Does the Public Need Protection from Itself?

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In December 1985, the US Food and Drug Administration (FDA)[1] announced its approval of an additional indication in the professional labeling for aspirin: "to reduce the risk of death and/or nonfatal myocardial infarction (MI) in patients with a previous infarction or unstable angina pectoris." This is an important new indication for aspirin in addition to its previously approved indication in reducing the risk of recurrent transient ischemic attacks in men.

The results of seven studies—six randomized, placebo-controlled multicenter trials[2-7] in 10,816 post-MI patients and one[8] in 1,266 men with unstable angina—were the basis for this new indication. Aspirin therapy in the MI patients was associated with a 20% reduction in the risk of subsequent death or nonfatal reinfarction over the four-year study period. This amounted to a median absolute decrease of 3% from the 12% to 22% event rates in the placebo groups.

In the 12-week study of patients with unstable angina treated with aspirin, the reduction in risk was about 50%, a 5% absolute reduction in event rate from the 10% rate in the placebo group.

The dosage of aspirin in the post-MI studies ranged from 300 to 1,500 mg/day; 324 mg was used in the study of unstable angina. Because two[2,8] of the trials used under 325 mg/day of aspirin and because laboratory data indicate that such dosage "inhibits platelet function fully," the FDA concluded that 300 or 325 mg of aspirin daily (solid buffered, solid plain, or buffered solution) is "a reasonable dose that would minimize gastrointestinal adverse reactions."

What adverse reactions were in fact seen? According to the *FDA Drug Bulletin*[1] 1,000 mg/day of aspirin was associated with more stomach pain, heartburn, nausea, vomiting, and gross gastrointestinal bleeding than placebo was. Symptoms and signs of gastrointestinal irritation were not increased by the buffered aspirin in solution used in the unstable angina trial. In addition, at a dosage of 1,000 mg/day, aspirin use was associated with small increases in systolic and diastolic pressure, BUN, and uric acid concentration. The clinical importance of these findings is unclear, and the FDA reminds us that patients with marked hypertension or renal insufficiency had been excluded from the trial in which these findings were described.

Curious about the FDA decision to call professional, but not public, attention

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to these findings, I wrote, on January 28, 1986, to FDA Commissioner Frank E. Young. He replied:

> We believe the indication is clearly directed to patients who should be under a doctor's care for a condition (heart attack or unstable angina) that they cannot diagnose or treat alone. It is important to realize that we do not believe there are data to show that aspirin is useful in patients who have not been shown to have one of these manifestations of coronary artery disease, and is not recommended as prophylaxis for such people.

Soon afterward, a physician friend, aware of my interest in such matters, mailed me a booklet provided to him by the Glenbrook Laboratories Division of Sterling Drug, Inc. The cover read: "Reduce your risk of heart attack or stroke . . . with aspirin." The text inside explained unstable angina, heart attack, and stroke, listed risk factors for heart attack and stroke, described how aspirin can help patients by affecting platelet function, and briefly related the findings on which the FDA had based its approval for the new labeling. Stapled to the back cover were four packets of aspirin, each containing two tablets of 325 mg each. There was also a coupon for a 50-cent rebate on the purchase of 100 to 300 tablets of Bayer® aspirin.

Sometime thereafter, full page ads for Bayer aspirin began to appear in national media with the heading: "News that could help save your life is worth repeating." The ad reproduced in full a story by Philip M. Boffey in the *New York Times* of October 11, 1985, describing the FDA decision and its basis. At the bottom of the ad was the sentence: "If you are a high-risk patient, ask your doctor about recently approved preventative aspirin therapy for heart attack."

I was fascinated. The drug firm was, it seemed to me, flouting the FDA's expressed desire to tell doctors, but not consumers, about the new labeling. Visions of punitive measures, law suits, first-amendment arguments, and the like began to run through my head. But nothing happened until July 6, 1986, when Surgeon General C. Everett Koop appeared on the CBS News program "Face the Nation." According to a *New York Times* story, "Koop said . . . that people 40 years of age and over should take daily doses of aspirin to prevent heart disease . . . [Aspirin] increases the blood's ability to stay fluid, preventing clogged veins and arteries that can lead to heart attacks." The story further quoted Koop as saying, "I take one aspirin a day."

Koop's televised advice would seem to make it difficult for FDA to slap the wrist of any aspirin manufacturer who mounts a television or newspaper or magazine campaign to educate the public about aspirin's demonstrated merits. Will wrist slapping occur? More important, *should* it?

Commissioner Young is correct in emphasizing that the available data do not support the prophylactic use of aspirin, to prevent heart attacks and death, by people who have not had a heart attack or do not have unstable angina. But the public knows, or should know, that risks of heart attack and stroke rise in those who smoke, have hypertension, hypercholesterolemia, diabetes, obesity, or stress, or do not exercise enough. They have been told this by no less authoritative an organization than the American Heart Association. People in ever-in-

creasing numbers jog daily to prevent heart attacks despite the lack of proper trials to demonstrate the efficacy (and safety) of such athletic efforts. What about aspirin's safety? Like every other drug, aspirin is not without hazard, particularly in those whose sensitivity to aspirin is manifested by asthma or allergic rashes. Yet an aspirin a day poses only negligible risk for most people, which is more than one can say about either heart attacks or jogging.

One cannot help wondering whether the best approach is not to deprive the public of important new information about aspirin and cardiovascular disease but to clearly educate the public about what is definitely known, what is not known, and what the apparent costs and risks are of action and of inaction. People are polled about all sorts of matters. What would the public say if polled on this issue?

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