THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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Great news for afibbers with risk factors for stroke – on October 20 the FDA approved a replacement for warfarin (Coumadin). Dabigatran etexilate (Pradaxa) is a direct thrombin inhibitor that has been thoroughly evaluated in at least five clinical trials; the most recent being the RE-LY trial involving over 18,000 atrial fibrillation patients with one or more risk factors for ischemic stroke. Dabigatran, at 150 mg twice daily, was found to be more effective than warfarin in protecting against ischemic stroke and embolism, had one quarter the risk of hemorrhagic stroke, but a somewhat higher risk of heart attack. The new drug comes in two dosages – 150 mg twice daily for afibbers with normal kidney function, and 75 mg twice daily for those with impaired kidney function. Dabigatran is not recommended for patients with impaired liver function. However, as in the case for warfarin, there is no evidence whatsoever that the drug would be beneficial for ***lone*** *afibbers with no or, at the most, one moderate risk factor for ischemic stroke.*

Among the other good news – Japanese researchers report that a 3-day course of corticosteroids post-ablation markedly reduces the incidence of AF recurrence both short- and long-term. Success rates for catheter ablation of paroxysmal and persistent AF are steadily rising with an 85% complete success rate (no afib, no antiarrhythmics) for paroxysmal and 78% for persistent being reported by Japanese electrophysiologists. And, especially good news for persistent afibbers undergoing ablation, the success rate for these more difficult cases can be substantially improved by pre-procedure therapy with dofetilide (Tikosyn).

If you have not yet done so, I would encourage you to explore my new ***AFIB RESOURCES*** *section at http://afibbers.org/resources/index.htm. Here you will find in-depth information on topics vital to lone afibbers such as dealing with digestive problems, the importance of potassium, post-ablation care, living with warfarin, osteoporosis, endurance exercise, electrical cardioversion, etc.*

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 good health and lots of NSR,

Hans

Highlights

Long-term outcome of catheter ablation

TOKYO, JAPAN. Catheter ablations for atrial fibrillation are now being performed in many centers around the world and success rates are steadily improving. A group of Japanese electrophysiologists reports long-term (average 27 months) complete success rates (no afib, no antiarrhythmics) of 85% for paroxysmal and 78% for persistent afibbers.

Their study involved 574 consecutive patients with symptomatic AF who had failed therapy with antiarrhythmic drugs (AADs). The average age of the patients was 61 years, 78% were men, 79% had paroxysmal afib (episodes self-terminating within 7 days), and 21% had persistent afib (episodes lasting longer than 7 days but amenable to cardioversion). None had permanent afib. Most (78%) had no underlying heart disease and were thus lone afibbers; however, 27% of the entire group did suffer from hypertension.

All patients underwent an extensive pulmonary vein isolation procedure with additional lesions as required to terminate AF, atrial flutter and atrial tachycardia prior to completing the procedure. All procedures included a right atrial flutter ablation (cavotricuspid isthmus line). Anticoagulation was continued for 3 to 6 months following the procedure. No AADs were prescribed post-procedure for paroxysmal afibbers, but persistent afibbers were prescribed AADs for 3 months after. Patients were evaluated with Holter monitoring at 2, 6, 10, 14, 24, 36 and 48 weeks after discharge and every 3 months thereafter.

Thirty months after the initial procedure, 67.3% of paroxysmal afibbers and 59% of persistent ones were free of any atrial arrhythmia without the use of AADs. One or more repeat ablations were performed in 160 patients (repeat rate of 40%). At the end of follow-up (27 months from the final procedure) 85.2% of paroxysmal afibbers and 77.9% of persistent afibbers were free of arrhythmia without the use of AADs. Late recurrence of AF (more than 12 months after the procedure) occurred in 1.7% of patients.

There were no deaths associated with the procedures and the rate of major complications was 2.2%. Cardiac tamponade at 0.8% was the most frequent complication followed by transient air emboli (0.3%) which resolved spontaneously, and pyloric spasm at 0.3%. One patient experienced a stroke, but recovered fully within 2 days. Three patients experienced phrenic nerve injury but recovered fully. No cases of pulmonary vein stenosis were observed.

Miyazaki, S, et al. Long-term clinical outcome of extensive pulmonary vein isolation-based catheter ablation therapy in patients with paroxysmal and persistent atrial fibrillation. **Heart**, *August 18, 2010 [Epub ahead of print]*

Editor's comment: The results obtained by the Japanese EPs are highly encouraging and show that success rates (no afib, no AADs) for paroxysmal afibbers can now be expected to be 85% or higher at high volume centers. A major complication rate of 2.2% and a mortality rate of 0% attest to the safety of the extensive pulmonary vein isolation procedure.

Standard ECG may help predict risk of future AF

STANFORD, CALIFORNIA. Most people in developed countries probably have one or more standard 12-lead electrocardiograms (ECG) during their lifetime. Now researchers at Stanford University School of Medicine report that data from these ECGs may be useful in predicting future risk of developing atrial fibrillation.

The researchers reviewed (using a computerized system) 137,000 ECG recordings obtained from 42,751 patients during the period March 1987 to July 2000. The patients were followed for an average of 5.3 years during which 1,050 of them (2.4%) developed AF verified by ECGs. Being male was found to be the strongest risk factor, increasing risk by a factor of 4.4. Age was also important with the average age of participants developing afib being 67.5 years vs. 55.8 years for those who remained in sinus rhythm. African-Americans had an increased risk of developing afib, while Hispanics had a lower risk when compared to white Caucasians.

In studying the baseline ECGs and correcting for possible confounding variables, the researchers conclude that the following factors significantly increase the risk of developing AF.

Variable(1)	Hazard Ratio
Presence of PACs(2)	2.1
Abnormal P axis	1.9
Pindex > 35 ms(3)	1.7
Pmax > 120 ms(4)	1.6
Presence of PVCs(5)	1.5
PR interval > 200 ms	1.3

(1) See www.afibbers.org/resources/heartbeat101.pdf for explanation
(2) Premature atrial contractions
(3) Pindex is defined as the standard deviation of P-wave duration across the 12 leads and may reflect the heterogeneity of diseased atria.
(4) Maximum duration of the P-wave
(5) Premature ventricular contractions

The association between a high Pindex and AF risk was particularly strong in patients younger than 60 years (Hazard ratio of 5.3) and older than 90 years (Hazard ratio of 7.4). The researchers conclude that the Pindex, a measurement of disorganized atrial depolarization, is one of the strongest predictors of future atrial fibrillation.

Perez, MV, et al. Electrocardiographic predictors of atrial fibrillation. **American Heart Journal**, *Vol. 158, No. 4, October 2009, pp. 622-28*

Editor's comment: The finding that a Pindex > 35 ms confers a 5-fold increase in the risk of developing afib among people below the age of 60 years may be of particular interest if future research establishes a correlation between Pindex and certain lifestyles, environmental or dietary factors. The authors of the paper make this interesting comment – "*Atrial fibrillation has been growing at a pace rapid enough to be labeled an epidemic"*. Perhaps the medical research fraternity needs to address the question "WHY?" with greater vigor!

Calcium supplementation questioned

AUCKLAND, NEW ZEALAND. LAF Survey III (June 2001) uncovered a highly significant association between the intake of calcium supplements and episode duration for vagal afibbers – the higher the intake, the longer the episodes. It now appears that calcium supplementation on its own may have other deleterious effects.

Dr. Mark Bolland and colleagues from the University of Auckland, in a recent article published in the *British Medical Journal*, conclude that calcium supplementation (without concomitant supplementation with vitamin D) is associated with an increased risk of heart attack (myocardial infarction). The NZ study was a meta-analysis of 11 randomized, placebo-controlled trials of calcium supplementation (500 mg/day or more). The average age of the 12,000 study subjects was 72 years, 80% were female, and the average blood level of vitamin D3 (25-hydroxyvitamin D) was about 70 nmol/L or 28 ng/mL, well below the currently accepted "healthy level" of 50 – 70 ng/mL. During the 3- to 4-year follow-up 2.7% of patients in the calcium supplement group suffered a heart attack as compared to 2.2% in the placebo group. There was no significant association between calcium intake and stroke, sudden death or overall mortality.

The authors conclude that calcium supplementation without co-administration of vitamin D is associated with an increased risk of heart attack. They also point out that calcium supplementation by itself has marginal efficacy in the prevention of bone fracture. Finally, they suggest that the higher incidence of heart attacks observed in the calcium-supplement group may have been due to vascular calcification. Other researchers, however, doubt this as it would take longer than 3 to 4 years for arterial calcification to lead to myocardial infarction.

Bolland, MJ, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events. **British Medical Journal,** *July 29, 2010 [Epub ahead of print]*

Cleland, JGF, et al. Calcium supplements in people with osteoporosis. **British Medical Journal**, *July 29, 2010 (editorial) [Epub ahead of print]*

Editor's comments: It should not come as a surprise to readers that supplementation with calcium on its own is a bad idea. Ideally calcium should be obtained from dietary sources; however, if supplementation is needed then it should always be accompanied by adequate amounts of vitamin D3 (2000 – 4000 IU/day depending on actual serum level) and vitamin K2 (45 – 100 mcg of menaquinone-7). As far as I know, there is no medical evidence that supplementing with this combination increases the risk of heart attack, stroke or any other cause of death, but there is substantial evidence that supplementation with calcium + vitamin D3 increases bone mineral density and reduces fracture risk. For further reading see www.afibbers.org/resources/osteoporosis.htm

However, calcium + vitamin D supplementation is not the only way to decrease the risk of bone fractures. It is known that bone fractures are relatively uncommon in developing countries where

calcium intakes are low and relatively common in developed countries where calcium intakes are high, and many people supplement with calcium in order to ensure an adequate intake. Does this make sense? Dr. Christopher Nordin at the Institute of Medical and Veterinary Science believes it does. Dr. Nordin points out that it is not the total calcium intake which determines bone strength (density), but rather the difference between what is taken in and what is excreted. Research has shown that for each gram of animal protein consumed one milligram of calcium is lost in the urine. This means that a 40-gram reduction in animal protein intake reduces the urinary calcium loss by 40 mg which in turn corresponds to a reduction in calcium requirements of 200 mg (assuming an absorption of 20%). A reduction in sodium (salt) intake of 2.3 grams also reduces urinary calcium loss by 40 mg lowering requirements by another 200 mg. So a person with a low intake of protein and salt might have half the calcium requirements of a person eating a typical North American diet. This and the fact that developing countries generally get more sunshine (vitamin D) than developed countries go a long way towards explaining the difference in the incidence of osteoporosis and bone fractures between different cultures and individuals. Dr. Nordin concludes that there is no single, universal calcium requirement, only a requirement linked to the intake of other nutrients especially animal protein and sodium.[1]

[1] Nordin, B.E. Christopher. Calcium requirement is a sliding scale. American Journal of Clinical Nutrition, Vol. 71, June 2000, pp. 1381-83

Early tachycardia predicts AF recurrence

SEOUL, REPUBLIC OF KOREA. It is not uncommon to develop atrial tachycardia (regular heart rhythm in excess of 100 bpm) following catheter ablation for atrial fibrillation. Whether or not occurrence of atrial tachycardia (AT) in the first 3 months after the ablation is indicative of future failure is, however, not clear. A team of American and South Korean EPs now report that early occurrence of atrial tachycardia (EAT) is associated with a greater likelihood of late AF recurrence.

The study involved 352 consecutive patients (72% paroxysmal, 28% persistent) who underwent catheter ablation for AF using a combination of electrophysiological and anatomical mapping. All patients had a standard circumferential antral pulmonary vein isolation (PVI) procedure with the end point of complete isolation of the pulmonary veins. A right atrial flutter ablation (linear lesion at the cavotricuspid isthmus or CTI) was performed in patients who had evidence of AT or right atrial flutter prior to or during the procedure. Additional linear lesions were generated in the left atrium in case of arrhythmia persisting after electrical isolation of the pulmonary veins.

During the first 3 months following the procedure (blanking period), 56 patients (15.9%) developed EAT. These patients were older, had larger left atria, and a higher proportion of heart disease (27% vs 12%) and persistent AF (55% vs 23%). The procedure time was significantly longer in patients with EAT than in those without. EAT patients were also more likely to have undergone CTI ablation (74% vs 42%) and to show inducibility of AF or AT immediately after ablation (65% vs 36%).

During a 22-month follow-up period 41% of the patients who experienced AT during the 3-month blanking period had recurrent AF as compared to only 12% among the ablatees not experiencing EAT. In the group without EAT, 29% of persistent afibbers experienced recurrence vs only 7% among paroxysmal afibbers. Thirteen of 23 patients with late AF recurrence in the EAT group underwent repeat ablation an average of 9 months after the initial ablation. Final success rates after repeat procedures was 77% in the EAT group and 89% in those without EAT.

The researchers conclude that an early repeat procedure should be considered in patients with EAT who show positive inducibility immediately after the completion of the initial procedure.

Choi, JI, et al. Clinical significance of early recurrences of atrial tachycardia after atrial fibrillation ablation. **Journal of Cardiovascular Electrophysiology**, *June 25, 2010 [Epub ahead of print]*

Editor's comment: It is of interest to note that the atrial tachycardia first occurred anywhere between 1 and 84 days after ablation. It converted to normal sinus rhythm on its own in 9% of patients, but needed cardioversion in 41% and the use of antiarrhythmics in 50% of patients experiencing EAT.

Permanent AF associated with inflammation

CHIETI, ITALY. There is substantial evidence suggesting that atrial fibrosis (thickening and scarring of heart tissue) may precede the onset of atrial fibrillation and that fibrosis, in turn, is caused by inflammation. A group of Italian and Spanish researchers now report that the use of both steroidal antiinflammatory drugs (SAIDs) such as prednisolone and hydrocortisone and non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and naproxen are associated with an increased risk of developing chronic AF. NOTE: In this study "chronic" AF is defined as atrial fibrillation lasting longer than 7 days and would thus include both persistent and permanent AF.

The Italian/Spanish study involved 525 patients with paroxysmal and 1035 patients with chronic AF. When compared to a control group of 5000 non-afibbers, the current use of SAIDs was associated with a 2.5-fold increase in the incidence of chronic AF. The risk increased with increasing dose and was apparent even with short-term use (30 days or less). There was a small increase (37%) in the incidence of paroxysmal AF among SAIDs users as compared to the control group. The current use of NSAIDs was associated with a 44% increase in the incidence of chronic AF but no statistically significant increase in the risk of paroxysmal AF. The risk tended to disappear with discontinuation of NSAID use and was only apparent in patients without heart failure.

The researchers conclude, not that SAIDs or NSAIDs cause chronic AF, but rather that the inflammation and associated pain prompting the use of the drugs is the culprit. They further propose that systemic inflammation such as autoimmune and rheumatic disorders is an independent risk factor for atrial fibrosis and subsequent development of chronic AF. If this is indeed the case, then drugs inhibiting the renin-angiotensin system (ACE inhibitors, angiotensin II receptor blockers and aldosterone antagonists) may be useful in the prevention of chronic AF through their ability to prevent cardiac fibrosis.

De Caterina, R, et al. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. **Archives of Internal Medicine,** *Vol. 170, No. 16, September 13, 2010, pp. 1450-55*

Editor's comment: The study clearly shows that the current use of SAIDs and NSAIDs is associated with an increased risk of chronic (persistent and permanent) atrial fibrillation. The authors suggest that this association is due not to a detrimental effect of the drugs, but rather to the inflammation and associated pain prompting the use of SAIDs and NSAIDs in the first place. It seems to me that if this hypothesis is indeed true then one must also conclude that SAIDs and NSAIDs do not eliminate inflammation but merely mask its symptoms.

Pre-treatment with dofetilide improves ablation outcome

NEW YORK, NY. Pulmonary vein isolation (PVI) on its own is not very effective in eliminating persistent and permanent atrial fibrillation. In order to achieve a reasonable rate of success it is necessary to create additional linear lesions in the left atrium as well as targeting sites demonstrating complex fractionated electrograms. This is time-consuming and often leads to post-ablation atrial tachycardias, especially left atrial flutter. Electrophysiologists at the St. Luke's and Roosevelt hospitals now report that pre-ablation treatment with the antiarrhythmic dofetilide (Tikosyn) markedly improves PVI success rate in persistent afibbers.

Their clinical trial involved 71 consecutive patients with persistent AF who had been in continuous afib for a median of 6 months (at least 7 days but no longer than 1 year). The average age of the patients was 59 years, 73% were male, and the average time since diagnosis was 5 years. The outcome of the PVI procedure was compared to that in a group of 35 paroxysmal afibbers.

After achieving a documented INR of 2.0 or greater for at least 3 weeks, patients in the persistent AF group were treated with a minimum of 6 doses of dofetilide over a 3-day period while being monitored in hospital. If normal sinus rhythm (NSR) had not been restored after the last dose electrical cardioversion was performed. Dofetilide treatment was maintained until the PVI and for 1 to 3 months post-ablation. There was no interruption of

dofetilide therapy for the PVI procedure. During the time leading up to the ablation 79% of the patients transferred to paroxysmal AF, 18% had complete suppression of any type of AF, and the remaining 3% (2 patients) remained in persistent AF.

After an average wait time of 85 days all patients underwent a standard anatomically-guided PVI with complete electrical isolation of the pulmonary veins as the end point. Fifteen percent underwent an early repeat procedure prompted by recurrent AF. Six months following the procedure 76% of the group were free of AF without the use of antiarrhythmics. This success rate declined to 70% at 12 months. The 35 patients in the paroxysmal group underwent identical PVIs with an average success rate of 80% at 6 months and 75% at 12 months with a 14% repeat rate. The success rate at 6 months was substantially better (92%) among persistent afibbers whose afib was completely suppressed by the pre-ablation dofetilide treatment than among those who converted to paroxysmal AF (75%). Neither of the 2 patients who remained in persistent AF after dofetilide therapy were in NSR at 6 months post-ablation.

Neither age, gender, hypertension, left atrial size, dofetilide dose, duration of persistent AF, time since diagnosis, nor clinical response to dofetilide predicted outcome of the ablation. The only significant variable doing so was the decrease in P-wave duration observed on the electrocardiogram (ECG) prior to initial cardioversion vs that noted just prior to ablation. In patients having a successful PVI P-wave duration decreased by 15% (from 137 ms to 116.7 ms), while it only decreased by 6% (from 132.9 ms to 124.7 ms) in those whose ablation was unsuccessful. There was no significant change in P-wave duration over the 3-month pre-ablation period in the paroxysmal control group.

The researchers suggest that the decrease in P-wave duration associated with dofetilide treatment is an indication that the treatment resulted in reverse electrical remodeling of the left atrium, thus substantially increasing the chance of a successful PVI outcome. They conclude that pre-ablation dofetilide therapy may be a viable alternative to more extensive lesion creation following a standard PVI.

Khan, A, et al. Pulmonary vein isolation alone in patients with persistent atrial fibrillation: an ablation strategy facilitated by antiarrhythmic drug induced reverse remodeling. **Journal of Cardiovascular Electrophysiology**, *August 31, 2010 [Epub ahead of print]*

Editor's comment: The observation that pre-ablation dofetilide therapy increases the chance of a successful outcome of PVIs in the case of persistent AF is clearly of great importance and, if confirmed in larger trials, could herald a novel way of effectively dealing with persistent AF.

Prevention of post-ablation inflammation

Background

In 1997 Dr. Andrea Frustaci, MD and colleagues at the Catholic University of Rome made a fascinating discovery. They performed biopsies of the right atrium in 12 patients with LAF and found that 8 (67%) of them had evidence of a current or past inflammation in the heart tissue (myocarditis). They also checked 11 control subjects and found that none of their biopsy samples showed any signs of inflammation. The Italian researchers concluded that inflammation and its aftermath (fibrotic tissue) is a likely cause of LAF.

The inflammation was found to be active in 3 of the 8 patients. These patients were treated with the anti-inflammatory medication prednisone. They had no further LAF episodes over a 2-year follow-up. The remaining patients were treated with propafenone, sotalol, flecainide or amiodarone and had numerous LAF episodes over the next 2 years.

Through correspondence with Dr. Frustaci I learned that 2 more patients had later shown signs of active inflammation and had been successfully treated with prednisone. Dr. Frustaci concurred that a relapse of atrial inflammation could result in new episodes of LAF and that it is quite possible that all of the 12 LAF patients actually had signs of inflammation, but that the biopsy missed them in four of the cases[1,2].

In January 2002 Cleveland Clinic researchers reported that patients with AF, with or without structural heart disease, had significantly higher blood levels of the inflammation marker, C-reactive protein (CRP), than did controls (median value of 0.21 mg/dL versus 0.096 mg/dL). The average

value for LAF patients was 0.21 mg/dL, which was not significantly lower than that found in AF patients with structural heart disease (0.23 mg/dL). CRP levels were generally higher if the patients were actually in atrial fibrillation or had come out of an episode within 24 hours of sampling. These patients had average CRP values of 0.30 mg/dL as compared to 0.15 mg/dL for AF patients in sinus rhythm. It was also clear that patients with persistent AF had higher CRP values than patients with paroxysmal AF (0.34 mg/dL versus 0.18 mg/dL). The researchers concluded that AF might induce or be induced by an inflammation, which in turn may promote the persistence of AF[3].

Also in 2002 Greek researchers tested CRP levels in 50 paroxysmal AF patients who were actually in fibrillation at the time of sampling and compared results to those obtained for 50 people in normal sinus rhythm. The AF patients had a median CRP level of 0.80 mg/dL as compared to 0.04 mg/dL for controls. The researchers observed that AF patients who could not be cardioverted had a much higher average CRP level (2.12 mg/dL) than did patients who were successfully cardioverted (0.50 mg/dL). They also noted that patients with an enlarged left atrium had considerably less success in being cardioverted. They concluded that high CRP levels are strongly associated with the presence of AF and with a lower chance of successful cardioversion[4].

Although the preponderance of evidence relating to the association between inflammation and AF favour the hypothesis that inflammation causes AF, Prof. Haissaguerre and his group in Bordeaux did report in 2006 that being in sinus rhythm after catheter ablation was associated with a significant decline in CRP[5]. This would support the idea that AF causes inflammation. Nevertheless, the general consensus today is that inflammation is indeed the causative agent. This is further supported by the observation made by Finnish researchers that the incidence of AF following cardiac surgery can be significantly reduced by treatment with corticosteroids[6].

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Abstract

TSUKUBA, JAPAN. Japanese researchers report that post-ablation therapy with corticosteroids can reduce the incidence of AF recurrence both short- and long-term. Their randomized, double-blind study involved 125 paroxysmal afibbers 80% of whom had no structural heart disease (lone AF). The average age of the patients was 61 years, 80% were male, and the average number of years since diagnosis was 7. All patients underwent a pulmonary vein isolation (PVI) procedure using the double Lasso technique without a three-dimensional mapping system. Ten patients needed an additional roof line lesion and 7 needed isolation of the superior vena cava in order to terminate AF. All patients also underwent a right atrial flutter ablation.

Immediately following the procedure half the patients received an injection of placebo (0.9% saline) while the other half received an injection of hydrocortisone. Oral prednisolone was also administered to the hydrocortisone group for 3 days following the procedure.

During the first month following the ablation, 49% of the patients in the placebo group experienced AF recurrence as compared to only 27% in the corticosteroid group. The recurrence happened within the first 3 days post-procedure in 31% of the placebo group versus only 7% of the corticosteroid group. At the end of the 14-month follow-up period, 71% of the patients in the placebo group were free of AF without the use of antiarrhythmics as

compared to 85% in the corticosteroid group. The Japanese researchers also measured CRP levels and body (armpit) temperature in the study participants and made several interesting observations:

- During the initial 3 days following PVI the CRP and maximum body temperature were both significantly higher in the placebo group, clearly indicating that the corticosteroid therapy did indeed dampen post-procedure inflammation.

- Experiencing AF recurrence within the first 3 days post-procedure was associated with poorer long-term prognosis in the placebo group, but not in the corticosteroid group.

- Elevated post-procedure body temperature and CRP were both related to an increased incidence of immediate AF recurrence.

- Early AF recurrences occurring within 4 days to 1 month post-ablation were not associated with an inflammatory response indicating that a relatively short (3 days) course of corticosteroids is sufficient to markedly reduce long-term recurrence risk.

Koyama, T, et al. Prevention of atrial fibrillation recurrence with corticosteroids after radiofrequency catheter ablation. **Journal of the American College of Cardiology**, *Vol. 56, No. 18, October 26, 2010, pp. 1463-72*

Editor's comment: The Japanese study clearly confirms our long held conviction that it is very important to curtail inflammation after a PVI procedure. The hydrocortisone/prednisolone approach is certainly an excellent idea and should ideally be followed by an anti-inflammatory protocol using fish oil, *Zyflamend*, curcumin, beta-sitosterol, Boswellia or other natural anti-inflammatories.

Another important anti-inflammatory measure one should take is to avoid strenuous exercise for at least 4-6 weeks after the ablation. Strenuous and prolonged physical activity will markedly "fan the flames" of an inflammation and may also deplete important electrolytes, especially potassium and magnesium. Swedish sports medicine experts are adamant that exercise should be totally avoided whenever myocarditis (inflammation of the heart tissue) is suspected[1]. Very recently Greek researchers found that participants in a 36-hour long distance run experienced a 152-fold increase in CRP levels and an 8000-fold increase in the level of interleukin-6 (IL-6), another important marker of systemic inflammation. They conclude that the increases in the inflammation markers noted, "amount to a potent systemic inflammatory response"[2].

While not many afibbers will run a 36-hour marathon following their ablation, the Greek study, nevertheless, clearly supports the contention that prolonged, heavy exercise is very detrimental when it comes to preventing or combating an inflammation. I would suggest that no exercise at all would be the best approach for the first two weeks after the ablation followed by one or two daily walks for the next month or so. Jumping right into a strenuous physical activity program right after an ablation is, in my opinion, a very unwise thing to do and will more than likely lead to the need for another ablation.

In conclusion, I strongly believe that ensuring an adequate potassium intake, following a suitable anti-inflammatory protocol, and going very easy on the exercise for the first month, at least, can go a long way to preventing a miserable recovery period and may even help ensure the success of the ablation.

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RESEARCH REPORT

The Dabigatran Story

by Hans R. Larsen

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. It is therefore not surprising that a vast amount of medical research has been directed at finding a replacement for warfarin.

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 essentially focused on developing new pharmaceutical drugs which will inhibit specific coagulation factors. A new direct thrombin inhibitor dabigatran etexilate (Pradaxa) has successfully undergone 3 large-scale phase III trials for the treatment of deep vein thrombosis (DVT). A recent trial involving 502 AF patients with at least one additional risk factor for stroke found that 150 mg of dabigatran twice a day is as effective and safe as standard warfarin therapy.

In September 2009 a large group of researchers from 41 countries reported on the RE-LY trial involving over 18,000 atrial fibrillation patients who had one or more risk factors for stroke (average $CHADS_2$ score was 2.1). NOTE: 79% of the participants had hypertension, 32% had heart failure, 20% had experienced a prior heart attack or stroke, and 23% had diabetes. The study participants were randomly allocated to receive 110 or 150 mg of dabigatran twice daily or standard warfarin therapy (INR range aim of 2.0 to 3.0). The patients were re-examined 2 weeks and 1 and 2 months after randomization, every 3 months thereafter in the first year, and then every 4 months until the end of the 2-year follow-up period. The INR of warfarin users was checked monthly, but no monitoring of blood levels of dabigatran was required.

A comparison of the incidence of ischemic stroke and systemic embolism, hemorrhagic stroke, major bleeding, heart attack, and overall mortality is shown below:

Annual Incidence of Events, %

	Warfarin INR 2.0-3.0	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily
Ischemic stroke & embolism	1.69	1.53	1.10
Hemorrhagic stroke	0.38	0.12	0.10
Heart attack	0.53	0.72	0.74
Major bleeding	3.36	2.71	3.11
Overall mortality	4.13	3.75	3.64

It is clear that dabigatran, either at 110 mg or 150 mg twice daily, gives better protection against strokes (ischemic and hemorrhagic) and bleeding than does warfarin, although a slightly increased risk of heart attack (myocardial infarction) was noted at both levels of dabigatran. There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150 mg dose than with warfarin (1.51%/year versus 1.02%/year).

Adverse events were similar in the 3 groups except in the case of indigestion (dyspepsia) which was experienced by about 11.5% of dabigatran users versus only 5.8% among warfarin users. Several other direct thrombin inhibitors, most prominent among them, ximelagatran, proved to cause liver toxicity and, for this

reason, has not been approved by the FDA for treatment of atrial fibrillation. In this 2-year long trial there was no indication that dabigatran caused a greater elevation of liver enzymes (alanine aminotransferase and aspartate aminotransferase) than did warfarin.

The RE-LY investigators concluded that low-dose dabigatran (110 mg twice daily) is associated with an ischemic stroke rate similar to that experienced with warfarin, but results in a lower incidence of hemorrhagic stroke and major bleeding. High-dose dabigatran (150 mg twice daily) is superior to warfarin when it comes to preventing ischemic and hemorrhagic stroke, but has a similar rate of major hemorrhage. NOTE: The description of the financial ties between the authors of this report and the pharmaceutical industry takes up half a page of fine print![1]

In September 2010 a FDA advisory panel recommended that dabigatran be approved for stroke prevention in atrial fibrillation patients.[2] This was followed by full approval by the FDA on October 20, 2010.[3] The approval covered two doses – a twice daily 150-mg dose for patients with normal kidney function, and a twice daily 75-mg doses for elderly patients and those with impaired kidney function. Impaired kidney function (creatinine clearance level less than 30 mL/min) has been found to double the half-life of dabigatran and increase systemic exposure (area under the curve) by a factor of 6.[4] Thus it is assumed that 75 mg twice a day will be effective in preventing ischemic stroke without increasing bleeding risk in this patient group. However, there is no long-term clinical data to prove that this assumption is correct.

Ximelagatran, a first-generation direct thrombin inhibitor, was found to increase liver enzymes in about 5% of patients taking it. For this reason it was never approved for long-term use. The RE-LY trial specifically excluded participants with compromised liver function but there was no indication that liver function was affected by dabigatran. Nevertheless, dabigatran is not recommended for patients with impaired liver function.

One of the major disadvantages of warfarin is that it is metabolized by CYP 450 enzymes. These enzymes are also involved in the metabolism of numerous pharmaceutical drugs, common foods, and supplements thus setting the stage for many interactions that may increase or decrease the blood level of warfarin. CYP 450 enzymes are not involved in the metabolism of dabigatran so the potential for interactions is substantially less. As a matter of fact, the detailed monograph on dabigatran only cautions that its use may be contraindicated in conjunction with verapamil, amiodarone, quinidine, clopidogrel, aspirin, clarithromycin, and St. John's wort.[4] Another major advantage of dabigatran is that its use does not involve the constant monitoring of INR levels required when using warfarin. However, while warfarin-induced bleeding can be controlled with injection of vitamin K, there is no known antidote for dabigatran-induced hemorrhage. Thus patients involved in contact sports or prone to falls may not be good candidates for dabigatran. Dabigatran was approved in Canada and Europe more than a year ago and has been used extensively on a short-term basis following knee- and hip-replacement surgery.

All told, dabigatran would seem to be a viable replacement for warfarin (Coumadin) in atrial fibrillation patients with underlying heart disease and one or more risk factors for ischemic stroke. However, there is no evidence whatsoever that the drug would be beneficial for lone afibbers with no or, at the most, one moderate risk factor for stroke.

References

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Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
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