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Aspirin: Friend or Foe?

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It is estimated that more than 50 million Americans now take a daily aspirin (acetylsalicylic acid) for prevention of cardiovascular disease. This translates into roughly 10 billion to 20 billion tablets consumed annually in the US alone[1].

The 2006 *Guidelines for the Management of Patients with Atrial Fibrillation* recommends that afibbers with no risk factors for ischemic stroke (hypertension, diabetes, heart failure, left ventricular ejection fraction below 0.35, heart disease, rheumatic heart disease, thyrotoxicosis, prior heart attack, stroke or TIA, or presence of prosthetic heart valves) take 81 to 325 mg of aspirin daily for stroke prevention[2]. This research report will examine whether this is a reasonable recommendation.

Stroke Risk in Lone Atrial Fibrillation

Several major clinical trials and epidemiologic studies have concluded that atrial fibrillation is associated with an increased risk of ischemic stroke. Although this conclusion is likely valid for afibbers with heart disease and other risk factors, there is no evidence that lone afibbers with none of the above risk factors have an increased risk[3]. Medical experts are pretty unanimous on this point. Dr. Rodney Falk, MD of Boston University, a world-renowned expert on atrial fibrillation, says that the stroke risk in patients with lone atrial fibrillation is minimal[4]. Professor Michael D. Ezekowitz, MD of the Veterans Administration says, “patients with lone atrial fibrillation are not at higher risk for thromboembolism than the general population and can be managed without anticoagulation or anti-platelet therapy”[5]. Dr. Stephen L. Kopecky of the Mayo Clinic did the first study regarding stroke risk in patients with lone atrial fibrillation. He found that lone afibbers under the age of 60 years had an exceptionally low stroke risk (0.55%/person-year) and that this risk varied little whether the fibrillation was paroxysmal or permanent[6].

More recently, researchers at the Mayo Clinic published a study regarding the correlation between lone atrial fibrillation (LAF) and stroke risk and overall mortality. The study is remarkable in that it followed the participants for 30 years and thus gives a good indication of the long-term prognosis for untreated LAF. The study involved 46 residents of Olmsted County who were diagnosed with LAF at an average age of 45.8 years (range of 34-58 years). None of the participants had coronary artery disease, hypertension, diabetes, mitral valve prolapse, congestive heart failure, or any other condition that would increase their risk of ischemic stroke (cerebral infarction). None of the participants were treated with warfarin. They were followed until death or July 1, 2002. At time of last follow-up the average age was 74 years (range of 63-85 years). At the beginning of the study 76% of participants had paroxysmal afib and 24% had

the persistent variety; this changed to 59% paroxysmal and 41% persistent by the end of the study period. All participants were Caucasians and 83% were men.

The Mayo researchers made the following important observations:

1. The observed mortality rate among the afibbers over a 25-year period was substantially lower (15.9%) than the mortality expected in a group of age- and sex-matched white Minnesotans (32.5%).

2. The incidence of ischemic stroke (cerebral infarction) in the afib group was no greater (0.5%/person-year) than in the general population. The researchers conclude that, "This observation indicated that the pathophysiological mechanisms responsible for the development of a cerebrovascular event were unrelated to the continued presence of AF." In other words, LAF as such is not associated with an increased risk of stroke[7].

So why should lone afibbers, with no risk factors for stroke, worry about an increased risk of ischemic stroke? They probably should not, but the authors of the latest guidelines obviously believe that they should.

Ischemic Stroke

There are two types of ischemic stroke – thrombotic and embolic. Both involve the obstruction and subsequent stoppage of the blood supply to an area of the brain (infarction). However, the mechanism by which the obstruction occurs differs.

A thrombotic stroke involves the formation of atherosclerotic plaque and subsequent narrowing and clot (thrombus) formation at the point of obstruction. In an embolic stroke, on the other hand, the obstruction is caused by the lodging of an embolus (blood clot or atherosclerotic plaque) formed in the heart or in an artery outside the brain. Cardiogenic emboli (blood clots originating in the heart) can form on heart valves, particularly prosthetic ones, or as a result of mitral stenosis. Cardiogenic emboli can also originate from the walls of the heart as a result of a heart attack (myocardial infarction), atrial fibrillation or congestive heart failure or from a benign atrial tumour (myxoma).

By far, the majority of strokes occurring in atrial fibrillation are cardioembolic. Anticoagulation with warfarin provides significant protection against this type of stroke, while antiplatelet therapy with aspirin has very limited effect[8]. This should come as no great surprise since thrombi originating in the left atrium tend to be rich in fibrin rather than in platelets[9]. The magic number of 22% reduction in ischemic stroke, eg. from about 2.8%/year to 2.2%/year in a 70-year-old male with hypertension, is often mentioned in connection with aspirin prophylaxis. However, there is now some doubt whether this observed risk reduction is related to AF at all. Dr. Gregory Lip of the University of Birmingham recently made the following observation in an editorial discussing the merits of prescribing aspirin for patients with atrial fibrillation:

> *"Since AF frequently co-exists with vascular disease, it is likely that we are seeing an effect of aspirin on vascular disease, rather than on stroke associated with AF per se. Also, thrombogenesis in AF is largely coagulation-related and the platelet abnormalities in AF, where present, are not much more than that seen with the associated vascular disease alone*."[10]

He also questions the soundness of the 2006 Guidelines with the following statement:

> *"Many guidelines still recommend aspirin for 'low-risk' patients with AF, but the recent Japanese Atrial Fibrillation stroke trial even questions this approach, showing that aspirin was no better (or perhaps worse) than placebo in low-risk AF patients. Indeed, the use of aspirin may be to treat (or reassure) the prescriber, rather than the patient*."[10]

Aspirin in Stroke Prevention

There is no evidence that daily aspirin consumption protects against a first ischemic stroke[11]. As a matter of fact, there is now evidence that it may do more harm than good in low-risk patients with atrial fibrillation. In a 2005 study of 871 low-risk AF patients Japanese researchers conclude that daily aspirin therapy (150-200 mg/day) in this group is neither effective nor safe. They actually observed more cardiovascular deaths, strokes and TIAs in the aspirin group than in the placebo group. In addition, fatal or major bleeding was found to be more frequent in the aspirin group than in the placebo group. Overall, the incidence of strokes, deaths and other adverse events was 42% greater in the aspirin group than in the placebo group. The trial was stopped early since the probability that aspirin would prove superior to placebo in stroke prevention, if it continued, was deemed to be vanishingly small[12].

Aspirin in Prevention of Heart Attacks

In 2003, five clinical trials designed to determine the benefits of aspirin therapy in the prevention of a first heart attack were reviewed in a study funded by Bayer, the manufacturer of aspirin[13]. Two of the trials, the Physicians Health Study and the British Doctors Trials, involved a total of 27,210 healthy men aged 40-84 years. The participants were followed for a mean of 5 and 6 years respectively. The rate of nonfatal heart attack was 0.28% per year in the aspirin group and 0.40% per year in the placebo group; that is, an absolute risk reduction of 0.12% or a relative risk reduction of 30%. Two other studies involving men and women at high risk for cardiovascular disease revealed an incidence rate of 0.53% per year for nonfatal heart attack in the aspirin group versus 0.76% in the placebo group; that is, an absolute risk reduction of 0.23% or a relative risk reduction of 31%.

Considering that the risk of hemorrhagic stroke and fatal bleeding is about 0.2% per year, and that of major gastrointestinal bleeding is about 0.5% per year, it is clear that long-term aspirin therapy for the prevention of a first heart attack (primary prevention) is not appropriate. This is recognized in the FDA's 2003 decision not to approve aspirin for long-term use in the **primary prevention** of heart attacks[14].

More recently, researchers at the University of Alabama performed a meta-analysis of six clinical trials involving 47,293 aspirin users and 45,580 controls not on aspirin who had no prior indication of cardiovascular disease. This study differed from the previously discussed one in that it included data from the recently completed Women's Health Study. The dosage of aspirin involved in the trials varied from 75 mg/day to 500 mg/day. The researchers conclude that regular aspirin use reduces the relative risk of experiencing a first non-fatal heart attack by 24%, that of developing coronary heart disease by 23%, and reduces the risk of any cardiovascular event by 15% (relative). No risk reduction was observed for stroke, cardiovascular mortality or all-cause mortality. The authors conclude that their analysis supports the current industry recommendation for the use of aspirin for primary prevention in patients with a high risk of cardiovascular disease (10-year risk of 6% or higher). Unfortunately, they completely ignore the downside of aspirin usage – a substantially increased risk of hemorrhagic stroke and major gastrointestinal bleeding. (NOTE: This study was funded by Bayer, the major manufacturer of aspirin).[11]

A meta-analysis of 5 of the 6 trials discussed above clearly shows that long-term aspirin usage increases the relative risk of hemorrhagic stroke (stroke caused by a burst blood vessel) by about 40% and the risk of major gastrointestinal bleeding by 70%. Thus, it would seem prudent to keep in mind the conclusion of the U.S. Preventive Services Task Force, "Patients at low risk for coronary heart disease probably do not benefit from and may even be harmed by aspirin because the risk for adverse events may exceed the benefits of chemoprevention."[15]

Aspirin does, however, have a significant role to play in preventing death when a first heart attack is actually experienced. Several large-scale trials have shown that taking as aspirin as soon as possible after feeling the first symptoms of a heart attack can reduce the risk of dying by 23%. Medical doctors at the Texas Southwestern Medical School have found that the aspirin should be chewed rather than swallowed whole in order to minimize the time it takes for it to take effect. Aspirin works by blocking the synthesis of thromboxane, a metabolite of arachidonic acid, which is involved in the formation of blood clots. Aspirin enters the blood stream very quickly and swallowing a chewed tablet with water was found to inhibit thromboxane formation by 50% after 5 minutes and by 90% after 14 minutes[16].

There are several useful tools available on the Internet for determining your risk of future coronary heart disease. You can find two at
http://www.intmed.mcw.edu/clincalc/heartrisk.html
http://www.med-decisions.com

Optimum Dosage of Aspirin

Although people with low risk for future coronary heart disease events would likely not benefit from a daily aspirin, there are groups of patients who would indeed do so, especially patients who have already suffered a thrombotic stroke or a heart attack. An obvious question is how much aspirin is required on a daily basis to achieve optimum protection? A recent review by a team of French and American physicians provides a plausible answer.

One 300-mg dose of aspirin irreversibly destroys the ability of platelets to form the aggregates that are involved in thrombotic, ischemic stroke. The platelets recover their ability to aggregate at a rate of about 10% a day. Thus, a prophylactic regimen of a one-time, 325-mg dose (standard dosage) followed by a daily dose of 81 mg (baby aspirin) or even half a baby aspirin would provide the full beneficial effect of aspirin as far as prevention of secondary cardiovascular events is concerned. Limited data suggest that 100 mg of aspirin every other day is also effective in suppressing platelet function.

The 300-mg loading dose, if taken in oral form, is effective within about an hour of ingestion. However, absorption and complete destruction of platelet activity can be achieved in half this time by chewing the tablet, or by taking the aspirin in the form of Alka-Seltzer[1].

The authors of this study point out that no clinical trial has ever demonstrated that taking large doses of aspirin on a daily basis is more effective than smaller doses over the range of 30 mg to 1300 mg a day[1].

Safety of Aspirin

Aspirin is not innocuous. It can cause serious bleeding in the gastrointestinal tract and can aggravate existing ulcers. The estimated death rate from gastrointestinal (GI) bleeding ranges from 8-12% of all cases. Researchers at Oxford University have released the results of a very large study aimed at establishing the magnitude of aspirin-related bleeding incidents. They carefully studied the results of 24 major randomized clinical trials involving almost 66,000 participants. They conclude that when treated for a year 2.47% of aspirin users develop GI bleeding as compared to 1.42% among placebo users. Put in terms of the 50 million Americans now taking aspirin this means that the excess incidence of GI bleeding attributable to aspirin would be 525,000 and the excess mortality would be 50,000 every year. The researchers also investigated whether lower dosages of aspirin would be safer. They found that they were not. The incidence of GI bleeding among low-dose aspirin users was 2.30% compared with 1.45% for placebo users. Somewhat surprisingly, the study also found that enterically-coated or otherwise modified formulations were no safer than standard aspirin. The increase in GI bleeding among users of modified formulations was 93% as compared to 68% for all aspirin users and 59% for low-dose users. The researchers conclude that patients and their physicians need to consider

the trade-off between the benefits and harms of long-term aspirin use. Dr. Martin Tramer of the Geneva University Hospitals in Switzerland wholeheartedly agrees with this conclusion and adds, "It may be more appropriate for some people to eat an apple rather than an aspirin a day."[17,18]

A study of 1225 patients with indications of adverse drug reactions admitted to two large British hospitals found that 18% of these reactions was associated with aspirin usage and most frequently involved gastrointestinal bleeding or peptic ulceration. The mortality among patients admitted with aspirin-related adverse events was 8%[19].

Although the above-mentioned Oxford study found no reduction of adverse events comparing low-dose aspirin vs. regular dose, other studies have found that low-dose is safer. The Dutch TIA study observed a bleeding incident rate of 2.6% in patients taking 30 mg/day vs. 3.2% in those taking 283 mg/day. The CURE trial observed a bleeding incident rate of 1.56% for daily doses of less than 100 mg vs. 2.29% for doses greater than 100 mg[1].

Overall, the evidence and common sense tend to support the conclusion that less is safer. The combined data from the TIA and CURE trials indicate that about 350,000 major bleeding events could be avoided every year in the US alone by using 81 mg/day instead of 325 mg/day for long-term prophylaxis.

The Oxford study discussed above also noted that neither enteric-coated nor buffered aspirin formulations decreased bleeding risk. This outcome was also reported in a study carried out by researchers at Boston University School of Medicine. The researchers conclude that the increase in risk (comparing aspirin and non-aspirin users) of major upper gastrointestinal bleeding was 2.6-fold for plain aspirin, 2.7-fold for enteric-coated aspirin, and 3.1-fold for buffered aspirin. They did not observe any significant differences in risk attributable to the three aspirin forms according to bleeding site (gastric vs. duodenal). Their conclusion was, "*Use of low doses of enteric-coated or buffered aspirin carries a three-fold increase in the risk of major upper gastrointestinal bleeding. The assumption that these formulations are less harmful than plain aspirin may be mistaken*."[20]

Alternative Options for Stroke Prevention

As discussed above, aspirin is largely ineffective in preventing the formation of fibrin-rich thrombi (clots) such as those involved in cardioembolic, ischemic stroke. Thus, if the aim is to prevent this kind of stroke, then the emphasis should be on supplementing with agents that reduce fibrinogen level or increase fibrinolytic activity (fibrin breakdown) rather than with agents that inhibit platelet aggregation. The most important of such supplements are niacin (vitamin B3), fish oils, vitamin C, and nattokinase.

Niacin

A clinical trial involving patients with peripheral arterial disease who supplemented with niacin for one year (2 x 1500 mg daily) observed a significant decrease (18%) in fibrinogen level and a remarkable 60% decrease in prothrombin Fragments 1 and 2. Corresponding numbers for warfarin therapy was 0% drop in fibrinogen level and a 48% drop in prothrombin Fragments 1 and 2[21].

Fish Oils

Studies carried out in 1994 by South African researchers concluded that fish oil (6 grams/day) reduces the level of coagulation factors V and VII in healthy men and women and also reduces factor X and fibrinogen levels in women[22]. Researchers at the University of Oslo have found that fish oil supplementation is effective in reducing fibrinogen levels in men. Their study involved 64 healthy men between the ages of 35 and 45 years. The men were randomized to receive olive oil capsules or fish oil capsules daily for 6 weeks. The fish oil capsules supplied a daily intake of EPA (eicosapentaenoic acid) of 3.6 grams and a daily intake of DHA (docosahexaenoic acid) of 2.9 grams. At the end of the study period, the average fibrinogen levels had dropped by

13% (from 2.73 g/L to 2.37 g/L). The researchers conclude that the antithrombotic (blood clot preventing) effect of fish oils may be due to their ability to lower fibrinogen levels[23].

Vitamin C
A clinical trial involving 40 patients who had suffered a previous heart attack examined the effect of vitamin C supplementation on fibrinolytic activity. An intake of 1000 mg of ascorbic acid twice a day resulted in an increase in serum ascorbic acid of 96% and a 45% increase in fibrinolytic activity. A second group of patients with acute myocardial infarction (recent heart attack) were also given 2 x 1000 mg of vitamin C daily with the result that serum ascorbic acid level rose by 94%, while fibrinolytic activity increased by 63%[24]. NOTE: Vitamin C should be taken in combination with the bioflavonoids with which it normally occurs in nature.

Nattokinase
Nattokinase is a potent enzyme that is highly effective in dissolving blood clots (thrombi). It works both by dissolving the blood clot directly and by inactivating plasminogen activator inhibitor type 1 (PAI-1), a strong inhibitor of fibrinolysis[25]. Nattokinase is a highly purified extract from natto, a traditional fermented cheese-like food that has been used in Japan for centuries. Dr. Hiroyuki Sumi discovered nattokinase in 1980 and established that it was highly effective in dissolving blood clots[26].

Animal experiments have shown that nattokinase is about four times as effective as the body's endogenous "blood clot dissolver" plasmin[27]. Other research has clearly shown that nattokinase prevents the formation of blood clots on injured artery walls[28,29]. Some researchers believe it is superior to conventional clot-dissolving drugs such as urokinase. Other researchers have found that it contains ACE inhibitors and, in large doses, is highly effective in lowering blood pressure in hypertensive individuals[30]. The beneficial effects of nattokinase persist for 18 hours or more and positive effects have been observed with as little as 50 mg[31].

A clinical trial involving 204 airline passengers at high risk for venous thrombosis was recently carried out to determine if a combination of nattokinase and pycnogenol (a water extract from the bark of the French maritime pine) would prevent venous thrombosis. The incidence of venous thrombosis in the nattokinase/pycnogenol group was 0% as compared to 7.6% in the control group[32].

These findings add to the evidence of nattokinase's effectiveness in preventing thrombosis. Deep vein thrombosis is caused by blood stagnation in the veins, particularly in the legs. There is evidence that a significant source of blood clots in permanent afibbers with cardiovascular disease is the left atrial appendage where blood tends to stagnate during atrial fibrillation. It would seem likely that nattokinase might also be effective in preventing the formation of cardioembolic clots in the left atrial appendage.

Optional Supplements
It would make little sense to just focus on a natural stroke prevention program that only addresses the risk of embolic stroke when thrombotic stroke is actually more prevalent. So, it would be prudent to add natural platelet aggregation inhibitors to the above regimen. These would include folic acid, vitamin B6 and vitamin B12 for homocysteine reduction as well as vitamin E, potassium, magnesium and ginkgo biloba.

Conclusion

The recommendation (2006 *Guidelines for the Management of Patients with Atrial Fibrillation)* that lone afibbers with no risk factors for stroke should be treated with 81 to 325 mg/day of aspirin does not stand up to closer scrutiny and is not supported by clinical evidence. As a matter of fact, there is now evidence that following the recommendation may do more harm than good.

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