CLINICAL DECISIONS
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"Doctor, Should I Keep Taking an Aspirin a Day?"

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Man Who Takes Low-Dose Aspirin Every Day

Amanda Fernandes, M.D.

Mr. Evans is a 72-year-old white man who visits your clinic for routine follow-up. His medical history is notable for hypertension and hyperlipidemia, and he began taking aspirin (81 mg daily), prescribed for primary prevention of coronary heart disease and stroke, approximately 5 years ago. He tells you that he recently heard a news report that daily aspirin may be harmful, and he wonders whether he should stop taking it. His other medications include hydrochlorothiazide (12.5 mg daily) and simvastatin (40 mg daily; also initially prescribed approximately 5 years ago). His body-mass index (the weight in kilograms divided by the square of the height in meters) is 30.

Mr. Evans has never smoked; he drinks one or two beers on the weekend. He reports that he reluctantly accompanies his wife on a 30-minute walk about three times a week. He has no known family history of coronary heart disease. His father once had a devastating stroke, and he is afraid of something similar happening to him.

A review of systems is unremarkable. Mr. Evans had recently received a diagnosis of external hemorrhoids after noticing blood in the toilet. The bleeding stopped after he started taking laxatives. His blood pressure is 130/72, and his physical examination is unremarkable.

TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the published literature, your own experience, published guidelines, and other information sources.

1. **Recommend continuing aspirin.**
2. **Recommend discontinuing aspirin.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

OPTION 1

Recommend Continuing Aspirin

John W. McEvoy, M.B., B.Ch., M.H.S.

It's fair to say that aspirin for the primary prevention of cardiovascular disease has become increasingly hard to defend, particularly in the wake of three recent clinical trials.[1-3] However, I believe that there remains sufficient equipoise in the evidence to consider recommending aspirin in selected situations.[4]

First of all, meta-analyses of the totality of data, including the recent clinical trials, consistently show that low-dose aspirin reduces the incidence of nonfatal myocardial infarction and nonfatal cardiovascular disease.[5,6] For those who argue that evidence for the benefit of aspirin in reducing nonfatal myocardial infarction has waned in the most recent trials,[6] I would counter that the diagnostic criteria for myocardial infarction and the sensitivity of the biomarkers used have changed substantially over the years. The markedly lower incidence of myocardial infarction among participants randomly assigned

to aspirin that is evident in older trials, which relied on electrocardiography and less sensitive biomarkers (e.g., creatine kinase), continues to demand our respect, since those trials most likely captured larger myocardial infarctions. In contrast, modern trials have used more sensitive biomarkers such as elevated levels of troponin, which often represent myocardial injury rather than the type-1 form of myocardial infarction that involves atherosclerotic plaque rupture, for which aspirin provides a benefit. Furthermore, adherence to aspirin was poor (between 60 and 70%) in the three 2018 trials,[1-3] with a substantial number of crossovers from placebo to aspirin, and the as-treated analyses,[2] although hypothesis generating, continued to show a significantly lower incidence of nonfatal myocardial infarction among those who received aspirin than among those who did not.

What about end points related to death? Although prophylactic aspirin did not reduce the incidence of fatal cardiovascular disease or death in contemporary trials (note that it has never been reliably shown to increase mortality, even in the Aspirin in Reducing Events in the Elderly [ASPREE] trial[1]), one must also consider that the case fatality rate from myocardial infarction has fallen dramatically[7] and that with relatively short periods of follow-up, recent trials were underpowered to evaluate mortality outcomes. Furthermore, trials of relatively short duration are less likely to capture downstream complications of myocardial infarction, such as ischemic cardiomyopathy, which can have a long latency period and therefore require extended follow-up of 10 years or more to detect clinical sequelae.

Without doubt, aspirin causes bleeding. Patients need to be told this. However, most bleeding is mild, and the absolute risk of fatal or intracranial bleeding during treatment with aspirin is far lower than the absolute risk of having a cardiovascular event. Furthermore, even if the number needed to treat with aspirin to prevent nonfatal cardiovascular disease is approximately equal to the number needed to harm to cause bleeding,[5] most patients prefer to avoid a heart attack or an atheroembolic stroke than a bleeding episode.[8]

If we assume that Mr. Evans's lipid levels are normal, since he is receiving simvastatin, this 72-year-old man has an estimated 10-year risk of cardiovascular disease of 20 to 25%. Despite the findings of the ASPREE trial (which showed no overall benefit of aspirin for primary prevention among adults who were more than 70 years of age),[1] I do not think that Mr. Evans's age automatically rules aspirin out, since the totality of data does not suggest a significant modification of the effect of low-dose aspirin according to age.[6,9] Therefore, after you discuss the risks and benefits with Mr. Evans, if he wants to continue taking aspirin for primary prevention, I think that approach is reasonable — with the following caveat: no longer can aspirin be started and then forgotten. Rather, regular (at least annual) reappraisal of the risks and benefits is needed. For persons in whom the most likely complications that will develop in the next year will be cardiovascular and who wish to continue taking low-dose aspirin after a discussion of potential risks and benefits, I believe that it is reasonable to continue aspirin. For those who have competing noncardiovascular conditions, or in whom such conditions are likely to develop, I believe that reappraisal of the aspirin regimen with the patient might then no longer justify its use for primary prevention.

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

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OPTION 2

Recommend Discontinuing Aspirin

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The first thing to ask before deciding whether Mr. Evans should continue taking aspirin is whether there is a role for aspirin in primary prevention at all. The answer to that question is not straightforward. The cardiovascular benefits associated with aspirin for primary prevention are modest and are countered by an increase in major bleeding.[10] Although the European Society of Cardiology does not recommend antiplatelet therapy in patients who are free of overt cardiovascular disease,[11] the U.S. Preventive Services Task Force recommends initiation of aspirin treatment depending on age and 10-year risk of cardiovascular disease.[12]

Recently, the 2019 American College of Cardiology–American Heart Association guideline on primary prevention of cardiovascular disease recommended a more restrictive use of aspirin.[4] This change in the U.S. recommendations was probably due to the results of three trials of aspirin for primary prevention published in 2018.[2,3,13] Two of the trials did not show any lower risk of major cardiovascular events with aspirin than with placebo,[2,13] and all three studies showed a significantly greater risk of major bleeding with aspirin. A meta-analysis of all published studies on aspirin for primary prevention showed that the cardiovascular benefits associated with aspirin were modest and equally balanced by major bleeding (0.38% absolute risk reduction in cardiovascular events and 0.47% increase in major bleeding).[5]

Mr. Evans is a 72-year-old man with a healthy lifestyle but with an increased risk of cardiovascular events, given his hypertension and hyperlipidemia. We do not know his cholesterol levels, but his 10-year risk of cardiovascular disease is greater than 20% if we estimate his cholesterol level to be 190 mg per deciliter (4.9 mmol per liter). It has been suggested that patients at high risk for cardiovascular events may benefit the most from preventive aspirin use. However, in the recently published meta-analysis,[5] aspirin use was associated with reductions in cardiovascular events and increases in major bleeding both in populations with low cardiovascular risk and in those with high cardiovascular risk.

Few elderly persons were included in the primary prevention trials before the recent ASPREE trial. In this trial, the median age of participants at the time of randomization was 74.[13] Here the use of aspirin did not result in a lower risk of cardiovascular disease than placebo but did result in a significantly higher risk of major bleeding. On the basis of this trial, aspirin would be of no benefit to Mr. Evans, but the risk of harm would be considerable.

Patient preferences should always be taken into consideration. Mr. Evans very much fears having a stroke and would probably be willing to take the risk of some bleeding if it means that he can prevent a stroke. Does aspirin protect against stroke? Studies have shown that aspirin primarily lowers the risk of nonfatal myocardial infarction and ischemic stroke, with little or no effect on the risk of total stroke (ischemic and hemorrhagic combined). Given the increased risk of intracranial bleeding with aspirin, I would recommend not prescribing aspirin and instead focusing on controlling his blood pressure, reducing his cholesterol level, and encouraging him to live a healthy lifestyle to protect against a stroke.

What else might influence our decision? The bleeding from his external hemorrhoids, which had stopped while he was still taking aspirin, is probably of little importance. If this had been major gastrointestinal bleeding, the arguments for stopping aspirin would have been even stronger.

In summary, if Mr. Evans were my patient, I would recommend that he stop taking aspirin. The absolute benefit associated with aspirin in this elderly man is small, if any, and is accompanied by a substantial increase in the risk of major bleeding.

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