EDITORIAL

Should Aspirin Be Used for Primary Prevention in the Post-Statin Era?

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Between 1853 and 1897, German chemists learned to efficiently combine sodium salicylate with acetyl chloride to produce acetylsalicylic acid. That compound, trademarked as aspirin, proved to be a remarkable antiinflammatory and antithrombotic agent and one of the most widely used drugs in pharmaceutical history.

As the medical community's understanding of platelet biology and atherothrombosis evolved, it became clear that aspirin was highly effective in the secondary prevention of cardiovascular events. Subsequent large-scale primary prevention trials, including the Physicians' Health Study and the Women's Health Study, provided evidence of small-to-modest cardiovascular benefits in high-risk patients, albeit with an increased risk of bleeding.[1,2] Yet these and other early prevention trials of aspirin were conducted at a time when smoking was common, blood pressure control suboptimal, and aggressive lipid lowering rare. Thus, the risks and benefits of prophylactic aspirin in current preventive practice remain uncertain, as do standards for dose and duration.[3] This calculus is further complicated by data suggesting that the use of aspirin may lower the incidence of colorectal cancers.[4]

In this issue of the *Journal* and in a recent issue of the *Lancet*, results are reported for three primary prevention trials of aspirin: the ASCEND (A Study of Cardiovascular Events in Diabetes) trial,[5] which involved participants with diabetes; the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial,[6] which was intended to involve high-risk participants without diabetes; and the ASPREE (Aspirin in Reducing Events in the Elderly) trial,[7-9] which involved older participants. These new trials share a common theme in that they address the level of risk, if any, that justifies the use of aspirin for primary prevention in current practice.

In the ASCEND trial, 15,480 participants with diabetes were randomly assigned to receive aspirin at a dose of 100 mg daily or matching placebo. During a mean follow-up of 7.4 years, the rate of serious vascular events was 8.5% with aspirin as compared with 9.6% with placebo (rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01); thus, the use of aspirin was associated with a 12% decrease in the rate of serious vascular events. This benefit, however, came at the cost of a 29% increase in the rate of major bleeding events (4.1% with aspirin vs. 3.2% with placebo; rate ratio, 1.29; 95% CI, 1.09 to 1.52, P=0.003). When weighing the vascular benefit against the bleeding risk, it is important to recognize that the definition of myocardial infarction in contemporary trials often includes small ischemic events that can be detected only on high-sensitivity cardiac-enzyme testing. If such small myocardial events and episodes of transient ischemic attack are excluded from the primary end point of serious vascular events, the net benefit–risk ratio for aspirin among high-risk participants with diabetes becomes smaller still. In the ASCEND trial, all-cause mortality was neutral between the trial groups (rate ratio, 0.94; 95% CI, 0.85 to 1.04).

The ARRIVE trial was intended to investigate the role of aspirin at a dose of 100 mg daily as compared with placebo for the primary prevention of cardiovascular events among high-risk participants without diabetes. However, during 5 years of follow-up among 12,546 participants,

the observed 10-year risk estimates were substantially lower than predicted. Thus, in interpreting the results of the ARRIVE trial, the participants should be considered to have low to moderate risk. In this context, the results are consistent with the results of previous trials, in which the use of aspirin conferred no vascular benefit but resulted in a significant increase in the risk of bleeding complications. In the intention-to-treat analysis of the ARRIVE trial, the incidence of the composite primary outcome of myocardial infarction, stroke, unstable angina, transient ischemic attack, or death from cardiovascular causes was 4.3% with aspirin and 4.5% with placebo (hazard ratio, 0.96; 95% CI, 0.81 to 1.13; P=0.60), whereas the incidence of gastrointestinal bleeding events with aspirin was twice the incidence with placebo (hazard ratio, 2.1; 95% CI, 1.36 to 3.28; P<0.001). In a per-protocol analysis that partially addressed differences between the trial groups in adherence to the trial regimen (but may have introduced bias), the results were more optimistic with respect to a benefit of aspirin. In the ARRIVE trial, there was no significant difference between the trial groups in the rate of fatal bleeding events, and all-cause mortality was again neutral between the two groups (hazard ratio, 0.99; 95% CI, 0.80 to 1.24; P=0.95).

The results of the ASPREE trial were published in three separate articles. The trial involved 19,114 participants in Australia and the United States who were 70 years of age or older and were free from cardiovascular disease, dementia, and disability at trial entry. The participants were randomly assigned to receive 100 mg per day of enteric-coated aspirin or placebo and were followed for up to 5 years. In the ASPREE trial, the use of aspirin conferred no benefit with respect to the prespecified composite primary end point of death, dementia, or persistent physical disability, an issue of considerable importance in the elderly (hazard ratio with aspirin vs. placebo, 1.01; 95% CI, 0.92 to 1.11; P=0.79). Of the primary end-point events that occurred, half were death, 30% dementia, and 20% persistent physical disability. Similar to the ARRIVE trial, the ASPREE trial showed no evidence of a cardiovascular benefit of aspirin (hazard ratio for cardiovascular disease with aspirin vs. placebo, 0.95; 95% CI, 0.83 to 1.08), yet the risk of major bleeding was again higher with aspirin than with placebo (hazard ratio, 1.39; 95% CI, 1.18 to 1.62; P<0.001).

With regard to other outcomes in the ASPREE trial, the investigators report that the rate of the secondary end point of death from any cause was potentially higher with aspirin than with placebo (hazard ratio, 1.14; 95% CI, 1.01 to 1.29). This finding is at odds with the results of previous primary prevention trials of aspirin and with the results of the ASCEND and ARRIVE trials (Fig. 1). The potentially higher mortality with aspirin was limited to the Australian cohort and was driven by an unexpectedly higher risk of cancer-related death with aspirin than with placebo (hazard ratio, 1.31; 95% CI, 1.10 to 1.56). These latter data should be interpreted with caution. In the ASPREE trial, the observed higher cancer-related mortality with aspirin was not specific to cancer site or pathologic type, and the potential adverse effect of aspirin on the incidence of cancer was of smaller magnitude than the effect on the incidence of fatal cancer; in contrast, in the ASCEND trial, which had a longer average follow-up time than the ASPREE trial, no increase or decrease in the rate of cancer was observed with the use of aspirin. Data on cancer from the ARRIVE trial have not yet been reported. Given such uncertainty and given the long latencies for cancer, continued follow-up from all three trials would help to robustly address hypotheses regarding benefits or harms of aspirin on the occurrence of site-specific cancer.

With regard to patient care, the results of these contemporary aspirin trials, which showed minimal benefits and consistent bleeding risks, should be considered alongside the results of contemporary statin trials. In primary prevention trials, the use of statins was associated with a 25% decrease in the risk of major vascular events for every 1 mmol per liter decrease in the low-density lipoprotein cholesterol level (rate ratio with statin vs. placebo, 0.75; 95% CI, 0.69 to 0.82).[10] This statistically certain benefit was associated with an enviable safety profile and was not associated with the bleeding complications seen with aspirin. The percentage of participants who were taking statins in the ASPREE, ARRIVE, and ASCEND trials was 34%, 43%, and 75%, respectively.

What can we conclude about the use of aspirin for prophylaxis 150 years after its chemical synthesis? For secondary prevention, in which risk is determined largely by the extent of atherosclerotic disease, the benefits of aspirin outweigh

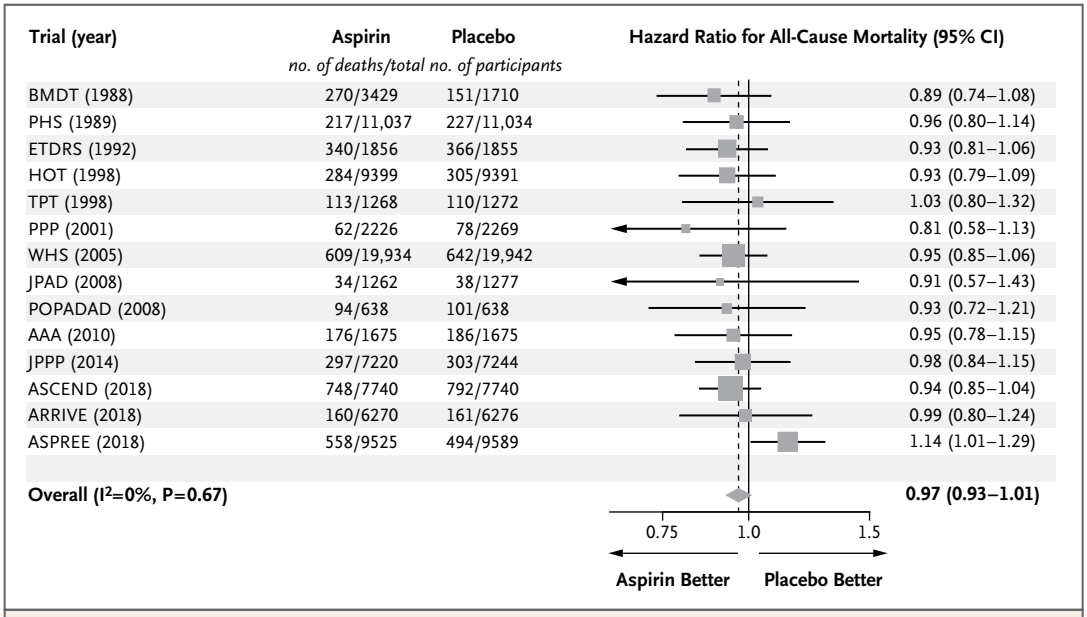

Figure 1. Aspirin and All-Cause Mortality in 14 Primary Prevention Trials.

BMDT denotes British Male Doctors Trial, PHS Physicians' Health Study, ETDRS Early Treatment Diabetic Retinopathy Study, HOT Hypertension Optimal Treatment, TPT Thrombosis Prevention Trial, PPP Primary Prevention Project, WHS Women's Health Study, JPAD Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes, POPADAD Prevention of Progression of Arterial Disease and Diabetes, AAA Aspirin for Asymptomatic Atherosclerosis, JPPP Japanese Primary Prevention Project, ASCEND A Study of Cardiovascular Events in Diabetes, ARRIVE Aspirin to Reduce Risk of Initial Vascular Events, and ASPREE Aspirin in Reducing Events in the Elderly. The meta-analysis was performed with a random effects model (I^2=0% for heterogeneity, P=0.67). The boxes indicate the hazard ratio for all-cause mortality in each trial, with box size proportional to sample size. The diamond indicates the overall hazard ratio and its confidence interval. Arrows on the lines for 95% confidence intervals indicate that the limit is beyond the scale.

the risks of bleeding. In contrast, for primary prevention, in which risk is determined largely by age and the presence or absence of diabetes, the benefit–risk ratio for prophylactic aspirin in current practice is exceptionally small. Thus, beyond diet maintenance, exercise, and smoking cessation, the best strategy for the use of aspirin in the primary prevention of cardiovascular disease may simply be to prescribe a statin instead.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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