

## CORRESPONDENCE



## Aspirin in the Prevention of Cardiovascular Disease in Women

**TO THE EDITOR:** Ridker et al. (March 31 issue)<sup>1</sup> conclude that primary prophylaxis with aspirin to prevent myocardial infarction is ineffective in young, healthy women. However, the majority of patients in this study (84.5 percent) had a 10-year risk of less than 5 percent for an incident myocardial infarction and therefore would not have received aspirin as primary prophylaxis, according to the American Heart Association guidelines. The American Heart Association published recommendations in 2002 stating that aspirin should be used as primary prevention for coronary events in persons with a 10-year risk of an incident myocardial infarction that is greater than 10 percent.<sup>2</sup> Although the results of the study by Ridker et al. are interesting, we need a trial based on practice according to current, established guidelines.

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1. Ridker PM, Cook NR, Lee I-M, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:293-304.
2. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation* 2002;106:388-91.

**TO THE EDITOR:** The press coverage of the study by Ridker et al. indicated that aspirin does not prevent heart attacks in women. This message is consistent with the abstract's concluding statement, "In this large, primary-prevention trial among women, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction." However, this conclusion is misleading. A more accurate statement would be that very-low-dose aspirin (100 mg every other day) is not effective in preventing myocardial infarction in women.

In the Primary Prevention Project trial,<sup>1</sup> 100 mg of aspirin per day was effective in preventing myocardial infarction in women and in men. However, in the Hypertension Optimal Treatment trial,<sup>2</sup> 75 mg of aspirin per day was effective as prevention in men but ineffective in women. It would not be unreasonable to conclude from these three trials that the minimum dose of aspirin needed for a cardioprotective effect is higher in women than in men and is greater than 75 mg per day. The study by Ridker et al. did not establish that aspirin is ineffective in preventing myocardial infarction in women.

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1. de Gaetano G, Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001;357:89-95. [Erratum, *Lancet* 2001;357:1134.]
2. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62.

### THIS WEEK'S LETTERS

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**THE AUTHORS REPLY:** Dr. Schwartz correctly notes that the majority of the participants in the Women's Health Study were at low risk for coronary heart disease, as measured by the Framingham risk score. However, 1100 participants did have a risk of coronary heart disease that was 10 percent or greater. Among these high-risk participants, the findings were consistent with the overall findings of the trial, with no significant benefit with respect to the primary end point of major cardiovascular events for women taking aspirin as compared with those taking placebo (61 events in the aspirin group and 60 in the placebo group,  $P=0.74$ ); there was a benefit for total stroke (17 events vs. 32, respectively;  $P=0.04$ ) and a trend toward benefit for ischemic stroke (16 vs. 29,  $P=0.07$ ), and there was no benefit for myocardial infarction (32 vs. 23,  $P=0.15$ ). Thus, although overall the population had a low risk of cardiovascular events, it is important to note that there was no evidence of a modification of the effect of aspirin according to levels of the Framingham risk score in our study.

Dr. Dalen is correct in pointing out that our trial

demonstrated that the specific dose of 100 mg of aspirin every other day was not associated with a reduction in myocardial infarction overall, and he raises the important question of whether this very low dose was inadequate to produce a cardioprotective effect in women. Although we agree that it is certainly possible that the dose was inadequate, there was no direct evidence to support this in the Women's Health Study. We showed that levels of thromboxane and prostacyclin were reduced with 100 mg of aspirin every other day; we observed the expected increased risk of gastrointestinal bleeding, hemorrhagic stroke, nongastrointestinal bleeding, and peptic ulcer, and 100 mg every other day was adequate both to lower the risk of stroke overall and to lower the risk of myocardial infarction as well as stroke in women 65 years of age or older. However, the issue of the lowest effective dose in both women and men requires further research.

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## The Ubiquilin 1 Gene and Alzheimer's Disease

**TO THE EDITOR:** Bertram et al. (March 3 issue)<sup>1</sup> report that in two family-based cohorts, a genetic variant of the UBQ-8i single-nucleotide polymorphism on chromosome 9q22 putatively increased the risk of Alzheimer's disease in an additive disease model. We attempted replication in a similarly ascertained but independent family-based data set based on 288 families in which linkage to microsatellites at 9q22.1 and 9q34.2 was demonstrated in a genome scan.<sup>2</sup> In addition, we analyzed a previously described independent data set based on patients with Alzheimer's disease and 1005 controls.<sup>3</sup>

We found no association between the risk of Alzheimer's disease and UBQ-8i, or any of six additional single-nucleotide polymorphisms within the *UBQLN1* gene, in either of the independent data sets. However, using age at onset as the trait of interest, we found a significant association between the putative UBQ-8i risk allele and an older age at onset in a recessive-disease model only in our case-control data set (Table 1). We found an additional, significant effect related to age at onset only in our family-based data set with a different single-nucleotide polymorphism in *UBQLN1*. Thus, although we

found no evidence of risk with any single-nucleotide polymorphism in *UBQLN1*, our results suggest that age at onset may be germane and that additional, detailed examination of *UBQLN1*, including a search for the functional variant (or variants), is warranted.

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1. Bertram L, Hiltunen M, Parkinson BS, et al. Family-based association between Alzheimer's disease and variants in *UBQLN1*. *N Engl J Med* 2005;352:884-94.
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3. van der Walt JM, Dementieva YA, Martin ER, et al. Analysis of European mitochondrial haplogroups with Alzheimer disease risk. *Neurosci Lett* 2004;365:28-32.