

THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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A group of researchers from Sweden's prestigious Karolinska Institute reports a strong inverse correlation between magnesium intake and the risk of suffering an ischemic stroke. In practical terms, their findings translate into a 36 to 54% risk reduction associated with supplementation with 400 to 600 mg a day of elemental magnesium. There is also evidence that a higher intake of magnesium is linked with a significant increase in bone mass (about 2% per 100 mg/day extra intake of elemental magnesium).

Other researchers report that high serum levels of vitamin E are correlated with a significantly lower recurrence of AF following electrical cardioversion, and that a high intake of fish oils is associated with a reduced risk of developing AF. These are three more examples of the importance of an adequate intake of vitamins and minerals.

Also in this issue we report on the safety of iodine supplementation, on a link between rheumatoid arthritis and AF, and on firm repudiation of the idea that the term "lone atrial fibrillation" is inappropriate for afibbers over the age of 60 years.

And finally, 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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may prove beneficial in reducing the frequency of AF episodes."

My conclusion that oxidative stress is an important factor in AF was partly based on the findings of a group of Cleveland Clinic researchers who concluded that AF patients show signs of extensive oxidative injury to their myofibrillar creatine kinase (MM-CK). MM-CK is involved in the control of the contraction of individual heart cells (myocytes). The researchers later followed up their initial findings with an experiment designed to show whether reducing the level of peroxynitrite through the use of an antioxidant (vitamin C) would prevent surgery-induced AF. Their clinical trial involved 50 bypass surgery patients who were given 2 grams of ascorbic acid (extended release) the night prior to their surgery, followed by 500 mg doses twice daily for 5 days following surgery. The incidence of postoperative AF in the vitamin C group was 16.3% as compared to 34.9% in a comparable group not given vitamin C.

Vitamin E prevents AF recurrence

ROME, ITALY. In my first book *Lone Atrial Fibrillation: Towards a Cure* published 10 years ago, I made the comment "I propose that excessive oxidative stress, caused by reactive oxygen species at the upper part of the left atrium, could be a major cause of ectopic (premature) beats and subsequent atrial fibrillation (AF) episodes. If this is indeed the case, then supplementation with vitamin C and the two most effective dietary neutralizers of reactive oxygen species, gamma-tocopherol and lycopene,

Now researchers at the Sapienza University of Rome report that persistent afibbers with high serum levels of vitamin E prior to cardioversion are significantly more likely to remain in normal sinus rhythm (NSR) after cardioversion than are those with low levels. Their clinical trial involved 144 patients with persistent AF (average age of 71 years, 61% male). Almost 90% of study participants had hypertension, 13% had diabetes, and 9% had suffered a heart attack – so not a terribly healthy group. After 4 weeks of anticoagulation with warfarin, all patients underwent biphasic electrical cardioversion starting with a 100 Joule shock. If AF returned within 15 minutes, amiodarone (150 mg) was administered intravenously and the shock was repeated. Patients in whom AF remained even after a 200 J shock, or who experienced immediate recurrence of AF in spite of amiodarone and a second shock were defined as failures and were excluded from the study.

The patients were followed with weekly electrocardiograms and monthly Holter monitoring for 3 months or until first AF recurrence. They were maintained on antiarrhythmics (53% on amiodarone, 32% on flecainide or propafenone, and 11% on sotalol) and 45% also took an ACE inhibitor or angiotensin II receptor blocker. Three months after cardioversion 94 patients (65%) were still in NSR, while 50 patients (35%) had experienced AF recurrence.

The only two variables independently affecting outcome was serum vitamin E level (measured as micromol/mmol cholesterol) and hs-CRP (C-reactive protein). Somewhat surprisingly, the use of antiarrhythmics did not affect outcome. Patients who remained in NSR had an average vitamin E (alpha-tocopherol) level of 5.0 micromol/mmol cholesterol, while those who experienced recurrence had an average level of 3.1. Patients with an alpha-tocopherol level below 4.1 were 2.4 times more likely to experience AF recurrence than were those with a level above 4.1, after adjusting for all other variables that could possibly affect outcome. Vitamin E level was found to be inversely proportional to the levels of urinary 8-isoprostaglandin F₂alpha and soluble NOX₂-derived peptides, both markers of oxidative stress.

The Italian researchers conclude that low vitamin E levels are associated with AF recurrence in patients undergoing cardioversion. They also suggest that the underlying cause of recurrence is oxidative

stress which is, at least partially, counteracted by vitamin E. Thus their recommendation to carry out further trials to see if vitamin E supplementation would be of benefit in the prevention of AF recurrence after electrical cardioversion.

Ferro, D, et al. Serum levels of vitamin E are associated with early recurrence of atrial fibrillation after electrical cardioversion. Circulation Arrhythmia and Electrophysiology, February 23, 2012 [Epub ahead of print]

Editor's comment: It is to be hoped that researchers following up on the above findings will use gamma-tocopherol, in combination with vitamin C, rather than just alpha-tocopherol in any clinical trials to evaluate the benefits of vitamin E supplementation prior to cardioversion. Gamma-tocopherol is the most common form of vitamin E in the diet and constitutes 30-50% of total vitamin E levels in human skin, muscle, and adipose (fat) tissue. Alpha-tocopherol, on the other hand, is much less common in the diet, but is the main and, in many cases, the only component of vitamin E supplements. Dr. Bruce Ames and his colleagues at the University of California suggest that gamma-tocopherol may be significantly more effective in combating cancer, heart disease, and neurodegenerative disease than is alpha-tocopherol. Experimenting on human macrophages (scavenger cells) and cells from human lung tissue (epithelial cells), they found that gamma-tocopherol is at least three times more effective in inhibiting the synthesis of prostaglandin E₂ (PGE₂) than is alpha-tocopherol. PGE₂, a marker of oxidative stress, plays a key role in promoting inflammation and its associated diseases such as cancer and cardiovascular disease. These findings, combined with recent evidence that blood plasma concentrations of gamma-tocopherol, but not alpha-tocopherol, are inversely correlated with the incidence of heart disease, prompt the researchers to speculate that gamma-tocopherol may actually be more important in disease prevention than is alpha-tocopherol. They conclude "*It may be that the inclusion of both alpha- and gamma-tocopherols in vitamin E supplements is more effective in human disease prevention, especially considering that alpha-tocopherol supplementation depresses gamma-tocopherol in human plasma and adipose tissue.*"[1]

Patients awaiting cardioversion are usually placed on warfarin therapy 3 to 4 weeks prior to the procedure. Thus any interaction between warfarin and vitamin E would clearly be of concern. However, there is no evidence 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.[2]

[1] Jiang, Qing, et al. *Gamma-tocopherol and its major metabolite, in contrast to alpha-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. Proceedings of the National Academy of Sciences USA, Vol. 97, No. 21, October 10, 2000, pp. 11494-99*

[2] Kim, JM and White, RH. *Effect of vitamin E on the anticoagulant response to warfarin. American Journal of Cardiology, Vol. 77, No. 7, March 1, 1996, pp. 545-46*

Iodine alert

TIANJIN, CHINA. Many alternative health practitioners and web sites promote supplementation with iodine in amounts vastly exceeding the recommended daily allowance (RDA) of 150 microgram/day and the official North American upper safe limit of 1100 microgram/day. Some iodine supplementation proponents recommend daily intakes of 20,000 to 50,000 microgram/day. Among purported benefits, improved thyroid function and the prevention or cure of breast cancer, hemorrhoids and migraine headaches. High-dose iodine supplementation is also claimed to strengthen the immune system, prevent the growth of harmful bacteria in the gut, and flushes out chemical toxins from the body (including fluoride, lead and mercury). An obvious question, is it safe to supplement with 20 to 50 times the official safe limit?

A recent study carried out in Denmark concludes that the incidence of hypothyroidism (low thyroid gland functioning) has increased since mandatory iodization of household salt was implemented in 2000 and two studies, one Danish and one Chinese, warn of a possible connection between an increase in thyroid cancer and increased iodine intake.[1-3]

Now a group of researchers at the School of Public Health in Tianjin report that high intakes of iodine are associated with the development of subclinical hypothyroidism. Their 4-week double-blind, placebo-controlled clinical trial included 140 healthy young men and 116 healthy young women with normal thyroid function with an average age of 22 years. The study participants were randomly assigned to one of 12 groups according to the amount of supplemental iodine prescribed (covering the range from 0 microgram/day to 2000 microgram/day of elemental iodine in the form of potassium iodide). In addition to iodine from supplements, the participants also ingested an average 110 microgram/day from the diet and 258 microgram/day from iodized salt.

At the 2-week mark urinary iodine excretion had nearly doubled in the group receiving 400 microgram/day of supplemental iodine, while it had increased by a factor of 6 in the group supplementing with 2000 microgram/day. The serum concentration of free triiodothyronine (FT₃) did not change significantly over the 4-week trial period irrespective of iodine intake. However, at 4 weeks free thyroxine (FT₄) concentrations were significantly lower in the 500, 750, 1250 and 1500 microgram/day supplementation groups when compared to the placebo group and the 200 and 400 microgram/day groups. The most noticeable change in serum thyroid hormones involved thyroid-stimulating hormone (TSH). At the end of the 4-week study period, TSH concentrations were significantly higher (4.4 mIU/L) in the 1250, 1500, 1750 and 2000 microgram/day supplementation groups than in the placebo group (2.4 mIU/L). Although the "official" normal range of TSH is 0.2 to 5.5 mIU/L, there is growing evidence that a range of 0.5 to 3.5 mIU/L would be more realistic, with values above 3.5 mIU/L indicating hypothyroidism.

The Chinese researchers conclude that 5% of study participants supplementing with 400 microgram/day and 47% of those supplementing with 2000 microgram/day developed subclinical hypothyroidism during the 4-week trial. They suggest that the total daily intake of iodine (from diet, salt and supplements) should not exceed 800 microgram/day in healthy individuals.

Sang, Z, et al. Exploration of the safe upper level of iodine intake in euthyroid Chinese adults: a randomized double-blind trial. American Journal of Clinical Nutrition, Vol. 95, 2012, pp. 367-73

Editor's comment: The finding that iodine supplementation may be associated with the development of hypothyroidism is unexpected and somewhat counterintuitive since a high iodine intake is generally associated with improved thyroid health. Several afibbers have also found iodine

supplementation beneficial (see our LAF bulletin board at <http://www.afibbers.net/forum/list.php?9> for details). Nevertheless, it would seem prudent to keep an eye on TSH levels if supplementing with iodine and perhaps to rethink high-dose iodine supplementation altogether if already diagnosed with clinical hypothyroidism.

[1] Laurberg, P, et al. Iodine fortification of salt and thyroid disease in Denmark. *Ugeskr Laeger*, Vol. 173,

No. 50, December 12, 2011, pp. 3264-70 [article in Danish – English abstract only]

[2] Blomberg, M, et al. Thyroid cancer in Denmark 1943-2008, before and after iodine supplementation. *International Journal of Cancer*, February 15, 2012 [Epub ahead of print]

[3] Wang, Y and Wang, W. Increasing incidence of thyroid cancer in Shanghai, China, 1983-2007. *Asia Pacific Journal of Public Health*, February 16, 2012 [Epub ahead of print]

Magnesium in stroke prevention

STOCKHOLM, SWEDEN. Magnesium is of key importance to human health. It participates in over 300 enzymatic reactions in the body. A deficiency has been linked to conditions such as irregular heartbeat, asthma, emphysema, cardiovascular disease, high blood pressure, mitral valve prolapse, stroke and heart attack, diabetes, fibromyalgia, glaucoma, migraine, kidney stones, osteoporosis, and probably many more. Magnesium is particularly important when it comes to ensuring the health of the heart and bones. About 99% of the body's magnesium stores are found in the bones and tissues and heart tissue is particularly rich in this important mineral. Only 1% of the body's magnesium is actually present in the blood so a standard blood analysis is a very poor way of determining overall magnesium status.

The RDA (Recommended Dietary Allowance) is 420 mg/day for men and 320 mg/day for women. Unfortunately, recent surveys have shown that many Americans have a dietary intake of 200 mg/day or less. A study found that 74% of a cohort of 2000 elderly men and women did not consume the recommended amount. This same study also concluded that a high magnesium intake is associated with a significantly higher bone density in older white men and women. Every 100 mg/day extra intake of magnesium was found to correspond to a 2% increase in whole-body bone mass. Almonds, nuts, blackstrap molasses, wheat bran and wheat germ are good sources of magnesium; however, many people will, no doubt, prefer to take a magnesium supplement as an easy and reliable way of assuring an adequate daily intake. Up to 800 mg/day of elemental magnesium is probably safe; however, people with kidney disease or severe heart disease should not supplement with magnesium without their doctor's approval.

A group of nutritional researchers at the Karolinska Institute now report that higher magnesium intakes

are associated with a significantly reduced risk of suffering an ischemic stroke. Their meta-analysis covered 7 prospective studies involving 241,378 participants and 6,477 cases of stroke, about 5100 of which were ischemic (caused by a blockage in an artery). The remaining strokes were hemorrhagic (caused by rupture of an artery), or of unknown origin. All studies compared stroke risk with at least 3 different levels of magnesium intake ranging from less than 186 mg/day to 575 mg/day and included adjustments for potential confounders such as age, sex, smoking, hypertension and diabetes; most also corrected for body mass index, physical activity and alcohol consumption. The conclusion of the meta-analysis was that the risk of ischemic stroke decreases by 9% for each 100 mg/day of additional magnesium intake. Thus, if a person with a daily intake of 200 mg (typical intake in North America) were to increase their intake by 400 mg/day they would decrease their risk of suffering an ischemic stroke by 36%.

In an accompanying editorial, Drs. Song and Liu of Harvard Medical School point out that researchers have been studying the role of magnesium in cardiovascular health for nearly 80 years, ever since Zwillingner in 1935 reported that intravenous injection of magnesium sulfate suppressed digitalis-induced cardiac arrhythmia in humans. They suggest that the time has come to perform a large, double-blind and placebo-controlled randomized trial of magnesium for the primary prevention of cardiovascular disease. They conclude with the comment "*Without a large trial that directly defines cardiovascular disease as a primary outcome, it is safe to predict that another 8 decades will go by while generations of nutritional scientists continue to debate magnesium's efficacy for the primary prevention of cardiovascular disease.*"

Larsson, SC, et al. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. **American Journal of Clinical Nutrition**, Vol. 95, 2012, pp. 362-66

Song, Y and Liu, S. *Magnesium for cardiovascular health: time for intervention. American Journal of Clinical Nutrition, Vol. 95, 2012, pp. 269-70*

Editor's comment: Many afibbers are already supplementing with 400 to 600 mg/day of elemental magnesium thus potentially reducing their risk of ischemic stroke by 36 to 54%. This is clearly highly

significant and using magnesium supplementation to achieve it avoids the many adverse effects of aspirin and warfarin, and would have the added benefit of potentially preventing or reversing osteoporosis by increasing whole-body bone mass by about 8%.

Atrial fibrillation linked to rheumatoid arthritis

COPENHAGEN, DENMARK. It is well established that rheumatoid arthritis (RA) is associated with an increased risk of heart attack (myocardial infarction) and heart failure. Now Danish researchers report that RA is also associated with an increased risk of atrial fibrillation (AF) and stroke (ischemic and hemorrhagic). Their study included the entire Danish populations over the age of 15 years at January 1, 1997. After eliminating about 100,000 persons with previous AF, stroke or RA, the study cohort was 4,182,335 people. The members of the cohort were followed for 13 years or until death, emigration or the diagnosis of RA, AF or stroke.

During follow-up, 18,247 participants were diagnosed with RA. The diagnosis was made at an average age of 59 years and most (70%) of RA patients were women. Also during follow-up, a total of 165,343 cohort members, including 718 with RA, experienced a stroke (ischemic or hemorrhagic) and 156,484 including 774 with RA were diagnosed with AF. The incidence rate of AF was found to be 0.82%/year in RA patients and 0.6%/year in the general population, corresponding to an age- and sex-adjusted incidence rate ratio of 1.41. In other words, patients with RA had a 41% (relative) increased risk of being diagnosed with AF than did a member of the general population. The incidence of stroke was 0.76%/year in RA patients and 0.57%/year in the general population, corresponding to an age- and sex-adjusted

incidence rate ratio of 1.32 or a 32% (relative) increased risk of suffering a stroke when compared to the general population.

The relative risk of RA patients being diagnosed with AF or stroke was 3-fold higher among younger patients (age below 50 years) than among older ones. However, the actual incidence of AF in people below the age of 50 years was very low (below 0.05%/year). The researchers conclude that RA is associated with an increased risk of AF and stroke and recommend that RA patients be routinely checked for AF.

Lindhardsen, J, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis. British Medical Journal, March 8, 2012 [Epub ahead of print]

Editor's comment: It is not surprising that RA patients are more likely to be diagnosed with AF than are members of the general population. After all, the two conditions share several characteristics including the likely presence of systemic inflammation, heart disease, heart failure, and atherosclerosis. The question is, "Is a 40% (relative) increase in risk of being diagnosed with AF really relevant?" Essentially, the results of the Danish study mean that, in a group of RA patients, 8 out of 1000 will develop AF during a 1-year follow-up as compared to 6 members of the general population.

Is there an age limit for lone AF?

MAASTRICHT, THE NETHERLANDS. Most definitions of lone atrial fibrillation (LAF) use the age of 60 years as a cutoff point beyond which the condition is no longer lone. I have always felt that, while it may make some sense to use biological age as a cutoff, it makes no sense at all to use chronological age for this purpose. This opinion is echoed by Lars Frost, MD of Aarhus University

Hospital in Denmark who expressed it thus. *Cardiologists with strong political influence have suggested that a diagnosis of lone atrial fibrillation should be restricted to patients less than 60 years of age, although there is no evidence of any threshold values by age regarding the risk of stroke in patients with atrial fibrillation – or in any other medical condition for that matter.[1]*

A group of international researchers from Canada, France, Germany, Greece and the Netherlands now confirms that the cardiovascular outcome in patients with idiopathic (no known cause) atrial fibrillation

(AF) may be closer related to the “biological age” of the cardiovascular system (primarily expressed as left atrial enlargement) than to one’s “calendar age”.

Classification of Atrial Fibrillation

Heart disease related AF

The vast majority of cases of AF are associated with underlying heart disease, in particular:

- * Heart valve disease
- * Coronary artery disease
- * Ventricular hypertrophy (thickening of left ventricle walls)
- * Cardiomyopathy (weakening of heart muscle leading to heart failure)
- * Hypertension (elevated blood pressure)
- * Sick sinus syndrome
- * Pericarditis (inflammation of the sac surrounding the heart)
- * Myocarditis (inflammation of the heart muscle).

Most episodes associated with heart disease are adrenergic in nature thus explaining the tendency of cardiologists to prescribe beta-blockers as a first line treatment for AF.

Non-valvular AF

Non-valvular AF is AF occurring in the absence of rheumatic mitral valve disease, mitral valve repair, or the presence of a prosthetic heart valve. About 70% of all cases of AF are non-valvular.

Lone AF

Lone AF is AF occurring in the absence of clinical or echocardiographic findings of cardiovascular disease (including hypertension), related pulmonary disease, or cardiac abnormalities such as valve problems or gross enlargement (> 50 mm) of the left atrium. A cutoff point of 60 to 65 years of age is usually specified as well.

Idiopathic AF

Idiopathic means “of no known cause”, so idiopathic AF is essentially lone AF not associated with any known cause. The most important known causes of LAF (heart disease has already been ruled out) are thyroid disorders, hypoglycemia, pheochromocytoma, chromosomal abnormalities (genetic connection), serious electrolyte imbalances, Conn’s syndrome (hyperaldosteronism), binge drinking, recreational drug use (especially cocaine), and treatment with pharmaceutical drugs including digoxin and certain drugs used in the treatment of asthma, emphysema and bronchitis. I suspect most members of www.afibbers.org would be classified as having idiopathic rather than lone AF.

The researchers involved in the study used the following definition for idiopathic AF:

- Absence of cardiovascular disease (including coronary and valvular disease)
- Absence of hypertension defined as a systolic blood pressure greater than or equal to 140 mmHg, a diastolic pressure greater than or equal to 90 mmHg, or the use of antihypertensive drugs.
- Absence of left ventricular hypertrophy
- No history of diabetes
- Total fasting cholesterol less than 6.4 mmol/L (248 mg/dL)
- No history of coronary artery disease or angina
- No previous heart attack, stroke, heart surgery, evidence of heart failure, or a left ventricular ejection fraction of less than 50%
- No present or past evidence of thyroid or pulmonary disease
- No cancer or significant renal dysfunction.

NOTE: Age was not included in this definition of idiopathic AF.

A total of 3978 AF patients taking part in the Euro Heart Survey were screened and 119 (3%) were found to meet the above strict criteria for idiopathic AF. The average (mean) age of the 119 study participants was 58 years (48% were older than 60 years) and 72% were male. Persistent and permanent AF, not unexpectedly, were more common among older patients (66%) than in the younger group (age under 60 years) where 34% had non-paroxysmal AF. There was no statistically significant difference in the time since diagnosis or in the left atrium size between the older and younger groups. However, left atrial size was significantly higher among persistent and permanent afibbers (average of 42 mm) than among paroxysmal ones (average of 38 mm). Despite the fact that all patients had a low stroke risk, 44% in the younger group and 65% in the older group had been prescribed warfarin or other vitamin K antagonists. No strokes or other cardiovascular events occurred in the groups during the 1-year follow-up.

The characteristics of the 119 patients were compared to a group of 152 matched AF patients fulfilling the criteria for idiopathic AF except for the presence of hypertension (treated or untreated). There were no significant differences in baseline characteristics between the two groups. However, 5 patients (6%) in the hypertension group suffered a

stroke during follow-up indicating that hypertension on its own confers a substantial stroke risk. NOTE: None of the 5 stroke victims were anticoagulated.

The researchers conclude that idiopathic AF, even if diagnosed at an advanced age, is not associated with significant atrial enlargement, AF progression (from paroxysmal to persistent/permanent), or an adverse short-term prognosis. In contrast, elevated blood pressure seems to imply a worse prognosis even if not associated with atrial enlargement. Therefore, a yet to be defined cutoff for blood pressure rather than age should be used when defining idiopathic AF.

Weijls, B, et al. Idiopathic atrial fibrillation revisited in a large longitudinal clinical cohort. Europace, Vol. 14, 2012, pp. 184-90

Wyse, DG. Idiopathic atrial fibrillation: a rose by any other name? Europace, Vol. 14, 2012, pp. 151-52

Editor's comment: Most members of www.afibbers.org probably have idiopathic rather than lone AF. Thus it is reassuring to see that chronological age as such is not related to prognosis or risk of stroke. However, hypertension (treated or untreated) clearly increases the risk of stroke even in otherwise idiopathic afibbers, so it would be prudent for such patients to take appropriate measures for stroke prevention. See www.afibbers.org/resources/stroke_prevention.pdf
[1] Frost, L. Lone atrial fibrillation – good, bad, or ugly? *Circulation*, Vol. 115, 2007, pp. 3040-41

Routine screening for AF

EDINBURGH, SCOTLAND. With 3 new anticoagulants recently approved for stroke prevention in atrial fibrillation (AF), it is perhaps not surprising that the push is on to increase the number of patients who are prescribed warfarin, dabigatran, rivaroxaban or apixaban. At a recent consensus conference organized by the Royal College of Physicians of Edinburgh, the participants approved the following statement:

Screening for AF in people of 65 or older satisfies the UK National Screening Committee criteria for a screening programme and such a national screening programme should be undertaken in the UK.

The conference participants also agreed that the most cost effective screening method would be routine pulse checking of people over the age of 65 years by GPs, followed by electrocardiogram examination for those with an irregular pulse.

Among other statements made at the conference: –

- *Atrial fibrillation is easily treated with drugs such as warfarin.* Obviously the conference participants had no personal experience with AF or they would have realized that for the majority of afibbers it is the vastly diminished quality of life that is the main problem and this certainly is not “fixed” by prescribing anticoagulants. As Professor Philippe Coumel MD stated in the foreword to my book, “for the patient the symptom

(atrial fibrillation) is the major issue whereas the physician's main concern is the potential arrhythmia-related risk, in particular stroke rather than discomfort."

- *Aspirin is ineffective in stroke prevention in people with atrial fibrillation and should not be used.* Aspirin may have some minor benefit in the prevention of strokes involving blockages associated with platelet-rich clots (thrombi) as it prevents platelet aggregation and subsequent clot formation. However, the blood clots (cardiogenic emboli) associated with AF originate in the left atrium or left atrial appendage and are fibrin-rich and their formation is not prevented by aspirin. This is not really rocket science, but it is good to see it finally recognized by stroke specialists.
- *It is estimated that 5000 strokes (presumably ischemic) and 2000 premature deaths (presumably per year) could be avoided through effective detection and treatment.* When considering this statement it is hugely important to realize that treatment with warfarin or any of the newer anticoagulants carry significant risks (hemorrhagic stroke and major bleeding).

A study carried out by a team of researchers from Massachusetts General Hospital, University of California, and Kaiser Permanente of Northern California casts serious doubt on the benefits of prescribing warfarin to AF patients at low risk for ischemic stroke. The study involved 13,559 patients with non-valvular atrial fibrillation who were followed for 6 years, accumulating a total of over 66,000 person-years of actual experience on warfarin usage in AF. At entry to the study about 53% of the patients were on warfarin.

In past studies aimed at proving the benefits of warfarin therapy among afibbers the focus has been entirely on the prevention of ischemic stroke with no, or very scant, attention paid to the harm done by the drug. The California study takes a bold step forward in this respect in that it introduces a new concept "net clinical benefit". In other words, it considers both the benefit (reduction in ischemic stroke) and harm (increase in hemorrhagic stroke)

in administering the drug. Net clinical benefit (NCB) is defined as:

$$\text{NCB} = (\text{TE rate off warfarin} - \text{TE rate on warfarin}) - W \times (\text{ICH rate on warfarin} - \text{ICH rate off warfarin})$$

TE rate is the annualized rate of thromboembolic events (ischemic stroke and systemic emboli).

W is a weighting factor designed to reflect the fact that the consequences of a hemorrhagic stroke (intracranial bleeding) are far more serious than that of an ischemic stroke. The authors used a W equal to 1.5.

ICH rate is the annualized rate of intracranial bleeding (incl. hemorrhagic stroke).

During the 6-year follow-up there were 407 thromboembolic events, 93% of which were ischemic strokes, in the total group treated with warfarin vs. 685 in patients not receiving warfarin, resulting in annualized TE rates of 1.25% and 2.29% respectively. ICH rates were 0.33% and 0.57% respectively. Not surprisingly, the net clinical benefit of warfarin therapy was highest for patients with a serious risk of stroke and negligible to negative in other cases. Thus, afibbers with a CHADS₂ score (this score assigns 1 point each for congestive heart failure, hypertension, age 75 years or older and diabetes, and 2 points for previous stroke or TIA) of zero (no risk factors for stroke) had a NCB of -0.11% indicating that for this group, which includes most lone afibbers, warfarin therapy is actually more likely to be harmful than beneficial. The likelihood of harm was particularly strong among those aged 65 years or less where the NCB was -0.25%. On the other hand, for patients over the age of 85 years, NCB was a positive 2.34% and for those who had already suffered a stroke it was 2.48%.

The researchers conclude that the net benefit of warfarin therapy is essentially zero in atrial fibrillation patients with a CHADS₂ score of 0 or 1, i.e. with, at the most, one risk factor for ischemic stroke.[1]

Christie, Bryan. *People over 65 should be screened for atrial fibrillation, say stroke specialists. British Medical Journal, Vol. 344, 2012, p. e1644*

Editor’s comment: Unfortunately, as is the case for breast and prostate cancer, it is likely that a routine screening program for atrial fibrillation will lead to

over-treatment and, as discussed above, a negative net clinical benefit, particularly when it comes to lone afibbers with no or, at the most, one risk factor for ischemic stroke.

[1] Singer, DE, et al. *The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Annals of Internal medicine, Vol. 151, September 1, 2009, pp. 297-305*

Dabigatran and catheter ablation

KANSAS CITY, KANSAS. Catheter ablation for atrial fibrillation (AF) is associated with an approximately 1% risk of procedure-related ischemic stroke. The risk arises from the formation of blood clots (thrombi) on catheters and sheaths as well as from the stagnation of blood in the left atrial appendage. It is also possible that char formed on catheters due to overheating may be dislodged and carried to the small arteries in the brain where they, like the above-mentioned thrombi, may cause a stroke.

In order to prevent a procedure-related stroke, prospective ablation patients are placed on warfarin (INR 2.0-3.0) for two months prior to the procedure. Warfarin is usually discontinued a day or two before the ablation and replaced with heparin, which is also infused during the procedure. After a couple of days “bridging” with heparin, warfarin therapy is reintroduced and the patients are maintained on this for 3 to 6 months post-procedure.

A group of American and Italian electrophysiologists (EPs) have found that not discontinuing warfarin prior to and during the ablation procedure essentially eliminates the risk of procedure-related ischemic stroke. The researchers also found that patients, in the proper INR range and not experiencing AF on the day of the procedure, do not need a pre-procedure transesophageal echocardiogram (TEE).

Now a group of American and Italian EPs specializing in catheter ablation report on their investigation aimed at determining if it would be possible to replace warfarin with dabigatran (Pradaxa) in the period prior to, during and following radiofrequency catheter ablation for atrial fibrillation (AF). Their study included 290 patients with AF with an average age of 60 years with 79% being male. Most (57%) were paroxysmal and 52% had hypertension, while 20% had been diagnosed with sleep apnea and 17% had coronary artery disease.

The study participants were randomly assigned to a group (145 patients) which received uninterrupted warfarin therapy for 30 days prior to and during the procedure, and for 3 to 6 months following (warfarin group), or to a group (145 patients) which received dabigatran (150 mg twice daily) for 30 days prior to and after the procedure, but did not receive their morning dose on the day of the procedure (dabigatran group). Patients in both groups underwent a standard pulmonary vein antrum isolation procedure with additional lesions as required. They all received unfractionated heparin before transseptal puncture and as required to maintain an activated clotting time (ACT) of between 300 and 400 seconds while the catheters remained in the left atrium.

Complication rates for the two groups are given below.

Complication	Warfarin Group	Dabigatran Group
Thromboembolism*	0%	2%
Major bleeding	1%	6%
Minor bleeding	6%	8%
Thromboembolism + bleeding	6%	16%

*Transient ischemic attack (TIA) or ischemic stroke. These complications all occurred in persistent afibbers treated with dabigatran.

No hemorrhagic strokes or deaths were observed in either group. The researchers conclude that the

use of dabigatran (odds ratio: 2.76) and age over 75 years (odds ratio: 3.82) were independent

predictors of bleeding and thromboembolic complications. The authors of the report conclude that continuation of dabigatran during the periprocedural period (immediately before, during and immediately after) is associated with an

increased risk of complications compared with uninterrupted warfarin therapy.

Lakkireddy, D, Natale, A, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation. Journal of the American College of Cardiology, Vol. 59, No. 13, March 27, 2012

Fish oils help prevent AF

BOSTON, MASSACHUSETTS. Experimental studies suggest that long-chain omega-3 (n-3) polyunsaturated fatty acids (n-3 PUFA) may help prevent the development of atrial fibrillation (AF). However, most studies involving humans have used food frequency questionnaires to estimate the intake of the three main n-3 PUFAs – eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). EPA, DPA and DHA are the main components of fish oil extracted from the **tissue** of oily fish such as herring, salmon and tuna.

A group of researchers from Harvard Medical School, Harvard School of Public Health, University of Western Australia, University of Washington, University of New Mexico, Fred Hutchinson Cancer Research Center, and Brigham and Women's Hospital now reports the results of a major study (funded by the National Heart, Lung, and Blood Institute in the US) aimed at determining the association between actual circulating blood levels (measured in the phospholipid fraction) of n-3 PUFAs and the development of AF in an older population.

The study included 1330 men and 1996 women who were free of AF and heart failure at enrolment in 1992 to 1993. During 31,169 person-years of follow-up, 789 participants were diagnosed with AF. After extensive adjustment for likely confounders (demographic, cardiovascular, and lifestyle risk factors), the researchers conclude that having an average n-3 PUFA level (measured as percentage of total phospholipid fatty acids in blood plasma) of 6.3% is associated with a 29% reduced risk of developing AF when compared to a total n-3 PUFA level of 2.9%. This corresponds to a risk decrease of 9% for each 1% increase in n-3 PUFA level.

An analysis of the effect of the individual components of n-3 PUFA (EPA, DPA and DHA) showed that only the association with DHA was statistically significant with a corrected risk reduction of 23% at an average phospholipid level of 4.4% as compared to a level of 2.0%, corresponding to an approximate 10% reduction in risk for each 1% increase in DHA level. The researchers point out that DHA is present in significantly higher (3- to 9-fold higher) levels in heart tissue (myocardial membranes) than are EPA and DPA. DHA has, in separate studies, been found to augment vagal activity, lower heart rate and blood pressure, and to favorably modulate myocytes ion channels.

The researchers conclude that higher circulation levels of n-3 PUFAs and, in particular, DHA are associated with a reduced risk of developing AF in older adults and recommend further studies to determine whether an increased dietary intake of n-3 PUFAs (fish oils) would be effective in the primary prevention of AF.

Wu, JHY, et al. Association of plasma phospholipid long-chain omega-3 fatty acids with incident atrial fibrillation in older adults. Circulation, Vol. 125, March 6, 2012, pp. 1084-93

Editor's comment: In considering the conclusions reached in the above study, it should be kept in mind that they are not necessarily applicable to the prevention of lone AF in younger, healthy people. Not only were the participants in the above study older (average age of 74 years at baseline) but almost half had hypertension, 20% had coronary heart disease, and 15% had diabetes. Furthermore, endurance athletes and other highly physically active people are likely to develop the vagal form of AF, for which fish oil supplementation may not be beneficial. For more on the association between fish oils and arrhythmia prevention see www.oilofpisces.com/arrhythmias.html.

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