

THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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For some reason, perhaps related to the use of potassium cyanide on death row, the medical profession and a large part of the general public view any oral or intravenous use of potassium with suspicion, if not outright fear. An example is the fact that it is unlawful to manufacture and sell multivitamins, and specific potassium supplements, containing more than 99 mg of potassium per tablet. This is clearly ridiculous in view of the fact that the recommended daily intake of potassium (elemental) is 4700 mg. A study from the Netherlands concluded that the average daily intake in the US and Canada is 2800 and 3000 mg/day respectively – well short of the recommended 4700 mg. The Dutch researchers estimate that attaining the recommended intake could reduce the risk of dying from a stroke or heart disease by 8 - 15% and 6 - 11% respectively (Archives of Internal Medicine, Vol. 170, No. 16, September 13, 2010, pp. 1501-02). Of course, many afibbers, myself included, have found potassium supplementation hugely beneficial in banishing PVCs, PACs, and even afib itself.

Now a group of German researchers report that intravenous infusion of a magnesium/potassium solution prior to cardioversion of persistent AF reduces the shock energy required to achieve normal sinus rhythm, and improves the immediate success rate of the procedure. This new study lends further credence to our long held belief that being replete in magnesium and potassium prior to cardioversion is extremely important.

Also in this issue – inflammation and impaired blood flow through the left atrial appendage increases the risk of clot formation, clinical trial results of two new anticoagulants (rivaroxaban and apixaban), yoga helps prevent AF episodes, and the use of proton pump inhibitors such as Nexium (esomeprazole) can lead to severe magnesium deficiency.

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 truly appreciated.

Wishing you lots of NSR,

Hans

Highlights

Rivaroxaban: New challenger to warfarin	p. 2
Catheter ablation as first-line therapy	p. 3
Cardioversion and ablation outcome	p. 4
Fish oils aid NSR after cardioversion	p. 5
Magnesium/potassium infusion	p. 6
Atrial fibrillation and dementia	p. 6
Apixaban – A new anticoagulant?	p. 7
NEWS BRIEFS	p. 8

Left atrial appendage and risk of stroke

ROME, ITALY. Although lone atrial fibrillation (LAF) as such is not a risk factor for ischemic stroke, the likelihood of suffering a stroke or transient ischemic attack (TIA) increases if the LAF is accompanied by heart disease, presence of prosthetic heart valves, hypertension (blood pressure greater than 160/90 mm Hg), diabetes, low left ventricular ejection fraction (< 45%) or a history of stroke, TIA, heart attack or peripheral vascular embolism.

A group of Italian medical researchers now report that an elevated level of the inflammation marker C-reactive protein (CRP) and a reduced blood flow through the left atrial appendage (LAA) are associated with an increased risk of forming blood clots (thrombi) in the left atrium. Their study included 150 patients (46% men, age ranging between 53 and 77 years) with persistent, non-valvular atrial fibrillation (AF). Prior to their scheduled electrical cardioversion, all patients underwent transesophageal echocardiography (TEE) and had blood samples drawn for later analysis. Examination of the echocardiograms revealed the existence of dense spontaneous echo contrast (SEC) in 52 patients. SEC is considered to be the origin of thrombi and is seen as a swirling pattern (fog) on the TEE; the denser the pattern the more likely it is that a clot will eventually develop. Nine patients were found to have a thrombus in the LAA and were excluded from further evaluation. The remaining 98 patients had no dense SEC. It is interesting that 85% of study participants were on warfarin, which is supposed to prevent clot formation.

Analysis of blood samples drawn prior to cardioversion showed that the presence of dense SEC was directly associated with elevated levels of C-reactive protein, D-dimer and fibrinogen. Examination of the echocardiogram revealed that the presence of dense SEC was strongly associated with a low velocity of blood flow in the LAA and significantly related with an enlarged left atrium. Somewhat surprisingly, left ventricular ejection fraction did not seem to affect LAA flow velocity. After correcting for possible confounders,

a multivariate analysis showed that only LAA flow velocity and CRP level were associated with the presence of dense SEC at a level achieving statistical significance.

The researchers conclude that patients with low LAA velocity (less than 0.25 m/sec) have a 19-fold increased risk of harboring dense SEC as compared to those with normal flow velocity. Similarly, a CRP level above 3 mg/L (0.3 mg/dL) was associated with a 3.4-fold increased risk of dense SEC.

Cianfrocca, C, Santini, M, et al. C-reactive protein and left atrial appendage velocity are independent determinants of the risk of thrombogenesis in patients with atrial fibrillation. International Journal of Cardiology, Vol. 142, 2010, pp. 22-28

Editor's comment: The finding that a low LAA flow velocity is associated with a greater risk of forming dense SEC and blood clots is not surprising. Blood stasis, such as also found in deep vein thrombosis, is an obvious incubator of thrombi. What is somewhat surprising is the finding that left ventricular ejection fraction is not associated with SEC formation. Seeing that the left ventricle abuts the LAA, one would expect that a more forceful left ventricular ejection would result in a greater LAA emptying velocity. The finding that a high CRP level (inflammation) is associated with an increased risk of dense SEC once again emphasizes the importance of knowing one's CRP level and, if necessary, reduce it through the use of natural anti-inflammatories such as *Zyflamend*, ginger, curcumin, vitamin C, beta-sitosterol, boswellia or *Moducare*.

Rivaroxaban: A new challenger to warfarin

DURHAM, NORTH CAROLINA. Although there is no evidence that otherwise healthy lone afibbers have an increased risk of ischemic stroke, it is clear that atrial fibrillation (AF) patients with heart failure, diabetes or hypertension have a significantly increased risk and this risk is further magnified if the patient has already suffered a heart attack or stroke. To date, oral anticoagulation with vitamin K antagonists such as warfarin (Coumadin) is still considered to be the best preventive therapy for patients at risk for stroke. Unfortunately, warfarin interacts with many foods and drugs and treatment requires constant, costly monitoring. Its use also substantially increases the risk of hemorrhagic stroke and major internal bleeding, particularly in

older people, a group that, ironically, is also most at risk for an ischemic stroke. Effective warfarin therapy is based on maintaining an INR (international normalized ratio) between 2.0 and 3.0. In real life this ratio is only achieved on a continuous basis in about 50 to 60% of patients. Too low a ratio increases the risk of ischemic stroke, while too high a ratio increases the risk of hemorrhagic stroke and major bleeding.

Warfarin acts by inhibiting the activation of the vitamin K-dependent coagulation factors V, VII, and X in the extrinsic and common pathways of the coagulation cascade. Research aimed at replacing warfarin has focused on developing new

pharmaceutical drugs which will inhibit specific coagulation factors. A new entry to the field is rivaroxaban (Xarelto) a direct inhibitor of factor Xa, the first member of the common pathway in the coagulation cascade.

Like dabigatran (Pradaxa), rivaroxaban was initially approved for temporary use following hip and knee operations. A very large study (ROCKET AF) evaluating rivaroxaban for stroke protection in AF patients has now been completed. The study included over 14,000 patients with nonvalvular AF treated at 1178 participating sites in 45 countries. The average (median) age of the patients was 73 years and 40% were female. Most of the study participants had persistent (probably including permanent) AF and had a CHADS₂ score of at least 2 (mean score of 3.5). All in all, the trial involved a group of very sick people – in no way comparable to a group of otherwise healthy afibbers. Over 90% of the group had hypertension, 63% had heart failure, and 55% had experienced a prior stroke or transient ischemic attack (TIA).

The study participants were randomized to receive standard therapy with oral warfarin (INR range of 2.0 – 3.0) or 20 mg/day of rivaroxaban (15 mg/day for patients with kidney disorder). All patients also received a placebo pill and regular INR checks to blind them to the treatment received. The warfarin-treated patients were within INR target range 55% of the time. During an average follow-up of about 2 years, 188 patients (1.7%/year) in the rivaroxaban group experienced a stroke, TIA or systemic embolism as compared to 241 patients (2.2%/year) in the warfarin group. Major and non-major

clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9%/year) and in 1449 patients (14.5%/year) in the warfarin group. The incidence of hemorrhagic stroke (intracranial hemorrhage) and fatal bleeding was significantly less in the rivaroxaban group (0.5% and 0.2%/year) than in the warfarin group (0.7% and 0.5%/year). However, the incidence of major gastrointestinal (GI) bleeding was higher in the rivaroxaban group (3.2%/year) than in the warfarin group (2.2%/year).

About 23% of participants dropped out of the study before its completion. The rate of ischemic stroke, TIA and systemic embolism during a median 117 days of follow-up was 4.7% in the rivaroxaban drop-out group and 4.3% in the warfarin drop-out group. The ROCKET AF investigators conclude that rivaroxaban is non-inferior to warfarin in the treatment of AF patients at moderate to high risk of stroke. NOTE: This study was funded by Johnson & Johnson and Bayer, and all the investigators had substantial financial ties to the pharmaceutical industry.

Patel, MR, Califf, RM, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine, August 10, 2011 [Epub ahead of print]

Editor's comment: Rivaroxaban is currently approved by the FDA for prevention of deep vein thrombosis after knee- or hip-replacement surgery. However, the FDA has asked for more data before approving the drug for stroke prevention in atrial fibrillation. Their main concern is that patients in the warfarin group were only within the specified INR range 55% of the time.

Catheter ablation as first-line therapy

BERN, SWITZERLAND. It is generally assumed that candidates for catheter ablation of atrial fibrillation (AF) have failed therapy with at least one antiarrhythmic drug (AAD). However, recently published guidelines allow for *AF ablation as an initial therapy prior to AAD in symptomatic paroxysmal AF patients with no significant underlying heart disease, who remain highly symptomatic, despite rate control, and reject AAD therapy.*

Now a group of electrophysiologists at the University Hospital in Bern reports that ablation success rates are higher in patients who go directly to an ablation than in those who try one or more

antiarrhythmic drugs before going the ablation route. Their study involved 434 AF patients with an average age of 58 years. The majority (68%) had paroxysmal AF, 56% had lone AF, 53% had hypertension, and 78% were male. The majority (362 patients – 83%) had tried at least one antiarrhythmic drug without success prior to being scheduled for ablation, while the remaining 72 patients (17%) went straight for the ablation. The members of the drug group (AAD group) had suffered from AF for a considerably longer period (78 months vs. 52 months) prior to ablation than had the ablation first group (ablation group). They were also more likely to have had cardioversions

and hospitalizations than were members of the ablation group.

All study participants underwent a circumferential pulmonary vein isolation (CPVI) procedure with additional lesions as required and were then followed for an average of 16 months (from last procedure) during which time ECGs, event recording, or Holter monitoring was used to determine success or failure of the procedure. ECGs were also done to confirm symptomatic episodes reported by patients. After excluding atrial tachyarrhythmias (AF, atrial flutter, and atrial tachycardia) during a 3-month blanking period, 59% of the ablation group was in normal sinus rhythm vs. 39% in the AAD group (with or without antiarrhythmic therapy). An enlarged left atrium (parasternal diameter) and female gender were associated with a poorer success rate.

A second CPVI was performed in 38% of the AAD group vs 21% of the ablation group. An average of

16 months following the last procedure, the final complete success rates (no AF, no antiarrhythmics) in the AAD group and ablation group were 41% and 63% respectively. The partial success rate (no AF, but still on antiarrhythmics after 3-month blanking period) was 23% for the AAD group and 15% for the ablation group.

The Swiss researchers conclude that performing catheter ablation at an earlier stage of AF progression results in a significantly higher success rate and a reduced need for repeat procedures.

Tanner, H, Delacretaz, E, et al. Catheter ablation of atrial fibrillation as first-line therapy – a single-centre experience. Europace, Vol. 13, 2011, pp. 646-53

Editor's comment: The findings of this study make imminent sense in that, the longer AF is allowed to continue, the more extensive electrical and structural remodeling there is likely to be, resulting in a poorer outcome of catheter ablation.

Cardioversion strategy improves ablation outcome

SALT LAKE CITY, UTAH. Early recurrence of atrial tachyarrhythmias (atrial flutter, atrial fibrillation and atrial tachycardia) is common among atrial fibrillation (AF) patients having undergone radiofrequency catheter ablation. Some studies have found that as many as 50% of patients experience recurrence during the first 3 months following their procedure (blanking period), with most recurrences occurring during the first 4 weeks. Evidence regarding the effect of early recurrence on long-term outcome is somewhat conflicting, but a reasonable estimate is that about half of early recurrences will not affect long-term outcome. Of course, knowing which early recurrence will affect long-term outcome and which won't is the \$64,000 question.

Electrophysiologists at the University of Utah and the Intermountain Medical Center now suggest that implementing a strategy of prompt cardioversion in the case of recurrence during the 3-month blanking period will markedly improve long-term outcome. Their clinical trial included 1304 patients who underwent a total of 1759 ablations (35% repeat rate). The mean patient age was 65 years, 58% were male, 52.6% had paroxysmal, 26.4% had persistent, and 21% had permanent (long-standing persistent) AF. Following their catheter ablation all patients were instructed to watch for symptoms of

arrhythmia recurrence and to take their pulse daily. If the pulse was irregular or exceeded 100 bpm, they were asked to present themselves for evaluation at the hospital the same day or the next business day in a fasting state.

Prompt (within 24 to 48 hours) cardioversion was performed as deemed necessary. A total of 515 cardioversions were performed for occurrence of post-ablation AF or flutter with 65% of procedures being done in patients with persistent or permanent AF. Nearly 50% of recurrences occurred in the first month post-ablation, 64% occurred in the first 90 days, and 24% occurred after a period of 6 months. Eighty percent of afibbers requiring cardioversion during the blanking period needed more than one procedure.

After a year of follow-up, 78% of the patients who had needed cardioversion were in normal sinus rhythm. Overall, 75.6% of patients experiencing arrhythmia within the first 90 days following ablation were in sinus rhythm without the use of antiarrhythmics at the 1-year mark.

The Utah researchers conclude that a strategy of prompt cardioversion in case of arrhythmia recurrence during the first 6 months following

catheter ablation markedly improves long-term outcome.

Malasana, G, Bunch, TJ, et al. *A strategy of rapid cardioversion minimizes the significance of early recurrent atrial tachyarrhythmias after ablation for atrial fibrillation. Journal of Cardiovascular Electrophysiology, Vol. 22, July 2011, pp. 761-66*

Editor's comment: These findings are clearly of great importance and would indicate that prompt cardioversion of atrial arrhythmias occurring within 90 days of a catheter ablation results in a better long-term prognosis. In practical terms this would mean that an afibber who experiences an episode lasting longer than say 2 to 4 hours should promptly present for cardioversion.

Fish oils help maintain sinus rhythm after cardioversion

BRESCIA, ITALY. There is evidence that n-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main components of fish oil, have antiarrhythmic effects and may help reduce sudden cardiac death. Several clinical and epidemiological studies have evaluated the effect of fish oil supplementation on the development and progression of atrial fibrillation (AF), but results have been inconclusive.

Now a team of Italian researchers reports that persistent AF patients treated with fish oil for at least 4 weeks prior to electrical cardioversion maintain normal sinus rhythm (NSR) for a considerably longer period post-conversion than do patients given placebo. Their randomized, double-blind, placebo-controlled, parallel arm clinical trial included 199 patients with persistent AF who had suffered relapse after at least one previous cardioversion. The average age of the patients was 70 years, 67% were male, 35% had diabetes, and 90% had structural heart disease, thus leaving only 10% with lone AF. All patients were on warfarin, amiodarone (200 mg/day) and an ACE inhibitor for at least 4 weeks prior to the planned cardioversion.

At the start of the study (at least 4 weeks before cardioversion), patients were randomized to a fish oil group or a control group. Members of the fish oil group received a 1-gram fish oil capsule twice daily providing a total daily intake of 920 mg of EPA and 760 mg of DHA in the form of ethyl esters (OMACOR). The control group received an identical-looking olive oil capsule twice daily. All patients underwent biphasic electrical cardioversion using an initial shock energy of 100 joule followed by a second and third 200-joule shock if the first one did not achieve NSR.

In the fish oil group, 78% of patients converted after the first shock, while only 33% in the control group did so. At the 1-year follow-up, 62% of fish oil

group members were still in NSR as compared to only 36% in the placebo group. The Italian researchers conclude that fish oil supplementation for at least 4 weeks prior to electrical cardioversion markedly improves long-term maintenance of NSR in a group of persistent AF patients (90% with structural heart disease) on amiodarone and ACE inhibitor/angiotensin receptor blocker therapy.

In an accompanying editorial, Drs Camm and Savelieva of St. George's University of London emphasize that trials of fish oil supplementation have produced inconsistent results when it comes to AF. They suggest that the positive results in the Italian study may be due to the concomitant treatment with amiodarone and ACE inhibitors/angiotensin receptor blockers and/or to the fact that fish oils may be more effective in patients with extensive, long-established heart disease. They point out that "*the ability of PUFAs to increase parasympathetic tone may theoretically be proarrhythmic in younger individuals with normal hearts in whom a vagal component may play a role in promoting AF. The proportion of such patients with lone AF or mild cardiovascular disease was higher in the studies that failed to demonstrate a benefit from PUFA therapy.*"

Nodari, S, Dei Cass, L, et al. *n-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion. Circulation, Vol. 124, September 6, 2011, pp. 1100-06*

Camm, AJ and Savelieva, I. *Fish oil for secondary prevention of atrial fibrillation – should we still believe in its antiarrhythmic effect? Circulation, Vol. 124, September 6, 2011, pp. 1093-96*

Editor's comment: Although not necessarily applicable to all lone afibbers, it is possible that adrenergic and mixed persistent afibbers could benefit from fish oil supplementation (for at least 4 weeks) prior to electrocardioversion, especially if taken in combination with a suitable antiarrhythmic drug. It is interesting that no adverse events relating to fish oil supplementation were observed

during the trial, thus confirming that it is safe to supplement with fish oils when on warfarin therapy.

For more on fish oils and AF please see www.oilofpisces.com/arrhythmias.html.

Magnesium/potassium infusion improves cardioversion results

HAMBURG, GERMANY. The immediate success rate of electrical cardioversion for persistent atrial fibrillation (AF) varies between 64% and 96%. Unfortunately, of patients successfully converted to normal sinus rhythm (NSR), as few as 25% are still in NSR a year following their conversion. There is evidence that lone afibbers tend to be deficient in magnesium and that being replete in potassium is important in ensuring a successful cardioversion.

Researchers at the University Hospital Hamburg now report that pretreatment with a magnesium/potassium (Mg/K) solution significantly improves the outcome of electrical cardioversion. Their randomized clinical trial comprised 170 patients (71% men) with an average age of 67 years. The participants had persistent AF and the episode for which cardioversion was planned had lasted at least 78 hours. The average pre-procedure (baseline) serum level of potassium and magnesium were both at or below normal ranges.

The study participants were randomized into two groups with one group (86 patients) acting as controls and the other group (84 patients) receiving a Mg/K solution providing 34 mg of elemental magnesium (2.772 mEq) and 108 mg of elemental potassium (2.774 mEq) prior to cardioversion. Successful biphasic cardioversion was achieved in 86% of the control group vs. 96.4% in the Mg/K infusion group. Furthermore, the shock energy required to effect conversion was substantially lower in the Mg/K group. In this group, 51.2% of

participants converted at the relatively low energy input of 75 joule as compared to a conversion rate of only 29.1% in the control group.

The authors conclude that pretreatment with intravenous Mg/K significantly reduces the shock energy required to achieve restoration of NSR and also improves the immediate success rate of the cardioversion procedure.

Sultan, A, Willems, St, et al. Intravenous administration of magnesium and potassium solution lowers energy levels and increases success rates electrically cardioverting atrial fibrillation. Journal of Cardiovascular Electrophysiology, August 4, 2011 [Epub ahead of print]

Editor's comment: This study again confirms that afibbers tend to be low in magnesium. The average baseline serum level of Mg in the 170 patients was 0.85 mg/dL or 0.34 mmol/L. The normal range is 1.5 to 2.3 mg/dL or 0.75 to 0.95 mmol/L. It would have been interesting if the authors had provided follow-up data to see if the longevity of NSR was affected by the Mg/K pretreatment infusion. It would, of course, also have been hugely interesting if the cardioverted participants had been randomly assigned to oral Mg/K supplementation or placebo post-procedure to see if continuous Mg/K supplementation would extend their time in NSR.

NOTE: The amount of magnesium infused (34 mg elemental) is very low and hardly likely to have any effect. Also, the baseline level of magnesium is way below normal. I suspect a couple of typos and have contacted the authors for clarification.

Atrial fibrillation and dementia

SEATTLE, WASHINGTON. Senile dementia is a growing problem in both the developed and developing world. It is estimated that there are currently 30 million people with dementia worldwide with 4.6 million new cases being diagnosed annually. The number of people with dementia in the USA in the year 2002 was estimated at 3.4 million with 2.4 million of these individuals having

Alzheimer's disease (AD). The estimated costs associated with AD (in the USA) are \$172 billion each year. This is clearly a very serious problem!

About 20% of AD cases are associated with genetic mutations, but many other risk factors have been implicated. Among them:

- Advanced age
- Oxidative stress, vitamin deficiency, poor diet
- Low antioxidant levels
- Atherosclerosis and cardiovascular disease
- Diabetes

- Elevated homocysteine level
- Vitamin B12 and folate deficiency
- Low intake of omega-3 fatty acids (fish oil)
- Hypertension
- Exposure to pesticides and herbicides

Now researchers at the University of Washington report an association between dementia, including AD, and atrial fibrillation (AF). Their study included 3045 participants in the Adult Changes in Thought (ACT) study who were without dementia or prior stroke at enrolment beginning in 1994. The median age at study entry was 74 years, 60% of participants were women, and 38% had completed college. Twenty-two percent had coronary heart disease or heart failure, 32% were being treated for hypertension, 26% were obese, and 9% had diabetes at baseline. None of the participants had dementia or AD when enrolled, but 132 (4.3%) had documented AF at baseline. These patients were more likely to have cardiovascular risk factors and diseases than were those without AF at baseline.

During an average (mean) follow-up of 6.8 years, an additional 370 participants (12%) were diagnosed with AF and 572 (18.8%) developed dementia, including 449 (14.7%) with possible or probably AD. The incidence (annual rate of diagnosis) of AD in participants with AF was 4.8% vs. 2.5% in those without AF. Corresponding numbers for AD were 3.8% and 2.0%.

After adjusting for gender, education level, hypertension, diabetes, coronary heart disease, heart failure, and history of stroke or TIA, the researchers conclude that AF is associated with a 38% relative increase in the risk of all-cause dementia and a relative increase in the risk of AD of 50%. In absolute terms, this corresponds to about

a 1%/year increase in the risk of developing dementia associated with AF.

The researchers speculate that the observed association may be due to decreased blood flow to the brain during AF, or to silent mini-strokes. They also point out that AF and dementia share underlying risk factors such as inflammation and cardiovascular disease. However, they admit that the prevalence of heart disease in the study population was based on self-reporting, which may be inaccurate. Also, information about valvular heart disease and echocardiographic findings such as left atrial enlargement and impaired systolic function, which are associated with development of AF, was not available.

Dublin, S, Larson, EB, et al. Atrial fibrillation and risk of dementia. Journal of the American Geriatrics Society, Vol. 59, August 2011, pp. 1369-75

Editor's comment: This study concludes that AF is associated with an approximately 1% per year absolute increase in the risk of developing dementia, mostly Alzheimer's disease among a group of elderly participants (average age at enrolment was 74 years) in the ACT study. Inasmuch as all participants were over the age of 65 years at time of enrolment, the results of the study cannot be extrapolated to a younger group of otherwise healthy afibbers. Nevertheless, taking precautions against developing dementia or AD would obviously be prudent. For more on this see www.yourhealthbase.com/Alzheimer's.htm www.yourhealthbase.com/Alzheimer's_Prevention.htm

Apixaban – Another warfarin replacement?

DURHAM, NORTH CAROLINA. Although there is no evidence that otherwise healthy lone afibbers have an increased risk of ischemic stroke, it is clear that atrial fibrillation (AF) patients with heart failure, diabetes or hypertension have a significantly increased risk and this risk is further magnified if the patient has already suffered a heart attack or stroke. To date, oral anticoagulation with vitamin K antagonists such as warfarin (Coumadin) is still considered to be the best preventive therapy for patients at risk for stroke. Unfortunately, warfarin interacts with many foods and drugs and treatment requires constant, costly monitoring. Its use also

substantially increases the risk of hemorrhagic stroke and major internal bleeding, particularly in older people, a group that, ironically, is also most at risk for an ischemic stroke. Effective warfarin therapy is based on maintaining an INR (international normalized ratio) between 2.0 and 3.0. In real life this ratio is only achieved on a continuous basis in about 50 to 60% of patients. Too low a ratio increases the risk of ischemic stroke, while too high a ratio increases the risk of hemorrhagic stroke and major bleeding.

Warfarin acts by inhibiting the activation of the vitamin K-dependent coagulation factors V, VII, and X in the extrinsic and common pathways of the coagulation cascade. Research aimed at replacing warfarin has focused on developing new pharmaceutical drugs which will inhibit specific coagulation factors. A latest entry to the field is apixaban (Eliquis) a direct inhibitor of factor Xa, the first member of the common pathway in the coagulation cascade.

A study comparing apixaban (5 mg twice daily) with aspirin (81 – 324 mg/day) in a group of 5600 AF patients found that apixaban reduced the relative risk of stroke and systemic embolism by about 50% when compared to aspirin (yearly event rates 1.6% with apixaban and 3.7% with aspirin) without significantly increasing the risk of major bleeding.

A very large scale study (ARISTOTLE) comparing apixaban to warfarin has now been completed. It involved 18,200 patients with AF and at least one additional risk factor for ischemic stroke. The average (median) age of the patients was 70 years and 35% were female. Most of the participants (85%) had persistent or permanent AF and had a CHADS₂ score of at least 1 (mean score of 2.1). All in all, the trial involved a group of very sick people, in no way comparable to a group of otherwise healthy afibbers. Almost 90% were being treated for hypertension, 35% had heart failure or abnormally low left ventricular ejection fraction, over 30% had experienced a prior heart attack, stroke, TIA (transient ischemic attack) or systemic embolism, and 25% had diabetes. None of the study participants had a CHADS₂ score of 0.

The participants were randomized to receive standard therapy with oral warfarin (INR range of 2.0 to 3.0) or 5 mg twice daily of apixaban (2.5 mg twice daily for elderly or frail persons and those with impaired kidney function). The warfarin-treated patients were within INR target range 66% of the time (median value). During an average (median) follow-up of 1.8 years, 212 patients (1.3%/year) in the apixaban group experienced a stroke, TIA or systemic embolism as compared to 265 patients (1.6%/year) in the warfarin group. The rate of major bleeding was 2.13%/year in the apixaban group compared to 3.09%/year in the warfarin group. The incidence of hemorrhagic stroke (intracranial bleeding) was 0.24%/year in the apixaban group compared to 0.47%/year in the warfarin group. The incidence of major gastrointestinal bleeding was 0.76%/year in the apixaban group and 0.86%/year in the warfarin group. Overall, 1009 patients (6.13%/year) in the apixaban group and 1168 patients (7.20%/year) in the warfarin group died (from any cause) or suffered a stroke, systemic embolism or major bleeding during follow-up.

The ARISTOTLE AF investigators conclude that apixaban is superior to warfarin in regard to preventing stroke and systemic embolism and non-inferior in all other aspects where a comparison was made. NOTE: This study was funded by Bristol-Myers Squibb and Pfizer and all the investigators have substantial financial ties to the pharmaceutical industry.

Granger, CB, Wallentin, L, et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine, September 4, 2011 [Epub ahead of print]

NEWS BRIEFS

Canadians are deficient in vitamin D

Plasma concentrations of vitamin D (25-hydroxy vitamin D) were measured in 5,306 Canadians and supplement use was ascertained via household interviews. The prevalence of 25(OH)D concentrations below 50 nmol/L was 37.2% overall and 60.7% in non-whites. During winter time the prevalence of vitamin D insufficiency [25 (OH) D concentrations below 50 nmol/L] was 19% in supplement users vs. 37% in non-users. Among those supplementing with more than 400 IU/day, vitamin D insufficiency was 10% or less year round. The University of Saskatchewan researchers reporting the study conclude that vitamin D sufficiency cannot be attained by relying on food sources or sun exposure, but only through supplementation.

Whiting, SJ, et al. The vitamin D status of Canadian relative to the 2011 Dietary Reference Intakes: an examination in children and adults with and without supplement use. American Journal of Clinical Nutrition, Vol. 94, 2011, pp. 128-35

Dronedarone (Multaq) trial halted

Dronedarone is approved as an antiarrhythmic drug for patients with paroxysmal atrial fibrillation (AF). The manufacturer (Sanofi-Aventis) recently announced that its PALLAS phase III trial investigating the use of the drug in permanent afibbers had been halted. The trial involved 3149 patients – 70% with permanent AF of over

2 years duration and 70% with heart failure (NYHA Class I to III at baseline). The study participants were randomly assigned to receive placebo or two 400-mg dronedarone tablets to be taken with morning and evening meals. The trial was halted early due to a statistically significant doubling of overall deaths, cardiovascular deaths, strokes, and hospitalization for heart failure. Dronedarone has now made the FDA “watch list” 5 times regarding concerns for an increased risk of congestive heart failure, torsades de pointes (a sometimes fatal cardiac arrhythmia), increased bleeding risk when taken concurrent with warfarin, and a risk of liver failure. French health authorities have concluded that the efficacy of dronedarone is “insufficient”.

<http://www.theheart.org/article/1255799/print.do>

<http://www.theheart.org/article/1254325/print.do>

<http://www.theheart.org/article/1251405/print.do>

Yoga helps prevent AF episodes

A team led by Dr. Dhanunjaya Lakkireddy at the University of Kansas Hospital reports that regular yoga practice reduces the frequency of AF episodes. The study included 49 paroxysmal afibbers who, after a 3-month control phase (to establish baseline AF burden), participated in a 3-month supervised yoga program consisting of breathing exercises, yoga postures, meditation and relaxation. The number of AF episodes was significantly reduced during the yoga-intervention period as compared to the control phase (average of 2.1 episodes vs. 3.8 episodes). In addition, 22% of participants had no episodes at all during the yoga program. The research team also noted that the yoga-intervention was associated with a “drastic” improvement in quality of life and significantly reduced anxiety and depression scores. They suggest that yoga may help prevent the peaks of sympathetic and parasympathetic tone that precede AF episodes.

<http://www.theheart.org/article/1204423/print.do>

Magnesium deficiency associated with Nexium

The proton pump inhibitor (PPI) Nexium (esomeprazole) is often prescribed for gastroesophageal reflux disease (GERD), a condition not uncommon among afibbers. Dutch physicians recently reported a case of a 76-year-old woman who presented with muscle cramps and lethargy. Blood analysis showed evidence of very low levels of magnesium (0.18 mmol/L), calcium (1.26 mmol/L), potassium (3.2 mmol/L), and parathyroid hormone (0.9 pmol/L). She was started on intravenous calcium and magnesium supplementation. After 3 days her levels of magnesium, calcium, potassium and parathyroid hormone normalized and her symptoms improved. The Nexium was discontinued and magnesium and calcium levels remained in the normal range. Subsequently, GERD symptoms reappeared and Nexium therapy was reinstated. Within 4 weeks the blood (serum) level of magnesium dropped to 0.4 mmol/L (normal range of 0.65 - 1.05 mmol/L). The Dutch physicians conclude that the use of PPIs is associated with a substantial risk of inducing severe magnesium deficiency.

Kuipers, et al. Hypomagnesaemia due to use of proton pump inhibitors – a review. Netherlands Journal of Medicine, Vol. 67, May 2009, pp. 169-72

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