

# THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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*This month's issue features an in-depth discussion of the pros and cons of taking a daily aspirin for stroke prevention. There is no evidence that aspirin prevents a first, ischemic stroke in healthy individuals with no specific risk factors for stroke. Nor is there any evidence that lone afibbers, with no specific risk factors, have an increased risk of ischemic stroke.*

*Thus, I have always found it puzzling why the 2001 Guidelines for the Management of Patients with Atrial Fibrillation recommended that lone afibbers receive no stroke prevention therapy – or a daily aspirin, while the 2006 Guidelines specify aspirin or warfarin, with no option of a non-pharmaceutical approach.*

*A thorough search for any medical evidence that could possibly have motivated the change turned up no supporting information. As a matter of fact, it turned up a surprising amount of evidence that concludes the daily aspirin ritual may do more harm than good in individuals at low risk for ischemic stroke.*

*Also in this issue we report on the epidemic growth of atrial fibrillation confirmed in a recent study in Scotland, that fish oils have been found to be entirely safe even if taken with aspirin or warfarin, Spanish researchers report on the trial of a new anticoagulant combination that is safer and more effective than warfarin, and finally, a fascinating study reveals how quickly and effectively supplementation with fish oils causes beneficial changes in heart cell membrane structure.*

*If you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to defray the cost of maintaining the web site and bulletin board. You can find the store at <http://www.afibbers.org/vitamins.htm> - your continuing support is very much appreciated.*

*Wishing you good health and lots of NSR,*

**Hans**

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## Status of AF in Scotland

GLASGOW, UNITED KINGDOM. A group of researchers has just completed a study aimed at determining the prevalence (total number of cases of a disease in a given population at a specific point in time) and incidence (total number of new cases of

a disease diagnosed during a specific time period – usually a year) of atrial fibrillation (AF) in Scotland. The study involved 55 primary care practices serving a total of 362,155 patients. The researchers determined the overall prevalence of AF (NOTE: no distinction was made between heart disease-related AF and lone AF) to be 0.94% in men and 0.79% in women. The **prevalence** increased markedly with age from 0.03% in individuals less than 45 years of age to 7.1% in persons over the age of 85 years. An 18% lower prevalence was found among socio-economically deprived individuals compared to affluent individuals (as measured by postal code of residence). It is possible that this difference is related to the shorter life expectancy of deprived individuals, or to the fact that affluent patients are more likely to receive electrocardiograms.

Other studies have concluded that the prevalence of AF among men and women between the ages of 75 and 84 years has risen from 7.3% to 9.5% in men and from 6.2% to 7.2% in women over the period 1994-1998. Most of the AF patients involved in the study had heart disease (32%) and/or hypertension (25%), while less than 5% had suffered a stroke.

The **incidence** (new cases per year) of AF rose from 0.01% in men below the age of 45 years to 0.04% in those between the ages of 65 and 74 years, and peaked at 0.09% for those aged 85 years and older. The corresponding numbers for women were 0%, 0.03%, and 0.07% respectively.

Most AF patients (71%) received rate control medication such as beta-blockers (28%), calcium channel blockers (42%), or digoxin (43%). Only 20% received an antiarrhythmic drug (amiodarone – 12%, sotalol – 6%). The researchers point out that the use of digoxin has decreased from 70% in 1996 to 43% in 2001. In this study, women were 25% more likely than men to be prescribed digoxin. Antithrombotic therapy was prescribed for 78% (aspirin – 44% and warfarin – 42%).

In an accompanying editorial Gregory Lip and colleagues at Birmingham University conclude that *AF is certainly the new “epidemic”* with 15.9 million people in the US alone expected to have the disease by 2050. Other studies have concluded that the lifetime risk of developing AF is now 24% in men and 22% in women at age 55 years.

*Murphy, NF, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart, Vol. 93, 2007, pp. 606-12*  
*Lip, GYH, et al. Atrial fibrillation – the growing epidemic. Heart, Vol. 93, 2007, pp. 542-43*

**Editor’s comment:** It is particularly gratifying to note that the use of digoxin has declined by 39% from 1996 to 2001. Digoxin is not as effective for rate control, as are beta- and calcium channel blockers and should never be taken by lone afibbers. Also, it is good to see the growing awareness of the fact that AF has now reached epidemic proportions. It is unfortunate that this study, like many others, did not distinguish between lone and heart disease-related AF. Of interest is the finding that the overall prevalence of AF was almost equal among men and women (ratio 54:46) whereas lone afib is significantly more prevalent among men (80:20).

## Fish oils are safe!

LOUISVILLE, KENTUCKY. Harold Bays, MD at the Louisville Metabolic and Atherosclerosis Research Center has addressed the question, “Does therapy with fish oils rich in omega-3 fatty acids increase the risk of bleeding, and are they contraindicated in patients treated with antiplatelet and anticoagulant therapies?” Dr. Bays concludes that clinical trial evidence does not support the idea that fish oils (EPA [eicosapentaenoic acid] and DHA [docosahexaenoic acid]) increase bleeding, even when given in combination with aspirin or warfarin. He also makes two other interesting observations:

- Fish oils inhibit thrombosis and may thus decrease the risk of ischemic stroke. However, one needs to take at least 1000 mg of EPA + DHA (not just 1000 mg of fish oil) a day to achieve significant cardiovascular benefits.
- It may be wise to stop fish oil supplementation 4-7 days prior to major surgery, except in the case of coronary artery bypass surgery where continued supplementation may help

prevent post-procedure atrial fibrillation.

Dr. Bays also addressed the question, “Do prescription and/or supplement omega-3 fatty acid products contain excessive vitamin or toxins, such as mercury, polychlorinated biphenyls, dioxin, or other contaminants, in sufficient concentrations to pose a potential health risk?” Again, his answer is negative. This conclusion is largely based on a 2006 ConsumerLab evaluation of 42 commercially available fish oil supplements. All but two were found to contain the amount of EPA and DHA stated on the label, were free of mercury, PCBs and dioxins, and were not oxidized (rancid). Among the brands that passed the ConsumerLab evaluation were Carlson, Coromega, Metagenics, Nordic Naturals, Kirkland and Puritan Pride.

Dr. Bays cautions that a high fish oil intake through the consumption of large amounts of fish may present a risk for environmental toxin exposure, especially methylmercury, PCBs, organochlorine pesticides and dioxins. He points out that oxidized mercury is insoluble in oil, so would not be expected

to represent a significant toxicity risk in fish oil supplements.

In an accompanying editorial Dr. William Harris of the University of South Dakota emphatically endorses Dr. Bays' conclusion that fish oils do not increase bleeding risk even if taken in combination with aspirin or warfarin.

*Bays, HE. Safety considerations with omega-3 fatty acid therapy. American Journal of Cardiology, Vol. 99, No. 6A, March 19, 2007, pp. 35C-43C*

*Harris, WS. Omega-3 fatty acids and bleeding – Cause for concern? American Journal of Cardiology, Vol. 99, No. 6A, March 19, 2007, pp. 44C-46C*

**Editor's comment:** The finding that fish oils do not increase bleeding and can safely be taken in combination with aspirin and warfarin is very reassuring as is the conclusion that 95% of fish oils supplements sold in health food stores are pure and safe.

## New antiplatelet/anticoagulation combination for AF patients

MADRID, SPAIN. Triflusal is an antiplatelet agent similar to aspirin, but not derived from acetylsalicylic acid. Several clinical trials in Europe have found it equivalent to aspirin in its ability to prevent cardiovascular events, but less likely to cause internal bleeding. Clinical trials have shown that 600 mg/day of triflusal is equivalent to 300 mg/day of aspirin as far as clinical efficacy is concerned.

Spanish researchers have just completed a clinical trial aimed at comparing the efficacy and safety of full-dose warfarin therapy (INR = 2.0-3.0) and a combination of triflusal (600 mg/day) with a reduced warfarin dose (INR = 1.25-2.0 or 1.4-2.4 if classified as high-risk). The trial involved 967 patients with atrial fibrillation, about 40% of which had hypertension and 10% had ischemic heart disease. The majority (77%) of trial participants were younger than 75 years of age. The researchers noted that older patients needed significantly less warfarin (1.9 mg/day vs. 2.1 mg/day) than younger patients to stay within INR range in the warfarin only group of the trial as well as in the triflusal/warfarin group (1.45 mg/day vs. 1.7 mg/day).

At the end of the trial the researchers made the following observations:

- For trial participants with no prior embolism, the total percentage of serious adverse events (fatal and non-fatal ischemic or hemorrhagic stroke/TIA, systemic embolism, heart attack, sudden death, and death from bleeding) in the elderly group (75 years of age or older) receiving warfarin alone was 4.6%/year vs. 1.8%/year in the younger group. The corresponding numbers for patients on the combination (triflusal + warfarin) were

substantially lower at 1.1%/year and 0.8%/year respectively.

- For trial participants with prior embolism, the event rate in the warfarin only group was 11.1%/year in the older group vs. 4.6%/year in the younger group. Corresponding numbers for the combination were 5.0%/year and 3.4%/year.
- Survival of elderly patients was substantially higher in the combination group. This was largely due to the fact that those in the warfarin group experienced more intracranial bleeding events (hemorrhagic stroke) than did those in the combination group (3.1% vs. 0.2%). Elderly warfarin group participants also suffered more fatalities from internal bleeding (2.1%/year vs. 0.3%/year in combination group). The non-fatal gastric bleeding rate was, however, higher in the combination group. The authors of the study point out that, in their experience, patients treated with warfarin alone tend to have more, usually fatal, intracranial bleeding complications, while those receiving combined therapy tend to experience more non-fatal upper gastrointestinal bleeding.

The Spanish researchers conclude that combination therapy (triflusal + low-dose warfarin) significantly reduces vascular events and bleeding mortality in elderly patients.

*Perez-Gomez, F, et al. Antithrombotic therapy in elderly patients with atrial fibrillation: Effects and bleeding*

complications. **European Heart Journal**, Vol. 28, 2007, pp. 996-1003

**Editor's comment:** It is interesting to note that, while the percentage of events (outcome rate) for patients on combination therapy is fairly low (2.3% and 1.5%) in both older and younger patients, the

outcome rate is quite different for those on warfarin. Here the outcome rate is 7% for the older patients versus 2.5% for younger ones, again proving that warfarin alone is a poor choice for older afibbers. Triflusal, unfortunately, is not available in North America.

## Fish oil incorporation in myocardial tissue

ADELAIDE, AUSTRALIA. There is ample evidence that increased fish or fish oil consumption is associated with a reduced risk of cardiac mortality, especially sudden death. It is believed that this benefit arises from the incorporation of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into the phospholipid membrane of cardiomyocytes (heart cells).

Australian researchers recently reported some very exciting findings regarding the actual mechanism and effectiveness of increasing the EPA + DHA content of myocytes and erythrocytes (red blood cells) by daily supplementation with fish oil. Their study involved 60 patients scheduled for on-pump bypass surgery and/or valve repair. The patients were divided into six groups of 10 patients and received supplements as follows:

- Group 1     6 grams/day EPA + DHA (50:50) for 7 days prior to surgery
- Group 2     6 grams/day EPA + DHA (50:50) for 14 days prior to surgery
- Group 3     6 grams/day EPA + DHA (50:50) for 21 days prior to surgery
- Group 4     6 grams/day of alpha-linolenic acid (ALA) in the form of flax oil for 21 days prior to surgery
- Group 5     6 grams/day of olive oil for 21 days prior to surgery
- Group 6     no supplements

Blood samples and biopsy specimens from the right atrium were taken during surgery. The samples were analyzed for fatty acid content and the following results obtained:

	<u>Baseline Control Group</u>	<u>Fish oil 21 days</u>	<u>Flax oil 21 days</u>	<u>Olive oil 21 days</u>
<b>Myocytes</b>				
<b>Fatty acid content</b>				
<b>% of total fatty acids</b>				
EPA	0.49	2.97	0.75	0.55
DHA	4.83	8.52	5.18	5.39
EPA + DHA	5.31	11.50	5.93	5.94
ALA	0.13	0.15	0.34	0.13
Arachidonic acid	20.84	15.99	20.01	20.02
<b>Erythrocytes</b>				
EPA	0.71	3.14	1.20	0.84
DHA	4.44	7.56	4.53	5.25
EPA + DHA	5.15	10.70	5.73	6.09
ALA	0.11	0.09	0.30	0.11
Arachidonic acid	14.21	11.67	14.36	14.51

The above results lead to the following observations:

- Fish oil supplementation for 21 days resulted in a substantial increase in

both EPA (500%) and DHA concentration (76%) in cardiomyocytes. This was mirrored by a proportional increase in red blood cells (340% for EPA and 70% for DHA).

- The increase in EPA + DHA was at the expense of a decrease in pro-inflammatory omega-6 arachidonic acid of 23% in the fish oil group (21 days). Supplementation with flax or olive oil had no effect on arachidonic acid levels.
- Supplementation (for 21 days) with flax oil (alpha linolenic acid) increased myocyte EPA concentration by a statistically insignificant 53% and DHA concentration by only 7% indicating that the efficiency of ALA conversion to EPA, and especially DHA, is low.
- No significant differences were found between the olive oil group and the control group.
- Analysis of data obtained after an average 10 days of fish oil supplementation showed that DHA is initially incorporated into heart cells at a rate twice that of EPA.

No excessive bleeding during surgery was observed for any of the groups involved in the study.

The researchers conclude that daily supplementation with 6 grams of EPA + DHA rapidly increases the EPA + DHA content of cardiomyocyte phospholipid membranes at the expense of a decrease in arachidonic acid level. They point out that these optimal rates of EPA + DHA incorporation are not likely to be matched at lower doses of fish oil. They also make the interesting suggestion that high-dose fish oil supplementation could be beneficial for patients recovering from a heart attack.

*Metcalf, RG, et al. Effects of fish-oil supplementation on myocardial fatty acids in humans. American Journal of Clinical Nutrition, Vol. 85, 2007, pp. 1222-28*

**Editor's comment:** The finding that high-dose fish oil supplementation rapidly increases myocyte membrane concentrations of EPA and DHA is indeed fascinating and could be of extreme interest to afibbers. Long-chain omega-3 fatty acids like EPA and DHA are known to increase membrane fluidity which may, in turn, be beneficial for afibbers. The relationship between omega-3 and omega-6 fatty acids and AF was first discussed in 2002 in an essay by Erling Waller about the path he took in order to vanquish his afib which had plagued him for

10 years. I would like to share Erling's thoughts with you.

*"After much study about cardiac cells, and the significance of cell membrane integrity and cellular energy in maintaining NSR, I finally focused in on the nutritional requirements of cells and the all important issues of omega-6 to omega-3 ratio, EPA and DHA fish oils, coenzyme Q10, l-carnitine, and magnesium.*

*Omega-3 (w3) and omega-6 (w6) are families of the essential polyunsaturated fats. They are essential in the diet because they are required and the body can't produce them. Probably everyone consumes too much w6 fats relative to the w3s since they are abundant in our food supply. The task for me was to know the sources and reduce their intake. The principal sources of w6s and w3s in our foods are the vegetable oils such as soybean, safflower, sunflower, canola, etc. If the food label lists polyunsaturated fats it's w6 and w3. The ratio of w6 to w3 in these food oils is too high to be conducive to health, and the methods used in extracting the oils make them unsuitable for consumption. "Virgin" applied to olive oil implies that gentle, low heat, non-destructive methods were used in extracting the oil, I've never seen that word used for other oils in our food. By reducing food oils and other common sources of polyunsaturates, and by adding supplemental w3s in the form of EPA/DHA fish oils I was able to improve my ratio. I have never aimed for a certain daily amount of w6, and would have a hard time doing so – I just watch my step. I figure that if I just stay low on most foods with oils I will still be getting plenty of w6, a required nutrient. But by doing so my intake of w3 is reduced. The most important w3s, EPA/DHA, are not in these oils anyway. They are either made in the body from other w3s in food (which for many is problematic), or they need to be supplemented. I usually take daily 4 capsules of fish oil providing 720 mg EPA and 500 mg DHA, but some days only 2 or 3 capsules. For a long time I was taking more than I am now. I absolutely stay away from hydrogenated oils which seem to be everywhere in processed foods. Hydrogenation produces "trans" fats with a molecular shape that screws up cell membranes. The book "Fats that Heal, Fats that Kill" by Udo Erasmus is powerful knowledge. Some days I only take 2 capsules, some days none, but I'm out of the woods now (in a maintenance mode) and am enjoying being less fussy about these things."*

## Pros and cons of vigorous exercise

DALLAS, TEXAS. The American Heart Association, in collaboration with the American College of Sports Medicine, has issued a consensus statement regarding the benefits and dangers of vigorous exercise. The groups agree that habitual exercise delays the development of atherosclerosis and reduces the incidence of coronary heart disease. On the other hand, vigorous physical activity can also transiently increase the risk of heart attack (acute myocardial infarction) and sudden cardiac death (SCD), particularly in individuals who are normally sedentary. Snow shoveling is highlighted as a particularly dangerous activity for normally sedentary individuals.

Highlights of the statement are:

- Among college athletes and other young people who die during exercise, the most common pathological findings are hereditary or congenital cardiovascular abnormalities such as Marfan syndrome, mitral valve prolapse, and arrhythmias.
- Among older people, the most common cause of exercise-related death is coronary artery disease with evidence of acute, coronary plaque disruption. Increased platelet activation has been reported in sedentary individuals who engage in unaccustomed high-intensity exercise but not in physically conditioned athletes.
- The incidence of exercise-related death is low among high school and college athletes with an estimated absolute risk of about 1 per 133,000 men and 1 per 769,000 women athletes. A recent Italian study found a sudden death rate of 1 per 33,000 young athletes a year.
- The incidence of exercise-related deaths in healthy older adults is also quite low with estimates ranging from 1 death per year for every 7,620 joggers to 1 death per 82,000 members of a fitness club. Nearly half of these deaths were among members who exercised infrequently or less than once a week. The estimated risk of an exercise-related heart attack ranges from 1 per 593 to 1 per 3,852 in apparently healthy, middle-aged men.
- The death rate related to exercise among patients with diagnosed heart disease is estimated at 1 per 116,402 exercise-hours. Although low, this number is 8 times higher than the corresponding number for healthy individuals.
- Vigorous exercise, while being beneficial in the long term for healthy adults, increases the risk of SCD by a factor of about 8 when compared to the SCD incidence during sedentary activities. The risk increase is particularly pronounced in normally sedentary individuals who engage in strenuous activity.
- Between 4 and 10% of heart attacks experienced by healthy individuals occurred within an hour of stopping vigorous exercise. For patients with coronary heart disease, the relative risk of cardiac arrest during vigorous exercise is estimated at 6 to 164 times greater than expected without exertion. The post-exercise risk of a heart attack is 50 times higher for sedentary individuals than for those who habitually exercise vigorously.
- Habitual vigorous exercise appears to reduce the overall risk of coronary artery disease in healthy adults; however, it may increase both exercise- and non-exercise-related sudden death in young people with cardiovascular disease.
- SCD and heart attacks occur more frequently in the morning than in the afternoon; however, there is no compelling evidence that this is related to time of exercise.
- Young athletes should be screened for cardiac abnormalities before participating in athletics. Doing so resulted in a decrease of 89% in SCD

among young Italian athletes. Older adults at risk for coronary artery disease should also be screened prior to undertaking a vigorous training program. This is particularly important for diabetics.

- Patients with known heart disease should include at least 5 minutes each of warm-up and cool-down in their training session in order to avoid inducing cardiac ischemia.

The statement concludes that habitual physical exercise is substantially more likely to be beneficial than harmful in healthy individuals with no underlying heart disease. It is also likely that exercise is more beneficial than harmful for older adults with heart disease, but beginning an exercise program requires close supervision and prior screening. *“Consequently, physical activity should be encouraged for most individuals in accordance with the Centers for Disease Control and Prevention/ACSM recommendations for at least 30 minutes of moderate-intensity physical activity such as brisk walking on most, preferably all, days of the week.”*

Thompson, PD, et al. *Exercise and acute cardiovascular events: Placing the risk into perspective. Circulation, Vol. 115, May 1, 2007, pp. 2358-68*

**Editor’s comment:** It is clear that moderate to vigorous daily exercise has long-term beneficial effects on cardiovascular and pulmonary health. The danger of death or heart attack during or after exercise is low in healthy adolescents and adults who regularly exercise. However, young athletes need to be screened for heart disease prior to engaging in strenuous athletics. Regular exercise is still recommended for adults with heart disease, but these individuals should be checked by their doctor before beginning a training program and should start out slowly, as should normally sedentary individuals who wish to become physically fit. Habitually exercising adults, particularly men, should also bear in mind that too prolonged and vigorous physical activity may increase the risk of developing atrial fibrillation by a factor of 5. For those individuals with atherosclerosis, it is of interest that fish oil has been found to improve plaque stability[1].

[1] Thies, F, et al. *Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. The Lancet, Vol. 361, February 8, 2003, pp. 477-85*

## RESEARCH REPORT

### Aspirin: Friend or Foe?

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/clinicalc/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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