Should You Take Aspirin to Prevent Heart Attack?

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"Nothing is Simple."—Harry Rowe Mimno,
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Abstract—The majority of physicians in the USA recommend aspirin for prevention of *first* heart attacks to almost everyone over the age of 50, even though women have not been included in the clinical trials of aspirin. While aspirin does prevent about 1/3 of first heart attacks, its side-effects are so severe as to cause a higher death rate overall than placebo. Non-fatal side-effects, such as internal bleeding and cataracts, are significant after years of aspirin use. The major study on which most recommendations are based did not utilize aspirin alone; therefore, the calcium and magnesium present in the buffered aspirin actually taken may have been responsible for some of the beneficial effects. Supplemental magnesium and vitamin E have been shown to be more effective than aspirin in lowering heart attack rates as well as overall death rates. Aspirin does reduce the incident of *second* heart attacks by about 1/5 when taken for a few weeks. Supplemental magnesium and coenzyme Q10 have been shown to be more effective than aspirin in treatment of cardiovascular disease.

Keywords: Aspirin—heart attack—cardiovascular disease—stroke—vitamin E—coenzyme Q10—magnesium—potassium.

Introduction

Recent advice given in books and articles for general audiences is contradictory. Many practicing cardiologists and other physicians still do not understand the findings in clinical studies and believe that this was all settled 10 years ago. Flaws have been claimed to exist in some of the largest and formerly best-regarded studies, including the supposed lack of an exact specification of what was taken that was supposed to be aspirin. As a result, studies of the supposed benefits of aspirin in preventing heart attacks continued during the 1990s. A skeptical examination of the benefits of aspirin attributed to the peer-reviewed medical literature shows frequent misinterpretation or worse by writers for lay audiences. This article will show that careful examination of original peer-reviewed papers will allow you to draw conclusions about who could benefit by taking aspirin which are at odds with some strongly held opinions. (The mean-
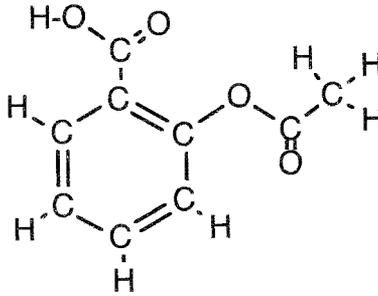
Fig. 1. Structural formula of aspirin (acetylsalicylic acid or ASA).

ing of medical terms may be found in ordinary or medical dictionaries, or
www.netscope.drkoop.com/search/query/ asp.)

What Is Aspirin?

The structural formula for aspirin is shown in Figure 1. The most common
chemical name for this organic compound is acetylsalicylic acid (ASA). There
are at least 32 other names for it, mostly trade names (Windholz, 1976). It was
first synthesized by Carl R. Gerhardt in 1853 (Mustard, 1982). The major ther-
apeutic use of ASA in providing relief from the pain of rheumatoid arthritis
was recognized by Felix Hoffman, an employee of Bayer AG, in 1897, who
administered ASA to his father, who tolerated ASA much better than other sal-
icylates already in use. ASA was not "invented" in 1897 as in the book *The As-
pirin Wars* (hereafter *Wars,* Mann & Plummer, 1991) (*Wars,* p. 7 and cover).
First trademarked in 1899 by Bayer AG (Vane & Botting, 1992), Leverkusen,
Germany, the name Aspirin™ became a generic term for ASA in the manner of
Kleenex and Frigidaire. For most of a century aspirin has been the preferred
treatment for arthritis pain and has been used for headache, fever, and, in the
last decade, prevention of heart attacks. It has been called the most successful
drug in history. A decade ago 1 in 5 Americans took aspirin every day (*Wars,*
cover).

   Not until the 1970s was the mode of action of aspirin worked out! Sir John
Vane was awarded the Nobel Prize for uncovering the mode of action of ASA
(Feinman, 1993). ASA inhibits the enzyme cyclooxygenase, preventing the
cells of the body from making certain prostaglandins that cause inflammation
and other ones that cause the clumping of blood platelets to form clots. The
clots, or thromboses, are responsible for "ischemic events," which are the local
anemias, or blood shortages, caused by blockage of arteries. When these are
coronary arteries, the blockages are called "heart attacks" of the myocardial
infarction (MI) type. The common slogan "aspirin thins the blood" is not
strictly true; aspirin prevents clot formation by platelets.

   The ASA content of a standard aspirin tablet is 325 mg. Extra-strength or

arthritis-strength tablets contain 500 mg. For other uses tablets containing 160 and 81 mg are available. Enteric-coated aspirin tablets resist the acidic environment of the stomach; the aspirin is absorbed in the alkaline small intestine. You would not expect "fast, *fast*, FAST relief of headache" with these, but some studies showed that stomach erosions and ulcers were less frequent (McDonald, 1982). "Buffered" aspirin is no faster than plain aspirin (*Wars,* p. 164) and only slightly less irritating, if at all (www.mayohealth.org). Besides containing 325 mg of ASA, a Bufferin™ tablet has an actual alkali content of 158 mg of calcium carbonate, 63 mg of magnesium oxide, and 34 mg of magnesium carbonate; the latter pair provide a total of 48 mg of magnesium, which may be important for preventing heart attacks. Bayer Aspirin with Stomach Guard is the same.

Primary vs. Secondary Prevention of Heart Attacks

One must be skeptical about any recommendation for or against aspirin that does not distinguish between primary and secondary prevention. Primary means that people not at any particular risk of MI may prevent a fraction of potential MIs from occurring by taking small doses of aspirin for a long period. Any side effects of aspirin can be serious if people begin taking it at age 45–50 and continue for 30–40 years. Secondary prevention means that actual victims of MI or unstable angina, a high-risk group, may prevent a fraction of further cardiovascular problems by taking moderate doses of aspirin for a limited period. Any recommendation for or against aspirin that does not make the distinction can be disregarded as superficial.

The Aspirin Wars distinguished between primary prevention of first heart attacks and secondary prevention on p. 11 quite well and described the U.S. Food and Drug Administration (FDA) decision to allow advertising for second heart attacks, but not for first heart attacks, due to an unusual number of strokes in the aspirin-using group in a large study on primary prevention, a prescient decision. But by p. 334 in *Wars:*

Aspirin is the drug of doctors' dreams. It is hugely effective. One aspirin a day, or every other day, will save hundreds of thousands of lives a year. It can be taken safely by more people than almost any other drug … It is likely to remain the only heart attack preventive sold in grocery stores for years to come.

Surrogate End Points in Clinical Trials: Are We Being Misled?

This is the title of an unusual paper by Fleming and DeMets (1996). Clinical trials are the standard scientific method for evaluating a new drug or a new use for an old drug. The true end point in most trials would be cure of a disease or condition, or, at least, reduction of symptoms, as indicated by longer lifespan of good quality. A surrogate end point is a laboratory measurement or a physi-

cal sign used as a convenient substitute for a clinically meaningful end point that measures survival directly. Changes induced by a therapy on a surrogate end point are supposed to reflect changes in a clinically real end point, but all too often, they do not.

Examples of surrogate end points are reduction of cholesterol level or blood pressure, two parameters easy to measure in the short term. A meta-analysis of 50 cholesterol-lowering interventions, including diet, resins, and lovastatin, showed that cholesterol levels were lowered an average of 10%, but there was a 1% increase in overall mortality. (This should not have been a surprise, since high blood cholesterol level and low LDL + HDL/HDL ratio are merely correlated with cardiovascular trouble, not an actual cause of it, as homocysteine is; McCully & McCully, 2000, and references to peer-reviewed papers therein). A meta-analysis of trials of calcium channel blockers, even though they really do lower blood pressure, showed possibly harmful effects overall. In addition, two antiarrythmia drugs approved by the FDA, encainide and flecainide, clearly suppressed arrythmias, probably as seen by electrocardiograms, as the surrogate end point. However, it was found that 3 times as many patients in the drug group died as in the placebo group.

In evaluating aspirin, it is, therefore, not enough to show reduction in the rate of MI or other undesirable vascular events; one must determine total death rates for a reasonable period of several years in order to find whether some toxic effect of aspirin is countering a positive effect on MI. On the other hand, one does not want to carry on for too many years since the ultimate death rates of treatment and placebo groups converge—to 100%.

Whisper Down the Alley

This is one name for a grade-school game in which someone in a classroom whispers a phrase of a few words to the nearest student, who whispers the same phrase (supposedly) to the next student. The output of the 30th or so student is compared with the input and all have a good laugh, since the two are never equal.

Adult scientists are not supposed to scramble the input—but some do.

A massive meta-analysis of 25 completed clinical trials of secondary prevention of MI was reported in the *British Medical Journal* (*BMJ*) in 1988 (Antiplatelet Trialists' Collaboration, 1988). The title: "Secondary Prevention of Vascular Disease by Prolonged Antiplatelet Treatment," makes clear that most of the patients involved had already suffered from MI, transient ischemic attack, unstable angina, or minor stroke. "Antiplatelet Treatment" indicates that aspirin was not the only drug tested; these facts are, of course, confirmed in the text and tables, of which one of the key tables is reproduced here as Figure 2. Note that only 12 of the trials employed aspirin alone. Overall reduction in mortality was about 25%, mostly in the first 2 years of treatment. A special note was made that men aged 55–74 with no history of vascular disease for whom aspirin treatment was actually primary showed no difference in mortality.
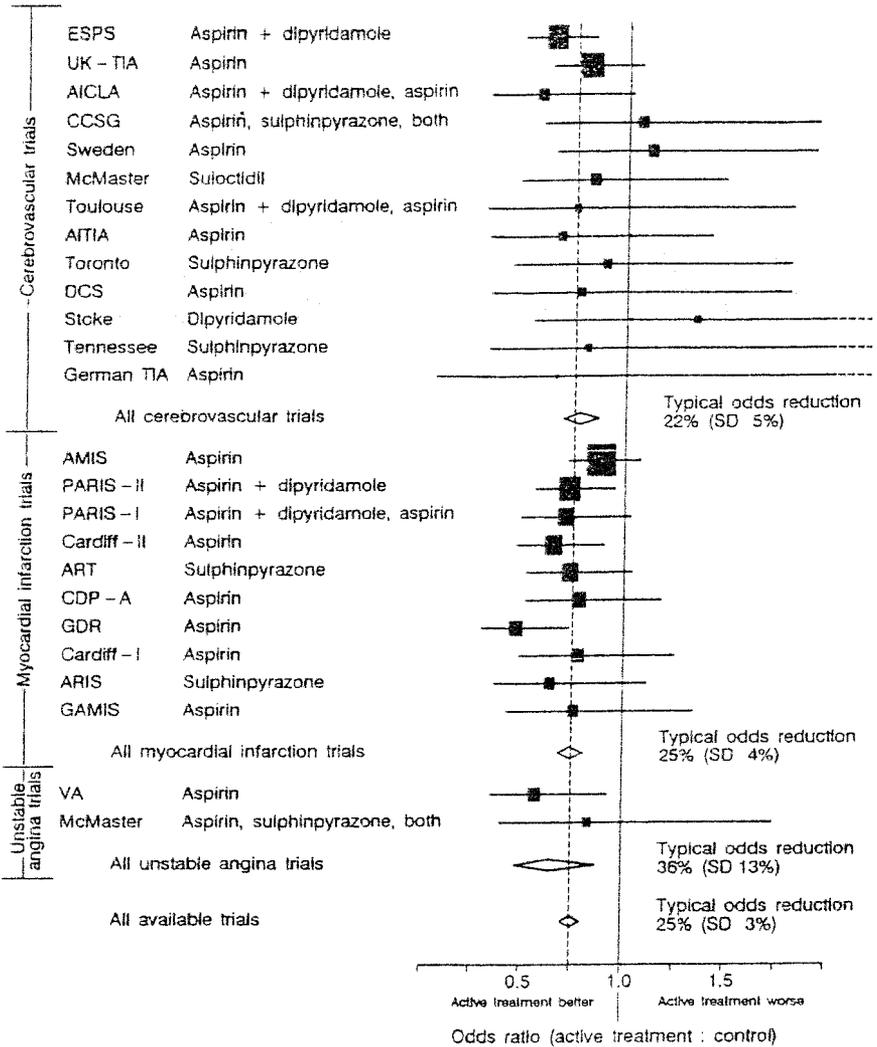
Fig. 2. Meta-analysis of antiplatelet treatment from McCully & McCully (1999). Odds ratios (active treatment : control) for first stroke, myocardial infarction, or vascular death during scheduled treatment period in completed antiplatelet trials. Filled square: Trial results and 99% confidence intervals (area of square proportional to amount of information contributed). Open diamond: Overview results and 95% confidence intervals. Dashed vertical line represents odds ratio of 0.75 suggested by overview of all trial results. Solid vertical line represents odds ratio of unity (no treatment effect).

This *BMJ* article was cited in *Science,* a publication of the American Association for the Advancement of Science, with reproduction of that same figure, as an excellent example of how to do a meta-analysis, along with an explanation of how to do one (Mann, 1990). The secondary nature of the trials was in-

dicated only by the word "recurrence," and the end point was implied to be only "heart attack," while the legend (in Figure 2) includes as end points MI, stroke, and other vascular death.

The *Science* article was cited by Dean Radin in the book *The Conscious Universe* as an example of the power of meta-analysis (Radin, 1997). Now Radin wrote implying that *only* aspirin was involved, and *only* for heart attacks, and the secondary nature of the treatment was not mentioned at all, which led me to believe, when I read this, that I should have continued using aspirin myself after all.

Recommendations for You to Take Aspirin for Primary Prevention of Heart Attacks

In publications for the general public there are a number of sources of advice to take aspirin for primary prevention of heart attacks. Here are a few:

Consumer Reports (*CR*), with ⊕5 million subscribers and ⊕20 million readers, recommended that postmenopausal women, men over 35 with risk factors such as smoking cigarettes, and possibly men over 45 without risk factors all take aspirin. No dose level was given, although the study quoted was based on "one 'aspirin' tablet every other day," and the use of enteric coated aspirin was advised only if uncoated aspirin caused damage to the stomach. "The ... study found that one aspirin tablet every other day cut the rate of initial heart attacks almost in half ... The implications were stunning." But then *CR* was very cautious, noting that the clinical study they were citing showed significantly more hemorrhagic strokes (rupture of blood vessel in the brain), ulcers, and allergic reactions, and that no benefit was observed in another trial on healthy male physicians in the UK (*Consumer Reports,* 1988). While the studies used did not get proper citations, the first was certainly the Physicians Health Study in which 22,071 male physicians were studied for 5 years (Steering Committee of the Physicians Health Study Research Group, 1989; hereafter PHS 89.)

Julian Whitaker, MD, in his popular newsletter *Health & Healing,* properly referenced PHS 89 and recommended that everyone take aspirin for primary protection from MI, but at the rate of 162 mg every other day, or 81 mg every day, half the dose used in PHS 89. While the study involved only male physicians, Whitaker did not restrict his recommendations to males. Whitaker wrote that the usual side effects of aspirin could be avoided by taking the low dose he recommended with a meal (Whitaker, 1996).[1]

In the February, 2000 issue of Life Extension magazine, the recommendation for taking 81 mg of aspirin per day with food is unequivocal:

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[1] Dr. Whitaker is one of the most courageous advocates of new or alternate treatments for many conditions. He has risked life, liberty, and financial ruin in trying to protect other practitioners from the FDA and in campaigning for easy availability of supplements.

A lot of people in alternative medicine criticize The Life Extension Foundation for recommending the daily use of low-dose aspirin, but The Foundation stands firm on the recommendations it made in 1983: most healthy people should take low-dose aspirin to specifically reduce their risk of heart attack. Aspirin may protect in ways that supplements do not. (Knorr, 2000)

Of the 34 references cited at the end of the article in such a way that one cannot tell which one backs each aspect of the article, just nine are to peer-reviewed journals. PHS 89 is not cited, nor is any peer-reviewed paper that shows lower total mortality in low-risk subjects. The article is cleverly laid out with a large space taken up by artwork so that it ends on the top half of its last page. The bottom half of the page is an advertisement for Life Extension Foundation's brand of aspirin. Does this fact make you skeptical?

Recommendations for You Not to Take Aspirin for Primary Prevention of Heart Attacks

From an anonymous author on a website (www.internetwks.com/pauling/lie/mag.html):

We have been told that all the aspirin studies that 'prove' an aspirin a day keeps a heart attack away—were with buffered aspirin, i.e., with added magnesium. Our sources point out that it is unlikely that further studies using 'plain' aspirin will be undertaken because preliminary studies always show 'plain' aspirin does not show the same protective effect against heart attacks. So if you still believe what you read in the mass media, make sure that your daily aspirin is buffered! (Or much better yet, take a magnesium tablet instead!)

From the editors of the newsletter *What doctors don't tell you* (McTaggart, 1995):

Possibly the largest collaborative study ever performed in medicine, this meta-analysis (*Antiplatelet Trialists' Collaboration, 1994*) pooled the results of some 174 clinical trials from around the world, testing an aggregate of 110,000 patients … The overview was designed to determine whether medium-dose aspirin (75 mg to 325 mg per day) … could prevent … nonfatal heart attacks, strokes, or deaths in [mostly] high-risk patients …. The researchers reckoned that this sort of therapy reduced the risk of [premature] death [a solid endpoint] from one of these causes by one-sixth …. This isn't the case with low-risk patients; the study showed that among those taking aspirin as 'primary prevention', although heart attacks were reduced by a third, there was a 'non-significant' increase in nonfatal strokes. However, that increase was cited as 21% (hardly a 'non-significant' increase in our view) …. However, the study makes quite clear that for low-risk people or for those with so-called risk factors like high cholesterol, hypertension, or smoking, but without vascular disease, there is no evidence that this so-called preventive therapy does any good. In fact, the risks (particularly of hemorrhage or stroke) may outweigh the benefits. Therefore, there is no scientific justification for your doctor's view that you should start taking aspirin just in case.

And from William Campbell Douglass, Jr., MD:

I'm sure you've heard about the study [PHS 89] showing that an aspirin a day prevents heart attacks. In that study, men who took a daily aspirin had 47% [sic] fewer heart attacks than men who didn't. What you haven't heard, and what I'm sure the aspirin companies don't want you to know, is that the subjects in that study took buffered aspirin— aspirin mixed with magnesium. Numerous studies have proven that magnesium has a powerful protective effect on your heart. It dilates blood vessels … aids potassium absorption into your cells (preventing heartbeat irregularities) … acts as a natural blood thinner … and keeps your blood cells from clumping together [the anti-platelet effect]; indeed autopsies of heart attack victims almost always find a magnesium deficiency! …. Not only that, but recent studies link aspirin to macular degeneration—the # 1 cause of blindness in people over the age of 55! But the biggest strike against aspirin may come from the very study touting its heart benefits. If you read the study's fine print, you'll find that even though the group taking aspirin had 47% fewer heart attacks, there was no difference in the death rates of the two groups. That means that death from other causes was 47% higher in the aspirin group! So stop taking that daily aspirin! Stick to magnesium instead. (Douglass, 1988)

Are these people crazy? Not entirely. Now we know enough to divide the original question that is the title of this article into two separate questions: on primary as distinct from secondary prevention of heart attacks. Let us go to the peer-reviewed literature to answer the first of the properly posed questions:

TABLE 1
Actual Deaths in PHS 89 Trial From PHS 89.

Cause[a]	Aspirin group	Placebo group	Relative risk	95% Confidence interval	P value
Total cardiovascular deaths[b]	81	83	0.96	0.60–1.54	.87
Acute myocardial infarction (410)	10	28	0.31	0.14–0.68	.004
Other ischemic heart disease (411–414)	24	25	0.97	0.60–1.55	.89
Sudden death (798)	22	12	1.96	0.91–4.22	.09
Stroke (430, 431, 434, 436)[c]	10	7	1.44	0.54–3.88	.47
Other cardiovascular (402, 421, 424, 425, 428, 429, 437, 440, 441)	15	11	1.38	0.62–3.05	.43
Total noncardiovascular deaths	124[d]	133	0.93	0.72–1.20	.59
Total deaths with confirmed cause	205	216	0.95	0.79–1.15	.60
Total deaths[e]	217	227	0.96	0.80–1.14	.64
Person-years of observation	54,894.6	54,864.2	—	—	—

[a] Numbers are code numbers of the International Classification of Diseases, ninth revision.
[b] All fatal cardiovascular events are included, regardless of previous nonfatal events.
[c] This category includes ischemic (three in the aspirin group and three in the placebo group), hemorrhagic (seven aspirin and two placebo), and unknown cause (zero aspirin and two placebo).
[d] This category includes one death due to gastrointestinal hemorrhage.
[e] Additional events that could not be confirmed because records were not available included 23 deaths (12 aspirin and 11 placebo), of which 11 were suspected to be cardiovascular (seven aspirin and four placebo) and 12 noncardiovascular (five aspirin and seven placebo).

Should You Take Aspirin to Prevent a First Heart Attack?

The Antiplatelet Trialists' Collaboration (1988) reported there were some low-risk men aged 55–74 for whom aspirin treatment was actually primary. The paper concludes with the opinion that the absolute benefits in primary prevention of MI were uncertain because they might be outweighed by a small increase in cerebral or other serious hemorrhagic disease. "Thus only for patients with an appropriate history of vascular disease is there at present clear evidence that antiplatelet treatment reduces the overall incidence of fatal or disabling vascular disease." This opinion recognizes that the real end point is life extension, not merely minimizing MIs.

Table 1 is reproduced from PHS 89. This massive study on 22,071 male physicians, half taking 325 mg of "aspirin" every other day, showed that total deaths in the aspirin group over the 5-year period of the study were 4% fewer total deaths than in the placebo group ($P = .64$); thus the difference was not considered significant. A big reduction in fatal MIs of 69% ($P = .004$) was countered by nearly equal increases in the totals for sudden death ($P = .09$), stroke, and other cardiovascular deaths. The reduction in MI was seen only in those aged ≥ 50. Using the end point of life extension, not MI, there was hardly any benefit from taking aspirin. With respect to nonfatal bleeding of several types, the aspirin group had a relative risk of 1.32 ($P = .00001$). Furthermore, 48 in the aspirin group and 28 in the placebo group required blood transfusions ($P = .02$, all 95% conf.). There really was a significant ($P < .00001$) reduction in nonfatal MIs of 44%. But what did this mean in real benefit? It meant that in a 1-year period the chance of having a nonfatal MI was cut from 0.44% to 0.25%.

There is no doubt that PHS 89 used Bufferin, not aspirin. Monthly calendar packs containing either Bufferin or placebo were provided by Bristol-Myers Products. Domenick Mellace of Bristol-Myers was acknowledged for his logistic support. Bristol-Myers contrived to have a 1.5 page advertisement placed just ahead of this paper in the journal, in which advertisement they were careful to advertise Bufferin only for secondary prevention as directed by the FDA. Is it possible that the reduction in MIs was due to the magnesium present in the Bufferin and not the ASA content?

By 1994 the Antiplatelet Trialists' Collaboration published a meta-analysis that was now up to 100,000 patients, of whom 30,000 were in the low-risk category (Antiplatelet Trialists' Collaboration, 1994). The doses were 75–325 mg of ASA per day, but the exact source of the ASA was not given. "There was no clear evidence on the balance of risks and benefits of antiplatelet therapy in primary prevention in low-risk subjects." In fact a graph was shown with "% free from a vascular event," including fatal, as the ordinate, and "years to first vascular event" as the abscissa. For low risk subjects after 4 years the treated group had 0.4% fewer events, that is, 4 per 1,000. But this included all of the antiplatelet treatments, including 2 trials with drugs that were more effective than aspirin, so it is likely that aspirin was of no benefit in low-risk subjects.

Randomized clinical trials testing aspirin in 5,011 elderly people, 58% of whom were women, mean age 72 years, followed for a mean of 4.2 years, showed that use of aspirin caused a fourfold increase in hemorrhagic stroke (P = .003) and a 1.6- to 1.8-fold increase in ischemic stroke (Kronmal et al., 1998).

Based on the Nurses' Health Study involving 79,319 women aged 34–59 years at the beginning, the role of aspirin in primary prevention of stroke was uncertain (Iso et al., 1999). This was based on a questionnaire, so the reduction, mostly in older women, of large-artery occlusive infarction by half (1 to 6 aspirin per week) or a doubling of the risk of hemorrhage (15 or more aspirin per week) might have included the use of a large fraction of buffered aspirin. This was not thought important. Total death rates were not included.

"No conventionally used prophylactic aspirin regimen seems free of the risk of peptic ulcer complications … Alka-Seltzer may be associated with higher risk (2×) and enteric-coated aspirin with lower risk (0.5×) compared with plain aspirin" (Weil et al., 1995). Users of aspirin for long periods to relieve arthritis pain have suffered so badly from side effects that a multitude of alternates, such as ibuprofen and naproxen, were introduced.

And, most recently, reported in 1998, a study of about 5,500 physicians in the UK on primary prevention of ischemic heart disease (which causes MIs) was carried out with 75 mg of aspirin daily in a controlled-release formulation for a median time of 7 years. The main effect of aspirin was a 32% reduction in nonfatal MI (less effective than PHS 89, which used double the dose), but there was an increase of 12% in fatal MI leading to an overall rise in death from all causes of 6%, which was not considered significant (Meade, 1998). The absolute reduction in all MIs per year was 0.23%. Note that there is a 10% increase in overall death rate in the aspirin group in this study compared with the Bufferin group in PHS 89. Could this "nonsignificant" difference have been a lack of the beneficial effect of the magnesium in Bufferin? Another difference from PHS 89 is that the men in this study were recruited from the quintile considered to be at highest risk for MI based on heredity, smoking, blood pressure, and obesity; but this is still a lower risk group than the one composed of actual victims of MI.

If delaying death is the real end point, not reduction in heart attacks per se, then it seems pointless to take aspirin for primary protection, with its certainty of obnoxious side effects, which may include gastritis, peptic ulcer, other internal bleeding, hemorrhagic stroke, fatal MI, and sudden death, to which has been added wet macular degeneration (in 1988) and 2–5 times the risk of cataracts in those people who were ≤ 55 and then took aspirin for ≥ 10 years (Cumming & Mitchell, 1998), *in trade* for a probable reduction of only 0.2% absolute per year in total (mostly nonfatal) MIs, especially when safer alternatives exist, such as magnesium.

Now it is time to ask the more difficult question…

Should You Take Aspirin to Prevent a Second Heart Attack?

Five earlier studies on secondary prevention of MI by ASA were reported from 1974 to 1980. There was said to be no beneficial effect overall (Gent & Carter, 1982). One multicenter study, nevertheless, the earliest of this type I have seen, had positive results. A single daily dose of 300 mg of aspirin in a gelatin capsule or a similar-looking placebo was to be taken before breakfast to ensure rapid absorption by 1,239 men who had had a recent MI. The aspirin group showed a reduction in total mortality of 12% at 6 months, 25% in 1 year, and 28% at 2 years. The authors modestly acknowledged that the results were statistically inconclusive, but they were in the range of what was observed in later trials. The much larger size of the later trials was needed to obtain results that would be statistically solid (Elwood et al., 1974).

Reported in 1988, the second International Study of Infarct Survival (ISIS-2) Collaborative Group in the UK determined the effect of aspirin vs. placebo in 17,187 people entering 417 hospitals after the onset of suspected acute MI. The aspirin used was clearly stated to be 162.5 mg in an enteric-coated tablet given daily for 1 month. All-cause mortality was said to be similar to vascular mortality. After 5 weeks aspirin produced 23% fewer vascular deaths overall ($2P < .00001$), cut MIs from an absolute value of 2% to 1%, cut nonfatal stroke from 0.6% to 0.3%, and did not cause any increase in cerebral hemorrhages. Survival rates after 2 years were 81.7% in the aspirin group vs. 80.0 % on placebo (ISIS-2, 1988).

In 1988 the Antiplatelet Trialists' Collaboration (1988) on 29,000 patients, a majority with a history of transient ischemic attack, stroke, unstable angina, or MI, were treated by a variety of methods, including with $\geq$ 300 mg ASA daily, which did not differ greatly in results from other drug regimens employed in the trials, as shown by this meta-analysis (see Figure 2). The authors thought that vascular mortality was reduced by 1/6, and nonfatal vascular undesirable events by 1/3 in high-risk patients. By 1994, now up to 70,000 high-risk patients, the Antiplatelet Trialists' Collaboration (1994) found similar results, but now the daily aspirin dose was 75–325 mg.

By 1998 ISIS-2 was still following 6,213 high-risk patients in the UK of the 17,187 originally in the trial. During the first 35 days of follow-up, the use of aspirin during the first month reduced the death rate by 22%. Hence all of the survival benefit of an early, 1-month course of oral aspirin (162.5 mg enteric coated, daily) seemed to accrue during the first month, with little further benefit between day 36 and the end of year 10, by when the death rate was down 1% relative to placebo (Baigent et al., 1998).

This then was the background of the North of England Aspirin Guideline Development Group's recommendations to physicians: Aspirin should be used in patients with acute MI at 150 mg daily for one month, then 75 mg daily for several years. In patients with MI, anginas, stroke, or transient ischemic attack, aspirin should be used at 75 mg daily for several years. There was no evidence that higher doses were more effective (Eccles, Fremantle, & Mason,

1998). The group did not mention either buffer or enteric coating. The latter seems desirable to this writer.

So the answer for secondary protection from recurrence of several types of undesirable vascular conditions is Yes, take aspirin in low doses, and not forever, in order to obtain a moderate (16–22%) protection from fatal MI. Take the first aspirin tablet, not enteric-coated, in a hurry; have small sealed packs in your home and car. Switch then to enteric-coated tablets, and consider stopping in 4–6 weeks if you do not have further attacks.

But is aspirin the best protection there is, either from the standpoint of effectiveness or freedom from side effects? Probably not.

What Else Could You Take to Prevent Heart Attacks?

Vitamin E for Primary Protection

The Nurses Health Study involved 87,245 female nurses aged 34–59 in 1980, who were free from diagnosed cardiovascular disease and cancer, and who completed dietary questionnaires every 2 years up to 8 years. Women who took vitamin E supplements containing, on average, 200 IU (International Units) for more than 2 years had 41% fewer instances of coronary disease of several types, and overall mortality 13% lower than those who did not ($P =$ .05) (Stampfer et al., 1993). The amount of vitamin E in multivitamin capsules at that time was typically ≤ 30 IU. It could not be ascertained whether the vitamin E supplements were mixed isomers (*d, l*) or the 1.36 times more active *d* form.

The Health Professionals Follow-up Study involving ⊕40,000 males aged 40–75 in 1986 who were free of diagnosed coronary heart disease, diabetes, or hypercholesteremia completed detailed dietary questionnaires every 2 years until 1990. Men who took 100–250 IU of vitamin E as supplements for 2–10 years had 37% fewer instances of coronary disease of several types, including fatal ($P =$ .05). Higher doses of vitamin E were no more effective. By contrast, the intake of vitamin C and beta-carotene did not lower risk (Rimm et al., 1993).

These results are far more impressive than the ones for aspirin, especially because side effects were so minimal as not to be mentioned. And vitamin E *could* be bought at almost any grocery store.

Vitamin E for Secondary Protection

The Cambridge Heart Antioxidant Study [CHAOS (English humor?)] was a single-center, double-blind, placebo-controlled study with 2,002 patients who had angiographically proven coronary atherosclerosis (fatty deposits). Doses of 400 or 800 IU of natural vitamin E were used in half, and the group was followed for a median of 510 days. Vitamin E gave a significant reduction in non-fatal MI of 77% ($P =$ .005); however, there was a nonsignificant excess (18%, $P =$ .61) of cardiovascular deaths in the combined vitamin E groups. However,

the lower dose of vitamin was better on both counts, including a 13% lower death rate on 400 IU than on placebo versus a 35% higher death rate on 800 IU. The lower dose of vitamin E gave 86% fewer nonfatal MIs and the higher dose 52% fewer. So here, too, vitamin E is far more effective than aspirin, and, again, side effects were negligible at the lower dose (Stephens et al., 1996). These latter data do not appear in the abstract, showing the bias of the authors, as did their measurements of total serum cholesterol, rather than of the more meaningful homocysteine.

The recent GISSI-P trial used 300 mg of synthetic (*d, l*) vitamin E (GISSI-P Investigators, 1999). In the composite end point of death and nonfatal MI, vitamin E reduced risk by a barely significant 11% (Brown, 1999). Since the subjects were already eating a "Mediterranean Diet" high in vitamin E, with olive oil, which aids in absorption of vitamin E (McCully & McCully, 1999, and references to peer-reviewed papers therein), perhaps this result is not surprising. Again, measurements of total serum cholesterol, HDL, LDL, and triglycerides showed no changes at all.

Magnesium for Primary Protection

The Caerphilly Heart Disease Study of men aged 45–59 years at the beginning of a 5-year period examined the relation of magnesium in the diet to the incidence of MIs, both fatal and nonfatal. Of the 627 men in the study, 38 suffered MIs. The mean daily intake of magnesium in these was 12% lower than in men who did not have MIs (Elwood et al., 1992). This is a difference of about 38 mg per day, less than the amount in a Bufferin tablet. The inverse relation of magnesium concentrations in drinking water to rate of heart attacks has been noted many times (Purvis & Mohaved, 1999).

The usual recommendations for dietary supplements are to take 300–600 mg of magnesium in a compound (not the metal) daily with food (Miller, 1999). The most common form in which to take magnesium is as the compound magnesium oxide, one of the alkalis in Bufferin, but equally persuasive is advice to take it as potassium magnesium aspartate for fast absorption (Douglass, 1995). Women at risk of osteoporosis are advised to take also about twice the mass of calcium (Lieberman & Bruning, 1990). But calcium, as well as vitamin D and phosphates, increase the amount of magnesium needed (Seelig, 1980). Mildred S. Seelig, MD, also wrote that the typical daily intake of magnesium in American college students was 250 mg, not ≥ 385 mg recommended for a 140-lb woman, or ≥ 500 mg for a 185-lb man. Unfortunately, I have not found a report on a large clinical study on primary protection using magnesium supplements in humans.

A prospective study of 10-year duration in 400 "high-risk" subjects (selected about as in Weil et al., 1995), of whom 93.5% were male, living in Moradabad, India, was carried out by assigning half the group to a high-magnesium diet (1,142 mg per day vs. 418 mg in the control group from fruits, green vegetables, cereals, and nuts) and tracking medical events. The high-magnesium

group had 35% fewer deaths from all causes ($P < .001$) and a 61% reduction of nonfatal cardiovascular events ($P < .001$), including a 54% reduction in strokes (Singh, 1990). Unfortunately, this report was marred by a number of arithmetical errors in the table of results. There was also a confounding factor in that the high-magnesium diet was also a high calcium diet (880 vs. 512 mg daily) and a high-potassium diet (3,080 vs. 548 mg daily). Since serum levels of magnesium and potassium were raised and those of calcium were not, it is most likely that the magnesium and potassium were responsible for the differences in outcomes, which also included significant reductions in serum total cholesterol and glucose.

Use of magnesium supplements in many people is probably justified by inference based on their effectiveness on secondary prevention, the clinical experience of a number of physicians, the drinking water studies, and the above diet study. The diet study would support using potassium magnesium aspartate as the supplement most resembling the high-magnesium diet.

Magnesium for Secondary Protection

In a double-blind, placebo-controlled study involving 273 patients with suspected acute MI, 74 received placebo, while 130 received 1.2 g of magnesium as the chloride intravenously during 24 hours, followed by 0.3 g in the next 24 hours. Treatments were begun within 3 hours of hospital admission. During the first 4 weeks after treatment mortality was 7% in the magnesium group and 19% in the placebo group, a reduction of 63% ($P = .045$). In the magnesium group 21% of the patients had arrhythmias that needed treatment vs. 47% in the placebo group, a reduction of 55% ($P = .004$). No adverse effects of intravenous magnesium were observed (Rasmussen et al., 1986).

Reported in 1992, the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) on 2,316 patients with suspected acute MI found a 24% reduction ($P = .05$) in 28-day mortality from treatment with intravenous magnesium sulfate (Woods et al., 1992). Reported in 1995, the Fourth International Study of Infarct Survival (ISIS-4) showed *no* benefit of similar treatment of 29,000 patients (ISIS-4 Collaborative Group, 1995).

By 1996 the discrepancy was explained as follows: LIMIT-2 was double-blind and placebo controlled, and only 30% of the patients had received treatment for thrombosis (streptokinase) by the time magnesium was begun, on average 3 hours after onset of symptoms. ISIS-4 was nonblinded; had no placebo, the alternate treatments being the drugs isosorbide mononitrate or captopril; 70% of the patients had received treatment (which raises blood magnesium concentrations) for thrombosis (clotting in major blood vessel); and 94% had received aspirin by the time magnesium was begun, on average 8 hours after onset of symptoms. It is interesting that captopril is a product of Bristol-Myers Squibb, the sponsor of ISIS-4, at a cost of about $10 million (Baxter, Sumeray, & Walker, 1996).

A study appeared simultaneously involving 194 patients considered unsuit-

able for treatment for thrombosis. In-hospital mortality was 4.2% in the magnesium group and 17.3% in controls, a reduction of 76% (Baxter, Sumeray, & Walker, 1996).

Where confounding treatments are absent, rapid treatment of patients suffering from MI with intravenous magnesium is of great benefit in secondary prevention, not only of MI, but of arrhythmias. The three studies not confounded showed, on average, a greater 4-week benefit than from aspirin, and LIMIT-2 showed that concurrent aspirin did not change the outcome. Side effects of magnesium were minimal and could be avoided altogether by controlling the rate of administration.

The medical establishment has accepted the role of oral magnesium supplements in countering hypertension, MI, congestive heart failure, and arrhythmias (Lauler, 1989).

Coenzyme Q10 for Primary Protection

Coenzyme Q10 is an oily organic compound, like vitamin E, and is found in every cell of the body. It has a number of functions, among which are preventing the oxidation of LDL and transporting oxygen from hemoglobin into the parts of cells where ATP, the main source of cellular energy, can be formed. Sharing its status with magnesium, the value of oral coenzyme Q10 supplements for better health in a low-risk population has not been investigated in large-scale controlled experiments (Overvad et al., 1999). Its use in older people with some definite symptoms, such as congestive heart failure, is probably justified by inference based on its effectiveness on secondary prevention, and the clinical experience of a number of physicians. For details, see the website of The International Coenzyme Q10 Association (wwwcsi.unian.it).

Coenzyme Q10 for Secondary Protection

The New York Heart Association (NYHA) has grouped heart failure into four classes of severity. A cardiac patient in class IV, the most serious, is unable to perform any physical act without discomfort, and symptoms of heart failure, including anginal pain, may be present even at rest. Cardiologists know that such patients are on a relentless downhill course to death in spite of all conventional therapy. In a study in which all patients in hospitals were in NYHA classes III and IV and all received conventional therapy (bypass surgery, digitalis, diuretics, vasodilators), about 25% survived for 3 years. The patients treated with Coenzyme Q10 had a 75% survival rate. Putting this finding in the same form as used above, the reduction in 3-year death rate was 67%! (Folkers, 1985, 1986)

Congestive heart failure is always characterized by an energy depletion status correlated with lowered coenzyme Q10 levels. In a 1-year double-blind trial, 641 patients of mean age 67 with chronic congestive heart failure (NYAS classes III and IV) were randomly assigned to receive either 2 mg/kg (⊕100 mg) daily of coenzyme Q10 or placebo. The number of patients who required

hospitalization for worsening heart failure was 38% lower ($P < .001$) in the Q10 group; the incidence of pulmonary edema was cut by 61%, and of cardiac asthma was cut by 51% (both $P < .001$) (Morisco, Trimarco, & Condorelli, 1993). A similar study on 2,500 patients showed only 0.5% with side effects thought due to Q10.

Summing Up

Not only the medical adviser to Consumers Union (CU), but also some health professionals who recommend aspirin, believe that there is a "high-risk" but not-yet-diagnosed population who should take aspirin for *primary* prevention of heart attack. You may check for yourself in the studies cited— often there is no such group. True, males ≥ 50 years old are at higher risk than males or females ≤ 50, but those males ≥ 50 are actually the low risk group in most of the large studies on health professionals. The study with the most favorable results in terms of reducing MIs, PHS 89, used Bufferin, which contains a significant amount of magnesium, not plain aspirin. This fact was lost on CU, as well as many others, including Abramowicz (2000), who cited PHS 89 and did not believe that the later European studies that utilized plain aspirin were valid.

There is no consensus even among cardiologists that use of aspirin in the general population is advisable. For one, Prof. F. Verheught, Dept. Cardiology, University Hospital, Nijmegen, Netherlands, warned that use of aspirin for primary prevention was inadvisable because its use was investigated only in men, that the risk of nonfatal MI is <0.5% per year [and would be cut only by 0.2%], and that there was risk of gastric discomfort and bleeding (Kmietowicz, 1998). The studies on low-risk males were carried on for 5–7 years. Based on life-expectancies, advice to take aspirin beginning at age 50 would mean ⊕30 years of exposure to its side effects.

The story is the same for diabetic patients: in primary studies the hazards exceed the benefits. However, because of their higher platelet turnover, diabetics who take aspirin for secondary prevention may benefit from higher doses— 300 mg of enteric-coated aspirin daily (Yudkin, 1995).

Vitamin E is both more effective and safer than aspirin, and its value in primary protection has been demonstrated in both men and women.

Magnesium intake is inversely correlated with incidence of cardiovascular problems, the effect being more pronounced in men than in women. Up to at least 1,100 mg daily along with up to 3,000 mg of potassium is strongly protective in the primary sense and unarguably protective in the secondary sense (Patki, et al., 1990).

In *secondary* protection, aspirin has a limited but definite value and does not have to be taken forever; most of the benefit is obtained in the first month. Based on available evidence, aspirin is preferred for the majority of stroke or myocardial infarction (heart attack) patients at risk of *recurrences,* according to The American Heart Association. But studies have shown that vitamin E,

magnesium, omega-3 fatty acids (Guallar, et al., 1999), and coenzyme Q10 each provide much greater benefits than aspirin with lesser side effects. Not even the skeptical website www.quackwatch.com disagrees with this.

Lowering homocysteine levels may be of the greatest value in preventing cardiovascular disease (McCully & McCully, 1999, and references to peer-reviewed papers therein), and both vitamin E and magnesium have roles in lowering those levels or preventing oxidation of LDL cholesterol.

A skeptical outlook is of great value in evaluating medical claims of most types. Medical advice with no citations to peer-reviewed papers on well-controlled studies can be ignored. You should spot-check the original papers, but beware of the Internet trap—you can get abstracts free, but it is more difficult or costly to obtain the full papers from websites. While all of the peer-reviewed papers in this field seem very honestly presented in detail, some important facts often do not appear in the abstracts, and some studies were contrived or abstracted to favor a preconceived result.

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Disclaimer

Any recommendations herein are based on studies published in peer-reviewed scientific journals. I am not an MD and cannot engage in the practice of medicine. (My degrees are: BS in Chemistry from the Philadelphia College of Pharmacy and Science, and a PhD in Organic Chemistry from the Massachusetts Institute of Technology. My experience includes about 10 years of exploratory drug development at the former and 4 years at the Massachusetts College of Pharmacy.)

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