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Natural Approaches to Stroke Prevention

Effective prevention of thrombosis and stroke involves one or both of two approaches:

- Eliminate or reduce artery wall dysfunctionality, atrial inflammation and blood stasis
- Use drugs or natural substances to prevent thrombosis.

Apart from regular exercise, it is not immediately obvious what can be done about reducing blood stasis in the left atrial appendage (LAA); so potential thrombus formation in the LAA is probably best prevented by the use of drugs or natural substances.

While most pharmaceutical drugs are quite specific in their thrombosis preventing action, several natural approaches not only inhibit specific promoters of platelet aggregation and coagulation, but also help to reduce inflammation and artery wall dysfunctionality.

Vitamin B Cocktail

A daily vitamin B cocktail (vitamin B6, vitamin B12 and folic acid) is among the most important supplements that an afibber, or anyone else for that matter, can take. The vitamin B cocktail effectively lowers the level of homocysteine in the blood. High levels of homocysteine, a sulfur-containing amino acid, is associated with an increased risk of stroke and is also involved in numerous other disease conditions:

- A group of American researchers has found that a high blood level of homocysteine is associated with an increased risk of stroke even after adjusting for other known risk factors such as advanced age, hypertension, smoking, diabetes, heart disease, and atrial fibrillation. The researchers found that those of the 1947 study participants who had homocysteine levels greater than 14.2 micromol/L had an 82% greater incidence of stroke over the 10-year study period than did participants with an level of 9.25 micromol/L or less. It is interesting that the average annual stroke incidence among the study participants (average age of 70 years) was 0.8%[1].

- Dutch researchers have found that high homocysteine levels are associated with a significantly higher risk of both stroke and heart attack. Their study involved 7983 elderly subjects who had their homocysteine level measured in July 1993. By December 1994, 120 of the participants had suffered a stroke and 104 had experienced a heart attack. The researchers found that stroke and heart attack risk increased linearly with an increase in homocysteine level so that a 1 micromol/L increase in homocysteine corresponded to a 6-7% increase in risk of stroke or heart attack. Study participants with

the highest homocysteine level had a two times higher risk of stroke than did those with the lowest level after adjusting for age, sex, smoking, hypertension, cholesterol level, and diabetes. The increased stroke risk applied to both ischemic and hemorrhagic stroke and was further increased by the presence of hypertension. It is interesting to note that the annual incidence of stroke in the group was 1.0%[2].

There are numerous other studies attesting to the association between high homocysteine levels and stroke risk. Many have found associations between high homocysteine levels and other disorders making homocysteine one of the top villains on the health scene.

- Swiss researchers have observed a strong association between coronary artery disease and high homocysteine levels. They found that an increase of just 5 micromol/L corresponds to an increased risk of coronary artery disease of 60% in men and 80% in women. They also found that homocysteine levels increased in a linear fashion among 631 patients undergoing angiography from 9.2 micromol/L for patients with no coronary disease to 12.4 micromol/L in patients with three-vessel disease[3].

- Taiwanese researchers have found a strong link between high homocysteine levels and the presence of endothelial dysfunction and atherosclerosis. Perhaps not surprisingly, they also found that a high-protein meal will markedly elevate homocysteine levels. Fortunately, they also found that 5 weeks supplementation with the vitamin B cocktail reduces this protein-meal-induced homocysteine rise quite significantly[4].

- Researchers at the Boston University School of Medicine report that people with a homocysteine level above 14 micromol/L have nearly twice the risk of developing Alzheimer's disease as do people with lower levels. They also determined that a 5 micromol/L increase in homocysteine level corresponds to a 40% increased risk of Alzheimer's[5].

- Italian researchers have observed a strong correlation between elevated homocysteine levels and the incidence of deep vein thrombosis (DVT). They found that the incidence of DVT was twice as high among people with high homocysteine levels as among those with low levels[6]. This finding is particularly intriguing when considering that DVT is associated with blood stagnation in the veins of the legs. Blood stagnation is also a key factor in the formation of blood clots in the left atrial appendage (LAA). Thus it would seem likely that high homocysteine levels maybe involved in thrombosis originating in the LAA and by inference, that measures that will prevent DVT and/or lower homocysteine levels will also have a salutary effect on LAA thrombosis.

- American researchers have established that the normal blood level of homocysteine is about 10-12 micromol/L. (NOTE: "Normal" does not necessarily equate with "healthy"). Heart disease and stroke patients often have levels of 15 micromol/L or higher and elevated levels have also been observed among patients with intermittent claudication, hypothyroidism, lupus erythematosus, venous thrombosis, and psoriasis. High homocysteine levels are also common among patients taking medications such as methotrexate, levodopa, niacin, phenytoin (Dilantin), carbamazepine, and theophylline[7].

- Norwegian researchers have found that for every 5.0 micromol/L that the blood level of homocysteine exceeds 9.0 micromol/L, cardiovascular mortality increases by 50%, cancer mortality by 26%, and death from other causes (respiratory, gastrointestinal and central nervous system diseases) by 104%. They conclude that high homocysteine levels have a pervasive negative effect on longevity[8].

By now it should be clear that homocysteine is a very bad actor indeed and that maintaining low blood levels is important. Taking steps to do so is particularly important for people eating a high-protein diet. Taiwanese researchers have found that consuming a high-protein meal rapidly increases homocysteine level to 20 micromol/L or more while at the same time constricting arterial blood flow[4].

Fortunately, it is easy, inexpensive, and safe to reduce homocysteine levels by regular supplementation with the vitamin B cocktail. "Regular" is a key term here. It takes about 4 to 5 weeks of supplementation to achieve maximum homocysteine reduction and much longer than that to reverse endothelial dysfunction. There is also evidence that homocysteine levels tend to rise again if daily supplementation is discontinued[9]. Numerous researchers have investigated just how much of the cocktail is required to achieve optimum results.

- Researchers at the Cleveland Clinic observed that a combination of 400 micrograms/day of folic acid plus 12.5 mg/day of vitamin B6 plus 500 micrograms/day of vitamin B12 reduced homocysteine levels in heart disease patients from an average of 13.8 micromol/L to 9.6 micromol/L over a 90-day period[10].

- Taiwanese researchers found that healthy women who supplemented with 5 mg/day of folic acid, 100 mg of vitamin B6, and 500 micrograms/day of vitamin B12 reduced their homocysteine level to 5.2 micromol/L after 5 weeks[4].

Other researchers have evaluated different protocols, but overall it would seem that 400-800 micrograms/day of folic acid plus 10-100 mg/day of vitamin B6 plus 500-1000 micrograms/day of vitamin B12 (a sublingual tablet is best) will do the trick. Recent research has shown that the commonly used folic acid supplement (pteroylmonoglutamate) may not be converted to folate if doses above 400 micrograms are taken. It is not known what the long-term effects of an accumulation of unconverted pteroylmonoglutamate might be, so unless under a doctor's supervision, it would be prudent not to exceed a folic acid supplement intake of 400 micrograms/day or to use a natural folate supplement such as L-5-methyltetrahydrofolate[11].

Although there is evidence that homocysteine reduces plasmin activity (ability to dissolve blood clots) it is not clear whether the main beneficial effect of the vitamin B cocktail in stroke prevention is a lowering of homocysteine or a reduction in the level of the thrombin-antithrombin III complex and a partial inhibition of thrombin generation[12].

In closing, high homocysteine levels are associated with inflammation. Inflammation is a key player in lone atrial fibrillation[13]. Is it possible that reducing homocysteine levels with the vitamin B cocktail would also reduce afib episode frequency?

Vitamin B6 (Pyridoxine)

There is considerable evidence that low blood levels of vitamin B6 or, rather, its metabolite pyridoxal-5'-phosphate (PLP, P5P) are associated with an increased risk of stroke. This risk increase is independent of homocysteine level[14,15]. There is also evidence that low vitamin B6 levels increase the risk of deep vein thrombosis[6].

South African and Turkish researchers have found that vitamin B6 supplementation is effective in increasing bleeding time by about 65% and that the underlying mechanism involves a significant reduction in platelet aggregation through inhibition of both ADP (adenosine diphosphate)- and epinephrine-induced aggregation[16,17]. The Turkish researchers found that daily supplementation with about 350 mg (5 mg/kg) of vitamin B6 reduced ADP-induced aggregation by 48% and epinephrine-induced aggregation by 41%[17]. The South African researchers

achieved similar results using 2 x 100 mg per day of vitamin B6 and also noted that B6 did not inhibit prostacyclin production[16].

Italian researchers have noted that people with low levels of vitamin B6 (less than 33.2 nanomol/L of PLP) have twice the risk of developing deep vein thrombosis than do people with levels above 46.5 nanomol/L[6]. The finding that high vitamin B6 levels may be protective against deep vein thrombosis is of particular interest to afibbers. It is highly likely that the mechanism (blood coagulation or inadequate fibrinolysis) involved in deep vein thrombosis is very similar to the mechanism involved in thrombus formation in the left atrial appendage. Thus, if vitamin B6 is protective against deep vein thrombosis, it may also be protective against thrombosis and stroke in atrial fibrillation.

Canadian researchers have found that supplementation with 100 mg/day of vitamin B6 for 10 weeks is associated with a 146% improvement in endothelial function in heart transplant patients[18]. More recently, researchers at the Harvard Medical School and the Massachusetts General Hospital discovered a strong association between stroke risk and blood level of PLP. This increased risk of stroke with low PLP levels was entirely independent of homocysteine levels confirming that vitamin B6, on its own, has significant stroke prevention properties. The researchers found that study participants with a plasma level of PLP of more than 80 nanomol/L had a 90% lower risk of stroke and transient ischemic attacks (TIAs) than did participants with a level below 20 nanomol/L. The risk decrease was independent of the presence of other risk factors such as hypertension, diabetes, and atrial fibrillation[15]. The researchers also noted a strong inverse correlation between C-reactive protein level and PLP level indicating that vitamin B6 may also have strong anti-inflammatory properties – an added plus for afibbers.

The 90% relative reduction in stroke risk among people with high PLP levels is very significant and compares extremely favourably with the oft-quoted relative risk reduction afforded by warfarin (64%) and aspirin (25%). Clearly, ensuring adequate blood levels of PLP is a must for all afibbers. Vitamin B6 is converted to its active metabolite PLP in the liver and there is some evidence that the liver can only handle about 50 mg of vitamin B6 at a time. Experiments have shown that the plasma concentration of PLP does not increase further if 100 mg rather than 50 mg of pyridoxine is ingested at any one time. So it is assumed that the conversion to PLP is limited by the liver's conversion capacity[19]. Other experiments have shown that supplementing (orally) with 40 mg of vitamin B6 will increase average plasma concentration from about 23 nmol/L (range: 18-37 nmol/L) to about 230 nmol/L within 3 days of beginning supplementation. No further increases were observed with 40 mg/day supplementation for a 12-week period[20].

The 230 nmol/L concentration achieved is well above the 80 nmol/L concentration associated with the 90% reduction in stroke risk observed by the Harvard researchers[15]. So 40-50 mg/day would seem to be sufficient for stroke protection and is considered entirely safe[20].

Vitamin B6 itself is, however, water-soluble and any excess is totally eliminated in the urine within about 9 hours. To keep the vitamin B concentration up, it would be necessary to take two or three 50 mg doses per day. However, in the case of stroke protection, one 50 mg dose per day is likely to be quite adequate, as PLP concentration does not vary much during the day once steady state conditions are achieved. Adequate amounts of vitamin B2 and magnesium are required in order to convert vitamin B6 to PLP. NOTE: If taking the vitamin B cocktail, there is no need for additional vitamin B6 in order to reap the benefits of its stroke prevention properties.

Vitamin C

Vitamin C is a powerful antioxidant and as such helps to prevent oxidative stress, a major underlying cause of thrombosis and reperfusion injury. A low intake of vitamin C has been linked to a doubling of the risk of dying from a stroke[21,22]. Finnish researchers recently reported that

low vitamin C levels are also associated with an increased risk of actually having a stroke whether ischemic (caused by a blood clot) or hemorrhagic (caused by a burst blood vessel). Their study involved 2419 randomly selected middle-aged men (42 to 60 years of age) with no history of stroke at the baseline examination. The men were followed for an average of 10.4 years during which time 96 ischemic and 24 hemorrhagic strokes were documented. This corresponds to a total stroke incidence of 0.5% per year.

After adjusting for age, month of examination (vitamin C levels tend to vary with the seasons), body mass index, systolic blood pressure, smoking, alcohol consumption, total cholesterol level, and presence of diabetes or exercise-induced angina, the researchers observed that men with a plasma vitamin C level below 28.4 micromol/L had twice the risk of having a stroke when compared to men with a level above 65 micromol/L. The association was particularly pronounced among hypertensive men where low vitamin C levels were associated with a 2.6 times higher risk and among overweight men where low levels were associated with a 2.7-fold risk increase. The researchers have also observed a significant association between low vitamin C levels and elevated blood pressure (hypertension). They conclude that a low vitamin C level is an independent risk factor for both ischemic and hemorrhagic stroke, especially among hypertensive and overweight men. They call for clinical trials to test the efficacy of vitamin C supplements in the prevention of stroke among hypertensive and overweight (BMI greater than 25 kg/sq m) and obese men[23].

It is likely that vitamin C's stroke protection properties are associated with its ability to

- reduce endothelial dysfunction;
- reduce the level of von Willebrand factor;
- reduce the level of plasminogen activation inhibitor-1 (PAI-1)

Greek researchers have observed that daily supplementation with 2000 mg of vitamin C plus 800 IU of vitamin E markedly reduces plasma levels of PAI-1 and von Willebrand factor in smokers[24]. High PAI-1 levels are associated with a reduction in fibrinolytic activity and high von Willebrand factor levels are associated with enhanced coagulation. Another group of Greek researchers found that daily supplementation with 2000 mg of vitamin C for 4 weeks significantly reduced endothelial dysfunction and decreased the level of von Willebrand factor in a group of patients with diabetes and coronary artery disease. The level of tissue plasminogen activator (tPA) was also decreased corresponding to a decrease in fibrinolytic activity in this group of patients[25]. Other researchers have found that daily supplementation with 2 x 1000 mg of vitamin C for 6 months increases serum ascorbic acid levels by about 96%, increases fibrinolytic activity by 45-63%, and decreases platelet adhesive index by 27%[26]. The recently completed Rotterdam study found clear evidence that a high dietary intake of vitamin C significantly reduces the risk of ischemic stroke, especially among smokers[27]. It is interesting to note that the average incidence of ischemic stroke among the 5,197 participants in the Rotterdam study was 0.7% per year.

Researchers at Cambridge University have confirmed that high blood levels of vitamin C (ascorbic acid) protect against stroke. Their study involved 20,649 men and women between the ages of 40 and 79 years when enrolled during the period 1993-1997. None of the participants had suffered a prior stroke. Blood samples were drawn and analyzed for ascorbic acid content at baseline and participants were then followed for an average of 10 years. During this time a total of 448 strokes occurred corresponding to an average annual stroke rate of 0.2%.

After adjusting for the possible effects of gender, age, smoking, BMI, blood pressure, cholesterol, physical activity, diabetes, heart attack, social class, alcohol consumption, and supplement use the researchers conclude that study participants whose blood plasma levels of vitamin C were

above 66 micromol/L had a 42% lower risk of stroke than did those whose levels were below 41 micromol/L. They also observed a 17% reduction in stroke for every 20-micromol/L increase in plasma vitamin C concentration. A 20-micromol/L increase in plasma vitamin C concentration can be achieved by adding one additional serving of fruit and vegetables daily.

It is also of interest to note that six times as many study participants in the high plasma vitamin C group were supplementing with vitamin C as compared to those in the low plasma vitamin C group (10.5% vs 1.9%).[146]

An average reduction in stroke risk of 42% is indeed impressive and compares favourably with the 25-30% relative risk reduction often quoted for aspirin, and the 50-65% reduction attributed to warfarin, especially since increasing one's vitamin C intake is not associated with any adverse effects. The Cambridge researchers point out that vitamin C has a very short half-life in the blood (about 30 minutes), so spreading one's intake (whether through foods or supplements) throughout the day is essential. Tissue saturation with vitamin C (about 70 micromol/L in plasma) can be obtained by supplementing with 300-500 mg of vitamin C three times a day.

Vitamin E

Vitamin E is a powerful, fat-soluble antioxidant that, together with vitamin C, protects cells against oxidative stress, an important underlying cause of stroke and cardiovascular disease. There is considerable epidemiologic evidence that supplementing with 100 IU/day or more of vitamin E is effective in reducing the incidence of heart disease by about 40% and the incidence of ischemic stroke by about 30%[28,29]. Larger daily intakes of vitamin E (800 IU/day) have been associated with a 77% reduction in the incidence of non-fatal heart attacks[30]. Other studies have concluded that vitamin E supplementation with 100 IU or more is effective in slowing the progression of atherosclerosis[31].

While there is little doubt about the benefit of vitamin E in **preventing** cardiovascular disease, two recent clinical trials concluded that it is not effective in **reversing** existing disease[32,33]. This is not really surprising. The main effect of antioxidants is that they help prevent (delay) the initiation of disease. They are not effective, certainly not in the amounts used in the trials, in reversing or even slowing down the progression of disease once it has taken hold. This is very basic antioxidant theory, but a point that seems to be ignored by many medical researchers. There are numerous studies that have shown vitamin E and Vitamin C to be effective in **preventing** many different conditions, but very few that have shown a curative effect.

Vitamin E produces its beneficial effects through three separate mechanisms:

- Prevention of lipid peroxidation, especially of low-density lipoprotein (LDL) cholesterol
- Improvement of endothelial function
- Inhibition of platelet aggregation and coagulation.

Vitamin E has been found to prevent or reverse endothelial dysfunction, especially in patients with cardiovascular disease, diabetes or high cholesterol level. It preserves or enhances the ability of endothelial tissue to produce nitric oxide and reduces the tendency of monocytes to adhere to vessel walls[34].

Vitamin E (100 IU/day) has been found to reduce platelet aggregation by inhibiting the release of arachidonic acid and thromboxane A2[35]. Researchers at the Boston University School of Medicine found that a specific enzyme, protein kinase C (PKC), found in platelets will induce platelet aggregation and adhesion when stimulated by certain compounds. The researchers also discovered that supplementation with vitamin E will completely suppress this negative effect of PKC. Their experiment involved 15 volunteers who were given 400, 800 or 1200 IU/day of

vitamin E for a 14-day period. The vitamin E content of the volunteers' platelets increased from 38.9 pmol/100 million platelets to 81.2, 96.0 and 160.5 pmol/100 million platelets respectively. PKC stimulation was completely inhibited at all three levels of vitamin E supplementation. The researchers conclude that vitamin E's ability to inhibit PKC stimulation and subsequent platelet aggregation and adhesion is an additional, beneficial effect that is not related to its ability to protect LDL against oxidation[36].

Other researchers have found that vitamin E profoundly inhibits platelet aggregation without affecting clotting time as measured with the prothrombin time test[37]. Yet, others have observed that vitamin E increases prostacyclin production and decreases von Willebrand factor activity[38]. Supplementation with 600 mg/day of vitamin E has been found to markedly decrease (by 25%) the blood level of prothrombin fragments 1 and 2[39]. This would indicate that vitamin E can affect the common pathway in the coagulation cascade to possibly lengthen bleeding time. There is no indication that vitamin E affects the level of vitamin K-dependent coagulation factors except in people with certain specific coagulation disorders. There is also no indication that vitamin E alters the coagulation pattern in normal, warfarin-treated patients, so there is no reason to shun vitamin E supplementation when taking warfarin[40].

It is clear that vitamin E has a profound inhibitory effect on platelet aggregation and possibly some minor effect on thrombin generation. These effects, as well as its proven ability to combat oxidative stress and prevent or reverse endothelial dysfunction, are undoubtedly what underlies vitamin E's observed ability to reduce the incidence of ischemic stroke by about 30%.

It is interesting that combining vitamin E (300 mg/day) with vitamin C (600 mg/day), selenium (75 micrograms/day) and beta-carotene (27 mg/day) has an even more pronounced effect on platelet aggregation than does vitamin E alone. Finnish researchers found that supplementing with the above "cocktail" for 5 months reduced serum lipid peroxides by 20%, ADP-induced platelet aggregation by 24%, ATP release during aggregation by 42%, and produced an astounding 51% reduction in platelet-produced thromboxane B2[41].

The bottom line is that vitamin E is effective in preventing thrombosis related to platelet aggregation, is safe, does not cause bleeding, and does not interact with warfarin except possibly in some patients with specific coagulation disorders. An appropriate daily dose for stroke prevention is 400-600 IU/day. Vitamin E should always be taken in its natural form as the whole complex based primarily on gamma-tocopherol and in combination with vitamin C (3 x 300-500 mg/day).

Niacin (Vitamin B3)

Patients with peripheral arterial disease (PAD) have a high risk of stroke so are usually treated with warfarin. A recent clinical trial involving PAD patients found that warfarin therapy (INR 1.5-2.0) resulted in a significant drop in coagulation factor VIIc (18% drop as compared to placebo group) and in the level of prothrombin fragments 1 and 2 (48% drop as compared to placebo group). No significant decreases in fibrinogen or von Willebrand factor were observed.

As part of the trial a separate group of PAD patients were given 2 x 1500 mg of niacin (vitamin B3) daily. After one year, there was a significant 14% decrease in fibrinogen and a remarkable 60% decrease in prothrombin fragments 1 and 2. There was no effect on the level of von Willebrand factor. The researchers involved in the trial conclude that high-dose niacin has a potentially beneficial effect on coagulation parameters in patients with established PAD[42].

Lycopene

The carotenoid lycopene is a powerful antioxidant, particularly abundant in tomatoes. There is evidence that it helps prevent lung and prostate cancer[43,44]. Italian researchers have reported an inverse correlation between blood level of lycopene and the severity of atherosclerosis and peripheral vascular disease (intermittent claudication)[45]. Austrian researchers have reported that elderly people with microangiopathy-related cerebral damage have significantly higher blood levels of fibrinogen and significantly lower levels of lycopene and vitamin E[46].

Finnish researchers recently reported that middle-aged men with low lycopene levels have a 3.3-fold higher risk of suffering a heart attack or stroke than do men with normal levels. They also found that the intima-media thickness of the common carotid artery wall (a measurement of atherosclerosis) was 18% higher in men with a low lycopene level. They conclude that low levels of lycopene may play a role in the early stages of atherogenesis (endothelial dysfunction)[47].

It is not clear exactly how lycopene exerts its protective effects in cancer, heart disease and stroke; however, it is known that it is the most effective neutralizer of singlet oxygen, a powerful free radical[48]. Lycopene can be obtained from tomatoes or, even better, from processed tomato products such as tomato paste and juice. Supplements are also effective in increasing blood levels of lycopene[49].

Magnesium

Not only is magnesium effective in reducing ectopic beats and to some extent atrial fibrillation episodes as well, there is now also emerging evidence that it may help protect against ischemic stroke. Austrian researchers recently investigated the association between serum magnesium levels and the risk of having an ischemic stroke or needing carotid revascularization (removal of the inner wall of the carotid artery or the placement of a stent to restore blood flow through the carotid artery). Their study involved 323 patients with advanced atherosclerosis (symptomatic peripheral artery disease and intermittent claudication). The patients (197 men and 126 women with an average age of 68 years) had their serum magnesium level measured and were then followed for 20 months. At the end of the study period, 35 patients had suffered an ischemic stroke or had needed revascularization or both. The researchers found that patients with a serum magnesium level below 0.76 mmol/L had a three times higher risk of experiencing a neurological event (stroke or revascularization) than did patients with a magnesium level of more than 0.84 mmol/L. Although these results, obtained in patients with advanced atherosclerosis, may not be directly applicable to lone afibbers they certainly do indicate that magnesium could play an important role in stroke prevention[50].

American researchers have reported that magnesium supplementation helps prevent the formation of blood clots in patients with coronary artery disease[51]. There is also evidence that magnesium injections given within 6 hours of suffering an ischemic stroke can markedly reduce stroke damage[52]. It is possible that magnesium may also, in a more indirect way, help to protect against stroke by preventing hypertension, a recognized risk factor for stroke. Researchers at the Harvard Medical School have reported that men whose daily magnesium intake is less than 250 mg/day have a 50% greater risk of developing hypertension than do men whose daily intake exceeds 400 mg[53]. Dutch researchers have found that magnesium supplementation is effective in lowering both systolic and diastolic blood pressure in women with moderate hypertension[54]. There is also evidence that magnesium supplementation is effective in reversing endothelial dysfunction, a recognized risk factor for stroke[55].

Potassium

Several studies have observed that low potassium levels are associated with a greater mortality from stroke. American researchers have found that the risk of having a stroke also increases with low potassium levels. Their study involved 5600 men and women over that age of 65 years who were free of stroke at enrollment in 1990-93. All participants underwent a thorough medical examination at baseline, completed a food frequency questionnaire, and had blood serum potassium level determined. After 4 to 8 years of follow-up, a total of 473 strokes (404 ischemic) had occurred in the group. The researchers found that participants on diuretics had a 2.5 times increased risk of stroke if their serum level of potassium was below 4.1 mEq/L. Participants who were not taking diuretics were found to have a 50 % increased risk of stroke if their dietary potassium intake was less than 2340 mg/day[56,57].

Researchers at the Harvard Medical School studied 43,738 male health professionals. During 8 years of follow-up, 328 strokes (210 ischemic, 70 hemorrhagic, 48 unspecified) were observed. They found that men whose daily intake of potassium (as obtained from a food frequency questionnaire) averaged 4.3 grams/day had a 38% lower risk of experiencing a stroke than did men whose average daily intake was below 2.4 grams/day. Men who supplemented with potassium also had a substantially reduced risk of stroke, particularly if they were also taking diuretics (non-potassium-sparing)[58]. Harvard researchers have also found a substantially lower stroke risk among women with a high intake of calcium, magnesium, and potassium[59].

As in the case of magnesium, it is also possible that potassium acts indirectly to protect against stroke through its pronounced effect on blood pressure. Researchers at the Johns Hopkins University School of Medicine have come out in favour of using supplementation with potassium in the treatment and prevention of hypertension (high blood pressure). A group of seven medical researchers reviewed 33 randomized, controlled supplementation trials involving over 2600 participants. They conclude that potassium supplementation is effective in lowering both systolic and diastolic blood pressure. The average observed decrease in hypertensive patients was 4.4 mm Hg and 2.5 mm Hg for systolic and diastolic pressure respectively. In people with normal blood pressure, the observed decreases were 1.8 mm and 1.0 mm. The amount of elemental potassium used in the studies varied from 60 mmol (2300 milligrams) to 120 mmol (4700 milligrams) daily. Sixty mmol of potassium is equivalent to 4.5 grams of potassium chloride, 6 grams of potassium bicarbonate, 15 grams (about 4 teaspoons) of potassium gluconate or 20 grams of potassium citrate. Oral potassium supplementation appeared to be well tolerated in all the studies examined. The researchers conclude that potassium supplementation "should be considered as part of recommendations for prevention and treatment of hypertension." Potassium supplementation is particularly important in people who are unable to reduce their intake of sodium[60].

Medical researchers at the Erasmus University Medical School in the Netherlands have discovered a natural mineral salt, which significantly lowers blood pressure in people suffering from mild to moderate hypertension. The salt, SagaSalt (Akzo Nobel), occurs naturally in Iceland and contains 41% sodium chloride, 41% potassium chloride, 17% magnesium salts, and 1% trace minerals. The researchers tested the salt in a randomized, double-blind, placebo-controlled trial involving 100 men and women aged 55 to 75 years. Half the group used the mineral salt in food preparation and at the table while the other half used common table salt (sodium chloride). After 8 weeks, the average blood pressure in the mineral salt group had fallen significantly. The systolic blood pressure (mean of measurement at weeks 8, 16 and 24) fell by 7.6 mm Hg and the diastolic pressure by 3.3 mm Hg in the mineral salt group as compared with the control group. The researchers conclude that replacing common table salt with a low sodium, high potassium, high magnesium mineral salt is an effective way of lowering blood pressure in older people suffering from mild to moderate hypertension[61].

Italian researchers have found that excessively high potassium levels increase stroke risk significantly[62]. Thus it is important to maintain potassium levels within a fairly narrow range. This should not be a problem if the kidneys are functioning normally. However, if kidney disease is present or potassium-sparing diuretics (spironolactone, triamterene) are used, then medical advice and extreme caution are advised if potassium supplementation or a switch to a high-potassium diet is contemplated.

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[63]. 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[64].

In January 2001, researchers at the Harvard Medical School reported that women who consumed fish even just once a week reduced their stroke risk substantially. Their study involved 79,839 female nurses who were between the ages of 34 and 59 years at the start of the study in 1980. After 14 years of follow-up, a total of 574 strokes had occurred in the group. Most of the strokes (303) were ischemic, i.e. caused by a blood clot. There were also 181 hemorrhagic strokes, i.e. caused by a ruptured artery and 90 strokes of undetermined origin. After adjusting for age, smoking and other cardiovascular risk factors, the researchers concluded that women who ate fish once a week lowered their risk of having a stroke of any kind by 22% and those who consumed fish 5 or more times a week reduced their risk by 52%. They ascribe the protective effect of fish consumption to the commensurate intake of fish oils. They estimate that women whose intake is 0.5 gram/day or more have a 30% lower risk of suffering a stroke than do women whose intake is below about 0.1 gram/day. There was no evidence that women with a high fish or fish oil consumption have an increased risk of hemorrhagic stroke. The researchers believe that the protective effects of fish oils are due to their ability to inhibit platelet aggregation, lower blood viscosity, suppress the formation of leukotrienes, reduce fibrinogen levels, and reduce blood pressure levels and insulin resistance. They also note that the beneficial effects of fish consumption were substantially more pronounced among women who did not take aspirin on a regular basis[65].

Shortly after the release of the Harvard study, researchers at the Harvard School of Public Health released the results of another study involving male health professionals. Over 43,000 male health professionals aged 40 to 75 years were enrolled in the study in 1986. During a 12-year follow-up period, 608 strokes occurred (377 ischemic, 106 hemorrhagic, and 125 strokes of unknown origin). The participants completed food frequency questionnaires in 1986, 1990 and 1994. Men who consumed fish at least once a month had a 44% lower risk of having an ischemic stroke than did men who consumed fish less than once per month. No significant association were found between fish or long chain omega-3 PUFA (polyunsaturated fatty acid) intake and the risk of hemorrhagic stroke, but a possible association could not be ruled out due to the relatively small number of hemorrhagic strokes that occurred in the group. The optimum protection was achieved at fish consumption once per week and more frequent fish consumption (5 or more times a week) did not reduce stroke risk further. The protective effect of fish consumption was not significantly affected by the use of aspirin or vitamin E supplements (about 25% of participants used aspirin for stroke protection and about 20% supplemented with vitamin

E). The researchers calculated the intake of PUFAs (EPA and DHA) from fish and found that significant protection against ischemic stroke was achieved at a daily fish oil intake of between 50 mg and 200 mg. The level of daily intake of alpha-linolenic acid did not affect stroke risk. Additional fish oil supplementation did not reduce risk of ischemic stroke any further[66].

It is likely that some strokes, particularly in afibbers with hypertension or heart disease, may be caused by the dislodgement of fragments of atherosclerotic plaque from the walls of the arteries. Researchers at the University of Southampton did a clinical trial to see if fish oil supplementation would improve plaque stability and thus help prevent heart attack and stroke. Their study involved 162 patients who were awaiting carotid endarterectomy (an operation involving the removal of atherosclerotic deposits from the carotid artery feeding the brain). The patients were randomly allocated to receive a placebo, fish oil or sunflower oil daily from the time they entered the study until the endarterectomy during which atherosclerotic plaque was removed for analysis. The placebo capsules contained an 80:20 blend of palm and soybean oils (a composition which closely matches that of the average UK diet); the sunflower oil capsules contained 1 gram of sunflower oil plus 1 mg of vitamin E (alpha-tocopherol); the fish oil capsules contained 1 gram of fish oil and 1 mg of vitamin E. The participants took 6 capsules daily providing a total to 3.6 grams linoleic acid (in the sunflower oil capsules) or 850 mg of EPA + 500 mg of DHA in the fish oil capsules.

The duration of supplementation varied between 7 and 189 days with the median being 42 days. Upon analysis of the removed plaque the researchers found that the supplemented fish oil (EPA and DHA) had been readily incorporated into the plaques and had resulted in favourable changes. Plaque from fish oil-treated patients tended to have thick fibrous caps and no signs of inflammation indicating more stability. Plaques from the control and sunflower oil groups, on the other hand, tended to have thin fibrous caps and signs of inflammation indicating less stability. The number of macrophages (large scavenger cells) in the plaque of fish oil-treated patients was also significantly less than the number observed in the control and sunflower oil groups. The researchers conclude that the increased plaque stability observed in the fish oil-treated patients could explain the reduction in fatal and non-fatal heart attacks and strokes associated with an increased intake of fish oils[67].

Italian researchers have concluded that fish oils are highly effective in preventing sudden cardiac death and point out that supplementation with fish oils shows its beneficial effect within a few weeks. They also emphasize that it is unlikely that the biological effects of fish oils would vary depending on source (oily fish or fish oil supplement)[68].

Some doctors and cardiologists caution against supplementing with fish oils if also taking warfarin or a daily aspirin. This concern would seem to be unwarranted. Norwegian medical researchers have found that fish oil supplementation does not increase the bleeding tendency in heart disease patients receiving aspirin or warfarin. Their study involved 511 patients who had undergone coronary artery bypass surgery. On the second day after the operation, half the patients were assigned in a random fashion to receive either a placebo or 4 grams of fish oil per day (providing 2 g/day of EPA, 1.3 g/day of DHA, and 14.8 mg/day of vitamin E). At the same time, the patients were also randomized to receive 300 mg of aspirin per day or warfarin aimed at achieving an INR of 2.5 to 4.2. The patients were evaluated every 3 months and questioned about bleeding episodes for the duration of the 9-month study period. The researchers concluded that fish oil supplementation did not result in a statistically significant increase in bleeding episodes in either the aspirin group or in the warfarin group[69].

It is clear that oily fish and fish oils are effective in stroke prevention with a relative risk reduction of 40-50% as compared to the 64% and 25% observed for warfarin and aspirin respectively.
Other research has shown that fish and fish oils are highly protective against heart attacks, sudden cardiac death, and cardiovascular disease in general. However, there is, unfortunately, a

flip side to this. Some fish can have mercury levels exceeding the current US standard of 1.0 ppm. Many more species of fish exceed the Canadian and New Zealand limit of 0.5 ppm. To be on the safe side, it is best to eat fish and shellfish with an average mercury content of less than 0.10 ppm. Unfortunately, there are not too many species left that fulfill this requirement. King crab, scallops, catfish, salmon (fresh, frozen and canned), oysters, shrimps, clams, flounder, and sole are all good choices. Salmon is my favourite because of its combination of a low mercury content with a high level of beneficial EPA and DHA. The following species should be avoided – tilefish, swordfish, king mackerel, shark, grouper, tuna, American lobster, halibut, pollock, sablefish, and Dungeness and blue crab. Limited sampling of the following also indicated high mercury levels – red snapper, marlin, orange roughy, and saltwater bass. Atlantic cod, haddock, mahi mahi, and ocean perch have mercury levels around 0.18 ppm, so should be eaten in moderation.

As more and more fish species join the "polluted list", it clearly becomes increasingly advantageous to use fish oil supplements rather than eating fish on a regular basis. However, caution is definitely in order here. All fish oil preparations are not created equal. Some contain impurities like mercury, dioxin or PCBs and others are rancid or become rancid if stored for any length of time. If you use fish oil supplements in gel capsules, you can check for rancidity be cutting open the capsule and smelling the contents. If there is any smell associated with the oil at all, then it is rancid and should not be used.

I have checked many fish oil preparations and have now taken Coromega (www.Coromega.com) for several years. The Norwegian company Pronova Biocare supplies the raw fish oil from which Coromega produces its product. The fish oil used in the Coromega product is, in turn, derived from the raw fish oil through a 3-stage process of purification and concentration that complies with European standards of Good Manufacturing Practice. This process yields oils that are highly refined and therefore represent a pharmaceutical preparation in which potential impurities, such as PCBs, mercury, other heavy metals, and dioxins, are effectively removed, as are pesticide residues, unwanted fatty acids, and oxidation products. Coromega is emulsified to improve absorption and is packaged in individual foil pouches to prevent oxidation. Each pouch contains 350 mg of EPA and 230 mg of DHA as well as 3 IU of vitamin E serving as an antioxidant. James Donadio, MD of the Mayo Clinic, has evaluated Coromega extensively and highly recommends it. One pouch a day provides the recommended daily intake of EPA and DHA and is adequate for general health maintenance. However, Dr. Donadio recommends 2 pouches a day for heart disease and stroke prevention, 3 pouches a day for reduction of triglycerides, 5 pouches a day for alleviating symptoms of rheumatoid arthritis, and 5 pouches a day for patients with IgA nephropathy (a common kidney disorder) or end stage renal disease[70].

Additional information on Coromega can be found at www.coromega.com and information about other fish oils may be found at www.consumerlab.com/results/omega3.asp.

Garlic

In the early 1990s, German researchers reported that daily supplementation with garlic tablets (800 mg/day) significantly reduced platelet aggregation (down by 56% after 4 weeks of supplementation) and diastolic blood pressure (down by 9.5%)[71,72]. These findings were later confirmed by American researchers who found that aged garlic extract (7.2 grams/day) inhibited platelet aggregation and platelet adherence to fibrinogen[73,74]. Other researchers have found that aged garlic extract helps prevent endothelial cell injury, inhibits lipid peroxidation and oxidative modification of LDL cholesterol, and reduces reperfusion damage after an ischemic stroke[75]. German researchers, after a 4-year clinical trial, concluded that garlic inhibits platelet aggregation, enhances fibrinolysis, decreases blood plasma viscosity, increases HDL cholesterol level by an average of 8% while lowering LDL level by 4%, and decreases blood pressure by an

average of 7%. The researchers conclude that these benefits of garlic supplementation translate into a reduction of cardiovascular risk for stroke and heart attack of more than 50%[76].

Garlic, in many ways, acts similarly to aspirin. Garlic supplements should therefore, not be taken in combination with aspirin or warfarin[77,78].

Ginkgo Biloba

Animal experiments have shown that pre-treatment with ginkgo biloba extract substantially lessens the damaging effect of an ischemic stroke and that this beneficial effect persists even if the ginkgo biloba is given up to 2 hours after the stroke occurred[79]. It is believed that ginkgo biloba exerts its beneficial effects through its strong antioxidant properties, its ability to increase nitric oxide synthesis and vasodilatation, its beneficial effect on blood pressure, and its ability to increase cerebral blood flow[80,81].

A group of American researchers have reviewed the current state of the art in regard to ginkgo biloba and conclude that the herb shows promise in the treatment of Alzheimer's disease, traumatic brain injury, tinnitus, macular degeneration, and ischemic stroke. They recommend caution in giving ginkgo biloba to patients taking anticoagulants such as warfarin[82].

Coenzyme Q10 (Ubiquinone)

Animal experiments and a few small human studies have shown that coenzyme Q10 may help protect against ischemic stroke. There is also anecdotal evidence that taking 400 mg of coenzyme Q10 (with fat) immediately after suffering a stroke may markedly reduce the damage. About 100 mg a day (with fat or a fatty meal) is likely needed to provide meaningful protection against heart attack and ischemic stroke[83,84].

L-Arginine

Researchers at Stanford University School of Medicine have found that supplementation with the amino acid L-arginine is highly effective in reversing endothelial dysfunction. It has been established that L-arginine is the precursor for endothelium-derived nitric oxide (EDNO). EDNO, in turn, is a potent vasodilator and inhibits platelet aggregation and the adherence of circulating blood cells to blood vessel walls. L-arginine administration, either orally or intravenously, has been found useful in preventing and reversing atherosclerosis, in increasing coronary blood flow in heart disease patients, in alleviating intermittent claudication, and in improving functional status of heart failure patients. L-arginine infusions have been found to lower blood pressure and to inhibit restenosis (reclosing of arteries) after balloon angioplasty[85].

British researchers have found that intravenous administration of L-arginine to patients who have just undergone carotid endarterectomy (removal of the inner part of the artery wall including adhering clots and atherosclerotic plaque) markedly reduced post-operative formation of blood clots as measured by Doppler ultrasound. They ascribe this beneficial effect to the known ability of L-arginine to reduce platelet aggregation and adhesion[86].

The findings that L-arginine reduces platelet aggregation and adhesion, while at the same time increasing nitric oxide synthesis and reversing endothelial dysfunction, should make this common amino acid a good candidate for a highly effective, natural stroke prevention supplement. Unfortunately, I am not aware of any clinical trials that have evaluated its effectiveness.

The most commonly used dosage of L-arginine is between 6 and 30 grams per day.

Red Wine & Trans-Resveratrol

Several studies have shown that moderate red wine consumption protects against heart attacks and stroke. The beneficial effect of wine consumption can be quite substantial. One study found that young women (aged 15 to 44 years) who consumed about 12 grams of alcohol per day (approximately 1 glass of wine) had a 45% lower risk of experiencing an ischemic stroke than did women who did not drink wine[87]. Red wine increases HDL cholesterol levels, helps prevent LDL cholesterol oxidation, and inhibits platelet aggregation[88-91]. There is also credible evidence from animal experiments that red wine effectively prevents homocysteine-induced endothelial dysfunction[92].

It is now clear that it is not the alcohol, but rather the polyphenol content of red wine that is responsible for its benefits. Polyphenols are exceptionally strong antioxidants. One component, resveratrol, has an antioxidant capacity 20 to 50 times greater than that of vitamins C and E and is now touted as a powerful cancer-preventing agent. Resveratrol also inhibits platelet aggregation and interferes with the release of inflammatory compounds. Red wine extract, as such, is also a potent initiator of NO (nitric oxide) production in endothelial tissue.

Afibbers have been found to have low levels of NO in their blood both during rest and exercise[93,94]. It has also been observed that NO levels are particularly low in the left atrium and left atrial appendage and some researchers believe that this could translate into a greater risk for stroke as NO has strong antithrombotic properties[95,96]. Red wine polyphenols have been found to increase NO production from endothelial cells[97].

Extensive research has shown that resveratrol is highly effective in preventing stroke damage and that both resveratrol and quercetin (a bioflavonoid found in red wine) significantly inhibit the synthesis of tissue factor, the component in the blood that initiates blood coagulation via the extrinsic pathway[98-100]. Inasmuch as thrombus formation in the left atrial appendage is probably initiated via the extrinsic pathway, it is likely that red wine, trans-resveratrol and quercetin would be highly effective in reducing stroke risk among afibbers.

Tea & Flavonoids

Dutch researchers have observed that habitual tea drinking provides strong protection against stroke. Their study involved 552 men aged 50 to 69 years at baseline. During a 15-year follow-up, 42 of the participants suffered a stroke. An analysis of dietary data showed that men who consumed more than 4.7 cups of tea per day have a 69% lower risk of having a stroke than did men who drank 2.6 cups per day or less. The researchers believe that the protective effect of black tea is due to its high content of flavonoids (mainly quercetin). They calculate that men with a daily flavonoid intake of 28.6 mg or more have a 73% lower risk of suffering a stroke than do men with a lower intake (less than 18.3 mg/day). The researches have previously reported that a high intake of flavonoids also protects elderly men against coronary heart disease[101].

Animal experiments have shown that pre-treatment with green tea extract can reduce stroke damage (infarct size) by as much as 60%[102]. Cell culture experiments have shown that quercetin is highly effective on its own in reducing stroke damage[103].

Drinking 5 cups of tea per day may not be everybody's "cup of tea"; however, powerful green tea extracts are available in supplement form. It is likely that supplementing with 100-200 mg of quercetin before each meal would have a similar, beneficial effect.

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[104]. 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[105].

Animal experiments have shown that nattokinase is about four times as effective as the body's endogenous "blood clot dissolver" plasmin[106]. Other research has clearly shown that nattokinase prevents the formation of blood clots on injured artery walls[107,108]. 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[109]. The beneficial effects of nattokinase persist for 18 hours or more and positive effects have been observed with as little as 50 mg[110]. Martin Milner, ND, professor of cardiovascular and pulmonary medicine at the National College of Naturopathic Medicine and Bastyr University, has this to say about Nattokinase: "Natto and nattokinase represent the most exciting new development in the prevention and treatment of cardiovascular related diseases. We have finally found a potent natural agent that can thin and dissolve clots effectively, with relative safety and without side effects."[111]

Researchers at the Changhua Christian Hospital in Taiwan report that nattokinase inhibits the synthesis of fibrinogen and coagulation factors VII and VIII. Elevated fibrinogen levels are associated with increased blood viscosity and an increased risk of cardiovascular disease (CVD). There is also evidence that elevated levels of factors VII and VIII are associated with atherosclerosis and coronary heart disease. The Changhua study involved 15 healthy controls, 15 patients with CVD or at least 2 risk factors for CVD, and 15 patients undergoing dialysis for chronic kidney disease (a known risk factor for CVD). At the beginning of the study (baseline) the levels of fibrinogen, factor VII and factor VIII in the three groups were as follows:

-	Controls	CVD Group	Dialysis Group
Fibrinogen, mg/dL	335.0	376.2	433.5
Factor VII, IU	122.5	139.7	154.8
Factor VIII, IU	106.1	156.7	236.3

All study participants ingested 2 nattokinase capsules a day (2000 fibrinolysis units per capsule) for 2 months. At the end of this period levels of fibrinogen had decreased by 9% in the healthy group, by 7% in the CVD group, and by 10% in the dialysis group. Corresponding declines in factor VII level in the 3 groups were 14%, 13% and 7% and for factor VIII 17%, 19% and 19% respectively. No adverse events or increases in uric acid level were observed during the trial.

However, 18% of participants noticed a drop in blood pressure and/or increased vitality. Thirteen percent noticed an improvement in bowel function and 11% reported a lessening of shoulder-neck ache. The Taiwanese researchers conclude that supplementation with nattokinase would have a beneficial effect on risk factors associated with CVD through its reduction in fibrinogen, factor VII and factor VIII levels.[145]

This study confirms that nattokinase is effective in preventing the formation of fibrin-rich blood clots such as those associated with venous thromboembolism and atrial fibrillation (blood stagnation in left atrium or left atrial appendage). Although nattokinase also reduces the level of factor VIII I am not aware of any evidence that it would also reduce the formation of platelet-rich clots (plaque).

Pinokinase

Pinokinase is a recently developed proprietary blend of nattokinase and pycnogenol specifically aimed at preventing edema and venous thrombosis during long-haul flights. Pycnogenol is a water extract from the bark of French maritime pine and had been found effective in controlling edema. It is a strong antioxidant, has significant anti-inflammatory effects, and increases capillary wall resistance. Flite Tabs, the brand name pinokinase preparation, contains 150 mg of a proprietary mixture of nattokinase and pycnogenol and is manufactured by Aidan in Tempe, Arizona. (www.aidanproducts.com).

A group of British and Italian researchers recently reported that pinokinase (Flite Tabs) is indeed effective in preventing edema and venous thrombosis. Their clinical trial involved 204 airline passengers at high risk for venous thrombosis traveling between London and New York (a 7-8 hour flight). Half the passengers were randomized to receive 2 capsules of Flite Tabs two hours before the flight with 250 ml of water. The other half of the experimental group received placebo capsules in a similar fashion. The presence of blood clots in the veins of the leg was determined with ultrasound scanning within 90 minutes of the beginning and completion of the flight. The degree of edema experienced during the flight was determined through a combined edema score including ankle circumference, discomfort, subjective swelling, and a standard edema test.

The researchers observed no thrombotic events in the Flite Tabs group, but discovered 5 cases of deep vein thrombosis and 2 cases of superficial thrombosis in the control group. Thus the total incidence of venous thrombosis was 7.6% in the control group versus 0% in the Flite Tabs group. The average edema score increased by 12% in the control group after the flight, but decreased by 15% in the Flite Tabs group. The researchers conclude that Flite Tabs are effective in controlling edema and reducing thrombotic events during long-haul flights[112].

These very recent 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 very effective in preventing thrombosis in the left atrial appendage.

Exercise

The body's coagulation system is constantly on the alert ready to spring into action at the first sign of bleeding. Coagulation factors are always present in the blood and, if not under strict control, can initiate inappropriate thrombosis. One of the most effective control mechanisms is the clearance and inactivation of activated coagulation factors by circulating the blood through the liver. Swiftly flowing blood is highly effective in dispersing activated factors not yet incorporated into the platelet aggregate and growing clot. The protective effect of flowing blood is clear when considering the increased risk of thrombosis associated with blood stagnation (stasis).

Exercise and physical activity, in general, is highly effective in increasing blood flow and the associated removal of activated coagulation factors in the liver. Thus, it is not surprising that a high level of physical fitness and regular physical activity have been associated with a substantially decreased risk of ischemic stroke. Doctors at a UK hospital have concluded that lifelong exercise provides a very significant protection against stroke. People who had been involved in vigorous exercise (running, swimming, cycling, playing tennis or squash) between the ages of 15 and 40 years were found to have a five times lower risk of suffering a stroke than had people who had never done any vigorous exercise. Being engaged in vigorous exercise between the ages of 15 and 25 years was found to be particularly beneficial but even people who began exercising in their forties or early fifties derived significant benefit. Interestingly enough, people

who had just recently taken up walking for exercise were also found to be three times less likely to suffer from a stroke than were sedentary people[113].

American researchers involved in the Framingham Study have concluded that older men who maintain a medium level of physical activity reduce their risk of having a stroke by almost 60%[114]. Researchers at the Cooper Institute and the West Texas A & M University followed over 16,000 men (aged 40 to 87 years at baseline) over a 10-year period and found that highly fit men (as determined via a treadmill test) had a 68% lower risk of dying from stroke than did men in the least fit group (bottom 20%). Moderately fit men had a 63% lower risk than did the least fit men. These risk reductions were not changed even after correcting for other known risk factors such as smoking, alcohol consumption, hypertension, diabetes, body mass index, and parental history of coronary heart disease[115].

Icelandic researchers have found that men who continued to engage in leisure-time physical activity after the age of 40 years reduced their risk of ischemic stroke by 38%[116]. Finnish researchers have observed that unfit men (maximum oxygen consumption during exercise (VO(2)max less than 25.2 mL/kg per minute) have a 3.5 times greater risk of suffering an ischemic stroke than do fit men (VO(2)max greater than 35.3 mL/kg per minute). They conclude that low cardiorespiratory fitness is in the same league as high blood pressure, obesity, smoking, and excessive alcohol consumption as a risk factor for stroke[117].

Physical activity is also protective against ischemic stroke (and other forms of stroke) in women. Researchers at the Harvard School of Public Health followed over 72,000 female nurses for 8 years and found that those who were highly physically active on a regular basis reduced their risk of ischemic stroke by 50% as compared to nurses who were generally physically inactive. This reduction was observed after adjusting for other known risk factors for stroke including age, obesity, and hypertension. Moderate intensity activities such as walking were also found to be effective with regular, brisk walking associated with a 40% reduction in the risk of ischemic stroke[118].

It is clear that there is much evidence that regular, moderate to vigorous physical activity is highly protective against ischemic stroke with an independent risk reduction somewhere between 40 and 70% even when corrected for other known risk factors for stroke. Some very recent research has, however, found that vigorous exercise when actually in afib, including when in persistent or permanent afib, may not be a good idea. It seems that platelet activation, an important step in the coagulation process, is enhanced during heavy physical activity when in afib. No increase in platelet activation was observed during moderate exercise[144]. Vigorous exercise also increases cortisol level and vagal tone so moderation is also important in avoiding afib episodes, especially among vagal afibbers.

Anti-inflammatories

There is considerable evidence that a systemic inflammation is directly involved in atherosclerosis, angina, peripheral arterial disease (intermittent claudication), diabetes, depression, and most common cancers[119-124]. Very recent research has added stroke to the list of diseases involving inflammation[125]. It is probably not an overstatement to conclude that 90% of all that ails us is caused by an underlying inflammation.

So why are we so inflamed? There are several possible explanations:

- Our lifestyle often emphasizes factors that are known to initiate inflammation – mental, emotional and physical stress, vigorous exercise, alcohol consumption, mercury

poisoning (mostly from dental amalgams), and oxidative stress. Inflammation can also be initiated by a bacterial, viral or fungal infection.

- Many common foods are inflammatory given the right conditions. The excessively high ratio of omega-6 polyunsaturated fatty acids to omega-3 fatty acids found in our modern diet favours the production of inflammatory prostaglandins, which certainly does not help matters[126].

- Childhood exposure to bacteria and viruses has been sharply curtailed through vaccinations and an excessive preoccupation with cleanliness. According to the "hygiene hypothesis", this has created an imbalance in the body's T-cells (key immune system defenders) so that the ones that promote inflammation have become dominant[127].

So how can inflammation be eliminated? Clearly, a two-pronged approach is required:

- The factors that initiate inflammation must be avoided.
- The immune system must be rebalanced to prevent an excessive inflammatory response.

There are several approaches to dealing with a persistent inflammation. One involves rebalancing the immune system itself. Lymphocytes, a specialized kind of white blood cells, are important components of the immune system. They can be subdivided into B-lymphocytes, which produce antibodies, and T-lymphocytes (helper T-cells), which help identify foreign cells and antigens so that killer cells can dispose of them. T-cells come in two varieties – TH1 cells and TH2 cells. TH1 cells produce lymphokines that enhance the ability of the immune system to kill viruses, bacteria, fungi, and parasites. TH2 cells are involved in allergic reactions and release interleukin-6 (IL-6), a powerful marker of inflammation. A healthy immune system has an optimum balance of TH1 and TH2 cells. The results of too many TH2 cells are autoimmune diseases, allergies, inflammation and pain, while not enough TH1 cells can lead to cancer and infectious diseases[128].

Extensive research carried out at the University of Stellenbosch in South Africa has shown that a proprietary mixture of plant sterols and sterolins (Moducare) is very effective in increasing TH1 cell production (the "good" T cells) and decreasing TH2 cell production (the "bad" T cells). Moducare also normalizes the ratio between DHEA and cortisol[125]. Moducare has strong anti-inflammatory effects and sharply reduces IL-6 production. It has been found useful in the treatment of chronic viral infections, tuberculosis, and HIV infection[129]. Also, it has been found to reduce the inflammatory response associated with excessive physical exertion[130]. The recommended dosage of Moducare is two capsules one hour before the main meals for the first month and then one capsule one hour before breakfast, lunch and dinner.

Adjusting the ratio between pro-inflammatory eicosanoids and anti-inflammatory eicosanoids is another important approach to combating inflammation. Fish oil or rather its main component, the omega-3 fatty acids, EPA and DHA, is very effective in shifting the balance. EPA and DHA compete with arachidonic acid (the main omega-6 fatty acid in the body) for the enzymes required in the synthesis of eicosanoids. Having a surplus of EPA and DHA favours the production of anti-inflammatory eicosanoids while having a surplus of arachidonic acid favours the production of inflammatory eicosanoids.

There are several other natural substances that may be beneficial in reducing inflammation.

- Boswellia (Boswellia serrata, Frankincense) - This resin obtained from the Boswellia serrata tree has been used as an anti-inflammatory in Ayurvedic medicine for centuries. Recent research has found it to be highly effective in the treatment of ulcerative colitis,

Crohn's disease and asthma[131-133].

- Curcumin – The yellow pigment of turmeric is as effective as cortisone in combating acute inflammation[134,135]. The recommended dosage is 400 mg three times daily preferably on an empty stomach[134].

- Bromelain – A mixture of enzymes found in pineapple has been found effective in the treatment of the inflammatory disease, rheumatoid arthritis[134,136]. The recommended dosage is 250-750 mg/day[134].

- Ginger (Zingiber officinalis) – It is a strong antioxidant that inhibits the formation of inflammatory compounds. It has been found highly useful in the treatment of rheumatoid arthritis[134,137]. The recommended dosage (fresh ginger root) is 8-10 grams/day[134].

- Pancreatic enzymes – These have been found to be beneficial in the treatment of chronic inflammatory conditions such as rheumatoid arthritis[138]. They should be taken before meals.

- Probiotics – A recent review of the benefits of probiotics (Lactobacillus and Bifidobacterium) concluded that the modification of gut microflora by probiotic therapy might help alleviate inflammatory diseases such as arthritis and inflammatory bowel disease[139].

- Antioxidants – Last, but certainly not least, it is very important to ensure an adequate daily intake of the major antioxidants (vitamin C, vitamin E, selenium, beta-carotene, proanthocyanidins and alpha-lipoic acid). They all help to combat oxidative stress, a potent source of inflammation.

Prednisone is the main pharmaceutical drug used in treating an acute inflammation. It has the potential for serious adverse reactions and its use is generally not recommended for extended periods of time. An unfavourable benefit/risk ratio also applies to the use of aspirin and other NSAIDs to combat inflammation. They do not get at the root cause of the inflammation and can cause serious bleeding complications.

Cholesterol-lowering (statin) drugs have been found effective in decreasing the levels of markers of inflammation and in reducing endothelial dysfunction[140,141]. There is also emerging evidence the statin drugs can lengthen the period between afib episodes. This effect is thought to be due to their anti-inflammatory actions and perhaps due to their ability to modulate the fatty acid composition and physiochemical properties of cell membranes, with resultant alterations in transmembrane ion channel properties[142].

Unfortunately, statin drugs come with many potentially serious side effects including memory loss, liver dysfunction, myopathy, rhabdomyolysis, and possibly cancer. Statin drugs also reduce coenzyme Q10 levels possibly leading to impaired cardiac function and congestive heart failure[143].

Conclusion

It is clear then that there is an astounding array of highly effective natural approaches to stroke prevention with some of them offering protection equal to or surpassing that of conventional pharmaceutical drugs such as aspirin and warfarin. What is more, the natural approaches do not

increase the risk of hemorrhagic stroke or major bleeding – serious side effects of antithrombotic pharmaceutical drugs.

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