Letters to the Editor must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Authors of letters selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication. Please submit three typewritten, double-spaced copies of the letter to Herbert L. Fred, MD, % the Circulation Editorial Office. Letters will not be returned.

**Correspondence**

**Throw Away the Aspirin and Take Nonsteroidal Anti-Inflammatory Drugs for the Primary Prevention of Myocardial Infarction**

To the Editor:

We read with interest the article by Kurth et al, postulating that regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) inhibits the protective benefits of aspirin against first myocardial infarction (MI). We sought to explore this unexpected finding further. Given the trial’s virtually complete follow-up of all patients at regular time intervals, the small amount of variability in NSAID use between follow-up questionnaires, and the absence of potential confounders, we were able to derive reasonable estimates of the 5-year risks of MI using information from Tables 3 and 4 of Kurth et al, which are presented in the Table below. It is apparent that NSAID use was a statistically significant effect modifier ($P=0.016$ for likelihood ratio test of interaction from logistic regression); the differences in risks between the placebo group and the aspirin group were 1.0%, 1.0%, and –2.8% for none, intermittent, and regular NSAID use, respectively. However, the test for interaction analysis was based on a very small number of MIs occurring among participants using $\geq 60$ days/year of NSAIDs, 1 in the placebo group and 6 in the aspirin group. The 5-year risk of MI in the 200 participants taking no aspirin but $\geq 60$ days/year of NSAIDs was only 0.5%, less than half of the 1.2% risk among $\geq 50$ participants taking aspirin alone. An alternate postulate arising from these data is that aspirin avoidance, not NSAID avoidance, would be the best strategy for primary prevention of MI. Because the significance attained by the test of interaction was more likely due to the extremely low risk of MI than to the increased risk among participants taking both aspirin and $\geq 60$ days/year of NSAIDs, the authors’ interpretation and our alternate interpretation of the data are questionable. Moreover, had a single additional participant taking $\geq 60$ days/year of NSAIDs in the placebo group experienced an MI, the test of interaction would not have reached statistical significance ($P=0.054$).

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**Response**

Eliasziw and Hill provide an intriguing alternative explanation for our findings. However, their explorations represent data-derived hypothesis formulation. Further, we disagree that our finding was “unexpected.” Indeed, Catella-Lawson et al provided a cogent and plausible biological mechanism that was supported by findings of an observational study by MacDonald and Wei. In a *priori* hypothesis testing, we found that regular, but not intermittent, use of NSAIDs inhibits the clinical benefit of aspirin on first myocardial infarction (MI). We discussed the limitation of the small number of MI cases in exposure subgroups and emphasized other potential limitations including chance, bias, and confounding.

Eliasziw and Hill created an *a posteriori* data scenario that would yield a “nonsignificant” likelihood ratio test for the interaction between aspirin and other NSAIDs ($P=0.054$) with respect to first MI. Because the $P$ value is influenced by sample size, the 0.05 cutoff should not reflect the only judgment of a “true” effect. Instead, biological plausibility and findings of other studies should also be taken into account.

Eliasziw and Hill postulate that aspirin avoidance would be the best strategy for primary prevention of MI from post hoc subgroup analyses of observational data. The totality of evidence on this question includes randomized data from the aspirin component of the Physicians’ Health Study, which was terminated early by the independent Data Safety Monitoring Board principally as a result of the emergence of a statistically extreme 44% reduction in risk of a first MI. Since that time, 4 additional randomized trials have been published, 3 of which also indicate a benefit of aspirin. Most recently, a meta-analysis of these trials demonstrates a statistically extreme 32% reduction in risk of a first MI among apparently healthy subjects randomized to aspirin.

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**Estimated 5-Year Risk of MI in Kurth et al Cohort**

<table>
<thead>
<tr>
<th>NSAID Use</th>
<th>Placebo (n/N)</th>
<th>Aspirin (n/N)</th>
<th>5-Year Risk Difference</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.2% (193/8773)</td>
<td>1.2% (107/8917)</td>
<td>1.0%</td>
<td>(0.6% to 1.4%)</td>
</tr>
<tr>
<td>1–59 d/y</td>
<td>2.5% (44/1760)</td>
<td>1.5% (26/1733)</td>
<td>1.0%</td>
<td>(0.07% to 1.9%)</td>
</tr>
<tr>
<td>$\geq 60$ d/y</td>
<td>0.5% (1/200)</td>
<td>3.3% (6/182)</td>
<td>–2.8%</td>
<td>(–5.6% to –0.03%)</td>
</tr>
</tbody>
</table>

$n$ indicates number of MIs over mean follow-up of 5 years; $N$, estimated average number of participants followed for 5 years; and d/y, days per year.


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Michael "Tex" Eliasziw and Michael D. Hill

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