Lone Atrial Fibrillation

Toward a Cure – Volume VI

By

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PUBLISHED BY:

INTERNATIONAL HEALTH NEWS

www.yourhealthbase.com

Lone Atrial Fibrillation: Toward a Cure – Volume VI
published by: International Health News
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First Printing – March 2009

ISBN 978-0-9809242-0-6

Printed and bound in Canada

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Introduction

Since the publication of *Lone Atrial Fibrillation: Towards a Cure* in December 2002 research into atrial fibrillation has grown exponentially. This emphasis on AF research is not coincidental. Recent studies conclude that more than 5.5 million Americans and Europeans now suffer from atrial fibrillation and that the incidence of the disorder increased by 300% between 1986 and 1996. Another study reached the sobering conclusion that one out of every four men and women over the age of 55 years will develop atrial fibrillation during their lifetime. It is estimated that about 20% of all AF patients have lone atrial fibrillation, that is, atrial fibrillation without any underlying heart disease. Truly an epidemic of enormous proportions!

Over the past year **The AFIB Report** has kept subscribers informed of new developments in atrial fibrillation research as reported in the leading journals such as *Journal of Cardiovascular Electrophysiology, Pacing and Clinical Electrophysiology, Circulation*, etc. The subjects covered in our journal summaries range from details of the latest ablation procedures, their outcome and potential complications, to the safety and efficacy of antiarrhythmic drugs. The latest insights into the mechanism of atrial fibrillation as well as important information about stroke risk and prevention are also covered. In addition, *The AFIB Report* has, in detail, covered the results of our most recent LAF survey dealing with the effectiveness of ablation and surgical procedures for eliminating LAF. Numerous afibbers have found ways of controlling their afib through means other than ablation and surgery and have shared their experiences in the section on Elimination/Reduction Protocols.

Truly, the 2008 issues of *The AFIB Report* are a treasure trove of immensely valuable information. Unfortunately the vast volume of data contained in the newsletter makes it very difficult to quickly and conveniently locate a particular piece of information. My new book ***Lone Atrial Fibrillation: Toward a Cure – Volume VI***, hopefully, solves this problem. Its 216 pages contain all the information published in the 2008 issues arranged in logical sections. The comprehensive subject index makes it easy to find the elusive, but important information you know is there – somewhere! In addition, the wealth of important new LAF information contained in *Lone Atrial Fibrillation: Toward a Cure – Volume VI* makes it an ideal and essential companion to *Lone Atrial Fibrillation: Towards a Cure* and *Lone Atrial Fibrillation: Toward A Cure – Volumes II, III, IV, and V*.

This book would not have been possible without the whole-hearted support of my wife Judi who was instrumental in seeing it come to fruition. Without her word processing skills, editing advice, and encouragement I couldn't have accomplished it.

My gratitude also to the many afibbers who participated in the 2008 ablation/maze survey and other previous surveys – thereby helping fellow afibbers find a way to manage their condition. Finally, a huge thank you to the many enthusiastic and caring contributors to the Bulletin Board, and to the subscribers to *The AFIB Report* without whose support my research would not have been possible.

Hans R. Larsen
Victoria, BC, Canada
March 2009

Journal Summaries

Incidence & Management

Is there an age limit for PVI ablation?

PALO ALTO, CALIFORNIA. The prevalence of atrial fibrillation among individuals 75 years or older is about 15%. Clearly it is important to answer the question, "Is PVI ablation safe and effective for this age group?" A team of electrophysiologists from the Cleveland Clinic, Marin General Hospital, and the Umberto I Hospital in Italy have pooled their outcome results for a total of 174 patients over 75 years of age who underwent pulmonary vein antrum isolation and isolation of the superior vena cava guided by mapping of electrically active areas and intracardiac echocardiography.

The patients were followed for an average of 20 months by serial event recorder transmissions. The immediate complete success rate (no afib, no antiarrhythmics) was 73%. An additional 16 patients (out of 20) were afib-free after a second procedure (repeat rate of 16%) bringing total success rate to 82%. An additional 18 patients maintained sinus rhythm with the use of previously ineffective antiarrhythmics resulting in a partial success rate of 10%. During the 194 procedures, 1 patient suffered a stroke, 3 experienced groin hematomas, and 1 suffered a hemothorax secondary to right internal jugular vein catheterization. No tamponade, atrial-esophageal fistula, or pulmonary vein stenosis were reported.

During the first 3 months, 3 patients experienced a thromboembolic event despite being on warfarin. However, in 2 cases their INR was below 2.0. In the third case, the patients had the stroke 2 days after undergoing cardioversion and it is suggested that the atrial thrombus (blood clot) was secondary to the atrial stunning that follows direct current cardioversion.

The researchers point out that their common strategy is to discontinue warfarin after 3 months in all patients whose left atrial mechanical function is normal provided they have not experienced recurrence of AF. This would seem to be safe and appropriate since no thromboembolic events were observed over a 16-month period in the group that discontinued warfarin. The conclusion drawn from the study is that, "*PVI appears to be a safe and effective treatment strategy for the eradication of AF in septuagenarians. Medium- to long-term success can be achieved in most patients, and the overall rate of complications is low.*"

Corrado, A, et al. Efficacy, safety, and outcome of atrial fibrillation ablation in septuagenarians. **Journal of Cardiovascular Electrophysiology,** *Vol. 19, August 2008, pp. 807-11*

Hurwitz, JL. Atrial fibrillation treatment in the elderly. **Journal of Cardiovascular Electrophysiology**, *Vol. 19, August 2008, pp. 812-14 (editorial comment)*

Editor's comment: The finding that pulmonary vein ablation is safe and effective even for patients over the age of 75 years is certainly welcome news. Although the participants in the study did not have lone afib (68% had structural heart disease and 24% coronary artery disease) and 65% had a CHADS score of 2 or higher, there is no reason to believe that the researchers' conclusion would not be applicable to lone afibbers who could perhaps expect an even better outcome.

Eight million Chinese join the ranks with AF

BEIJING, CHINA. It is estimated that 2.5 million people in the USA and 4.3 million individuals in the EU suffer from atrial fibrillation (AF). Up until now, it has not been clear whether AF is a disease related to Western civilization and lifestyle, or whether it is a worldwide phenomenon. Chinese researchers now provide a partial answer. A large-scale epidemiological study involving more than 29,000 individuals from 13 provinces and 14 ethnic groups in China found an age-adjusted AF rate of 0.61%, suggesting that approximately 8 million adults in China have AF. This prevalence is very similar to that observed in the USA and Europe, thus pretty well laying to rest the idea that AF is somehow related to Western lifestyle and diet.

The Chinese researchers confirmed that the risk of AF increases with age and is more prevalent among men. The percentages of nonvalvular AF, valvular AF, and lone AF were 65%, 13%, and 22% respectively. Hypertension and heart failure were the most common underlying comorbidities in hospitalized AF patients – the majority (76%) of whom had nonvalvular AF with the remaining 24% having valvular AF. Thus, it would appear that lone afibbers are not hospitalized in China.

The incidence of ischemic stroke was high among non-hospitalized individuals with AF at a rate of 12.1% a year vs. 2.1% a year in the general population. Among hospitalized patients with nonvalvular AF, the rate was even higher and dramatically dependent on age. Thus, the average incidence was 4.3% in patients younger than 40 years, but almost 33% in those 80 years of age or older. The main risk factors for stroke in hospitalized patients were found to be hypertension, high systolic blood pressure, diabetes, left atrial thrombi, and age at or above 75 years.

The epidemiological study found that only 2.7% of AF patients were on warfarin and none had their INR monitored on a regular basis. A study involving 828 patients with nonvalvular AF found that warfarin therapy

was twice as effective as aspirin therapy (150 – 160 mg/day) in preventing ischemic stroke.
Hu, D and Sun, Y. Epidemiology, risk factors for stroke, and management of atrial fibrillation in China. **Journal of the American College of Cardiology**, *Vol. 52, No. 10, September 2, 2008, pp. 865-68*

Gender distribution in lone atrial fibrillation

ROCHESTER, MINNESOTA. Our LAF surveys have consistently found a greater proportion of men (75-80%) than women among respondents. An early survey (August 2002) also suggested the possibility that lone atrial fibrillation may be an inherited disorder in many cases. The survey found that 43 of 100 respondents (43%) had at least one close relative with cardiac arrhythmia. The most common carrier was the mother who accounted for 30% of the relatives, siblings 26%, and fathers 23%. Permanent afibbers reported the mother to be the carrier in 71% of cases. Researchers at the Mayo Clinic now confirm that LAF is indeed more common among men and that there is a definite familial connection.

Their study included 192 unrelated lone afibbers who were divided into 3 groups. Group 1 consisted of 114 afibbers who had no relatives with atrial fibrillation (sporadic LAF), group 2 consisted of 44 afibbers who had 1 first- or second-degree relative with LAF (possibly familial LAF), and group 3 consisted of 34 afibbers who had 2 or more relatives with LAF (confirmed familial LAF). Thus, out of the total study population of 192 lone afibbers, 41% had a least one relative with LAF.

The proportion of men in groups 1, 2, and 3 were 82%, 84%, and 62% respectively. Sporadic LAF was more common among men (62%) than among women (51%). It was also clear that those with familial LAF (group 3) were more likely to have permanent afib (27%) than were those of groups 1 and 2 (8.2% and 6.8% respectively). As far as gender differences are concerned, the researchers observed that women afibbers were more likely to report palpitations and being awakened by palpitations at night than were men. Women were also more likely to have paroxysmal LAF (76% vs. 64% for men) and less likely to have persistent afib (11% vs. 25% for men).
The researchers conclude that the greater incidence of sporadic LAF among men would be partially due to x-linked recessive inheritance in which women, including the mother, may be asymptomatic carriers. They also conclude that sporadic and familial LAF are clinically indistinguishable.
Chen, LY, et al. Lone atrial fibrillation: influence of familial disease on gender predilection. **Journal of Cardiovascular Electrophysiology**, *Vol. 19, August 2008, pp. 802-06*

Editor's comment: The Mayo Clinic study found that 41% of the 192 study participants had at least one first- or second-degree relative with LAF. This percentage is almost identical to the 43% observed in our August 2002 LAF survey. The male to female ratio of 79:21 found in the Mayo Clinic study is also very close to the 78:22 ratio found in our 2007ablation/maze survey. Comparing the above numbers gives a feeling of comfort that the findings reported in our surveys do indeed reflect the "real world".

Mechanistic Insights

Metabolism in atrial fibrillation

LONDON/CAMBRIDGE, UNITED KINGDOM. While much research has been done to analyze and describe the mechanism of the disorganized electrical activity underlying atrial fibrillation, the possibility of a dysfunctional metabolism playing a major role seems to have been overlooked. This may now change with some exciting new discoveries made by a group of researchers from the University of Cambridge and King's College, London. The researchers used two very powerful techniques (proteomics and metabolomics) to determine the impact of cardiac metabolism on the initiation and persistence of atrial fibrillation. Their very recent paper (February 2008) is highly technical and to understand their findings it is necessary to bone up on a few definitions.

Metabolism is the set of chemical reactions that occur in living organisms in order to maintain life. These reactions are catalyzed and regulated by enzymes and can be divided into two major categories: - *catabolism* which involves the breakdown of large molecules and produces energy, and *anabolism* which uses energy to produce component of cells such as proteins and nucleic acids.

Glycolysis is the initial process in the breakdown (catabolism) of larger carbohydrate molecules into smaller units. It results in the production of pyrovate for the citric acid cycle (Krebs cycle, TCA cycle) of energy production and ATP (adenosine 5'-triphosphate), the body's main energy transporter.

Ketone bodies (acetoacetate, acetone, and beta-hydroxybutyrate) are produced when fatty acids are broken down in the liver and kidney to produce energy for use in the heart and brain.

Proteomics is the study of the function and structure of proteins. It uses highly sophisticated methods such as gel electrophoresis and mass spectrometry to separate and analyze the proteins and their structure.

Metabolomics is the study and identification of small-molecule metabolites generated by specific cellular processes (such as atrial fibrillation).

The British researchers compared metabolic variables in three groups of patients.

- Group SR – Patients in normal sinus rhythm prior to undergoing valve (nonrheumatic) surgery
- Group AF – Patients in permanent afib prior to undergoing valve surgery.
- Group SR-AF – Patients who developed afib after coronary artery bypass surgery.

The researchers extracted cardiac issue from all three groups during surgery and then looked for differences in protein and enzyme expression using proteomics and metabolomics. When comparing group SR with group AF they noted that heart tissue from group AF had higher levels of beta-hydroxybutyrate (a ketone body) and the ketogenic amino acids tyrosine and leucine. Group AF also had a significantly higher level of glycine and a higher fumarate/succinate ratio. Structural damage inflicted by prolonged AF was also evident as was depletion of the antioxidant protein peroxiredoxin 1 and a reduced level of ANP (atrial natriuretic peptide) precursor.

Looking at heart tissue from patients who developed afib after bypass surgery, the researchers observed that these patients had significantly reduced levels of glucose, beta-hydroxybutyrate, and acetate (a ketone body). They also noted that those who developed AF after surgery (bypass or valve) had a reduced glucose/acetate ratio and that their ratio of glycolytic end products (alanine, lactate) to lipoid metabolism end products (acetate) correlated positively with time of onset of post-operative AF (the lower the ratio, the earlier the onset of AF).
There is evidence that AF is associated with a high-energy demand and that this may explain many of the permanent changes in the atria resulting from permanent AF. There is also evidence that ketone bodies may be a main source of this energy during permanent AF.

The researchers conclude that ketone bodies play an important role in atrial fibrillation and that a discordant regulation of energy metabolites precedes the onset of AF after surgery.
Mayr, M, et al. Combined metabolomic and proteomic analysis of human atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 51, No. 5, February 5, 2008, pp. 585-94*

Editor's comment: While these findings are most interesting and exciting, it is not at all clear how to interpret and take advantage of them. Most important, there is obviously no evidence that they apply to lone afibbers since all participants had underlying heart disease. The finding that bypass surgery patients who go into afib after their surgery are very low in ketone bodies (fatty acid breakdown products) during surgery ties in with recent findings that giving these patients fish oil supplements prior to the operation markedly reduce the risk of afib development.

The observation that valve surgery patients in permanent afib had a higher level of ketone bodies (during surgery) than did those in normal sinus rhythm support the hypothesis that the heart's energy demand is substantially increased during permanent afib and that much of this demand is met by burning fatty acids rather than glucose. This intriguing and most welcome research raises many important questions, but most of all, is hopefully the beginning of a trend to look for the causes of atrial fibrillation.

Progression of paroxysmal AF

FLORENCE, ITALY. Paroxysmal (intermittent, self-terminating) atrial fibrillation may over time progress to persistent or permanent afib (episodes lasting 7 days or longer). It is not clear why some paroxysmal afibbers progress to the persistent variety, while other remain paroxysmal for decades. A group of American and Italian researchers now provide at least a partial answer to this question.

Their study involved 330 patients with a history of paroxysmal AF (mean age of 70 years, 61% male) who had had a pacemaker implanted to deal with bradycardia (slow heart beat). Most study participants had underlying heart disease, but 21% were lone afibbers. The pacemaker (Medtronic AT501) automatically recorded the daily burden (duration) of afib and tachycardia for an average of 400 days. After a mean interval of 147 days, 24% of the patients progressed to persistent afib. The researchers made the following interesting observations.

- The prevalence of lone atrial fibrillation (LAF) did not differ between the group that remained in paroxysmal afib and the one that progressed to persistent afib.

- Patients with congestive heart failure were significantly more likely to progress to persistent AF.

- Patients destined to progress to persistent AF experienced a higher daily afib burden and a higher probability of experiencing afib on any given day than those in the paroxysmal group.

- The mean daily afib burden in the group destined for progression to persistent AF increased by about 14 seconds/day, while it stayed relatively constant in the group that remained paroxysmal.

- Lone afibbers experienced significantly more PACs (premature atrial beats, ectopics) than did patients with CVD.

However, the incidence of these ectopics decreased over time.

- The conversion to persistent afib occurred suddenly and was often preceded by a period of normal sinus rhythm.

- It is possible that treatment with ACE inhibitors or angiotensin receptor blockers (ARBs) may slow down the remodeling that underlies progression to persistent AF.

The researchers conclude that, "Our results suggest that functional electrical remodeling may not impact all patients or inevitably lead to increasing AT/AF burden and persistent AF. In fact, a large proportion of patients may not increase their AT/AF burden, particularly in the absence of CVD."

Saksena, S, et al. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. American Heart Journal, *Vol. 154, November 2007, pp. 884-92*

Editor's comment: This study indicates that a steady progression of afib burden (longer and more frequent episodes) may lead to persistent afib. Thus, if such a trend is noted, it may be worth trying an ACE inhibitor or an ARB.

Is lone AF recurrence inevitable?

BARCELONA, SPAIN. Lone atrial fibrillation (LAF) is defined as AF occurring in the absence of structural heart disease. Idiopathic AF is defined as lone AF of no known cause; ie. thyroid disorders, hemochromatosis, alcoholism, and electrolyte disturbances have been ruled out. Although LAF patients, in most cases idiopathic, constitute between 10 and 30% of all afib patients, comparatively few studies have been done dealing specifically with this condition. A recently released study by researchers at the University of Barcelona is, hopefully, a harbinger of a trend to focus greater efforts on determining the causes and likely progression of LAF.

The study involved 98 patients (71% men with an average age of 48 years) who were admitted to the University hospital's emergency room with AF of no known cause (idiopathic). Most (64.3%) had experienced previous episodes, while the remaining 35.7% showed up with their first episode. Half the patients reverted spontaneously to normal sinus rhythm (NSR) or did so after oral flecainide administration (classified as paroxysmal afibbers), while the other half required electrical cardioversion to convert (classified as persistent afibbers). First-occurrence patients were discharged with no medication, while recurrent patients were

discharged on whatever medications they had used prior to the index episode (the episode at which they first were admitted to the ER), or on a class 1C antiarrhythmic (mostly flecainide). Patients for whom class 1C drugs had clearly not worked were recommended to try amiodarone. None of the patients were discharged with a prescription for anticoagulants (warfarin).

During the following 6 months, 57% of the entire patient group experienced at least one subsequent afib episode. Recurrent afib was more common among those with prior episodes before the index episode (65.1%) than among "first-onset" patients (34.9%); this despite the fact that 70% of the "veteran" afibbers were taking antiarrhythmics. As a matter of fact, taking amiodarone or a class 1C antiarrhythmic did not significantly influence the risk of recurrence in this group. The researchers also observed that an enlarged left atrium (dilated anteroposterior LA diameter) was associated with a 30% increased risk of AF recurrence. However, they found no association between recurrence risk and afib type (paroxysmal or persistent).

They conclude that for lone (idiopathic) afibbers who have a recurrent episode and an enlarged left atrium (indexed for body surface area), the probability of another episode is about 90% despite the use of antiarrhythmics. On the other hand, the probability of another episode is only 30% in a patient with normal LA diameter who has just experienced one episode.

Arriagada, G, et al. Predictors of arrhythmia recurrence in patients with lone atrial fibrillation. Europace*, Vol. 10, 2008, pp. 9-14*

Editor's comment: Several findings stand out in this excellent report:

- First-onset patients were not put on medication after their first episode. This is in accordance with the 2001 ACC/AHA/ESC recommendations.
- No patients were prescribed warfarin.
- The use of antiarrhythmics was not effective in preventing further episodes in most cases.

Of particular interest is the finding that first-time afibbers with a non-dilated left atrium have only a 30% chance of experiencing another episode in the 6 months following the first one. My guess is that these patients may well be able to hold off subsequent episodes for a long time through trigger avoidance, supplementation, and dietary and lifestyle changes.

Role of fibrosis in atrial fibrillation

MONTREAL, CANADA. According to the late Professor Philippe Coumel, three conditions must be met in order for atrial fibrillation to occur:

1. The myocardium (heart tissue) must be capable of being triggered into and sustaining an episode. In other words, it must provide an electrophysiological substrate that is suitable for AF initiation and maintenance.
2. The autonomic nervous system must be out of balance.
3. A trigger or precipitating event capable of initiating an episode must be present.

Researchers at the Montreal Heart Institute believe that cardiac fibrosis (formation of scar tissue in response to injury) is an important feature in the development of an "afib friendly" substrate. Tissue fibrosis results from an accumulation of fibrillar collagen deposits which themselves are formed in a repair process aimed at replacing degenerating myocardial tissue. Fibrosis is associated with aging, dilated cardiomyopathy, mitral valve disease, and possibly myocardial ischemia (angina).

However, fibrosis and increased collagen deposition have also been observed in lone afibbers. Fibrosis interferes with the normal progression of the sine wave from the sinoatrial node to the atrioventricular node by impairing the transfer of the impulse from myocyte (heart muscle cell) to myocyte. The researchers point out that the renin-angiotensin-aldosterone system (RAAS) is involved in the formation of myocardial fibrosis and that patients with primary hyperaldosteronism (Conn's syndrome) have a significantly increased incidence of atrial fibrillation. They also point out that locally produced angiotensin II is associated with the formation of collagen deposits and fibrosis.

Mechanical stretch of cardiac muscle fibers induces collagen synthesis and increased angiotensin II production, thus creating structural remodeling that further promotes afib (AF begets AF). The researchers reason that, if the production of collagen deposits and fibrosis could be slowed or even reversed, then it may be possible to eliminate or at least control AF. They suggest that ACE inhibitors (lisinopril, enalapril, ramipril), angiotensin II type 1 receptor blockers (valsartan, irbesartan, losartan), and aldosterone antagonists (spironolactone, eplerenone, canrenone) may be useful in preventing fibrosis and thus denying the atria the electrophysiological substrate necessary for initiating and sustaining an AF episode.

Burstein, B and Nattel, S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 51, No. 8, February 26, 2008, pp. 802-09*

Editor's comment: Although the observation that angiotensin II is involved in cardiac fibrosis is not new, the finding that patients with primary hyperaldosteronism have a substantially increased incidence of atrial fibrillation is certainly of considerable interest. I was eventually (after 14 years of afib) diagnosed with primary hyperaldosteronism (see http://www.afibbers.org/conference/session26.pdf for details), but my attempts to reverse the resulting fibrosis with spironolactone were not successful. Now, after reading the article by Burstein and Nattel, I cannot help wondering if earlier intervention with an ACE inhibitor, angiotensin II receptor blocker, or aldosterone antagonist might have saved me a lot of trouble. Certainly, I would strongly recommend that all new-onset afibbers include an aldosterone:renin ratio test, or even just a renin measurement in their initial evaluation. An abnormally high ratio, or an abnormally low renin level should alert the patient and their physician to the possible presence of primary hyperaldosteronism. If primary hyperaldosteronism is indeed diagnosed, then treatment with an ACE inhibitor, angiotensin II receptor blocker, or aldosterone antagonist may well be worth trying before embarking on stronger measures, especially for newly diagnosed afibbers. NOTE: Primary hyperaldosteronism results in potassium wasting, so supplementation with potassium may also be necessary. However, combining ACE inhibitors, etc. with potassium should only be undertaken in close cooperation with a physician.

Afib begets afib – Or does it?

WARREN, NEW JERSEY. Animal experiments have shown that continued pacing of the heart makes paroxysmal (intermittent, self-converting) atrial fibrillation (AF) progress to persistent (episodes lasting longer than 7 days needing cardioversion) and permanent AF. Hence the expression "afib begets afib". The question is, "Do these findings apply to humans"? After all, patients with paroxysmal AF do not have their heart constantly paced and do spend often long periods in normal sinus rhythm. A group of electrophysiologists at the University of Florence, Italy, the Robert Wood Johnson School of Medicine, and Medtronic Inc. (a major manufacturer of pacemakers and implantable cardioverter/defibrillators) now provides at least a partial answer to this question.

Their study involved 330 patients with a history of paroxysmal AF and bradycardia (mean age of 70 years, 61% male). All suffered from heart failure to varying degrees and had had a pacemaker (Medtronic Model AT501) installed prior to the study. Most patients (79%) experienced some form of cardiovascular disease with 61% having hypertension; thus, the proportion of lone afibbers was insignificant and the results of the study may not apply to lone afibbers. After an average follow-up of one year and 3 months, 24% of the study participants had converted to persistent afib with the median time to conversion being 9 months (103

days). The researchers noted the following important differences between the patients who remained in paroxysmal AF (Group 1) and those who progressed to persistent AF (Group 2).

- Prior to conversion to persistent afib, patients in Group 2 were more likely to experience afib on any given day and had a higher average afib burden (no. of episodes x duration) than did those in Group 1.

- Prior to conversion to persistent afib, there was a significant linear increase in daily afib burden (mean increase of 14 sec/day) in Group 2, but no increase (on average) in Group 1.

- The transition from paroxysmal to persistent afib in Group 2 was quite abrupt and was preceded by a few days of normal sinus rhythm.

- The increase in afib burden over time was substantially higher among patients with cardiovascular disease (average 0.18 min/day) than among those with no cardiovascular disease (CVD) where the burden actually declined slightly over time (average –0.06 min/day). Patients with CVD were also more likely to progress to persistent AF.

- Atrial premature beats (PACs) were more frequent in patients without CVD, but decreased with time in all patients.

The researchers conclude that structural remodeling (substrate modification) is critical to the transition to persistent afib. The changes to the substrate may involve fibrosis, apoptosis (cell death), and altered cellular junction proteins. In an accompanying editorial, electrophysiologists at the Tufts-New England Medical Center suggest that the renin angiotensin aldosterone system (RAAS) may play a significant role in the substrate modification and that ACE inhibitors and/or angiotensin receptor blockers may help slow down the structural remodeling. They also suggest that targeting just the pulmonary veins during an ablation (pulmonary vein isolation) is unlikely to suffice in the case of persistent or permanent AF.

Saksena, S, et al. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. American Heart Journal, *Vol. 154, No. 5, November 2007, pp.884-92*

Homoud, MK and Estes, M. Shedding new light on the pathophysiology of conversion of paroxysmal atrial fibrillation into persistent atrial fibrillation. American Heart Journal, *Vol. 154, No. 5, November 2007, pp.801-04*

Editor's comment: In considering the above findings it should be kept in mind that the study did not involve a significant proportion of lone

afibbers. Nevertheless, the mechanism underlying the progression from paroxysmal to persistent AF (substrate modification) is likely to be similar. If increasing afib burden is indeed a universal sign of progression, then lone afibbers who experience such an increase may wish to consider medication with an ACE inhibitor (lisinopril, enalapril, ramipril) or an angiotensin receptor blocker (losartan, valsartan, irbesartan) in order to slow down structural remodeling. Although there is no published evidence to support this, it is also possible that proteolytic enzymes (Serrapeptase, Wobenzym, nattokinase) may be useful in slowing down, or perhaps even reversing, the fibrosis component of substrate modification and thereby help prevent progression to persistent AF.

Gender differences in arrhythmia

TAMPA, FLORIDA. Surveys of lone afibbers generally find that the ratio of men to women is about 80:20. It is by no means clear why this is indeed the case, but the proportion of afib induced by sustained, vigorous endurance exercise would likely be higher among men. If all cases of atrial fibrillation (AF) are considered, including those involving heart disease, men have a 50% higher risk of developing AF than do women. The overall prevalence of AF is, however, higher among women because they tend to outlive men.

Other significant differences between men and women when it comes to arrhythmias and the heart in general were summarized in a recent study carried out by cardiologists at the University of South Florida. Among the highlights are:

- The average resting heart rate in women is about 3-5 bpm faster than in men. This may be due to an intrinsic difference in the sinus node.

- Women have longer QT (corrected) intervals than men. NOTE: The QT interval is the duration of the activation (contraction) and recovery of the ventricular myocardium. A prolonged QT interval is associated with ventricular arrhythmias.

- Women are more likely to suffer from supraventricular tachycardia (SVT). Research has shown that SVT episodes are more common during the luteal phase of the menstrual cycle when progesterone levels are elevated.

- Inappropriate sinus tachycardia (inappropriately high heart rate at rest [over 100 bpm] and during stress) is also more common among women and is thought to involve abnormal

autonomic regulation of the sinus node. Editor's comment: Inappropriate sinus tachycardia is also fairly common after an ablation, perhaps indicating that an ablation can result in a temporary, abnormal regulation of the sinus node.

- Women with AF are more likely than men to suffer an embolic stroke; however, they are also more likely to experience a major bleeding event if taking warfarin, so stroke prevention in women is particularly challenging. Women with paroxysmal AF tend to have longer episodes and a higher average heart rate during an episode.

- Pulmonary vein isolation (ablation) procedures are equally effective in men and women.

- Women are more likely to experience Torsades de Pointes (a distinctive form of ventricular tachycardia associated with a prolonged QT interval). This means that class 1C antiarrhythmics (flecainide and propafenone) are the preferred antiarrhythmics for women since they do not increase the QT interval. Amiodarone, sotalol, dofetilide and disopyramide may, on the other hand, increase the QT interval and should be used with caution in women.

- In the United States sudden cardiac death (SCD) claims between 300,000 and 400,000 victims every year. The incidence among women is only half of that among men and occurs 10-20 years later in life.

- The risk of SVT increases during pregnancy and during the post-partum period.

The Florida researchers conclude that there are important differences in the presentation and clinical course "of many cardiovascular disorders in men and women. It is important for health care providers to be aware of these differences to provide optimal care for their patients".

Yarnoz, MJ and Curtis, AB. More reasons why men and women are not the same (gender differences in electrophysiology and arrhythmias). American Journal of Cardiology, *Vol. 101, 2008, pp. 1291-96*

Seasonal variation in AF episodes

LUBLIN, POLAND. It has been known since the time of Hippocrates that the weather (atmospheric conditions) influences people's mood and health. As far back as the first half of the 19th century, Polish researchers reported an association between short-term weather changes and a

worsening of angina, increased incidence of heart attacks, and more pronounced fluctuations in blood pressure. More recent research has shown that levels of the stress hormone cortisol are lower at high barometric pressures and that lower levels are associated with a lessening of depression. So, conceivably, a person with elevated cortisol levels would feel better on a sunny day.

Now Polish researchers report that weather conditions also affect the incidence of paroxysmal afib episodes. Their study involved 739 patients (52% females, average age of 65 years, range of 18-91 years) who were admitted to hospital because of an AF episode during the period 2005-2006. Patients with acute coronary syndrome, myocarditis, pericarditis, thyrotoxicosis, and respiratory problems were excluded from the study, as were those who had recently suffered a heart attack.

The researchers correlated the number of patients admitted each day with air temperature, atmospheric pressure, wind speed and cloudiness, and also investigated the effect of approaching cold fronts and warm fronts. On average, there was one admission per day related to afib episodes. However, there were 9 days on which 4 patients were admitted and 4 days on which 5 patients were admitted. There was a seasonal effect with more cases (2.4/day) reported in the winter (December to February) than in the spring and summer (1.7 cases/day during the period May to August).

The most interesting correlation though was between the approach of a cold front and the number of afib-related hospital admissions. All the high admission days (4-5 cases/day) occurred 24-36 hours prior to the arrival of a cold front. The researchers speculate that the effect may be due to the electromagnetic waves created in deep low-pressure systems and storm centers. These waves travel at the speed of light, whereas the front itself moves at 10-50 km/hr, thus explaining why the effect of an approaching cold front would be felt 24-36 hours in advance. The researchers found no relationship between afib incidence and the approach of a warm front. However, they did notice that periods of constant high atmospheric pressure were associated with a significant decline in hospital admissions for AF.

Gluszak, A, et al. Episodes of atrial fibrillation and meteorological conditions. Kardiologia Polska, *Vol. 66, September 2008, pp. 958-63*

Editor's comment: The speculation that a temporary increase in exposure to electromagnetic radiation may precipitate afib episodes is indeed an interesting one and, if proven correct, could perhaps partly explain the current AF epidemic, which certainly coincides with a vast increase in our exposure to electromagnetic radiation. As way of explanation the Polish researchers make the following remarks:

"Electromagnetic waves penetrate into the tissue to a depth depending on the electric resistance and wavelength. In the very low frequency generated by atmospheric conditions (up to 10 MHz) living tissue acts as a conductor in which an alternating electric field produces Foucault eddy currents practically induced in the entire body. These phenomena were also reported by Kozlowski, who claimed that electromagnetic field effects in the body tissues involve stimulation of particles and atomic movements which cause chemical reactions and bioelectric processes. Induction of these changes occurs in electromagnetic field of relatively low intensities. This was also underlined by Hessmann-Kosaris, who reported that even weak electromagnetic fields may affect metabolic processes of cells and cellular membranes".

New insights into the mechanism of lone AF

ATHENS, GREECE. Researchers at the University of Athens have just published an article regarding the association between lone atrial fibrillation (LAF) and inflammation and oxidative stress. The paper is highly technical, but could contain some important clues in relation to the development and recurrence of persistent LAF. In order to summarize the article it is necessary to become familiar with some technical terms.

Description of Terms

Markers of Inflammation

- **Cytokine** – A chemical messenger protein released by white blood cells to facilitate communication by immune system cells.
- **CRP (C-reactive protein)** – A general indicator of systemic inflammation and infection.
- **TNF (tumour necrosis factor alpha)** – A cytokine that promotes the inflammatory response which in turn causes many of the problems associated with autoimmune disorders such as rheumatoid arthritis, Crohn's disease, asthma, psoriasis, etc.
- **IL-6 (interleukin-6)** – A cytokine secreted by macrophages (large white blood cells that destroy or ingest foreign substances) to stimulate immune response to trauma.
- **IL-10 (interleukin-10)** – An anti-inflammatory cytokine that can inhibit the production of inflammatory cytokines such as TNF.

- **sICAM-1 (soluble intercellular adhesion molecule-1)** – An important biomarker of inflammatory processes, especially in atherosclerosis and cancer.
- **sVCAM-1 (soluble vascular cell adhesion molecule-1)** – An important biomarker of inflammatory processes, particularly those involving endothelial cells (cells lining the heart and blood vessels). There is evidence that fish oil can decrease SVCAM levels in men over the age of 55 years.

Markers of Oxidative Stress

- **Malondialdehyde (MDA)** – A prominent marker of oxidative stress formed by the oxidation of polyunsaturated fatty acids.
- **Nitrotyrosine (NT)** – A marker for cell damage and inflammation caused by reactive nitrogen species (nitrogen oxide and peroxynitrite).

The Greek study involved 41 afibbers with persistent LAF (average age of 47 years, 27 males, 14 females). All participants were carefully screened to rule out hypertension, heart failure, coronary artery disease, valvular heart disease, myocarditis, and any other cardiomyopathy. Patients with diabetes, thyroid dysfunction, active inflammation, cancer, infection, renal failure, obstructive pulmonary disease, or alcohol or drug abuse were also excluded from the study. Thus, the study group truly consisted of otherwise healthy lone afibbers. A group of 41 equally healthy volunteers (matched for age, gender, and body mass) served as control (group C).

All study participants had blood samples drawn at baseline (24 hours before pharmaceutical conversion, or 1 hour before electrocardioversion) and at 1 hour, 24 hours, 1, 2, 4 and 6 weeks after cardioversion. All samples were analyzed for the above-mentioned biomarkers for inflammation and oxidative stress. Pharmaceutical conversion was attempted with amiodarone and all participants (except the control group) remained on amiodarone during the study period. During the 12-month follow-up after cardioversion, 25 of the participants remained in sinus rhythm except for 7 who experienced short episodes of afib (group A). Among the remaining participants, 8 had recurrence of persistent afib, 4 experienced episodes lasting longer than 30% of total ECG recording time, and 4 had paroxysmal episodes lasting longer than 6 hours (group B). In other words, cardioversion was largely successful in group A, but unsuccessful in group B. The results of the blood analyses were as follows:

Baseline Values

- CRP levels were higher in group B than in groups A and C (no difference between A and C).

- TNF levels were higher in group B than in group A and both were elevated compared to group C.
- IL-6 was undetectable in controls, but 3 times higher in group B than in group A.
- IL-10 was lower in group B than in group A, but both were significantly higher than in the control group.
- sICAM-1 was highest in group B, followed by group A and controls.
- sVCAM-1 was about the same in groups A and C, but substantially lower in group B.
- MDA levels were significantly higher than controls in groups A and B with group B levels being twice as high as those in group A.
- NT levels were significantly higher than controls in groups A and B with group B levels being about 50% higher than in group A.

From the above data it is clear that recurrence of afib was associated with a higher level of inflammation and oxidative stress.

Comparing the changes in the biomarkers evaluated post-cardioversion, the researchers conclude that the following markers could reliably (80% certainty) distinguish between afibbers who would largely remain in sinus rhythm (group A) and those who would not (group B). Thus, maintenance of sinus rhythm was associated with a low baseline level of MDA, a low level of IL-6 one week after cardioversion, and low levels of sICAM-1 and NT two weeks after cardioversion. The most reliable and potent markers of success were a greater than 36.1% decrease in IL-6 one week after cardioversion, a decrease in sICAM-1 of more than 5.2% two weeks following cardioversion, and a decrease in NT of more than 22.2% two weeks after cardioversion.

The researchers conclude that there is an association between persistent lone atrial fibrillation and the presence of oxidative stress and inflammation. They also point out that CRP is not a useful marker when it comes to LAF. Unfortunately, they also state, "*It is still unclear whether the elevated levels of inflammatory and oxidative markers have a causative relation to AF or they are epiphenomena of the arrhythmia*". In other words, it is not clear which is the "chicken" and which is the "egg".
Leftheriotis, DI, et al. The predictive value of inflammatory and oxidative markers following the successful cardioversion of persistent lone atrial fibrillation. International Journal of Cardiology, *July 18, 2008 [Epub ahead of print]*

Editor's comment: Inflammation and oxidative stress have long been associated with atrial fibrillation. However, this is the first study to prove that the association is present in true lone afib and thus is not due to

comorbid heart disease. The uncertainty as to whether the inflammation and oxidative stress causes afib or whether the continued presence of afib causes oxidative stress and inflammation, of course, makes it difficult to translate the findings of the study to practical advice for afibbers. It seems intuitively possible that inflammation could be either the cause or effect of afib, but it is a little harder to visualize how the presence of afib could result in oxidative stress. Perhaps the most likely explanation is that we are dealing with a vicious cycle in which inflammation and oxidative stress begets afib and afib begets inflammation and perhaps, oxidative stress. In this case, it should be possible to break the cycle either by cardioversion, or by dampening inflammation and oxidative stress. Since both systemic inflammation and oxidative stress have been implicated in a wide range of diseases and disorders, it would seem prudent for all afibbers to supplement with antioxidants (vitamin C, vitamin E, selenium, coenzyme Q-10, alpha-lipoic acid, etc) and anti-inflammatories (fish oils, Zyflamend, beta-sitosterol, bromelain, curcumin, boswellia, quercetin, Moducare).

Risk Factors & Triggers

Risk factors for lone atrial fibrillation

BARCELONA, SPAIN. While much research is being done to find new, improved methods of treating atrial fibrillation (AF), very little research is done to determine the causes of the AF epidemic. Hopefully, recent work undertaken at the University of Barcelona will help reverse the balance. The Spanish researchers determined height, physical activity level, and left atrial size in a group of 107 lone atrial fibrillation (LAF) patients and compared their results to those in a group of age- and sex-matched healthy individuals without AF. In their discussion, the researchers make the following statements of particular interest:

- "*The rise (in atrial fibrillation cases) is not due exclusively to population aging or to the higher prevalence of obesity."*
- *"The prevalence of LAF ranges from around 2-10% in the AF population and may reach 30% in patients seeking medical attention."*
- *"LAF was defined as AF in the absence of any identifiable cause of the arrhythmia."*
- *"Atrial fibrillation was considered of 'vagal' origin when it occurred at least 80% of times during sleep and/or in post-prandial situation and 'adrenergic' when it occurred at least 80% of the time during high physical exertion and/or in situations of stress. The remaining patients were classified as suffering 'random' AF."*

The researchers measured the height, weight, and left atrial size of each study participant and also had all participants complete a validated questionnaire to determine their accumulated lifetime physical activity. Physical activity was classified into four levels – sedentary, light, moderate, and heavy. Light activities included standing and slow walking; moderate included activities that increased heart rate slightly and perhaps resulted in light perspiration, but which did not result in exhaustion; heavy activities included vigorous exercise that significantly increased heart rate. The accumulated lifetime hours of all occupational and exercise/sports activities for each level were calculated for each participant, taking into account their duration and frequency.

Forty-three percent of the LAF patients were admitted to the emergency department with a first episode of AF, while the remaining 57% had experienced previous episodes. Average age at admission was 48 years (NOTE: Our survey of 625 afibbers recorded an average age of 48 years at diagnosis). The majority (69%) of the participants were male and most (70%) had vagal AF.

The researchers observed a strong correlation between height and LAF prevalence with taller individuals (average height of 186 cm) being up to 17 times more likely to experience LAF than shorter individuals (average height of 160 cm). NOTE: Our first LAF survey in 2001 found an average height of 183 cm among male afibbers. PC's later survey (LAFS-11) found an average height of male afibbers of 181 cm as compared to a population mean of 175 cm. Thus, the correlation between height and LAF risk is well established and is likely associated with the larger atrial size accompanying tallness.

A larger left atrium (left atrial anteroposterior diameter) was associated with a 40% increased risk of LAF. The most striking finding was the association between LAF risk and accumulated moderate and heavy physical activity. Those with a lifetime accumulated moderate plus heavy physical activity of more than 9300 hours had 15 times the prevalence of LAF than did those with less than 2100 hours accumulated. More than 564 hours of accumulated heavy, vigorous physical activity was associated with a 7 times increased prevalence of LAF.

The researchers speculate that the negative effects of moderate and particularly vigorous physical activity may be related to the chronic volume and pressure overload caused by the increased activity. They conclude, "*The fact that physical activity is a risk factor for AF does not argue against exercise as a way of preventing coronary artery disease. It only offers a word of caution suggesting that the benefits obtained by physical activity, if excessively intense and over a great many hours, may be counteracted by the risk of AF.*"

Mont, L, et al. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace, *Vol. 10, 2008, pp. 15-20*

Alcohol consumption linked to atrial flutter

SAN FRANCISCO, CALIFORNIA. It is well established that binge drinking and long-term alcohol abuse are risk factors for atrial fibrillation. Now researchers at the University of California report that alcohol consumption is also a significant risk factor for right atrial flutter (AFL), at least in persons at or below the age of sixty years. Their study involved 195 patients (121 with atrial fibrillation and 74 with AFL) who presented for

cardioversion or ablation over a two-year period. A control group consisting of 132 patients with SVT (supraventricular tachycardia) and 54 with no known arrhythmia were also included. About 13% of participants had coronary artery disease or congestive heart failure, and 28% had hypertension.

The researchers found a strong correlation between daily alcohol consumption and the prevalence of AFL in those at or below the age of 60 years. After correcting for potential confounders (gender, race, hypertension, congestive heart failure, coronary artery disease, and body mass index) the researchers conclude that daily alcohol consumption (1-2 drinks per day) is associated with an 11 times greater prevalence of AFL. No such relationship was found among patients older than 60 years nor among those with atrial fibrillation. The California researchers also observed a strong correlation between daily alcohol intake and a shorter atrial effective refractory period (AERP) in the right atrium and speculate that a shorter AERP may facilitate the initiation of AFL by allowing propagation of a critically-timed premature atrial complex (PAC).

Marcus, GM, et al. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. **PACE**, *Vol. 31, March 2008, pp. 266-72*

Helicobacter pylori and atrial fibrillation

ROCHESTER, MINNESOTA. In 2005 Italian researchers reported that patients with atrial fibrillation tended to have a higher level of IgG antibodies to *Helicobacter pylori* (seropositive) than did healthy volunteers. They speculated that the *H pylori* bacterium may adversely affect the NA^+/K^+-ATPase pump responsible for maintaining homeostatic balance in individual heart cells. A disturbance of this balance may trigger AF by creating abnormal automaticity or triggered activity that causes a depolarization delay, which can result in very rapid premature atrial contractions (PACs), a forerunner for a full-blown afib episode.[1]

Researchers at the Mayo Clinic have now followed up on these findings. Their study included 743 patients who were admitted to the clinic because of suspected cardiovascular disease and underwent coronary angiography or an electrophysiologic study. All patients were also tested for IgG antibodies to *H pylori.* Those who had one or more electrocardiograms showing afib during the study period (1994 to 2001) were included in the AF group (83 patients in total). The researchers found that patients with afib were more likely to seropositive for *H pylori* than were non-afibbers (65% vs. 55%). Paroxysmal afibbers (62% of group) were seropositive in 65% of cases, persistent afibbers (22%) were seropositive in 67% of cases, and permanent afibbers (67%) were seropositive in 67% of cases.

The association between seropositivity and AF varied significantly with age. In patients less than 50 years of age, the incidence of AF was 8% in the seropositive group versus 0% in the seronegative group; however, in older patients (more than 70 years of age), there was no significant difference in incidence (17.5% among seropositive versus 15.4% among seronegative patients).

There was no association between the level of the systemic inflammation marker CRP (C-reactive protein) and *H pylori* status, which is somewhat surprising since *H pylori* infection causes chronic gastric inflammation. Nevertheless, the researchers conclude that ectopy within pulmonary veins may be aggravated by inflammation in the esophagus or stomach caused by a chronic *H pylori* infection. They suggest further studies and routine assessment of *H pylori* status in younger patients with atrial fibrillation.

Bunch, TJ, et al. Frequency of Helicobacter pylori seropositivity and C-reactive protein increase in atrial fibrillation in patients undergoing coronary angiography. American Journal of Cardiology, *Vol. 101, 2008, pp. 848-51*

Editor's comment: There is little question that *H pylori* is a bad actor when it comes to stomach ulcers and perhaps, stomach cancer. However, whether its elimination will "cure" or prevent afib is still very much an open question, but one that further Mayo Clinic studies will, hopefully, help answer. In the meantime, routine elimination of *H pylori*, except in the case of stomach ulcers, may not be the smartest idea for an afibber. Nine years ago Dr. Martin Blaser of the Department of Veterans Affairs warned that a lack of *H pylori* may be behind the recent increase in the incidence of gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal cancer. Dr. Blaser points out that the human stomach and *H pylori* have lived in harmony for millions of years. However, recently the incidence of *H pylori* colonization has declined in the Western world because of, among other reasons, the excessive use of antibiotics in children. This decline has been accompanied by a substantial increase in GERD and esophageal cancer. GERD is uncommon in countries where most people are colonized ("infected") by *H pylori*. Dr. Blaser believes that the most common strain of *H pylori* (cag+) is protective against GERD, Barrett's esophagus, and esophageal cancer but can promote stomach ulcers and cancer. He believes *H pylori* exerts its effect by regulating acid secretion in different parts of the stomach.[2]

[1] Montenero, AS, et al. Helicobacter pylori and atrial fibrillation: a possible pathogenic link. Heart, Vol. 91, July 2005, pp. 960-61

[2] Blaser, Martin J. Hypothesis: The changing relationship of Helicobacter pylori and humans: implications for health and disease. Journal of Infectious Diseases, Vol. 179, June 1999, pp.1523-30

Metabolic syndrome implicated in atrial fibrillation

NIIGATA, JAPAN. Metabolic syndrome (MS) is defined as a combination of risk factors for atherosclerosis including obesity, high blood pressure (hypertension), insulin resistance (glucose intolerance), and dyslipidemia (elevated cholesterol and triglycerides). The diagnosis of MS is made when at least 3 of the following criteria are met:

- Elevated body mass index (BMI) – greater than 30 kg/sq m*
- Elevated triglycerides – greater than 150 mg/dL
- Low high-density cholesterol (HDL) – less than 40 mg/dL in men and 50 mg/dL in women
- Elevated blood pressure – greater than 130/85 and/or history of treated hypertension
- Impaired glucose tolerance

*NOTE: Because the incidence of obesity in Japan is only 2-3% as compared to 20-30% in western countries, a cut-off value for obesity of only 25 kg/square meter was used in this study.

A group of American and Japanese researchers now report that metabolic syndrome is not only a risk factor for atherosclerosis and cardiovascular disease, but also significantly increases the risk of developing atrial fibrillation (AF). Their study involved 28,449 Japanese men and women enrolled in the Niigata Association for Comprehensive Health Promotion and Research Study. The mean age of enrolment in the study was 59 years and 66% of participants were women. At baseline MS was diagnosed in 13-16% (depending on definition of impaired glucose tolerance) of the participants, but none had AF. After a 4.5-year follow-up period, AF had been diagnosed in 265 subjects corresponding to an annual incidence rate of 0.41% in men and 0.13% in women. The annual incidence rate of AF was 0.19% in participants without MS and 0.33% in those with MS, thus indicating that MS along with age and gender (males were 3 times more likely to develop AF than were women) are potent risk factors for AF.

The risk of developing AF increased with the number of MS components diagnosed in individual participants. The relative risk increase associated with the components were as follows:

- Obesity – 64%
- Hypertension – 69%
- Low HDL cholesterol – 52%
- Impaired glucose tolerance – 44%

An elevated level of triglycerides was not associated with an increased risk of AF. The researchers speculate that inflammation and oxidative stress may be common factors in both MS and AF and that hypertension and obesity can cause atrial stretch and dilation resulting in a structural substrate predisposing to AF.
Watanabe, H, et al. Metabolic syndrome and risk of development of atrial fibrillation. Circulation, *Vol. 117, March 11, 2008, pp. 1255-60*

Fosamax (alendronate) implicated in AF

SEATTLE, WASHINGTON. A recent (2007) clinical trial of once-a-year osteoporosis treatment with zoledronic acid (a bisphosphonate) revealed that this treatment significantly increased the risk of atrial fibrillation from 0.5% to 1.3%, or a 2.6-fold risk increase. The obvious question at the time was, "Do more common orally-administered bisphosphonates such as alendronate (Fosamax) also increase the risk of atrial fibrillation in postmenopausal women with osteoporosis?" Clinicians at the University of Washington in Seattle, the University of California, and the Center for Health Studies, Group Health also in Seattle now provide an answer to this question.

Their study involved 719 women with diagnosed afib and 966 matched controls who had been receiving health care at Group Health for a median of 20 years. The median age was 75 years for afib patients and 71 years for controls. The women were observed for a 6-month period during which 45.6% were diagnosed with persistent or recurrent paroxysmal AF – 41.6% experienced just one self-terminating episode and 11.5% were found to have permanent AF. Women who had ever used alendronate (irrespective of how long they had used it, or how much their cumulative intake had been) were found to have an average 86% greater relative risk of being diagnosed with afib. The risk of being diagnosed with permanent afib was almost 6 times greater among ever users of alendronate than among those never using it. The relative risk increase for women with persistent/recurring afib was 25% and for those with just one self-terminating episode the increase was 93%. Adjustment for possible confounding variables such as cardiovascular disease, BMI, cholesterol levels, estrogen therapy, osteoporosis, etc. did not change these risk estimates. However, the researchers did note that the combined use of alendronate and statin drugs was associated with a 13-times increased risk of developing AF.

The researchers conclude that 3% of the AF diagnoses made during the 6-month study can be attributed to alendronate use. They further state that the benefits of fracture prevention in high-risk patients will generally outweigh the possible risk of AF. However, in women with only modestly increased fracture risk the benefits may be less clear.

Heckbert, SR, et al. Use of alendronate and risk of incident atrial fibrillation in women. **Archives of Internal Medicine,** *Vol. 168, No. 8, April 28, 2008, pp. 826-31*

Editor's comment: Alendronate (Fosamax) can also cause stomach ulcers, particularly in combination with naproxen and has been strongly implicated in rotting of the jawbone after dental work. Add a substantial risk of atrial fibrillation and it is clear that alendronate is by no means an innocuous drug. Fortunately, there are highly effective alternative means of preventing and treating osteoporosis. Lifestyle changes and supplementation with calcium, magnesium, strontium, boron, zinc and vitamins C, D and K can go a long way towards dealing effectively with osteopenia (the forerunner of osteoporosis) and osteoporosis itself. You can find out more about the natural approach at http://www.yourhealthbase.com/osteoporosis.htm

Lifestyle, stress and AF

BOLOGNA, ITALY. In our first LAF Survey (February 2001) one of the questions related to the circumstances preceding the very first episode of afib. The most common trigger for the first one was emotional or work-related stress (26%) followed by physical overexertion at 24%. Caffeine, alcohol, and ice-cold drinks were next at 10%, 6%, and 8% respectively. A later survey dealt with the triggers of subsequent episodes. Here again, stress and anxiety were high on the list with 94% of adrenergic, 56% of mixed, and 29% of vagal afibbers listing anxiety and emotional and work-related stress as important trigger factors. Caffeine was listed as a trigger for 23% with 31% of adrenergic afibbers experiencing this trigger factor. It is known that both stress and caffeine lead to an increase in sympathetic dominance, so it is not surprising that adrenergic afibbers are particularly vulnerable to stress and caffeine.

A group of Italian researchers now confirm that stressful periods are indeed powerful initiators of a first atrial fibrillation (AF) episode. Their study involved 400 patients (51% men) who presented with a first episode of AF. Their average age was 54 years, and none of them had underlying heart disease. After admission and cardioversion (as needed), the patients were asked how many cups of coffee (espresso) they drank per day and also questioned as to their alcohol and chocolate consumption, smoking habits, physical activity level, and their body mass index (BMI) and waist-to-hip ratio was measured. Finally, all patients underwent a series of cognitive tests to evaluate acute psychological stress during the past 7-30 days. A control group matched for age and gender was selected and evaluated as above.

The researchers found that AF patients had a significantly higher mean life acute stress score (64 LCU) during the week preceding the first

episode when compared to the control group (34 LCU). As a matter of fact, the group with a LCU between 75 and 100 had twice the risk of developing afib than did the group with an LCU between 0 and 25. Coffee was another potent trigger with participants drinking more than 3 cups of espresso a day being 3 times more likely to develop afib than were those drinking just 2 cups a day. Obesity (BMI greater than 30) was associated with a relative 61% increase in the risk of experiencing a first afib episode. The researchers found no significant correlations between afib risk and alcohol and chocolate consumption, cigarette smoking, and level of physical activity. They also made the following interesting observations:

- Forty-seven percent of the patients converted spontaneously to normal sinus rhythm within the first 48 hours. Patients with a recent acute stressful event showed the highest probability of spontaneous conversion.
- An increase in coffee consumption was noted in the days after the stressful event and this increase was more pronounced among patients who were not habitual coffee drinkers.

The researchers identify high espresso coffee consumption, a recent acute stressful event, and obesity as independent risk factors for the development of acute lone AF. They also suggest that reducing coffee consumption and avoiding obesity may lead to a reduction in the incidence of AF.

Mattioli, AV, et al. Effect of coffee consumption, lifestyle and acute life stress in the development of acute lone atrial fibrillation. Journal of Cardiovascular Medicine, *Vol. 9, No. 8, 2008, pp. 794-98*

Editor's comment: The finding that emotional and work-related stress is a trigger factor for afib episodes is not surprising. Nor is it surprising that caffeine was fingered as a culprit. Caffeine consumption results in the release of norepinephrine, the nervous system transmitter that increases sympathetic (adrenergic) activity. Thus adrenergic and mixed afibbers would be vulnerable to over-consumption of caffeine, while it would be expected to affect vagal afibbers much less or not at all. Recent discussions on the Bulletin Board have produced the suggestion that the AF-promoting effects of coffee may be due to the pesticides it contains rather than to the caffeine as such. It is possible that this may be largely true for vagal afibbers, but I don't believe the caffeine effect can be dismissed as far as adrenergic and mixed afibbers are concerned. Nevertheless, drinking organically-grown coffee would certainly be a prudent measure for all afibbers who regularly indulge.

Risk factors for lone atrial fibrillation

UTRECHT, THE NETHERLANDS. The majority (80-90%) of all patients with atrial fibrillation (AF) have some type of cardiovascular disease or abnormality that can explain the cause of their AF. Thus heart disease-related AF involves an arrhythmogenic substrate, that is, an atria which is diseased, has been stretched, or contains a substantial amount of fibrotic tissue likely formed by long-term inflammation.

On the other hand, ***lone*** atrial fibrillation, does not involve diseased or otherwise compromised atria, but is rather an "electrical" problem where certain triggers initiate afib episodes through their action on especially sensitive foci mostly located in and around the entrances of the pulmonary veins into the left atrium. This explains why lone afibbers have normal life expectancy, a low stroke risk, and why paroxysmal (intermittent) afib rarely progresses to persistent or permanent. However, for AF patients with diseased atria (arrhythmogenic substrate) the situation is quite different. These patients have a substantially greater stroke risk, higher mortality, and are much more likely to progress from paroxysmal to permanent AF.

While heart disease is, by definition, not a cause of lone AF, there are other known causes. First among these are electrolyte disturbances (particularly deficiencies in magnesium and potassium) and autonomic nervous system imbalances. However, alcohol consumption, especially binge drinking, and cocaine and certain pharmaceutical drugs can also increase the risk of lone afib. Thyroid disorders can be an underlying cause, as can hypoglycemia and an excessive consumption of tyramine-containing foods. It is also clear that chromosomal abnormalities can increase the risk of lone afib. A recent LAF survey revealed that 43% of 100 respondents had a close relative with cardiac arrhythmia – so the "genetic connection" is by no means uncommon. Finally, there is also evidence that the rare disease pheochromocytoma can cause AF to develop. Once all these possible causes have been ruled out, ***lone*** atrial fibrillation becomes "idiopathic" which really is the proper designation for the type of afib most "members" of www.afibbers.org experience.

Lately, several additional initiators of lone AF have been discovered. In a recent review by Dutch researchers it is pointed out that obesity, obstructive sleep apnea (OSA), increased pulse pressure (the difference between systolic [pumping] and diastolic [filling] blood pressure), systemic inflammation, and long-term participation in vigorous endurance sports have all been associated with an increased risk of developing AF.

Obese people (BMI greater than 30) have been found to have twice the risk of developing lone afib when compared to those with normal body weight (BMI between 18.5 and 25 kg/sq.m). Similarly, the presence of

OSA increases afib risk by a factor of 2. Several studies have found a clear association between systemic inflammation (high levels of hs C-reactive protein and interleukins) and the presence of lone AF, but it is not clear whether inflammation causes afib or afib results in inflammation.
Schoonderwoerd, BA, et al. New risk factors for atrial fibrillation: causes of 'not-so-lone atrial fibrillation'. **Europace**, *Vol. 10, 2008, pp. 668-73*

Editor's comment: Although it is of great interest to discover additional possible causes of afib, the great majority of lone afibbers do not have any of these conditions, so the most important causes of the ***lone*** afib epidemic are still to be discovered.

Cardioversion

Metoprolol improves cardioversion results

STOCKHOLM, SWEDEN. Electrical cardioversion is often used in an attempt to convert persistent afibbers to normal sinus rhythm (NSR). Unfortunately, the relapse rate is high and even with the use of class I or class III antiarrhythmic drugs, only about 50% of electro-cardioverted patients remain in NSR for 6 months or longer.

Researchers at the Karolinska Institute now report that pretreatment with the beta-blocker metoprolol (time-release version, Toprol XL) significantly improves the success rate for cardioversion. Their study involved 168 persistent afibbers who were randomized to receive metoprolol or a placebo starting at least a week prior to cardioversion (NOTE: only about 15% of the study participants were lone afibbers). On average, the participants were on metoprolol or placebo for 28 days prior to cardioversion and they were also prescribed warfarin (INR 2.1 – 3.0) for at least 3 weeks before and 6 weeks after cardioversion. The starting dose of metoprolol was 50 mg/day with a 50 mg stepwise increase to a target dose of 200 mg once a day.

The participants were checked with an ECG 2 hours after cardioversion and then every week for 6 weeks, and then 3 and 6 months after cardioversion. During the first 6 weeks, 49% in the metoprolol group and 47% in the placebo group developed afib again and were given a second cardioversion. At the 6-month checkup, 46% of patients in the metoprolol group were still in NSR as compared to only 26% in the placebo group. It is also of interest to note that while 8% of placebo group members relapsed into afib within 2 hours of their first cardioversion, none of the patients in the metoprolol group did.

Nergardh, AK, et al. Maintenance of sinus rhythm with metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation. **European Heart Journal**, *Vol. 28, 2007, pp. 1351-57*

Editor's comment: It is likely that the metoprolol pretreatment would be beneficial for adrenergic and perhaps mixed afibbers, but it is not at all clear that it would benefit vagal, persistent afibbers. Researchers at the Mayo Clinic have reported that a high blood level of C-reactive protein (CRP), a marker of systemic inflammation, prior to cardioversion is associated with a greater probability of afib recurrence within one month. There is also evidence that a low level of potassium is associated with poorer outcome of cardioversion. Thus, combating inflammation with

Moducare or beta-sitosterol, and supplementing with potassium and magnesium prior to cardioversion may improve both the short- and long-term outcome of the procedure.

Improved cardioversion results

Persistent afib can be converted to normal sinus rhythm (NSR) by electrical cardioversion. Unfortunately, the bliss of NSR is often short-lived. Italian researchers now report that flecainide and a combination of amiodarone and flecainide are safe and effective in maintaining NSR after cardioversion in patients with persistent afib and hypertension. Their trial showed that flecainide on its own maintained NSR in 88% of patients, while the combination maintained it in 80% at the 6-month check-up. In comparison, only 33% of patients on sotalol or amiodarone alone were still in NSR at the 6-month follow-up. The researchers also found that adding an angiotensin II receptor blocker (losartan, valsartan, irbesartan, candesartan) to the medication regimen was highly effective in maintaining NSR.

Journal of Cardiovascular Electrophysiology, *Vol. 18, Suppl. 2, October 2007, Abstract 11.3, p. S23 and Abstract 11.5, p. S24*

Magnesium aids in cardioversion

HARTFORD, CONNECTICUT. Intravenous ibutilide (Corvert) is often used to chemically convert atrial fibrillation and atrial flutter to normal sinus rhythm. Unfortunately, the procedure only works in about 50% of cases and is accompanied by a 4% risk of developing Torsade de Pointes, a sometimes fatal ventricular arrhythmia. Researchers at the University of Connecticut now report that adding 4 grams of intravenous magnesium sulfate to the ibutilide protocol (2 grams before the first ibutilide dose and 2 grams over half an hour after the final ibutilide dose) will increase the odds of a successful conversion by a factor of 3.

The clinical trial included 229 patients who presented for cardioversion of atrial fibrillation (80%) or atrial flutter. Of these, 88% received ibutilide by itself, 87 patients received between 1 and 3 grams of intravenous magnesium sulfate, and the remaining 54 patients received a total of 4 grams of magnesium sulfate during the administration of ibutilide. The average age of the patients was about 66 years and most had hypertension or underlying heart disease. Only one case of Torsade de Pointes was observed during the trial and that involved a patient who was receiving ibutilide only. The beneficial effect of the addition of 1-3 grams of magnesium was not statistically significant indicating that at least 4 grams is needed.

The researchers speculate that the benefits of concomitant use of magnesium sulfate are related to magnesium's ability to increase intracellular potassium concentrations and regulate intracellular calcium concentrations.

Tercius, AJ, et al. Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. **PACE**, *Vol. 30, November 2007, pp. 1331-35*

Editor's comment: Although there were very few lone afibbers in the study group, there is no reason to believe that the addition of magnesium sulfate to the ibutilide protocol would not benefit them as well. Also, if the beneficial effect of magnesium is related to its ability to increase intracellular potassium concentrations and regulate calcium concentrations, then it would seem logical that adding magnesium to cardioversion protocols involving other antiarrhythmics, or even electrical cardioversion, would also be beneficial. Perhaps having a warm bath with plenty of Epsom salt when using the on-demand (pill-in-the-pocket) approach with flecainide or propafenone may improve the odds of a quick conversion.

New drug for conversion of AF

MONTREAL, CANADA. Although most atrial fibrillation (AF) episodes experienced by lone afibbers are self-terminating, some do require medical intervention in order to convert to normal sinus rhythm (NSR). Electrical cardioversion has an immediate success rate of about 90%. But only 25-50% of patients remain in NSR for a year. The efficacy is improved if patients are replete in potassium when the conversion is attempted and is very much decreased if the patient is on digoxin (Lanoxin) at the time of the cardioversion.

Pharmacologic conversion is also used and employs intravenous infusions of such drugs as ibutilide (Corvert), flecainide (Tambocor), and propafenone (Rythmol). Although these drugs result in conversion in 30-60% of cases, they must be used with caution as they can cause dangerous ventricular arrhythmias and serious hypotension. A group of researchers from Canada, Scandinavia and the United States recently completed a phase III clinical trial to evaluate the safety and effectiveness of vernakalant hydrochloride (RSD1235). Vernakalant is an atrium-selective potassium and sodium channel blocker and has, in animal studies, been found to prolong the atrial refractory period.

The clinical trial involved 336 patients enrolled at 44 different centers. The patients were divided into two groups. Group I (220 patients) consisted of AF patients who had been in afib for 3 hours to 7 days, while Group II (116 patients) was made up of those who had been in afib for 8

to 45 days. None of the patients had heart failure (class IV), had experienced a heart attack, or had previously failed electrical cardioversion. They were randomized to receive a 10-minute infusion of vernakalant (3.0 mg/kg) or placebo followed by a 15-minute observation period. If conversion to NSR was not achieved, an additional dose of vernakalant (2.0 mg/kg) or placebo was administered. Patients were then observed in the hospital for a minimum of 8 hours.

Successful conversion was defined as converting to NSR for at least one minute within 90 minutes of the initiation of drug infusion. In Group I (short-duration AF), 51.7% of patients were successfully converted as compared to 4% in the placebo group. Most (76%) of those who converted with vernakalant did so with a single dose and within a median time of 11 minutes. All but one of the 75 patients who converted remained in NSR for more than 24 hours. The success rate in Group II was much lower at 7.9% among vernakalant-infused patients, and 0% among those receiving placebo.

There was a clear trend for the procedure to be more successful the shorter time the patient had been in afib. Thus, those who were treated no more than 48 hours from the onset of their episode experienced a 62.1% conversion rate versus 4.9% with placebo. Overall, 83 of the 221 patients (37.6%) given vernakalant successfully converted versus 2.6% in the placebo group. There were no reports of torsade de pointes or ventricular fibrillation during the first 24 hours after infusion; however, three patients did develop serious adverse events (hypotension and heart block) probably related to vernakalant administration. Minor adverse effects included impaired sense of taste experienced by almost 30% of patients treated with vernakalant, sneezing experienced by 16%, nausea by 9%, and hypotension by 6.3%.

The researchers conclude that vernakalant is safe and effective for conversion of short-duration atrial fibrillation. NOTE: This study was sponsored by the manufacturer of vernakalant, and 8 of the 13 authors had received financial compensation form the manufacturer and/or other pharmaceutical companies.

Roy, D, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation. Circulation, *Vol. 117, March 25, 2008, pp. 1518-25*

Editor's comment: Vernakalant would appear to be a useful drug for intravenous, pharmacological conversion of short-duration afib. However, it does require a trip to the ER so most lone afibbers would likely be better off using the pill-in-the-pocket approach (with flecainide or propafenone), which has a conversion effectiveness around 90%.

Elevated CRP = cardioversion failure

IOANNINA, GREECE. Several studies have uncovered an association between elevated levels of the inflammation marker C-reactive protein (CRP) and atrial fibrillation (AF). Inflammatory markers, mainly CRP, have been related to the risk of developing AF, the persistence of AF (paroxysmal, persistent, permanent), recurrence after cardioversion, and left atrium enlargement. Now Greek researchers weigh in with a study designed to determine the relationship between CRP level prior to cardioversion and time to first recurrent afib episode.

The study included 60 patients with persistent afib between the ages of 61 and 75 years, 60% of whom were men. The participants were free of valvular heart disease, congestive heart failure, prior heart attack, and thyroid dysfunction, so were a relatively healthy group although not classified as lone afibbers. A significant exclusion criteria was that the patients could not have been taking antioxidants or multivitamins. They had their CRP level measured prior to direct current cardioversion and were given amiodarone after the conversion (200 mg/day x 3 during first week, 200 mg/day x 2 during second week, and 200 mg/day thereafter). Patients who did not convert or who reverted back to AF within an hour were excluded from further follow-up.

The researchers found a clear correlation between CRP level and the percentage of patients who remained in sinus rhythm over the 3-year follow-up period. In the group of patients with a CRP level less than 0.43 mg/dL (4.3 mg/L), 45% were still in sinus rhythm at the end of 3 years. The corresponding figures for CRP levels between 0.43 and 0.8 mg/dL and CRP level greater than 0.8 mg/dL were 13% and 17% respectively. The researchers conclude that baseline CRP levels can be used to estimate the likelihood of persistent afibbers remaining in sinus rhythm after undergoing a successful electrical cardioversion.

Korantzopoulos, P, et al. Long-term prognostic value of baseline C-reactive protein in predicting recurrence of atrial fibrillation after electrical cardioversion. **PACE**, *Vol. 31, October 2008, pp. 1272-76*

Editor's comment: This study adds to the evidence of a close association between inflammation, as measured by CRP level, and the risk and persistence of AF. Although it is not entirely clear whether inflammation causes AF or AF causes inflammation, it would seem prudent for afibbers to maintain their CRP levels as low as possible. This can be achieved by regular supplementation with such natural anti-inflammatories as Zyflamend, beta-sitosterol, bromelain, curcumin, boswellia, Moducare, quercetin, and fish oil.

Natural Treatments & Prevention

N-acetylcysteine helps prevent post-operative AF

ISPARTA, TURKEY. N-acetylcysteine (NAC) has anti-inflammatory properties and is the precursor of glutathione, the body's main indigenous antioxidant. It is effective in counteracting the effects of acetaminophen (Tylenol, Paracetamol) poisoning and is protective against kidney damage caused by exposure to x-ray dyes (contrast media). Turkish researchers now report that NAC is also highly effective in preventing post-operative atrial fibrillation (AF). The development of AF following cardiac valve surgery and coronary artery bypass surgery is quite common affecting between 10% and 65% of patients. Considering that well over 500,000 bypass operations (half of which are likely unnecessary) are performed each year in the US alone, post-operative AF is clearly a major problem.

The Turkish researchers reasoned that since cardiac surgery is accompanied by inflammation, substantially increased oxidative stress, and a loss of glutathione, it would perhaps be beneficial to pre- and post-treat patients with a potent antioxidant and glutathione precursor such as NAC. Their randomized, double-blind, placebo-controlled clinical trial involved 115 patients 107 of which underwent bypass surgery alone, while the remaining 8 underwent valve surgery with or without accompanying bypass surgery.

Half of the study participants received an intravenous infusion of NAC one hour prior to their procedure followed by an infusion for 48 hours after the procedure. The amount of NAC infused prior to surgery was 50 mg/kg (3500 mg for a person weighing 70 kg – 154 lbs), while the amount infused during the 2 days following the procedure was 50 mg/kg per day. The other half of the group just received a standard saline infusion. All patients were monitored with 12-lead electrocardiography. No side effects of NAC administration were observed.

During follow-up 21.1% of patients in the placebo (saline infusion) group developed AF as compared to only 5.2% in the NAC-treated group – a 4-fold reduction in risk. All afib episodes converted to sinus rhythm either spontaneously or with the use of amiodarone. The researchers conclude that pre- and post-treatment with NAC substantially reduces the risk of post-operative AF and speculate that NAC therapy may be of value in AF patients.

Ozaydin, M, et al. N-acetylcysteine for the prevention of postoperative atrial fibrillation. European Heart Journal, *Vol. 29, 2008, pp. 625-31*

Editor's comment: There is little question that bypass surgery is a potent "recruiting ground" for afib patients. Whether or not these patients go on to have subsequent episodes is not clear, but certainly, anything that will help prevent that first episode is most welcome. Could regular supplementation with NAC help prevent future episodes? I am not aware of any evidence to this effect, but it certainly is an intriguing possibility. It is, unfortunately, not clear from the article whether the NAC was infused in a saline solution or in an aqueous solution. If indeed it was infused in the aqueous form (no salt), then it is possible that the observed benefits of NAC were at least partly due to the lack of salt (sodium chloride) in the infusion. Somehow, it does not seem like a great idea to infuse a salt solution after the patient has suffered the significant potassium loss always accompanying cardiac surgery.

PUFAs reduce surgery-induced AF

Atrial fibrillation is a common complication of coronary bypass-graft surgery (CABG). Polyunsaturated fatty acids (PUFAs), notably fish oils, have significant anti-inflammatory, anti-arrhythmic, and anti-thrombotic properties. Slovakian researchers recently completed a clinical trial to see if pre-treatment with PUFAs would reduce the incidence of post-CABG atrial fibrillation. Their study involved 44 patients undergoing CABG. Half of them received 2 grams/day of PUFA for 5 days prior to surgery until discharge from hospital. In this group 18% developed post-procedure afib as compared to 50% in the group not receiving PUFA treatment. There was also a significant difference in the average duration of hospitalization between the two groups – 9.3 days for the PUFA group vs 11.5 days for the non-PUFA group.

Journal of Cardiovascular Electrophysiology, *Vol. 18, Suppl. 2, October 2007, Abstract 24.5, p. S59*

New Chinese medicine-based antiarrhythmic

HONG KONG, CHINA. The contraction (depolarization) and resting (repolarization) periods of the heart cells are determined by the balance of the inward flow of calcium ions and the outward flow of potassium (K) ions. The major outward K currents are I_{Kur} (ultrarapid delayed rectified K+ current) and I_{to} (transient outward K+ current). The Class III antiarrhythmics (amiodarone, sotalol and dobutilide) work by blocking the outward K+ currents so as to increase the resting period (ERP) during which afib cannot be initiated. Ideally, only the K+ currents in the atria would be blocked since blocking them in the ventricles can lead to arrhythmias (proarrhythmic effects) and lengthening of the corrected QT interval (long-QT syndrome). I_{Kur} is only present in the atria, so a drug that would block only I_{Kur} would be a highly desirable antiarrhythmic.

Researchers at the University of Hong Kong now report that they may have found such a "drug" in the natural flavone, acacetin, derived from the traditional Chinese medicine *Xuelianhua*. Their experiments, so far, have only involved human heart cells and various animals, but are intriguing nevertheless. The researchers found that acacetin is non-toxic even when administered in relatively large doses. They also observed that it does not prolong the corrected QT interval in isolated rabbit hearts. Most importantly, they found that acacetin was highly effective in blocking both I_{Kur} and I_{to}, prolonged the atrial effective resting period (AERP), and prevented the induction of atrial fibrillation in dogs. As an added bonus, acacetin was also found to block the I_{Kach} (acetylcholine-activated K+ current), which may be instrumental in the initiation of vagally-induced afib.

Other research has shown that acacetin has anti-inflammatory effects, is an effective antioxidant, and exhibits anti-cancer effects in human prostate and lung cancer – truly a "super drug". The Chinese researchers conclude that oral acacetin is a promising agent for the prevention and treatment of atrial fibrillation.

Li, GR, et al. Acacetin, a natural flavone, selectively inhibits human atrial repolarization potassium currents and prevents atrial fibrillation in dogs. Circulation, *Vol. 117, May 13, 2008, pp. 2449-57*

Editor's comment: I usually do not report on cell culture and animal experiments since there is a distinct possibility that their results may not apply to humans. Nevertheless, I found the results of this study so fascinating that I decided to make an exception. As far as I know, acacetin is not available outside the laboratory, but *Xuelianhua* might be. Of course, there is no way of knowing whether this whole botanical medicine may have similar effects to the highly concentrated extract acacetin.

Walking helps prevent atrial fibrillation

BOSTON, MASSACHUSETTS. Although the average age at diagnosis of **lone** atrial fibrillation (LAF) is about 47 years, by far the majority of AF patients are diagnosed at age 65 years or older. Studies have shown that the 10-year risk of a 65-year-old developing AF is about 20%. Researchers at Harvard Medical School now report that older people can substantially reduce this risk by engaging in light to moderate exercise on a regular basis.

Their study included 5446 adults aged 65 years or older who enrolled in the Cardiovascular Health Study in 1989-1990. The participants were examined at baseline and every year for the 12-year follow-up period. About half the participants had hypertension, about 20% had coronary

heart disease, 25% had chronic pulmonary disease, and about 18% had diabetes when entering the study. During the follow-up, 1061 new cases of AF were diagnosed either during the annual ECG recordings or from hospital discharge records. Thus, about 1 in 5 participants developed AF during the follow-up. At the start of the study and at the 3rd and 7th annual visits usual leisure-time activity (kcal per week), usual exercise intensity, and usual walking habits were assessed.

The researchers observed that study participants who walked 60 or more city blocks (3-4 miles) a week had half the risk of developing AF than did those who walked 4 blocks or less a week. Walking pace was also important with people walking at speeds greater than 3 mph (4.8 km/hr) having half the risk of those walking at speeds less than 2 mph (3.2 km/hr). Regular engagement in leisure-time activities was also protective with participants expending in excess of 1840 kcal/week having a 36% lower risk of developing AF than those expending less than 35 kcal/week.

The relationship between exercise intensity and AF risk was U-shaped, that is, a low level of exercise and high intensity exercise were significantly less protective than was a moderate level of exercise which reduced AF risk by about 28% (compared to no exercise at all). NOTE: All the above risk reduction estimates have been adjusted for age, gender, race, education level, smoking status, alcohol use, use of beta-blockers, and the presence of coronary heart disease, chronic pulmonary disease and diabetes.

The researchers noted that having suffered a heart attack or having congestive heart failure increased the risk of developing AF by almost 5 times. They also point out that physical activity lowers blood pressure and resting heart rate, and improves glucose control, cholesterol levels, and mental well-being. They conclude that moderate physical exercise, especially walking, is associated with a significantly lower AF incidence in older adults.

Mozaffarian, D, et al. Physical activity and incidence of atrial fibrillation in older adults. **Circulation**, *Vol. 118, August 19, 2008, pp. 800-07*

Editor's comment: It is likely that the study underestimated the prevalence of paroxysmal AF, particularly the asymptomatic kind since ECGs were only obtained once a year or upon hospital admission. Nevertheless, walking half a mile a day at a brisk pace would seem to be a small price to pay to reduce the risk of non-lone atrial fibrillation by about 50%.

Prevention & Treatment with Antiarrhythmics

Genetic connection with response to antiarrhythmic drugs

NASHVILLE, TENNESSEE. There is increasing evidence that the renin-angiotensin-aldosterone system (RAAS) is involved in atrial fibrillation. (NOTE: This has been discussed in the Conference Room – Sessions 2 and 26). There is also recent evidence that the angiotensin-converting enzyme (ACE) has at least three common genetic variations (DD, II and ID) that can affect its blood level and activity. Thus, the DD variation increases ACE activity by 50%, while the ID variation increases it by 25%. This increase in activity has been associated with an elevated risk of experiencing a heart attack or suffering cardiac arrest.

Researchers at Vanderbilt University recently set out to determine if variations in the ACE gene could account for some of the differences experienced by afibbers in response to treatment with common antiarrhythmic drugs. Their study included 213 AF patients (34% were lone afibbers and 41% had hypertension). All patients measured their symptomatic afib burden (duration x frequency x score for severity) before and after being treated with an antiarrhythmic. If their burden decreased by 75% or more, then they were classified as responders. If their burden did not change or reduced by less than 75%, then they were classified as non-responders, and another drug was tried. The frequency of the three polymorphisms of the ACE gene was 25% for the DD mutation, 30% for the II variation, and 45% for the ID variation. Thus, at least 60% of the study participants had one or two D alleles (gene versions) corresponding to higher levels and increased activity of the ACE when compared to the activity of II ACE.

The response to common class I and III antiarrhythmics (flecainide, propafenone, sotalol) in lone afibbers was 95% in patients with the II allele, 59% in those with the ID allele, and 53% in those with the DD genotype (amiodarone efficacy was not affected by genotype). Put it another way, 31% of study participants did not derive benefit because of an unfavourable variation in their ACE gene. So it is clear that in a fair number of cases a lone afibber will not be able to find an antiarrhythmic that works for them simply because of their genetic make-up. The researchers speculate that patients with one or two D alleles might

benefit from adding an ACE inhibitor to their antiarrhythmic in order to compensate for the increased activity of their ACE gene.
Darbar, D, et al. ACE I/D polymorphism modulates symptomatic response to antiarrhythmic drug therapy in patients with lone atrial fibrillation. Heart Rhythm, *Vol. 4, June 2007, pp: 743-49*

Editor's comment: It is indeed welcome to see the continuing interest in linking the RAAS to lone atrial fibrillation. I am personally convinced that there is a strong link for many afibbers (including myself). However, until it is sorted out afibbers who have experienced no luck with propafenone (Rythmol) or flecainide (Tambocor) may consider asking their prescribing physician if they could run a trial with an ACE inhibitor in addition to their antiarrhythmic – lisinopril (Zestril, Prinivin) at 10 mg/day may be a good start. Of course, an even better approach would be to be tested for the ACE gene variations before adding an inhibitor, but for most afibbers this would probably be difficult to arrange.
http://www.afibbers.org/conference/session2.pdf
http://www.afibbers.org/conference/session26.pdf

Most vagal afibbers receive wrong medication

MAASTRICHT, THE NETHERLANDS. There is still widespread denial among North American cardiologists as to the existence of vagally-mediated AF (atrial fibrillation) and a pronounced tendency to treat all AF patients the same. Hopefully, this will now change with the publication of the results of the Euro Heart Study. This study involved over 5000 AF patients treated in 182 hospitals in 25 different countries.

A total of 1517 of the patients experienced paroxysmal (intermittent) afib and was studied in detail. Among this group, 42% (640 patients) had a distinct, physician-verified, autonomic pattern as far as triggering an episode was concerned. Another 35% reported no clear trigger patterns, while in the remaining 23%; the physician did not verify the presence of triggers. The authors of the study classified the trigger pattern as vagal if episodes occurred after a meal or during the night, and as adrenergic if initiated by exercise or emotional stress. Afibbers with no clear trigger pattern were classified as mixed.

Sixteen percent of the group had lone AF defined as afib without the presence of hypertension, coronary artery disease, or heart failure. Somewhat surprisingly, the researchers found no difference in the incidence of heart disease among vagal and adrenergic afibbers. Among the group with clearly defined trigger patterns, 18% were classified as vagal, 46% as adrenergic, and the remaining 36% as mixed. (NOTE: The distribution in our most recent LAF survey was 30% vagal, 6% adrenergic, and 64% mixed).

The major conclusions reached from the study are as follows:

- Exercise and emotional stress were the most common triggers followed by electrolyte imbalances, and alcohol and caffeine consumption.

- The majority (72%) of vagal afibbers received non-recommended drugs (beta-blockers, sotalol, digoxin or propafenone) – 57% were prescribed beta-blockers or sotalol.

- Vagal afibbers who were prescribed non-recommended drugs were more likely to progress to persistent or permanent AF than were vagal afibbers prescribed recommended drugs (primarily flecainide). After 1 year of follow-up, 19% of vagal afibbers prescribed non-recommended drugs had developed persistent or permanent afib as compared to 0% in the group prescribed correct drugs.

- Among adrenergic afibbers, 20% did not receive the medication recommended in the 2006 ACC/AHS/ESC Guidelines for the Management of Atrial Fibrillation. However, there was no indication that the type of medication affected progression to persistent or permanent in this group.

- Quality of care would appear to vary considerably between the regions in Europe. In the Mediterranean region 41% of patients received the recommended treatment as compared to 20% in Central Europe, and only 19% in Western Europe. Similarly, in the Mediterranean region physicians verified the presence of triggers in 75% of cases as compared to 79% in Central Europe and only 46% in Western Europe. *Editor's comment*: It would seem that afib care in Western Europe is substandard, but probably no worse than in North America.

- The authors point out that beta-blockers are often given in conjunction with class 1C antiarrhythmics (flecainide and propafenone) in order to prevent 1:1 conduction in the case of atrial flutter induced by the class 1C drug. They suggest that verapamil and diltiazem could be used as safer alternatives.

The authors conclude, "*Physicians do not seem to choose rhythm or rate control medication based upon autonomic trigger pattern of AF. However, the role of autonomic influences should be taken into*

consideration in order to achieve an optimal management of the disease as non-recommended treatment may result in aggravation of the arrhythmia."

de Vos, CB, et al. Autonomic trigger patterns and anti-arrhythmic treatment of paroxysmal atrial fibrillation: data from the Euro Heart Survey. European Heart Journal, *Vol. 29, 2008, pp. 632-39*

Editor's comment: Although not specifically directed at lone AF, this new European study is clearly a landmark and emphasizes the importance of determining trigger pattern (vagal, adrenergic or mixed) before prescribing medication for paroxysmal afibbers. It is interesting that our first LAF Survey (February 2001) revealed that 50% of vagal afibbers had been prescribed non-recommended drugs. This resulted in an average afib burden (# of episodes times their duration) more than twice as high than the burden among vagal afibbers taking flecainide or disopyramide. As far as propafenone (Rythmol) is concerned, the situation may not be as clear-cut as suggested in the Euro Heart Study. Some vagal afibbers have found this drug quite useful. Some fairly recent research have found that the degree of beta-blocking effect exhibited by propafenone depends markedly on how fast it is metabolized, so this may explain why it works for some vagal afibbers, while it is contraindicated in most others.

Statin drugs are dangerous

WASHINGTON, DC. Well over a thousand cases of rhabdomyolysis (an often fatal muscle disease) caused by the ingestion of statin drugs (atorvastatin [Lipitor], simvastatin [Zocor], lovastatin [Mevacor], pravastatin [Pravachol]) have been reported. Now the FDA has issued a warning not to take more than 20 mg/day of simvastatin if also taking amiodarone since doing so will markedly increase the risk of rhabdomyolysis. The warning also applies to the combination of simvastatin and ezetimibe (Vytorin) and the combination of simvastatin and extended-release niacin (Simcor). The FDA press release states that:

- The risk of rhabdomyolysis is increased when higher doses of simvastatin are administered with amiodarone. The precise mechanism is unknown, but is related to the fact that amiodarone inhibits the cytochrome P450 3A4 (CYP3A4) enzyme. This is the same enzyme that metabolizes simvastatin. Prescribers should consider use of another statin for patients taking amiodarone, or initiating amiodarone therapy, who require simvastatin doses greater than 20 mg daily to meet their lipid goals.

- Rhabdomyolysis has been reported with all statins. Predisposing risk factors for rhabdomyolysis include

advanced age (greater than 65 years), uncontrolled hypothyroidism, and renal impairment.

- The FDA does not have data on how varying the dose of amiodarone in patients taking simvastatin affects the risk of developing rhabdomyolysis.

http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm

Editor's comment: If a combination of amiodarone and 20 mg/day or more of simvastatin is dangerous enough to require a warning, how dangerous is amiodarone plus 10 mg/day? Who knows? The FDA does not seem to. What is perhaps more disturbing is that the FDA has no data regarding the effect of amiodarone dosage on rhabdomyolysis incidence when combined with simvastatin. Could simvastatin combined with a loading dose of amiodarone (800 – 1600 mg/day) be vastly more dangerous than the combination of simvastatin and an amiodarone maintenance dose of 200 – 400 mg/day? Nobody knows, so afibbers on or contemplating amiodarone should be very careful about also taking statin drugs, particularly simvastatin.

Antiarrhythmics vs. ablation

HAMILTON, CANADA. Current guidelines for the management of atrial fibrillation (AF) recommend first-line treatment with antiarrhythmics. However, the efficacy of antiarrhythmics such as sotalol, propafenone, and flecainide in preventing recurrence over a one-year period is only about 50% or less. Amiodarone is somewhat more effective (prevents recurrence in about 65% of cases), but comes with serious potential side effects. Researchers at McMaster University now report on a study to determine the relative efficacy of radiofrequency (RF) ablation and treatment with antiarrhythmics.

Their study involved a meta-analysis of 6 randomized trials comparing RF ablation with antiarrhythmic mediations in the treatment of AF. About two-thirds of the patients involved in the trials had structural heart disease and most had paroxysmal or persistent afib. Most of the trials were performed at high volume centers, with expert operators performing the ablations. A total of 348 patients were assigned to receive antiarrhythmics (sotalol, class I agents or amiodarone), while 345 were assigned to undergo a PVI followed by linear ablation and ablation of fractionated electrograms as appropriate. Touch-up procedures were allowed within the blanking period of the trials (first 2 to 3 months after ablation).

At the end of the one-year follow-up period, only 27% of the drug-treated patients were still in sinus rhythm as compared to 76% in the ablation group – a relative risk reduction for recurrence of 65% for ablation vs. drug treatment. The researchers suggest that their findings raise a couple of interesting questions:

- *Should we wait for patients to fail antiarrhythmic medications before recommending catheter ablation?*
- *Is it possible that catheter ablation as a first-line treatment for AF will yield better results?*

Nair, GM, et al. A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. Journal of Cardiovascular Electrophysiology, *September 3, 2008 [Epub ahead of print]*

Editor's comment: It should be kept in mind that the above conclusions may not necessarily apply to lone afibbers. Class I drugs (flecainide, propafenone, disopyramide) can be quite effective in lone afibbers, but afib patients with underlying heart disease they may be dangerous. Thus, sotalol and amiodarone are the primary antiarrhythmics used among AF patients with underlying heart disease. The benefits of antiarrhythmics were evaluated in LAF Surveys 2 and 14. Class I drugs were found effective by about 55% of users in Survey 2 and by about 40% in Survey 14. Amiodarone was found effective by about 65% and sotalol by 32% in Survey 14. In considering the results of the meta-analysis, it should also be kept in mind that the ablations were performed by highly skilled operators. Personally, I would think that there would be little difference in efficacy between treatment with antiarrhythmics and ablations carried out by less experienced EPs.

Prevention & Treatment with Other Drugs

Safety of digoxin questioned

OSLO, NORWAY. Digoxin (digitalis, Lanoxin) is widely used in the treatment of heart failure in order to increase the force of heart muscle contractions (positive inotropic effect) and reduce heart rate (ventricular rate). This results in an increase in exercise capacity, but digoxin treatment has no effect on overall survival in heart failure patients. This raises the question, "Are the beneficial inotropic benefits of the drug counterbalanced by serious adverse effects?"

A team of American, Norwegian and Swedish researchers now provides a preliminary answer to this question. Their study involved 7329 participants in the SPORTIF III and IV trials aimed at comparing the effectiveness of the anticoagulants warfarin (Coumadin) and ximelagatran in afib patients. About 53% of participants were on digoxin throughout the study.

The researchers found a higher mortality (6.5%) in the digoxin group than in the group not using digoxin (4.1%). After adjusting for confounding variables, they conclude that digoxin users have a 53% (relative) higher mortality than do non-users. They suggest that in heart failure patients the adverse effects are counterbalanced by the positive inotropic effect, whereas in AF patients, who do not benefit from the inotropic effect, the adverse effects of digoxin dominate and lead to the 53% relative increase in mortality among users.

Gjesdal, K, et al. Digitalis: a dangerous drug in atrial fibrillation? Heart, *Vol. 94, 2008, pp. 191-96*

Editor's comment: In my 2001 book *Lone Atrial Fibrillation: Towards A Cure* I called digoxin "the medicine from hell" and warned that it should never be used by lone afibbers as it has been found to increase episode frequency and promote the conversion of paroxysmal afib to the permanent version. The above finding that digoxin also increases mortality among afibbers only strengthens my conviction that this is indeed a drug to be avoided.

Ablation - Procedures

Improved pulmonary vein isolation technique

CLEVELAND, OHIO. By far the majority of atrial fibrillation triggers are located in or around the pulmonary veins making pulmonary vein isolation (PVI) and pulmonary vein antrum isolation (PVAI) highly successful techniques for eliminating afib. Nevertheless, the procedures are not always successful with one of the reasons being that some triggers are located outside the ablation rings formed around the pulmonary veins.

EPs at the Cleveland Clinic estimate that the superior vena cava (large vein that carries the de-oxygenated blood from the upper half of the body to the right atrium) harbors about 6-8% of these extraneous (to the pulmonary veins) triggers. In a recent clinical trial they investigated the feasibility and safety of adding isolation of the superior vena cava (SVC) to the standard PVAI procedure as a means of improving overall success rate. The trial involved 407 afibbers with an average age of 55 years of which 51% had the paroxysmal variety, 39% were in permanent afib, and the remaining 10% had persistent afib.

The participants were divided into two groups – Group I consisting of 190 patients who had undergone an initial PVAI followed by a search for triggers in the SVC, and Group II who underwent a PVAI followed by empirical SVC isolation. Twenty-four patients (12%) in Group I exhibited triggers in the SVC (accompanied by triggers in the right superior pulmonary vein) that were successfully isolated leaving all 24 patients arrhythmia free for an average of 450 days post-procedure. Among the 217 Group II patients, 208 (96%) exhibited SVC potentials. These were successfully isolated by segmental ablation (approximately 50%) of the SVC circumference in 59% of patients. Complete ablation of the circumference was necessary in 19% of patients, and in 18% of patients complete isolation was not possible owing to excessive phrenic nerve stimulation.

During follow-up, 16% of all patients experienced afib recurrence. Six percent underwent successful PVAI or SVC touch-up procedures bringing the overall total success rate to 90%. The remaining 10% achieved satisfactory control of their afib through the use of previously ineffective antiarrhythmic drugs.

The Cleveland researchers conclude that the SVC harbors the majority of afib triggers outside the pulmonary veins, and that SVC isolation is feasible and safe and should be considered as a standard adjunct to a regular PVAI. They found no evidence of SVC stenosis, but warn that SVC isolation may not be possible in all patients due to the danger of phrenic nerve injury.

Arruda, M, et al. Electrical isolation of the superior vena cava. **Journal of Cardiovascular Electrophysiology**, *Vol. 18, December 2007, pp. 1261-66*

Successful application of *Stereotaxis* system

HOUSTON, TEXAS. The *Stereotaxis Niobe* system is a magnetically-guided, remotely-controlled system for performing radiofrequency (RF) ablation. It is usually combined with the CartoMerge system and a CT scan to provide accurate mapping and precise catheter location. The main advantages of the system are the substantially improved mapping accuracy, greater flexibility of the catheter enabling its tip to reach areas in the left atrium which may be difficult to reach with a manually-guided catheter, and the fact that the catheter movement can be controlled remotely, thus substantially reducing radiation exposure to the operator. It is expected that the use of the *Stereotaxis* system will significantly improve the outcome of RF ablations, even if carried out by relatively inexperienced electrophysiologists.

EPs at the Ohio State University Medical Center and the University of Texas now report on the case of a 72-year-old man experiencing daily episodes of atrial tachycardia causing palpitations and shortness of breath. The patients underwent a RF ablation using the *Stereotaxis* system with a 4-mm tip *Navistar-RMT* catheter. The operators located the source of the tachycardia and isolated it with 5 lesions (burns). The total procedure time was close to 5 hours (275 minutes) with a fluoroscopy time of 29 minutes. After the ablation it was no longer possible to induce the tachycardia. The authors of the report conclude that, "*From our experience in general, and this case in particular (where the entire mapping and ablation procedure was performed safely, effectively, and efficiently with remote navigation), we feel that Stereotaxis Niobe MNS potentially has wide applicability in the area of interventional ablation therapy of complex cardiac arrhythmias.*"

Mehta, R, et al. Successful ablation of focal left atrial tachycardia using Stereotaxis Niobe remote magnetic navigation system. **Europace**, *Vol. 10, 2008, pp. 280-83*

Editor's comment: Although one large study undertaken at the Cleveland Clinic found significant shortcomings with the *Stereotaxis* system when used in pulmonary vein isolation, it is expected that these shortcomings (inadequate lesion depth and charring at catheter tip) have been overcome through the development of an irrigated catheter. Other studies have confirmed the advantages of the system in achieving

immediate success in eliminating arrhythmias, but a definitive study of the long-term success rate of the system for PVI is still awaited.

Flutter ablation with *Stereotaxis* system

LEIPZIG, GERMANY. Radiofrequency (RF) catheter ablation of common right atrial flutter (cavotricuspid isthmus-dependent – CTI) is a comparatively simple procedure with a success rate of about 95%. Because the location of the electrical circuit involved in the flutter is so well-established, this procedure lends itself particularly well to the use of electroanatomical (CARTO) mapping. German researchers now report on their evaluation of a new system combining the CART-RMT mapping system with the Stereotaxis NIOBE II remote magnetic navigation system. The Stereotaxis system makes use of two stationary magnets (one of each side of the patient) that controls the movement of a magnetically-tipped RF ablation catheter. The system is operated remotely so the operator's exposure to x-ray radiation from fluoroscopy is minimized. An earlier version of the NIOBE II system used a 4-mm catheter, but the German researchers used a new, flexible-tip, 8-mm (non-irrigated) catheter.

The clinical trial involved 26 patients (23 men, mean age of 65 years). At the time of the ablation, 20 were in flutter (19 counter-clockwise and 1 clockwise), and the remaining 6 were in sinus rhythm. In the case of one patient, a conventional ablation had to be performed because of technical difficulties with the NIOBE system. Among the remaining 25 patients, 24 were successfully ablated (acute success rate of 95%). One patient had to be ablated with a conventional catheter before complete isthmus block could be achieved. The procedure, RF application, and fluoroscopy times were 80 minutes, 31 minutes, and 11 minutes respectively in the first group of 14 patients. In the remaining patients, the corresponding times were 45 minutes, 20 minutes, and 7.2 minutes respectively indicating a steep learning curve – in other words, the new technique is relatively easy to learn.

Compared to the conventional RF flutter ablation procedure, the fluoroscopy time was reduced by 43%, but overall procedure time did not change. There were no major complications in the group of 26 patients treated with the new system; however, significant charring was observed in 19% of patients. The researchers conclude that ablation of right atrial flutter with the NIOBE II/CARTOMERGE system is safe, feasible, and effective. However, they do make the following qualifying statement, "*This study was conducted to assess the acute results of RF catheter ablation using remote MNS and an 8-mm tip magnetic catheter. Therefore, no comment on the long-term outcome of this system for the ablation of AFL can be made*."

Arya, A, et al. Initial clinical experience with a remote magnetic catheter navigation system for ablation of cavotricuspid isthmus-dependent right atrial flutter. **PACE**, *Vol. 31, May 2008, pp. 597603*

Editor's comment: The combined Stereotaxis/CartoMerge system has now undergone at least 9 trials that I am aware of. All, but one, have shown good safety and impressive results as far as **acute** success is concerned. However, somewhat curiously, I am not aware of any trials that have reported on the long-term success of the procedure. Dr. Carlo Pappone and colleagues in Milan, Italy performed the first trial of the system in atrial fibrillation patients more than 2 years ago. The acute success rate, as measured by the lack of electrical conduction between the pulmonary veins and the left atrium shortly after placing the last ablation lesion, was an impressive 95%. However, as far as I know, long-term follow-up has not yet been reported, although there has been ample time to do so. Several studies have shown that **acute** success does by no means guarantee **long-term** success. As a matter of fact, long-term success (6 months or longer) may be as low as 50% even with a 95% acute success rate. Even though the Stereotaxis/CartoMerge system certainly looks like a winner, long-term data are still required to prove its ultimate efficacy.

Evaluation of Hansen Sensei robotic system

CLEVELAND, OHIO. The success of a pulmonary vein isolation (PVI) ablation depends on the location and quality of the lesions (burns) imparted during the procedure. Lesion quality, in turn, depends on such factors as catheter design, duration of burn, power (wattage) applied during the burn (for RF ablations), the pressure applied to the catheter during the burn, and last, but certainly not least, the stability of the catheter during the burn. The ultimate aim of lesion creation is to form a barrier preventing the propagation of electrical impulses throughout the entire thickness of the heart wall – without penetrating the wall in the process (tamponade) – very exacting work indeed!

The process (mapping) used in determining the location of the lesion(s) may involve the determination of electrical potentials or the location of anatomical features using electroanatomical (CARTO) mapping now increasingly associated with an overlay of a CT or MRI scan (CartoMerge). The actual ablation process is performed by the electrophysiologist (EP) who is standing next to the patient and manually directing a catheter, which extends from the femoral vein in the groin to the left atrium. Needless to say, this process takes great manual dexterity and experience and tends to produce very uneven results largely related to the skill of the EP.

Not surprisingly, a great deal of effort has been expended on coming up with ablation systems that will "level the playing field" by inserting a robot between the EP and the tip of the ablation catheter. Two such systems are now under evaluation. The **Stereotaxis system** uses a catheter with a magnetic head, which can be easily maneuvered to any location in the atria by controlling (remotely) the magnetic flux from 3 electromagnets placed to the right and left of the body (at heart level) and above the head. The **Hansen Sensei system** uses a robotic arm (placed next to the patient at groin level), which essentially guides a flexible sheath (tube) extending from the groin to the atria through the femoral vein. The ablation catheter is threaded through the sheath with only the tip (1 cm) extending from the sheath. The movement of the sheath can be very closely controlled by the robotic arm which, in turn, can be precisely controlled by the EP sitting at a remotely located console. Both systems have the great advantage of limiting radiation exposure to the operator by a factor of 10 or more.

A group of expert EPs (including Dr. Andrea Natale, Pr. Michel Haissaguerre, Pr. Pierre Jais, Dr. Walid Saliba, Dr. David Burkhart, Dr. Vivek Reddy, Dr. Luigi Di Biase, et al) now report on the first full scale evaluation of the Hansen Sensei system. The study involved 40 atrial fibrillation patients of which 90% had lone atrial fibrillation. The patients were recruited at 3 centers (Bordeaux, Coburg and Prague); their average age was 57 years, and most (75%) had paroxysmal afib with the remaining 25% having persistent afib. Twenty-three patients also had typical right atrial flutter. The patients (29 men and 11 women) underwent a pulmonary vein antrum isolation using CARTO mapping, ICE guidance, and the Hansen Sensei system. The 23 patients with flutter also underwent a right atrial flutter ablation. Total average procedure time for the afib ablation was about 3 hours with an ablation time of 106 minutes and fluoroscopy time of 83 minutes. The patients were followed for 12 months at which time 34 (85%) were free of any arrhythmia without antiarrhythmics, while 13% were free of arrhythmia while taking previously ineffective antiarrhythmics. There was one (2.5%) pericardial effusion associated with the use of the Hansen Sensei system.

The EPs conclude that the use of the robotic catheter remote control system for transseptal puncture and endocardial navigation and ablation is safe and feasible, and give results similar to those obtained by EPs using manual guidance. (Editor's note: Only the very best EPs would obtain a 98% complete and partial success rate with just one ablation). NOTE: This study was supported by a grant from Hansen Medical, Inc.

Saliba, W, et al. Atrial fibrillation ablation using a robotic catheter remote control system. **Journal of the American College of Cardiology**, *Vol. 51, June 24, 2008, pp. 2407-11*

Callans, DJ. Can we improve upon human performance in the electrophysiology laboratory? **Journal of the American College of Cardiology**, *Vol. 51, June 24, 2008, pp. 2412-13*

Editor's comment: This is indeed a very exciting study which, in contrast to other studies involving robotic guidance, actually presents long-term outcome results. It would seem that the Hansen Sensei system pretty well solves all the problems involved in creating "perfect" lesions except the one that besets all robotic systems – that of pressure control. However, work is apparently underway to develop a suitable pressure sensor that will hopefully solve this problem and perfectly emulate the pressure exerted by the hands of a skilled EP.

Vagal denervation may cure afib

The atrial fibrillation epidemic is clearly not confined to North America and Western Europe. It would seem that Russian EPs/cardiologists are also very active in the field of AF research. A team from the State Research Institute of Circulation Pathology in Novosibirsk reports that vagal denervation (destruction of vagal nerve endings) in the left atrium may be as effective as pulmonary vein isolation in curing AF. Vagal nerve endings are highly concentrated in the four ganglionated plexi (fat pads) found in the left atrium. (NOTE: There are three ganglionated plexi in the right atrium). The clinical trial involved 58 patients with drug-refractory afib of which 36% had the permanent variety. All patients underwent ablation of the four ganglionated plexi in the left atrium with no attempt to isolate the pulmonary veins. An average of 7 months after the procedure, 86% of the patients were free of afib without medications. The researchers observed a significant increase in resting heart rate after the procedure and also noted that heart rate variability parameters had changed with an increase in the sympathetic/parasympathetic ratio being quite evident.

Journal of Cardiovascular Electrophysiology, *Vol. 18, Suppl. 2, October 2007, Abstract 16.1, p. S36*

Ablation end-point testing not reliable

HAMBURG, GERMANY. It is common practice for electrophysiologists doing pulmonary vein isolations (PVIs) to check the quality of their work by using burst pacing to try to induce atrial fibrillation, or other atrial tachycardias, after the completion of the ablation. If atrial tachycardias are not inducible, the procedure is often considered complete and successful. German researchers now report that post-procedural non-inducibility is in no way a reliable indication of long-term success (avoidance of future atrial tachyarrhythmias).

The study included 60 patients (45 men and 15 women) with paroxysmal AF. The majority (85%) had no underlying structural heart disease, but 33% had a history of hypertension. The patients all underwent a PVI using electroanatomical mapping (CARTO, Pappone method) to create two continuous lesion circles (CCLs) around the right and left pulmonary veins. The completeness of electrical isolation was checked with two Lasso catheters within the ipsilateral (same side) pulmonary veins at least 30 minutes after completion of the ablation.

Atrial arrhythmia inducibility was then evaluated using 10-second burst pacing from the coronary sinus. Seventeen (28%) of the 60 patients (group II) developed sustained atrial tachyarrhythmias (AF in 8 patients, common-type atrial flutter in 6 patients, and left macro re-entrant atrial tachycardia in 3 patients). The remaining 43 patients (72%) did not develop tachyarrhythmias after burst pacing (group I). The researchers observed that the area encircled by the CCLs was significantly smaller in group II than in group I. There was also a trend for group II members to have a larger left atrial volume and area than found among group I members.

After an average follow-up of 16 months, 18 of the 43 patients (42%) in group I had experienced one or more episodes of atrial tachycardia (13 with recurrent AF and 5 with new atrial tachycardia with stable cycle length). In group II, 7 of 17 patients (41%) experienced atrial tachycardia (2 with recurrent AF and 5 with new atrial tachycardia with stable cycle length). All 25 patients with recurrent tachycardia underwent a repeat procedure and all showed signs of recovered electrical conduction between the pulmonary veins and the left atrium. Following the repeat procedure, 91% of group I and 94% of group II remained in stable sinus rhythm during the subsequent follow-up period of 21 months.
The researchers conclude that non-inducibility of post-procedural atrial tachyarrhythmia does not predict long-term success in paroxysmal afibbers having undergone a PVI. They also conclude that inducibility is associated with smaller isolated areas around the pulmonary veins.
Satomi, K, et al. Inducibility of atrial tachyarrhythmias after circumferential pulmonary vein isolation in patients with paroxysmal atrial fibrillation: clinical predictor and outcome during follow-up. **Europace**, *Vol. 10, 2008, pp. 949-54*

Editor's comment: It is interesting that the initial (first procedure) success rate was only about 58%, thus indicating that about half of all afibbers undergoing a PVI can count on needing a "touch-up" procedure before they are cured. It is also of interest that the immediate success rate as indicated by post-procedural non-inducibility is not a measure of long-term success. This should be kept in mind when evaluating trials of new catheters and robot-assisted ablation systems since such trials often

equate success with lack of conduction or inducibility immediately following the procedure.

Mesh catheter looks promising

FERRARA, ITALY. Currently radiofrequency (RF) pulmonary vein isolation (PVI) procedures employ 2 or 3 separate catheters for mapping, ablating and guidance. Manoeuvring 3 catheters in the small left atrium is very challenging indeed. Furthermore, the ablation rings burned around the pulmonary veins are produced one "dot" at a time, making the process time-consuming, while leaving the distinct possibility of gaps in the rings which can reinitiate afib. The use of the so-called cryo-balloon catheter makes it possible to produce an unbroken lesion ring, but still requires separate mapping.

Scientists and engineers at Bard Electrophysiology have now developed a new "mesh" catheter designed to perform both the mapping and ablation. The catheter looks somewhat like a metal-mesh balloon when expanded – it is, of course, deflated when it is advanced to the left atrium through a sheath (tube) inserted in the femoral vein. One part of the catheter is able to provide high definition voltage (potential) maps to guide the ablation and to check on its completeness, while a 6-mm band of electrodes (separated into 4 quadrants) delivers radiofrequency energy to create an unbroken ablation line around the edges of each pulmonary vein.

Italian EPs now report the first use of the *Mesh-Bard* catheter on a 45-year-old female afibbers who lapsed back into afib after an initially successful standard (CARTO) RF PVI. After remapping the left atrium, the EPs found evidence of lesion gaps in the left inferior and right superior veins. A repeat ablation was performed using the *Mesh-Bard* catheter. One single 5-minute RF application in each vein eliminated the offending potentials. The overall procedure time was 2 hours with only 12 minutes of fluoroscopy time. The patient was discharged after 2 days with no antiarrhythmic therapy and has been in normal sinus rhythm for 3 months.

More recently, an EP in Liverpool (Broadgreen Heart and Chest Centre) used the *Mesh-Bard* catheter on 2 AF patients and found it to be efficient and safe with a significantly shorter procedure time than current standard PVI procedures.

Pratola, C, et al. Paroxysmal atrial fibrillation ablation with the multipolar mapping and ablation catheter (Mesh-Bard). **PACE**, *Vol. 31, June 2008, pp. 753-56*

Editor's comment: The new *Mesh-Bard* catheter looks to be a well thought out device that should materially reduce procedure time while

providing more complete lesions, thus hopefully, reducing the need for repeat ablations. However, there is, as yet, no long-term data as to its ultimate success rate, nor is there sufficient data to pronounce on its safety, especially in regard to pulmonary vein stenosis and phrenic nerve injury. It is also clear that while the catheter may be successful in dealing with paroxysmal afib, which originates in the pulmonary veins, there is no evidence that it is also useful in ablations involving persistent and permanent afib.

Improvements in cryoablation

Cryoablation uses a nitrogen-cooled, rather than an electrically-heated, catheter to create ablation lesions in or around the pulmonary veins. The advantage of cryoablation is that the danger of pulmonary vein stenosis and atrioesophageal fistula is eliminated. A possible disadvantage is that cryo lesions may be less durable than those created via the application of radiofrequency energy. German researchers treated 94 afibbers (including 41 lone afibbers) with cryoablation using a newly developed 23 or 28 mm balloon catheter. NOTE: The advantage of a balloon catheter is that it produces a continuous ring-shaped lesion with just one or two applications. After a mean follow-up of 6 months (including 8 touch-ups), 77% of patients were free of afib. However, 4 patients (4%) developed phrenic nerve palsy, which disappeared over a 6-month period.

Journal of Cardiovascular Electrophysiology*, Vol. 18, Suppl. 2, October 2007, Abstract 16.7, p. S39*

Evaluation of new cryo-balloon technique

BAD NAUHEIM, GERMANY. In 1998 Professor Michel Haissaguerre at the Hopital Cardiologique du Haut Leveque in Bordeaux reported that paroxysmal atrial fibrillation was mainly triggered by "rogue" cell clusters in the pulmonary veins. Early ablation techniques aimed at isolating the pulmonary veins from the left atrium by using radiofrequency (RF) energy to "burn" a ring of lesions just inside the vein. Unfortunately, this led to several cases of pulmonary veins stenosis (narrowing of the diameter of a vein by 50% or more). Thus, newer RF ablation techniques place the lesion ring in the left atrium itself rather than inside the veins, thus avoiding the danger of stenosis.

Nevertheless, placing a complete lesion ring just inside the vein is still theoretically at least, the best way of ensuring a complete electrical barrier between the potentials originating in the veins and the left atrium itself. The search for a technique that could achieve this without the danger of stenosis eventually led to the development of cryoablation in which a catheter or inflated balloon (cryo-balloon) cooled with liquid

nitrogen is used to create the lesion ring. Early experiments showed that lesions created with cryoablation did not cause pulmonary vein stenosis.

German electrophysiologists now report on the evaluation of a new cryo-balloon device (*Arctic Front*, Cryocath, Quebec, Canada) and an 8-mm cryo-catheter (*Freezor Max*) also developed by Cryocath. Their clinical trial involved 293 patients with paroxysmal afib and 53 with persistent afib. The average age of the patients was 59 years (62% male). They had suffered from symptomatic afib for an average of 7 years and had tried at least two antiarrhythmic drugs with no success. Forty-five percent of the study participants had hypertension and another 17% had mild heart disease, but none had advanced structural heart disease.

The patients all underwent pulmonary vein isolation using either a 23-mm or a 28-mm diameter balloon (when inflated) and the 8-mm catheter as required to reach spots missed by the balloons. The procedure was performed under conscious sedation using electrophysiological mapping with Lasso catheters and fluoroscopy as needed. Total average procedure time was about 3 hours (170 minutes), fluoroscopy time averaged 40 minutes, and total cryo application averaged 46 minutes. Each vein, on average, received 2.8 cryo-balloon applications lasting about 5 minutes each. All patients remained on warfarin and antiarrhythmic medication for the first 3 months following the procedure (blanking period).

After the blanking period patients were scheduled for quarterly follow-up visits, which included 7-day Holter ECG recordings. After an average 12-month follow-up, 74% of paroxysmal afibbers had experienced no recurrence of AF without the use of antiarrhythmics. NOTE: A total of 79 paroxysmal afibbers were lost to follow-up for one reason or another; thus, the success rate based on the total number of patients undergoing the initial ablation is probably somewhere between 54% and 74%. The success rate among persistent afibbers was only 42%. The main adverse event during the trial was phrenic nerve palsy (PNP), which was observed in 26 patients (11%) during ablation of the right superior vein. Most (90%) of PNPs occurred during the use of the 23-mm balloon. All cases of PNP were fully resolved in less than a year. No cases of stenosis, atrioesophageal fistula, stroke or death occurred, but 2 patients (0.8%) did develop left atrial flutter during the blanking period. No other atrial tachycardia or flutter developed during follow-up.

The German researchers conclude that cryoablation is safe and effective for paroxysmal afibbers, but not recommended for those with persistent AF. NOTE: Five of the 16 authors of this paper had received financial support from Cryocath.

Neumann, T, et al. Circumferential pulmonary vein isolation with the cryoballoon technique. **Journal of the American College of Cardiology**, *Vol. 52, July 22, 2008, pp. 273-78*

Editor's comment: This large-scale trial of ablation using the cryo-balloon technique confirms that the procedure is safe and reasonably effective for paroxysmal afibbers, but much less so for persistent afibbers. This is not really too surprising since the cryo-balloon technique only addresses isolation of the pulmonary veins, but does not involve linear ablations and other substrate modifications necessary to adequately deal with persistent AF. It is, unfortunately, not clear from the article why only 214 of the original 293 paroxysmal afibbers were followed up in arriving at the 74% success rate. Thus, the quoted success rate would seem to be a bit uncertain and could, presumably, be as low as 55%.

Ablation - Complications

Atrial flutter after ablation

ANN ARBOR, MICHIGAN. Left atrial flutter and supraventricular tachycardia are not uncommon complications of otherwise successful pulmonary vein isolations (PVIs). The incidence of these tachycardias is highly dependent on the protocol used in the ablation procedure. Thus, about 3% of patients treated with the Haissaguerre method (segmental pulmonary vein isolation) can expect to develop a left atrial tachycardia (LAT). In contrast, 20-30% of patients undergoing a circumferential anatomical pulmonary vein isolation (Pappone method) with widely encircling PV lines plus mitral and roof lines may develop LAT.

Electrophysiologists at the University of Michigan report on their investigation of 78 patients who underwent an ablation for LAT after having undergone a circumferential anatomical PVI using the 3-dimensional CARTO mapping system. The researchers mapped a total of 155 LATs and found that 88% were the re-entry type, while 12% were of focal origin. They also noted that 96% of the re-entrant LATs were associated with gaps in ablation lines created during the original PVI. Repeated catheter ablations were successful in eliminating the LATs in 85% of the 78 patients with the most common ablation targets being the mitral isthmus, the left atrial roof, and the septum separating the right and left atrium.

At the 13-month follow-up 77% of the 78 patients were free of afib and LATs without the use of antiarrhythmics. The Michigan EPs conclude that it should be possible to reduce the incidence of LATs by ensuring complete isolation of the pulmonary veins, limiting the number of linear lesions, and ensuring the absence of gaps.

Chae, S, et al. Atrial tachycardia after circumferential pulmonary vein ablation of atrial fibrillation. Journal of the American College of Cardiology, *Vol. 50, No. 18, October 30, 2007, pp. 1781-87*

Daubert, JP. Iatrogenic left atrial tachycardias. Journal of the American College of Cardiology, *Vol. 50, No. 18, October 30, 2007, pp. 1788-90*

Editor's comment: The "revelation" that 20-30% of patients undergoing a circumferential PVI may develop a post-procedure left atrial tachycardia (flutter or SVT) is indeed discouraging and again emphasizes the need of carefully considering one's options and choosing a highly skilled EP for the procedure. NOTE: Both Dr. Natale and Profs. Haissaguerre and Jais

use the segmental procedure, which is associated with the lowest incidence of LATs.

LAA thrombi rare in PVI patients

CLEVELAND, OHIO. Suffering a stroke during or after a pulmonary vein isolation (PVI) procedure is fairly rare (approximately 1.5% incidence rate), but obviously constitutes a serious complication. To avoid stroke during the procedure, patients are usually pre-screened for clots in the left atrium (LA) and left atrial appendage (LAA) using CT scanning and/or transesophageal echocardiography (TEE). In addition, heparin is used during the procedure and warfarin after to avoid post-procedural stroke. It is not known just how frequent LA or LAA clots are found in patients prior to their PVI.

Electrophysiologists at the Cleveland Clinic have just published the results of a study involving 1221 afibbers who underwent a pulmonary vein antrum isolation during the period 2000-2004. All patients underwent a pre-procedure CT scan and 60 also underwent a TEE. Nine patients were found to have a thrombus (clot) in the LAA as per the CT scan; however, when checked with TEE only three were actually clots, while the remaining 6 were smoke-like echo.

Two of the 3 patients had permanent afib with an average left ventricular ejection fraction (LVEF) of 48%, while the sole paroxysmal afibbers with a clot had an ejection fraction of only 25%. Thus, no paroxysmal afibbers with an ejection fraction of 50% or greater (normal) experienced LAA thrombi. Inasmuch as lone afibbers, by definition, have normal LVEFs (50% or greater), there were no incidences of LAA clots in paroxysmal, lone afibbers. It is likely that the two permanent afibbers had underlying heart disease (average LVEF was 48%), so it is probably safe to assume that even permanent, lone afibbers would be very unlikely to have thrombi in the LAA.

The Cleveland EPs conclude that a pre-procedure CT scan may be all that is required and that the use of TEE may not be needed in the case of paroxysmal afibbers with normal (50% or greater) LVEF.

Khan, MN, et al. Low incidence of left atrial or left atrial appendage thrombus in patients with paroxysmal atrial fibrillation and normal EF who present for pulmonary vein antrum isolation procedure. **Journal of Cardiovascular Electrophysiology**, *Vol. 19, April 2008, pp. 356-58*

Editor's comment: This is good news indeed and confirms earlier research that lone afibbers are not prone to clot development in the LAA. As far as the CT scan or TEE is concerned, if given the choice, I would personally prefer the TEE so as to avoid the radiation inherent in CT

scanning and the potential adverse effects of the contrast medium (x-ray dye) used during the scan.

Complications in AF ablation

BALTIMORE, MARYLAND. Although the risk of dying during or after a RF ablation for atrial fibrillation is infinitesimally small, the risk of major complications is not negligible. A recent worldwide survey found a major complications rate of 6%, while a just published Italian study found a rate of 3.9%. A study at the Cleveland Clinic (400 patients) found a moderate-to-severe stenosis rate of 0.25%, a stroke/TIA rate of 0.8%, and the risk of tamponade at 0.5% for a total major event rate of 1.6%. In contrast, an Austrian study involving only 75 patients found a serious adverse event rate of 12%.

Electrophysiologists at Johns Hopkins Hospital in Baltimore now report on their complication rate in a series of 517 patients treated for atrial fibrillation by RF ablation during the period 2001 to 2007. Up until January 2003 the segmental (Haissaguerre) procedure was used. It was replaced by the circumferential (Pappone, CARTO) method and in March 2005 the CartoMerge system (combining CARTO and CT scan or MRI images) was added. The 517 patients underwent a total of 641 procedures (24% repeat rate). Overall success rate was not reported, but an earlier report from Johns Hopkins involving 200 patients gave the complete success rate as 28% after one procedure and 41% after multiple procedures. The most common major complications are listed below:

Stroke	7	1.1 %
Tamponade	8	1.2 %
Vascular injury	11	1.7 %
Pulmonary vein occlusion	1	0.2 %
Hemothorax	2	0.3 %
Heart block	1	0.2 %
Acute lung injury	1	0.2 %
Mitral valve injury	1	0.1 %
	32	5.0%

The researchers found an overall major complication rate of 5.0%. The rate was higher (6.0%) for patients over the age of 70 years and for women (7.8%). They conclude that complication rates for AF ablation remain significant.

Spragg, DD, et al. Complications of catheter ablation for atrial fibrillation: incidence and predictors. **Journal of Cardiovascular Electrophysiology**, *Vol. 19, June 2008, pp. 627-31*

Atrioesophageal fistula avoidance

MAINZ, GERMANY. The accidental creation of a fistula (hole) between the back wall of the left atrium and the esophagus is a rare but often fatal complication of pulmonary vein ablation. In early 2005 it was estimated that about 20 cases had occurred worldwide which would correspond to an incidence of 0.05% or less. The creation of an atrioesophageal fistula would appear to be more common when using the circumferential (Pappone) ablation approach than when using the segmental (Haissaguerre/Natale) approach. Clearly, avoiding lesion creation in the part of the left atrium that abuts the esophagus would be an effective way of avoiding a fistula, but would doing so reduce the likelihood of the ablation being successful? A team of German researchers recently set out to answer this question.

Their clinical trial involved 43 paroxysmal afibbers (28 men, 15 women) with an average age of 62 years. Seventy percent of the patients had idiopathic afib (lone afib of no known cause). The study participants were divided into 2 groups. Group A underwent a standard segmental pulmonary vein isolation (PVI) creating lesions to completely isolate (electrically) each pulmonary vein from the left atrium regardless of the anatomical relationship between the ablation sites and the esophagus. An average of 3.7 veins were successfully isolated and 67% of the patients had all veins completely isolated.

During the ablation of the remaining patients (Group B) special care was taken to avoid ablation over the esophagus (a stomach tube was inserted in the esophagus so that its location was clearly visible in fluoroscopy imaging). In Group B only 55% of the patients had all veins successfully isolated and the mean number of successfully isolated veins was 3.2. The study participants were followed up with ECGs and extended Holter monitoring for a minimum of 6 months. At the end of 3 months, 90% of patients in Group A and 95% of those in Group B were afib-free. Corresponding numbers at 6 months were 81% and 82%. However, one patient in Group A and 4 in Group B were treated with amiodarone. Assuming this treatment was continued would result in a complete success rate (no afib, no antiarrhythmics) of 76% in Group A and 64% in Group B.

The researchers also compared the outcome in patients where the PVI was performed without relevant changes due to the location of the esophagus and in those in which the ablation strategy was adjusted due to the proximity of the esophagus to the pulmonary veins. The freedom from afib (with or without antiarrhythmics) in the two groups after 6 months was 85% and 75% respectively. The researchers conclude that avoiding lesion creation in the vicinity of the esophagus does not have a

significant effect on afib recurrence rate during short-term and mid-term follow-up.

Kettering, K, et al. Segmental pulmonary vein ablation: success rates with and without exclusion of areas adjacent to the esophagus. **PACE**, *Vol. 31, June 2008, pp. 652-59*

Ablation - Outcome

Cryoablation outcome

MAASTRICHT, THE NETHERLANDS. Pulmonary vein isolation (PVI) using cryoablation is a procedure very similar to the standard PVI using radiofrequency energy for lesion creation except that it uses a nitrogen-cooled (–90° C) catheter rather than an electrically-heated catheter. Cryoablation is potentially safer than RF ablation in that the risk of pulmonary vein stenosis and esophageal injury is pretty well non-existent. The procedure also has the advantage that, since no pain is felt during lesion creation, it does not require conscious sedation or anaesthesia.

EPs at the Academic Hospital in Maastricht recently reported on the long-term success of the procedure. Their study included 70 patients (54 men and 16 women), 77% of whom had lone AF with the remaining having arterial hypertension (14%) or minimal heart disease (9%). The age of the patients ranged between 21 and 65 years (average of 40 years), their average left atrial diameter was 38 mm, and the left ventricular ejection fraction averaged 59% – in other words, a pretty healthy group. The patients had all failed one or two antiarrhythmic drugs (none had been on amiodarone), and had suffered from symptomatic afib episodes for an average of 4 years.

All patients underwent a segmental PVI using cryoablation. The Maastricht EPs were able to locate the specific offending vein(s) in 14% of cases and isolated only that vein or veins. In other cases, all veins were targeted. The patients were followed for an average of 33 months; the first 180 days via a transtelephonic event recorder and the following months via periodic Holter monitoring. At the end of the follow-up period, 49% were still in sinus rhythm without the use of antiarrhythmics, 22% were afib-free with the use of antiarrhythmics, 11% were improved more than 50% with the use of antiarrhythmics, and the remaining 18% had not benefited from the procedure. The researchers point out that the 10 patients in which the offending vein could be identified were all free of afib at the end of the follow-up period. They make the following interesting statement:

> *Atrial fibrillation is a disease with different stages. In early stages, paroxysmal and nonsustained episodes are the rule. In this stage, the triggers, mostly located in the pulmonary veins, are the main culprit of AF. Over*

> *time, atrial remodeling starts to occur, and more substrate becomes available to sustain longer episodes. Therefore, self-perpetuation of AF (AF begets AF) leads to the idea that a treatment strategy employed early in the disease would be more likely to succeed.*

The average procedure time was almost 6 hours with a fluoroscopy time of 88 minutes. One patient suffered a stroke during or after the procedure, another experienced a pulmonary embolism, and a third experienced transient phrenic nerve paralysis. No cases of stenosis or esophageal injury were detected.

Moreira, W, et al. Long-term follow-up after cryothermic ostial pulmonary vein isolation in paroxysmal atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 51, No. 8, February 26, 2008, pp. 850-55*

Editor's comment: A total success rate of 49% in a group of prime PVI candidates is not impressive; thus, there would seem to be no advantage of choosing cryoablation over a RF ablation carried out by a top-rated EP.

Long-term success of circumferential PVI

SYDNEY, AUSTRALIA. Circumferential anatomical pulmonary vein isolation (CAPVI or Pappone method) is an increasingly popular approach to curing AF via radiofrequency ablation. 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.

Researchers at the University of Sydney now report on the long-term success of the procedure in persistent and permanent afibbers. Their study involved 45 (80%) male afibbers and 11 female with either persistent (69.6%) or permanent (30.4%) afib who had failed an average of 2 antiarrhythmic drugs. The mean age of the patients was 56 years and they had suffered from afib from 1 to 12 years (average of 6.4 years). Nine patients (16.1%) had structural heart disease, 3.6% had coronary artery disease, 66.1% had hypertension, and 10% had impaired left ventricular systolic function.

All patients underwent a circumferential PVI guided by the CARTO electroanatomical mapping system with a merged, three-dimensional CT image of the heart. Lesions were positioned about one centimetre from the edge (ostia) of the pulmonary veins where they join the left atrium. The endpoint of the ablation was electrical isolation (from the left atrium) of all the pulmonary veins as measured with a Lasso mapping catheter. A

linear ablation (roof line) was added in 57% of patients and 25% also underwent a right atrial flutter ablation. Antiarrhythmics were continued for the first month after the procedure and then discontinued if there were no afib recurrences. Repeat procedures were common with 28.6% undergoing two procedures, 8.9% undergoing 3 procedures, and 1.8% undergoing 4 procedures. Four major complications, one each – stroke, TIA, tamponade, and atrio-esophageal fistula – were observed during the 86 procedures.

After a follow-up of 13 to 30 months (average of 21.6 months), 53.6% of the ablated patients were in normal sinus rhythm (NSR) without the use of antiarrhythmics, 32.1% were in NSR with the aid of antiarrhythmics, and the remaining 14.3% still experienced afib episodes; thus, according to our usual way of grading success, 53.6% of the procedures (including repeats) were complete successes, 32.1% were partial successes, and 14.3% were failures.

Early recurrence (symptomatic episodes within the first 90 days following the procedure) was quite common after the initial procedure (46.4%) as was late recurrence (symptomatic episodes more than 90 days post-procedure), which was experienced by 69.6%. Ten percent developed flutter after the initial PVI and required an extra procedure to correct this. After the final procedure 23.3% had an early recurrence, and 46.4% had a late recurrence. Most late recurrences occurred within 12 months of the procedure. The researchers observed that female afibbers and those with afib of long standing were more likely to experience recurrences. They also noted that experiencing late recurrence was not precluded by the absence of early recurrences.

Seow, SC, et al. Efficacy and late recurrences with wide electrical pulmonary vein isolation for persistent and permanent atrial fibrillation. **Europace,** *Vol. 9, 2007, pp. 1129-33*

Editor's comment: A final complete success rate (after repeat ablations) at 53.6% is not impressive, but probably about average for other than top-ranked institutions/EPs.

Long-term success of pulmonary vein isolation

ATHENS, GREECE. Pulmonary vein isolation (PVI) is now a well-established procedure for "curing" atrial fibrillation. Acute success rates (elimination of electrical potentials between pulmonary veins and the left atrium), measured shortly after lesion completion, are indeed impressive and often quoted as between 90 and 100%. Unfortunately, this does not mean that 90-100% of afibbers undergoing a PVI are free of afib for the remainder of their life, or even for the first 6 months after the procedure. A team of American and Greek researchers now provide the first evidence

that long-term (over 3 years) success rates are substantially less than generally believed.

Their study involved 39 patients (average age of 52 years, 87% male) with symptomatic paroxysmal atrial fibrillation (about 30% with LAF and 50% with hypertension). All patients underwent a first segmental PVI (antral in 4 cases) and were then followed for an average 3.5 years (minimum of 3 years). Total pulmonary vein isolation was verified in all cases before catheter withdrawal. During the follow-up, the team made the following observations:

- Ninety-two percent of all patients experienced at least one AF recurrence within 3 to 42 months of the initial procedure (first 2 months were considered a blanking period); 22% of these episodes were within the third month, 22% between months 3 and 12, and the remaining 56% occurred more than 12 months after the first procedure. This equates to a complete long-term success rate of 8% after just one ablation.

- Twenty-five of the 36 patients with recurrence (69%) underwent a second ablation. Among these, 10 patients (40%) experienced no relapse, while the remaining 15 (60%) were either classified as failures (60%), or went on to undergo a third ablation which was successful in 67% of cases. (NOTE: 80% of patients undergoing the third ablation had the circumferential procedure).

- Overall, the long-term (longer than 3 years) success rates were 21.4% for patients undergoing just one procedure, 52.6% for those undergoing two, and 66.7% for those who underwent 3 procedures. However, symptomatic improvement was reported in 67% of all patients.

The team concludes that, 3.5 years (on average, but minimum 3 years) after the initial procedure, 46% of study participants were free of afib, while 67% experienced symptomatic improvement. To accomplish this, almost half of the patients had a second procedure, and 15% underwent a third.

Katritsis, D, et al. Long-term follow-up after radiofrequency catheter ablation for atrial fibrillation. Europace*, Vol. 10, 2008, pp. 419-24*

Editor's comment: The long-term success rates found in this study are indeed sobering. It should be kept in mind though that the ablations were not performed at top-ranked institutions where success rates would be expected to be significantly higher. Nevertheless, the study clearly shows

that follow-up ablations may be the norm rather that the exception, and also makes it abundantly clear that acute success is in no way related to long-term success.

Early recurrence of AF not a good sign

It is generally believed that early recurrence of afib following a pulmonary vein isolation (PVI) procedure is not necessarily indicative of long-term failure. Arrhythmia specialists in Rio de Janeiro, Brazil, however, question this belief. Their clinical trial involved 121 afibbers (72% lone) who underwent PV antrum isolation guided by ICE (Natale method). Thirty percent of patients experienced one or more afib episodes during the first 6 weeks following their PVI. The late recurrence (after 21 months of follow-up) in this group was 51% as compared to only 7% in the groups of 91 patients who had not experienced episodes in the 6 weeks following their PVI.

Journal of Cardiovascular Electrophysiology*, Vol. 18, Suppl. 2, October 2007, Abstract 17.4, p. S41*

Left atrium function after RF ablation

BARCELONA, SPAIN. Many afibbers, myself included, have wondered just how efficient the pumping action of the left atrium is after undergoing an extensive RF ablation. Researchers at the University of Barcelona obviously wondered about this too and now report on a clinical trial to find the answer. They measured the left atrial ejection fraction (LA EF%) using cardiac magnetic resonance imaging (MRI) in 55 patients (in normal sinus rhythm) who had undergone one or more circumferential pulmonary vein ablations for paroxysmal or persistent AF. The researchers defined LA EP% as (LAmax – LAmin/LAmax) x 100 where LAmax is the volume of the left atrium immediately before the mitral valve opens to allow blood flow into the left ventricle, and LAmin is the volume immediately after closure of the mitral valve.

MRI was performed prior to the ablation and 4-6 months following the ablation. After an average of 1.2 ablations, 60% of the patients were in normal sinus rhythm (NSR) without the use of antiarrhythmics, 9% were in NSR with the use of antiarrhythmics, and the remaining 31% were still experiencing episodes. Patients were prescribed an antiarrhythmic for the first 4 weeks following the procedure and remained on warfarin for a minimum of 2 months post-procedure.

The researchers found that the LA EF% increased or remained stable in 68% of the patients whose ablation had been successful (with or without antiarrhythmics). In contrast, patients whose ablation had not been successful experienced an average drop of 11% in their LA EF%,

indicating that the contractibility of the left atrium had been impaired by the unsuccessful ablation. The decline in LA EF% was associated with a smaller decrease in LAmin after the ablation among patients with an unsuccessful procedure than among those with a successful one. The contractibility of the left atrial appendage was not affected by the ablation irrespective of outcome.

Perea, RJ, et al. Left atrial contractibility is preserved after successful circumferential pulmonary vein ablation in patients with atrial fibrillation. Journal of Cardiovascular Electrophysiology, *Vol. 19, April 2008, pp. 374-79*

Editor's comment: It is indeed comforting to know that the pumping action of the left atrium and the left atrial appendage is not likely to be impaired following a successful RF ablation.

Variables affecting PVI success

BARCELONA, SPAIN. It is known that the success or failure of a circumferential pulmonary vein ablation (Pappone method) depends on the amount of existing left atrial scarring observed during mapping, the area ablated in the left atrium, whether or not vagal denervation is performed, and the absence of AF inducibility after the procedure. There is also some evidence that the success rate in the case of non-paroxysmal (persistent and permanent) AF is less than that observed for paroxysmal AF.

Spanish researchers now add to our knowledge regarding pre-procedure factors that affect the final outcome of an anatomically-guided (CARTO) circumferential PVI (CPVA). Their study involved 148 patients, of which the majority (60.8%) had paroxysmal afib, while the remaining had either persistent (23.6%) or permanent (15.6%). The average age was 52 years and 82% were male. Eighty percent experienced lone atrial fibrillation (no underlying structural heart disease) and 33.8% had hypertension.

The patients all underwent a standard CPVA procedure using the CARTO mapping system and an 8-mm irrigated *Navistar* catheter. The procedure involved lesions encircling both left- and right-sided pulmonary veins as well as linear lesions along the posterior wall of the left atrium and along the mitral isthmus. The patients were followed for an average of 13 months at which time 73.6% were free of afib recurrences. A second procedure was needed in 22 patients (14.8%) because of recurrent afib or the development of left atrial flutter (9.5%), and a third procedure was needed in 4 patients (overall 18% repeat rate). Two patients suffered a TIA during the procedure, 6 developed post-procedural pericarditis, and 3 experienced cardiac tamponade, thus resulting in an overall major complication rate of 7.4%.

The researchers noted that the success rate of the procedure was negatively affected by advanced age, hypertension, permanent afib, elevated left atrial antero-posterior diameter (LAD), and elevated left ventricular end-systolic diameter. However, in multivariable analysis only hypertension (2.8 times risk) and elevated LAD (1.1 times risk) proved to be independent predictors of failure. They conclude that patients with a LAD at or below 45 mm and no hypertension could expect a favourable outcome in at least 85% of cases, while among those with hypertension and an enlarged left atrium (LAD >45 mm), a success rate of only about 50% could be expected.

Berruezo, A, et al. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. European Heart Journal, *Vol. 28, 2007, pp. 836-41*

Editor's comment: The finding that hypertension is associated with an almost three times greater likelihood of failure is indeed a sobering one. It is known that hypertension causes left atrial enlargement and fibrosis, but it is not clear whether controlling hypertension (through medications or supplements) will result in a better outcome.

Left atrial scarring predicts ablation failure

CLEVELAND, OHIO. Both electrophysiological and anatomical mapping has shown that a significant proportion of afibbers have significant scarring in the left atrium. Researchers at the Cleveland Clinic now report that such scarring is a strong predictor of failure of the pulmonary vein antrum isolation (PVAI) procedure for the elimination of AF. Their study involved 700 patients who underwent a PVAI during the period January 2002 to August 2003. The average age of the patients was 53 years and a little over half had lone AF (no structural heart disease). All underwent a standard PVAI guided by intracardiac echocardiography (ICE). Prior to creating the ablation lesions, the electrical potentials of the left atrium wall were carefully mapped using a multipolar Lasso catheter (later checked by the use of a NaviStar (CARTO) catheter).

Areas with no electrical activity were classified as scarred tissue and patients exhibiting 3 or more such areas were classified as having left atrial scarring (LAS). On average, scar tissue covered about 21% of the total left atrium surface area. The 42 patients (6%) with LAS had, on average, a larger left atrium diameter, a lower left ventricular ejection fraction, and a much higher level of C-reactive protein (CRP) – 5.93 mg/L vs 0.31 mg/L in the non-LAS group. NOTE: A CRP level of 0.31 mg/L is at the lower end of the normal range thus indicating that the majority of afibbers in the non-LAS group (94% of total) did not have an elevated CRP level. There was also a trend for LAS patients to be less likely to have paroxysmal afib (26% vs 40% in the non-LAS group), but this trend was

not statistically significant. Mean age, AF duration, and the incidence of structural heart disease were no different in the two groups.

All patients were prescribed an antiarrhythmic (dofetilide, flecainide, propafenone or sotalol) for a 2-month period (blanking period) after the completion of the PVAI and were then followed for an average of 16 months. The complete success rate (no afib, no antiarrhythmics) was 81% in the non-LAS group, but only 43% in the LAS group. Of the patients with afib recurrence, 17 of 24 in the LAS group and 117 of 128 in the non-LAS group underwent a second procedure. Complete success rate after the repeat procedure was 52% in LAS patients and 90% in non-LAS patients.

The researchers conclude that the presence of LAS is a strong predictor of PVAI failure with patients experiencing LAS having a 3.4 times greater risk of failure than non-LAS patients. They suggest that for those with LAS combining ablation with long-term drug therapy may be the most effective approach. It is also possible that more extensive ablation of the left atrial wall itself may prove helpful.

Verma, A, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. Journal of the American College of Cardiology, *Vol. 45, No. 2, January 18, 2005, pp. 285-92*

Editor's comment: Left atrial scarring, unfortunately, can only be determined by an electrophysiologic study, so it is not possible to say whether a patient is a good candidate for pulmonary vein ablation before the procedure is actually underway. None of the study participants had undergone a previous catheter ablation, so from this study it is not possible to conclude whether scar tissue originating from previous ablation(s) may also reduce the chance of success.

Early recurrence and final ablation outcome

VIENNA, AUSTRIA. Early recurrence of afib (within 48 hours of procedure completion) is not uncommon following a pulmonary vein isolation (PVI) procedure. However, it is not known whether early recurrence is associated with a poorer long-term prognosis. EPs at the Medical University of Vienna recently completed a study to investigate this.

The study included 234 patients undergoing catheter ablation for symptomatic paroxysmal or persistent AF. The average age of the patients was 57 years, 72% were men and 71% had paroxysmal AF with 82% experiencing daily or weekly episodes. Twenty-two percent had structural heart disease, so the majority (78%) of the group would be classified as lone afibbers. Thirty-five percent of the group underwent a segmental PVI (Haissaguerre method), while the remaining 65%

underwent an anatomically-guided (CARTO) circumferential PVI (Pappone method) including roof line and mitral isthmus line. Total procedure time was 173 minutes for the segmental procedure versus 142 minutes for the circumferential procedure with total fluoroscopy times of 64 and 46 minutes respectively.

Early afib recurrence (within 48 hours) was observed in 37% of the segmental group patients versus 46% in the circumferential group. After an average (median) follow-up of 12.7 months, 35% of study participants were free of afib without the use of antiarrhythmics, 23% were free of afib while on antiarrhythmics that had previously failed, and the remaining 42% still experienced episodes. Among paroxysmal afibbers, 64% were free of afib (with or without antiarrhythmics) at the end of the follow-up as compared to only 45% of persistent afibbers.

Early recurrence was a significant predictor of failure. Among paroxysmal afibbers, the long-term success rate (with and without antiarrhythmics) was 70% for those without early recurrence and 53% for those with early recurrence. Corresponding numbers for persistent afibbers were 59% and 32%. Early recurrence was a predictor of failure in both the segmental PVI group and in the circumferential group. Overall, ablated afibbers who experienced early recurrence experienced twice the risk of failure, as did those not experiencing early recurrence. However, the researchers emphasize that, despite this, 46% of those who experienced early recurrence still were free of afib at the end of the study period.
Richter, B, et al. Frequency of recurrence of atrial fibrillation within 48 hours after ablation and its impact on long-term outcome. American Journal of Cardiology*, Vol. 101, 2008, pp. 843-47*

Editor's comment: The success rates in this study are certainly not impressive (complete success rate of 35% after one procedure); however, there was no significant difference between the outcome of segmental (Haissaguerre) and circumferential (Pappone) procedures. It is of interest that the characteristics of the Vienna group – age at ablation: 57 years, male: 72%, and paroxysmal: 71% – are quite similar to those of the 516 afibbers responding to the 2007 ablation/maze survey. Here the average age at ablation was 56 years with 78% being male, and 78% being paroxysmal. The complete success rate achieved by the Austrian group (35%) is also very close to the average success rate (34%) found in the 2007 survey.

Predicting AF occurrence following ablation

BOSTON, MASSACHUSETTS. Success rates for pulmonary vein isolation (PVI) vary widely and depend primarily on the skill and experience of the electrophysiologist (EP) performing the ablation. In order to ensure

optimum results it is common practice to measure the electrical potential between the pulmonary veins and the left atrium outside of the ablation rings after completing the procedure. If potentials are still present, thus indicating incomplete isolation, the ablation is continued until no potentials are evident. At this point, some EPs consider the procedure complete, while others do a "final check" by trying to induce afib by rapid burst pacing of the atrium often accompanied by infusion of isoproterenol, a drug capable of inducing atrial fibrillation. If AF can be induced, then further ablation is carried out, if necessary on the left atrium wall and roof, the superior vena cava, etc. Only when AF can no longer be induced is the procedure deemed complete. Unfortunately, the lack of inducibility does not ensure long-term freedom from afib recurrence; thus, the search continues for a method to predict long-term success before the ablation procedure is terminated.

A group of researchers from Harvard Medical School and McGill University now report that trying to induce AF by administering an external shock (as done in electrocardioversion) to the ablatee after burst pacing and isoproterenol infusion may help in determining the need for further ablation, or the continued use of antiarrhythmics, in order to achieve long-term success. The study included 116 patients who underwent PVIs guided by electroanatomical mapping (CARTO, Pappone method). For 17 of the patients it was their second procedure. Following PV isolation, AF could be induced in 19 patients (16%) with burst pacing with or without isoproterenol. Nine of these patients were rendered non-inducible through further ablation. Burst pacing induced atrial tachycardia in 26 patients, 20 of whom were successfully ablated for this arrhythmia. Subsequent to the burst pacing, 81 patients in whom AF could not be induced were given a 30 J external shock timed to the peak of the R wave (most vulnerable time for initiation of AF). Among these patients, 16 went into afib, while in the remaining 65 (80%) afib could not be induced.

After an average follow-up of 16 months, 54% of ablatees in whom AF could be induced either by burst pacing or shock had experienced recurrent AF vs. only 21% among non-inducible patients. Comparing only those who were non-inducible by burst pacing and underwent subsequent shock, the recurrence rate at one year was 60% in patients who went into afib after the shock vs. only 18% in those who did not. The researchers conclude that administering a shock at the end of the procedure to ablatees who were non-inducible by burst pacing (with or without isoproterenol) may help to guide post-procedure management so as to reduce the incidence of recurrence. They also note that besides inducibility, mitral regurgitation was also associated with a poorer long-term success. Experiencing paroxysmal (intermittent) afib was, however, associated with a significantly better long-term prognosis than having persistent or permanent afib.

Wylie, JV, et al. Inducibility of atrial fibrillation with a synchronized external low energy shock post-pulmonary vein isolation predicts recurrent atrial fibrillation. Journal of Cardiovascular Electrophysiology *[Epub ahead of press]*
Ilkhanoff, L and Goldberger, JL. Recurrent atrial fibrillation after ablation. Journal of Cardiovascular Electrophysiology *[Epub ahead of press] (editorial comment)*

Editor's comment: This study clearly demonstrates that equating complete isolation of the pulmonary veins at the end of the procedure with long-term success is not realistic. Thus, results of studies using this endpoint as proof of the capability of new catheters, robot-assisted systems, etc. should be taken with a very large grain of salt indeed.

Late AF recurrence after pulmonary vein isolation

NEW YORK, NY. Most successfully ablated afibbers, myself included, do wonder sometimes if their cure is permanent or whether "the beast" will eventually rear its ugly head again. Researchers at the St. Luke's-Roosevelt Hospital Center now report on the long-term "durability" of initially successful pulmonary vein isolation (PVI) procedures.

Their study involved 350 consecutive patients (65% male) with paroxysmal (86%) or persistent (14%) atrial fibrillation. The authors do not state the proportion of lone afibbers in the group; however, 41% had hypertension, 29% had hyperlipidemia, and 15% had coronary artery disease. All patients underwent a standard PVI with no additional lesions. At the end of the first year following the procedure, 264 patients (75%) were still in normal sinus rhythm without the use of antiarrhythmics. These patients were followed for an additional 34 months (on average) during which time 20 paroxysmal (8.7%) and 3 persistent (8.8%) afibbers experienced recurrent bouts of symptomatic afib. The risk of recurrence was substantially higher among those with hypertension (70% vs. 39%) and hyperlipidemia (61% vs. 30%). None of the 264 patients were taking antiarrhythmics; however, 57% were on beta-blockers, 48% on statins, 14% on ACE inhibitors, and 10% on angiotensin II receptor blockers.

An actuarial calculation concluded that the recurrence rate was 5.8% at 2 years, 8.8% at 3 years, 13% at 4 years, and 25% at 5 years. However, the authors point out that the number of observations made at the 4- and 5-year marks were not sufficient to achieve statistical significance.

Eighteen of the 23 patients with late recurrence underwent a repeat PVI with additional linear lesions as necessary. In each case, mapping showed that electrical conduction had been re-established between the left atrium and at least one pulmonary vein. The researchers conclude that recurrence of afib after a seemingly successful PVI is related to one or more of the following factors:

- Presence of hypertension and/or hyperlipidemia (elevated levels of LDL cholesterol and/or triglycerides).
- Resumption of electrical connection at previously ablated sites.
- Failure to target all pulmonary veins during the initial ablation.
- Emergence of triggers outside the areas encircled by the PVI procedure.
- Progression of heart disease and modification of atrial substrate that would promote AF.

Shah, AN, et al. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. Journal of Cardiovascular Electrophysiology, *Vol. 19, July 2008, pp. 661-67*

Editor's comment: When considering the above conclusion that about 9% of afibbers undergoing an initially successful PVI can expect to be back in afib within 3 years, it should be kept in mind that this conclusion is unlikely to apply to a healthy lone afibbers without hypertension or hyperlipidemia who had their ablation performed by a highly skilled EP, especially if this EP took the time to look for triggers outside the pulmonary veins and eliminate them. I am not aware of any published data on this, but from my own survey (and gut feel), I would be very surprised if the percentage of lone afibbers who go back into afib after 3-5 years would exceed 3% - assuming that their PVI was performed by a highly skilled EP. Incidentally, the 9% figure for long-term relapse is very similar to the published figure of 8% for the Cox maze procedure.

Early recurrence and long-term failure

BORDEAUX, FRANCE. It is generally accepted that experiencing one or more afib episodes in the first month following a pulmonary vein isolation (PVI) procedure (early recurrence) is not a good sign and may indicate that the ablation was not successful. Thus, the question arises, "Should patients who experience episodes of AF (or atrial tachycardia) shortly after their first ablation be re-ablated within the first month, or would it be better to wait at least 3 months before undergoing a repeat ablation?" A recent trial carried out at the Hopital Cardiologique du Haut-Leveque set out to answer this question.

The trial included 302 afib patients who had their first PVI between January 2004 and September 2007. The average age of the patients was 55 years and about 82% were male. Most of the patients (83%) would be classified as having lone atrial fibrillation and were about evenly split between paroxysmal and persistent afibbers. All trial participants underwent a PVI guided by electrophysiological mapping (Haissaguerre

method) as well as a cavotricuspid isthmus ablation to prevent post-procedure right atrial flutter. Additional focal ablations and linear lesions were applied as necessary to achieve non-inducibility of AF by burst pacing at the end of the procedure.

Of the 302 patients ablated, 144 (48%) experienced no recurrence during the first month and received no further follow-up. NOTE: An early recurrence was defined as an episode of AF, atrial tachycardia, or ectopic activity lasting 3 minutes or more. Early recurrence was significantly associated with a lower left ventricular ejection fraction (60% vs. 65%) and longer duration of AF (87 months vs. 61 months). Of the remaining 158 patients with early recurrence, 7 could not be followed up for various reasons. Thus, 151 patients were available for the study to determine the merits, or otherwise, of repeat ablation within the first month following the initial procedure.

A total of 61 patients underwent an early re-ablation. After an 11-month follow-up, 49% experienced no further afib or tachycardia episodes. Among the 90 patients with early recurrence who did not undergo an early re-ablation, only 9% experienced no further arrhythmia incidence, with the remaining 91% requiring a repeat procedure. As far as a third procedure is concerned, this was needed by 36% of the group undergoing the early re-ablation and by 33% of the group undergoing late re-ablation.

Overall, the early re-ablation group underwent an average of 2.5 procedures, while the late re-ablation group underwent 2.2 procedures on average. The indication for a second ablation for AF was 50% of cases, atrial tachycardia was 46%, and incessant atrial ectopy was 4% of cases. The Bordeaux researchers conclude that the vast majority (91%) of afibbers who experience a recurrence within the first month after their initial PVI will have late occurrences as well. They also state that,

> *"Contrary to current thinking, early re-ablation within the first month is not deleterious, as there are fewer clinical recurrences compared with patients without early re-ablation. In all patients who have a second procedure, whether early or late, the rate of further ablation for clinical recurrences was the same; however, the total number of needed ablations was significantly higher in patients with early re-ablation".*

The following statement from the report is also of interest:

> *"Radiofrequency ablation has a proinflammatory effect leading to cellular dysfunction and is potentially pro-arrhythmogenic. Moreover, AF ablation modifies the*

> *autonomic nervous system by reducing vagal activity and increasing sympathetic activity that may explain these ER (early recurrences) after the procedure, due to changes on the atrial substrate"*.

Lellouche, N, et al. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early reablation. **Journal of Cardiovascular Electrophysiology**, *Vol. 19, June 2008, pp. 599-605*

Editor's comment: The initial procedure success rate reported here (48%) for the Bordeaux group is in line with the 46% reported in the 2007 ablation survey. The complete success rate after a second follow-up ablation would appear to be 83%, which is somewhat better than the 73% observed in our survey.

Surgical Procedures

Tachycardia after Cox maze

BIRMINGHAM, ALABAMA. The development of right or left atrial flutter/tachycardia after an otherwise successful PVI (pulmonary vein isolation) procedure is not uncommon. Most of these arrhythmias disappear on their own, but some persist and require a follow-up ablation. Surgeons at the University of Alabama now report that post-procedural tachycardias are also fairly common after Cox III maze procedures. Their study included 143 patients who had undergone the procedure during the period 1996 to 2005.

All patients were checked for arrhythmias at 2 and 8 weeks postoperatively; those experiencing palpitations at the 8-week check-up were monitored intensively with Holter monitors or event recorders and, if the tachyarrhythmia persisted, they underwent an electrophysiologic study and catheter ablation. A total of 22 patients (15%) were found to have developed a tachycardia that persisted for more than 8 weeks. Another 10 (7%) developed atrial fibrillation that was treated with medication. The electrophysiologic study of the 22 patients showed the presence of a total of 25 arrhythmias – 15 in the right atrium and 10 in the left atrium. The right atrial arrhythmias were evenly divided between the common counterclockwise right atrial flutter and macroreentrant right atrial arrhythmias that did not involve the cavotricuspid isthmus. Three of the left atrial tachycardias involved reentry around the mitral valve annulus, and the remaining 7 were mapped to the roof of the left atrium. It is of interest that the lesions around the mitral valve annulus were created with cryoablation. All post-operative flutter/tachycardias were successfully treated with standard catheter ablation and the patients have now been arrhythmia-free for over 3 years.

The Alabama surgeons conclude that the occurrence of post-operative flutter/tachycardia after a maze procedure is related to gaps in lesions lines either in the line itself or at the end of a line where it abuts an anatomic boundary.

McElderry, HT, et al. Proarrhythmic aspects of atrial fibrillation surgery. Circulation, *Vol. 117, January 15, 2008, pp. 155-62*

Editor's comment: It would appear that tachycardia/flutter may occur fairly often (10-30%) following both Cox maze procedures and PVIs. Fortunately, most of these arrhythmias disappear on their own, but some may require follow-up ablations which are usually successful.

Stroke Risk Factors

Platelet activation in acute atrial fibrillation

MAYWOOD, ILLINOIS. It is not known whether atrial fibrillation as such results in a hypercoagulable state that could increase the risk of ischemic stroke. A group of cardiovascular researchers at Loyola University Medical Center now provides an intriguing insight into this question.

Their study involved 22 patients with paroxysmal afib who were scheduled to undergo radiofrequency catheter ablation. The patients did not have left ventricular dysfunction, rheumatic valve disease, mitral valve prolapse, or any significant valvular regurgitation; however, about 30% had hypertension and about 14% had diabetes. The study participants were divided into two groups of 14 (Group A) and 8 patients (Group B) respectively. The only statistically significant difference between the two groups was a greater preponderance of men (93%) in Group A than in Group B (50%).

All patients were in sinus rhythm when the study began and had sheaths (tubes) inserted in the femoral veins and coronary sinus (via the right internal jugular vein) for collection of blood samples. Atrial fibrillation was induced for 15 minutes by burst pacing (330 bpm or a cycle length of 180 ms) in Group A resulting in a ventricular rate (heart beat) of 121 bpm. In Group B atrial pacing to achieve a ventricular rate at 120 bpm without going into afib was applied for 15 minutes. Analysis of blood samples taken at the coronary sinus in Group A revealed increased platelet activation and thrombin generation as well as reduced nitrogen oxide production when compared with Group B. The blood sample (systemic) taken from the femoral vein did not change with pacing indicating that the effect is localized to the heart – at least for the first 15 minutes.

The researchers conclude that their findings may help explain why short episodes of atrial fibrillation predispose to stroke, especially in patients with underlying vascular disease such as diabetes and hypertension.

Akar, JG, et al. Acute onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. Journal of the American College of Cardiology, *Vol. 51, May 6, 2008, pp. 1790-93*

Editor's comment: Obviously, the question is "Do these findings apply to lone afibbers without hypertension and diabetes?" Unfortunately, the researchers did not separate out the effects due to hypertensive/diabetic subjects vs. those with no stroke risk factors, so it is impossible to say and, in all fairness, the study population really was not large enough to allow such a separation. However, the results of this study would

certainly support the supplementation with natural antiplatelet agents such as vitamins C, E, B3 and B6, and fish oils, some of which would also have an inhibitory effect on the formation of prothrombin. Nattokinase would not have any effect on platelet activation or prothrombin or thrombin formation, but would be effective in increasing fibrinolytic actively and thereby prevent blood clots from forming.

Lifestyle and stroke risk

BOSTON, MASSACHUSETTS. There is overwhelming evidence that maintaining a healthy lifestyle (not smoking, eating a healthy diet, engaging in regular, moderate exercise, and maintaining optimal body weight) can reduce the risk of cancer, diabetes, and cardiovascular disease more than any other intervention.

Researchers at the Harvard Medical School now report that a healthy lifestyle also materially reduces the risk of suffering a stroke, particularly one caused by a blood clot or the rupture of atherosclerotic plaque (ischemic stroke). The Harvard researchers describe a low-risk lifestyle as:

- Not smoking
- A body mass index < 25 kg/m^2
- At least 30 minutes/day of moderate physical activity
- Modest alcohol consumption (5-30 g/day for men, 5-15 g/day for women)
- Scoring within the top 40% of a healthy diet score

A healthy diet was defined as follows:

- High intake of vegetables, fruits, nuts, soy and cereal fiber
- High ratio of chicken plus fish to red meat
- High ratio of polyunsaturated to saturated fat
- Low intake of *trans*-fatty acids
- Daily supplementation with multivitamins for 5 years or more

The Harvard lifestyle/stroke risk study is a very large one involving 43,685 men enrolled in the Health Professionals Follow-up Study (begun in 1986) and 71,243 women from the Nurses' Health Study (begun in 1976). All participants were free of cancer and cardiovascular disease at baseline. The mean age at baseline (study entry) was 50 years for women and 54 years for men.

During follow-up, a total of 994 strokes (600 ischemic, 161 hemorrhagic [caused by a burst blood vessel], and 233 of unknown type) were documented among male participants. A total of 1559 strokes (853

ischemic, 278 hemorrhagic, and 428 of unknown type) were documented among female participants. Women with all 5 low-risk factors as defined above were found to have an 81% lower risk of suffering a stroke (79% lower risk of suffering an ischemic stroke) compared with women who had none of these low-risk factors, i.e. a highly unhealthy lifestyle. Corresponding risk reductions for men were 69% for total stroke and 80% for ischemic stroke. Unfortunately, only 2% of women and 4% of men had all 5 low-risk factors. Heavy smoking was, by far, the most significant risk factor for stroke followed by obesity (BMI over 30 kg/m^2), lack of exercise, and excessive alcohol consumption.

Adherence to a healthy diet was clearly more important for women than for men with the very worst diet increasing total stroke risk by 47%, ischemic stroke risk by 33%, and hemorrhagic stroke risk by 70% among women. Corresponding figures for men were 16%, 16%, and 10%. The researchers conclude that 47% of all strokes (54% of ischemic strokes) among women can be attributed to lack of adherence to a low-risk lifestyle. Corresponding figures for men are 35% and 52%.

Chiuve, SE, et al. Primary prevention of stroke by healthy lifestyle. Circulation, *Vol. 118, August 26, 2008, pp. 947-54*

Gorelick, PB. Primary prevention of stroke – Impact of health lifestyle. Circulation, *Vol. 118, August 26, 2008, pp. 904-06 (editorial)*

Editor's comment: It is not clear how many person-years were involved in these follow-up studies. However, assuming that follow-up was completed in 2006 (last dietary evaluation was in 2002) would result in a maximum follow-up for women (nurses) of 2.14 million (30 x 71243) person-years and 0.87 million (20 x 43685) persons-years for men (health professionals). Thus, total stroke rates would be 0.11%/year for men and 0.07% for women. These are indeed very low rates when compared to the oft-quoted rate of 1%/year among the general US population. I noticed this discrepancy in a 14-year follow-up study of the health professionals published in 2003. Following is an explanation provided by Dr. Ka He, the lead author (personal communication to me, November 30, 2003):

The annual incidence of new and recurrent stroke in the US is about 700,000 according to the American Stroke Association. Based on a population of 270,000,000 the annual rate is 0.26 per 100 person-years, or 0.26% per year. Stroke risk, of course, increases with age so it would clearly be higher if, for example, only people over 50 years of age were considered. Says Dr. He, "*In our study, we only count the first event not recurrent stroke. Also, the participants are all healthcare professionals. They are health-conscious and relatively healthy (they were free from any CVD and diabetes). I would not be surprised if there is relatively low rate of stroke in our cohort.*"

Stroke Prevention

Genetic testing for patients on warfarin

SALT LAKE CITY, UTAH. Patients on warfarin need to be monitored regularly to ensure that the INR (International Normalized Ratio) of their blood is within the therapeutic range of 2.0 to 3.0. Values lower than this increase the risk of ischemic stroke (stroke caused by blockage of small arteries), while values above about 4.0 increase the risk of serious internal bleeding and hemorrhagic stroke (stroke caused by rupture of small arteries). It is estimated that the target range of 2.0 to 3.0 is only achieved in about 50% of all patients at any one time. Not surprisingly, warfarin is the second most common drug implicated in emergency room visits for adverse drug reactions.

It is clear that any protocol that would increase the time patients spend within the therapeutic range would be most welcome. Preliminary studies have shown that certain gene variations significantly affect the rate at which warfarin is metabolized and thus the INR. The FDA recently approved a new genetic test designed to determine the presence or absence of three genes affecting warfarin metabolism [CYP2C9 *2, CYP2C9 *3, and VKORC1(C1173T)].

Researchers at the University of Utah School of Medicine now report on the first trial of genotype-guided warfarin dosing. Two hundred patients starting on warfarin were randomized into a standard treatment arm and the genotype-guided arm. Patients in the standard arm were given 10 mg/day of warfarin for the first two days, 5 mg/day for the third day, and then an adjusted dosage based on their day 3 INR value. Patients in the genotype-guided arm were given an initial dose of from 2 to 16 mg/day for two days as determined by an algorithm taking into account age, weight, gender, and the presence or absence of the variant genotypes. Dosage was halved on day 3 and then adjusted according to INR. The adjustment was calculated as the ratio of the estimated individual weekly maintenance dose determined with the algorithm to the standard weekly dose. INR measurements were made on days 0, 3, 5, 8, 21, 60, and 90.

Somewhat surprisingly, the use of the genotype algorithm did not reduce the time patients had an INR outside the therapeutic range. In both cases, patients were outside the range about 30% of the time pretty evenly split between being too high and too low. It should be pointed out that the study participants were hospitalized, so likely received better care

and follow-up than if they had been outpatients. The researchers did notice that patients in the genotype arm required slightly fewer dose adjustments than did those in the standard arm. They also observed that patients who carried both the CYP2C9 and the VKORC1 variants had a greater risk of experiencing an INR greater than 4 than did those without these two gene variants. They recommend further, much larger (at least 2000 patients) trials to further evaluate their findings.

Anderson, JL, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. **Circulation,** *Vol. 116, November 27, 2007, pp. 2563-70*

Editor's comment: This study clearly shows that genotype-guided warfarin therapy does not reduce the time spent outside the recommended INR range of 2.0 to 3.0. It is possible that identifying carriers of both the gene variants may avoid some cases of overdosing, but this particular study did not have the statistical power to prove this. Says the lead investigator of the study, Dr. Jeffrey Anderson, " I think this approach has a lot of promise for the future, but it's maybe not ready for right now." Dr. Raymond Gibbons of the Mayo Clinic shares this view, "I definitely do not think doctors should rush out there and start giving genetic tests to all the patients they want to put on warfarin at the moment. Maybe one day this will happen, and yes, it does make sense, but we need evidence that it will have a real benefit, and that's not there yet."
http://www.theheart.org/printArticle.do?primaryKey=826363

Vitamin C protects against stroke

CAMBRIDGE, UNITED KINGDOM. Researchers at Cambridge University have confirmed that high blood levels of vitamin C (ascorbic acid) protect against stroke. Their study involved 20,649 men and women between the ages of 40 and 79 years when enrolled during the period 1993-1997. None of the participants had suffered a prior stroke. Blood samples were drawn and analyzed for ascorbic acid content at baseline and participants were then followed for an average of 10 years. During this time a total of 448 strokes occurred corresponding to an average annual stroke rate of 0.2%.

After adjusting for the possible effects of gender, age, smoking, BMI, blood pressure, cholesterol, physical activity, diabetes, heart attack, social class, alcohol consumption, and supplement use the researchers conclude that study participants whose blood plasma levels of vitamin C were above 66 micromol/L had a 42% lower risk of stroke than did those whose levels were below 41 micromol/L. They also observed a 17% reduction in stroke for every 20-micromol/L increase in plasma vitamin C concentration. A 20-micromol/L increase in plasma vitamin C

concentration can be achieved by adding one additional serving of fruit and vegetables daily.

It is also of interest to note that six times as many study participants in the high plasma vitamin C group were supplementing with vitamin C as compared to those in the low plasma vitamin C group (10.5% vs 1.9%).
Myint, PK, et al. Plasma vitamin C concentrations predict risk of incident stroke over 10 years in 20,649 participants of the European Prospective Investigation into Cancer. American Journal of Clinical Nutrition, *Vol. 87, January 1, 2008, pp. 64-69*

Editor's comment: An average reduction in stroke risk of 42% is indeed impressive and compares favourably with the 25-30% relative risk reduction often quoted for aspirin, and the 50-55% reduction attributed to warfarin, especially since increasing one's vitamin C intake is not associated with any adverse effects. The Cambridge researchers point out that vitamin C has a very short half-life in the blood (about 30 minutes), so spreading one's intake (whether through foods or supplements) throughout the day is essential.

Perils of aspirin discontinuation

LAUSANNE, SWITZERLAND. It is estimated that more than 50 million Americans now take a daily aspirin for the prevention of cardiovascular disease. While there is evidence that this practice may help prevent heart attacks in high-risk populations, there is no evidence that it may help prevent a first stroke or TIA (transient ischemic attack) in low-risk patients such as lone afibbers. Nevertheless, the ritual of the daily aspirin is clearly very popular and it is therefore of concern that interrupting this ritual may result in an increased risk of stroke.

Researchers at the University Hospital in Lausanne report a 3-fold increased risk of ischemic stroke in a group of high-risk patients who discontinued their aspirin therapy prior to scheduled surgery, because they experienced bleeding complications or interactions with other drugs, or because they or their physician decided that they no longer needed the aspirin. The study included 309 patients with an average age of 72 years who had suffered a recent stroke or TIA, and a control group of 309 patients who had a history of stroke or TIA, but had not suffered an event in the last 6 months. Neither group was particularly healthy with about 70% having hypertension, and 36% and 18% (control group) respectively having coronary heart disease. Thirteen participants in the patient group and 4 in the control group had discontinued aspirin at least 4 weeks prior to their TIA or stroke (patient group) or 4 weeks prior to being interviewed (control group).

The researchers found (after correcting for possible confounding variables such as coronary heart disease) that those who discontinued aspirin were 3.4 times more likely to experience a TIA or ischemic stroke than were patients who remained on the aspirin. Seventy percent of the strokes occurred within 10 days after discontinuation (mean: 9 days). The researchers conclude that the discontinuation of aspirin therapy could increase the risk of ischemic stroke in patients with multiple cardiovascular risk factors, mainly in those with coronary heart disease.

Maulaz, AB, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Archives of Neurology, *Vol. 62, August 2005, pp. 1217-20*

Llinas, RH. Could discontinuation of aspirin therapy be a trigger for stroke? Nature Clinical Practice Neurology, *Vol. 2, June 2006, pp. 300-01*

Editor's comment: The patient groups evaluated in this study had multiple cardiovascular risk factors including hypertension, coronary heart disease, and diabetes. Thus, it is not at all clear whether the increased stroke risk accompanying aspirin withdrawal applies to afibbers with no underlying heart disease or other stroke risk factors. My guess would be that it probably does not. Nevertheless, if an afibber wishes to wean off the daily aspirin it may be prudent to replace it, at least for a couple of months, with one or more natural antiplatelet aggregation agents such as vitamin C, vitamin E, vitamin B6, niacin, fish oil, ginkgo biloba, or garlic.

Gamma-tocopherol in stroke prevention

MELBOURNE, AUSTRALIA. Natural vitamin E is not a single compound but a complex of at least four tocopherols (*alpha, beta, delta, and gamma*) and four tocotrienols (*alpha, beta, delta, and gamma*). *Alpha*-tocopherol is the predominant form found in human blood, while *gamma*-tocopherol is the predominant form found in food. Based on the finding that *alpha*-tocopherol is the most abundant form in blood, scientists concluded that it was also the most active and beneficial form. This led to the formulation of vitamin supplements based solely on *alpha*-tocopherol, and later to the synthesis and marketing of synthetic (*dl*-) *alpha*-tocopheryl acetate. *Dl-alpha*-tocopheryl acetate also quickly became the preferred form used in clinical trials aimed at evaluating the benefits of vitamin E, particularly in regard to cardiovascular disease.

A team of Australian and Chinese researchers now suggests that *gamma*-tocopherol may be significantly more effective than *alpha*-tocopherol and may be particularly beneficial in stroke prevention. Their clinical trial included 39 healthy volunteers (19 men and 20 women) between the ages of 20 and 40 years. The participants were randomly assigned to supplement with a placebo, or 100 mg/day or 200 mg/day of pure *gamma*-tocopherol. Blood samples were drawn for analysis at the beginning and end of the 5-week trial. Supplementation clearly increased *gamma*-tocopherol concentrations in blood serum from 5.3 to 16.8

mg/mL in the case of the 100-mg/day dose, and from 5.4 to 30.1 mg/mL in the case of the 200-mg/day dose. The serum concentration of *alpha*-tocopherol did not change significantly during the trial.

The researchers also noted a significant decrease in platelet activation, LDL cholesterol level, platelet aggregation, and mean platelet volume. They also made the following interesting observations:

- *"Several independent investigations have demonstrated that the blood concentration of gamma-tocopherol, not alpha-tocopherol, was negatively correlated to the incidence of coronary heart disease."*

- *"Supplementation with large amounts of alpha-tocopherol was shown to increase the breakdown and decrease blood concentrations of gamma-tocopherol."*

- Both natural and synthetic *alpha*-tocopherol suppresses serum *gamma*-tocopherol. The resulting imbalance between *alpha*- and *gamma*-tocopherol may have significant health consequences.

The researchers conclude that the results of their study suggest, "*that the daily consumption of small amounts of gamma-tocopherol, in conjunction with usual dietary intake from mixed food sources may provide protection from oxidative damage and prevent thrombosis*."
Singh, I, et al. Effects of gamma-tocopherol supplementation on thrombotic risk factors. Asia Pacific Journal of Clinical Nutrition, *Vol. 16, No. 3, 2007, pp. 422-28*

Editor's comment: The results of this study support my own long-held belief that supplements, especially vitamins and antioxidants, should always be taken in a formulation that mimics, as close as possible, the way the vitamin/antioxidant is found in nature. Thus, vitamin C should always be taken with the bioflavonoids with which it is associated in nature. B vitamins should always be taken as the whole complex, as should vitamin E with emphasis on natural *gamma*-tocopherol. The finding that *gamma*-tocopherol helps prevent thrombosis logically leads to the conclusion that it may also be effective in preventing transient ischemic attacks (TIAs) and ischemic stroke.

Bleeding risk with warfarin

BOSTON, MASSACHUSETTS. Clinical trials carried out in 1994 concluded that the use of warfarin in atrial fibrillation (AF) patients was relatively safe with an annual rate of major hemorrhage of 1.3%. Major hemorrhage is defined as a fatal bleeding incident, a bleeding incident

requiring hospitalization with transfusion of 2 or more units of packed red blood cells, or a bleeding incident involving a critical site (intracranial, intraspinal, pericardial, intraocular, etc). The average annual reduction in ischemic stroke rate in the five 1994 trials was 1.8% for patients over the age of 75 years with no risk factors for stroke, and 6.9% for those with one or more risk factors. Thus, it was concluded that treating older patients with warfarin had a favourable benefit/risk ratio.

Elaine Hylek and colleagues at the Boston University School of Medicine now question this conclusion. Their recently completed clinical trial involved 472 AF patients with an average age of 77 years (32% were 80 years or older). Forty-seven percent of the patients were women and 91% had one or more risk factors for ischemic stroke (75% had hypertension and 35% had coronary artery disease). After being admitted with a first AF episode (59%), a recurrent episode (35%), or permanent AF (6%) all study participants were prescribed warfarin with an INR target of 2.0 – 3.0. Management of warfarin dosage was carried out by the hospital's own anti-coagulation clinic. More than 10,000 INR measurements were made during the 1-year follow-up period. The time spent within the prescribed INR range (2.0 – 3.0) was only 58% with 29% being spent below 2.0 and 13% above 3.0.

The overall incidence of major hemorrhage was 7.2% and that of intracranial hemorrhage (hemorrhagic stroke) was 2.5%. A third of the hemorrhagic strokes were fatal and 89% of them occurred in patients 75 years or older. The incidence of major hemorrhage was particularly high (13.1%) among patients 80 years or older. Age and an INR greater than 4 were strong risk factors and 58% of the major hemorrhages occurred within the first 90 days after initiation of warfarin therapy. Concomitant use of aspirin was also a significant risk factor for major bleeding and there was no indication that taking 81 mg/day was any safer than taking the standard 325 mg/day.

During the study 26% of participants aged 80 years or older were taken off warfarin – 81% because of safety concerns and 19% because they regained normal sinus rhythm. The Boston researchers conclude that the risk of major bleeding among older AF patients on warfarin has been significantly underestimated in previous trials. They also point out that the rate of bleeding observed in their closely controlled clinical trial would likely be significantly lower than that experienced in the "real world".

In an accompanying editorial Dr. George Wyse of the Health Sciences Center in Calgary, Canada states, "*there is reason to be sceptical about net benefit when warfarin is used in some elderly patients with AF.*" Dr. Wyse also points out that warfarin therapy would appear to be over-utilized in patients with low to moderate risk of ischemic stroke. A recent

European study found that 50% of AF patients with no risk factors for stroke were being treated with warfarin or similar anticoagulants.

Hylek, EM, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation, *Vol. 115, May 29, 2007, pp. 2689-96*

Wyse, DG. Bleeding while starting anticoagulation for thromboembolism prophylaxis in elderly patients with atrial fibrillation. Circulation, *Vol. 115, May 29, 2007, pp. 2684-86*

Editor's comment: This study adds to the growing evidence that warfarin therapy is far from ideal for AF patients. It would appear to be over-prescribed for patients who don't need it and of no overall benefit for older patients with one or more risk factors for ischemic stroke.

Gender differences in aspirin effectiveness

UTRECHT, THE NETHERLANDS. Aspirin has been found effective in the prevention of heart attack (myocardial infarction), ischemic stroke, and cardiovascular death in patients who have already experienced a heart attack or stroke. Its benefits in primary prevention, that is in the prevention of a first heart attack or stroke, are much less clear. Researchers at the University Medical Center in Utrecht have just published a major study aimed at determining the benefits and risks of taking a daily aspirin for primary prevention of cardiovascular events. Taking into account all major studies on the subject as well as discharge statistics from Dutch hospitals, the researchers developed a computer model for predicting the risk of a first heart attack, ischemic stroke, hemorrhagic stroke, major gastrointestinal bleeding, and death in four specific age groups of men and women who were, or were not, taking aspirin on a daily basis.

Using a 55-year-old man with no cardiovascular risk factors as an example, they found an annual incidence of a first heart attack to be 0.40%/year with no aspirin and 0.28%/year with daily aspirin, or a relative risk decrease of 30%. There was no decrease in risk of a first ischemic stroke, but the relative risk increase of a first hemorrhagic stroke was 42%, and that of major gastrointestinal bleeding 42%. The daily aspirin did not prevent a first heart attack in 55-year-old women, but did reduce the risk of ischemic stroke from 0.07%/year to 0.05%/year, or a relative risk reduction of 24%. However, this benefit was offset by a relative risk increase of hemorrhagic stroke of 5% and of major gastrointestinal bleeding of 70%.

Overall, the researchers concluded that the risk involved in the daily aspirin ritual outweighs the benefit in healthy 55-year-old women. A healthy 55-year-old man may gain 3 days of "Quality Adjusted Life Years" (QALY) over a 10-year period by taking aspirin on a daily basis.

The net benefits of daily aspirin usage increased with increasing age and the presence of cardiovascular risk factors. For healthy men, the gain in QALY over a 10-year period was 9 days at age 65 years and 15 days at age 75 years. Corresponding numbers for women were a loss of one day at age 65 years and a gain of 6 days at age 75. However, for men with 5 times normal cardiovascular risk the net gain in QALY over a 10-year period was 34 days at age 55, 68 days at age 65, and 108 days at age 75. Corresponding numbers for women were 2 days, 12 days, and 38 days.

The researchers conclude that for most women aspirin treatment results in increased health care costs and worse health outcomes. However, for women 65 years or older with 5-times-increased cardiovascular risk, aspirin may have a favourable benefit/risk ratio. The benefits for healthy men are not impressive until age 75, but daily aspirin would generally seem to be beneficial for men with moderate or high risk for cardiovascular disease.

Greving, JP, et al. Cost-effectiveness of aspirin treatment in the primary prevention of cardiovascular disease events in subgroups based on age, gender, and varying cardiovascular risk. Circulation, *Vol. 117, June 3, 2008, pp. 2875-83*

Mosca, L. Aspirin chemoprevention – one size does not fit all. Circulation, *Vol. 117, June 3, 2008, pp. 2844-46*

Editor's comment: The major "take-home" message from this study is that one size does definitely not fit all when it comes to using aspirin for prevention of a first cardiovascular event. In general, aspirin may benefit men with a 10-year cardiovascular disease risk greater than 10% and women with a 10-year cardiovascular disease risk greater then 15%.

Vitamin C and warfarin

NEWCASTLE, UNITED KINGDOM. The evidence regarding a possible interaction between warfarin (Coumadin) and vitamin C is conflicting. A reduction in INR (shortening of bleeding time) was noted in 2 separate cases involving patients supplementing with 2 grams/day of vitamin C and an unspecified amount respectively. In contrast, a trial in which 5 patients supplemented with 1 gram/day for 14 days revealed no effect of vitamin C on INR. Another trial involving patients given 1 gram/day of vitamin C for 6 months demonstrated no change in required warfarin dosage compared with control patients not supplementing with vitamin C.

Finally, a trial involving 19 warfarin-treated patients given 3, 5, or 10 grams of vitamin C for 7 days showed no clinically important changes in INR, but did result in a 17.5% drop in total plasma warfarin concentration. The researchers involved in this study attribute the decreased absorption of warfarin to the loose stools or diarrhea often accompanying high vitamin C intakes.

A group of researchers at the University of Newcastle now report that normal dietary intakes of vitamin C (20-600 mg/day; 92 mg/day average) has no effect on warfarin clearance from the blood and thus is unlikely to affect INR. Their study involved 57 patients (31 males) who were receiving warfarin.

Wynne, H, et al. Dietary related plasma vitamin C concentration has no effect on anticoagulation response to warfarin. Thrombosis Research, *Vol. 118, 2006, pp. 501-04*

Editor's comment: The evidence regarding a possible effect of vitamin C on warfarin clearance and INR is clearly mixed. It would seem though that, while relatively small doses would be expected to have no effect, large doses (3-10 grams/day) may decrease plasma concentrations of warfarin and thus could potentially lead to a drop in INR. From the sparse data available, it would appear that the drop would be relatively minor (from 2.5 to 2.1, for example) and could safely be compensated for by a slight increase in warfarin dosage. In my opinion continuing supplementation (on a steady basis) with 3 x 500 mg/day of vitamin C when on warfarin would be far more beneficial than detrimental.

Warfarin replacements on the horizon

MAGDEBURG, GERMANY. 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 and 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 is being 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 essentially focuses on developing new pharmaceutical drugs which will inhibit specific coagulation factors. Among the more promising agents are:

- **Direct thrombin inhibitors** – The first of these, ximelagatran, showed great promise as a one-size-fits-all, once-a-day effective anticoagulant. Unfortunately, it was found to be

toxic to the liver and is now only approved (in Europe) for short-term use such as after knee replacement surgery. A newer direct thrombin inhibitor dabigatran etexilate (Pradax) 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. A very large phase II trial has just finished enrolment of 18,000 AF patients. In this study 2 doses of dabigatran (110 and 150 mg twice a day) will be compared to warfarin therapy. Results are expected by 2009. It is noteworthy that no studies, so far, have observed any excess liver toxicity associated with dabigatran.

- **Direct inhibitors of activated factor X** – two drugs, rivaroxaban and apixaban, are currently being investigated for stroke prevention in AF patients in 2 very large clinical trials involving 14,000 and 15,000 patients respectively. Rivaroxaban would appear to be the most promising of the two. Trials in over 1,000 patients with DVT found that 10-30 mg twice a day and 40 mg once a day were equally effective and had a low rate of bleeding and adverse events, and no sign of liver toxicity. However, lower doses may be required for patients with renal (kidney) impairment. Other activated factor X inhibitors include otamixaban and betrixaban and an extract from the nematode hookworm (NAP5), which is actually the most potent inhibitor identified so far.

- **Inhibitors of endocardial remodeling** – there is some indication that inhibitors of endocardial remodeling (fibrosis) may be useful in stroke prevention either alone or in combination with one of the above-mentioned drugs. Foremost in the research in this area are the angiotensin II type I receptor blockers (ARBs) which have been found to help block atrial thrombus formation.

The researchers conclude that, "novel anticoagulants or hybrid therapy with a combination of anticoagulants with inhibitors of endocardial remodeling like angiotensin II receptor blockers appear to be attractive future perspective approaches".

Hammwohner, M and Goette, A. Will warfarin soon be passé? New approaches to stroke prevention in atrial fibrillation. Journal of Cardiovascular Pharmacology, *Vol. 52, July 2008, pp. 18-27*

Editor's comment: It is indeed encouraging to see that a substantial research effort is being directed at replacing warfarin which, in my opinion, is very far from being an ideal stroke prevention remedy. I would not be surprised if a combination of dabigatran and an ARB such as losartan or irbesartan would turn out to be a winner with perhaps rivaroxaban being the "dark horse". It is very unfortunate that equal effort is not being put into carrying out phase III trials with such natural stroke prevention agents as magnesium, potassium, fish oils, nattokinase, vitamin C, vitamin E, niacin, and vitamin B6.

Role of Exercise

Exercise capacity after PVI

MILAN, ITALY. According to the Italian National Eligibility Guidelines for Continuing Sport Participation, patients with symptomatic atrial fibrillation and those on anticoagulation are prohibited from participating in competitive sports. Thus, it is of considerable interest to establish whether competitive athletes with afib can meet eligibility requirements after a successful pulmonary vein ablation (PVI). Researchers at the University of Milan now report on a clinical trial to determine this.

The trial involved 20 male athletes (average age of 44 years) who, after participating in competitive sports (cycling, long-distance running, soccer, and skiing) for an average of 25 years, had been disqualified because of symptomatic lone AF. Fourteen (70%) of the athletes experienced paroxysmal LAF, while the remaining 6 had the persistent variety. The study participants had suffered from afib for an average of 3 years and had failed 3 or 4 antiarrhythmic drugs (quinidine, flecainide, propafenone, and sotalol). They often experienced episodes during training. The impact of afib on the physical performance of the athletes was assessed by comparing pre-ablation maximal exercise performance (MEP) with post-ablation MEP, as well as with the average MEP measured in a group of matched athletes without AF.

All study participants underwent a segmental PVI accompanied by a flutter ablation, if indicated. At least 3 months after the first procedure, all participants underwent a planned second electrophysiology study and re-isolation of veins that had regained conductivity. The researchers noted that 81% of 77 veins isolated during the first procedure had regained some conductivity. Five patients (25%) needed a third procedure to achieve complete isolation. During a 3-year follow-up, 90% of the group were free of afib without the use of antiarrhythmics, and the remaining 2 patients were still experiencing infrequent, short episodes. All study participants were able to resume full training and met eligibility requirements 6 months after their final procedure.

The athletes underwent stress testing pre- and post-ablation. Prior to the first ablation the average MEP was 183 W with athletes experiencing afib during the stress test having a lower MEP (176 W) than those remaining in normal sinus rhythm (207 W). After the final ablation the average MEP in the group was 218 W, still somewhat lower than the average 231 W

recorded among matched athletes who had never experienced AF. It is of interest to note that 65% of study participants went into afib during training indicating adrenergic dominance, while at the same time 78% experienced episodes at night indicating vagal dominance.

In an accompanying editorial, Dr. Rachel Lampert of the Yale University School of Medicine gives an elegant explanation for this seeming paradox. Says Dr. Lampert,

> *"Data have also shown that sympathetic stimulation decreases atrial effective refractory period. Most relevant to the situation of the trained athlete are studies demonstrating that sympathetic activation acts synergistically with vagal stimulation to shorten the atrial refractory period further than either branch of the autonomic nervous system acting alone."*
>
> *"These findings imply that while both adrenergic and vagal activity can induce AF, the interaction between high levels of sympathetic and parasympathetic activity is particularly arrhythmogenic, a situation analogous to intense exercise in the trained athlete."*

Furlanello, F, et al. Radiofrequency catheter ablation of atrial fibrillation in athletes referred for disabling symptoms preventing usual training schedule and sport competition. Journal of Cardiovascular Electrophysiology*, published online, February 8, 2008*
Lampert, R. Atrial fibrillation in athletes: toward more effective therapy and better understanding. Journal of Cardiovascular Electrophysiology*, published online, March 21, 2008*

Editor's comment: It is clearly of great comfort to competitive athletes that it is possible to restore their ability to compete through extensive pulmonary vein isolation. Whether they will achieve their full pre-afib capacity is open to question since the average MEP after ablation was still only 218 W as compared to the 231 W measured in a group of matched non-afib athletes. The observation that intense exercise increases activation of both the sympathetic (adrenergic) and parasympathetic (vagal) nervous system resulting in a shortened atrial refractory period is of particular interest in explaining why competing athletes are more prone to developing lone afib than are less intense exercisers. Finally, the finding that 81% of ablated veins had regained some conductivity after the initial ablation goes a long way toward explaining the now quite common need for a "touch-up" ablation.

AF and long-term endurance sports practice

BARCELONA. SPAIN. Several studies have concluded that long-term participation in vigorous, sustained exercise (sports) increases the risk of developing lone atrial fibrillation (LAF). A group of Spanish researchers now confirm this connection. Their study included 183 male marathon runners (between the ages of 20 and 60 years) who had participated in the 1990 Barcelona marathon and joined the study between 1990 and 1992. The annual incidence of LAF in this group was compared to the incidence in a group of 290 largely sedentary men recruited from a general population study conducted in 1994-96.

The two groups were followed for 12 years and 6 years respectively. At the end of the follow-up period, 9 of the marathon runners and 2 of the control subjects had developed LAF. This corresponds to an annual incidence of 0.43% among the athletes as compared to 0.11% among the sedentary men.

The researchers conclude that the overall incidence of LAF among marathon runners is still relatively low at less than 0.5%/year, but distinctively higher than the incidence associated with a more sedentary lifestyle. The only statistically significant difference between athletes who developed afib and those who did not was a larger inferosuperior left atrial diameter in the afibbers. However, as the measurement of atrial dimensions was done after the diagnosis of LAF, it is not clear whether the enlargement helped precipitate the atrial fibrillation, or the atrial fibrillation caused the enlargement.

Molina, L, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. Europace, *Vol. 10, 2008, pp. 618-23*

Editor's comment: There would seem to be little doubt now that long-term, vigorous endurance exercise is a risk factor for the development of LAF. Whether a risk increase of 0.3%/year over that of sedentary men is acceptable is clearly a decision to be made by each athlete. Unfortunately, it is unlikely that endurance athletes worry about developing LAF until it is too late. It is interesting that the Spanish researchers use the following definition for LAF: "*Lone atrial fibrillation is characterized by the presence of atrial fibrillation in the absence of structural heart disease or other identifiable causes of arrhythmia such as hypertension, hyperthyroidism, or alcohol use*." This definition is actually more akin to the definition of idiopathic atrial fibrillation, i.e. afib with no known cause, but close to the definition we generally use.

The two faces of marathon running

ESSEN, GERMANY. It is well established that regular physical exercise reduces the risk of cardiovascular disease, but it is equally well

established that vigorous exercise increases the short-term risk of coronary events (heart attack and stroke), especially among elderly people not accustomed to exercise. A group of German researchers have now taken a look at the cardiovascular risk profile of 108 apparently healthy male marathon (42 km) runners aged 50 years or older and with at least 5 marathons under their belt. Not surprisingly, they found that the marathon runners' Framingham risk score (7%) was significantly lower than the score in a group of healthy age-matched controls (11%). Marathon runners experienced a 52% higher HDL cholesterol level, an 18% lower LDL cholesterol level, a 15% lower body mass index, and a 12% lower systolic blood pressure as well as a significantly lower resting heart rate (65 bpm vs 76 bpm). Coronary artery calcification (CAC) score was similar in marathon runners and age-matched men; however, when CAC scores were compared for marathon runners and age-matched men with a similar low Framingham risk score, then 36% of marathon runners were found to have a CAC score of 100 or higher as compared to only 22% in the control group.

MRI studies of the marathon runners indicated that 12% had late gadolinium enhancement (LGE), a marker of cardiovascular damage. Overall, LGE was associated with high CAC scores and an increased number of completed marathons. During a mean follow-up of 21 months, 4 coronary events occurred among the runners, 2 of which required resuscitation.

The researchers conclude that marathon running does not seem to protect against atherosclerosis as indicated by a high CAC score and may, in fact, exacerbate the problem due to excessive vascular oxidative stress, and frequent bursts of inflammatory cytokines experienced during long-distance running. The authors conclude that, *"Regular marathon running has a beneficial effect on the cardiovascular risk factor profile but the extent of calcified coronary plaque is underestimated from that risk factor profile, with 36% of marathon runners aged 50 years or greater having a CAC score of 100 or greater and 9% of these requiring coronary revascularization during two years of follow-up. Advanced CAC scores seem to contribute to increased myocardial damage and appear to impair outcome. Frequent marathon running may not protect these athletes from the risk of coronary events."*

Mohlenkamp, S, et al. Running: the risk of coronary events. **European Heart Journal**, *Vol. 29, 2008, pp. 1903-10*
Schmermund, A, et al. The risk of marathon runners – live it up, run fast, die young? **European Heart Journal**, *Vol. 29, 2008, pp. 1800-02 (editorial)*

Editor's comment: This study adds to the evidence that exercise in moderation is good, while vigorous exercise taken to extremes may produce unhealthy stress on the cardiovascular system.

Role of Inflammation

Inflammation in AF: Cause or effect?

HOUSTON, TEXAS. 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 conclude 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[1].

In January 2002 two research papers were published that clearly support the inflammation connection[2,3]. Both papers, one by American researchers (Cleveland Clinic) and one by Greek researchers, report a significant association between the level of C-reactive protein (CRP), a marker of inflammation, and the presence and severity of LAF.

The Cleveland researchers found that patients with AF, with or without structural heart disease, had significantly higher blood levels of 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 conclude that AF might induce or be induced by an inflammation, which in turn may promote the persistence of AF[2].

The 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 conclude that high CRP levels are strongly associated with the presence of AF and with a lower chance of successful cardioversion[3].

In a recent review of these and other studies researchers at Baylor College of Medicine conclude that inflammation plays a significant role in the perpetuation and maintenance of atrial fibrillation. They point out that inflammation is a potent risk factor for stroke and suggest that it would be advisable to reduce it. Statin drugs are known to have anti-inflammatory properties, but their role in actually preventing AF is not clear. The use of glucocorticoids (dexamethasone, cortisone, methylprednisolone) has been found effective in reducing CRP levels and post-operative afib. There is also some evidence that pharmacological conversion with propafenone is more effective and longer lasting if methylprednisolone is added to the protocol. The addition of methylprednisolone was also found to decrease CRP levels by 80%. Finally, it is possible that ACE inhibitors and angiotensin receptor blockers may help prevent inflammation-induced atrial remodeling and thereby reduce the risk of paroxysmal afib becoming permanent.

The Baylor College researchers conclude that the preponderance of evidence supports the conclusion that inflammation is an independent risk factor for the initiation and maintenance of AF, but do caution that it is still not clear whether inflammation causes AF or AF causes inflammation[4].

In order to answer this question Turkish researchers recently carried out an experiment in which an attempt was made to induce atrial fibrillation in 39 patients undergoing an electrophysiologic study for syncope (fainting) of undetermined origin or palpitations with no documented arrhythmias. None of the participants had been diagnosed with afib, or acute or chronic inflammatory diseases. CRP levels were measured before the EP study as well as 6 and 24 hours after the study. The researchers were able to induce afib in 18 patients leaving the remaining 21 patients as a control group. CRP levels at baseline were not significantly different between the two groups (2.8 mg/L vs 4.5 mg/L or 0.28 mg/dL and 0.45 mg/dL).

However, 24 hours after the procedure CRP increased in both groups. To 3.9 mg/L (0.39 mg/dL) in the control group compared to 10.0 mg/L (1.0 mg/dL) in the group in which afib was induced (average episode duration was 4.8 hours). The Turkish researchers conclude that the induction of afib was accompanied by a significant inflammatory process and that

even the EPS study by itself caused an increase in CRP (in the control group).[5]

References

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2. Chung, Mina K., et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation, Vol. 104, December 11, 2001, pp. 2886-91
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4. Issac, TT, et al. Role of inflammation in initiation and perpetuation of atrial fibrillation. Journal of the American College of Cardiology, Vol. 50, November 20, 2007, pp. 2021-28
5. Pirat, B, et al. Comparison of C-reactive protein levels in patients who do and do not develop atrial fibrillation during electrophysiologic study. American Journal of Cardiology, Vol. 100, 2007, pp. 1552-55

Editor's comment: It is obviously not clear whether atrial fibrillation is a consequence of inflammation or inflammation is a consequence of AF. However, it is known that inflammation is associated with remodeling of the atrium, which again is associated with perpetuation of the arrhythmia. Thus, it is clear that if an afibbers has signs of a systemic inflammation (CRP level above about 1.6 mg/L (0.16 mg/dL) steps should be taken to eliminate this inflammation. Apart from cutting out obvious inflammation triggers such as alcohol and caffeine, it would also be prudent to refrain from vigorous exercise and workouts until the inflammation has subsided. Supplementation with natural anti-inflammatories such as *Moducare*, curcumin, beta-sitosterol or *Zyflamend* is also an essential step in eliminating systemic inflammation and reducing CRP level.

Inflammation and atrial fibrillation

LINKOPING, SWEDEN. It is well recognized that there is a significant association between the level of the inflammatory markers C-reactive protein (CRP), and interleukin-6 (IL-6) and atrial fibrillation (AF) in general. However, it is not clear whether inflammation causes AF or AF causes inflammation. There is also evidence that the observed relationship between inflammation and AF is due not to afib as such, but rather to the comorbid conditions (heart disease, hypertension) that generally accompany it. Swedish researchers now add the results of a small pilot study to the knowledge base regarding AF and inflammation.

Their study involved 28 patients scheduled for radiofrequency ablation. Ten had paroxysmal AF, while 8 had permanent AF. None had structural

heart disease or inflammatory conditions. The control group consisted of 10 patients with Wolf-Parkinson-White (WPW) syndrome and no evidence of AF. After catheterization, but before ablation all patients had blood samples drawn from the femoral vein, right atrium, coronary sinus, and the left and right pulmonary veins. The level of CRP, IL-6, and IL-8 (interleukin-8) were measured in the samples.

All study participants were found to have normal levels of CRP and IL-6, thus confirming that lone AF is not associated with an increased CRP or IL-6 level. The level of IL-8, however, was elevated in participants with permanent AF, specifically in the samples from the femoral vein, right atrium, and coronary sinus. Surprisingly, the IL-8 level was not elevated in the samples from the pulmonary veins. The researchers conclude that permanent AF is associated with a systemic inflammation, perhaps caused by vascular endothelial damage or dysfunction. They also speculate that IL-8 may somehow be consumed during passage through the lungs. Their final conclusion is that, "*Taken together, these data seem to support the concept that the elevated levels of C-reactive protein and IL-6 in patients with AF reported in other studies were likely related to the presence of other co-morbid conditions that existed in these patient cohorts rather than to AF itself.*"

In an accompanying editorial two researchers point out that the increase in IL-8 may be related to endothelial activation, perhaps due to local perturbations in shear stress related to the irregular and fast heart rate experienced in permanent afib.

Liuba, I, et al. Source of inflammatory markers in patients with atrial fibrillation. **Europace**, *Vol. 10, 2008, pp. 848-53*
Melenovsky V and Lip, GYH. Interleukin-8 and atrial fibrillation. **Europace**, *Vol. 10, 2008, pp. 784-85 (editorial)*

Ablation-associated inflammation

SAN FRANCISCO, CALIFORNIA. There is substantial evidence that any kind of catheterization or surgical procedure involving the heart causes an inflammatory response. There is also evidence that inflammation can cause arrhythmia. Finally, it has been observed that recurrent afib episodes are fairly common in the first 3 months following a pulmonary vein isolation (PVI) procedure and the occurrence of such episodes is not necessarily indicative of long-term failure.

A group of electrophysiologists at the University of California now report that the level of the inflammation marker CRP increased significantly in a group of ablated afibbers who experienced recurrent episodes within the first 7 weeks following the procedure. A similar increase in CRP was not seen in afibbers who did not experience any afib episodes during their

first 7 weeks of recovery. The CRP level in both groups declined between the 7-week follow-up period and a second follow-up at 26 weeks.

The researchers conclude that the extent of left atrial tissue damage inherent in curative AF ablation generates a protracted inflammatory state with proarrhythmic effects.
McCabe, JM, et al. Protracted CRP elevation after atrial fibrillation ablation. PACE, *Vol. 31, September 2008, pp. 1146-51*

Editor's comment: I am still not sure in my own mind whether the association between elevated CRP levels and afib is due to inflammation causing afib or afib causing inflammation. However, assuming that inflammation is indeed the causative factor, then it would make sense to take steps to dampen the post-ablation inflammation by supplementing with natural anti-inflammatories such as Zyflamend, beta-sitosterol, bromelain, curcumin, boswellia, Moducare, quercetin, and fish oil.

Odds and Ends

Case studies with the experts

BOSTON, MASSACHUSETTS. A special satellite symposium was held during the 2007 Heart Rhythm Society meeting. During the symposium 5 experts (Eric Prystowsky MD, Pierre Jais MD, Peter Kowey MD, Stanley Nattel MD, and Jeremy Ruskin MD) discussed various aspects of atrial fibrillation (NOTE: Their comments are not specifically aimed at lone AF). Following are some highlights from the discussion.

- **Re: Aspirin vs. warfarin for stroke prevention**
  Comment: "*Of course, you have the discussion with the patients and the patients do generally make the right decision, but I think there is a tendency among many physicians to be somewhat aggressive in many cases and decide to prescribe warfarin just to be on the safe side. That's not fair either*."

- **Re: Damage to atrium due to long-term AF**
  Summary: The atrial rate is increased about 10-fold in persistent afib. This causes a calcium overload which the body compensates for by inactivating calcium channels. This results in a shortening of the refractory period (AERP) making it more likely that afib will persist. Animal experiments have also shown that persistent/permanent afib increases fibrosis and collagen expression in the heart.

- **Re: Choice of antiarrhythmic drugs**
  Comments: "*In people with minimal or no structural heart disease, drugs with minimal organ toxicity are preferred, such as flecainide, propafenone, and sotalol; amiodarone and dofetilide are second-line choices*."

  "*We talked about cardiac risks, but we can't forget extracardiac risks, and beta blockers, propafenone, sotalol, and dofetilide are all pretty much equivalent and fairly low. Amiodarone is by far the worst. So in the AF management guidelines, there's a pretty simple general rule. The rule is that amiodarone is kept in reserve because of its significant risk of extracardiac toxicity, particularly with longer term therapy, so it's not a first-line drug unless the risks of the alternatives are too high*."

Prystowsky, EN, et al. Case studies with the experts: Management decisions in atrial fibrillation. Journal of Cardiovascular Electrophysiology, *Vol. 19, Suppl. 1, 2008, pp. S1-S12*

Fish oils and heart rate variability

BOSTON, MASSACHUSETTS. Heart rate variability (the variation in the interval between heart beats) is a powerful indicator of the state of the autonomic nervous system (ANS). The variation in the heart beat interval is usually measured via a 5-minute electrocardiogram or 24-hour Holter monitoring. The original and still commonly used measure for the variation is referred to as SDNN which is the standard deviation of the heart beat intervals, that is, the square root of the variance. Most scientific work on heart rate variability (HRV) now uses power spectral density (PSD) analysis to relate the relatively simple measurement of beat to beat variability to the state of the autonomic nervous system. PSD analysis uses a mathematical technique (fast Fourier transform) to determine how the power (variance in heart beat interval) is distributed across different frequency bands. There is now general agreement that the power in the low frequency band (LF) from 0.04 to 0.15 Hz (cycles/second) is an indication of sympathetic (adrenergic) branch activity and that the power in the high frequency band (HF) from 0.15 to 0.40 Hz is primarily an indication of parasympathetic (vagal) activity. It follows that the ratio of LF/HF is a measure of the balance of the autonomic nervous system with a higher number indicating an excess of adrenergic activity and a lower number indicating an excess of vagal activity.

Other important measures derived from HRV analysis include the Poincare ratio and the short-term fractal scaling exponent (DFA1) which are related to sinoatrial node firing patterns. A low Poincare ratio and/or a high DFA1 correspond to a less erratic heart beat (more normal sinoatrial firing).

A low heart rate variability has been implicated in sudden cardiac death, ventricular fibrillation, angina, heart attack, atherosclerosis, and other heart-related problems. HRV analysis has been used extensively in the study of atrial fibrillation. LAF episodes can be divided into two groups – those that are preceded by an increase in LF power and a decrease in HF power consistent with an increase in sympathetic (adrenergic) tone, and those that are preceded by a decrease in LF power and an increase in HF power consistent with an increase in parasympathetic (vagal) tone. The changes in HRV are apparent at least 5 minutes before the actual episode.

A team of researchers from Harvard Medical School, Washington University School of Medicine, Wake Forest University School of Medicine, and the University of Washington now reports that the consumption of oily fish and fish oils strongly influences HRV. Their study involved 4465 older men and women (average age at enrolment of 72 years) who were enrolled in 1989-1990 and then followed for 10 years. At enrolment all participants were given a resting 12-lead ECG or a 24-hour Holter monitor recording and information about their intake of fish and fish oils over the past year was obtained. The researchers observed a significant correlation between the intake of broiled or baked fish (especially tuna) and HRV. They also observed a strong correlation between plasma levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and HRV.

Study participants with a high broiled/baked fish intake experienced a greater HRV (higher SDNN) than those with a lower intake. They also showed lower LF power (lower adrenergic stimulation of the ANS) and higher HF power (increased vagal dominance of the ANS), thus resulting in a lower LF/HF ratio, again suggestive of vagal dominance. High fish consumers also had a lower Poincare ratio and a higher DFA1 indicating a more stable sinoatrial firing pattern. These correlations were also evident when comparing HRV variables with the intake of EPA + DHA. The researchers did not observe any correlation between HRV and the intake of fried (non-fatty) fish.

During the follow-up period, 542 deaths occurred related to cardiovascular causes (1.1%/person-year). The researchers found that high values of SDNN and DFA1 were associated with a 1.1% and 8.4% respectively reduced risk of cardiovascular death, while a low Poincare ratio was associated with a 5.9% risk reduction. They conclude that an increased intake of oily fish (or EPA + DHA) have significant beneficial effects on parameters influencing HRV, specifically an increase in vagal tone, modulation of adrenergic-mediated baroreceptor activity, and improved sinoatrial node function. NOTE: The average daily intake of EPA + DHA ranged from 47 mg to 927 mg.

Mozaffarian, D, et al. Dietary fish and omega-3 fatty acid consumption and heart rate variability in US adults. Circulation, *Vol. 117, March 4, 2008, pp. 1130-37*

Editor's comment: The confirmation that a high intake of EPA + DHA is associated with a decreased risk of cardiovascular death is indeed encouraging. However, the finding that a high oily fish/fish oil consumption is associated with vagal (parasympathetic) dominance may be less welcome news to vagal afibbers, especially since a high fish oil intake has also been associated with a lower resting heart rate.

PACs and coughing

WAKEFIELD, RHODE ISLAND. Dr. Neil Brandon, a cardiologist in Rhode Island, reports on the case of 3 patients who were observed to have a single premature atrial contraction (PAC) immediately preceding a cough. In discussing his findings with colleagues, he found that several physicians had noted a similar association including two cardiologists who had experienced it themselves. Dr. Brandon speculates that a PAC arising in the atrium near the phrenic nerve may trigger the cough reflex in susceptible patients and points out that patients sometime cough during an atrial fibrillation procedure. He also suggests that otherwise unexplained coughing may be due to asymptomatic PACs.

Brandon, N. Premature atrial contraction as an etiology for cough. Chest, *Vol. 133, 2008, p. 828*

Research Reports

Endurance Exercise – Is It Worth It?

Hans R. Larsen

There is ample evidence that being physically fit reduces the risk of heart disease, stroke, metabolic syndrome, osteoporosis, hypertension, diabetes, prostate cancer, breast cancer, colon cancer, depression, anxiety, and many other conditions. There is also evidence that physically fit people live longer than do sedentary people. It is also clear that the only way to become and remain physically fit is by being physically active. The question is, "How much physical activity is required to be considered fit, and is there such a thing as overdoing the physical fitness"?

How Much is Enough?

Ten years ago researchers at the Royal Free Hospital School of Medicine in London, England reported that middle-aged men who regularly engaged in light to moderate physical activity experienced a 40-50% lower mortality than did those who were largely inactive.[1] Researchers at Harvard Medical School found that women who walked for at least one hour a week at a moderate pace had a 50% lower risk of developing coronary artery disease than did those who did not walk regularly. The pace of walking (exercise intensity) was found to be less important than the time spent in walking, and increasing pace or walking time (beyond 1.5 hours/week) did not provide added protection.[2] Clearly, regular exercise is important, but how much is required and what are the optimum ways of getting it?

An expert panel endorsed by the American Heart Association and the American College of Sports Medicine recommends that all healthy adults aged 18 to 65 years engage in at least 30 minutes of moderate-intensity aerobic physical activity on 5 days each week, or vigorous-intensity aerobic activity for a minimum of 20 minutes on 3 days of the week. Combinations of moderate and vigorous exercise are also acceptable and the 30 minutes of moderate physical activity can be met, for example, by 3 individual bouts of 10 minutes each. The panel emphasizes that physical exercise over and above the recommend minimum can be expected to lead to reduced premature mortality and further health improvements, particularly in regard to cardiovascular health. The panel also recommends activities that maintain and increase muscular strength for a minimum of 2 days each week. Such activities would include stair climbing, weight training, and weight-bearing callisthenics.

The intensity of physical exercise is usually expressed in terms of energy expenditure which, in turn, is expressed in metabolic equivalents (MET). One MET represents an individual's energy expenditure while sitting

quietly for 1 minute (equivalent to about 1.2 kilocalories/minute for a person weighing 160 lbs). Moderate activity is associated with a MET equivalent of 3-6 METs per minute, while vigorous exercise is associated with METs greater than 6. METs for some common activities are given below:

Walking at 3 mph (5.0 km/h)	3.3 MET
Walking at very brisk pace of 4 mph (6.4 km/h)	5.0 MET
Bicycling, flat surface, 10-12 mph (16-19 km/h)	6.0 MET
Bicycling, fast, 14-16 mph (22-26 km/h)	10.0 MET
Golfing (walking and pulling clubs)	4.3 MET
Swimming (leisurely)	6.0 MET
Swimming (moderate to hard)	8.0-11.0 MET
Hiking at moderate pace with light or no pack	7.0 MET
Hiking at steep grades and heavy pack	7.5-9.0 MET
Jogging at 5 mph (8 km/h)	8.0 MET
Cross-country skiing (slow)	7.0 MET
Cross-country skiing (fast)	9.0 MET
Competitive soccer	10.0 MET

Thus, 30 minutes of walking at 3.0 mph would accumulate 99 METs (3.3x30) and jogging for 20 minutes at 5 mph would accumulate 160 METs (8x20). The panel suggests a minimum weekly MET accumulation of 450 to 750 METs be achieved through specific physical exercise.

The panel makes the interesting observation that exercise is relatively ineffective in achieving weight loss, but that a very much increased level of activity is required to maintain a weight loss achieved by other means. They also acknowledge that the risk of musculoskeletal injury increases substantially with increased physical activity and can affect as many as 55% of people involved in jogging programs and US Army basic training. The risk of cardiac arrest and heart attack also increases during vigorous physical exercise, especially among infrequent exercisers. Nevertheless, the panel concludes that, in the case of healthy individuals, the benefits of regular moderate to vigorous physical activity far outweighs the risks. They also suggest that healthy men and women do not need to consult with a physician or other healthcare provider prior to embarking on a regular exercise program. However, those with cardiovascular disease, diabetes, or other chronic diseases should clearly do so.[3]

I an accompanying article Miriam Nelson of Tufts University and other members of a separate panel outline physical activity recommendations for those above the age of 65 years and adults aged 50-64 years with clinically significant chronic disease conditions or functional limitations. The recommendations are identical to those discussed above, except that the definition of *moderate* and *vigorous* exercise is tailored to the

individual's basic fitness level rather than given as specific MET targets.[4]

How Much is Too Much?

So, regular exercise is clearly a good thing, but like all good things it can be overdone. British researchers followed 20 veteran athletes for 12 years and concluded that high intensity lifelong endurance exercise is associated with altered cardiac structure and function, especially the development of left ventricular hypertrophy (thickening of the muscles of the left ventricle) and profound bradycardia. Two of the athletes ended up having to have a pacemaker implanted.[5] NOTE: Endurance exercise is usually defined as vigorous exercise for more than 45 minutes per session.

Swedish sports medicine experts found that elderly men with a lifelong history of regular, very strenuous exercise were more likely to suffer from complex ventricular arrhythmias than were men who had been only moderately physically active.[6]

A recent study involving 134 former Swiss professional cyclists concluded that these former athletes were more likely to suffer from sinus node disease and atrial fibrillation and flutter than were an age-matched group of golfers. The two groups were examined at age 66 years, which for the cyclists was an average of 38 years from their last professional race (Tour de Suisse). The Swiss researchers also observed that ventricular tachycardias were more common in the cyclists than in the golfers (15% vs 3%). They conclude that, "The elderly athlete may not be as healthy as believed."[7]

In 1998 Jouko Karjalainen and colleagues at the University of Helsinki reported that the prevalence of lone atrial fibrillation in a group of elite orienteers was 6 times higher than in a control group of less active men (5.3% vs 0.9%). The first afib episode among the orienteers occurred at a mean age of 52 years after an average training history of 36 years. Although the orienteers were more likely to develop lone atrial fibrillation, they were significantly less likely to develop heart disease (2.7% vs 7.5% in control group) and experienced lower mortality during the observation period (1.7% vs 8.5% in control group). The Finnish researchers conclude that vigorous, long-term endurance exercise is associated with atrial fibrillation in healthy, middle-aged men despite protecting against coronary heart disease and premature death. They speculate that the increased risk for afib is related to enhanced vagal tone, atrial enlargement, and left ventricular hypertrophy.[8]

Medical researchers at the University of Barcelona have found that men who engage in vigorous physical exercise of many years have an

increased risk of developing lone (vagal) atrial fibrillation. A review of the records of 1160 patients seen at an outpatient arrhythmia clinic revealed that the incidence of lone AF among long-term exercisers was 60% as compared to only 15% in the general population of Catalonia.[9] The same group of researchers also concluded that lone afib was about 3 times more prevalent among men who reported former and current sport practice than among men who did not. They observed a particularly strong correlation for men who reported more than 1500 hours of lifetime sports activities.[10]

More recent research by the Spanish group confirmed the strong association between LAF risk and accumulated moderate and heavy physical activity. Those with a lifetime accumulated moderate plus heavy physical activity of more than 9300 hours had 15 times the prevalence of LAF than did those with less than 2100 hours accumulated. More than 564 hours of accumulated heavy, vigorous physical activity was associated with a 7 times increased prevalence of LAF.

The researchers speculate that the negative effects of moderate and particularly vigorous physical activity may be related to the chronic volume and pressure overload caused by the increased activity. They conclude,

> *"The fact that physical activity is a risk factor for AF does not argue against exercise as a way of preventing coronary artery disease. It only offers a word of caution suggesting that the benefits obtained by physical activity, if excessively intense and over a great many hours, may be counteracted by the risk of AF."*[11]

The evidence that heavy, sustained physical exercise is associated with an increased risk of lone atrial fibrillation is indeed substantial. The only study disputing this connection is the one carried out by Antonio Pelliccia and colleagues at the National Institute of Sports Medicine in Rome. These researchers found no difference in the prevalence of atrial fibrillation in a group of competitive athletes as compared to the general population.[12] However, the average age of this group of athletes (24 years) was substantially lower than the average age in the studies discussed earlier, so the results are not comparable, especially since it is well known that the incidence of afib increases with age, and that the average age at diagnosis is about 48 years for lone afibbers.

Why would long-term, vigorous endurance exercise increase the risk of developing atrial fibrillation? Long-term endurance training profoundly affects the body's physiology. Among other things it significantly reduces the heart rate and testosterone levels.[13,14] It is also known that, while exercise in the short-term increases adrenergic tone, its long-term effect

is an increase in vagal tone.[15,16] Vigorous, long-term endurance exercise has also been associated with an increased risk of inflammation. Greek researchers observed that participants in a 36-hour long distance run experienced a 152-fold increase in C-reactive protein (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".[17] Finally, there is ample evidence that long-term endurance training tends to increase the size of the left atrium and is also likely to lead to left ventricular hypertrophy.[5,7,8]

Taken together, all these effects of vigorous, long-term endurance training is likely to combine to form a potent breeding ground for the development of atrial fibrillation. It would seem logical that continuing vigorous endurance training after experiencing a first afib episode would be a poor choice.

Several studies have found a convincing association between inflammation and afib.[18] There is also evidence that vigorous endurance sports such as participating in marathons can result in a very pronounced systemic inflammation.[17] Andrea Frustaci and colleagues at the Catholic University of Rome have found that inflammation of the heart lining (myocarditis) is an almost universal feature among lone afibbers.[19] Further exercise will fan an inflammation and Swedish sports medicine experts are adamant that exercise should be avoided when myocarditis is suspected.[20]

Does Detraining Help Prevent AF?

Does refraining from heavy exercise actually work for lone afibbers? Says the late Professor Philippe Coumel,

> "*It is known that in well-trained people suffering from vagal AF, the first step of therapy should be deconditioning by discontinuing high-level training. It may be sufficient to bring about an improvement in the patient and it is often a necessary adjuvant to facilitate pharmacological therapy.*"[21]

In the same paper Dr. Coumel also makes the following statement of interest to vagal afibbers,

> "*Not only are beta-blockers ineffective,* [for vagal afibbers] *but they usually make patients worse and inhibit the efficacy of antiarrhythmics.*"

British researchers support Dr. Coumel's observation about the beneficial effects of detraining. They report the case of a 53-year-old athlete whose

symptoms of palpitations, ectopics, and atrial tachycardia completely resolved after detraining.[22] Spanish researchers report that detraining for 2-4 weeks results in an increase in heart rate and adrenergic tone – both changes beneficial in regards to vagally-induced afib.[23] At least one member of our afib group has found that forgoing exercise one week out of every four significantly reduced his frequency of episodes. Of course, abruptly ceasing all exercise may carry with it a whole new set of problems, so a gradual approach is definitely in order. This might be worth experimenting with if you are a vagal afibber.

There is some evidence that patients who have been ablated for right atrial flutter are more likely (81% increased risk) to develop atrial fibrillation post-ablation if they have a history of active engagement in endurance sports. Those continuing endurance sports after their ablation are also more likely (68% increased risk) to develop post-ablation AF. The Belgian researchers reporting these findings conclude that there is a 10% and 11% increased risk of developing AF per weekly hour of sport performed pre- and post-ablation for flutter.[24]

Several ablated afibbers who resumed their pre-ablation training schedule too early have reported a relapse and required a second ablation to achieve a final cure. There is now evidence that repeat ablations may be the norm rather than the exception for competitive athletes with afib. Italian researchers found it took an average of 2.3 PVIs to prevent afib recurrences in athletes who had been disqualified from competition due to their afib.[25,26]

Somewhat paradoxically, actions that may promote afib in vagal afibbers may also help to terminate an episode already in progress. About 27% of male vagal afibbers reported (in LAF Survey 14) that they were able to terminate an afib episode by exercise. This finding is supported by a case history involving a 45-year-old physician with vagally-mediated, paroxysmal AF. The patient was able to convert to normal sinus rhythm by exercising for 20 minutes on a cross-country ski machine (pulse rate of 170 bpm).[27]

Conclusion

So, is exercise good or bad? There is no question that the overall benefits of a regular, moderate exercise program far outweigh any possible adverse effects. However, when it comes to long-term, vigorous endurance exercise, the benefit/risk ratio is less clear. Such exercise can lead to undesirable cardiac modifications and an increased risk of developing atrial fibrillation. In those who already experience vagally-mediated afib, refraining from such exercises, or substantially cutting back may prove highly beneficial. To again quote Professor Coumel,

"Excessive training is harmful when it exaggeratedly modifies the ANS balance beyond the sympathetic and parasympathetic physiological values. It is a major mistake to think that the man in the street must be as trained and fit as the professional sportsman. Any common sense driver knows that if he wants to make his car last, he must avoid handling it as a rally or Formula One driver."[28]

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Elimination/Reduction Protocols

CASE A

Female afibber – **56 years** of age with **vagal AF** of **10 years standing;** no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **48**
Afib burden in 6 months prior to starting protocol: **192 hrs**.
No. of episodes in 6 months after starting protocol: **2**
Afib burden in 6 months after starting protocol: **2 hrs.**
Time on protocol: **6 months**
Still need to avoid triggers?: **Yes, but much less so**

Main components of effective protocol

Trigger avoidance: **MSG, aspartame, and other excitatory food additives, caffeine, high glycemic index foods, heavy evening meals, dehydration**
Diet changes: **Elimination of wheat and adopted Zone diet**
Supplementation: **Magnesium, potassium, taurine, coenzyme Q10**
Drug therapy: **None**
Stress management: **Relaxation therapy, breathing exercises**
Approaches to shorten episodes: **Light exercise, hydrotherapy (ice baths, icy water on hands, hot/cold showers)**
Approaches to reduce ectopics: **Supplementation with magnesium, potassium, and taurine, low-sodium V8 juice**

Background and details of protocol

I was having increased episodes with the use of Toprol XL which my doctor prescribed. I had taken the drug for 2 years. I began suffering with PACs and ectopics everyday as well. During that time I was faithfully avoiding every trigger I could. My situation only got worse. The first thing I did was to purchase Hans' book. I determined, with the help of his book, the web site, and the people participating on the Bulletin Board, that I was probably vagal and needed to eliminate the beta-blocker. I stopped the beta-blocker (slowly) at the same time I began experimenting with adding supplements. I experimented with dosages of magnesium to determine my bowel tolerance.

I had always taken calcium and fish oil. I stopped those because my research indicated those could be counter productive. All the while I had changed my diet and continued to exercise, but not

with the vengeance I used to. I eat breakfast now; I never used to. I eliminated bread and have increased my veggies. I'm not a fruit eater, but admittedly I have always had a lousy diet. I avoid triggers, watch my diet, exercise, drink lots of water and take my supplements. My biggest trigger is a large meal, especially in the evening. I try to walk or stay active at night after a meal. All this with my EPs blessing. He has given me Toprol for pill-in-the-pocket usage, but I have yet to use them. I am an avid golfer and will play in the heat of the day. I am very careful to avoid becoming dehydrated all the time, but especially when I am out golfing. I carry my own bag and walk, so I'm loaded down with water. All of these are taken after food: one 500-mg magnesium in the morning and one in the evening one 500-mg taurine in the morning and one in the evening. All of these are in the morning only - 1 multi, 500 mg Vit C, 100 mg of potassium, 150 mg CoQ10, 325 mg aspirin (doctor's continued wish, although I have only age and afib as risk factors) I know some of these doses (taurine, Vit C, mag) are low, but they are currently working. Perhaps I can increase them if things change. I started out purchasing my supplements at the corner drug store out of frustration. Once my current supply is gone, I fully intend to use the services for Hans' supplements. My education has included the need to be careful with supplements and I need to purchase the best forms of the products I take. I have yet to avoid an activity or an opportunity because of afib. Once, I played a round of golf while in afib. It did affect my putting! I think a positive attitude will go a long way in meeting this condition head on. Lastly, I'm very lucky because my condition is mild compared to many. I know from reading postings that some people suffer far more than I do. For that, I am grateful, but I have compassion for those who are not as fortunate.

CASE B

Female afibber – **47 years** of age with **vagal AF** of **25 years standing**; no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **Permanent**
Afib burden in 6 months prior to starting protocol: **Permanent**
No. of episodes in recent 6 months after starting protocol: **0**
Afib burden in 6 months after starting protocol: **0**
Time on protocol: **7 ½ years**
Episodes since protocol implementation: **3 episodes lasting approx. 2 hours each early on**
Still need to avoid triggers?: **No**

Main components of effective protocol

Trigger avoidance: **MSG, aspartame, alcohol, caffeine, dehydration, high glycemic index foods**
Diet changes: **Changed to paleo diet**
Supplementation: **None**
Drug therapy: **None**
Stress management: **None**
Approaches to shorten episodes: **Not applicable**
Approaches to reduce ectopics: **Paleo diet**

Background and details of protocol

I experienced AF at 22 years of age. It came out of the blue after the birth of my first son. Unfortunately, sometimes when it happened I would pass out. Witnesses said I convulsed, so the diagnosis came as epilepsy. I was put on anticonvulsants which never worked. In the beginning my AF was maybe twice or three times a week. Always at rest. It was short-lived, well the really fast racing part was short lived – maybe 2 to 4 hours (in the end it could go on for days, then became permanent). Every so often I would visit my GP and complain, but was told it was just palpitations and I was being over anxious. So decided they must be panic attacks and gave up on doctors.

Nine years later I was finally diagnosed with atrial fibrillation and was put on digoxin which I stayed on for 10 years. In 2000 I finally saw a new cardiologist who said that I should never have been put on digoxin. I was then put on Rythmol (propafenone) and when this did not work sotalol, flecainide, and atenolol followed.

All these drugs had terrible side effects, so in December 2001 I stopped taking all medications. In October of 2000 I had started a program of trigger elimination (notably MSG and food additives) and had also adopted the paleo diet. In hindsight my diet had been very refined which led to leaky gut (with no digestive symptoms) so that my body was very low on all nutrients. The paleo diet cut out the problem foods, helped heal the gut, and didn't feed bad bacteria and allowed good bacteria to flourish, thus allowing absorptions of all the major nutrients. Excitatory neurotransmitters such as MSG, aspartame, etc. played havoc since there were not enough minerals, vitamins, etc to make inhibitory neurotransmitters, hormones, etc. and the liver was under undue stress and unable to break down and eliminate toxins. Starchy foods such as grains and potatoes played havoc with blood sugar levels as there were no glycogen stores in the liver or muscle to fall back on. This was verified by hair tissue analysis which showed that I was still low on all minerals except vitamin K which was very high (and had an inverse ratio with Na – very low), meaning that K is not readily available for use in the body. The lack of available K meant it was difficult for insulin to be delivered into cell walls for storage, and also couldn't polarize nerve impulses. As mineral levels increased the problems subsided. Obviously, the whole scenario is a lot more complex than discussed above; however, it is my opinion that my AF was a culmination of long-term malnutrition that could not be sorted out by taking supplements since they could not be metabolized, and the underlying reasons had to be dealt with first.

Since then I have played around with my diet, as after curing my AF, I became aware of reactive hypoglycemia. Happily, I have overcome this, but of course, I have to stick to my paleo diet. I prefer it this way since I have regained my health. I have cured more than just AF – don't suffer from fibromyalgia, headaches, tremors, seizures, and fainting. The only thing I have not solved is low blood pressure, but I can live with that!

CASE C

Male afibber – **52 years** of age with **vagal AF** of **4 years standing**; no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **7 (including one lasting 2.5 months)**
Afib burden in 6 months prior to starting protocol: **Average 7 hours/episode except for one lasting 2.5 mos.**
No. of episodes in 6 months after starting protocol: **0**
Afib burden in 6 months after starting protocol: **None**
Time on protocol: **43 months**
Episodes since protocol implementation: **4 episodes (3 of 0.7 hrs, 1 of 20 hrs)**
Still need to avoid triggers?: **No**

Main components of effective protocol

Trigger avoidance: **None**
Diet changes: **None**
Supplementation: **Magnesium, potassium, taurine**
Drug therapy: **Pill-in-pocket flecainide**
Stress management: **None**
Approaches to shorten episodes: **Pill-in-pocket flecainide**
Approaches to reduce ectopics: **Supplementation with magnesium, potassium and taurine**

Background and details of protocol

I am a vagal afibber and a life-long exerciser. I am sufficiently fit to compete annually in a 13-mile race up Pike's Peak (14,100', 4,300m elevation, 7850' elevation gain). In the summer of 2004 several days after a long training day on a 14'er, I woke up with a rapid, irregular heart beat and was subsequently diagnosed with lone atrial fibrillation. During the next 2 months I experienced 5 more classically vagal episodes starting around 3 AM. These either converted on their own or converted with exercise after about 7 hours. The next episode, however, lasted 2.5 months, but I was eventually able to convert it by taking 300 mg of flecainide (conversion took 20 hours).

Early on, I found the LAF Bulletin Board and purchased Hans' first book. I looked at low potassium (hypokalemia) as a potential issue. Prior to afib, I'd had two annual blood tests with serum potassium levels at the low end of normal - 3.5 mmol/l. The day of my first episode, my level was 3.2 in the ER. Five days later it was 4.2 in the doctor's office.

My conclusion was that I had intermittent hypokalemia. I set out to design a supplement program that would keep my serum K above 4.2. This program includes 3 grams of potassium as citrate, 0.8 grams magnesium as glycinate and 4 grams of taurine per day. All doses are divided and taken morning and evening around meal time. I proposed to my EP that I use on-demand flecainide as a back-up in case the supplements failed. He agreed.

After ending the 2.5-month episode, I started supplements. Here are the subsequent episodes:

1. 1 month – 3 AM episode, converted 20 hours after taking 300 mg flecainide
2. 4.5 months – midnight episode, converted 20 minutes after taking 300 mg flecainide
3. 5.5 months – 3 AM episode, converted 20 minutes after taking 300 mg flecainide
4. 2.5 years – 11 PM episode, in vagal period after sexual climax. Converted 50 minutes after taking 300 mg flecainide.

Notes – prior to episodes 2 & 3, I'd run out of taurine and not bothered to replace it. Episode 4 occurred, 3 days after ceasing all supplements. This was evidence that all three supplements are essential for me. Episode 2 was a bit unusual, as I'd snow-shoed for 4 hours through heavy snow with a 75-pound pack and then spent 6 hours of hard work constructing a snow cave. It came on after I'd gone to bed. Normally I would crush the flecainide in warm water, however all I had was partially frozen water bottle. I chewed the flecainide tablets and washed them down with near freezing water – still effective.

When I started the supplement program, I also started a monitoring program with a Polar S810 heart rate monitor and a FreezeFramer heart rate monitor. Using them I was able to count PAC and PVC rates/hour. PAC's typically run 0-2/hr and PVC's 0-20/hr. My monitoring concept is that an increase in ectopic rates will foreshadow afib. The results could also be used to "tweak" the supplement program.

For anyone copying this program, I recommend BUN and creatinine tests to make sure your kidneys are OK. Also start slowly with the supplements and gradually increase dosages.

A couple of other, perhaps unrelated notes. When I was out of rhythm for 2.5 months, I gained 20 lbs (9.1 kg). I decided a good

approach to losing weight would be to keep my blood sugar low and level. I purchased the most accurate home glucometer I could find – Bayer Ascencia Contour. I sampled my blood sugar 45 minutes (usually maximum spike) after eating and would modify my meals such that I'd keep this spike to around 100 or 110 mg/dL (6.1 mmol/l) or less. This allowed me to drop the excess weight in around 2 months. This did not have any bearing on my success at keeping afib in remission, I only include it for general information.

The reason I stopped all supplements prior to episode 4 is that I thought I might be allergic to the fillers in the pills. I subsequently underwent an Elisa IgE/IgG test and determined that I was allergic to wheat, dairy, eggs, soy, almonds, grapes … These were the source of my allergy, not the pills.

I have had a regular meditation habit for many years (before and after I ended up with afib). I have not seen any effect afib by meditation.

In summary, I'm very happy with my program. I am still very active, exercising on the excessive side of moderate. However I no longer train for endurance activities and try to keep my heart rate under 130 BPM during daily exercise (in fact, a lot of my exercise is in the 100 to 110 BPM range). However, I have done long hard days of exercise with high HR without adverse effect. I just try not to make it too regular a habit and limit them to FUN activities – not training. I do pay attention to my early morning resting HR. If it is elevated by 10 BPM or more, it is a sign that: 1) I've over done it the day before, or 2) I'm coming down with some illness. In either case, I take it very easy.

CASE D

Female afibber – **65 years** of age with **vagal AF** of **7 years standing;** no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **4-5**
Afib burden in 6 months prior to starting protocol: **4 hrs**
No. of episodes in 6 months after starting protocol: **0**
Afib burden in 6 months after starting protocol: **0 hrs**
Time on protocol: **58 months**
Episodes since protocol implementation: **3 episodes (from ½ to 12 hrs)**
Still need to avoid triggers?: **No**

Main components of effective protocol

Trigger avoidance: **MSG, caffeine, high glycemic index foods, dehydration, emotional stress**
Diet changes: **Eliminated gluten and wheat. Sharply reduced intake of dairy products. Switched to paleo diet.**
Supplementation: **Magnesium, potassium, taurine, low-sodium V8 juice**
Drug therapy: **Lisinopril (Zestril) – 10 mg/day**
Stress management: **Avoided stressful relationships**
Approaches to shorten episodes: **None**
Approaches to reduce ectopics: **Low-sodium V8 juice and potassium supplementation**

Background and details of protocol

My first brush with afib was in late '99 while working a stressful job. I was 57 years old, seriously overweight, had that year gone through a lot of stressful life changes, was eating poorly [whatever I could pick up in the convenience store I worked in], it was hot weather and I had no air conditioning, and I was surviving on coffee. I had a couple of short episodes that went away before I could get to a doctor, and of course when I did get to the doctor he found nothing wrong. Then I had one that did not go away, and ended up in the hospital for 3 days. I changed jobs after that, and worked more normal hours, dropped the coffee and ate better [more vegetables, less junk], and had no more afib until August 2000, when I was hospitalized again with another "just-won't-go-away" episode. This again was associated with caffeine [green tea this time, dozens of cups of it, trying to stay awake at work] and hot weather, compounded by lack of sleep. After that I dropped caffeine altogether, and got an air conditioner.

For the next several years I had short episodes occasionally, but they always went away by themselves, and in any case, I was getting turned off by hospital emergency rooms. I had learned a little about using computers by that time, and was researching better nutrition. I retired and moved back to Maine, and eventually got my own computer, and found Hans' site. Here I found there were a lot of people taking various drugs, and none of these drugs seemed to be curing their afib. They were still getting afib attacks, trading drug advice, going on different drugs, and still getting afib. Some of them were talking about, and some even resorting to, heart surgery. I couldn't blame them for doing this, because their afib had started small and gradually increased until it ruled their lives. I was afraid mine would do that too.

Worse yet, by no means all of those ablation patients had gotten rid of their afib either. Two of them had had near-death experiences, and I was pretty sure that the reason there were not more stories like that was because most ablations that went bad had resulted in death, and of course, we are not very likely to hear from those people. And then there were 2 people posting who claimed to have gotten rid of their afib by diet and supplements. These were Fran and Erling.

Well, I thought, if these 2 people so different from one another can do that, maybe I can too. Food choices are something I can control. So I changed to a mostly paleo diet, and sent away for some Carlson's magnesium glycinate. At first I still did get some short, mild afib episodes, but then I began seeing posts about low sodium V8 juice, 850 mg potassium per 8 oz. glass. I was having trouble consuming enough vegetables and fruits to get in 3-5 grams K a day, and this seemed like just what I needed, and sure enough it was. The taurine I added later when I began to experience loose bowels from my usual dosage of magnesium glycinate.

The Paleo Diet

The paleo diet is based on the premise that the human body thrives best on the diet of our hunter/gatherer forebears of 10,000 years ago, ie. before the introduction of agriculture. The proponents of the diet point out that the human genomic make-up is very slow to change and has not had a chance to adjust to the very major changes in diet that have occurred since the Stone Age. The hunter/gatherers of the
Stone Age consumed a diet based on fish and meat from wild animals, vegetables, berries, fruits and nuts. Grains and dairy

products were not available. The paleo diet thus emphasizes the above food sources and excludes dairy products, grains, starchy vegetables, sugar and legumes, and of course, chemical food additives. The paleo diet is described in detail in the book "The Paleo Diet" by Loren Cordain, PhD or at www.paleodiet.com

Concerning those few short, mild episodes, I think a lot of what paleo did for me was eliminate postprandial hypoglycemia. A paleo diet pretty much prohibits high glycemic load foods. Jackie and others had called my attention to the fact that a lot of my afib symptoms were the same symptoms as those of reactive hypoglycemia - shaky, lightheadedness, cold sweat, panic - and sure enough, the minor episodes I got soon after converting to paleo lacked just those features. I wasn't sorry to see them go.

Also, I need to mention that those last episodes, mild though they were, appeared right after use of a seasoning containing MSG. I had never had an afib episode that I could tie to MSG before, but then I had never been without it for any period of time before either. For all I really know, they could have all had to do with MSG, in combination with stress, hypoglycemia, dehydration, electrolyte deficiency, caffeine, and any of the other myriad stressors of modern life.

Any paleo diet purist will point out that I ingest a lot of stuff that isn't paleo. The V8 certainly isn't, and neither are the supplements I take. I do eat a little cheese, too, though not the plasticized processed cheese. I cannot afford organic food, so I make do with what I can find in the local supermarket, cheapest first. I go out to eat sometimes, and on those occasions I commit excesses like baked potato and gravy, or bread on sandwiches. I cheat outrageously sometimes, too, particularly with chocolate baked goods.

Speaking of bread, gravy, and bakery goodies, if I hadn't gone to paleo I would also never have realized that I have a bad reaction to wheat. Since taking up the paleo diet my antacid consumption has gone way down, except when I eat anything with wheat in it. That will have me eating antacids for a good 12 hours and sometimes more.

Another good thing about the paleo diet is that I fit the classic profile for insulin resistance - fat, high blood pressure, relatively inactive, cholesterol a bit on the high side - and the paleo diet is good for insulin resistance. I hope to avoid type 2 diabetes this way, or at least to slow it down.

For those concerned about whether my afib is "really cured", I do not think I can expect to be cured of needing proper nutrition, any more than cars are cured of needing gasoline. I don't think I am going to ever again be just like I was in my 20's either. To use the same metaphor, old cars are never again just like they were when new.

I think afib is one of the long latency deficiency diseases, and that is why, in most people, it does not appear until a relatively 'older' age, and why it appears in the context of stress so often. I am still old, fat, and lame in the knees, but I don't have afib any more. If I can do this, you can too.

CASE E

Male afibber – **47 years** of age with **mixed AF** of **12 years standing;** no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **45**
Afib burden in 6 months prior to starting protocol: **630 hrs**
No. of episodes in 6 months after starting protocol: **3**
Afib burden in 6 months after starting protocol: **30 hrs**
Time on protocol: **28 months**
Still need to avoid triggers?: **Yes**

Main components of effective protocol

Trigger avoidance: **MSG, high glycemic index foods, heavy evening meals, stress, physical overexertion, alcohol, mercury (tuna)**
Diet changes: **Zone diet and 4-5 small meals throughout day**
Supplementation: **Magnesium, potassium, taurine, fish oil, coenzyme Q10**
Drug therapy: **Beta-blocker + flecainide**
Stress management: **Regular exercise**
Approaches to shorten episodes: **On-demand beta-blocker + flecainide**
Approaches to reduce ectopics: **Beta-blocker**

Background and details of protocol

I started off with the recommendations in your website and publications. Largely a change in lifestyle with emphasis on taking things a bit easier, avoiding large meals (especially at bedtime) and taking the above supplements, including large doses of fish oil (3 500-mg enteric-coated fish oil capsules and one large fish oil gel cap daily). I also had some benefits from eliminating all tuna (mercury issue) and limiting swordfish to about once/month. Anecdotally, I believe this helped. Also, I believe MSG was a trigger and tried to avoid this. Later, I discovered that a diet with lots of protein and complex carbs (similar to zone diet) was helpful.

Typically I have a hearty breakfast with eggs and some type of low-fat meat (Canadian bacon or turkey sausage or bacon) and some kind of fresh fruit. Just before (late afternoon) exercise, yogurt mixed with more fruit. After exercise a protein shake mixed with a banana and some nuts.

Then I try to have a healthy Zone diet type dinner in the evening (meat about the size of a deck of cards and a vegetable). I try to

have no bread whatsoever. I also drink about 3 liters of water daily and steer clear of all refined sugar products.

The above protocol was helpful, but I was still having persistent attacks which inhibited my ability to exercise in the day (adrenergic attack) or would wake me up in the middle of the night (vagal). Generally, once the attack went from persistent arrhythmia to full afib, they would go on all night and convert sometime from late morning to early afternoon. Some attacks lasted almost 24 hours. I worked through a cardiologist, who put me on a few beta-blockers and we finally settled on Toprol - 4 x 25 mg. I experimented with the timing of taking the pills and try to take a pill around 11:00, 2:00, 5:00 and 8:00. This helped with the daytime attacks but still not satisfactory. Also would "bite" one or two metoprolol during daytime attacks and this seemed to help me convert back within a couple of hours. Unfortunately, the night time attacks were no better. Metoprolol would not help with evening attacks, and may have made some worse. Many sleepless nights were spent listening to the "frog in my chest trying to get out".

I strongly considered ablation, but wanted to give procedure development more time so I opted for flecainide. Flecainide proved to be the final "plank" needed for my program. This worked in two ways. The dosage (3 x 50 mg/day) strongly curtailed the frequency of the attacks. Secondly, if I do get an episode, I have taken up to five additional pills (about three is sufficient most of the time) and will convert in 2-4 hours) - I don't believe I have had a single monster 20-24 hr attack since. Added benefit at this point was "normal sinus rhythm promotes more normal rhythm" - it felt like, over time, the attacks become fewer and fewer, which I think is due to some restoration of "normal" heart circuitry.

So to summarize my (largely successful but not perfect) program (in order of perceived effectiveness/benefit is): - 150 mg flecainide - timed to take most in the evening to address vagal attacks; additional "bite down" flecainide to convert if full afib attack occurs; 100 mg Toprol - timed to keep adrenergic attacks (and PACs) to a minimum; additional "bite down" of 25-50 mg of metoprolol if attacks are adrenergic (daytime); strong magnesium and potassium supplementation; avoidance of heavy meals or heavy drinking to avoid vagal attacks; avoidance of severe mental or emotional stress - over working; avoidance of mercury and MSG; heavy doses of fish oil; sitting up or standing during the onset of a vagal attack (i.e. lots of PACs or persistent

arrhythmia); sitting down during onset of adrenergic attack; Zone-type diet; exercise (weight training) and cardio exercise (possible since I started taking flecainide); listening to your own body - sense when you are more susceptible and be proactive. And finally, take responsibility for your own "cure" - our current medical establishment will only do so much.

CASE F

Female afibber – **60 years** of age with **vagal AF** of **6 years standing;** no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **25**
Afib burden in 6 months prior to starting protocol: **1000 hrs**
No. of episodes in 6 months after starting protocol: **0**
Afib burden in 6 months after starting protocol: **0 hrs**
Time on protocol: **33 months**
Still need to avoid triggers?: **Yes**

Main components of effective protocol

Trigger avoidance: **MSG, aspartame, alcohol, caffeine, high glycemic index foods, heavy evening meals, dehydration, sleeping on left side**
Diet changes: **Eliminated gluten and wheat, modified paleo diet.**
Supplementation: **Magnesium + taurine**
Drug therapy: **None**
Stress management: **Breathing exercises, yoga**
Approaches to shorten episodes: **-**
Approaches to reduce ectopics: **Supplementation with magnesium + taurine**

Background and details of protocol

I began supplementing with magnesium and taurine almost 2 years ago. I was already supplementing with omega-3 oil, Multibionta, coenzyme Q10, vitamin E, etc., but did not notice any difference until the taurine was added. I now supplement with 4 grams a day. I adopted a modified paleo diet and after having tests for allergies gave up eating wheat and gluten products as I reacted badly to them during the tests. This has resulted in no afib at all for 33 months. Once my cardiologist took me off warfarin, I had an immediate improvement to what remained of my GERD problem. This had already been helped by the supplements. Within a month of stopping the warfarin, the GERD disappeared completely and has not returned. My dietary regimen is very strict and absolute avoidance of triggers is a must, but it continues to be worth the effort.

CASE G

Female afibber – **67 years** of age with **vagal AF** of **3 years standing**; no underlying heart disease
No. of episodes in 6 months prior to starting protocol: **4**
Afib burden in 6 months prior to starting protocol: **20 hrs**
No. of episodes in 6 months after starting protocol: **3**
Afib burden in 6 months after starting protocol: **37 hrs**
Time on protocol: **26 months**
Still need to avoid triggers?: **Yes**

Main components of effective protocol

Trigger avoidance: **MSG, aspartame, alcohol, caffeine, high glycemic index foods, heavy evening meals, dehydration, stress, sleeping on left side**
Diet changes: **Elimination of wheat and gluten, modified paleo diet**
Supplementation: **Magnesium, potassium, taurine, coenzyme Q10, B vitamins, low sodium V-8 juice, L-Theanine as needed.**
Drug therapy: **None**
Stress management: **Relaxation**
Underlying disease conditions: **Digestive problems and hypoglycemia**
Approaches to shorten episodes: **Resting, magnesium, potassium, taurine**
Approaches to reduce ectopics: **Magnesium, potassium, taurine, low sodium V-8 juice, L-Theanine**

Background and details of protocol

In retrospect I believe that I had episodes of afib before being diagnosed in September 2005. After being diagnosed I had such severe reactions to medications for afib that I determined to learn all I could about afib and its possible causes and possible natural means of eliminating or reducing episodes.

My first goal was to determine my nutrient and mineral intake on a daily basis. I did an extensive project to find the areas where my body was not in balance. In June 2006 after an afib episode I recorded everything I ate and drank for 20 days on a program called www.fitday.com. The information was invaluable to me. The program showed me the nutrients derived from my intake of food and clearly showed me what I was lacking.

In those 20 days I discovered that I was getting some nutrients in excess through food and decided not to supplement them. I

made the decision to take individual supplements for those I was lacking instead of a multi. I also added the recommended supplements for afib.

I changed my lifestyle and eating habits and did my best to eat good, nutritious food with extra protein, veggies of all types especially green, limited or stopped my intake of grains, low sodium V-8 juice for potassium. I did lose over 30 pounds when I changed to whole foods and was concerned about my low weight. However, I have maintained my weight at about 120-123 lbs and feel great. I have been able to find gluten free bread and other gluten free foods which add more calories and fiber (which is very important to the digestive system.) After I completed the project I was able to make an educated decision about adding particular supplements that I lacked in my daily foods. I believe the lack of proper food nutrients is a big part of what causes afib and will continue to watch the foods that I eat and the things I drink.

Conclusion: I believe this was a positive experience, although not a cure as evident in outbreaks of afib since October 2007. I strongly believe the reasons for the outbreak were directly connected with my straying from my protocol whether consciously or unconsciously. I also remind myself that many things factor into what causes afib and it might not be my protocol failure at all. Recently I went back on FITDAY to check my nutrients again and discovered that I was not getting the RDA of 4700 mg of potassium a day through my foods and the supplements. So, I have now made it an important point to get that on a daily basis. I feel it is very important for the body to be in balance and for a person to be as healthy as possible so episodes of afib will be easier to endure for the overall person.

Listed below are the supplements I am currently taking. Some I have increased since the last protocol posting and I have so indicated. I choose not to take a multi vitamin but to continue targeting those I'm missing in my food. I'm careful to take recommended afib supplements religiously. I have explained the other supplements I'm taking and why.

Magnesium – Chelated – 200 mg x 3 per day.
Q-Absorb Co-Q10 – 100 mg @ 1 per day
D - "Source Natural" Vitamin. D, 1,000 IU 4 x a day = 4,000 IU per day

E - "NOW" Gamma E Complex @ 400 IU 1 x day
C - “Country Life” Vitamin C with Rose Hips, 1000 mg x 3 per day = 3,000 mg
NOTE: If I feel a cold coming on I increase my Vitamin C another 1,000-2,000 mg per day
B’s - Super B Complex by “Wellness Resources” includes all of the "B's" RDA requirements. One per day.
B-12 Sublingual one per day under tongue.
Zinc – “Natural Factors”, Chelate 25 mg @ 1 per day
Potassium Gluconate – “NOW Brand” 540 mg, powder (1 tsp), 4-5 tsp per day in water or juice.
Taurine - “NOW Brand” 500 mg X 6 a day- If I have a stressful day or afib episode I increase another 1,000 mg. *I believe Taurine is the main supplement that slows my heart rate during afib.*
RXOmega-3 Factors EPA 400 mg, DHA 200 Mg x 2 a day
“Michael Murray's Brand”
Glucosamine Sulfate 2 @ 750 mg – (for knees)
”Cran Clearance” Cranberry concentrate pill form - 680 mg @ 1 per day - for a healthy urinary tract.
L-Theanine – When needed for stress or during an afib episode.

With this regime of minerals and supplements, diet changes and avoiding stress as much as possible I went for 1 1/2 years with no sign of afib. Then on Oct. 13th 2007 I had a six-hour episode which self converted. Since October of 2007 I have had four afib episodes, March - 2008 – 17 hours; May 2008 - 9 hours, July 2008 – 21 hours and October 22 – 7 hours. I believe all were related to food, stress and digestive issues.

Ablation/Maze Survey – 2008

2008 Ablation/Maze Survey

The 2008 Ablation/Maze Survey produced 323 responses, 162 of which were updates to responses submitted in earlier surveys. Combining the 516 respondents to earlier surveys with the 161 new respondents contributing their experience in 2008 results in a total database of 677 patients having undergone a total of 1045 procedures.

The survey results are discussed in three sections. The first covers definition of terms and the general background of the respondents. The second section deals with the details and results of radiofrequency (RF) catheter ablation procedures, while the third section to be published in the February 2009 issue covers the details and results of other procedures (cryoablation, maze procedure, mini-maze procedure, and AV node ablation and pacemaker implantation).

PART 1 – DEFINITIONS AND BACKGROUND

Definition of Terms

Types of Atrial Fibrillation

- **Paroxysmal –** Episodes occurring intermittently and tending to terminate spontaneously - usually within 48 hours.
- **Persistent** – Episodes lasting longer than 7 days and not terminating spontaneously, but can be terminated with chemical or electrical cardioversion.
- **Permanent** – Constant (chronic, 24/7) afib not amenable to effective termination by cardioversion.
- **Adrenergic** – Episodes occurring almost exclusively during daytime, often in connection with exercise or emotional or work-related stress.
- **Vagal** – Episodes tending to occur during rest, at night or after a meal. Alcohol and cold drinks are common triggers.
- **Mixed (random) –** Episodes occur anytime and do not consistently fit the adrenergic or vagal pattern.

Procedures

- **Focal ablation** – The original radiofrequency (RF) ablation procedure in which specific active foci of aberrant impulses are located and ablated.
- **Pulmonary vein ablation (PVA) –** An ablation procedure in which a ring of scar tissue is placed just inside the pulmonary veins where they enter the left atrium. The original PVA carries a high risk of pulmonary vein stenosis, so it is rarely used in its original form anymore. Thus, the term PVA is now associated with ablation around the pulmonary veins when a more specific description (SPVI, CAPVI or PVAI) is not used by the EP or the exact type of pulmonary vein isolation procedure is not known by the respondent.
- **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 eliminate sources of afib located outside the pulmonary veins.
- **Right atrial flutter ablation –** This procedure involves the application of radiofrequency energy to create a block of the cavotricuspid isthmus in the right atrium so as to interrupt

the flutter circuit. A right atrial flutter ablation is usually successful in eliminating the flutter, but rarely helps eliminate atrial fibrillation and may even, in some cases, initiate the development of atrial fibrillation.

- **Left atrial flutter ablation –** Left atrial flutter is a common complication of ablation for atrial fibrillation. It most often resolves on its own, but if not it may be necessary to re-enter the left atrium, locate the offending circuit, and block it via radiofrequency catheter ablation.
- **Cryoablation –** In this procedure a nitrogen-cooled or argon-cooled, rather than electrically-heated, catheter is used to create the ablation lesions.
- **Maze procedure** – The original surgical procedure, the full maze or Cox procedure, used a cut-and-sew protocol for creating lesions forming a "maze" that conducted the electrical impulse from the SA to the AV node, while at the same time interrupting any "rogue" circuits. The cut-and-sew method has now largely been replaced by the use of RF-powered devices, but cryosurgery, microwave application, and high-intensity focused ultrasound (HIFU) have all been tried as well and are preferred by some surgeons. Creating the full set of maze lesions usually requires open-heart surgery and the use of a heart/lung machine.
- **Mini-maze procedure –** The so-called mini-maze procedure also involves lesions on the outside of the heart wall, but access to the heart is through incisions between the ribs rather than via open-heart surgery. The mini-maze may involve the creation of the full maze set of lesions, but usually focuses on pulmonary vein isolation. The procedure does not involve the use of a heart/lung machine and lesions are usually created by the application of RF energy or cryoenergy.
- **AV node ablation + pacemaker –** In this procedure the AV node (the ventricular beat controller) is isolated from any extraneous impulses through cauterization of surrounding tissue, and the ventricles are fed their "marching order" through an implanted pacemaker. The procedure does not eliminate atrial fibrillation, but makes it substantially less noticeable. Patients who have undergone AV node ablation and pacemaker installation are entirely dependent on the pacemaker and are usually on warfarin for life.

Statistical Terms

- **N** – The number of respondents in a sample.

- **Mean** – The average value for a group of data, i.e. the sum of the values of all data points divided by the number of data points.
- **Median** – The value in the middle of a group of data, i.e. the value above which half of all individual values can be found and below which the remaining 50% can be found.
- **Statistical significance** – In this study average values are considered different if the probability of the difference arising by chance is less than 5 in 100 using the two-tailed t-test. This is expressed as "p" being equal to 0.5 or less. Lower values of p are indicative of a greater certainty that observed differences are truly significant.

All statistical tests were carried out using the *GraphPad Instat* program (GraphPad Software Inc, San Diego, CA).

Definition of Success

The success of the procedures is (unless otherwise noted) judged at least 6 months after the completion of the procedure. It is defined in two ways:

Subjectively – The afibber's own opinion as to whether the procedure was completely successful, partially successful, or not successful at all

Objectively – The following criteria are used to define success objectively:

- Complete success – No afib episodes, no antiarrhythmics, consistent sinus rhythm
- Partial success – No afib episodes, but on antiarrhythmics to maintain consistent sinus rhythm
- Failure – Afib episodes still occurring with or without the use of antiarrhythmics
- Uncertain – Cases where insufficient data was available or where less than 6 months had gone by since the procedure.

Overview of Procedures

The procedures used to cure atrial fibrillation can be divided into two groups: – **catheterization procedures** and **surgical procedures**. Both types involve the creation of lesions on the heart wall (right and/or left atrium) in order to stop the propagation of impulses not involved in

conducting the heart beat "signal" from the sino-atrial (SA) node to the atrio-ventricular (AV) node.

Catheterization procedures create the lesions from the inside via an ablation catheter threaded through the femoral vein and are performed by electrophysiologists (EPs). Surgical procedures create the lesions from the outside and access is either through incisions between the ribs or may involve open-heart surgery and the use of a heart/lung machine. Surgical procedures are carried out by cardiothoracic surgeons.

The overwhelming majority of catheterization procedures use radiofrequency (RF) energy to create the lesions, but some EPs prefer the use of nitrogen-cooled catheters (cryoablation) rather than RF-powered ones due to their reduced risk of creating pulmonary vein stenosis.

The original surgical procedure, the full maze or Cox procedure, used a cut and sew protocol for creating lesions forming a "maze" that conducted the electrical impulse from the SA to the AV node, while at the same time interrupting any "rogue" circuits. The cut and sew method has now largely been replaced by the use of RF-powered devices, but cryosurgery, microwave application, and high-intensity focused ultrasound (HIFU) have all been tried as well and are preferred by some surgeons.

The so-called mini-maze procedure also involves lesions on the outside of the heart wall, but access to the heart is through incisions between the ribs rather than via open-heart surgery. The mini-maze may involve the creation of the full maze set of lesions, but usually focuses on pulmonary vein isolation. The procedure does not involve the use of a heart/lung machine.

Most of the rogue electrical impulses that create afib originate in the area where the pulmonary veins join the left atrium. Thus, all catheterization procedures aimed at curing afib involve electrical isolation of the pulmonary veins from the left atrium wall. Depending on the origin of the afib, catheterization procedures may also involve ablations of the superior vena cava and coronary sinus (thoracic veins), linear ablation of the left atrial roof, and a standard cavotricuspid isthmus (right flutter) ablation.

Surgical procedures, except for the full maze, also focus on isolating the pulmonary veins, but in addition may involve lesion creation at specific spots located by mapping, removal of the left atrial appendage, and disconnection of the ligaments of Marshall – a potent source of vagal input.

Evaluation of Background Data

Distribution of Procedures

Six hundred and seventy-seven afibbers responded to the survey and provided data for a total of 1045 procedures distributed as follows:

TABLE 1

	Number of Procedures				
RF Ablation Procedures	1st	2nd	3rd	Further	Total
Focal ablation	52	26	7	0	85
Pulmonary vein ablation (PVA)	191	71	15	1	278
Segmental pulmonary vein ablation	65	37	10	0	112
Circumferential pulmonary vein ablation	55	23	5	2	85
Pulmonary vein antrum isolation	127	37	13	3	180
Right atrial flutter ablation	50	17	6	0	73
Left atrial flutter ablation	5	6	4	0	15
Ablation for supraventricular tachycardia	4	2	2	0	8
Ablation procedure unknown	62	32	9	13	116
Total RF ablation procedures	**611**	**251**	**71**	**19**	**952**
Other Procedures					
Cryoablation	8	4	0	0	12
Maze procedure	20	3	1	2	26
Mini-maze procedure	29	3	6	2	40
AV node ablation + pacemaker	9	3	1	2	15
Total other procedures	**66**	**13**	**8**	**6**	**93**
GRAND TOTAL	**677**	**264**	**79**	**25**	**1045**
% undergoing procedure	**100**	**39**	**12**	**4**	

The majority of procedures (90%) were radiofrequency (RF) ablation procedures. Thirty-nine percent of the 677 respondents underwent a second procedure, 12% a third procedure, and 4% underwent further procedures. The most widely used AF ablation procedure was the generic pulmonary vein ablation (PVA) followed by the pulmonary vein antrum isolation (Natale), the segmental PVI (Haissaguerre), and the circumferential PVI (Pappone).

General Background of Respondents

TABLE 2

Demographics	Male	Female	Total
Gender distribution, %	78	22	100
Average (median) age*, yrs	58	59	58
Median age at diagnosis, yrs(1)	47	49	48
Age range at diagnosis, yrs(1)	5-74	10-79	5-79
Years since diagnosis(1)	8	8	8
Years since diagnosis (range)	1-45	1-44	1-45
Underlying heart disease, %	9	7	8
LAF confirmed by diagnosis, %	92	90	92
Median age at last proc., yrs(1)	56	56	56
Age range (last proc.), yrs(1)	26-81	26-85	26-85

* At time of completing survey
(1) From 2007 ablation/maze survey

There are no significant differences between males and females as far as demographic variables are concerned.

Afib Type and Burden

A total of 584 respondents had provided detailed information regarding their type of AF (adrenergic, mixed, vagal) prior to their procedure. The distribution was as follows:

TABLE 3

Type of AF	Male	Female	Total
No. of respondents	453	131	584
Adrenergic, %	5	4	5
Mixed, %	43	48	44
Vagal, %	25	24	24
Total paroxysmal, %	72	76	73
Persistent, %	10	10	10
Permanent, %	17	15	17
TOTAL	**100**	**100**	**100**

NOTE: 93 respondents were uncertain as to which type they had

The majority of the 2008 respondents (73%) had paroxysmal AF, while 10% had persistent, and 17% had permanent AF. Mixed (random) AF was the most common paroxysmal type for both sexes followed by vagal and adrenergic.

Although not specifically dealt with in this survey, the 2007 survey did provide data concerning the frequency of episodes and the total burden (frequency x duration) experienced among 478 afibbers.

The majority of respondents (79%) experienced episodes at least once a week and 40% were in afib every day (including permanent afibbers). Only 6% of those seeking a cure through ablation or surgical procedures had episodes less frequent than once a month. This indicates that most afibbers only opt for a procedure when the frequency of episodes becomes intolerable or permanent AF becomes a reality.

The median duration of paroxysmal episodes was 9 hours with a wide range of from a few minutes to 120 hours. There was no statistically significant difference in afib burden between paroxysmal afibbers taking antiarrhythmics or blockers and those taking no medications on a continuous basis.

The total average (median) burden over a 3-month period was 208 hours for mixed afibbers, 163 hours for vagal afibbers, and 104 hours for adrenergic.

PART 2 – RADIOFREQUENCY ABLATION

Demographics

A total of 552 afibbers underwent a RF ablation of the left atrium for the purpose of curing afib as their first procedure. The majority of the 481 respondents who knew their type of afib had the paroxysmal form (74%), 10% had persistent afib, while the remaining 16% were in permanent afib. Among the 352 paroxysmal afibbers who were aware of the initiating circumstances for their episodes, 58% characterized themselves as mixed, 35% were vagal, and 7% were adrenergic.

Twenty-three percent of respondents were female. Six percent of respondents had been diagnosed with heart disease.

Initial Procedure Results

Only afibbers who had undergone their first RF ablation at least 6 months prior to completing the survey questionnaire were considered in this evaluation in order to avoid making premature conclusions as to success. Thus, 475 afibbers who knew the outcome of their first ablation were included. Results are presented in the table below.

TABLE 4

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Ablation Results				
Adrenergic	20	44	6	50
Mixed	188	35	6	58
Vagal	99	33	3	64
Paroxysmal - not sure	49	24	7	69
Total paroxysmal	356	33	6	61
Persistent	42	46	8	46
Permanent	70	42	5	53
Not sure	7	29	14	57
Grand total	**475**	**34**	**5**	**61**
Other Possible Variables				
Underlying heart disease	30	20	7	73
Outcome for males	367	36	4	61
Outcome for females	108	28	10	62

The overall rate of complete success (no afib, no antiarrhythmics) for a first RF ablation was 34%. The rate of partial success (no afib, but on antiarrhythmics) was 5%, and the overall failure rate was a disappointing 61%. There were no statistically significant differences in success or failure rates between the three types of paroxysmal AF (adrenergic, mixed and vagal). The failure rate for afibbers with underlying heart disease was somewhat higher than the average; however, this difference was not statistically significant, nor was the difference in complete success between male and female ablatees.

The overall complete success rate (34%) for the initial RF ablation is clearly disappointing. However, as previous surveys have shown, success rates are mostly dependent on the skill and experience of the EP performing the procedure. The possible influence of episode duration and frequency on procedure outcome was evaluated in the 2007 ablation/maze survey. Episode duration, somewhat surprisingly, did not play a statistically significant role in determining the outcome of the first ablation. The risk of failure did, however, increase with increasing episode frequency. Afibbers who experienced episodes every week or more frequently had a 65% risk of failure, while those with less frequent episodes had a failure risk of 49%. This difference is statistically significant ($p = 0.03$) and may indicate that ablation should be considered if episode frequency approaches once a week. However, in assessing the validity of any possible correlation such as this, it should always be kept in mind that the overriding factor in any evaluation of ablation success is the EP performing the procedure.

Second and Third Procedure Results

Only afibbers who had undergone their 2nd and 3rd afib ablations at least 6 months prior to completing the survey and were certain of the outcome were included in this tabulation in order to avoid making premature conclusions as to success. Results are presented in the table below.

TABLE 5

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Procedure outcome				
1st procedure	475	34	5	61
2nd procedure	193	34	5	61
3rd procedure	46	35	17	48
Total/Average	**714**	**34**	**6**	**60**

The percentage of complete success of the 2nd and 3rd procedures is not significantly different from that of the first procedure, thus supporting the claim by many EPs that a follow-up procedure is not materially different from the initial procedure. The remainder of this section will thus combine the results for all RF afib ablation procedures for which the outcome is known (after a 6-month wait period) including the 4th, 5th and 6th procedures.

It is of interest to note that the rate of partial success (no afib, but on antiarrhythmic drugs) is substantially higher after the 3rd procedure than after the 1st and 2nd procedures (17% vs. 5%). This difference is statistically highly significant and may indicate that the chance of antiarrhythmics working is greater after multiple ablations.

Procedure Outcome – RF Ablation

Outcome of Procedures

TABLE 6

	Complete Success, %				
	1998-2004	2005	2006	2007-2008	1998-2008
Procedure	Success,%	Success,%	Success,%	Success,%	Success,%
Focal ablation	11	30	33	33	19
PV ablation (PVA)	19	37	26	43	28
Segmental PVI	32	43	43	41	40
Circumferential PVI	30	20	18	67	34
Antrum PVI (PVAI)	52	63	63	59	59
Unspecified	11	18	11	38	18
Total/Average	**24**	**39**	**33**	**48**	**34**
# of procedures	276	148	140	165	729

The average complete success rate for 729 individual left atrium RF ablation procedures (including 4th, 5th, and 6th) performed during the period 1998-2008 was 34%. Complete success rates have doubled from the average 24% observed for the 1998-2004 period to 48% for the year 2007 and first 4 months of 2008. This remarkable improvement in single procedure success is reflected in an overall average increase in final (complete) success rate from 47% in the period 1998-2004 to 66% in the period 2007-2008.

The most successful procedure is clearly the pulmonary vein antrum isolation procedure (Natale method) with an average single procedure success rate of 59%. The second most successful procedure was the segmental PVI (Haissaguerre method) as practiced in Bordeaux and several other clinics with an average single procedure success rate of 40%. The circumferential PVI (Pappone method) had an overall success rate of 34%, but improved markedly in the last year or so to reach an average complete success rate of 67%. This remarkable improvement could be due to the introduction of more reliable mapping procedures, the increasing experience of the EPs performing the procedure, but could also be due to a preference for selecting paroxysmal afibbers for the procedure. In the period 2007-2008, 95% of patients undergoing the circumferential procedure had the paroxysmal form of AF. In contrast, only 65% of patients undergoing the pulmonary vein antrum isolation procedure had paroxysmal. Similarly, only 62% of afibbers treated with the segmental procedure had paroxysmal AF.

The usage pattern of the different procedures in relation to the type of afib ablated is further explored in Table 7.

TABLE 7

Success Rate – Single Procedure, 2005-2008

		Procedure Use, %			Complete Success Rate, %		
Procedure	# in Group	Parox	Persist	Perm	Parox	Persist	Perm
Focal ablation	28	71	7	21	35	100	0
PV ablation (PVA)	129	79	12	9	36	38	18
Segmental PVI	85	74	12	14	40	40	58
Circumferential PVI	50	90	6	4	36	67	0
Antrum PVI (PVAI)	99	65	7	28	69	57	46
Unspecified	51	76	6	18	21	100	0
Total/Average		75	9	15	41	51	32
# in group	442	333	41	68	137	21	22

It is clear that the circumferential PVI is primarily used in paroxysmal afib and has an average success rate for this type (36%). The PVAI procedure, on the other hand, has an excellent success rate for both paroxysmal (69%) and permanent (46%) afib, and only 65% of patients undergoing this procedure had paroxysmal afib. The best success rate for permanent afib (58%) was observed for the segmental PVI, no doubt, because 67% of the procedures were carried out by the Bordeaux team of Profs. Haissaguerre and Jais. Similarly, the 46% success rate for single procedure PVAI for permanent afib is, no doubt, due to the fact that 66% of the procedures were carried out by Dr. Natale. The average success rate for persistent afib was surprisingly high at 51%. I have no explanation for this other than the fact that most procedures for persistent afib were carried out at top-ranked institutions.

Adverse Events

The 2008 ablation/maze survey did not specifically enquire about adverse events. However, the 2006 survey did and since the incidence of adverse events is an important consideration in deciding on an ablation, I have repeated the results of the 2006 survey.

The table below shows the incidence of adverse events that occurred during or shortly following 358 RF ablation procedures performed during the period 1998-2006. Fifty-nine percent of all procedures were not accompanied by an adverse event, while 41% were associated with one or more events.

TABLE 8

	1998-2004			2005-2006			1998-2006		
Event, %	Compl Succ	Part Succ	Failure	Compl Succ	Part Succ	Failure	Compl Succ	Part Succ	Failure
None	74	63	55	69	30	48	71	50	52
One or more, %	26	38	45	31	70	52	29	50	48
Total, %	100	100	100	100	100	100	100	100	100

It is clear that the risk of adverse events is substantially higher in the case of a failed ablation (48%) than in the case of a successful one (29%). This difference is statistically very significant (p=0.002). About 70% of all adverse events reported were fully resolved at the time the survey was completed.

The following table shows the distribution of events. The percentage of events relates to the number of procedures (not the total number of events). Thus, the sum of adverse events and no adverse events may not always equal 100% since some procedures were accompanied by more than one adverse event.

TABLE 9

	1998-2004			2005-2006			1998-2006			
	Comp. Succ.	Part. Succ.	Fail.	Comp. Succ.	Part. Succ.	Fail.	Comp. Succ.	Part. Succ.	Fail.	Total Events
None, %	74	63	55	69	30	48	71	50	52	**59**
Hematoma, %	13	13	19	14	10	21	13	12	20	**17**
TIA, %	2	0	1	0	0	1	1	0	1	**1**
Stroke, %	0	0	2	0	0	0	0	0	1	**1**
PV stenosis, %	2	0	6	0	10	0	1	4	4	**3**
Pericarditis, %	0	0	3	3	10	1	1	4	3	**2**
Tamponade< %	0	0	2	0	0	0	0	0	2	**1**
Fistula, %	2	0	0	0	0	0	1	0	0	**0**
Left flutter, %	2	31	12	8	20	21	5	27	15	**12**
Right flutter, %	2	0	8	3	30	8	2	12	8	**6**
Minor events, %	5	0	3	7	10	1	6	4	3	**4**
Life-threat, %	0	0	1	0	0	0	0	0	1	**0**
Permanent, %	0	0	2	0	0	0	0	0	1	**1**
Adv. events, %	**26**	**44**	**59**	**34**	**90**	**55**	**30**	**62**	**57**	**47**

Over the period 1998-2006 hematoma in the groin and thigh area was the most common adverse effect at 17%.

Fortunately, this adverse event was short-lived and was completely resolved at the time the survey was submitted. The second most common adverse event was the development of post-procedural left atrial tachycardia/flutter. This complication arose in 44 of 358 procedures (12%). The left atrial tachycardia/flutter resolved on its own in about 40% of cases, but 6 (14%) ablatees underwent another ablation to deal with it.

Post-procedure right atrial flutter was reported by 22 ablatees (6%) and 8 (36%) subsequently underwent an ablation to eliminate it.

In the remaining 64% the right atrial flutter was temporary and resolved itself prior to completion of the survey. NOTE: One hundred and fourteen (32%) of all ablation procedures included a right atrial flutter ablation as a precautionary measure.

Minor reversible events occurred during 4% of all procedures, pulmonary vein stenosis during 2.5%, and stroke and TIA accounted for 0.6% and 0.8% respectively. Tamponade (piercing of the heart wall) occurred during 3 procedures and thus accounted for 0.8% of events, pericarditis (inflammation of the heart wall) followed 8 procedures (2.1%), and one ablatee experienced a non-fatal fistula (0.3%). One respondent sustained permanent damage to the mitral valve, and another experienced a life-threatening event.

Afib Episodes after Procedure(s)

Questions about the occurrence of afib episodes after each procedure were not included in the 2008 survey, so the results from the 2006 survey are repeated below.

TABLE 10

	# in Group	Complete Success, %	Partial Success, %	Failure, %
Continuing afib episodes				
None	156	69	33	8
Less than 1 month	83	12	27	21
One month	21	7	3	3
Two months	30	6	7	7
Three months	21	3	3	5
More than 3 months	155	2	27	56
Total	466	100	100	100

Complete success was associated with only an 11% incidence of continuing afib episodes after the first, often unstable month. Failure, on the other hand, was associated with a 68% incidence of continuing episodes after the first month. This difference was extremely significant ($p < 0.0001$). It is also evident that experiencing episodes beyond 3 months post-procedure is a strong indicator of ultimate failure. While only 2% of successfully ablated afibbers experienced episodes beyond 3 months, 56% of those ultimately unsuccessful did. These findings support the observation made by Italian researchers that patients who continue to have episodes beyond the first month post-procedure only have a 10% probability of eventual cure[1].

Recovery Time

A question about recovery time was not included in the 2008 ablation/maze survey, so the results from the 2006 survey are repeated below.

TABLE 11

	# in Group	Complete Success,%	Partial Success,%	Failure,%	Average,%
Time to full recovery					
Less than 1 month	96	28	29	33	31
1-2 months	84	26	25	28	27
2-3 months	54	24	8	14	17
More than 3 months	75	21	38	25	24
Total	309	100	100	100	100

About 58% of all ablatees recovered fully in less than 2 months, but 24% took longer than 3 months to return to their pre-ablation level of stamina.

Patient Outcome

Four hundred and sixty-one patients had undergone only RF ablation procedures in order to cure their AF, knew the outcome of their final procedure, and had gone at least 6 months since that last procedure. The average (median) observation period after the most recent ablation was 18 months with a range of 6 months to 11 years.

Two hundred and fifty-six of the 461 respondents (56%) were no longer experiencing afib episodes and were no longer taking antiarrhythmic drugs (compete success). Ten percent were also afib-free, but only with the help of antiarrhythmics (partial success), while the remaining 156 (34%) were still experiencing episodes with or without the use of antiarrhythmics. Thus, the overall outcome after an average 1.5 procedures per patient was as follows:

	Objective Judgment	Subjective Judgment
Complete success	56%	64%
Partial success	10%	20%
Failure	34%	16%
TOTAL	100%	100%

The subjectively judged success rate is clearly higher than actually warranted by the actual outcome. It is likely that some afibbers

considered their procedure a success even though they still experienced episodes, but generally of lesser frequency and/or shorter duration. Many also were less sensitive to former triggers adding to the feeling of success.

In interpreting the objective judgment numbers, it should be kept in mind that they are applicable to the 11-year period 1998-2008. If only the latest period 2007-2008 is considered, then the percentages become:

	Objective Judgment
Complete success	66%
Partial success	8%
Failure	26%
TOTAL	100%

Trigger Avoidance

While 79% of successful ablatees no longer needed to avoid previous triggers, only 23% of those having undergone an unsuccessful procedure were so lucky. Nevertheless, it would seem that any ablation, whether successful or not, does help to reduce trigger sensitivity.

TABLE 12

	# in Group	Complete Success,%	Partial Success,%	Failure,%	Average,%
Trigger avoidance					
No longer necessary	264	79	51	23	57
Still necessary	85	5	16	42	18
Much less sensitive	72	10	18	24	16
Uncertain	39	6	14	11	8
Total	**460**	**100**	**100**	**100**	**100**

Changes in Heart Rate

The 2008 ablation/maze survey did not enquire about post-procedural changes in heart rate. However, the 2007 survey did and produced the following results. Changes in resting heart rate after RF ablation were quite common among paroxysmal and persistent afibbers.

TABLE 13

	# in Group	Complete Success.%	Partial Success.%	Failure.%	Average.%
Heart rate change					
Increase	137	67	56	41	57
No change	67	23	36	33	28
Decrease	36	10	8	26	15
Total	**240**	**100**	**100**	**100**	**100**

The most frequent post-procedural change was an increase in heart rate (experienced by 57%). This increase was most common among afibbers who had undergone successful procedure(s) (67%) and least common among those whose procedures had failed to cure the afib (41%). This difference was statistically significant (p=0.04). A decrease in heart rate was fairly rare among successfully ablated afibbers (10%), but more common (26%) among those whose procedure had failed.

The reason for the increase in heart rate after an ablation is that a significant portion of vagal nerve endings is damaged during the RF ablation procedure. Because the vagal nerves imbedded in the myocardium serve as "speed controllers" counteracting the adrenergic influence, a reduction in the number of effective vagal nerves would be expected to lead to an increased heart rate. Thus, it is possible that a more "aggressive" ablation, as indicated by a higher heart rate after the procedure, is more likely to be successful. However, this is speculation on my part and obviously assumes that the "aggression" is directed at the right spots on the atrium walls and pulmonary vein ostia.

It is generally assumed that the increase is temporary, however, this may not always be the case. A mini-survey (2006 survey) of 25 afibbers who had experienced a significant increase (average of 20 bpm) in post-procedure resting heart rate revealed that for 13 out of 25 respondents (52%) the heart rate was still significantly elevated a year or more after the last procedure. From personal experience I know that a substantial increase in heart rate (to 90 bpm or higher) can be very uncomfortable, so it is to be hoped that afib researchers will eventually address this problem.

Post-Procedural Arrhythmias

One hundred and forty-seven afibbers provided data as to whether they had experienced episodes of ectopics (PACs and PVCs), supraventricular tachycardia (SVT) including inappropriate sinus tachycardia, or flutter beyond 6 months following their final left atrium ablation procedure for

the purpose of curing afib. When completing the survey they had five choices in answering the questions:

1. Do you still experience ectopics?
2. Do you still experience tachycardia?
3. Do you still experience flutter?

The five possible answers were:

- Yes
- No
- No, but did experience episodes for **some time** following the procedure
- No, **never** did experience episodes after the procedure
- Not sure

The answers were evaluated against the following two variables:

- Success of left atrium ablation procedure
- Previous or concomitant right atrial flutter ablation

The results are presented in Tables 14 to 16.

TABLE 14

Post-Procedure Ectopics

	# in group	Never,%	No, %	Sometimes,%	Yes,%	Unsure,%
Outcome of ablation(1)						
Complete success	103	2	29	8	50	12
Failure	34	0	21	0	71	9
Right flutter ablations						
No previous ablation	73	3	22	7	59	10
Right flutter (2)	74	4	24	7	50	15

(1) Outcome of final RF ablation in the left atrium
(2) Right atrial flutter ablation as part of left atrium ablation, or separate procedure preceding final left atrium ablation

It is clear that continuing to experience episodes of ectopic beats (PACs and PVCs) even 6 months following a left atrium ablation procedure is very common with 50% of ablatees having undergone a successful procedure, and 71% of those whose procedure had failed experiencing ectopics. This difference is statistically significant and shows that an increase in ectopic episodes goes hand in hand with a failed procedure. It is also clear that even a successful ablation does not solve the problem of ectopics, but merely prevents them from precipitating afib. The idea has been advanced that the ectopic beats originate in the pulmonary veins,

but cannot initiate afib, because the electrical impulse generated by them is unable to cross the barrier (lesions) isolating the veins from the left atrium. I posed this possibility to Prof. Pierre Jais and his reply was, "*In my opinion, you cannot feel ectopics from the isolated veins. There is no atrial contraction associated with the isolated beat*". It is thus likely that the source of the ectopics is the atrium wall itself and that an additional ablation may be required in order to deal with them. However, I should point out that many afibbers have found that supplementation with magnesium/potassium/taurine significantly reduces ectopics.

There was no indication that having a right atrial flutter ablation prior to or during the left atrium ablation reduced the incidence of ectopics.

TABLE 15

Post-Procedure Tachycardia

	# in group	Never,%	No,%	Sometimes,%	Yes, %	Unsure,%
Outcome of ablation(1)						
Complete success	103	7	70	10	12	2
Failure	34	6	41	3	44	6
Right flutter ablations						
No previous ablation	73	4	66	7	19	4
Right flutter (2)	74	9	59	9	22	0

(1) Outcome of final RF ablation in the left atrium
(2) Right atrial flutter ablation as part of left atrium ablation, or separate procedure preceding final left atrium ablation

Tachycardia is a less common post-procedural complication than ectopics and unless actually diagnosed may be mistaken for flutter or vice versa. Again, it is clear that a failed left atrium ablation is associated with a substantially higher risk of experiencing post-procedural tachycardia than if the procedure is successful (44% vs. 12%). Having undergone a right atrial flutter ablation as part of or prior to the left atrium ablation did not affect the incidence of post-procedure tachycardia.

TABLE 16

Post-Procedure Flutter

	# in group	Never,%	No, %	Sometimes,%	Yes,%	Unsure,%
Outcome of ablation(1)						
Complete success	103	11	72	5	7	6
Failure	34	0	32	3	41	24
Right flutter ablations						
No previous ablation	73	7	62	5	14	12
Right flutter (2)	74	9	62	5	15	8

(1) Outcome of final RF ablation in the left atrium
(2) Right atrial flutter ablation as part of left atrium ablation, or separate procedure preceding final left atrium ablation

The incidence of post-procedure flutter is substantially higher in the case of a failed left atrium ablation than in the case of a successful one (41% vs. 7%). Unfortunately, I have no data to enable me to determine whether the flutter originated in the left or right atrium. However, the finding that having undergone a right atrial flutter ablation made no difference to the incidence of post-procedural flutter may indicate that most of the post-procedure flutter was left atrial flutter.

Other RF Ablation Procedures

Ablation for Supraventricular Tachycardia

Eight afibbers had undergone an ablation for supraventricular tachycardia (SVT), 4 as their first procedure and 4 following a left atrium ablation procedure. All but one (performed after a left atrium AF ablation) were successful.

Left Atrial Flutter Ablation

Five respondents had received a diagnosis of left atrial flutter as being the likely cause of their afib and underwent an ablation for this condition as their first procedure. Four of the respondents knew the outcome of the procedure and had gone at least 6 months since the procedure. One of the procedures was partially successful (no afib, but still on antiarrhythmics), but the other 3 were not. Two of the three went on to have PVIs, both of which successfully eliminated their afib.

It is estimated that about 10% of afibbers undergoing a PVI develop left atrial flutter or tachycardia following the procedure. If the flutter or tachycardia develops within the first week following the procedure, it is usually transient and requires no treatment. However, it may develop as much as 2-3 months post-procedure and, in this case, treatment is usually required. Treatment may involve re-isolation of the pulmonary veins or the placement of linear ablation lesions to interrupt the flutter circuit.

Ten respondents underwent a left atrial flutter ablation subsequent to a PVI. There is insufficient data to determine the success of these ablations as far as elimination of the flutter is concerned.

Right Atrial Flutter Ablation

Seventy-three respondents had undergone a right atrial flutter ablation either as an initial procedure (50 respondents) or as a follow-up after a PVI, mini-maze or unsuccessful right atrial flutter ablation (23 respondents). In addition, 254 left atrium ablation procedures included a routine right atrial flutter ablation, while 379 did not. The need for a subsequent right atrial flutter ablation was 0.8% in the group having undergone the routine flutter ablation versus 1.8% in the group that did not. This difference was not statistically significant.

Forty-seven of the 50 respondents who underwent a right atrial flutter ablation as their first procedure reported the outcome at least 6 months after their procedure. Five of the procedures were completely successful in eliminating the afib (11%) and 4 (9%) were partially successful (still on antiarrhythmics). Thus, in 80% of cases an initial right atrial flutter ablation failed to eliminate the underlying AF (with or without antiarrhythmics). Somewhat surprisingly, 11% of afibbers underwent a second, and even a third, right atrial flutter ablation in further attempts to cure their afib.

In this regard, it should be mentioned that only 2 of the original 50 initial procedures were carried out at top-ranked RF ablation institutions and both were followed by standard PVI ablations. All told, 56% of initial right atrial flutter ablations were followed by standard RF pulmonary vein ablations.

Atrial flutter and AF are similar in that they both involve abnormal, sustained, rapid contractions of the heart's upper chambers (atria). In atrial flutter the atria contract 220 to 350 times a minute in an orderly rhythm. In AF the rate of contraction may be as high as 500 beats/minute and the rhythm is totally chaotic. The two arrhythmias can both occur as a result of an enlarged atrium or in the aftermath of open-heart surgery, but the mechanism underlying them is quite different. Nevertheless, they can coexist in the same patient and one may convert to the other.

Because the location of the origin of atrial flutter, at least in the common type, is so well known and consistent from patient to patient radio frequency catheter ablation can be used with considerable success to permanently eradicate atrial flutter. Unfortunately, this procedure is unlikely to cure AF, which may often coexist with atrial flutter. There is also some evidence that atrial flutter patients who have a successful ablation increase their risk of later developing AF by 10-22%. So undergoing RF ablation for atrial flutter may not remove the necessity of dealing with AF.

Because of the close connection between AF and atrial flutter, it was quite common, in the early days of ablation, to perform an atrial flutter ablation in the hope that it would cure the AF. The atrial flutter ablation involves only the right atrium so there is no need to pierce the septum to the left atrium as is done in a PVI.

After the 1998 discovery that 80-90% of paroxysmal episodes originate in the left atrium near the pulmonary veins, the use of the right atrial flutter ablation in an attempt to cure AF became less common, but the procedure is still used as a first attempt in patients with a combination of AF and flutter. It is, of course, also used in patients suffering from right atrial flutter only.

Quality of Life

Although the main concern of the medical profession when it comes to lone atrial fibrillation is stroke risk, the overwhelming concern of the patient is quality of life. As all afibbers know, being in permanent afib or awaiting the next episode in a state of anxiety has a devastating effect on ones quality of life and radically changes the life of those nearest and dearest to us.

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 1.5 procedures) is 56%. 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 66%. Further considering that, according to the 2007 ablation/maze survey, 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.

Performance Rating

Previous ablation/maze surveys have all arrived at the conclusion that the most important factor in determining the outcome of a RF ablation is the skill and experience of the EP performing it. In order to provide some guidance in regard to the likelihood of undergoing a successful left atrium

AF ablation at a particular institution, I have developed a Performance Rating scheme. This rating takes into account the success rates reported by afibbers treated at specific institutions and by specific EPs. The rating is calculated using the following rating scores:

Success Score

- Completely successful left atrium ablation score = 10
- Partially successful left atrium ablation score = 5
- Failed ablation (continuing afib episodes) score = 0

Please note that in this evaluation of 729 single RF left atrium afib ablation procedures, a procedure is not considered a failure unless followed by another RF left atrium afib ablation or continued afib episodes. The subsequent occurrence of left or right atrial flutter or tachycardia is treated here as an adverse event and not as an ablation failure.

It is clear that a performance rating is not very indicative in cases where just one or two procedures have been performed. Thus, performance ratings have only been established for institutions that had reports on 6 or more procedures. The results from 28 institutions with 6 or more procedures are presented in the table below.

TABLE 17

Rank	No. of Proced.	Rating	Institution
1	7	7.1	Cleveland Clinic, Weston, FL
2	83	6.4	Cleveland Clinic, OH
3	55	5.9	California Pacific Medical Center, San Francisco *
4	14	5.7	Mayo Clinic, Rochester, MN
5	8	5.0	Freeman Hospital, Newcastle, UK
6	11	5.0	Medical University of South Carolina (MUSC)
7	20	5.0	University of Pennsylvania
8	6	5.0	Johns Hopkins University Hospital
9	73	4.7	Hopital Card. du Haut Leveque, Bordeaux, FR
10	7	4.3	Loyola Medical Center, Maywood, IL
11	14	4.3	Good Samaritan Hospital, Los Angeles
12	6	4.2	Aurora/Sinai Medical Center, Milwaukee, WI
13	11	3.6	Sequoia Hospital, Redwood City, CA
14	13	3.5	University of Michigan
15	14	3.2	NYU Medical Center, NY
16	11	2.7	Centinela Hospital, Inglewood, CA
17	22	2.3	Royal Jubilee Hospital, Victoria, BC
18	10	2.0	University of California at San Diego
19	11	1.8	St. Paul's Hospital, Vancouver, BC
20	9	1.7	University of Alabama, Birmingham
21	12	1.7	St. Bartholomew's, London, UK
22	7	1.4	Hollywood Hospital, Perth, Australia
23	7	1.4	Northwestern Memorial Hospital, Chicago, IL
24	7	1.4	Southampton Hospital, UK
25	9	1.1	Massachusetts General Hospital, Boston
26	6	0.8	Scottsdale Healthcare, Osborn, AZ
27	13	0.8	Brigham and Women's Hospital, Boston, MA
28	14	0.4	Texas Heart Institute, Houston

* Includes procedures carried out by Drs. Natale and Hao at Marin General Hospital

The first 15 institutions (performance rating of 3.0 or higher) in the above table account for close to 50% of all left atrium RF ablation procedures performed; their performance is evaluated in detail in Table 18 (ranked by complete success rate).

TABLE 18

Single Procedure Success – Top-Ranked Institutions

Rank	Institution	# of Procedures	Rating	Success Rate, % Complete	Partial	Failure
1	Cleveland Clinic, OH	83	6.4	61	6	33
2	Cleveland Clinic, FL	7	7.1	57	29	14
3	California Pacific(1)	55	5.9	56	5	38
4	Mayo Clinic, MN	14	5.7	50	14	36
5	Freeman Hospital	8	5.0	50	0	50
6	Bordeaux	73	4.7	47	1	52
7	MUSC	11	5.0	45	9	45
8	U of Pennsylvania	20	5.0	45	10	45
9	Good Samaritan	14	4.3	43	0	57
10	Loyola	7	4.3	43	0	57
11	Sequoia	11	3.6	36	0	64
12	Johns Hopkins	6	5.0	33	33	33
13	Aurora/Sinai	6	4.2	33	17	50
14	U of Michigan	13	3.5	31	8	62
15	NYU	14	3.2	29	7	64
Grand Total – Top-ranked		**342**	**5.3**	**50**	**6**	**44**
Other Institutions		**387**	**2.4**	**21**	**5**	**74**
All Institutions		**729**	**3.7**	**34**	**6**	**60**

(1) Includes procedures carried out by Drs. Natale and Hao at Marin General

The electrophysiologists performing the procedures in the above 15 institutions are as follows:

Institution	Electrophysiologists
Cleveland Clinic, OH	Drs. Andrea Natale*, Robert Schweikert**, Walid Saliba, Patrick Tchou, Oussama Wazni
Cleveland Clinic, FL	Dr. Sergio Pinski
California Pacific	Drs. Andrea Natale, Steven Hao
Mayo Clinic, Rochester, MN	Drs. Douglas Packer, Thomas Munger, Paul Friedman, Peter Brady
Freeman, Newcastle, UK	Dr. Stephen Furniss***
Bordeaux, France	Drs. Michel Haissaguerre, Pierre Jais
MUSC	Dr. Marcus Wharton
University of Pennsylvania	Drs. David Callans, Frank Marchlinski, David Lin
Good Samaritan, Los Angeles	Drs. Anil Bhandari, Neala Hunter, David Cannom, Mark Girski
Loyola Medical, Maywood, IL	Drs. David Wilber, Albert Lin
Sequoia, Redwood City, CA	Drs. Rob Patrawala, Roger Winkle
Johns Hopkins	Drs. Hugh Calkins, Ronald Berger

Aurora/Sinai, Milwaukee, WI	Dr. Jasbir Sra
University of Michigan	Drs. Fred Morady, Hakan Oral, Frank Pelosi, Eric Good
NYU Medical Center	Dr. Larry Chinitz

NOTE: 90% of the procedures performed at the Cleveland Clinic, OH were done by Dr. Natale or Dr. Schweikert

* Now at St. David's Medical Center, Austin, TX and California Pacific Medical Center, San Francisco
** Now at Akron General Medical Center, OH
*** Now at Eastbourne General Hospital, East Sussex, UK

The average performance rating for the top-ranked institutions is 5.3 as compared to 2.4 for the remaining institutions (387 single procedures). In evaluating the results for the top-ranked institutions it should be kept in mind that some may have a greater load of "difficult cases" than do others. Table 19 shows the relative proportion of paroxysmal, persistent, and permanent afibbers treated at the top-ranked institutions.

The statistics presented in Table18 are indeed sobering. Undergoing a single RF ablation procedure of the left atrium at an institution not included in the top 15 is associated with an average complete success rate of 21%, a partial success rate of 5%, and a failure rate of 74%.

Despite this overall bleak picture for "other" institutions, there would appear to be some good performers in this group, bearing in mind that the number of procedures upon which this conclusion is based is extremely limited.

Electrophysiologist	#of Procedures	Complete Success
Dr. Jonathan Steinberg [1]	5	80%
Dr. Chun Hwang [2]	4	50%
Dr. Yaariv Khaykin [3]	3	100%
Dr. David Fitzgerald [4]	3	67%

[1] St. Luke's Hospital, NYC
[2] Utah Valley Hospital, Provo, UT
[3] Southlake Hospital, Newmarket, ON, Canada
[4] Wake Forest University Medical Center, Winston-Salem, NC

TABLE 19

Types of afib treated – Top-ranked institutions

	# of Procedures	Paroxysmal,%	Persistent,%	Permanent,%
Cleveland Clinic, OH	83	69	7	24
Cleveland Clinic, FL	7	100	0	0
California Pacific *	55	63	2	35
Mayo Clinic, MN	14	100	0	0
Freeman Hospital	8	100	0	0
Bordeaux	73	70	15	15
MUSC	11	100	0	0
U of Pennsylvania	20	85	10	5
Good Samaritan	14	54	23	23
Loyola	7	86	0	14
Sequoia	11	64	18	18
Johns Hopkins	6	100	0	0
Aurora/Sinai	6	67	0	33
U of Michigan	13	85	8	8
NYU	14	100	0	0
Grand Total – Top	**342**	**74**	**8**	**18**
Other Institutions	**387**	**80**	**9**	**11**
All Institutions	**729**	**77**	**9**	**14**

* Includes procedures carried out by Drs. Natale and Hao at Marin General

It is clear that a significant percentage of procedures performed at the Cleveland Clinic in Ohio (31%), Hopital Cardiologique du Haut Leveque in Bordeaux (30%), California Pacific Medical Center in San Francisco (37%), Good Samaritan Hospital in Los Angeles (46%), and Sequoia Hospital in Redwood City, CA (36%) involved patients with permanent or persistent afib. In contrast, the cases treated at Freeman Hospital in Newcastle, UK, the Cleveland Clinic in Weston, FL, Medical University of South Carolina, NYU Medical Center, Johns Hopkins, and the Mayo Clinic in Rochester did not include any permanent or persistent afibbers.

Final Outcome

The ultimate measure of success for the individual patient is, of course, whether or not they are cured of afib irrespective of how many procedures it takes. In other words, the crucial question to an afibber seeking a solution is, "If I go to institution X what are my chances of getting cured?"

This part of the evaluation includes 461 individual patients whose last reported procedures were RF ablations in the left atrium for the purpose of curing AF. All patients reported their afib status 6 months following

their last procedure. The patients underwent a total of 729 procedures at 168 different institutions. A substantial number of the 200 repeat ablations were performed at institutions other than the ones doing the original procedure, so as far as this evaluation is concerned, a total of 531 patients were treated. Results of the evaluation are presented in Table 20.

TABLE 20

Final Performance Rating – Top-Ranked Institutions

Rank	Institution	# of Proced	# of Patients	Repeat Rate,%	Success Rate, % Compl	Part	Fail
1	Cleveland Clinic, OH	83	72	15	72	7	21
2	Bordeaux	73	47	55	72	2	26
3	California Pacific	55	46	20	67	7	26
4	Cleveland Clinic, FL	7	6	17	67	33	0
5	Freeman Hospital	8	6	33	67	0	33
6	Mayo Clinic, MN	14	11	27	64	18	18
7	MUSC	11	8	38	63	13	25
8	Good Samaritan	14	10	40	60	0	40
9	U of Pennsylvania	20	16	25	56	13	31
10	Loyola	7	6	17	50	0	50
11	Sequoia	11	8	38	50	0	50
12	Aurora/Sinai	6	4	50	50	25	25
13	Johns Hopkins	6	5	20	40	40	20
14	U of Michigan	13	9	44	44	11	44
15	NYU	14	8	63	38	13	50
Grand Total – Top-ranked		**342**	**262**	**30**	**65**	**8**	**27**
Other Institutions		**387**	**269**	**44**	**32**	**7**	**61**
All Institutions		**729**	**531**	**37**	**48**	**8**	**44**

NOTES:
Ranking is by highest % of patients achieving complete elimination of afib without use of antiarrhythmics.
Repeat rate is calculated as # of repeat ablations divided by # of initial procedures performed at the institutions.
First repeat procedure on patients who came to the institution from another one is not counted as a repeat.

The average complete success rate for the 15 top-ranked institutions is 65% with a failure rate of 27%. This compares to a complete success rate of 32%, and a failure rate of 61% at other than top-ranked institutions. The average repeat rate is 30% at top-ranked institutions versus 44% at other institutions.

In evaluating the results of the final performance rating it should be kept in mind that they, in order to optimize the statistical power of the survey, reflect the 11-year period 1998-2008. Techniques and outcomes have improved markedly from the period 1998-2004 to the period 2007-2008.

For example, the final success rate for the three top-rated RF ablation centers (Cleveland Clinic (Ohio), Hopital Cardiologique du Haut Leveque (Bordeaux), and California Pacific Medical center (San Francisco)) has increased almost 10% to average 82% for the period 2007-2008. A very encouraging trend indeed!

The repeat rate of 55% at Hopital Cardiologique Haut Leveque in Bordeaux is particularly high. This is likely due to the fact that most patients treated in Bordeaux have traveled long distances to get there and probably do not fancy repeating the trip. Thus, the Bordeaux team, at least until recently, used to perform a touch-up procedure as soon as one week following the initial procedure if the patient showed any signs at all that the ablation had not been successful. Over half of the repeat procedures done in Bordeaux were performed within the first month following the initial procedure. Since the first 3 months following an ablation is usually considered a blanking period where irregular heart activity is common without necessarily predicting ultimate failure, it is likely that some of the repeat procedures may not have been necessary, but were done anyway in order to ensure, as far as possible, that the patient returned home cured.

Comparison with Other Surveys

At least 6 surveys of PVI procedure success rates have now been published. The most recent one done by J.D. Fisher and colleagues at the Montefiore Medical Center in New York compiled the results of ablations performed in major centers around the world and reported in 200 peer-reviewed medical articles and covered a total of 23,000 AF patients.[2] Another large study, the Cappato Study, published in 2005 involved 8745 patients treated at 90 different institutions world-wide.[3] The outcome experience at the Cleveland Clinic, Ohio was presented for 323 patients who underwent a PVI for drug-resistant AF.[4] The University of Michigan experience (755 patients) was presented in a 2006 paper by *Oral, et al*[5], while Johns Hopkins Hospital outlined their PVI outcomes for 200 PVI procedures in a 2006 study authored by *Cheema, et al*.[6] Finally, also in 2006, a group of Danish electrophysiologists outlined their results of a study involving 100 patients who underwent a PVI using either the Haissaguerre or Pappone method.[7]

A comparison of the results from these surveys and the 2008 ablation/maze survey is presented in Tables 21 and 22. Table 21 summarizes the results of initial procedures, while Table 22 summarizes final outcome, that is, outcome after repeat ablations as required.

TABLE 21

Outcome after initial procedure						
		# of	Initial Success Rate,%			Observ.
Survey	Institution	Proced	Compl	Part	Fail	period, mos.
TOP-RANKED INSTITUTIONS						
Bhargava[3]	Cleveland Clinic, OH	323	71	0	29	6
Afibbers.org	Cleveland Clinic, OH	72	63	7	31	6
Afibbers.org	15 top-ranked	342	50	6	44	6
OTHER INSTITUTIONS						
Nilsson[6]	Copenhagen Univ.	100	17	0	83	3
Afibbers.org	Other	387	21	5	74	6

There are, unfortunately, only two studies, other than the afibbers.org survey (2008 ablation/maze survey), that have provided data for initial procedure outcome. Complete success after one ablation varies from 17% to 71% with the afibbers.org survey finding a rate of 50% for top-ranked institutions and 21% for other institutions.

TABLE 22

Outcome after final procedure							
		# of	Final Success Rate,%			Repeat	Observ.
Survey	Institution	Patients	Compl	Part	Fail	Rate, %	period,mos.
TOP-RANKED INSTITUTIONS							
Bhargava[4]	Cleveland, OH	323	83	0	17	12	12
Afibbers.org	Cleveland, OH	72	72	7	21	15	6
Oral[5]	Univ. Michigan	755	73	?	?	?	12
Cappato[3]	Top-ranked (world)	3244	64	16	20	27	12
Fisher[2]	Major (world)	23000	63	12	25	25	6
Afibbers.org	15 top-ranked	262	65	8	27	30	6
OTHER INSTITUTIONS							
Cheema[6]	Johns Hopkins	200	41	11	48	32	12
Nilsson[7]	Copenhagen Univ.	100	44	?	?	74	12
Afibbers.org	Other	269	32	7	61	61	6

The final outcome results are somewhat better documented with a recent world-wide survey of major institutions involving 23,000 patients finding an average complete success rate of 63%, a partial success rate of 12%, a failure rate of 25%, and a repeat rate of 25%. This compares well with our results for top-ranked institutions of a 65% complete success rate, an 8% partial success rate, a 27% failure rate, and a 30% repeat rate.

Summary

- The 2008 ablation/maze survey included 611 respondents who had undergone a total of 952 RF ablation procedures. The outcome of 729 of these procedures was known (status reported at least 6 months following the procedure).

- The overall objectively-rated complete success rate (no afib, no drugs) for 461 afibbers after an average of 1.5 procedures per patient was 56%, partial success was achieved in 10% of cases, and 34% of all afibbers who underwent one or more RF ablations continued to experience AF episodes.

- The subjective judgment of success by ablatees was somewhat more favourable with 64% feeling that the end result was total success, 20% claiming partial success, and 16% judging their procedures as a failure.

- The objectively rated complete success rate for a **single** RF ablation procedure was 34%, that of partial success 5%, and that of failure 61% when averaged over the years 1998-2008. For the more recent period 2007-2008, the complete success rate for a **single** RF ablation procedure averaged 48%. This remarkable improvement in single procedure success is reflected in an overall average increase in final (complete) success rate from 47% in the period 1998-2004 to 66% in the period 2007-2008.

- The average complete success rate for the 15 top-ranked RF ablation centers was 65% with a failure rate of 27% for the period 1998-2008. This compares to a complete success rate of 32%, and a failure rate of 61% at other than top-ranked institutions. This clearly indicates that the all-important factor in determining the outcome of an RF ablation is the skill and experience of the EP performing it. Techniques and outcomes have improved markedly from the period 1998-2004 to the period 2007-2008. For example, the final success rate for the three top-rated RF ablation centers (Cleveland Clinic (Ohio), Hopital Cardiologique du Haut Leveque (Bordeaux), and California Pacific Medical center (San Francisco)) has increased almost 10% to average 82% for the period 2007-2008. A very encouraging

trend indeed! The average repeat rate was 30% at top-ranked institutions versus 44% at other institutions.

- Forty-one percent of 358 RF ablation procedures were accompanied by an adverse event, the most common (17%) being temporary hematoma in the thigh area. Left atrial tachycardia was also a fairly common adverse effect (12%), but resolved by itself in about 50% of cases. Stroke and TIA were rare at 0.6% and 0.8% respectively. About two-thirds of all adverse events were fully resolved at the time the survey was completed. Successful ablations were much less likely to be accompanied by an adverse event than were unsuccessful ones. NOTE: This data is from the 2006 ablation/maze survey.

- There were no significant differences in success and adverse event rates between a first and subsequent RF ablations, perhaps indicating that the technical difficulty in performing them is pretty much the same.

- The majority (79%) of respondents experienced AF episodes at least weekly prior to their ablation. [From 2007 survey]

- There was no evidence that age at diagnosis and ablation, gender, years of afib, or type of paroxysmal afib affected the outcome to a significant degree. However, more frequent episodes were associated with a lower success rate. [From 2007 survey]

- The most successful procedure for the period 2005-2008 was the pulmonary vein antrum isolation procedure (Natale method) with a single procedure complete success rate of 62% (paroxysmal, persistent and permanent combined). The segmental PVI (Haissaguerre method) was the second-most successful procedure with an average complete success rate of 42%.

- A significant majority (69%) of afibbers who had a completely successful ablation experienced no AF episodes at all after the procedure. Only 8% of those "doomed to failure" experienced no episodes at all after their procedure. Only 2% of completely successful ablatees experienced episodes for more than 3 months after the procedure, while 56% of unsuccessful ablatees did so. Thus, if AF episodes continue beyond 3 months the procedure is almost certainly a failure. On the other hand, if no AF episodes occur during the first

month then the procedure is likely to be a success. [From 2007 survey]

- Almost 60% of ablatees recovered fully in less than 2 months, but 24% took longer than 3 months to return to their pre-ablation level of stamina. NOTE: This data is from the 2006 ablation/maze survey.

- Most (96%) of afibbers who had a completely successful ablation did not continue with warfarin, but 13% of them continued to use natural stroke prevention remedies such as fish oil, nattokinase, vitamin E and ginkgo biloba. Seventeen percent took a daily aspirin for stroke prevention. In contrast, 36% of ablatees with a failed procedure continued on warfarin. [From 2007 survey]

- While 79% of successful ablatees no longer needed to avoid previous triggers, only 23% of those having undergone an unsuccessful ablation were so lucky. Nevertheless, it would seem that any ablation, whether successful or not, does help to reduce trigger sensitivity.

- The incidence of post-procedure ectopics (PACs and PVCs) even 6 months or more following the procedure was high at 50% for completely successful ablations and 71% for failed procedures, a difference that is statistically significant. There was no indication that having undergone a right atrial flutter ablation prior to or during the left atrium ablation reduced the incidence of ectopics.

- The incidence of post-procedure tachycardia (SVT and inappropriate sinus tachycardia) was 12% for completely successful and 44% for failed ablations. Having undergone a right atrial flutter ablation as part of or prior to the left atrium ablation did not affect the incidence of post-procedure tachycardia.

- The incidence of post-procedure flutter was 7% for a completely successful ablation and 41% for an unsuccessful one. Having undergone a prior right atrial flutter ablation made no difference to the post-procedure incidence of flutter perhaps indicating that most of the post-procedure flutter was left atrial flutter.

- Even an unsuccessful ablation resulted in a significant reduction in episode frequency in 74% of cases and in 75%

of cases was associated with a significant decrease in episode duration. Overall, 70% of unsuccessfully ablated patients experienced a 50% or better decrease in their afib burden. [From 2007 survey]

- Considering a 50% or greater reduction in afib burden (frequency x duration) as an indicator of improvement, it is estimated that close to 90% of RF ablations were ultimately successful in improving quality of life. [From 2007 survey]

- A post-ablation increase in heart rate was a common occurrence. This phenomenon was more prevalent among successful ablatees (67%) than among those whose ablation had failed (41%). This may indicate that a more aggressive approach (increased destruction of vagal nerve endings) is associated with a better outcome. [From 2007 survey]

Conclusion

I have made every effort to ensure that the calculations and conclusions made in this survey are correct. I have observed good internal consistency in the data and am comforted by the fact that the success rates found in this 2008 LAF Ablation/Maze Survey agree reasonably well with those found in published studies. The LAF survey is based on a total of 729 procedures performed on 461 individual patients, not an overly large number, but enough to draw reasonably valid conclusions in general terms. Where the survey results become less "solid" are in the evaluation of the success rates of individual electrophysiologists and institutions. The ratings of the Cleveland Clinic and the Hopital Cardiologique, Bordeaux are probably reasonably indicative since they involve a reasonably large number of patients, but ratings based on just 5 or 6 patients are clearly much less reliable, and it is quite possible that larger samples would produce different results.

Nevertheless, there is still a considerable gap in outcomes between top-ranked institutions and other centers. By far the best chance of success can be had at the top-ranked institutions, particularly one of the top three. That said, it is also clear that most, probably as many as 90%, of RF ablations result in a significant improvement in quality of life whether they are completely successful or not. This also means that 10% of all afibbers embarking on the ablation path can expect no improvement and in a significant proportion, a worsening of afib or a major adverse event.

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Acknowledgement

This survey obviously would not have been possible without the wholehearted (pun intended) cooperation of the almost 700 afibbers who have responded to this or previous surveys. On behalf of our fellow afibbers, ex-afibbers and myself, I would like to extend a sincere thank you to all respondents.

PART 3 – PROCEDURES OTHER THAN RF ABLATION

Overview of Procedures

The procedures used to cure atrial fibrillation can be divided into two groups – **catheterization procedures** and **surgical procedures**. Both types involve the creation of lesions on the heart wall (right and/or left atrium) in order to stop the propagation of impulses not involved in conducting the heart beat "signal" from the sino-atrial (SA) node to the atrio-ventricular (AV) node.

Catheterization procedures create the lesions from the inside via an ablation catheter threaded through the femoral vein and are performed by electrophysiologists (EPs). Surgical procedures create the lesions from the outside and access is either through incisions between the ribs or may involve open-heart surgery and the use of a heart/lung machine. Surgical procedures are carried out by cardiothoracic surgeons.

The original surgical procedure, the full maze or Cox procedure, used a cut and sew protocol for creating lesions forming a "maze" that conducted the electrical impulse from the SA to the AV node, while at the same time interrupting any "rogue" circuits. The cut and sew method has now largely been replaced by the use of RF-powered devices, but cryosurgery, microwave application, and high-intensity focused ultrasound (HIFU) have all been tried as well and are preferred by some surgeons.

The so-called mini-maze procedure also involves lesions on the outside of the heart wall, but access to the heart is through incisions between the ribs rather than via open-heart surgery. The mini-maze may involve the creation of the full maze set of lesions, but usually focuses on pulmonary vein isolation. The procedure does not involve the use of a heart/lung machine.

Most of the rogue electrical impulses that create afib originate in the area where the pulmonary veins join the left atrium. Thus, all catheterization procedures aimed at curing afib involve electrical isolation of the pulmonary veins from the left atrium wall. Depending on the origin of the afib, catheterization procedures may also involve ablations of the superior vena cava and coronary sinus (thoracic veins), linear ablation of the left atrial roof, and a standard cavotricuspid isthmus (right flutter) ablation.

Surgical procedures, except for the full maze, also focus on isolating the pulmonary veins, but in addition may involve lesion creation at specific

spots located by mapping, removal of the left atrial appendage, and disconnection of the ligaments of Marshall – a potent source of vagal input.

The procedures covered in this part of the survey are cryoablation, AV node ablation + pacemaker installation, the maze procedure, and the so-called "mini-maze" procedure (thoracoscopic epicardial pulmonary vein isolation). The main difference between the full maze and the mini-maze procedure is the method of access to the heart. The maze involves a 6-12 inch long cut through the breastbone, while the mini-maze provides access through two or more 2-inch incisions between the ribs. Another important difference is that the maze procedure requires the use of a heart/lung machine, while the mini-maze does not.

Evaluation of Background Data

Eighty-seven afibbers had undergone one or more surgical procedures (maze, mini-maze, AV node + pacemaker installation) or cryoablations. The distribution of these procedures is detailed in Table 23 below.

TABLE 23

	No. of Procedures				
Procedures	1st	2nd	3rd	Further	Total
Cryoablation	8	4	0	0	12
Maze procedure	20	3	1	2	26
Mini-maze procedure	29	4	6	2	41
AV node ablation + pacemaker	9	3	1	2	15
Total	**66**	**14**	**8**	**6**	**94**
RF ablation*	21	18	10	5	54
Total procedures	**87**	**32**	**18**	**11**	**148**

* RF ablations performed before or after cryoablation, maze, mini-maze, or AV node ablation + pacemaker implantation procedure.

Sixty-six respondents had undergone a surgical procedure or cryoablation as the initial attempt to cure their afib. Another 21 had theirs following an initial RF ablation – right atrial flutter (2), PVI or focal ablation (19).

General Background of Respondents

The general background data for the 87 respondents whose treatments for the purpose of curing atrial fibrillation included one or more cryoablation, maze, mini-maze or AV node ablations is given in Table 24.

TABLE 24

Demographics	Male	Female	Total/Average
Gender distribution, %	80	20	100
Average (median) age*, yrs.	62	61	62
Underlying heart disease, %	22	29	23
LAF confirmed by diagnosis, %	100	100	100
Afib Type			
Adrenergic, %	1	6	2
Mixed, %	37	50	39
Vagal, %	18	6	15
Uncertain, %	12	6	11
Total paroxysmal, %	68	69	68
Persistent, %	7	19	10
Permanent, %	25	13	23
Total	**100**	**100**	**100**

* At time of completing questionnaire

The only statistically significant difference between this group and the group undergoing RF ablations is the considerably higher incidence of underlying heart disease (23% vs 8%).

The majority of the cryoablation/maze group had paroxysmal afib (68%). Mixed (random) AF was the most common type of paroxysmal afib, followed by vagal and adrenergic. There were no statistically significant differences in afib type between this group and the RF ablation group.

Cryoablation

The cryoablation procedure is similar to the standard RF ablation procedure except that the ablation catheter is cooled by liquid nitrogen or argon rather than electrically heated. The advantage of cryoablation is that it reduces procedure stroke risk and does not create pulmonary vein stenosis even if the ablation is done inside the pulmonary veins.

Eight paroxysmal afibbers with no underlying heart disease (7 male, 1 female) had undergone cryoablation as their first procedure. Three of these procedures were fully successful (no afib, no drugs) giving a first procedure complete success rate of 38%.

Three of the unsuccessful ablatees went on to have other procedures – 2 had another cryoablation of which one was a success, while the third had an unsuccessful PVI procedure. The 2 remaining unsuccessful ablatees went on to have RF ablations, one of which was successful. Two

respondents underwent a cryoablation following a failed PVI. One was partially successful (afib controlled with antiarrhythmics).

The outcome (at least 6 months after procedure) was known for 12 cryoablation procedures. Four (33%) were fully successful and one (9%) was partly successful. The average single procedure complete success rate for cryoablation is thus 33%, not significantly different from the average single procedure complete success rate for PVI procedures at 34%. There is insufficient data to say what the final success rate would be after repeated cryoablations.

AV Node Ablation + Pacemaker Implantation

Palpitations, elevated heart rate, and other major symptoms of an atrial fibrillation episode are associated with rapid and irregular contractions of the left ventricle rather than with the actual "quivering" of the left atrium. So, although the root cause of AF is found in the left atrium, its symptomatic effects can, to a large extent, be eliminated by isolating the AV node (the ventricular beat controller) from impulses originating in the left atrium and feeding the ventricles their "marching orders" from an implanted pacemaker. AV node ablation + pacemaker installation is a relatively simple procedure and is therefore mostly successful. It does also provide substantial symptom relief allowing afibbers to live a fairly normal life. Nevertheless, the procedure is considered a last resort for the following reasons:

- It does nothing to stop the fibrillation in the atrium and may, in fact, hasten the progression to permanent AF.
- It does not reduce stroke risk as do successful PVIs and maze procedures. Thus, the patient must continue on warfarin for life.
- It makes the patient dependent on the pacemaker. If it or the leads malfunction, or the battery runs out the patient may die.
- It does little to prevent the fatigue and reduced exercise capacity felt by some afibbers during an episode.

Fourteen respondents (36% female) underwent AV node ablation + pacemaker implantation procedures. One had a second procedure to replace a pacemaker lead after 6 years. Of the 14 patients, 29% had underlying heart disease; the median age of the patients was 65 years.

Nine patients underwent the AV node ablation as their first procedure in an attempt to alleviate their afib symptoms (44% had underlying heart disease and 60% had permanent afib). Six patients had no further follow-up, while of the remaining three, one had a pacemaker replacement (6 years after the initial one), one had a PVI (partially successful), and one had a maze procedure (partially successful) with no further follow-up.

Two respondents underwent their AV node ablation following a failed PVI and a failed maze procedure respectively. One respondent had his procedure after 2 failed focal ablations, and one had his as a fifth procedure after 3 PVIs and a mini-maze. Finally, one respondent had his AV node procedure after 3 failed right atrial flutter ablations and 3 failed PVIs.

It is somewhat difficult to evaluate the success of an AV node ablation + pacemaker implantation since it, at best, provides symptomatic relief only. Eighty percent of respondents felt (subjectively) that their procedure had been a success, while the remaining 20% felt that it had been partially successful.

Based on this small sample of 14 respondents, it is clear that AV node ablation + pacemaker installation is usually a successful procedure and provides significant symptomatic relief even though it does not eliminate AF. Nevertheless, it is still the procedure of last resort.

Maze Procedure

Twenty-six respondents reported having undergone a full maze procedure – 20 as their initial procedure, 5 after failed PVIs or focal ablations, and 1 after an AV node ablation + pacemaker implantation. The maze group differed significantly from the group of 552 afibbers who underwent catheter ablation. While the percentage of patients in the RF ablation group who had underlying heart disease was only 6%, it was 35% in the maze group. Also, while the percentage of patients having permanent afib was only 15% in the ablation group, it was 33% in the maze group. Both differences were statistically highly significant.

Five of the 26 procedures were cryo-maze. In other words, the maze lesions were applied with a nitrogen-cooled or argon-cooled catheter rather than with RF energy or the cut-and-sew approach. Only 2 of these procedures were successful. One of the unsuccessful patients went on to undergo a pulmonary vein isolation procedure with Dr. Natale, which was a complete success.

Twenty-three patients had gone 6 months or more following their maze procedure and knew the outcome. It is problematical, perhaps even unwise, to pronounce on success rates with only 23 procedures in the sample. Nevertheless, as with catheterization procedures, there would appear to be a definite trend for procedures performed by top-ranked cardiac surgeons to be more successful than those performed by less prominent ones.

TABLE 25

	# of	Success Rate,%		
Surgeon	Procedures	Complete	Partial	Failure
Top-ranked	8	88	0	13
Other	15	33	7	60
Total	23	52	4	43

It is, of course, open to argument who is and who is not "top-ranked", but I do believe that the surgeons in the above group (Drs. Niv Ad, Ralph Damiano, Dale Geiss, Marc Gillinov and Patrick McCarthy) would all fall in this category.

The complete success rate for top-ranked surgeons is thus 88%, very close to the oft-quoted 90% success rate for maze procedures[1,2]. However, the complete success rate for other than top-ranked surgeons is only 33%, very close to the 34% found for other than top-ranked EPs performing RF ablation procedures.

Our results, albeit based on a very small sample, lead to the conclusion that, just as in the case of conventional PVIs, the choice of surgeon or EP is the all-important variable with the type of procedure playing a lesser role in the final outcome.

As reported in the 2006 Ablation/Maze Survey, 7 out of 12 (58%) of patients undergoing the maze procedure experienced one or more adverse events, some of them quite serious. Two suffered a transient ischemic attack (TIA, mini-stroke), one reported excessive fluid retention, and one pericarditis. This rate of serious adverse events is higher than experienced in any other procedure.

A comparison of objective and subjective success rates show that the respondents' subjective impression of outcome is identical to the actual (objective evaluation) when it comes to complete success (no afib, no antiarrhythmics). However, it would seem that respondents were more likely to feel that even a failed procedure (still experiencing afib episodes) was at least partially successful.

	Objective	Subjective
Complete success	52%	52%
Partial success	4%	26%
Failure	43%	22%
Total	**99%**	**100%**

As far as post-procedure problems (trigger avoidance, ectopics, tachycardia, flutter) are concerned, it is clear (Table 26) that a successful maze procedure is far less likely to be accompanied by post-procedure problems than is an unsuccessful one. Although a similar trend was observed for catheter ablations, it is far more pronounced for the full maze procedure.

TABLE 26

Variable *	Complete Success	Failure
Still need to avoid triggers	15%	100%
Still have ectopics	33%	100%
Still have tachycardia	17%	100%
Still have flutter	0%	33%

* As observed at least 6 months following the procedure

The full maze procedure performed by a top-ranked cardiac surgeon provides the best chance of being cured of afib with one single procedure. However, full maze procedures performed by less skilled surgeons tend to be considerably less successful. This, combined with the potential for significant adverse effects (especially associated with the use of the heart/lung machine), would lead one to the conclusion that it may be "overkill" for a paroxysmal afibber, with no underlying heart disease, to select the full maze over a conventional radiofrequency PVI or mini-maze procedure.

This conclusion is supported by the following quote from an article reporting the results of 130 Cox-maze IV procedures, "It is a weakness of this study that we did not examine pulmonary vein isolation in patients who had lone AF. Further data are needed to evaluate the efficacy of this procedure in this group. However, our historical results with the cut-and-sew procedure (Cox-Maze III) had higher success rates in patients who had AF associated with concomitant cardiac pathology as opposed to those who had lone AF".[1]

Of course, the full maze procedure is obviously preferred if other heart surgery is needed.

Mini-Maze Procedure

Forty-one respondents (17% female) reported undergoing a mini-maze procedure, 29 as their initial procedure and 12 after one or more failed radiofrequency (RF) PVIs. The 12 patients had undergone a total of 22 PVIs before their mini-maze. Only 3 of the failed PVIs were performed at top-ranked institutions. A total of 8 patients underwent PVIs (7) or AV node ablation + pacemaker implantation (1) following a failed mini-maze. There were no repeat mini-mazes. The incidence of underlying heart disease was significantly higher in the mini-maze group than in the RF ablation group (20% vs. 6%).

The majority of procedures (84%) used RF energy in creating the ablation lesions, 13% used microwave energy, and the remaining 3% (1 procedure) used high-intensity focused ultrasound (HIFU). The HIFU procedure was unsuccessful as were 3 of the microwave procedures.

The final outcome at least 6 months following the procedure was known for 31 procedures. Of these, 13 were carried out by 4 top-ranked cardiac surgeons.

- Dr. Randall Wolf, University of Cincinnati Hospital - 8 procedures
- Dr. Michael Mack, Medical City, Dallas, TX - 3 procedures
- Dr. James Cox*, Ohio State University Hospital - 1 procedure
- Dr. Adam Saltman**, University of Massachusetts - 1 procedure

* Now medical director at ATS Medical Inc, Minneapolis, MN
** Now at Maimonides Medical Center, Brooklyn, NY

RF-powered catheters or clamps were used for lesion creation in all procedures. The outcomes are presented in Table 27.

TABLE 27

	# of	Success Rate,%		
Surgeon	Procedures	Complete	Partial	Failure
Top-ranked	13	62	8	31
Other	18	50	6	44
Total	31	55	6	39

The average complete success rate for top-ranked cardiothoracic surgeons is 62%. This is very close to the initial procedure complete success rate of 61% experienced at the Cleveland Clinic, but significantly better than the average 50% single procedure complete success rate obtained at the 15 top-ranked RF ablation institutions. Considering both

top-ranked and other institutions, the 55% average complete success rate for the mini-maze is clearly superior to the average single procedure success rate of 34% for RF ablation.

The standard RF ablation can, of course, be repeated, whereas I have not seen any example of full maze and mini-maze patients being given the option of undergoing a second procedure if the initial one fails. The complete success rate after an average of 1.5 RF ablation procedures is 65% for the 15 top-ranked centers and is now 82% at the 3 top-ranked centers – Cleveland Clinic, OH, Hopital Cardiologique du Haut Leveque, Bordeaux, and California Pacific Medical Center, San Francisco. The overall mini-maze success rate of 50% with other than top-ranked surgeons is, however, superior to the "other institutions" RF ablation complete success rate of 32% after repeat ablations.

A mini-maze procedure performed by a top-ranked cardiac surgeon provides the second-best chance (after the full maze procedure) of being cured of afib with one single procedure, although the Cleveland Clinic single procedure success rate of 61% is very close. It is also likely that even a mini-maze performed by a less than top-ranked surgeon will have a substantially better outcome than a standard RF ablation performed by a less than top-ranked EP.

The incidence of adverse events (as per the 2006 survey) tended to be slightly higher than for RF ablations and involved pneumonia (9%), tamponade (4%), serious hemorrhage (4%), and subcutaneous nerve pain (4%). As far as post-procedure problems (trigger avoidance, ectopics, tachycardia and flutter) are concerned, it is clear (see Table 28) that a successful mini-maze procedure is far less likely to be accompanied by post-procedure problems than is an unsuccessful one. A similar trend has also been observed for the maze procedure and RF ablations.

TABLE 28

Variable *	Complete Success	Failure
Still need to avoid triggers	6%	63%
Still have ectopics	25%	100%
Still have tachycardia	10%	40%
Still have flutter	10%	75%

* As observed at least 6 months following the procedure

Published Studies on Effectiveness

Several studies have been published regarding the efficacy of the mini-maze procedure with complete success rates (no afib, no antiarrhythmics) varying between 58% and 91%.

- A group of cardiothoracic surgeons (including Dr. Randall Wolf) reported on the success of 27 mini-mazes performed in 2003-2004. The complete success rate (no afib, no antiarrhythmics) after 3 months was 65%, which compares well with the 62% observed in this survey for top-ranked surgeons. The average hospital stay was 3.3 days and the average procedure time was about 3 hours[3].

- A group led by Drs. James Edgerton and Michael Mack of the Medical City, Dallas Hospital presented at the 2008 Annual Meeting of the American Association for Thoracic Surgery the results of a study involving 150 patients. The majority (55%) of the patients treated had paroxysmal afib, 20% had persistent afib, and the remaining 25% had the permanent variety. The patients were followed for 6 months at which time 58% were in normal sinus rhythm without the use of antiarrhythmics (complete success). The complete success rate for paroxysmal afibbers was 70% versus only 40% for persistent and permanent ones. Procedural adverse events were significantly worse than for standard RF ablations with 2 patients (1.3%) dying on the operating table, 4 patients (2.7%) developing a new heart block, and 2 patients (1.3%) suffering phrenic nerve palsy[4].

- Cardiothoracic surgeons at the Ohio State University treated 32 patients with persistent or permanent afib with laparoscopic full maze procedures and observed a complete success rate of 88%[5].

- A group of American and Japanese cardiothoracic surgeons treated 20 patients (80% paroxysmal, 20% persistent) with the mini-maze procedure and observed a complete success rate of 85% after 6 months. No major adverse events were reported[6].

- An American team based in Florida treated 100 lone afibbers (64% paroxysmal, 11% persistent, 25% permanent) with a mini-maze procedure using microwave energy for lesion creation[7]. The complete success rate after 6 months was only 31% and adverse effects were serious (3 patients died

following the procedure, 2 patients experienced a TIA (mini-stroke), and 2 had a stroke). These results confirm the survey findings of a 25% success rate with microwave energy (based on a sample of only 4 patients).

- A team at the Nebraska Heart Hospital treated 22 paroxysmal afibbers with a mini-maze procedure and observed a complete success rate of 91% after an average follow-up of 18 months[8].

Summary

A total of 94 procedures, other than the conventional RF ablation (PVI), were performed in attempts to eliminate AF. The following observations were made:

- The outcome (at least 6 months after procedure) was known for 12 cryoablation procedures. Four (33%) were fully successful and one (9%) was partly successful. The average single procedure complete success rate of cryoablation is thus 33%, not significantly different from the average single procedure complete success rate of PVI procedures at 34%. There is insufficient data to say what the final success rate would be after repeated cryoablations.

- It is not possible, based on a small sample, to evaluate the success rate of an AV node + pacemaker implantation since it, at best, provides symptomatic relief only. Eighty percent of respondents felt (subjectively) that their procedure had been a success, while the remaining 20% felt that it has been partially successful. Thus, based on a small sample of 14 respondents it would appear that AV node ablation + pacemaker installation is usually a successful procedure and provides significant symptomatic relief even though it does not eliminate the fibrillation of the atria. Nevertheless, it is still the procedure of last resort.

- The full maze procedure performed by a top-ranked cardiac surgeon provides the best chance of being cured of afib with one single procedure (complete success rate of 88%). However, full maze procedures performed by less skilled surgeons tend to be considerably less successful. This, combined with the potential for significant adverse events

(especially associated with the use of the heart/lung machine), would lead one to the conclusion that it may be "overkill" for a paroxysmal afibbers, with no underlying heart disease, to select the full maze over a conventional RF ablation or mini-maze procedure.

- A mini-maze procedure performed by a top-ranked cardiac surgeon provides the second-best chance of being cured of afib with one single procedure. It is also likely that even a mini-maze performed by a less than top-ranked surgeon will have a substantially better outcome than a single standard RF ablation performed by a less than top-ranked EP. However, the risk of adverse effects accompanying the mini-maze procedure is somewhat higher than for RF ablations.

This concludes the evaluation of the 2008 Ablation/Maze Survey. Again, my sincere thanks to all those who participated. A special thanks goes to Mellanie True Hills for providing the references regarding the effectiveness of the mini-maze procedure.

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Appendix A

Glossary of Medical Terms

Ablation
A procedure for destroying heart tissue that is creating abnormal electrical impulses.

Accessory pathway
A collection of muscle fibres that bypass the normal pathway for electrical impulses going from the atria to the ventricles through the atrioventricular (AV) node.

ACE inhibitor
A pharmaceutical drug that inhibits the enzyme which converts angiotensin I to angiotensin II.

Acetylcholine
The neurotransmitter released at parasympathetic (vagus) nerve endings.

Acidosis
A condition in which the blood is excessively acidic (pH below 7.38). It is caused by an imbalance in the bicarbonate-carbonic acid buffer system that keeps the pH of blood within a very narrow range.

Acute
Of rapid onset, severe symptoms and short duration.

Adenoma
A benign tumour of epithelial origin.

Adrenaline
See Epinephrine.

Adrenergic
Pertaining to the sympathetic branch of the autonomic nervous system.

Adrenergic LAF
Lone atrial fibrillation triggered by excessive sympathetic stimulation.

Adrenergic tone
The strength or vigour of the sympathetic branch of the autonomic nervous system.

ADP (adenosine diphosphate)
A compound involved in energy transfer within cells. It consists of adenine, ribose and two phosphate groups.

Afferent
Pertaining to nerves or neurons that carry impulses (information) from an organ to the brain or spinal cord (See also efferent).

Alkalosis
A condition in which the blood is excessively alkaline (pH above 7.44). It is caused by an imbalance in the bicarbonate-carbonic acid buffer system that keeps the pH of blood within a very narrow range.

Aneurysm
A bulge formed by dilation of the wall of the heart or blood vessel.

Angina pectoris
Pain in the center of the chest, which is induced by exercise and relieved by rest. Angina occurs when the demand for blood exceeds the supply and is usually caused by atherosclerosis of the coronary arteries.

Antiarrhythmic
Pharmaceutical drug designed to prevent abnormal heart rhythms or to convert abnormal rhythms to normal sinus rhythm.

Anticoagulant
Pharmaceutical drug designed to prevent blood clotting.

APC [activated protein-C resistance]
A condition caused by the presence of a mutation of blood coagulation factor V (factor V Leiden). APC is associated with an increased risk of venous thromboembolism.

Apoptosis
Self-destruction (suicide) of individual cells to avoid a threat to the survival of the organism as a whole.

Arrhythmia
An abnormal heart rhythm.

Atherosclerosis
The development of fatty plaque and scar tissue on the inner wall of the arteries – eventually leading to obstruction of blood flow and an increased risk of thrombosis.

Artery
A blood vessel that carries blood away from the heart.

Atria
The two upper chambers of the heart. The right atrium receives returning blood from the body and the left atrium receives oxygenated blood from the lungs.

Atrial appendages
Small pouches connected to the right and left atria. The left atrial appendage (LAA) is associated with the generation of blood clots during atrial fibrillation.

Atrial fibrillation
A chaotic movement of electrical impulses across the atria leading to a loss of synchrony between the atria and the ventricles.

Atrial flutter
An abnormal, sustained, rapid contraction of the atria. The rhythm is rapid, but regular as opposed to atrial fibrillation where it is rapid and irregular.

Atrial natriuretic peptide [ANP]
A hormone formed in the atria. ANP is involved in regulating blood pressure and salt and water balance in body fluids.

Atrial refractory period [ARP]
See Refractory period

Atrioventricular (AV) node
A set of specialized heart cells that conducts the normal electrical impulses from the atria to the ventricles.

Auscultation
The act of listening for sounds in the body to ascertain the functioning of the heart, lungs, abdomen and other organs (usually done with a stethoscope).

Autonomic nervous system [ANS]
The part of the central nervous system that is not under conscious control (involuntary). It controls the body's internal organs including the heart and digestive system and is responsible for regulating blood pressure.

AV node ablation
Full or partial destruction (by ablation) of the AV node's ability to conduct signals between the atria and ventricles. A permanent pacemaker is required after AV node ablation.

Baroreceptors
Specialized muscle cells located in the walls of the heart and major arteries. They "measure" blood pressure by stretching or relaxing as blood flows past them.

Beta-blocker
A pharmaceutical drug which blocks the receptor sites for the neurotransmitters (catecholamines) used by the sympathetic (adrenergic) branch of the autonomous nervous system.

Bigeminy
An abnormal heart rhythm in which a normal heartbeat (originating from the SA node) is followed by an ectopic beat (originating outside the SA node) in rapid succession.

Biopsy
The removal of a small piece of living tissue from the body for microscopic examination. Biopsy is often carried out with a special hollow needle (needle biopsy) to minimize invasiveness and discomfort.

BMI [body mass index]
Equals a person's weight (in kilograms) divided by height in meters squared (BMI= kg/m^2). A BMI between 18.5 and 24.9 is ideal; above 25 is overweight and above 30 is obese.

Bradycardia
An abnormally slow heart beat.

Brain natriuretic peptide [BNP]
A hormone released almost exclusively from the ventricular myocardium. Elevated levels may indicate heart failure.

Bundle of His
A small bundle of specialized cardiac muscle fibres connecting the AV node with the upper part of the ventricles.

Calcium-channel blocker
A pharmaceutical drug that inhibits the flow of calcium ions through or across cell membranes. It is used in the treatment of stroke and certain heart conditions.

Carcinoma
A malignant tumour of epithelial origin.

Cardiogenic
Originating in the heart

Cardiogenic emboli
Blood clots originating in the heart

Cardioversion
The conversion of an irregular heart rhythm to normal sinus rhythm. Cardioversion can be done with drugs or through an electric shock administered to the chest area.

Carotid artery
The artery that carries blood from the heart to the brain. It is situated in the front of the neck.

Catecholamines
A group of chemical compounds (amines) derived from tyramine and tyrosine. The group includes epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine.

Catheter
A tube designed to be inserted into a narrow opening or hollow organ such as the urinary bladder or a vein. The catheter is used to drain fluids or to allow the insertion of special instruments used for imaging or ablation.

Catheter ablation
Destruction of tissue by the application of electrical current, usually at radio frequencies, via a catheter threaded through a vein to reach the area to be ablated (AV node, pulmonary veins, “hot spots” in the atria).

Cerebrovascular event
See Stroke.

Chronic
Persisting over a long period of time.

Circumferential pulmonary vein isolation [CPVI]
An ablation procedure involving the creation of two rings of lesions in the left atrium; one completely enclosing the left pulmonary veins and another completely enclosing the right pulmonary veins; the two rings are usually joined by a linear lesion. Also known as the Pappone method.

Coagulation (of blood)
Process whereby blood is converted from a liquid to a solid state.

Comorbidity
A disease condition accompanied by one or more unrelated disease conditions.

Congestive heart failure [CHF]
Failure of the heart to pump sufficiently strongly to prevent the accumulation of fluid in the lungs.

Coronary arteries
The arteries that supply the heart itself with oxygenated blood.

Cortex
The outer part of the adrenal gland. Aldosterone, cortisol and DHEA (dehydroepiandrosterone) are synthesized here.

Couplet
An abnormal heart rhythm involving two ectopic beats in a row.

CRP (C-reactive protein)
A general indicator of systemic inflammation and infection.

Cytokine
A chemical messenger protein released by white blood cells to facilitate communication by immune system cells.

Deep vein thrombosis [DVT]
A condition where a blood clot is formed in a deep vein, usually in the legs.

Depolarization
The sudden surge of ions across heart cell membranes that initiates the contraction of the heart.

Diastolic
Pertaining to the time period between fillings of the ventricles. The diastolic pressure is the lower of the two readings reported when measuring blood pressure.

Diuretic
An agent that increases the excretion of urine.

Docosahexaenoic acid [DHA]
A main component of fish oils.

Echocardiogram
An ultrasound picture of the heart as it beats.

Ectopic beat
A heart beat that is initiated at a location other than the sinoatrial node. The junction between the left atrium and the pulmonary veins is a primary spawning ground for ectopic beats.

Edema
Swelling caused by an abnormal accumulation of fluid in body tissues.

Efferent
Pertaining to nerves or neurons that carry impulses (instructions for action) from the brain or spinal cord to a target organ or muscle.

Ejection fraction
The proportion of the blood volume in the left ventricle that is actually pumped out in each

heartbeat. The proportion for a healthy heart is 50-60 per cent. A value of 40 per cent or below indicates ventricular dysfunction.

Electrocardiogram [ECG]
A recording of the electrical activity of the heart during contraction.

Electrolytes
Chemical substances that dissociate into two or more ions when dissolved in water.

Embolism
A condition in which a blood clot becomes lodged in an artery and obstructs the flow of blood [embolic].

Endarterectomy
Surgical removal of the inner lining of an artery that is clogged with atherosclerotic build-up.

Endogenous
Originating from within an organism, cell or tissue.

Endothelium
The single layer of cells that line the heart, blood vessels and lymphatic vessels [endothelial].

Enzyme
A protein-based substance (catalyst) that speeds up the rate of a biological reaction without being consumed in the process.

Epidemiology
Dealing with the study of the causes, distribution and control of diseases in populations [epidemiologic].

Eicosapentaenoic acid [EPA]
A main component of fish oils

Epithelium
Membranous tissue that covers most internal and external surfaces of the body and its organs [epithelial].

Exogenous
Derived or developed from outside the body, originating externally.

Epinephrine
A hormone secreted by the medulla of the adrenal gland. Also known as adrenaline.

Factor V Leiden
A mutation in blood coagulation factor V that results in an increased tendency to blood clotting – especially deep vein thrombosis.

Fibrillation
Rapid and chaotic beating of the heart.

Fibrinolysis
The process by which blood clots are removed from the circulation. It involves digestion of insoluble fibrin by the endogenous enzyme plasmin [fibrinolytic].

Focal Ablation
The original radio frequency ablation procedure in which specific active foci of aberrant

impulses are located and ablated.

Framingham Heart Study
A large epidemiologic study begun in 1948 with the purpose of discovering the causes of heart disease and stroke. The study now involves thousands of men and women and their offspring from the town of Framingham in Massachusetts.

Gastrointestinal
Relating to the stomach and intestines [gastrointestinal tract].

Glucose tolerance test
A test used in the diagnosis of diabetes and impaired glucose tolerance. It measures how well the body deals with sugar (glucose).

Glycemic index
A measure of how much and how quickly glucose is released and absorbed from a carbohydrate food. Pure glucose has a value of 100.

Heart failure
See Congestive heart failure.

Heart rate variability [HRV]
A measure of the beat- to-beat variability in heart rate.

Hematoma
A localized swelling of blood resulting from a break in a blood vessel.

Hemorrhagic stroke
See Stroke

Holter monitor
A portable device for measuring heart rhythm over a 24-hour period.

Homocysteine
A sulphur-containing amino acid used by the body in cellular metabolism and the manufacture of proteins.

Hyperhomocysteinemia
An elevated blood level of homocysteine.

Hyperlipidemia
An excess of fats or lipids in the blood.

Hypertension
A blood pressure that is persistently above the upper limit of the reference range (140/90).

Hyperthyroidism
An overactive thyroid gland. The condition is characterized by increased metabolic rate, high blood pressure and a rapid heartbeat.

Hypocalcemia
An abnormally low blood level of calcium.

Hypoglycemia
A lack of glucose in the blood stream. The condition can cause sweating, mental confusion, atrial fibrillation and muscle weakness.

Hypokalemia
An abnormally low blood level of potassium.

Hypomagnesemia
An abnormally low blood level of magnesium.

Hyponatremia
An abnormally low blood level of sodium

Hypotension
An abnormally low blood pressure.

Hypothyroidism
An underactive thyroid gland. The condition is characterized by fatigue, hair loss, feeling cold, constipation and skin pallor.

ICD
Implantable cardioverter-defibrillator.

Idiopathic
Of no known cause.

IL-6 (interleukin-6)
A cytokine secreted by macrophages (large white blood cells that destroy or ingest foreign substances) to stimulate immune response to trauma.

IL-10 (interleukin-10)
An anti-inflammatory cytokine that can inhibit the production of inflammatory cytokines such as TNF.

Incidence
The extent or frequency of occurrence.

Infarction
Localized cell death (necrosis) resulting from obstruction of the blood supply.

INR
International Normalized Ratio. A measure of the blood's tendency to coagulate (form clots) when on warfarin (Coumadin). A normal INR is 1.0. Warfarin dose is usually adjusted to give an INR between 2.0 and 3.0.

Intermittent claudication
Muscle pain, usually in the calf muscles, that is brought on by exercise and relieved by rest. It is usually caused by atherosclerosis of the arteries feeding the affected limb.

Intracardiac Echocardiography [ICE]
An ultrasound technique for visualizing the inside of heart chambers.

Intracellular
Situated or occurring inside a cell.

Intracranial
Within the head.

Ion
An electrically charged atom or molecule.

Ion channel
A pore in a cell's membrane that provides a channel for ions to cross the membrane.

Ischemia
Inadequate blood flow to the heart or other body parts [ischemic].

Ischemic stroke
See Stroke

Left atrial appendage
See Atrial appendages.

Left ventricular dysfunction
Inadequate pumping capacity of the left ventricle. Characterized by a left ventricular ejection fraction below 40 per cent.

Macrophages
Large scavenger cells found in connective tissue and in many major organs and tissues including the liver, lymph nodes, spleen, bone marrow and central nervous system.

Malondialdehyde (MDA)
A prominent marker of oxidative stress formed by the oxidation of polyunsaturated fatty acids.

Mast cells
Large cells in connective tissue that release heparin, histamine and serotonin in response to inflammation or allergens.

Maze procedure
A surgical procedure that involves the creation of a pattern of scar tissue to contain and channel the heart's electrical impulses and thereby prevent atrial fibrillation.

Medulla
The inner part of the adrenal gland. Epinephrine and norepinephrine are synthesized here.

Mitral stenosis
A narrowing of the opening of the mitral valve.

Mitral valve
A valve that allows blood to flow between the left atrium and the left ventricle while preventing back flow.

Mitral valve prolapse [MVP]
A usually benign abnormality of the mitral valve resulting in regurgitation (back flow) of blood from the left ventricle to the left atrium.

Monocyte
A variety of white blood cells whose purpose is to ingest foreign particles such as bacteria and tissue debris.

Mortality
Incidence of death in a given period.

Myocardial infarction [heart attack]
Destruction of heart tissue resulting from obstruction of the blood supply to the heart muscle.

Myocarditis
An acute or chronic inflammation of the heart muscle.

Myocardium
The middle of the three layers that form the wall of the heart. It is composed of muscle fibres.

Myocyte
A muscle cell.

Myxoma
Benign gelatinous tumour of connective tissue. Atrial myxoma most commonly involves a tumour in the left atrium.

Necrosis
Death of cells through injury, disease or obstruction of blood supply.

Neutropenia
Decrease in the number of neutrophils (a type of white blood cell) resulting in an increased susceptibility to infection.

Nitric oxide [NO]
A colourless gas produced in cellular metabolism. It is involved in oxygen transport to tissues, the transmission of nerve impulses and the relaxation of blood vessel walls.

Nitrotyrosine
A marker for cell damage and inflammation caused by reactive nitrogen species (nitrogen oxide and peroxynitrite).

Non-valvular atrial fibrillation
Atrial fibrillation that is not caused by malfunctioning or damaged heart valves.

Norepinephrine
The neurotransmitter released at sympathetic (adrenergic) nerve endings. Also known as noradrenaline.

Normal sinus rhythm [NSR]
The normal rhythm of the heart when beats are initiated only at the sinoatrial node.

Ostial PVI
A pulmonary vein isolation procedure where the ablation lesions are placed in the left atrium around the openings of the pulmonary veins rather than inside the pulmonary veins. The ostial procedure eliminates or sharply reduces the risk of pulmonary vein stenosis.

On-demand approach
A method of self-terminating atrial fibrillation episodes. It involves taking propafenone or flecainide immediately following the start of the episode. Also known as the pill-in-the-pocket approach.

Oxidative stress
A condition that occurs when the body's natural antioxidant defences are overwhelmed by reactive oxygen species and other free radicals.

Pacemaker
An implanted device meant to provide small electric shocks to the heart to initiate heartbeats (contractions) at a predetermined rate.

Palpitation
A sensation of a rapid, irregular heart beat.

Parasympathetic
Pertaining to the parasympathetic branch of the autonomic nervous system.

Paroxysmal
Occurring at intervals (intermittent).

Peripheral arterial disease [PAD]
Atherosclerosis in arteries other than the coronary arteries. Intermittent claudication may occur if the atherosclerotic deposits are blocking the arteries feeding the legs.

Permanent LAF
Continuous lone atrial fibrillation that does not respond to cardioversion.

Persistent LAF
Lone atrial fibrillation episodes lasting more than seven days, but amenable to cardioversion.

Pheochromocytoma
A tumour of the adrenal gland that produces epinephrine and norepinephrine.

Platelet
Blood cell involved in the initiation of blood clotting [thrombocyte].

Platelet inhibitor
A drug that prevents the aggregation of platelets.

Plaque
A build-up of cholesterol and fatty substances on the inner lining of arteries.

Postprandial
Occurring after a meal, especially dinner.

Premature atrial complex [PAC]
A premature heart beat originating in the atrium other than at the sinoatrial node.

Premature ventricular complex [PVC]
A premature heart beat originating below the atrioventricular node, often in the ventricular muscle itself.

Prevalence
The total number of cases of a disease in a given population at a specific time.

Proarrhythmic
Capable of inducing arrhythmia.

Prophylaxis
Action taken to prevent disease [prophylactic].

Prostaglandin
A hormonelike compound synthesized in the body from 20-carbon unsaturated fatty acids, notably arachidonic acid. Prostaglandins are involved in a wide range of physiological functions including control of blood pressure, contraction of smooth muscle and modulation of inflammation.

Prothrombin time
A measure of the blood's tendency to clot when medicated with warfarin. See INR.

PUFA
Polyunsaturated fatty acid.

Pulmonary embolism
A blood clot lodged in the pulmonary artery.

Pulmonary vein ablation [PVA]
Ablation of sources of ectopic heartbeats located at the junction of the left atrium and the pulmonary veins.

Pulmonary vein isolation [PVI]
Isolation of the pulmonary veins from the left atrium by ablating (generating lesions) a ring around each pulmonary vein.

Pulmonary veins
The veins draining oxygenated blood from the lungs to the left atrium.

Pulse pressure
Difference between systolic and diastolic blood pressure

Purkinje fibres
A group of specialized heart cells that conduct electrical impulses in the ventricles.

QT Interval
The duration of the activation and recovery of the ventricular myocardium. A prolonged QT interval is associated with ventricular arrhythmias.

Refractory period
The rest period following a contraction of the heart muscle. The cell does not respond to stimulation during this period.

Reperfusion
The restoration of blood flow to an organ or tissue that has had its blood supply cut off due to a stroke or heart attack. Reperfusion is associated with increased free radical activity.

Rheumatic heart disease
Heart disease caused by rheumatic fever.

Run
An abnormal heart rhythm characterized by four or more ectopic beats in a row.

sICAM-1 (soluble intercellular adhesion molecule-1)
An important biomarker of inflammatory processes, especially in atherosclerosis and cancer.

Sinoatrial (sinus) node
The specialized (pacemaker) tissue that initiates a heart beat. It is located near the top of the right atrium.

Sinus rhythm
See Normal sinus rhythm.

Stasis
Stagnation or cessation of flow; for example, of blood or lymph fluid.

Stenosis
A constriction or narrowing of a duct or passage; for example, pulmonary vein stenosis.

Stroke
An event that damages nerve cells in the brain. It is caused by

an interruption of the oxygen supply to the brain due to a blood clot (ischemic stroke) or a burst blood vessel (hemorrhagic stroke).

Subcutaneous
Beneath the skin.

Supraventricular
Located above the ventricles, that is in the atria or atrioventricular node.

Supraventricular tachycardia [SVT]
A rapid, but regular heart rate caused by a fault in the conduction system around the atrioventricular node.

Suture
The closure of a wound or incision with material such as silk or catgut. The term is also used to describe the material used in closing the wound or incision.

sVCAM-1 (soluble vascular cell adhesion molecule-1)
An important biomarker of inflammatory processes, particularly those involving endothelial cells (cells lining the heart and blood vessels). There is evidence that fish oil can decrease sVCAM levels in men over the age of 55 years.

Sympathetic
Pertaining to the sympathetic branch of the autonomic nervous system.

Systemic
Relating to or affecting the body as a whole.

Systolic
Pertaining to the time at which the ventricles contract. The systolic pressure is the higher of the two readings reported when measuring blood pressure.

T-cells
A specialized kind of white blood cells (lymphocytes) that help identify foreign cells and antigens so that killer cells can dispose of them.

Tachycardia
A rapid, but regular heart beat usually in excess of 100 bpm.

Tamponade
Compression of the heart caused by the build-up of fluid or blood in the space between the sac (pericardium) surrounding the heart and the heart muscle (myocardium) itself.

Thallium stress test
A test used to assess the blood flow through the coronary arteries before and after exercise.

Thrombosis
A condition in which blood changes from a liquid to a solid state, i.e. forms a clot [thrombotic].

Thrombus
A blood clot.

Thrombolysis
The dissolution of a blood clot by the infusion of an enzyme, such as streptokinase, into the blood [thrombolytic].

Thyrotoxicosis
A serious condition resulting from an excess of thyroid hormones.

TNF (tumour necrosis factor alpha)
A cytokine that promotes the inflammatory response which in turn causes many of the problems associated with autoimmune disorders such as rheumatoid arthritis, Crohn's disease, asthma, psoriasis, etc.

Transesophageal
Through or across the esophagus. The term is often applied to a special form of echocardiography used to check for blood clots in the left atrial appendage.

Torsade de Pointes
A distinctive form of ventricular tachycardia associated with a prolonged QT interval.

Transient ischemic attacks (TIAs)
A sudden, temporary loss of neurological function caused by blockage of small arteries supplying blood to the brain (mini-stroke).

Transthoracic
Through or across the chest. The term applies to the standard form of echocardiography.

Tricuspid valve
A valve that allows blood to pass between the right atrium and the right ventricle.

Trigeminy
An abnormal heart rhythm in which every third beat is ectopic (originating outside the SA node).

Triplet
An abnormal heart rhythm involving three ectopic beats in a row.

Vagal
Pertaining to the parasympathetic branch of the autonomic nervous system.

Vagal LAF
Lone atrial fibrillation triggered by excessive parasympathetic stimulation.

Vagal tone
The strength or vigour of the parasympathetic branch of the autonomic nervous system.

Vasodilatation
An increase in the diameter of blood vessels, especially arteries. It is brought about by a relaxation of vessel walls mediated, for example, by nitric oxide.

Vagus nerve
The tenth cranial nerve originating in the brain stem. It enervates the heart, gastrointestinal tract and larynx (voice box).

Valsalva manoeuvre
A manoeuvre that increases vagal tone. It is performed by attempting to forcibly exhale while keeping the mouth and nose closed for about 15-30 seconds. It may sometimes help to abort an episode of supraventricular tachycardia or adrenergic LAF.

Vein
A blood vessel that carries blood towards the heart.

Vena cava
The large vein(s) that returns blood from the body to the heart (right atrium).

Ventricles
The two lower chambers of the heart.

Ventricular fibrillation
An often-fatal cardiac arrhythmia characterized by rapid, irregular fibrillation of the ventricles. Ventricular fibrillation is the main cause of sudden cardiac death (cardiac arrest).

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