Response

Eliaszw 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 MacDonal 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.

Eliaszw 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.

Eliaszw 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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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 ≥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 ≥60 days/year of NSAIDs was only 0.5%, less than half of the 1.2% risk among 8917 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 ≥60 days/year of NSAIDs, the authors’ interpretation and our alternate interpretation of the data are questionable. Moreover, had a single additional participant taking ≥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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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>≥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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