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FDA Comes Out Against Aspirin To Prevent First Heart Attacks

In the latest development in a long-simmering debate, the FDA has announced that aspirin should not be marketed for the prevention of a first heart attack or stroke in people with no history of cardiovascular disease. The announcement follows FDA's rejection on Friday of Bayer Healthcare's decade-old petition requesting approval of a primary prevention indication. [PDF of FDA rejection letter]

Aspirin is still widely used for primary prevention. Many physicians, including cardiologists, recommend it for some of their patients. The American Heart Association currently supports the use of aspirin for primary prevention when recommended by a physician in high risk patients. (There is widespread agreement that for secondary prevention the benefits of aspirin outweigh the risks and should be used to prevent a second heart attack or stroke after an earlier cardiovascular event.)

In its statement the FDA said it had "reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In

fact, there are serious risks associated with the use of aspirin, including increased risk of bleeding in the stomach and brain." The FDA reaffirmed the use of aspirin in secondary prevention.

Cardiologist Sanjay Kaul, who often serves as an FDA consultant and advisory committee member, offered the following comment:

> There have been 9 primary prevention trials evaluating the role of aspirin in CVD. Not a single trial has been positive so far. When the data are pooled together in a meta-analysis, there is a small, but statistically significant, benefit which is counterbalanced by an equally small but statistically significant risk of bleeding. On balance, the totality of evidence does not yield a favorable benefit-risk ratio for aspirin in primary prevention. FDA declined to approve aspirin for primary prevention in 2003. Overall, I agree with the FDA's stance. The tough task ahead for professional societies is to acknowledge the tepid evidentiary support for their guideline recommendations. Equally challenging a task is that patients will have to recalibrate their opinions about aspirin for primary prevention of CV disease.

Ethan Weiss, a cardiologist at the University of California, San Francisco, sent the following comment:

> The FDA Consumer Update on Aspirin for primary prevention reopens a discussion that has gone on in some form or other since the late 1980's. The

publication of the Physician's Heath Study in 1989 led to a series of trials designed to examine the benefits of low-dose aspirin for primary prevention of cardiovascular events. The FDA response letter to Bayer provides detail on the trials and the results. The letter concludes: "While there is some evidence that aspirin may be associated with a reduction of nonfatal MIs, this finding has not been consistently demonstrated across trials."

In my opinion, this is a reasonable conclusion. It also happens to be at odds with the most recent guidelines from both the AHA/ACC (2002) as well as the USPSTF (2011). This leaves physicians and patients in a difficult place. In my own practice, I have reserved aspirin for primary prevention for only the highest risk patients. The evidence provided in the letter from the FDA to Bayer is very compelling and will certainly make me think before recommending aspirin for primary prevention in low and moderate risk patients. However, most everyone agrees that aspirin is beneficial in secondary prevention. Presumably, the clear benefit here derives from the increased risk of second events in this population. The thinking has always been that if you can identify the patients who are at high risk for their incident event, aspirin may reduce the risk similar to its effect in secondary prevention. Yet, as the FDA letter states, trials have failed to demonstrate benefit in high risk primary prevention patients even those with diabetes which is considered a CHD risk equivalent in many guidelines. Clearly there is room for more study. However, given the numbers of patients and the associated costs of such trials, it seems unlikely we will get an answer soon if ever. Perhaps the lesson

is that we do not yet know how to predict high risk primary prevention patients and that resources and efforts should be focused on how to define high risk before spending more money on trials designed to test an intervention in a high risk population.