60)	1.15 (0.82–1.63)
≥60 d/y	6	2.81 (1.23–6.41)	2.86 (1.25–6.56)	2.84 (1.24–6.52)	1	0.21 (0.03–1.52)	0.21 (0.03–1.48)	0.20 (0.03–1.46)

\*Adjusted for age at baseline (5-year increments).

†Model 1: adjusted for baseline information on age, body mass index, exercise, history of arthritis, smoking status, and randomized  $\beta$ -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.

were 1.12 (95% CI, 0.73 to 1.74) for NSAID use on 1 to 59 d/y and 2.61 (95% CI, 1.14 to 5.98) for NSAID use on ≥60 d/y compared with no NSAID use. For the placebo group, the RRs of MI were 1.09 (95% CI, 0.78 to 1.54) for NSAID use on 1 to 59 d/y and 0.21 (0.03 to 1.49) for NSAID use on ≥60 d/y compared with never use. Additional adjustment for risk factors for MI did not attenuate the RR associated with aspirin and regular NSAID use.

### Discussion

In subgroup analyses of data from a large randomized trial, we found a >2-fold increased risk of MI among participants randomized to aspirin who also took other NSAIDs on ≥60 d/y. Participants randomized to placebo who used NSAIDs regularly had a nonsignificantly reduced risk of MI. These results are compatible with the possibility that NSAIDs inhibit the clinical benefits of aspirin on first MI. We found no association between intermittent use of NSAIDs (between 1 and 59 d/y) and subsequent development of MI among aspirin or placebo users.

Aspirin reduces the incidence of first and recurrent MI<sup>1,4</sup> by its ability to irreversibly block COX-1. This inhibits production of thromboxane A<sub>2</sub> and thus increases platelet inhibition.<sup>18</sup> This effect lasts for the lifetime of the platelet. Nonselective NSAIDs also inhibit platelet activity of COX-1,<sup>8</sup> but this effect does not persist throughout the dosing interval.<sup>9</sup> Aspirin and NSAIDs share a common docking site on COX-1, providing the possibility of competitive interaction. Basic research findings,<sup>19,20</sup> a crossover study in healthy subjects,<sup>12</sup> and 1 observational study<sup>13</sup> support this hypothesis. In the crossover study by Catella-Lawson et al,<sup>12</sup>

concomitant administration of 400 mg ibuprofen every morning antagonized the irreversible platelet inhibition of COX-1 induced by 81 mg aspirin. This inhibition could be bypassed, such as when aspirin was given before a single dose of ibuprofen. Intake of enteric-coated ibuprofen 3 times/d inhibited the effect of aspirin on platelets, even when the aspirin was taken before the ibuprofen. No interaction was found between concomitant intake of aspirin and rofecoxib, acetaminophen, or diclofenac.

A recent observational study of secondary prevention by MacDonald and Wei<sup>13</sup> identified 7107 patients from Scotland who were discharged after first admission for cardiovascular diseases and followed them up for 8 years. Four discharge groups were compared: low-dose (<325 mg) aspirin alone, aspirin plus ibuprofen, aspirin plus diclofenac, and aspirin plus another NSAID. Compared with users of aspirin alone, those also using ibuprofen had a relative risk of 1.73 (95% CI, 1.05 to 2.84) for cardiovascular mortality. Combined use of aspirin and diclofenac or other NSAIDs did not increase the risk. Although the authors could control for several potential confounding factors, the nature of their data did not allow them to control for lifestyle factors such as smoking and exercise.

The strengths of our study include the large number of endpoints and participants, randomized data on aspirin use, prospectively collected data on NSAID use, and confirmation of MI by medical record review. We incorporated change of NSAID use over time in our analyses, and we could differentiate between the effects of intermittent and regular NSAID use. We performed sensitivity analyses on a different NSAID use cutoff and included MI events that occurred before the end of the study but could not be included in the final report

**TABLE 4. RRs and Their 95% CIs of MI According to Randomized Treatment Assignment and Time-Varying NSAID Use**

	Age-Adjusted* RR (95% CI)	Model 1† RR (95% CI)	Model 2‡ RR (95% CI)
Placebo	1.00	1.00	1.00
Placebo+1–59 NSAIDs	1.14 (0.82–1.59)	1.12 (0.79–1.57)	1.13 (0.80–1.58)
Placebo+≥60 NSAIDs	0.22 (0.03–1.55)	0.22 (0.03–1.54)	0.21 (0.03–1.50)
Aspirin	0.55 (0.43–0.70)	0.55 (0.43–0.70)	0.56 (0.44–0.72)
Aspirin+1–59 NSAIDs	0.67 (0.44–1.01)	0.68 (0.45–1.03)	0.69 (0.46–1.05)
Aspirin+≥60 NSAIDs	1.49 (0.66–3.37)	1.53 (0.68–3.46)	1.57 (0.70–3.56)

\*Adjusted for age at baseline (5-year increments).

†Model 1: adjusted for baseline information on age, body mass index, exercise, history of arthritis, smoking status, and randomized  $\beta$ -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.

of the aspirin arm of the PHS.<sup>1</sup> Both sensitivity analyses led to similar results. Furthermore, the PHS study population was relatively homogeneous, which reduces confounding by several variables, including access to medical care, educational attainment, and socioeconomic status.

Our study has several limitations. In contrast to the randomized data on aspirin, the data on NSAID use were observational. Thus, bias and confounding are plausible alternative explanations for the findings, although this is limited by the prospective method of data collection and adjustment for a large number of covariates. In addition, all post hoc subgroup findings raise the possibility of chance as a plausible alternative explanation, a concern mitigated by the mechanistic plausibility of the hypothesis of competitive interaction between aspirin and NSAIDs. We had no information on the brand and dosage of the NSAIDs used and thus can give only average effects over all NSAIDs. During the study period, however, ibuprofen was a widely used non-aspirin NSAID in the US market.<sup>21</sup> Because the study participants were apparently healthy at baseline, relatively few used NSAIDs regularly. In addition, few MIs occurred in the exposed groups. This is reflected by the wide range of the CIs around the relative risks. Thus, these relative risks should be interpreted with caution. Biological plausibility must also be taken into account. This is particularly true for the relative risks in the placebo and high NSAID-intake group, in which only 1 MI occurred. Although some controversy exists regarding a possible cardioprotective effect of the nonselective NSAID naproxen,<sup>22–25</sup> an overall cardioprotective effect of NSAIDs is not expected.<sup>9</sup>

Another limitation to the generalizability of our findings involves the nature of the cohort, which included only male US physicians, 92% of whom were Caucasian. We have no reason to believe, however, that the study population and the general population differ with respect to the mechanism by which aspirin and NSAIDs may interact. The data on all covariates were collected by self-administered questionnaires. Although physicians are likely to provide health-related information accurately,<sup>26</sup> random misclassification is plausible.

In summary, these randomized data on aspirin use and prospective observational subgroup data on NSAID use over a mean follow-up period of 5 years are compatible with the possibility that regular but not intermittent use of NSAIDs inhibits the clinical benefits of aspirin on first MI.

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