THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

NUMBER 101 **JULY/AUGUST 2010** **10th YEAR**

Welcome to our summer issue – or winter issue for our Aussie and Kiwi subscribers!

The good news is that researchers at the Mayo Clinic have confirmed that otherwise healthy lone afibbers have a very low risk of cardioembolic stroke or TIA. Further good news – more than 80% of afibbers who experienced no AF recurrence during the first year following their PVI are still in normal sinus rhythm 5 years later, a successful ablation markedly improves quality of life, and electrical cardioversion is generally safe for lone afibbers. The not-so-good news is that left atrial flutter is a fairly common complication of pulmonary vein isolation using the circumferential (Pappone) protocol, dronedarone (Multaq) is not as safe and effective as the spin doctors would have us believe, and ablation using high intensity focused ultrasound (HIFU) may be quick but is also highly dangerous.

As an added bonus, in our new "Supplement News" section we report that vitamin K2 is effective in preventing certain cancers, that vitamin/mineral supplements are safe, and that lycopene supplements, while perhaps being effective in the prevention of prostate cancer, should be used with caution, if at all, in cases of established prostate cancer.

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 a safe and enjoyable summer with lots of NSR,

Hans

Highlights

Long-term success of AF ablation

PHILADELPHIA, PENNSYLVANIA. Apart from our 2009 Ablation/Maze Survey there is little published data on the long-term outcome of initially successful pulmonary vein isolation (PVI) procedures. Electrophysiologists at the University of Pennsylvania now report on the 5-year outcome for 123 afibbers who had undergone a PVI, plus additional lesions as needed, during the period 2001 to 2003 and had remained afib-free for one year following the procedure without the use of antiarrhythmics. The mean age of the study participants was 54 years, 80% were male, 85% had paroxysmal AF with the remaining 15% having the persistent variety.

A total of 239 patients underwent a segmental PVI and 59% of these patients were afib-free (without antiarrhythmics) without further intervention one year after their initial procedure. Among the 123 one-year "veterans", 84% continued to remain afib-free for 3 years after their initial PVI. The percentage of afib-free participants decreased to 77% at year 4 and 71% at year 5 indicating a recurrence rate of approximately 7% a year.

Persistent afibbers had a 2.8-fold increase in the risk of experiencing a recurrence and older afibbers

(57years) had a 10% greater risk of relapsing than did younger ones (52 years). There was also some indication that a larger left atrial size was associated with a poorer outcome. There was no association between operator experience and long-term success. NOTE: More than likely operator experience would nevertheless be highly important in determining 1-year outcome.

A total of 35 patients experienced recurrent AF an average of 3.3 years after the index procedure. Ten had fewer than 6 episodes a year, while the remaining 25 continued to experience AF episodes despite re-initiation of antiarrhythmics. Fifteen of these patients underwent a repeat ablation an average of 3 years following their initial procedure and 73% remained afib-free 3 years after their second procedure. Including patients who had a second ablation in the total, the 4- and 5-year complete success rates (no AF and no antiarrhythmics) becomes 89% and 81% respectively. In all cases, the recurrence of AF was due to previously ablated pulmonary veins reconnecting electrically with the left atrium.

Tzou, WS, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. **Circulation: Arrhythmia and Electrophysiology**, *Vol. 3, June 2010, pp. 237-42*

Editor's comment: It is of interest to compare the above results with those obtained in the 2009 Ablation/Maze Survey. Here 66 afibbers who had remained in normal sinus rhythm for 6 months following their last procedure were followed for up to 7 years. Complete success rate was 83% at year 3-4 and 86% at year 5-6, thus comparable to the 89% and 81% observed in the University of Pennsylvania study. The long-term success rate in our survey was, however, highly dependent on operator experience and the absence of AF episodes during the first 6 months following the procedure.

Quality of life after ablation

ROCHESTER, MINNESOTA. It is well established that people with atrial fibrillation have impaired quality of life (QoL). What has not been investigated is the extent to which a successful or unsuccessful catheter ablation impacts on QoL. Researchers at the Mayo Clinic have just reported the results of a study involving 323 afibbers who had undergone one or more ablations with the intent of curing AF. All patients underwent circumferential pulmonary vein isolation with additional lesion lines as needed. Two years after their last procedure, 233 patients (72%) were afib-free without the use of antiarrhythmics (complete success), 48 patients (15%) were able to remain in sinus rhythm with the aid of previously ineffective antiarrhythmics (partial success), and the remaining 42 patients (13%) were still having afib episodes (failure). Eighteen percent of the groups underwent a repeat ablation an average of two years after their initial procedure.

All study participants completed QoL questionnaires prior to their first ablation and 2 years after their last procedure. Health-related QoL was assessed with the Medical Outcomes Study Short Form-36 (SF-36) which measures health on 8 different scales with a range from 0 (worst health) to 100 best health). The participants also completed the Mayo AF-Specific Symptom Inventory (MAFSI) which seeks to determine frequency of common AF symptoms (palpitations, dizziness, shortness of breath, fatigue, etc) over a 6-month period using a scale of 0 (never) to 4 (always).

The average baseline (prior to ablation) SF-36 score was 64 increasing to 81 three months after the procedure and maintaining this level at the 1- and 2-year marks. The physical component score of SF-36 increased from 59 to 76 and the mental component score rose from 65 to 80. The increase in these scores was somewhat less for patients experiencing recurrences and significantly less for those still taking antiarrhythmics. Improvement in QoL was also significantly less for afibbers who remained on warfarin. Frequency of common AF symptoms as measured by MAFSI decreased from 14 prior to the ablation to 5 following. Symptoms improvements were particularly marked in the case of palpitations, tiredness, and ability to exercise. The degree of improvement in symptoms as measured with the MAFSI scale depended highly on ablation outcome. In the case of complete success (no AF, no antiarrhythmics) the improvement averaged 9.5 points as compared to only 5.6 points among participants still needing antiarrhythmics for control, and 3.4 points among those experiencing AF recurrence. Being on warfarin 2 years following ablation reduced SF-36 score by an average of 10 points, while being obese reduced it by 6.8 points. A total of 43 patients

experienced major procedural complications. These, somewhat surprisingly, did not affect QoL at 2 years post-procedure.

Wokhlu, A, et al. Long-term quality of life after ablation of atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 55, No. 21, May 25, 2010, pp. 2308-16*

Editor's comment: The conclusion of the Mayo Clinic study that a RF ablation improves QoL to some extent irrespective of outcome supports the conclusion from our 2007 Ablation/Maze Survey. "*Considering quality of life improvement rather than strictly success or failure of RF ablation procedures, it becomes clear that even a failed ablation may improve life quality. The average complete success rate found in this survey (after an average 1.3 procedures) is 54%. Adding to this partial success (where afib is kept at bay with antiarrhythmics) brings the percentage of afibbers whose lives have been improved through RF ablation to 65%. Further considering that about 70% of ablatees whose procedure failed still reduced their afib burden by at least 50% brings one to the conclusion that RF ablation, whether successful or not, is likely to improve quality of life in close to 90% of those undergoing the procedure. A significant portion of the remaining 10% may, however, see a worsening of their condition or may experience a serious adverse event."*

Inflammation implicated in AF development

BOSTON, MASSACHUSETTS. Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence in the general population is increasing rapidly. There is substantial evidence that AF is associated with systemic inflammation as measured via C-reactive protein (CRP) level; however, until now it has not been clear whether inflammation causes AF or AF results in inflammation. Researchers at Harvard Medical School now provide conclusive evidence that systemic inflammation precedes the development of AF in women. Their study involved 24,734 women who were part of the ongoing Women's Health Study (WHS) begun in 1993. At baseline, the participants (female health professionals between the ages of 49 and 59 years) completed health questionnaires and had blood samples drawn for analysis of three biomarkers for inflammation – CRP, slCAM-1 and fibrinogen. NOTE: slCAM-1 is soluble intercellular adhesion molecule-1, an inflammatory molecule associated with atherosclerosis.

During the 14-year follow-up period, 747 women developed AF (94% lone AF). The researchers found a clear correlation between elevated inflammation markers at baseline and the risk of developing AF. Assigning 1 point each for CRP level above 3.4 mg/L (0.34 mg/dL), slCAM-1 level above 373 ng/mL, and fibrinogen level above 382 mg/dL, the researchers observed that women with 1 point had a 22% increased risk of developing AF compared to women with 0 points (none of the inflammation markers above the cut-off points). Women with a 2-point score had a 32% increased risk, and those with a 3-point score had a 59% increased risk after adjusting for possible confounding variables including smoking, blood pressure, body mass index, diabetes, hypercholesterolemia, exercise, alcohol consumption, and race/ethnicity. The actual number of newly diagnosed afibbers per 1000 person-years was 1.66 for an inflammation score of 0, 2.2 for a score of 1, 2.73 for a score of 2, and 3.25 for a score of 3.

The researchers conclude that, "*markers of inflammation were independently associated with incident AF in initially healthy, middle-aged women, even after controlling for traditional risk factors. These findings suggest that inflammation may be involved in the pathogenesis of AF.*"
Conen, D, et al. A multimarker approach to assess the influence of inflammation on the incidence of atrial fibrillation in women. **European Heart Journal**, *May 25, 2010 [Epub ahead of print]*

Editor's comment: There is overwhelming evidence of an association between systemic inflammation and atrial fibrillation. The Harvard study clearly supports the hypothesis that inflammation causes AF rather than vice versa. Although this study in no way proves that existing afib can be reduced or eliminated by eliminating systemic inflammation, it certainly would be advisable to do so, preferably through the use of such natural anti-inflammatories as curcumin, bromelain, ginger, beta-sitosterol, boswellia, fish oil, *Zyflamend* or *Moducare*.

Left atrial flutter induced by catheter ablation

SAN DIEGO, CALIFORNIA. The three most commonly used procedures for isolation of aberrant electrical impulses originating in the pulmonary veins are:

- **Segmental pulmonary vein isolation (SPVI or Haissaguerre procedure) –** In this procedure electrophysiological mapping (using a multipolar Lasso catheter) is used to locate the pathways taken by aberrant impulses from the pulmonary veins and these pathways are then eliminated by ablation around the veins approximately 5 to 10 mm from the ostium of the veins.
- **Circumferential anatomical pulmonary vein isolation (CAPVI or Pappone procedure) –** In this procedure anatomical mapping (CARTO) is used to establish the exact location of the pulmonary veins. Two rings of lesions are then created in the left atrium - one completely encircling the left pulmonary veins and another completely encircling the right pulmonary veins; the two rings are usually joined by a linear lesion.
- **Pulmonary vein antrum isolation (PVAI or Natale procedure) –** This procedure is a variant of the Haissaguerre procedure. It involves locating aberrant pathways through electrophysiological mapping (using a multipolar Lasso catheter) and ablating these pathways guided by an ultrasound (ICE) catheter. The ablation is performed as close as possible to the outside edge (antrum) of the junction between the pulmonary veins and the atrial wall. All four pulmonary veins as well as the superior vena cava (if indicated) are isolated during the procedure.
- All three variants of the PVI procedure may be followed by focal ablations involving other areas of the atrium wall or creation of linear lesions in order to isolate sources of afib located outside the pulmonary veins.

There is growing concern that the use of linear ablations may have unintended effects, in particular, the creation of iatrogenic (procedure-caused) arrhythmias such as left atrial flutter. Electrophysiologists at the University of California Medical School now confirm that linear ablation is indeed associated with an increased risk of post-procedural left atrial flutter. Their clinical trial included 66 consecutive patients with paroxysmal lone AF (73% male, average age of 57 years and average duration of AF of 5.6 years). The patients were randomized to receive a segmental PVI including a right atrial flutter ablation or a circumferential, anatomically guided PVI with a lesion line (roof line) connecting the left and right rings encircling the pulmonary veins as well as a mitral isthmus line connecting the mitral valve annulus with the left encircling ring. Total fluoroscopy time (radiation exposure) was 73 minutes in the segmental group vs. 91 minutes in the circumferential group.

All patients were followed up at 1, 3, 6, 12 and 24 months following the ablation and every 12 months thereafter. Before the 6- and 12-month follow-up visits, patients were continually monitored for 2 weeks to spot any arrhythmia occurrence. Sixteen months after the initial procedure 58% of patients in the segmental group were free of all atrial arrhythmias and off all antiarrhythmic drugs. The corresponding number for the circumferential group was 52%. Thirty percent of patients in the segmental group underwent a repeat PVI after which 85% remained in normal sinus rhythm without the use of antiarrhythmics. In the circumferential group, 40% underwent a repeat procedure after which 85% remained free of AF without the use of antiarrhythmics.

Following the initial procedure, paroxysmal AF recurred in 14 patients in the segmental group and in 8 patients in the circumferential group. However, another 6 patients in the circumferential group developed left atrial flutter and 2 developed both left atrial flutter and experienced recurrence of paroxysmal AF as well. Six patients underwent a follow-up ablation for left atrial flutter of which 5 were immediately successful and one required a repeat procedure. Three complications occurred among the 66 patients (4.5%) – 1 femoral hematoma, 1 femoral pseudoaneurysm, and 1 pericardial effusion with tamponade, all of which were successfully resolved. The researchers conclude that linear lesions, in particular the mitral isthmus line, are associated with a greater

incidence of left atrial flutter, should be avoided whenever possible, and should not be used in the initial ablation of patients with paroxysmal AF and structurally sound hearts.

Sawhney, N, et al. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. **Circulation: Arrhythmia and Electrophysiology**, *Vol. 3, June 2010, pp. 243-48*

Safety of electrical cardioversion

VANCOUVER, CANADA. A study carried out by physicians at St. Paul's Hospital in Vancouver concludes that electrical cardioversion of patients with atrial fibrillation or atrial flutter has a very low rate of long-term complications. During the period January 1, 2000 until September 2007, 1233 such patients made 1820 visits to the emergency departments at St. Paul's and Mt. St. Joseph's hospitals. Of these, 400 underwent electrical cardioversion. Most (72%) needed only one shock to revert to normal sinus rhythm (NSR) and 68% needed only 100 joule energy or less to convert. A formal chart review was done for 141 of the 400 patients yielding the following patient characteristics:

- Average age – 57 years
- Male sex – 75%
- Lone atrial fibrillation – 74%
- Admitted with atrial fibrillation – 87%
- Admitted with atrial flutter – 13%
- Average heart rate at admission – 122 bpm
- Average blood pressure at admission – 127/80
- Percent having a $CHADS_2$ score of 0 – 61%
- Percent having a $CHADS_2$ score of 1 – 37%

Most patients (94%) were cardioverted within 24 hours of the onset of their symptomatic episode with only 3.5% failing to regain NSR. The length of stay in the emergency department ranged from 1.4 to 22.8 hours with a median time of 4 hours. All 400 patients were followed for 30 days after their cardioversion. During this time no patients died, experienced a stroke, or had a thromboembolic event. Only 22 patients (5.5%) made a follow-up visit to an emergency department and of these, six (1.5%) required a repeat cardioversion.

The emergency physicians conclude that electrical cardioversion is safe for up to 30 days for both atrial fibrillation and atrial flutter. However, they do point out that the patient population involved in the study were relatively young, had mostly lone AF, had a low risk of stroke (low $CHADS_2$ score), and had been in AF or flutter for only a short time. Thus their findings may not apply to sicker patients.

Scheuermeyer, FX, et al. Thirty-day outcomes of emergency department patients undergoing electrical cardioversion for atrial fibrillation or flutter. **Academic Emergency Medicine**, *Vol. 17, April 2010, pp. 408-15*

Editor's comment: The majority (94%) of patients involved in the study had been in afib or atrial flutter for less than 24 hours. Thus it is difficult to extrapolate the results to the cardioversion of persistent afibbers who often have been in afib for 7 days or more. It is interesting that a recent study concluded that electrical cardioversion was most effective if carried out between 24 and 36 hours following the onset of an afib episode.

Dronedarone (Multaq) – Is it all hype?

LOS ANGELES, CALIFORNIA. Amiodarone (Cordarone) is the most effective antiarrhythmic drug on the market today, although a recent trial found that its efficacy in keeping atrial fibrillation patients afib-free for a year is only 34%. Apart from questionable efficacy, amiodarone also has a long list of potentially very serious side effects including thyrotoxicosis, hypothyroidism, pulmonary toxicity (fatal in 10% of cases), liver toxicity, optic

neuropathy (including loss of vision), and blurred vision.

The amiodarone molecule contains 37.5% by weight of iodine and it is widely believed that it is the iodine that causes most of the adverse effects of the drug. Thus, it is not surprising that much research has been devoted to finding a drug similar to amiodarone (a benzofuran derivative), but without the iodine component. This recently resulted in the development of dronedarone (Multaq). Dronedarone has undergone several large-scale clinical trials, which, with the exception of one (ANDROMEDA) involving patients with severe congestive heart failure, have found it to be safe and with no significant adverse effects after one year of use. However, an increase in serum creatinine level (an indicator of possible kidney toxicity) has been observed in some trials, as have gastrointestinal problems like diarrhea, nausea and vomiting.

Two large-scale clinical trials (EURIDIS and ADONIS) evaluated the effect of 400 mg of dronedarone twice a day in 1237 AF patients. At the end of the trial (12 months from the start), 24.8% of the placebo group were still in normal sinus rhythm as compared to 35.9% in the dronedarone group.

A more recent trial (ATHENA) involved 4628 patients with paroxysmal or persistent AF or flutter and, in most cases, hypertension (85%), structural heart disease (60%), or coronary artery disease (31%). The trial participants were randomized to receive 400 mg of dronedarone twice a day or a placebo and were then followed for an average of 21 months resulting in approximately 4000 patient-years of observation. The purpose of the trial was to investigate whether dronedarone therapy would significantly reduce all-cause mortality and rehospitalization for cardiovascular causes. In other words, the "endpoint" chosen was primarily of interest to the health care system rather than to the patient who would be more interested in knowing whether the drug would reduce the recurrence of AF or flutter, or the overall burden (number of episodes times their duration). The overall mortality in the placebo group was 3.0% vs. 2.5% in the dronedarone group – a non-statistically significant and not terribly impressive relative reduction of 17%. Cardiovascular-related hospitalizations were 19% in the placebo group vs. 15% in the dronedarone group – again, a fairly modest relative reduction of 21%.

A group of cardiologists from the Cedar-Sinai Medical Center and the University of California has now taken a critical look at the trials underlying the FDA approval of dronedarone for the prevention of cardiovascular hospitalization related to AF or flutter. Among their most pertinent comments are:

- The antiarrhythmic effects of dronedarone are quite modest compared with placebo and only half as effective compared with amiodarone.

- The ANDROMEDA trial showed that dronedarone worsened heart failure and the drug now carries a black box warning regarding its use in heart failure patients.

- Reasons for hospital admissions in the ATHENA trial were not clearly delineated and it is not at all clear that hospitalizations for AF or flutter recurrence were a major contributor.

- The DIONYSOS study, which compared dronedarone (400 mg twice/day) with amiodarone (200 mg/day), found that 42% of patients in the amiodarone group experienced AF recurrence over a 6-month period as compared to 63% in the dronedarone group. However, dronedarone was associated with a reduced risk of thyroid problems, sleep disorders, and tremors, but the risk of adverse gastrointestinal events increased.

The authors conclude that the available data support only limited use of dronedarone for select patient populations, mostly as a second- or third-line agent in lieu of amiodarone. For lone afibbers the preferred antiarrhythmics would be flecainide, propafenone and sotalol as recommended in the current guidelines for the management of AF. They caution against indiscriminate use of dronedarone.
Singh, D, et al. Dronedarone for atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 55, No. 15, April 13, 2010, pp. 1569-76*

Editor's comment: Not surprisingly, the publication of the above article with its criticism of the ATHENA trial and the suggestion that dronedarone may be more hype than substance caused a considerable stir within the cardiology community. Dr. Sanjay Kaul, the lead author of the article, defended his position and clarified it with comments such as:[1]

- *"Limitations in the design and execution of the ATHENA trial raise questions about the quality of its data and cast doubts on their relevance to clinical practice."*

- *"I am not convinced that dronedarone offers us a safer alternative."*
- *"In my mind, the patient population that was selected in the ATHENA trial does not represent what we see in clinical practice."*

Dr. George Wyse of the University of Calgary is also sceptical of the ATHENA results. Says he, "*To me that argues strongly against the favourable impact of dronedarone having anything to do with preventing atrial fibrillation.*"[1]

The investigators involved in the ATHENA trial all come out strongly in favor of dronedarone. However, their enthusiasm should perhaps be tempered by the fact that most, if not all, of them had financial ties to the maker of dronedarone, Sanofi-Aventis and numerous other pharmaceutical companies. Finally, it is doubtful that dronedarone therapy is cost-effective. At a cost of $9 per day per patient, keeping 2314 patients on dronedarone for 21 months would cost $13,303,000. Doing so would avoid 184 hospital admissions. In other words, the cost of avoiding one hospital admission through the use of dronedarone would be $72,300 – hardly a bargain!

[1] http://www.theheart.org/article/1065123/print.do

HIFU ablation found unsafe

HAMBURG, GERMANY. High intensity focused ultrasound (HIFU) is used successfully in the treatment of prostate cancer. Early trials also found it effective in the ablation of atrial fibrillation. The procedure is similar to that used in a standard pulmonary vein isolation (PVI) using radiofrequency energy except that the lesion-creating catheter is in the form of an inflatable balloon equipped with a 9 MHz ultrasound crystal which, when turned on, generates the heat necessary to create a complete lesion ring in less than a minute. Thus, the HIFU technique has the advantage of short procedure time and minimal radiation exposure (mean fluoroscopy time of about 30 minutes). Unfortunately, the HIFU procedure is also associated with the potential for serious adverse events such as phrenic nerve injury and the creation of esophageal ulcers or an, mostly fatal, atrioesophageal fistula (a hole between the heart and the esophagus).

Electrophysiologists at the Asklepios Klink St. Georg recently completed a trial to see if implementing a stringent safety protocol when performing HIFU ablations would reduce the number and severity of adverse events. Their trial involved 28 patients with paroxysmal (19) or persistent (9) atrial fibrillation of 6 years standing. The average age of the patients was 63 years and 18 (64%) were male. A temperature probe was inserted in the esophagus prior to the start of ablation which used a 20, 25 or 30 mm diameter sonication ring at an acoustic power setting of 45 watt. The effectiveness of the HIFU application in achieving electrical isolation of the pulmonary veins was measured with a Lasso catheter inserted in the ablated vein. A safety algorithm was used to ensure that tissue temperatures, especially esophageal temperature, did not exceed certain specified limits.

Complete acute isolation of all pulmonary veins was achieved in 9 patients (32%) using HIFU only with the addition of radiofrequency ablation bringing the total number of patients having all veins isolated to 16 or 57%. Eleven of 13 HIFU ablations (85%) were aborted prematurely because of dislodgement of the catheter or because of excessive esophageal temperatures. Adverse effects were significant with 21% experiencing transient or persistent phrenic nerve palsy (corresponding incidence for radiofrequency ablation is less than 0.1%). Esophageal ulcers were observed in two (8%) of patients undergoing post-procedure endoscopy, one patient died due to an atrioesophageal fistula, and one died of unexplained causes 49 days following the procedure. The authors conclude that, "*application of HIFU energy for PVI in humans cannot be advised at this point in time.*"

Neven, K, et al. Fatal end of a safety algorithm for pulmonary vein isolation with use of high-intensity focused ultrasound. **Circulation: Arrhythmia and Electrophysiology**, *Vol. 3, June 2010, pp. 260-65*

Editor's comment: If you are ever offered a PVI procedure involving HIFU, please say NO THANKS.

Predicting risk of cardioembolic stroke

ROCHESTER, MINNESOTA. About 50% of strokes occurring in atrial fibrillation (AF) patients are cardioembolic in nature and usually related to thrombus (blood clot) formation in the left atrial appendage (LAA). Such strokes are best prevented by anticoagulation with warfarin. NOTE: In my personal opinion, nattokinase would likely be an even better choice for preventing cardioembolic strokes. The other 50% of strokes are either thrombotic (most often involving rupture of atherosclerotic plaque) or hemorrhagic in nature. The optimum way of preventing thrombotic stroke is through the use of antiplatelet agents such as aspirin or clopidogrel. Thus, it is important to know if a patient is at increased risk of cardioembolic stroke and thus may need warfarin, or has no increased risk in which antiplatelet therapy may be a better choice.

The presence of thrombi in the LAA can be established with reasonable accuracy by doing a transesophageal echocardiography (TEE) in which the ultrasound probe is placed in the esophagus rather than on the chest as is the case in standard transthoracic echocardiography. TEE will show the presence of existing thrombi and will also detect spontaneous echocardiographic contrast (SEC) – a pattern of "smoke-like", slow-swirling, echodensities in the LAA or left atrium. SEC is believed to be the genesis of thrombi.

Electrophysiologists at the Mayo Clinic recently reported a study aimed at developing a scoring system which would predict the likelihood of finding thrombi in the LAA. Their study involved 110 patients with nonvalvular AF (not on warfarin) in whom thrombi had been detected in the LAA (cases) and 387 patients with nonvalvular AF (not on warfarin) in whom no thrombi had been detected during TEE (controls). Statistically significant differences between the two groups included the following:

	Cases	Controls
Permanent AF	43%	11%
AF duration >1 year	55%	11%
Congestive heart failure	64%	21%
Diabetes	31%	16%
Prior TIA/stroke	39%	13%
Presence of SEC	92%	41%
Left ventricular ejection fraction	44%	53%

The average $CHADS_2$ score (a commonly used indicator of stroke risk) was also significantly higher among cases (mean = 2.8) than among controls (mean = 1.6). The incidence of LAA thrombi was not related to age, gender or the presence of hypertension. Thus, while age above 75 years is considered a risk factor in the $CHADS_2$ score, there was no indication that advanced age is associated with an increased risk of LAA thrombi. Based on their findings, the Mayo researchers propose a new algorithm for predicting the presence of LAA thrombi and commensurate risk of cardioembolic stroke or TIA.

A prior stroke or TIA, permanent AF, diabetes, and AF duration longer than 48 hours would each be allocated 1 point, while the presence of SEC, congestive heart failure, and AF duration longer than one year would be allocated 2 points each. Therefore, LAA thrombi risk would be graded from 0 to 10 by this new system which has yet to receive a catchy acronym. A separate analysis showed the presence of SEC and congestive heart failure to be, by far, the most predictive of LAA thrombi (odds ratios of 9.68 and 5.12 respectively). The Mayo researchers point out that prior research has shown that if TEE detects no thrombi in the LAA the risk of a cardioembolic stroke is pretty close to zero.

Wysokinski, WE, et al. Predicting left atrial thrombi in atrial fibrillation. **American Heart Journal,** *Vol. 159, April 2010, pp. 665-71*

SUPPLEMENT NEWS

Vitamin K in cancer prevention

HEIDELBERG, GERMANY. There is abundant evidence that vitamin K is a crucial factor in the maintenance of bone mass and the prevention of arterial calcification. Natural vitamin K comes in two forms – vitamin K1 (phylloquinone) and vitamin K2 (menaquinone). Vitamin K1 is found in green leafy vegetables whereas the main source of vitamin K2 is meat and dairy products, especially cheese. A team of researchers from the German Cancer Research Center and the Harvard School of Public Health now report that vitamin K2 is also effective in preventing certain cancers. Their study included 11,438 men and 19,902 women aged 35 to 64 years at enrolment (1994-1998) who were free of cancer. The participants completed detailed food-frequency questionnaires at baseline and were then followed for 10 years. At the end of the follow-up, 1755 participants had developed cancer and 458 had died from the disease. The three most common cancers among men were prostate cancer (2.9%), colorectal cancer (1.0%), and lung cancer (0.8%), while among women breast cancer (2.8%), colorectal cancer (0.5%), and melanoma (0.4%) were the most common. The percentages of men who died from prostate, colorectal and lung cancer during the follow-up period were 4.6%, 27%, and 72% respectively. Corresponding numbers for women were 7.5%, 32%, and 0% for breast cancer, colorectal cancer, and melanoma. The dietary intake of phylloquinones (vitamin K1) did not affect cancer incidence or mortality. However, a high intake (greater than 46 micrograms/day) of menaquinones (vitamin K2) was associated with a significantly lower incidence of prostate cancer and lung cancer among men. After adjusting for possible confounding factors, the researchers observed that men who consumed 46 micrograms/day or more of menaquinones had a 35% lower risk of developing prostate cancer than did those who consumed less than 26 micrograms/day. A high intake of menaquinone was also associated with a 62% lower risk of developing lung cancer. The major source of menaquinones was cheese with an intake of 40 grams/day or more being highly protective. Among participants who did develop cancer, a high vitamin K2 intake was associated with a 28% reduced risk of dying from cancer. There was no statistically significant association between vitamin K intake and overall cancer incidence and mortality among women; this is explained by the finding that vitamin K intake did not affect the incidence of breast cancer, the most common cancer among women.

Nimptsch, K, et al. Dietary vitamin K intake in relation to cancer incidence and mortality. American Journal of Clinical Nutrition, Vol. 91, May 2010, pp. 1348-58

Supplements are safe

SEATTLE, WASHINGTON. A team of researchers from the University of Washington and the Fred Hutchinson Cancer Research Center has concluded an investigation of the safety of 20 supplements – vitamin A, beta-carotene, vitamin D, thiamine, niacin, vitamin B6, vitamin B12, folic acid, iron, magnesium, zinc, selenium, chromium, fiber, glucosamine, chondroitin, saw palmetto, Gingko biloba, garlic, and fish oil. Their study involved 77,000 men and women aged 50 to 76 years who lived in western Washington State when enrolled during the period October 2000 until December 2002. The participants were queried about their supplement use during the 10-year period preceding enrolment and were classified as non-users, low users or high users depending on the frequency and duration of their supplement use. During the follow-up through December 31, 2006 a total of 3,577 participants died. After adjustment for age and sex, the following supplements were associated with a statistically significant lower mortality:

Vitamin A (retinol)
Beta-carotene
Thiamine
Niacin
Vitamin B6
Vitamin B12
Folic acid
Magnesium
Zinc
Selenium
Ginkgo biloba

However, after further adjustment for a long list of potential confounders (education, smoking, physical activity, self-rated health, and a calculated morbidity score) the associations were no longer statistically significant except in the case of glucosamine and chondroitin where high users had a significantly lower mortality than did non-users. There was also a trend for a high fish oil intake to be associated with a 17% reduced risk of death. Previous studies have noted that the use of glucosamine and chondroitin is associated with a reduced risk of lung and colorectal cancer and that chondroitin may slow down the progression of heart disease.

Pocobelli, G, et al. Total mortality risk in relation to use of less-common dietary supplements. American Journal of Clinical Nutrition, Vol. 91, June 2010, pp. 1791-1800

Lycopene and prostate cancer

CLERMONT-FERRAND, FRANCE. There is substantial evidence that processed tomato products (tomato paste and sauce) protects against the development of prostate cancer. It is widely believed that the active factor is lycopene, the component responsible for the red color of tomatoes. Lycopene is a potent antioxidant which accumulates in the prostate where it could protect DNA from oxidative damage, the starting point for cancer development. French researchers now report on a clinical trial aimed at determining if Lycopene on its own (in supplement form) has the same beneficial effects as processed tomato products. The trial involved 30 healthy men aged 50 to 70 years who were randomly assigned to receive a red tomato paste providing 16 mg/day of lycopene, a yellow tomato paste containing no lycopene, or a pure lycopene supplement providing 16 mg/day of lycopene. After a 2-week consumption the blood serum concentration of lycopene was 0.78 micromol/microgram of plasma triglycerides in the red tomato group, 0.31 in the yellow tomato group, and 0.87 in the lycopene supplement group. Thus this part of the trial showed that lycopene from a supplement is absorbed equally well as that from tomato paste. There was no difference in PSA and IGF-1 levels following supplementation or consumption of tomato paste.

The second part of the trial involved incubating LNCaP prostate cancer cells with blood serum obtained after 2 weeks of lycopene supplementation or tomato paste consumption. A total of 45 genes involved in prostate cancer were then checked to see if they were significantly up- or down-regulated compared to placebo. The activity of 7 genes had changed markedly:

- *Cyclin-D1* – a cell cycle regulator
- *p53* – a gene associated with stress response
- *Nrf-2* – a gene associated with stress response
- *Bax:Bcl-2* ratio – an indicator of degree of apoptosis
- *IGFBP-3* – the main binding protein for IGF-1 in plasma. Regulates cell growth, proliferation and apoptosis in an IGF-1-independent manner
- *c-Fos* – increases metastatic potential
- *uPAR* – increases matrix degradation by inducing the activity of metalloproteinases involved in metastasis.

In prostate cancer cells incubated with sera from men having consumed red tomato paste, cyclin-D1, p53 and Nrf-2 were down-regulated (activity decreased), while the Bax:Bcl-2 ratio and IGFBP-3 activity were up-regulated. These changes are all beneficial and may wholly or partly explain the beneficial effects of processed tomato products on prostate cancer development and progression. In prostate cancer cells incubated with sera from men having taken the lycopene supplement, IGFBP-3, c-Fos, and uPAR were all up-regulated. While the up-regulation of IGFBP-3 is beneficial, the increased activity of c-Fos and uPAR is anything but. The French researchers conclude that pure lycopene should be used with caution in the case of aggressive prostate cancers. Up-regulation of the Bax:Bcl-2 ratio was also observed in the case of yellow tomato paste indicating that the beneficial effects of tomato products is unlikely to be solely due to lycopene.

Editor's comment: This clinical trial confirms that the consumption of processed tomato products induces favorable changes in genes associated with prostate cancer. It also confirms that pure lycopene up-regulates IGFBP-3 and thus may help prevent prostate cancer; however, it should be used with caution if at all in cases of established prostate cancer. Processed tomato products are likely to be beneficial for both prevention and slowing progression of prostate cancer.

Talvas, J, et al. Differential effects of lycopene consumed in tomato paste and lycopene in the form of a purified extract on target genes of cancer prostatic cells. American Journal of Clinical Nutrition, Vol. 91, June 2010, pp. 1761-1724

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Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@afibbers.org World Wide Web: http://www.afibbers.org