Vitamin B6 is much in the news and is hugely important for lone afibbers. A deficiency is associated with increased inflammation and oxidative stress, both important players in the afib saga. There is now also evidence that a B6 deficiency substantially increases the risk of a heart attack and that supplementation with as little as 50 mg/day can reduce the risk of suffering an ischemic stroke by 90%. This is a “must take” supplement!

Data regarding the long-term success of catheter ablations is now appearing and is not encouraging. However, our own survey involving 88 afibbers who had gone at least 4 years afib-free since their latest procedure paints a much brighter picture and proves once again that the expertise and experience of the EP performing the procedure not only affects short-term results, but is crucial in determining long-term outcome.

Also in this issue we report on a new ablation catheter which improves success rate, that patients with hypertension can decrease their risk of developing afib by using an angiotensin II-receptor blocker to control blood pressure, that mastic gum can help eradicate Helicobacter pylori, and much more.

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

**Vitamin B6 deficiency associated with inflammation**

BOSTON, MASSACHUSETTS. Systemic inflammation and oxidative stress have both been implicated in atrial fibrillation. The recent findings, by Dr. Jian Shen and colleagues at Tufts University, that a vitamin B6 deficiency is associated with an increase in the inflammatory marker C-reactive protein (CRP) and with a common marker of oxidative stress, are thus of interest to afibbers.

The study involved 1205 adults of Puerto Rican descent (aged 45 to 75 years) living in Massachusetts. The researchers measured plasma levels of pyridoxal-5’-phosphate (PLP), the main metabolite of vitamin B6, and urinary levels of 8-hydroxydeoxyguanosine (8-OHdG), an indicator of oxidative stress. Participants were allocated to one of four quartiles depending on their plasma PLP level – quartile 1 was 5.5 to 28.3 nmol/L, quartile 2 was 28.4 to 42.4 nmol/L, quartile 3 was 42.5 to 65.2 nmol/L, and quartile 4 was 65.3 to 737 nmol/L. A clear correlation between PLP quartile and CRP level was observed, with quartile 1 members having an average CRP level of 4.7 mg/L (0.4 mg/dL) as compared to a level of 2.5 mg/L (0.25 mg/dL) found among those in quartile 4.
Urinary 8-OHdG level was also significantly associated with PLP level, with members of quartile 1 having a concentration of 124 ng/mg creatinine as compared to 108 ng/mg creatinine in quartile 4. Participants in the highest quartile of PLP also had lower fasting glucose and HbA1c (glycated hemoglobin) levels than did those in the lower quartiles. Higher PLP levels were associated with higher intakes of vitamin B6, folate, vitamin B12, vitamins C and E, and a higher intake of vegetables. Finally, the presence of chronic conditions such as metabolic syndrome, obesity, and type 2 diabetes was strongly associated with lower PLP concentrations.


**Editor's comment:** It is becoming increasingly clear that having an adequate level of plasma PLP is of significant importance to afibbers. This study shows a strong correlation between low PLP level and increased inflammation and oxidative stress. Another study discussed later on in this issue reveals a correlation between low PLP levels and the risk of heart attack. Perhaps most important, several studies have found a strong correlation between low PLP levels and the risk of ischemic stroke and transient ischemic attacks (TIAs). Researchers at Harvard Medical School compared PLP levels in stroke patients and matched controls and found that study participants with a plasma level of PLP of more than 80 nanomol/L had a 90% lower risk of stroke and transient ischemic attacks (TIAs) than did participants with a level below 20 nanomol/L. The risk decrease was independent of the presence of other risk factors such as hypertension, diabetes, and atrial fibrillation[1].

The 90% relative reduction in stroke risk among people with high PLP levels is very significant and compares extremely favourably with the oft-quoted relative risk reduction afforded by warfarin (64%) and aspirin (25%). Clearly, ensuring adequate blood levels of PLP is a must for all afibbers. Vitamin B6 is converted to its active metabolite PLP in the liver and there is some evidence that the liver can only handle about 50 mg of pyridoxine at a time. Experiments have shown that the plasma concentration of PLP does not increase further if 100 mg rather than 50 mg of pyridoxine are ingested at any one time. So it is assumed that the conversion to PLP is limited by the liver's conversion capacity[2]. Other experiments have shown that supplementing (orally) with 40 mg of vitamin B6 will increase average plasma concentration from about 23 nmol/L (range: 18-37 nmol/L) to about 230 nmol/L within 3 days of beginning supplementation. No further increases were observed with 40 mg/day supplementation for a 12-week period[3].

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


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**Is catheter ablation a permanent cure for AF?**

VENEZIA, ITALY. Most clinical trials and studies of the efficacy of catheter ablation for atrial fibrillation (AF) have very limited follow-up and evidence concerning long-term maintenance of normal sinus rhythm (NSR) is scarce indeed. A group of Italian electrophysiologists have just published the results of a study involving follow-ups as long as 6 years. Between February 2001 and October 2003, 229 patients with paroxysmal or persistent AF underwent a single radiofrequency (RF) procedure (segmental approach in 83 patients and anatomical [CARTO] approach in 146 patients). At the 12-month follow-up point, 177 (58% paroxysmal and 42% persistent) of these patients had not experienced any afib or flutter. However, 19% used antiarrhythmics to maintain NSR, thus giving a complete success rate (no afib, no antiarrhythmics) of 58% for the original 229 patients.

The 177 patients (57% had no underlying heart disease) who remained free of afib one year after the ablation were followed for up to 6 years. The percentages of study participants who experienced afib recurrence at the end of the specified year are given below:
Afib-free survival was similar in patients with paroxysmal AF and in those with persistent AF, and there was no difference in afib-free survival between those on antiarrhythmics and those not on these drugs. There was a trend for afibbers with a small left atrium to be more likely to maintain NSR. There was no difference in long-term outcome between patients who had been treated with the segmental protocol and those who had undergone an anatomically-guided ablation.

The recurrent arrhythmias in patients who had paroxysmal AF prior to their ablation were mostly (75%) paroxysmal in nature, but in 25% of originally paroxysmal afibbers, the recurrent arrhythmia was permanent. In the case of originally persistent afibbers, 21% of recurrent arrhythmias were paroxysmal, 48% were persistent, and 31% were permanent. After 4 years, 58.2% of patients (45% of the original 229) were free from arrhythmia with (18.6%) or without (39.6%) the use of antiarrhythmics. The authors of the study conclude that, “Data from published studies and from our experience seem to confirm that success over a 12-month follow-up does not necessarily guarantee long-term success, and that the early hope of AF ablation being a ‘curative’ procedure continues to be shattered by the harsh reality that AF does in fact recur after a several-month blanking period.”

NOTE: The authors point out that their experience with the segmental protocol was limited, perhaps explaining why the outcome of the segmental protocol was not superior to that of the anatomically-guided one.


Editor’s comment: The conclusion of this study is certainly not encouraging and is in sharp contrast to the conclusion reached in our 2009 ablation/maze survey involving 88 afibbers who had gone at least 4 years since their latest ablation procedure. “Of the 88 respondents undergoing RF ablation, 55 (63%) underwent only a single procedure, while 33 (37%) underwent 2 or more procedures for the purpose of curing AF. The most widely used and most successful procedure for paroxysmal AF was the pulmonary vein antrum isolation procedure developed by Dr. Andrea Natale followed by the segmental pulmonary vein ablation (Haissaguerre technique), which was especially successful among persistent and permanent afibbers.

The most important variable determining long-term success was whether or not a respondent had an initially successful procedure, i.e. they remained in sinus rhythm without the use of antiarrhythmics during the last 6 months of the 12-month period following their final procedure (index period). This, in turn, was dependent on the ranking of the institution at which the final procedure was performed, and on the incidence of AF during the first 6 months following the final procedure (blanking period).

In conclusion, the long-term prognosis for an afib-free future with no antiarrhythmics after an initially successful catheter ablation is excellent with 87% of paroxysmal afibbers and 82% of persistent and permanent afibbers achieving this enviable state in the period 5 to 6 years following their final procedure. In comparison, in the initially unsuccessful group only 33% of paroxysmal afibbers and 33% of persistent and permanent afibbers achieved this status.

There is also encouraging news for those afibbers whose final procedure was not successful. At the end of year 4, 27% of respondents were still experiencing afib episodes. However, their frequency was down by 95% from pre-procedure levels and the total time spent in afib was down from 7% to 0.2% for paroxysmal afibbers. The reduction in afib burden from pre-procedure days to year 4 was 97% and this decline was pretty well universal with only 1 of 16 respondents reporting an increase in burden. The decline in afib frequency and burden continued throughout years 5 and 6, but then suffered a slight reversal in years 7-10.
Progression from paroxysmal to persistent AF

MAASTRICHT, THE NETHERLANDS. The possibility of paroxysmal (intermittent, spontaneously converting) AF progressing over time to persistent (episodes lasting longer than 7 days or requiring cardioversion) or permanent (chronic, not amenable to cardioversion) AF is of concern to all afibbers. A study just released by Dr. Maurits Allessie and colleagues at Maastricht University conclude that about 15% of patients with paroxysmal or new-onset AF progress to persistent over a one-year period.

Their study involved 1219 paroxysmal afibbers participating in the Euro Heart Survey on AF who were followed for one year following their enrolment. Progression occurred in 178 patients (15%). There were 203 lone afibbers in the study population and among these progression occurred in only 14 patients (7%).

The major baseline characteristics predicting progression were hypertension, history of heart failure, chronic obstructive pulmonary disease (COPD), history of stroke or TIA, and age above 75 years. These factors are similar to those involved in determining the CHADS2 score for stroke risk, so it is not surprising that participants with a high CHADS2 score also had an increased risk of AF progression. Several medications (digoxin, ACE inhibitors, and diuretics) increased risk of progression, while angiotensin II receptor blockers decreased the risk. There was no indication that antiarrhythmic drugs had any effect on risk of progression, but patients on warfarin were more likely to progress, possibly related to the fact that they likely had a higher CHADS2 score. Patients whose AF progressed to persistent were more likely to be hospitalized for cardiovascular problems, were more likely to suffer a stroke or TIA, and were also more likely to undergo electrical cardioversion during the follow-up year.

Based on their findings, the Dutch researchers developed a scoring system (HATCH) for predicting the risk of progression. The formula for the HATCH score is similar to that of the CHADS2 score and allocates points as follows:

- Hypertension – 1 point
- Age > 75 years – 1 point
- COPD – 1 point
- Heart failure – 2 points
- Stroke or TIA – 2 points

A re-examination of the baseline data showed that, among patients with a HATCH score of 0, only 6% progressed to persistent AF, while among those with a HATCH score above 5 almost 50% progressed to persistent.


Editor’s comment: A 2005 Canadian study concluded that 25% of patients originally diagnosed with paroxysmal afib progress to permanent within 5 years of initial diagnosis. Major risk factors for progression were aortic stenosis, an enlarged left atrium, moderate to severe mitral regurgitation and cardiomyopathy.[1] A 2005 survey of 188 lone afibbers concluded that the risk of progression from paroxysmal to permanent was associated with a family history of AF, having undergone one or more cardioversions, having developed hypertension after diagnosis, and having an enlarged left atrium.[2]


Comparison of antiarrhythmic therapy and ablation

MAYWOOD, ILLINOIS. Antiarrhythmic drug therapy (ADT) is usually the first approach to dealing with atrial fibrillation. However, the long-term efficacy of antiarrhythmics is not great with 60 to 80% of patients on sotalol, propafenone or flecainide experiencing recurrence within one year when first exposed to these drugs. Having failed one antiarrhythmic increases the risk of failing another one with recurrence rates now approaching 80 to 90% within one year. Amiodarone is the
exception to this with a one-year recurrence rate of 30 to 40%. However, amiodarone has the potential for very serious adverse effects.

A large group of electrophysiologists from 15 centers in the USA, 2 in Europe, and 1 each in Canada and Latin America now attempts to answer the question – *Having failed one antiarrhythmic drug, is it worth trying another, or is catheter ablation a better option?*

Their study involved 167 paroxysmal afibbers who had all failed therapy with at least one antiarrhythmic and who experienced at least 3 afib episodes in the 6 months prior to being randomized to undergo catheter ablation (106 patients) or try a different antiarrhythmic (61 patients). Both groups consisted mainly of lone paroxysmal afibbers (90% in ablation group and 85% in ADT group). The average age of patients was 56 years and about 65% were male. Fifty percent had been treated (ineffectively) with propafenone prior to joining the study, while 35% had taken sotalol, and 28% flecainide.

The 61 patients in the ADT group were assigned to a not previously administered antiarrhythmic (dofetilide, flecainide, propafenone, sotalol, or quinidine) and followed for 9 months. The study protocol did not allow the use of amiodarone. Patients in the ADT group were allowed to opt for an ablation after 90 days of ineffectual ADT – 36 patients (54%) chose to do so within 3 to 5 months of being assigned to ADT.

The patients assigned to ablation underwent a circumferential pulmonary vein isolation procedure (Pappone protocol) with additional lesion lines placed at the discretion of the EP. A repeat procedure was performed in 13 patients (12.6%) within 80 days of the initial ablation.

At the end of the 9-month effectiveness evaluation period, 66% of the participants in the ablation group remained afib-free as compared to 16% in the ADT group. Major adverse events occurred in 4.9% of the ablation group and in 8.8% in the ADT group. Quality of life scores, while being similar in the two groups prior to randomization, improved substantially within 3 months following ablation, but remained unchanged in the ADT group. The researchers conclude that, “Among patients with paroxysmal AF who had not responded to at least 1 antiarrhythmic drug, the use of catheter ablation compared with ADT resulted in a longer time to treatment failure during the 9-month follow-up period.”


**Editor’s comment:** This study certainly provides convincing evidence that, if a first antiarrhythmic drug fails to control paroxysmal AF episodes, a catheter ablation is a better second step than trying another antiarrhythmic. However, this may not apply to everyone. For example, if a vagal afibber has had no success with sotalol or propafenone, which both have beta-blocking properties, it is not inconceivable that flecainide might be effective in a “second try”. It is also possible that long-term therapy with amiodarone might approach the efficacy of ablation, but the risk of adverse effects would be substantially higher and quality of life would no doubt be lower.

### New ablation catheter improves success rate

**LEIPZIG, GERMANY.** In 2008 Hans Kottkamp and colleagues at the University of Leipzig Heart Center reported on their experience using the Agilis NXT (St. Jude Medical) bi-directional, manually-steerable sheath for catheter guidance in ablation for atrial fibrillation. They compared ease of operation and final results with those obtained using a conventional fixed transseptal sheath (*Mullins* by Cook Medical Inc) in a group of 166 AF patients of which 50% were lone afibbers. They found that, while 77% of patients in the Agilis group were in normal sinus rhythm (NSR) 6 months following their procedure, only 56% of those in the Mullins group were in NSR 6 months post-procedure.

The Leipzig group and their Swiss colleagues at the Hirslanden Heart Center in Zurich now report the outcome of a trial of the Agilis NXT manually-steerable sheath in 674 consecutive patients treated for AF. The average age of the group of patients was 57 years, 69% were male, 85% had paroxysmal AF, 15% had persistent AF, and the average number of years since diagnosis was four. Only 6% of patients had coronary heart disease or left ventricular dysfunction, but 50% had arterial
hypertension. During a 7-day Holter before ablation the paroxysmal afibbers had an average (median) of 2 episodes lasting a total (median) of 21 hours.

All participants underwent an anatomically-guided pulmonary vein isolation procedure using CARTO mapping (Pappone protocol) and an irrigated Navi-Star Thermocool ablation catheter (Biosense Webster). In paroxysmal afibbers only the pulmonary veins were isolated (one ring around the right pulmonary veins and one around the left veins). In persistent afibbers additional ablation lines were placed between the circular lesions along the roof of the left atrium as well as between the circular lesions and the mitral annulus. Seven-day Holter recordings were done immediately following completion of the procedure as well as 3, 6 and 12 months after the ablation. Any post-procedure arrhythmia lasting longer than 30 seconds was classified as recurrence, and those occurring during the initial Holter monitoring period were defined as early recurrence.

About 52% of patients experienced early recurrence and doing so was closely associated with still having afib episodes one year after the ablation. At the 12-month follow-up, 75.7% of patients having undergone a single procedure were afib-free without the use of antiarrhythmics. The success rate was markedly higher in patients who had not experienced early recurrence (91%) than in those who had experienced early recurrence (success rate at 12 months was 58.6%). There was no significant difference in success rates between paroxysmal and persistent afibbers.

Thirteen patients (1.8%) experienced major complications during or immediately after the procedure. Six (0.9%) experienced tamponade (puncture of the heart wall), 1 suffered a TIA or stroke, and 3 had groin vascular complications requiring surgery. There were no deaths and no cases of pulmonary vein stenosis, phrenic nerve palsy, or atrioesophageal fistulas. Early recurrence, arterial hypertension, and a left atrial diameter greater than 55 mm predicted failure at the 12-month follow-up mark.


Editor’s comment: The complete 1-year success rate (75.7%) after a single circumferential PVI procedure is remarkable indeed and bodes well for the use of steerable rather than fixed sheaths. It should be noted that the Agilis sheath can be manipulated either manually or by remote control.

Hypertension and atrial fibrillation

BASEL, SWITZERLAND. Patients with hypertension (elevated blood pressure) are usually treated with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARBs), or calcium channel blockers, sometimes accompanied by diuretics. Some studies suggest that drugs which interfere with the renin-angiotensin system may be favorable because of their beneficial affect on atrial remodeling. A group of researchers from the Basel University Hospital and Boston University Medical Center has just completed a study to determine if some anti-hypertensive drugs are better than others in preventing the development of atrial fibrillation among patients with hypertension.

Their study included 4,661 patients with AF and 18,642 matched controls all derived from a total population of 682,993 patients with elevated blood pressure, but no history of arrhythmias, ischemic heart disease or congestive heart failure. Almost two-thirds of the case patients were 70 years or older when they received their initial afib diagnosis and 47% were men. Obese patients with hypertension had a 71% greater risk of being diagnosed with AF.

Using treatment with calcium channel blockers as the reference point, the researchers observed that patients receiving beta-blockers had a 22% reduced risk of developing AF, those on ACE inhibitors a 25% reduced risk, and those on ARBs a 29% reduced risk. The researchers conclude that exclusive therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for AF compared with calcium channel blocker therapy in patients with mild to moderate hypertension (those whose hypertension can be controlled with just one drug).

Editor’s comment: It would seem that treatment with an ARB such as valsartan (Diovan) or losartan (Cozaar) may be the best bet for patients with hypertension who wish to reduce their risk of developing AFib. In this connection, it is of interest that ARBs have been found to reduce brain natriuretic peptide (BNP), a high level of which is strongly related to the risk of developing AF. In looking at the baseline characteristics of the study participants, it is of interest to note that over 40% suffered from depression, almost 90% had been on antibiotics, and close to 70% were overweight or obese – not a very healthy bunch!

Trauma and warfarin use

NASHVILLE, TENNESSEE. Surgeons have long been aware that trauma patients on warfarin (Coumadin) have significantly poorer survival than do those who are not anticoagulated at the time of their accident. In order to determine more precisely exactly how dangerous being on warfarin is, Dr. Lesly Dossett and colleagues at Vanderbilt University Medical Center reviewed the records of 1,230,422 trauma patients listed in the National Trauma Databank maintained by the American College of Surgeons. They found that 36,270 of the patients were on warfarin when their trauma occurred. After adjusting for comorbidities associated with warfarin, they found that its use increased trauma-related mortality by 30%. The Vanderbilt team also noted that the use of warfarin had almost doubled in the period 2002 to 2006. Overall, 2.3% of the patient population was on warfarin in 2002 as compared to 4.0% in 2006. Among patients over the age of 65 years warfarin usage increased from 7.3% in 2002 to 12.8% in 2006.


ODDS AND ENDS

Mastic gum may eradicate Helicobacter pylori

CHIOS, GREECE. Helicobacter pylori infections are common and are associated with indigestion, gastritis (inflammation of the stomach lining), peptic ulcer, and stomach cancer. In 1983 two Australian physicians discovered that the H. pylori bacterium can be permanently eradicated with a course of antibiotics and proton pump inhibitors (PPIs). Although the therapy is effective it does have side effects that many patients find intolerable. A group of Greek gastroenterologists now report that mastic gum (a natural resin excreted for the mastic bush) is effective in eradicating H. pylori. Their study involved 52 patients who suffered from H. pylori infection as diagnosed with upper gastrointestinal endoscopy and confirmed with a urea breath test (UBT). The patients were randomly assigned to receive one of four treatments:

- Group A – 350 mg mastic gum 3 times daily for 14 days;
- Group B – 1000 mg mastic gum 3 times daily for 14 days;
- Group C – 350 mg mastic gum 3 times daily + 20 mg pantoprazole (a PPI) for 14 days;
- Group D – 1 g amoxicillin + 500 mg clarithromycin + 20 mg pantoprazole twice daily for 10 days.

Five weeks after completion of the treatment UBT was repeated. This showed that 31% of group A, 39% of group B, and 92% of group D had achieved total eradication of H. pylori. None of those in group C achieved eradication. The researchers speculate that mastic gum requires an acidic environment to be effective and that the addition of a PPI is therefore counterproductive. They conclude that mastic gum may be a reasonable alternative for patients who are unable to tolerate the standard triple antibiotic therapy.


Editor’s comment: For a discussion of the use of mastic gum in H. pylori eradication please see Conference Room Session 65 at www.afibbers.org/conference/session65.pdf. It is interesting that mastic gum may require an acidic environment to work effectively. If this is indeed the case, then combining mastic gum with betaine hydrochloride may result in more effective eradication in those with low stomach acid.
**Vitamin B12 deficiency implicated in hypothyroidism**

KARACHI, PAKISTAN. There is evidence that an under-active thyroid gland (hypothyroidism) may be associated with lone atrial fibrillation. One of our early LAF surveys showed that 45% of respondents had a low basal temperature and 40% of these had actually been diagnosed with hypothyroidism. Impaired memory, depression, numbness, and generalized weakness are common symptoms of hypothyroidism. Researchers at the Aga Khan University in Pakistan recently discovered that 40% of 116 patients with an under-active thyroid gland also had a vitamin B12 deficiency – a B12 level below 200 pg/mL. Twenty-four of the 46 patients diagnosed as being deficient received monthly intramuscular vitamin B12 injections and 14 (58%) of them noted a significant improvement in their symptoms. However, among 21 patients with normal B12 levels who also received monthly injections, 40% reported a significant improvement in their symptoms after 6 months of injections – perhaps indicating a significant placebo effect, or the possibility that the currently established lower limit of the reference range for vitamin B12 is too low. The researchers conclude that all hypothyroid patients should be screened for vitamin B12 deficiency and, if necessary, be given B12 injections to normalize their levels.


**Vitamin B6 protects against heart attacks**

BOSTON, MASSACHUSETTS. There is growing evidence that an adequate vitamin B6 status is important in the prevention of coronary artery disease. Researchers at Harvard Medical School report that a high fasting plasma concentration of pyridoxal-5'-phosphate (PLP) is associated with a significantly reduced risk of suffering a fatal or non-fatal heart attack (myocardial infarction). PLP is the main form of vitamin B6 found in circulating blood. The Harvard study included 33,000 women participating in the Nurses’ Health Study. Over a 10-year period following the PLP measurement, 239 suffered a heart attack. The researchers found that women in the highest quartile of PLP concentration had a 78% lower risk of suffering a heart attack than did those in the lowest quartile. The risk reduction was particularly impressive (95%) in women who were under the age of 60 years at time of blood sampling. PLP concentration was directly correlated with dietary intake of vitamin B6 and inversely correlated with homocysteine level.